Overview

Diagnosis: Gallium scan
Biomarkers
Treatment: Carcinoid syndrome (complete)
Carcinoids (complete)
Genetics:
Trials: NETTER (PRRT)
Immunotherapy
Novel drugs- FGFR
Improve use of drugs we have
Increasing incidence of NETs

NET Incidence Increasing Faster Than Other Neoplasms (SEER data, 1973-2004)

Abbreviation: SEER, Surveillance, Epidemiology, and End Results.

第二最常见的GI tract癌症

- 第二最常见的GI tract癌症，位于结肠直肠癌之后

- 观察到的诊断NET发病率在过去30年里增加了5倍。

- 大约有100,000名患者正在美国生活与NETs相伴（这超过了胃和胰腺癌的总和）

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February 21, 2014 -- German researchers have confirmed the efficacy of PET/CT with the radiopharmaceutical gallium-68 (Ga-68) DOTATATE for detecting the recurrence of neuroendocrine tumors (NETs), in a study published in the February issue of *Radiology*.

PET/CT with Ga-68 DOTATATE achieved high sensitivity (90%) and good specificity (82%) for determining the recurrence of NETs. It also ruled out recurrence with a high negative predictive value (90%), according to lead author Dr. Alexander Haug, from Ludwig Maximilian University, and colleagues.

Dr. Thomas Odorisio and Colleagues examined several biomarkers—serum neurokinin A, chromogranin A, serotonin, and pancreastatin—that all reflect tumor burden in neuroendocrine tumors. They sought to determine whether their levels correlate with survival in surgically managed small bowel (SBNETs) and pancreatic neuroendocrine tumors (PNETs).

Higher pancreastatin levels are significantly associated with worse outcomes in SBNETs and PNETs. This effect is independent of age, primary tumor site, and presence of nodal or metastatic disease. Pancreastatin provides valuable prognostic information and identifies surgical patients at high risk of recurrence who could benefit most from novel therapies. IF levels normalize after surgery it is a good sign.


**Pancreastatin** is a 49 amino acid peptide produced by degradation of Chromo-granin A. It inhibits Chromogranin A and Parathyroid Hormone release. **Pancreastatin** also inhibits release of Somatostatin upon glucose stimulation. It may also control carbohydrate metabolism and hyperglycemia.
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Sandostatin approved in 1988 by FDA for symptom control of carcinoid syndrome—no other options

For pancreatic Nets two approved drugs, Affinitor and Sunitinib since 2011, no approved drugs to delay progression yet for all other carcinoids
On August 3, 2015 Lexicon Pharmaceuticals, Inc. announced that the pivotal TELESTAR Phase III clinical trial met its primary endpoint, showing the benefit of oral telotristat etiprate in treating cancer patients with carcinoid syndrome that is not adequately controlled by the current standard of care. Telotristat etiprate was discovered using Lexicon’s gene science, based on Nobel Prize-winning technology, and is the company’s first discovery to complete a pivotal Phase III clinical trial. If approved, telotristat etiprate would be the first oral treatment successfully developed for carcinoid syndrome and the first addition to the standard of care in more than 16 years.

Top-line results from the Phase III study show that patients who added telotristat etiprate to the standard of care at both the 250 mg and 500 mg doses experienced a statistically significant reduction from baseline compared to placebo in the average number of daily bowel movements over the 12-week study period (p<0.001), meeting the study’s primary endpoint.

(Source: Company website)

Oral pill that can help symptoms of refractory carcinoid syndrome
On May 21, 2015 Novartis announced that the Phase III study of Afinitor® (everolimus) tablets plus best supportive care in patients with advanced nonfunctional neuroendocrine tumors (NET) of gastrointestinal (GI) or lung origin met its primary endpoint: significant extension of progression-free survival (PFS) compared to placebo plus best supportive care. The RADIANT-4 study is part of one of the largest clinical trial programs in NET.

"We look forward to presenting the findings from the RADIANT-4 trial of everolimus, which has the potential to become an important treatment option for patients with advanced nonfunctional GI or lung NET," said Alessandro Riva, MD, Global Head, Novartis Oncology Development and Medical Affairs. "The results will serve as the basis of planned worldwide regulatory filings for everolimus in these two types of NET, bringing us closer to our goal of offering Afinitor for these patients." (Source: Company website)

Oral pill that can help prolong progression free survival in advanced GI or lung NET patients
Increased Efficacy but Added Toxicity with Bevacizumab plus Everolimus in pNETs

150 patients with advanced pNETs were randomly assigned to receive 10 mg daily of everolimus with or without 10 mg/kg of bevacizumab every 2 weeks, in addition to depot octreotide acetate.

The combination was associated with a significant improvement in median progression-free survival (PFS) compared with everolimus alone (16.7 vs. 14.0 months). The combination was also associated with a significant improvement in response rate, with responses observed in 31% of patients receiving everolimus plus bevacizumab compared with 12% of patients receiving everolimus alone (p = 0.005).

However no difference in overall survival was seen and 81% of patients had side effects on combination


EFFECTIVE BUT SIDE EFFECTS: May need to look at less intense maintenance or ways to predict who really benefits from combination
New therapies on horizon: Evaluate role of Surgery

- Bowel resection
- Removal of mesenteric nodes,
- Lysis of adhesions
- Debulk liver disease
- Control hormonal symptoms
  removal of PNET

 Instituto de Cancerología Roswell Park

In a Distal Pancreatectomy procedure with Splenectomy, the tail of the pancreas containing the tumor and the spleen are removed.

Lysis of adhesions that may cause pain and bowel obstruction.

Left hepatectomy
Aggressive liver-directed therapy for GI carcinoids

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Genetics:
Genes play a role in small bowel carcinoid!

- Because the disease has long been considered randomly occurring rather than inherited, people with a family history are not typically screened.
- Heredity accounts for up to 35 percent of small intestinal carcinoid, a rare digestive cancer, according to findings from a team at the National Institutes of Health.

Conducted at the NIH Clinical Center, the study screened 181 people from 33 families, each with at least two cases of small intestinal carcinoid. The researchers discovered the disease in 23 people who had not yet developed symptoms, and successfully removed all tumors in 21 of those people.

Sei et al July 2015; Volume 149, Issue 1, Pages 67–78

Call for info: 1-866-444-2214
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FIRST PIVOTAL PHASE III STUDY EVALUATING 177Lu-DOTATATE IN MIDGUT NEUROENDOCRINE TUMOURS

Lutathera (or 177Lu-DOTATATE) is a novel compound currently under development for the treatment of midgut neuroendocrine tumours. Lutathera belongs to an emerging form of treatments called peptide receptor radionuclide therapy (PRRT) which involves targeting carcinoid tumors with radiolabeled somatostatin analogue peptides.

**Primary endpoint:** Progression free survival

**Update:** The first patient was enrolled in July 2012. The study will randomize 230 patients, 1:1 to each arm. 36 EU and 15 US sites. Accrual is complete. The Analysis of primary endpoint (PFS) shall start after 74 evaluable and centrally confirmed events.

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**TREATMENT AND ASSESSMENTS**

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<tr>
<th></th>
<th>dose 1</th>
<th>dose 2</th>
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<th>dose 4</th>
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<td>Sandostatin LAR Arm</td>
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**n=115**

**60 mg Octreotide LAR treatment every 4 weeks**

**n=115**

**PROGRESSION FREE SURVIVAL BY RECIST EVERY 12 WEEKS**
Dr. Pamela Kunz at Stanford
Dr. Michael Morse at Duke

Examining role of newer immunotherapy agents in NET patients.
Expect to open both this year and details to follow!!!!!!!
Nintedanib – oral FGFR inhibitor trial open!

Roswell Park: Dr. Iyer (lead site)
Ohio State: Dr. Shah
MSKCC: Dr. Reidy

NCCN grant funded study of an oral fibroblast growth factor inhibitor given twice daily in progressing carcinoid patients in combination with Sandostatin or Somatuline.

**Primary endpoint:** progression free survival
Expect 30 patients in 2 years
**Contact:** Cathy Grande at 845 8309
Studies of optimal somatostatin analogue dose and schedule continue

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<td>1.5±0.3</td>
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Our group is studying immune effects of SS analogues in the laboratory and in patients
Take away

A lot has happened and continues to happen in this field- Stay informed!

The success of the trials and this event is because of you- Participate when you can!

We want to help you LIVE with this disease- Let us know how we can help you!

DVDs from last years event are available outside- Feel free to grab one!
Thank you to all patients and caregivers for what you teach us everyday, the sponsors for your generous support, our NET patient care team and organizing crew for their hard work!