A Pilot Study To Evaluate Patient Experience with the Somatostatin Analogs Octreotide Long Acting Release and Lanreotide during the Treatment of Advanced, Nonfunctional, Well Differentiated Neuroendocrine Tumors

PROTOCOL FACE PAGE FOR
MSK NON THERAPEUTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

OneMSK Sites	
Manhattan	All Protocol Activities
Basking Ridge	All Protocol Activities
Bergen	All Protocol Activities
Commack	All Protocol Activities
Monmouth	All Protocol Activities
Westchester	All Protocol Activities
Nassau	All Protocol Activities

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Title of Study: A pilot study to evaluate patient experience with the somatostatin analogs (SSA) octreotide long acting release (LAR) and lanreotide during the treatment of advanced, nonfunctional, well differentiated neuroendocrine tumors (WDNETs)

Study Centers: Memorial Sloan Kettering Cancer Center (MSKCC)

Trial Phase: Pilot study

Clinical Indication: Well differentiated neuroendocrine tumors (WDNETs)

Trial Type: Two-arm randomized design

Type of control: No treatment control

Route of administration: Each patient on study will receive three injections of intramuscular (IM) octreotide LAR and three injections of deep subcutaneous (subq) lanreotide

Trial blinding: No trial blinding

Number of trial subjects: 50 patients

Estimated duration of trial: Approximately 30 months from the time the first subject signs the informed consent until the final consenting subject's last visit

Study Design:

This will be a two-arm, randomized, pilot study of 50 patients. Patients presenting with advanced WDNETs, recommended to begin SSA therapy by their provider, will be eligible to participate. As described in the protocol schema below, patients will be randomized to the order in which they receive two standard-of-care SSA by monthly injection (i.e. octreotide LAR before lanreotide, or lanreotide before octreotide LAR). Randomization will occur centrally at MSKCC on day of protocol enrollment. Our nursing staff will administer all injections; octreotide LAR will be manually prepped in clinic just prior to injection, and lanreotide will be sent from pharmacy in a prefilled syringe. Patients will receive three monthly injections of one SSA (drug A), followed by three monthly injections of the other SSA (drug B).

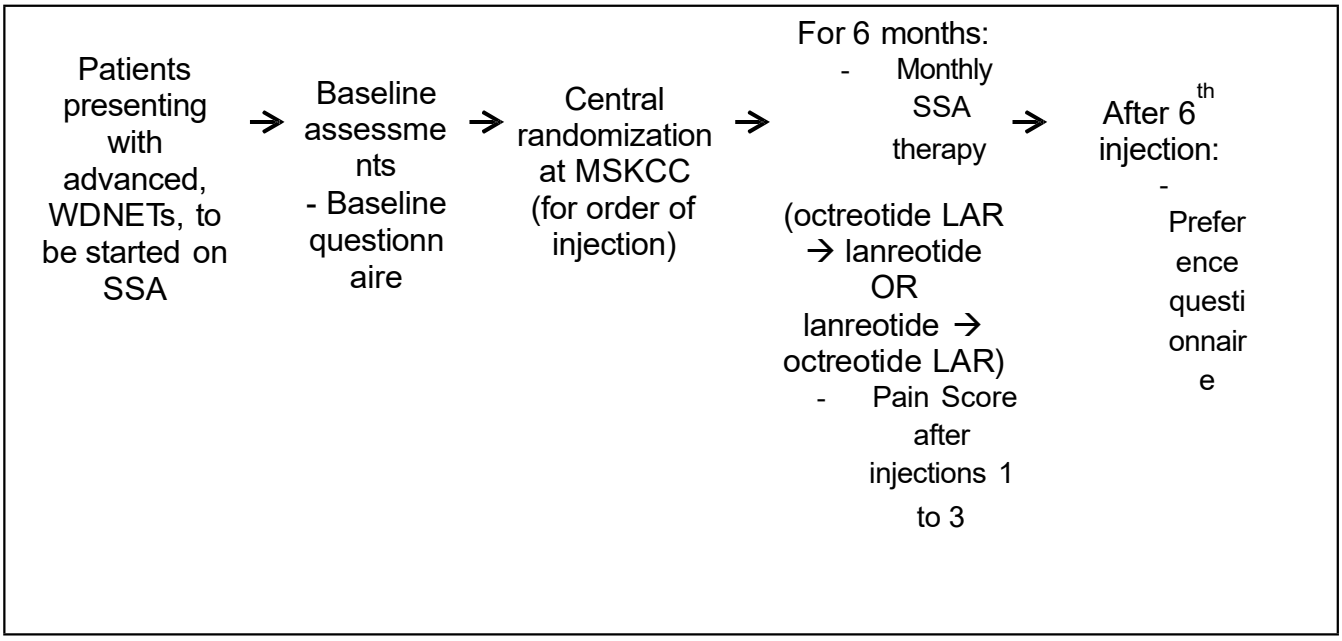
The study participation period for each patient is 6 months from the date of beginning treatment. There will be 4 time periods:

1. Pre-treatment evaluation on day of protocol enrollment at which time a baseline questionnaire will be completed.
2. SSA injections #1, 2, and 3 (with drug A) every 28 (+/- 3) days with numeric pain score (0 to 10) obtained in clinic and by diary following injection.
3. SSA injections #4, 5, and 6 (with "drug B") every 28 (+/- 3) days.
4. End of study evaluation after SSA injection #6, at which time a preference questionnaire will be completed by all patients.

After completion of this study, if patients are recommended to continue SSA therapy, they will continue on octreotide LAR moving forward which is on MSK formulary without restrictions.

We anticipate accrual of 1 to 2 patients per month, with accrual to this study completed in 24 to 36 months.

Protocol Schema:



2.1 OBJECTIVES AND SCIENTIFIC AIMS Overview: Octreotide LAR has been used since the early 1990's to slow tumor growth. The original registration was for control of hormone-related symptoms, however prolonged progression-free survival (PFS) has been shown in a randomized, double-blind, placebo-controlled trial. However, octreotide LAR has not been specifically registered with the FDA for this specific purpose.

Based on the more recently published registration trial, lanreotide has been specifically FDA-approved for tumor control of well differentiated NETs. NCCN guidelines regard these two agents as equally acceptable treatment options. However, the average sales price (ASP) of one dose of octreotide LAR is $3362, while the ASP of lanreotide is $6157. These shots are given every 4 weeks. So the annual costs are $43,706 versus $80,041, or $36,335 per patient per year. This difference is likely to increase further, as generic versions of octreotide LAR are expected on the market shortly. Furthermore, due to both increasing incidence and prevalence of NETs, plus the fact that these agents are often taken for many years by patients, the potential for financial toxicity associated with lanreotide is considerable.

We believe that the increased cost of lanreotide relative to octreotide LAR is not warranted, and on the GI Oncology Service we use octreotide LAR unless there is a specific contraindication which favors lanreotide. Both agents are on the MSK formulary (lanreotide available with restrictions).

A major marketing point of lanreotide is the claim that the injection is more comfortable for patients. Octreotide is given as an intramuscular injection, while lanreotide is given as a "deep subq injection," although the designation of "deep" subq is unique to this agent and is not well defined. We hypothesize that patients will find little or no subjective difference between these two injections. A demonstration of this is likely to have a significant impact on the treatment of NETs in practice in this country and abroad. There is considerable interest in this topic and this study within the NET community.

The purpose of this study is to evaluate patient experience with the SSA octreotide LAR and lanreotide. In this study, patient experience is defined as the pain experienced with the drug injections, as octreotide LAR is administered IM, and lanreotide is administered deep subq. This will be directly evaluated through the primary objective. We will also try to further understand other aspects of patient experience by studying drug preference and financial toxicity with our secondary objectives. We have developed our own questionnaires to study some of these secondary objectives, as there are no validated questionnaires available to address these issues for this patient population.

- Primary objective: To compare injection site pain experienced with octreotide LAR and lanreotide.
- Primary endpoint: Comparison of mean pain score over the first three injections of either octreotide LAR or lanreotide.
- Secondary objectives:
    - To evaluate if patients have a preference for octreotide LAR or lanreotide.
    - To evaluate patient willingness to pay for preferred SSA therapy.
    - To quantify amount of time spent by nurses in clinic to prepare SSA injections.
- Secondary endpoints:
    - Patient-reported preference of octreotide LAR vs lanreotide assessed after six months of therapy by post-treatment questionnaire.
    - Patient-reported willingness to pay for preferred therapy, assessed by post-treatment questionnaire.
    - Nursing-reported measurement of time spent preparing SSA injections in clinic.

3.1 BACKGROUND AND RATIONALE

3.2 Well differentiated neuroendocrine tumors (WDNETs)

WDNETs are an uncommon and heterogeneous group of neoplasms that arise throughout the body, most commonly in the lung and gastrointestinal tract.[1] These tumors are subdivided into carcinoid tumors and pancreatic neuroendocrine tumors (panNETs); panNETs are the second most common tumor of the pancreas, and represent 1-2% of all pancreatic neoplasms.[2,3] Carcinoid tumors develop from the neuroendocrine tissues of the aerodigestive tract, and panNETs develop from the endocrine tissues of the pancreas (i.e. islets of Langerhans). This group of WDNETs is both morphologically and clinically distinct from high grade neuroendocrine carcinomas, tumors that are characterized by an extremely aggressive behavior and are treated along small cell lung cancer paradigms with platinum-based chemotherapy.[4] Epidemiological data from the last 30 years has demonstrated that the incidence of NETs continues to rise, while there have been no significant changes in survival from this disease.[5,6]

Although the majority of WDNETs are slow growing, after the development of metastatic disease (most commonly, in the liver), median survival ranges from 2 to 5 years, and most patients with liver metastases will die from disease.[7] A subset of carcinoid tumors (less than 10%) and panNETs (just over 30%) are functional tumors and produce clinical syndromes due to excessive hormone secretion. Functional carcinoid tumors classically release serotonin and can cause "carcinoid syndrome." The release of serotonin can cause hot red flushing of the face, severe diarrhea, and wheezing; rarely, the deposition of serotonin in the heart can cause cardiac disease.[8] Functional panNETs are classified by the hormones they hypersecrete, and include insulinoma (secrete insulin and cause hypoglycemia), gastrinoma (secrete gastrin and cause

Zollinger-Ellison syndrome, which is characterized by severe peptic ulcer disease), glucagonoma (secrete glucagon and cause hyperglycemia), and vasoactive intestinal polypeptide (VIPoma, secrete VIP and cause severe secretory diarrhea).[3,9-11] Non-functional WDNETs are tumors that do not secrete hormones or the products they secrete do not cause a clinical syndrome; examples include pancreatic polypeptide, chromogranin A, ghrelin, neurotensin, subunits of chorionic gonadotropin, and neuron-specific enolase.[11] Metastatic disease is a common presentation for the majority of patients with WDNETs, especially those with non-functioning tumors given the absence of clinical symptoms that would warrant earlier clinical evaluation.[7]

Asymptomatic patients diagnosed with advanced, metastatic WDNETs are often monitored initially, however with time, often their disease will progress and require treatment. The typical indications for therapy are pain and symptoms due to tumor bulk, symptoms from hormone secretion for functional tumors, high tumor burden, or progression of disease under observation.[9] Given the heterogeneous clinical presentations and complex spectrum of aggressiveness of WDNETs, their treatment is challenging, and requires multimodality management with surgeons, interventional radiologists, medical oncologists, endocrinologists and gastroenterologists.

There are multiple systemic therapy options available for the treatment of metastatic WDNETs. These systemic options include SSA, targeted agents, and sometimes (usually in the setting of grade transformation) cytotoxic chemotherapy. SSA is often the first choice for treatment, and there are currently two options (both listed on NCCN guidelines): octreotide LAR or lanreotide. Of note, lanreotide is the only SSA that is approved by the FDA for the treatment of tumor control in non-functional gastroenteropancreatic NETs (GEP-NETs), based on the results of the CLARINET study (see Section 3.2.2). However, it is believed that octreotide LAR and lanreotide are biochemically similar, and at MSK, given the much higher retail price/institutional drug cost of lanreotide (see Section 3.2.3), lanreotide is not routinely offered to our patients. Lanreotide is currently available on the MSK formulary *with restrictions*; specifically, use of lanreotide requires approval from the P&T Chair or designee, and is restricted to patients receiving anticoagulation, or a personal history of bleeding from the intended injection site, or insufficient soft tissue mass.

To date, no investigation has previously been undertaken to look at differences in one SSA versus the other. While it is believed that both octreotide LAR and lanreotide are biochemically similar and likely offer similar control of disease, these drugs differ in terms of mode of administration, and it has been suggested that this difference may impact patient experience and drug preference. The purpose of this study is to investigate the patient experience with these two SSA; we hypothesize that there is unlikely to be a meaningful difference, as octreotide LAR is administered IM, and lanreotide is administered “deep subq.” However, if there is a meaningful difference in patient experience, with lanreotide being preferred by patients, we believe it could justify the higher cost of this drug to the institution and impact our use of lanreotide at MSK, when treating patients with WDNETs. We are limiting this study to patients with non-functional tumors to maintain a homogenous patient population, and to eliminate other biases that could impact patient experience.

3.3 Somatostatin analog therapy

Somatostatin and its synthetic analogs (i.e. octreotide and lanreotide) bind to G-protein couple receptors on the cell surface to exert their effects. There are five known subtypes of somatostatin

receptors, SST1-SST5, and binding of somatostatin to these receptors can inhibit the release of hormones and secretory proteins and also stall tumor growth, offering cytostatic control.

The majority of WDNETs express somatostatin receptors (most commonly SST2) on their surface and are octreotide avid on SSA scintigraphy (i.e. Octreoscan™).[12,13] In octreotide positive disease, SSA are often used first line, as they are well tolerated, treat functional symptoms (in those tumors that are hormone secreting), and have been demonstrated to have an anti-proliferative, cytostatic effect on the growth of tumor.

3.3.1 SSA and control of symptoms from hormone secretion

Therapy with octreotide and lanreotide has revolutionized the way we care for patients with hormone producing, functional WDNETs. In the earliest study of SSA in patients with carcinoid syndrome, 25 patients with metastatic carcinoid tumors were treated with short-acting octreotide (150 mcg subq three times a day); 18/25 (72%) patients experienced a decrease of 50% or more in their urinary 5-HIAA levels, and 7/24 (29%) patients who reported flushing experienced complete relief of treatment, while 4/25 (16%) patients who reported considerable diarrhea experienced complete relief. In many subsequent studies, both partial and complete relief of carcinoid syndrome symptoms has been demonstrated in the majority of patients studied.[14-20]

As previously discussed, functional panNETs include insulinomas, gastrinomas, glucagonomas, and VIPomas. SSA appear to be highly useful in the treatment of functional symptoms from VIPomas and glucagonomas, with an improvement seem in secretory diarrhea in VIPomas and an improvement in necrolytic migratory erythema, a characteristic blistering skin rash, in glucagonomas.[21-23] However, although insulinomas and gastrinomas are the most common types of functional panNETs, SSA appear to have a more limited role in controlling their hormone-related symptoms. In particular, when initiating SSA therapy on insulinomas, close monitoring of glucose levels is required, as there can be transient worsening of hypoglycemia; hypoglycemia can occur as nearly half of insulinomas do not express SST2 and SSA therapy can blunt a compensatory glucagon response.[9] In gastrinomas, rather than SSA, proton pump inhibitors are the preferred treatment to blunt the effects of excessive gastric acid production.

3.3.2 SSA and control of tumor growth

In addition to treating hormone-related symptoms in functional tumors, octreotide and lanreotide have a role in controlling tumor growth of non-functional as well as functional tumors. As previously discussed, observation alone is generally pursued for patients with asymptomatic, advanced, unresectable WDNETs and small volume disease, as disease may remain indolent for months to years; SSA therapy is subsequently initiated when there is evidence of clinically meaningful tumor progression.

The earliest studies investigating a cytostatic role for SSA included patients with many types of NETs. In one phase II trial, 34 patients with advanced NETs were treated with octreotide as antineoplastic therapy after clear objective disease progression; with a median follow-up of 29 months, the median survival for this patient population from the start of octreotide therapy had not been reached.[24] In this study, 17/34 (50%) patients had disease stabilization for a minimum of two months based on CT imaging. In another prospective study, 21 patients with metastatic GEP-NETs were treated with short-acting octreotide 200 micrograms three times a day; no patients

had documented tumor shrinkage, and the most favorable response was stability of disease in 5/21 (24%) patients.[25]

The first randomized data to support an antiproliferative role for octreotide in the treatment of NETs came from the phase III PROMID study; this study included only midgut NETs and not panNETs.[26] In this study, 85 patients were randomized to either placebo or octreotide LAR 30 mg IM every month until progression of disease or death. The primary endpoint was time to tumor progression (TTP), and the investigators observed a significant difference in TTP in the octreotide LAR and placebo groups (14.3 months versus 6 months, p=0.000072). In clinical practice and by NCCN guidelines, physicians were extrapolating the use of octreotide in midgut tumors to use in panNETs but no prospective randomized data exist.[27]

The CLARINET study, however, confirmed the antiproliferative effect of SSA in GEP- NETs.[28] In this double-blind, placebo-controlled, multinational study in patients with low or intermediate grade, well or moderately differentiated NETs (45% panNETs), 204 patients were randomized to receive an extended-release aqueous-gel formulation of lanreotide (Autogel) at a dose of 120 mg or placebo once every 28 days for 96 weeks; the primary endpoint was progression-free survival (PFS), defined as time to disease progression or death. The authors observed that lanreotide was associated with significantly prolonged PFS in comparison to placebo (median not reached versus median of 18 months, p<0.001).There were no significant differences between the two groups in quality of life or overall survival. The most common adverse event was diarrhea, which was more prevalent in patients receiving lanreotide (26% in the lanreotide group and 9% in the placebo group). The CLARINET study confirmed that in comparison to placebo, lanreotide is safely tolerated and significantly prolongs PFS in patients with metastatic NETs; based on these findings, lanreotide is the only SSA that is FDA-approved for tumor control in non-functional GEP-NETs.

Of note, while lanreotide is the only SSA FDA approved for cytostatic tumor control in the treatment of NETs (given the trial design of CLARINET and PROMID), octreotide LAR is believed to have similar efficacy in controlling tumor growth based on the available data and identical mechanism of action of the two drugs.[28] Per NCCN guidelines, either octreotide LAR or lanreotide are listed as treatment options for cytostatic control of octreotide avid disease.

3.3.3 Octreotide LAR vs lanreotide: similarities and differences

Both octreotide LAR and lanreotide are 8 amino acid synthetic analogues of somatostatin. Both drugs have the same mechanism of action and are designed to bind the somatostatin receptor, but have a longer half-life than somatostatin. Both drugs display a greater affinity for the SST2 and SST5 receptors. In the currently available formulations, both drugs are administered monthly. Although no trial has directly compared octreotide LAR and lanreotide for efficacy or tolerability, the assumption based on their mechanism of action is that the two drugs are identical, and similarly offer symptomatic and as well as cytostatic control in NETs.

Though these drugs have many similarities biochemically, they differ in three key ways: preparation, mode of administration, and cost, which may influence patient experience and preference for drug.

Preparation: Octreotide LAR is manually mixed in clinic; both the powder and diluents must first

reach room temperature, and then the powder must be completely saturated and uniformly suspended in the diluent *immediately* prior to injection. It is estimated by our nurses that this entire preparation period takes approximately seven minutes on average for each octreotide LAR injection administered in the clinic setting. To contrast, lanreotide is administered subcutaneously, and is an aqueous gel that comes in a prefilled syringe, requiring no in-clinic preparation. Given the very high volume of RN/nurse-only visits for SSA injections in our clinics providing care to NET patients, and the time requirements necessary to prepare octreotide LAR injections in specific, we now have a weekly clinic led by our nurses during which patients receive their monthly SSA injections. The amount of time spent by nurses preparing and mixing these injections while also assessing patients just prior to and after injection administration has never been quantified in a prospective fashion.

Mode of administration: Octreotide LAR is administered **IM** while lanreotide is administered **deep subq**. It has been reported that up to 50% of patients receive injection site pain with octreotide LAR (with up to 5% developing hematomas at the injection site).[Reference: Octreotide LAR drug manual - Novartis] In comparison, about 20% of patients receiving lanreotide report injection site pain.[Reference: Lanreotide drug manual - Ipsen] This “injection site pain” has never been quantified from the patient’s perspective. However, on this limited data, it is assumed that lanreotide is less painful for patients, and may be the preferred SSA by patients; these assumptions have not been studied to date.

Cost: There is also a cost difference between octreotide LAR and lanreotide, with an average sales price (as of October 2016) of approximately $3362 each month for a typical dose of octreotide LAR (20 mg) and $6157 each month for a typical dose of lanreotide (120 mg).[Reference: Centers for Medicare and Medicaid Services Manufacturer reporting of Average Sales Price data]. Given the results of CLARINET, over the period of time a patient may be on lanreotide (>2 years), this cost differential in retail price of lanreotide could easily exceed $67,000 per patient.

Given increased cost-sharing, through co-payments, co-insurance, and high deductible insurance plans, all patients, including those who are well-insured, are at risk for experiencing the burden of high cost cancer treatments. Looking at US prices for new cancer drugs, these prices have soared from approximately $170 per month of therapy in the 1970s, to $10,000 per month as of 2014.[29] Through prior investigation, it has been shown that these higher drug costs can result in decreased adherence, increased bankruptcy, as well as personal sacrifice.[30,31](National Survey of Households affected by Cancer) Looking specifically in advanced cancer patients, it has been demonstrated that 1 in 4 patients abandoned their cancer drugs when out-of-pocket costs exceeded $500 – a “*side effect”* of cancer treatment the American Society of Clinical Oncology (ASCO) has termed “financial toxicity.”

In prior experience at MSK, when two drugs have demonstrable equal efficacy but real cost differences (for example in colorectal cancer: ziv-aflibercept and bevacizumab, cetuximab and panitumumab), we have recognized and acknowledged that there are not two equivalent regimens (i.e. offering all options and leaving the decision of which drug to use to the treating physician); rather, we have recognized there is really only one appropriate regimen, and neither ziv-aflibercept nor cetuximab are on our formulary and available for use by providers at MSK.

Similarly, at this time, in an effort to control and limit costs, octreotide LAR is available on MSK

formulary for all patients and lanreotide is available on MSK formulary with restrictions, limited to those receiving anticoagulation, with a personal history of bleeding from the intended injection site, or with insufficient soft tissue mass to administer the shot. It is of note that MSK is one of the only institutions that does not have lanreotide freely available and current practice in the community and at other centers is changing to use lanreotide more frequently despite the higher retail price, particularly as it is now approved by the FDA for tumor control. Unlike the above examples in colorectal cancer, we recognize that the differences in drug administration between octreotide LAR and lanreotide could impact patient experience and drug preference. In our opinion, an improvement in patient experience could change the *value* of lanreotide (if lanreotide is in fact preferred by our patients), and impact our decision to use lanreotide without restrictions at MSK. For this reason, we have developed this pilot study, to evaluate the question "does patient experience impact choice for a particular SSA?" Given our belief that there is minimal difference in patient experience between an IM and deep subq injection, we hypothesize that there will not be a difference in patient experience between the two SSA to justify our inclusion of lanreotide onto the MSK formulary without restrictions.

In order to answer the above question and study our hypothesis, this pilot study will evaluate the pain or discomfort experienced during SSA administration, to quantify the toxicity that may impact experience and drive patient drug preference. Through a questionnaire we have developed specific for this study (Appendix C), as there are no available validated questionnaires, patients will indicate their level of preference for these injections. In addition, we will study "financial toxicity," and collect data on patient willingness to pay for a preferred drug.

Ultimately, we believe that the findings from this pilot study will illustrate that patients will find little or no subjective difference between octreotide LAR and lanreotide injections. The data collected from this pilot study will be directly applicable in our practice here at MSK, and for the community of providers caring for patients with WDNETs, as well as for patients with this cancer.

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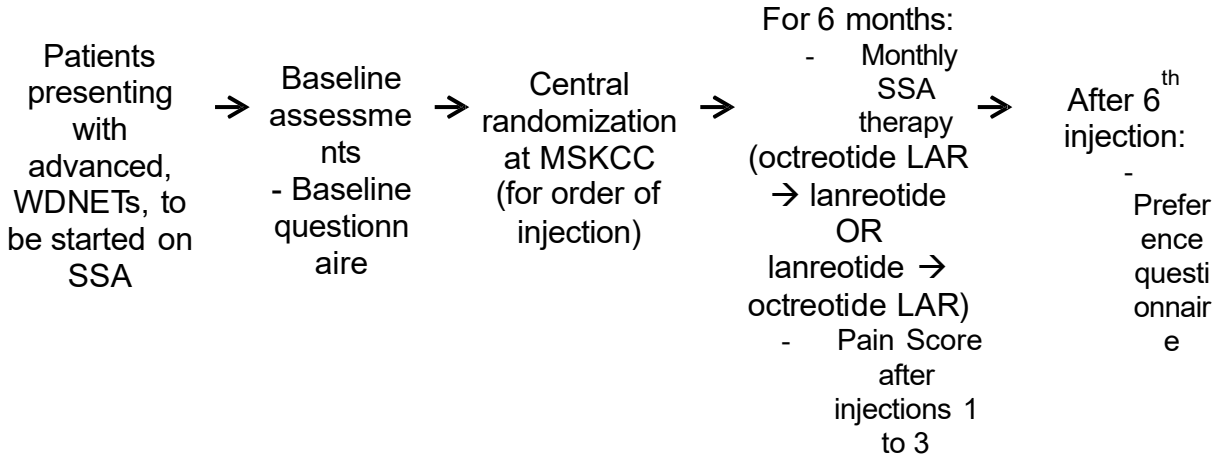
4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This is a single institution, prospective, pilot study to evaluate pain experienced following injection and patient preference of SSA therapy when treated with octreotide LAR and lanreotide during the management of advanced WDNETs. Please refer to table 1 for the protocol design and schema:

Table 1: Protocol schema



4.3 Intervention

This will be a two-arm randomized pilot study of 50 patients who will be randomized to receive octreotide LAR followed by lanreotide (n=25) or lanreotide followed by octreotide LAR (n=25). Patients presenting with advanced WDNETs, recommended to begin SSA therapy by their provider, will be eligible to participate. Patients will receive a total of 6 months of SSA therapy on trial, three octreotide LAR injections and three lanreotide injections; the injections will be separated by 28 (+/- 3) days. For the purposes of this study, these drugs will be referred to as “drug A” (drug given in months 1 to 3) and “drug B” (drug given in months 4 to 6). Our nursing staff will administer all injections in the outpatient clinic setting; octreotide LAR will be manually prepped in clinic just prior to injection, and lanreotide will be sent from pharmacy to clinic in a prefilled syringe.

On day of trial enrollment, after signing informed consent, patients will complete a baseline questionnaire (Appendix A). This baseline questionnaire will assess financial burden of health care, and whether a patient is concerned, prior to beginning any treatment, about pain or discomfort with the SSA injection.

The study participation period for each patient is 6 months from the date of beginning treatment and includes 4 time periods (pre-treatment evaluation on day of protocol enrollment, monthly injections of drug A for three months, monthly injections of drug B for three months, and an end of study evaluation after injection #6 at which time a preference questionnaire will be completed). At the first three visits when patients receive drug A, a pain score will be collected (0 to 10 numeric scale). Please refer to Appendix B for the post-treatment questionnaire that patients will complete immediately after injection, and to Appendix D for the diary patients will complete at home prior to returning for their next injection. As is standard practice at our institution, prior to every SSA injection, a baseline pain score using this same scale will be obtained by the nurse administering the injection. The end of study preference questionnaire (Appendix C) will evaluate which drug patients preferred and how much they preferred a certain drug. The preference questionnaire will also evaluate the topic of financial burden and willingness to pay, asking patients to quantify how much extra money per injection they believe their preferred drug is worth.

5.0 CRITERIA FOR SUBJECT ELIGIBILITY

5.1 Subject Inclusion Criteria

1. Willing and able to provide written informed consent for the trial
2. ≥ 18 years of age
3. Histologically- or cytologically- confirmed locally advanced or metastatic WDNET
4. SSA therapy is recommended by physician for disease management, and has not yet begun
5. ECOG performance status of 0, 1, or 2

5.2 Subject Exclusion Criteria

1. Currently participating in a study of an investigational agent
2. Prior chemotherapy, targeted small molecule therapy within 2 weeks prior to study Day 1 or not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent
   *Note: Subjects with ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia are an exception to this criterion and may qualify for the study
3. No concurrent chemotherapy or targeted small molecule therapy
4. If received major surgery, not recovered adequately from the toxicity and/or complications from the intervention prior to starting the study
5. Known additional malignancy that is progressing or requires active treatment
6. Active infection requiring systemic therapy
7. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial

6.0 RECRUITMENT PLAN

This study will be available to all patients seen at MSKCC, who meet the eligibility criteria outlined in section 5.0.

Potential research subjects will be identified by doctors from the gastrointestinal medical oncology clinics at MSKCC. The principal investigator or a member of the treatment team will discuss the study with the patient. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. All eligible patients, regardless of sex and race, will be approached for participation. The investigators are aware of the NIH policy concerning inclusion of women and minorities in clinical research populations.

Participation in the study is completely voluntary. Patients will be required to read, agree to, and sign an IRB-approved informed consent form prior to registration on this trial; registration is described in section 12.2. Patients will not receive payment for their participation on this study. Patients are free to withdraw from the study without consequence at any time.

7.1 ASSESSMENT/EVALUATION PLAN

The following assessments will be performed in this study:

Period	Screening (<28 days[2])	Treatment (6 SSA injections)[1]	Post-treatment (After injection #6)
Informed consent	x		
Medical history	x		
Physical examination	x		
Vital signs/Performance status[3]	x		
Review and report medications	x		
Central randomization at MSKCC (to order receiving octreotide LAR and lanreotide) after enrollment on study	x		
Octreotide LAR or Lanreotide injection		x	
Baseline questionnaire (AppendixA)	x (day of protocol entry)		
Post-injection pain assessment (AppendixB)		x (after injections 1, 2, and 3)	
Pain Diary (Appendix D)		x	
End of study preference questionnaire (Appendix C)			x

1. Each injection must be given 28 (+/-3) days apart
2. Procedures must be performed within 28 days prior to first SSA injection
3. Vital signs to include heart rate, respiratoryrate, blood pressure, height, and weight

8.1 TOXICITIES/SIDE EFFECTS

There are no investigational drugs in this trial - both octreotide LAR and lanreotide are standard of care treatment options for WDNETs. Both octreotide LAR and lanreotide will be administered by their approved mode of administration (IM for octreotide LAR, deep subq for lanreotide). For these reasons, patients on this study are not anticipated to experience side effects or toxicities from these drugs beyond those that are already known.

The side effects of octreotide LAR that may occur include:

Common (>20%):

- Slow heart rate
- Fatigue, malaise
- Headache
- Fever
- Dizziness
- High blood sugar
- Abdominal pain
- Loose bowel movements

- Nausea
- Flatulence
- Gallstones
- Upper respiratory infections

Occasional (4-20%)

- Itching
- Muscle and/or joint aches
- High blood pressure
- Irregular heart rhythms
- Pain
- Rash
- Heartburn
- Fatty bowel movements
- Low red blood cell counts
- Ear aches
- Kidney stones
- Sweating

Rare and Serious (<3%)

- Heart failure
- Depression
- Hallucinations
- Low blood sugars
- Difficulty swallowing
- Changes in taste
- Incontinence
- Tremor
- Vision changes
- Ringing of the ears
- Anaphylaxis
- Bile duct infection (cholangitis)
- Diabetes mellitus
- Fatty liver
- GI bleeding
- Pancreatitis
- Syncope/loss of consciousness

The side effects of lanreotide that may occur include:

Common (>20%):

- Diarrhea
- Abdominal pain
- Vomiting
- Gall stones

Occasional (4-20%)

- Slow heart rate
- High blood pressure

- Headache
- High or low blood sugars
- Flatulence
- Nausea
- Low red blood cell count
- Muscle or joint pains
- Dizziness
- Depression
- Loose bowel movements
- Constipation

Rare and Serious (<3%)

- Gall bladder infection
- Hypersensitivity reaction
- Low thyroid function
- Pancreatitis
- Cardiac valve abnormalities

The interventions that are being performed in this trial, specifically, baseline, post-treatment, as well as preference questionnaires, do not pose any potential toxicities or side effects to enrolled patients.

9.1 PRIMARY OUTCOMES

The following are tests and/or measures to be carried out during this pilot study:

For patients:

1. **Baseline questionnaire:** This questionnaire is provided in Appendix A and will be completed in clinic by all enrolled patients on the day that they provide informed consent to participate in this study. This questionnaire assesses financial burden of health care, and whether a patient is concerned, prior to beginning any treatment, about pain or discomfort with the SSA injection.

2. **Post-treatment questionnaire (after the first 3 injections):** Patients will rate, on a numeric scale of 0 to 10, with 0 being “No pain” to 10 being “Worst pain ever” the pain or discomfort experienced with the SSA injection (Appendix B). Patients will rate their pain following injection by the nurse who administered the injection.

3. **Pain Score Diary:** Patients will rate, on a numeric scale of 0 to 10, with 0 being “No pain” to 10 being “Worst pain ever” the pain or discomfort experienced with the SSA injection (Appendix D). Patients will rate their pain at home each day prior to returning to clinic for their next injection.

4. **Preference questionnaire:** This questionnaire is provided in Appendix C. This questionnaire asks 2 questions to evaluate level of preference for drug A or B, and how much extra money per injection a patient feels the preferred drug would be worth.

For nursing:

1. **Time for injection preparation:** Nurses will use a stopwatch to measure the amount time they spend preparing octreotide LAR and lanreotide injections. Start time will be the time the RN opens the package of the drug; octreotide LAR injections will be prepared in the room while the patient is undergoing nursing assessment. The end time will be as soon as the nurse discards the needle in the sharps container. A secure data spreadsheet will be maintained on the MSK server to collect this information for each monthly injection for enrolled patients. Coordination of this study objective will be by Elizabeth Cruz, RN, Co-PI on this study.

10.0 CRITERIA FOR REMOVAL FROM STUDY

In the absence of serious toxicity or complications, all patients will continue on study for 6 months (through completion of post-treatment questionnaire. In the absence of adverse event(s), patients may continue on study until one of the following criteria applies:

- Progression of disease warranting switch off of SSA therapy
- Development of an intercurrent medical condition or need for concomitant treatment that precludes further participation in the trial
- Unacceptable toxicity or any adverse event that precludes further participation in the trial
- The investigator removes the patient from the trial in the best interests of the patient
- Patient death
- Study completion or discontinuation for any reason
- Patient withdraws consent to continued participation in the trial or is lost to follow up

If consent is withdrawn, the subject can continue to receive SSA therapy off of protocol under the care of his/her treating physician, however the subject will not receive any further study observation.

11.1 BIOSTATISTICS

This is a pilot study to evaluate patient preferences for therapy with the commercially available SSA octreotide LAR and lanreotide. Fifty patients with WDNETs will be accrued to this study. We expect to accrue 2-3 patients per month, with accrual completed in 24 months. This study is a two-arm randomized design, in which patients will be randomized to the order in which they receive octreotide LAR and lanreotide in six separate monthly injections (randomization described in section 12.2).

Twenty-five patients will receive three monthly injections of octreotide LAR followed by three monthly injections of lanreotide, and 25 patients will receive three monthly injections of lanreotide followed by three monthly injections of octreotide LAR. The study participation period for each patient is 6 months from the date of beginning treatment and includes 4 time periods (pre-treatment evaluation on day of protocol enrollment, monthly injections of drug A for three months, monthly injections of drug B for three months, and an end of study evaluation after injection #6 at which time the preference questionnaire will be completed). Injection site pain will be assessed after each of the first 3 injections (with drug A) using a numeric 0 to 10 pain scale. For the primary objective of this study, all patients are expected to be included (i.e. all patients are expected to have data for the first 3 injections). In the unlikely event that patients drop-out before we get the data for the entire 6 months of this protocol, any patients that are removed will not be evaluable for our secondary objectives.

Primary objective: To compare injection site pain experienced with octreotide LAR and lanreotide.

Primary endpoint: Comparison of mean pain score over the first three injections of either octreotide LAR or lanreotide., With 25 patients per group, using a two-sample t-test we have 80% power to detect a mean score difference of 1.6 with a two-sided type I error of 0.05 assuming a standard deviation of 2 for both groups. The standard deviation of 2 was chosen based on internal pilot data of pain scores obtained from 20 patients receiving octreotide LAR. The mean score difference of 1.6 is the minimal detectable difference based on the proposed design and sample size and is considered to be clinically meaningful by the investigators of this study based on prior evaluation of the smallest meaningful and clinically significant change than can be identified using numeric and pictorial pain scales.[34] For the actual analysis, nonparametric tests such as Wilcoxon rank sum test will be used to compare the two groups in terms of their pain scores averaged over the 3 time-points. To account for correlation between the pain scores obtained after injections 1, 2, and 3, as a secondary analysis for the primary objective, repeated measures ANCOVA (adjusting for the baseline pain score) and/or Friedman's test will also be employed. In this study, mean pain score will be calculated among all non-missing data.

Secondary objectives:

1. To evaluate if patients have a preference for octreotide LAR or lanreotide.

2. To evaluate patient willingness to pay for preferred SSA therapy.

3. To quantify amount of time spent by nurses in clinic to prepare octreotide LAR and lanreotide injections.

Secondary endpoints:

1. Patient-reported preference of octreotide LAR versus lanreotide assessed after six months of therapy by post-treatment questionnaire (Appendix C). Patients will be asked their level of preference for either drug A or B with a Likert scale (i.e. no preference for one drug over the other, mild preference for drug A, strong preference for drug A, mild preference for drug B, strong preference for drug B). Preference of one drug over the other will be summarized descriptively.

2. Patient willingness to pay extra for preferred therapy measured in question format in the preference questionnaire (7 choices: $0, $1-50, $51-100, $101-200, $201-500, $501-1000, more than $1000). We will summarize patient willingness to pay (how much extra money per injection they believe the preferred drug is worth) using descriptive statistics after review of the answers provided in the preference questionnaire. We will use this data to evaluate whether or not the level of preference has a relationship to the amount of money people are willing to pay for a preferred therapy. This relationship will be assessed using the Spearman rank correlation coefficient. Due to small sample sizes this analysis is exploratory in nature.

3. Measurement of time nurses spend preparing octreotide LAR injections in clinic. We will summarize the average (with range) of time spent preparing either octreotide LAR or lanreotide injections for the patients included in this study.

12.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

12.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

12.3 Randomization

This is a pilot study in which patients are randomized to the order in which they receive three monthly injections of octreotide LAR and lanreotide. After eligibility is established

and consent is obtained, patients will be registered in the Protocol Participant Registration (PPR) system, and randomized to order octreotide LAR → lanreotide (n=25) or lanreotide → octreotide LAR (n=25) using the Clinical Research Database (CRDBi-Multicenter). If a patient is pending registration based on limited available information, randomization will occur after all completed documentation is received. A patient may be registered as pending for up to 30 days from the initial registration submission to PPR. Randomization will be completed at MSKCC and accomplished by the method of random permutated block. Since this is an unblinded study, all study investigators may view randomization in the CRDBi-Multicenter.

13.1 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secure database (Clinical Research Database, CRDB). Source documentation will be available to support the computerized patient record.

13.2 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent, and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

13.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: http://mskweb5.mskcc.org/intranet/_assets/_tables/content/359689/Data_safety%20Monitoring07.pdf

There are several different mechanisms bywhich clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, and there are two institutional committees that are responsible for monitoring the activities of our

clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

14.1 PROTECTION OF HUMAN SUBJECTS

All the patients will be required to sign an IRB-approved informed consent document and will have all their questions fully addressed before enrolling in the study. During the informed consent process, it will be made clear to the patient that participation is voluntary. All the data will be confidential, maintained in a password protected electronic database and will comply with all HIPAA guidelines.

Benefits: While on study, participating patients may identify a more preferable SSA drug and have the opportunity to receive this drug moving forward. It is also possible that from the results of this pilot study, we will be able to characterize, in broader terms, patient preference for SSA therapy. This information may guide both patients and clinicians in the future when they are making a similar therapy decision (i.e. whether to begin octreotide LAR or lanreotide when needing to start a SSA).

Risks: None beyond side effects/toxicities associated with SSA, which are standard-of-care therapy for WDNETs.

Costs: The patient will be responsible for the costs of standard medical care, including all drug and drug administration fees and all hospitalizations, even for complications of treatment. Patients will be notified of the co-pay associated with octreotide LAR and lanreotide and will have this information available prior to signing consent to this trial, as patients will have varying co-pays for these drugs that may impact their decision to enroll on this trial.

Incentives: No incentives will be offered to patients/subjects for participation in the study.

Alternatives/options for treatment: Patients may be eligible for other investigational studies, standard treatment options (including SSA off of trial), or focus on palliative care options.

Confidentiality: Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patient's name or any other personally identifying information will not be used in reports or publications resulting from this study. The Food and Drug Administration or other authorized agencies (e.g., qualified monitors) may review patients' records and pathology slides, as required.

14.2 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure

of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

14.3 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

For all other trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:
The CRDB SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office.

14.2.1

There is no additional SAE reporting information as no investigational drug is being studied in this trial.

15.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

16.0 REFERENCES

1. Kunz PL, Reidy-Lagunes D, Anthony LB, et al. Consensus guidelines for the management and treatment of neuroendocrine tumors. *Pancreas.* May 2013;42(4):557-577.
2. Dumlu EG, Karakoc D, Ozdemir A. Nonfunctional Pancreatic Neuroendocrine Tumors: Advances in Diagnosis, Management and Controversies. *International surgery.* Jan 15 2015.
3. Metz DC, Jensen RT. Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. *Gastroenterology.* Nov 2008;135(5):1469-1492.
4. Moertel CG, Kvols LK, Oconnell MJ, Rubin J. Treatment of Neuroendocrine Carcinomas with Combined Etoposide and Cisplatin - Evidence of Major Therapeutic Activity in the Anaplastic Variants of These Neoplasms. *Cancer.* Jul 15 1991;68(2):227-232.
5. Modlin IM, Oberg K, Chung DC, et al. Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncol.* Jan 2008;9(1):61-72.
6. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer.* Feb 15 2003;97(4):934-959.
7. Yao JC, Hassan M, Phan A, et al. One hundred years after "Carcinoid": Epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *Journal of Clinical Oncology.* Jun 20 2008;26(18):3063-3072.
8. Vinik A, Feliberti E, Perry RR. Carcinoid Tumors. In: De Groot LJ, Beck-Peccoz P, Chrousos G, et al., eds. *Endotext*. South Dartmouth (MA)2000.
9. Reidy-Lagunes DL. Systemic Therapy for Advanced Pancreatic Neuroendocrine Tumors: An Update. *J Natl Compr Canc Ne.* Jun 2012;10(6):777-783.
10. Castellano D, Grande E, Valle J, et al. Expert consensus for the management of advanced or metastatic pancreatic neuroendocrine and carcinoid tumors. *Cancer chemotherapy and pharmacology.* Dec 6 2014.
11. Jensen RT, Berna MJ, Bingham DB, Norton JA. Inherited pancreatic endocrine tumor syndromes: advances in molecular pathogenesis, diagnosis, management, and controversies. *Cancer.* Oct 1 2008;113(7 Suppl):1807-1843.
12. Reubi JC, Waser B. Concomitant expression of several peptide receptors in neuroendocrine tumours: molecular basis for in vivo multireceptor tumour targeting. *European journal of nuclear medicine and molecular imaging.* May 2003;30(5):781-793.
13. Oberg KE, Reubi JC, Kwekkeboom DJ, Krenning EP. Role of somatostatins in gastroenteropancreatic neuroendocrine tumor development and therapy. *Gastroenterology.* Sep 2010;139(3):742-753, 753 e741.
14. di Bartolomeo M, Bajetta E, Buzzoni R, et al. Clinical efficacy of octreotide in the treatment of metastatic neuroendocrine tumors. A study by the Italian Trials in Medical Oncology Group. *Cancer.* Jan 15 1996;77(2):402-408.
15. Oberg K, Norheim I, Theodorsson E. Treatment of malignant midgut carcinoid tumours with a long-acting somatostatin analogue octreotide. *Acta oncologica.* 1991;30(4):503-507.
16. Janson ET, Oberg K. Long-term management of the carcinoid syndrome. Treatment with octreotide alone and in combination with alpha-interferon. *Acta oncologica.* 1993;32(2):225-229.
17. Anthony L, Vinik AI. Evaluating the characteristics and the management of patients with neuroendocrine tumors receiving octreotide LAR during a 6-year period. *Pancreas.* Oct 2011;40(7):987-994.
18. Ruszniewski P, Ducreux M, Chayvialle JA, et al. Treatment of the carcinoid syndrome with the longacting somatostatin analogue lanreotide: a prospective study in 39 patients. *Gut.* Aug 1996;39(2):279-283.

19. Tomassetti P, Migliori M, Gullo L. Slow-release lanreotide treatment in endocrine gastrointestinal tumors. *The American journal of gastroenterology.* Sep 1998;93(9):1468-1471.
20. Toumpanakis C, Garland J, Marelli L, et al. Long-term results of patients with malignant carcinoid syndrome receiving octreotide LAR. *Alimentary pharmacology & therapeutics.* Oct 2009;30(7):733-740.
21. Kraenzlin ME, Ch'ng JL, Wood SM, Carr DH, Bloom SR. Long-term treatment of a VIPoma with somatostatin analogue resulting in remission of symptoms and possible shrinkage of metastases. *Gastroenterology.* Jan 1985;88(1 Pt 1):185-187.
22. Nikou GC, Toubanakis C, Nikolaou P, et al. VIPomas: an update in diagnosis and management in a series of 11 patients. *Hepato-gastroenterology.* Jul-Aug 2005;52(64):1259-1265.
23. Frankton S, Bloom SR. Gastrointestinal endocrine tumours. Glucagonomas. *Bailliere's clinical gastroenterology.* Dec 1996;10(4):697-705.
24. Saltz L, Trochanowski B, Buckley M, et al. Octreotide as an antineoplastic agent in the treatment of functional and nonfunctional neuroendocrine tumors. *Cancer.* Jul 1 1993;72(1):244-248.
25. Arnold R, Neuhaus C, Benning R, et al. Somatostatin analog sandostatin and inhibition of tumor growth in patients with metastatic endocrine gastroenteropancreatic tumors. *World journal of surgery.* Jul-Aug 1993;17(4):511-519.
26. Rinke A, Muller 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.* Oct 1 2009;27(28):4656-4663.
27. Clark OH, Benson AB, 3rd, Berlin JD, et al. NCCN Clinical Practice Guidelines in Oncology: neuroendocrine tumors. *Journal of the National Comprehensive Cancer Network : JNCCN.* Jul 2009;7(7):712-747.
28. Caplin ME, Pavel M, Cwikla JB, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *The New England journal of medicine.* Jul 17 2014;371(3):224-233.
29. Saltz LB. Perspectives on Cost and Value in Cancer Care. *JAMA oncology.* Jan 2016;2(1):19-21.
30. Hsu J, Price M, Huang J, et al. Unintended consequences of caps on medicare drug benefits. *New Engl J Med.* Jun 1 2006;354(22):2349-2359.
31. Wong YN, Meropol NJ, Speier W, Sargent D, Goldberg RM, Beck JR. Cost Implications of New Treatments for Advanced Colorectal Cancer. *Cancer.* May 15 2009;115(10):2081-2091.
32. Herr KA, Garand L. Assessment and measurement of pain in older adults. *Clin Geriatr Med.* Aug 2001;17(3):457-+.
33. Wong DL, Baker CM. Pain in children: comparison of assessment scales. *Pediatric nursing.* Jan-Feb 1988;14(1):9-17.
34. von Baeyer CL. Children's self-report of pain intensity: what we know, where we are headed. *Pain research & management.* Jan-Feb 2009;14(1):39-45.

17.0 APPENDICES

Appendix A: Baseline Patient Questionnaire

Appendix B: Post-treatment Questionnaire

Appendix C: Preference Questionnaire

Appendix D: Pain Score Diary