MANAGEMENT OF PANCREATIC NEUROENDOCRINE TUMORS

5.1.15
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DISCLOSURES:

- Support for clinical trials
  - Genentech (drug only)
  - Novartis
  - Lexicon

- Advisory Board (uncompensated)
  - Novartis
  - Celgene
  - Lexicon
Tumors arising from enterochromaffin cells located in neuroendocrine tissue throughout the body.

NETs can be functional or nonfunctional and include a heterogeneous group of neoplasms:

- Medullary thyroid carcinoma
- Pancreatic neuroendocrine tumors (islet cell carcinomas)
- Carcinoid tumors (well-diff NET)
- Pheochromocytoma/paraganglioma
- Poorly differentiated/small cell/large cell NET
- Merkel cell carcinoma


NET incidence of NETs increasing

US SEER data show a 5-fold increase in the past 30 years

NEUROENDOCRINE TUMORS (NET): A DIVERSE GROUP OF MALIGNANCIES

- Characterized by:
  - site of origin
  - ability to make biologically active peptides
  - histological grade

- Express somatostatin receptors and neuroendocrine markers (CGA, NSE)

References:

TUMORS CAN TYPICALLY BE IDENTIFIED BY CT/MRI SCAN AND OCTREOSCAN™

MOLECULAR IMAGING

- Novel radiopharmaceuticals for imaging
  - Anatomical localization with PET/CT, CT or MRI
  - High grade: 18F-FDG-PET
  - Low grade:
    - $^{111}$In-pentetreotide (SRS) (80% sensitivity)—but not
      - Insulinomas (50%), Small tumors, Poorly diff tumor
    - Also, $^{111}$In-DOTA-lanreotide, 99Tc-HYNIC-TOC
    - Ga68-labeled SSA (up to 90% sensitivity)
      - Ga68-DOTATATE, DOTATOC, DOTANOC
      - Higher SSTR affinity
    - 18F-DOPA
    - 5-HTP-PET (pancreatic NET?)
    - Gastrin receptor scintigraphy (CCK2)
- Functional imaging for selection of patients who may benefit from receptor-based therapies

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dehHerder, 2014

GA68 DOTATOC PET-CT (INVESTIGATIONAL):

Negative study
Liver met and pancreatic 1°

Courtesy of Thomas Hope, MD (UCSF)
NEUROENDOCRINE (NE) TUMORS OF THE GI TRACT: CLASSIFICATION

• **Functioning**: clinical syndrome due to hormone (<30%)
  - serotonin, substance P, gastrin, insulin, glucagon, somatostatin, vasoactive intestinal peptide, growth hormone-releasing factor, adrenocorticotropic hormone
  - Multiple hormones possible, as is conversion from nonfunctional to functional over time

• **Nonfunctioning**: no specific symptoms
  - may also secrete hormones
    - (pancreatic polypeptide)
The only curative treatment for early-stage disease involves a multidisciplinary approach, surgery remains although the optimal clinical management of PNETs tumors vulnerable to hormone targeted therapies. This avidity can assist in diagnosis and may make some somatostatin receptors and uptake hormones strongly (5). PETs possess especially strong hormone receptors, such as analogues) as the primary therapeutic approach. Some with hormonal treatment with octreotide (somatostatin *OUIFQBTU
USFBUNFOUPQUJPOTGPS1&5TIBWFCFFOMJNJUFE

Treatment groups of increasing malignant potential (19,22). parameters to classify pancreatic endocrine tumors into proved to be highly predictive of patient outcome and nuclear grade and prognosis (24). The TNM system has studies have demonstrated a correlation between overall metastasis and local or metastasis (5). Nuclear expression and cytokeratin 19 immunostaining (5,23). Peptide angioinvasion, and possibly CD44 isoform upregulated status, necrosis, mitotic activity, perineural invasion and helpful in determining prognosis are tumor size and functional differentiated neuroendocrine carcinomas, on the basis well-differentiated neuroendocrine tumors or poorly- stratification. PETs are graded into 1 of 3 tiers, either as standardize current diagnostic and management procedures diagnosis, or at least have the potential to metastasize in neoplasms is acknowledged and enforced. The fact is that PETs (186)

Table 2 WHO 2010 classification and grading of PETs (5,21)

<table>
<thead>
<tr>
<th>Classification/Grade</th>
<th>Mitotic count (per 10 hpf)</th>
<th>Ki-67 Index (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NET-G1</td>
<td>&lt;2</td>
<td>&lt;3</td>
</tr>
<tr>
<td>NET-G2</td>
<td>2-20</td>
<td>3-20</td>
</tr>
<tr>
<td>NEC-G3</td>
<td>&gt;20</td>
<td>&gt;20</td>
</tr>
</tbody>
</table>

NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; hpf, high power field; 10 HPF =2 mm², at least 40 fields (at 400x magnification) evaluated in areas of highest mitotic density.

Well-differentiated = G1 and G2

Poorly-differentiated= G3


Kulke, et al. JCO, 2011; 29: 934-943
Low- and intermediate grade tumors (G1/2) are grouped as well-differentiated NET
- Reference to grade or differentiation required in path report (Ki 67 or mitotic rate)

- NOT black and white—spectrum in terms of behavior

- Doesn’t account for discordance between K67/mitotic rate/morphology
  - Scheme evolving
  - Core biopsy ideal
    - FNA may be OK for pancreas (McCall, et al. 2013)

- Rebiopsy if behavior not consistent with path
  - Potential for heterogeneity

- Cut-off for true high grade unclear
  - Large cell/small cell, Ki 67>55%?
  - Well diff morphology, Ki 67 20-55%?
**DECISION TREE: NET**

- **NET**
  - Well-differentiated
    - "carcinoid"
  - Poorly-differentiated
    - PNET
    - Paraganglioma/pheochromocytoma
    - Platinum-based CTx

**UNKNOWN PRIMARY IN ≥15%:**

**DOES IDENTIFYING TYPE OF TUMOR MATTER? YES**

- Prevents complications (SB tumors)
- Treatment options and response to treatment depends on primary site
  - Everolimus/sunitinib for PNET
  - Chemotherapy for PNET?
- Access to clinical trials

- Molecular mechanisms underlying tumor progression different?
PANCREATIC NET (PNET)

- Incidence has increased over last several decades
  - 0.2 to 0.4 per 100,000 per year
  - ≈1.5% pancreatic cancers (=400-1200 cases/yr)
  - Increases with age; peaks in 7th decade, median age ≈60
  - 10% of all pancreatic cancers by prevalence

- Arise from islets of Langerhans (usually well-differentiated)

- Evenly distributed between head, body and tail

- Most are well-differentiated (<10% G3)

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PANCREATIC NET (PNET)

- Most (≈70%) are nonfunctional
  - Functional: insulinoma > gastrinoma > glucagonomas
    > VIPomas > somatostatinomas > others
    - 90% of insulinomas are benign (excellent outcome)
    - Insulinomas and gastrinomas more common in younger pt
    - Glucagonomas and serotonin-producing tumors more common in elderly
  - Pancreatic polypeptide production common and asymptomatic (nonfunctional)

- 55-70% metastatic at diagnosis
  - Median OS stage IV 2-6 yr
Tuberous sclerosis (inactivation of transcription factors at a nuclear level MENIN, is involved in different functions, such as the von Recklinghausen's von Hippel–Lindau disease tumor suppressor is controversial (not well understood, and the exact role of MENIN as a component of a family history. How mutations lead to cancer is the occurrence of PETs is multiple endocrine neoplasia type I (MEN1), an autosomal dominant disorder. The most frequent inherited syndrome associated with 1300 different germline mutations have been described. Mutation of MENIN allowed an improved description of its interaction with JUND and MLL (enhancing p27KIP1 and p18INK4c function) and result is a negative control of the cell cycle (inactivating mutation of a TSG located on chromosome 11q13). Ten exons constitute the gene, and the corresponding protein, named Menin. About 10% of PETs occur as a part. The recent description of the crystal structure of Menin shows that it is a member of a family of proteins involved in chromatin remodelling. Menin plays a role in transcriptional regulation and cell cycle control. Menin interacts with several partners, including JunD, SMAD3, SMAD4, and p27KIP1/p16INK4a. Menin is involved in the regulation of cell cycle progression by promoting the expression of p27KIP1 and p18INK4c, which are inhibitors of cyclin-dependent kinases. Menin also interacts with JUND, a transcription factor that regulates the expression of genes involved in cell cycle control. The precise role of Menin in cancer remains to be elucidated, but it is clear that alterations in the Menin gene play a significant role in the development of MEN1 syndrome. MEN1 is a genetic syndrome associated with inherited pancreatic endocrine tumours, including clinical features and molecular defects.

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Gene function main molecular consequences</th>
<th>Major clinicals features</th>
<th>Patients with PET (%)</th>
<th>PET subtype</th>
<th>Metastatic PET (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple endocrine neoplasia type I</td>
<td>Menin (11q13)</td>
<td>Oncosuppressor Deregulation of JunD, SMAD3 p27KIP1/p16INK4a</td>
<td>Two or more between: a) GEP-NET b) Parathyroid adenomas c) Pituitary adenoma</td>
<td>20–100%</td>
<td>100% NF 54% Gastrinomas 15% Insulinomas 3% Glucagonomas 1% GFRomas or VIPomas</td>
<td>80–100% NF</td>
</tr>
<tr>
<td>von Hippel–Lindau disease</td>
<td>VHL (3p25–26)</td>
<td>Oncosuppressor Overexpression of HIF and VEGF</td>
<td>One or two between: a) Retinal or cerebellar hemangioblastomas b) Renal cell carcinoma c) Pheochromocytoma</td>
<td>5–17%</td>
<td>Rare</td>
<td>Duodenal somatostatinomas (1–10%) Insulinomas (&lt;1%)</td>
</tr>
<tr>
<td>von Recklinghausen's disease</td>
<td>NF1 (17q11.2)</td>
<td>Oncosuppressor Deregulation of Ras pathway (mTOR)</td>
<td>a) Café-au-lait skin spots b) Neurofibromas of any type and localisation</td>
<td>Very rare</td>
<td>Mainly NF</td>
<td>–</td>
</tr>
<tr>
<td>Tuberous sclerosis complex</td>
<td>TSC1 (9q34)</td>
<td>Oncosuppressor Deregulation of mTOR pathway</td>
<td>a) Skin alterations b) Renal angiomylipomas c) Multiple and diffuse hamartomas d) Neurological alterations</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

GEP-NET, gastroenteropancreatic neuroendocrine tumour; PET, pancreatic neuroendocrine tumour; NF, non-functioning.

- Most common neoplasm is parathyroid hyperplasia (98% of patients), followed panNET(50%), pituitary adenomas (35%), and/or lung/thymus carcinoid tumors (10%).
  - NF tumors most common PNET
  - Gastrinomas and insulinomas are the most common functional tumors
  - Often multiple

- Type 2 gastric carcinoid tumors common in MEN1 patients with gastrinoma.

MEN1
MEN1

- Adrenal tumors also increased in MEN1
- HyperPTH usually treated before PNET in patients with MEN1
- Role of surgery for multifocal PNET controversial in MEN1
  - Symptomatic functional tumors refractory to medical management
  - Tumor larger than 1–2 cm in size
  - Tumor with relatively rapid rate of growth over 6–12 months
  - Endoscopy with EUS is recommended prior to pancreatic surgery

PNETS: GENETICS (SPORADIC TUMORS)

- Sporadic (90%) well diff tumors
  - DAXX/ATRX (43%), MEN1 (44%), and mTOR (14%) pathway genes are frequently altered in sporadic PNET

Table 1. Comparison of commonly mutated genes in PanNETs and PDAC based on 68 PanNETs and 114 PDACs.

<table>
<thead>
<tr>
<th>Genes*</th>
<th>PanNET</th>
<th>PDAC†</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN1</td>
<td>44%</td>
<td>0%</td>
</tr>
<tr>
<td>DAXX, ATRX</td>
<td>43%</td>
<td>0%</td>
</tr>
<tr>
<td>Genes in mTOR pathway</td>
<td>15%</td>
<td>0.80%</td>
</tr>
<tr>
<td>TP53</td>
<td>3%</td>
<td>85%</td>
</tr>
<tr>
<td>KRAS</td>
<td>0%</td>
<td>100%</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>0%</td>
<td>25%</td>
</tr>
<tr>
<td>TGFB1, SMAD2, SMAD4</td>
<td>0%</td>
<td>38%</td>
</tr>
</tbody>
</table>

[Table 1. Comparison of commonly mutated genes in PanNETs and PDAC based on 68 PanNETs and 114 PDACs.]

PNET GENETICS

- *Prognostic value* of specific mutations unclear
  - Conflicting data

- *Predictive value* of specific alterations unclear

Pancreatic NETs
RESECTABLE DISEASE
WORK-UP

- Multiphasic CT or MRI
- CGA (elevated in 60% of PNET)
- As appropriate: somatostatin scintigraphy, EUS, +/- additional biochemical evaluation
  - Gastrin
  - Insulin, proinsulin, c-peptide, FBS
  - Glucagon
  - Pancreatic polypeptide
  - VIP
  - Somatostatin
  - Calcitonin
  - PThrP
  - RARE: GHRH, ACTH, 24 hr urine 5HIAA, LH, renin, IGF2, etc


TREATMENT: SURGICAL RESECTION

- Type of surgery depends on location of tumor
  - Enucleation
  - Distal pancreatectomy
  - Central pancreatectomy
  - Whipple (pancreatic duodenectomy)
  - Total pancreatectomy

- Curative surgery, TNM stage and grade are predictors of survival

- No role for adjuvant therapy
PNET SURVIVAL BY STAGE (N=926)

No at risk

<table>
<thead>
<tr>
<th>Stage</th>
<th>N</th>
<th>148</th>
<th>130</th>
<th>126</th>
<th>128</th>
<th>85</th>
<th>84</th>
<th>4</th>
<th>26</th>
<th>23</th>
<th>16</th>
<th>12</th>
<th>6</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>N</td>
<td>130</td>
<td>126</td>
<td>128</td>
<td>128</td>
<td>85</td>
<td>84</td>
<td>4</td>
<td>26</td>
<td>23</td>
<td>16</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>II</td>
<td>N</td>
<td>130</td>
<td>126</td>
<td>128</td>
<td>128</td>
<td>85</td>
<td>84</td>
<td>4</td>
<td>26</td>
<td>23</td>
<td>16</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>III</td>
<td>N</td>
<td>130</td>
<td>126</td>
<td>128</td>
<td>128</td>
<td>85</td>
<td>84</td>
<td>4</td>
<td>26</td>
<td>23</td>
<td>16</td>
<td>12</td>
<td>6</td>
</tr>
</tbody>
</table>

Rindi et al. JNCI 2014

METASTATIC DISEASE
LIVER-DOMINANT METASTATIC DISEASE (NO RCT)

- Resection of known disease if possible (≥90%)
  - Median OS 10 yr (retrospective 339 pt)
    - Benefits greatest if <25% liver involvement or symptomatic high volume disease (vs hepatic arterial therapy)
    - Recurrence 95% at 5 yr, 99% at 10 yr
  - 10 year OS 50% if RO or R1 resection (172 pt)
    - 15% R1; 10% RFA alone; 13% RFA plus surgery
    - Thoracic primary associated with worse outcome on multivariate analysis (less so for late recurrence)
    - Late recurrence an issue (annual scan for life?)
      - Glazer, et al. HBP (Oxford), 2010

Pancreatic NETs

ADVANCED UNRESECTABLE DISEASE
UNRESECTABLE DISEASE: INDICATIONS FOR THERAPY

Well-differentiated NET

Control of hormone-mediated symptoms

Progressive disease (need for anti-tumor effect)

Ability to resect all known disease

*Patient selection is key!*

SOMATOSTATIN (SST)

- Bioactive neuropeptide
  - Prepro→SST-14 and SST-28 (Short t½)

- Produced and acts locally:
  - Glandular and exocrine secretions:
    - Inhibits GH/ACTH/TSH release
    - Pan-inhibitor of GI tract hormone release (insulin, glucagon)
    - Inhibits release of gastric acid, amylase
  - Antiproliferative

- Mediates inhibitory effects thru 5 GCPR (SSTR 1-5)
  - Expressed throughout CNS, GI tract, endocrine/exocrine glands, & immune/inflammatory cells

*Schmid et al. Mol Cell Endocrinol 2008;286:69–74*;
### REGULATORY ACTION OF SOMATOSTATIN RECEPTORS

<table>
<thead>
<tr>
<th>Action</th>
<th>SST₁</th>
<th>SST₂</th>
<th>SST₃</th>
<th>SST₄</th>
<th>SST₅</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antisecretory</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-angiogenic</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiproliferative/Inhibit cell cycle (G1 arrest)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction of apoptosis</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Effects probably SSTR subtype- and tissue-specific; may reflect interaction between two or more receptor types (e.g. SSTR subtypes and/or other GPCR, eg D2R)*


### SOMATOSTATIN ANALOGS (SSTA) AND NETS

- SSTa indicated for the treatment of hormone-mediated sx¹:
  - Octreotide (SQ)/Octreotide LAR (IM q mo)
    - Sandostatin®, Sandostatin LAR®
    - Approved for acromegaly and carcinoid syndrome
  - Lanreotide (SQ q 14d)/Lanreotide autogel (SQ q mo)
    - Approved for acromegaly (Somatuline) and for tumor control of well diff NETS in US (including PNETs)
  - sstr 2, 5 (high) > sstr 3 > sstr 1, 4 (low)
  - Both afford ≈70% symptomatic response rate

SUMMARY: SYMPTOM CONTROL

Use caution when treating patients with insulin-excess!!!
Not always SSTR (+), can worsen sx


SPECIFIC SYNDROMES: GASTRINOMA

- Recurrent peptic ulcers from hypergastrinemia (ZES), diarrhea, reflux
- Typically located in duodenum (usually malignant)

- Work-up
  - Basal gastrin level (+/- stimulated)—fasting 10x ULN and pH <2 (if off PPI)
    - r/o PPI, achlorhydria, antacids
  - Multiphasic CT/MRI
  - As indicated: somatostatin scintigraphy, EUS, other biochemical evaluation

- Manage gastrin hypersecretion with PPI and somatostatin analogs
- Local disease- include periduodenal LN dissection

SPECIFIC SYNDROMES: INSULINOMA

- 1.5-4 per 1,000,000
  - Located in pancreas, usually small and solitary
- 90% are benign
- 90% sporadic
  - 5% associated with MEN1 (NF, gastrinoma, insulinoma) or VHL
    - More likely to be malignant
  - Malignant insulinoma 10 yr OS <20%

SPECIFIC SYNDROMES: INSULINOMA

- Neuroglycopenic symptoms usually dominate the clinical picture
  - Confusion, altered consciousness
- Worst in early am or late at night (after prolonged fast)
  - Post prandial hypoglycemia can be seen (weakness, sweating)
- Can be worsened by exercise, alcohol, low cal diet, drugs
- Weight gain in 20-40% of patients
LOCALIZATION OF INSULINOMA

- Low glucose (+/- after 48-72 hr fast); high insulin, proinsulin, c-peptide
- Imaging (+) pancreatic mass (>80%< 2cm)
  - CT or MRI or angiography or EUS (less commonly THPVS, SACS test etc)—detects up to 75%
  - Intraoperative US (detects >90%) and/or palpation

TREATMENT OF HYPOGLYCEMIA: ACUTE

- Frequent glucose monitoring
- Reduce exercise
- Frequent carbohydrate meals (D5 or D10 gtt)
- Cornstarch (q 3 hr 24/7)
- Diazoxide
  - 200-600 mg/d
- Prn Glucagon injections
- Octreotide (if SSTR imaging (+))
TREATMENT OF INSULINOMA

- Resection is gold standard for localized disease
  - Enucleation (56%)
  - Distal pancreatectomy (32%), Whipple (3%), subtotal pancreatectomy (<3%)
  - Open procedures preferred (mortality 4%)
    - 7% recurrence


PNET SURVIVAL BY FUNCTIONAL STATUS (N=926)

Rindi et al. JNCI 2014
TREATMENT OF INSULINOMAS

- Laparoscopic: benign, small and/or body and tail
- LN dissection usually not performed
- Radical resection: multiple, >4 cm, not well encapsulated, and/or near main pancreatic duct

- Poor surgical candidates
  - EtOH ablation
  - CT guided RFA
  - embolization

SPECIFIC SYNDROMES: VIPOMA

- Watery diarrhea, hypokalemia, achlorhydria (WDHA syndrome)
  - High volume (often >3 liters/d)
  - Usually malignant and located in pancreas

- Work-up
  - Check electrolytes, VIP level, multiphasic CT or MRI
  - As appropriate: somatostatin scintigraphy, EUS, +/- additional biochemical evaluation

  - Stabilized with IVF and electrolytes and SSTa

  - Local dissection: Include LN dissection
**SPECIFIC SYNDROMES: GLUCAGONOMA**

- Usually in the pancreatic tail
- Diabetes/glucose intolerance, weight loss +/- migratory necrolytic erythema (perineum, trunk, extremities)
- Work-up
  - Glucagon level, multiphasic CT or MRI
  - As appropriate: somatostatin scintigraphy, EUS, +/- additional biochemical evaluation
- Stabilize glucose with IVF and SSTa
  - Treat diabetes as appropriate
- Local dissection: Include LN dissection

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**UNRESECTABLE DISEASE: INDICATIONS FOR THERAPY**

- **Well-differentiated NET**

- Control of hormone-mediated symptoms
- Progressive disease (need for anti-tumor effect)

Ability to resect all known disease

*Patient selection is key!*

---

RATIONALE FOR ARTERIAL THERAPY

- 75% of blood supply to normal liver via portal vein
- Malignant liver tumors supplied almost exclusively by hepatic artery
- Arterial embolization preferentially targets malignant lesions
- Perfusion of malignant lesions 5-17 fold higher than normal liver tissue

LIVER –DIRECTED THERAPY

- HAE/HACE/Y90-SIRT
- Symptomatic improvement >50%
- Radiologic response in ≈50%

NO RCT to guide selection of therapy

TREATMENT OPTIONS-SYSTEMIC THERAPY

- Somatostatin analogs
- PRRT
- Chemotherapy
- VEGF inhibitors
- mTOR inhibitors

CLARINET: PHASE 3, RANDOMIZED, DOUBLE-BLIND STUDY OF LANREOTIDE VS PLACEBO IN PATIENTS WITH NON-FUNCTIONAL WELL-DIFFERENTIATED NET

Eligibility criteria:
- Well-differentiated NET (pancreas, midgut, hindgut)
- Nonfunctional
- ECOG 0-2
- Ki67<10%
- SSTR(+)
- No prior SSA therapy

Lanreotide 120 mg deep SQ q 28 d x 96 wk

Placebo

N=200

Caplin, et al. NEJM, 2014
The hazard ratio was derived from a Cox proportional-hazards model with terms included to adjust for baseline characteristics. Kaplan–Meier curves were compared with the use of a stratified log-rank test, with stratification according to the presence or absence of tumor progression at baseline and the receipt or nonreceipt of previous therapy. The midgut was defined as the small intestine and appendix, and the hindgut was defined as the large intestine, rectum, anal canal, and anus. Post hoc analyses confirmed that there were no significant between-group differences at baseline. The midgut was defined as the small intestine and appendix, and the hindgut was defined as the large intestine, rectum, anal canal, and anus.

Two patients in each group had gastrinomas. The median progression-free survival was 18.0 months (95% CI, 12.1–24.0) in the lanreotide group and 33.0% (95% CI, 23.0 to 43.3) in the placebo group. More patients in the placebo group than in the lanreotide group had centrally assessed disease progression. The hazard ratio was 0.47 (95% CI, 0.30–0.73; P<0.001 for the comparison of progression-free survival).

Table 1. Baseline Demographic and Disease Characteristics of the Patients (Intention-to-Treat Population)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lanreotide (N=101)</th>
<th>Placebo (N=103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex — no. (%)</td>
<td>53 (52)</td>
<td>54 (52)</td>
</tr>
<tr>
<td>Age — yr</td>
<td>63.3±9.8</td>
<td>62.2±11.1</td>
</tr>
<tr>
<td>Time since diagnosis — mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>32.6±46.1</td>
<td>34.4±41.4</td>
</tr>
<tr>
<td>Median</td>
<td>13.2</td>
<td>16.3</td>
</tr>
<tr>
<td>Prior treatment for neuroendocrine tumor — no. (%)</td>
<td>16 (16)</td>
<td>16 (16)</td>
</tr>
<tr>
<td>Primary tumor resected — no. (%)</td>
<td>40 (40)</td>
<td>39 (38)</td>
</tr>
<tr>
<td>Origin of neuroendocrine tumor — no. (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>42 (42)</td>
<td>49 (48)</td>
</tr>
<tr>
<td>Midgut</td>
<td>33 (33)</td>
<td>40 (39)</td>
</tr>
<tr>
<td>Hindgut</td>
<td>11 (11)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Unknown or other</td>
<td>15 (15)</td>
<td>11 (11)</td>
</tr>
<tr>
<td>Tumor progression — no. (%)</td>
<td>4 (4)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Tumor grade — no. (%)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1: Ki-67 0–2%</td>
<td>69 (68)</td>
<td>72 (70)</td>
</tr>
<tr>
<td>2: Ki-67 3–10%</td>
<td>32 (32)</td>
<td>29 (28)</td>
</tr>
<tr>
<td>Data missing</td>
<td>0</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>
tumor volumes greater than 10%.
grade 1 tumors and few patients had hepatic
It was made up almost entirely of patients with
tumors, the study was narrowly focused so that
compared with placebo in patients with midgut
significantly prolonged time to tumor progression
with Metastatic Neuroendocrine Midgut Tumors
in PROMID.
Crine tumors are based largely on findings from
Control of advanced enteropancreatic neuroendo-
ning the use of somatostatin analogues for con-
in patients with neuroendocrine tumors.
shorter progression-free survival. These differ-
dimensional measure of the same tumor re-
in PROMID and the unidimensional RECIST,
this cannot be confirmed. Moreover, disease-
tients with stable disease. How
it seems unlikely, considering the shorter time
in our study had stable disease at baseline, and
since the median time to diagnosis was longer
PROMID, had, in general, more indolent tumors,
be made with caution, it seems likely that the
sons of the findings from these two studies must
in a study population of patients with entero-
showed an antiproliferative effect of lanreotide
Current clinical practice guidelines regard
however, in cases in which evi-
Although PROMID showed a sig-
H o w e v e r , i n c a s e s i n w h i c h 

Our study principally examined the prevention of dis-
appear to support this approach. However, our
of progression-free survival in this group may
Gate for deferred treatment, and the long period
and see" policy) may be appropriate. The placebo

Study treatment–related adverse events
in ≥5% of patients

Withdrawal because of adverse event related
to study treatment

S A F E T Y :

Withdrawal because of adverse event related

Lanreotide
Placebo

to study treatment
1 (1)
0

Study treatment–related adverse events
in ≥5% of patients

Table

Diarrhea
26 (26)
9 (9)

Abdominal pain
14 (14)
2 (2)

Cholelithiasis
10 (10)
3 (3)

Flatulence
8 (8)
5 (5)

Injection-site pain
7 (7)
3 (3)

Nausea
7 (7)
2 (2)

Vomiting
7 (7)
0

Headache
5 (5)
2 (2)

Lethargy
5 (5)
1 (1)

Hyperglycemia
5 (5)
0

Decreased level of pancreatic enzymes
5 (5)
0

CLARINET: TAKE HOME POINTS

 Lanreotide improves PFS in nonfunctional well-diff NET (Ki 67<10%)
  Median PFS 18 mo v NR (P<0.001)

 No Δ 2 yr OS
  o Extension study confounds interpretation

 Excellent median PFS in control group argues for watch and wait

 Enriched for patients with SD
  o 95% of patients had SD by RECIST in the 3-6 mo before study drug.

 Value Ki 67>10%? Pt with PD?

 FDA APPROVED 12/2014 to improve PFS of well- or
  moderately diff advanced GEP-NETs
TREATMENT OPTIONS: SYSTEMIC THERAPY

Peptide receptor radiotherapy (PRRT)

- Potential value (e.g. \[^{177}\text{Lu} \text{-DOTA 0,Tyr3}\text{octreotate or }^{90}\text{Y-DOTATOC}\]) in pt with high tumor uptake on somatostatin receptor scintigraphy
  - Other radioconjugates under study
- Symptom control, SD, and/or radiographic responses (4-30%) have been reported
- No prospective RCT evaluating toxicity/anti-tumor efficacy

CHEMOTHERAPY

- Anaplastic/poorly diff: 50% RR (platinum-based)
- Well-differentiated NET: No accepted standard treatment
  - Carcinoids: RR<20%
  - PNET:
    - inconsistent RR (6-40%) with streptozotocin-based therapy (Moertel, et al. 1992, NEJM; Cheng and Saltz, 1999, Cancer)
    - 70% RR in 1st line PNET (retrospective, n=30) with capecitabine/temozolomide (Strosberg, et al. Cancer 2011)
- Treatment related toxicity often limiting
TEMOZOLOMIDE-BASED CHEMOTHERAPY: SUMMARY

- Activity in NET
  - May be dose/schedule/partner-dependent
  - 3+ regimens under study
  - May be MGMT-dependent
    - Definition of high vs. low?
  - May be disease-dependent: PNET vs carcinoid
    - 70% RR in 30 PNET (retrospective) with capecitabine/temozolomide
  - May be site-dependent (e.g. thymic vs bronchial vs SB)

- Toxicity may be schedule-dependent
- Utility of MGMT testing needs prospective validation

- Prospective, randomized trials are needed!
- Not approved for this indication

ECOG 2211: RANDOMIZED PHASE II STUDY OF CAPECITABINE/TEMOZOLOMIDE VS TEMOZOLOMIDE ALONE IN ADVANCED, PROGRESSIVE, WELL-DIFFERENTIATED PNET

Eligibility criteria:
- Well-differentiated PNET
- Disease progression in past 12 months
- ECOG 0/1

1:1 Randomization

N=145

Stratify:
- Prior everolimus
- Prior sunitinib
- Concurrent octreotide

Capecitabine/temozolomide

Temozolomide

1stEP: PFS

Up to 13 cycles
Advanced PanNETs

**VEGF PATHWAY INHIBITOR**

---

**VEGF AND NET**

- NETs are highly vascular and express VEGF and its receptors
- VEGF expression correlates with metastases and decreased progression free survival (PFS)
- In preclinical models, VEGF is a valid target for therapy
  - VEGF RTK inhibitors active in RIPTAg model

PHASE 3, RANDOMIZED, DOUBLE-BLIND STUDY OF SUNITINIB VS PLACEBO IN PATIENTS WITH ADVANCED, PROGRESSIVE, WELL-DIFFERENTIATED PNET

Eligibility criteria:
- Well-differentiated PNET
- Disease progression in past 12 months
- ECOG 0/1

N=340 planned (171 actual)
Closed early

Sunitinib 37.5 mg PO Q day w/o breaks

1:1

1°EP: PFS

Placebo*

*With best supportive care

Somatostatin analogs permitted in both arms

After trial closure all patients became candidates for open-label sunitinib in trial NCT00443534 or NCT00428220

Raymond, et al. NEJM, 2011

PROGRESSION-FREE SURVIVAL (PRIMARY ENDPOINT)

Median PFS
- Sunitinib 11.4 months (95% CI 7.4, 19.8)
- Placebo 5.5 months (95% CI 3.6, 7.4)

HR=0.418 (95% CI 0.263, 0.662)
P<.001

SUMMARY

- **Sunitinib improves PFS in progressive, well-differentiated pNET**
  - Benefit across subgroups (including on-study and prior SSA)
  - PR rate low (9%)
  - QOL preserved
    - Hypertension, fatigue, diarrhea, nausea
  - Overall survival data should be interpreted with caution (70% X-over)
    - Longer f/u needed
  - **FDA-approved for progressive PNET indication in May 11’**

- **Unanswered questions:**
  - Optimal role/sequence in context of other “available” therapies (e.g. SIRT, everolimus, PRRT, chemotherapy)?
  - Value in other low-grade NET (e.g. carcinoid)?

### Advanced PanNETs

**MTOR PATHWAY INHIBITOR**
MTOR PATHWAY AS A TARGET FOR THERAPY IN NET

- mTOR has a central role in a number of proliferation pathways

- Abnormalities in the mTOR pathway are involved in the development of some NETs
  - TSC-2 is negative regulator of mTOR
  - mTOR components mutated in 15%

- mTOR signaling promotes cell metabolism, angiogenesis, and cell proliferation

RADIANT-3: EVEROLIMUS VS. PLACEBO IN ADVANCED PANCREATIC NET

Patients with advanced pNET PD w/ 12 mo n=410^*

Randomize

1:1

Cross over

Everolimus 10 mg/d + best supportive care^*

Placebo + best supportive care^*

Treatment continued until progression

Randomization Aug. 2007 – May. 2009

*concurrent somatostatin analogs allowed

1° EP PFS (inv-reported)

Yao, et al. NEJM, 2011
PFS BY INVESTIGATOR REVIEW

Kaplan-Meier medians PFS
Everolimus: 11.0 months
Placebo: 4.6 months
Hazard ratio = 0.35; 95% CI [0.27-0.45]
\( P \)-value: <0.0001

No. of patients still at risk

<table>
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<tr>
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<th>Everolimus</th>
<th>Placebo</th>
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<tbody>
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<td>189</td>
<td>203</td>
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\( P \)-value obtained from stratified one-sided log rank test
Hazard ratio is obtained from stratified unadjusted Cox model

SUMMARY: EVEROLIMUS IN PNET

• Everolimus therapy resulted in a significant 6.4 month increase in median PFS
  - 4.6 months v 11.0 months
  - No OS benefit

• Stability more common than significant shrinkage
  - 4.8% RR with RAD vs 2% with placebo

• Everolimus has an acceptable safety profile
  o Mouth sores, rash, hyperglycemia, hyperlipidemia, hypophosphatemia

• Approved by FDA for progressive PNET in May 11’
• Relationship between response and mutational status unknown
## EFFICACY IN SUNITINIB OR EVEROLIMUS IN PNET RANDOMIZED TRIALS

<table>
<thead>
<tr>
<th></th>
<th>Sunitinib (n=171)</th>
<th>Everolimus (n=410)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>11.4 mos</td>
<td>11.0 mos</td>
</tr>
<tr>
<td>(vs. 5.5 mos in placebo arm)</td>
<td></td>
<td>(vs 4.6 mos in placebo arm)</td>
</tr>
<tr>
<td>Overall Response Rate (RECIST)</td>
<td>9.3%</td>
<td>5%</td>
</tr>
<tr>
<td>Partial Response or Stable Disease</td>
<td>72%</td>
<td>78%</td>
</tr>
<tr>
<td>Survival Advantage Demonstrated?</td>
<td>No*</td>
<td>No*</td>
</tr>
</tbody>
</table>

Raymond, et al. NEJM, 2011  
Yao, et al. NEJM, 2011

*Pts receiving placebo in either study had opportunity to receive study drug following progression

## COMBINATION MTOR INHIBITOR + VEGF INHIBITOR

**PH II TEMSIROLIMUS + BEVACIZUMAB IN PROGRESSIVE PANNETS**

Advanced, progressive G1/G2 pancreatic NETs (n=55)  
Temsolimus 25mg IV days 1, 8, 15, 22  
Bevacizumab 10 mg/kg days 1, 15  
Repeat Q28 days

| Confirmed PR | 23 (41%) |
| 6-month PFS  | 79%      |
| Med PFS      | 13.2 mo  |
| 12-month PFS | 48%      |

Most common grade 3 to 4 adverse events: hypertension (21%), fatigue (16%), lymphopenia (14%), and hyperglycemia (14%).

Hobday. JCO 2014
CALGB 80701: RANDOMIZED PHASE II STUDY OF EVEROLIMUS ALONE OR IN COMBINATION WITH BEVACIZUMAB, IN PATIENTS WITH ADVANCED PANCREATIC NET (OPEN 10/2010, KULKE, PI)

138 pts

Opened: October 2010
Closed to accrual– results pending

Arm 1: Everolimus 10 mg po qd + octreotide LAR

Arm 2: Everolimus 10 mg po qd + Bevacizumab 10 mg/kg IV q 2 wks + octreotide LAR

Primary Endpoint:
INV –report PFS

SUMMARY: ADVANCED WELL-DIFF PANCREATIC NET

- Liver resection associated with prolonged survival but is not curative
- Asymptomatic patients with stable unresectable disease and low tumor burden can be observed and monitored
- SSTa have documented antitumor activity in well diff NET
- Sequential therapy with targeted agents (everolimus or sunitinib) in patients with symptoms, clinically significant tumor burden, and/or progressive PNET
  - Stabilization >>> shrinkage
  - Neither agent has been shown to improve overall survival
  - Optimal sequence unknown
  - No established role in carcinoid
- Chemotherapy often considered when tumor response required or when patients have failed targeted agents (PNET>>CARC)
Conclusions

- Major advances in understanding and treatment of NET in past 10 years
- Treatment needs to be individualized, weighing the risks of therapy vs potential benefit
  - Predictive markers are needed
  - PNET ≠ Carcinoid
  - Benefit of targeted agents relative to PRRT, SSTα, chemotherapy, and/or liver-directed therapy unknown
  - Optimal sequence unknown
  - Eventual resistance to therapy is the rule

NEXT STEPS

- Optimize sequence
- Explore mechanisms of resistance
- “personalized” medicine
  - DAXX/ATRX
  - MEN
  - mTOR
  - Other?
- Molecular imaging
- Novel therapies