A phase II/III randomized double-blind study of octreotide acetate LAR with axitinib versus octreotide acetate LAR with placebo in patients with advanced G1-G2 NETs of non-pancreatic origin (AXINET trial-GETNE-1107).

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Background: Angiogenesis plays an important role in NET development and progression. Axitinib is a potent and selective VEGFR-1,2,3 inhibitor, with proven activity against several vascular-dependent solid tumors. The aim of this randomized, double-blind phase II/III study was to assess the efficacy of axitinib in patients with advanced G1-2 extra-pancreatic NETs. **Methods:** Eligible pts were randomized (1:1) to receive octreotide LAR (30 mg IM q4w) with axitinib (5 mg BID) or placebo BID until disease progression or unacceptable toxicity. Pteswere stratified by time from diagnosis to study entry (> or < 12m), primary tumor site (GI tract vs non-GI) and Ki-67 index (< 5% vs > 5%). Prior therapy with SSA, IFN and up to 2 lines of systemic treatment was allowed, but not prior VEGF- or VEGFR-targeted drugs. Clinical and/or radiological disease progression within 12 months prior to study entry was required. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), time to progression, overall response rate (ORR), duration of response, biochemical response and safety. **Results:** 256 pts were randomized (106 in the Phase II part, and 150 additional pts in the Phase III part), 126 to axitinib and 130 to placebo. The main characteristics of the study population were: median age 61 years (range: 21-85), 52% male, PS 0-1 (64-35%), G1-2 (29%-71%), primary tumor site GI (40%)-Lung (17%)-Other (32%). Prior therapies included: SSA (46%), everolimus (13%), chemotherapy (13%), TACE (5%) and PRRT (2%). ORR was significantly higher in axitinib- vs placebo-treated patients (17.5% vs 3.8%, p = 0.0004). PFS per investigator assessment also favored axitinib vs placebo-treated patients, although the difference did not reach statistical significance (median PFS 17.2 vs 12.3 months, respectively, HR 0.816, p = 0.169). Grade 3-4 treatment-related AEs occurred more frequently in the axitinib vs placebo arm (52% vs 13.8%), and included hypertension (21% vs 6 %), cardiac disorders (3.2% vs 0.7%), diarrhoea (13% vs 1.5 %), asthenia (9% vs 3%) and nausea&-vomiting (2% vs 0.7%). There were 3 treatment-related deaths, 1 in the axitinib arm (cardiac failure) and 2 in the placebo arm (myocardial infarction and hepatorenal syndrome). **Conclusions:** Although the study failed to demonstrate a significant PFS benefit per investigator assessment, axitinib in combination with octreotide LAR demonstrated activity and had a tolerable safety profile in patients with advanced G1-2 extra-pancreatic NETs. Data base cleaning and central blinded radiological PFS assessment are currently ongoing. Clinical trial information: NCT01744249. Research Sponsor: Pfizer.

Discordance between central versus local response assessments in neuroendocrine tumor (NET) patients (pts) enrolled in A021202.

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Background: Assessment of tumor response in extrapancreatic NETs with metastases can be very challenging. Previous studies suggest a high degree of discordance between local and central imaging reviews, which has implications for clinical practice and trial design. **Methods:** Serial images archived from a randomized phase II trial (A021202) of pazopanib vs placebo in progressive non-pancreatic NETs were evaluated by central review, with real-time review conducted at the time of locally interpreted progressive disease (PD). The primary endpoint of the trial was progression-free survival (PFS) by central review. Discordances between central (Alliance Imaging Core Laboratory) and local (investigator-reported) reviews were assessed. Scan-level and pt-level results across both treatment arms were evaluated. Kappa tests were used to test concordance based on source of review. **Results:** 151 pts had a total of 724 scans with response adjudication by both local and central RECIST review. Discordance was observed in both directions. Overall, 20% of scans (143/724) had discordant classifications. The most common discordances were: stable disease (SD) on local vs. PD on central review (82/143=57%), and PD on local vs. SD on central review (32/143=22%). On a pt level, 78 of 151 pts (52%) had discordant reviews; 8 had >1 type of discordance. Overall, 30% of pts (N=45) had a determination of PD on central review, but SD or better on local review, potentially resulting in excessive exposure to therapy. In contrast, 20% (N=30) were classified as PD on local read but SD or better on real-time central review (which did not necessarily translate into an abbreviated course of treatment). Cohen's kappa statistics revealed only moderate concordance between local and central reviewers both at the scan (K=0.48, 95% CI: 0.42 – 0.55) and pt (K=0.41, 95% CI: 0.32 – 0.5) levels, with no significant influence by treatment arm, primary tumor site, tumor functionality, histology, differentiation or primary disease spread. **Conclusions:** Discordance was observed in both directions, where 30% of pts were potentially kept on study drug too long (based on central read), and 20% would have been taken off study treatment early for local PD were it not for real-time central review. Although this bidirectional discordance did not affect the overall findings of the PFS outcome between arms in the trial, these analyses highlight the high prevalence of discordance, the potential to negatively influence treatment duration in both directions, and the need for more straightforward methods of assessing treatment response in carcinoid. Support: U10CA180821, U10CA180882, U24CA196171; NETRF Investigator Award; https://acknowledgments.alliancefound.org Clinical trial information: NCT01841736. Research Sponsor: U.S. National Institutes of Health.

Radiographic response of desmoplastic mesenteric lesions to peptide receptor radionuclide therapy (PRRT).

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Background: ^{177}Lu-dotatate PRRT is indicated in well-differentiated, SSTR+ small bowel NETs. These tumors often metastasize to mesenteric lymph nodes and produce a desmoplastic reaction, consisting of tumor cells mixed with fibrotic tissue. We hypothesized that in patients treated with ^{177}Lu-dotatate, mesenteric tumors would remain stable even as liver tumor size changes were observed. **Methods:** We retrospectively reviewed the records of all patients treated with ^{177}Lu-dotatate between 4/2018 and 12/2019. Among patients with desmoplastic mesenteric tumors and liver metastases, we evaluated changes in tumor size of mesenteric and liver lesions based on pre and post-treatment radiology reports. Due to the infrequency of objective radiographic response (ORR), any reported changes in tumor size were considered significant. Scans were subsequently reviewed by a radiologist to confirm findings. **Results:** 21 patients met the inclusion criteria: 9 had evidence of shrinkage of liver lesion(s), 1 report described mild progression of liver lesions, 7 described stable hepatic disease and 4 described mixed hepatic progression/response. 2 of the patients with hepatic tumor shrinkage met criteria for PR by RECIST 1.1. Desmoplastic mesenteric lesions remained unchanged in size, regardless of the changes detected on liver lesions. **Conclusions:** ^{177}Lu-dotatate does not impact desmoplastic mesenteric tumors typically associated with midgut NETs. Patients whose disease is confined to desmoplastic mesenteric lesions are unlikely to respond radiographically to PRRT. Moreover, the inclusion of desmoplastic mesenteric lesions as target lesions in RECIST measurements increases rates of disease stability versus response or progression. Research Sponsor: None.

363 **Poster Session**

A clinical score (CS) for patients with well-differentiated neuroendocrine tumors (WD NETs) under consideration for peptide receptor radionuclide therapy (PRRT) with Lu 177-dotatate.

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Background: Despite the benefit of PRRT for patients with WD NETs, questions remain regarding sequencing and optimal patient selection for the treatment. We developed a CS at Vanderbilt Ingram Cancer Center (VICC) that we hoped would predict outcomes for patients with WD NETs receiving PRRT. **Methods:** Patients with progressive WD NETs (N = 146) under consideration for PRRT with Lu 177-dotatate between 3/1/2016-3/17/2020 at VICC (N = 122) and Rush Medical Center (RMC) (N = 24) were scored. The CS included 5 categories: available non-PRRT treatments for tumor type, prior systemic treatments, patient symptoms, tumor burden in critical organs and peritoneal carcinomatosis presence. All categories were scored from 0-2 except the peritoneal carcinomatosis category which was scored from 0-1; scoring criteria were determined by the VICC NET tumor board. All patients at VICC were prospectively scored, while patients from RMC were scored retrospectively with the investigator blinded to patient outcomes. The primary outcome, progression-free survival (PFS) was estimated by the Kaplan-Meier method; a Cox proportional-hazards model adjusting primary tumor site, tumor grade and number of PRRT doses administered (none, 1-2 doses or 3-4 doses) was used to analyze effect of CS. **Results:** Median patient age was 62.7 while median CS was 5 (range 1-8); the most common primary tumor sites were small intestinal (N = 81) and pancreatic (N = 37). A total of 101 patients and 31 patients received 3-4 doses and no doses of PRRT, respectively. On multivariable analysis, in patients treated with 3-4 doses of PRRT, for each 2-point increase in CS, the estimated hazard ratio (HR) for PFS was 3.26 (95% confidence interval (CI) 2.05-5.19). On multivariable analysis, in patients who received no doses of PRRT, for each 2-point increase in CS, the estimated HR for PFS was 1.37 (95% CI .78-2.41). **Conclusions:** Among patients treated with 3-4 doses PRRT, those with lower CS had better PFS with the treatment compared to patients with higher CS. This PFS difference, based upon CS, was not observed in patients who did not receive PRRT, suggesting the predictive utility of the CS for patients with WD NETs receiving PRRT with Lu 177-dotatate. Though the CS needs to be validated, it is the first of its kind reported. Research Sponsor: U.S. National Institutes of Health.

Real-world efficacy and safety of peptide receptor radionuclide therapy (PRRT) in gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

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Background: PRRT with ^{177}Lu-Dotatate (Lutathera) is a radiolabeled somatostatin analog indicated treatment of somatostatin receptor (STTR) positive GEP-NETs. The study aims to establish the efficacy and safety of PRRT in GEP-NETs in a real-world setting. **Methods:** We conducted an observational, retrospective, multicentric study of 40 patients with GEP-NET treated with PRRT belonging to GGNET (Galician Research Group on Neuroendocrine Tumors) network at Nuclear Medicine Department of Santiago de Compostela University Hospital (Spain). Patients characteristics, overall survival (OS), progression-free survival (PFS), overall response rate (ORR) and toxicity data were retrospectively collected and analyzed. **Results:** Data from 40 patients (pts) treated between 2016 and 2020 were recorded in this study. Median age was 63.5 years (range 41-85) and 55% were male. The baseline ECOG PS 0/1/2 was 15 (37.5%)/16 (40%)/9 (22.5%). Tumor location was intestinal 26 pts (65%), pancreas in 11 pts (27.5%) and unknown origin in 3 pts (7.5%). 25 pts (62.5%) were none functioning. Tumor grade G1/G2/G3 were 17 pts (42.5%)/ 20 pts (50%)/ 3 pts (7.5%), and Ki 67 $<$ 2/3-20/ $>$ 20%/unknown was 11 pts (27.5%)/ 21 pts (52.5%)/ 3 pts (7.5%)/ 5 pts (12.5%), respectively. The most frequent site of metastasis was liver in 32 pts (80%), lymph nodes in 19 pts (47.5%), peritoneum 11 pts (27.5%) and bone 10 pts (25%). Surgery: 22 pts (55%) primary tumor surgery and 8 pts (20%) metastasectomy. Previous systemic treatments included somatostatin analogs (SSA) in 40 pts (100%), everolimus in 26 pts (65%) and sunitnib in 11 pts (27.5%), others 7 pts (17.5%). 34 pts (85%) completed 4 cycles of treatment (6 pts (15%) non-complete due to premature death). 35 pts were evaluable for early response (after 2 cycles of treatment). Early ORR and DCR were 2.8% and 74.2%, respectively. 26 pts were evaluable after finishing treatment (6 pts premature death and 8 pending evaluation). ORR and DCR were 19.2% and 92.3%. With a median follow up of 21 months, 14 pts (35%) had died. Median OS was not reached (NR) and median PFS was 27.2 m (95% CI 16.0-38.4m). Tumor grade G1-2 ($p < 0.001$), Ki 67 $<$20% ($p = 0.002$), primary tumor surgery ($p = 0.039$) and metastasectomy ($p = 0.030$) were associated with prolonged PFS. Mild adverse events were most frequent after the 1o doses in 27.5% patients, and medium-term toxicity was present in 25.6%, mainly hematological, G1-G2 25.6%, and G3 5%. **Conclusions:** ^{177}Lu-Dotatate is a safe and effective treatment for those patients diagnosed with metastatic GEP-NET and positive somatostatin receptors, with an excellent clinical and radiological response. Furthermore, we have identified some predictive factors to OS that should be taken into consideration. Research Sponsor: None.

365 **Poster Session**

Cost of treatment change among patients with neuroendocrine tumors (NET) treated originally with somatostatin analogs.

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Background: Understanding the economic implications of changes in treatment among patients with NET will be important as treatment sequencing continues to evolve. This study describes treatment characteristics and healthcare costs prior to and following treatment change from somatostatin analog (SSA) monotherapy to another therapy among a privately-insured NET patient population in the U.S. **Methods:** Patients with newly diagnosed NET and treated with SSA monotherapy were extracted from IBM MarketScan claims databases in 1/1/2014-3/31/2019. NET treatment change was captured ≥30 days after SSA start date (earliest new treatment = index date). Healthcare costs (reimbursed amount in 2019 dollars) were reported for 1, 3, and 6 months pre- and post-index intervals. **Results:** A total of 1,122 NET patients with SSA monotherapy were identified; 305 had further treatment changes (mean age: 58 years; female: 52%; metastatic disease at NET diagnosis: 49%). The majority of patients started on octreotide (81%) vs lanreotide (19%). Common treatment changes included alternate SSA (38%), targeted therapy (everolimus or sunitinib) (30%) or chemotherapy (23%). Fewer than 10% of patients were treated with PRRT ^{177}Lu-dotatate or telotristat and 1% with a combination. Total healthcare cost increased from $12,376 to $25,647 (mean difference = $13,272 ±$24,189, $p<0.001$) for 1 month before/after treatment change, from $36,395 to $59,324 ($22,929 ±$41,764, $p<0.001$) for 3 months before/after, and from $66,786 to $109,224 ($42,438 ±$98,875, $p<0.001$) for 6 months before/after. Patients changing to targeted therapy had the largest 1 month interval cost increase ($19,677 ±$19,023, $p<0.001$) compared with patients changing to alternate SSA ($10,240 ±$14,112, $p<0.001$) and to chemotherapy ($4,057 ±$20,566, $p=0.155$). The differences were driven by increases in outpatient services and pharmacy prescriptions. **Conclusions:** The setting of rising costs after treatment change from SSA indicates treatment costs as the key driver, rather than NET disease severity. Future studies should investigate the clinical effectiveness of switching from SSA relative to the economic burden imposed by treatment change. Research Sponsor: Ipsen Biopharmaceuticals.

Temozolomide and capecitabine (CAPTEM) is effective in metastatic well-differentiated gastrointestinal neuroendocrine tumors.

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Background: The study aimed to evaluate patients' outcomes and prognosis with metastatic gastrointestinal neuroendocrine tumors (mgNET) who treated temozolomide and capecitabine (CAPTEM). **Methods:** The data of forty-three patients were retrospectively evaluated. Clinico-pathological features and treatment approaches were recorded. Kaplan-Meier analysis was used for overall survival (OS) and progression-free survival (PFS). Prognostic factors were assessed with Cox-regression analysis. **Results:** Median age was 59 (27-85) years. The number of male and female patients was 23 (%53.5) and 20 (%46.5), respectively. Pancreas (%51.2) was the most common site of the tumor. The number of patients with well- and poorly-differentiated mgNET was 38 (%88.4) and 5 (%11.6), respectively. The most common metastatic sites were liver (%62.8), lymph node (%58.1), and bone (%18.6). Eleven (%25.6) of the patients previously had undergone surgery, and some patients received radiotherapy (%9.5), chemotherapy (%19), and nuclear therapy (%9.3). Also, patients received octreotide (%86) or lanreotide (%14) with CAPTEM. In patients with well-differentiated mgNET, median PFS was 17.4 months, and disease control ratio % 79.4 (%3-complete response, %38.2-partial response, and %38.2-stable response). No response observed in patients with poorly differianted mgNET, and the median PFS was calculated as 4.5 months. Grade 1-2 toxicity was observed in 34 (%79.1) of the patients, and grade 3-4 toxicity in 8 (%18.6). Four (%9.5) patients discontinued therapy for the toxicity. The most common toxicities were anemia (%37.2), thrombocytopenia (%25.6), and fatigue (%16.3). At a median follow-up of 33.8 (2.9-172.73) months, the ratio of five-years OS was %61. In multivariate analysis; gender (p=0.008), age (p=0.007), and Ki-67 levels (p=0.011) were a statistically significant for OS. However, the site of the tumor (p=0.186), number of metastatic sites (p=0.255), and type of somatostatin receptor ligand (p=0.903) were not. **Conclusions:** In the study, we showed that CAPTEM + somatostatin receptor ligands (octreotide or lanreotide) were effective and well-tolerated in patients with well-differentiated mgNET. But, it was not effective in patients with poorly-differentiated mgNET. Male gender, aged over 60 years, and tumor with a high level of Ki-67 were negative prognostic factors. Research Sponsor: None.

367 **Poster Session**

Tumor burden in serotonin secreting pancreatic neuroendocrine tumors after initiating telotristat ethyl.

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Background: Pancreatic neuroendocrine tumors (pNETs) characterized by high serotonin levels and carcinoid syndrome (CS) are rare. We evaluated tumor burden in a subgroup of patients with pNETS from the real-world TELEACE study before and after initiating telotristat ethyl (TE) in US clinical practice. **Methods:** Detailed methods of the TELEACE study have been reported previously. This was a retrospective, single arm, pre-post physician panel-based chart review of patients who received TE for at least 6 months. Descriptive statistics analyzed demographic, clinical, laboratory and radiological data extracted from medical charts of TELEACE patients with pNETS. **Results:** Fifty-two patients with pNETS initiating TE were eligible for this analysis. The average age at the time of TE initiation was 60+10.4 years; 64% were males. The majority of patients had well-differentiated (60%) tumors and low-grade (54%) tumor status. Patients received TE for an average of 11.5+7.84 months, and 21% were still receiving TE at the time of data extraction. Diarrhea and flushing were the most common CS symptoms recorded at the time of TE initiation. Urinary 5-HIAA levels were reported for 9 patients before and for 2 patients after TE initiation. Mean (median) 5-HIAA levels before and after TE initiation were 693 (211) and 22 (22) μmol/24h, respectively. Significant mean reduction in tumor size of 0.67 cm after TE initiation (P = 0.017) was observed. **Conclusions:** This subgroup analysis of the TELEACE study population showed that the addition of TE to somatostatin analog treatment may positively impact tumor burden for patients with functional pNETs. Research Sponsor: Lexicon Pharmaceuticals (now TerSera Therapeutics USA).

Treatment response and clinical outcomes of well-differentiated high-grade neuroendocrine tumors to 177Lu-DOTATATE.

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Background: ^{177}Lu-DOTATATE is an approved therapy for somatostatin receptor (sstr) positive gastroenteropancreatic neuroendocrine tumors (NETs). There are little data available on response and outcomes for well differentiated (WD) high grade (HG) NETs treated with ^{177}Lu-DOTATATE. **Methods:** Pts with WD HGNETs treated with ^{177}Lu-DOTATATE at MSK from 2018-2020 were identified. Demographics, response to treatment, and progression-free survival (PFS) were determined. In pts with archival tumor tissue, next-generation sequencing (NGS) was performed through an institutional platform (MSK-IMPACT). **Results:** 19 pts were identified (mean age 54, 63% female). Site of tumor origin included: pancreas (14/19, 74%), small bowel (2/19, 10.5%), rectal (2/19, 10.5%), lung (1/19, 5%). Average tumor Ki-67 was 34.8 (range 22-56). All tumors were sstr avid on pre-treatment Ga68-DOTATATE PET/CT; none of the patients had sstr negative lesions detected. Median number of prior treatments (systemic and/or liver-directed) was 4 (range 2-7). All pts had progressive disease prior to initiation of ^{177}Lu-DOTATATE. 13 pts (68%) completed all four treatment cycles; treatment was incomplete in 6 pts due to treatment-related toxicities (n = 3) and clinical progression (n = 3). Best response by radiographic report was available in 16 patients (84%):10/16 (63%) with partial response, 1/16 (6%) with stable disease, 5/16 (31%) with disease progression. One pt with stable disease as best response received two additional cycles of ^{177}Lu-DOTATATE at progression. Median PFS (from date of first treatment with ^{177}Lu-DOTATATE until progression/death) was 11.1 months (95% CI 10.6 to NA). Five pts (26%) experienced dose modifying toxicity with ^{177}Lu-DOTATATE. The most common treatment-related toxicities were thrombocytopenia (9 pts, 47%; G3/4 in 1 pt, 5%), anemia (7 pts, 37%; G3/4 in 2 pts, 10.5%), leukopenia (6 pts, 32%; G3/4 in 0 pts), and AST/ALT elevation (4 pts, 21%; G3/4 in 0 pts). NGS results were available in the tumor tissue of 13 pts (68%). The most commonly observed alterations were in MEN1 (6/13, 46%) and DAXX (4/13, 31%). No RB1 alterations were identified. **Conclusions:** We observed a meaningful disease control rate of 69% during treatment of WD HGNETs with ^{177}Lu-DOTATATE. In this heavily pre-treated population, more than half of pts received all four treatment cycles with treatment-related toxicities largely bone-marrow related, as expected, based on historical data. As would be expected in sstr avid tumors, the vast majority had alterations in chromatin remodeling genes (MEN1, DAXX) consistent with WD NETs, with no RB1 alterations identified. Research Sponsor: Cycle for Survival.

369 **Poster Session**

Phase Ib/II study of pembrolizumab with lanreotide depot for advanced, progressive gastroenteropancreatic neuroendocrine tumors (PLANET).

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Background: Pembrolizumab has antitumor activity in a subset of GEP-NETs patients. We hypothesized that the lanreotide, by its antitumor effects and reduction of serotonin, a modulator of immunity, would synergize with pembrolizumab in low/intermediate grade GEPNETs. **Methods:** GEP-NETs patients who had progressed on a prior somatostatin analogue received lanreotide 90mg sq and pembrolizumab 200mg IV every 3 weeks until progressive disease or intolerable toxicity. The primary endpoint was ORR at any time on study and secondary endpoints were PFS and OS. **Results:** 22 patients were treated (F/M 10/12; Caucasian/AA/other 10/7/5; GI/pancreatic 14/8; median Ki67 5%, median time since diagnosis 5.3 yrs (IQR 2.3-7.9 yrs)). Prior octreotide LAR/lanreotide/both was administered to 20/1/1. Patients had a median of 2 prior systemic therapies (range 1-9) and six had prior locoregional therapy and 3 external beam radiotherapy. Of the 12 tumors analyzed thus far, 4 had detectable PD-L1 expression and 11 had detectable TILs. A median of 6 pembrolizumab doses (range 2-15) and 7 lanreotide doses (range 2-15) were administered. Six patients experienced treatment related SAEs (abdominal pain, pneumonitis, colitis, and hyperglycemia, all related to the pembrolizumab). Selected treatment related adverse events included: Hypothyroidism 23%, colitis 9%, hyperglycemia 14%, and pneumonitis 5%. Best response by RECIST 1.1 was SD/PD/Not available:39/52/9% and by irRECIST was 43/48/9%. Median PFS was 5.4 months (95% CI 1.7-8.3 mo). The median overall survival at a median follow-up of 15 months was not reached. Peripheral blood immunologic correlates will be reported subsequently. **Conclusions:** In a population of GEP-NET patients, progressing on a median of 2 prior therapies, including prior somatostatin analogue therapy, a minority of whom had PD-L1 expressing tumors, the combination of lanreotide and pembrolizumab produced stable disease in approximately 40% of patients. No new safety signals were identified. Clinical trial information: NCT03043664. Research Sponsor: Ipsen, Merck.

370 **Poster Session**

Efficacy of ipilimumab and nivolumab in patients with high-grade neuroendocrine neoplasms.

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Background: Dual checkpoint inhibitor therapy with anti-PD-1 and ant-CTLA-4 therapy has shown promising results in patients with high-grade NENs, demonstrating varying response rates of 9 – 44%. More data are needed to evaluate the true response in a real-world cohort of patients. **Methods:** Retrospective study of all patients with high-grade neuroendocrine neoplasms treated at the Moffitt Cancer Center and Mayo Clinic between 9/2017 and 7/2020 who received combination therapy with ipilimumab and nivolumab. Primary endpoint was objective response rate. **Results:** 34 patients met eligibility criteria for evaluation. Patients had received an average of 2 lines of therapy prior to treatment with ipilimumab/nivolumab, including at least one cytotoxic chemotherapy regimen. 27 (79.4%) of patients had poorly differentiated NECs and 7 (20.6%) had well-differentiated high grade NETs. The most common primary site (10, 29.4%) was pancreas; other primary sites of disease included unknown primary (n = 9), colon (n = 5), uterus (n = 3), anorectum (n = 2), esophagus (n = 2), cervix (n = 1), stomach (n = 1), and small intestine (n = 1). 5 patients (14.7%) exhibited a best response of PR per RECIST 1.1 criteria, 9 (26.5%) SD, and 17 (50%) PD: 3 patients did not have a follow-up scan and discontinued treatment shortly after initiation due to clinical progression. ORR was 14.7% and DCR was 41.2%. Median PFS was 1 month (95% CI, 0.45 – 1.55); median OS from time of treatment initiation was 5.0 months (95% CI, 3.42 – 6.59) and median OS from diagnosis was 14.0 months (95% CI, 1.49 – 26.51). Median duration on treatment was 1 month (range 0 – 10 months). 26 patients discontinued treatment for progression, 4 patients for toxicity, and 4 remain on treatment at the time of data cut off. 12 patients (35%) experienced grade 3 and 4 treatment-emergent toxicities: liver transaminitis, elevated blood bilirubin, arthralgia, myalgia, peripheral sensory neuropathy, lower extremity edema, confusion, diarrhea, encephalopathy, acute kidney injury, rhabdomyolysis, myocarditis, and colitis. **Conclusions:** The ipilimumab and nivolumab regimen has modest activity in aggressive and heavily pretreated high-grade NENs who have progressed on prior cytotoxic chemotherapy. Use of this regimen may be considered in patients with particularly aggressive, refractory high-grade NENs. Research Sponsor: None.

The role of systemic inflammatory factors in gastroenteropancreatic neuroendocrine tumors (GEP-NETs) treated with peptide receptor radionuclide therapy (PRRT).

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Background: Inflammation plays a key role in the pathophysiology of many diseases, including cancer. Systemic inflammatory factors have been validated as indicators of ongoing systemic inflammation that could be predictive markers of poor prognosis for oncological outcomes. However, it is unknown the prognostic impact of systemic inflammation markers in patients with GEP-NETs treated with PRRT. **Methods:** We conducted an observational, retrospective, multicentric study of 40 patients with GEP-NET treated with PRRT belonging to GGNET (Galician Research Group on Neuroendocrine Tumors) network at Nuclear Medicine Department of Santiago de Compostela University Hospital (Spain). The systemic inflammatory markers were calculated as follows: NLR = neutrophil count/lymphocyte count, PLR = platelet count/lymphocyte count, MLR= monocyte count/lymphocyte count, ALB= albumin levels and dNLR = neutrophil count/ (leucocytes count – neutrophils count). For the calculation of the different ratios, baseline analysis and after the second dose were used. The cut-off values were determined as the median of each values, correlating them with progression-free survival (PFS). **Results:** Data from 40 patients (pts) treated between 2016 and 2020 were recorded. Median age was 63.5 years (range 41-85) and 55% were male. Baseline ECOG PS 0/1/2 was 15 (37.5%)/16 (40%)/9 (22.5%). Tumor location was intestinal 26 pts (65%), pancreas 11 pts (27.5%) and unknown origin 3 pts (7.5%). 15 pts (37.5%) were functioning. Tumor grade G1/G2/G3 were 17 pts (42.5%)/ 20 pts (50%)/ 3 pts (7.5%), and Ki 67 <2/ 3-20/>20%/unknown were 11 pts (27.5%)/ 21 pts (52.5%)/ 3 pts (7.5%)/ 5 pts (12.5%), respectively. The most frequent site of metastasis was liver 32 pts (80%), lymph nodes 19 pts (47.5%), peritoneum 11 pts (27.5%) and bone 10 pts (25%). Surgery: 22 pts (55%) primary tumor surgery and 8 pts (20%) metastasectomy. Previous systemic treatments included somatostatin analogs (SSA) 40 pts (100%), everolimus 26 pts (65%) and sunitnib 11 pts (27.5%), others 7 pts (17.5%). The baseline cutoff-values for NLR was 2.61, for PLR 110.14, for MLR 0.31, for ALB 4.2. and for dNLR 1.71. The cutoff-values after the 2nd dose for NLR was 2.3, for PLR 2.15, for MLR 0.3, for ALB 4.2 and for dNLR 1.48. With a median follow up of 21 months, 14 pts (35%) had died. Median PFS was 27.2 m (95% CI 16.0-38.4m) and OS was not reached (NR). Pts with baseline higher NLR (>2.61 vs. <2.61) had a significantly lower PFS: 15.8 m vs. NR (HR 0.181; 95% CI 0.051-0.638, p=0.03), which was also true for pts with elevated dNLR (>1.71 vs. <1.71): PFS 15.8 m vs. NR (HR 0.174; 0.049-0.614, p=0.03). Baseline PLR, ALB, MLR and NLR, PLR, ALB, dNLR and MLR values after the 2nd dose was not statistically significant for PFS. **Conclusions:** We have identified that baseline NLR and dNRL are significant predictive factors in patients with GEP-NETs treated with PRRT. Research Sponsor: None.

Copy number alterations in plasma cell-free DNA from metastatic gastroenteropancreatic neuroendocrine neoplasms.

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Background: Recent studies, including our proof-of-concept study, demonstrated the possibility to detect tumor-derived molecular alterations in cell-free DNA (cfDNA) from plasma of patients with a gastroenteropancreatic neuroendocrine neoplasm (GEP-NEN). More in-depth evaluation of the biomarker potential of cfDNA in GEP-NENs is warranted, since highly sensitive and specific blood-based biomarkers are an important unmet need for this tumor type. The aim of our study was to detect tumor-associated copy number alterations (CNAs) in cfDNA from GEP-NEN patients to molecularly characterize the tumor and to estimate tumor fraction, as a measure of tumor burden, and to evaluate changes in these parameters over time. **Methods:** Metastatic GEP-NEN patients were included within NETwerk, a multi-institutional network of nine hospitals in Belgium. Clinicopathological data were collected to correlate experimental and clinical findings. Plasma samples were collected from all patients and cfDNA was extracted and subjected to shallow whole-genome sequencing (WGS). Detection of CNAs and estimation of tumor fraction, based on the sequencing data, were performed using the R-based tool ichorCNA. **Results:** In total, 80 samples of 29 metastatic GEP-NEN patients were analyzed using shallow WGS. All patients had a well-differentiated GEP-NEN of Grade 1/2 and primary sites were pancreas (N = 15), small intestine (N = 9), colon (N = 1), caecum (N = 1), ileocaecal valve (N = 1), pylorus (N = 1) and unknown (N = 1). Median number of samples per patient was two, with a median time between first and last sampling of six months. In 25 cfDNA samples from nine patients (31%), CNAs with tumor fractions higher than 3% could be detected. The primary tumor site of all CNA-positive patients was pancreas, corresponding to 60% of included pancreatic NEN (PNEN) patients. Six of the CNA-positive patients were included at initiation of everolimus treatment. The detected CNA patterns were similar to the copy number profiles of PNENs described in literature, e.g. whole-chromosome gains of chromosomes 5, 7, 9, 12, 13, 14, 19 and 20. CNA profiles were relatively stable over time, although in two patients new alterations did arise. Tumor fractions changed over time, which could be linked to changes in tumor burden, tumor progression and treatment response according to RECIST1.1 criteria and will be further examined, including in additional samples that are being collected. **Conclusions:** Cell-free DNA of metastatic GEP-NEN patients contains CNAs that correspond to CNA profiles seen in tumor tissue samples. CNAs can be used to quantify the tumor fraction in cfDNA over time, which will be linked to tumor progression in our ongoing study, particularly in the promising subgroup of PNEN patients. Research Sponsor: Kom op tegen Kanker (Stand up to Cancer, the Flemish cancer society), Other Government Agency.

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Ampullary neuroendocrine tumors: A window into a rare tumor using a national database.

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Background: Ampullary neuroendocrine tumors (NET) make up < 1% of all gastrointestinal NETs. Information about their behavior and prognosis is reliant on small case series. This study set out to describe the population of patients who are diagnosed with ampullary NETs and compare them to patients with duodenal and pancreatic head NETs. **Methods:** The National Cancer Database (2004 – 2016) was queried for patients with ampullary, duodenal, and pancreatic head NETs. Clinicopathologic and treatment characteristics were compared. Subset analysis was performed on patients who underwent surgery. Kaplan Meier (KM) analysis and Cox regression were used to analyze the survival of patients with ampullary NETs. **Results:** Overall, 872 patients were identified with ampullary NET, 9692 with duodenal NET, and 6562 with pancreatic head NET. Patients with ampullary NET had an average age of 60.9 +/- 14.5 years, were evenly split among men and women (N = 437, 50.1% vs N = 435, 49.9%, respectively), and primarily Caucasian (N = 663, 76.0%). 72.1% underwent local tumor destruction or surgery (N = 629). Most did not receive radiation (N = 832, 95.4%), chemotherapy (N = 627, 71.9%), or hormone therapy (N = 788, 90.4%). Patients with ampullary NETs had more poorly differentiated tumors (N = 119, 13.6%) than patients with duodenal (N = 159, 1.6%) or pancreatic head (N = 602, 9.2%) NETs. Patients with ampullary NETs had more positive lymph nodes (N = 288, 33%) than patients with duodenal (N = 915, 9.4%) or pancreatic head (N = 1381, 21%) NETs. At five years, the overall survival for patients with ampullary, duodenal, and pancreatic head NETs was 57%, 68%, and 46%, respectively. Within the surgical population, five-year survival for patients with ampullary (N = 367), duodenal (N = 991), and pancreatic head (N = 1961) NETs was 60%, 74%, and 72%, respectively. When compared, there was a statistically significant difference between the mean overall survival of patients with ampullary (98 +/- 4.7 months), duodenal (112 +/- 2.5 months), and pancreatic head (108 +/- 1.7 months) NETs ($p < 0.001$). In the cox regression analysis, sex, Charlson-Deyo score, lymph node positivity, lymph-vascular invasion, mitotic rate, chromogranin A level, 5-HIAA level, and tumor size did not correlate with survival. Increasing age (HR 1.04, CI 1.01 – 1.07, p = 0.008) and worse tumor differentiation (poorly differentiated HR 3.33, CI 1.38 – 8.04, p = 0.008 and undifferentiated HR 8.31, CI 2.77 – 24.92, $p < 0.001$ compared to well differentiated) were associated with increased mortality. **Conclusions:** This study sheds light on a rare tumor histology. When compared to patients who underwent surgical resection for duodenal or pancreatic head NETs, patients with ampullary NETs had a significantly worse prognosis. Identifying prognostic factors allows us to create more concrete treatment recommendations and provide patients with improved prognostic information. Research Sponsor: None.

Incidence and patterns of secondary malignancies in patients with neuroendocrine neoplasms: A SEER database analysis.

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Background: Neuroendocrine tumors (NETs) are comprised of a group of biologically and clinically heterogenous malignancies arising from a variety of anatomic sites, the majority of which lie within the gastrointestinal tract. Prior literature has reported on the association between NETs and other primary malignancies (OPM), most of which also end up being within the gastrointestinal tract, but these studies are limited by small sample sizes. We aim to further analyze the association of NETs and OPM on a larger scale using a population-based cancer registry. **Methods:** Malignant primary cancer with NET features were identified from the Surveillance Epidemiology and Ends Results (SEER) registry between 1975 and 2017. The histology/behavior of NET included carcinoid tumor, neuroendocrine carcinoma, pancreatic endocrine tumor, atypical carcinoid tumor, and other including insulinoma, glucagonoma, gastrinoma, VIPoma, somatostatinoma and enterochromaffin cell carcinoid. First NET observation from each patient was examined. Patients with NET were grouped into three categories: only one primary cancer with NET, first primary cancer with NET and first primary cancer without NET based on sequence number of primary cancer recorded in SEER. Distribution of NET between gastrointestinal (GI) and non-GI sites was described. Demographics were compared by NET sequence group and between GI and non-GI sites. **Results:** 45,896 patients with NET were analyzed (77.9% Caucasian, 47.0% male, median age 62.0 years). More than half (65.7%) of the NETs were observed in GI sites. Within the GI tract, 31.3% were in the small intestine, 25.1% in the rectum, 16.6% in pancreatobiliary, and $<$ 11% in other GI locations. Age at NET diagnosis was younger in those with GI NETs (median 60.0 vs 65.0, $p < 0.001$). 71.2% of NET found in only cancer diagnosis, 10.4% of NET in first followed by a second primary malignancy, and 18.4% in a non-NET primary followed by NET. Mean age was 58.9 for NET primary only, 61.0 for NET primary first and 68.3 for non-NET primary first ($p < 0.0001$). More Caucasian patients had non-NET primary first (82.3%) compared to NET primary only (76.9%) and NET primary first (75.5%). No gender differences were observed amongst the three groups. Carcinoid tumor histology was more prevalent in NET primary first (78.6%) compared to NET primary only (67.3%) and non-NET primary first (66.6%), while neuroendocrine carcinoma histology was more prevalent in NET only (27.4%) and non-NET first (29.3%) compared to NET first. **Conclusions:** 28.8% of patients with NETs were found to have OPM, either preceding or following their NET diagnosis. It is imperative that patients with NET undergo age-appropriate cancer screening to help identify any concurrent malignancies. Further research is warranted to identify the location of such additional malignancies and the timeframe in which they occur in relation to the NET. Research Sponsor: None.

TPS375 **Trials in Progress Poster Session**

A phase I study of safety and immunogenicity of survivin long peptide vaccine (SurVaxM) in patients (pts) with metastatic neuroendocrine tumors (NETs).

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Background: Metastatic neuroendocrine tumors (NETs) have a poor prognosis and there are limited options after first-line treatment with somatostatin analogues (SSA)/chemotherapy. Therefore, new therapies are urgently needed. Survivin is an intracellular protein that alters cell division, function of cell death proteases and inhibits apoptosis. It is undetectable in adult cells and expressed in many tumors, making it an ideal target. SurVaxM is a 15 amino acid synthetic peptide vaccine. It stimulates antigen presentation via intracellular cell-surface target recognition and induces CD8+ & CD4+ T cells and IgG production. It was well tolerated in a phase I trial in recurrent glioma pts (Fenstermaker et al., Neurooncol; 2014). Prelim analysis from a phase II study in glioma patients (pts) showed its efficacy (Ahluwalia et al., Neurooncol; 2018). Targeting survivin in NETs is based on our work with tissue microarrays from gastroenteropancreatic (GEP) and lung NETs that showed that its expression correlated with a worse overall survival (Hanif et al., Oncotarget; 2020). We have an ongoing single-arm phase I trial evaluating the safety and immunogenicity of SurVaxM in metastatic NETs. **Methods:** Ten eligible pts with any grade metastatic GEP/lung origin NETs that are survivin positive by immunohistochemistry and have progression on SSA within the last 6 months on two CT scans >4 weeks apart per RECIST v1.1 are being enrolled. Pts receive a fixed dose of 500 mcg of SurVaxM in Montanide ISA 51 subcutaneously along with 100 mcg of GM-CSF q2 weeks X 4 doses. SSA is continued at the same dose as before. Pts free of progression and toxicity at 6 months get extra doses of SurVaxM q12 weeks, up to 1 year. Subjects are assessed continuously for safety per NCI CTCAEv5.0. Response assessment via CT scans per RECIST v1.1 q12 weeks. Primary objective is to assess safety of SurVaxM +/- SSA. Secondary objectives are to assess overall response rate, progression free survival, duration of response and vaccine immunological response (anti-survivin antibody titers and survivin-specific CD8 T-cell responses). Safety analysis is per Pocock stopping boundary with the assumption of true toxicity of 0.2 and unacceptable toxicity of 0.3 at a significance level of 0.05.To this date, eight patients were screened out of which five patients were enrolled. One patient did not meet the eligibility criterion due to negative survivin staining and the other two did not meet the RECIST v1.1 progression criterion. Of the five pts enrolled, two were of lung origin, two of GEP, and the remainder one of thymic origin. Three pts had high grade neuroendocrine carcinoma, one patient had atypical bronchial tumor and one with low-grade NET. Currently, two pts remain on the study. The enrollment is ongoing. The trial is funded by The Neuroendocrine Tumor Research Foundation. Research Sponsor: The Neuroendocrine Tumor Research Foundation (NETRF).

TPS376 **Trials in Progress Poster Session**

Phase II trial of the CDK4/6 inhibitor abemaciclib in patients (pts) with advanced and refractory well-differentiated gastroenteropancreatic neuroendocrine tumors (GEP NETs).

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Background: Despite advances in the treatment of advanced GEP NETs, long-term disease control remains a challenge. Overexpression and altered regulation of cyclin-dependent kinases (CDK) 4 and 6 have been observed in multiple subtypes of GEP NETs. Preclinical studies have demonstrated that the CDK 4/6 inhibitor palbociclib reduces growth of pancreatic NET cell lines and levels of phosphorylated retinoblastoma protein *in vitro*. Moreover, the drug significantly inhibited tumor growth *in vivo* in pancreatic NET xenograft models. Abemaciclib is a selective small molecule CDK 4/6 inhibitor, approved for the treatment of HR+ HER2– metastatic breast cancer. Clinical activity and central nervous system penetration of the drug have been observed in several tumor types in clinical trials, including partial response in one pt with metastatic small intestinal NET. We have developed a Phase 2 trial of abemaciclib in GEP NETs to evaluate its efficacy and safety in these rare cancers. **Methods:** This is an investigator-initiated non-randomized phase 2 trial using a two-stage design. Eligible pts have metastatic or locally advanced unresectable well-differentiated grade 1-2 GEP NETs, ECOG PS 0-2, and must have progressed on at least one line of systemic therapy. Prior or concurrent treatment with somatostatin analogs is allowed,. Abemaciclib is administered at a dose of 200 mg orally every 12 hours continuously in 28-day cycles. Dose reductions for toxicities are allowed to level -1 (150 mg) and -2 (100 mg). Primary endpoint is objective response rate (ORR) by RECIST v1.1. Secondary endpoints include progression free survival (PFS), overall survival (OS), and toxicity. A two-stage design with 88% power to detect an increase in ORR to 20% with abemaciclib at the 1-sided 0.05 level would require a total of 37 patients. Stage 1 will include 20 patients, and if one response is seen among these patients, the study will continue to enroll another 17 patients. The trial was activated in January 2020, and 3 patients have been enrolled to date. Available archival tumor tissue and molecular profiling data are collected for future correlative studies including assessment of response biomarkers. Research Sponsor: Eli Lilly.