SOMATOSTATIN ANALOGUES FOR THE MANAGEMENT OF NEUROENDOCRINE TUMOURS

Effective Date: March, 2015

The recommendations contained in this guideline are a consensus of the Alberta Provincial Endocrine Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.
BACKGROUND

Neuroendocrine tumours (NETs) are a relatively rare family of tumours, occurring at a rate of about 5.25 cases per 100,000. The most common primary site of NETs are the ileum and pancreas, but they can arise throughout the GI tract, lungs, thyroid, parathyroid, adrenal glands, and pituitary gland. Patients with well-differentiated low and inter-mediate grade NETs often have a relatively good prognosis, while those with poorly-differentiated, high grade NETs fare less well. These tumors are often classified as functioning or nonfunctioning, the latter of which do not present with hormone hypersecretion and are often found as a bulky tumour with metastatic disease. Functioning NETs are often found earlier and may have a better prognosis.

Somatostatin analogues (Octreotide and Lanreotide), are commonly used in the treatment of functional NET’s to manage symptoms associated with hormonal hypersecretion. Somatostatin regulates hormones and inhibits tumour secretions. Somatostatin analogues have been shown to control the production of hormones such as growth hormone (GH) and insulin-like growth factor 1 (IGF-1), and also have an antitumor effect as suggested by the PROMID and CLARINET studies. The purpose of this guideline is to provide evidence-based recommendations on the use of somatostatin analogues for NETs and to define which patients are candidates for treatment with these agents. The American Joint Committee on Cancer (AJCC; 7th edition, 2010) staging for NETs can be found in Appendix A.

GUIDELINE QUESTIONS

- Are somatostatin analogues effective for symptom management in secretory syndromes resulting from neuroendocrine tumours? If so, for which patients and what are the appropriate dosing regimens?
- Are somatostatin analogues effective in delaying tumor progression among patients with neuroendocrine tumours? If so, for which patients and what are the appropriate dosing regimens?
- Are somatostatin analogues effective for the management of carcinoid heart disease? If so, for which patients and what are the appropriate dosing regimens?
- Is octreotide effective for the management of symptoms secondary to elevated calcitonin in medullary thyroid carcinoma? If so, for which patients and what is the appropriate dosing regimen?

DEVELOPMENT AND REVISION HISTORY

This guideline was reviewed and endorsed by the Alberta Provincial Endocrine Tumour Team. Members of the Alberta Provincial Endocrine Tumour Team include medical oncologists, endocrinologists, surgeons, and nurses. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Endocrine Tumour Team and a Knowledge Management Specialist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in November, 2013. This guideline was revised in March, 2015.

SEARCH STRATEGY

The PubMed database was searched (1965 through 2013 May) for relevant publications using the following search terms: octreotide AND neuroendocrine tumour. Results were limited to randomized controlled trials and phase II-III clinical trials. Thirty-eight citations were returned in PubMed. Excluded from these were retrospective studies, case studies, studies published before 2001, and those that did not
report response or survival outcomes, leaving a total of ten studies. The American Society of Clinical Oncology (ASCO) meeting abstracts database was searched (2009 through 2012 March) for relevant abstracts; five abstracts (phase III trials) were identified. In total, 15 studies were used as evidence to inform the recommendations on tumour control and symptom management.

Additional searches were conducted of the PubMED database for studies on the use of octreotide for carcinoid heart disease, malignant bowel obstruction, and increased calcitonin levels in medullary thyroid carcinoma. The searches included studies involving patients with any type malignancy (i.e., not limited to neuroendocrine tumours). The key words octreotide AND carcinoid heart disease or malignant bowel obstruction or calcitonin were used. Available data is presented in the discussion section.

For the 2014 update of the guideline the PubMed, MEDLINE and EMBASE databases were searched (2013 through 2014 October) for relevant publications using the following search terms: octreotide AND neuroendocrine tumour. In addition, the databases were searched (2009 through 2014 October) for relevant publications using the following search terms: lanreotide AND neuroendocrine tumour. A total of five additional studies were relevant and are summarized in the tables in Appendix B.

TARGET POPULATION

The recommendations in this guideline apply to patients diagnosed with NETs of the gastrointestinal tract, pancreas, lungs, thyroid, parathyroid, adrenal glands, and pituitary gland, and NETs of unknown origin.

RECOMMENDATIONS

Described below are indications for the use of somatostatin analogues in neuroendocrine tumours (NETs).

1. Management of symptomatic secretory syndromes.
   - Somatostatin analogues are recommended for symptom control in patients with secretory syndromes, resulting from, carcinoid syndrome, and gastrinomas, insulinomas, somatostatinomas, glucagonomas, and VIPomas with locoregional and metastatic disease.
     - Octreotide dosing for symptom control: A trial of octreotide 100-250 mcg SC TID for 1-2 weeks followed by introduction of octreotide LAR 20-30 mg IM every 4 weeks.
     - Dose and frequency may be increased for symptom control, as needed.
     - Short-acting octreotide can be added to octreotide LAR for rapid relief of symptoms or for breakthrough symptoms.
     - Lanreotide dosing for symptom control:
       - Somatuline LA 30 mg IM every 10 – 14 days
       - Somatuline Autogel 60 – 120 mg SQ every 28 days

2. Tumour control.
   - Octreotide LAR has been shown in the PROMID study to slow tumour progression, as compared to placebo, in patients with locoregional unresectable or metastatic well-differentiated (low grade) NETs of mid-gut origin and those of unknown origin believed to be a mid-gut primary. Therefore, octreotide LAR should be considered for its anti tumour effect in patients with locoregional unresectable or metastatic well-differentiated (low grade) mid-gut NETs whose disease is progressing regardless of functional status of the tumour.
     - Octreotide LAR dosing for tumour control: 30 mg IM every 4 weeks. Note: therapeutic levels of octreotide would not be expected to be reached for 10-14 days after LAR injection.
Octreotide has not been compared to placebo in the phase III setting in patients with poorly-differentiated mid-gut NETs or other NETs (i.e., non-mid-gut primaries) with locoregional unresectable disease or distant metastases.

Lanreotide has been shown in the CLARINET study to slow prolong progression free survival in comparison to placebo in patients with advanced well to moderately differentiated, nonfunctioning somatostatin receptor positive neuroendocrine tumors.

- Lanreotide dosing for tumor control: 120 mg SC injection every 28 days


- Octreotide is used to treat carcinoid crises.
  - Octreotide dosing for carcinoid heart disease: bolus of 100-500 mcg IV or by infusion; urgent situations may require high doses and up to 54,000 mcg has been reported.

- There is a paucity of data on the use of octreotide for the prevention of carcinoid heart disease in patients with carcinoid tumours. However, given the life-threatening nature of carcinoid heart disease and the relative safety of octreotide, use of octreotide should be considered in this setting.
  - Patients with 5-HIAA levels greater than 50 mg/24 hours should be considered in this setting.
  - Dosing for the prevention of carcinoid heart disease: octreotide LAR 20-30 mg IV every 4 weeks.

4. Management of symptoms secondary to elevated calcitonin in medullary thyroid carcinoma.

- Octreotide has been shown to relieve symptoms associated with elevated calcitonin levels in patients with medullary thyroid carcinoma. Therefore, octreotide is recommended to manage symptoms (i.e., diarrhea) in patients with elevated calcitonin levels in medullary thyroid carcinoma.
  - Octreotide dosing for symptoms associated with metastatic medullary thyroid cancer: A trial of daily octreotide 100-250 TID mcg SC for 1-2 weeks with subsequent introduction of monthly octreotide LAR at a dose of 20-30 mg IM every 4 weeks. Octreotide can be given long-term without significant adverse effects.

DISCUSSION

Management of Symptomatic Secretory Syndromes

Octreotide and lanreotide have been shown to improve symptoms associated with hypersecretory syndromes in patients with NETs. A small prospective study of 14 patients with functional metastatic gastroenteropancreatic neuroendocrine tumors (VIPoma, glucagonoma, gastrinoma, pancreatic and midgut carcinoids, and medullary thyroid carcinoma) examined the efficacy of octreotide therapy for 6 months. Efficacy was defined as a reduction in diarrhea and changes in 5-HIAA and CgA levels. Median urinary 5-HIAA and the number of stools decreased significantly (p=0.016 and p=0.009); decreases in CgA levels did not reach statistically significance (p=0.14). In another small study, 9 patients with pancreatic NETs and 9 patients with metastatic carcinoid tumors were treated with octreotide, administered subcutaneously twice daily for 3 days, continuing for 2 to 12 months in patients with a response. Nearly all patients with a gastrinoma or glucagonoma responded with reduced hormone secretions, improved diarrhea, and improved skin lesions; however, in carcinoid syndrome, clinical efficacy was partial and inconstant. Similar results have been reported elsewhere.

A double-blind randomized trial compared octreotide LAR at 10, 20, and 30 mg every 4 weeks with open-label SC octreotide every 8 hours in 79 patients with carcinoid syndrome and showed that the responses
in each of the four study arms were comparable (SC, 58.3%; 10 mg, 66.7%; 20 mg, 71.4%; 30 mg, 61.9%; P≥.72 for all pairwise comparisons). Stool frequency was also similar between groups, while flushing episodes were best controlled in the 20-mg LAR and SC groups. A phase II trial combining 5-FU with LAR octreotide (20 mg monthly) in patients with advanced/metastatic well-differentiated NETs of the gastrointestinal tract (n=29) reported symptom relief in 60% of patients. A biochemical response (i.e., CgA levels) was observed in 48% of patients.

Based on the available data, octreotide is recommended for symptom control in patients with secretory syndromes, resulting from gastric NETs, carcinoid syndrome, and gastrinomas, insulinomas, somatostatinomas, glucagonomas, and VIPomas with locoregional disease or metastatic disease. The use of octreotide in this setting is supported elsewhere in Canada and in the United States. A trial of subcutaneous dose of 100-250 mcg three times per day for 1-2 weeks followed by intramuscular octreotide LAR 20-30 mg every 4 weeks is recommended. Similar dosing has been recommended elsewhere for use in this setting. Dose and frequency may be increased for symptom control, as needed. Short-acting octreotide can be added to octreotide LAR for rapid relief of symptoms or for breakthrough symptoms.

### Tumour Control

Octreotide LAR has also been shown to slow tumour progression, as compared to placebo, in patients with locoregional unresectable or metastatic well-differentiated (low grade) NETs. The largest trial to date, the PROMID trial, is a phase III randomized controlled trial, comparing octreotide LAR (30 mg IM monthly) with placebo in patients with well-differentiated NETs of the midgut (n=85). The trial demonstrated both a greater rate of stable disease at 6 months (66.7% vs. 37.2%) and longer progression-free survival (14.3 vs. 6 months; p<.000072) in the octreotide-treated group, as compared to placebo. Octreotide has not been compared to placebo in the phase III setting in patients with poorly-differentiated mid-gut NETs or other NETs (i.e., non-mid-gut primaries) with locoregional unresectable disease or distant metastases.

Based on the available data, octreotide LAR is recommended in patients with locoregional unresectable or metastatic well-differentiated (low grade) mid-gut NETs. Use of octreotide in this setting is supported elsewhere in Canada. Recommended dosing for tumour control is LAR 30 mg IM every 4 weeks. Due to a lack of data, octreotide is not recommended for patients with poorly-differentiated mid-gut NETs or other NETs (i.e., non-mid-gut primaries) with locoregional unresectable disease or distant metastases for the purpose of tumor control.

More recently, the CLARINET trial investigated lanreotide in a randomized controlled trial of well to moderately differentiated enteropancreatic neuroendocrine tumours (grade 1 or 2). Lanreotide was shown to significantly prolong progression-free survival compared to placebo (median not reached for lanreotide group vs. 18.0 months for placebo, p<0.001; hazard ratio for progression or death 0.47, 95% CI 0.30-0.73). At 24 months the estimated progression-free survival rate for the lanreotide group was 65.1% and 33.0% for the placebo group.

### Management of Carcinoid Heart Disease

Carcinoid heart disease results from exposure of the heart to high levels of tumour-derived vasoactive substances, such as serotonin, resulting in endocardial damage. Ventricular failure can occur. 5-HIAA levels; levels greater than 50 mg/24 hours are associated with an increased risk of developing carcinoid heart disease. Octreotide is recommended for the treatment of carcinoid heart disease based on its...
The use of octreotide in the prophylactic setting is controversial because there is a paucity of data on its use in patients with carcinoid tumours in this setting. Based on consensus, the prophylactic use of octreotide should be considered in patients with carcinoid tumours. Canadian consensus guidelines recommend that early intervention with octreotide should be considered, given that toxicity is low and the morbidity and mortality rates associated with carcinoid heart disease are high. Patients with 5-HIAA levels greater than 50 mg/24 hours should be considered for octreotide therapy, with the goal of normalizing 5-HIAA 24-hour urine excretion, if possible. A dose of 20-30 mg IV every 4 weeks is recommended for the prevention of carcinoid heart disease.

Management of Symptoms Secondary to Elevated Calcitonin in Medullary Thyroid Carcinoma

Octreotide has been shown to relieve symptoms associated with elevated calcitonin levels in patients with medullary thyroid carcinoma. A prospective study, among 22 patients with persistent or relapsed metastatic medullary thyroid carcinoma, evaluated the long-term use of somatostatin analogs. Following surgery, patients had an elevated serum calcitonin level (252-69482 pg/ml). Daily octreotide (0.4-1.0 mg SC) or monthly octreotide LAR (20-30 mg IM for 3-21 months) was given, along with systemic chemotherapy with or without external radiotherapy. Pre-existing diarrhea was improved in 8 patients (36.4% partial response), and remained stable in 10 patients. Calcitonin concentrations decreased more than 25% in 18% of patients (4 of 22). Another somatostatin analog, lanreotide (slow-release), was shown to improve symptoms in seven patients with advanced and symptomatic medullary thyroid carcinoma. The number and intensity of bowel movements and flushing episodes decreased in nearly all patients (7 of 8) and plasma calcitonin levels decreased significantly in nearly all patients (6 of 7); the magnitude of decrease was 50% or more in half of these patients. Similar results have been reported elsewhere.

Based on the available evidence, octreotide is recommended to manage symptoms (i.e., diarrhea) in patients with elevated calcitonin levels in medullary thyroid carcinoma. The recommended octreotide dosing in this setting is 100-250 TID mcg SC or monthly octreotide LAR at a dose of 20-30 mg IM every 4 weeks. Octreotide can be given long-term without significant adverse effects.
GLOSSARY OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>AHS</td>
<td>Alberta Health Services</td>
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<td>ASCO</td>
<td>American Society of Clinical Oncology</td>
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<td>BCCA</td>
<td>British Columbia Cancer Agency</td>
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<tr>
<td>BID</td>
<td>two times a day</td>
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<td>CCO</td>
<td>Cancer Care Ontario</td>
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<td>CgA</td>
<td>chromogranin A</td>
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<td>GH</td>
<td>growth hormone</td>
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<tr>
<td>5-HIAA</td>
<td>5-hydroxyindoleacetic acid</td>
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<tr>
<td>IGF-1</td>
<td>insulin-like growth factor 1</td>
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<tr>
<td>IM</td>
<td>intramuscular</td>
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<tr>
<td>LAR</td>
<td>octreotide acetate injection, long acting</td>
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<td>NET</td>
<td>neuroendocrine tumour</td>
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<tr>
<td>PO</td>
<td>orally</td>
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<tr>
<td>SC</td>
<td>subcutaneously</td>
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<tr>
<td>TID</td>
<td>three times a day</td>
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DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2016. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Endocrine Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Endocrine Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.
REFERENCES


ADDITIONAL REFERENCES


APPENDIX A: AJCC STAGING (7th EDITION, 2010) FOR NEUROENDOCRINE TUMOURS

Neuroendocrine Tumour of the Stomach

Primary Tumour (T)
Tx: primary tumour cannot be assessed
T0: No evidence of primary tumour
Tis: Carcinoma in situ/dysplasia (tumour size less than 0.5 mm), confined to mucosa
T1: Tumour invades lamina propria or submucosa and 1 cm or less in size
T2: Tumour invades muscularis propria or more than 1 cm in size
T3: Tumour penetrates subserosa
T4: Tumour invades visceral peritoneum (serosal) or other organs or adjacent structures
For any T, add (m) for multiple tumours

Regional Lymph Nodes (N)
Nx: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Regional lymph node metastases

Distant Metastasis (M)
M0: No distant metastasis
M1: Distant metastasis

Neuroendocrine Tumour of the Duodenum/Ampulla/Jejunum/Ileum

Primary Tumour (T)
Tx: primary tumour cannot be assessed
T0: No evidence of primary tumour
T1: Tumour invades lamina propria or submucosa and size 1 cm or less (small intestinal tumours); tumour size 1 cm or less (ampullary tumours)
T2: Tumour invades muscularis propria or size greater than 1 cm (small intestinal tumours); tumour greater than 1 cm (ampullary tumours)
T3: Tumour invades through the muscularis propria into subserosal tissue without penetration of overlying serosa (jejunal or ileal tumours) or invades pancreas or retroperitoneum (ampullary or duodenal tumours) or into non-peritonealized tissues
T4: Tumour invades visceral peritoneum (serosa) or invades other organs
For any T, add (m) for multiple tumours

Regional Lymph Nodes (N)
Nx: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Regional lymph node metastases

Distant Metastasis (M)
M0: No distant metastasis
M1: Distant metastasis
Neuroendocrine Tumour of the Colon or Rectum

Primary Tumour (T)
Tx: primary tumour cannot be assessed
T0: No evidence of primary tumour
T1: Tumour invades lamina propria or submucosa and size 2 cm or less
  T1a: Tumour size less than 1 cm in greatest dimension
  T1b: Tumour size 1-2 cm in greatest dimension
T2: Tumour invades muscularis propria or size greater than 2 cm with invasion of lamina propria or submucosa
T3: Tumour invades through the muscularis propria into the subserosa, or into non-peritonealized pericolic or perirectal tissues
T4: Tumour invades peritoneum or other organs
For any T, add (m) for multiple tumours

Regional Lymph Nodes (N)
Nx: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Regional lymph node metastases

Distant Metastasis (M)
M0: No distant metastasis
M1: Distant metastasis

Neuroendocrine Tumour of the Pancreas

Primary Tumour (T)
Tx: primary tumour cannot be assessed
T0: No evidence of primary tumour
Tis: Carcinoma in situ
T1: Tumour limited to the pancreas, 2 cm or less in greatest dimension
T2: Tumour limited to the pancreas, more than 2 cm in greatest dimension
T3: Tumour extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4: Tumour involves the celiac axis or the superior mesenteric artery (unresectable primary tumour)

Regional Lymph Nodes (N)
Nx: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Regional lymph node metastases

Distant Metastasis (M)
M0: No distant metastasis
M1: Distant metastasis
Appendiceal Carcinoid Tumour

Primary Tumour (T)
Tx: primary tumour cannot be assessed
T0: No evidence of primary tumour
T1: Tumour 2 cm or less in greatest dimension
   T1a: Tumour 1 cm or less in greatest dimension
   T1b: Tumour more than 1 cm but not more than 2 cm
T2: Tumour more than 2 cm but not more than 4 cm or with extension to the cecum
T3: Tumour more than 4 cm or with extension to the ileum
T4: Tumour directly invades other adjacent organs or structures, e.g., abdominal wall and skeletal muscle

Regional Lymph Nodes (N)
Nx: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Regional lymph node metastases

Distant Metastasis (M)
M0: No distant metastasis
M1: Distant metastasis

Neuroendocrine Tumour of the Adrenal Gland

Primary Tumour (T)
Tx: primary tumour cannot be assessed
T0: No evidence of primary tumour
T1: Tumour 5 cm or less in greatest dimension, no extra-adrenal invasion
T2: Tumour greater than 5 cm, no extra-adrenal invasion
T3: Tumour of any size with local invasion, but not invading adjacent organs
T4: Tumour of any size with invasion of adjacent organs

Regional Lymph Nodes (N)
Nx: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Regional lymph node metastases

Distant Metastasis (M)
M0: No distant metastasis
M1: Distant metastasis
## Table 1: Clinical studies

<table>
<thead>
<tr>
<th>Author (trial)</th>
<th>Design</th>
<th>Treatments</th>
<th>Patients (n)</th>
<th>Response</th>
<th>Survival</th>
<th>Adverse events</th>
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<tbody>
<tr>
<td><strong>OCTREOTIDE</strong></td>
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<tr>
<td>Li J. 2014</td>
<td>phase II</td>
<td>IP regimen: irinotecan 180 mg/m² on d1, and cisplatin 50 mg/m² on d1, q 2 wks for 6 cycles (n=40)</td>
<td>NET (n=40)</td>
<td></td>
<td></td>
<td>PFS (med after chemotherapy): 3.1 mo octreotide LAR vs 4.1 mo no octreotide LAR, p=0.908</td>
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<tr>
<td>Bajetta E. 2013</td>
<td>phase II</td>
<td>octreotide LAR (30 mg q 28 d) + everolimus (10 mg/d)</td>
<td>advanced well differentiated gastroenteropancreatic- NET (n=50)</td>
<td>ORR: 20% CR: 4% (n=2) PR: 16% (n=8) SD: 72% (n=36)</td>
<td>TTP(med): 16.3 mo</td>
<td>Gr 3 skin rash: 1 pt stomatitis: 8% (n=4) diarrhea: 22% (n=11)</td>
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<tr>
<td>Wolin EW. 2013</td>
<td>phase III</td>
<td>1. P arm: pasireotide LAR (60 mg IM q 28 d)</td>
<td>NET (n=110)</td>
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<td>PFS (med): 11.8 mo P arm vs. 6.8 mo O arm (HR=0.46; p=0.045)</td>
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<tr>
<td>Pavel ME. 2011</td>
<td>phase III RCT</td>
<td>EO: everolimus (10 mg/d PO) + octreotide LAR (30 mg IM q 4 wks)</td>
<td>NET, advanced low-intermed grade w/ radiologic progression in the past 12 mo (n=429)</td>
<td>CgA response: overall 46% EO vs. 29% PO 5-HIAA response: overall 61% EO vs. 47% PO</td>
<td></td>
<td>stomatitis: 62% EO vs. 14% PO rash: 37% EO vs. 12% PO fatigue: 31% EO vs. 23% PO diarrhoea: 27% EO vs. 16% PO</td>
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**Comments:**

- **PFS (med after chemotherapy):**
  - 3.1 mo octreotide LAR vs 4.1 mo no octreotide LAR, p=0.908

- **Adverse events:**
  - Gr 3-4 for entire regimen:
    - Neutropenia: 50%
    - Leukopenia: 35%
    - Nausea/vomiting: 7.5%
    - Diarrhea: 5%
    - Anorexia: 5%

- **Symptom response (6-mo):**
  - 21% (n=9/43) P arm vs. 27% (n=12/45) O arm, OR: 0.73 (95% CI 0.27-1.97; p=0.53)

- **PFS (med):**
  - 16.4 mo EO vs. 11.3 mo PO (HR progress/death: 0.77; 95% CI 0.59-1.00; p=0.026)

- **Subgroup:**
  - Disease site (n=307)
    - Sm int PFS (med): ↑ 4.6 mo
    - Lung PFS (med): ↑ 8.0 mo
    - Colorec PFS (med): ↑ 23.3 m

**Prog factors for med PFS:**

- Stomatitis: 62% EO vs. 14% PO
- Rash: 37% EO vs. 12% PO
- Fatigue: 31% EO vs. 23% PO
- Diarrhoea: 27% EO vs. 16% PO
<table>
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<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rinke A. 2009&lt;sup&gt;7,35&lt;/sup&gt; (PROMID) (JCO article + ASCO abstract)</td>
<td>phase III RCT</td>
<td>1. octreotide LAR (30 mg IM monthly) (n=85)</td>
<td>well-differentiated NET primary site midgut or unknown primary believed to be of midgut if a primary within pancreas, chest; elsewhere was excluded; tx-naive</td>
<td>SD (6-mo): 66.7% octreo vs. 37.2% placebo</td>
<td>PFS (med): 14.3 mo octreo vs. 6 mo placebo (HR 0.34; p&lt;0.0001)</td>
<td>Most frequent severe: hematopoietic system (octreotide 5 pts vs. placebo 1 patient) fatigue and fever (octreotide 8 pts vs. placebo 2 pts) WHO Gr 2-4: more often in the octreotide arm (diarrhea, flatulence)</td>
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<tr>
<td>Arnold R. 2005&lt;sup&gt;56&lt;/sup&gt; (abstract)</td>
<td>phase III</td>
<td>1. octreotide + IFN-alpha</td>
<td>progressive metastatic NET (n=125) primary site foregut (mainly pancreatic) and the midgut</td>
<td>PR (12-mo): 5.7% SD (12-mo): 15.2% (no diff b/t arms)</td>
<td>OS (med): 54 mo O+IFN vs. 32 mo O alone</td>
<td></td>
</tr>
<tr>
<td>Yao JC. 2008&lt;sup&gt;37&lt;/sup&gt; (RADIANT-1)</td>
<td>phase II</td>
<td>1. everolimus (5 mg/d) + octreotide LAR (30 mg q 4 wks) (n=66)</td>
<td>NET, advanced low-intermed Gr primary site (%) pancreas 48% sm intestine 27% lung 7% gastric 2% thymus 2% rectum 5% renal 2% unknown 8%</td>
<td>whole group: PR: 22% (n=13) SD: 70% (n=42)</td>
<td>PFS whole group (med): 13.8 mo OS (med): not reached OS (1-yr): 83%; (2-yr): 81% Subgroup (SD vs. progressive) PFS (med): 17 mo SD vs. 11.5 mo progressive disease; p&lt;0.01</td>
<td>most common: mild aphthous ulceration Gr 3-4 (≥10% pts): diarrhea, 11% fatigue, 11% hypophosphatemia, 11%</td>
</tr>
<tr>
<td>Author (trial)</td>
<td>Design</td>
<td>Treatments</td>
<td>Patients (n)</td>
<td>Response</td>
<td>Survival</td>
<td>Adverse events</td>
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<tr>
<td>Savelli G. 2012&lt;sup&gt;16&lt;/sup&gt;</td>
<td>phase Ila</td>
<td>(90)Y-DOTATOC advanced stage well differentiated gastro-entero-PNET (n=38)</td>
<td>primary site (%) pancreas 17% ileum 5% duodenum 1% rectum 1% renal 2% breast 1% unknown 13%</td>
<td>PR: 43.6%  SD: 25.6%</td>
<td>PFS (med): 22.3 mo</td>
<td>main toxicity: renal (3 pts with chronic renal failure) mild hematologic toxicity (Gr 1-3) affected most of the patients.</td>
</tr>
<tr>
<td>Imhof A. 2011&lt;sup&gt;10&lt;/sup&gt;</td>
<td>phase II open label</td>
<td>[(90)Y-DOTA]-TOC octreotide (3.7 GBq/m² per injection; 1 injection per cycle)</td>
<td>advanced/ meta-static carcinoid 43% sm intestine 56% bronchus 18% lg intestine 9% upper gut 1.5% other 2.5% unknown 14% PNET 34% rare NET 9.3% unknown 16.7%</td>
<td>Morphologic 34.1% (n=378) Biochemical 15.5% (n=172) Clinical 20.7% (n=329)</td>
<td>OS (23-mo): 54.9% Median OS: 94.6 mo OS predictors: age, previous surgery, previous chemo, Liver mets, bone mets, and response</td>
<td>Gr 3-4 hematologic: 12.8% (142) Gr 4-5 renal (permanent): 9.2% (103)</td>
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<tr>
<td>Claringbold PG. 2011&lt;sup&gt;10&lt;/sup&gt;</td>
<td>phase II</td>
<td>capecitabine (1,650 mg/m²/d for 14 days + (177)Lu-octreotate (7.8 GBq 8-weekly) x 4 cycles * 2.4 Gy per cycle to kidneys; 4.8 Gy per cycle to liver</td>
<td>disseminated, progressive, unresectable NET (n=33) primary site (%) sm intestine 39% unknown 18% pancreas 9% lung 6% colon 6% other 21%</td>
<td>CR: 0% PR: 24% SD: 70%</td>
<td>PFS (med): not reached, 16 mo OS (med): not reached, 16 mo OS (1-yr): 91% (75-98%) OS (2-yr): 88% (71-96%)</td>
<td>Gr 3 thrombocytopenia: 1 pt nephrotoxicity: none</td>
</tr>
<tr>
<td>Brizzi MP. 2009&lt;sup&gt;7&lt;/sup&gt;</td>
<td>phase II</td>
<td>5FU (200 mg/m² IV daily) + LAR octreotide (20 mg) advanced/ meta-static well-diff NET (n=29)</td>
<td>PR: 24.1% (n=7) SD: 69.0% (n=20)</td>
<td>PFS (med): 22.6 mo OS (med): not reached</td>
<td></td>
<td>diarrhea 65.4% hand-foot syndrome 34.5%</td>
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<td>Seregni E. 2010&lt;sup&gt;11&lt;/sup&gt;</td>
<td>phase II</td>
<td>([177]Lu)DOTA-TATE (5.55 GBq) and [(90)Y]DOTA-TATE (2.6 GBq) alternating x 4 cycles</td>
<td>refractory NET (n=26)</td>
<td>PR: 67% (n=10) at 3-4 mos post</td>
<td>Symptom relief: 60% (9/15 pts)</td>
<td>Leukocytopenia Gr 1-2: 2 pts</td>
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<tr>
<td>Cwikla JB. 2010&lt;sup&gt;12&lt;/sup&gt;</td>
<td>phase II</td>
<td>[(90)Y]DOTA-TATE</td>
<td>progressive gastroentero-PNET (n=56)</td>
<td>Radiologic: PR: 23% (n=13) SD: 77% (n=43) Clinical: PR: 72% (n=43) SD: 16% (n=9)</td>
<td>OS (med): 22 mo (9.5 mo in early PD; 23.5 mo in PR / SD)</td>
<td>Gr 2-3 renal toxicity: 5 patients</td>
</tr>
<tr>
<td>Waldherr C. 2001&lt;sup&gt;43&lt;/sup&gt;</td>
<td>phase II</td>
<td>[(90)Y-DOTA]-TOC (6000 MBq/m2 x 4 injections) q 6 wks</td>
<td>gastroentero-pancreatic NET (n=41)</td>
<td>Overall: 36% for endocrine NET CR: 2% (1 pt) PR: 22% (n=9)</td>
<td>OS (2-yr): 76% Reduction of symptoms: 83% Reduction in pain: 100% of those w/morphine-depend pain</td>
<td>Gr 3 pancytopenia: 5%</td>
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<tr>
<td>Caplin, M.E. *</td>
<td>phase III RCT</td>
<td>1) extended-release aqueous-gel formulation of lanreotide (120 mg) q 28 days for 96 wks (n=101)</td>
<td>advanced, well-differentiated or moderately differentiated, nonfunctioning, somatostatin receptor-positive NET (n=204)</td>
<td>CgA reduction ≥50%: 42% (n= 27/64) lanreotide vs. 5% (n=3/64) placebo, p&lt;0.001</td>
<td>PFS (med): not reached lanreotide vs. 18.0 mo placebo, p&lt;0.001</td>
<td>Most common: diarrhea: 26% lanreotide and 9% placebo</td>
</tr>
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<td>Martin-Richard M.</td>
<td>phase II</td>
<td>lanreotide autogel, 120 mg q 28 days over 12 mo</td>
<td>progressive NET (n=30)</td>
<td>SD: 89% (n=24) PR: 4% (n=1)</td>
<td>PFS (med): 12.9 mo (95% CI 7.9-16.5)</td>
<td>most common: diarrhea: 40% asthenia: 20% flatulence: 10% injection- site pain: 10% 1 pt had severe event (aerophagia) and 1 pt had a serious event (acute renal failure)</td>
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<td>Primary tumour midgut 40% pancreatic 27%</td>
<td>CgA normalised/ decreased by ≥30% at 8 wks: 70%</td>
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</tbody>
</table>

2) placebo q 28 days for 96 wks (n=103)

primary site (%)
lanreotide vs. placebo
pancreas 42% vs. 48%
midgut 33% vs. 39%
hindgut 11% vs. 3%
unknown/other 15% vs.11%

PFS (24 mo): 65.1% (95% CI 54.0-74.1) lanreotide vs. 33.0% (95% CI 23.0-43.3) placebo

cholelithiasis) in the lanreotide group and one event (bile duct stenosis) in the placebo group

**Abbreviations:** ASCO = American Society of Clinical Oncology; CI = confidence interval; CR = complete response; Gr = grade; HR = hazard ratio; mo = months; NET = neuroendocrine tumour; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression free survival; PR = partial response; pt = patient; SD = stable disease; TTP = time to progression