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NET Disease Management: Innovation in a Rapidly Changing Landscape

The North American Neuroendocrine Tumour Society (NANETS) is a medical society established by healthcare professionals dedicated to advancing the field of neuroendocrine tumour (NET) disease management. Each year, NANETS brings physicians, allied healthcare providers, researchers and students together at its international symposium, the largest professional NET disease meeting of medical professionals in North America. The Canadian Oncology Societies (COS) reports here on some of the most significant presentations, accompanied by commentaries from oncology experts on the practice implications of these latest developments.

Neuroendocrine tumour (NET) disease is rare and complex, presenting a double challenge: medical professionals are likely to see only a few cases in the course of their careers, and treatment advances are occurring quickly. The NANETS annual symposium provides an opportunity to exchange new knowledge about diagnosis and treatment, bringing together medical professionals with firsthand experience in managing the disease.

Among the key topics discussed at the 2017 meeting were advances in somatostatin inhibitors for carcinoid syndrome (CS), peptide receptor radionuclide therapy (PRRT), and developments in targeted therapies and immunotherapy. In his keynote address, Dr. Drew Pardoll from Johns Hopkins Hospital discussed recent studies showing that patients who previously had very poor outcomes are now effectively cured, in some instances, with immunotherapy approaches. Sessions also focused on the roles played by members of multidisciplinary cancer care teams, especially as oral therapies become more common; debated the merits of surgery for less advanced disease; and anticipated the impact of new imaging technologies. Patient-reported outcomes and quality-of-life data had a strong presence at the meeting.

SETTING THE STAGE

Significant advances have been made in the treatment of NETs over the past few years. Recent randomized studies of octreotide long-acting repeatable (LAR), lanreotide, everolimus and sunitinib in well-differentiated NETs have demonstrated prolongation of progression-free survival (PFS) compared with placebo. Functional tumours actively secrete hormones and cause clinical symptoms, notably CS. Somatostatin analogues have long been used to control hormone-induced symptoms in patients with NETs, and are being investigated as antiproliferative agents for patients with well-differentiated metastatic disease. Several important clinical trials are already changing practice. In the CLARINET phase 3 trial,[1] lanreotide was found to improve PFS compared to placebo in patients with gastroenteropancreatic (GEP) NETs. The RADIANT-4 trial[2] compared everolimus to placebo in patients with progressive gastrointestinal (GI) or lung NETs and found everolimus offered better PFS. The NETTER trial,[3] focused on patients with midgut NETs, concluding that ^{177}Lu-DOTATATE brought substantial improvement in PFS compared with high-dose octreotide. Regarding CS, the TELESTAR study[4] found that treatment with telotristat ethyl (TE), an oral serotonin inhibitor, was associated with a significant reduction in bowel movements per day, and the TELECAST study[5] supported the safety and efficacy of TE. The NANETS 2017 symposium included followup and secondary analysis of data from these trials.

CARCINOID SYNDROME

NETs can release large amounts of hormones into the blood, causing numerous problems. CS most commonly arises from carcinoid tumours of the digestive tract. It is caused by elevated circulating levels of serotonin that stimulate the secretion of small bowel fluid and electrolytes. Common symptoms include diarrhea and flushing; some patients may also experience abdominal pain and carcinoid heart disease.[6,7] Treatment of CS involves somatostatin analogues. Somatostatin itself only lingers in the circulation for a few hours. Formulations of somatostatin that can remain viable in the circulation for longer have been developed for NET treatment. However, some patients may require additional treatment, notably for diarrhea and elevated levels of levels of urinary 5-hydroxyindoleacetic acid (5-HIAA).

Telotristat ethyl (TE) inhibits tryptophan hydroxylase, the rate-limiting enzyme in serotonin synthesis.[8] In the TELESTAR (Telotristat Etiprate for Somatostatin Analogue Not Adequately Controlled Carcinoid Syndrome) trial, TE was found to significantly reduce the frequency of bowel movements in patients with bowel frequency not adequately controlled with somatostatin analogues,[9] leading to accelerated approval by the US FDA (Food and Drug Administration). The trial included patients with CS experiencing ≥4 bowel movements (BMs) per day while on somatostatin analogue (SSA) therapy. Patients received either TE 250 mg, TE 500 mg or placebo, each 3 times per day.

The randomized double-blind placebo-controlled TELECAST (Telotristat Ethyl for Carcinoid Syndrome Therapy) study was conducted to provide further data on safety and efficacy.[5] Inclusion criteria differed somewhat

between the 2 studies. In TELECAST, the 2 treatment arms involved TE 250 mg 3 times a day or 500 mg 3 times a day. Primary endpoints for safety were the emergence of adverse events (AEs), and for efficacy, the change in 24-hour urinary 5-HIAA by week 12, along with bowel movement frequency, flushing, abdominal pain and quality of life. At week 12, patients in the placebo arm had an increase in urinary levels of 5-HIAA of 97%, while levels were reduced by 33% in the 250-mg arm and 76% in the 500-mg arm. TE also demonstrated reductions in the frequency of bowel movements compared to placebo. Following the double-blind portion of the study, patients were invited to participate in a 36-week open-label extension period, receiving the higher (500 mg 3 times daily) dose.

The NANETS 2017 symposium included analysis by Dr. Marianne Pavel from Friedrich-Alexander University in Germany, of the TELECAST open-label extension trial. As well, Dr. Joseph Dillon presented further analysis of the TELESTAR trial.

Marianne Pavel et al presented results from the TELECAST extension trial. Safety and efficacy were assessed up to week 48. No new safety signals were observed in the open-label extension period. Improvements in European Organisation for Research and Treatment of Cancer Quality of Life

Commentary: carcinoid syndrome

Following the NANETS Symposium, COS asked **Dr. Rachel Goodwin,** Medical Oncologist at The Ottawa Hospital Cancer Centre, to comment on the relevance of these new analyses of TELECAST and TELESTAR trials:

Neuroendocrine tumours are rare, but their incidence is increasing.[13] Appoximately 30–40% of GI NETs are functional, with carcinoid being the most common syndrome.[14] As presented at NANETS 2017, patients with liver disorder, enlarged lymph nodes, or abdominal mass are 2 to 4 times more likely to have preexisting CS prior to diagnosis; this confirms our previous clinical suspicion that CS is linked to bulk of disease. Despite being on long-acting somatostatin analogues, some patients continue to suffer from multiple bowel movements per day. Symptoms can also reoccur after many years with disease. Carcinoid diarrhea negatively impacts patient's quality of life by limiting social interactions and the ability to work.[15,16] Prior to TE, physicians would rely on less convenient methods, such as short-acting octreotide injections, or less mechanism-specific solutions, such as loperamide and narcotics, to control diarrhea.

The TELESTAR study concluded that in patients with CS and ≥4 BMs not adequately controlled by somatostatin analogues, treatment with TE resulted in significant reductions in BM frequency and urinary 5-HIAA, thus reflecting tryptophan hydroxylase (TPH) inhibition. BM frequency was reduced by approximately 2 per day. Reflecting these findings, patients reported improved quality of life using the EORTC QLQ-C30 diarrhea subscale, but no difference in global health scores were observed. This confirms a meaningful impact on patients. Side effects were manageable: mild nausea and asymptomatic increases in gamma glutamyl transpeptidase (GGT). The 250 mg TID dose is most often prescribed by physicians given the similar efficacy and better toxicity profile compared to the 500 mg TID dose. Some questions arising from this trial included: Is the efficacy sustainable beyond the 12-week period? Do new toxicities emerge with extended use? Does the drug work to reduce carcinoid diarrhea with less frequent baseline BMs? and finally, Does the mechanism of action reduce other symptoms of CS? The TELECAST study set out to answer the above questions.

Patients included in TELECAST differed from those in TELESTAR and had to be experiencing on average ≤4 BMs/day and have at least 1 other carcinoid sign or symptom on a stable dose of SSA (or ≥1 symptom or ≥4 BMs if not on SSA) during a 12-week double-blind treatment period (placebo/250 mg TID/500 mg TID) followed by a 36-week open-label extension with the 500 mg TID dose. Special-interest AEs based on the mechanism of the drug and prior data included depression, hepatic enzyme abnormalities, and GI disorders. During the double-blind period, treatment-emergent AEs (TEAEs) in the extension study were comparable. There was no increase in depression-related AEs on TE compared to placebo. Rare increases in alanine transaminase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST) and GGT were transient and normalized after drug discontinuation, with no associated hyperbilirubinemia. GI disorders were common (about 40%–60% patients), however there was no dose-dependent or drug-dependent relationship between TE and GI symptoms. Forty percent of patients on TE were considered durable responders (≥30% reduction in daily BMs for ≥50% of the time). There was no statistically significant change in cutaneous flushing with TE use. In summary, TE provides a safe, convenient and effective means of treating CS-related diarrhea in well-differentiated metastatic NET patients. It is not known yet if the reduction in urinary 5-HIAA seen with this class of drug will result in decreased valvular heart disease and mesenteric fibrosis.

Questionnaire-Core 30 (EORTC QLQ-C30) diarrhea scores on TE were 10–21 points at week 12 and 17–18 points at week 24 and week 48. TE was found to be well-tolerated, and reductions in urinary 5-HIAA and improvements in diarrhea scores were maintained with TE over 48 weeks.[10]

Dr. Joseph Dillon from the University of Iowa presented further analysis of time to sustained response in the TELESTAR trial. The first occurrence of sustained response was defined as the time from the first dose to the first day of a continuous 14 days of ≥30% reduction from baseline in bowel movement frequency during the double-blind trial period. The time to the first sustained response in the TELESTAR study was examined among treatment groups; Cox regression was used to analyze hazard ratios and the log-rank test for treatment comparisons.

Each treatment arm had 45 patients. Sustained improvement in bowel movement frequency over the 12-week double-blind trial period was achieved in 34, 31 and 19 patients, respectively, in the TE 250 mg, TE 500 mg and placebo groups. Median time to sustained ≥30% improvement was 3 to 4 weeks with TE at both dosing levels, and no median was reached on placebo. Hazard ratio estimates suggest that treatment with TE increases the likelihood of a more than 2-fold sustained improvement in bowel movement frequency as compared with placebo. The first day of sustained improvements occurred within 5 days (25th percentile) and 73 days (75th percentile) of treatment initiation. Time to sustained clinical benefit with TE may vary across patients. Some patients experienced initiation of sustained improvement in bowel movement frequency within days of beginning treatment, whereas the median time on therapy for this effect was 3 to 4 weeks.[11]

One of the difficulties in CS is predicting which patients are most likely to develop the syndrome. Patients may experience delays in diagnosis of 5 to 7 years from symptom onset, as symptoms are mistaken for other diseases. At NANETS 2017, Beilei Cai et al presented a claims database case-control study matching newly-diagnosed patients with GI NETs without CS (controls) to patients with CS (cases), based on NET diagnosis date. The aim was to detect factors predictive of CS prior to diagnosis among GI NET patients.

The most frequently observed conditions, other than symptoms or diagnoses known to be associated with CS, within 1 year prior to the index date were assessed. A total of 1,004 GI NET patients were identified, of which 251 (25%) had CS and 753 (75%) were controls. Three factors prior to CS diagnosis were associated with higher CS risk, including liver disorder (odds ratio 95% CI: 3.38 [2.07–5.51]), enlarged lymph nodes (2.13 [1.10–4.11]) and abdominal mass (3.79 [1.87–7.69]). This study suggests that patients diagnosed with CS are 2 to 4 times as likely to have a pre-existing diagnosis of a liver disorder, enlarged lymph nodes or abdominal mass within the year preceding CS diagnosis, compared to those without CS. These findings may aid physicians in diagnosing CS patients earlier.[12]

METASTATIC DISEASE

The management of patients with liver metastases from gastropancreatic (GEP)-NETs involves several specialties: surgery, medical oncology, radiotherapy, interventional radiology and nuclear oncology. The options available to an individual patient depend primarily on the extent of metastases. Surgery is the only treatment associated with curing liver involvement, however the extent of liver metastases precludes the surgical option for many patients. Medical and radiologic approaches are being explored, with an emphasis on their ability to shrink tumours, which might for some then permit surgical resection of the liver lesions, while for others will help to relieve symptoms and slow progression.

Somatostatin analogues

The standard of care for differentiated somatostatin receptor-expressing metastasized nonresectable midgut, pancreatic-or unknown origin NETs involves LAR SSAs. Randomized phase 3, multicentre trials demonstrated that LAR octreotide and lanreotide depot can significantly prolong PFS in a heterogeneous population of patients with GEP-NETs.[17]

More from CLARINET

At the 2017 NANETS symposium, Edward Molin et al presented findings from an open-label extension of the CLARINET trial whose primary objective was to evaluate long-term safety and efficacy of lanreotide. The main efficacy endpoint was PFS, measured from the time of core study randomization to death or disease progression.[18]

In the CLARINET study, lanreotide depot (Autogel®), a prolonged-release, supersaturated aqueous gel formulation, 120 mg every 28 days, was found to significantly improve PFS vs placebo in metastatic grade 1/2 enteropancreatic NETs. Patients in the trial had received no prior somatostatin analogue treatment, and no other prior medical therapies, in the previous 6 months. They were randomized to lanreotide 120 mg (n=101) or placebo (n=103) for 96 weeks, or until death/progressive disease (RECIST 1.0). Following the CLARINET trial, patients with stable disease in the core study were invited to continue lanreotide in the open-label extension. Interim analysis showed continued antitumour effects. The final PFS analyses were presented at the NANETS symposium. The final open-label study population comprised 89 patients (lanreotide-lanreotide 42; placebo-lanreotide 47); 38% had pancreatic and 38% midgut NETs. During the extension, 40% of those continuing lanreotide and 47% of those of switched to lanreotide had treatment-related AEs. Diarrhea was more common in the placebo-lanreotide group than in the lanreotide-lanreotide group (25% vs 9%). No new safety concerns were identified. Median PFS was 38.5 months (95% CI: 30.9, 59.4) and varied with tumour origin and prior therapy. The CLARINET open-label extension indicates sustained antitumour effects with lanreotide 120 mg in enteropancreatic NETs, irrespective of tumour origin, and suggests benefits with lanreotide as early treatment.[18]

Alexandria Phan et al presented results of a pooled analysis of the safety and tolerability of lanreotide depot to analyze safety in functioning and nonfunctioning NETs. Analysis included followup data on the extended open-label phase of CLARINET, further analysis of the CLARINET study itself, and the ELECT study. It confirms a persistent antitumour response to lanreotide in patients with nonfunctional advanced NETs of the GI tract. Of 378 patients, 90% received lanreotide 120 mg and 10% received ≤90 mg. Overall AE and serious AE profiles were similar across all groups, although treatment-related AEs were higher in lanreotide patients vs placebo patients. GI events were most frequent (56%, excluding diarrhea; 28% reported diarrhea, excluding in ELECT double-blind and initial open-label phases), with abdominal pain being the most common individual AE and treatment-related AE. There were 32 serious AEs reported among 18 patients, the most common being abdominal pain and cholelithiasis (3 each). No withdrawals were due to GI AEs, no deaths were considered treatment-related, and no additional safety signals were reported in >12-month vs ≤6-month data.

This safety analysis demonstrates a consistent safety profile and, together with reported efficacy, supports the positive benefit-risk profile of lanreotide in NETs.[19]

PEPTIDE RECEPTOR RADIONUCLIDE THERAPY

Somatostatin receptor-expressing NETs can also be treated with PRRT, a molecular-targeted therapy which uses a somatostatin analogue similar to octreotide, coupled with a radionuclide-emitting beta radiation. Among responders (<35%), significant increases in overall survival (OS) have been seen. Extensive liver metastases are a negative predictor for PFS.[20]

At NANETS 2017, **Dr. Wouter van des Zwan** et al from the Rotterdam Cohort presented PFS and OS results for a cohort of patients with metastasized and/or inoperable GEP or bronchial NETs treated and retreated with the PRRT ^{177}-Lu-DOTATATE.[21] The efficacy and toxicity of salvage PRRT were assessed over long-term followup.

Patients with GEP-NETs were selected for re-(re)-treatment if they had shown benefit (defined as stable disease + partial response + complete response using Response Evaluation Criteria In Solid Tumors [RECIST 1.1]) from initial PRRT and had renewed progression. Salvage PRRT took place between 2003–2015, with followup until end 2016. The intended dose for re-(re)-treatment was 14.8 GBq (400 mCi) divided over 2 administrations. Total intended cumulative dose per patient for the initial treatment (I-PRRT) was 29.6 GBq (800 mCi), for re-treatment (R-PRRT) 44.4 GBq (1200 mCi) and for re-re-treatment (RR-PRRT) 59.2 GBq (1600 mCi). Median followup was 91 months. Patients were re-treated with a median cumulative dose of 14.9 GBq (range 3.7–16.2 GBq) and re-re-treated with a median cumulative dose of 15.0 GBq (range 3.8–15.3 GBq). After I-PRRT (n=181), the median PFS was 33 (95% CI [30.4, 35.6]) months. Median PFS after R-PRRT was 14 (n=133; 95% CI [11.7, 16.3]) months and OS was 26 (n=181; 95% CI [18.9, 33.1]) months. Median PFS and OS after RR-PRRT were 14 (n=12; 95% CI [9.8, 18.2]) months and 29 (n=14; 95% CI [4.6, 53.4]) months. Overall, the OS was 77 months (95% CI [63.1, 91.0]).

AEs included grade 3–4 bone marrow toxicity, seen in 10.0%, 7.7% and 7.1% after I-PRRT, R-PRRT and RR-PRRT, respectively. Severe long-term hematologic toxicity included 2 cases of acute myeloid leukemia (AML) and 1 myelodysplastic syndrome (MDS), a prevalence not higher than previously reported. No PRRT-related grade 3–4 nephrotoxicity was observed. The authors concluded that salvage PRRT with ^{177}-Lu-DOTATATE is a feasible treatment option in patients with a good response after I-PRRT.[21]

A systematic literature review of octreotide's antitumour effects in NETs was presented by **Dr. Stephanie Barrows** at NANETS 2017 that included clinical trials and observational studies published or presented up to January 2017.

Commentary: CLARINET

COS had a chance to discuss these results with **Dr. Alexandria Phan** at the meeting. She pointed out that the studies raise the question of a potential need to reclassify nonfunctional disease according to whether it is asymptomatic or associated with biomarker elevation. "There is a subgroup of patient," she said, "larger than we expect, with nonfunctional pancreatic NETs that still have elevated chromogranin A and 5-HIAA. In treating patients with somatuline or lanreotide, those with elevated chromogranin A and 5-HIAA respond, correlating with better progression-free survival." Asked about when to initiate systemic therapy in patients with asymptomatic metastatic GI NETs, Dr. Phan concluded the decision depends somewhat on the expectations of the patient and treating physician. "But for patients with asymptomatic, low-burden, nonprogressing disease, data exist for potential use of lanreotide to treat earlier rather than later. The placebo arm of the CLARINET study was no treatment, or watch-and-wait, and the treatment arm demonstrated potential evidence that treating earlier may bring improved progression-free survival." In the CLARINET study, quality of life appeared unchanged, which makes it more acceptable to use in nonprogressing patients.

Octreotide is currently approved in the US only for carcinoid symptom control, not tumour control. Of 42 articles/abstracts identified, 13 unique studies compared octreotide with active or no treatment. Two of the 13 studies were clinical trials, and 11 were observational studies. The phase 3 PROMID clinical trial showed that octreotide LAR significantly prolonged time to tumour progression compared with placebo in patients with functionally active and inactive metastatic midgut NETs (hazard ratio [HR], 0.34; 95% confidence interval [CI], 0.20–0.59),[22] but no difference in OS was observed.[23] Retrospective observational studies found octreotide LAR treatment was associated with significantly longer OS than no octreotide LAR treatment for patients with distant metastases (HR, 0.68; 95% CI, 0.55–0.84), but not for those with local/regional disease.[24,25] Another retrospective study found that ≤20 mg octreotide LAR was associated with significantly worse OS than 21–30 mg (HR, 2.00; 95% CI, 1.32–3.04), but that doses ≥30 mg did not significantly improve OS.[26] The clinical trials and observational studies with informative evidence seem to support octreotide LAR's antitumour effect on time to tumour progression or OS. This review revealed the rarity of studies assessing octreotide's antitumour effect, an area where future research is warranted.[27]

TARGETED THERAPIES

Novel targeted therapies such as everolimus (RADIANT-3[and -2 and -4]) and sunitinib have been introduced in the clinical management of G1 and G2 NETs. Findings of the 3 RADIANT studies were consistent with the role of everolimus in prolonging PFS and not in achieving tumour shrinkage[28,2]. In the trial with sunitinib, tumour shrinkage rate in patients with pancreatic NET was low; only 9% of those treated with sunitinib achieved an objective response according to the RECIST criteria.[29] Another potential targeted treatment is vascular endothelial growth factor (VEGF) inhibitor, though the trial with bevacizumab brought disappointing results in terms of tumour shrinkage.[30] Trials combining everolimus and bevacizumab have failed to demonstrate improved efficacy.[31]

Cabozantinib is a tyrosine kinase inhibitor that acts on many targets, including MET, which is associated with decreased OS in pNETs, and VEGF receptors, which appear active in advanced disease. At NANETS 2017, **Dr. Jennifer A. Chan** from the Dana-Farber Cancer Institute in Boston reported encouraging results from a phase 2 trial of cabozantinib in patients with advanced carcinoid and pancreatic neuroendocrine tumours (pNETs), with clinical benefit seen in 90% of patients with pNETs and 78% of patients with carcinoid tumours. The primary endpoint was response rate (RECIST 1.1). Median PFS was 21.8 months (95% CI, 8.5–32.0 mo) in patients with pNET and 31.4 months (95% CI, 8.5 mo–NR) in patients with carcinoid. In patients completing ≥1 cycle, 81% (43/53) of patients required dose reduction from the initial 60 mg dose, and 21% discontinued treatment due to adverse effects. Treatment with cabozantinib was associated with objective tumour response and encouraging PFS duration in patients with advanced carcinoid and pNET. While dose reduction was common, treatment was tolerable. A randomized phase 3 trial to confirm activity of cabozantinib in carcinoid and pNET is being developed through the Alliance for Clinical Trials in Oncology.[32]

RADIOTHERAPY AND SURGICAL APPROACHES

Surgical approaches to treatment of NETs include liver resection or occlusion of the portal vein in the tumour-bearing liver lobe.[33] In NET patients with liver disease only, or with liver-dominant metastases, locoregional approaches such as ablative techniques or intraarterial therapies can be proposed in place of upfront surgery with a cytoreductive aim, leading to lesion resectability and a 5-year survival rate of 50%.[34]

NET hepatic metastases are characterized by a high rate of vascularization, as opposed to many other liver primary or secondary malignancies. Vascularization of NETs liver metastases depends mostly on the hepatic artery.[35] Arterially-directed interventional strategies, such as transarterial embolization (TAE) and transarterial chemoembolization (TACE) with a radiologically-controlled percutaneous technique, have been widely investigated and adopted during the past decade for the treatment of NETs liver metastases. These strategies have generated encouraging outcomes in term of survival, response and quality of life.[36] Hepatic TAE selectively catheterizes and obstructs the hepatic artery supplying tumour lesions to achieve ischemia and necrosis of neoplastic cells. On radiologic evaluation, TAE has been shown to improve biophysical markers, palliate symptoms and shrink tumour lesions.[37] In contrast to TAE, TACE combines blockage of the tumour blood supply with intra-arterial administration of cytotoxic drugs. In clinical practice, TACE is preferred over TAE in patients with NET with the worst prognostic factors, such as foregut origin (lung or pancreas) and poorly differentiated NETs.[38] This treatment has shown effective results in patients with metastatic liver disease, with reported OS values of 3–4 years and objective response of about 75%. Notably, response to TACE is higher when treatment is used as a first-line therapy, and liver involvement is lower. Combining results obtained with TAE and TACE, the rates of symptomatic response ranges from 39 to 95%.[39] The 2 techniques appear comparable.

At the 2017 NANETS symposium, **Dr. Michael Soulen** presented results of the Randomized Embolization Trial for NeuroEndocrine Tumour Metastases To The Liver (RETNET).[40] Neuroendocrine tumours are the second most common GI malignancy after colon cancer, and between 40% and 90% of these patients either present with or go on to develop liver metastases. This is a major determinant of symptoms and survival. Clinical and imaging response rates to embolotherapy are in the 50% to 70% range. Current National Comprehensive Cancer Network

(NCCN), NANETS, and European Neuroendocrine Tumor Society (ENETS) guidelines support embolotherapy for symptomatic or progressive hepatic metastases, but provide no recommendation about how to choose among the available techniques of embolization (TAE, TACE, transarterial radioembolization [TARE]). A practice survey in the United States found that all methods of embolization are used equally.[41]

Dr. Soulen described the design of an international investigator-initiated prospective controlled comparison of standard embolotherapy techniques for liver metastases. Results may help to refine treatment guidelines by identifying superior or inferior techniques. The primary hypothesis is that chemoembolization will be nearly twice as durable as bland embolization. Called RETNET, this open-label, multicentre, randomized comparison of 3 standard techniques of embolotherapy for neuroendocrine liver metastases is currently accruing at collaborating centres in the US, France, Argentina, Canada and Australia, with the aim of randomizing 180 subjects to 3 arms: TAE, conventional TACE (cTACE) and TACE with non-resorbable drug-eluting beads (DEB-TACE). Eligible participants will have liver-dominant neuroendocrine tumour(s) that are symptomatic or progressive, or a liver tumour burden of >25% of the liver volume without the need for documented progression.

Team CommNETS and Team ENETS with (standing) conference Co-Chairs, Dr. Michael Soulen and Dr. Simron Singh.

PHOTO COURTESY OF NANETS

No concomitant anticancer therapy (other than octreotide analogues) is allowed. The primary endpoint is hepatic progression-free survival (HPFS) by central review.[40]

LOCAL TREATMENT APPROACHES

For more localized metastases, a number of different treatment options are employed. At NANETS 2017, **Dr. Taymeyah Al-Toubah** presented a retrospective analysis of outcomes in patients with unifocal progression treated to compare

Surgical treatment

COS discussed current thinking about surgery in an interview with **Dr. Eric Nakakura** from the University of California at San Francisco. His presentation at the symposium explored how much surgery is enough in midgut NETs. "I had 3 take-home messages," he told us. "The first is that we use a lot of vague terminology to describe NETs in our field. In the title of my talk I use the term midgut, and I showed that this is very imprecise — even small intestine is a very imprecise term. The disease we're really dealing with here is ileal NET, which is a very distinct, defined process. In effect, this is the disease we're dealing with in most cases of NET. These are tumours that arise in the small intestine, they're frequently multifocal, they're very hard to diagnose because they're small, but they spread to the lymph nodes and cause a mesenteric mass that leads to a lot of the patient morbidity and problems we see."

Dr. Nakakura emphasized the importance of surgically removing the mesenteric mass, which can cause obstruction and ischemia of the intestine. "It's very important to recognize ileal NETs and consider removing them." In patients with ileal NETs, surgery should aim to remove the primary tumour, the lymph nodes in the region, and the mesenteric mass. "Removing the mesenteric mass has to be done very carefully," he stressed, "because it's located on the superior mesenteric vessels, and injuring these can lead to problems with eating and digestion." He recognizes the controversy around using minimally invasive or laparoscopic techniques, but considers that when done properly, many patients can be managed with very small incisions. "I think this is something to seriously consider in patients with advanced disease that's unresectable, who still have the primary tumour in place. Many of these patients will run into problems with the primary tumour as the mesenteric mass causes obstruction or ischemia. When that happens, the patients can't eat, and when they can't eat, you can't treat. There are a lot of promising treatments, such as PRRT, which can control liver and bone metastases, but they have no effect on the mesenteric mass, which can cause a lot of the problems in these patients." If a patient is obstructed, they cannot receive therapies such as PRRT or agents currently in clinical trials.

Dr. Nakakura stressed the importance of asking patients with advanced disease whether they are losing weight, having trouble eating, or feeling pain or cramps after they eat. "If the answer is yes, you have to consider removing that primary tumour, because they may run into problems with obstruction in the near future."

New guidelines on postsurgical followup

Dr. Eva Segelov, from Monash Health and Monash University in Australia, presented the combined COMMNETS (Commonwealth Neuroendocrine Tumour Group)/NANETS consensus guidelines for the followup of surgically resected patients after resection of GI or small-intestine NETs.[43] They concentrate on patients who have NETs that have not metastasized, either in the small bowel or pancreas. "This is a combined consensus expert guideline," said Dr. Segelov in an interview with COS, "that provides a slightly different view from the current guidelines on how patients should be followed up once they've had curative surgery for a small-bowel NET. They undertook a very large population-based cohort study with colleagues at the Institute for Clinical Evaluative Sciences in Canada and looked at followup received by almost 1000 patients who had resected small-bowel and pancreatic NETs."

Results indicated that NETs can recur much later — even beyond 10 years — than what most people consider adequate followup. "We also found," said Dr. Segelov, "that imaging to detect recurrence was most often done earlier, which doesn't really reflect the pattern of recurrence." As a result of the population series, the guidelines recommend far longer followup and fewer investigations, especially in the initial followup period. "We also identified a subgroup of patients that appear to have such a good outcome that followup wasn't justified." Dr. Segelov hopes that the new guidelines are more patient-friendly and cost-effective than previous recommendations. "We found that pancreatic NETs come back earlier than small-bowel NETs. That was a finding that has been hinted at before, but never shown in such a large series. So, our pattern of followup," she concludes, "should perhaps be different according to the site of the NET."

surgical resection, radiofrequency ablation (RFA), hepatic arterial embolization (HAE), and radiation to control discrete sites of progression, allowing patients to continue their existing therapy, and sparing them toxicities of a new systemic treatment.[42] Records were reviewed for 59 patients treated at a large referral centre between 2014 and 2017 who underwent local treatment for progressive metastatic GEP-NETs in the setting of widespread metastases. Patients undergoing lobar HAE or cytoreductive hepatic surgery were not included. The primary endpoint was time to new systemic therapy. Secondary endpoints included time to any additional intervention (systemic or local), PFS and side effects of treatment.

Of the 59 patients, 27% underwent resection, 29% RFA, 25% external beam radiation, and 19% selective HAE. With a median followup of 17 months, 19 patients (32.2%) eventually progressed and received salvage systemic treatment, and 6 patients (10.2%) progressed and received further local treatment. Median time to new systemic treatment was 42 months (95% CI, 9.7–74.3 months). Median time to any additional intervention was 21 months (95% CI, 11.4–30.6 months). Four patients died, all of whom had progressed and received further systemic treatment. In this group, control of local sites of progression enabled the majority of patients to remain on their existing systemic treatment and avoid potential toxicities associated with salvage systemic therapy.[42]

QUALITY OF LIFE

The advent of new oral therapies as the standard of care for metastatic NETs raises the issue of how to best manage AEs and ensure the safety of patients taking these therapies.

Dr. Alia Thawer, the oral chemotherapy pharmacist at the Sunnybrook Odette Cancer Centre in Toronto, performed a literature review to define the timing, grade and management of toxicities experienced by patients treated with everolimus.[44] A proactive telephone followup algorithm was developed based on literature review and the clinical experience of the interdisciplinary team. The algorithm was piloted in 16 patients, who received proactive callbacks from the pharmacist using the standardized algorithm.

All patients had at least 1 drug-related AE, and 10% had grade 3 AEs. Proactive followup identified 61% of all drug-related AEs and 54% of grade 3 toxicities; 43% of proactive calls using the algorithm resulted in treatment interruptions, while 5% resulted in urgent clinic or emergency room (ER) referrals. Dose reductions were made in 69% of patients. The most common AEs were fatigue (14%), stomatitis (13%), infections (13%), rash (11%) and nausea (9%). Median time (in days) to onset of stomatitis was 13, rash 29, diarrhea 35, fatigue 46, hyperglycemia 55, hyperlipidemia 79, infections 98 and pneumonitis 165. The most common reason for patients to be referred to the ER was infections.

These results led the team to adapt the algorithm and include assessment and interventions related to fatigue and nausea following these results. The algorithm provides standardized proactive monitoring for patients treated with everolimus and can serve as a tool to improve patient safety. Proactive followup resulted in early identification and management of AEs, with a low rate of referrals for urgent assessment.[44]

Neuroendocrine tumour progression is associated with deterioration in quality of life, both due to tumour and

Diagnosis and prognosis

Dr. Thomas Hope from the University of California at San Francisco presented at the NANETS symposium on advances in functional imaging that stand to improve the precision of diagnosis and treatment in NETs.[46] The approval in 2016 of Gallium-68 DOTATATE positron emission tomography (PET) scan in the US has already changed the way patients are imaged and staged.

In an interview with COS at NANETS, Dr. Hope described the prospects for improvement with next-generation imaging.

"The Gallium-68 DOTATATE PET scan allows you to see obviously the location of tumours much better, but more importantly, allows you to see whether patients have somatostatin receptors on their tumours, which is becoming a very important piece of management because of the development of targeted therapy or peptide receptor radionuclide therapy."

"Conventional imaging, like CT [computed tomography] or MRI [magnetic resonance imaging], is really very good at anatomic imaging, so if you can see the anatomy of a mass in the liver, you can delineate it. Things like hepatobiliary phase MRI are actually better than somatostatin receptor PET. But when you don't know where the disease is, in particular when it's small and extrahepatic, somatostatin receptor PET is useful for 2 things: 1 is demonstrating that it is real disease. If you see a small node that has uptake, that's definitely a tumour, whereas a sub-centimetre node on CT could be anything; that specificity really adds value. The other use is in osseous disease: somatostatin receptor PET has a huge benefit in the evaluation of bone disease, as we're seeing a lot more osseous metastatic disease than we have previously."

"Conventional imaging and somatostatin receptor PET play a combined role in the staging of patients. Once you know where the disease is, you can then choose CT or MRI to follow that disease appropriately. If it involves mesenteric nodes, then CT is very good at following the change in size over time; in liver disease, MRI is really good; if it's bone disease, which you can't see on conventional imaging, then you might want to follow it with somatostatin receptor PET. The 2 have a complementary benefit in terms of following patients."

hormone-related symptoms. At NANETS 2017, **Dr. Jonathan Strosberg** from the H. Lee Moffitt Cancer Center presented a study of quality of life in the NETTER-1 clinical trial[45] to determine the impact of treatment on time to deterioration in health-related quality of life (HRQoL). The NETTER-1 trial is an international phase 3 study that enrolled patients with progressive, somatostatin receptor-positive midgut neuroendocrine tumours, and randomized them to receive treatment with either ^{177}Lu-DOTATATE or high-dose (60 mg) octreotide LAR. Two EORTC questionnaires were used to determine the impact of treatment on HRQoL.

Patients completed the questionnaires at baseline and every 12 weeks thereafter until progression was centrally confirmed. The time to deterioration was defined as the time (in months) between randomization and the first QoL deterioration ≥10 points for each patient in the corresponding domain scale. Time to QoL deterioration was significantly longer in the ^{177}Lu-DOTATATE arm vs the control arm for global health status, physical functioning, role functioning, fatigue, pain, diarrhea, disease-related worries and body image. In the other domains, time to deterioration did not reach statistical significance between the arms. The analysis demonstrates that ^{177}Lu-DOTATATE provides a significant quality-of-life benefit for patients with progressive midgut NETs compared to high-dose octreotide, in addition to the meaningful increase in PFS already reported.[45]

WHAT'S NEXT...

With the various treatment modalities becoming available, there is a need for more and better knowledge about combining and sequencing therapies. **Dr. Tim Asmis,** from the Ottawa Hospital Cancer Centre, particularly noted the difference of opinion regarding the appropriateness of observation or surgery for asymptomatic nonfunctional small pancreatic NETs that had no evidence of lymph node or distant metastases. "In Canada, we have a consensus guideline written a few years ago that did argue that, for patients with tumours less than 2 cm, observation is an appropriate strategy," Dr. Asmis told COS in an interview at the symposium. "However, we heard a fair number of dissenting opinions from the audience [at the symposium], with some who would argue that upfront surgery was indicated. Anywhere in medicine where you have such a wide variation of opinions, it really is a call to action to perform more research, where we can have more data so that there is less controversy, and we can present our patients with hopefully

some form of consensus."

Dr. Simron Singh, from Sunnybrook Health Sciences Centre, cochair of the 2017 NANETS symposium, along with Dr. David Metz and Dr. Michael Soulen from the University of Pennsylvania, summed up the take-away messages from the meeting in an interview with COS:

"We've seen a growth in this conference year after year. Specific themes that have really resonated for me at this conference have been the increased multidisciplinary practice of neuroendocrine tumours. We've been talking about this for a long time, but there were a lot of good sessions that really integrated roles that various team members play in the care of neuroendocrine cancers. We saw a lot on the advances in PRRT and attempts to understand how PRRT can be integrated into the care pathway. We heard about some of the new trials that are taking place and some of the new treatments that are being developed. We debated about surgical [techniques] and the role of surgery in neuroendocrine cancer. We talked about quality of life. I'm especially pleased at the number of Canadian speakers, bringing Canadian research and Canadian perspectives."

References

1. Caplin ME, Pavel M, Ćwikla JB, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med* 2014;371:224–33.
2. Yao JC, Fazio N, Singh S, et al. Everolimus for the treatment of advanced nonfunctional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet* 2016;387:968–77.
3. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 trial of177Lu-DOTATATEfor midgut neuroendocrine tumors. *N Engl J Med* 2017;376:125–35.
4. Kulke MH, Hörsch D, Caplin ME, et al. Telotristat ethyl, a tryptophan hydroxylase inhibitor for the treatment of carcinoid syndrome. *J Clin Oncol* 2017;35:14–23.
5. Pavel M, Gross D, Benavent M, et al. Efficacy and safety results of telotristat ethyl in patients with carcinoid syndrome during the double-blind treatment period of the TELECAST phase 3 clinical trial. Presented at: North American Neuroendocrine Tumor Society meeting; September 30–October 1, 2016; Jackson, WY. Abstract 174.
6. Strosberg J, Weber J, Feldman M, et al. Above-label doses of octreotide-LAR in patients with metastatic small intestinal carcinoid tumors. *Gastrointest Cancer Res* 2013;6(3):81–85.
7. Kulke MH, Mayer RJ. Carcinoid tumors. N Engl J Med 1999;340(11):858–868.
8. Liu Q, Yang Q, Sun W, et al. Discovery and characterization of novel tryptophan hydroxylase inhibitors that selectively inhibit serotonin synthesis in the gastrointestinal tract. *J Pharmacol Exp Ther* 2008;325(1):47–55.
9. Kulke M, Hörsch D, Caplin M, et al. Telotristat etiprate is effective in treating patients with carcinoid syndrome that is inadequately controlled by somatostatin analog therapy: the phase III TELESTAR clinical trial. Presented at: European Cancer Congress; September 25–29, 2015; Vienna, Austria. Abstract 37LBA.
10. Pavel M, Benavent M, Perros P, et al. Poster presented at: NANETS Annual Symposium; October 19–21, 2017; Philadelphia, PA. https://www.nanets.net/nanets_cd/2017/pdfs/C14.pdf. Abstract C-14.
11. Dillon JS, Kulke MH, Pavel M, et al. () Time to sustained improvement in bowel movement frequency with telotristat ethyl: analysis of the Phase 3 TELESTAR study. Poster presented at: NANETS Annual Symposium; October 19–21, 2017; Philadelphia, PA. https://www.nanets.net/nanets_cd/2017/pdfs/C5.pdf. Abstract C-5.
12. Cai B, Broder MS, Chang E, et al (Predictive factors of carcinoid syndrome (CS) among patients with gastrointestinal neuroendocrine tumors (GI NETs). Poster presented at: NANETS Annual Symposium; October 19–21, 2017; Philadelphia, PA. https://www.nanets.net/nanets_cd/2017/pdfs/P1.pdf. Abstract P-1.
13. Mocellin S, and Nitti D. Gastrointestinal carcinoid: epidemiological and survival evidence from a large population-based study (n= 25 531). *Annals of Oncology* 2013;24(12): 3040-4.
14. Halperin DM, Shen C, Dasari A, et al. Frequency of carcinoid syndrome at neuroendocrine tumour diagnosis: a population-based study. *The Lancet Oncology.* 2017;18(4):525-34.
15. Beaumont JL, Cella D, Phan AT, et al. Comparison of health-related quality of life in patients with neuroendocrine tumors with quality of life in the general US population. *Pancreas.* 2012;41(3):461-6.
16. Singh S, Granberg D, Wolin E, et al. Patient-reported burden of a neuroendocrine tumor (NET) diagnosis: results from the first global survey of patients with NETs. *Journal of Global Oncology.* 2016;3(1):43-53.
17. Caplin ME, Pavel M, Ćwikła JB, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med* 2014;371:224–33.
18. Molin E, Pavel ME, Ćwikła JB,et al Final progression-free survival analyses for lanreotide autogel/depot 120 mg in metastatic enteropancreatic neuroendocrine tumors: the CLARINET extension study. Poster presented at: NANETS Annual Symposium; October 19–21, 2017; Philadelphia, PA. https://www.nanets.net/nanets_cd/2017/pdfs/C22.pdf. Abstract C-22.
19. Phan A, Wolin EM, Fisher Jr GA, et al. Safety and tolerability of lanreotide autogel/depot in patients with neuroendocrine tumors: pooled analysis of clinical studies. Poster presented at: NANETS Annual Symposium; October 19–21, 2017; Philadelphia, PA. (https://www.nanets.net/nanets_cd/2017/pdfs/C15.pdf. Abstract C-15.
20. Kwekkeboom DJ, de Herder WW, Kam BL, et al. Treatment with the radiolabeled somatostatin analog [177Lu-DOTA0,Tyr3]octreotate: toxicity, efficacy, and survival. *J Clin Oncol* 2008;26:2124–30.
21. van des Zwan W, Brabander T, Kam B, et al. PFS and OS after salvage peptide receptor radionuclide therapy (PRRT) with 177Lu[DOTA0,Tyr3]octreotate in Patients with GastroEnteroPancreatic or Bronchial NeuroEndocrine Tumours (GEP-NETs) – The Rotterdam Cohort. Poster presented at: NANETS Annual Symposium; October 19–21, 2017; Philadelphia, PA. https://www.nanets.net/nanets_cd/2017/pdfs/C36.pdf. Abstract C-36.
22. Rinke A, Müller HH, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol* 2009;27(28):4656–63.
23. Rinke A, Wittenberg M, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors (PROMID): Results of Long-Term Survival. *Neuroendocrinology* 2017;104(1):26–32.
24. Shen C, Shih YC, Xu Y, Yao JC. Octreotide long-acting repeatable use among elderly patients with carcinoid syndrome and survival outcomes: a population-based analysis. *Cancer* 2014;120(13):2039–49.
25. Shen C, Shih YC, Xu Y, Yao JC. Octreotide long-acting repeatable among elderly patients with neuroendocrine tumors: a survival analysis of SEER-Medicare data. *Cancer Epidemiol Biomarkers Prev* 2015;24(11):1656–65.
26. Shen C, Xu Y, Dasari A, et al. Octreotide LAR dosage and survival among elderly patients with distant-stage neuroendocrine tumors. *Oncologist* 2016;21(3):308–13.
27. Barrows SM, Cai B, Wright K, et al. Systematic literature review of octreotide's antitumor effects in neuroendocrine tumors. Poster presented at: NANETS Annual Symposium; October 19–21, 2017; Philadelphia, PA. https://www.nanets.net/nanets_cd/2017/pdfs/C3.pdf. Abstract C-3.
28. Pavel ME, Hainsworth JD, Baudin E, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. *Lancet* 2011;378:2005–12.
29. Raymond E, Dahan L Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med* 2011;364:501–13.
30. Yao JC, Phan A, Hoff PM, et al. Targeting vascular endothelial growth factor in advanced carcinoid tumor: a random assignment phase II study of depot octreotide with bevacizumab and pegylated interferon alpha-2b. *J Clin Oncol* 2008;26:1316–23.

31. Kulke MH, Niedzwiecki D, Foster NR, et al. Randomized phase II study of everolimus (E) versus everolimus plus bevacizumab (E+B) in patients (Pts) with locally advanced or metastatic pancreatic neuroendocrine tumors (pNET), CALGB 80701 (Alliance). Proceedings of the 2015 ASCO Annual meeting. *J Clin Oncol* 2015;33:15S, abs 4005.
32. Chan J, Faris J, Murphy J, et al. Phase II trial of cabozantinib in patients with carcinoid and pancreatic neuroendocrine tumors. Poster presented at: NANETS Annual Symposium; October 19–21, 2017; Philadelphia, PA. https://www.nanets.net/nanets_cd/2017/pdfs/C4.pdf. Abstract C-4.
33. Schnitzbauer AA, Lang SA, Goessmann H, et al. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. *Ann Surg* 2012;255:405–14.
34. Ho AS, Picus J, Darcy MD, et al. Long-term outcome after chemoembolization and embolization of hepatic metastatic lesions from neuroendocrine tumors. *Am J Roentgenol* 2007;188:1201–7.
35. Vogl TJ, Naguib NN, Zangos S, et al. Liver metastases of neuroendocrine carcinomas: interventional treatment via transarterial embolization, chemoembolization and thermal ablation. *Eur J Radiol* 2009;72:517–28.
36. Toumpanakis C, Meyer T, Caplin ME. Cytotoxic treatment including embolization/chemoembolization for neuroendocrine tumours. *Best Pract Res Clin Endocrinol Metab* 2007;21:131–44.
37. Del Prete M, Fiore F, Modica R, et al. Hepatic arterial embolization in patients with neuroendocrine tumors. *J Exp Clin Cancer Res* 2014;33–43.
38. Pericleous M, Caplin ME, Tsochatzis E, et al. Hepatic artery embolization in advanced neuroendocrine tumors: efficacy and long-term outcomes. *Asia Pac J Clin Oncol* 2016;12:61–9.
39. Dong XD, Carr BI. Hepatic artery chemoembolization for the treatment of liver metastases from neuroendocrine tumors: a long-term follow-up in 123 patients. *Med Oncol* 2011;28 suppl 1:S286–90.
40. Soulen M. Randomized embolization trial for neuroendocrine tumor metastases to the liver (RETNET). Poster presented at: NANETS Annual Symposium; October 19–21, 2017; Philadelphia, PA. https://www.nanets.net/nanets_cd/2017/pdfs/T6.pdf. Abstract T-6.
41. Gaba RC. Chemoembolization practice patterns and technical methods among interventional radiologists: results of an online survey. *AJR Am J Roentgenol* 2012;198(3):692–9.

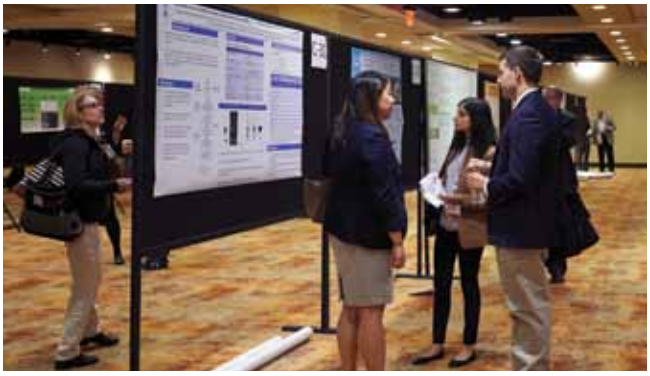

PHOTO COURTESY OF NANETS

42. Al-Toubah T, Cives M, Anaya D, et al. () Outcomes of locoregional treatment for unifocal progression in widespread metastatic gastroenteropancreatic neuroendocrine tumors. Poster presented at: NANETS Annual Symposium; October 19–21, 2017; Philadelphia, PA. https://www.nanets.net/nanets_cd/2017/pdfs/C2.pdf. Abstract C-2.
43. Singh S, Moody L, Chan DL, et al. Follow-up recommendations for completely resected gastroenteropancreatic neuroendocrine tumours (GEP-NETs): consensus guidelines from the Commonwealth Neuroendocrine Tumour Collaboration (CommNETS) in conjunction with the North American Neuroendocrine Tumour Society (NANETS). Presented at: NANETS Annual Symposium; October 19–21, 2017; Philadelphia, PA. Submitted for publication.
44. Thawer A, Chan, Leake J, et al. Pharmacist-led development of an adverse event (AE) management algorithm for the proactive monitoring of patients with neuroendocrine tumours (NETs) on everolimus. Poster presented at: NANETS Annual Symposium; October 19–21, 2017; Philadelphia, PA. https://www.nanets.net/nanets_cd/2017/pdfs/C18.pdf.
45. Strosberg et al. QOL improvements in NETTER-1 phase III trial in patients with progressive midgut neuroendocrine tumors. Poster presented at: NANETS Annual Symposium; October 19–21, 2017; Philadelphia, PA. https://www.nanets.net/nanets_cd/2017/pdfs/C33.pdf. Abstract C-33.
46. Hope T. Personalizing therapy for NETs with functional imaging. Presented at: NANETS Annual Symposium; October 19–21, 2017; Philadelphia, PA.