ACS Cancer Research Program (CRP) Educational Series

Emerging Diagnostic and Treatment Opportunities for Neuroendocrine Tumors of the Gastrointestinal

March 11, 2021
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Emerging Diagnostic and Treatment Opportunities for Neuroendocrine Tumors of the Gastrointestinal - Disclosures Reported

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Wake Forest Baptist Health

Flavio Rocha, MD, FACS, FSSO – Nothing to disclose
Oregon Health & Science University/Knight Cancer Institute

Delphine Chen, MD – Nothing to disclose
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Jonathon McConathy, MD, PhD – honorarium and research support for consulting at Eli Lilly/Avid, honorarium for consulting at GE Healthcare, honorarium and research support for consulting at Blue Earth Diagnostics, research support for clinical trial at Cytosite Biopharma, honorarium for consulting at ImaginAb, honorarium for consulting at Canon Medical

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American College of Surgeons

Linda Zheng – Nothing to disclose
American College of Surgeons
Program Objectives

Target Audience
- Breast surgeons
- Cancer registrars
- Colorectal surgeons
- General surgeons
- Nurses
- Nurse practitioners
- Other advanced practice professionals
- Physician assistants
- Physicians in cancer accredited centers and programs
- Surgical oncologists

Learning Objectives
- Outline the context of these innovations for both primary and metastatic neuroendocrine tumors.
- Discuss the impact of the changes to diagnosis and treatment on patient outcomes.
- Understand the indications and rationale for new imaging modalities and chemotherapy options for patients with gastrointestinal neuroendocrine tumors.
Moderators

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Co-leader GI Oncology and Co-leader Phase I Program  
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Modern Imaging for NETs

Jonathan McConathy, MD, PhD
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Director, Division of Molecular Imaging and Therapeutics
Disclosures

- Eli Lilly/Avid: honorarium, research support
- GE Healthcare: honorarium
- Blue Earth Diagnostics: honorarium
- Cytosite Biopharma: research support
- ImaginAb: honorarium, research support
- Canon Medical: honorarium
Imaging modalities for neuroendocrine tumors

CT
- Arterial and venous phases, thin slices

MRI
- Arterial, venous, hepatobiliary phases
- Excellent for liver evaluation

Endoscopic ultrasound
- Allows biopsy of primary tumor and regional lymph nodes

Molecular imaging
- Tumor localization, whole body staging
- Monitoring response to therapy
- Therapy planning for theranostics

FDA approved molecular imaging agents for NETs

**Somatostatin receptor ligands**

- [^{68}Ga]DOTATATE, [^{64}Cu]DOTATATE, [^{68}Ga]DOTATOC

**Norepinephrine transporter substrates**

- [^{123/131}I]MIBG

**Glucose metabolism (glycolysis)**

- [^{18}F]FDG
Molecular imaging based on type of NET

**Lung**
- Carcinoid \(\rightarrow\) SSTR-PET
- Small cell \(\rightarrow\) \[^{18}F\]FDG
- Large cell \(\rightarrow\) \[^{18}F\]FDG

**Pancreas**
- Islet cell tumors \(\rightarrow\) SSTR-PET

**Gastrointestinal**
- Midgut most common \(\rightarrow\) SSTR-PET

**Autonomic nervous system**
- Pheochromocytoma \(\rightarrow\) \[^{123}I\]MIBG
- Paraganglioma \(\rightarrow\) SSTR-PET
- Neuroblastoma \(\rightarrow\) \[^{123}I\]MIBG

**Medullary thyroid cancer** \(\rightarrow\) question mark

**Merkel cell cancer** \(\rightarrow\) \[^{18}F\]FDG
### SSTR-PET versus FDG-PET

#### Table 1 | Characteristics of neuroendocrine tumours

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Well-differentiated neuroendocrine tumour or carcinoma</th>
<th>Poorly differentiated neuroendocrine carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour grade*</td>
<td>1 (low)</td>
<td>2 (intermediate)</td>
</tr>
<tr>
<td></td>
<td>3 (high)</td>
<td></td>
</tr>
<tr>
<td>Ki67 index (%) and/or mitotic count (per 10 HPF)</td>
<td>Ki67 &lt;3% and &lt;2 mitoses</td>
<td>Ki67 3–20% or 2–20 mitoses</td>
</tr>
<tr>
<td></td>
<td>Ki67 &gt;20% or &gt;20 mitoses</td>
<td></td>
</tr>
<tr>
<td>Clinical course and findings on CT or MRI</td>
<td>Indolent course</td>
<td>Intermediate</td>
</tr>
<tr>
<td></td>
<td>Rapid growth</td>
<td></td>
</tr>
<tr>
<td>Incidence FDG-PET-positive lesions‡</td>
<td>Lower</td>
<td>Intermediate</td>
</tr>
<tr>
<td></td>
<td>Higher</td>
<td>Higher</td>
</tr>
<tr>
<td>Somatostatin receptor expression‡</td>
<td>Higher</td>
<td>Intermediate</td>
</tr>
<tr>
<td></td>
<td>Lower</td>
<td></td>
</tr>
<tr>
<td>Prognosis</td>
<td>Relatively good</td>
<td>Intermediate</td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td></td>
</tr>
</tbody>
</table>


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Diagnostic performance of $^{68}$GaDOTATATE-PET for NETs

- Highest sensitivity for well-differentiated NETs
  - Sensitivity = 97%, specificity = 95%

- Changes management in ~40% of patients with NETs (usually due to new lesion detection)

- In a prospective comparison for GEP-NETs, $^{68}$GaDOTATATE-PET/CT detected 95% of lesions compared to 45% for CT/MRI and 31% for $^{111}$Inpentetreotide

- Higher sensitivity than contrast-enhanced CT alone for finding NETs of unknown primary (94% versus 63% in one study)


59-year-old-woman with metastatic NET thought to arise from the small bowel. Prior studies have not identified the location of the primary tumor.
DOTATATE-PET/CT
34-year-old-woman with hepatic NET metastasis with no known primary tumor.

\[^{68}\text{Ga}]\text{DOTATE-PET/CT MIP}\]
DOTATATE-PET/CT

Diagnosis
A. Left lobe hepatic mass; biopsy:
   - Neuroendocrine carcinoma.
   - Ki-67 proliferative index 40-50%.
67 year old man with hepatic neuroendocrine tumor metastasis being considered for possible resection of a chest wall metastasis

- \(^{68}\)GaDOTATATE-PET/CT is requested for staging

Histology of biopsy: neuroendocrine carcinoma with numerous mitoses and non-focal necrosis
FDG-PET/CT
Planar $^{123}$I MIBG

52 year old man undergoing staging for pheochromocytoma
[\textsuperscript{123}I]MIBG-SPECT/CT

Planar

SPECT

Fusion

CT
Theranostics and radionuclide therapy for cancer

- Radiopharmaceuticals can selectively deliver radioactivity to cancer cells
- Some radiopharmaceuticals can be labeled for imaging and for therapy: **theranostic approach**
- Radionuclide therapies can succeed after other therapies fail.
- Imaging often guides therapy by demonstrating the entire tumor burden expresses the therapeutic target
Theranostics and radionuclide therapy for cancer

• Radiopharmaceuticals can selectively deliver radioactivity to cancer cells.

• Some radiopharmaceuticals can be labeled for imaging and for therapy: **theranostic approach**

• Radionuclide therapies can succeed after other therapies fail.

• Imaging often guides therapy by demonstrating the entire tumor burden expresses the therapeutic target.

[68Ga]DOTATATE-PET for diagnostic imaging
Theranostics and radionuclide therapy for cancer

- Radiopharmaceuticals can selectively deliver radioactivity to cancer cells
- Some radiopharmaceuticals can be labeled for imaging and for therapy: **theranostic approach**
- Radionuclide therapies can succeed after other therapies fail.
- Imaging often guides therapy by demonstrating the entire tumor burden expresses the therapeutic target
Accurate diagnostic imaging is key to using theranostics.

A. DOTATATE-PET MIP
   Metastatic small bowel NET

B. PET

C. DOTATATE-PET
   Fusion

D. T2 SSFSE

E. DOTATATE-PET
   hepatobiliary phase fusion

F. hepatobiliary phase fusion

G. DOTATATE-PET/MRI with hepatobiliary phase contrast MRI

H. diffusion (b=700)
Key points

- Anatomic imaging with (CT, MRI) and molecular imaging (FDG, SSTR-PET, MIBG) play important roles in diagnostic imaging of NETs.

- Type of NET and grade influence optimal molecular imaging technique.

- Theranostics extends imaging beyond detection alone to characterize the entire tumor volume for therapeutic targets.
Surgical Treatment of NETS

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Director of Pancreatobiliary Disease Center
Assistant Professor of Surgery
University of Alabama, Birmingham
Raising incidence

Dasari. JAMA Onc. 2017
Brenner. NEJM. 2007
Earlier Detection

Dasari. JAMA Onc. 2017
2017 WHO classifications

Table 1. WHO classifications

<table>
<thead>
<tr>
<th>WHO Classification</th>
<th>Cumulative Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well Differentiated</td>
<td></td>
</tr>
<tr>
<td>NET G1</td>
<td></td>
</tr>
<tr>
<td>NET G2</td>
<td></td>
</tr>
<tr>
<td>Poorly Different</td>
<td></td>
</tr>
<tr>
<td>NEC</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Basturk et al., Am J Surg Pathol. 2015
Localized Pancreatic Disease
Overall survival by surgical procedure

OS by surgery type for patients with PNETs ≤ 2 cm

Survival Advantage for Resection of PNET

Hill. Cancer. 2009
Who should be resected?

- Symptomatic patients
  - Functional tumors
  - Non-functional with symptoms
- Asymptomatic tumors
  - non-functional tumors?

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Major Clinical Symptom</th>
<th>Predominant Hormone</th>
<th>Malignant Potential</th>
<th>Other Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrinoma</td>
<td>Recurrent peptic ulcer</td>
<td>Gastrin</td>
<td>Very high</td>
<td>Diarrhea/steatorrhea</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>Hypoglycemia (fasting or nocturnal)</td>
<td>Insulin</td>
<td>Low (5-10%)</td>
<td>Catecholamine excess</td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>Diabetes mellitus, Migratory necrolytic erythema</td>
<td>Glucagon</td>
<td>Very high</td>
<td>Panhypoaaminoaciduria, Thromboembolism, Weight loss</td>
</tr>
<tr>
<td>VIPoma</td>
<td>Watery diarrhea, hypokalemia, achlorhydria (WDHA syndrome)</td>
<td>Vasoactive intestinal polypeptide (VIP)</td>
<td>High</td>
<td>Metabolic acidosis, Hyperglycemia, Hypercalcemia, Flushing</td>
</tr>
<tr>
<td>Somatostatinoma</td>
<td>Diabetes mellitus</td>
<td>Somatostatin</td>
<td>Very high</td>
<td>Hypochlorhydria, Weight loss, Gall bladder disease</td>
</tr>
<tr>
<td>PPoma</td>
<td>Hepatomegaly, Abdominal pain</td>
<td>Pancreatic polypeptide (PP)</td>
<td>Very high</td>
<td>Occasional watery diarrhea</td>
</tr>
</tbody>
</table>
NF-PNET: non-operative management

- Multiple retrospective, single institution studies evaluating incidentally discovered small NF-PNET
- Non-operative management vs resection
- No change in survival at various reported cut-offs (<2, 3, 4 cm)
- Currently widely accepted 2cm cutoff amongst pancreas surgeons for resection, 1cm for observation

Gaujoux. J Clin Endo Metab. 2013
Tanaka. Ann Surg Onc. 2021
Localized GI Disease
**Gastric NETs**

<table>
<thead>
<tr>
<th>Relative frequency</th>
<th>Gastric NETs/carcinoids</th>
<th>Gastric NECs (poorly differentiated NENs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>70%-80%</td>
<td>14%-25%</td>
</tr>
<tr>
<td>Type 2</td>
<td>5%-6%</td>
<td>6%-8%</td>
</tr>
<tr>
<td>Type 3</td>
<td>14%-25%</td>
<td>6%-8%</td>
</tr>
<tr>
<td>Type 4</td>
<td></td>
<td>6%-8%</td>
</tr>
</tbody>
</table>

**Features**
- Mostly small (<1-2 cm) and multiple
- Mostly small (<1-2 cm) and multiple
- Solitary often >2 cm
- Solitary mostly exulcerated, >2 cm

**Associated conditions**
- CAG
- MEN1/ZES
- No
- No

**Histology**
- Well differentiated G1
- Well differentiated G1
- Well/moderate differentiated G2
- Poorly differentiated G3

**Serum gastrin**
- (Very) high
- (Very) high
- Normal
- (Mostly) normal

**Gastric pH**
- Anacidic
- Hyperacidic
- Normal
- (Mostly) normal

**Metastases**
- <10%
- 10%-30%
- 50%-100%
- 80%-100%

**Tumor-related death**
- No
- <10%
- 25%-30%
- ≥50%

---

Local resection

Resect gastrinoma

<2cm

>2cm

Anatomic resection


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Duodenal

- <1cm: Endoscopic treatment
  - <3% recurrence
- >2cm, peri-ampullary, or R1 endo: Resection
- 1-2cm: Tailored approach

<table>
<thead>
<tr>
<th>Case series</th>
<th>Patients (n)</th>
<th>Tumors (n)</th>
<th>Recurred (n)</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al. 2014</td>
<td>38</td>
<td>41</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>Shroff et al. 2015</td>
<td>20</td>
<td>20</td>
<td>0</td>
<td>26</td>
</tr>
<tr>
<td>Gincul et al 2016</td>
<td>29</td>
<td>32</td>
<td>2</td>
<td>56</td>
</tr>
<tr>
<td>Park et al. 2018</td>
<td>15</td>
<td>15</td>
<td>0</td>
<td>26</td>
</tr>
<tr>
<td>Jung et al. 2015</td>
<td>14</td>
<td>14</td>
<td>0</td>
<td>42</td>
</tr>
<tr>
<td>Untch et al. 2014</td>
<td>12</td>
<td>12</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Kim et al. 2017</td>
<td>25</td>
<td>26</td>
<td>0</td>
<td>24</td>
</tr>
<tr>
<td>Matusomot et al. 2014</td>
<td>7</td>
<td>9</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>Mullen et al. 2005</td>
<td>6</td>
<td>6</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td>Matsumoto et al. 2013</td>
<td>7</td>
<td>7</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Osera et al. 2016</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>22</td>
</tr>
</tbody>
</table>

Klemm. J GI Cancer. 2021
Small bowel

- 50% multifocal, 72% within 100cm of terminal ileum
- Present as pain, obstruction, carcinoid syndrome
- Open resection including lymph nodes down to branching of segmental vessels, run length of bowel
- Consider cholecystectomy if expecting SSA treatment (stage IV)
  - ~20% on SSA will need it
Appendiceal

- Appendectomy for <1cm
  - No surveillance if N0, R0
- >2cm gets right hemicolecotomy
  - Standard surveillance
- 1-2cm tailored approach

<table>
<thead>
<tr>
<th>Size</th>
<th>Guideline Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1cm</td>
<td>Tumor located at the appendiceal base</td>
</tr>
<tr>
<td></td>
<td>Mesoappendiceal invasion &gt;3 mm</td>
</tr>
<tr>
<td>1-2cm</td>
<td>Young patients&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>World Health Organization grade: G2</td>
</tr>
<tr>
<td></td>
<td>Vascular (V1) or lymph vessel (L1) invasion</td>
</tr>
<tr>
<td></td>
<td>Mesoappendiceal invasion &gt;3 mm</td>
</tr>
</tbody>
</table>

<sup>a</sup>There is an increased risk of incomplete resection or late recurrence.

## Carcinoid Crisis

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (n)</th>
<th>Octreotide dose</th>
<th>Crises Rate</th>
<th>Take-away</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinney et al (2010)</td>
<td>45 intraop vs 67 no dose</td>
<td>30-4000 μg (median 350 μg)</td>
<td>0% vs 10%</td>
<td>Octreotide seemed to help</td>
</tr>
<tr>
<td>Massimino et al (2013)</td>
<td>87 preop dose vs 10 no dose</td>
<td>100-1100 μg (median 500 μg) preop + PRN bolus</td>
<td>24% (19% hypo, 5% strict definition)</td>
<td>no difference if octreotide used</td>
</tr>
<tr>
<td>Woltering et al (2016)</td>
<td>179</td>
<td>500 μg/h peri-op infusion + PRN bolus</td>
<td>3.4%</td>
<td>Low rate suggests helpful</td>
</tr>
<tr>
<td>Condron et al (2016)</td>
<td>127</td>
<td>500 μg/h peri-op infusion + PRN bolus</td>
<td>30%*</td>
<td>No change from prior study, no benefit</td>
</tr>
</tbody>
</table>

Howe. Pancreas. 2017
Areas of controversy

• What to do with 1-2cm nonfunctional pNETs
• Cytoreduction of metastatic disease (R0 vs R1 vs R2)
• Resection of primary tumor when metastatic not resectable
• Resection of G3 neuroendocrine
Conclusions

• Neuroendocrine Tumors are relatively uncommon
  • Increasing in incidence due to rise in cross sectional imaging

• Functional pancreatic lesions and most GI NETs should be resected in the appropriately staged patient.

• Non-functional pancreatic lesions tend to be larger and present with metastatic disease, however in those with small, localized, incidentally discovered lesions, imaging follow-up may be a reasonable course of action depending on the:
  • Patients functional status
  • Size and presentation of the tumor
  • Anticipated technical aspects of the operation
  • Change in size over time
Novel Targeted Therapeutics for NETs

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Wil B. Nelp, MD Endowed Professorship in Nuclear Medicine
University of Washington
Director of Molecular Imaging, Seattle Cancer Care Alliance

Emerging Diagnostic and Treatment Opportunities for Neuroendocrine Tumors of the Gastrointestinal Tract
American College of Surgeons Cancer Research Program
March 11, 2021
Neuroendocrine tumor treatment options

- Surgery
- Liver-targeted therapies
- Chemotherapy/systemic therapy
- Radiation therapy
- Peptide receptor radionuclide therapy (PRRT)
Basis of PRRT

- Somatostatin receptor targeting, predominantly SSTR2 agonists
- Highly expressed in well-differentiated gastroenteropancreatic (GEP) NETs (80-100%)

- Lu-177 dotatate (Lutathera®) approved in the US 2018 (NETTER-1)
- Indicated for somatostatin-positive GEP-NETs (foregut, midgut, hindgut)
- Off-label use in other neuroendocrine neoplasms
  - Lung carcinoid
  - Paraganglioma/pheochromocytoma
  - Neuroendocrine-differentiated prostate cancer

Strosberg et al, NEJM 2017;376:125-35
Novel targeted therapeutics for NETs: Radiopharmaceuticals

- Response based on DNA double-strand breaks induced by delivered radioactivity
- Radiopharmaceutical development still based on somatostatin receptor targeting
  - Beta-emitter labeled somatostatin agonists
    - Lu-177, Y-90
    - Multiple listed clinical trials
  - Alpha-emitter labeled somatostatin analogs
    - Ac-225, Pb-212, Ra-223, At-211
    - Shorter radiation delivery distance
    - $^{212}$Pb-DOTAMTATE (clinicaltrials.gov NCT03466216)
  - Lu-177 labeled somatostatin antagonists
    - $^{177}$Lu-OPS201 (clinicaltrials.gov NCT02592707)

Images taken/modified from https://www.cdc.gov/nceh/radiation/isotopes.html#alpha
Partial response with progression after β emitter PRRT

Novel targeted therapeutics for NETs: Combination therapies

- Sensitizers to radiation therapy: blocking DNA repair mechanisms to enhance DNA damage effects
  - Ribonucleotide reductase inhibitors: Triapine (clinicaltrials.gov NCT04234568)
  - DNA PK inhibitor: Paposertib (clinicaltrials.gov NCT04750954)
  - PARP inhibitors: Olaparib (clinicaltrials.gov NCT04086485)

- Immunotherapy combinations: Increase tumor antigen exposure from radiation damage
  - Promising results with external beam radiation therapy and immunotherapy
  - No active trials listed yet for GEP-NETs
  - One trial listed for small cell lung cancer (PRRT with nivolumab, clinicaltrials.gov NCT03325816)
    - Initial assessment in small number of patients affirms tolerability
Case

- 36-year-old man with well-differentiated (grade 1) metastatic neuroendocrine tumor of the rectosigmoid colon to liver and bone as well as poorly differentiated neuroendocrine carcinoma liver metastases

- Presentation: 6 weeks abdominal pain, early satiety, reflux, decreased appetite, and constipation
- Liver biopsy: metastatic neuroendocrine carcinoma, large cell type with several foci of poorly differentiated epithelioid malignancy, Ki-67 11%, WHO grade 2
- Colonoscopy with rectosigmoid colon mass biopsy: well-differentiated neuroendocrine neoplasm, WHO grade 1, Ki-67 <3%
Management

- Requires opiates for pain control, worsening constipation
- Treated initially with carboplatin/etoposide (c/b SBO, conservatively managed)
- Atezolizumab added with cycle 2
- Octreotide added 2 months later together with carboplatin, etoposide, and atezolizumab
- FDG PET demonstrated progression 2 months after starting octreotide
- Switched from carbo/etoposide to cap/tem, received one cycle
- To be treated concurrently with PRRT and atezolizumab per Multidisciplinary NET Tumor Board discussion
Baseline Scans

$^{18}$F-FDG PET/CT (MIP)  

$^{68}$Ga-dotatate PET/CT (MIP)
Diffuse Liver Involvement and Enlargement
Rectosigmoid colon mass not apparent on $^{18}$F-FDG PET/CT
Diffuse mesenteric and serosal bowel involvement
Small osseous metastases

Arterial and portal venous phase CT
Response to 4 cycles $^{177}$Lu-dotatate: $^{18}$F-FDG

Baseline  
After 2 cycles  
After 4 cycles
Response to 4 cycles $^{177}$Lu-dotatate: $^{68}$Ga-dotatate

Baseline

After 2 cycles

After 4 cycles
Marked response in mesentery

- Baseline
- After 2 cycles
- After 4 cycles
Symptoms post-PRRT

- No longer requires pain medication
- No further episodes of obstruction
- Energy levels and activities back to baseline
  - Can travel full day without requiring breaks or naps
- Continues on atezolizumab and octreotide
Acknowledgements

- NM Staff at Seattle Cancer Care Alliance
  - Zack Scherzer, CNMT
  - Larisa Toderas, CNMT
- SCCA NET Tumor Board Multidisciplinary Group
  Co-Chairs David Zhen, Medical Oncology, and Delphine Chen, Nuclear Medicine
  Admin: Maggie Eng-Johnson, GI Oncology Service Line Manager
  Gabi Chiorean  Gentry King  Manuela Matesan  Alan Failor
  Bill Harris   Lindsay Hannan  Sanaz Behnia  Mara Roth
  Kit Wong      Jonathan Sham  David Lewis  Jim Apisarnthanarax
  Andrew Coveler  Jim Park  Hubert Vesselle  Pharmacy Team
  Stacey Cohen  Venu Pillarisetty  Robert Miyaoka
  Veena Shankaran
Ongoing Key Clinical Trials NET
Focus on Cooperative Groups
NET Case Presentation

Caio Max S. Rocha Lima, MD
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Co-leader GI Oncology and Co-leader Phase I Program
Wake Forest School of Medicine
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A Phase 2 Study of XL184 (Cabozantinib) in Combination with Nivolumab and Ipilimumab for the Treatment of Poorly Differentiated Neuroendocrine Carcinomas

NCI Program: ETCN CATCH UP 20

Key Eligibility Criteria

- Poorly-differentiated neuroendocrine neoplasms per 2018 WHO classification, with the exception of small cell lung cancer and Merkel cell carcinoma. All variations of poorly differentiated neuroendocrine carcinoma (small cell, large cell and mixed cells) are eligible.
- Failure of only one line systemic treatment.
- Patients must have measurable disease per RECIST 1.1
- Patients must have lesions that can be safely biopsied and be willing to have a pretreatment and an on-treatment biopsy (after 1 month of treatment with the combination regimen).

Accrual: As of 05-Mar-2021

<table>
<thead>
<tr>
<th>Step Type</th>
<th>Planned</th>
<th>Actual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>30</td>
<td>11</td>
</tr>
</tbody>
</table>
Randomized, Double-Blinded Phase III Study of CABozantinib Versus Placebo IN Patients with Advanced NEuroendocrine Tumors After Progression on Prior Therapy (CABINET)

Key Eligibility Criteria

- Well- or moderately-differentiated neuroendocrine tumor of pancreatic or non-pancreatic origin
- Target lesion disease progression by RECIST v1.1
- Patients must have measurable disease per RECIST 1.1
- Progression or intolerance of $\geq 1$ prior therapy (except somatostatin analogs)
Randomized Phase II Study of Platinum and Etoposide Versus Temozolomide and Capecitabine in Patients with Advanced G3 Non-Small Cell Gastroenteropancreatic Neuroendocrine Tumors including Poorly Differentiated Neuroendocrine Carcinomas and Well-Differentiated Neuroendocrine Neoplasms
ECOG-ACRIN (Lead), NRG, SWOG, ALLIANCE

Accrual: As of 05-Mar-2021

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<tbody>
<tr>
<td>Intervention</td>
<td>80</td>
<td>66</td>
</tr>
</tbody>
</table>

- Advanced and unresectable or metastatic GEP NEC either known or suspected to be of GI origin
- Ki-67 proliferative index of 20-100% OR at least 10 mitotic figures per 10 high powered fields
- Measurable disease per RECIST 1.1
- No prior therapy: chemotherapy, targeted therapy, PRRT(prior somatostatin analogs allowed)
Case NET-
Initial Presentation

• 58 yo male 02.20.2013 presented to emergency room with severe abdominal pain and dx with acute pancreatitis.
• He was referred to Wake Forest one week later because of a tail of pancreas mass.
Case NET Additional Work Up

• EUS revealed a large mass in the pancreatic tail.
  • FNA revealed endocrine neoplasm with extensive clear cell features.
• Tumor Markers WNL
Surgical Procedure on 4/10/2013

• Distal pancreatectomy, splenectomy.
• Partial gastrectomy.
• Partial colectomy (splenic flexure).
• Left adrenalectomy.
• Omentectomy.
Pathology

• HISTOLOGIC TYPE: Well-differentiated endocrine neoplasm with clear cell features.

• MITOTIC ACTIVITY: Mitoses per 10 HPF: 5

• Ki 67 (?)

• TUMOR NECROSIS: Not identified

• MICROSCOPIC TUMOR EXTENSION: No involvement of stomach or spleen identified. The tumor invades muscularis propria of colon

MARGINS: Margins uninvolved by tumor.
Gastro-entero-pancreatic NENs WHO classification, 2019

- **Neuroendocrine tumor, G1**
  - Well differentiated morphology
  - Mitotic index <2 and Ki-67 index <3%
  - Low grade of malignancy

- **Neuroendocrine tumor, G2**
  - Well differentiated morphology
  - Mitotic index 2-20 and/or Ki-67 index 3-20%
  - Intermediate grade of malignancy

- **Neuroendocrine tumor, G3**
  - Well differentiated morphology
  - Mitotic index >20 and/or Ki-67 index >20%
  - High grade of malignancy

- **Neuroendocrine carcinoma**
  - Large cell type
  - Small cell type
  - High grade of malignancy

- **Mixed neuroendocrine-non neuroendocrine neoplasm (MiNEN)**
Adjuvant Therapy Was Not Recommended
**Surveillance 5/22/2014 CT scan**

**Patient Asymptomatic**

- Ill-defined region of hyperenhancement within the pancreatic neck

A 1.5 x 1.6 cm rounded, hyperenhancing lesion is present within segment 6 of the liver and a second hyperenhancing area slightly more laterally in segment 6

07/03/2014 MRI Confirmed the neck of the pancreas hyperenhancement.
Two lesions in hepatic segment 6 with early arterial enhancement and restricted diffusion consistent with metastatic disease
Pancreatic NET

- Somatostatin analog
- Everolimus
- Sunitinib
- Capecitabine/ Temozolomide
- PRRT (Based on somatostatin receptor expression)
- Hepatic arterial embolization
Hepatic arterial embolization:

- Appropriate for liver-dominant metastases
- May be palliative for carcinoid syndrome
- TACE x TARE x Bland embolization
- Meta-analysis studying data from six retrospective studies favor TACE in survival (similar tumor burden and tumor grade among all the studies).
- The three studies that included RECIST data found no difference in the treatment responses.
Management of Hepatic Metastasis

• 10/17/2014 - 12/11/2017 TACE x 3.
• No systemic therapy recommended
Further Progression

- MRI 11/13/2017
  - Increase in size and conspicuity of the arterial phase enhancement of hepatic segment 2 and 6 lesions concerning for underlying viable tumor
  - Enlarged 3.0 cm periportal lymph node
3/22/2018 Ga68 Dotatate

- Uptake in segment 2 and 6
- Uptake in porta hepatis LN
Pancreatic NET

- Somatostatin analog
- Everolimus
- Sunitinib
- Capecitabine/ Temozolomide
- PRRT (Based on somatostatin receptor expression)
Time to Progression: Octreotide LAR vs Placebo

Octreotide LAR: 42 patients / 26 events
Median 14.3 months [95% CI: 11.0–28.8]

Placebo: 43 patients / 40 events
Median 6.0 months [95% CI: 3.7–9.4]

Proportion Without Progression

P = 0.000072
HR = 0.34 [95% CI: 0.20–0.59]

CLARINET Subgroup Analysis (ITT): Midgut vs. pNET

N=204 adults with well- or moderately differentiated, metastatic, and/or locally advanced unresectable GEP-NETs, and Ki-67 <10%

Lanreotide Depot 120 mg (fixed dose) vs placebo every 28 days

Midgut NETs (n = 73)
Lanreotide Autogel vs placebo
p = 0.0091, HR = 0.35 (95% CI: 0.16, 0.80)

Lanreotide 120 mg
8 events / 33 patients median, not reached
Placebo
21 events / 40 patients median, 21.1 months [95% CI: 17.0, NC]

pNET (n = 91)
Lanreotide Autogel vs placebo
p = 0.0637, HR = 0.58 (95% CI: 0.32, 1.04)

Lanreotide 120 mg
18 events / 42 patients median, not reached
Placebo
31 events / 49 patients median, 12.1 months [95% CI: 9.4, 18.3]


Wake Forest Baptist Medical Center
Systemic Therapy

- Octreotide LAR Monthly at an outside institution
- 2/19/2018 - 05/2020

- Radiologic progression 06/2020 but no new complaints
06/14/20: MR liver

Worsening porta-hepatis LN

Worsening segment 2
06/30/20 PET GA-68 DOTATATE

Increased/worsening Ga-68 DOTATATE avid periportal nodal conglomerate and hepatic metastatic lesions
No new DOTATATE avid disease identified
Pancreatic NET

- Continue somatostatin analog at higher dose
- Everolimus
- Sunitinib
- Capecitabine/ Temozolomide
- PRRT (Based on somatostatin receptor expression)
Progression-Free Survival

Inoperable, somatostatin receptor +, midgut NET, progressive under Octreotide LAR 30mg (label use)

N = 229 (ITT)
Number of events: 90

- $^{177}$Lu-Dotatate: 23
- Oct 60 mg LAR: 67

Hazard ratio: **0.21** [0.129 – 0.338]
p < 0.0001

79% reduction in the risk of disease progression/death

Overall Survival (Interim Analysis)

N = 229 (ITT)
Number of deaths: 40

- $^{177}$Lu-Dotatate: 14
- Oct 60 mg LAR: 26

RR 18% x 3% favoring PRRT
p = 0.0008

Hazard ratio: **0.398**
[0.21 – 0.77]
P = **0.0043**

Second-line Systemic Therapy

- Lutetium (Lu 177) dotatate every two months at our institution and continuation of octreotide LAR with a local oncologist
Conclusions

• Many options for metastatic/unresectable PNEN patients
• No data comparing head to head the available options
• Unmet need of randomized data to guide sequence of treatments
• Unmet need of predictive markers for treatment selection
Cancer Programs Webinar Series

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- NAPBC Best Practices Webinar Series: Quality in Action – 6 webinars
- NAPRC: Practical Tips, Pearls, and Advice from the Trenches – 1 webinar
- CAnswer Forum LIVE 2021 – 6 webinars
- ACS Cancer Research Program (CRP) Educational Series - 6 webinars

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