Navigating Targeted Therapies and PRRT

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HARVARD MEDICAL SCHOOL

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Outline

- What are targeted therapies and peptide receptor radionuclide therapy (PRRT) and how do they work?
- What are the outcomes and side effects associated with targeted therapies and PRRT?
- When are targeted therapies and PRRT considered as a treatment option?

Overview of Treatment Options for Neuroendocrine Cancers

Systemic Therapy

- Drugs that enter the bloodstream to treat cancer cells throughout the body
- Typically used for disease that cannot be removed with surgery or has spread
- Can reduce disease burden, slow growth, improve symptoms related to disease

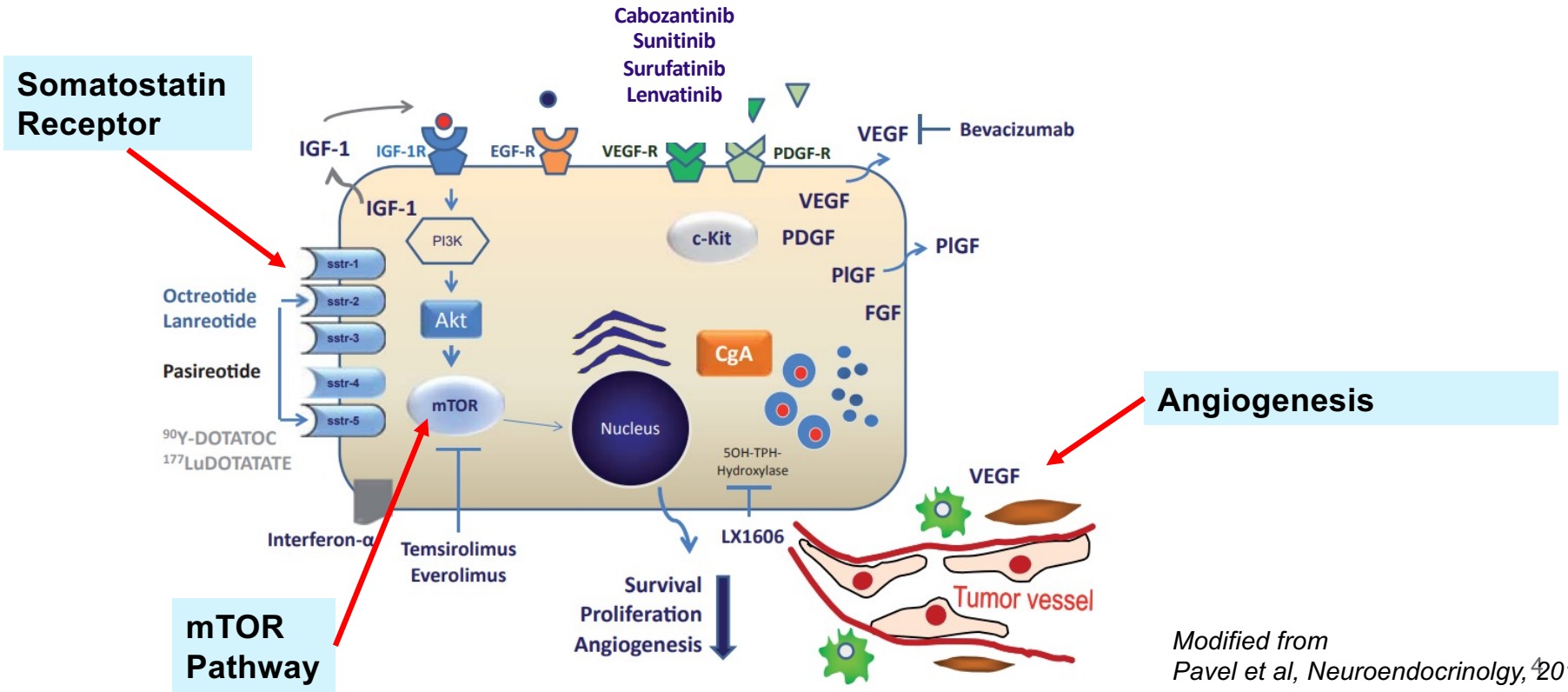
Well-differentiated NET

- Somatostatin analogs
- Peptide receptor radionuclide therapy
- Molecularly targeted therapy
- Chemotherapy

Poorly differentiated NEC

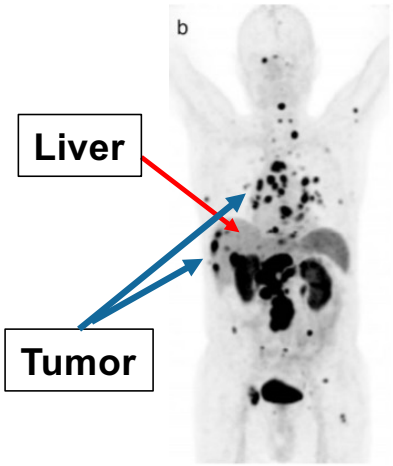
- Chemotherapy
- Consider immunotherapy

Targets For Treatment of NET



Modified from
Pavel et al, Neuroendocrinolgy, 2012

Somatostatin Receptors and NET



- Somatostatin receptors (SSTR) are present on the surface of >80% of well-differentiated GI and pancreatic NET cells, less frequent in lung NET (~40%)
- Lesions are considered SSTR positive if uptake on dotatate PET CT is higher than background liver

Deroose et al, *J Nucl Med*, 2016

PRRT for NET

PRRT enables delivery of tumoricidal doses of radioactivity to SSTR-positive NET by pairing a somatostatin receptor ligand with a radionuclide

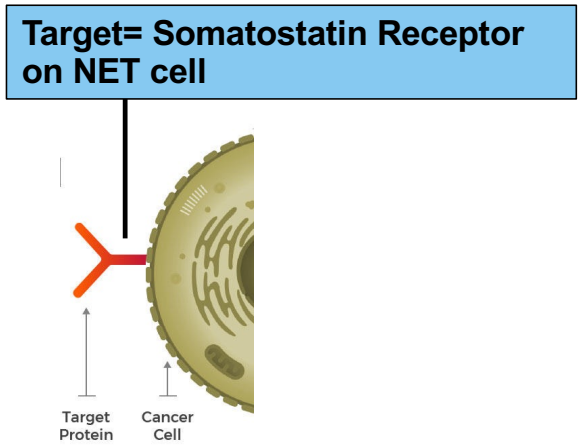


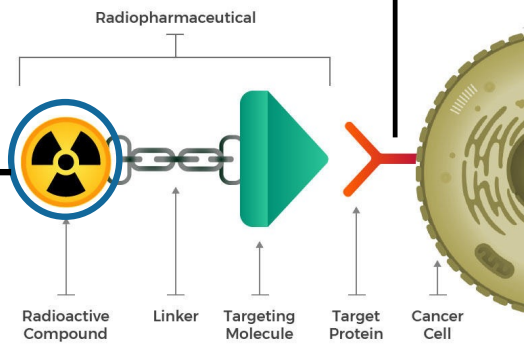
Image from NCI

PRRT for NET

PRRT enables delivery of tumoricidal doses of radioactivity to SSTR-positive NET by pairing a somatostatin receptor ligand with a radionuclide

Target= Somatostatin Receptor on NET cell

Chelator: Cage to bind radionuclide to ligand to ensure stability, delivery to target



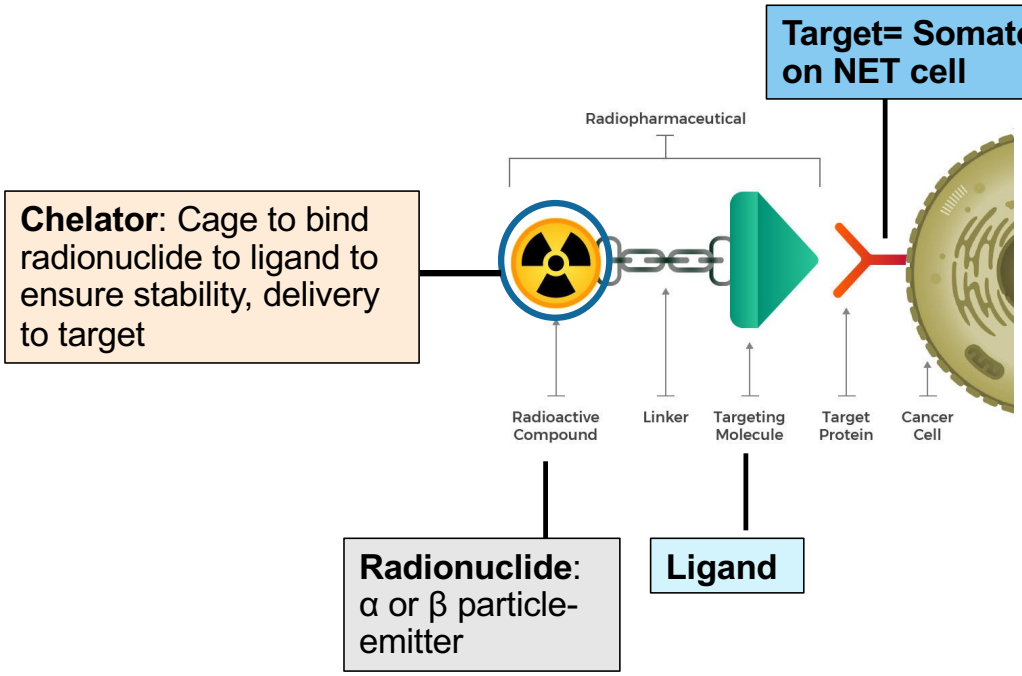
Radionuclide: α or β particle-emitter

Ligand

Image from NCI

PRRT for NET

PRRT enables delivery of tumoricidal doses of radioactivity to SSTR-positive NET by pairing a somatostatin agonist or antagonist with a radionuclide



^{177}Lu-DOTATATE

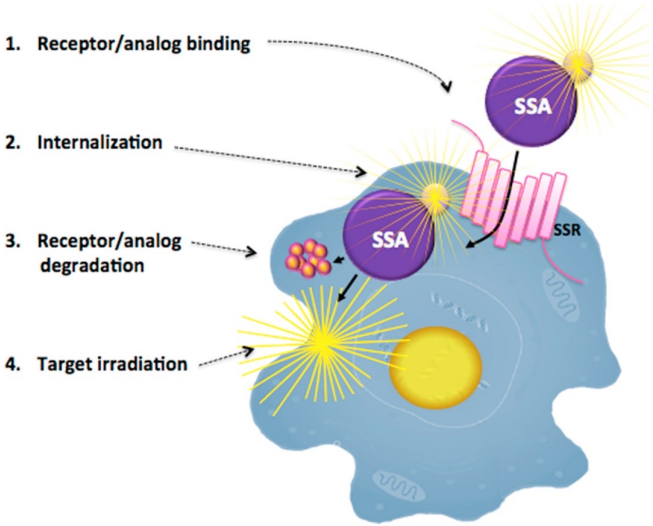
Radionuclide

Ligand= Somatostatin Agonist

Chelator

Image from NCI

PRRT for NET



- **^{177}Lu-dotatate** binds to somatostatin receptors (SSTR) on NET cells, is internalized and releases radiation to cause tumor cell death

- **^{177}Lu-dotatate** is approved for treatment of SSTR+ GI and pancreatic NET
  - Administered every 8 weeks x 4 cycles with or without monthly SSA
  - Amino acids are given to protect kidneys
  - Radiation safety precautions during and following treatment

- **Benefits of ^{177}Lu-dotatate**
  - Can slow disease progression
  - Can lead to tumor shrinkage – particularly if higher grade or if pancreatic NET
  - Can improve hormone-related symptoms

- **Side effects:** fatigue, nausea, vomiting, diarrhea, low risk of myelodysplasia or leukemia

When is PRRT recommended?

- **^{177}Lu-dotatate is often utilized for patients with GI or pancreatic NET after progression has occurred on a somatostatin analog**

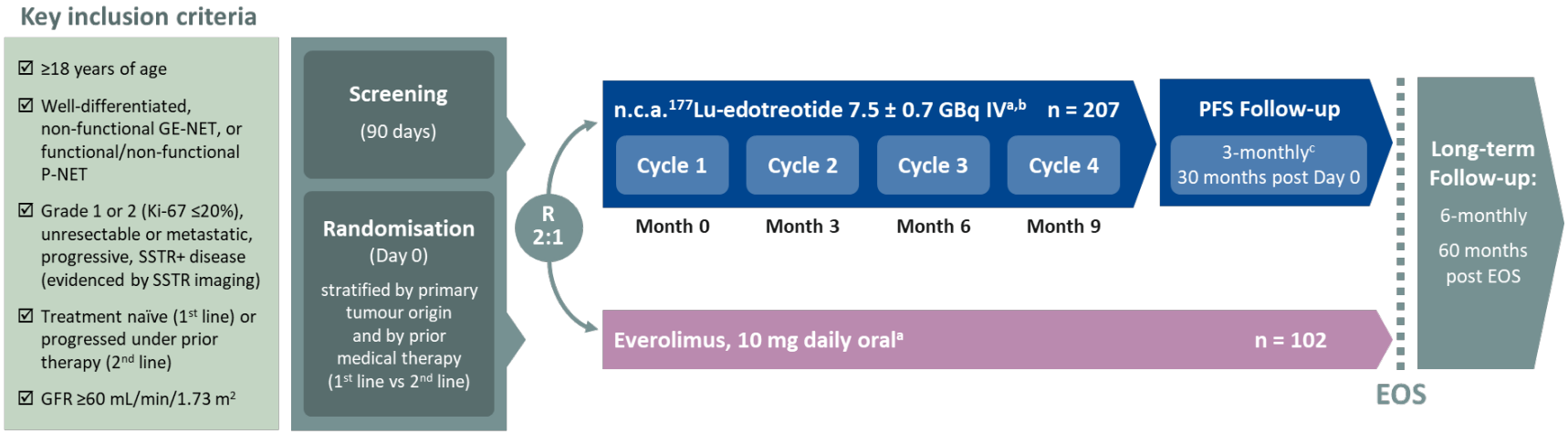
- **^{177}Lu-dotatate can be utilized in some cases of high-grade 2 or grade 3 (Ki-67 ≥ 10%) GI or pancreatic NET, particularly if there is a high burden of disease**

- **Retreatment with ^{177}Lu-dotatate can be considered in cases when there has been a durable benefit to the first course of PRRT** (>1 year of disease control)

- **Clinical trials are evaluating efficacy of repeat PRRT with ^{177}Lu-dotatate or ^{225}Ac-dotatate in patients with GI or pancreatic NET**

^{177}Lu-Edotreotide in G1-G2 GEP-NET

COMPETE Trial



Capdevila et al., ESMO 2025

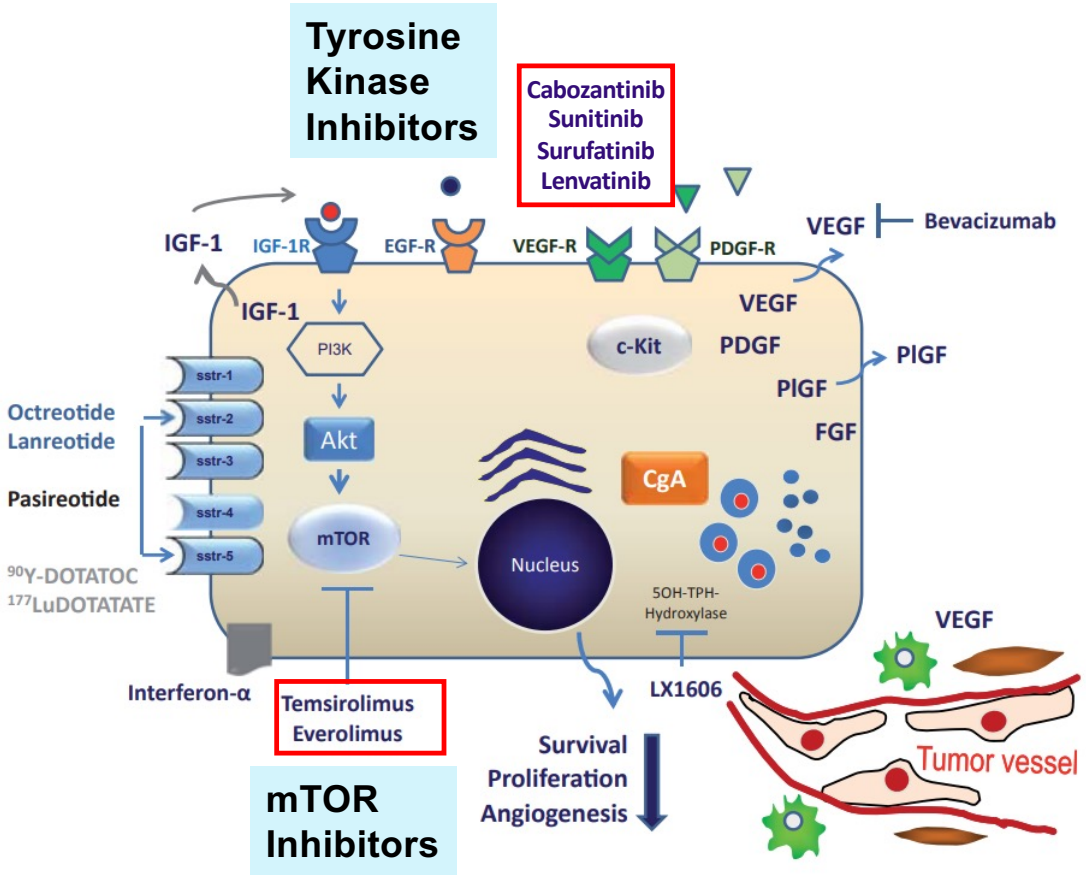
Primary endpoint: PFS[d] (per RECIST 1.1 by BICR)
Secondary endpoints: ORR, OS, DCR, DDC, HRQoL, safety, and tolerability

- **^{177}Lu-edotreotide improves Progression-Free Survival in patients with GI or pancreatic NET compared with everolimus**
- Currently under review at FDA….

Molecularly Targeted Therapy for NET

Dana-Farber Cancer Institute

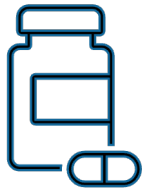
Molecularly Targeted Agents For Treatment of NET



- Molecularly targeted agents block signaling pathways in cells responsible for survival, growth, and formation of blood vessels

Modified from
Pavel et al, Neuroendocrinolgy, 2012

Everolimus



- **Everolimus is an mTOR inhibitor** that works by blocking the mTOR pathway that is responsible for regulating cell growth and metabolism
- **Benefits of everolimus:**
  - **Can slow disease progression** (growth and spread to new areas) in pancreatic NET and nonfunctional GI and lung NET
- **Administered as tablets taken daily by mouth**

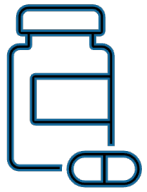
- **Side effects**: fatigue, mouth sores, rash, hyperglycemia, decreased appetite, diarrhea, lung inflammation, swelling, taste changes

Cabozantinib

- **Cabozantinib is a tyrosine kinase inhibitor** that works by blocking multiple receptors (VEGF receptor, MET, AXL, RET) that are responsible for blood vessel formation, tumor growth and spread
- **Benefits of cabozantinib**
  - Can slow disease progression of pancreatic NET and extra-pancreatic NET (GI, lung, unknown primary sites, thymus, and other rare primary sites)
  - Can lead to tumor shrinkage in some cases (pancreatic NET)
- **Administered as tablets taken daily by mouth**

- **Side effects:** fatigue, diarrhea, high blood pressure, discomfort and redness in the palms and soles, mouth sores, decreased appetite, weight loss, taste changes

Sunitinib



- **Sunitinib is a tyrosine kinase inhibitor** that works by blocking multiple receptors (VEGF receptor, PDGFR, c-KIT, RET) that are responsible for blood vessel formation, tumor growth and spread
- **Benefits of sunitinib**
  - Can slow disease progression of pancreatic NET
- **Administered as tablets taken daily by mouth**

- **Side effects:** fatigue, diarrhea, high blood pressure, discomfort and redness in the palms and soles, mouth sores, loss of appetite, weight loss, taste changes

Belzutifan

- **Belzutifan is a HIF-2α inhibitor** that works by preventing HIF-2α from activating genes that control growth and recruitment of new tumor blood vessels

- **Benefits of belzutifan**
  - Can shrink and slow disease progression of pancreatic NET associated with germline *VHL* mutations; pheochromocytoma/paraganglioma
- **Administered as tablets taken daily by mouth**

- **Side effects:** anemia, hypoxia, fatigue, dyspnea, headache, dizziness, visual changes, musculoskeletal pain

When are molecularly targeted agents recommended?

- **Everolimus or TKIs are typically utilized after progression on other therapies including somatostatin analogs or PRRT**
- **Choice of agents depends on factors including other medical conditions, treatment side effect profile, primary tumor site**
- **Doses may need to be adjusted due to side effects**
- **Treatment with molecularly targeted agents continues until disease progression or discontinuation for other reasons**

Important Considerations in Management of Neuroendocrine Cancers

Tumor-related Factors

- **Primary tumor location**
- **Pathology**
  Differentiation
  Grade
- **Stage** (extent of disease)
- **Locations of spread**
- **Somatostatin receptor (SSTR) expression**
- **Functional status**: presence or absence of symptoms related to hormones secreted by the cancer

Important Considerations in Management of Neuroendocrine Cancers

Patient-related Factors

- **Age**
- **Medical history and other medical conditions**
- **Performance status**
- **Symptoms** related to disease burden or hormones secreted by neuroendocrine tumors
- **Preferences** regarding therapy

Important Considerations in Management of Neuroendocrine Cancers

Treatment-related Factors

- **Side effects**
- **Administration** – oral, intravenous, intramuscular, subcutaneous
- **Schedule / frequency of treatment**
- **Availability of therapy**
- **Cost considerations**

Options for Tumor Control in Advanced NET

	Somatostatin Analogs	Targeted therapy	Peptide Receptor Radionuclide Therapy	Cytotoxic chemotherapy
Agents	**Octreotide Lanreotide**	**Everolimus TKIs: Cabozantinib, Sunitinib**	**Lu-177 dotatate**	**Alkylating agents (temozolomide- and streptozocin- based regimens)**
Primary tumor location	GI and pancreatic NET (SSTR+) Consider for lung NET (SSTR+)	Pancreatic NET (everolimus, cabozantinib, sunitinib) Extra-pancreatic NET (everolimus, cabozantinib)	GI and pancreatic NET (SSTR+) Consider for lung NET (SSTR+)	Pancreatic NET Lung NET
Treatment outcome	Improves hormone syndrome Slows progression	• Slows progression • Some shrinkage with cabozantinib in pancreatic NET	• Slows progression • Shrinkage, esp. if pancreatic NET and higher grade	• Slows progression • Shrinkage, esp. if pancreatic NET and higher grade
Side effects	Hyperglycemia, cholelithiasis, diarrhea, bloating, pancreatic exocrine insufficiency	Everolimus: hyperglycemia, stomatitis, edema, pneumonitis TKIs: fatigue, diarrhea, hypertension, mouth sores, redness and pain in palms/soles	Fatigue, diarrhea, nausea, thrombocytopenia, risk of MDS, leukemia	Nausea, fatigue, vomiting, constipation, diarrhea, neutropenia, thrombocytopenia

Navigating Targeted Therapies and PRRT for NET

Somatostatin Analogs	Targeted therapy	Peptide Receptor Radionuclide Therapy	Cytotoxic chemotherapy

- PRRT with ^{177}Lu-dotatate is often utilized for advanced GI or pancreatic NETs following progression on SSA; can be utilized as initial therapy for high G2 or G3 disease particularly when there is high burden of disease

- Molecularly targeted therapies for progressing NETs include
  - Everolimus
  - TKIs: cabozantinib or sunitinib
  - Belzutifan (VHL disease)

- Treatment selection must be individualized and made with multidisciplinary input

Thank you!