

ABSTRACTS

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B-1

Development of innovative in vitro and in vivo patient-derived cancer models for translational studies in G1/G2 gastroenteropancreatic neuroendocrine tumors

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BACKGROUND

Well-differentiated gastroenteropancreatic neuroendocrine tumors (GEP-NETs) grow slowly but are nonetheless lethal when advanced. Despite progress, effective systemic treatments for GEP-NETs remain limited. A key barrier is the scarcity of clinically relevant models that accurately reflect human GEP-NET biology. To address this important gap, we have conducted the following studies.

METHODS

Doxycycline (Dox)-inducible TP53R273H and SV40LT lentiviruses, marked with EGFP, were generated, and characterized. Cells digested from 21 surgically resected primary or metastatic tissues of G1/G2 GEP-NETs were transduced with these lentiviruses to produce Dox-inducible genetically modified PDOs (GM PDOs). GM PDOs from PanNETs transduced with luciferase lentivirus were injected into pancreata of NSG mice to generate orthotopic GM PDO-derived xenografts (GM PDXs). The genetic and biological signatures of GM PDOs were examined and compared to their original tumor cells through WGS and RNA-seq analyses. Cell growth rates of GM PDOs cultured with Dox-on, and Dox-off conditions were quantified by measuring EGFP fluorescence intensity. Tumor growth of GM PDXs was monitored through bioluminescence imaging. Expression of NET markers, Ki67, p53 (R273H), and SV40LT in GM PDOs with Dox-on and Dox-off conditions, their original tumors and GM PDXs was measured by IHC staining.

RESULTS

A total of 12 GM PDOs were successfully generated, including 6 out of 10 PanNETs (60%), 5 out of 10 intestinal NETs (50%), and 1 gastrinoma (100%), achieving an overall success rate of 57%. WGS results showed that these GM PDOs maintained chromosome copy number and structure variants, gene mutations and tumor mutational burdens, of their original tumors. Cell proliferation of GM PDOs accelerated with Dox treatment; Dox withdrawal stopped TP53R273H and SV40LT expression, slowed cell growth, decreased Ki67 expression, and restored CHGA, SYP and SSTR2 expression and cell signaling pathways, suggesting that the effects of Dox-inducible p53R273H and SV40LT proteins on biological changes in GM PDOs were reversible, demonstrating that GM PDOs in Dox-off condition were similar to the original tumors. Furthermore, one orthotopic GM PDX model from a G2 PanNET was successfully generated, in which luminescent density gradually but significantly increased from 2 to 8 weeks post-injection. Histologic examination and IHC staining results confirmed GM PDX lesions with strong expression of CHGA, SYP and SSTR2 proteins.

CONCLUSIONS

Innovative in vitro and in vivo patient-derived cancer models that could recapitulate the genomic and biological features of human G1/G2 GEP-NETs were successfully developed for the first time. These models yield unique materials enabling translational studies in GEP-NETs.

ABSTRACT ID 28437



B-2

Spatial Transcriptomics of Multifocal Ileal Neuroendocrine Tumors Reveals Tumor Heterogeneity based on Tumor Microenvironment and New Biomarkers

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BACKGROUND

Ileal neuroendocrine tumors (i-NETs) are characterized by a high incidence of multiple primary tumors (>30-40%) and production of serotonin/other hormones. Recent whole genome sequencing analyses revealed an absence of shared somatic variations among synchronous primary tumors, so the mechanisms underlying multifocal tumor development are not known. In this study, we evaluated gene expression patterns of multifocal i-NETs with spatial resolution in order to develop new hypotheses about tumorigenesis focusing on the tumor microenvironment.

METHODS

FFPE blocks of surgically resected specimens from 4 patients with multifocal i-NETs were used. Tissue microarrays were constructed from 72 cores (18 one-mm cores per patient). Spatial gene expression libraries were constructed using Visium v1 (10x Genomics). A total of 8,295 spots were analyzed: a median of 3,102 genes, 5,944 UMI counts per spot, and a total of 16,778 genes were detected in each capture area. R packages including Seurat, clusterProfiler, and monocle3 were used for data analysis.

RESULTS

Spatial transcriptomics analysis reliably captured spatial information of malignant and non-malignant cells in distinct tissue compartments within the ileum and regional lymph node/mesenteric masses. Unsupervised clustering demonstrated differences of the i-NET in various microenvironments—mucosa, submucosa, muscularis propria, and intranodal/perinodal regions of the lymph node/mesenteric masses. In all 4 patients, gene expressions of tumor cells in the mucosa were similar among multifocal tumors while tumor cells in other microenvironments clustered separately. Trajectory analysis was consistent with the supposition that tumors in the mucosa are likely the origin of i-NETs found in the other microenvironments. Tumor cells in all microenvironments exhibited characteristic gene expression patterns of serotonin receptors (HTR1B, HTR1D, and HTR7), ghrelin receptor (GHSR), GIP receptor (GIPR). Over-representation or enrichment analysis found that tumor cells in the mucosa or those with potential for metastasis exhibited overexpression of specific gene sets, including genes related to lipid metabolism.

CONCLUSIONS

This is the first spatial transcriptomics analysis of multifocal i-NETs revealing similarities among tumors located in the mucosa and distinct clustering of tumors situated in other microenvironments. The finding that tumor heterogeneity in multifocal i-NETs varies depending on the microenvironment has not been previously described. The spatial data also reveal known, as well as, new biomarkers of i-NETs. In particular, we identified serotonin and other hormone receptors—some of which may be tumor specific—suggesting possible endocrine/paracrine signaling in i-NETs.

ABSTRACT ID 28490



B-3

Investigating the Role of Oncometabolites in von Hippel Lindau disease-related Pancreatic Neuroendocrine Neoplasms

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BACKGROUND

Von Hippel Lindau (VHL)-related pancreatic neuroendocrine tumors (PNETs) are distinct from sporadic PNETs (sPNETs), exhibiting unique genetic and clinical traits. Pseudohypoxia, resulting from VHL protein deficiency, leads to robust metabolic shift. Yet, its effect on vPNET neoplastic drive remains elusive.

METHODS

Metabolomics analysis was performed on vPNETs and sporadic PNET (sPNET) samples through LC-MS. Data were processed using MetaboAnalyst. Single nucleus RNA sequencing (snRNA-seq) analysis was conducted on eight samples (five sPNETs and three vPNETs), including clustering and annotation via the Seurat package, copy number alteration analysis, pathway enrichment analyses, cell trajectory, and pseudo-time analysis. Immunofluorescence staining was carried out on tumor samples using synaptophysin and ADORA2B antibodies.

RESULTS

In unbiased metabolomic profiling of vPNETs (n=3) and sPNETs (n=5), we found elevated adenosine monophosphate (AMP) levels in vPNETs that were redetected in a validation cohort. Through snRNA-seq, we identified malignant NE cells in each sample. Copy number alteration analysis revealed distinct changes in vPNET, with copy number losses in chromosomes 4 and 5, while sPNET showed gains in chromosomes 4, 5, 17, 19, and 20. Transcriptome-based pathway analysis of malignant cells demonstrated enrichment of hypoxia, glycolysis, apoptosis, and the PI3K-AKT-MTOR pathways in vPNET vs. sPNET. Pseudo-time analysis showed the origin and progression of malignant cells from non-malignant neuroendocrine cells. In our multi-omics analysis, combining metabolomics with snRNA-seq data, we found that purine metabolism was enriched in the top 50 variance metabolites corresponding to hypoxia-related genes. Immunofluorescence studies demonstrated a weak but positive expression of the adenosine 2B receptor expression on neuroendocrine cells.

CONCLUSIONS

We revealed the possible involvement of the adenosine pathway in the pro-tumoral drive of vPNET and characterized distinct cell types and genetic alterations between vPNETs and sPNETs. Our findings shed light on metabolic and cellular disparities between these tumor subtypes, offering insights for targeted therapeutic strategies.

ABSTRACT ID 28541

B-4

Hedgehog signaling drives glial cell plasticity and oncogenic reprogramming in gastroenteropancreatic neuroendocrine tumors

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BACKGROUND

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) represent heterogeneous malignancies whose cellular origins remain poorly understood. *Men1*-driven reprogramming of neural crest-derived glial cells was recently implicated in GEP-NET development. In these studies, hyperactivation of the Sonic hedgehog (SHH) signaling pathway known to pattern neural crest cell fate coincided with the neuroendocrine phenotype in mice. Here, we investigated the hypothesis that loss of MENIN encoded by the *MEN1* gene promotes SHH-mediated reprogramming of enteric glial cells to acquire a neuroendocrine cell fate.

METHODS

Men1 was deleted in glial cells by expressing Cre recombinase downstream of the human glial fibrillary acidic protein promoter (*GFAP^{ΔMen1}*). Hedgehog (HH) activation of *Men1*-deficient glial cells was blocked by deleting the gene encoding primary ciliary protein KIF3A required for transducing SHH signaling. The resulting *GFAP^{ΔMen1}* mice were evaluated for NET development and dysregulated hormone activity. Induction of HH signaling was confirmed in primary enteric glial cultures upon *Men1* silencing. Hyperactivation of SHH in human and mouse GEP-NETs was evaluated by immunofluorescent staining and western blot. Human and mouse tumoroids were treated with an agonist and inhibitors of HH signaling and evaluated for ERK/AKT activation, proliferation, and transcript fluctuations indicative of neural crest cell reprogramming.

RESULTS

GFAP^{ΔMen1} mice developed NETs in the pancreas, pituitary, and small intestine. Impaired SHH activation in *GFAP⁺/Men1^{-/-}* cells abolished the development of NETs and restored hormone levels to that of wild type mice. *Men1* silencing in enteric glial cultures stimulated HH signaling and upregulated the expression of neural progenitor and neuroendocrine transcripts coincident with downregulation of glial lineage genes. Human and mouse GEP-NETs overexpressed SHH and HH pathway components. Functionally, SHH treatment activated ERK/AKT signaling, cell proliferation, and the expression of neuroendocrine transcripts in GEP-NET tumoroids whereas pharmacological inhibition of HH signaling reversed these effects.

CONCLUSIONS

Our observations implicate neural crest-derived glial cells as potential neuroendocrine cell precursors that are susceptible to transformation through increased HH signaling upon loss of MENIN. These studies warrant future investigation into the delivery of Hedgehog inhibitors in the adjuvant setting for the treatment of GEP-NETs.

ABSTRACT ID 28549

B-5

Single-nucleus transcriptome profiling of enterochromaffin cells in SI-NET patients

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BACKGROUND

Small intestinal neuroendocrine tumors (SI-NETs) are one of the major cancer subtypes of the small bowel. Their putative cells-of-origin are enterochromaffin cells, which account for less than 1% of the intestinal epithelium. Enterochromaffin cells are a specialized type of enteroendocrine cells that synthesize, store and secrete ~90% of the serotonin (5-hydroxytryptamine or 5-HT) in the human body. The low tumor mutational burden and the presence of only few recurrent genomic driver alterations in SI-NETs have motivated the search for other potential causes of SI-NET pathogenesis, including transcriptomic and epigenomic profiling of these lesions. These studies have been limited, however, by the lack of a reference for enterochromaffin cells. The goal of this project has been to characterize the gene expression landscape of enterochromaffin cells in the ileum of SI-NET patients, and to form a reference for cancer-to-normal cell comparisons.

METHODS

Our sample cohort consisted of 21 fresh-frozen normal ileum specimens from 12 multi- and 9 unifocal SI-NET patients. To identify subpopulations of enterochromaffin cells within each sample, single-nucleus RNA (snRNA) sequencing was performed using 10x Chromium Single Cell 5' High-Throughput v2 technology. Seurat v5 and Harmony R packages were used for the data analysis and integration of the samples, respectively. The identification of enterochromaffin cells in our data was based on four cell markers: SLC18A1, TPH1, CHGA and CHGB.

RESULTS

A total of 142,362 high-quality nuclei were available for our analysis. After the integration of snRNA sequencing data from all 21 normal ileum samples, five most variable genes identified were *DEFA5*, *CNTNAP2*, *DEFA6*, *CHGA*, and *CTNNA2*. For example, *DEFA5* and *DEFA6* are known cell markers for Paneth cells, and *CHGA* for enteroendocrine cells. We successfully detected an enteroendocrine cell cluster in our integrated data set, which included 877 nuclei, and located enterochromaffin cells within this cluster. We are currently calculating the total number of enterochromaffin cells in our data set, and subsequently, we will assess their transcriptomic profile.

CONCLUSIONS

Our results indicate that snRNA sequencing can capture enterochromaffin cells within normal ileal tissue. We will next use the transcriptomic profile of enterochromaffin cells as a reference for cancer-to-normal cell comparisons in a cohort of 10 SI-NETs. A better understanding of the cellular and molecular mechanisms that underlie SI-NETs is essential for the non-invasive management, early detection and prevention of these tumors.

ABSTRACT ID 28589

B-6

A novel hormone based anti-SSTR bispecific T-cell engager for the treatment of neuroendocrine tumors

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BACKGROUND

Somatostatin receptor 2 (SSTR2) is overexpressed in well-differentiated NETs. We designed a novel bispecific T-cell engager targeting SSTR2 via Somatostatin-14, the hormone that physiologically binds the SSTR2, linked with a scFV-based anti-CD3.

METHODS

The recombinant protein was expressed in *Trichoplusia-ni* cells, isolated and characterized by chromatography. Flow cytometry and Image Stream flow cytometry were used to determine the interaction of the molecule with CD3 and SSTR2. Target 293T cells were stably transduced to concurrently express SSTR2 and GFP or GFP only. Effector CD3+ T cells and target cells were co-incubated in the absence or presence of the engager at different concentrations. The formation of immune synapses was assessed by measuring actin rearrangement in T-cell target cell doublets and LFA-1 expression using ImageStream and IncuCyte. The engager-induced T-cell activation and cytotoxicity were evaluated by ELISA and real-time quantitative live-cell imaging. Tumor-infiltrating lymphocytes (TILs) from different tumor regions and autologous tumoroids from pancreatic NET liver metastasis were cocultured in the presence of the molecule at serial concentrations and the engager-induced activation of TILs was measured by ELISA.

RESULTS

The T-cell engager was detected by flow cytometry on approximately 85% of T-cells at a concentration of 100nM. The engager interaction with SSTR2+ and its subsequent internalization was detected by image stream between 100nM and 20nM. The induction of immunological synapses by the engager, measured as actin rearrangement and LFA-1 expression on T-cells, was significantly higher in the presence of the receptor compared to the control. IFN- γ , TNF- α and Granzyme-B secretion was significantly higher when the T-cells were co-cultured with SSTR+ 293T cells in the presence of the engager at 100nM and 20 nM as compared with conditions using SSTR- 293T cells or in absence of the molecule. Additionally, the 20nM and 100nM engager exhibited cytotoxic activity when added to SSTR+ 293T cell cultures in the presence of T-cells in a dose dependent way. The engager was also able to elicit IFN-gamma secretion by TILs when co-cultured with autologous tumoroids at concentrations of 20nM, 60nM, and 100nM. Notably, this effect was retained when TILs failing to show cytotoxic activity per se were co-cultured with autologous tumoroids.

CONCLUSIONS

To our knowledge, this is the first T-cell engager to incorporate a hormone in one binding site, exerting a dose-dependent cytotoxic activity against SSTR2-expressing cells. This molecule can elicit a TIL response against autologous tumoroids from patient with well differentiated NET, restoring the antitumor potential of bystander TILs.

ABSTRACT ID 28592

B-7

The Role of Cancer Associated Fibroblasts on the Growth of Pancreatic Neuroendocrine Tumors

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BACKGROUND

Pancreatic Neuroendocrine Tumors (pNETs) have a rising incidence rate in the United States with a 23% five-year survival for patients with metastatic disease. These patients have few therapeutic options. The Tumor Microenvironment (TME) is composed of various cell populations interacting to promote tumor development and cancer progression. Among them are Cancer Associated Fibroblasts (CAFs) that are involved in increased cancer cell proliferation, extra cellular matrix remodeling, and treatment resistance. We hypothesize that CAFs contribute to increased pNET growth through factor secretion.

METHODS

A co-culture study was conducted using pNET cell lines (BON-1 & NT-18P) in patient derived serum-depleted fibroblast conditioned media (FCM) isolated from pancreas tumors of grades 1, 2, and 3 (CAF 1, CAF 2, CAF 3 respectively), compared to both serum containing (Normal) and serum depleted (Experimental) controls. Cell proliferation was measured through cell-titer glo assays, clonogenic assays, and cell cycle studies. FCM assessment was performed through media fractionation separated by four molecular weight cut-offs, followed by mass spectrometry for identification of pro-growth factors secreted by CAFs. Finally, bulk RNA sequencing on FCM conditioned cells was used to observe gene expression variances compared to control cells.

RESULTS

FCM conditioned cells demonstrate higher cell proliferation over seven days in comparison to cells grown in serum free control media for both cell lines (NT-18P: +55% for CAF 1, +56% for CAF 2, +60% for CAF 3). FCM treated cells also demonstrated increased colony formation (NT-18P: CAF 2= 33 colonies, CAF 3= 51 colonies) while no measurable colonies formed in the experimental control. There was no statistical difference in tumor cell growth based on grade. NT-18P cells demonstrated an increased number of proliferating cells in G2 mitotic state in FCM conditions (NT-18P: CAF 1= 14% CAF 2= 26%, CAF 3= 14% vs Control= 11%). Media fractionation data showcases highest proliferative rate among cells treated with the highest molecular weight fraction of the FCM (+50 kDa), further validated by mass spectrometry. RNA sequencing analysis is ongoing.

CONCLUSIONS

CAFs contribute to increased growth and proliferation among pNET cells, independent of grade. Our work demonstrates CAF secreted factors with larger molecular weights have a greater influence towards increased cell proliferation. Understanding the role of pNET CAFs may lead to identification of biomarkers that serve as therapeutic targets against pNET development.

ABSTRACT ID 28593

B-8

Surface calreticulin induction by doxorubicin in a patient derived xenograft model of pancreatic neuroendocrine carcinoma

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BACKGROUND

Pancreatic neuroendocrine neoplasms are categorized as either well-differentiated (PNETs) or poorly differentiated (PNECs). PNETs have lower proliferative rates and often overexpress somatostatin receptors (SSTRs), enabling SSTR-targeted theragnostics. In contrast, PNECs are highly proliferative, often do not express SSTRs, and the 5-year patient mortality rate is over 50%. Therefore, new treatment options for patients with PNECs and SSTR-negative PNETs are needed. Calreticulin (CALR) is a protein linked to endoplasmic reticular (ER) calcium homeostasis and immunogenic cell death. Upon sufficient cellular insult, CALR can translocate from the ER to the cell surface. Surface CALR can be targeted with theragnostic agents for tumor imaging and potential treatment. Herein, we hypothesized that doxorubicin, a common agent to trigger CALR surface translocation, could induce surface CALR in a PNEC patient-derived xenograft model (PDX).

METHODS

The PNEC PDX used in this study was derived from a surgically resected PNEC. Multiple generations were histologically validated by a surgical pathologist using H&E, chromogranin, synaptophysin, and Ki-67 staining. Tumors were grown subcutaneously in mice following an approved IACUC protocol, and at approximately 250mm³ tumor volume, mice were randomized and treated with either saline, 0.22mg/kg intratumoral doxorubicin, or 10mg/kg intraperitoneal doxorubicin (n=6/group). Tumors were harvested 24h after intratumoral or 48h after intraperitoneal treatment. Tumors were halved and analyzed for surface CALR by immunofluorescence and flow cytometry. A fixable live/dead stain was included for flow. Surface CALR detected by immunofluorescence was quantified in FIJI and flow cytometry data was analyzed in FlowJo. Statistics were calculated in SPSS using an ANOVA with Tukey post hoc test.

RESULTS

Immunofluorescence revealed that tumors treated with intratumoral doxorubicin had a background-subtracted mean raw integrated density for surface CALR expression of 8.7×10^9 , versus 7.2×10^9 for both saline and intraperitoneal doxorubicin ($p < 0.001$). In parallel, flow cytometry analysis showed tumors treated with intratumoral doxorubicin had 26.5% of live cells (49.5% total cells) expressing surface CALR, compared to 7.9% of live cells (17.4% total cells) expressing surface CALR in the saline group ($p = 0.032$). Tumors treated with intraperitoneal doxorubicin had 9.6% live cells (28.8% total cells) with surface CALR.

CONCLUSIONS

We found that surface CALR expression was increased in PNEC PDXs 24h after administration of intratumoral doxorubicin compared to saline injected tumors. Systemically administered doxorubicin did not significantly increase surface CALR expression, which suggests other delivery methods or inductions agents may be preferred to induce surface CALR prior to theragnostic targeting.

ABSTRACT ID 28596

B-9

Establishment of a long term gastric neuroendocrine tumor organoid and matched patient derived xenograft

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BACKGROUND

Gastric neuroendocrine neoplasms (gNENs) are a rare subset of neuroendocrine tumors. Treatment development has been limited due to low patient trial accrual and a lack of accurate study models. Herein we describe the creation of stable G3 gNEN patient tumor organoid (PTO) and patient derived xenograft (PDX) lines from a primary tumor.

METHODS

Patient tissue was procured fresh from a clinically indicated surgery at the NIH. Tissue was freshly dissociated into cell suspension, then seeded for long term growth. Passaging occurred as organoids reached >100 μM . PDX establishment was attempted using freshly dissected tissue fragments implanted subcutaneously into NSG mice. Following PDX establishment, PTOs were established from the PDX (PDX-PTO) in a similar manner as patient tissue. Similarly, PTOs were used to establish a new PDX (PTO-PDX). Therapeutic screening on PTOs was performed at passages 0, 3, 6, 9, and 12 and on PDX-PTOs at passage 0. Immunohistochemistry and whole genome sequencing was performed on both PTO and PDX tissues.

RESULTS

A patient with a germline MEN1 mutation and a history of previous neuroendocrine tumors underwent a gastrectomy in 2023. The patient had previously progressed while on sunitinib. Sequencing analysis did not detect pathogenic mutations, with several other genes of unknown significance detected. Tumor pathology detected neuroendocrine features, with a $\text{ki67} = 30\%$. PTOs from patient tumor have reached >15 passages, with $\text{ki67} > 50\%$. PDX growth of passage 1 (p1) implants remained non-palpable until day 300, upon which one tumor mass began exponential growth, reaching 1000 mm^3 at day 330 and progressed to 3,000 mm^3 by day 360, which was then resected to establish p2 tumors. Currently expanding in vivo p2 tumors reached 500 mm^3 -1,000 mm^3 volumes within ~100 days post-implantation which is estimated to have a doubled growth rate compared to p1. Furthermore, PTO-PDX engraftment has demonstrated an approximate 50% acceleration in tumor growth compared to p1 PDX, reaching 500 mm^3 at day 210 compared to day 320 for p1 PDX. All organoids and tissues have displayed histopathologic, molecular, and genomic signatures consistent with well-differentiated neuroendocrine tumors, including $\text{Ki67} > 50\%$ and prominent Chromogranin A and Synaptophysin

immunostaining of gNENs. Therapy screening has demonstrated sensitivity towards everolimus, cabozantinib, and capecitabine/temozolomide therapy, while it is resistant towards sunitinib.

CONCLUSIONS

Long term culture of a matched gNEN PTO, PDX, PTO-PDX, and PDX-PTO remains ongoing and demonstrates promising growth, establishment, and therapy response. Future work will focus on maintaining genomic and phenotypic stability during culture and cryopreservation.

ABSTRACT ID 28668

B-10

Development of GEP-NEN Patient Derived Organoids for Long Term Culture and Therapy Screening

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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 and investigational therapies. The second group was grown for long-term expansion and biobanking, followed by characterization using immunohistochemistry for chromogranin A, synaptophysin, and ki67 and genetic profiling at passages 0, 3, and 6 to ensure tumor cell maintenance.

RESULTS

From March 2023–July 2024, thirty patients provided 69 tumors for PTO development. These included small intestine (n=10), pancreatic (n=19), and gastric (n=1) neuroendocrine tumors derived from both primary and metastatic origins. Ongoing short-term culture (³3 passages) was successful for 51/69 (74%) of specimens while long term culture (³6 passages) was successful in 18/69 (26%) of specimens, with an average passage time of 3–4 weeks. Passaging time and number was significantly correlated with tumor grade, with grade 2 and 3 organoids capable of more and faster passages. PTOs maintained immunohistochemical characteristics of the parent tumor types including neuroendocrine tumor cell markers and grade and demonstrated similar genetic profiles across passages. Early-stage therapeutic screening was successfully performed for 52/55 (95%) tumors, demonstrating dose-dependent and clinically dose relevant sensitivity towards chemotherapy and small molecule inhibitor therapies including capecitabine:temozolomide, everolimus, cabozantinib and sunitinib. Treatment efficacy could also be stratified based on origin and tumor grade, with higher grade tumors more sensitive to

chemotherapy regimens when compared to lower grade tumors. Finally, PTOs responded based on VHL mutation status to Belzutifan and demonstrated resistance towards previously deployed clinical regimens.

CONCLUSIONS

Development of GEP-NEN PTOs is feasible for standard of care therapy testing. The establishment of large-scale prospective clinical PTO cohorts will allow integration of molecular biological characteristics and immediate treatment responses in cancer patients, reducing the time of the clinic-bench-clinic cycle, and thus help develop a platform for personalized oncology therapy.

ABSTRACT ID 28670

B-11

Phosphoproteomic Mass Spectrometry Reveals A Novel Therapeutic Target in Well-Differentiated Gastroenteropancreatic Neuroendocrine Tumors

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BACKGROUND

Though surgical debulking is an accepted therapeutic strategy for gastroenteropancreatic neuroendocrine tumors (GEP NETs), most patients will develop liver recurrence limiting overall survival, highlighting need for additional therapy. Given limited utility of mutational analysis to identify new drug targets, we sought to employ novel techniques to unveil tumor signaling pathways and kinases of interest.

METHODS

Phospho- and total proteomic analysis was performed on snap-frozen small bowel NET (SBNET) and pancreatic NET (PNET) liver metastases and adjacent normal liver. Identified phosphorylation sites were back-mapped onto upstream kinases using the *Kinase Library*, a computational motif dataset of the entire human serine/threonine kinome, and used to nominate kinases driving these tumors based on statistically significant enriched substrates in the mass-spec dataset.

Small molecule inhibitors were selected based on candidate kinase targets, and patient-derived organoids (PDOs) were generated for pharmacologic testing. PDOs were treated for 96-hours, with drug response measured by CellTiter-Glo and fluorescent imaging.

RESULTS

Liver metastases and adjacent liver parenchyma were obtained from 9 SBNET patients (Grade I n=6, Grade II n=3) and 4 PNET patients (Grade I n=1, Grade II n=3), with identification of ~19,000 peptides and 2,176 independent phosphopeptides. Number and distribution of total peptides/proteins detected by mass spectrometry were similar between metastatic NETs and hepatic parenchyma. Mean abundance of phosphopeptides in NET samples increased by over 2-fold. After computational analysis of tumor-enriched phosphosites, several kinase signatures emerged including regulators of MAPK signaling, protein secretion, and activation of a casein kinase (CK) 1 isoform. We selected CX-4945 (silmitasertib), a casein-kinase 2 inhibitor, for PDO validation, as CK1 has no available clinically relevant inhibitors.

PDOs were derived from 13 unique PNET metastases from 3 patients and 8 unique SBNET metastases from 3 patients. Establishment rate was 84.6% (11/13) for PNET and 75% (6/8) for SBNET.

IHC demonstrated GEP-NET marker expression in PDOs. Silmitasertib exhibited an IC_{50} 0.18-0.75 μ M in SBNETs and IC_{50} 0.79-4.75 μ M in PNETS.

CONCLUSIONS

Phospho-MS reveals novel signal dysregulation in well-differentiated GEP-NET liver metastases. Our data suggests that CK-2 inhibition has potential efficacy for Grade I and Grade II SBNETs and PNETs.

ABSTRACT ID 28672



B-12

Combination of angiogenesis and HIF-2 α blockade: synergistic pair worth exploring in neuroendocrine tumors

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BACKGROUND

Inhibition of angiogenesis via vascular endothelial growth factor receptor (VEGFR) blockade has revealed therapeutic efficacy in advanced neuroendocrine tumors (NETs), most recently with Cabozantinib in the CABINET trial. Belzutifan, a hypoxia-inducible factor (HIF)-2 α inhibitor, has demonstrated activity in Von Hippel-Lindau (VHL)-associated pancreatic NETs (pNETs). Evidence has also shown that VHL gene impairment by promoter methylation and deletion occurs in nearly 25% of sporadic pNETs. The HIF pathway regulates several oncogenes related to proliferation, angiogenesis, invasion, and metastasis including VEGF. Interaction between angiogenesis and the hypoxia signaling pathway presents an opportunity to repress VEGF at both the transcription and receptor level.

METHODS

BON and QGP (human pNET) and STC-1 (mouse small bowel NET) cell lines were used. For hypoxia experiments, cells were maintained in a hypoxic incubator set to 3.0% O₂ and 5.5% CO₂. Cells were treated with serial dilutions of Belzutifan and Cabozantinib ranging from 250 μ M to 7.8 μ M and 100 μ M to 3.1 μ M, respectively. Drug interaction and synergy were analyzed using the SynergyFinder Plus platform. The Zero Interaction Potency (ZIP) synergy score was calculated for each cell line at varying drug concentrations under both normoxic and hypoxic conditions. Cell viability was measured using MTT and trypan blue exclusion assays after 48 hours. DMSO and untreated cells served as controls. Additionally, spheroids from each cell line were treated with Belzutifan, Cabozantinib, and their combination and placed in hypoxia for 48 hours. HIF-2 α expression levels were analyzed via Western blot.

RESULTS

The combination of Belzutifan and Cabozantinib demonstrated varying synergy across BON, QGP, and STC-1 cell lines under normoxic and hypoxic conditions. In BON cells, moderate synergy was observed in hypoxia (ZIP: 34.74) and normoxia (ZIP: 27.26), with cell viability significantly reduced under hypoxia (50.10% at the highest concentration). Strong drug synergy was observed in QGP cells under both hypoxia (ZIP: 168.01) and normoxia (ZIP: 131.03). STC-1 cells showed moderate synergy under hypoxia (ZIP: 36.89), but minimal synergy under normoxia (ZIP: 0.90). Western blot analysis revealed that HIF-2 α expression decreased as drug concentrations increased in hypoxic conditions. Cell viability and spheroid drug synergy studies confirmed that combination treatment led to highest cell death in hypoxia.

CONCLUSIONS

The combination of Belzutifan and Cabozantinib demonstrates strong synergy in QGP cells and moderate synergy in BON and STC-1 cells. The reduction in HIF-2 α expression and increased cell death with combination treatment in hypoxia support further exploration of this treatment.

ABSTRACT ID 28676



B-13

Transcriptome alterations in pancreatic neuroendocrine tumors among those living with adverse social determinants of health

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BACKGROUND

There are disparities in survival among patients with pancreatic neuroendocrine tumors (pNET) based on race and adverse social determinants of health (SDOH) (rurality, unmarried). The biologic mechanism of these factors is unknown.

METHODS

At our institution, we constructed a cohort of patients (Table 1) who underwent surgical resection for Grade 1 or 2 pNETs (2006 and 2022). We identified black patients (self-identified race) and matched them to white patients (by age, sex, and tumor grade). Formalin-fixed, paraffin-embedded (FFPE) pNET specimens were sequenced by Illumina NextSeq550. We created a linear regression of differentially-expressed genes (DEGs) predicting each adverse neighborhood level SDOH based on patient billing address census data and controlling for race, BMI, smoking, and year of surgery. Gene Set Enrichment Analyses were then completed to determine if these DEGs were enriched in known biologic pathways (significant normalized enrichment scores (NES) p value: <0.05, q-value: <0.05).

RESULTS

A total of 24 patients were analyzed (11 Black, 13 White). At the time of surgery, the median (interquartile range) age was 62 years (51-69), 16 (67%) were female, and 18 (75%) had grade 1 disease. The median tumor size was 2.7 cm (1.5-4.1) and the median Area Deprivation Index (ADI) was 60th percentile. A total of 145 DEGs were identified across 5 adverse SDOH domains. Compared to controls, those living in lower-income neighborhoods demonstrated significant suppression of immune-related biologic processes such as lymphocyte and leukocyte activation; this was accompanied by significant activation of metabolic processes such as small molecule and organic acid metabolic processing. Those living in areas with lower educational attainment had enhanced activation of cellular metabolism and processing, and cellular communication. Those living in areas with higher uninsured rates had increased expression of cellular metal ion homeostasis pathway. Those living in areas with higher ADI displayed activation of catabolic processes including fatty acid oxidation accompanied by noticeable suppression of lymphocyte activation.

Table 1: Demographics of patients with pancreatic neuroendocrine tumors (pNETs)

	Overall	Black (n=11)	White (n=13)
Tumor size (median, IQR, cm)	2.7 [1.5-4.1]	3 [1.5-4.3]	2 [1.5-4]
Neighborhood level metrics (median, IQR)			
National ADI (percentile)	60 [51-78]	78 [68-93]	55 [49-62]
Uninsurance rate	14.7% [11.8-18.9]	18.1%[13.0-19.5]	13.6% [11.0-15.6]
Income	\$48,170 [37,648-57,018]	\$35,446 [32,332-51,980]	\$49,427 [45,864-57,500]
High School Graduation Rate	88.5% [84.1-96.6]	87.0% [77.2-95.4]	90.0%[85.3-96.3]

CONCLUSIONS

Significant biologic changes were seen in pNET gene expression of patients living in neighborhoods characterized by adverse SDOH. The pathways most effected centered on suppressed immune response and heightened catabolism.

ABSTRACT ID 28679



B-14

Deletion of Notch1 inhibits pancreatic neuroendocrine tumor growth *in vivo*

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BACKGROUND

Pancreatic neuroendocrine tumors (pNETs) are uncommon neoplasms developing from islet cells in the pancreas. Current studies show that Notch1 plays an essential role in the development of pNETs. Notch1 signaling is a cell-cell communication pathway responsible for regulating cell growth, differentiation, and cell fate determination. We hypothesized that Notch1 signaling plays a significant role in pNET progression.

METHODS

We generated a Notch1 pNET cell line, BON-N1-KO, using CRISPR-Cas9 technology. Successful Notch1 knockout was confirmed by Sanger sequencing and Western blot analysis. To assess tumor growth *in vivo*, we subcutaneously implanted wildtype (WT) BO and BON-N1-KO into different groups of nude mice. The study included 12 mice (6 males and 6 females), with three replicates per group. Tumor sizes were measured twice weekly using calipers. When tumors reached a volume of approximately 180mm³, the mice were euthanized. The tumors were then sectioned for Ki-67 immunohistochemistry staining. To obtain a comprehensive view of signaling pathways affected by Notch1 deletion, we performed proteomic analysis using Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) followed with Ingenuity Pathway Analysis (IPA).

RESULTS

Deletion of Notch1 significantly inhibited tumor growth in both sex. At day 58, the average WT BON tumor size in female was 124.88 mm³, compared to 20.23 mm³ in BON-N1-KO ($p = 0.001$). In contrast, at day 36, the average WT BON tumor size in male was 132.02 mm³, compared to 23.65 mm³ in BON-N1-KO ($p = 0.04$). Ki-67 staining showed no significant difference between the BON and BON-N1-KO groups. Principal Component Analysis (PCA) of the proteomics data reveals distinct clustering between WT BON and BON-N1-KO groups. IPA identified the EIF2 signaling pathway as the most significantly affected by Notch1 deletion ($p = 7.34e-10$). Furthermore, molecular and cellular function analysis indicated significant differences between WT BON and BON-N1-KO groups in "cell death and survival" ($p = 9.93e-3 - 4.12e-11$) and "cellular growth and proliferation" ($p = 1.03e-2 - 2.06e-8$) processes.

CONCLUSIONS

Knockout of Notch1 signaling in pNET cells inhibit tumor growth *in vivo*. Our data suggest that this inhibitory effect highlighting the potential of Notch1 as a therapeutic target.

ABSTRACT ID 28701



B-15

CDK4/6 and MEK are actionable, therapeutic targets in pancreatic and lung neuroendocrine tumors (NETs)

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BACKGROUND

Neuroendocrine tumors (NETs) are slow growing tumors whose incidence has risen precipitously compared to all other malignancies. These tumors develop via transformation of neuroendocrine cells throughout the body; however, they are predominantly found in the pancreas, lungs, and intestines. NETs are extremely slow-growing tumors that respond poorly to traditional anti-cancer therapies, and unfortunately patients with unresectable or partially resectable tumors will inevitably progress on the currently approved therapies. Therefore, there is a critical need to identify new drugs and/or combination therapies for treating resistant tumors. Our group has shown that pancreatic NETs (pNETs) overexpress an oncogenic Rab-like GTPase, RABL6A. RABL6A upregulates many kinases, such as CDK4/6, MEK, and AKT whose hyperactivation is a key feature of pNET and lung NET pathogenesis. Monotherapies targeting these kinases individually have not been effective when tested in pNET patients. We hypothesized that combination therapy targeting both CDK4/6 and MEK together would have synergistic antitumor activity against pNETs and lung NETs.

METHODS

Anti-tumor effects of the drugs – vehicle control, CDK4/6 inhibitor (palbociclib), MEK inhibitor (mirdametinib), or the combination – were measured *in vitro* in cultured pNET and lung NET cells via cell cycle, cell survival, and drug synergy assays. Western blotting of phosphorylated RB1 protein evaluated activity of the drugs against their target. The *in vivo* activity of the drugs, alone or combined, was measured in xenograft tumors of each NET type (BON1 and H727) in immune-deficient NSG mice.

RESULTS

Dual CDK4/6-MEK inhibitor therapy was highly synergistic *in vitro* where it caused robust pNET cell cycle arrest and cell death relative to single drug controls. The combination was also synergistic at nanomolar doses against a lung NET cell line, H727. Importantly, molecular assays showed the CDK4/6-MEK inhibitor combination effectively inactivated the targeted pathway, as measured by RB1 protein hypo-phosphorylation. In animals bearing pNET xenografts, the CDK4/6-MEK inhibitor combination significantly slowed tumor growth and yielded a 6-fold extension in average mouse survival (~120 days versus 20 days for vehicle control). Pilot drug studies of H727 lung NET xenografts showed significant anti-tumor activity of MEK inhibition alone.

CONCLUSIONS

Combination therapy targeting CDK4/6 and MEK kinases effectively inhibits NET growth *in vitro* and *in vivo*, suggesting it could be a valuable treatment option for NET patients. To date, most analyses have been conducted in pNET models; therefore, future studies will be expanded to more deeply examine the anti-tumor activities of CDK4/6 and MEK inhibitors in lung NET models.

ABSTRACT ID 28786

B-16

Comparison of pulmonary versus extra-pulmonary small cell neuroendocrine carcinomas demonstrate distinct genomic alterations

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BACKGROUND

Small cell neuroendocrine carcinomas (SC-NECs) are uncommon but aggressive tumors with poor prognosis. Although both small cell lung cancer (SCLC) and extrapulmonary small cell NEC (EP-SC-NEC) have similar histological and morphological characteristics, whether they are biologically distinct is still unknown. We assessed and compared the genomic profiles of SCLC and EP-SC-NECs to identify distinct mutations that may allow for more personalized therapeutic options.

METHODS

Patients with a histological diagnosis of SC-NEC were identified from the de-identified Tempus real-world multimodal database and stratified by primary tumor site and categorized as SCLC or EP-SC-NEC. Patient demographic/clinical characteristics and genomic/transcriptomic data were described as N (%) or median (IQR), min, and max and compared between groups by Chi-squared/Fisher's Exact tests or Wilcoxon rank-sum tests, as applicable. The prevalence of somatic mutations (SNVs, CNVs, and Fusions) was compared similarly, with a false-discovery rate correction for multiple comparisons. Analyses were two-sided, with statistical significance evaluated at the 0.05 alpha level.

RESULTS

228 SCLC vs 186 EP-SC-NEC were compared. The two groups did not differ in age, race, or ethnicity when diagnosed. SCLC samples had significantly higher median TMB than EP-SC-NEC samples (5.0 vs 3.4 mut/MB, $p < 0.001$). MSI-H was rare in both groups (SCLC 0.4% vs EP-SC-NEC 2.7%, $p = 0.10$). There were significant differences in SNVs with *TP53*, *RB1*, *EGFR*, and *NOTCH1* mutations more common and *TERT*, *ARID1A*, *APC*, *FOXA1*, and *CTNNB1* mutations less common in SCLC ($q < 0.05$). SCLC also had significantly fewer *CCNE1* amplifications than EP-SC-NEC. Pathogenic fusions were also more frequent in EP-SC-NEC vs SCLC ($q < 0.001$), with 24% of EP-SC-NEC fusions being *TMPRSS2-ERG*.

CONCLUSIONS

Despite the histological and morphological overlap between SCLC and EP-SC-NECs, our data revealed heterogeneous molecular characteristics between both groups. These distinct molecular signatures could impact therapeutic decisions for SC-NEC according to their site of origin.

ABSTRACT ID 28477



B-17

Molecular landscape of extra-pulmonary small cell neuroendocrine carcinomas based on site of origin

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BACKGROUND

Extrapulmonary small cell neuroendocrine carcinomas (EP-SC-NECs) are uncommon but aggressive malignancies. Although they are treated with similar chemotherapy regimens, their distinct genomic profiles have not been fully explored. We aimed to investigate the genomic profile of these tumors to characterize distinct molecular subgroups of EP-SC-NECs and to identify mutations that could enable more personalized therapy.

METHODS

Patients with a diagnosis of SC-NEC that originated outside the lung were selected from the de-identified Tempus real-world multimodal database. Patients were further stratified by primary tumor site into gastrointestinal (GI), genitourinary (GU), head and neck (H&N), and gynecological origin (GYN). Patient demographic/clinical characteristics and genomic/transcriptomic data were described as N (%) or median (IQR), min, and max and compared between primary tumor site groups by Chi-squared/Fisher's Exact tests or Kruskal-Wallis rank-sum test, as applicable. The prevalence of somatic mutations (SNVs, CNVs, and Fusions) was compared similarly, with a false-discovery rate correction for multiple comparisons. Analyses were two-sided, with statistical significance evaluated at the 0.05 alpha level.

RESULTS

186 patient samples (61 GI, 95 GU, 23 GYN, and 7 H&N) were identified. Age at diagnosis significantly differed between the subtypes, with GYN having the youngest age at diagnosis. There was no difference in race and ethnicity between groups. GI and GU SC-NECs have higher median TMB, and results were significant when comparing GI to GYN SC-NECs (3.8 vs 2.1 mut/MB, $p=0.026$). MSI-H was rare in all groups, with no significant differences. There were differences in CNVs among the four groups, with H&N having the highest frequency of *PAX8*, *RET*, and *SLC3F5* deletions, while GYN and H&N SC-NECs had higher rates of *CDKN1B* amplification. However, these were not significant after correction for multiple testing. There were also significant differences in SNVs between the four groups, in which *TP53* and *RB1* mutations were more common in GI and GU compared to GYN and H&N SC-NECs ($q<0.001$ and 0.087 , respectively). GI SC-NECs had more frequent *KRAS* and *APC* mutations

($q < 0.001$ and 0.002 , respectively), while GU SC-NECs had more *TERT* mutations compared to other groups ($q < 0.001$).

CONCLUSIONS

Our results demonstrated that EP-SC-NEC possess distinct heterogeneous genomic profiles associated with different primary origins despite their histological and morphological similarities. These distinct molecular signatures could impact precision therapeutic decisions for EP-SC-NEC according to their primary site of origin.

ABSTRACT ID 28478



B-18

Uncovering genomic differences between small and large cell extra-pulmonary neuroendocrine carcinomas

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BACKGROUND

Extra-pulmonary neuroendocrine carcinomas (EP-NECs) are rare and aggressive cancers that include two morphological subtypes: large cell NEC (LC-NEC) and small cell NEC (SC-NEC). Although they are treated with similar chemotherapy regimens, they are distinct diseases, and their genomic profiles have not been compared. We investigated the genomic profile of the extrapulmonary LC-NEC and SC-NEC to identify mutations that could enable more personalized therapy.

METHODS

Patients diagnosed with poorly differentiated extra-pulmonary NECs (LC-NEC and SC-NEC subtypes) were selected from the de-identified Tempus real-world multimodal database. Patient demographic/clinical characteristics and genomic/transcriptomic data were described as N (%) or median (IQR), min, and max and compared between subgroups by Chi-squared/Fisher's Exact tests or Wilcoxon rank-sum tests, as applicable. The prevalence of somatic mutations (SNVs, CNVs, and Fusions) was described and compared similarly, with a false-discovery rate correction for multiple comparisons. Analyses were two-sided, with statistical significance evaluated at the 0.05 alpha level.

RESULTS

307 patient samples (121 LC-NECs and 186 SC-NECs) were identified. There was no difference in race and ethnicity between LC and SC NECs. There were no significant differences in median TMB between LC and SC-NECs (3.1 vs 3.4 mut/Mb, p=0.2, respectively); the majority had low TMB (<10 mut/Mb). LC-NECs had higher frequency of deletions vs SC-NECs in *CDKN2A* (12% vs 1.6%, q=0.002), *CDKN2B* (12% vs 1.6%, q=0.002), and *MTAP* (9.9% vs 1.1%, q=0.002). SC-NECs had more frequent *RB1* loss compared to LC-NECs, although not significant after correction for multiple testing (16% vs 7.4%, q=0.2). LC-NECs have more common *CCND1*, *FGF3*, *FGF4*, *KDM5A*, *NOTCH1*, and *MYC* amplifications, but less common *SDHC*, *SLAMF1*, *FCGR2A*, *FCGR3A*, and *NIT1* amplifications compared to SC-NECs. SNVs in *APC*, *KRAS*, *BRAF*, *DAXX*, *NOTCH1*, and *SMARCA4* mutations were more common in LC-NECs, while *RB1*, *TERT*, and *FOXA1* mutations were more common in SC-NECs.

CONCLUSIONS

Our results demonstrated that EP-NECs display a broad pattern of genomic alterations according to their histological subtypes. These distinct molecular signatures could impact the development of future precision therapeutics for SC-NECs and LC-NECs.

ABSTRACT ID 28479

B-19

Activity of nab-Sirolimus Alone or in Combination with Cabozantinib, Octreotide, or Talazoparib in Nonclinical Neuroendocrine Tumor Models

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BACKGROUND

The phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway is strongly implicated in the pathogenesis and progression of neuroendocrine tumors (NETs). *nab*-Sirolimus, an injectable form of albumin-bound sirolimus, demonstrates greater tumor drug accumulation, mTOR target inhibition, and antitumor activity in human tumor models compared to conventional mTOR inhibitors including everolimus. This study utilized NET cell lines for *in vitro* and *in vivo* evaluation of the anti-proliferative and antitumor activity of *nab*-sirolimus as a single agent or in combination with targeted agents with known activity in NETs.

METHODS

In vitro cell viability assays evaluated the anti-proliferative effect of *nab*-sirolimus (20 or 80 nM) alone or in combination with clinically relevant concentrations (0.037 to 80 µM) of talazoparib, octreotide, or cabozantinib in 3 different NET cell lines: BON-1 (human pancreatic), NCI-H209 (human small cell lung carcinoma), and STC-1 (murine gastrointestinal). BON-1 was subsequently selected for *in vivo* evaluation. Athymic nude mice (N=8 per group) bearing subcutaneous (SC) BON-1 xenografts were treated with either saline, or clinically equivalent relevant doses of *nab*-sirolimus, cabozantinib, octreotide, or talazoparib alone or in combination for 6 weeks to assess antitumor activity (**Table**).

RESULTS

In vitro, *nab*-sirolimus showed anti-proliferative effects as a single agent across all 3 NET cell lines and additive effects were observed in combination with talazoparib and cabozantinib. In BON-1 xenografts, *nab*-sirolimus demonstrated greater antitumor activity compared to other single agent treatments, and significant additive effects were observed when *nab*-sirolimus was combined with cabozantinib, octreotide, or talazoparib (**Table**).

Table. Antitumor Activity of nab-Sirolimus Alone or in Combination in BON-1 Xenografts

Treatment	TGI ^a (P-value) ^b
nab-Sirolimus 5mg/kg, IV weekly	77%
Cabozantinib-5 5 mg/kg, PO daily	44% (0.0019)
Cabozantinib-15 15 mg/kg, PO daily	66% (0.2646)
Octreotide 0.1 mg/kg, SC daily	12% (0.0012)
Talazoparib 0.33 mg/kg, PO daily	35% (0.0371)
nab-Sirolimus+Cabozantinib-5	86% (0.0002)
nab-Sirolimus+Cabozantinib-15	89% (0.0290)
nab-Sirolimus+Octreotide	81% (0.0006)
nab-Sirolimus+Talazoparib	90% (0.0075)

IV=intravenous; PO=oral; TGI=tumor growth inhibition.

^aTGI is percent versus saline on Day 33.

^bP-value (ANOVA) for single agents=comparison with nab-sirolimus;

P-value for combinations=comparison with non-nab-sirolimus component.

CONCLUSIONS

Single agent nab-sirolimus showed significant *in vitro* and *in vivo* activity in NET lines. Combinations of nab-sirolimus with other targeted agents demonstrated additive anti-proliferative and antitumor activity; however, the magnitude of response for select combinations compared with single agent activity warrants further investigation.

ABSTRACT ID 28547

B-20

Spatial analysis of the tumor microenvironment in pancreatic neuroendocrine tumors

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BACKGROUND

Pancreatic neuroendocrine tumors (PanNETs) represent a heterogeneous group of neoplasms with an increasing incidence, posing a significant clinical challenge. Their clinical presentation, natural history, and prognosis vary widely, underscoring the critical need for precise prognostic biomarkers and effective treatment strategies, including systemic and targeted therapies. Recent advances in genetic and epigenetic research have identified novel PanNET subtypes and validated several prognostic biomarkers, such as the detection of alternative lengthening of telomeres (ALT) and ATRX/DAXX protein loss through immunohistochemistry. However, our understanding of tumor microenvironment (TME) dynamics, particularly the role of tumor architecture and spatially organized immunological processes, remains limited. We utilized advanced technologies to explore the spatial relationships between PanNET subtypes and systematically analyze the information encoded within both the tumor and the intact TME.

METHODS

Tissue microarrays (TMAs) comprising 62 non-functional PanNETs were constructed, with each case sampled from intratumoral and peritumoral regions. Detection of ALT was performed using both a telomere-specific FISH assay and a novel chromogenic in situ assay developed by our team. Protein expression levels of ATRX, DAXX, ARX, and PDX1 were evaluated through immunohistochemistry. To maintain spatial context, unbiased whole transcriptome profiling was conducted on 38 cases using the Visium platform by 10X Genomics. Additionally, a multiplex immunofluorescent assay was optimized on the Lunaphore COMET platform for comprehensive immune cell analysis. Data integration and multi-modal, multi-scale analyses were facilitated using Giotto Suite, a technology-agnostic spatial multi-omics analysis platform.

RESULTS

Overall, ALT was detected in 40% of the cases. Multiplex immunofluorescence identified a variety of immune cell populations, while Visium spatial transcriptomics provided comprehensive profiles for 38 cases (19 ALT-positive and 19 ALT-negative). On average, 400 Visium spots were captured per TMA core, with 83% of the cores achieving a median of over 1,500 genes per spot. The dataset included expression of canonical epithelial, immune, and stromal marker genes, and deconvolution of spots is underway using a single-cell RNA sequencing reference dataset. Z-stack batch effects were minimal across experiments. Image registration was also performed for integration between these spatial

datasets and immunohistochemical and histological markers. These integrated analyses aim to reveal spatial architectural differences between ALT-positive and ALT-negative cases, potentially uncovering key biological pathways.

CONCLUSIONS

This study aims to elucidate specific tumor and TME spatial characteristics, correlating with biomarkers to enhance prognosis and identify therapeutic targets. Integration of spatial data with molecular insights promises to advance personalized medicine for patients.

ABSTRACT ID 28569



B-21

Therapeutic Targeting of SDHB-Deficient Tumors

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BACKGROUND

Pheochromocytomas and Paragangliomas (PPGLs) are rare neuroendocrine tumors arising from the adrenal medulla and extra-adrenal paraganglia, respectively. About 40% of PPGLs are hereditary, and nearly half of these caused by germline mutation of a succinate dehydrogenase (SDH) subunit. Pathogenic succinate dehydrogenase subunit B (*SDHB*) mutation confers increased risk for metastasis. Unfortunately, treatments for metastatic PPGL remain palliative. Hence, discovering novel therapeutic avenues that improve the prognosis for metastatic *SDHB*-PPGL patients is an urgent unmet need.

METHODS

To explore the function of *SDHB* in cells and human PPGLs, we (i) conducted bulk mRNAseq on UOK269, a human *SDHB*-deficient renal cell carcinoma line, and *SDHB* reconstituted UOK269 (UOK269WT) cells (n=3), and (ii) interrogated gene expression in the publicly available PPGL (n=178) Cancer Genome Atlas (TCGA) database. Gene Ontology (GO) analysis identified pathways altered by *SDHB* deficiency. Additionally, we performed cell viability assays, Hoechst and Ethidium Homodimer I (EthD-1) staining, following compound treatment (t=72h), and automated image acquisition and analysis (Operetta, PerkinElmer). ANOVA or paired t-tests were used for statistical analysis, as appropriate.

RESULTS

GO analysis revealed that UOK269 cells exhibit enhanced expression of nutrient transporters, including many solute carrier (SLC) transporters; likely reflecting adaptive metabolic activity due to *SDHB* deficiency. Notably, altered SLC transporter expression is also present in human *SDHB*-deficient PPGLs (TCGA dataset). Among these, we identified SLC35F2, which demonstrates ~4-fold increased expression in *SDHB*-deficient PPGLs, as an attractive potential therapeutic target for *SDHB*-deficient PPGLs. The SLC35F2 transporter is required for cytotoxic activity of the chemotherapeutic compound YM155. Furthermore, YM155 acts by promoting DNA damage, a pathway of increased susceptibility in SDH-deficient cells. Indeed, YM155 cytotoxicity against UOK269 was ~10-fold enhanced. Importantly, chemical inhibition of SDH complex activity in UOK269WT cells with 3-NPA, to mimic *SDHB*-deficiency, conferred increased YM155 sensitivity. Finally, YM155 cytotoxicity was found to be increased against *SDHB*-deficient mouse primary renal tubule cells. Mechanically, YM155 treatment results in increased DNA damage (γ-H2AX) in *SDHB*-deficient UOK269 cells.

CONCLUSIONS

We identified SLC35F2 as a potential therapeutic target for *SDHB*-deficient tumors. Specifically, this transporter is upregulated in human *SDHB*-deficient PPGLs and is responsible for cellular import of the chemotherapeutic compound YM155. Critically, YM155 demonstrated preferential cytotoxicity towards *SDHB*-deficient cells, in part related to impaired DNA damage repair. This preferential cytotoxicity of YM155 towards *SDHB*-deficient cells was observed in both tumor cell lines and primary cell cultures. Collectively, these data indicate that *SDHB*-deficient cells exhibit unique chemical sensitivities which have potential to be therapeutically leveraged.

ABSTRACT ID 28571



B-22

TILs from panNET liver metastases: in search of novel adoptive transfer strategies for the treatment of NETs

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BACKGROUND

The anti-tumor activity of tumor-infiltrating lymphocytes (TILs) in NETs is currently unknown.

METHODS

We collected matched blood, FFPE and cryopreserved or fresh samples of liver metastases from 29 patients with well-differentiated panNETs (7 G1;19 G2;3 G3). FFPE samples were subjected to WES and RNAseq to predict number and identity of tumor neoantigens. IHC was used to assess HLA-I and HLA-II expression in tumor samples, and findings were validated by TMA in an independent cohort of 49 panNETs. Digital quantification of CD3+ staining was performed using the Aperio tool. Multi-region analysis of individual tumor samples was carried out and in vitro-mapped TILs outgrowth was contrasted with tumor zonal characteristics. TILs were expanded up to 105 days and weekly enumerated and phenotyped by flow cytometry. TCR sequencing was performed to assess over time TCR skewing. The Seahorse technology was used to evaluate TILs' metabolism. TILs deriving from different tumor regions were co-cultured with autologous tumoroids to assess their antitumor activity. Secretion of IFN- γ and Granzyme-B was measured by ELISA.

RESULTS

PanNET liver metastases exhibited a relatively low mutational and neoantigen burden (median of 12 pathogenetic variants per sample; median of 3 HLA-I and 4 HLA-II predicted neoantigens per sample). HLA-I and HLA-II expression was retained in 28/29 and 0/29 samples respectively. By TMA, HLA-I and HLA-II expression was observed in 36/49 and 0/49 samples. PreREP-sufficient numbers of TILs were reached in 18/29 patients (62%). TILs' outgrowth was independent of clinical parameters, being

instead significantly correlated with T cell density by IHC ($p<0.05$) and TLS presence ($p<0.01$). Wide differences were observed in T cell yield according to the different tumor regions analyzed. T cells were the predominant population in the TILs cultures at the time of cryopreservation with CD4+/CD8+ T cells ratio of 5:1. We observed a switch in CD8+ T cell differentiation (from TE to TEM) after 2 weeks of culture. Such a switch was accompanied by a metabolic reprogramming, with reduced efficiency of OXPHOS overtime. When cocultured with autologous tumoroids, TILs deriving from different tumor regions exhibited heterogeneous antitumor activity, spanning from no tumor recognition to massive production of pro-inflammatory cytokines and up-regulation of activation markers such as CD69/CD39. TILs showing anti-tumor reactivity were able to infiltrate co-cultured tumoroids and displayed a significantly higher respiratory capacity and glycolytic capacity. TILs not showing anti-tumor reactivity showed a higher presence of CD8+ Tregs.

CONCLUSIONS

PreREP sufficient TIL numbers were reached in approximately 60% of cases. TILs comprise both anti-tumor reactive clones and bystander lymphocytes. Isolation and expansion of tumor-reactive TILs may enhance the efficacy of TILs adoptive transfer.

ABSTRACT ID 28607



B-23

A Novel Nonpeptide Drug Conjugate (NDC) for the Treatment of Somatostatin Receptor 2-Expressing Tumors

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BACKGROUND

Somatostatin receptor 2 (SST2) is an established target for the treatment of neuroendocrine tumors (NETs) and a potentially useful one for many other solid tumors including breast cancer, melanoma, thyroid cancer, and meningioma. Here, we provide the first report of CRN09682, a non-radioactive, nonpeptide drug-conjugate (NDC) optimized for the delivery of a cytotoxic MMAE payload to SST2-expressing tumors.

METHODS

CRN09682 was developed by linking a small molecule, nonpeptide SST2 agonist with the cytotoxic drug monomethyl auristatin E (MMAE) via a spacer and a cleavable linker. SST2 activation was assessed by monitoring cAMP production in SST2-expressing CHO cells using a cAMP HTRF assay. CRN09682-SST2 complex internalization and endosomal localization were evaluated using the PathHunter β -arrestin recruitment assay and the PathHunter ENDO-EA pharmacotraficking assay, respectively. The SST2 expressing small cell lung cancer (SCLC) cell lines NCI-H524, NCI-H69 and the SST2 receptor null cells H460 were treated with CRN09682 to characterize the anti-proliferative effects in vitro. The plasma stability of CRN09682 was investigated in vitro and in vivo. Intratumoral concentrations of CRN09682 and MMAE were determined in NCI-H524 xenografts (CDX). Anti-tumor activity of CRN09682 was characterized in NCI-H524 and NCI-H69 CDX models.

RESULTS

CRN09682 activated SST2 G-protein signaling and induced internalization with low nanomolar potency. In vitro, the anti-proliferative effect of CRN09682 was comparable to MMAE alone. Co-incubation with an SST2 antagonist blocked the anti-proliferative response and CRN09682 had no effect in H460 cells. CRN09682 was stable in mouse, dog, and human plasma. In vivo, CRN09682 displayed a half-life of 7.4 h in mouse, 1.1 h in rats and 7.1 h in dogs. MMAE plasma concentrations remained below 1% of total injected NDC. Biodistribution studies in NCI-H524 CDX model demonstrated high tumor uptake for CRN09682 and rapid MMAE release within the tumors. MMAE accumulated and remained in the tumor for up to 10 days. CRN09682 demonstrated dose-dependent anti-tumor activity in CDX models without significant weight loss, whereas the analog with no SST2 agonist activity did not inhibit tumor growth.

CONCLUSIONS

These data demonstrate the potent anti-tumor activity of CRN09682, a first-in-class NDC targeting SST2 expressing solid tumors. CRN09682 could provide a novel alternative for the treatment of NETs and other SST2-expressing tumors. CRN09682 is expected to enter a Phase I clinical trial in 2025.

ABSTRACT ID 28646

B-24

Cell-free methylation signatures non-invasively distinguish patients with MEN1 and provide insights into the biology underlying dpNETs

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BACKGROUND

Multiple Endocrine Neoplasia Type 1 (MEN1) is highly penetrant autosomal dominant disorder in which ~85% patients develop duodenopancreatic neuroendocrine tumors (dpNETs), the most common cause of MEN1-related death. While most MEN1-related dpNETs have an indolent course, 15-25% of these tumors develop distant metastases associated with poor survival. Given widespread access to genetic testing, patients are typically diagnosed prior to the development of dpNETs or while the tumor is still localized. Biomarkers identifying aggressive dpNETs with metastatic potential, therefore, would provide an opportunity for risk stratification and early intervention to prevent metastases in this population. In this pilot study, we hypothesized that the plasma cell free methylome (cfMe) can non-invasively distinguish localized from metastatic dpNETs in patients with MEN1.

METHODS

Plasma cfDNA from patients with wild type germline MEN1 with sporadic primary hyperparathyroidism (HPT) ($n = 4$) and MEN1 with localized ($n = 6$) or metastatic ($n = 4$) dpNETs underwent whole genome bisulfite sequencing (WGBS). Paired tumor-leukocyte DNA was sequenced when available (localized $n = 1$; metastatic $n = 3$). Reads were aligned to GRCh38 and methylation calls were extracted using Bismark. Data were smoothed across nearby CpG sites using bsseq and sites with $< 5\times$ coverage in all samples were removed. Global methylation was assessed with MethylKit, differentially methylated regions (DMR) were called with bsseq using a t statistic cutoff of 4.6 and filtered to include ≥ 3 CpGs and a mean difference > 0.2 .

RESULTS

No differences were observed in global methylation between patients with or without MEN1. 112 DMR were identified in MEN1 including hypermethylation of the promoters for *MEG3*, *PDX1*, and *CDKN1B* as well as hypomethylation of the *MGMT* promoter. Preliminary comparisons of MEN1 patients with localized versus metastatic dpNETs revealed 138 DMR, including hypomethylation of the *SOCS3* promoter in metastatic dpNETs. Intriguingly, overexpression of *SOCS3*, a negative regulator the JAK2/STAT3 pathway, has been associated with cancer stemness and therapeutic resistance in other malignancies. Paired plasma and tissue had concordant methylomes.

CONCLUSIONS

In this feasibility study, we demonstrate that (1) cfMe non-invasively recapitulates epigenetic signatures previously associated with MEN1 dpNETs and (2) differentially methylated regulatory motifs in plasma cfME distinguish localized from metastatic dpNETs. Collectively, these findings hold promise for developing non-invasive biomarkers for the early detection and prognostication of MEN1 associated dpNETS. Furthermore, detection of specific DMR, e.g. SOCS3, may provide insights into the biology underlying metastatic dpNETs as well as inform therapy selection.

ABSTRACT ID 28654

B-25

NETest® 2.0 – A Decade of Innovation in Neuroendocrine Tumor/Neoplasm Diagnostics

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BACKGROUND

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are challenging to diagnose and manage. We introduced the NETest in 2013, a liquid biopsy that quantifies mRNA expression of 51 NET-specific genes in blood using real-time PCR (NETest® 1.0). The test leverages a proprietary blood collection to stabilize RNA and perform RT-PCR on RNA isolated from whole blood, followed by supervised machine learning (ML) algorithms. The 0-100 algorithm was scaled to adjudicate patient results against cutoffs of 20, 40, and 80. A result >20 correlated with a NET diagnosis a result of 40-79 correlated with a high probability of disease progression, with >80, identifying those most at risk. Over the next decade, we continued efforts to train the ML classifiers to simplify test outputs, optimize sensitivity and specificity of NET diagnosis and prognostication (NETest 2.0).

METHODS

qPCR measurements were used to train two supervised classifiers for diagnostic and prognostic scores. Unlike NETest 1.0, the algorithms used were different. The diagnostic classifier was trained on 78 controls (healthy individuals) and 162 NETs to distinguish NETs from controls; the prognostic classifier was trained on 134 patients with stable disease (SD) and 61 patients with progressive disease (PD) to differentiate stable from progressive NET. In all cases, 80% was retained for model training; 20% was used for performance evaluation. The predictive performance was assessed using sensitivity, specificity, and Area under Received Operating Characteristic Curve (AUROC). Trained models were validated in two independent sets of patients. Validation Set I (Controls vs. NETs) consisted of 555 NETs and 186 controls, while Validation Set II (Stable vs. Progressive) comprised 294 patients with image-confirmed SD and 149 with PD.

RESULTS

Results are reported from the two validation sets (Set I-Diagnostic: $n=741$; Set II-Prognostic: $n=443$). The diagnostic algorithm achieved an AUROC of 0.92, 93% sensitivity, 82% specificity, and 90% overall accuracy for distinguishing NETs from controls. The prognostic algorithm demonstrated an AUROC of 0.81, 67% sensitivity, 87% specificity and 80% overall accuracy for distinguishing stable from progressive disease. In head-to-head comparisons versus NETest 1.0, the overall diagnostic accuracy was significantly better using NETest 2.0 ($p=1 \times 10^{-15}$) as was the prognostic accuracy ($p=1.5 \times 10^{-5}$).

CONCLUSIONS

NETest 2.0 was trained on 240 samples and validated in 741 (diagnostic) and 443 (prognostic) patients, respectively. NETest 2.0 simplified the disease scoring system exhibiting improved diagnostic and prognostic capabilities over NETest 1.0. This optimized, validated blood-based molecular tool provides a powerful approach for diagnostic, prognostic and patient monitoring.

ABSTRACT ID 28660

B-26

Leveraging Cell Mass Measurements To Assess Drug Efficacy For Gastroenteropancreatic Neuroendocrine Tumor Liver Metastases And Advanced Adrenocortical Carcinoma

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BACKGROUND

Although surgical debulking is an accepted therapeutic strategy for selected patients with metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) or adrenocortical carcinoma (ACC), recurrence is the rule rather than the exception. Current preclinical models struggle with translational applicability and access to tissue at time of surgery has limited high-throughput utility for new drug discovery. To address this unmet need, we investigated single tumor cell mass measurements curated with inline machine-learning based image classification using tissue from the operating room to identify candidate drugs for a personalized medicine approach.

METHODS

Tumor biopsies from metastatic small bowel neuroendocrine tumors (SBNET) and pancreatic neuroendocrine tumors (PNET) liver metastases and advanced ACC tumors were collected intraoperatively. Tumor cells were isolated from tumor biopsies and assessed for viability utilizing CellTiter-Glo and flow cytometry. Cells were treated with FDA-approved drugs including everolimus, etoposide, doxorubicin, and cisplatin. Drug response was measured post-treatment upon passing single cell suspensions through a suspended microchannel resonator (SMR) to assess cell mass. Brightfield images were captured as cells passed through the SMR and annotated using machine-learning based classification to identify intact cells from debris particles for assessment of drug response. Drug response was assigned a value between 0 and 100, with >50 indicating a significant response to the treatment. Patient clinical response to therapy was defined by RECIST criteria.

RESULTS

Tumor biopsies were collected from 13 SBNET patients with median cell purity 76% (95% CI 70-92%) and median viability 92% (95% CI 90-95%), 6 PNET patients with median cell purity 70% (95% CI 50-88%) and median viability 92% (95% CI 60-97%), and 9 ACC patients with median cell purity 65% (95% CI 10-80%) and median viability 96% (95% CI 90-99%). Drug treatments were successfully performed in 69% SBNET samples, 66% PNET samples, and 66% ACC samples. For GEP-NETs, 63% SBNET and 100% PNET samples demonstrated significant drug response to everolimus. For ACC, treatment with etoposide, doxorubicin, and cisplatin demonstrated significant drug response in 40%, 33%, and 40% of samples, respectively. This lack of response to etoposide, doxorubicin, and cisplatin aligned with these patients' clinical disease progression despite previous treatment with these drugs.

CONCLUSIONS

This study indicates drug efficacy may be assessed using single-cell mass measurements of tumor cells. This methodology carries implications for selecting personalized therapies to optimize treatment plans for patients with metastatic neuroendocrine tumors and adrenocortical carcinoma.

ABSTRACT ID 28674



B-27

Use of patient-derived pre-clinical models to identify new and effective treatments for neuroendocrine tumors

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BACKGROUND

Neuroendocrine tumors (NETs) arise in different organs and are heterogeneous with limited treatment options. Preclinical models established from patient tumor specimens enable precision oncology by assessing the response to various drug treatments. Herein, we aim to develop patient-derived organoids (PDOs) and xenografts (PDXs) for NETs and use them to identify new treatment approaches.

METHODS

We established two pre-clinical models: patient-derived organoids (PDOs) and patient-derived xenografts ex-ovo (PDXovo), using fresh surgical samples from patients with gastroenteropancreatic NETs. To establish PDOs, the fresh tumor tissue sample is dissociated in single-cell suspension, and the cells are seeded in 384-well plates coated with chemically defined hydrogel. To assess the PDOs' progression and drug response, we use Chromalive™ non-toxic dyes to monitor the organoids' metabolic state, ER stress, and apoptosis. High-content imaging of the PDOs is done using an automated spinning disk confocal microscope (Opera Phenix, Revvity), and the image analysis uses customized algorithms. To establish NET patient-derived xenograft ex-ovo (PDXovo) models, we engraft small tumor tissue fragments into the chorioallantoic membrane of avian embryos. High-frequency ultrasound imaging (HF-US) is used to measure changes in tumor volume and vascularity. PDXovos are harvested and characterized at the endpoint using immunostaining and molecular biology approaches.

RESULTS

PDOs and PDXovos were established with a success rate of >95% and a take rate of >90%, respectively. We used NET PDOs from primary tumors (small intestine, pancreas, and cecum) and metastases (liver, lymph node) for high-throughput drug screening of clinically approved drugs alone and in combination with therapies currently used for GEP-NET. We have identified BH3-mimetics that inhibit anti-apoptosis proteins and augment the efficacy of clinically approved therapies for NETs.

We established over 160 PDXovos originating from 21 primary tumors and metastases. HF-US scanning of the PDXovos revealed successful tumor growth and vascularization. PDXovos were immunostained for neuroendocrine markers, such as chromogranin A, and markers of proliferation and apoptosis. We found that PDXovos resemble the tumor architecture and morphology of the corresponding patient tumor sample. We are currently evaluating the efficacy of the BH3-mimetics drug combinations using the PDXovo models to corroborate our findings further.

CONCLUSIONS

Overall, this study showed that we can reproducibly derive NET preclinical models on a large scale. Moreover, we have identified a new class of drugs for NETs, which we are further evaluating. Utilizing the dual approach of PDOs/PDXovo preclinical models will enable us to identify new potential treatments for patients with NETs.

ABSTRACT ID 28678



B-28

Stratification of neuroendocrine tumors for ecto-5-nucleotidase expression for clinical trials

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BACKGROUND

The recent development of small molecules inhibitors and neutralizing antibodies targeted against the enzyme ecto-5-nucleotidase (NT5E) is potentially applicable to the treatment of neuroendocrine neoplasms (NEN). NT5E is known to convert AMP to adenosine. Increased levels of NT5E are linked to worse outcomes in lung, pancreas, and stomach cancer. Phase 2 clinical trials for NT5E inhibitors are currently ongoing for the treatment of gastrointestinal cancers. We have previously quantified circulating levels of adenosine, AMP and NT5E levels in NEN patients and reported significant differences between patients with NEN tumors and control non cancer patients. The purpose of this study was to quantify NT5E levels in NEN tumors directly, determine cohort variations, and demonstrate patient/tumor specific screening for clinical trials.

METHODS

The Louisiana State University Health Science Center – New Orleans Neuroendocrine Cancer tissue repository was queried for unfixed cryopreserved 1) primary small bowel NEN tumors (N=30), 2) matched small bowel primary and liver metastatic NEN tumors (N=9), and 3) normal small bowel tissue (N=10). Available tumors and normal tissues were homogenized and quantified for NT5E by commercial ELISA.

RESULTS

NT5E levels were significantly higher in G2 and G3 primary small bowel NEN tumors ($p < 0.01$) but not in G1 tumors ($p = 0.41$) when compared to normal small bowel tissue. In contrast, liver NEN metastatic tumors NT5E levels did not increase with grade and were significantly lower when compared to matched G2 and G3 small bowel primary tumors.

CONCLUSIONS

NT5E expression levels correlated with primary NEN tumor grade but not metastatic liver grade. This observation correlates with literature reporting NT5E role in cancer progression and metastasis. Consequently, NT5E small molecule inhibitors or NT5E neutralizing antibodies have the potential to benefit patients with moderate and high-grade primary tumors by targeting metastatic growth.

ABSTRACT ID 28688

C-1

NP-101 in Combination with Nivolumab and Ipilimumab in Metastatic Extra-pulmonary Neuroendocrine Carcinomas (EP-NECs): A Pilot Study

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BACKGROUND

Extrapulmonary Neuroendocrine Carcinomas (EP-NECs) are a heterogeneous group of rare tumors with poor clinical outcomes. These patients have limited treatment options after progression on first-line platinum-based chemotherapy. Although dual immune checkpoint inhibitors (ICPIs) with anti-CTLA-4 and anti-PD-1 blockade have significantly improved outcomes for several solid tumors, they demonstrated modest activity for EP-NECs with 9–26% response rates and low survival rates. Preliminary data demonstrated that NP-101 (Thymoquinone) enhances T-cell infiltration and is synergistic with dual ICPIs in NECs' cellular models. This pilot study evaluated the safety and feasibility of a novel drug (NP-101) plus nivolumab and ipilimumab in patients with metastatic EP-NECs refractory to first-line platinum-based chemotherapy.

METHODS

This is a single-arm pilot study (NCTNCT05262556) in which patients with metastatic EP-NECs received NP-101 (oral capsules), 3000mg daily, plus ICPIs (intravenous nivolumab 3 mg/kg and ipilimumab 1 mg/kg) every 3 weeks for 4 cycles. Responders resumed NP-101 with the same daily dose (3000mg daily), plus maintenance biweekly nivolumab (240 mg), and completed 24 weeks of treatment. Treatment-related adverse events (TR-AEs) were characterized according to CTCAE v4.03. The response rate was estimated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 as the ratio of responders to the total number of patients and reported along with its Clopper-Pearson Confidence Interval.

RESULTS

Twelve patients received ≥ 1 dose of NP-101 and nivolumab plus ipilimumab. There were no dose limiting toxicities (DLTs). Grade 1/2 TR-AEs occurred in 100% (12/12) of patients. The most common G1/2 TR-AEs were fatigue (75%), nausea (41.7%), pruritus (41.7%), muscle weakness (33.3%), vomiting (25%), arthritis (25%), and abdominal pain (25%). 58.3% (7/12) of patients experienced grade 3/4 TR-AEs including rash (33.3%), nausea (16.7%), vomiting (16.7%), and transaminitis (16.6%). No treatment-related Grade 5 toxicities or deaths were recorded. The objective response rate (ORR) was 41.7% (2/12 CR + 3/12 PR; 95% CI:15.2-72.3%) for all patients and 50% (2/8 CR + 2/8 PR, 95% CI: 0.16- 0.84) for patients with NEC of gastrointestinal origin. The median duration of response was 13.9 months (range: 1.4-15.2 months). Median OS was not estimable with the current follow-up data and is still in progress.

CONCLUSIONS

The combination of NP-101 plus dual ICPIs (nivolumab and ipilimumab) was safe and well-tolerated with preliminary evidence of anti-neoplastic activity. A randomized phase II clinical trial studying the combination is now under development.

ABSTRACT ID 28480



C-2

Preliminary clinical activity of surufatinib combined with octreotide LAR in patients with G1/2 gastroenteropancreatic neuroendocrine tumor (GEP-NET)

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BACKGROUND

Surufatinib targets VEGFR1-3, FGFR1 and CSF1R, is a novel oral tyrosine kinase inhibitor (TKI) with dual antiangiogenic and immunomodulatory activities. It has been approved for the treatment of well-differentiated neuroendocrine tumors. Octreotide LAR, a somatostatin analogue, has been approved for the treatment of G1/G2 GEP-NET. This study aims to investigate the efficacy and safety of surufatinib combined with octreotide LAR in the treatment of G1/G2 GEP-NET.

METHODS

This single-arm, prospective, open-label phase II clinical study included patients aged 18-75 years with unresectable locally advanced or distant metastasis G1/G2 GEP-NET, ECOG PS 0-1, and adequate organ and bone marrow function. Patients received surufatinib (300 mg, po, qd) and octreotide LAR (30mg, sc, q4w) until disease progression or unacceptable toxicity. The primary endpoint was 6-month progression-free survival (PFS) rate. The secondary endpoints were PFS, overall survival (OS), objective response rate (ORR), disease control rate (DCR) and safety.

RESULTS

As of August 5, 2024, 8 patients were enrolled, and 7 were assessable, with a median age of 59 years (range 40-66), and 57.1% females. Most were G2 (71.4%) with a median Ki-67 index of 5% (range: 2-10%). The primary sites included rectum (42.9%), pancreas (28.6%), gastric (14.3) and small intestine (14.3%). All of them had liver metastases. 28.6% had prior anti-tumor therapy. With 15.7 months median follow-up, the 6-month and 12-month PFS rates were 100.0% and 66.7% (95%CI 37.9-100.0%). 2 patients progressed, 5 remain on treatment, 4 beyond 14 months (24.6, 20.1, 14.9, 14.2 months). The ORR and DCR were 28.6% and 100.0%, respectively. The most common treatment-related adverse events (TRAEs) were proteinuria (62.5%), lactate dehydrogenase increased (37.5%) and thyroid stimulating hormone increased (37.5%). Grade 3 TRAEs were proteinuria (12.5%) and hypertension (12.5%). No grade 4 TRAEs or deaths were reported.

CONCLUSIONS

This first study demonstrates promising antitumor activity and manageable safety of surufatinib plus octreotide LAR in G1/2 GEP-NET patients. The results support further evaluation of the therapy in a larger population. This trial is ongoing and updated data will be presented in the future.

ABSTRACT ID 28484

C-3

Prolonged Response to Dabrafenib/Trametinib in Metastatic Well-Differentiated Grade 3 Pancreatic Neuroendocrine Tumor (NET G3) with BRAF V600E Mutation

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BACKGROUND

Treatment of metastatic pancreatic neuroendocrine tumors (pancNETs), particularly well-differentiated grade 2 (G2) and grade 3 (G3), often presents a dilemma in choosing from multiple similarly efficacious therapies. Data on targeted therapies for specific molecular alterations in these tumor types is limited. This report presents BRAF-targeted therapy as a therapeutic option for metastatic pancNET G3. Studies regarding the prevalence of targetable alterations and efficacy of related treatments across gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are also reviewed.

METHODS

This is a case report of a patient with well-differentiated G3 pancNET (Ki-67 index of 37%) metastatic to liver, lung, lymph node, and scalp (soft tissue) treated with dabrafenib/trametinib (D/T) in the presence of a BRAF V600E mutation detected in tumor tissue. A (non-systemic) literature review accompanies the case.

RESULTS

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

CONCLUSIONS

Molecular testing for targetable alterations should be undertaken for all GEP-NENs, particularly in those grades of disease (G2 and G3). Identifying targetable alterations can provide extensive periods of disease control to add to the treatment armamentarium for these malignancies.

ABSTRACT ID 28494



C-4

Comparison of survival outcomes and hypoglycemic control in patients receiving systemic therapy for malignant insulinoma

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BACKGROUND

Malignant insulinoma is a rare neuroendocrine tumor characterized by inappropriate autonomous insulin secretion. The aim of this retrospective review was to evaluate the therapeutic efficacy of various systemic therapies in terms of survival outcomes and clinical management of refractory hypoglycemia.

METHODS

Patients receiving systemic therapy for metastatic or locally advanced, unresectable insulinoma at Mayo Clinic from 1992 to 2024 were retrospectively analyzed. Treatment history, clinical characteristics, and outcomes were collected. Median progression-free survival (mPFS) was calculated from the start date of therapy until documented radiographic progression. Median overall survival (OS) was calculated from the start date of therapy until death or last contact. Determination of hypoglycemic control was based on physician assessment of improvement, stability, or worsening in the severity and frequency of hypoglycemic episodes after initiation of systemic therapy. Survival analysis via Kaplan-Meier method and tests of statistical significance were completed in RStudio.

RESULTS

Fifty-seven patients (male=31) met inclusion criteria. Median age was 52.6 years (range 18-83). Two (3.5%) had MEN1 syndrome. Forty-four (77%) had de-novo metastatic disease. Fifty-two (91.2%) had liver metastases, 11 (19.3%) had distant metastases, and 4 (7%) had regional lymph node metastasis only. Half (50.9%) underwent surgical resection of the primary tumor. Twenty-six (45.6%) underwent liver debulking surgery. Six (10.5%) received ablation or embolization to the primary tumor. Thirty-four (59.6%) received ablation or embolization to liver metastases. Fifteen (26.3%) received radiation therapy. Systemic therapies received included somatostatin analog (71.9%), Everolimus (42.1%), Capecitabine and Temozolomide [CAPTEM] (38.5%), Radioligand Therapy [RLT] (33.3%), Streptozocin-based chemotherapy (14%), other chemotherapy (33.3%), tyrosine kinase inhibitors [TKIs] (7.0%), and immunotherapy (5.2%). mOS and mPFS differed for each systemic therapy (**Table 1**). Durable improvement in hypoglycemic episodes was observed in 93% of patients receiving RLT (**Table 1**). The majority of patients had improvement in hypoglycemia with initiation of CAPTEM (70%) or mTOR inhibitor (61.9%).

Table 1: Survival outcomes and hypoglycemic control for each systemic therapy.

Therapy	Number of Patients	mPFS (months)	mOS (months)	Percent of patients with durable improvement in hypoglycemia
CAPTEM	30	8.13	81.67	70.00
Other chemotherapy	25	5.03	15.23	21.05
Everolimus	24	29.90	74.07	61.90
RLT	22	12.40	49.73	93.33
Somatostatin analog	51	15.00	84.67	35.71
Streptozocin	8	4.32	8.35	33.33

CONCLUSIONS

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

ABSTRACT ID 28537



C-5

Once-daily Oral Paltusotine in the Treatment of Patients With Carcinoid Syndrome: Results From a Phase 2, Randomized, Parallel-Group Study

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BACKGROUND

Paltusotine is a once-daily, oral, nonpeptide, selective SST2 receptor agonist in development for the treatment of acromegaly and carcinoid syndrome (CS).

METHODS

This open-label, multicenter, dose-ranging study examined the safety, tolerability, pharmacokinetics, and exploratory efficacy of paltusotine in patients with CS. Eligible patients had documented, well-differentiated, grade I or II NETs (eg, GEP-NETs, bronchial NETs) with CS. Patients who were somatostatin receptor ligand (SRL) treatment naïve or currently untreated and actively symptomatic (average of ≥ 4 bowel movement [BMs] per day or > 2 flushing episodes per day in ≥ 2 days over 2-week period) and patients with symptom control on SRLs who demonstrated symptom worsening after SRL washout were randomly assigned to receive once-daily oral paltusotine 40 mg or 80 mg for 8 weeks. Exploratory efficacy was assessed using a daily symptom diary. Meaningful within-patient change (MPWC) thresholds were derived using FDA-recommended methods: for daily BM frequency -0.90 to -1.10 (single threshold: -0.90) and for daily flushing frequency -1.70 to -1.85 (single threshold: -1.80).

RESULTS

Thirty-six patients (n=9 treatment naïve or currently untreated; n=27 SRL washout) were enrolled. Entry criteria were met by 22 patients for flushing and 25 patients for BM. Among Week 8 completers (n=30), mean reduction from baseline in daily BM frequency was -1.1, and in daily flushing frequency it was -1.7. In patients with > 3 BMs per day at baseline, mean excess daily BM frequency decreased from 2.0 to 0.8 (-60%). In patients with > 1 flushing episode per day at baseline, mean daily flushing frequency decreased from 3.2 to 1.2 (-63%). Mean daily frequency of urgent BM episodes decreased from 1.1 to 0.4 (-64%); mean abdominal pain severity (worst pain score, scale from 0-10) decreased from 2.5 to 1.2 (-52%); and mean flushing severity (worst flushing score, scale from 0-10) decreased from 3.7 to 1.5 (-59%). During treatment, paltusotine dose was increased (per protocol) in 9 patients. Among patients meeting entry criteria for the corresponding symptom, 40% (10/25) met the daily BM frequency MWPC threshold of -0.90 and 59% (13/22) the daily flushing frequency MWPC threshold of -1.80. No severe or

serious adverse events (AEs) were considered treatment related. Two patients discontinued the study due to AEs (encephalopathy and bowel obstruction; not drug related). No new safety signals were identified.

CONCLUSIONS

In this phase 2 study, treatment with once-daily, oral paltusotine reduced the frequency and severity of CS symptoms and was well tolerated, justifying further clinical development.

ABSTRACT ID 28555



C-6

Evaluation of Switching SSAs on GI-NET Progression – Experience at an Academic Medical Center

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BACKGROUND

Long-acting somatostatin analogs (SSAs), available as lanreotide and octreotide LAR, are the standard of care first-line therapy for metastatic gastrointestinal well-differentiated neuroendocrine tumors (GI-NETs). On initial progression, we have noted a practice of switching patients to the alternate long-acting SSA as second-line therapy. With the availability of several FDA-approved second-line therapies, including PRRT, we sought to evaluate the efficacy of this practice, which is not well supported by available literature.

METHODS

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

RESULTS

Among 37 patients identified with alternating SSAs, the median age at first SSA initiation was 61.0 years old (IQR 50.0–65.0). SSAs were commonly transitioned due to disease progression (54.1%), medication intolerance (16.2%), symptom control (16.2%), and medication logistical issues, including administration difficulties (13.5%). Although 20 patients progressed, only 19 were available for evaluation due to loss of follow-up. In the 19 patients who transitioned SSAs due to disease progression, all patients were initially on octreotide LAR before transitioning to lanreotide. After transitioning to a second SSA, the median overall survival was 97 days (95% CI, 73–147). Progression was due to imaging progression in 84.2% of patients and serologic/clinical progression in 8.1%.

Table 1: Demographic and clinical characteristics of SSA transitions

	NET Patients (n = 37)
Median age, years (IQR)	61.0 (50.0-65.0)
Male, n (%)	20 (54.1)
Primary site, n (%)	
Small bowel	11 (29.7)
Pancreas	5 (13.5)
Colon/Rectum	5 (13.5)
Other/unknown	16 (43.2)
WHO Differentiation, n (%)	
Grade 1	7 (18.9)
Grade 2	2 (5.4)
Grade 3	0 (0)
Unknown	28 (75.7)

CONCLUSIONS

This real-world cohort demonstrates the limited activity of switching SSAs in patients with progressive disease following first-line treatment with SSAs in the metastatic GI-NET population. This practice has been noted in our region, and we sought to evaluate its efficacy in this limited retrospective study. Switching SSAs on progression is not well supported by previous literature, and with the availability of several FDA-approved second-line therapies, our study does not support its use.

ABSTRACT ID 28566

C-7

Cabozantinib therapy in patients with previously treated well differentiated grade 3 neuroendocrine tumors (G3 NETs)

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BACKGROUND

G3 NETs are a recently recognized entity among well differentiated neuroendocrine tumors but little is known about the optimal therapy sequencing, especially in later lines. Small studies have suggested benefit of multikinase inhibitors in G3 NETs. Recently, PRRT was shown to be an effective therapy for G3 NETs in a prospective trial and other trials are ongoing. The efficacy of later line therapy is unclear. In this study, we report on an expanded cohort of heavily pretreated patients with G3 NETs treated with cabozantinib.

METHODS

Cases of patients with G3 NETs treated with cabozantinib were identified using the search tools of the Mayo Clinic electronic medical record. Information on baseline patient and tumor characteristics, tolerability and efficacy were extracted.

RESULTS

Eleven patients (4 women, 7 men), median age 61 years (range 40 – 79) met inclusion criteria. Seven had pancreatic primary tumor; one each had duodenal, small bowel, rectal and a NET of unknown primary. The median Ki-67 was 15.5 (range 0.89 – 55) on the initial biopsy and 51.4 (range 23.4 – 97) on a repeat biopsy prior to starting cabozantinib. Nine patients had genomic studies completed and 2 had TMB > 200 m/Mb, presumably temozolomide-induced hypermutated state. Nine patients had prior somatostatin analogs, six had prior PRRT and all patients had prior CAPTEM before starting cabozantinib. Nine patients had other chemotherapy prior to cabozantinib (all had irinotecan or oxaliplatin regimens). Four patients had everolimus and 1 patient (with high TMB) had immunotherapy without a response. Five patients had an objective response, but one has not had follow up imaging. Nine patients progressed but 2 patients died shortly after starting therapy. The median mPFS was 2.8 months (range 2.2 – 14) and the median OS from start date of cabozantinib was 24.5. Two patients had to discontinue cabozantinib for toxicity and 3 needed a dose reduction.

CONCLUSIONS

Cabozantinib appears to have antitumor activity in this small cohort of extensively pretreated mostly pancreatic G3 NET patients. Although the overall mPFS is modest, some patients had both a profound imaging response and encouragingly long PFS despite very high nuclear grade. Cabozantinib may be a viable option for patients with advanced and heavily pretreated G3 NETs and further studies are warranted.

ABSTRACT ID 28613

C-8

Temozolomide Induced Hypermutation in Pancreatic Neuroendocrine Tumors: A Case Series

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BACKGROUND

Based on the current data, well-differentiated NETs generally do not respond to immune checkpoint inhibitors (ICIs). However, ongoing research is exploring strategies to transform these immunologically "cold" tumors into "hot" tumors (i.e. NETs). Temozolomide (TMZ) is an alkylating agent that induces DNA methylation at the O6 position of guanine, leading to mismatched base pairing, DNA replication errors, and cell death. Prolonged exposure to TMZ can cause defects in DNA polymerase and mismatch repair (MMR) genes, resulting in a hypermutated phenotype, characterized by a high tumor mutational burden (TMB-H). This phenomenon is well-documented in gliomas, where TMZ-induced hypermutation arises from acquired MMR defects during treatment. Although rare, similar hypermutations have been observed in NETs following TMZ treatment, raising the question of whether these patients might respond to ICI therapy. In this study, we present a series of NETs that developed an ultra-hypermutated phenotype after TMZ exposure.

METHODS

We conducted a retrospective chart review across all three Mayo Clinic sites, focusing on patients with advanced well-differentiated NETs treated with CAPTEM who were found to be TMB-H and/or microsatellite instability-high (MSI-H) through standard molecular testing. Clinical characteristics and outcomes were extracted from electronic medical records.

RESULTS

Seven patients were identified with ultra-hypermutated TMB (>100 mut/Mb) following TMZ exposure. The median age at diagnosis was 57 years (range 44-63), with the majority being males (n=5). All patients had metastatic pancreatic NETs (G2, n=4; G3, n=3). CAPTEM was administered either as first (n=3) or second-line (n=4) therapy. The median number of CAPTEM cycles was 12 (range 5-15), with a median cumulative dose of TMZ of 2250 mg/m². Next-generation sequencing (NGS) was performed post-progression on CAPTEM using either tissue-based assays (n=6) or blood samples (n=2). The median TMB in this cohort was 189 mut/Mb (102-2134 mut/Mb). The majority of patients were microsatellite stable (MSS, n=6), with one patient being MSI-H. Six patients initiated immunotherapy: one patient remains disease-free (TMB=2134 mut/Mb, MSI-H) after 2 years on Nivolumab/Ipilimumab, one patient achieved stable disease as their best response but progressed after 6 months, and three patients experienced disease progression after 4 cycles of ICIs.

CONCLUSIONS

This case series illustrates that despite TMZ-induced hypermutation and elevated TMB, the majority of patients do not respond to ICI therapy. Further research is needed to understand the molecular changes occurring within neuroendocrine tumor cells in this context, which may help identify strategies to generate immunogenicity in these historically “cold” tumors. This research also suggests that NGS and mismatch repair testing are warranted in pancreatic NETs.

ABSTRACT ID 28616

C-9

Updated Results of CABINET Trial/Alliance A021602: Cabozantinib Versus Placebo for Advanced Neuroendocrine Tumors (NET) after Progression on Prior Therapy

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BACKGROUND

NETs are sensitive to VEGF pathway inhibitors. We compared cabozantinib (CABO), a multi-kinase inhibitor targeting VEGFR, c-MET, AXL and RET, with placebo (PB) in a phase 3 trial including previously treated patients (pts) with advanced NET (NCT03375320). The study was stopped early and unblinded, per DSMB recommendations, based on interim results showing improvement in PFS by local radiology assessment (ESMO 2023). Final analyses of PFS by blinded independent central review (BICR), objective response rate (ORR), subgroup analyses, and safety are presented.

METHODS

Pts with locally advanced or metastatic extra-pancreatic NET (epNET) or pancreatic NET (pNET) were randomized 2:1 in separately powered cohorts to receive CABO 60 mg daily vs PB. Eligibility: progression by RECIST within 12 months (mo) prior to registration, ≥ 1 prior therapy. Prespecified primary endpoint: PFS by BICR. Secondary endpoints: ORR, overall survival (OS), safety.

RESULTS

203 pts with epNET and 95 pts with pNET were randomized through the data cutoff of 8/24/2023. Primary tumor sites for pts with epNET included GI tract 57%, lung 19%, unknown 12%. In both cohorts, CABO significantly improved PFS by BICR and resulted in higher confirmed ORR (Table). Across clinical subgroups, including primary tumor site and prior anticancer therapy, PFS favored CABO. Grade 3+ treatment-related adverse events (AEs) were higher in the CABO arm; no new safety signals were noted. The most common \geq grade 3 treatment-related adverse events in the epNET cohort included

hypertension (21%), fatigue (13%) and diarrhea (11%); in the pNET cohort, they included hypertension (22%), fatigue (11%) and thromboembolic events (11%).

Table. Progression-free survival and objective tumor response by BICR of patients enrolled in the epNET and pNET cohorts

	CABO - epNET (N=134)	PB - epNET (N=69)	CABO - pNET (N=64)	PB - pNET (N=31)
Median PFS (BICR), months	8.5	4.0	13.8	4.5
Stratified HR (95% CI)	0.38 (0.25-0.58)	Ref	0.23 (0.12-0.42)	Ref
Stratified log-rank p-value	p<0.0001		p<0.0001	
Confirmed ORR (BICR), n (%)				
Partial response	7 (5%)	0	12 (19%)	0
Stable disease	87 (65%)	37 (54%)	39 (61%)	17 (55%)
Progressive disease	15 (11%)	24 (35%)	5 (8%)	12 (39%)
Not evaluable/missing	25 (19%)	8 (12%)	8 (13%)	2 (6%)

CONCLUSIONS

CABO demonstrates significant improvement in PFS by BICR in epNET and pNET. AEs are consistent with the known safety profile of CABO. CABO may be a new treatment option for pts with previously treated, advanced NET.

ABSTRACT ID 28623



C-10

RZ358 (Ersodetug) as a Novel Therapy for Hypoglycemia due to Tumor Hyperinsulinism: Outcomes from an Expanded Access Program for Compassionate Use

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BACKGROUND

Tumor hyperinsulinism (tumorHI) occurs when insulin or related paraneoplastic substances produced in excess by tumors stimulate the insulin receptor, leading to excessive signaling and hypoglycemia. TumorHI arises from two types of neoplasms: pancreatic neuroendocrine tumors (pNETs), i.e. insulinomas, and a variety of other tumors, which can oversecrete forms of IGF-2. The associated hypoglycemia is often life-threatening and current means of managing hypoglycemia produces significant morbidity. Tumor-directed therapies are often ineffective at controlling severe hypoglycemia in advanced disease. Hence, there is a significant unmet medical need for better hypoglycemia-directed therapies for tumorHI.

Ersodetug, a fully human monoclonal antibody that allosterically binds the insulin receptor and negatively modulates signaling by insulin or related hormones, is a novel therapy with a mechanistic potential to treat any congenital and acquired forms of HI. It is currently being investigated in a global Phase 3 study (sunRIZE) for congenital HI, after favorable safety and efficacy outcomes were demonstrated in Phase 2 (RIZE study). This motivated development of an Expanded Access Program (EAP) that has included patients with severe hypoglycemia due to tumorHI.

Objective: To report the case experiences from a cohort of patients who have received RZ358 to treat tumorHI.

METHODS

Five adult patients (2M/3F) with refractory hypoglycemia due to metastatic insulin producing tumors received treatment with ersodetug after FDA/IRB-approval. At program entry, all patients required continuous parenteral dextrose, including 4 in a prolonged hospital setting. Ersodetug was initiated at 6 or 9mg/kg every 1-2 weeks (by 30-min intravenous infusion), and titrated to response, at physician discretion.

RESULTS

Ersodetug was generally safe and well-tolerated, and patients were able to stop or substantially reduce parenteral dextrose, enabling hospital discharge after initiating therapy. Four patients achieved complete discontinuation, and one achieved a 50% reduction in intravenous carbohydrate support after dose increase to 9mg/kg. Three patients achieved complete resolution of hypoglycemia within two weeks of starting treatment. More protracted responses occurred in patients who initially received ersodetug at a lower dose or frequency.

CONCLUSIONS

EAP for compassionate use provides real-world proof-of-concept for the use of ersodetug to treat hypoglycemia due to tumorHI. These observations are consistent with the known mechanism of action of ersodetug, pharmacology studies, and recent results from studies in congenital HI. A global, multi-center Phase 3 study in tumorHI patients is planned.

ABSTRACT ID 28673



C-11

Survivin and DLL-3 as predictors of survival in low-grade neuroendocrine tumor patients

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BACKGROUND

Neuroendocrine tumors (NETs) are increasing in incidence, but treatment options are limited. Emphasis on novel targeted agents and somatostatin receptor directed therapies is needed. To this end, we explored the expression of anti-apoptosis protein – survivin, and notch pathway regulator – DLL-3 in NETs as there are now agents to target these proteins in other clinical settings (glioblastoma multiforme and small cell lung cancer). They are being explored in high grade neuroendocrine carcinomas, but have not yet been well elucidated in low grade NETs as potential targets. We studied these biomarkers and correlated them with survival outcomes.

METHODS

With IRB approval, grade 1 and 2 NET patients who received chemotherapy: Temozolomide-based therapies, Everolimus, somatostatin analogous (SSAs) or Peptide Receptor Radionuclide Therapy (PRRT) and had survival follow-up of 3 years or longer were included. Their retrospectively banked tissue samples were stained for expression of survivin and DLL-3 using standardized methods. Correlation with 3-year overall survival (OS) was done in blinded fashion.

RESULTS

Twenty-five patients with NETs were included. Median age at diagnosis was 63.8 years (range: 46.1-79.7) and 52% were female. Primary tumor sites were lung (n=3), unknown (n=1) and gastrointestinal (GI) (n= 21). Survivin and DLL3 status was available for 24 and 20 patients respectively (missing cases had insufficient tumor cells for staining). Four patients had positive survivin staining: pancreas (n=2), colorectal (n=1), GI (n=1). Two patients had positive DLL3 expression: pancreas (n=1), lung (n=1). No patients were positive for both. The 3-year OS rate in survivin positive patients was lower than survivin negative patients [0.50 (95% CI 0.06- 0.84) vs 0.71 (95% CI 0.44- 0.87)], but this didn't reach significance. The 3-year OS rate for the two DLL3 positive patients was higher than that of the 18 DLL3 negative patients. [1.00 (95% CI 1.00-1.00) vs 0.82 (95% CI 0.54-0.94)]

Table 1: 3-year OS rates by survivin, DLL-3 and treatment regimen:

		3-yr OS Rate (95% CI)
Total		0.68 (0.43, 0.83)
Survivin	Negative (n= 20)	0.71 (0.44, 0.87)
	Positive (n =4)	0.50 (0.06, 0.84)
DLL3	Negative (n=18)	0.82 (0.54, 0.94)
	Positive (n=2)	1.00 (1.00, 1.00)
Chemo	Temozolomide + Capecitabine (n=14)	0.74 (0.38, 0.91)
	Temozolomide (n=1)	1.00 (1.00, 1.00)
	Everolimus (n=6)	0.67 (0.19, 0.90)
	None (n=4)	0.38 (0.01, 0.81)
Hormone	None (n=5)	0.75 (0.13, 0.96)
	Lanreotide (n=8)	0.50 (0.11, 0.80)
	Octreotide (n=1)	1.00 (1.00, 1.00)
	Sandostatin (n=11)	0.73 (0.37, 0.90)

CONCLUSIONS

Survivin and DLL3 can be therapeutic targets in NETs. Survivin positivity is more frequent in NECs, but can also be seen in low grade NETs and is correlated with lower 3-year OS. Larger studies are needed to explore therapeutic response to currently approved agents in these subsets.

ABSTRACT ID 28682

C-12

Updated Phase 1 data for the DLL3/CD3 IgG-like T-cell engager BI 764532 in DLL3-positive tumors: focus on extrapulmonary neuroendocrine carcinomas

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BACKGROUND

Delta-like ligand 3 (DLL3) is expressed on several cancers including extrapulmonary neuroendocrine carcinomas (epNECs). BI 764532 is a DLL3/CD3 immunoglobulin G (IgG)-like T-cell engager. This ongoing phase 1 trial (NCT04429087) aims to determine the maximum tolerated dose (MTD) and/or recommended dose for expansion of BI 764532 in patients with locally advanced/metastatic DLL3-positive small cell lung cancer, epNEC, or large cell neuroendocrine lung carcinoma. Other objectives include safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy (investigator review per Response Evaluation Criteria in Solid Tumors v1.1). Here, we focus on patients with epNEC.

METHODS

BI 764532 was given intravenously in four regimens: Regimen A (RA; fixed dose Q3W); Regimen B1 (RB1; fixed dose QW); and Regimens B2 and B3 (RB2 and RB3; step-in dose, followed by target dose). Treatment continued until disease progression, unacceptable toxicity, other withdrawal criteria, or maximum treatment duration (36 months).

RESULTS

As of August 14, 2023, 132 patients had received ≥ 1 dose of BI 764532 (RA: n=24; RB1: n=10; RB2: n=79; RB3: n=19). Most patients (60%) were male, median (range) age was 60 (32–81) years, and 28% and 71% had ECOG performance status of 0 and 1, respectively. Around half (48%) of patients had prior PD1/PD-L1 treatment, and 70% had ≥ 2 prior lines of treatment.

Dose-limiting toxicities were observed in one patient on RA (Grade 3 confusion) and five patients on RB2 (Grade 4 cytokine release syndrome [CRS], Grade 3 CRS, Grade 3 immune effector cell-associated neurotoxicity syndrome [ICANS], Grade 3 nervous system disorder, Grade 2 infusion-related reaction). MTD was not reached. Fifty-four patients with epNEC have been treated (gastrointestinal [GI]: n=28; genitourinary [GU]: n=18; unknown origin: n=7; missing: n=1). Treatment-related adverse events (TRAEs) were observed in 94% of patients (GI: 93%; GU: 94%), with 19% experiencing Grade ≥ 3 TRAEs (GI: 21%; GU: 17%). The most common TRAEs (any/Grade ≥ 3) were CRS (72%/4%), pyrexia (30%/0%), and dysgeusia (19%/0%). There was one Grade 5 TRAE (ICANS). Objective response rate/disease control rate in patients who received clinically active doses of BI 764532 was: overall (n=98): 28%/54%; epNEC group (n=41): 29%/49% (GI [n=21]: 29%/43%; GU [n=14]: 36%/57%; unknown origin [n=6]: 17%/50%). Seven (58%) of the responding patients with epNEC were still on treatment.

CONCLUSIONS

BI 764532 showed clinically manageable tolerability; MTD was not reached. Promising efficacy was observed in patients with epNEC. The study is ongoing, and updated efficacy and safety data will be presented.

ABSTRACT ID 28781



C-13

Patterns of long-term remission or apparent cure in a cohort of patients with grade 3 neuroendocrine neoplasms (NENs).

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BACKGROUND

Grade 3 disease is considered difficult or impossible to eradicate in most patients with NENs. We sought to describe the pathways to long term treatment-free survival or apparent cure in a cohort of tertiary care patients.

METHODS

A registry analysis identified NEN patients with 1) no imaging evidence of disease or 2) long-term nonprogressive disease without treatment, seen over the previous 23 years. Criteria included Ki-67 >20% or high-grade histology and no evidence of disease on no treatment for >5 years (stage I-III) or no evidence of disease progression or activity for at least 2 years (for stage IV disease).

RESULTS

A total of 51 patients (60.8% male, 39.2% female) were eligible for analysis. Whites consisted of 88.2% and African Americans were 11.8%. Most tumors were original diagnoses and originated in the head and neck area (31.6%) followed by GI (29.8%) and GU (22.8%). Pathology was poorly differentiated in 54.9% and mixed in 25.5% of the cases. Patient staging on initial presentation was 1 (27.5%), 2 (21.6%), 3 (19.6%) and 4 (31.4%).

Most common general treatments strategies included a combination of approaches (62.8%). Commonly used patterns were surgery and chemotherapy (32%) followed by chemotherapy and radiation (20%) and surgery as single treatment (14%). Most common first line treatments were curative surgery (62.7%) followed by localized radiation (21.6%), with only 7.8% of patients stopping treatment because of intolerance. Most second line treatments consisted of chemotherapy with platinum and etoposide (31.4%) with localized radiation (11.8%). Patients with metastatic disease on diagnosis were all treated with immunotherapy. Most patients underwent surgery followed by platinum chemotherapy. Only 5.9% of patients received a 4th and only 2% received a 6th treatment. Only 3.92% of patients were enrolled in a clinical trial.

Currently 84.3% of patients have no evidence of disease while 3.9% have long term stable disease. Most patients (78.4%) are alive as of last follow-up. A logistic regression model showed that patients with poorly differentiated histology and GU/head and neck origins had a statistically significant higher risk of death.

CONCLUSIONS

The most common road to cure or long-term remission for patients with grade 3 disease consists of surgery with platinum chemotherapy or radiation. The only pathway for those with metastatic disease included immunotherapy. Origin and histology affects survival despite apparent disease eradication. More analyses are ongoing.

ABSTRACT ID 28787



C-14

Approach Integrating ERCP with Radiofrequency Ablation for Long-term Management for metastatic pancreatic NET to biliary tree as klatskin tumor

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BACKGROUND

Introduction

Pancreatic neuroendocrine tumors (PNETs) are common pancreatic tumors with unclear molecular origins. Diagnosis involves testing and imaging, while a less favorable prognosis is associated with higher grade, metastasis, or larger size. Treatment at academic centers follows a 4-pronged approach: surgery, locoregional therapy, systemic therapy, and complication control. We present you a case of PNETs who underwent stenting for multiple episodes with RFA to the reduce the frequency of complication.

Case Report

A seventy-six-year-old white male was diagnosed with stage Ib well differentiated pancreatic neuroendocrine tumor WHO grade 2 in 2016 which was locally advanced. His Ki67 index was 17%. He was initially treated with 3 different chemotherapeutic regimens which includes Everolimus, Sinutinib and capecitabine+ temozolomide without significant response. He also received radiation to primary site. Afterwards, he was initiated on monthly lanreotide. He had undergone multiple ERCPs at another hospital but was not able to achieve biliary patency and was transferred to Thomas Hospital in Fairhope, AL. He presented in 2019 with ascending cholangitis with metastasis at the hepatic duct bifurcation in a Bismuth Type III anatomy.

METHODS

Procedure

He underwent ERCP with stent removal X 2. Stone and pus were extracted, and a covered self-expanding metal stent was placed. Since his initial ERCP, he had been treated with RFA primarily on a three-month basis. Typically, procedures begin with sweeping the tract clear of stones and debris which allows for a clearer cholangiogram and ensures the RFA energy treats the malignant tissue vice the debris. Priority for treatment is based on identifying the stricture that if treated allows for recruitment of the most liver. Cholangioscopy is usually required to place a wire across the stricture. Treatment is accomplished using 7 watts above the bifurcation. This setting is continued as the catheter is withdrawn in a stepwise fashion after each 90-second treatment and a 30-second pause. Once the proximal electrode is entirely within the common hepatic duct, the power is increased to 10 watts. After the entire stricture has been treated, the RFA catheter is removed, and a 9-12 mm extraction balloon is placed above the area treated. Again, three complete sweeps are completed.

In addition to the ERCPs, the patient also required a single stent to be placed by PTC to maintain liver segments 2 & 3 because it was not possible to pass a wire through the stricture at ERCP. His most recent configuration of stents is indicated in the picture below. This has required a total of 32 ERCP and as his cancer has progressed, they have become more frequent. His last procedure was last week and both the right and left hepatic ducts to the level of tertiary ducts were treated with good results.

Post-procedure

Reported adverse events included nausea post-procedure that resolved spontaneously. On two occasions he was hospitalized for supportive care to treat cholangitis. None of those events required the ICU. His overall survival since diagnosis is 7 years.

RESULTS

After undergoing ERCP with stent removal and subsequent treatment with radiofrequency ablation (RFA) primarily on a three-month basis, the patient has shown good results. The RFA procedures, coupled with stent placements, have required a total of 32 ERCPs, and despite some reported adverse events and hospitalizations for supportive care, the patient's overall survival since diagnosis is 7 years.

CONCLUSIONS

This case with a well-differentiated pancreatic neuroendocrine tumor WHO grade 2 showcases the challenges and complexities of managing such cases. Despite the multiple treatments and procedures, including stenting and radiofrequency ablation (RFA), the patient experienced some adverse events. However, the fact that the patient has shown an overall survival of 7 years since diagnosis highlights the resilience and ongoing efforts of the medical team in managing the condition.

ABSTRACT ID 28255



C-15

RECIST for the real world: Impact of Response Evaluation Criteria in Solid Tumors compared to standard radiology reports on physician decisions and patient satisfaction

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BACKGROUND

Neuroendocrine tumors (NETs) are slow-growing, so radiological assessment of tumor progression using standard evaluation is challenging. RECIST 1.1 is commonly used to assess the response to treatment in solid oncology clinical trials. This study aims to assess the impact of RECIST 1.1 in a standard of care setting and compare its use to routine radiology reports on physician decision making and patient satisfaction.

METHODS

We identified 50 patients (pts) from the Stanford NET clinic. We retrospectively used Stanford's Tumor Response Assessment Criteria (TRAC) and mintLesion™, FDA-approved software, to apply RECIST 1.1 criteria to CTs or MRIs performed as part of standard of care imaging. To assess the impact of TRAC compared to standard radiology reports on physician decision-making, 20 physicians reviewed 5 de-identified patient cases. Physicians received standard radiology reports and answered survey questions regarding disease response; subsequently, they received TRAC reports for the same cases and responded to the same questions. The survey evaluated their interpretation of both the standard radiology report and TRAC report, if TRAC report would prompt changes in treatment, and measured their confidence in their decisions, comparing rates and reasons for treatment change. To assess pt satisfaction and understanding of their standard radiology report compared to TRAC report, pts were asked to complete 2 surveys, first after they received their standard radiology report and second after they were given TRAC report reviewed by a provider.

RESULTS

Physician responses were analyzed using Kendall's W to assess agreement in survey responses after separately reviewing standard and TRAC reports. Across all cases we found that the overall agreement of responses to interpretation after reviewing the standard report (0.77) and TRAC report (0.81) were similar; although physicians agreed within each method, their responses differed between standard and TRAC reports. Agreement on treatment changes was higher after reviewing TRAC report (0.70) than standard report (0.55). Patient surveys were analyzed using Wilcoxon signed rank test.

Pts reported significantly improved understanding of their diagnosis ($p = 0.011$), felt more comfortable ($p < 0.001$), and were very satisfied with the way their imaging was explained with TRAC vs standard radiology report ($p < 0.001$).

CONCLUSIONS

Our study underscores the variability in physician interpretation of standard radiology reports and impact on treatment decisions in NETs. The results highlight several positive aspects of patient experience with TRAC compared to standard approach and suggests the benefits of using standardized response assessment for imaging in routine clinical practice.

ABSTRACT ID 28344



C-16

Targeted Alpha Therapy with ²¹²Pb-DOTAMTATE in subjects with advanced somatostatin receptor-expressing gastroenteropancreatic neuroendocrine tumors

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BACKGROUND

²¹²Pb-DOTAMTATE is a Targeted Alpha Therapy (TAT) in clinical development for subjects with SSTR+NETS. A Phase 1 dose-escalation study has already been completed. TAT holds the promise to improve outcomes versus Peptide Receptor Radionuclide Therapy (PRRT) with beta-emitters like ¹⁷⁷Lu-DOTATATE, currently considered standard of care for subjects with GEP-NETs.

METHODS

ALPHAMEDIX 02 is a Phase 2, open-label, multicenter study evaluating safety, tolerability and efficacy of ²¹²Pb-DOTAMTATE in PRRT-naïve (Cohort 1, N = 35) and PRRT-refractory (Cohort 2, N = 26) subjects with histologically confirmed unresectable or metastatic GEP-NETs, positive SSTR imaging and at least 1 site of measurable disease per RECIST 1.1. ²¹²Pb-DOTAMTATE was administered at 67.6 µCi/kg per cycle, every 8 weeks, for up to 4 cycles. Primary endpoints include overall response rate (ORR) per RECIST1.1, and incidence and severity of adverse events (AEs). Secondary endpoints include progression free survival, overall survival, and health-related quality of life. Initial results of the already completed Cohort 1 are presented.

RESULTS

In Cohort 1, 19 out of 35 subjects with metastatic SSTR+ GEP-NETs achieved a confirmed response (ORR 54.3% (95%CI: 38.2-69.5%)). In the Phase 1 trial, five out of eight PRRT-naïve subjects with SSTR+ GEP-NETs treated with the same regimen of ²¹²Pb-DOTAMTATE achieved a response (ORR 62.5% (30.6-86.3%)); the combined ORR from both studies is 55.8% (41.1-69.6%). Median Duration of Response (DOR) has not been reached in either study. Four out of four subjects (100%) with confirmed response in Phase 1 had a DOR of ≥ 12 months. In the ongoing Phase 2 study: so far 19 out of 19 subjects (100%) with confirmed response had a DOR of ≥ 6 months, and 10 out of 11 (91%) had a DOR of ≥ 12 months. Lymphocytopenia is a main cause of the 60% Grade 3 and 4 AEs reported overall in Cohort 1. Three deaths were reported as fatal AEs: underlying progressive disease (N = 2) and multiorgan failure/sepsis (N=1)

CONCLUSIONS

In PRRT-naïve subjects with SSTR+ unresectable or metastatic GEP-NETs, treatment with ^{212}Pb -DOTAMTATE was well-tolerated, with a safety profile consistent with the underlying disease and expected toxicities of radioligand therapy, similar to ^{177}Lu -DOTATATE. The 54.3% ORR in Cohort 1 (55.8% in pooled dataset) appears to be substantially higher than the ORR previously reported for ^{177}Lu -DOTATATE in the pivotal NETTER-1 study (18% (10–25%)).

ABSTRACT ID 28402



C-17

ACTION-1 phase Ib/3 trial of RYZ101 in gastroenteropancreatic neuroendocrine tumors progressing after ¹⁷⁷Lu somatostatin analogue therapy: Phase 1b safety/efficacy

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BACKGROUND

RYZ101 (²²⁵Ac-DOTATATE) is an alpha-emitting radiopharmaceutical in development for SSTR2+ solid tumors. Alpha-particles have a shorter path length/higher linear energy transfer than beta-particles, causing more frequent double-strand DNA breaks and potentially improved therapeutic index. ACTION-1 (NCT05477576) is a 2-part, global, randomized, controlled, open-label, phase 1b/3 trial of RYZ101 in advanced, well-differentiated SSTR+ gastroenteropancreatic neuroendocrine tumors (GEP-NETs) progressing after ¹⁷⁷Lu somatostatin analogue (SSA) therapy. Herein, we report updated results from the phase 1b portion of the trial.

METHODS

The phase 1b portion of the trial had a dose de-escalation/Bayesian optimal interval design with boundaries based on a dose-limiting toxicity (DLT) rate of 25%. Patients received RYZ101 IV every 8 weeks for 4 cycles. Planned dose levels (n=6/level): Level 0 (starting dose) 120 kBq/kg; Level -1 90 kBq/kg; Level -2 60 kBq/kg. DLT was assessed for 56 days after the first RYZ101 dose. Treatment-emergent adverse events (TEAEs) were graded by NCI-CTCAE v5.0. Dose de-escalation decisions/safety data were overseen by a Data Review Committee. Tumor response was assessed locally by RECIST v1.1.

RESULTS

17 patients have received at least one dose of RYZ101 at 120 kBq/kg (4 doses: 15 patients; 2 doses: 2 patients; median 8.3 MBq). Baseline characteristics: median age 63 years; male (n=11); ECOG PS 0/1 (n=10/7); primary tumor site GI/pancreas (n=12/5). As of 30 June 2023, the most frequent TEAEs were nausea (58.8%) and fatigue (52.9%). Serious adverse events (SAEs) were observed in 6 patients (none were treatment related); grade ≥3 AEs occurred in 9 patients (5 were treatment related). No AEs led to treatment discontinuation. 4 patients had TEAEs leading to dose modification, dose hold, and/or delays. The confirmed objective response rate was 29.4% (n=5; all partial responses); 1 patient

had an unconfirmed partial response. 8 patients (47.1%) had stable disease and 3 patients (17.6%) had progressive disease. Updated safety and efficacy data, including duration of response and progression-free survival, will be presented.

CONCLUSIONS

RYZ101 was well tolerated and a fixed dose of 10.2 MBq was declared the recommended phase 3 dose. Initial data suggest promising efficacy. Longer-term safety and efficacy data will be presented. Part 2 (phase 3) is enrolling and will compare RYZ101 at 10.2 MBq every 8 weeks for 4 cycles with standard of care in patients with advanced SSTR2+ GEP-NETs progressing following prior ¹⁷⁷Lu-labeled SSAs.

ABSTRACT ID 28436

C-18

DNA Damage Repair Mutational Status's Effect on Lu-177-DOTATATE in Combination with Olaparib in Metastatic SSTR+ GI Neuroendocrine Tumor: Preliminary Results

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BACKGROUND

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are somatostatin receptor (SSTR) expressing tumors that can be treated with Lu-177-DOTATATE. As ionizing radiation kills tumors via DNA damage, combination therapy with olaparib, a poly-ADP-ribose polymerase inhibitor (PARPi) may enhance Lu-177-DOTATATE's efficacy. In patients with BRCA mutations, PARPi act synergistically with intrinsic DNA-repair deficiencies causing synthetic lethality and is the proposed mechanism underlying PARPi's efficacy in these patients. However, the impact of patient's DDR mutational status on efficacy of this combination in GEP-NETs is unknown.

METHODS

In this standard 3+3 dose escalation, single-center phase 1/2 study (NCT04086485), Lu-177-DOTATATE is given at fixed dose of 200 mCi x 4 cycles with olaparib being escalated from dose level (DL) 1 at 50mg to 100mg (DL2), 200mg (DL3), and 300mg (DL4) bid. Olaparib dosing starts 2 days prior to Lu-177-DOTATATE until 28 days post, for a total of 30 days with each Lu-177-DOTATATE administration. Eligibility includes SSTR+ tumors and progressive disease by RECIST within 36 months of enrollment. Specific DNA-repair mutations such as BRCA are not required for eligibility but the data is collected. The study opened for enrollment in September 2022 and will require up to 33 patients for full accrual.

RESULTS

As of August 2024, 12 patients have been treated on study with 6 having completed therapy and have response data analyzed. Tumor location of origin for these 6 patients include 3 pancreas, 2 mid-gut, and 1 unknown (presumed mid-gut). Of these 6 patients, two have DDR mutations, with one having a pathogenic small nucleotide variation in BRCA2 (pNET) and another with ATM loss. The patient with BRCA2 mutation exhibited exceptional response that is seen after only 1 cycle of therapy, achieved scintigraphic CR in the liver by the second cycle, and achieved radiographic CR in the liver by the end of the 4th cycle. The other 5 patients including the one with ATM loss showed RECIST SD in this same time frame. Post-treatment dosimetry was performed after every cycle of Lu-177-DOTATATE and showed an average cumulative dose of 29.5 Gy to liver lesions in the BRCA2 patient and 48.5 Gy to liver lesions in the other 5 patients.

CONCLUSIONS

Preliminary data suggests that Lu-177-DOTATATE in combination with olaparib is effective in GEP-NET, and may be particularly effective in those with BRCA mutations.

ABSTRACT ID 28530

C-19

Safety of Lutetium-177 DOTATATE Treatment in Patients with Advanced Neuroendocrine Tumors and Extensive/Innumerable Bone Metastases

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BACKGROUND

Peptide receptor radionuclide therapy (PRRT) utilizing ¹⁷⁷Lu DOTATATE has led to a paradigm shift in advanced GEP NETs. As we gain more clinical experience with PRRT, we continue to understand more about treatment timing, sequencing of therapy, and optimal patient selection. One of the better-known toxicities of PRRT is bone marrow toxicity, namely cytopenias and treatment related myeloid neoplasms (t-MN). Of particular interest is whether bone marrow toxicity is accentuated in patients with extensive bone metastasis. We sought to build on this body of literature and evaluate the hematological safety as well as the efficacy ¹⁷⁷Lu-DOTATATE PRRT in the setting of advanced NETs with extensive/innumerable bone metastases.

METHODS

We retrospectively reviewed the medical records of all Mayo Clinic pts with extensive/innumerable osseous metastases, defined as >50 % skeletal involvement by somatostatin receptor (SSTR) positron emission tomography (PET), who were treated with ¹⁷⁷Lu DOTATATE. Patients' characteristics, along with laboratory results before, during, and after treatment were collected. Hematotoxicity was graded according to the NCI-CTCAE v5.

RESULTS

In total, 187 cycles of ¹⁷⁷Lu-DOTATATE PRRT were performed in 51 pts with extensive bony metastases. The median number of PRRT cycles was 4 (range 1-8), with a cumulative dose of 29.6 GBq (800mCi) (i.e. full dose) per patient. Three patients had dose reduction of 3.7 GBq (100 mCi) per cycle after the first cycle owing to hematological toxicity or renal dysfunction, and three patients had their PRRT cycles postponed allowing for hematological recovery. Out of 51 pts, 28(55%) pts experienced bone marrow toxicity of any grade after treatment with one or more cycles of PRRT. Significant G3-4 hematological toxicity was observed in 12(23.5%) patients (Thrombocytopenia 15.6%, anemia 13.7% and neutropenia 4%). Eight(15.7%) pts continued to experience cytopenia(s) of any grade one year post-PRRT. Regarding t-MNs, one patient developed therapy related myelodysplastic syndrome(2%), while two pts were found to have therapy related clonal cytopenias (t-CC)(4%). There was a significant difference in overall survival in those who developed hematotoxicity vs those who didn't (17.3 vs. 34.5 months).

CONCLUSIONS

In one of the largest institutional series of PRRT in patients with advanced NETs and extensive/innumerable bone metastases, moderate rates of grade 3-4 hematotoxicity were observed, although the majority were transient. Dose reductions were uncommon. Our study highlights the importance of carefully monitoring and assessing hematological parameters in patients being considered for ¹⁷⁷Lu DOTATATE PRRT with extensive/innumerable bone metastasis.

ABSTRACT ID 28539

C-20

Imaging, Clinical, and Safety Outcomes in Metastatic Neuroendocrine Tumor Patients Treated with Peptide Receptor Radionuclide Therapy in the Midwestern USA

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BACKGROUND

Multiple studies analyzing response to peptide receptor radionuclide therapy (PRRT) in metastatic neuroendocrine tumors (NETs) in the Australian and European populations have been published. However, data from US population is scant. This study, performed in a tertiary referral center in the Midwestern US, aims to assess the imaging, safety, and survival outcomes since the inception of this institution's PRRT program.

METHODS

This retrospective study included all consecutive metastatic NET patients treated with one or more doses of ¹⁷⁷Lu-Dotatate (Lutathera®) between March 2019 and April 2024, with a minimum follow-up period of 12 months. Primary endpoints included tumor response assessment using metabolic imaging tumor volume and RECIST v1.1, progression free survival (PFS), overall survival (OS), and safety profile. Secondary endpoints included analyzing trends of primary tumor location, metastatic sites, and tumor markers favoring disease progression.

RESULTS

A total of 42 patients [mean age (standard deviation), 66 + 5.6 years; 60% male; 88% Caucasians] including 27 (64.3%) gastrointestinal-NET, 13 (31%) pancreatic-NET, and 2 (4.8%) bronchial-NET patients were analyzed. 41 patients had WHO grade 1 or 2 NET (Ki-67<20%). Treatment response assessment at the end of follow-up period [median, 40 (27.5, 48) months] revealed partial response in 4 (9.5%), stable disease in 25 (59.5%), and disease progression in 13 (31%) patients, of which 12 patients died. The median progression-free and overall survivals were not reached at the end of follow-up period. 39 (92.6%) patients had grade 1 or 2 adverse effects. No treatment-related renal or liver dysfunction, myelodysplastic syndrome, or leukemia was reported. Transient lymphopenia and hyperglycemia were noted in 33 (78.6%) and 25 (59.5%) patients, respectively. Multivariable logistic regression analysis demonstrated no significant association of disease progression with primary or metastatic disease sites or pre-treatment Chromogranin A (CgA) levels. However, higher disease progression was noted in patients with grade 3 adverse effects (p=0.025) and higher post-treatment CgA levels (p=0.033).

Treatment cycles administered			
Four, n (%)	26 (61.9)	7 (16.7)	0.006
Three, n (%)	3 (7.1)	1 (2.4)	
Two, n (%)	0	3 (7.1)	
One, n (%)	0	2 (4.8)	
Common Terminology Criteria for Adverse Effects			
Grade 1 or 2	29 (100)	10 (76.9)	0.025
Grade 3	0	3 (23.1)	
Pre-treatment ChromograninA	107 (32,350)	360 (41,998)	0.305
Post-treatment ChromograninA	91.2 (46,232)	515 (148,1846)	0.033

CONCLUSIONS

The study supports the role of PRRT in favorable survival outcomes and safety profile in patients with metastatic NETs in a US-based population.

ABSTRACT ID 28542



C-21

Effect of Absorbed Dose on Toxicity and Tumor Response of Lu-177-DOTATATE With Olaparib in Gastroenteropancreatic Neuroendocrine Patients: Preliminary Results

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BACKGROUND

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are somatostatin receptor (SSTR) expressing tumors treated with Lu-177-DOTATATE. Olaparib is a poly-ADP-ribose polymerase inhibitor that blocks single-stranded DNA repair which may synergize with Lu-177-DOTATATE for both efficacy and toxicity. We present in-progress dosimetry results of a phase 1/2 trial testing this combination in metastatic GEP-NET.

METHODS

Three quantitative SPECT/CT scans (4, 24, 48 hours post-infusion) are performed in NCT04086485, a 3+3 dose escalation phase 1/2 study evaluating Lu-177-DOTATATE + olaparib. Lu-177-DOTATATE is given at fixed 200 mCi x 4 cycles while olaparib is escalated from 50mg to 100mg, 200mg, and 300mg bid. Dosimetry was performed using MIM's SurePlan MRT workflow. Regions of interest (ROIs) are drawn around all major organs and select tumors by an experienced Nuclear Medicine physician using MIM's automatic segmentation and PET Edge tool. Integrated time activity curves were obtained using both MIM's fitting functions and trapezoidal integration. The latter data and the voxel S-value convolution method in SurePlan was used to calculate absorbed doses. CT scans obtained at baseline, post 2-cycles, and post 4-cycles were used for RECIST tumor measurements.

RESULTS

By April 2024, 11 patients were treated (6 patients with 4 cycles, 3 with 3 cycles, and 2 with 1 cycle). Absorbed doses calculated with trapezoidal integration yielded results that were on average 34% higher than best fit method. For the 6 patients who completed therapy, 62 tumors lesions were contoured, of which 23 were official RECIST measurable lesions. For these 62 tumors, absorbed dose over all 4 cycles averaged 51.86 Gy (range: 0.77 to 248.85 Gy) per lesion. Per cycle average dose decreased over time (Cycles 1-4: 15.91, 13.57, 12.36, 11.29 Gy, respectively). No correlation was found between total absorbed dose or olaparib dose with change in RECIST diameter at studied re-staging time points. For toxicity, 3/9 (33%) evaluable patients had grade 1 creatinine elevation with average absorbed doses of 13.35 Gy (left) and 11.91 Gy (right) to kidneys, compared to 12.79 Gy and 11.02 Gy in the other 6 patients. One patient (11%) had grade 1 transaminase elevation with 5.85 Gy to the liver, compared to 25.14 Gy (range: 5.85 to 53.13 Gy) in others.

CONCLUSIONS

Preliminary data suggests that absorbed doses calculated via 3 time-point dosimetry do not correlate with tumor response or organ toxicity after 2 or 4 cycles in patients treated with Lu-177-DOTATATE and olaparib.

ABSTRACT ID 28545



C-22

Multicenter clinical registry of patients with a neuroendocrine tumor (NET) diagnosis receiving 177Lu-DOTATATE

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BACKGROUND

Since FDA and EMA approval of 177Lu-DOTATATE to treat advanced NETs, there has been rapid adoption of this therapy. To allow for collaboration and data centralization related to NET treatment with 177Lu-DOTATATE, two major US NET centers have partnered to create a NET registry compiling clinicopathologic, epidemiologic, radiologic, and molecular data for patients receiving 177Lu-DOTATATE therapy.

METHODS

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

RESULTS

As of 8/2024, the registry includes 479 patients (pts) who have received at least one dose of 177Lu-DOTATATE (sex: 238 female, 50%, race: 362 White/Caucasian, 75%). Site of origin includes: pancreas (183 pts, 38%), small bowel (164 pts, 34%), bronchial (30 pts, 6%), rectal (17 pts, 4%), paraganglioma-pheochromocytoma (9 pts, 2%), gastric (8 pts, 2%), other (28 pts, 6%), unknown (40 pts, 8%). Tumor grade at initial diagnosis: grade 1 (130 pts, 27%), grade 2 (246 pts, 51%), grade 3 (86 pts, 18%), unknown (17 pts, 4%). Most patients received 4 cycles of 177Lu-DOTATATE (326 pts, 68%).

CONCLUSIONS

This multicenter clinical registry represents a collaboration between two academic centers to study real-world outcomes for patients receiving 177Lu-DOTATATE therapy. Ongoing addition of eligible patients and project-relevant variables supports our effort to continuously expand the utility of this registry. As this registry grows, important questions related to the sequencing of 177Lu-DOTATATE in NET treatment as well as identifying biomarkers (clinicopathologic, radiologic, molecular) of response and resistance to 177Lu-DOTATATE can be addressed. Our shared goal is to advance our use of 177Lu-DOTATATE for this heterogeneous disease.

ABSTRACT ID 28591

C-23

Neuroendocrine tumor (NET) progression of disease during or within one year after completion of therapy with ¹⁷⁷Lu-DOTATATE

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BACKGROUND

The survival and response benefit of ¹⁷⁷Lu-DOTATATE to treat NETs is established by prospective trials. Further study of NETs with limited response to ¹⁷⁷Lu-DOTATATE remains. We report single-institution outcomes of patients with NETs that experienced disease progression during or within one year after completion of ¹⁷⁷Lu-DOTATATE.

METHODS

Patients with a NET diagnosis who received at least one ¹⁷⁷Lu-DOTATATE cycle were included. Demographics, clinicopathologic data, prior treatments, ¹⁷⁷Lu-DOTATATE treatment data, response (based on radiographic reports) were collected.

RESULTS

Among 284 treated patients, 105 (37%) progressed during or within one year after ¹⁷⁷Lu-DOTATATE therapy.

Among these patients (pts), 67 (64%) received all 4 cycles, with radiographic progression identified on average at 6.4 months (range 0-12) after therapy completion. Best response: partial response (34 pts, 51%), stable disease (14 pts, 21%), progressive disease (19 pts, 28%). Site of origin: pancreas (38 pts, 57%), small bowel (10 pts, 15%), lung (5 pts, 7%), rectal (3 pts, 4%), kidney (2 pts, 3%), gastric (1 pt, 1%), large intestine (1 pt, 1%), unknown (6 pts, 9%). Tumor grade (G): G1 (15 pts, 22%), G2 (37 pts, 55%), G3 (12 pts, 18%), unknown (3 pts, 4%). Mean number of prior treatments: 4.0 ± 2.1 (range 1-11).

Thirty-eight pts (36%) with progression received fewer than 4 cycles (1: 6 pts, 16%, 2: 17 pts, 45%, 3: 15 pts, 39%). In this cohort, radiographic progression was identified on average 3.2 months into therapy (range 0-12). Best response: partial response (10 pts, 26%), stable disease (6 pts, 16%), progressive disease (22, 58%). Site of origin: small bowel (14 pts, 37%), pancreas (9 pts, 24%), lung (7 pts, 18%), rectal (2 pts, 5%), appendix (1 pt, 3%), unknown (5 pts, 13%). Tumor grade: G1 (12 pts, 32%), G2 (21 pts, 55%), G3 (4 pts, 10%), unknown (1 pt, 3%). Mean number of prior treatments: 4.0 ± 2.6 (range 0-12). Reasons for early treatment discontinuation: radiographic/clinical progression (28 pts, 71%), hematologic toxicities (7 pts, 18%), bowel obstruction (1 pt, 3%), death (1 pt, 3%), infection (1 pt, 3%), ¹⁷⁷Lu-DOTATATE production delay (1 pt, 3%).

CONCLUSIONS

Among patients with disease progression during or soon after ¹⁷⁷Lu-DOTATATE completion, 64% received the full treatment course/4 cycles. Early progression was more commonly seen in G2/3 disease (74 pts, 70%). The most common reasons for therapy cessation prior to completion of 4 cycles were disease progression during treatment followed by therapy-related hematologic toxicities.

ABSTRACT ID 28603

C-24

Evaluating Time to Treatment Start for Patients Receiving Peptide Receptor Radioligand Therapy

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BACKGROUND

Background: Timeliness of treatment initiation has been shown in oncology settings to impact patients' overall survival. However, the multistep process from referral to therapy initiation is complex. This study evaluates the time from referral of patients with Neuroendocrine Tumors (NET) to their first infusion of Radiopharmaceutical Therapy (RPT) and determines if there are areas for timeliness improvement.

METHODS

We reviewed the electronic medical records of 10 patients who have received at least 1 cycle Lu177-DOTATATE (all inside referrals) between January 2023 and July 2024. As a comparator, we also reviewed 20 patients (10 inside referrals and 10 outside) who received Lu177-PSMA during this same time. The dates for the following events were recorded: referral to Nuclear Medicine (NM), presentation at the Tumor Board (TB), consultation with NM, insurance approval, and cycle 1 of RPT. The number of days between each event and the overall elapsed time between referral and cycle 1 were calculated.

RESULTS

The average elapsed time from referral to cycle 1 of Lu177-DOTATATE was 44 days with a standard deviation (SD) of 30 days. For Lu177-PSMA patients, inside referrals took an average of 51 days (SD 17 days) and outside referrals took 63 days (SD 32). The below table details the elapsed days between each workflow event:

	DOTATATE Days (SD)	PSMA Inside/Outside Days (SD)
TB discussion to referral	6 (11)	20, 25 (18, 22)
Referral to Consultation	11 (5)	7, 12 (12, 22)
Consultation to Insurance Approval	8 (13)	6, 7 (6, 9)
Insurance Approval to Treatment Start	23 (24)	17, 20 (12, 18)
Total Time from Referral to Treatment Start	44 (17)	51, 63 (17,32)

CONCLUSIONS

Compared to the patients receiving Lu177-PSMA, Lu177-DOTATATE patients had a lower elapsed time between referral and cycle 1 of RPT. This is likely due to the workflow differences between prostate cancer and NET referrals to NM. Patients with NETs are referred by an internal medical/surgical oncology provider and must always be presented at the TB with a recent DOTATATE PET before the referral to NM is placed, so it is assured the patient meets criteria for RPT. The most common cause for delay between referral and consultation was waiting for patients to call back for scheduling. Patients with Medicare had the shortest wait for insurance approval, while prior authorizations requiring peer-to-peer review had the longest delay. Common causes for delay to treatment start after insurance approval included hospitalizations and patient preference.

ABSTRACT ID 28604

C-25

Does Liver Tumor Morphology Predict Outcomes after LDT, PRRT or CapTem?

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BACKGROUND

Patients with metastatic neuroendocrine tumor (NET) have multiple options for liver-directed therapy (LDT) and systemic therapies. Post hoc analysis of NETTER-1 suggested that tumor size but not tumor burden predicted PFS after PRRT, whereas a multicenter analysis of LDT found that tumor burden was predictive. We analyzed imaging datasets from completed multicenter prospective clinical trials to investigate whether morphologic subgroups of NET liver metastatic disease based on lesion size, lesion number and tumor burden might be more optimally treated with liver-directed therapy vs systemic chemotherapy vs systemic radiotherapy.

METHODS

All images from the CapTem arm of EA2211 were reviewed and categorized for liver metastasis number, maximum lesion diameter, liver tumor burden, and size of up to five index lesions (N=67). A similar number of cases from the RETNET trial imaging archive (N=76) and from an institutional cohort of patients treated with PRRT (N=77) were analyzed. Morphologic categories were then correlated with RECIST response and PFS. Descriptive and graphical analyses were followed by multivariable modeling to test treatment by stratum interaction.

RESULTS

The objective response rates for LDT, PRRT and CapTem were 65%, 38% and 25% respectively ($p < 0.001$) with an odds ratio favoring LDT of 5.66. The respective median PFS were LDT 18.9 months [95% CI 16.3-24], PRRT 21.6 mo [14.3-26.7], and 16.6 [11.5-29] for CapTem ($p=0.99$ for all comparisons).

Lesion number, maximum lesion diameter, and liver tumor burden were not associated with differences in response or PFS for any of the three therapies or for the entire analyzed population as a whole. Lesion size as a continuous variable did not correlate with tumor response for any therapy ($p=0.4$).

CONCLUSIONS

Liver-directed therapy provides superior debulking to systemic therapies. PFS is similar for all three modalities. No morphologic features of liver metastases were identified that correlated with treatment outcome within a particular treatment modality nor to favor one over another when triaging patients.

ABSTRACT ID 28605

C-26

Incidence and Characterization of Carcinoid Crises post Embolization of Neuroendocrine Tumor Liver Metastases

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BACKGROUND

Transarterial embolization (TAE) of neuroendocrine tumor liver metastases (NETLMs) involves delivery of embolic agents into the hepatic arterial supply of the tumor. Embolotherapies, similar to surgical resection, of NETLMs may instigate a potentially life-threatening period of hemodynamic instability, termed a carcinoid crisis. Currently, this life-threatening complication is not reported or well-studied post NETLM embolizations. Further, there is poor evidence supporting the use of octreotide, the current prophylaxis and standard of care for these perioperative crises. However, the pathophysiology of these events remain unknown, contributing to the lack of standardized care. The aim of the current study is to investigate the incidence of carcinoid crises post embolotherapy and direct future studies addressing the management of carcinoid crises.

METHODS

Data were collected retrospectively from patients undergoing transarterial embolization (bland embolization, chemoembolization, and radioembolization) for a NETLM from January 1, 2010 to January 1, 2024 at the University of Kentucky. Continuous variables were analyzed using Student's independent t-tests, and categorical variables were analyzed using Fisher's Exact Test. A crisis was defined as an intra-procedural crisis as documented by the performing physician or clinically important hemodynamic instability (sustained systolic BP <80 or >180mmHg or sustained tachycardia >120bpm) not attributable to other factors within 48 hours post-procedure.

RESULTS

There were nine suspected crises of 211 procedures (4.3%) and 113 patients (8.0%). Eight of these occurred post-procedurally, three of which met the criteria for a SIRS response in the absence of infection. The management of these crises was highly variable with five patients receiving prophylactic octreotide and only two patients receiving octreotide during the crisis.

CONCLUSIONS

Carcinoid crises are life-threatening events and can occur post-procedurally for patients undergoing hepatic artery embolization of NETLMs. The incidence post-embolization of NETLMs observed in this study is lower than reported post-surgical resection (typically reported around 30-40%). The occurrence of SIRS responses supports a mechanism of distributive shock. There was no consistent management protocol utilized for the prevention or treatment of carcinoid crisis post-resection or post-embolization. Therefore, future studies should focus on developing a standardized protocol for periprocedural prophylaxis and management of carcinoid crisis.

C-27

A Pilot Study of Pembrolizumab and Peptide Receptor Radionuclide Therapy for Patients with Well-Differentiated Neuroendocrine Tumors and Symptomatic and/or Progressive Metastases

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BACKGROUND

Expected progression free survival (PFS) for patients with grade 3 well-differentiated neuroendocrine tumors 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 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 PD1 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 ¹⁷⁷Lu-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 were enrolled: 15 men, median age 60 years, median Ki-67 index 30% (range 11-70%), 6 patients with grade 2, 20 patients with grade 3 NET. Primary site: 15/26 pancreas, 6/26 small bowel, 3/26 lung, 2/26 other. As of August 15, 2024, 22/26 patients (84.6%) have been on study for at least 24 weeks, and 5/26 (19.2%) are still receiving pembrolizumab. Median follow-up was 13.7 mo. Grade 3 and 4 adverse events include anemia (n=2, 7.7%), neutropenia (n=2, 7.7%), and thrombocytopenia (n=1, 3.8%) related to PRRT, and diabetes mellitus (n=2, 7.7%) and hyponatremia (n=3, 11.5%) attributable to pembrolizumab. In terms of best radiographic response, 9/26 patients (34.6%) demonstrated partial response, 16/26 (61.5%) had stable disease, and 2/26 (7.7%) had disease progression, with 23/26 (88.5%) patients having achieved some shrinkage of their disease (median 24.2%, range 4.3-84.1%). Median PFS was 11.2 months (95% CI 8.6, 14.4 months). Overall, 21 patients discontinued participation due to disease progression (n=17), performance status deterioration (n=2), or completion of planned two years of pembrolizumab treatment (n=2). Updated safety, PFS, and ORR analyses will be reported.

CONCLUSIONS

In this pilot study of patients with well differentiated NET with Ki67>10%, combination treatment with ¹⁷⁷Lu-DOTATATE PRRT and pembrolizumab was well tolerated and associated with ORR 34.6% and mPFS 11.2 months. Additional research is needed to identify the patients most likely to benefit from combination therapy and to determine the incremental benefit of each component.

ABSTRACT ID 28609

C-28

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

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BACKGROUND

Neuroendocrine carcinoma (NEC) and grade 3 neuroendocrine tumors (NET) are aggressive, often unresectable malignancies with poor prognosis despite systemic therapies. Liver-directed therapies (LDT) may help control disease burden and reduce symptoms. Outcomes after LDT in this subset of patients with aggressive tumor biology are not well studied.

METHODS

Single center retrospective cohort study of all patients with grade 3 NET or NEC who underwent liver-directed therapy (LDT) from 2015 to 2024, including bland embolization (TAE), chemoembolization (TACE), and Yttrium-90 radioembolization (TARE). Clinicopathologic characteristics, radiologic response (modified Response Evaluation Criteria in Solid Tumors), adverse events, and progression free survival (PFS) were recorded. Local PFS ended with progression of the treated tumor; hepatic PFS ended with progression of any hepatic tumor; and overall PFS ended with progression of any disease.

RESULTS

20 NET patients (mean age 58, 40% male) underwent 30 LDT procedures (9 TAE, 12 TACE, 9 TARE), and 6 NEC patients (mean age 63, 67% male) underwent 13 LDT procedures (1 TAE, 4 TACE, 8 TARE) during the study period. In the NET group, median Ki-67 index was 28.5 (range 21-65), mean largest hepatic tumor diameter was 6.6cm, 35% had primary pancreatic tumors, 93% had bilobar hepatic metastases, and 90% had extrahepatic metastases. In the NEC group, median Ki-67 index was 55 (range 32-90), mean largest hepatic tumor diameter was 6.8cm, 17% had primary pancreatic tumors, 92% had bilobar hepatic metastases, and 46% had extrahepatic metastases. Radiologic response rates at 1 month post-LDT for both cohorts are listed in the table below ($p > 0.05$). On Kaplan-Meier analyses, median local, hepatic, and overall PFS for NET vs NEC were 6.7 vs 2.9 months ($p = 0.25$), 4.8 vs 1.5 months ($p = 0.21$), and 3.2 vs 1.5 months ($p = 0.33$), respectively. Adverse events were seen in 32.6%, most commonly post-embolization syndrome (27.9%) and hepatic infarct (18.6%). Carcinoid crisis was noted in 1 patient (2.4%).

CONCLUSIONS

Liver-directed therapies induce a durable local response in approximately 60% of grade 3 NET patients with median PFS of the treated tumor of 6.7 months. While not reaching significance in this small cohort study, outcomes in NEC patients appear worse, with approximately 31% local response rate and median PFS of 2.9 months.

ABSTRACT ID 28620

C-29

Initial Outcomes of Integrating Yttrium-90 Radioembolization with Capecitabine-Temozolomide for Grade 3 Liver-Dominant Metastatic Neuroendocrine Tumors

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BACKGROUND

Well-differentiated Grade 3 (G3) neuroendocrine tumors (NETs) are characterized by a high proliferative rate (Ki67 > 20%) with a prognosis between that of Grade 2 NETs and neuroendocrine carcinoma. Embolotherapy of G3 hepatic metastases has poor outcomes with median hepatic progression free survival (HPFS) of 4.9 months and overall survival (OS) of 9.3 months in a multicenter analysis. To improve these historical outcomes, an integrated protocol of radiosensitizing chemotherapy and radioembolization was developed.

METHODS

Patients with liver-dominant, well-differentiated G3 NET were treated with capecitabine 750 mg/m² twice daily for 14 days followed by 14 days off. Temozolomide 200 mg/m² daily x 5 days was given on days 10-14 of capecitabine (CapTem regimen). CapTem was given for a year or stopped at time of progression or intolerance if sooner. Simulation angiography with Tc99m-MAA SPECT was performed in the first cycle of CapTem. The dominant lobe was treated on day seven of the second cycle. Resin Y90 microspheres (SIR-Spheres) were administered using the body surface area method. For bilobar disease, the other lobe was treated in the third or fourth cycle. Clinical and laboratory assessment were done monthly and imaging every 3 months. PFS and OS were estimated by Kaplan-Meier method.

RESULTS

Seven patients had pancreatic NETs and one had an atypical lung carcinoid, with Ki67 21-70%. Two patients had extrahepatic metastasis. Median duration on CapTem was nine months (range 4-16 months). Thirteen radioembolizations were performed, with a median total dose per patient of 48 mCi (33-66 mCi). Grade three toxicities included ALT/AST elevation (n=2), hyperbilirubinemia (n=1), and anemia (n=1). There was one grade four thrombocytopenia, leading to CapTem hold and dose reduction. Median follow-up time from initiation of CapTem was 32 months. Four patients had partial response in the liver, two had stable disease, and two had progressive disease (ORR 50%). Median decrease in Chromogranin A was 58% (33-95%). All patients eventually developed intrahepatic progression. Median hepatic PFS was 9.3 months (2.8-40.5 months), and median extrahepatic PFS was 16.4 months. Multiple patients proceeded to alternative treatment regimens. Six patients died between 8-60 months from initiation of CapTem, with mOS of 30.8 months.

CONCLUSIONS

Integrated CapTemY90 chemotherapy and radioembolization showed acceptable toxicity, not greater than expected in this cohort of patients with G3 NETs. Hepatic and overall PFS suggest improved outcomes compared to that reported in the literature for G3 NETs treated with standard embolotherapy, noting that ours is a small cohort.

ABSTRACT ID 28641

C-30

Somatostatin receptor expression of gastroenteropancreatic neuroendocrine tumors: A comprehensive analysis of expression in the era of somatostatin receptor PET imaging

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BACKGROUND

There is limited data on somatostatin receptor (SSTR) expression of metastatic neuroendocrine tumors using modern imaging techniques and stratifying by primary site and tumor grade. Few studies evaluate the degree of SSTR expression and tumor heterogeneity. Understanding patterns of SSTR expression is essential when determining the relevance of cold and radiolabeled somatostatin analogs for a particular population of patients.

METHODS

A single-institutional retrospective analysis of metastatic well-differentiated G1-3 GEP-NET patients who underwent ⁶⁸Ga- or ⁶⁴Cu-DOTATATE PET imaging from September 2016 to June 2024 was performed.

RESULTS

A total of 1192 patients were considered eligible for this study. Among them, 26 (2.2%) had completely negative SSTR expression, and 27 (2.3%) had weak expression (less or equal to the normal liver). Up to 40 (3.4%) had a heterogenous expression: 26 (2.2%) displayed the coexistence of strongly avid lesions with the absence or near absence of SSTR uptake in measurable tumors (heterogenous strong), while 14 (1.2%) had a combination of absent and weakly expressing SSTR tumors (heterogenous low). An additional 9 cases with prior homogenous expression (0.8%) developed new SSTR-negative tumors along with disease progression, potentially indicating dedifferentiation.

The absent or heterogenous SSTR expression rates were greater in NET G3 than G1/G2 and in tumors originating outside the small bowel (midgut). Most NETs with absent or heterogenous SSTR expression were 18FDG avid.

CONCLUSIONS

The large majority of metastatic GEP-NETs demonstrate strong and relatively uniform SSTR expression, but approximately 8% are SSTR negative, weak, or heterogeneous. Higher than average rates of absent/heterogenous/weak SSTR expression occur in G3 NETs and lower rates among small intestine primaries.

ABSTRACT ID 28643

C-31

First-Line Efficacy of [177Lu]Lu-DOTA-TATE in Gastroenteropancreatic Neuroendocrine Tumors by Tumor Grade and Primary Origin: Phase 3 NETTER-2 Subgroup Analysis

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BACKGROUND

In the Phase 3 NETTER-2 study (NCT03972488), first-line [¹⁷⁷Lu]Lu-DOTA-TATE (hereafter ¹⁷⁷Lu-DOTATATE) significantly improved median progression-free survival (PFS) by 14 months and increased objective response rate (ORR) by 34% vs high-dose octreotide in patients with advanced, well-differentiated, Grade 2 (G2) and G3, gastroenteropancreatic neuroendocrine tumors (GEP-NETs). This preplanned subgroup analysis examined efficacy by NET grade (G2, G3) and NET origin (pancreas, small intestine [SI]).

METHODS

Patients were randomized to 4 cycles of ¹⁷⁷Lu-DOTATATE (4 × 7.4 GBq) + 30 mg octreotide long-acting release (LAR) every 8 weeks (Q8W) during ¹⁷⁷Lu-DOTATATE treatment then Q4W (n=151), or 60 mg octreotide LAR Q4W (n=75). Efficacy parameters (PFS, ORR, duration of response [DOR], time to response [TTR]) were centrally assessed (RECIST 1.1).

RESULTS

For PFS and ORR, a clinical benefit in favor of ¹⁷⁷Lu-DOTATATE was evident across subgroups (Table). In the ¹⁷⁷Lu-DOTATATE arm, median PFS was shorter for patients with G3 vs G2 and pancreatic NETs (pNETs) vs SI-NETs. ORR was high in patients with G3 and G2 and higher in pNETs vs SI-NETs. Among

65 patients with complete/partial response to ¹⁷⁷Lu-DOTATATE, median TTR was ~5.8 months (m) for all 4 subgroups, and median DOR (95% confidence interval) was 24.9 m (23.3, not estimable [NE]) in G2 NETs, 19.3 m (17.8, NE) in G3 NETs, 18.4 m (11.3, 23.3) in pNETs and NE for SI-NETs. The low number of responders in the control arm (n=7) precluded DOR and TTR subgroup analyses.

Efficacy outcomes by subgroup

Tumor subgroup	PFS event/n (%)	Median PFS* (95% CI), m	Responders /n	ORR (95% CI), %
G2: ¹⁷⁷Lu-DOTATATE	29/99 (29.3)	29.0 (21.8, NE)	40/99	40.4 (30.7, 50.7)
G2: Control	25/48 (52.1)	13.8 (8.4, 19.3)	5/48	10.4 (3.5, 22.7)
G3: ¹⁷⁷Lu-DOTATATE	26/52 (50.0)	22.2 (13.9, 27.8)	25/52	48.1 (34.0, 62.4)
G3: Control	21/27 (77.8)	5.6 (3.7, 8.9)	2/27	7.4 (0.9, 24.3)
Pancreas: ¹⁷⁷Lu-DOTATATE	39/82 (47.6)	19.4 (16.6, 24.9)	42/82	51.2 (39.9, 62.4)
Pancreas: Control	27/41 (65.9)	8.5 (3.8, 16.6)	5/41	12.2 (4.1, 26.2)
SI: ¹⁷⁷Lu-DOTATATE	11/45 (24.4)	29.0 (21.8, NE)	12/45	26.7 (14.6, 41.9)
SI: Control	10/21 (47.6)	8.4 (5.4, NE)	1/21	4.8 (0.1, 23.8)
*Kaplan-Meier estimate.				

CONCLUSIONS

First-line ¹⁷⁷Lu-DOTATATE efficacy was maintained across NET grades (G2, G3) and locations (pancreas, SI). ¹⁷⁷Lu-DOTATATE should be considered a standard of care for this population.

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ABSTRACT ID 28651



C-32

Outcomes of Peptide Receptor Radionuclide Therapy (PRRT) with ¹⁷⁷Lu-DOTATATE in Patients with Malignant Pheochromocytoma (PCC) and Paraganglioma (PGL): A Single Institution Retrospective Study

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BACKGROUND

Peptide receptor radionuclide therapy (PRRT) has emerged as a promising treatment option, showing improvements in both survival and the management of cancer-related symptoms in malignant PPGL. This study aimed to evaluate the outcomes of PRRT in patients with metastatic PPGL, based on a single-institution experience.

METHODS

Records of patients with advanced PPGL who received their initial dose of PRRT between May 2019 and February 2024 were retrospectively reviewed. Patient characteristics, prior treatments, imaging response based on RECIST 1.1, biochemical response, symptomatic response to catecholamine-induced symptoms, toxicity profiles within the first 8-12 weeks and 12-24 weeks following PRRT, PFS, and OS outcomes were assessed.

RESULTS

Our study included 12 patients, involving 7 (58.3%, 7/12) had PCC and 5 (41.7%, 5/12) had PGL. Seven patients (58.3%, 7/12) had germline mutations. The median age was 52.5 years (range: 41-68), and the mean follow-up time was 28.4 ± 16.3 months. One patient (8.3%, 1/12) discontinued PRRT due to disease progression and worsening condition, 11 (91.7%, 11/12) completed the 4 cycles. Two patients (16.7%, 2/12) received PRRT as their initial systemic therapy, and 2 (16.7%, 2/12) were re-challenged with PRRT, totaling 8 cycles. Partial response (8.3, 1/12) or stable disease (67.7%, 8/12) was observed in 9 (75%, 9/12), including 1 who received PRRT as an initial treatment, 5 who were previously stable, and 3 who had progressive disease before PRRT. Symptomatic improvement was seen in 9 (75%, 9/12), and 2 (16.7%, 2/12) remained stable. The mean duration of PRRT response was 20.1 ± 13.9 months.

Following PRRT, 5 patients (41.7%, 5/12) underwent additional systemic therapies. The mean time to initiate the additional treatments after PRRT was 10.2 ± 7.3 months. The most common symptom

following PRRT was grade 1 fatigue (83.3%, 10/12). Grade 3 and 4 hemotoxicities were reported in 2 patients (16.7%, 2/12), 1 with thrombocytopenia and 1 with myelodysplastic syndrome, respectively. No moderate or severe nephrotoxicity was reported. Two patients (16.7%, 2/12) experienced hypertensive crises during or right after PRRT cycles; 1 had a history of hypertensive crises. The median OS was 54.8 months (95% CI: 15.832- 93.768). The median PFS was 18.0 months (95% CI: 0.008 - 35.932).

CONCLUSIONS

Our findings suggest that PRRT yielded promising therapeutic outcomes in the management of both cancer and cancer-related symptoms. Although hypertensive crises were observed in a small number of cases, the treatment was overall well-tolerated, with fatigue being the most frequently reported symptom following PRRT.

ABSTRACT ID 28653



C-33

Corticosteroid prophylaxis did not decrease tumor flare reaction in high-risk neuroendocrine tumors patients treated with ¹⁷⁷Lu-DOTATATE

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BACKGROUND

Since ¹⁷⁷Lu-DOTATATE was approved for patients with somatostatin receptor (SSTR)-positive gastroenteropancreatic neuroendocrine tumors, a tumor flare reactions including increased pain and small bowel obstruction (SBO) have been reported. A retrospective review of 22 patients treated with ¹⁷⁷Lu-DOTATATE, who were deemed to be high risk for SBO due to mesenteric and peritoneal disease burden, found that 6% of patients experienced at least 1 episode of SBO within 3 months of treatment (Strosberg, et al., 2021). Another review found that in 12 patients treated with ¹⁷⁷Lu-DOTATATE, 5 patients experienced a flare reaction including increased pain and SBO (Salner, et al., 2020). Both reviews report some success of both treatment of the flare reaction with corticosteroids and use of prophylactic corticosteroids to prevent flare reaction with future doses of ¹⁷⁷Lu-DOTATATE..

METHODS

We identified adult patients with NETs who were treated with ¹⁷⁷Lu-DOTATATE who received corticosteroids as prophylaxis for a flare reaction due to high burden of disease, significant peritoneal or mesenteric disease, or disease involvement of critical structures under IRB approval at Vanderbilt-Ingram Cancer Center. Variables including demographics, diagnosis, treatment history, and outcomes were collected within a RedCAP database.

RESULTS

Forty-one patients were identified, 51% female, with a median age of 66 (39,84). The primary disease site was small intestine (76%), with 58% of those patients being grade 1. The majority of patients (88%) received corticosteroids prior to the initiation of ¹⁷⁷Lu-DOTATATE, while 12% of patients received corticosteroids due to having a previous tumor flare after ¹⁷⁷Lu-DOTATATE administration. The majority of corticosteroid courses (98%) were for 7 days. Despite corticosteroid prophylaxis, 32% of patients still experienced a tumor flare event, with 3 patients (7%) experiencing multiple tumor flare events. SBO occurred in 10% of patients, increased pain in 27% of patients, and vision changes in 2% of patients. Adverse events (AEs) due to corticosteroids occurred in 20% of patients, with the most common AEs being hyperglycemia and insomnia. Most AEs were grade 1 or 2, however, there was one grade 3 duodenal ulcer hemorrhage requiring hospitalization and intervention.

CONCLUSIONS

Short-course corticosteroid prophylaxis to prevent tumor flare reaction in high-risk patients with neuroendocrine tumors treated with ¹⁷⁷Lu-DOTATATE did not appear to decrease the incidence of

tumor flare reactions compared to previously reported numbers. Randomized, placebo-controlled trials looking at the use of corticosteroids to prevent tumor flare reaction in patients treated with ¹⁷⁷Lu-DOTATATE are needed to fully elucidate the safety and efficacy of corticosteroids used in this setting.

ABSTRACT ID 28661

C-34

Peptide Receptor Radionuclide Therapy with ¹⁷⁷Lu-DOTATATE: A Single Center Experience

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BACKGROUND

¹⁷⁷Lu-DOTATATE peptide receptor radionuclide therapy (PRRT) is approved for treatment of metastatic gastroenteropancreatic (GEP) neuroendocrine tumors (NETs). Here we report our single institution experience with PRRT.

METHODS

A retrospective review of patients who received ¹⁷⁷Lu-DOTATATE at our institution was performed. Demographics, clinical and laboratory values, and post-treatment outcomes were reviewed. RECIST 1.1 and CTCAE version 5.0 guidelines were used to evaluate radiographic response and grade treatment toxicities respectively.

RESULTS

Between 2018 and 2024, 195 patients were treated with ¹⁷⁷Lu-DOTATATE. Median follow-up was 21 months. Breakdown of primary site and grading of NETs are provided in Table 1. The median and mean SUVmax of the hottest lesion on DOTATATE-PET was 41.9 and 51.5 (IQR 28.3–60.3). 106 (54%) patients had non-functional tumors. In terms of marrow toxicity, the WBC decreased by 29%±28%, platelets by 36%±27% and hemoglobin by 11%±12% during treatment. eGFR fell by an average of 7%±28% at any point in time after treatment. G3/4 anemia was observed in 10/195 (5%), G3/G4 thrombocytopenia in 6/195 (3%), 8/195 (4%) patients developed G3/G4 leukopenia. Also 7/195 (4%) patients developed G3/G4 ascites and 2/195 (1%) developed AML (1 G4 and 1 G5). 142 (72%) patients were kept on SSAs after PRRT. 19 (10%) patients were re-treated. In terms of efficacy, and radiographic response: 1 (0.5%) CR, 64 (33%) PR, 106 (54%) SD, and 15 (8%) PD. Median PFS (mPFS) for SBNET was 32 (23–38) months, mPFS for PNET was 19 (14–27) months, and mPFS for patients with other/unknown primary tumor was 27 (18–40) months, p=0.02. By grade, the mPFS for G1 was 42 (25–52) months, G2 26 (21–32) months and G3 14 (12–20) months, p <0.001. Also, the mPFS for patients ³ 70 years old was 28 (19–38) months, and for patients < 70 years old was 24 (20–31) months p = 0.459.

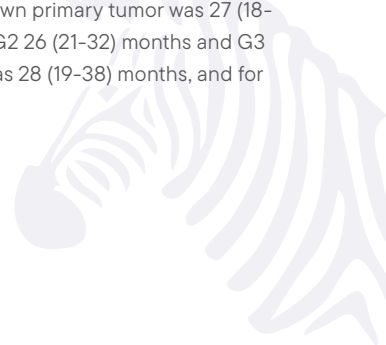


Table 1: Breakdown of primary site and grading of NETs.

Site of primary tumor	
Small intestine	80 (41%)
Pancreas	65 (33%)
Bronchial and other	50 (26%)
Grade of NETs	
Grade 1	51 (26%)
Grade 2	98 (50%)
Grade 3	31 (16%)

CONCLUSIONS

Our results mirror published results, with shorter PFS in patients with higher grade disease, and PNET compared to SBNET. Older patients had a similar PFS compared to younger patients overall. The most common toxicity was marrow toxicity, and two patients developed AML after treatment.

ABSTRACT ID 28667

C-35

Small bowel obstruction incidence in Lu177 PRRT patients had no impact on overall survival

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BACKGROUND

Small bowel obstruction (SBO) is an observed complication associated with Lu177 peptide receptor radioligand therapy (PRRT). Recent studies estimate that SBO occurs in 6% of patients receiving PRRT, likely by inducing mesenteric inflammation. However, the impact of SBO after PRRT on overall survival and post-treatment survival is not well understood. Many patients who receive PRRT may undergo abdominal surgery as part of their cancer treatment, which is an independent risk factor for SBO. This further complicates the care of these patients and emphasizes the need to better understand the impact of SBO on survival after PRRT.

METHODS

The Louisiana State University Health Science Center – New Orleans Neuroendocrine Cancer Data repository was queried for incidence of small bowel obstruction following Lu177 peptide receptor radioligand therapy. Dates of surgery, PRRT, small bowel obstruction, and death were extracted, collated and analyzed.

RESULTS

Between 2008 to 2024, a total of 298 NEN patients received Lu177 PRRT. Small bowel obstructions was reported in 18 patients (6%). The average time between PRRT and SBO was 303±62 days and ranged significantly between patients (32-859days). The majority (14of18) of patients had had a small bowel resection prior to PRRT. The average time between surgery and PRRT was 1224±327days (275-4941days). There was no significant difference in overall survival between patients who developed an SBO (1807±276days) and those that did not (1838±250days). In contrast, survival post PRRT was significantly lower in patients with SBO (440±108days) when compared to those without (759±111days p=0.025). In patients that had PRRT after surgery, overall survival (1846±96) was not significantly different when compared to PRRT only (1628±124 p= not significant). In contrast, survival after PRRT was greater in patients receiving PRRT following surgery (491±189) when compared to PRRT only (and 211±69 p<0.05).

CONCLUSIONS

The incidence of SBO after PRRT in NEN patients is similar to that observed with other cancers following radiation therapy. Our study found no difference in overall survival between patients who had SBO versus those who did not. However, SBO negatively impacts survival post PRRT. Recent studies have shown success with corticosteroid therapy in treating post-PRRT SBO, with a small subset of

patients requiring surgery. Future studies on this topic will focus on treatments post SBO to better define optimal treatment algorithms. We also plan to expand the data set to include incidence of SBO in patients without PRRT.

ABSTRACT ID 28681

C-36

Safety and Efficacy of Peptide Receptor Radionuclide Therapy in Thymic Neuroendocrine Neoplasms: A Single-Institutional Case Series

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BACKGROUND

Primary neuroendocrine neoplasms (NENs) of the thymus are rare and aggressive. In advanced stages, treatment is limited to chemotherapy and targeted therapies, which have limited efficacy. Peptide Receptor Radioligand Therapy (PRRT) has shown improved outcomes in advanced gastroenteropancreatic NENs (GEPNETs) leading to its FDA approval in 2018. NCCN guidelines recommend considering PRRT for thymic NETS, if SSTR positive upon disease progression on octreotide analogs. However, the safety and efficacy of PRRT for thymic NENs remain unknown.

METHODS

We conducted a retrospective review of our IRB-approved institutional registry of patients with NENs to identify those with thymic NENs who had received PRRT. We reviewed patient, tumor, and treatment characteristics, time to progression after PRRT and toxicity. We used the National Cancer Institute Common Terminology Criteria for Adverse Events version 5 (CTCAE) to grade adverse events. Median progression-free survival (PFS) was estimated using the Kaplan-Meier method.

RESULTS

Eight patients with thymic NENs were identified in our registry between 2001 – 2023, of which five received PRRT. The median age at time of first PRRT was 53 (IQR 51–60) years. The majority were White (5/5, 100%) and male (4/5, 80%). Pathologically, most patients had atypical carcinoid (3/5, 60%) followed by typical carcinoid (1/5, 20%) and large cell neuroendocrine carcinoma (1/5, 20%). Prior to PRRT, patients received a median of 3 (IQR 1–3) therapies; including surgical resection (4/5, 80%), chemotherapy (3/5, 60%), external beam radiation (2/5, 40%). Of the five patients, 3/5 (60%) received Lu177-DOTATATE PRRT, 1/5 (20%) received Y90-DOTATOC PRRT, and 1/5 (20%) received both. Patients received a median of 4 cycles of PRRT (IQR 3–4) and a median cumulative dose of 772 mCi (IQR 668 – 784 mCi). At first restaging scan after PRRT, 1/5 (20%) patients had stable disease and 4/5 (80%) patients had progressive disease. Median PFS after PRRT was 6 months. The longest PFS observed was 52 months in a patient with typical thymic carcinoid. We did not identify CTCAE grade 3 or higher renal or hematological adverse effects over a median follow up of 24 months.

CONCLUSIONS

Our case series highlights the need for large prospective studies to investigate the safety and efficacy of PRRT in TNETs and identify sub-groups more likely to benefit. The current analysis is limited by small sample size, retrospective design, and lack of pre-treatment imaging data.

ABSTRACT ID 28687

C-37

Preliminary safety and efficacy data of [²¹²Pb]VMT- α -NET in somatostatin receptor 2 (SSTR2) expressing neuroendocrine tumors (NETs)

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BACKGROUND

Despite the introduction of Lutathera, there remains an unmet medical need for new front-line therapies for advanced NETs. In this Phase I study, [²¹²Pb]VMT- α -NET, a novel targeted alpha radionuclide therapy (TAT) to SSTR2, is being investigated for safety and efficacy in PRRT-naïve patients with SSTR2 expressing tumors. Here we present initial results from the first two dose escalation cohorts.

METHODS

This is a first-in-human dose-escalation study to determine the safety, pharmacokinetics, and preliminary efficacy of [²¹²Pb]VMT- α -NET in adult NETs of any grade, Small Cell Lung Cancer, Pheochromocytoma and Paraganglioma with progressive disease as assessed by RECIST 1.1. (NCT05636618).

The Phase 1 of the trial includes four escalating cohorts and follows a Bayesian modified toxicity probability interval (mTPI-2) design. The first two cohorts incorporate dosimetry evaluations with the therapeutic surrogate [²⁰³Pb]VMT- α -NET prior to receiving up to 4 treatment cycles of [²¹²Pb]VMT- α -NET with injected activity of 92.5 MBq (2.5 mCi) or 185 MBq (5 mCi) for Cohort 1 or 2, respectively. Reno-protective amino acids are co-administered with [²¹²Pb]VMT- α -NET. DLT assessment period is defined as the first 6 weeks of cycle 1. Safety is assessed weekly during cycle 1 and bi-weekly for subsequent cycles. The total in-trial follow-up period will be 18 months following the final administration. Efficacy will be assessed by RECIST 1.1 criteria. The primary objective is to evaluate the tolerability of [²¹²Pb]VMT- α -NET, collection and measurement of radioactive blood and urine PK samples at specific timepoints, and determination of the recommended phase 2 dose of [²¹²Pb]VMT- α -NET in PRRT naïve participants with NETs.

RESULTS

A total of 9 patients were enrolled (2 in cohort 1 and 7 cohort in 2). There were no DLTs or grade 3 AEs for Cohort 1 (92.5 MBq (2.5 mCi). 4/33 TEAEs were grade 2 AEs (elevated Amylase, fatigue, nausea and urinary tract infection). Cohort 2 Safety Monitoring Committee (SMC) meeting was held on July 17th, 2024, with no DLTs. There were 2 grade 3 AEs (diarrhea, syncope), 4 grade 2 AEs (fatigue, nausea, presyncope and weight loss). The most frequent TEAE were in descending order: nausea, alopecia, diarrhea and fatigue. No nephrotoxicity was reported in either cohort. One patient discontinued due to progressive disease.

CONCLUSIONS

[212Pb]VMT- α -NET is safe up to 185 MBq (5 mCi) dose level, and the SMC supported dose escalate to cohort 3 at 277.5 MBq (7.5 mCi) following a mandatory FDA review in fall. Cohort 2 remains open for dose level expansion.

ABSTRACT ID 28690

C-38

Radioactivity in drained body cavity fluid following peptide receptor radionuclide therapy with ¹⁷⁷Lu DOTATATE in patients with advanced neuroendocrine tumors

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BACKGROUND

Peptide receptor radionuclide therapy (PRRT) is an established therapy option for patients with advanced and metastatic neuroendocrine tumors (NETs) with proven efficacy both early and later in the course of the malignancy. The only FDA approved PRRT currently is ¹⁷⁷Lu DOTATATE (Lutathera). Body cavity fluid collections, especially ascites, frequently occur in patients with advanced NETs and drainage is often required. Little is known about radioactivity in drained body cavity fluid collections following PRRT.

METHODS

Patients with NETs undergoing therapeutic or diagnostic drainage procedures for symptomatic body cavity fluid collections in the days immediately following PRRT were identified using the institution's electronic medical record. The radioactivity in the drained body cavity fluid was measured using a Capintec dose calibrator.

RESULTS

Four patients, all with small bowel NETs, were included in the analysis. In three cases peritoneal fluid/ascites was tested and in one patient, pleural effusion. Three patients had fluid cytology assessment, and one had positive cytology with malignant cells present. The median time from PRRT administration to fluid drainage was 1 day (range: 0-3). The radioactivity detected in the fluid is detailed in the table.

Table

Patient (fluid type)	Total volume drained/ volume sampled (mL)	Activity in sample (μCi)	Total calculated activity (μCi)
1 (ascites)	4200/88	31.2	1489
2 (ascites)	4500/50	5.5	495
3 (pleural)	500/40	11.2	140
4 (ascites)	7400/58	74.6	9517

CONCLUSIONS

Body cavity fluid collections are common among patients with advanced NETs. The detected radioactivity in drained body cavity fluid following PRRT does not represent a significant exposure hazard, but radiation protection practices should be followed when handling radioactive bodily fluids. When handling radioactive bodily fluids, standard precautions are sufficient to protect yourself from contamination. To protect yourself from external radiation exposure radiation protection practices such as minimize your time around, increase your distance from, and potentially shield the radioactive material.

ABSTRACT ID 28693

C-39

Dosimetry-guided ¹³¹I-mIBG Therapy in a Hemodialysis-Dependent Paraganglioma Patient

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BACKGROUND

A 63 year old male patient with paraganglioma, type 2 diabetes mellitus, hypertension, and end stage renal disease requiring hemodialysis (HD) was referred to our clinic for radiopharmaceutical therapy which was indicated based on progressive disease by imaging, increasing pain, and increasing Chromogranin A levels. ¹²³I-mIBG scintigraphy showed high mIBG uptake in the mass without any additional disease sites.

Because mIBG is not considered dialyzable, study of ¹³¹I-mIBG in patients undergoing hemodialysis is limited, and 2008 European Association of Nuclear Medicine (EANM) guidelines list renal insufficiency requiring dialysis as an absolute contraindication for ¹³¹I-mIBG treatment. Consequentially, extensive pre-treatment dosimetry was performed to calculate a safe reduced therapeutic activity for the patient. This abstract summarizes the successful administration of this therapy.

METHODS

Planar and SPECT/CT-based dosimetry was performed to calculate the absorbed dose to the lungs, liver, kidneys, bone marrow, and retroperitoneal mass.

The patient was admitted to the hospital to accommodate hemodialysis and radiation safety. 204.6 MBq ¹³¹I-iokebenguane (high-specific activity mIBG) was administered for dosimetry. Whole-body planar images and single-bed SPECT/CT images of the upper abdomen were obtained at 1, 24, 72, and 168 hours post-administration. Images were acquired on a Philips Precedence SPECT/CT (Philips Healthcare, Milpitas, CA, USA), and an I-¹³¹ standard was used for quantitative calibration.

OLINDA/EXM 2.0 was used to calculate organ doses from the planar images using the Adult Male Model, and bone marrow and lesion doses were calculated from SPECT/CT using the Unit Density Sphere Model.

RESULTS

A total treatment activity of 6689 MBq was chosen to limit the bone marrow dose to 3 Gy. Ultimately, 6553 MBq of ¹³¹I-iokebenguane was administered over two treatments, 4070 MBq and 2483 MBq 90 days apart, providing an estimated lesion dose of 38.5 Gy.

Despite treating with 17.7% of the maximum approved activity, the lesion responded to treatment based on CT volume measurements. Two months before the therapy, the lesion was 165 ml. At dosimetry and treatment 1, the volume increased to 203 ml. Three months later at treatment 2, the volume decreased to 153 ml, and another 3 months later, a follow-up CT showed a volume of 132 ml. Importantly, the

patient did not experience any hematologic or other toxicity. Additionally, the radiation safety precautions to the staff were manageable with appropriate education facilitating limited exposure.

CONCLUSIONS

Dosimetry-guided treatment with ¹³¹I-mIBG in patients requiring hemodialysis is feasible. With appropriate activity reduction, the treatment can be effective with limited side effects.

Abstract ID 28696

C-40

Implementation of dosimetry in clinical Lu177-DOTATATE therapy

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BACKGROUND

While generally well tolerated, Lu-177 DOTATATE therapy can result in adverse effects such as renal toxicity or myelosuppression. Because of this, our institution has implemented post-therapy dosimetry for specific patients at risk of receiving elevated normal-tissue dose. Despite the fact that radiation dose is the mechanism for cytotoxic effects, clinical implementation of dosimetry is challenging due to a lack of validated tolerance dose limits for radiopharmaceutical therapy.

This abstract summarizes our experience incorporating dosimetry into clinical Lu-177 DOTATATE therapy.

METHODS

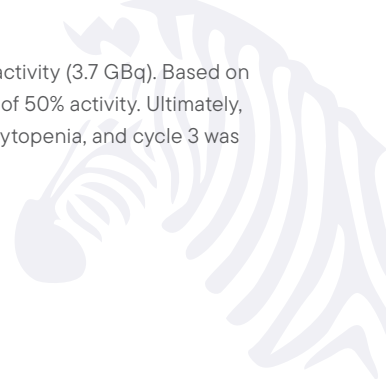
To date, dosimetry was performed on four patients due to: re-treatment (n=2), single kidney (n=1), and poor kidney function (n=1). Post-therapy dosimetry was performed using quantitative SPECT/CT acquired 4, 24, 48, and 72 hrs post-injection. Absorbed dose to kidneys, lungs, liver, and representative regions of bone marrow was calculated using voxel-based dosimetry (MIM Software Inc., Cleveland, OH). Single-cycle absorbed dose was extrapolated to estimate total dose from multiple cycles and compared to tolerance dose limits used in EBRT or other therapies.

RESULTS

Reference dose limits and mean dose per injected activity for each patient are shown in Table 1. Of the four patients, two potentially exceeded the limits.

Patient 1 was a re-treatment case who received an additional 2 cycles based on a bone marrow dose of 3.1 Gy and kidney dose of 22.4 Gy.

Patient 4 had poor kidney function and was therefore treated with 50% activity (3.7 GBq). Based on dosimetry, the patient was protocolled to receive a maximum of 4 cycles of 50% activity. Ultimately, cycle 2 was reduced by another 50% (1.9 GBq) due to grade 3 thrombocytopenia, and cycle 3 was postponed due to grade 3 anemia.



	Gy/GBq		
	Liver (<30 Gy)	Bone Marrow (<2 Gy)	Kidneys (<23 Gy)
1 - retreatment	0.205	0.069*	0.505*
2 - retreatment	0.133	0.037	0.460
3 - single kidney	0.109	0.025	0.729
4 - low kidney function	0.109	0.175*	1.638*

CONCLUSIONS

Because there are no well-established normal organ dose limits for Lu-DOTATATE, the dosimetry results are always considered along with other clinical factors. When dosimetry suggests low normal tissue doses, we are given confidence to proceed with the maximally approved activity per cycle. However, when normal organ doses exceed limits, we carefully consider the overall clinical scenario before change in management.

This preliminary data is limited to a single institution and more information from larger studies and long-term follow up is needed to establish generalizable recommendations for clinical implementation of dosimetry in radiopharmaceutical therapy.

ABSTRACT ID 28704

C-41

Long-term Survival Outcomes After Minimally Invasive Surgery for Ileal Neuroendocrine Tumors

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BACKGROUND

Ileal neuroendocrine tumors (i-NETs) are characterized by their multifocality and bulky mesenteric mass. Although various guidelines mention possible benefits of using minimally invasive surgery (MIS) for i-NETs, none offer recommendations regarding specific techniques or established criteria for patient selection. Having shown that MIS utilizing a hand-access port device has favorable short-term outcomes and achieves the goals of surgery for i-NETs, we sought to analyze long-term survival outcomes of MIS.

METHODS

One hundred sixty-eight patients who underwent resection of primary i-NETs at a single institution between January 2007 and February 2023 were retrospectively studied. Patients were categorized into the MIS or open surgery cohort on an intention-to-treat basis. Open surgery was selected mainly based on the need for hepatectomy or bulky mesenteric mass resection. Overall survival was analyzed using log-rank tests with propensity-score matching (PSM) and Cox proportional hazards regression. PSM was performed to reduce standardized mean differences of the variables to less than 0.2.

RESULTS

One hundred twenty-nine (77%) patients underwent MIS and thirty-nine (23%) underwent open surgery. Twenty-seven MIS patients were converted to an open procedure. The median follow-up time was 49 mos (IQR = 23, 87 mos). In the PSM cohorts, overall survival did not differ significantly between the MIS and open surgery cohorts (median 99 mos [95% CI 91-NA] vs. 103 mos [86-NA]; $p = 0.77$, HR 0.87 [95% CI 0.33-2.2]; $p = 0.77$).

Table. Surgical outcomes in the propensity-score-matched cohorts.

Characteristic	N	Surgical Procedure, N (%)		p-value*
		Open, N = 31	MIS, N = 55	
Incomplete mesenteric lymph node dissection	86	6 (19)	10 (18)	1
Microscopically positive mesenteric margin	86	5 (16)	11 (20)	0.77
Complete mesenteric lymph node dissection	86	20 (65)	34 (62)	1
Estimated blood loss (ml), median (IQR)	82	100 (35,150)	50 (20,100)	0.0071
Postoperative complications \geq G3	86	2 (6.5)	2 (3.6)	0.9
Length of stay (days), Median (IQR)	86	6 (5, 7)	5 (4,7)	0.098
Survival status Dead	86	7 (23)	13 (24)	1
Follow-up months, Median (IQR)	86	46 (16, 82)	53 (33, 79)	0.31

SSA, Somatostatin analogue; PRRT, Peptide receptor radionuclide therapy.

* Wilcoxon rank-sum or Fisher's exact test were used.

CONCLUSIONS

MIS is an alternative to open surgery for i-NETs, achieving similar short- and long-term oncological outcomes, and less blood loss. Bulky mesenteric mass and plan for concurrent liver resection are potential criteria for open surgery.

ABSTRACT ID 28492

C-42

Loss of MGMT protein expression by immunohistochemistry is associated with response to capecitabine/temozolomide in neuroendocrine neoplasms (NENs)

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BACKGROUND

A recent prospective phase II study (ECOG-ACRIN E2211) demonstrated that O6-methylguanine-DNA methyltransferase (MGMT) deficiency was associated with a significant response to capecitabine and temozolomide (CAPTEM) in pancreatic neuroendocrine neoplasms (NENs), however, routine MGMT analysis in NENs was not recommended. Our study sought to demonstrate whether loss of MGMT protein expression is associated with improved overall survival (OS) in patients receiving CAPTEM for NENs from various tumor sites.

METHODS

Paraffin-embedded tumor samples were evaluated by immunohistochemistry (IHC) using an MGMT monoclonal antibody. Intact MGMT protein expression (i.e., IHC positivity) was defined as any staining intensity (>1+) in $\geq 36\%$ of neoplastic cells, according to an internal validation study. IHC and pyrosequencing for MGMT promotor methylation was performed in an independent cohort of 58 NENs. Real-world OS was extrapolated from insurance claims data with Kaplan-Meier estimates from the date of first CAPTEM administration to the last date of contact.

RESULTS

The study cohort included 80 patients (42 men, 38 women) with a median age of 57 years [range: 19-89]). They had various NENs (33 pancreatic, 17 intestinal, 7 pulmonary, 8 other, and 15 of unknown origin) treated with CAPTEM. The median OS for the 48 patients with MGMT negative tumors was 31 months compared to 17.5 months for the 32 patients whose tumors were MGMT positive by IHC (HR: 1.75 [95% CI: 1.066-2.87], $p=0.025$). IHC results from the independent cohort of 58 NENs showed only 43% concordance with pyrosequencing results.

CONCLUSIONS

MGMT promotor status by IHC may be a clinically useful indicator that predicts improved OS for NENs treated with CAPTEM but does not reliably correlate with the findings of MGMT promotor methylation by pyrosequencing.

ABSTRACT ID 28493

C-43

To Treat or Not to Treat: Resection of Primary Pancreatic Neuroendocrine Tumors in the Metastatic Setting

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BACKGROUND

The pancreas is the most common site of origin for neuroendocrine tumors (NETS). Half are stage 4 at diagnosis. For NETS from small bowel primaries, surgical resection of the primary tumor is the standard of care even when metastatic and is associated with increased overall survival. In contrast, the benefit of resecting pNETs in the metastatic setting is unclear. Pancreatic surgery is higher risk and has more long-term morbidity than bowel resection. Current practice guidelines reflect considerable uncertainty about the role of primary pancreatic tumor resection in the metastatic setting. To better understand current pNET natural history and develop an evidence base for further study of pancreas-directed therapies, we compared progression and overall survival of a cohort of metastatic pNET patients who underwent resection of their primary tumor with those who did not.

METHODS

The healthcare system database was searched to find all patients presenting with metastatic primary pancreatic neuroendocrine tumors with at least 2 years of follow up. Patients were divided into two groups based on whether their primary tumor was resected or not. Co-primary outcome measures of progression free survival (PFS) and overall survival (OS) were estimated by Kaplan-Meier in each group and compared using the log rank test. Other variables of interest were tumor grade, type of resection, toxicities and adverse events with and without resection, and other therapies.

RESULTS

Overall, 292 patients with primary metastatic pNETs were analyzed. 159 underwent resection of their primary tumor and 133 did not. For the co-primary endpoints, median PFS for patients with unresected vs. resected primary tumors was 8.5 vs 38.1 months, HR 2.38, $p < 0.0001$. Median OS for unresected vs. resected primary tumors was 45.6 vs.190 months, HR 5.59, $p < 0.0001$.

CONCLUSIONS

Resection of the primary tumor in patients presenting with metastatic pancreatic NETs is associated with considerable improvements in PFS and OS. Additional multivariate analyses to incorporate the affect of tumor grade, type of resection, and other therapies will be performed. Adverse events associated with resection vs. no resection will be analyzed.

ABSTRACT ID 28572

C-44

Incidence and prognostic analysis of neuroendocrine differentiation in CRC, GC, ESCC and BTC cohorts

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BACKGROUND

Neuroendocrine differentiated (NED) occurs in various non-neuroendocrine organs and is associated with unique clinical profiles, disease progression, and poor prognosis. However, there are few relevant studies worldwide to explore the clinical characteristics of NED. This study aims to clarify the pathological features and prognostic significance of NED and provide reference for clinical diagnosis and treatment.

METHODS

Patients (18-75 years) with cancers including colorectal, gastric, pancreatic, esophagus and cholangiocarcinoma, were analyzed post-surgery. Criteria for inclusion were normal organ function and no pre-surgery neoadjuvant therapy. Tumors were staged postoperatively using AJCC 8th criteria (stages I-III), followed by standard adjuvant chemotherapy. NED markers like Chromogranin A, Synaptophysin, and CD56 were detected in tumors via immunohistochemical staining.

RESULTS

Between January 2017 and June 2018, over 450 cases were enrolled. Initial analysis included 59 CRC, 70 GC (36 gastric tubular adenocarcinoma [GAC] and 34 gastric signet ring cell carcinoma [GSRC]), 50 ESCC and 49 BTC samples. NED markers were positive in 9 (15.3%) CRC, 10 (27.8%) GAC, 18 (52.9%) GSRC, 5 (10.0%) ESCC and 19 (38.8%) BTC samples. Patients with positive NED markers had worse outcomes, the mOS (negative vs positive) were NA (95%CI 41.2-NA) vs 33.4 (95%CI 13.4-NA) months (mo) in CRC, NA (95%CI 33.5-NA) vs 25.2 (95%CI 19.5-NA) mo in GAC and 40.2 (95%CI 16.1-NA) vs 16.2 (95%CI 8.8-NA) mo in ESCC. In the BTC cohort, NEC marker expression status had little impact on prognosis, with mOS 61.6 (95%CI 38.7-NA) vs NA (95%CI 21.5-NA) mo. Interestingly, patients with positive NED markers for GSRC had a better prognosis, the mOS (negative vs positive) was 22.35 (95%CI 14.9-36.9) vs NA (95%CI 18.0-NA)..

CONCLUSIONS

This study reveals a significant occurrence of neuroendocrine differentiation in CRC, GC, ESCC and BTC. In CRC, GAC and ESCC, patients with positive NED markers had worse prognosis, suggesting that new treatment strategies are needed for these patients.

ABSTRACT ID 28574

C-45

Interaction Between Race and Insurance Coverage for Gastroenteropancreatic Neuroendocrine Tumor Outcomes

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BACKGROUND

While the incidence of common solid tumors has decreased over the last few decades, that of Gastroenteropancreatic Neuroendocrine tumors (GEP-NETs) has steadily risen. Disparities in access and outcomes from GEP-NETs are described for minorities and those with low socioeconomic status. Health insurance is the primary gateway to healthcare access in the United States, and significantly affects patient outcomes. We aim to study the differential impact of the lack of health insurance by race on survival of patients with GEP-NETs.

METHODS

Using the US Neuroendocrine Tumor Study Group (USNETSG) database of patients with surgically resected neuroendocrine tumors, we performed a retrospective cohort study of adult patients recently diagnosed with GEP-NETs (2005-2016). Health insurance categories consisted of Uninsured/Unknown (UI), Government Insurance (GI), and Private Insurance (PI) patients. We performed univariate and multivariate Cox proportional hazard (Cox PH) analyses to evaluate the impact of health insurance on progression-free (PFS), recurrence-free (RFS) and overall survival (OS), adjusting for patient and tumor-specific characteristics. We also performed a stratified multivariate analysis by Black and White race.

RESULTS

We identified 1605 patients for our analysis. Mean age was 57.2 (SD 13.48). 225 patients (14%) identified as Black and 1,283 (80%) identified as White. Predominant tumor location was the foregut (83%; Whites 67% vs Blacks 44%) and midgut (17%; Blacks 37% vs Whites 26%). Black had higher incidences of hypertension (67% vs 48%) and diabetes (28% vs 19%); ($p < 0.001$) 979 patients (63%) were PIP, 556 GIP (29%), and 70 UIP (8.6%). Univariate CoxPH for overall survival (OS) showed that compared to PIP, UIP [HR = 2.99 (1.97, 4.53, $P < 0.001$)] and GIP had worse OS [HR=1.53 (1.18, 1.99), $P = 0.001$]. Multivariate CoxPH analysis results showed UIP had a worse OS: [HR=2.52 (1.03, 6.20), $p = 0.044$]; while GIP OS was

not significantly different from PIP: [HR=0.80 (0.49, 1.31), p=0.37]. When stratified by race, White UIP patients had worse OS than White PIP [HR=3.16 (1.44, 6.92), p<0.01] but Black UIP patients were not significantly different in survival from Black PIP [HR=6.12 (0.62, 60.96) p=0.12]. There were no significant differences in PFS or RFS by insurance status.

CONCLUSIONS

Health insurance is an important predictor of overall survival of GEP NETs. While there was no demonstrable difference in GEP-NET OS when stratifying for race, uninsured patients demonstrated worse overall survival compared to patients with government or private insurance.

ABSTRACT ID 28686



C-46

Clinical utility of preoperative DOTATATE-PET in small bowel neuroendocrine tumors

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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 retrospective single institution cohort study was performed between January 2013 and December 2023. All adult patients diagnosed with well-differentiated primary SBNET, grade 1-3, with or without distant metastasis who underwent primary tumor resection and had preoperative DOTATATE-PET imaging were included. Preoperative imaging reports and final pathology reports were reviewed and compared. Patient characteristics, pathologic tumor characteristics and imaging characteristics were analyzed. Nodal upstaging was defined as pathologic finding of more positive lymph nodes than identified on DOTATATE-PET. Usual descriptive statistics were applied.

RESULTS

A total of 162 patients with well-differentiated grade 1-3 SBNET were identified, of which 53 (33%) had preoperative DOTATATE-PET imaging included for analysis. Most patients were male (58%) with mean age at diagnosis of 61 years (SD 11.1). Pathologic evaluation of resected specimens identified multifocal tumor in 45% of patients (n=24) and lymph node (LN) metastasis in 91% (n=48). Preoperative DOTATATE-PET identified multifocal SBNET in 19% (n=10) and LN metastasis in 85% (n=45). Imaging was accurate in identifying the number of tumors in 53% of patients and LNs in 17% of cases. Surgical resection resulted in nodal upstaging in 72% of patients (n=38). Median number of LN examined was 18 (IQR 3-48), with a higher positive LN ratio in patients with nodal upstaging (33% vs 14%, $p < 0.05$). There was a higher proportion of nodal upstaging in patients with $Ki67 < 3$ compared to $Ki67 \geq 3$ (55% vs 42%, $p=0.14$) and presence of lymphovascular invasion (92% vs 5%, respectively, $p=0.04$). Mean follow-up time after surgery was 37 months (SD=27). Post-operative disease progression was noted in 44% (n=17) with nodal upstaging and in 20% (n=3) without nodal upstaging ($p=0.09$). DOTATATE-PET to identify multifocal SBNET had a sensitivity of 38% and specificity of 97%.

CONCLUSIONS

Although DOTATATE-PET can identify multifocal SBNET with high specificity, its sensitivity remains poor and it cannot accurately predict lymph node burden. Given that nodal upstaging may be associated with disease progression, a comprehensive preoperative assessment of SBNET patients should integrate multiple modalities and potentially machine-learning for better prognostication.

ABSTRACT ID 28689



C-47

Response After Neoadjuvant Therapy for Pancreatic Neuroendocrine Tumors

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BACKGROUND

Neoadjuvant therapy (NAT) has been widely employed in PDAC to downsize tumors. However, data to support the routine use of NAT in advanced PNET is limited. This study aims to investigate the objective response rate (ORR) of cytotoxic NAT in advanced PNET.

METHODS

We performed a retrospective review of patients with PNETs who underwent cytotoxic NAT followed by surgical resection at a high-volume tertiary cancer center from January 2009 to August 2023. Demographic and clinicopathologic characteristics were evaluated. ORR was defined as $\geq 30\%$ reduction in serum Chromogranin A (CgA) or hormone level in functional-PNET, partial radiographic response per RESIST v1.1 criteria, and/or tumor downgrading after NAT. Secondary endpoints were progression free survival (PFS) and overall survival (OS).

RESULTS

This cohort of 34 patients had a median follow-up of 42 months (IQR 18–99). 25 (74%) patients had metastatic disease at presentation (Table 1). 26 (76%) patients received neoadjuvant CAPTEM, 2 (6%) received Everolimus, 2 (6%) received Etoposide+Cisplatin, 2 (6%) received Streptozotocin+5-FU+Leucovorin, 1 (3%) received Sunitinib, and 1 (3%) received Evacizumab.

23 (68%) underwent resection of all visible lesions. 11 (32%) underwent cytoreductive surgery with $>70\%$ debulking. 18 (53%) had progression of disease after resection with a median PFS of 33 months (IQR 5–43). Median OS of the cohort was not reached. 3 (9%) patients died due to disease (median resection to death was 58 months). ORR after NAT for the entire cohort was 76% (26 patients). 20 (59%) showed a response by serum biomarker, 10 (29%) by reduction in tumor grade, and 9 (26%) by RESIST criteria. 4 (12%) patients showed response by all 3 criteria; they all received CAPTEM.

Table 1. Study Cohort Demographic and Clinicopathological Characteristics

Cohort Characteristics	N=34(%)
Median Age, yrs(IQR)	56(45-63)
Sex	
Male	15(44%)
Female	19(56%)
Race	
White	31(91%)
Black	2(6%)
Other	1(3%)
Ethnicity	
Hispanic	32(94%)
Non-Hispanic	2(6%)
Tumor Grade	
G1	8(23%)
G2	21(62%)
G3	5(15%)
Surgical Procedure for primary tumor	
Distal Pancreatectomy	21(62%)
Pancreatoduodenectomy	9(26%)
Total Pancreatectomy	4(12%)
Median largest primary tumor Size, cm(IQR)	5.0(3.4-8.0)
Primary Tumor Margin	
RO	23(68%)
R1	11(32%)
Nodal Metastasis	
NO	11(32%)
N1	23(68%)
Distant Metastasis	
M0	9(26%)
M1	25(74%)
Liver	20(59%)
Multiple sites	5(15%)
Neoadjuvant Cytotoxic Regimen	26(76%)
CAPTEM	2(6%)
Streptozotocin, 5-FU, Leucovorin	2(6%)
Everolimus	1(3%)
Evacizumab	1(3%)
Sunitinib	2(6%)
Etoposide, Cisplatin	

CONCLUSIONS

For advanced PNETs, NAT was associated with an ORR of 76%. NAT allowed for surgical resection in patients with advanced metastatic disease and provided durable PFS and OS.

ABSTRACT ID 28692



C-48

Impact of Hospital Type and Location on Survival Outcomes for Patients with Well-Differentiated G1/G2 Pancreatic Neuroendocrine Tumors

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BACKGROUND

Well-differentiated nonfunctional pancreatic neuroendocrine tumors (PanNETs) require multimodal and multidisciplinary management; therefore, treatment facility type and location may impact patient outcomes. This study examines how facility type and geographic factors are associated with survival for patients with well-differentiated PanNETs.

METHODS

A retrospective cohort study utilizing the National Cancer Database from 2004–2021 to identify patients with well-differentiated G1/G2 nonfunctional PanNETs was performed. Variables included demographic characteristics, insurance status, distance traveled, pathological stage, and treatment modalities (surgery, chemotherapy, radiotherapy, hormonal therapy). The primary outcome was overall survival (OS) and association between survival and treatment facility type and location. Multivariable Cox proportional hazards models were used to identify factors independently associated with mortality.

RESULTS

Of 21,473 patients included in the analysis, 23.2% were treated at community hospitals, 17% at integrated hospitals, and 51.8% at academic hospitals. Patients at community hospitals had lower 15-year survival rates (40% vs. 47% at integrated; 49% at academic hospitals, $p < 0.001$). Survival rates varied significantly by hospital distance, with traveling >250 miles showing the highest 15-year survival (59% vs. 47% within 12.5 miles; 49% 12.5–250 miles, $p < 0.001$). Kaplan-Meier curves indicated inferior outcomes for patients treated at community hospitals <250 miles of their residence, with nearly 4 years less median survival time. Univariable Cox analysis revealed that receiving treatment at a community hospital <250 miles was associated with $>50\%$ risk of mortality (HR=1.52, 95%CI 1.42–1.62, $p < 0.001$). Mortality risk was elevated for patients treated at low-volume hospitals and those with higher tumor stages, as well as higher tumor grade with G2-tumors associated with nearly 40% higher risk of mortality compared to G1-tumors (HR=1.39, 95% CI 1.31–1.49, $p < 0.001$). Primary tumor resection and private insurance were associated with a significant reduction in mortality risk. On MVA, the main protective and risk factors remained significant. Treatment at a community hospital was associated with a 9% increase in mortality (HR=1.09, 95%CI 1.01–1.17, $p = 0.018$). Primary tumor resection was associated

with a 67% reduction in mortality (HR=0.33, 95%CI 0.31-0.35, p<0.001). Other significant factors included age >65yrs, male sex, higher stage and grade, low-volume hospitals, and insurance status.

CONCLUSIONS

Traveling longer distances to specialized, high-volume centers and primary tumor resection are associated with improved OS for patients with well-differentiated PanNETs. These findings underscore the value of access to centralized care at high-volume, specialized hospitals, especially for advanced-stage PanNETs. Future studies examining the utility of interdisciplinary care for patients without access to academic or integrated centers may be of benefit.

ABSTRACT ID 28703



C-49

National trends in surgical management of T1N0 well-differentiated pancreatic neuroendocrine tumors (PNET) and age-specific survival

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BACKGROUND

Prior studies on the surgical resection of T1N0 pancreatic neuroendocrine tumors (WD-PNET) remain controversial. The present study uses the Surveillance Epidemiology and End Results (SEER) dataset to explore association with surgical management on survival, factors that contribute to allocation of surgery, and subgroup analysis for younger and older cohorts.

METHODS

We performed a retrospective analysis of microscopically confirmed T1N0 WD-PNET with known surgical history diagnosed from 2010–2021 and divided them into surgical (SG) and non-surgical (NSG) groups. The 12-year period was divided into 3-year blocks (P1–P4). Surgical methods include local excision (LE), partial pancreatectomy +/- gastrectomy/duodenectomy (PP), total pancreatectomy +/- subtotal gastrectomy/duodenectomy (TP), and extended pancreatoduodenectomy (EP). We assessed trends in surgical management with descriptive statistics and one-way anova, factors associated with surgical allocation using multivariable logistic regression, association of surgery with overall survival (OS) using multivariable cox-regression analysis.

RESULTS

N=1,766 patients diagnosed between 2010–2021 met criteria for T1N0 WD-PNET (SG:N=565 vs NSG:N=1,201). The median age was 60.0 years in SG vs 66.0 years in NSG. PP (52.5%) was the most common resection method followed by LE (9.5%), TP (4.5%), and EP (0.4%). The number of cases increased over time (P1: 96, P2:409, P3: 548, P4: 713). Surgical resection rates decreased significantly over time ($p < 0.001$) from 91.3% in 2010 to 49.2% in 2021.

Tumor size $>1\text{cm}$ (OR1.57[1.22–2.03], $p < 0.001$) and body/tail location (OR 1.37[1.04– 1.79], $p=0.03$) increased likelihood of proceeding to the operating room, but advanced age decreased likelihood (50–75 years: OR 0.63[0.47–0.84], $p<0.01$; >75 years: OR 0.21[0.14–0.32], $p<0.001$).

Lower OS was seen with advanced age (50–75 years: 3.59[1.74–7.44], $p<0.001$; 75+ years: 9.50[4.32–20.91], $p<0.001$). SG had higher OS (HR 0.48[0.34–0.70], $p < 0.001$) compared to NSG. Subgroup analysis showed that SG had higher OS in 50–75 year olds (HR 0.40 [0.26–0.63], $p < 0.001$), but not in extremes of age (<50 years: HR 2.01 [0.21–18.85], $p = 0.41$; > 75 years: HR 0.53 [0.24–1.16], $p = 0.11$). Even so, the 5– year absolute difference in survival was marginal (4%) in the 50–75 year old cohorts.

CONCLUSIONS

Since 2010, the number of patients diagnosed with T1N0 WD-PNET increased and surgical resection rates significantly decreased. Surgery shows marginal 5- year absolute survival over no-surgery in cohorts 50-75 years with no significant difference in OS in extremes of age. Results suggest patients 75+ may defer surgery to be spared post-operative morbidity while younger patients (<50 years) may opt for active surveillance in select cases.

ABSTRACT ID 28705



P-1

Rare germline variants in MEN1, TSC1, ATM, and MSH2 are associated with higher risk of pancreatic neuroendocrine tumors

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BACKGROUND

Pancreatic neuroendocrine tumors (pNETs) comprise ~2% of all pancreatic malignancies, with pancreatic ductal adenocarcinoma (PDAC) being the most common type. The etiology of pNET is poorly understood, including an incomplete understanding of the heritable genetic factors. We investigated whether genes associated with PDAC susceptibility also predispose to pNET. We further verified associations for genes implicated in pNET development from smaller studies by performing the largest study to date on pNETs.

METHODS

We used a case-control design involving 842 pathologically confirmed incident pNET cases from the Mayo Clinic Biospecimen Resource for Pancreas Research and 52,760 control patients without pancreas cancer from the Mayo Clinic Biobank. Whole-exome sequencing was performed using germline DNA obtained from the participants. We evaluated eleven candidate genes known to be associated with PDAC (*APC*, *ATM*, *BRCA1*, *BRCA2*, *CDKN2A*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, *PMS2*, *STK11*, *TP53*) and another six genes implicated in pNET (*MEN1*, *MEN2/RET*, *NF1*, *TSC1*, *TSC2*, *VHL*). We classified rare variants (minor allele frequency < 0.001) in these genes as pathogenic or likely pathogenic (P/LP) based on the American College of Medical Genetics and Genomics and the Association for Molecular Pathology consensus guidelines. Unconditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs), adjusting for age, sex, and the top two principal components of genetic ancestry. We computed two-tailed p-values using gene-burden test with SKAT-O, adjusting for multiple comparisons.

RESULTS

Germline P/LP variant carrier frequency was higher in the pNET cases (10%) than in the control patients (3%). We found a higher risk of pNET in patients who carry a P/LP variant in *MEN1* (OR = 56.7, 95% CI: 34.0-94.6, $p = 5.0 \times 10^{-38}$), *TSC2* (OR = 62.9, 95% CI: 12.7-312.0, $p = 3.6 \times 10^{-5}$), *ATM* (OR = 2.6, 95% CI: 1.7-4.0, $p = 0.0001$), or *MSH2* (OR = 9.0, 95% CI: 2.7-30.2, $p = 0.002$). No other significant association was observed.

CONCLUSIONS

Our results show that germline P/LP variants in *MEN1*, *TSC2*, *ATM*, and *MSH2* are associated with a higher risk of pNET. We did not find significant associations for *APC*, *BRCA1*, *BRCA2*, *CDKN2A*, *MLH1*, *MSH6*, *PALB2*, *PMS2*, *STK11*, *TP53*, *MEN2/RET*, *NF1*, *TSC1*, or *VHL*. These findings are important for genetic risk assessment, genetic counseling, early detection of pNET through screening in genetically defined high-risk patients and might inform therapy selection for certain patients. Genetic testing of all pNET patients would be necessary for familial risk assessment.

ABSTRACT ID 28299



P-2

Novel pathogenic germline variants (PGV) identified in pancreatic neuroendocrine neoplasm (PNEN) patients during genetic testing

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BACKGROUND

Poor outcomes in pancreatic cancer are in part due to the inability to identify patients with early-stage disease. Prevention strategies have focused on identifying high risk patients through genetic susceptibility genes associated with the development of pancreatic cancer. Invitae® initiated The Detect Hereditary Pancreatic Cancer program through which patients diagnosed with pancreatic ductal adenocarcinoma (PDAC) or pancreatic neuroendocrine neoplasm (PNEN) were offered no charge genetic testing. Approximately 10% of PNENs are due to germline mutations often as part of an inherited genetic syndrome. Here we report the incidence of pathogenic germline variants (PGVs) in PNEN patients enrolled in the program.

METHODS

Patients diagnosed with PDAC or PNEN seen at Cedars-Sinai and underwent genetic testing between 9/5/2019 and 2/15/2022 with either the Invitae® Common Hereditary Cancers Panel (42-47 genes) or Multi-Cancer Panel (80-84 genes) with the option to add on genes associated with chronic pancreatitis (CFTR, CASR, CTRC, CPA1, PRSS1, SPINK1) were identified. Demographic data including age, gender, ancestry, family history and cancer stage were collected and assessed retrospectively. The incidence of PGVs in PNEN patients was evaluated.

RESULTS

A total of 129 PNEN patients (median age, 58 years; 47.3% female; 75.4% white; 81.3% with family history of cancer; 52.8% stage IV) had germline testing performed. PGVs were found in 14.7% (19/129) of PNEN. The pancreatitis panel was added to 39 PNEN and PGVs in these genes were detected in 7.7% (3/39) of PNEN. CFTR alterations, identified in 5.1% (2/39) of PNEN, were the most common pancreatitis-associated gene in which PGVs were found in PNEN. Alterations in MUTYH, associated with polyposis syndrome, were the most frequently detected in PNEN (3.9%, 5/129) and were less prevalent in PDAC (1.8%, 21/1203). DNA or base repair PGVs were found in 7% (9/129) of PNEN.

Prevalence of PGVs in PNEN

	Variable	PNEN (N=129)
Patients with PGVs		19 (14.7%)
Pancreatitis gene PGVs (N=39)	CFTR	2 (5.1%)
	PRSS1	1 (2.6%)
DNA/Base Repair gene PGVs (N=129)	ATM	1 (0.8%)
	CHEK2	1 (0.8%)
	FANCA	1 (0.8%)
	MUTYH	5 (3.9%)
	RAD50	1 (0.8%)

All PGVs identified are monoallelic.

CONCLUSIONS

PGVs in PNENs were more common than previously reported. This suggests that germline testing for pancreatic NENs may play a role in standard of care management of these patients. Although biallelic loss of MUTYH is associated with colorectal polyposis and risk of colorectal cancer, this study suggests further evaluation into monoallelic pathogenic MUTYH alterations as a potential risk factor for PNEN.

ABSTRACT ID 28488

P-3

Sexual dimorphism in Small Intestinal NETS: Any association with development of mesenteric metastases?

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BACKGROUND

- SI-NET-linked mesenteric and hepatic metastases are associated with increased morbidity and mortality.
- Mesenteric fibrosis risk increases in women around menopause. (Blažević et al. 2022)

Aim: analyse sexual dimorphism in a large cohort of patients with SI-NET.

METHODS

849 SI-NET patient database (recruited 2009-2021).

- Parameters analysed: age, sex, grade, stage, presence of mesenteric metastases and size, presence of fibrosis and urinary 5HIAA.
- Survival analysis conducted for male and female patients, mesenteric metastases, mesenteric fibrosis and tumour multifocality.

RESULTS

- 54% patients were male.
- Male sex ($p = 0.048$) and age of diagnosis ($p = 0.048$) were statistically significant predictors of mesenteric metastases.
- Median survival time did not differ significantly based on sex.
- Mesenteric metastases presence increased with age for males and females being statistically significant for females only.

CONCLUSIONS

- Elderly females have higher prevalence of mesenteric metastases that may be linked to the effect of sex hormones post-menopausal.
- Investigating sex hormone level in patients and expression of receptors in tissue will elucidate further on the role of pre-menopausal status in mesenteric fibrosis protection.

ABSTRACT ID 28507

P-4

Think NENs Global Education Program on Neuroendocrine Neoplasms Diagnostics and Management for Primary Care Physicians

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BACKGROUND

Neuroendocrine neoplasms (NENs) are complex neoplasms with increasing incidence and prevalence worldwide that can originate in various organs, but most commonly in the gastrointestinal tract and the respiratory system.

Previously INCA demonstrated via a Survey of Challenges in Access to Diagnostics and Treatment for NET Patients (SCAN) survey significant challenges in NEN patient management: a long mean time to diagnosis of 5 years; and almost half, 46%, were advanced stage IV at diagnosis. SCAN also underlines the important role primary care physicians (PCPs) play in NENs detection and care – with 19% of HCPs alerting a diagnostic test and 44% of them actively involved in the ongoing monitoring of NEN patients.

METHODS

A team of medical experts in NENs, PCPs and patient advocates from across the globe developed Think NENs Global Educational Program. NEN leaders working with PCP partners provided a framework of particular knowledge around NEN that was further streamlined into a format deemed suitable for PCP learning. The free online training includes everything PCPs need to know about diagnostics, treatment and care of patients with NENs. Its objective is to equip PCPs with competence and skills in detecting and managing NENs in primary care, including referral pathways.

RESULTS

Think NENs Global Educational Program for PCPs includes 1 main module of 3 videos providing concise knowledge about neuroendocrine cancer diagnosis and managing patients via Q&A sessions between PCPs and neuroendocrine neoplasm (NEN) experts from around the world, as well as 13 supplementary videos on common NEN types, the impact of treatments and genetic NENs. Upon successful completion of exam, the main module can provide 1 UEMS-EACCME® credit, which has a reciprocal agreement of mutual recognition of credits with the American Medical Association. The program provides heightened diagnostic awareness and skills to evaluate the common diagnostic pitfalls in the most frequent type of clinical diagnostic scenarios in primary care. It also maps the common NEN treatments and their implications that can be seen in primary care, as well as ways to

deal with them. The program is available in English, French, German, Italian, Portuguese and Spanish.

CONCLUSIONS

Delayed NEN diagnosis and suboptimal patient care are enduring global challenges. PCPs play a key role in NEN diagnostics and ongoing patient monitoring. Improved understanding of NENs among PCPs is of instrumental importance for improving patient diagnostic and care pathways, as well as patient outcomes. Continuous educational efforts should be employed to support PCPs in their practice.

ABSTRACT ID 28554



P-5

The exceptionally rare phenomenon of well-differentiated colon neuroendocrine tumors

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BACKGROUND

Colonic neuroendocrine tumors (NETs), excluding rectal NETs, are often described as relatively common and aggressive, with inferior median survival compared to other gastrointestinal (GI) primary sites. However, epidemiological databases may conflate well-differentiated NETs with poorly differentiated NECs, leading to a lack of precise data on the prevalence, clinical behavior, and prognosis of well-differentiated colonic NETs.

METHODS

We analyzed a large institutional database to identify patients with well-differentiated NETs originating in the colon, excluding rectal NETs. Cecal NETs were included, however ileocecal NETs (overlapping the ileocecal valve) were not. We assessed their prevalence compared to other primary sites, grade, stage, and prognosis.

RESULTS

Among 3639 patients with gastroenteropancreatic (GEP) NETs, only 19 (0.5%) had well-differentiated colonic NETs. This included 11 cecal and 8 sigmoid colon primaries (2 of them described as 'rectosigmoid'). No tumors originated in the ascending, transverse, or descending colon. Sigmoid NETs were typically early-stage polyps, discovered incidentally during colonoscopy. In contrast, 8 of the 11 cecal NETs metastasized ($p=0.04$), with 6 of these patients (55%) exhibiting carcinoid syndrome and none in the sigmoid cases ($p=0.01$).

CONCLUSIONS

Well-differentiated colon NETs are exceptionally rare, comprising approximately 0.5% of GEP-NETs. These tumors fall into two distinct categories: cecal NETs, which resemble ileal NETs in behavior, and sigmoid NETs, which appear to be quite similar to rectal NETs. The broad categorization of colonic 'NETs' in epidemiologic databases likely includes NECs, obscuring the true clinical picture.

ABSTRACT ID 28560

P-6

Epidemiological description of a patient's cohort with diagnosis of neuroendocrine tumors in a Colombian health care institution (CTIC)

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BACKGROUND

Neuroendocrine neoplasms (NENs) are considered rare tumors, but their incidence has significantly increased in recent years. In Colombia, there are few epidemiological descriptions of the population affected by this pathology.

METHODS

Descriptive analysis was conducted on patients with a confirmed histopathological diagnosis of neuroendocrine neoplasm who were evaluated in Colombian Health Care Institution (CTIC) over a two-year period, from July 2022 to July 2024. The analysis included demographic, epidemiological, tumor behavior, and histopathological characteristics.

RESULTS

47 cases were analyzed in total, with an ECOG: 0 - 1 reported in 91% of cases. The mean age was 63 years, Neuroendocrine Tumors (NETs) were more common than Neuroendocrine Carcinomas (NECs) (78,7% vs. 17%); within well-differentiated NETs 45,9% were grade 1, 45,9% grade 2 and 8,1% grade 3. Pancreas was the most frequent primary site (29,8%), followed by ileum (27,7%), and stomach (14,9%), in which were mostly NECs. Stages distribution is as follows: stage I: 20,9%, stage II: 4,7%, stage III 16,4% and stage IV 58,1%. Liver (81,5%), followed by retroperitoneum (33,3%), peritoneum (29,6%) are the most frequent sites of metastatic disease, and less frequently lung and bones (22,2%). In 15,6% of patients, symptoms consistent with carcinoid syndrome and/or elevated 5HIAA levels were reported in well-differentiated NETs. Second primary neoplasms were observed in almost 20% of the cases and 100% of them patients had a history of at least one first-degree relative with a diagnosis of some malignant disease.

Functional imaging was performed prior to systemic or surgical treatment in 57% of cases.

Chemotherapy was used 25,5% and somatostatin analogs 50% in patients treated. Lu-177-Dotatate Therapy was initiated in 4,3% of cases. The use of other targeted therapies such as cabozantinib, sunitinib, and everolimus, was less common. Primary tumor resection was performed in 50% of cases and mortality was observed in 8,5% of patients.

CONCLUSIONS

This descriptive analysis has identified these patients had similar characteristics as the general NENs population, as diagnosis age, carcinoid syndrome prevalence, and cases proportion were initially diagnosed as stage IV. In striking way, this cohort from a Colombian institution shows a higher proportion in cases of gastric NECs and second primary neoplasms. Overall, these findings highlight the importance of precise diagnostic evaluation to improve patient care. More analytical studies on a higher number of patients in the Colombian population are proposed for the future.

ABSTRACT ID 28567

P-7

Metastatic Neuroendocrine Tumors to the Breast: A Systematic Review

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BACKGROUND

Neuroendocrine neoplasms (NENs) are tumors primarily originated in the digestive system and lungs. These neoplasms are classified into two groups: neuroendocrine carcinomas (NECs), and neuroendocrine tumors (NETs). Metastases to the breast are rare, counting for only 1% of cases. The objective of this research was to characterize patients with breast metastatic NENs based on a literature review.

METHODS

A systematic review was conducted using PubMed, EMBASE, Lilacs, and OpenGrey databases, employing specific terms combined with Boolean operators, and limited to English and Spanish until July 2024. Case reports, case series, and cross-sectional studies documenting at least one case of breast metastatic NEN confirmed by histopathological study or functional imaging were included. The quality of the studies was assessed using an adapted Newcastle-Ottawa scale tool

RESULTS

Eighty-one articles reporting 138 cases of breast metastatic NENs were included with chronological increase in frequency. The mean age of the patients was 52.7 years, including 3 male cases out of 138. NETs were more common than NECs (82,6% vs. 14,5%). The small bowel was the most frequent primary site (45,3%), followed by lung (26,6%). Metastatic involvement to the breast alone is uncommon, the most frequent extramammary metastases were liver, lymphatic, lung and bone (87%). The median time from the onset of NEN-attributable symptoms to diagnosis was 8 months. In 27 patients (23,3%), the breast lesion was the initial clinical manifestation. About 23% of cases were initially misdiagnosed as primary breast tumor. Symptoms compatible with carcinoid syndrome were reported in 18 patients (21,4%). Breast ultrasound showed hypoechoic lesions with irregular margins in most of the cases, mammography revealed poorly defined margins and functional Imaging were used in 35 cases.

Regarding the treatment, chemotherapy was used in 57,4%, somatostatin analogs in 36,2% of patients. Primary tumor resection was performed in 74,6% of cases, and metastasis resection in 73,5%.

A lower progression free survival in CNEs is described, statistically significant and a trend that did not reach significance of lower overall survival

CONCLUSIONS

This systematic review has identified that these patients share several characteristics with the general NEN population, such as age at diagnosis and the prevalence of carcinoid syndrome. Additional metastases to other organs are common, and a significant proportion of cases were initially misdiagnosed as primary breast tumor. This is the first characterization of this population, and this finding highlights the importance of precise diagnostic evaluation to improve patient care and avoid misdiagnoses.

ABSTRACT ID 28568

P-8

Risk Factors Associated with Gastroenteropancreatic and Lung Neuroendocrine Tumors: A Nested Case-Control Study from The All of Us Research Program

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BACKGROUND

The incidence of neuroendocrine tumors (NETs) continues to increase worldwide, with a 4.5-fold increase between 1975 and 2019 in the USA. Gastroenteropancreatic (GEP) and lung NETs are the most common NET sites. However, the etiology of NETs remains inconclusive.

METHODS

Of 2,180 individuals, most cases and controls were non-Hispanic White (62.8%). The mean age at primary consent date was 63.01 (\pm 11.99) years in cases and controls. Females outnumbered males (61.0% vs. 39.0%) in cases and their matched controls. Among 366 cases, 118 (32.2%) had lung NETs and 248 (67.8%) had GEP NETs. Individuals with a family history of any cancer (OR, 1.43; 95%CI, 1.06 to 1.95, P=0.021), a past diagnosis of type 2 diabetes (OR, 1.46; 95%CI, 1.09 to 1.96, P=0.012) and any immune-mediated disease (OR, 1.40; 95%CI, 1.11 to 1.76, P=0.004) were at a higher risk of developing GEP or lung NETs. Male individuals with obesity, female individuals with genetic ancestries other than non-Hispanic White, having a family history of any cancer, and having a past medical history of type 2 diabetes or any immune-mediated disease were at a higher risk of developing GEP or Lung NETs.

RESULTS

Our study confirms a significant role of having a first-degree relative with any cancer and previous diagnosis of type 2 diabetes in the development of overall NETs and GEP NETs. Notably, we highlight for the first time, pre-existing diagnosis of any immune-mediated disease as a novel risk factor of developing NETs. These results suggest that the risk of developing NETs may be explained by both inheritable and environmental risk factors, with important site-specific differences in risk profiles by gender and race.

CONCLUSIONS

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 28590



P-9

Shared Care Model (SCM) in the Management of Neuroendocrine Neoplasms (NENs)- Patient Perspective

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BACKGROUND

Rural-urban disparities in NEN incidence and outcomes have been previously noted. Multidisciplinary expert management of NENs is consolidated to urban centers. SCMs can bring expert care closer to home. SCMs have been studied in cancer survivorship, but not in NENs. Patient perspectives on the current landscape, including their attitudes towards primary NEN care (PNC) versus NEN specialty centers (NSC), are pivotal to designing an optimal SCM.

METHODS

An anonymous 43 question survey developed on SurveyMonkey was reviewed initially by a patient focus group. It included multiple choice, select-all, and open responses. Domains included demographics, clinical characteristics, PNC vs NSC details and factors affecting patient satisfaction. The Canadian Neuroendocrine Tumour Society (CNETS) patient advocacy group's electronic mailing list was used for distribution during 2023-2024. Spearman's Regression was used for analysis.

RESULTS

96 Canadian NEN patients participated in the first round, predominantly female (73%) and >60yrs (70%). 56% identified their PNC provider as a NEN specialist. 36% have been referred to NSC, mostly for PRRT or second opinion. 50% report financial toxicity, 55% drove >4hrs, 70% took time away from work/activities, and 42% reported expenses >\$200/appointment to attend NSC. Despite this, 61% reported improved patient experience due to NSC involvement, whereas 84.5% were satisfied/somewhat satisfied with their PNC.

There was a significant ($p < 0.05$) association between increased financial toxicity and younger age, lower household income, more time spent away from work/activities attending NSC appointments, and high burden of physical symptoms. Factors valued in NSC included knowledge/skills and resource availability whereas ease of access, care closer to home, and continuity of providers were valued in PNC; Tumor board review significantly improved satisfaction with both ($p < 0.05$). Higher symptom burden correlated positively with NSC satisfaction, but negatively with PNC ($p < 0.05$). Most patients (74%) identified ability to access NSC as needed, while continuing with primary NEN care as the key to SCM.

CONCLUSIONS

To our knowledge, this is the first patient survey focusing on variables that rationalize the need for and determine the success of NEN SCM. We demonstrated the relative pros/cons of both PNC and NSC, including time and financial toxicity. Future SCMs should bring NSC expertise/resources closer to home by increasing knowledge/experience of PNCs, coordination between providers, and NEN tumor board access. Our sampling methods incurred bias towards well-connected CNETS patients. Hence, next steps in survey expansion to increase generalizability by targeting more diverse patient population via social media, clinics and patient support programs are underway.

ABSTRACT ID 28608



P-10

Disparities in the rising incidence of early-onset neuroendocrine neoplasms

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BACKGROUND

More young people are being diagnosed with neuroendocrine neoplasms (NENs) in recent years, but the epidemiology is not well understood. We aim to describe the incidence of early-onset NENs and differences by patient and tumor characteristics in the diverse California population.

METHODS

All patients with malignant NENs diagnosed from 1992-2019 in the population-based California Cancer Registry were identified by histology (ICD-O-3 code 8013, 8041-5, 8150-5, 8240-9). Patients diagnosed by age 49 were designated as early-onset. Annual age-adjusted incidence rates (AIRs) by patient or tumor characteristic were calculated, compared using incidence rate ratios (IRRs), and described using Joinpoint regression temporal trend and annual percent change (APC).

RESULTS

Among 12,266 early-onset NEN patients identified, the majority (55%) were women. Most (52%) identified as Non-Hispanic (NH) White, 28% Hispanic, 10% Asian/Pacific Islander (API), and 9% as NH Black. Half (50%) were diagnosed with local stage, 21% regional, and 29% distant metastases. Nearly half (46%) had a gastrointestinal primary, 29% pulmonary, 10% pancreatic, and 15% other site. Surprisingly, the AIRs of pulmonary NENs improved steadily during years 1992-2019 (APC -3.3), but the other primary sites rose statistically significantly by 1.1 to 6.9 percent annually. In recent years, the AIRs rose for all other subpopulations tested, with some significant disparities to note; faster for women (APC 8.4) than men (6.5), faster for Hispanic Californians (11.2) than any other race and ethnicity (3.2 to 6.1), faster for urban residents (7.5) than rural (3.1), and faster for residents in the lowest socioeconomic status neighborhoods (8.0) than highest (5.7). The final overall AIR in year 2019 is 2.85 per 100,000 person-years. During the most recent ten-year block, the AIRs differ across every racial and ethnic population, as presented in the Table.

Latest 10-year age adjusted incidence rates (AIR) from 2010–2019 by race and ethnicity and incidence rate ratio (row/column) with Tiwari 95% confidence interval

	API	Hispanic	NH Black	NH White
N:	640	1,960	476	2,433
AIR:	1.53	1.90	3.02	2.57
API	1	0.81 [0.73,0.88]	0.51 [0.45,0.57]	0.60 [0.55,0.65]
Hispanic	1.24 [1.14,1.36]	1	0.63 [0.57,0.70]	0.74 [0.70,0.79]
NH Black	1.97 [1.75,2.23]	1.59 [1.43,1.76]	1	1.18 [1.06,1.30]
NH White	1.68 [1.54,1.83]	1.35 [1.27,1.43]	0.85 [0.77,0.94]	1

CONCLUSIONS

We found incidence rates of early-onset NENs rising significantly for all extra-pulmonary primary sites, and differences by geographic location, socioeconomics, sex, and race and ethnicity. Reasons for these wide differences are unclear, and further research is underway to better understand the mechanisms causing disparities.

ABSTRACT ID 28612



P-11

Re-examining NCTN Clinical Trials for Sex Differences in Outcomes and Toxicities in Patients with Neuroendocrine Neoplasms

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BACKGROUND

Prior large epidemiologic and retrospective studies have shown sex-based differences in the epidemiology and treatment-related side effects of patients with neuroendocrine neoplasms (NEN). The purpose of this study was to examine sex differences in outcomes and toxicities in National Clinical Trial Network (NCTN) NEN clinical trials.

METHODS

We performed a retrospective analysis of three randomized trials for patients with NEN conducted through the NCTN: ECOG-ACRIN E2211 [Phase II capecitabine + temozolomide versus temozolomide in advanced pancreatic NEN], SWOG S0518 [Phase III Octreotide + IFN versus Octreotide + Bevacizumab in advanced gastrointestinal NEN], and Alliance CALGB 80701 [Phase II everolimus versus everolimus + bevacizumab in advanced pancreatic NEN]. We examined sex differences in progression free survival (PFS), overall survival (OS), response rate (RR), and treatment-related toxicities as measured through NCI Clinical Trial Adverse Event Criteria.

RESULTS

The total number of males (M) and females (F) in each trial were E2211 (N = 73 M and 60 F), S0518 (N = 192 M and 210 F), and CALGB 80701 (N = 84 M and 66 F). The number of M and F within each treatment arm were E2211 [Capecitabine + Temozolomide (N = 38 M and 30 F) vs Temozolomide (N = 35 M and 30 F)], S0518 [Octreotide + IFN (N = 90 M and 112 F) vs Octreotide + Bevacizumab (N = 102 M and 98 F)] and CALGB 80701 [Everolimus (N = 40 M and 35 F) vs Everolimus + Bevacizumab (N = 44 M and N = 31 F)]. There were no statistically significant sex differences in PFS, OS and RR within the treatment arms of E2211, S0518 and CALGB 80701 clinical trials. However, there were sex differences in treatment-related toxicities in CALGB 80701 but not in E2211 and S0518.

In CALGB 80701, there was a higher occurrence of cardiac-related toxicities among females in Everolimus treatment (20% vs 3%; $p=0.022$) but not in Everolimus + Bevacizumab. In E2211, hematological toxicities showed a trend of female predominance in both treatment arms but not statistically significant.

CONCLUSIONS

Sex differences were present in cardiac treatment-related toxicities in CALGB 80701. However, there were no other statistically significant sex-based differences in PFS, OS, RR in the three clinical trials examined. Our findings suggest that sex differences in treatment-related toxicities in NEN may be more prevalent than previously recognized and highlight the need for further study in this area.

ABSTRACT ID 28617



P-12

US NETs Clinical Trial Searches as Compared to SEER Prevalence Data from 2011-2021 Indicates Potential Areas of Unmet Needs

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BACKGROUND

A neuroendocrine tumors (NETs) clinical trial finder tool launched in Oct. 2023 by extending Ancora.ai, an AI-based clinical trial finder, to include NETs as a tumor type. Ancora.ai received over 2,500 searches for NETs trials. An analysis was conducted to see if US patient searches in Ancora.ai correlate to NETs prevalence data and perhaps indicate unmet needs.

METHODS

NETs prevalence data was calculated using incidence data from NCI's Surveillance, Epidemiology, and End Results (SEER) Research Database, version 17 Registries Nov. 2023 Sub (2000-2021). Prevalence data was analyzed on 93,808 NETs patient records from 2011-2021 using year of diagnosis and year of death. NETs sites were categorized using ICD-O-3 codes and Primary Site fields.

NETs trial finder de-identified US patient searches were extracted from Ancora.ai for a 2-year period covering a total of 2,475 records.

The comparison between NETs trial searches and NETs prevalence data was made using a percent of total records by NETs primary sites.

RESULTS

Ancora.ai searches are over-represented as compared to prevalence for Pancreas, Small Intestine, Paraganglioma and Pheochromocytoma sites. Ancora.ai searches are under-represented for Appendix and Rectum sites.

Comparison of US NETs Prevalence and Trial Searches by NETs Primary Site

Primary Site	SEER Prevalence (%)	Ancora.ai Searches (%)
Appendix	8.9%	1.1%
Lung	11.7%	12.4%
Others	17.5%	7.9%
Pancreas	12.0%	28.2%
Paraganglioma + Pheochromocytoma	0.5%	9.9%
Small Intestine	17.3%	24.8%
Stomach	6.8%	4.0%
Unknown	4.2%	5.0%
Rectum	17.4%	2.4%
Colon	3.7%	4.1%

Patients' interest in joining clinical trials captured in Ancora.ai were evaluated. The patients' responses were as follows: 69% "Yes", 2% "No", and 29% "Don't Know".

CONCLUSIONS

The NETs sites that Ancora.ai trial searches varied on possibly indicate where unmet needs lie and the impact of patient organizations on disseminating information on clinical trials. The large under-representation of Ancora.ai searches for Appendix and Rectum NETs as compared to prevalence can be explained by these patients' response to initial therapy and subsequent longer survival rates. The over-representation of Paraganglioma and Pheochromocytoma reflects the unmet need and impact of a patient organization, the Pheo Para Alliance, and their work to educate patients on the availability of clinical trials.

Finally, the over-representation of Pancreas and Small Intestine searches in Ancora.ai may indicate unmet needs and areas researchers should target, especially as 69% of those searching for NETs trials indicate interest in joining a clinical trial.

ABSTRACT ID 28622



P-13

Role of genetic alterations and tumor functionality in predicting peptide receptor radionuclide therapy effectiveness and survival in pancreatic neuroendocrine neoplasm

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BACKGROUND

Studies exploring the potential of genetic alterations and tumor functionality to predict treatment effectiveness and survival outcome in pancreatic neuroendocrine neoplasm (PNET) are limited. The objective of this study was to report on the genetic and functional tumor profiles, as well as to examine their association with peptide receptor radionuclide therapy (PRRT) treatment effectiveness and survival outcome in PNET patients.

METHODS

Patients diagnosed with PNET seen at Cedars-Sinai were identified. Data of race, ethnicity, tumor functionality, genetic testing results were collected retrospectively. The incidence of genetic alterations and functioning tumors were reported. Progression-free survival (PFS) for evaluating PRRT effectiveness was calculated for patients who received PRRT (n=28) while overall survival (OS) was calculated for the entire patient cohort (n=115). They were compared across groups stratified by somatic mutations, germline mutations, tumor functionality and PRRT treatment status.

RESULTS

Of 115 PNET patients, 60 had somatic testing results and 49 had germline testing results. Somatic variants were detected in 73.3% of patients (44/60). The most common somatic variants detected were MEN1(33.3%, 20/60), DAXX(18.3%, 11/60), CDKN2A(15.0%, 9/60), ATRX(11.7%, 7/60), CDKN2B(10.0%, 6/60) and TP53(8.3%, 5/60). Germline variants were detected in 20.4% of patients (10/49). The most frequently detected germline variant was APC (6.1%, 3/49). The most common functioning tumors were gastrinoma (9.6%, 11/115) and insulinoma (7.0%, 8/115). Shorter median PFS was associated with the presence of MEN1 (5.4 months), CDKN2A (9.1 months) and CDKN2B (3.0 months) mutations. Longer median OS was noted in ATRX (114.3 months), CDKN2A (78.0 months), CDKN2B (78.0 months) and DAXX (78.0 months) mutations while shorter median OS was noted in MEN1 (47.3 months) and TP53 (9.1 months) mutations. Longer median PFS (16.9 months) and median OS (69.3 months) were noted in patients with functioning tumors.

PFS/OS of PNEN

		Median PFS (months)	Median OS (months)	N (PFS/OS)
Somatic mutations	ATRX	0.9	114.3	3/7
	CDKN2A	9.1	78.0	6/9
	CDKN2B	3.0	78.0	5/6
	DAXX	18.4	78.0	5/11
	TP53	N/A	9.1	0/5
	MEN1	5.4	47.3	6/20
	Without somatic mutations	18.0	58.5	6/20
Tumor functionality	Functioning	16.9	69.3	8/23
	Non-functioning	13.8	33.5	20/92

PFS of ATRX/TP53 was not described due to small sample size.

CONCLUSIONS

The findings suggested that genetic alterations and tumor functionality could provide insights into predicting PRRT treatment effectiveness and survival outcome in PNEN patients. The incorporation of genetic and functional tumor profiling could potentially aid in better PNEN management. Further studies with larger sample sizes are needed to enhance the reliability of these results.

ABSTRACT ID 28691



P-14

Comparative Analysis of Characteristics and Outcomes of Patients with Early-Onset versus Average-Onset Small Bowel Neuroendocrine Tumors

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BACKGROUND

The global incidence of early-onset gastrointestinal cancers (GI) is increasing. Although patients with more common early-onset GI cancers, e.g. colorectal cancer, often present with more advanced disease and experience relatively worse outcomes; the characteristics and treatment outcomes for less common early-onset small bowel neuroendocrine tumors (SBNETs) have yet to be explored.

METHODS

We used the Surveillance, Epidemiology, and End Results (SEER) database to identify patients diagnosed with SBNETs from 2004-2021. Using ICD-0-3 SEER histology codes 8240/3, 8241/3, 8243/3, 8244/3, 8249/3, 8246/3), we restricted the sample to patients with SBNETs. Patients with poorly differentiated histology were excluded. We used the chi-square test to compare patients with early-onset SBNETs (EO-SBNETs, aged 30-49 years) and those with average-onset SBNETs (AO-SBNETs, aged \geq 50 years) for categorical variables including sex, race/ethnicity, treatment and stage at diagnosis. Survival estimates were determined by Kaplan Meier analysis. Level of statistical significance was set at $p < 0.05$.

RESULTS

A total of 3,713 patients with SBNETs were included in the analysis, of which, 925 (25%) were EO-SBNETs. Compared to patients in the AO-SBNETs group, EO-SBNETs patients were more likely to be females (51.1% vs 46.7%, $p=0.02$), non-Hispanic Black (20.8% vs 17.6%, $p=0.04$), Hispanic (13.6% vs 8.8%, $p<0.0001$) and less likely to be non-Hispanic White (60.8% vs 69.9%, $p<0.0001$). There were no observed differences in the stage at diagnosis between the EO-SBNETs and AO-SBNETs, i.e., localized disease (33.5% vs 31.0%, $p=0.15$), regional spread (41.9% vs 42.8%, $p=0.64$) and distant metastatic disease (20.9% vs 21.9%, $p=0.500$). Patients did not differ in receipt of treatment modalities, i.e., surgical resection (90.5% vs 89.1%, $p=0.25$), chemotherapy (5% vs 6.3%, $p=0.15$) and radiation therapy (1.4% vs 1%, $p=0.27$) comparing EO-SBNETs and AO-SBNETs respectively. In both unadjusted and models adjusting for age at diagnosis (stratified by 5-year intervals), race/ethnicity, sex, stage and socioeconomic status, early onset was significantly associated with better survival ($p<0.0001$).

CONCLUSIONS

To our knowledge, this is the first investigation related to characteristics and outcomes in EO-SBNETs. We noted significantly superior overall outcomes among EO-SBNETs despite no differences in stage and receipt of surgery compared to AO-SBNETs. These findings establish age at diagnosis as a significant prognostic factor for SBNETs. Further studies investigating the role of factors such as differences in tumor biology and patient preferences in receipt of other therapies besides surgery may be helpful in age adapted approach to the management of SBNETs.

ABSTRACT ID 28699

P-15

Surgery enhances the effectiveness of Peptide Receptor Radionuclide Therapy in metastatic Gastroenteropancreatic Neuroendocrine Tumors

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BACKGROUND

With the advent of Peptide Receptor Radionuclide Therapy (PRRT), the timing and sequence of surgery in the treatment of metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) merits further study. We hypothesized that surgery prior to PRRT might enhance its effectiveness in patients with metastatic GEP-NETs.

METHODS

Eighty-nine patients with metastatic well-differentiated GEP-NETs treated with ¹⁷⁷Lu- DOTATATE PRRT between 2018 and 2023 were included. Fifty-six patients underwent surgery (primary tumor resection and/or liver debulking) prior to PRRT and 33 patients did not. Primary outcome was progression-free survival (PFS) according to RECIST. Pre-treatment DOTATATE PET CT was used to calculate tumor volumes (TV).

RESULTS

The surgery and no-surgery groups were well-matched. Median PFS after PRRT was 15.6 months (IQR 9.1-22.7) in the no-surgery group compared to 26.1 months (IQR 12.7-38.1) in the surgery group ($p=0.04$). On subgroup analysis, median PFS was 18.1 months (IQR 11.9-38.4) in patients who underwent primary tumor resection only versus 26.2 months (IQR 14.0-38.1) in patients who underwent liver debulking ($p=0.04$). TV was lowest in patients who underwent liver debulking (median 146.07mL³) compared to no surgery (median 626.42mL³) ($p = 0.001$). On univariable analysis, TV < 138.8mL³ was associated with longer PFS (HR 2.03 [95% CI 0.95 – 4.34], $p=0.05$), with a median PFS of 38.1 months (IQR 16.9-41.3) versus 17.8 months (IQR 10.8-28.7).

CONCLUSIONS

Surgery may enhance the effectiveness of ^{177}Lu -DOTATATE in the treatment of metastatic well-differentiated GEP-NETs. This positive effect may be due to a lower tumor volume in patients after surgery. Our findings fortify the concept of using surgical debulking to improve systemic therapies such as PRRT.

ABSTRACT ID 28483



O-1

Hereditary Predisposition and Clinical Presentation of Patients with Pheochromocytomas and Paragangliomas: Insights from a Large Clinical Cohort

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BACKGROUND

Approximately 30–40% of paragangliomas (PGL) and pheochromocytomas (PCC) harbor an underlying hereditary cause. Early identification of at-risk individuals is imperative given the early-onset, aggressiveness of tumors, and other tumor/cancer risks associated with hereditary PGLs/PCCs. This study analyzes the clinical presentations and genetic histories of patients with PGL/PCC and/or hereditary risk to contribute to the expanding knowledge in this rare population.

METHODS

Retrospective chart review identified two cohorts of patients seen in cancer genetics clinics at an academic medical center and a safety-net hospital between August 2016 and December 2022. Cohort 1 consisted of patients with likely pathogenic/pathogenic variants (LPV/PV) in hereditary PGL/PCC predisposition genes (*FH*, *MAX*, *MEN1*, *NF1*, *RET*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, *TMEM127*, *VHL*). Cohort 2 consisted of patients with a personal history of a PGL/PCC. Demographics, personal/family history, and genetic testing outcomes were analyzed.

RESULTS

A total of 560 patients met study criteria (Cohort 1, n=364; Cohort 2, n=269). In Cohort 1, 77 (21.1%) patients had an incidental LPV/PV in a PGL/PCC gene. Nearly half (n=36, 46.8%) were in SDHx genes, with a majority in *SDHA* (n=21). In Cohort 2, 86 patients tested positive for 87 LPV/PV in a hereditary cancer predisposition gene). The SDHx genes were most likely to have a LPV/PV identified (*SDHB* n=24, *SDHD* n=23, *SDHA*=7). Patients at the safety-net hospital most frequently had an LPV/PV in syndromic genes (*VHL*, *NF1* and *FH*) compared to patients at the academic medical center.

CONCLUSIONS

Multigene panels identify patients at risk for hereditary PGL/PCC, many of whom are incidentally found. While *SDHA* LPV/PVs were the most frequent incidental finding, they were less common in patients with PGL/PCC, indicating the need for longitudinal studies to better understand the prevalence and penetrance of these tumors.

ABSTRACT ID 28300

O-2

Characterization of early-onset gastroenteropancreatic neuroendocrine neoplasms at UCSF

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BACKGROUND

Incidence rates of early-onset (age<50) neuroendocrine neoplasms (EO-NENs) in California are rising significantly across multiple organ sites. Recognizing the limitations of population-based registries (e.g. lack of detail regarding Ki67, grade progression, treatment sequence, functional status, germline findings), this study seeks to understand the incidence, clinicopathologic (CP), and demographic features of EO-NENs at UCSF.

METHODS

For this retrospective IRB-approved cohort study we identified 439 patients diagnosed with pancreatic NENs (panNENs) and 514 patients with gastrointestinal NENs (GI-NENs) between 2011 and 2023 (any stage, age, grade, or differentiation). Eligible patients are restricted to age < 50 at diagnosis. Chi-squared tests and Wilcoxon rank sum tests were used to test associations for categorical and continuous variables, respectively.

RESULTS

The study population consists of 132 with EO-panNENs and 120 with EO-GI-NENs. Preliminary results are available for EO-panNENs. (median follow-up 7.1 yr), which account for 30.1% of panNENs at UCSF: 50% female, 54.8% locoregional disease, and 70.8% White, 18.4% non-White, and 10.8 % "other". The majority of EO-panNENs occur in the tail (54.5%) and 95.8% are well differentiated. Additional CP characteristics are summarized in **Table 1**:

Characteristic	Total (<50 yrs old) (n= 132, 100%)	18-39 yrs old (n=47, 35.6%)	40 - 49 yrs old (n=85, 64.4%)	P value
Grade at Diagnosis:	103 (91.2)	37 (94.9)	66 (89.2)	
G1/G2 NET			6 (8.1)	
G3 NET	6 (5.3)	0 (0.0)	2 (2.7)	0.299
G3 NEC	4 (3.5)	2 (5.1)		
Grade Progression	15 (12.7)	5 (12.5)	10 (12.8)	1.000
Functional Tumor	29 (24.0)	16 (35.6)	13 (17.1)	0.039

Demographic and CP variables associated with EO-panNENs are similar in very young (18-39) and young (40-49) patients (including tumor size, initial Ki67, and metastases or grade progression at any point), with the exception of functional tumors being more prevalent in the very young. N=59/132 (44.7%) underwent germline testing; 22/59 (37.3%) tested positive (the most common mutations being in MEN1, BRCA1, CHEK2, MSH2, and MUTYH2).

CONCLUSIONS

EO-panNENs represent a growing subset of patients that warrants special attention. EO-panNENs account for 30% of cases at UCSF and are predominantly low-grade, well-differentiated, and locoregional at diagnosis. Of note, 37% of tested patients harbor a pathogenic/likely pathogenic mutation. Further analyses of treatment patterns and survival according to CP variables are pending, as is an analysis of EO-GI-NENs (which will be reported at the meeting). Advances in our understanding of EO-NENs should lead to clues regarding etiology, detection, and optimal treatment.

ABSTRACT ID 28495

O-3

Racial Disparities in End-of-Life Care Among Patients with Neuroendocrine Tumors

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BACKGROUND

Due to a slower course of disease and lack of awareness among care teams, end-of-life (EOL) care is typically underutilized in patients with Neuroendocrine tumors (NETs). Owing to a heavy symptom burden, patients with NETs often struggle due to lack of palliative care and eventually EOL care support. Prior studies have revealed that Black patients with advanced cancer are more likely to receive aggressive care and suffer a significant decline in quality of life at EOL. Similar data investigating racial differences in EOL among patients with NETs are lacking.

METHODS

The National Inpatient Sample (NIS) was queried between years 2016-2020 to identify all hospitalizations (regardless of site of origin) with NETs utilizing the appropriate ICD-10 codes (neuroendocrine carcinomas were excluded). Hospitalizations of White and Black patients with documented inpatient mortality events were extracted. Demographic and clinical data were analyzed using independent sample t-test, Chi-square test, and binary logistic regression (adjusted for age, gender, and Charlson comorbidity index or CCI).

RESULTS

A total of 6,265 hospitalizations with NETs were included, of which 5,125 (81.8%) and 1,140 (18.2%) had White and Black patients respectively. Black patients were younger, more likely to be females, and less likely to have a do not resuscitate (DNR) code status. There was no significant difference in CCI between the groups. Palliative care consultation was less likely to be performed among Black patients (adjusted OR=0.70, $p<.001$). Black patients also had longer mean length of stay in the hospital (10.25 vs 8.42 days, $p<.001$). Black patients were also more likely to receive aggressive care in the form of mechanical ventilation at EOL.



	White N=5125	Black N=1140	aOR (95% CI)	p-value
Age (in years)	67.67 ± 11.89	65.14 ± 11.29	-	<.001
Females	46.1%	50.9%	-	.004
CCI	15 (12.7)	5 (12.5)	10 (12.8)	.538
Mean length of stay	29 (24.0)	16 (35.6)	13 (17.1)	<.001
Palliative	62.6%	54.5%	0.70 (.61-.80)	<.001
DNR	64.9%	60.1%	0.80 (.70-.92)	.002
Blood transfusion	13.2%	15.4%	1.18 (.98-1.41)	.052
Mechanical ventilation	28.8%	38.6%	1.55 (1.35-1.77)	<.001
Vasopressor	9%	9.6%	1.07 (.86-1.33)	.47

CONCLUSIONS

This is the largest analysis demonstrating significant racial disparities in EOL care among patients with NETs. Black patients had longer inpatient stay, were less likely to receive inpatient palliative care consultation, have a DNR order and more likely to receive aggressive care at EOL. These findings may have implications for informing healthcare decision making for EOL care among Black patients with NETs.

ABSTRACT ID 28540

O-4

MEN1/DAXX alterations are associated with improved overall survival and treatment response in patients with pancreatic neuroendocrine tumors

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BACKGROUND

Alterations in the *MEN1* and *DAXX* genes are common in pancreatic neuroendocrine tumors (PNETs). Previous data show that *MEN1*- and *DAXX*- altered tumors show longer overall survival (OS) and these alterations may increase radiation efficacy in tumor cells. We explored the associations of *MEN1* and *DAXX* alterations with clinical outcomes in PNETs.

METHODS

A retrospective chart review was conducted. Patients with PNETs seen at University of Chicago between 2013 and 2023 with available tumor NGS results were included. Patients with MEN1 syndrome were excluded. Cases with deleterious alterations (truncating mutations, missense mutations considered pathogenic, copy number losses) in the *MEN1* and *DAXX* genes were considered as *MEN1/DAXX* altered (*MEN1/DAXX*^{at}). The primary outcome was OS. The secondary outcome was progression free survival (PFS), after peptide receptor radionuclide therapy (PRRT), capecitabine/temozolomide (CAPTEM), and metastases debulking. Kaplan-Meier estimations and Cox proportional hazards regression analysis were conducted.

RESULTS

62 patients were included. Median follow-up was 42.1 months (IQR, 28 – 67.6). 28 (45.2%) patients were *MEN1/DAXX*^{at}. At diagnosis, the *MEN1/DAXX*^wt (wild-type) and *MEN1/DAXX*^{at} groups had similar median age (55.5 years vs. 54.2 years; $p = 0.99$), presence of metastatic disease (26/34, 76.5%; vs. 22/28, 78.6% $p = 0.99$), extrahepatic metastases (12/34, 35.3%; vs. 11/28, 39.3% $p = 0.8$), or bone metastases (7/34, 20.6% vs. 2/28, 7.1%; $p = 0.17$). The *MEN1/DAXX*^wt group showed a higher proportion of grade 3 disease (vs. grade 1/2; 12/34, 35.3% vs. 2/28, 7.1%; $p = 0.01$). OS after diagnosis (19 deaths recorded) was longer in the *MEN1/DAXX*^{at} group (median NR vs. 53.8 months; HR, 0.39; 95% CI, 0.15 – 1.03; log-rank $p = 0.049$). In patients with metastatic disease ($N = 61$), OS was longer after diagnosis of metastases in the *MEN1/DAXX*^{at} group (median NR vs. 53.5 months; HR, 0.33; 95% CI, 0.12 – 0.89; $p = 0.03$). PFS was longer with PRRT in the *MEN1/DAXX*^{at} group ($N = 27$; 26.5 months vs. 12.9 months; HR, 0.30; 95% CI, 0.12 – 0.77; $p = 0.01$). PFS did not vary significantly for CAPTEM treatment ($N = 30$; 17.8 months vs. 12.4 months; HR, 0.65; 95% CI, 0.28 – 1.53; $p = 0.32$) or metastases debulking ($N = 38$; 14.5 months vs. 11.3 months; HR, 0.77, 95% CI, 0.38 – 1.55; $p = 0.46$).

CONCLUSIONS

MEN1/DAXX altered PNETs may represent a subtype with favorable prognosis. *MEN1/DAXX*^{wt} cases showed favorable response to PRRT. The clinical significance of these alterations in PNETs warrants further exploration.

ABSTRACT ID 28544



O-5

Peptide Receptor Radionuclide Therapy versus Capecitabine/ Temozolomide for the treatment of Metastatic Pancreatic Neuroendocrine Tumors

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BACKGROUND

Peptide Receptor Radionuclide Therapy (PRRT) and Capecitabine/Temozolomide (CAPTEM) are cornerstones of systemic therapy for metastatic pancreatic neuroendocrine tumors (PNETs). The best sequence of systemic therapies in PNETs is poorly understood. Herein we compare the efficacy of PRRT vs. CAPTEM as second line and beyond systemic therapies.

METHODS

Clinicopathologic, radiographic, and genomic data were captured for metastatic PNET patients seen at the University of Chicago between 2013 and 2023. The primary outcome was progression free survival (PFS) with PRRT/CAPTEM after progression on at least one prior line of systemic therapy. The secondary outcomes were objective response rate (ORR), time to response (TTR), and overall survival (OS). Outcomes were analyzed using Kaplan Meier estimations and Cox proportional hazards regression.

RESULTS

59 patients were included and median follow-up was 31.7 months. There was no difference in PFS between the PRRT (n = 29) and CAPTEM (n = 30) groups (21.90 months vs. 20.03 months; HR, 0.99; 95% CI, 0.56 – 1.74; p = 0.97). On subgroup analysis, PRRT had longer PFS in cases without extrahepatic metastases (n = 20; 26.47 months vs. 17.67 months; HR, 0.31; 95% CI, 0.10 – 0.92; p = 0.03) and cases with mutations in the *MEN1*, *DAXX*, and/or *ATRX* genes (n = 19; 28.43 months vs. 18.67 months; HR, 0.22; 95% CI, 0.06 – 0.85; p = 0.03). CAPTEM had longer PFS in patients with grade 3 disease (n = 13; 16.33 months vs. 7.83 months; HR, 0.13; 95% CI, 0.02 – 0.67; p = 0.02) and trended towards longer PFS in cases with bone metastases (n = 20; 28.60 months vs. 17.87 months; HR, 0.35; 95% CI, 0.11 – 1.18; p = 0.09). ORR did not vary significantly (PRRT, 8/23, 34.78%; vs. CAPTEM, 9/22, 40.91%; p = 0.67). CAPTEM responders showed shorter TTR (6.03 months vs. 11.15 months; log-rank p = 0.03). In patients who received both (PRRT first = 11; CAPTEM first = 12), OS did not vary based on the sequence (48.57 months vs. 50.07 months; HR, 1.20; p = 0.75).

CONCLUSIONS

PFS, ORR, and OS are similar when using PRRT vs. CAPTEM as 2nd line and beyond therapy for patients with metastatic PNETs. However, patients with *MEN1*, *DAXX*, and/or *ATRX* mutations or without extrahepatic metastases might further benefit from PRRT and patients with grade 3 disease from CAPTEM. Candidates for surgical debulking or those with tumor-induced symptoms may benefit from initial treatment with CAPTEM due to shorter TTR.

ABSTRACT ID 28546



O-6

Empowering Participation: Trends in APP/AHP Authorship and the Impact of Travel Grants in Neuroendocrine Tumor Research

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BACKGROUND

The involvement of Advanced Practice Providers (APPs) and Allied Health Professionals (AHPs) in academic research, particularly within the neuroendocrine tumor (NET) field, has gained increasing attention. To understand their expanding role in interdisciplinary research, it is crucial to evaluate trends in authorship and conference participation. This study examines APP/AHP authorship trends in abstracts submitted to NANETS from 2018 to 2023, assessing changes over time and comparing involvement before and after the introduction of travel grants.

METHODS

We analyzed 616 abstracts submitted between 2018 and 2023, categorizing them into those with APP/AHP authors (n=225) and those without (n=392). Travel grants, introduced in 2022, were awarded to 12 individuals in 2022 and 21 in 2023. We conducted a cross-tabulation analysis to compare APP/AHP involvement over the years, with statistical significance determined by pairwise comparisons ($p < 0.05$). Additionally, the percentage of APPs participating as attendees and speakers during this period was assessed, using mean and median values to identify trends.

RESULTS

The analysis revealed a significant increase in APP/AHP authorship, rising from 21 abstracts in 2018 to 66 in 2023 ($p < 0.0001$). First-author contributions also grew from 3 and 5 in 2018 and 2019, respectively, to 14 and 19 in 2022 and 2023 ($p < 0.002$). Five APP/AHPs who submitted first-author abstracts in 2022 and 2023 were first-time attendees who received travel grants. Meanwhile, the number of abstracts without APP/AHP authorship declined, suggesting broader inclusion of APPs/AHPs in research. Among the 33 travel grant recipients, 4 had previously attended NANETS conferences, and 5 first-time attendees in 2022 returned in 2023. The mean percentage of APP/AHP attendees per year was 11.93%, with a median of 12.83%. APP/AHP speakers had mean and median percentages of 11.05% and 11.17%, respectively. Despite the introduction of travel grants, these percentages remained consistent over the years, though overall APP/AHP engagement increased significantly.

CONCLUSIONS

This study highlights a significant upward trend in APP/AHP authorship and conference involvement in NANETS from 2018 to 2023. The introduction of travel grants in 2022 likely supported this increased participation, as seen by the return of first-time attendees and the rise in first-author contributions. This growing involvement underscores the need for academic institutions and industry partners to increase support and resources for APPs/AHPs, fostering greater inclusion and collaboration within the NET field. Further research is recommended to explore the full impact of these grants on research quality and scope.

ABSTRACT ID 28564

O-7

Elevated Cancer Testis Antigen Expression Corresponds to Immune Activation and Improved Survival in Small Bowel Neuroendocrine Tumors

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BACKGROUND

While immune checkpoint inhibition (ICI) has proven highly effective in management of many solid tumors, its effectiveness in small bowel neuroendocrine tumors (SBNET) remains limited. Elucidation of the tumor immune microenvironment may improve understanding of mechanisms of ICI resistance and drivers of response in SBNET, expanding our treatment options as incidence continues to increase. Thus, we performed bulk transcriptional and digital spatial profiling (DSP) to further characterize the SBNET immune microenvironment and its association with overall survival (OS).

METHODS

Clinicopathologic data and preserved tissue blocks of primary tumors were obtained from patients who underwent surgical resection for well-differentiated SBNET between 2003-2016. A Cox proportional hazards model was used for OS and multivariable analyses (MVA). Using the NanoString PanCancer Immune Panel, bulk transcriptional profiling was performed on RNA from the tissue blocks. A tissue microarray was created, and DSP was performed on 245 regions of interest, segmented using PanCK to delineate tumor from stroma.

RESULTS

Transcriptional analysis of 42 resected SBNET yielded dichotomization into high and low cancer testis antigen (CTA) expression during unsupervised clustering of gene expression. Elevated expression of interleukin and antitumoral chemokines and cytokines was demonstrated in CTA^{high} patients (n=12). Significant improvement in median OS was also observed in CTA^{high} patients (HR 0.211, 95%CI 0.059-0.751) and those with increased IL expression (HR 0.153, 95%CI 0.020-1.153). MVA, controlling for age, sex, metastatic disease, and Ki-67%, confirmed independent association of CTA^{high} status with improved OS (HR 0.183, 95%CI 0.041-0.818).

DSP on regions of tumor and adjacent normal small bowel revealed heterogeneous CTA expression between tumor, tumor stroma, normal tissue, and normal stroma, with elevated CTA expression primarily driven by tumor epithelium. Upregulation of genes involved in immune activation (HLA-DQB1, CD27), interferon response (IFNA4, IFIT3), and epigenetic regulation and chromatin remodeling (KDM6A, WDR5) was demonstrated in CTA^{high} tumors. Signals for increased immune cells (CD8⁺ cytotoxic T cells, activated NK cells) were exhibited in CTA^{high} tumor regions and their adjacent stroma. T cell receptor (TCR) profiling demonstrated increased TCR diversity in CTA^{high} tumor ($p=0.024$) and adjacent stroma ($p=0.022$) regions

CONCLUSIONS

Consistent with previous studies examining other disease sites, elevated CTA expression in resected SBNET is associated with increased anti-tumor immunity and improved overall survival. Augmentation of the peritumoral immune environment in CTA^{high} regions suggests a role for CTA expression in modulating tumor response. Targeted pathways to drive CTA expression may represent an opportunity to improve tumor sensitivity and response to immunotherapy in future trials.

ABSTRACT ID 28602



O-8

From Neuroendocrine Neoplasms to Sarcomas: How Genetic Testing Reveals Diagnostic Pitfalls

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BACKGROUND

Neuroendocrine neoplasms (NENs) are heterogeneous with wide range of histological differentiation. Chromogranin, synaptophysin, and INSM1 are commonly expressed in NEN. Round cell sarcomas, such as Ewing sarcoma (ES), and desmoplastic small round cell tumor (DSRCT), can overlap morphologically and immunohistochemically with NENs, complicating diagnosis. Herein, we describe four cases of high-grade NEN that were subsequently classified as round cell sarcoma.

METHODS

This single-institution case series retrospectively reviews four cases initially diagnosed as NENs and later identified as round cell sarcoma.

RESULTS

Three cases were originally diagnosed as neuroendocrine carcinoma (NEC) and one as a grade 3 well differentiated neuroendocrine tumor (G3 NET) (Table 1). All cases were referred from outside facility with further initial confirmation of pathology at our institution. Immunohistochemical (IHC) was positive for synaptophysin and chromogranin in all the cases except one (pt#4) where both stains were negative, but positive for INSM1 and CD56. Subsequent Next-Generation Sequencing (NGS) revealed genetic fusions indicative of round cell sarcomas: *EWSR1-WT1* in two cases, *EWSR1-FLI1* in one, and *EWSR1-PATZ1* in another, consistent with DSRCT, ES, and undifferentiated small round cell sarcoma, respectively. This led to treatment modifications in all patients except one who died shortly after the first dose of platinum and etoposide (EP). Interestingly, pt#1 and #3 had initial partial response to EP before quickly progressing thereafter.

Table 1: Summary of Cases

Case (Age/Sex)	Initial Dx/ subsequent Dx	Synaptophysin/ Chromogranin/INSM1	Ki-67 Index	Genetic Findings (method)
1 (33 M)	NEC/ES	+/-/+	~100%	EWSR1-FLI1 (Tissue and blood NGS AND FISH)
2 (63 F)	NEC/ undifferentiated round cell sarcoma	+/?/?	40%	EWSR1-PATZ1 (Tissue NGS)
3 (43 M)	NET G3/DSCRT	+/?/?	60%	EWSR1-WT1 (Tissue NGS)
4 (57 M)	NEC/DSCRT	-/?/?	80%	EWSR1-WT1 (Tissue NGS)

CONCLUSION

Sarcomas can express NET markers and be misdiagnosed as NENs. This case series underscores the critical role of NGS in the accurate diagnosis of NEN mimickers, which can significantly alter treatment decisions and outcomes.

ABSTRACT ID 28611



O-9

Improving PET Scan Report Clarity Using Radiotracer Information: A Physician Survey

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BACKGROUND

Advancements in PET imaging have introduced novel cancer-specific radiotracers (e.g. Ga-68 Dotatate for NETs) targeting unique cancer biomarkers and biological processes. Amid the rapid pace of oncology practice, essential details in PET scan reports, such as the radiotracer used and the clinical indication for a scan, may be overlooked by providers. Addressing this, we investigated the potential benefits of enhancing report clarity by including radiotracer information in the impression section of PET reports.

METHODS

Online surveys were sent to physicians and advanced practice providers across various medical and surgical specialties. An initial 15-question survey explored respondents' current PET report reading practices and opinions on the need for clarity improvement. Subsequently, a revised PET scan impression template was implemented, so that all reports would include a line in the impression stating the radiotracer used and the common clinical indications of this tracer (e.g. *This scan utilized a Ga-68 PSMA tracer, typically used for evaluating prostate cancer*). A follow-up survey assessed provider opinions on the utility of this new format.

RESULTS

Sixty-five providers participated in the initial survey and 23 in the follow-up. In the initial survey, a majority (58%) of participants emphasized the impression as the most important part of a PET report, with 38% "often" or "always" reading only the impression section. Simultaneously, more than half of respondents found it at least "sometimes" challenging to identify the radiotracer used in a scan or the clinical indication for the radiotracers used. Subsequently, only 32% of providers were at least "somewhat confident" in interpreting the findings of non-FDG PET scans, compared to the 67% who were at least "somewhat confident" in interpreting FDG-PETs. After introducing the new PET report template, a follow-up survey found that the addition of this new line in the impression improved physicians' ease of reading reports— 39% of respondents "strongly agreed" that it would reduce reading time, and 48% "strongly agreed" that it would improve report clarity and clinical utility. Overall, 73% anticipated that this change would increase their confidence in interpreting PET reports.

CONCLUSIONS

Our survey responses emphasize the need for improvements in the accessibility of radiotracer and clinical indication information. They support the inclusion of this information in the impression of PET reports, streamlining reading and improving the utility of PET reports for providers. Further education among oncology-associated specialties regarding novel PET tracers and their indications is an important next step.

ABSTRACT ID 28618



O-10

Demystifying DIPNECH: Initial Findings from a New Longitudinal Patient Registry

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BACKGROUND

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) was first characterized in 1992 with an initial case series describing 6 patients with neuroendocrine cell hyperplasia, with cough and dyspnea symptoms. Since that time, DIPNECH has remained a poorly understood and understudied entity with the largest series reporting 61 patients. Based on the prevalence of DIPNECH at our institution, we believe it may be more common than recognized. We therefore sought to further characterize this syndrome in a new longitudinal registry.

METHODS

We identified adult patients with confirmed DIPNECH under IRB approval at Vanderbilt-Ingram Cancer Center. Variables including demographics, symptom evolution, pathologic diagnosis, radiographic characteristics, treatment history, and outcomes were collected within a RedCAP database. Data analysis was conducted using R. Exploratory endpoints include correlation of baseline molecular biomarkers with clinical outcomes. Analysis of study objectives will be descriptive and hypothesis generating.

RESULTS

Sixty-one patients were identified, all female and a majority (77%) never smokers. Median age at symptom onset and diagnosis were 56 (44,64) and 61 (52,67) respectively. Prior to diagnosis, 82% of patients reported chronic cough, 48% dyspnea, 9.8% chest pain, 3.3% hemoptysis, and 1.6% recurrent pneumonia. No symptoms were reported in 6.6% of patients. Patients received many diagnoses before DIPNECH, including GERD (49%), asthma (41%), COPD (8.2%), and ILD (4.9%).

Imaging studies included CT (98%), 68-Ga or 64-Cu DOTATATE PET (61%), fluorodeoxyglucose-18 (FDG) PET (20%), and indium-111 (111-In) pentetate (6.6%). CT findings included mosaic attenuation (59%), multiple pulmonary nodules (90%), airway wall thickening (9.8%), and bronchiectasis (3.3%). On DOTATATE PET, 44% demonstrated avid disease, 7.7% mixed, and 49% no avidity.

Concurrent lung neuroendocrine tumors (Lu-NETs) were identified alongside DIPNECH in 70% of patients, with 86% typical carcinoids. More than half (58%) of these patients had multiple identified Lu-NETs.

Post-diagnosis, 48% were treated with somatostatin analogs (SSA), 38% observation alone, and 8.2% systemic steroids. Spirometry at diagnosis was restrictive in 24%, obstructive in 43%, and normal in 32%. After SSA, 71% of patients reported improvement in cough and 70% improvement in dyspnea.

There was no significant difference in post-treatment spirometry findings. Only one patient had died at time of submission, with a minimal median survival time of 8 years.

CONCLUSIONS

These findings highlight the indolent natural history of DIPNECH and the clinical challenges associated with its diagnosis. Similar to prior series, this registry suggests modest improvement in pulmonary symptoms with SSA treatment. DIPNECH remains a poorly understood diagnosis, and this registry will be expanded with other centers to better characterize disease burden and outcomes.

ABSTRACT ID 28666



O-11

Health-related quality of life issues in patients with non-metastatic neuroendocrine neoplasms persist after treatment

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BACKGROUND

Little is known about the prevalence of long-term symptoms for patients with a history of neuroendocrine neoplasms (NENs) following completion of their primary cancer treatment. We sought to understand the health-related quality of life (HRQOL) of patients with NENs after receiving treatment with curative intent in the Gastrointestinal Survivorship Clinic (GISC) at the University of California, San Francisco (UCSF).

METHODS

Self-reported HRQOL measures were obtained from the National Comprehensive Cancer Network (NCCN) Survivorship Assessment Questionnaire, which includes domains focused on fatigue, depression and anxiety, pain, sexual function, sleep, mental focus, exercise, and bowel function. Patients completed the questionnaire every 3 to 6 months prior to each appointment in the UCSF GISC. Responses to questions were either yes/no or rated on a scale from 0 to 10, with a score of 10 being the worst. Fatigue, anxiety, and pain were evaluated independently over time and compared by gender, age (<50, ≥50), and exercise frequency (<150 min/week, >150 min/week). Associations between patient characteristics and HRQOL were tested using linear mixed models fit to repeated measures within the patient, and by Pearson Chi-squared and Kruskal-Wallis tests at initial visit.

RESULTS

A total of 82 patients (48 women and 34 men) completed 312 NCCN questionnaires from 2016 to 2024. All patients were diagnosed with a localized neuroendocrine neoplasm and were undergoing surveillance after treatment. 32% of patients had a pancreatic primary. 33% of patients identified as non-White, 67% White and 99% were English speaking. At baseline visit, 35% of patients reported fatigue (mean score 3.2), 28% reported pain (mean score 1.7), 44% reported sleep problems, 18% reported anxiety (mean score 2.8), and 57% reported exercising >150 min per week. Over subsequent visits, women experienced worse fatigue ($p=0.007$), anxiety ($p=0.023$), and pain ($p=0.019$) compared to men. By age, there was no difference in fatigue and anxiety, however patients age<50 reported worse pain ($p=0.011$). Patients who reported exercising >150 min/week reported better fatigue ($p=0.001$), anxiety ($p=0.029$), and pain ($p=0.011$).

CONCLUSIONS

Despite completing their primary cancer treatment, patients with NENs continued to report ongoing HRQOL issues which persisted over time. Fatigue, anxiety, and pain were worse in women, but reported better in those who exercised. These findings support the importance of multidisciplinary survivorship care with a focus on lifestyle interventions. Identifying those patients with the greatest need will aid in resource allocation.

ABSTRACT ID 28671

O-12

The diagnostic accuracy of vasoactive intestinal peptide (VIP) for VIPoma

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BACKGROUND

VIPoma is a challenging diagnosis and depends on clinical variables, VIP concentrations, and advanced imaging. While VIP concentrations are commonly elevated in VIPoma, the optimal threshold for screening/ diagnostic purposes is not well defined. We aimed to study this in a single institution population.

METHODS

We obtained results from VIP test orders from 2011-2023 and reviewed the medical record for patients who had concentrations greater than the established reference limit of 75 pg/mL. We assessed the reason for VIP testing and for the presence of a VIPoma. Medical conditions previously reported to result in elevated VIP concentrations were also collected (small bowel resection, inflammatory bowel disease, and CKD).

We compared VIP concentrations between patients who did vs those who did not have a VIPoma (student's t-test with unequal variance) along with the medical conditions listed above. We then completed a binomial logistic regression analysis to determine the optimal threshold for VIP concentrations to predict a VIPoma. Once this was determined, we calculated the odds ratio of diagnosing a VIPoma at differing VIP thresholds.

RESULTS

76 patients met the selection criteria for elevated VIP concentration. Of these, twelve cases of VIPoma were diagnosed. All patients had chronic diarrhea and six of the patients had a previous diagnosis of a pancreatic neuroendocrine tumor that was being monitored for functional status. VIP concentrations were drawn for acute or episodic diarrhea along with flushing/ diaphoresis. However, VIPoma was not diagnosed in these clinical scenarios.

While the mean VIP concentration was increased in patients with a VIPoma relative to those without, the difference was not statistically significant for this dataset (433 pg/mL vs 224 pg/mL, p value=0.39). Our binomial regression analysis had an area under the curve (AUC) of 0.833 for an elevated VIP concentration to predict a VIPoma. When including the clinical indication for testing, the AUC increased to 0.875. The optimal VIP threshold was 211 pg/mL (OR 6.9, pval=0.02). Using the threshold of 75 pg/mL for an elevated VIP, the positive predictive value for a VIPoma was 0.16.

CONCLUSIONS

VIP concentrations are integral to the diagnosis of a VIPoma. However, elevated VIP concentrations are not specific for a VIPoma and most patients with an elevated VIP concentration do not have a VIPoma. We recommend that VIP only be drawn in certain clinical scenarios, such as chronic diarrhea and monitoring known neuroendocrine tumors, to avoid unnecessary medical investigations.

ABSTRACT ID 28684

O-13

Prevalence of CHIP Mutations in patients with Neuroendocrine Tumors and Role in Predicting Hematologic Toxicity to PRRT and Chemotherapy

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BACKGROUND

In our previous work, we found hematological toxicities from PRRT occur in those with clonal hematopoiesis of indeterminate potential (CHIP) mutations. CHIP mutations carry a formidable risk of progressing to myeloid neoplasia, particularly in cases featuring high-risk mutations. Supported by the NANETS grant, we sought to validate these findings in a larger, independent cohort of neuroendocrine tumors (NETs). We plan future analyses to correlate these findings with treatment options impacting hematopoiesis. Here, we present the molecular signature results prior to chemotherapy and PRRT exposure.

METHODS

Following IRB approval from both institutions, peripheral blood samples from treatment-naïve NET patients were submitted for CHIP mutation analysis. We utilized a 63-gene myeloid NGS panel and used a 2% VAF cutoff to identify CHIP. Extracted DNA was sequenced using anchored Multiplex PCR and Illumina technology, achieving >500X coverage and >98% of targeted regions showing >100X coverage. In future analyses, and with established access to longitudinal samples, we plan to calculate risk stratification scores to predict the risk of hematologic toxicities in these patients.

RESULTS

Here, we present the descriptive statistics of the treatment-naïve NET patients. A total of 102 patients were included in our study. The median age of the cohort was 60.5 years (range: 20–81), with 49 participants (48.04%) being female. Twenty-three (22.5%) patients harbored CHIP mutations (Table). The median age of CHIP+ patients was 65 years vs CHIP negative patients median age was 59 years; $p=0.0151$. Notably, 9/23 (39%) patients had baseline cytopenias. DNMT3A and TET2 were the most commonly mutated genes. Notably, mutations in high-risk genes [PPM1D (n=3), SF3B1 (n=2), JAK2 (n=1), TP53 (n=1), SF3B1 (n=2); Table] were observed in patients with no prior therapy exposure. Sixteen patients harbored multiple mutations.

Table: Common mutations in NET patients at baseline:

Total Patients with CHIP Mutations (N=23) and Total Unique Mutations (n=32)	
Standard Risk Mutations (N=23)	
DNMT3A	13
TET2	3
Others	7
High Risk Mutations (N=9)	
PPM1D	3
SF3B1	2
MPL	2
TP53	1
JAK2	1

CONCLUSIONS

The high baseline prevalence of high-risk CHIP mutations, which significantly elevate the risk of progressing to overt myeloid neoplasms, along with baseline cytopenia and the presence of multiple mutations in several patients, is concerning. The analysis is currently ongoing, and we will soon include post-treatment data to investigate the correlation between baseline CHIP mutations and the development of hematologic toxicities, bringing us a step closer to developing a risk prediction score for hematologic toxicity.

ABSTRACT ID 28694



O-14

Racial Inequities in Neuroendocrine Tumor Clinical Trial Enrollment in the United States

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BACKGROUND

The incidence of neuroendocrine tumors (NETs) continues to rise. Despite several therapeutic advances, racial inequities in outcomes among patients with NETs remain prevalent. We sought to investigate racial inequities in clinical trial enrolment in NET therapeutic clinical trials in the US.

METHODS

We extracted data from clinicaltrials.gov in July 2024 for all completed U.S.-based interventional clinical trials including patients with "neuroendocrine tumors". Only trials with race distribution in the database or in published reports were included. We extracted data on racial distribution of participants and compared them with the prevalence of NETs in respective categories of race using data from Surveillance, Epidemiology, and End Results (SEER; SEER 18 and SEER-Medicare) database. We then captured additional data related to the clinical trials such as site (single or multi-center), funding source (academic, National Cancer Institute (NCI) or industry), phase (1, 2 or 3), and number of participants.

RESULTS

A total of 88 NET therapeutic clinical trials were identified, of which, only 37 (42.5%) clinical trials reported breakdown of participants by race. A total of 2,101 trial participants across these 37 clinical trials were included in the analysis, of which majority were White (1772/2101, 84.3%), followed by other races (201/2101, 9.6%) and Black patients (128/2101, 6.1%). Black patients were significantly under-represented in clinical trials ($p < 0.01$, 6.1% v. 13.0%), compared to the 2018 SEER prevalence data. White patients were not found to be significantly over- or under-represented in clinical trials ($p = 0.11$, 84.3% v. 83.0%). On average, Black patients had higher rates of enrollment in academic (12.5%) and NCI-funded (26.6%) trials compared to other races (4.5% and 13.9%) and White (5.9% and 16.3%) patients ($p < 0.01$). Rates of enrollment in industry-funded trials were lowest for Black patients (60.9%) compared to other races (81.6%) and White (78.6%) patients ($p < 0.01$). Black patients were more likely to be represented in phase 2 clinical trials compared to phase 1 or 3 trials ($p < 0.01$) and on trials commenced after 2012 as opposed to those commenced before 2012 ($p < 0.01$).

CONCLUSIONS

Our analysis highlights that about 60% of NET therapeutic clinical trials in the US do not report a racial breakdown of participants. Black patients were significantly under-represented in NET clinical trials. Factors such as funding source, phase and year of trial commencement were notably associated with representation of Black patients. Our findings underscore the critical need to diversify clinical trial participation for patients with NETs in the US.

ABSTRACT ID 28695



O-15

Characterization of the Genomic and Immune Landscapes of 88 Cases of Pheochromocytomas and Paragangliomas: Implications for Development of Targeted Therapeutics

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BACKGROUND

Pheochromocytomas and paragangliomas (PCC/PGL) are rare neuroendocrine neoplasms (NENs) arising from the neural crest tissue. Evolution in the understanding of the biology of these tumors has revealed distinct molecular subtypes with therapeutic and prognostic implications. Due to the rarity of PCC/PGL, however, large-scale studies that integrate the transcriptomic and genomic data with the immune landscape are lacking. Herein, we identified the genomic and immune landscape of PCC/PGL and draw a comparison with other NENs.

METHODS

NENs (non-PCC/PGL: n=4105) and PCC/PGL (n=88) that underwent molecular profiling at Caris Life Sciences (Phoenix, AZ) were included. Tumor microenvironment (TME) composition was estimated using the quanTIseq method on bulk RNA sequencing data. Fishers Exact and Chi-squared tests were used to ascertain statistical significance with the Benjamini–Hochberg method used to correct for multiple comparisons ($q < 0.05$).

RESULTS

Among PCC/PGL, the most common genetic alterations were succinate dehydrogenase subunit B (SDHB) mutations (22.1%), followed by NF1 (11.8%), ATRX (9.9%), SDHD (6.9%) and RET (4.7%) mutations. We identified potentially targetable mutations (RET, FGFR1 and VHL) in 10.3% of patients (10/88). Of the 40 patients with available transcriptomic data, potentially targetable alterations (RET, CREM, NUMA1 and NTRK fusions) were identified in 4 patients (10%). PCC/PGL had significantly higher prevalence of SDHB (22.1% vs 0.27%), ATRX (9.9% vs 3.3%) and VHL (2.3% vs 0.4%) mutations, ARID1A deletions (3.5% vs 0.2%) and RET fusions (2.5% vs 0.2%) compared to other NENs (all $q < 0.05$). Additionally, we noted a higher prevalence of SMO, CSF1R, PDGFRB, AURKB, SMARCB1, MEN1 and NFKB2 amplifications among PCC/PGL (all $q < 0.05$). High tumor mutational burden (>10 mut/Mb) was more prevalent among other NENs compared to PCC/PGL (10.5% vs 1.1%, $q = 0.02$). M2 Macrophages (6.6% vs 3.5%) and B-cells (6.5% vs 4.6%) were enriched while neutrophils (0.9% vs 2.9%) and T-regulatory cells (0.9% vs 1.5%) were lower in PCC/PGL compared to other NEN tumors (all $q < 0.05$).

CONCLUSIONS

Comprehensive analysis of the genomic and immune landscape of PCC/PGL shows distinct differences from that of other NENs. We also noted distinct molecular and tumor immune cell microenvironment features between PCC/PGL and other NENs. These findings extend our understanding of the biology of PCC/PGL and merit further investigation for potential therapeutic and prognostic implications.

ABSTRACT ID 28697



T-1

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

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BACKGROUND

Neuroendocrine tumors (NETs; ~2% of all malignancies) commonly arise from the gastrointestinal (GI) tract, pancreas, and lung, often presenting as metastatic disease. The PI3K/Akt/mTOR pathway is implicated in the pathogenesis and progression of NETs. Everolimus, an oral mTOR inhibitor (mTORi), is an option for treatment of NETs of the GI tract, lung, or pancreas, but response rates observed in the RADIANT-3 and -4 studies were modest at 4–10%. *nab*-Sirolimus, an intravenous nanoparticle albumin-bound mTOR inhibitor (mTORi), is approved in the US for adults with advanced malignant perivascular epithelioid cell tumors based on a 39% response rate. Preclinical data demonstrated improved tumor accumulation, mTOR target inhibition, and tumor growth suppression of *nab*-sirolimus versus other mTORis. This study will evaluate efficacy and safety of *nab*-sirolimus in patients with advanced or metastatic NETs.

METHODS

This phase 2, multicenter, open-label, single-arm clinical study (NCT05997056) will enroll ~21 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 systemic therapy other than somatostatin analogs (SSTa). Patients with functional NETs are eligible if they have been on a stable dose of SSTa for ≥12 weeks and had disease progression during SSTa treatment. Eligible patients must have ≥1 measurable target lesion (per Response Evaluation Criteria in Solid Tumors [RECIST] v1.1), Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate organ function/hematologic parameters. Patients who have received a prior mTORi, including *nab*-sirolimus, or have tumors with known inactivating *TSC1* or *TSC2* alterations will be excluded. Patients will receive *nab*-sirolimus 100 mg/m² by intravenous infusion on days 1 and 8 of a 21-day cycle (Simon's 2-stage design). Treatment will continue until disease progression, unacceptable toxicity, or discontinuation based on investigator or patient discretion. The primary endpoint is investigator-assessed overall response rate per RECIST v1.1. Secondary endpoints include duration of response, disease control rate, time to response, progression-free survival, overall survival, and safety. Exploratory endpoints include correlation of baseline molecular biomarkers with clinical outcomes. Stage 1 enrollment will enroll 12 patients. If ≥1 response is achieved in Stage 1, the trial will continue with Stage 2 of enrollment.

RESULTS

To date, 9 patients have been enrolled in Stage 1 and ≥ 1 response has been achieved..

CONCLUSIONS

Stage 1 of enrollment is currently open. The criterion has been met for continuing to Stage 2 of enrollment.

ABSTRACT ID 28543



T-2

KinLET: Phase I Trial for Dose Determination and Pharmacokinetics Evaluation of [177Lu]Lu-edotreotide Radiopharmaceutical Therapy in Pediatric Participants with SSTR+ Tumors

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BACKGROUND

Current therapy options for pediatric patients with SSTR-positive solid tumors/lymphoma are limited. Considering the rarity of SSTR-positive tumors in the pediatric population, a broad patient screening effort is critical for this trial. Target tumors include neuroendocrine tumors, central nervous system tumors, lymphoma, peripheral primitive neuroectodermal tumors (Ewing family sarcomas), gastrointestinal sarcoma, or rhabdomyosarcoma.

METHODS

KinLET is a phase I, multicenter, open-label, interventional trial that aims to determine the appropriate pediatric dosage based on the safety profile and evaluate pharmacokinetics of [177Lu]Lu-edotreotide in pediatric participants with recurrent, progressive, or refractory SSTR-positive solid tumors and lymphoma. Furthermore, the anti-tumor activity by tumor type will be preliminarily assessed using the parameters objective response rate, overall survival, progression-free survival, and duration of response. The correlation between immunohistochemical SSTR expression and functional imaging will be determined. In addition, the safety of [177Lu]Lu-edotreotide RPT as monotherapy or following sequential standard of care will be evaluated and a quality-of-life evaluation will take place. At least 20 pediatric participants (≥2 to <18 years old) will be included in three sequential age cohorts.

Sequential Age Cohorts and Dose of [177Lu]Lu-edotreotide

	Cohort 1	Cohort 2	Cohort 3
Age	≥12 - <18 years	≥6 - <12 years	≥2 - <6 years
Number of participants*	≥6	≥6	≥6
Starting dose**	100 MBq/kg, at maximum 7.5 GBq	Based on at least cycle 1 data from 4 participants of Cohort 1***	Based on at least cycle 1 data from 4 participants of Cohort 2***

*Total ≥20 eligible participants; ≥6 of them with gastroenteropancreatic neuroendocrine tumors

**Dosing within each cohort based on at least cycle-1 data from 2 participants

***Decision by Data Monitoring Committee

Treatment will consist of two to six cycles of intravenous infusion of [¹⁷⁷Lu]Lu-EDOT (EDOT = edotreotide) at eight-week (± 2 w) intervals. For kidney protection, an arginine-lysine solution will be co-infused. Dosimetry assessments, based on SPECT/CT, whole-body planar imaging and blood radioactivity PK measurements will be assessed at several time points post [¹⁷⁷Lu]Lu-EDOT infusion.

For all cycles, the median kidney absorbed dose may not exceed 23 Gy and the median bone marrow dose should remain below 2 Gy. Cycles can be delayed for recovery from dose-modifying toxicity. Follow-up will consist of two years of monitoring for progression-free survival and an additional simplified follow-up for three years.

RESULTS

NA

CONCLUSIONS

Trial in progress, Clinical Trial Information: NCT06441331

ABSTRACT ID 28557

T-3

Phase 2 Dose Optimization Trial of Everolimus post Bland Hepatic Artery Embolization (Evero-Embo) in patients with Neuroendocrine Tumors.

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BACKGROUND

NETs are the second most common GI malignancy in the U.S., with an estimated prevalence of >170,000. Hepatic metastases are common with the 5-year overall survival < 25%. Treatment options include surgical resection and liver-directed therapies including hepatic artery embolization (HAE). Everolimus is approved for treating progressive NETs. The concurrent use of everolimus with HAE was previously reported NANETS 2021, C-41 [Gupta et al]. An analysis of 96 evero-embos was performed in 51 patients, 30/51 patients had 24 or more months of follow-up post-procedure. The median hPFS was 3.43 years with 95% confidence interval (2.85, 4.31 years). This compares to the literature median hPFS of 1.25 years for the HAE alone group in 155 patients reported [Chen et al].

METHODS

The primary objective is to determine whether the post-HAE optimal everolimus dose is 50% of the pre-HAE dose. This phase 2 open-label trial will include 9-12 well-differentiated, low-to-intermediate grade liver dominant NET patients who can tolerate an everolimus dose of at least 5 mg daily for a minimum of 5 days (to ensure steady-state levels) prior to bland HAE. Pre-HAE everolimus blood levels will be obtained prior to the procedure. Everolimus will resume at 48 hours post-procedure at 50% of the pre-procedure dose and continue for 30 days. Everolimus blood levels will be repeated between D7-D14. Subjects who cannot tolerate 50% everolimus dose reduction will be replaced. A QOL hepatobiliary cancers (FACT-Hep) survey will be done during pre-procedure and each clinic visit.

RESULTS

Pre- and post-procedure everolimus blood concentrations will be compared using a pairwise t-test. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting.

CONCLUSIONS

The expected outcome is that patients will be able to tolerate half the pre-procedural everolimus dose for at least 30 days based on institutional experience. The optimal post-bland HAE everolimus dosing is expected to be at least 5 mg every other day. Once the post-HAE everolimus dosing has been identified, a Phase III clinical trial comparing the evero-embo optimized dosing regimen to the superior treatment arm (bland vs TACE) identified in the RETNET clinical trial [Soulén et al] is feasible.

ABSTRACT ID 28610

T-4

Lipiodol Deposition in NET Liver Metastases during TACE using Pressure-Enabled versus Endhole Catheters: Pilot Data from a Randomized, Internally-Controlled Trial

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BACKGROUND

Intratumoral lipiodol deposition during transarterial chemoembolization (TACE) is an imaging biomarker for response and survival in hepatocellular carcinoma. Improving delivery of liquid therapeutics during TACE may also help improve neuroendocrine tumors (NETs) outcomes. Pressure-enabled delivery catheters (PED) overcome the high resistance and interstitial pressure within the tumor microvasculature compared to endhole catheters (EH). PED have been shown to increase deposition of solid particles in tumors. Enhanced delivery of a liquid agent such as emulsified lipiodol in TACE has yet to be investigated.

METHODS

Single-center, randomized, internally controlled comparison of endhole versus PED catheter for TACE of NET liver metastases. Patients with bilobar metastases planned for staged TACE were eligible starting February 2024. Patients were randomized for which catheter would be used for their first TACE, with the other catheter used in the second TACE. Pre-embolization CTA of the treated distribution was performed to delineate tumors. After TACE, a dual energy CT scan was performed at tube voltage 100/Sn150 kVp, and reconstructions of 40, 70, and 190 keV virtual mono-energetic images and iodine maps were created. Lipiodol deposition in tumors was analyzed using iodine maps.

		PED	Endhole
# of tumors treated		10	9
Mean diameter (cm)		3.5	3.2
Mean (max) iodine deposition density	Overall	84 (404)	94 (536)
	Patient 1	39 (126)	35 (94)
	Patient 2	39 (126)	86 (297)
	Patient 5	192 (890)	111 (768)

RESULTS

Five patients are enrolled and three have completed bilobar TACE. Ten lesions were treated with PED and 9 with EH among 6 chemoembolizations in the completed patients. All patients had bowel NETs (2 jejunum, 1 rectal) with Ki-67 of <2%, 5%, and 26%. Mean tumor diameter was 3.5cm (range 1.3-5.4cm) in PED and 3.2cm (1.2-5.8cm) in EH ($p=0.64$). Mean density of lipiodol deposited per PED-tumor was 84 mg/cm³ versus 94 mg/cm³ in EH-tumors ($p=0.71$). When assessing with intra-patient control (PED to EH for each patient), the patient with hypervascular tumors on CTA (Patient 5) showed greater lipiodol deposition with PED, whereas patients 1 and 2 with tumor enhancement similar or less than background liver showed equivalent and decreased lipiodol tumor deposition with PED, respectively. No difference in adverse events was observed between catheters

CONCLUSIONS

Pilot data show no difference in lipiodol deposition from TACE in NET liver metastases when treated with PED or EH catheter when assessed on a per-tumor basis. Inpatient analysis suggests a difference that may relate to underlying vascularity of metastases.

ABSTRACT ID 28621



T-5

Can NK1 antagonists and COX-2 inhibitors improve same-day discharge rates following chemoembolization?

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BACKGROUND

Observation after 40% of chemoembolization procedures, which places a burden on patients and families and adds to institutional costs for care. Standard pre-medications include corticosteroids, diphenhydramine, a 5-HT3 antagonist such as ondansetron as well as intra- and post-operative narcotics for pain control. Recent NCCN and ASCO guidelines for highly emetogenic therapies add a neurokinin receptor antagonist (e.g., fosprepitant), but these drugs are expensive. Additionally, recent trials have shown that pre-medication with a COX-2 inhibitor reduces post-operative pain scores and narcotic requirements. We investigated whether adding IV fosprepitant and ketorolac as pre-medications for liver embolization would improve same-day discharge rates without increasing the rate of unscheduled return visits, and if the resultant savings would offset the drug cost.

METHODS

Patient variables included tumor burden, amount of liver embolized, embolization of the gallbladder, chemoembolic dose, and particle size. Outcomes included need for pre-discharge narcotics and anti-emetics, same-day discharge, and unscheduled return visits. Data were collected on patients treated since January 2023, with the new premedication regimen instituted in 2024.

RESULTS

294 chemoembolizations were performed from Jan 2023 to the present. To date, 44 procedures have been analyzed, 18 with the new pre-medication scheme. 29 were segmental and 15 were lobar chemoembolizations using 100-300 micron microspheres, almost all had tumor burden < 25%.

Prophylaxis	Standard	NK-1 + COX-2
N	26	18
Post-op narcotics	13 (50%)	6 (33%)
Post-op antiemetics	11 (46%)	5 (28%)
Same day discharge	16 (62%)	17 (94%)
7-day return	0	0

CONCLUSIONS

These preliminary data suggests that pre-medication with a NK1 antagonist and a COX-2 inhibitor reduces the severity of post-embolization syndrome and substantially increases same-day discharge rates. Analysis of the full cohort will provide robust statistical power and a cost comparison between the two strategies.

ABSTRACT ID 28645



T-6

DAREON™-7: Phase 1 trial of BI 764532 (a delta-like ligand 3 [DLL3]-targeting T-cell engager) plus chemotherapy for DLL3+ neuroendocrine carcinomas

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BACKGROUND

Neuroendocrine carcinomas (NECs) have limited treatment options. Delta-like ligand 3 (DLL3) is highly expressed in NECs and is a promising treatment target. In an ongoing phase 1 trial (NCT04429087), BI 764532, a DLL3/CD3 immunoglobulin G (IgG)-like T-cell engager, was tolerable with promising activity in patients with DLL3-positive (+) tumors, including those with NECs. DAREON™-7 (NCT06132113) is a phase 1, open-label, dose-escalation (Part A) and dose-expansion (Part B) trial that aims to determine the maximum-tolerated dose (MTD), the recommended dose for expansion (RDE)/recommended phase 2 dose (RP2D), and the safety and efficacy of BI 764532 in combination with platinum and etoposide in patients with DLL3+ NEC.

METHODS

Part A: ~25 patients will receive intravenous BI 764532 (target dose after step-in dosing) plus carboplatin/etoposide until progression per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, intolerable toxicity, or for a maximum of 36 months. BI 764532 dose escalation will be guided by a Bayesian logistic regression model with overdose control. Part B: 2 cohorts (~15 patients each) will receive BI 764532 at RDE/RP2D + carboplatin/etoposide or cisplatin/etoposide (carboplatin/etoposide or cisplatin/etoposide are the most-used standard of care [SOC] regimens). Key inclusion criteria: Patients must have no prior systemic treatment for DLL3+ locally advanced or metastatic NEC (extrapulmonary or unknown primary) or large-cell NEC of the lung except for 1 cycle of standard platinum/etoposide regimen as first-line treatment prior to entering the treatment period of the trial; patients with localized NEC or resectable disease who received prior adjuvant therapy can participate in the trial if they experienced a treatment-free interval of >6 months prior to the diagnosis of metastatic disease; and patients must have at least 1 measurable lesion as defined per RECIST v1.1. Patients must be adequate candidates to receive platinum/etoposide as the SOC treatment.

Primary endpoints: Occurrence of dose-limiting toxicities (DLTs) in the MTD evaluation (Part A) and on-treatment (Part B) periods. Secondary endpoints: Occurrence of DLTs and adverse events during the on-treatment period (Part B), and efficacy measured by objective response and duration of response (Part B).

RESULTS

DAREON™-7 is currently enrolling.

CONCLUSIONS

Not applicable—the trial is currently in progress.

ABSTRACT ID 28655



T-7

Surgical Debulking Prior to Peptide Receptor Radionuclide Therapy in Patients with Well-Differentiated Gastroenteropancreatic Neuroendocrine Tumors

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BACKGROUND

Gastroenteropancreatic Neuroendocrine Tumors (GEPNETs) are among the most prevalent NETs in the US, with metastatic involvement in 50-75% of the cases. Liver failure secondary to metastatic disease is the leading cause of death in patients with GEPNETs. Although Peptide Receptor Radionuclide Therapy (PRRT) with ¹⁷⁷Lu-DOTATATE has become a transformative therapy for patients with GEPNETs, the cytoreductive potential of the treatment is modest. The post-hoc analysis from the NETTER-1 study identified a subset of patients with GEPNETs with one or more tumors >3 cm reduced progression-free survival (PFS). Surgical debulking is an established treatment for patients with metastatic GEPNETs with hepatic involvement with some series showing improved survival. However, complete surgical debulking is not always technically feasible. This pilot study aims to assess the feasibility and clinical impact of surgical debulking of tumors >3 cm prior to PRRT with ¹⁷⁷Lu-DOTATATE in patients with GEPNETs. Additionally, we will explore mechanistic impact of surgical debulking in changes in somatostatin receptor 2 (SSTR2) expression based on ⁶⁴Cu-DOTATATE PET/CT.

METHODS

This is a single institution pilot study to assess the objective response rate of the combination of standard of care treatment in GEPNET by first surgical debulking of tumors >3 cm followed by PRRT with ¹⁷⁷Lu-DOTATATE within 90 days of surgery. The study will enroll six patients with metastatic well-differentiated, grade 1-2 GEPNETs with adequate SSTR avidity defined as \geq liver SSTR uptake confirmed on a ⁶⁴Cu DOTATATE PET/CT. Only patients with hepatic metastases, and at least one large tumor >3 cm which is accessible for surgical resection, will be enrolled. All patients will be reviewed for study candidacy at a multidisciplinary neuroendocrine tumor board. Following surgery, patients will undergo a ⁶⁴Cu DOTATATE PET/CT within 12 weeks. All patients will then receive standard treatment with up to 4 cycles of ¹⁷⁷Lu-DOTATATE. The primary objective is to measure objective response rate of a combination of surgical debulking followed by PRRT. The secondary objective is to assess the radiomic profile including SSTR standardized uptake values of large (>3 cm) and non-large (<3 cm) tumors.

RESULTS

This study is open and enrolling

CONCLUSIONS

Trial in progress.

ABSTRACT ID 28685



T-8

Trial in Progress- Genetic Predisposition Testing Program for Pancreatic Neuroendocrine Neoplasms (PanNENs)

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BACKGROUND

The incidence of PanNENs is rising and varies by race/ethnicity, but the impact of genetic predisposition has not been fully elucidated. Preliminary studies suggest 17% of patients with well-differentiated pancreatic tumors harbor pathogenic germline alterations. Despite this, reflex germline testing is not routine. The consequences of a positive test remain controversial and the impact of patient and tumor characteristics is uncertain. This pilot study aims to further explore the rates of germline mutations in a diverse population of patients with PanNENs.

METHODS

This ongoing prospective multicenter study (IRB#22-37899) involves University of California medical centers in San Francisco (UCSF), Los Angeles (UCLA), and San Diego (UCSD) which serve a diverse (majority minority) population in the state; 300 evaluable patients will be enrolled (N=100 each center). Eligibility includes age ≥18, histologically/cytologically confirmed PanNEN, regardless of family history or prior germline testing, histologic grade, or stage. Exclusions include a primary language unsupported by our genetics department, active hematologic malignancy, or history of allogeneic bone marrow or stem cell transplant. UCSF Expanded Hereditary Cancer Panel is offered to those without prior large panel (N ≥80 genes) germline testing. Primary endpoint is rate of pathogenic/likely pathogenic germline mutations (PGM) in PanNENs. Secondary endpoints include: 1) Rates of different PGM overall and by race/ethnicity and other clinical variables (age, stage, grade, sex, campus); 2) Rates of different variants of unknown significance (VUS), overall and by race/ethnicity and other clinical variables; 3) Rate of declination for patients offered testing; 4) Rate of completion of testing for those who agree to testing. Exploratory endpoints include assessing the relationship between PGM/ somatic mutations and the consequences of a PGM (e.g. second cancers, cascade testing in family members).

RESULTS

Enrollment is complete at UCSF (4/2023-6/2024) and ongoing at the other centers. UCSF includes 102 patients, median age 52.5 years, 50% female, 65% non-Hispanic ethnicity, 64% White, 22% Asian, and 17% other race/unknown. Prior testing had been performed in 67% (68/102): 83% (57/68) with a large panel, thus 44% (45/102) were offered prospective testing

CONCLUSIONS

The impact of, race, ethnicity and sex on the rates of germline pathogenicity in panNENs is largely unknown. This ongoing multicenter pilot study aims to examine the rates of PGM and VUS in a diverse population of patients with PanNENs, while also exploring the attitudes of patients about genetic testing, and the consequences of a positive test.

ABSTRACT ID 28698

