

# Clinical Roundtable Monograph

Clinical Advances in Hematology & Oncology

April 2016

## Current Concepts in the Management of GEP-NETs: A Case Study Compendium

### Discussants



#### Renuka Iyer, MD

Associate Professor of Oncology  
Co-Director, Liver and Pancreas Tumor Center  
Section Chief for Gastrointestinal Oncology  
Roswell Park Cancer Institute  
Buffalo, New York



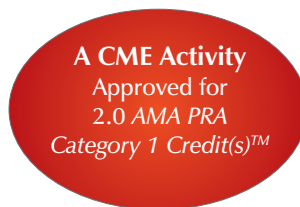
#### J. Philip Boudreaux, MD, FACS

Professor of Surgery, Division of Surgical Oncology  
LSU Health Sciences Center School of Medicine  
Department of Surgery  
New Orleans, Louisiana  
Chairman, Department of Surgery  
Ochsner Medical Center-Kenner Hospital  
Kenner, Louisiana



#### Fadi Braiteh, MD

Clinical Associate Professor of Medicine  
University of Nevada School of Medicine  
Las Vegas, Nevada



**Release Date:** April 2016

**Expiration Date:** April 30, 2017

**Estimated time to complete activity:** 2.0 hours

**Project ID:** 11303

**Abstract:** Available systemic treatment options for patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs) have expanded considerably in recent years. In patients with functional tumors, the overproduction of amines or peptide hormones may require treatment to relieve symptoms. Because many patients present with metastatic disease, therapy that inhibits tumor progression is also needed. Somatostatin analogs are used for controlling carcinoid syndrome, with recent studies also demonstrating their ability to inhibit disease progression. Drugs that inhibit angiogenesis or the mammalian target of rapamycin have demonstrated efficacy in pancreatic NETs, prolonging progression-free survival. New drugs under investigation include temozolomide, an alkylating agent that has demonstrated efficacy in combination with other agents. In addition, surgical resection and radiotherapy remain indispensable approaches for effective patient treatment. The availability of new treatments has raised questions regarding how to integrate them into practice. An important challenge now facing providers involves sequencing. Optimal sequencing of drugs for first-line and subsequent therapies must be considered. In patients with disseminated disease, questions may arise regarding which tumor or symptoms to address first. This discussion of case studies highlights current issues in the management of patients with GEP-NETs.

Supported through an educational grant from Ipsen Biopharmaceuticals, Inc.

Jointly provided by Postgraduate Institute for Medicine and Millennium Medical Publishing

## Target Audience

This activity has been designed to meet the educational needs of oncologists and nurses involved in the management of patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

## Statement of Need/Program Overview

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are epithelial neoplasms that originate from neuroendocrine cells. Functional tumors secrete peptides and/or neuroamines that induce clinical symptoms such as flushing, diarrhea, bronchospasm, and valvular heart disease. Patients with nonfunctional tumors may be asymptomatic or have symptoms resulting from tumor bulk. Many patients present with metastatic disease and require therapy that inhibits tumor progression. In recent years, treatment paradigms for GEP-NETs have been expanded by the somatostatin analogs octreotide and lanreotide depot/autogel. Other approved agents include everolimus and sunitinib. Patients with resectable tumors may benefit from surgery. The availability of new treatments has raised questions regarding how to integrate them into practice. Optimal sequencing of drugs for first-line and subsequent therapies must be considered. In patients with disseminated disease, questions may arise regarding which tumor or symptoms to address first.

## Educational Objectives

After completing this activity, the participant should be better able to:

- Analyze results from clinical trials evaluating new therapies and strategies in the management of GEP-NETs
- Discuss how to integrate new treatments into clinical practice
- Define the role of multidisciplinary care in the treatment of GEP-NETs
- Modify treatment based on patient outcomes

## Accreditation Statement

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Postgraduate Institute for Medicine and Millennium Medical Publishing, Inc. The Postgraduate Institute for Medicine is accredited by the ACCME to provide continuing medical education for physicians.

## Credit Designation

The Postgraduate Institute for Medicine designates this enduring material for a maximum of 2.00 *AMA PRA Category 1 Credit(s)*<sup>™</sup>. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

## Disclosure of Conflicts of Interest

Postgraduate Institute for Medicine (PIM) requires instructors, planners, managers, and other individuals who are in a position to control the content of this activity to disclose any real or apparent conflict of interest (COI) they may have as related to the content of this activity. All identified COI are thoroughly vetted and resolved according to PIM policy. PIM is committed to providing its learners with high-quality CME activities and related materials that promote improvements or quality in healthcare and not a specific proprietary business interest of a commercial interest.

The faculty reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:

**Renuka Iyer, MD**—Consultant: Ipsen Biopharmaceuticals, Inc.

**J. Philip Boudreaux, MD**—Consultant: Ipsen Biopharmaceuticals, Inc.

**Fadi Braiteh, MD**—Honoraria: Amgen, BIND Therapeutics, Boehringer In-

gelheim, Dendreon; Consulting or Advisory Role: Amgen, BIND Therapeutics, Boehringer Ingelheim, Dendreon, Incyte; Speakers Bureau: Amgen, Bayer, Boehringer Ingelheim; Research Funding: AbbVie (Inst), Amgen (Inst), Astra-Zeneca (Inst), Ipsen Biopharmaceuticals (Inst); Other Relationship: Celgene.

The planners and managers reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:

The following PIM planners and managers, Trace Hutchison, PharmD; Samantha Mattiucci, PharmD, CHCP; Judi Smelker-Mitchek, RN, BSN; and Jan Schultz, RN, MSN, CHCP hereby state that they or their spouse/life partner do not have any financial relationships or relationships to products or devices with any commercial interest related to the content of this activity of any amount during the past 12 months. Jacquelyn Matos: No real or apparent conflicts of interest to report. Maggie Merchant, PhD: No real or apparent conflicts of interest to report.

## Method of Participation

There are no fees for participating in and receiving CME credit for this activity. During the period April 2016 through April 30, 2017, participants must 1) read the learning objectives and faculty disclosures; 2) study the educational activity; 3) complete the post-test by recording the best answer to each question in the answer key on the evaluation form; 4) complete the evaluation form; and 5) mail or fax the evaluation form with answer key to Postgraduate Institute for Medicine. You may also complete the post-test online at [www.cmeuniversity.com](http://www.cmeuniversity.com). On the navigation menu, click on "Find Post-test/Evaluation by Course" and search by course ID 11303. Upon registering and successfully completing the post-test with a score of 75% or better and submitting the activity evaluation, your certificate will be made available immediately. Processing credit requests online will reduce the amount of paper used by nearly 100,000 sheets per year.

A statement of credit will be issued only upon receipt of a completed activity evaluation form and a completed post-test with a score of 75% or better. Your statement will be emailed to you within three weeks.

## Media

Monograph

## Disclosure of Unlabeled Use

This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. The planners of this activity do not recommend the use of any agent outside of the labeled indications. PIM, Millennium Medical Publishing, Inc., and Ipsen Biopharmaceuticals, Inc. do not recommend the use of any agent outside of the labeled indications.

The opinions expressed in the educational activity are those of the faculty and do not necessarily represent the views of the planners. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

## Disclaimer

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patient's conditions and possible contraindications or dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

## Disclaimer

Funding for this clinical roundtable monograph has been provided through an educational grant from Ipsen Biopharmaceuticals, Inc. Support of this monograph does not imply the supporter's agreement with the views expressed herein. Every effort has been made to ensure that drug usage and other information are presented accurately; however, the ultimate responsibility rests with the prescribing physician. Millennium Medical Publishing, Inc., the supporter, and the participants shall not be held responsible for errors or for any consequences arising from the use of information contained herein. Readers are strongly urged to consult any relevant primary literature. No claims or endorsements are made for any drug or compound at present under clinical investigation.

©2016 Millennium Medical Publishing, Inc., 611 Broadway, Suite 310, New York, NY 10012. Printed in the USA. All rights reserved, including the right of reproduction, in whole or in part, in any form.

# Current Concepts in the Management of GEP-NETs: Introduction

Renuka Iyer, MD

Associate Professor of Oncology

Co-Director, Liver and Pancreas Tumor Center

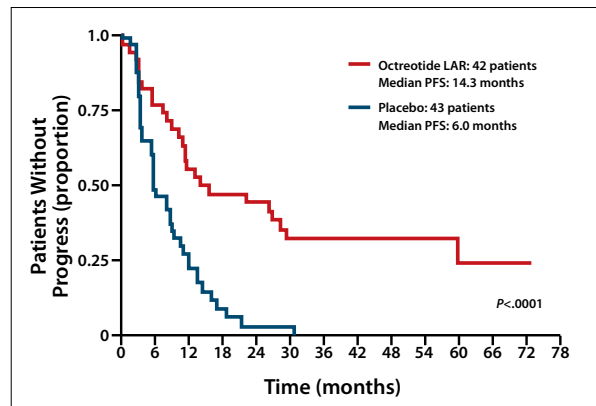
Section Chief for Gastrointestinal Oncology

Roswell Park Cancer Institute

Buffalo, New York

**G**astroenteropancreatic neuroendocrine tumors (GEP-NETs) are epithelial neoplasms that originate from neuroendocrine cells.<sup>1</sup> The category consists of 2 major types: carcinoid tumors of the gastrointestinal tract and pancreatic NETs. Functional tumors secrete peptides and/or neuroamines that induce clinical symptoms such as flushing, diarrhea, bronchospasm, and valvular heart disease. Patients with nonfunctional tumors may be asymptomatic or have symptoms resulting from tumor bulk. Although GEP-NETs are rare, their prevalence has increased during the last decade owing to improved diagnostic and imaging techniques. In recent years, treatment paradigms for GEP-NETs have been expanded by the development and validation of the somatostatin analogs octreotide and lanreotide depot/autogel. These groundbreaking agents bind to somatostatin receptors, displacing the activating peptide hormone and preventing downstream peptide release.

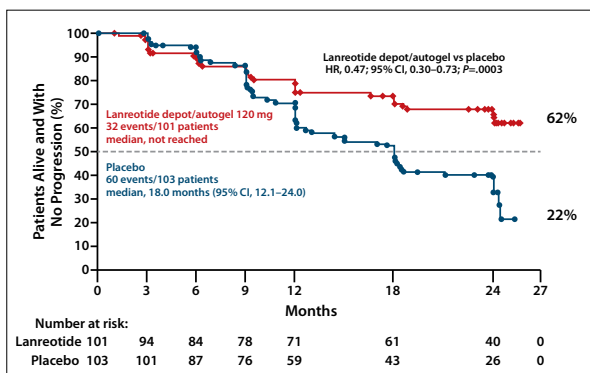
Octreotide was originally approved for the relief of symptoms in patients with functional NETs. Numerous single-arm clinical trials appeared to show that octreotide induced tumor stabilization, but the lack of a placebo control arm limited the interpretation of results. To provide decisive evidence regarding the activity of octreotide, the placebo-controlled, double-blind, phase 3b PROMID (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) study was conducted.<sup>2</sup> To improve the likelihood of demonstrating tumor control, the study included only treatment-naïve patients with well-differentiated midgut NETs and metastatic disease. Tumor grade was limited to a proliferation index of less than 2%. Eighty-five patients were randomized to octreotide long-acting release (LAR) vs placebo. The study demonstrated an improvement in progression-free survival (PFS) for patients treated with octreotide LAR (14.3 vs 6.0 months; hazard ratio [HR], 0.34; 95% CI, 0.20-0.59;  $P=0.00072$ ; Figure 1), with antiproliferative activity observed in both functional and nonfunctional tumors.



**Figure 1.** PFS in the PROMID trial, which enrolled patients with advanced midgut neuroendocrine tumors.

LAR, long-acting release; PFS, progression-free survival; PROMID, 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. Adapted from Rinke A et al. *J Clin Oncol*. 2009;27(28):4656-4663.<sup>2</sup>

The efficacy of somatostatin analogs in controlling NETs was further established in the CLARINET (Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors) study.<sup>3</sup> The phase 3 trial included a broader study population, enrolling 204 patients with nonfunctional, well- or moderately differentiated tumors; somatostatin receptor expression; and metastatic disease. Enrollment criteria permitted patients with higher-grade tumors that had a proliferation index of less than 10%. Tumors could originate in the midgut, hindgut, or pancreas or could be of unknown origin. Lanreotide depot/autogel was associated with a significant extension of median PFS (not reached vs 18.0 months; HR, 0.47; 95% CI, 0.30-0.73;  $P<.001$ ; Figure 2). The study clearly demonstrated that lanreotide depot/autogel delayed progression in patients with grade 1 or 2 enteropancreatic tumors and stable disease. Moreover, both octreotide and lanreotide have demonstrated very favorable safety profiles. Somatostatin analogs continue to be a cornerstone of GEP-NET therapy, particularly in the context of functional tumors.



**Figure 2.** Progression-free survival among the intent-to-treat population in the CLARINET trial, which enrolled patients with grade 1 or 2 GEP-NETs that were well-differentiated or moderately differentiated, nonfunctioning, and locally inoperable or metastatic.

CLARINET, Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors. GEP-NETs, gastroenteropancreatic neuroendocrine tumors. Adapted from Caplin ME et al. *N Engl J Med.* 2014;371(3):1556-1557.<sup>3</sup>

Everolimus, which inhibits the mammalian target of rapamycin (mTOR) pathway, and sunitinib, a multikinase inhibitor of angiogenesis receptors, are also approved to treat progressive pancreatic NETs.<sup>4,5</sup> Studies of temozolomide in combination with thalidomide, bevacizumab, or capecitabine have demonstrated efficacy with manageable tolerability in patients with pancreatic NETs.<sup>6-8</sup> Questions

remain regarding the best way to sequence octreotide, lanreotide depot/autogel, and other therapies, such as everolimus and sunitinib. The following sets of case studies are presented to elucidate current concepts and conundrums in treating patients with GEP-NETs.

### Disclosure

Dr Iyer is a consultant for Ipsen Biopharmaceuticals, Inc.

### References

- Eads JR, Meropol NJ. A new era for the systemic therapy of neuroendocrine tumors. *Oncologist.* 2012;17(3):326-338.
- Rinke A, Müller HH, Schade-Brittinger C, et al; PROMID Study Group. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol.* 2009;27(28):4656-4663.
- Caplin ME, Pavel M, Ruzsniiewski P. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med.* 2014;371(16):1556-1557.
- Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med.* 2011;364(6):514-523.
- Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med.* 2011;364(6):501-513.
- Chan JA, Stuart K, Earle CC, et al. Prospective study of bevacizumab plus temozolomide in patients with advanced neuroendocrine tumors. *J Clin Oncol.* 2012;30(24):2963-2968.
- Kulke MH, Stuart K, Enzinger PC, et al. Phase II study of temozolomide and thalidomide in patients with metastatic neuroendocrine tumors. *J Clin Oncol.* 2006;24(3):401-406.
- Strosberg JR, Fine RL, Choi J, et al. First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. *Cancer.* 2011;117(2):268-275.

## Cases in the Management of NETs: Focus on Sequencing Somatostatin Analogs

Renuka Iyer, MD

Associate Professor of Oncology

Co-Director, Liver and Pancreas Tumor Center

Section Chief for Gastrointestinal Oncology

Roswell Park Cancer Institute

Buffalo, New York

### CASE 1

A 59-year-old man presented with a 3 cm × 5 cm presacral mass that was identified by imaging performed for chronic left lower back pain (Figure 3). A biopsy identified the tumor as a well-differentiated carcinoid. Tumor markers were negative, but an octreotide scan showed positive uptake by the mass and the presacral lymph nodes, with a

focus in the left mediastinum. The patient was diagnosed with a metastatic, nonfunctional carcinoid tumor of unknown primary origin. Initial treatment consisted of octreotide LAR (30 mg) by intramuscular injection once every month.<sup>1</sup> The patient had stable disease that lasted approximately 3 years, which is slightly longer than the median for patients treated with octreotide LAR. After 36 doses, the patient's disease progressed.



**Figure 3.** A computed tomography scan showing the left sided presacral mass measuring 3 × 5 cm, as indicated by the arrow.

The patient's treatment was switched to lanreotide depot/autogel (120 mg) injected subcutaneously once a month, which resulted in stable disease for approximately 1 year.<sup>2</sup> The stabilization of disease suggested that the change to lanreotide depot/autogel was beneficial. After 13 doses of lanreotide, the patient progressed. Treatment with temozolomide combination therapy was recommended.<sup>3-5</sup> Later, the patient received irradiation to enlarged obturator lymph nodes. He developed liver metastases after a few months.

### Discussion

Somatostatin analogs are indicated by the National Comprehensive Cancer Network (NCCN) guidelines for slowly progressing disease.<sup>6</sup> However, the benefit of using them sequentially has not been well studied. Somatostatin analogs are similar in their binding sites, but have different molecules, chemical structures, pharmacokinetic profiles, and routes of delivery, which may result in improved efficacy when switching from one agent to another. This approach merits further study, especially given the limited approved therapies in this setting.

### CASE 2

A 62-year-old man presented with a left upper quadrant mass invading the spleen, retroperitoneal lymphadenopathy, and liver lesions that proved positive for metastasis on biopsy. At a community facility, he was diagnosed with a metastatic, well-differentiated, nonfunctional pancreatic NET. He received octreotide LAR at 20 mg intramuscularly once a month for 3 years, at which point his disease progressed.<sup>1</sup> Many community physicians use a 20-mg initial dose of octreotide LAR. The NCCN guidelines offer the choice of using 20 mg or 30 mg in the context of carcinoid syndrome.<sup>7</sup> In the PROMID study, disease



**Figure 4.** A computed tomography scan showing the left upper quadrant mass with splenic invasion and liver metastases.

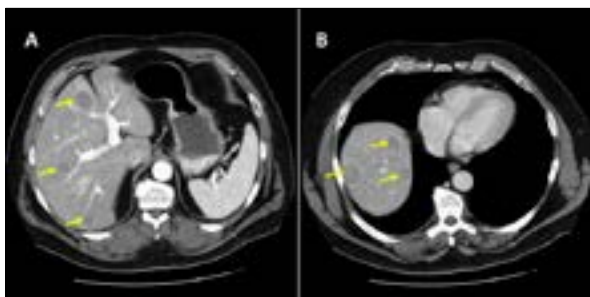
progression was inhibited by the 30-mg dose, as reflected in the increased PFS.<sup>1</sup>

The dose of octreotide LAR was increased to 30 mg once per month, and everolimus (10 mg once daily) was added to this treatment.<sup>8</sup> Imaging showed further progression, at which point the patient was referred to our center for treatment. His therapy was changed to temozolomide plus thalidomide in anticipation of tumor regression.<sup>4</sup> However, his disease progressed, so capecitabine plus temozolomide was initiated, and octreotide LAR (30 mg) was reinitiated.<sup>5</sup> The patient continued to experience disease progression, and the therapy was changed to lanreotide depot/autogel and sunitinib.<sup>9</sup>

The patient continued on this combination of lanreotide depot/autogel and sunitinib for approximately 10 months, during which time he received 9 doses of lanreotide depot/autogel. He had stable disease. It was unclear how much benefit was derived from which agent.

He then showed worsening of extrahepatic disease, with an increase in the size of the left upper quadrant mass, increased splenic invasion (Figure 4), and worsened ascites, although his liver metastases were stable. He was advised to continue lanreotide depot/autogel but to replace sunitinib with a combination of folinic acid/leucovorin, 5-fluorouracil, and oxaliplatin (FOLFOX). This chemotherapy combination was recommended based on concerns about the functionality of the spleen and the possible risk of infections from a likely impending peritoneal tunnel catheter. FOLFOX tends to have less of a myelosuppressive effect and is therefore associated with a lower risk of infection. At this point, the patient began treatment with a doctor who did not belong to our center, and he was lost to our follow-up.





**Figure 5.** Bilobar hepatic metastases, as indicated by the arrows, seen on computed tomography scans.

### Discussion

This case illustrates an aggressive metastatic pancreatic NET that progressed on synthetic somatostatin analogs, an mTOR inhibitor (everolimus), cytotoxic chemotherapy, and an anti-vascular endothelial growth factor targeted therapy (sunitinib). In addition, the case highlights the role of continuing somatostatin analogs in such NETs with nonindolent biology, an approach that should be prospectively evaluated. This patient was on concomitant somatostatin analogs while receiving the molecularly targeted agents. It was unclear how much benefit was attained with each agent. In the recent RADIANT-4 (RAD001 in Advanced Neuroendocrine Tumours, Fourth Trial) trial, everolimus showed a 7.1-month improvement in PFS compared with placebo in nonfunctional carcinoid tumors.<sup>10</sup> However, patients in this study were required to discontinue use of somatostatin analogs prior to study entry.

### CASE 3

A 61-year-old man showed symptoms of small-bowel obstruction. He underwent exploratory laparotomy and right hemicolectomy. The patient was diagnosed with a well-differentiated NET of the ileocecal valve along with involvement of several lymph nodes. Eight years after the hemicolectomy, computed tomography (CT) revealed bilobar hepatic disease (Figure 5), which was later confirmed to be positive on octreoscan. Octreotide LAR (30 mg) was initiated for metastatic midgut NET, and the patient underwent partial hepatic lobectomy with radiofrequency ablation of some liver lesions.<sup>1</sup>

Four years later, his liver metastases progressed, requiring treatment with yttrium-90 microspheres.<sup>11</sup> His dose of octreotide LAR was increased to 40 mg, as several studies suggested that octreotide LAR at doses exceeding 30 mg/month might be effective at preventing tumor progression without increased toxicity.<sup>12</sup> After 3 years, his liver metastases progressed, and his tumor markers increased. His treatment was changed to lanreotide depot/autogel at 120 mg. He also underwent bland embolization of liver lesions.

The patient developed asymptomatic splenic lesions and a lumbar vertebral (L2) lesion 6 months after starting treatment with lanreotide depot/autogel. However, he had stable disease elsewhere. The minimal, asymptomatic progression and predominantly stable disease led us to continue lanreotide depot/autogel and add bisphosphonates for the bone metastasis. To date, the patient has received 9 doses of lanreotide depot/autogel, with ongoing response in the liver. The long-term performance of lanreotide depot/autogel in this setting will be of interest.

### Discussion

As in cases 1 and 2, lanreotide depot/autogel might have had benefit after the patient progressed while receiving octreotide. The patient's liver disease stabilized after the switch from octreotide to lanreotide depot/autogel, and he continues to have an ongoing response in the liver while on lanreotide. It should be acknowledged that this patient received multiple liver-directed therapies before initiation of lanreotide depot/autogel. He underwent bland embolization of the liver lesions a few weeks after initiation of lanreotide depot/autogel. These liver-directed therapies might have partially contributed to the ongoing response in the liver. In any case, the site of metastases might be predictive of benefit with sequencing somatostatin analogs in advanced NETs. This strategy warrants further study.

### Disclosure

*Dr Iyer is a consultant for Ipsen Biopharmaceuticals, Inc.*

### References

1. Rinke A, Müller HH, Schade-Brittinger C, et al; PROMID Study Group. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol.* 2009;27(28):4656-4663.
2. Caplin ME, Pavel M, Ruzsniewski P. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med.* 2014;371(16):1556-1557.
3. Chan JA, Stuart K, Earle CC, et al. Prospective study of bevacizumab plus temozolomide in patients with advanced neuroendocrine tumors. *J Clin Oncol.* 2012;30(24):2963-2968.
4. Kulke MH, Stuart K, Enzinger PC, et al. Phase II study of temozolomide and thalidomide in patients with metastatic neuroendocrine tumors. *J Clin Oncol.* 2006;24(3):401-406.
5. Strosberg JR, Fine RL, Choi J, et al. First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. *Cancer.* 2011;117(2):268-275.
6. Kulke MH, Shah MH, Benson AB 3rd, et al; National comprehensive cancer network. Neuroendocrine tumors, version 1.2015. *J Natl Compr Canc Netw.* 2015;13(1):78-108.
7. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Neuroendocrine Tumors Version 1.2015. National Comprehensive Cancer Network. [http://www.nccn.org/professionals/physician\\_gls/pdf/neuroendocrine.pdf](http://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf). Updated November 11, 2014. Accessed March 15, 2016.
8. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med.* 2011;364(6):514-523.
9. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med.* 2011;364(6):501-513.

10. Yao JC, Fazio N, Singh S, et al; RAD001 in Advanced Neuroendocrine Tumours, Fourth Trial (RADIANT-4) Study Group. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2016;387(10022):968-977.
11. Rajekar H, Bogamanna K, Stubbs RS. Selective internal radiation therapy

- for gastrointestinal neuroendocrine tumour liver metastases: a new and effective modality for treatment. *Int J Hepatol*. 2011;2011:404916.
12. Broder MS, Beenhouwer D, Strosberg JR, Neary MP, Cherepanov D. Gastrointestinal neuroendocrine tumors treated with high dose octreotide-LAR: a systematic literature review. *World J Gastroenterol*. 2015;21(6):1945-1955

# Cases in the Management of GEP-NETs: The Use of Surgery, an Underutilized Option in the Management of Advanced-Stage NETs

J. Philip Boudreaux, MD, FACS  
Professor of Surgery, Division of Surgical Oncology  
LSU Health Sciences Center  
School of Medicine, Department of Surgery  
New Orleans, Louisiana  
Chairman, Department of Surgery  
Ochsner Medical Center-Kenner Hospital  
Kenner, Louisiana

## CASE 1

A 42-year-old woman had a 3-year history of flushing and diarrhea. She regularly rode horses, and her symptoms were exacerbated by this activity. Her previous health care providers had suggested that the hot flashes were attributable to premature menopause. A fall from a horse led to an imaging scan that showed a large tumor—measuring approximately 12 cm in diameter—in the central portion of her liver (Figure 6). A biopsy revealed that it was an endocrine tumor. Many tests and scans were performed, but the primary tumor site was never discovered. The patient was diagnosed with a well-differentiated NET of unknown primary origin. She underwent upper and lower endoscopy and a colonoscopy. The terminal ileum was not intubated or interrogated.

The patient was seen by an oncologist. Elevated levels of 5-hydroxyindoleacetic acid (5-HIAA) led to a diagnosis of carcinoid syndrome. The oncologist informed her that she was not a candidate for surgery and sent her to a specialist at a tertiary center, who enrolled her in a clinical trial. After approximately 3 months on blinded treatment, the disease progressed and the symptoms remained the same. This medical specialist told the patient that she was not a candidate for surgery. She began treatment with depot octreotide at 20 mg monthly. Symptoms persisted, so the dose was increased to 30 mg monthly.<sup>1</sup> At a different treatment center, she saw another oncologist who said she was not eligible for surgery and recommended yttrium-90 microsphere embolization to the liver.<sup>2</sup> After that treatment, her symptoms improved for approxi-

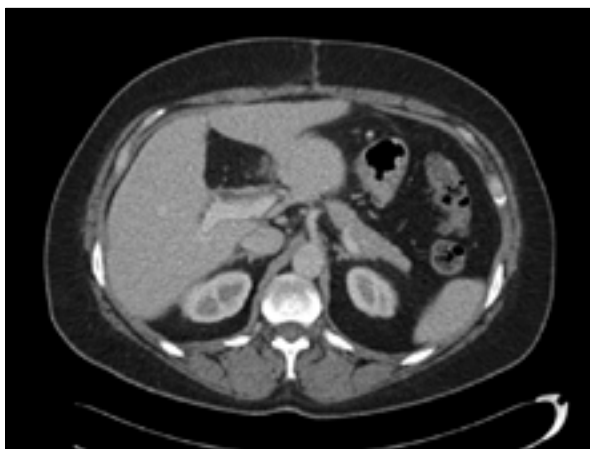


**Figure 6.** A preoperative image showing disease.

mately 3 months. It is noteworthy with this patient's care that the initial oncologist, as well as the next 2 specialists, told her that she was not a candidate for surgery. She was not evaluated by a surgeon at any of these visits.

The patient continued to experience flushing and diarrhea. She sought care from another physician, who suggested she might need a liver transplant. She visited the liver transplant center, but she was not evaluated by a transplant surgeon. She saw a physician who told her she was not a candidate for surgery and recommended chemotherapy. She declined chemotherapy and sought out another center.

She finally self-referred to our center, where she received a fourth opinion in a multidisciplinary setting. We deemed



**Figure 7.** A postoperative image showing no evidence of disease.

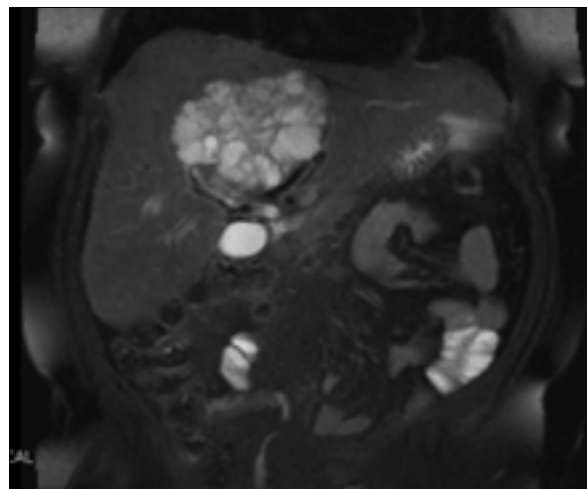
her operable and successfully removed the large tumor in the center of her liver. Interestingly, we found a 1-cm tumor in her terminal ileum, approximately 4 inches from her ileocecal valve. Therefore, she had a previously undiscovered primary tumor. As noted above, the terminal ileum was not interrogated during her initial assessments. She also had lymph node metastases, illustrating that a small tumor can and will metastasize. The tumor in her liver, as well as her primary tumor and nodes, were completely excised.

Now it has been 3 years since the surgery, and she has no evidence of disease (Figures 7 and 8). Her 5-HIAA and chromogranin A levels are normal, as are her CT scan and octreotide scan results. She continues treatment with a long-acting somatostatin analog administered monthly.

### **Discussion**

This patient was told she had incurable, unresectable disease and might need a liver transplant, partly because she was not evaluated by the proper clinicians. Another lesson here is that even a tumor as small as 1 cm can metastasize, which is contrary to the teachings found in most textbooks. This patient had a very large liver metastasis that originated from a 1-cm primary tumor.

This case underscores the point that a patient with carcinoid syndrome will most likely have a tumor somewhere in the small bowel. Sometimes, the tumor will only be discovered at surgery. However, other modalities that may be used include colonoscopy that can reach the terminal ileum and a small-bowel enteroscopy with a long scope. Why would we operate on her small bowel if her primary tumor is asymptomatic, with no symptoms of obstruction? Her symptoms were caused by the tumor burden in her liver and the large amount of serotonin it was producing. The natural history of bowel tumors is to eventually cause obstruction or bleeding. Without treatment, a patient will ultimately experience intestinal ischemia owing to mesenteric vascular encasement by metastatic lymph nodes



**Figure 8.** A postoperative image showing no evidence of disease.

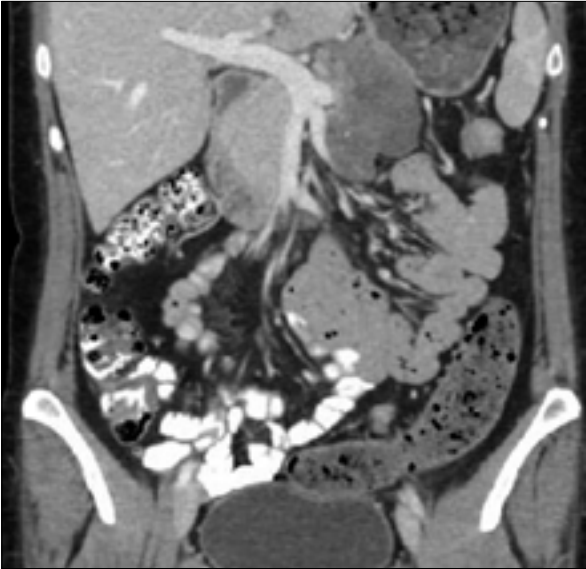
and gut failure. In contrast to the current paradigm, it is not necessary to wait for tumors to become symptomatic before considering surgery. This case also highlights the importance of having an experienced surgeon evaluate patients for tumor resectability. Medical oncologists may be unfamiliar with the available types of procedures and complementary modalities available, including irreversible electroporation (IRE) for “unresectable” tumors.

### **CASE 2**

A 40-year-old woman had vague abdominal pain. Imaging via CT revealed a 10-cm mass identified as a “poorly differentiated carcinoma” in the left upper quadrant retroperitoneum and tail of the pancreas (Figures 9 and 10). The mass involved the spleen and distorted the posterior aspect of the stomach. The patient had a solitary metastasis of the liver. Upon repeated laparoscopic lymph node biopsy, the mass was described as a well-differentiated pancreatic NET, with a Ki-67 proliferation index of 8%.<sup>3</sup> The mass was positive according to <sup>18</sup>F-fluorodeoxyglucose positron emission tomography but negative by octreotide scan. The patient underwent several cycles of systemic, platinum-based chemotherapy, which resulted in stable disease. She was explored for cytoreduction but considered ineligible for resection. She remained on chemotherapy.

Ten months later, she presented to our office, where our pathologist reviewed her biopsy slides. On this evaluation, the pathologist observed a well-differentiated NET with a much lower Ki-67 mitotic index of 1%. Additional analysis confirmed the original diagnosis of pancreatic NET. The patient underwent complete, R0 resection of her tumor with removal of the tail of the pancreas, a portion of the stomach, and the metastatic lesion in the liver. The biopsies showed a Ki-67 proliferation index of 30% for the primary tumor and 1% for the lymph node and liver metastases.





**Figure 9.** A preoperative scan showing a large pancreatic tumor encasing the splenic vein.

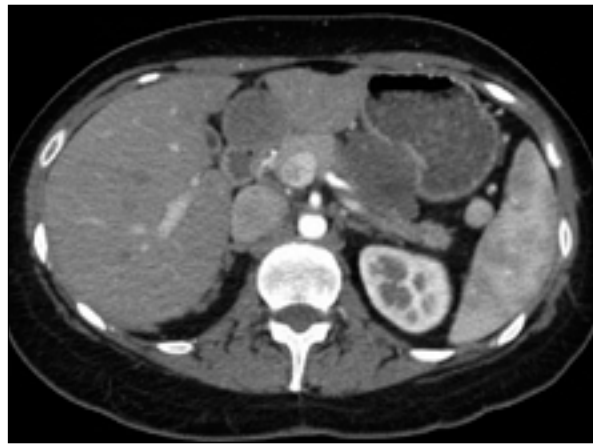
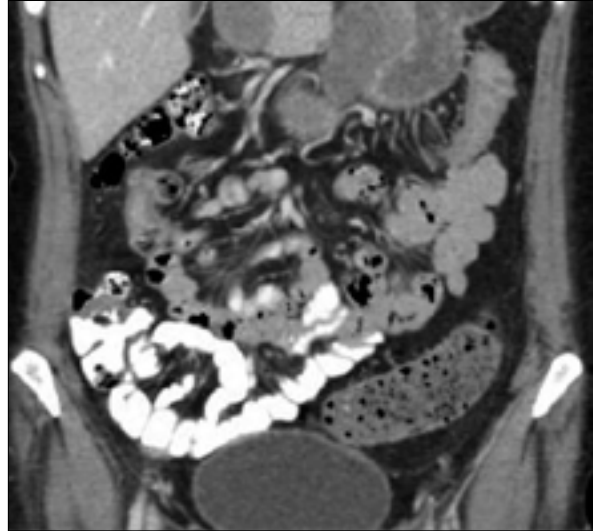
### Discussion

The lesson from this case is that the pathology for NETs can be difficult to ascertain, particularly if the specimen is inadequate. There may not be enough tissue to perform the required analysis, or the tissue may be partially investigated with only some of the necessary stains required for a definitive diagnosis. With this patient, the initial biopsy was not queried for synaptophysin, chromogranin, and several other markers for NETs. A diagnosis of “poorly differentiated carcinoma” is inadequate. As a result of the incorrect initial diagnosis, which was based on incomplete pathologic investigation, definitive therapy was delayed. Once again, unresectability was not determined in the setting of a multidisciplinary neuroendocrine tumor center.

### CASE 3

Many aspects of NET disease can be addressed in stages, rather than all at once. A 68-year-old woman had a history of typical symptoms of carcinoid syndrome associated with midgut NETs and bowel obstruction (Figure 11). She underwent emergency surgery for small-bowel obstruction after years of diarrhea and hot flashes. After the surgery, she was told that her remaining disease burden, which included a 9-cm liver metastasis and mesenteric nodal metastases, was inoperable (Figure 12). The patient’s surgeon and oncologist referred her to our multidisciplinary center for evaluation.

Our evaluation indicated that the disease burden in her mesentery could be excised and dissected away from the mesenteric vessels.<sup>4</sup> We also felt confident that the tumor in her liver could be resected, even though it was large. The patient began treatment with long-acting lan-



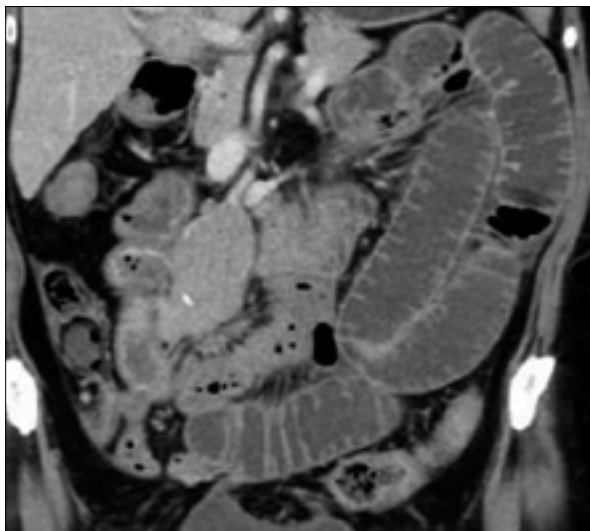
**Figure 10.** Preoperative scans showing the tumor invading the medial gastric wall.

reotide depot/autogel at 120 mg subcutaneously to delay the progression of her disease.<sup>1,5</sup> She also met with a nutritionist to devise a diet with foods that do not exacerbate diarrhea and other symptoms, while providing sufficient nourishment to enable a second surgery.

Six months later, the patient had stable disease. Her diarrhea had lessened but still persisted. She underwent gross R0 resection, with complete debulking of her mesentery to eliminate the risk of eventual intestinal ischemia.<sup>6</sup> The natural history of metastatic tumors in the base of the mesentery is to become symptomatic, eventually resulting in intestinal ischemia and gut failure. At 9 months after her debulking, the patient continues treatment with lanreotide depot/autogel. She remains asymptomatic, and has gained weight.

### Discussion

An important point illustrated by this case is that before the patient could undergo the second surgery, she not only needed to recover from her previous surgery but required nutritional resuscitation. Patients who are nutritionally

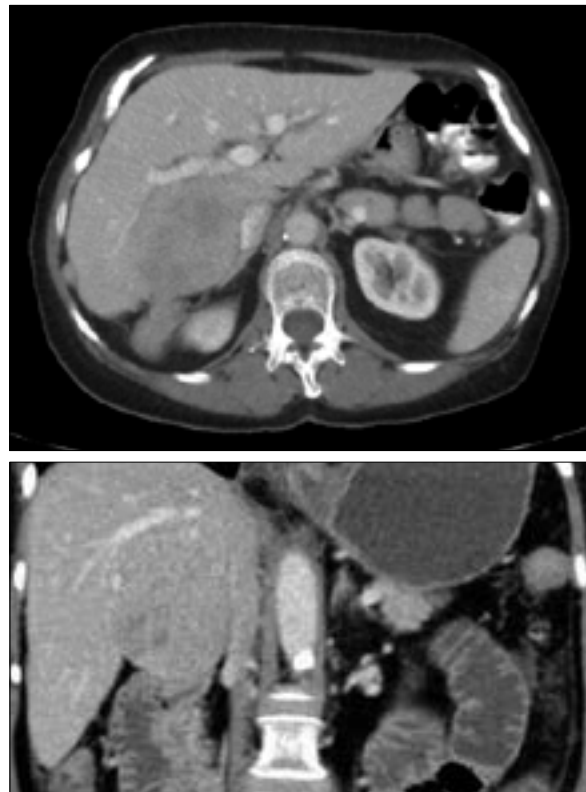


**Figure 11.** A preoperative scan showing partial bowel obstruction and a large mesenteric mass.

challenged are not great candidates for major surgery. The second surgery may be more involved than the first, and the patient must be as robust as possible to ensure good wound healing and have an adequate ability to fight infection. As a result of these requirements, a good nutritional evaluation is essential for patients who will undergo major resection.

Persistent diarrhea can lead to nutritional challenges, and is seen in patients who have had the ileocecal valve removed. Diarrhea can also persist in patients who have had large sections of the bowel removed owing to the presence of multiple tumors. In addition, long-acting somatostatin analogs can cause pancreatic insufficiency and steatorrhea. Diarrhea, a hallmark of carcinoid syndrome that results from high concentrations of serotonin and other vasoactive and bioactive amines, can be exacerbated by the wrong diet. Diarrhea can result from an unrecognized partial bowel obstruction caused by an unresected primary tumor. These multifactorial nutritional issues must be evaluated and corrected by health care providers who have experience with these types of patients. The cause of their diarrhea is not always easy to detect, and can be due to multiple factors. We often see patients who are not suitable for surgery but could be with the appropriate interventions.

We have found that prioritizing treatment is important. One hundred patients were referred to us under the classification of patients whose most promising treatment option was peptide receptor radionuclide therapy (PRRT).<sup>7</sup> PRRT involves radiolabeling of a somatostatin analog to direct radiation to NETs.<sup>8</sup> These patients were referred to us based on symptoms including abdominal pain, weight loss, bloating, and diarrhea, and had large bulky tumors in their livers. Some of them had lost 100 pounds. More than one-third of these patients had an occult bowel obstruction



**Figure 12.** Preoperative scans showing a large liver metastasis.

that was complete or nearly complete because their primary tumor had never been resected. The health care providers were so focused on the big tumors in the liver that they ignored the tumor in the small bowel. However, in many of these patients, the abdominal pain resulted from the bowel obstruction. In a typical scenario for these patients, we relieve the bowel obstruction and create a plan so they can eat well again and reverse their weight loss. At this point, when we believe the patient is physically ready, we address the large liver tumors surgically or in combination with other modalities of ablation, IRE, and embolization.

This approach underscores the need to prioritize the different treatment options and sequence them appropriately. A large tumor in the liver is a problem, but a tumor that is obstructing the bowel takes priority once it is recognized. Many of these patients come to us on narcotic patches for pain, and some have been contemplating hospice. After our intervention, 85% of these patients went home without the need for any narcotics, and 5% of those patients who were referred to us as stage 4 “terminal disease” went home with no evidence of disease.<sup>7</sup> In our series of more than 200 surgical resections for patients with midgut NETs with stage 4 disease, survival rates were 87% at 5 years, 77% at 10 years, and 41% at 20 years.<sup>9</sup> I know of no published medical regimen that can match those results. My colleagues and I believe that evaluation and treatment

in a dedicated multidisciplinary NET clinic offers patients the best chance for long-term survival. Surgical unresectability is best determined by those who perform these types of complex resections and cytoreductions on a daily basis.

### Disclosure

Dr Boudreaux serves on an advisory board to Ipsen Biopharmaceuticals, Inc.

### References

1. Rinke A, Müller HH, Schade-Brittinger C, et al; PROMID Study Group. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol*. 2009;27(28):4656-4663.
2. Rajekar H, Bogammana K, Stubbs RS. Selective internal radiation therapy

for gastrointestinal neuroendocrine tumour liver metastases: a new and effective modality for treatment. *Int J Hepatol*. 2011;2011:404916.

3. Klimstra DS, Modlin IR, Coppola D, Lloyd RV, Suster S. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. *Pancreas*. 2010;39(6):707-712.
4. Lyons JM, Lindholm E, Wang Y, et al. Extensive retroperitoneal carcinoid involving the mesenteric vasculature does not preclude effective cytoreduction. *Pancreas*. 2010;39(2):274-275.
5. Caplin ME, Pavel M, Ruzsniowski P. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med*. 2014;371(16):1556-1557.
6. Gulec SA, Mountcastle TS, Frey D, et al. Cytoreductive surgery in patients with advanced-stage carcinoid tumors. *Am Surg*. 2002;68(8):667-671.
7. Boudreaux JP, Putty B, Frey DJ, et al. Surgical treatment of advanced-stage carcinoid tumors: lessons learned. *Ann Surg*. 2005;241(6):839-845.
8. Kwekkeboom DJ, de Herder WW, Kam BL, et al. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3]octreotate: toxicity, efficacy, and survival. *J Clin Oncol*. 2008;26(13):2124-2130.
9. Boudreaux JP, Wang YZ, Diebold AE, et al. A single institution's experience with surgical cytoreduction of stage IV, well-differentiated, small bowel neuroendocrine tumors. *J Am Coll Surg*. 2014;218(4):837-844.

## Cases in the Management of GEP-NETs: Combination Regimens

Fadi Braiteh, MD  
Clinical Associate Professor of Medicine  
University of Nevada School of Medicine  
Las Vegas, Nevada

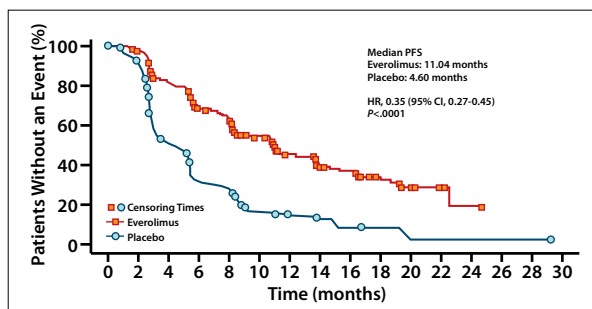
### CASE 1

A 43-year-old man presented to the emergency room with abdominal pain in November 2011. A CT scan revealed a mass in the uncinate process that was consistent with a pancreatic neoplasm. The CT scan also showed multiple hepatic metastases, pancreatic and portal hepatic lymphadenopathy, and apparent vascular invasion with involvement of the upper mesenteric vein, close to the venous confluence. Ultrasound performed the same day showed the hepatic masses, small gallbladder polyps, and periportal lymph nodes. A liver biopsy was positive for malignant cells and suggested neuroendocrine differentiation; however, no immunohistochemistry information was provided. A subsequent octreotide scan showed multiple foci of increased activity in the liver and abnormal foci of uptake in the upper abdomen, consistent with a primary pancreatic neoplasm. A bone scan performed in early December was negative for osteoblastic metastatic disease but suggested periodontal disease in the maxillary and mandibular alveolar ridge. Assessment of tumor markers suggested a nonsecreting pancreatic NET.

The patient was treated with octreotide LAR (30 mg) plus everolimus (10 mg daily; Figure 13).<sup>1,2</sup> The patient

received treatment during months 1, 13, 25, and 34 after diagnosis. In March 2012, a CT scan showed that the primary tumor and liver metastases were decreasing in size, with the dominant right hepatic lobe measuring 8.6 cm and the left hepatic lobe mass measuring 3.5 cm. The pancreatic head mass and the peripancreatic lymph node mass measured 1.3 cm each. Nearly 4 months later, a CT scan showed that the pancreatic head mass had increased to 3.3 cm. However, all other masses appeared stable or had decreased in size. The left hepatic lobe mass had decreased to 3.1 cm. The scan showed no evidence of new metastatic disease.

Treatment with octreotide and everolimus continued. CT scans revealed stable disease, with decreases in some of the tumors. The patient discontinued everolimus in February 2014. In March 2014, he underwent radioembolization to the right liver with yttrium-90. Magnetic resonance imaging (MRI) in August 2014 showed enhancing hepatic metastases throughout the liver and an irregular enhancing mass of 3.4 cm in the pancreatic head. In September 2014, the patient underwent a second radioembolization involving the segment 4 and segment 2/3 arteries. In the following month, second-line treatment of sunitinib (37.5 mg) was added to the octreotide (30 mg) regimen (Figure 14).<sup>3</sup>



**Figure 13.** Median PFS in the RADIANT-3 trial, which evaluated everolimus in patients with advanced low-grade or intermediate-grade pancreatic neuroendocrine tumors who had experienced radiographic progression in the previous 12 months. PFS, progression-free survival; RADIANT-3, RAD001 in Advanced Neuroendocrine Tumors, Third Trial. Adapted from Yao JC et al. *N Engl J Med.* 2011;364(6):514-523.<sup>2</sup>

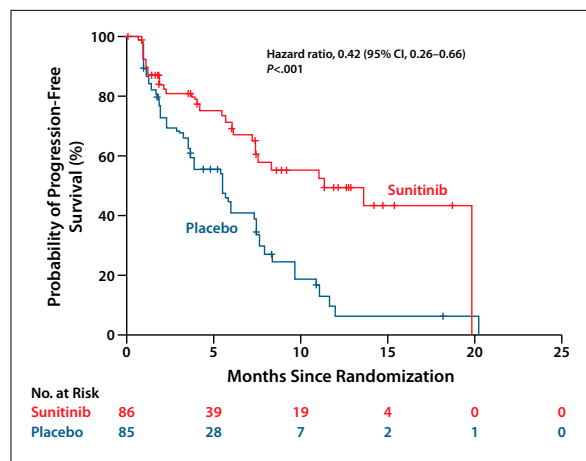
In late February 2015, a CT scan showed a decrease in disease burden, particularly in the right hepatic lobe. Several small nodules in the right lobe had resolved, and active disease sites in the left liver had decreased in size. The patient was rotated to lanreotide depot/autogel, with 4 courses given 1 month apart. The sunitinib dose was reduced to 5 days on, 2 days off owing to transaminitis.

In June 2015, CT revealed significant disease progression, with extensive liver metastases. Significant increases were noted in the left hepatic lobe metastasis and the pancreatic head mass. To control the disease progression, the patient received maintenance lanreotide depot/autogel once per month from July 2015 through February 2016. In addition, the patient was treated with BBI503, an experimental multi-kinase inhibitor that has demonstrated activity against cancer stem cells.<sup>4</sup> The patient received BBI503 approximately every 4 weeks. In September 2015, a CT scan showed a significant decrease in all liver metastases and a decrease in the pancreatic head mass from 4.7 cm to 4.2 cm. Two months later, although many tumors appeared stable, the CT scan showed confluent metastatic disease in the left lobe of the liver that had increased in size. In addition, a segment 5 lesion had increased from 3.4 cm × 2.7 cm to 6.3 cm × 5.1 cm.

The patient had undergone genetic profiling via next-generation sequencing. Results in late September 2015 showed amplification of RICTOR, a key component of the mTOR complex 2. As of January 2016, imaging showed a response as evidenced by a decrease in the tumor centers.

**CASE 2**

In April 2013, a 67-year-old woman was diagnosed with a well-differentiated carcinoid tumor. The tumor was negative for CK7 and CK20, but was positive for CDX2. The mitotic rate was not reported. Based on ultrasound, the patient also had multiple metastatic lesions measuring up



**Figure 14.** Progression-free survival in a phase 3 trial of sunitinib in patients with advanced, well-differentiated pancreatic neuroendocrine tumors. Adapted from Raymond E et al. *N Engl J Med.* 2011;364(6):501-513.<sup>3</sup>

to 3.0 cm. An abdominal CT scan demonstrated a large metastatic lesion in the right anterior liver with additional smaller lesions. In May 2013, an octreotide scan showed heterogeneous activity throughout the liver, with a large focus of increased uptake in the anterior right lobe. A bone density scan showed osteopenia of the spine, and the 24-hour urine 5-HIAA level was 3.2 mg. The levels of tumor marker chromogranin A and serotonin were 28 ng/mL and 520 ng/mL, respectively. In September 2013, MRI showed extensive liver lesions, of which the largest was in segment 4b, consistent with a hypervascular metastatic lesion of a carcinoid tumor. Transvaginal ultrasound showed uterine fibroids.

The patient received first-line treatment of high-dose octreotide LAR (30 mg) once per month.<sup>1</sup> In February 2014, CT imaging showed multiple hypervascular lesions throughout the right and left liver and early arterial enhancement with multiple lesions. The patient underwent radio-embolization in February 2014 and again 2 months later. In October 2014, a CT scan showed scattered hypoechoic, hypodense lesions throughout the liver measuring from 1.0 cm to 1.5 cm, as well as a left hepatic lesion of 1.5 cm × 1.2 cm and a hyperenhancing right hepatic lesion of 1.9 cm × 2.0 cm. A small sclerotic lesion within T10 and L1 of the spine was also noted, suggesting possible underlying metastatic disease. Biliary sludge was observed, and in December, the patient’s gallbladder was removed.

In February 2015, MRI showed disseminated hepatic metastases and the growth of previously observed masses. Second-line treatment consisting of lanreotide depot/autogel once every 4 weeks was initiated.<sup>5</sup> Three months later, the patient continued to show progressive disease with the appearance of a mesenteric mass and possible bone metastases. In late May, the patient was admitted to



the hospital for abdominal pain, where an esophagogastroduodenoscopy showed a normal mucosal appearance consistent with gastritis. A CT-guided liver biopsy in July showed recurrent/residual, well-differentiated carcinoid tumor with a Ki-67 mitotic index of 10%. The patient received a third radioembolization treatment directed to the liver tumor in July 2015. Genetic profiling was performed, but no targeted treatments were identified.

A CT scan performed in August suggested a reduction in viable tumor; however, the sclerotic lesion in the spine persisted and was deemed likely related to metastatic disease. Based on these results, sunitinib (37.5 mg) was added to treatment with lanreotide depot/autogel. After 2 weeks, the sunitinib therapy was discontinued and was replaced by everolimus, which was associated with stomatitis. An MRI of the liver performed prior to initiation of everolimus showed progressive hepatic metastases. The patient was under consideration for radioembolization to the untreated part of the liver or transarterial chemoembolization.

### CASE 3

A 47-year-old man experienced 2 months of nausea and vomiting combined with an unintentional weight loss of 25 pounds. A CT scan showed evidence of a mass in the tail of the pancreas that was invading the spleen. In May 2012, the pancreas and the spleen were removed, and the tumor was characterized as a well-differentiated pancreatic NET. The primary tumor measured 12.5 cm × 10.5 cm × 6.5 cm. CT scans performed in July 2012 revealed small hepatic metastases as well as a small subpleural nodule that was most likely benign. There were several nodes in the upper abdomen that did not show abnormal activity on octreotide scan. The neoplasm in the left upper quadrant of the liver was resected. The patient was treated with octreotide LAR (30 mg).<sup>1</sup>

In September, several masses of concern were visible by CT imaging. The overall appearance of the liver had changed, with a possible increase in the size of the multifocal vascular blush, but without discrete masses. In March 2013, imaging of the chest, abdomen, and pelvis failed to reveal any hypervascular lesions, consistent with a complete response based on Response Evaluation Criteria In Solid Tumors (RECIST) criteria.<sup>6</sup> An octreotide scan performed in August 2013 showed several foci of abnormal radiotracer in the liver, a result that was similar to a prior octreotide scan. No new metastatic disease was observed elsewhere. The gallbladder showed multiple gallstones without edema.

In October 2013, a CT scan showed no evidence of residual/recurrent metastatic disease. However, several months later, MRI showed more than 25 lesions that were

present in all segments of the liver. Although most lesions were smaller than 1.5 cm, the largest lesion measured 3.2 cm × 2.7 cm × 3.1 cm. The patient underwent laparoscopic cholecystectomy with radiofrequency ablation, which uncovered a metastatic NET with a Ki-67 mitotic index of 15%. In June 2014, CT imaging revealed multiple hyperdense lesions within the liver, with a dominant mass measuring 5.6 cm × 7.1 cm × 5.1 cm with inflammation. An octreotide scan in August 2014 showed abnormal uptake consistent with progressive metastatic disease based on size, number, and activity of lesions. At this point, sunitinib was added to the patient's octreotide therapy.<sup>3</sup> A CT scan showed a decrease in the left lobe mass from 6.9 cm × 5.7 cm to 4.2 cm × 3.5 cm, with developing necrosis. A mass in the right lobe had doubled in size.

In May 2015, a CT scan showed that the liver metastases, including the large mass on the dome of the liver, were growing. Multiple periportal lymph nodes were also enlarged. Second-line treatment was initiated in March 2015 and consisted of lanreotide depot/autogel plus sunitinib. Radioembolization was performed in July, with selective internal radiation therapy applied to the right lobe, and a second round of radioembolization was performed 2 months later. As of January 2016, the patient had achieved a partial response, with an estimated decrease in disease burden of 80%.

### Disclosure

*Dr Braiteh has received honoraria from Amgen, BIND Therapeutics, Boehringer Ingelheim, and Dendreon. He is a consultant or advisor for Amgen, BIND Therapeutics, Boehringer Ingelheim, Dendreon, and Incyte. He is on the speakers bureaus of Amgen, Bayer, and Boehringer Ingelheim. He has received funding for his institution from AbbVie, Amgen, AstraZeneca, and Ipsen Biopharmaceuticals. He has received other funding from Celgene.*

### References

1. Rinke A, Müller HH, Schade-Brittinger C, et al; PROMID Study Group. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol*. 2009;27(28):4656-4663.
2. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364(6):514-523.
3. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364(6):501-513.
4. Laurie SA, Jonker DJ, Edenfield WJ, et al. A phase 1 dose-escalation study of BBI503, a first-in-class cancer stemness kinase inhibitor in adult patients with advanced solid tumors [ASCO abstract 2527]. *J Clin Oncol*. 2014;32(suppl 5).
5. Caplin ME, Pavel M, Ruzsniowski P. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med*. 2014;371(16):1556-1557.
6. Therasse P, Arbuick SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst*. 2000;92(3):205-216.



# Slide Library

## GEP-NETs

- Epithelial neoplasms that originate from neuroendocrine cells
- Consist of 2 major types: carcinoid tumors of the gastrointestinal tract and pancreatic NETs
- Functional tumors secrete peptides and/or neuroamines that induce clinical symptoms such as flushing, diarrhea, bronchospasm, and valvular heart disease
- Patients with nonfunctional tumors may be asymptomatic or have symptoms resulting from tumor bulk

GEP-NETs, gastroenteropancreatic neuroendocrine tumors

## Somatostatin Analogs

- In recent years, treatment paradigms for GEP-NETs have been expanded by the somatostatin analogs octreotide and lanreotide depot/autogel
- These groundbreaking agents bind to somatostatin receptors, displacing the activating peptide hormone and preventing downstream peptide release

GEP-NETs, gastroenteropancreatic neuroendocrine tumors

## The PROMID Trial of Octreotide

- Phase 3b, placebo-controlled trial enrolling 85 treatment-naïve patients with well-differentiated midgut NETs and metastatic disease
- The study demonstrated an improvement in PFS for patients treated with octreotide LAR (14.3 vs 6.0 months; HR, 0.34; 95% CI, 0.20-0.55;  $P=0.00072$ ), with antiproliferative activity observed in both functional and nonfunctional tumors

HR, hazard ratio; LAR, long-acting release; PFS, progression-free survival; PROMID, Placebo-Controlled, Double-Blind, Phase 3b, Randomized Study of the Effect of Octreotide LAR in the Control of Tumor Growth in Patients With Metastatic, Well-Differentiated Midgut Tumors

## The CLARINET Trial of Lanreotide Depot/Autogel

- Phase 3, placebo-controlled trial enrolling 204 patients with nonfunctional, well- or moderately differentiated tumors; somatostatin receptor expression; and metastatic disease
- Enrollment criteria permitted patients with higher-grade tumors that had a proliferation index of less than 10%. Tumors could originate in the midgut, hindgut, or pancreas or could be of unknown origin
- Lanreotide depot/autogel was associated with a significant extension of median PFS (not reached vs 18.0 months; HR, 0.47; 95% CI, 0.30-0.73;  $P<.001$ )

CLARINET, Controlled Study of Lanreotide Depot/Injectional Response in Neuroendocrine Tumors

## Other Therapies in the Management of GEP-NETs

- Everolimus inhibits the mTOR pathway
- Sunitinib is a multikinase inhibitor of angiogenesis receptors
- Studies of temozolomide in combination with thalidomide, bevacizumab, or capecitabine have demonstrated efficacy with manageable tolerability in patients with pancreatic NETs

## Surgery and Radiotherapy

- Surgical resection and radiotherapy are indispensable approaches for effective patient treatment
- Evaluation and treatment in a dedicated multidisciplinary neuroendocrine tumor clinic offers patients the best chance for long-term survival
- Surgical unresectability is best determined by those who perform these types of complex resections and cytoreductions on a daily basis

For a free electronic download of these slides, please direct your browser to the following web address:  
<http://www.hematologyandoncology.net>

# Current Concepts in the Management of GEP-NETs: A Case Study Compendium

**CME Post-Test:** Circle the correct answer for each question below.

- In the PROMID trial, octreotide LAR was associated with a PFS of \_\_\_\_.
  - 8.6 months
  - 10.2 months
  - 14.3 months
  - Not reached
- In the CLARINET trial, lanreotide depot/autogel was associated with a PFS of \_\_\_\_.
  - 12.2 months
  - 14.6 months
  - 18.0 months
  - Not reached
- Which agent inhibits the mTOR pathway?
  - Capecitabine
  - Everolimus
  - Sunitinib
  - Temozolomide
- Which agent is a multikinase inhibitor of angiogenesis receptors?
  - Capecitabine
  - Everolimus
  - Sunitinib
  - Temozolomide
- Which symptom is a hallmark of carcinoid syndrome that results from high concentrations of serotonin and other vasoactive and bioactive amines?
  - Diarrhea
  - Nausea
  - Ulcers
  - Vertigo
- In a series of more than 200 surgical resections for patients with midgut NETs with stage 4 disease, what was the survival rate at 5 years?
  - 58%
  - 63%
  - 74%
  - 87%
- In the recent RADIANT-4 trial, everolimus showed a \_\_\_\_ improvement in PFS compared with placebo in nonfunctional carcinoid tumors.
  - 5.8-month
  - 6.2-month
  - 7.1-month
  - 8.5-month
- A patient with carcinoid syndrome will most likely have a tumor somewhere in the small bowel.
  - True
  - False
- Which of the following is NOT a sign of worsening of extrahepatic disease?
  - A decreased level of 5-HIAA
  - An increase in the size of the left upper quadrant mass
  - Increased splenic invasion
  - Worsened ascites
- Which of the following is a key component of the mTOR complex 2?
  - ERK
  - MEK
  - RICTOR
  - C-RAF

# Evaluation Form: Current Concepts in the Management of GEP-NETs: A Case Study Compendium

If you wish to receive acknowledgment for completing this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876. You may also complete the post-test online at [www.cmeuniversity.com](http://www.cmeuniversity.com). On the navigation menu, click on "Find Post-tests by Course" and search by **project ID 11303**. Upon successfully registering/logging in, completing the post-test and evaluation, your certificate will be made available immediately.

## 1. What degree best describes you?

- MD/DO  PA/PA-C  NP  RN  PharmD/RPh  PhD  
 Other, please specify:

## 2. What is your area of specialization?

- Oncology, Medical  Surgery/Surgical Oncology  Oncology, Radiation

## 3. Which of the following best describes your primary practice setting?

- Solo Practice  Group Practice  Government  
 University/teaching system  Community Hospital  
 HMO/managed care  Non-profit/community  I do not actively practice  
 Other, please specify:

## 4. How long have you been practicing medicine?

- More than 20 years  11-20 years  5-10 years  1-5 years  
 Less than 1 year  I do not directly provide care

## 5. Approximately how many patients do you see each week?

- Less than 50  50-99  100-149  150-199  200+  
 I do not directly provide care

## 6. How many patients do you currently see each week who have neuroendocrine tumors?

- Fewer than 5  6-15  16-25  26-35  36-45  46-55  
 56 or more  I do not directly provide care

## 7. Rate how well the activity supported your achievement of these learning objectives:

Analyze results from clinical trials evaluating new therapies and strategies in the management of GEP-NETs

- Strongly Agree  Agree  Neutral  Disagree  Strongly Disagree

Discuss how to integrate new treatments into clinical practice

- Strongly Agree  Agree  Neutral  Disagree  Strongly Disagree

Define the role of multidisciplinary care in the treatment of GEP-NETs

- Strongly Agree  Agree  Neutral  Disagree  Strongly Disagree

Modify treatment based on patient outcomes

- Strongly Agree  Agree  Neutral  Disagree  Strongly Disagree

## 8. Rate how well the activity achieved the following:

The faculty were effective in presenting the material

- Strongly Agree  Agree  Neutral  Disagree  Strongly Disagree

The content was evidence based

- Strongly Agree  Agree  Neutral  Disagree  Strongly Disagree

The educational material provided useful information for my practice

- Strongly Agree  Agree  Neutral  Disagree  Strongly Disagree

The activity enhanced my current knowledge base

- Strongly Agree  Agree  Neutral  Disagree  Strongly Disagree

The activity provided appropriate and effective opportunities for active learning (e.g., case studies, discussion, Q&A, etc.)

- Strongly Agree  Agree  Neutral  Disagree  Strongly Disagree

The opportunities provided to assess my own learning were appropriate (e.g., questions before, during or after the activity)

- Strongly Agree  Agree  Neutral  Disagree  Strongly Disagree

## 9. Based upon your participation in this activity, do you intend to change your practice behavior? (choose only one of the following options)

I do plan to implement changes in my practice based on the information presented

My current practice has been reinforced by the information presented

I need more information before I will change my practice

## 10. Thinking about how your participation in this activity will influence your patient care, how many of your patients are likely to benefit?

Please use a number (for example, 250):

## 11. If you plan to change your practice behavior, what type of changes do you plan to implement? (check all that apply)

- Apply latest guidelines  Choice of treatment/management approach  
 Change in pharmaceutical therapy  Change in current practice for referral  
 Change in nonpharmaceutical therapy  Change in differential diagnosis  
 Change in diagnostic testing  Other, please specify:

## 12. How confident are you that you will be able to make your intended changes?

- Very confident  Somewhat confident  Unsure  Not very confident

## 13. Which of the following do you anticipate will be the primary barrier to implementing these changes?

- Formulary restrictions  Insurance/financial issues  Time constraints  
 Lack of multidisciplinary support  System constraints  
 Treatment-related adverse events  Patient adherence/compliance  
 Other, please specify:

## 14. Was the content of this activity fair, balanced, objective and free of bias?

- Yes  No, please explain:

## 15. Please list any clinical issues/problems within your scope of practice you would like to see addressed in future educational activities:

## Request for Credit (\*required fields)

Name\* \_\_\_\_\_

Degree\* \_\_\_\_\_

Organization \_\_\_\_\_

Specialty\* \_\_\_\_\_

City, State, ZIP\* \_\_\_\_\_

Telephone \_\_\_\_\_ Fax \_\_\_\_\_

E-mail\* \_\_\_\_\_

Signature\* \_\_\_\_\_ Date\* \_\_\_\_\_

## For Physicians Only:

I certify my actual time spent to complete this educational activity to be:

- I participated in the entire activity and claim 2.00 credits.  
 I participated in only part of the activity and claim \_\_\_\_\_ credits.

## Post-test Answer Key

1	2	3	4	5	6	7	8	9	10