Penn Medicine

Current Therapies for Advanced Pancreatic Neuroendocrine Malignancy

South Florida GI Cancer Symposium

Jennifer Eads, MD
Professor of Medicine
Physician Lead GI Clinical Research
Director, Penn Neuroendocrine Tumor Program
Director, Penn National Clinical Trials Network

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Objectives

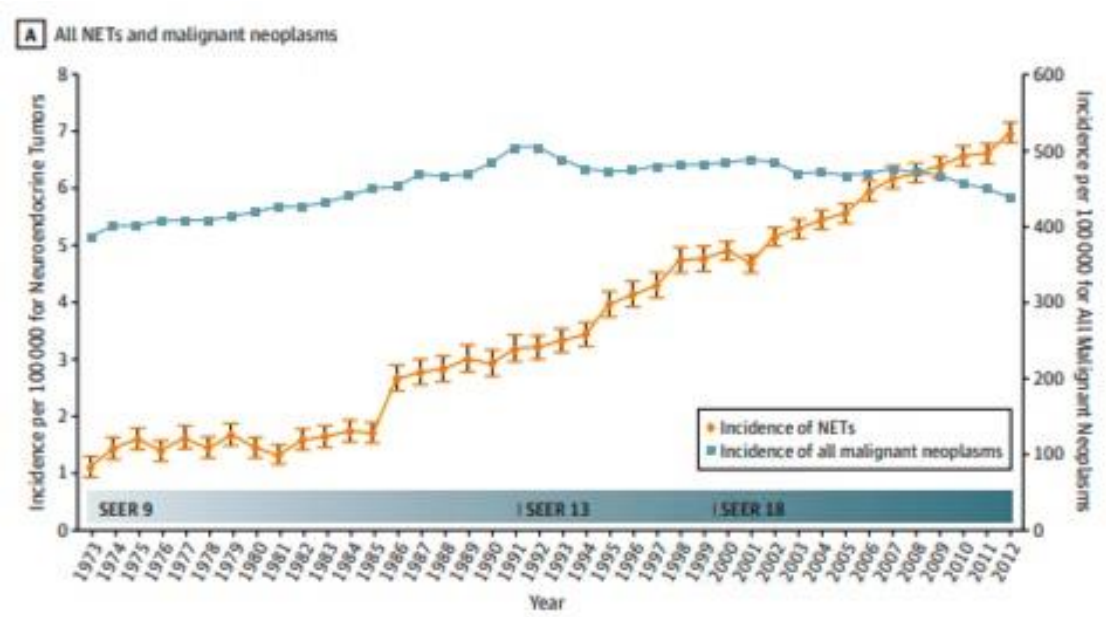
- Review the pathology, epidemiology and clinical presentation of patients with a well differentiated pancreatic neuroendocrine tumor
- Discuss the standard treatment approaches used for patients with well differentiated pancreatic neuroendocrine tumors as well as evolving treatment strategies
- Discuss treatment approaches for patients with neuroendocrine carcinomas of the pancreas

Overview of Neuroendocrine Tumors

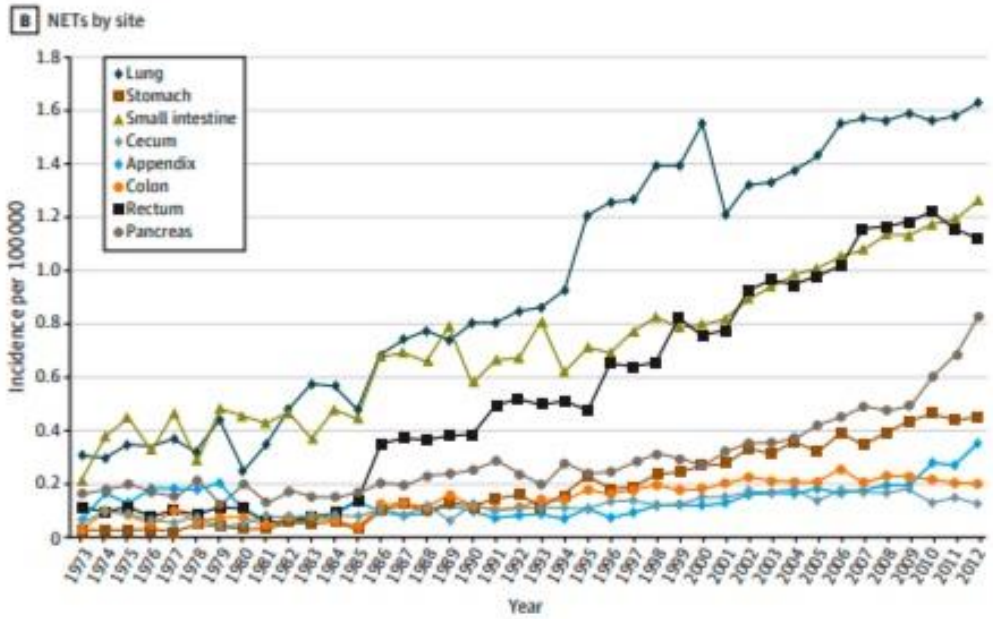
- Rare disease entity that may arise from neuroendocrine cells anywhere in the body
- Primarily gastrointestinal in origin
  - Pancreatic
  - Bowel (foregut, midgut and hindgut)
- Well-differentiated tumors have a relatively indolent disease course
- Poorly-differentiated tumors are aggressive with a poor prognosis
- There is a spectrum of disease

Well-differentiated NENs (GI/PNET)	**Ki-67**	**Mitotic Index**
Neuroendocrine tumor (NET) G1	< 3%	< 2/10 HPF
Neuroendocrine tumor (NET) G2	3-20%	2-20/10 HPF
Neuroendocrine tumor (NET) G3	> 20%	> 20/10 HPF
Poorly-differentiated NENs (GI/PNET)		
Poorly differentiated (NEC) G3	> 20%	
Small cell		
Large cell		
Lung NETs		
Typical Carcinoid of the Lung		< 2/10 HPF, no necrosis
Atypical Carcinoid of the Lung		2-10/10 HPF or necrosis

Incidence of NETs over a 40-year period



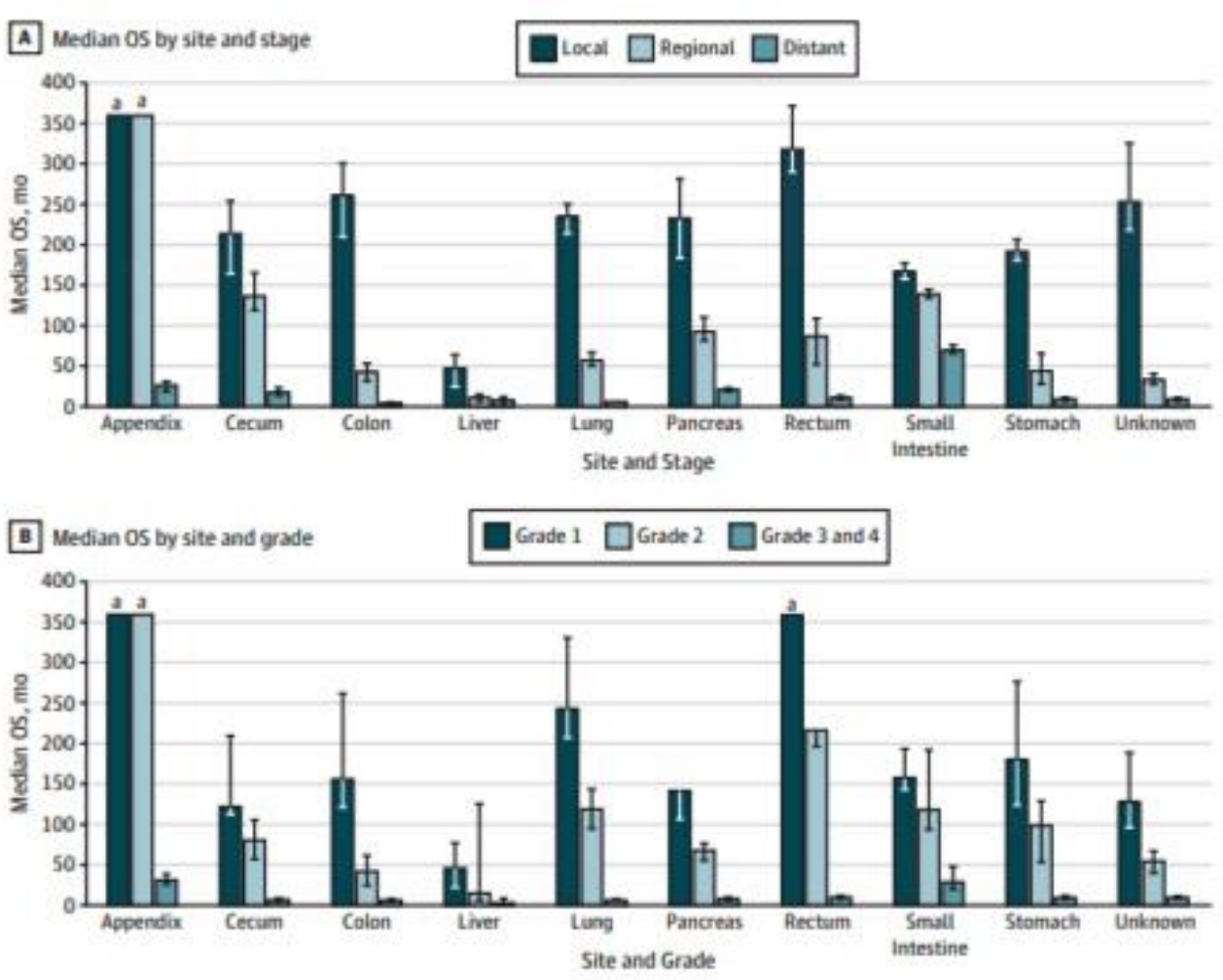
Disproportionate rise in neuroendocrine tumors over a 40-year period



Greatest rise in small bowel, rectal, lung and pancreatic primaries

Dasari A, et al. JAMA Oncol 2017

Survival Trends by Stage and Grade



Dasari A, et al, JAMA Oncol 2017

Pancreatic Neuroendocrine Tumors

Clinical Presentation of Pancreatic Neuroendocrine Tumors

- May be functional (hormone producing) or non-functional at the time of presentation
- Hormone produced may be useful as a tumor marker

Table 1. Subtypes of pancreatic neuroendocrine tumors with associated hormones and symptoms

Tumor type	Hormone produced	Clinical features
Gastrinoma	Gastrin	Recurrent peptic ulcers, diarrhea, steatorrhea
Insulinoma	Insulin	Hypoglycemia, catecholamine excess
Glucagonoma	Glucagon	Diabetes mellitus, migratory necrolytic erythema, weight loss, thromboembolism, panhypoaminoaciduria
VIPoma	VIP	Watery diarrhea, hypokalemia, achlorhydria, metabolic acidosis, hyperglycemia, flushing, hypercalcemia
Somatostatinoma	Somatostatin	Diabetes mellitus, diarrhea, steatorrhea, hypochlorhydria, weight loss, gallbladder disease
Pancreatic polypeptidoma	Pancreatic polypeptide	Hepatomegaly, abdominal pain, watery diarrhea

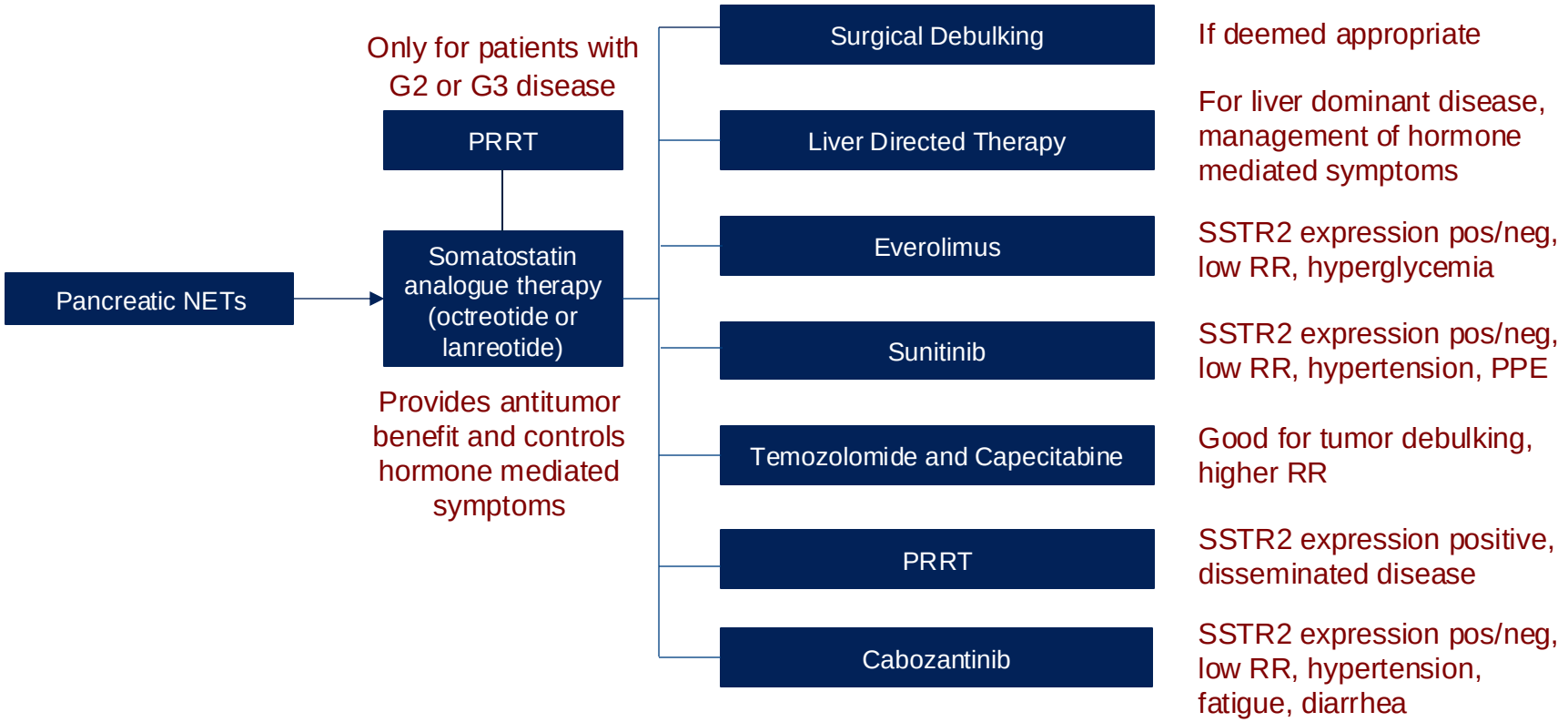
Abbreviation: VIP, vasoactive intestinal peptide.

Eads JR, Meropol NJ, The Oncologist, 2012

Genetics of Pancreatic Neuroendocrine Tumors

- Many pancreatic neuroendocrine tumors carry mutations:
  - DAXX or ATRX in 43%
  - MEN1 in 44%
  - mTOR pathway genes in 15%
- Key pathways involved include:
  - DNA damage repair
  - Chromatin remodeling
  - Telomere maintenance
  - mTOR signaling activation
- Associated genetic syndromes:
  - Multiple endocrine neoplasia-1 (MEN-1): hyperparathyroidism, pituitary adenomas, PNET
  - Von Hippel Lindau (VHL): renal cell carcinoma, CNS hemangioblastomas, PNET
    - Belzutifan is a HIF-2α inhibitor that can be used for patients with these tumors who are not yet appropriate for surgery

Approach to Neuroendocrine Tumors of the Pancreas



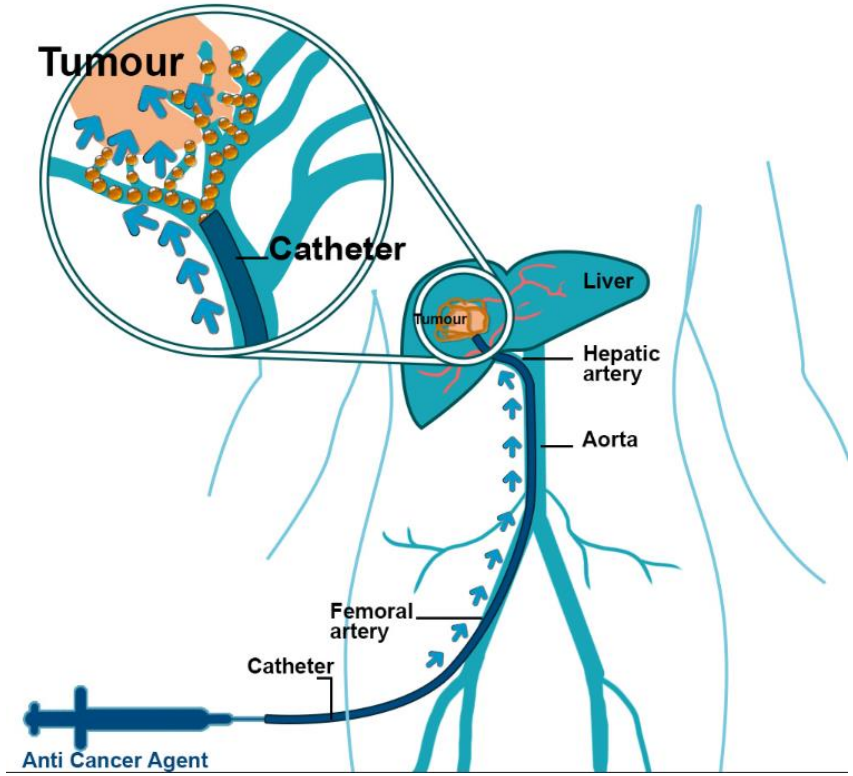
When is there a role for surgery or local management?

- Localized disease—surgery can be curative!
- Endoscopic resection
  - Standard for management of type I/II gastric carcinoids
  - May be appropriate for rectal neuroendocrine tumors
- Small bowel primaries are prone to obstruction
  - Required at the time of urgent/emergent presentation
  - Prevent future obstruction
  - Can minimize the desmoplastic reaction that can cause peritoneal fibrosis
- Tumor debulking utilized in the metastatic setting
  - Decrease tumor burden to “reset the clock”
  - Debulk to alleviate hormone mediated symptoms, pain
  - Debulk to prevent future complications

Liver Directed Therapy

- NCCN, NANETS and ENETS all recommend embolization therapy for progressive or symptomatic liver dominant disease

- General Approaches
  - Chemoembolization
  - Radioembolization
  - Bland Embolization
  - Drug-eluting beads should not be used



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RETNET Trial

- Randomized Embolization Trial for NeuroEndocrine Tumor Metastases to the Liver
  - clinicaltrials.gov identifier NCT02724540

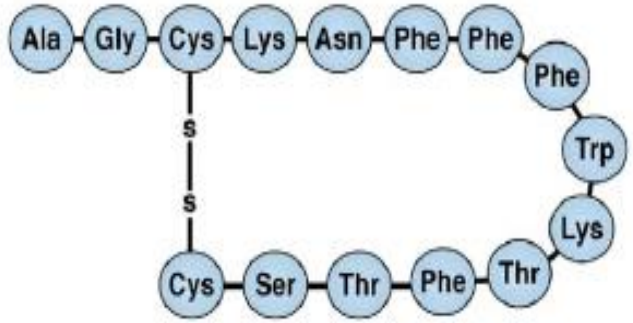
- Study Design and Aims
  - 180 patients randomized to bland, TACE or DEB-TACE
  - Is one more or less effective?
  - Is one more or less toxic?
  - Does one provide better or worse quality of life?

- First Safety Analysis
  - 4/10 patients in the DEB-TACE arm experienced major complications
    - DEB arm was closed due to toxicity

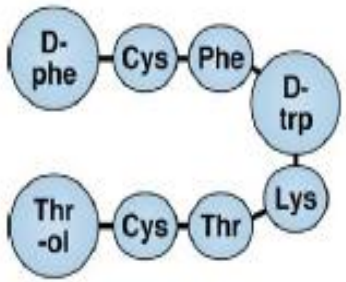
- NCCN guidelines changed as a result!! Accrual is nearly complete with results pending.

Somatostatin Receptor

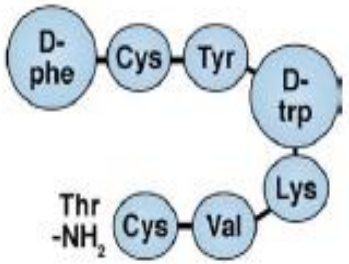
- Expressed in 80-100% of PNETs and carcinoids
- Five types of SSTRs
  - Higher and more diverse levels of expression in well differentiated tumor
- High levels of SSTR expression usually results in a positive octreotide scan or DOTATATE PET scan
- Serve both diagnostic and therapeutic purposes



Somatostatin



Octreotide acetate

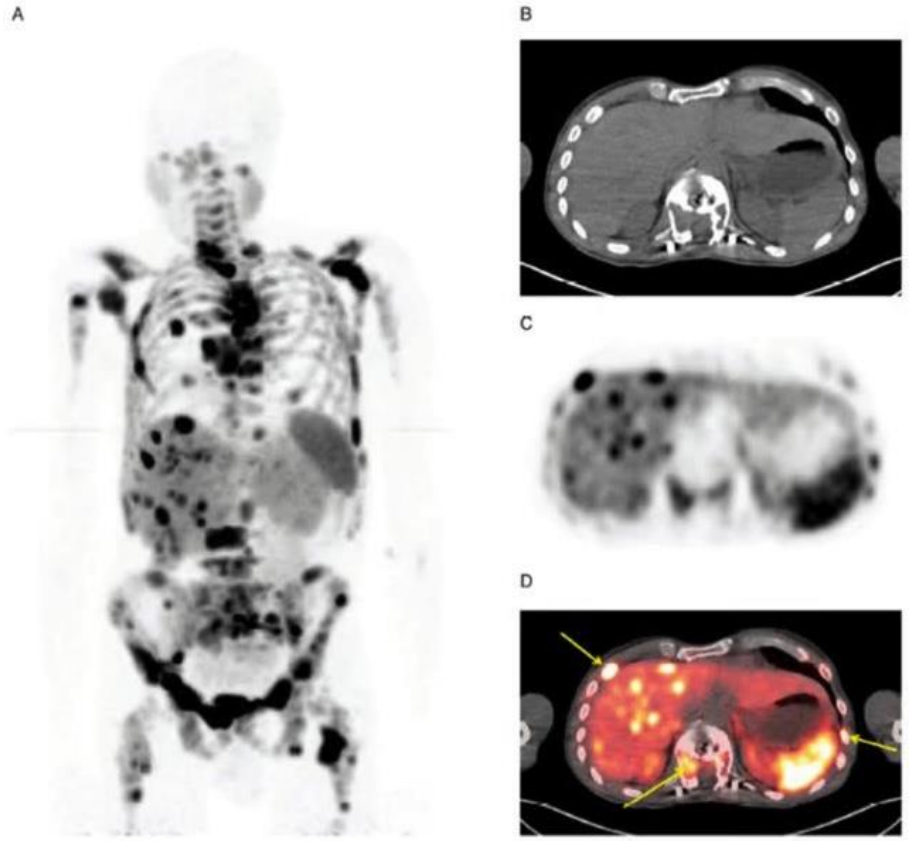


Lanreotide

Oberg KE et al, Gastroenterology 2010

DOTATATE PET Imaging

- Gold standard functional imaging test for NETs
  - Identification of unknown primary tumors
  - More refined detail regarding disease
  - Aid in distinguishing between more and less aggressive tumors
  - Aid in diagnosing a neuroendocrine tumor (elevated chromogranin)
  - Evaluate for PRRT candidacy



Somatostatin Analogue Therapy

- Initially utilized to aid in the treatment of carcinoid syndrome related symptoms
- More recently studies show anti-tumor efficacy

Study	Agent	Outcome
PROMID metastatic midgut G1/G2 carcinoid	Octreotide LAR 30 mg every 28 days	Time to Progression: 14.3 months (HR 0.42)
CLARINET metastatic midgut, hindgut, pancreatic and unknown primary G1/G2 NET	Lanreotide 120 mg SC every 28 days	Progression Free Survival: 38.5 months (HR 0.47)

Targeted Therapy

- Demonstrate variable activity in patients with pancreatic NETs vs bowel NETs

Study	Target	Agent	Outcome
RADIANT-3 met G1/G2 PNET	mTOR	Everolimus 10 mg orally once daily	Progression Free Survival: 11.0 months (HR 0.35)
RADIANT-4 met G1/G2 bowel NET	mTOR	Everolimus 10 mg orally once daily	Progression Free Survival: 11.0 months (HR 0.48)
Raymond et al. met G1/G2 PNET	PDGFR-α, PDGFR-β, c-kit, VEGFR-2, VEGFR-3	Sunitinib 37.5 mg orally once daily	Progression Free Survival: 11.5 months (HR 0.42)
CABINET met G1/G2 PNET met G1/G2 EP NET	VEGFR, c-MET, AXL, RET	Cabozantinib 60 mg orally once daily	Progression Free Survival 11.4 months (HR 0.27) 8.3 months (HR 0.45)

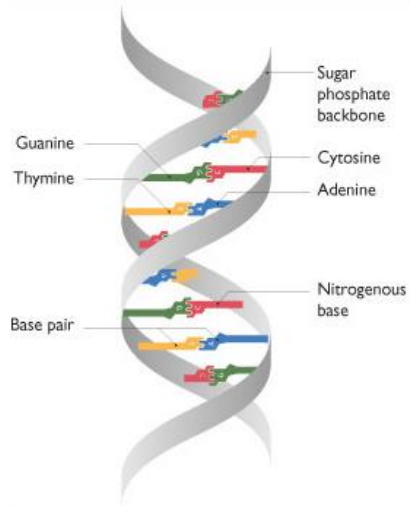
- Generally associated with response rates less than 10%

Yao JC et al, NEJM 2011; Yao JC et al, Lancet 2016; Raymond E et al, NEJM 2011; Chan JA NEJM 2024

Chemotherapy—Temozolomide in Neuroendocrine Tumors

- Mechanism of Action: DNA damaging agent (alkylating agent)
- Preclinical studies had demonstrated benefit of temozolomide based therapy in these tumors

	Pancreatic NET	Carcinoid
Temozolomide/ Thalidomide (n=26)	45%	7%
Temozolomide/ Bevacizumab (n=34)	24%	0%
Temozolomide/ Capecitabine (n=30) (retrospective)	70% PFS 18 months	



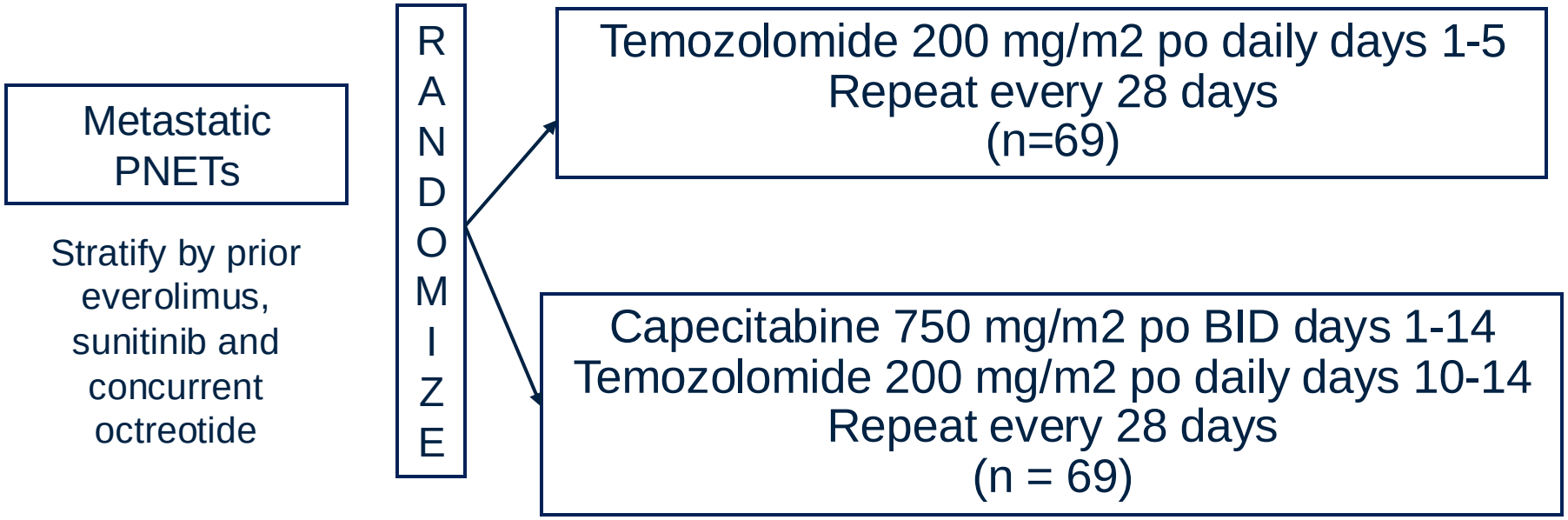
Temozolomide

O^6-methylguanine (O^6-mG)
Direct DNA repair with MGMT

N^7-methylguanine (N^7-mG) and
N^3-methyladenine (N^3-mA)
Base Excision Repair

Kulke M et al, J Clin Oncol 2006; Kulke M et al, J Clin Oncol 2006; Strosberg J et al, Cancer 2011

E2211—Temozolomide vs Temozolomide/Capecitabine in PNET



Progression Free Survival: 22.7 months vs 14.4 months (HR 0.58, p=0.023)

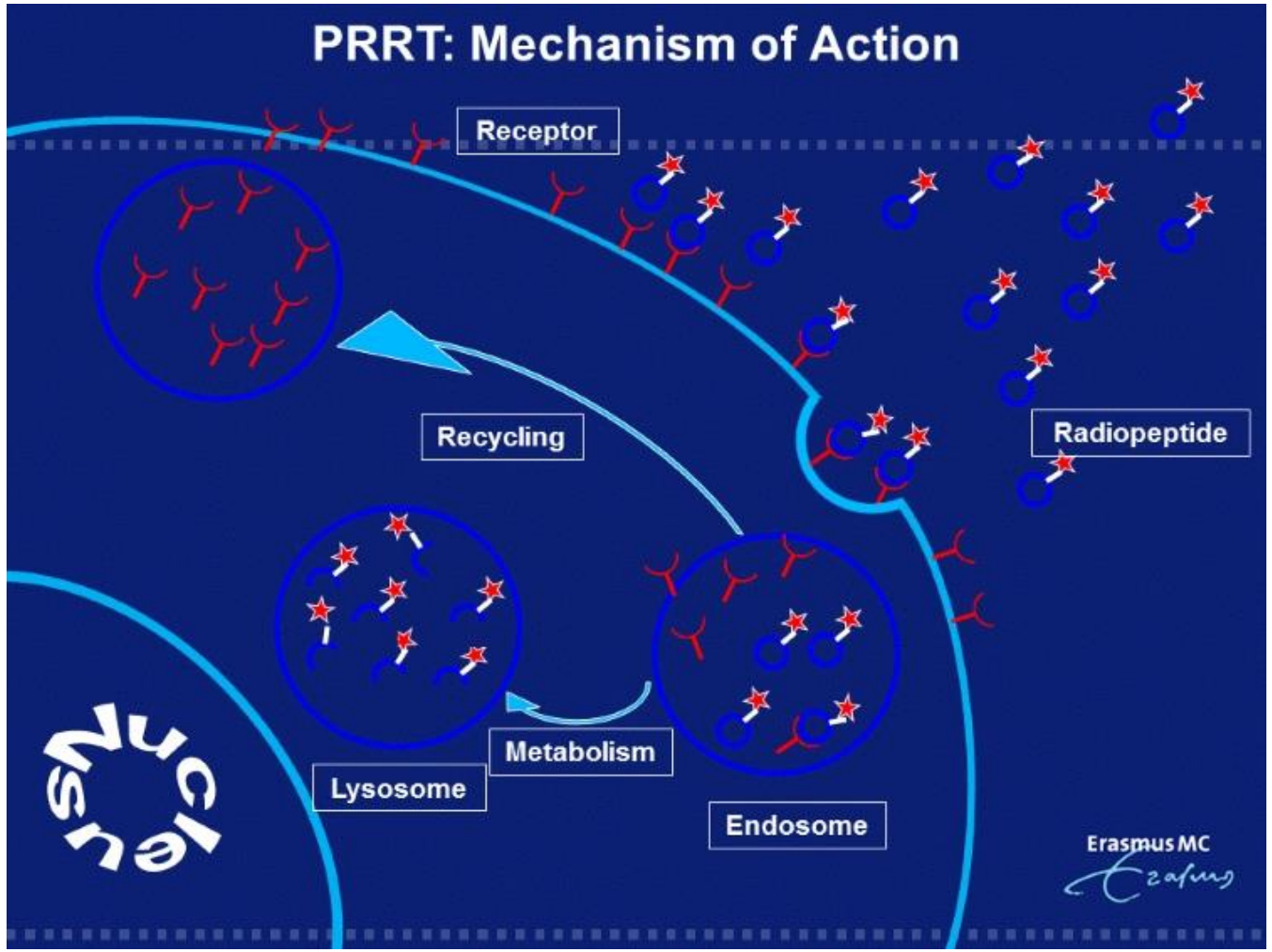
Overall Survival: not reached vs 38.0 months (HR 0.41, p=0.012)

Response Rate: 33.3% vs 27.8%; Disease Control Rate: 81.9% vs 68.1%

Kunz PL et al, J Clin Oncol 2023

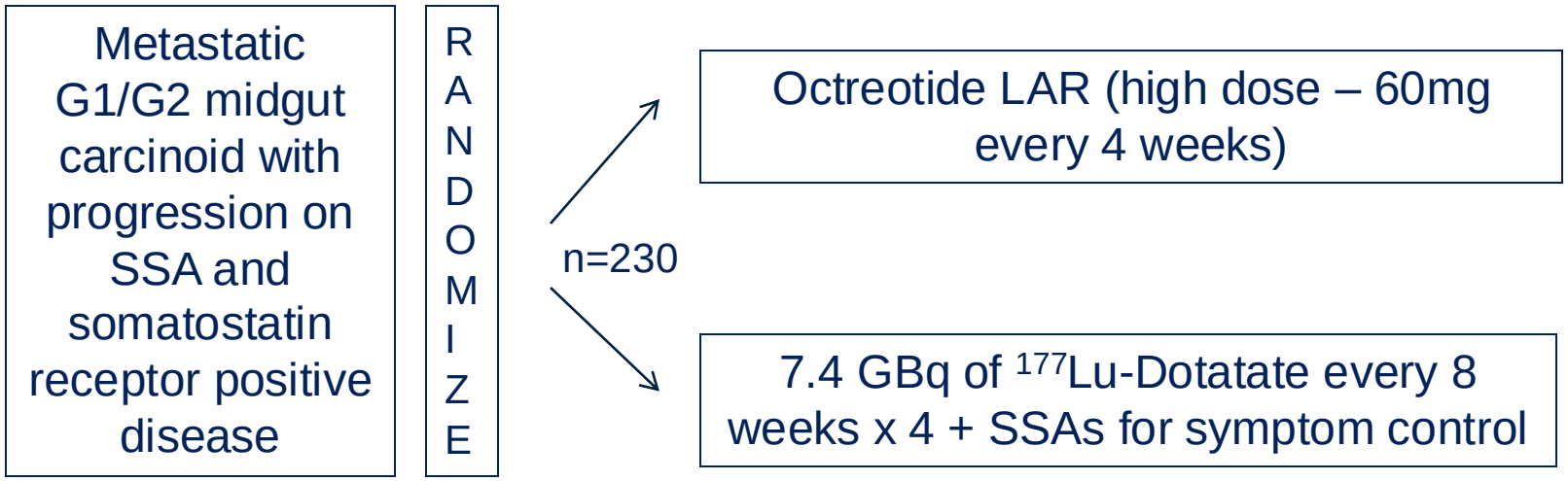
Peptide Receptor Radionuclide Therapy

- ^{177}Lu-DOTATATE is a radiolabeled derivative of octreotide that binds to somatostatin receptors
- Extensive experience in Europe in both carcinoid and PNETs
  - Rotterdam study of 310 patients showing a PFS of 33 months and an OS of 46 months
- Requires patient to have a positive octreotide scan or DOTATATE PET scan



Kwekkeboom DJ et al, JCO 2008; Breeman WAP and de Blois E, University Medical Center Rotterdam

NETTER-1—PRRT in Midgut Carcinoid



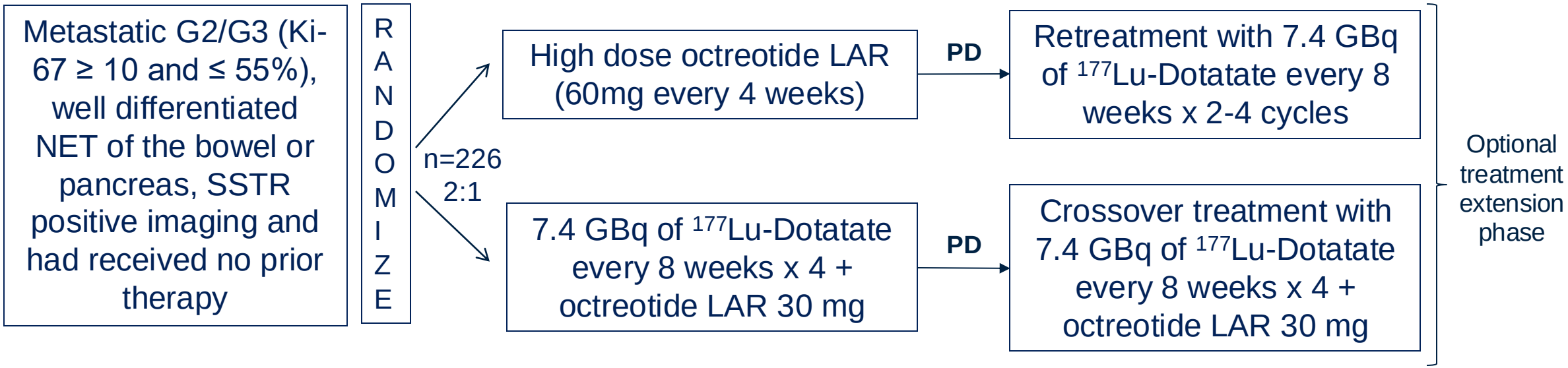
Progression Free Survival at 20 months: 65.2% vs 10.8%
Overall Survival: 48.0 months vs 36.3 months (HR 0.84, p=0.30)

Response Rate: 18% vs 3%

FDA approved in 2018 when evaluated in combination with European data—indication is for all patients with a GI or pancreatic NET that is avid on SSTR imaging

Strosberg J et al, NEJM 2017; Strosberg J et al, Lancet Oncol 2022

NETTER-2—PRRT in G2/G3 Neuroendocrine Tumors



Progression Free Survival: 22.8 months vs 8.5 months (HR 0.276, p<0.0001)

Response Rate: 43% vs 9.3%

While data were positive, is likely not broadly applicable to all G2/G3 patients

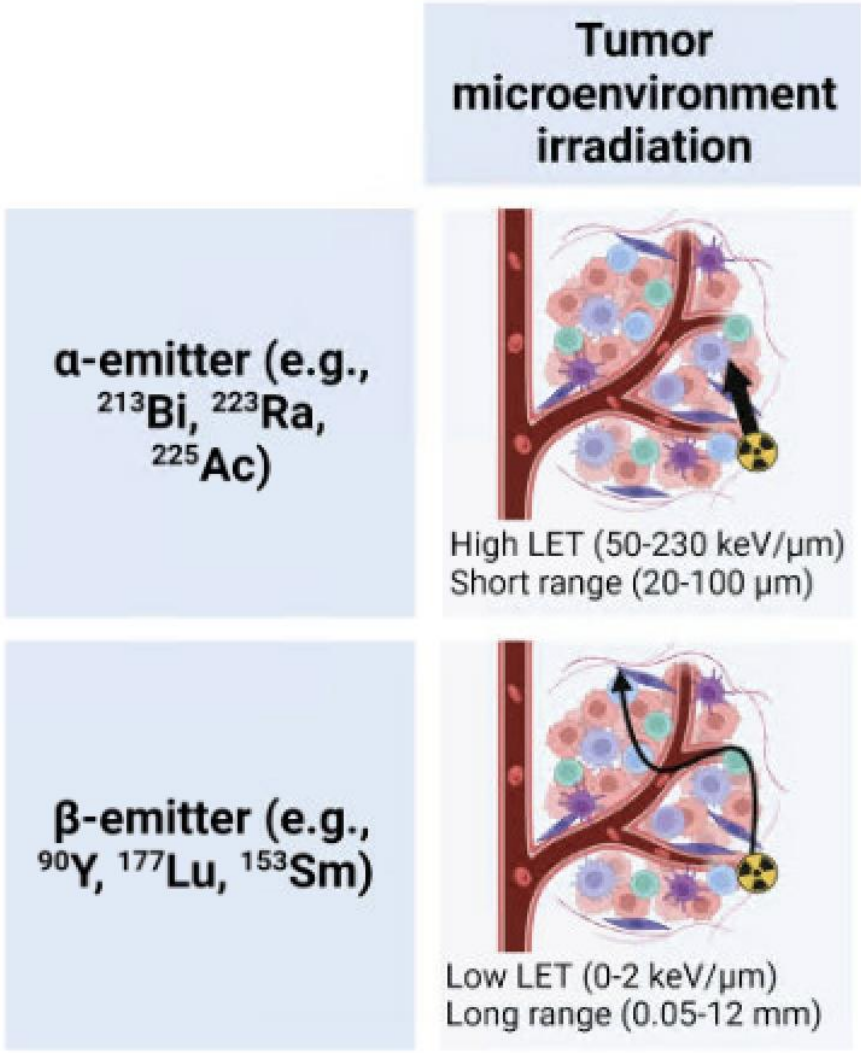
Singh S et al, ASCO GI 2024

Alpha Emitters as PRRT

- Higher linear energy transfer with alpha particles as compared to beta particles
- Results in greater degree of double strand DNA breaks
  - → greater cell death

- ^{212}Pb-DOTAMTATE assessed for safety, tolerability and efficacy

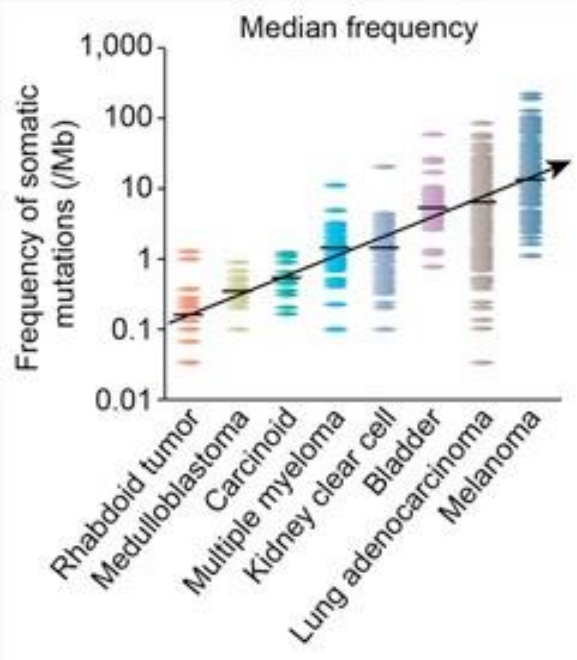
Study	Response Rate
ALPHAMEDIX-02	55.6%
NETTER-1	18%



Strosberg J et al, NEJM 2017; Strosberg J et al, ASCO 2024

Immunotherapy in Neuroendocrine Tumors

- Neuroendocrine tumors demonstrate a low tumor mutational burden

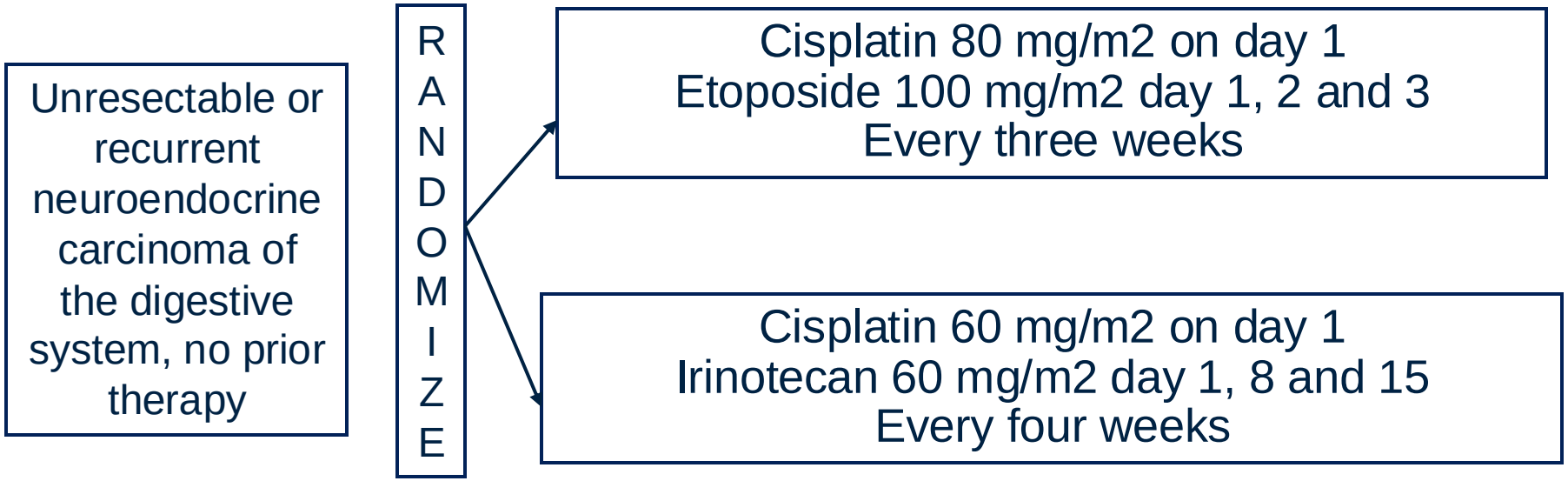


Study	Agents	Outcome
KEYNOTE-158 met NET of lung, appendix, colon, rectum, pancreas and small bowel	Pembrolizumab 200 mg IV every 3 weeks	Response Rate: 3.7%
DART-SWOG 1609 met G1/G2 NET	Nivolumab 240 mg IV every 2 weeks and Ipilimumab 1 mg/kg IV every 6 weeks	Response Rate: 0%
DUNE met G1/G2/G3 NET and pancreatic NET	Durvalumab 1500 mg IV and Tremelimumab 75 mg IV every x 4 → Durvalumab 1500 mg monotherapy	Response Rate: G1/G2 GI: 0% G1/G2 PNET: 6.3% G3 GI/PNET: 9.1%

Chauhan A, et al, Oncotarget 2018; Patel SP et al, Clin Can Res 2020; Strosberg J et al, Clin Can Res 2020; Capdevila J et al, Nat Commun 2023

Pancreatic Neuroendocrine Carcinoma

TOPIC-NEC—Cisplatin/Etoposide vs Cisplatin Irinotecan in NEC



Overall Survival: 12.5 months with EP vs 10.9 months with IP (HR 1.043, p=0.7968)

Progression Free Survival: 5.6 months with EP vs 5.1 months with IP (HR 1.060, p=0.7161)

Response Rate: 54.5% with EP vs 52.5% with IP (p=0.8732)

In a subgroup analysis, patients with pancreatic primaries (n=10) benefited more from EP

Morizane C et al, ASCO GI 2022

FOLFIRINOX for High Grade Neuroendocrine Neoplasms

- Retrospective analysis of 35 patients with high grade neuroendocrine neoplasms
  - 66% pancreatic, 6% ampullary
  - 71% NEC, 6% G3 NET, 23% MiNEN
  - 86% with metastatic disease

- Patients received front-line therapy with FOLFIRINOX

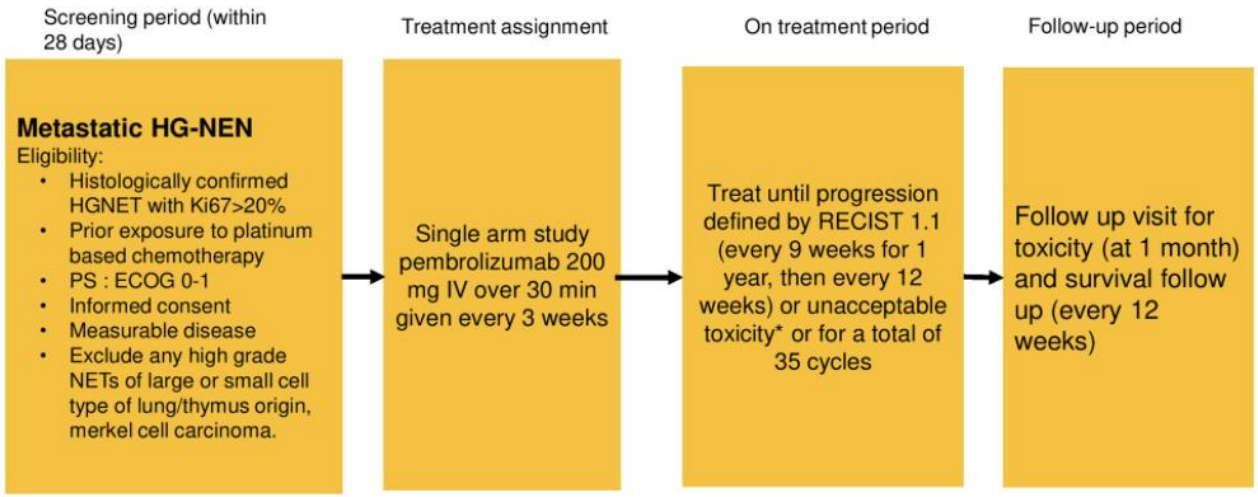
Response Rate 77%

Median PFS 12 months, Median OS 20.6 months

- Randomized phase II trial assessing FOLFIRINOX is ongoing (FOLFIRINEC)

Borghesani M et al, JNCCN 2024

Pembrolizumab—High Grade Neuroendocrine Carcinoma



* Pts may be treated beyond first progression under protocol defined circumstances

Primary endpoint: Overall Response Rate (ORR)
Secondary endpoints
- **Progression free survival (PFS)**
- **Overall survival (OS)**

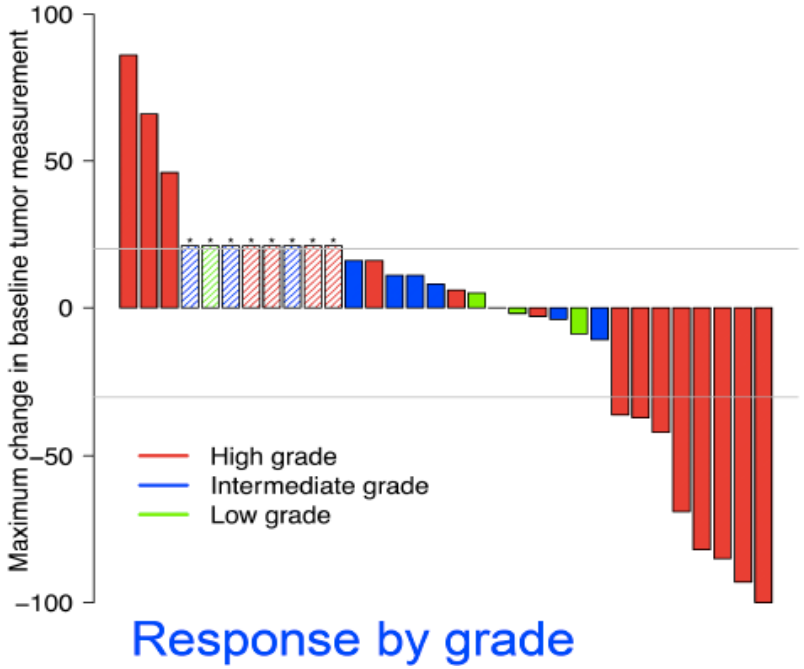
Best Overall Response	N (%)
Complete Response	0
Partial Response	**1 (4.7%)**
Stable Disease	3 (14.2%)
Progressive Disease	12 (57.1%)
Disease Control Rate (CR+PR+SD)	4 (19%)
Missing Scan	5 (23.8%)

- Total of 21 patients treated
- No apparent role for pembrolizumab as second line therapy in high grade neuroendocrine carcinoma

Vijayvergia N et al, ASCO 2018

DART-SWOG 1609

- Evaluated the combination of nivolumab and ipilimumab in a neuroendocrine cohort inclusive of Grade 1/2/3 tumors

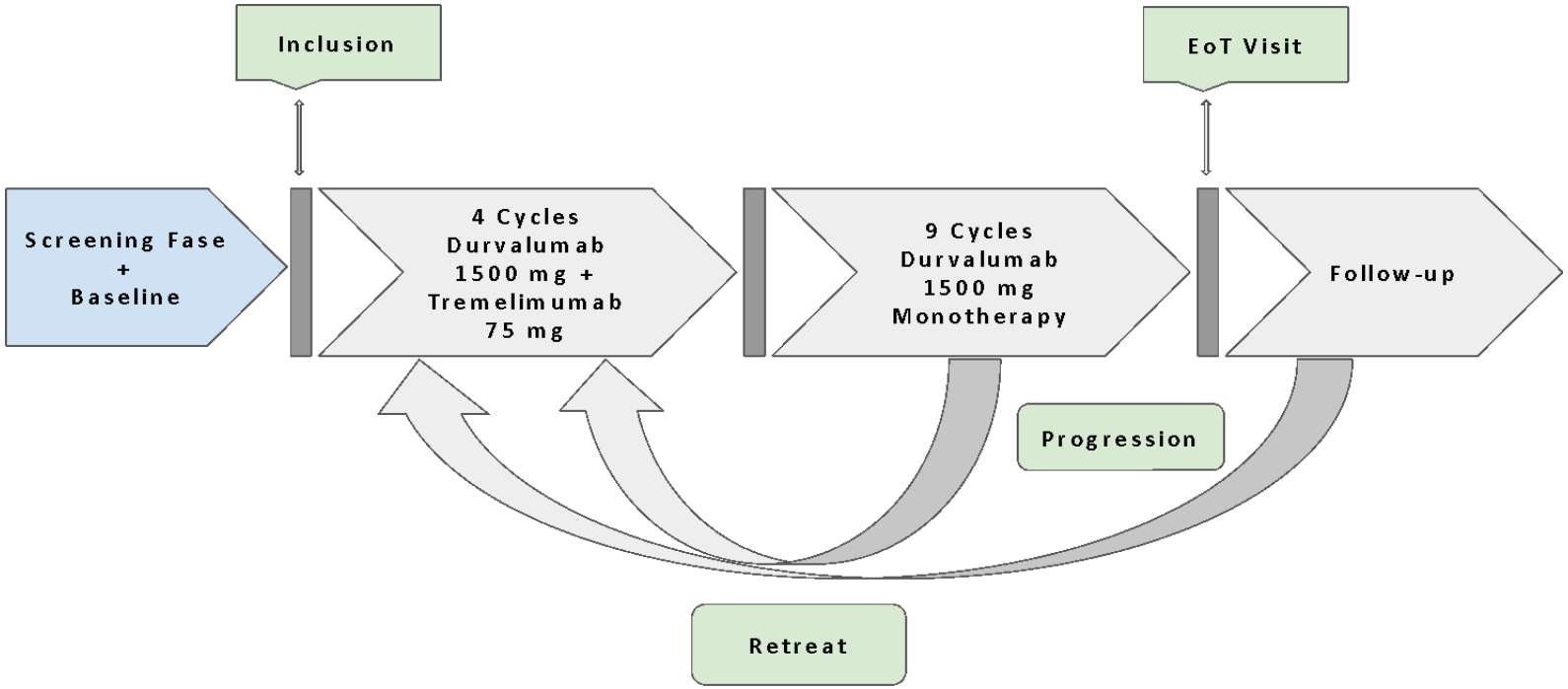


Patients enrolled: 32
- High grade: 18 (56%)
- Gastrointestinal: 15 (47%)

Response Rate
- Overall: 25%
- High grade: 44%
- Low/intermediate grade: 0%

Patel SP et al, Clin Cancer Res 2020

DUNE Trial—Durvalumab and Tremelimumab in Neuroendocrine Neoplasms



Multicohort study:

C1: Typical/atypical lung carcinoids. Prior therapy with somatostatin analogues and/or targeted therapies or chemotherapy

C2: G1/2 gastrointestinal. Prior treatment with somatostatin analogues and targeted therapy such as everolimus or radionucleotides

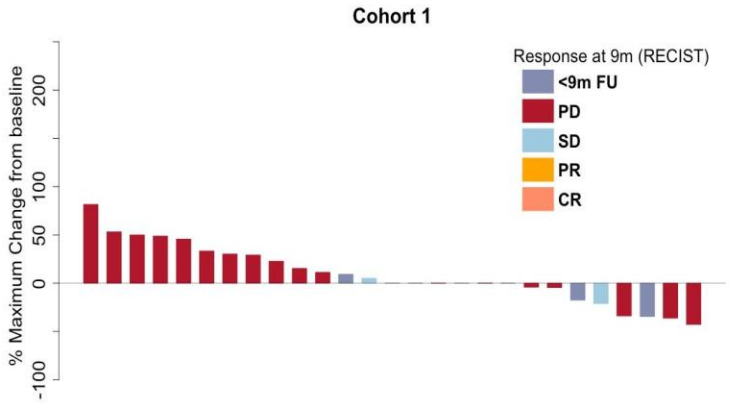
C3:G1/2 pancreatic. Prior treatment with chemotherapy, somatostatin analogues and targeted therapies. 2-4 systemic treatment lines

C4: G3 gastroenteropancreatic origin. After first line of chemotherapy with a platinum-based regimen

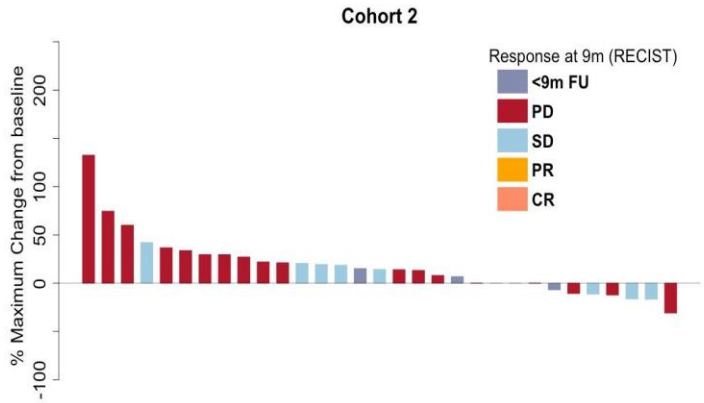
Capdevila J et al, ESMO 2020

DUNE Trial—Treatment Response

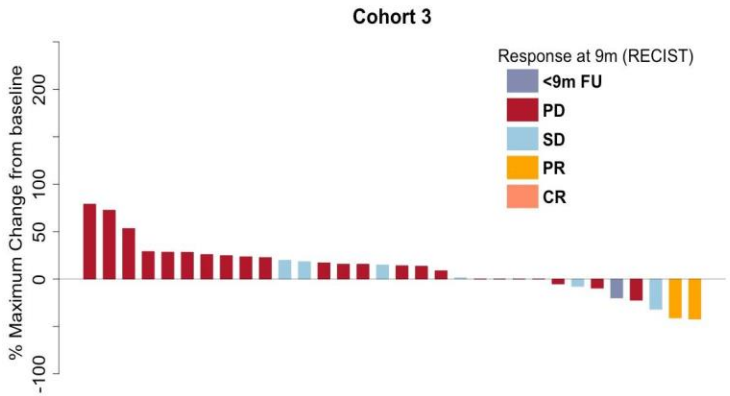
Cohort 1: Typical/atypical lung carcinoids



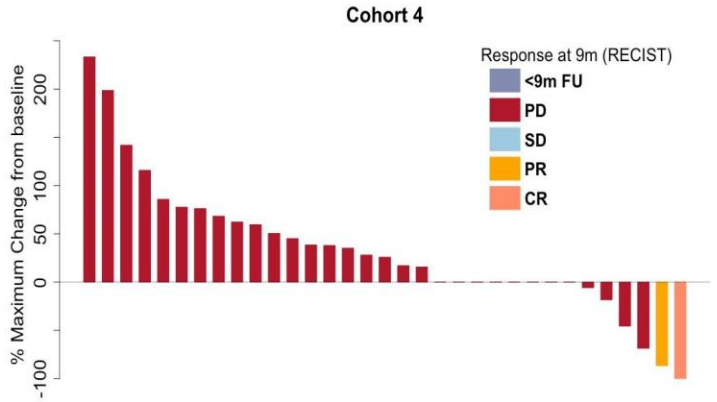
Cohort 2: G1/2 gastrointestinal



Cohort 3: G1/2 pancreatic



Cohort 4: G3 gastroenteropancreatic



- Clinical Benefit Rate at 9 months for pancreatic primaries (cohort 3): 25%
- Overall Survival Rate at 9 months for G3 gastroenteropancreatic primaries (cohort 4): 36.1%

Capdevila J et al, ESMO 2020

Ongoing Investigation

- A022001: Temozolomide/Capecitabine vs PRRT in pancreatic neuroendocrine tumors
- S2014: Adjuvant temozolomide/capecitabine in patients with resected, high risk pancreatic neuroendocrine tumors
- Multiple alpha emitters as PRRT
- RETNET: Favored modality of liver directed embolization therapy
- Chimeric Antigen Receptor Therapy (CAR-T)
- DLL3 targeted therapies in high grade neuroendocrine neoplasms
- Additional tyrosine kinase inhibitors such as zanzalintinib
- Non-peptide drug conjugates (targeting the somatostatin receptor)

Summary

- Front-line therapy for well differentiated patients with SSTR positive disease is a somatostatin analogue
  - May consider the addition of PRRT in G2/G3 patients—if it makes sense
- No data to determine subsequent sequencing of therapies
  - Consider degree of tumor burden
  - Is patient SSTR positive?
  - Do they have liver dominant disease?
  - What do their labs look like?
- We don’t combine therapies but rather sequence them
  - Managing this disease is a marathon not a sprint!
  - Options include surgery, SSAs, liver directed therapy, targeted therapy, PRRT, chemotherapy
- Limited options for poorly differentiated carcinomas but standard is platinum/etoposide, then directed by disease site or NGS/molecular findings
- Look for clinical trial options at any opportunity!!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