# FACTORS INFLUENCING SEQUENCE OF THERAPY FOR WELL DIFFERENTIATED NETS

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# OUTLINE

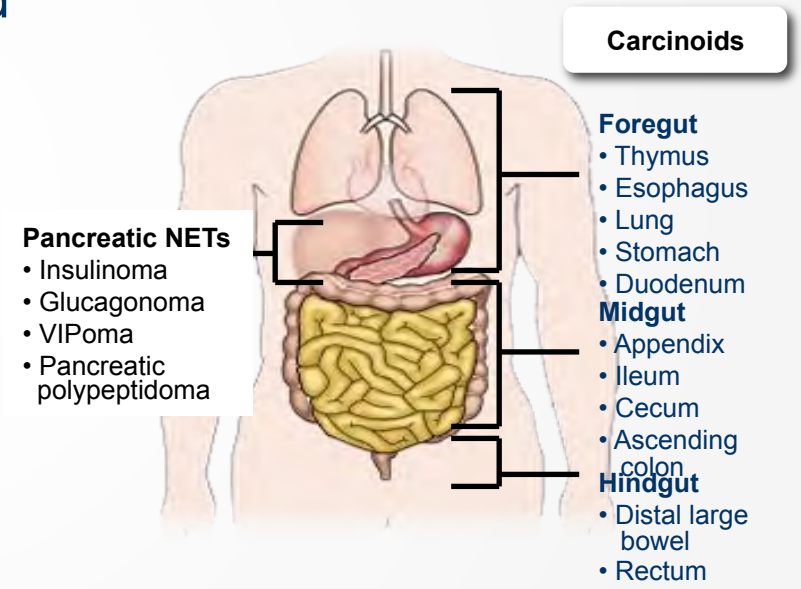
- Brief overview of neuroendocrine neoplasms
- Factors influencing choice of therapy
- Unanswered questions

# NEUROENDOCRINE TUMORS (NET): A DIVERSE GROUP OF MALIGNANCIES

NETs arise in various organs throughout the body

NETs can be functional or nonfunctional and include a heterogeneous group of neoplasms[1,2]

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




**References: 1.** Dorland's Medical Dictionary Web site. Available at: http://www.dorlands.com. Accessed November 10, 2008. 2. Modlin IM, Kidd M, Latich I,**2.** Zikusoka MN, Shapiro MD. Current status of gastrointestinal carcinoids. Gastroenterology. 2005;128:1717-1751.

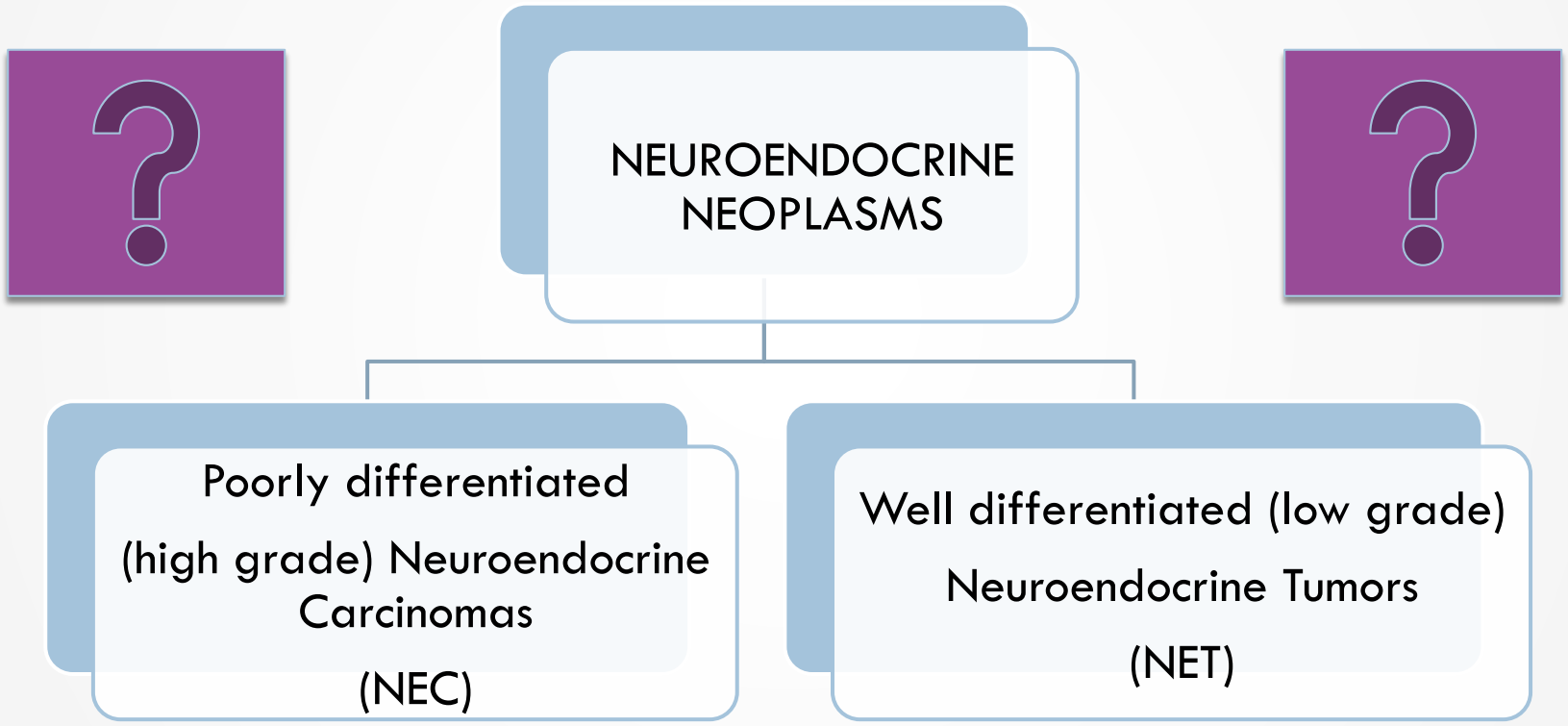
# NEUROENDOCRINE TUMORS (NET): A DIVERSE GROUP OF MALIGNANCIES

- Tumors express somatostatin receptors and neuroendocrine markers (CGA, NSE)

- Characterized by:
  - site of origin
  - ability to make peptides that cause symptoms
  - histological grade

# TUMOR-ASSOCIATED FACTORS THAT INFLUENCE CHOICE OF THERAPY

# WHAT IS THE TYPE (GRADE) OF TUMOR?



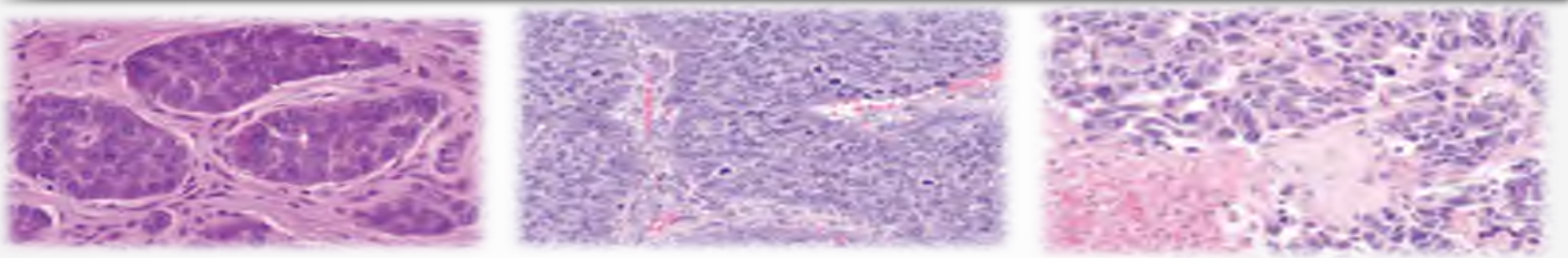
# SPECTRUM OF NEUROENDOCRINE TUMORS

**Well differentiated**

**Low Ki 67 (<20%)**

**Poorly differentiated**

**High Ki67 (20-100%)**



Mitotic Count and/or Ki67 proliferation index determine grade

**References: 1.** Strosberg JR, Nasir A, Hodul P, Kvols L. *GI Cancer Res*. 2008; 2:113-125. **2.** Klöppel G, Perren A, Heitz PU. *Ann Ny Acad Sci*. 2004; 1014:13-27.

# NET CLASSIFICATION: BASED ON REVIEW OF TUMOR BIOPSY

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

| Classification/Grade | Mitotic count (per 10 hpf) | Ki-67 Index (%) |
|---|---|---|
| NET-G1 | <2 | <3 |
| NET-G2 | 2-20 | 3-20 |
| NEC-G3 | >20 | >20 |

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

**Critically important to distinguish between:**

- **Well-differentiated = G1 and G2**
- **Poorly-differentiated= G3**

Kulke, et al. JCO, 2011; 29: 934-943
Moran et al. Am J Clin Pathol, 2009; 131: 206-221

# WHAT ELSE IS IMPORTANT ABOUT YOUR TUMOR?

- Where did the it start? (pancreas v other)
- Is it a “functional tumor” (making hormones that cause symptoms)
- How extensive is it?
  - Stage is determined by size, lymph nodes, metastases
  - Stage I-IV (IV=distant spread)

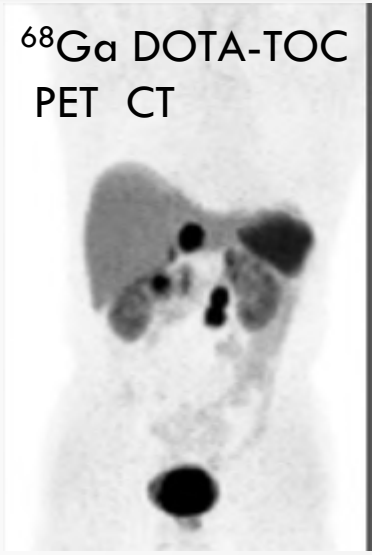
# WORK-UP: GASTROENTEROPANCREATIC (GEP)-NETS

- Multiphasic CT scan or MRI

- *As appropriate*:
  - Upper endoscopy (+/- ultrasound) /colonoscopy
  - Chromogranin (CGA)
  - +/- additional biochemical evaluation (blood/urine tests)
    - 24 hr urine 5HIAA
    - Gastrin, Insulin, Pancreatic polypeptide, etc.
  - somatostatin scintigraphy (G1/2)

# MOLECULAR IMAGING

- Novel radiopharmaceuticals for imaging well diff NET
  - Anatomical localization with PET/CT, CT or MRI
  - $^{111}$In-pentetreotide (SRS) (80% sensitivity)—but not
    - Insulinomas (50%), Small tumors, Poorly diff tumor
  - **Ga68-labeled SSA (up to 90% sensitivity)**
    - Ga68-DOTATATE, DOTATOC, DOTANOC
    - 68Ga-DOTA-JR11 under study
    - Higher SSTR affinity
  - Other conjugates under study




*Courtesy of T. Hope*

# MOLECULAR IMAGING: POTENTIAL ROLE

- Identification of unknown primary
- Staging
  - Rule out spread or assess extent of spread
- Assess changes over time
  - Bone metastases
  - Other sites
- “Functional” imaging for selection of patients who may benefit from receptor-based therapies (PRRT)

# GOALS OF THERAPY INFLUENCE CHOICE OF AGENT/MODALITY

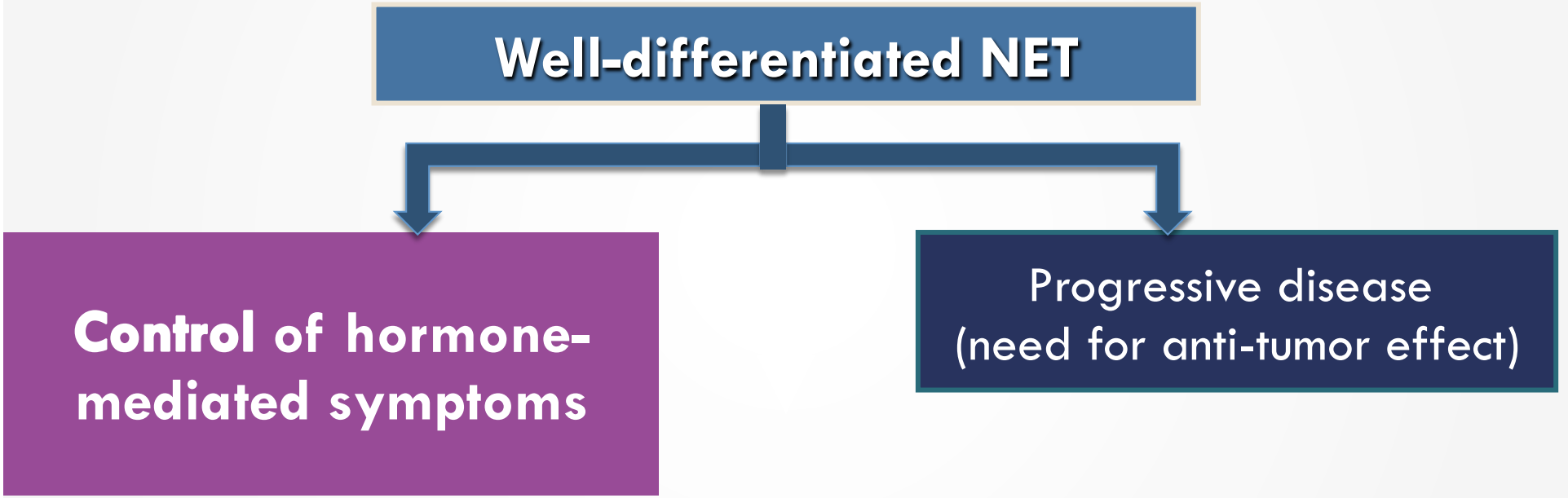
# QUESTIONS TO ASK

- Can all of the tumor be removed?
- Are there symptoms that need to be controlled?
- Is the tumor growing?

# LIVER-DOMINANT METASTATIC DISEASE (NO RANDOMIZED TRIALS)

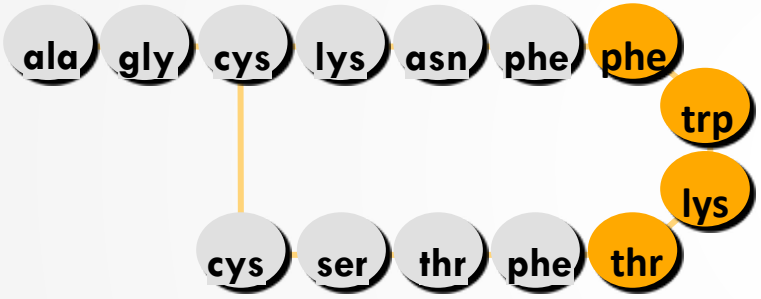
- Remove all known disease if possible (≥90%)
  - Controversial if Whipple required for pancreatic head mass
- Likely “resets” the clock (rather than cures)

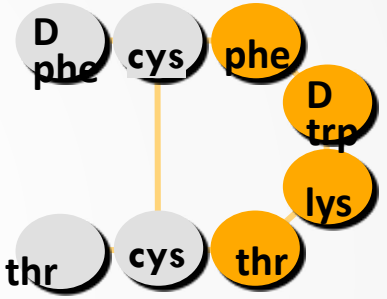
# ADVANCED DISEASE: INDICATIONS FOR THERAPY

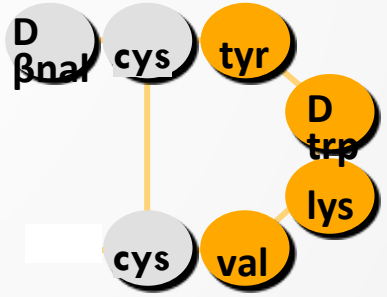



***Patient selection is key!***

# CONTROL OF HORMONAL SYNDROME: ANALOGUES OF SOMATOSTATIN




Amino acids essential for receptor binding

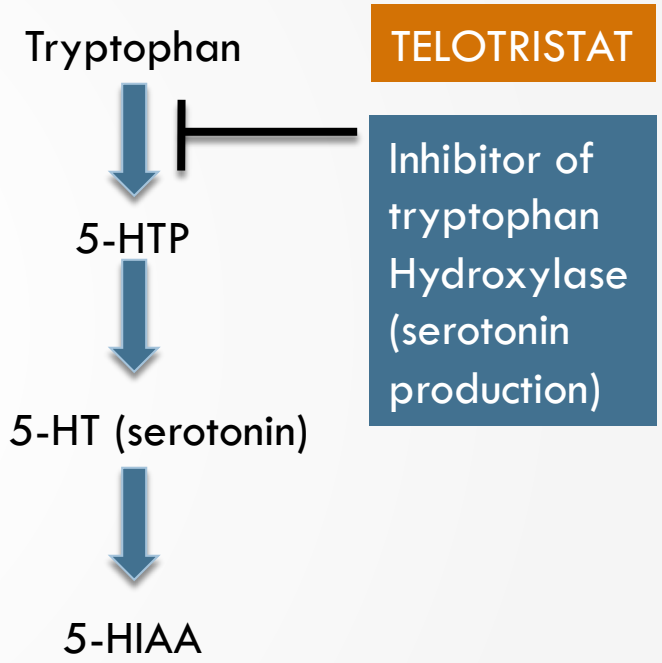
# SOMATOSTATIN ANALOGS (SSTA) AND NETS

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

1. Oberg et al. 2004. Ann Oncol; 15: 966—973; 2. Modlin et al. Alimentary Pharmacology & Therapeutics, 200

# TELOTRISTAT (ORAL AGENT) REDUCES DAILY BOWEL MOVEMENT FREQUENCY IN CARCINOID SYNDROME (TELOSTAR):

- Oral agent
- Randomized phase III trial
  - ↓bowel movements/day versus placebo (by about 1 BM/d) (*P*<0.001)
  - Reduction of urine 5HIAA

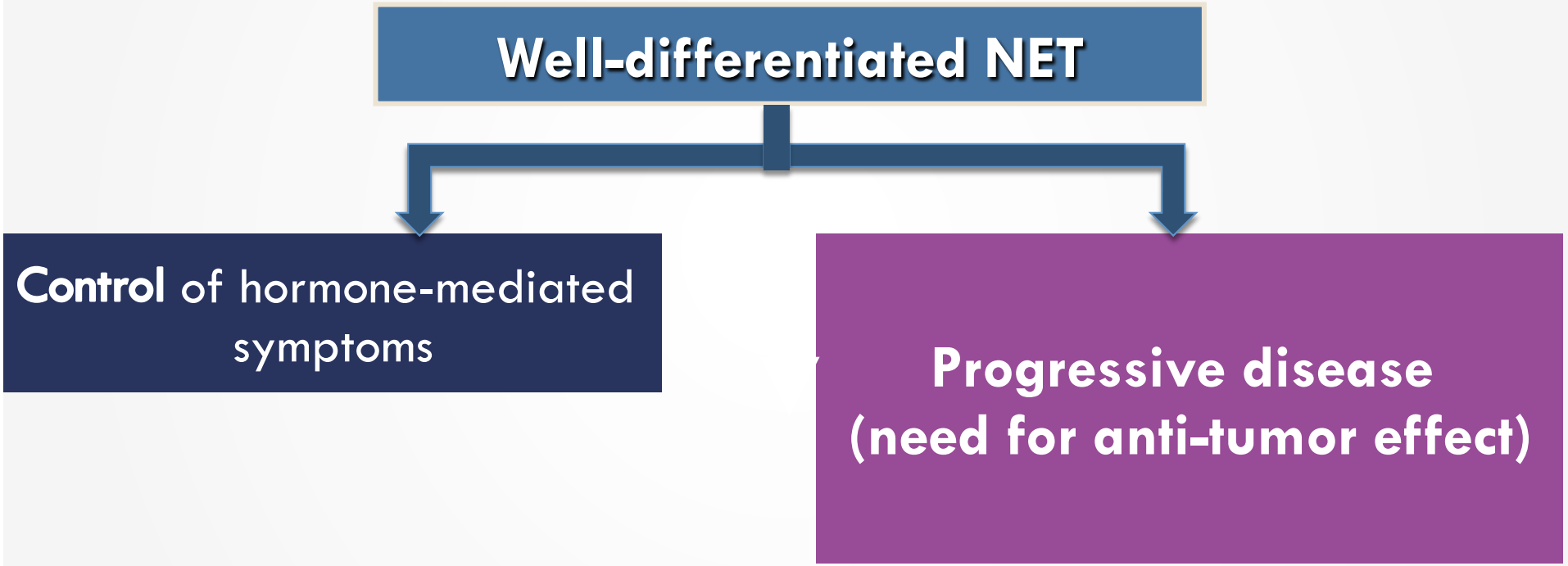



FDA review pending

**BM**, bowel movement; **SSA**, somatostatin analog

Kulke, et al. ESMO 2015

# ADVANCED DISEASE: INDICATIONS FOR THERAPY



# LIVER –DIRECTED THERAPY

- Resection (debulking)
- Ablation (surgical, percutaneous)

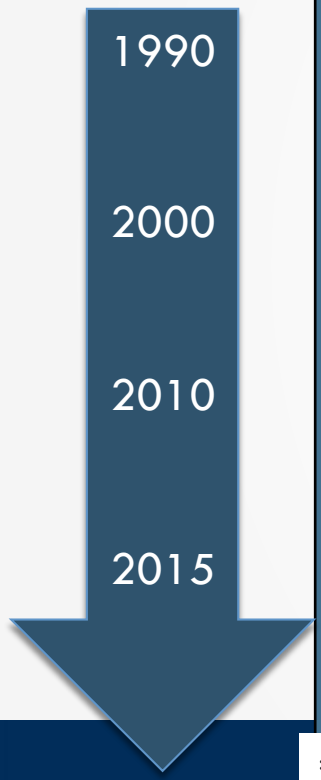
- Hepatic arterial embolization (HAE or TAE) or hepatic arterial chemoembolization (HACE or TACE) or selective internal radiation therapy (e.g. Y90-SIRT, Sir-spheres, theraspheres)

  - Symptomatic improvement >50%
  - Radiologic response in ≈50%
  - Careful in setting of prior Whipple for pancreatic tumor
  - *NO randomized controlled trials to guide selection of therapy*

# TREATMENT OPTIONS-SYSTEMIC (WHOLE BODY) THERAPY

- Somatostatin analogs SSA)
- Chemotherapy
- VEGF inhibitor (sunitinib)
- mTOR inhibitor (everolimus)
- PRRT (peptide receptor radionuclide therapy)
  - Radionuclide-labeled SSA

# SYSTEMIC THERAPY FOR WELL DIFF NET




| Chemotherapy | Biologics | SSA |
|---|---|---|
| Streptozocin (Moertel, 1992) (PNET) | | |
| TemCape Retrospective* (Strosberg, 2011) (Fine, 2013) (mostly used for PNET) | Everolimus (PNET) (Yao, 2011) Sunitinib (PNET) (Raymond, 2011) | Octreotide LAR* (midgut) (Rinke, 2009) |
| | Everolimus (GI/LUNG NET) (Yao, 2015) | Lanreotide (GEPNET) (Caplin, 2014) |
| | | Lu177 dotatate PRRT (midgut)* (Strosberg 2015) |

* not FDA-approved

# SOMATOSTATIN ANALOGS (SSA)

- **Octreotide** delays progression in well differentiated mid-gut carcinoids (80% with Ki67<2%)
  - Rinke et al, JCO 2009
  - Shrinkage is rare

- **Lanreotide** delays progression in well differentiated SSTR (+) GI and pancreas (GEP) NETs (Ki67<10%)
  - Caplin, et al. NEJM, 2014
  - Shrinkage is rare
  - FDA approved for this indication

# PRRT: NETTER-1 RANDOMIZED TRIAL IN MIDGUT NET ($^{177}$LU-DOTATATE V HIGH DOSE OCTREOTIDE)

- $^{177}$ Lu-DOTATATE delays progression compared to high dose octreotide in mid-gut NET refractory to standard dose somatostatin analog
  (median PFS: "Not reached" v 7 mo, p<0.0001, HR 0.21)

- Major shrinkage in 18% $^{177}$Lu-Dotatoc v 3 % control (p=0.0008)

- Most patients received all 4 doses
- Toxicity profile acceptable

FDA review pending

Midgut NET, Grade 1-2, progression on octreotide LAR 20-30 mg q 3-4 wk

Strosberg, et al. ECCO-ESMO 2015 Abstr#LBA6

# CHEMOTHERAPY

- Well-differentiated NET: No accepted standard treatment
  - Carcinoids: RR<20% (no standard chemo)
  - PNET: RR 35-70%
    - Capecitabine/temozolomide[1] often used
    - Results of E2211 pending (cape/tem v tem)

- Chemotherapy considered when tumor response required or when patients have failed targeted agents (PNET>>CARC)

1.Strosberg, et al. Cancer 2011

# TARGETED THERAPY

- **Sunitinib**: inhibits VEGF receptor signaling (and that of some other receptors)
  - Pill
  - Inhibits blood vessel growth
  - Delays tumor progression in panNETs (minimal shrinkage) by ≈6 mo
    - Fatigue, high blood pressure, GI side effects
    - Shrinkage rare
  - FDA approved for **PNET**
- Approved for patients with progressive disease

Raymond, et al. NEJM, 2011.

# TARGETED THERAPY

- **Everolimus**: inhibits mTOR signaling in tumors leading to slowing of tumor growth and delayed progression (minimal shrinkage) by ≈6-7 mo
  - Pill
  - FDA approved for PNET, GI and Lung NETS
    - Mouth sores, rash, diarrhea, high blood sugars, pneumonitis
    - Shrinkage rare
- Approved for patients with progressive disease

# TYPE OF EXPECTED BENEFIT DEPENDS ON THE THERAPY

| | Tumor progression | Major shrinkage rate |
|---|---|---|
| Octreotide/ lanreotide | Delays tumor progression | <5% |
| Everolimus | Delays tumor progression(6-7 mo) | <10% |
| Sunitinib (PNET) | Delays tumor progression (6 mo) | <10% |
| Cape/tem (PNET) | (no randomized data) | 35-70% |
| Liver directed (SIRT, TAE, TACE) | (no randomized data) | 50% |
| PRRT (mid-gut) | Delays tumor progression (2+ years?) | About 20% |

# ADDITIONAL FACTORS THAT INFLUENCE CHOICE OF THERAPY

# OTHER FACTORS THAT INFLUENCE DECISION-MAKING

| | |
|---|---|
| SSA (lanreotide, octreotide) | SSTR negative tumor (somatostatin scintigraphy)<br>Severely low heart rate?<br>Uncontrolled gall stone disease?<br>Prior intolerance to SSA |

# OTHER FACTORS THAT INFLUENCE DECISION-MAKING

| | |
|---|---|
| Everolimus | Bad diabetes<br>Interstitial lung disease<br>Nonhealing wound, planned surgery |
| Sunitinib | Uncontrolled high blood pressure, recent heart attack, history of stroke, recent bowel obstruction, uncontrolled thyroid disease; nonhealing wound/ planned surgery |

# OTHER FACTORS THAT INFLUENCE DECISION-MAKING

| | |
|---|---|
| Chemotherapy (cape/tem) | Minimal disease<br>Very slow growing disease (?)<br>Baseline low blood counts<br>Significant kidney or liver dysfunction<br>Very ill patient |

# OTHER FACTORS THAT INFLUENCE DECISION-MAKING

| | |
|---|---|
| Liver-directed therapy | Too much liver disease (>70%)<br>Too little liver disease (<15%)<br>CT contrast allergy<br>Lots of disease outside the liver<br>Prior Whipple procedure or biliary stent (due to risk of infection)<br>Baseline liver dysfunction, ascites<br>Prior liver–directed therapy? |

Also considered: Size and distribution of liver tumors

# OTHER FACTORS THAT INFLUENCE DECISION-MAKING

| | |
|---|---|
| PRRT | Significant kidney dysfunction<br>SSTR negative tumors<br>Low blood counts<br>Prior therapy? |

ALSO: Availability of PRRT?

# OPTIMAL SEQUENCE OF THERAPY IS UNCLEAR

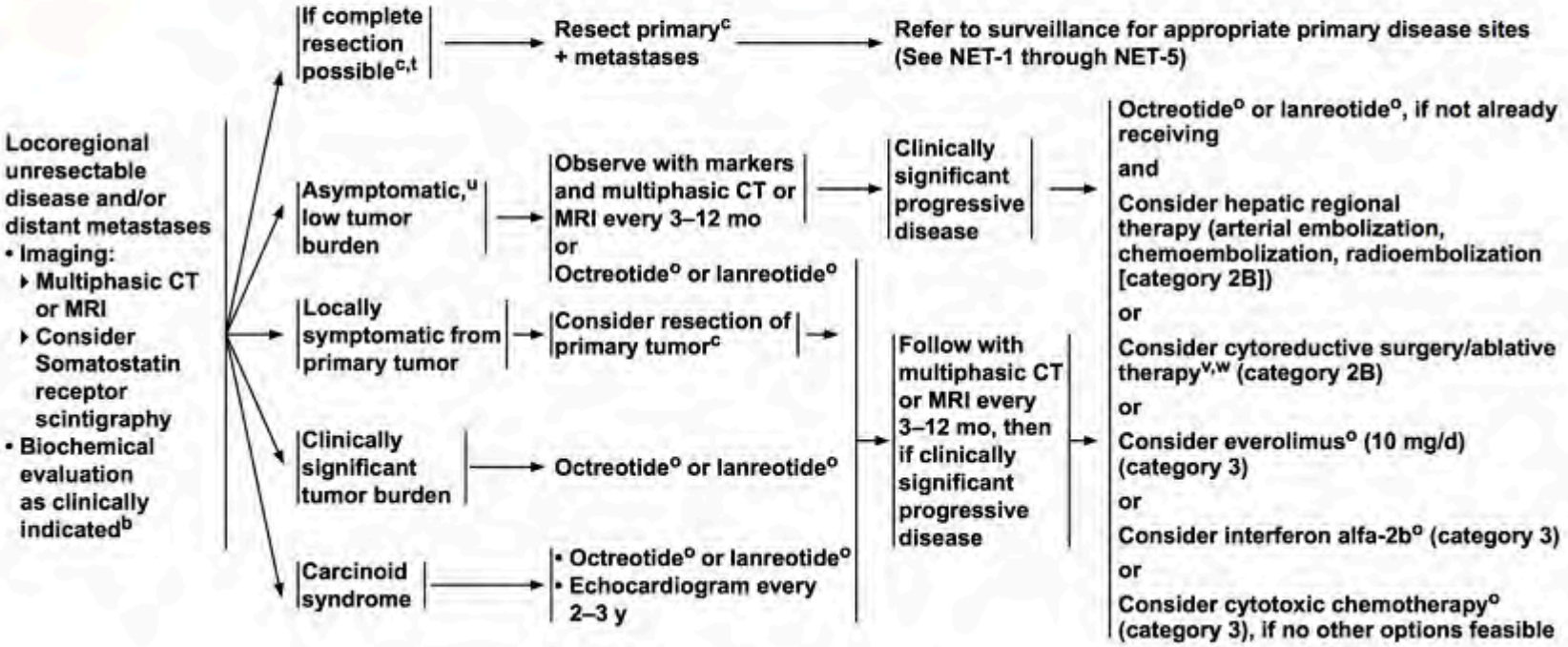
National Comprehensive Cancer Network®

# NCCN Guidelines Version 2.2016

## Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus (Carcinoid Tumors)

NCCN Guidelines Index
Neuroendocrine TOC
Discussion

### MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES[c]




Telotristat?

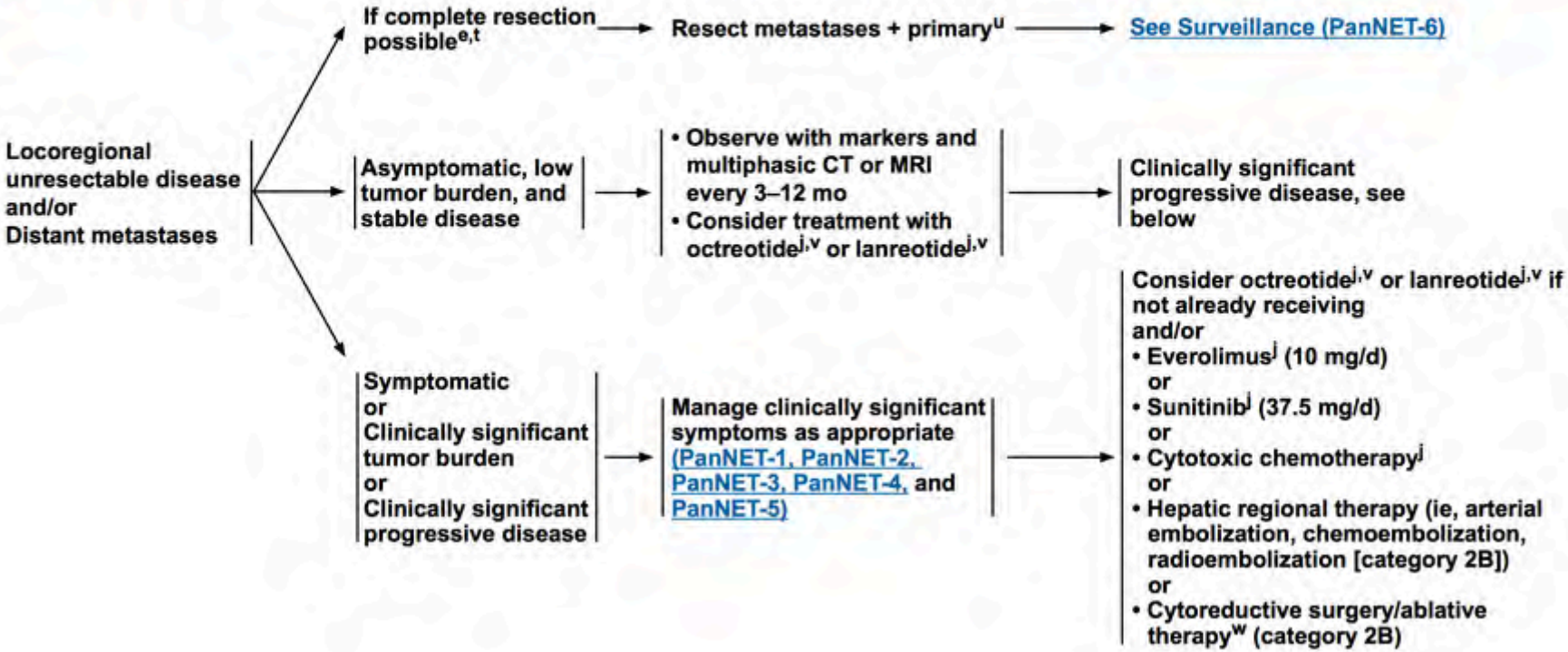
Lu177 Dotatate for midgut--PRRT?

National Comprehensive Cancer Network®

# NCCN Guidelines Version 2.2016
## Neuroendocrine Tumors of the Pancreas

NCCN Guidelines Index
Neuroendocrine TOC
Discussion

### MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES[e]



# MOVING FORWARD: UNANSWERED QUESTIONS

- If PRRT is approved by FDA…
  - What is the optimal sequence of therapy?
    - Liver-dominant disease v other
    - Considering efficacy, safety (long and short term), accessibility
  - What is the optimal number of treatments? Optimal radioconjugate? Optimal route of administration?
  - What is the role for PRRT in non-midgut NET? Poorly differentiated NEC?
- Can we use biomarkers to improve patient selection?
  - Blood? Imaging? Tumor biopsy?
- What is the best way to induce SHRINKAGE, not just STABILITY?
  - Optimal combinations of existing agents?
  - Role of novel agents?

# THE RESULTS OF CLINICAL TRIALS ADVANCE THE FIELD