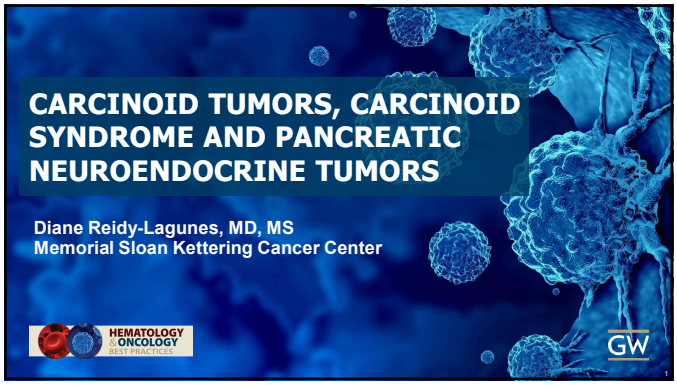


Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

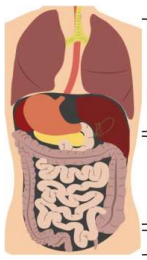
Agenda

- NETs and heterogenity
- Use of pathology and genetics to guide management
- Systemic therapy options in 2020
- A role for biomarkers to guide NET therapy (or lack thereof)
- "Legend" = important point

http://clicktoeditURL.com

NET Pearls: Location Matters!

Treatment and prognosis driven by where the tumor starts



Foregut
- Thymus
- Esophagus
- Lung
- Stomach
- Duodenum
- Pancreas

Midgut
- Appendix
- Ileum
- Cecum
- Ascending colon

Hindgut
- Distal bowel
- Rectum

Oronsky et al. (2017), *Neoplasia*

4

Pathology grading– most important prognostic tool but with problems

Uses differentiation status, cytologic grade

	Well-differentiated (NET)		Poorly-differentiated (NEC)
Tumor grade	1	2	3
Ki-67 index (%)	<3	3-20	>20
Mitotic count (per 10 HPF)	<2	2-20	>20

WHO, World Health Organization; NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; HPF, high-power field

Kartalis et al. (2015), Ann Gastroenterol

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WHO Classification of Pancreatic NE Neoplasms (2017)

Well differentiated NE tumor*

Grade	Mitoses	Ki-67 Index
G1	<2 / 10 HPF	<3%
G2	2-20 / 10 HPF	3-20%
G3**	>20 / 10 HPF	>20%

*Organoid architecture, "well differentiated" cytology, absence of non-neuroendocrine carcinoma components, may have components of G1 or G2, usually strong immunoexpression of general NE markers

**mitoses >20/10 HPF but usually <30/HPF; Ki 67 >20% but usually <55%

Poorly differentiated NE carcinoma*

Grade	Mitoses	Ki-67 Index
G3**	>20 / 10 HPF	>20%

*Small cell carcinoma and large cell NE carcinoma; less organoid architecture, classic cytology of small cell and large cell NE CA, absence of G1 or G2 NE components, may have non-neuroendocrine carcinoma components, less diffuse immunoexpression of general NE markers

**mitoses >20/10 HPF and usually >30/10 HPF; Ki67 >20% and usually >55%

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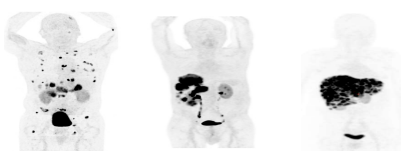
Symptoms of Neuroendocrine Tumors

- 85% of tumors are non-functional!
- A nonfunctional tumor can become functional –always assess for new symptoms particularly at progression
- Hormone w/u driven by clinical symptoms
  - Midgut and Lung
    - Carcinoid syndrome –flushing and diarrhea (24 hour 5hiaa, serum 5hiaa)
  - Pancreatic NETs
    - VIP
    - Insulin, Proinsulin
    - Gastrin
    - Glucagon
    - ACTH
    - Carcinoid syndrome –flushing, diarrhea (rare)- 24 hour 5hiaa, serum 5hiaa

Diagnostic Work-Up

- Cross-sectional imaging (CT Triphasic or MRI)
- Functional Imaging x1 (Somatostatin scintigraphy –i.e. Octreotide scan or Ga68DOTATATE)
- Biopsy
- Biomarkers? Unlikely to help
- Role of EUS? Capsule Endoscopy? Yield is low

Evolving Diagnostic Imaging GA68 DOTATATE



Ga 68 DOTATATE improved sensitivity compared to octreotide imaging

Radioactive diagnostic agent indicated for localization sst positive disease

Beware of comparing apples to oranges! Ga68 should not be compared to cross-sectional imaging to define extent of disease

Question 1

16 year-old boy has a resected 0.8 cm tumor of the appendix found incidentally at the time of acute appendicitis. Does any further work-up need to be done

A) Yes
B) No

Answer: NO

- Review of 200 patients at MSK suggest there is no role for right hemicolectomy or any other imaging for carcinoid <1.0 cm
- NCCN recommendations tumors >2.0 cm should be considered for right hemicolectomy
- Tumors between 1-2 cm with meso-appendiceal involvement might have LN involvement; in our data set NO patients with carcinoid of the appendix recurred (even with LN Involvement)

Question 2

75 year-old man has bilobar liver lesions and 3 cm RLQ mass in terminal ileum. The liver lesion is biopsied to be well differentiated low grade NET. He experiences flushing and diarrhea. He is started on octreotide LAR with improvement of his symptoms. He develops sudden onset acute n/v/abdominal pain and is found to be pSBO at the site of the primary tumor. What does the anesthesiologist have to worry about?

A) Cardiac history and risk for carcinoid heart
B) Carcinoid Crisis
C) Epinephrine surge and risk of hypertensive emergency
D) All of the above
E) none of the above
F) A+B

Genetics: Sequencing of NETs

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Mutations in well differentiated panNETs

- Whole-exome sequencing → targeted sequencing
- Early stage (59%), metastatic (41%)
  - Chromatin remodeling genes (MEN1/DAXX/ATRX)
  - mTOR pathway (PTEN, TSC2)
  - *Better prognosis with MEN1 + DAXX/ATRX mutated status

Jiao et al. (2011), *Science*

Jiao et al Science, 2011

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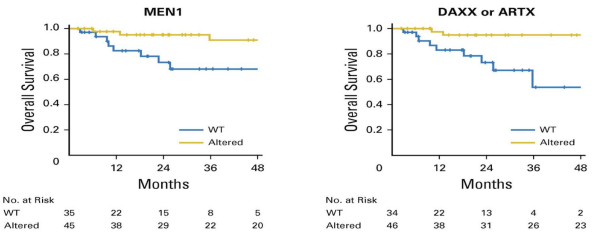
Next-generation sequencing of Pancreatic NETs



Raj et al JCO PO, 2018

Raj et al. (2018), JCO Precision Oncology

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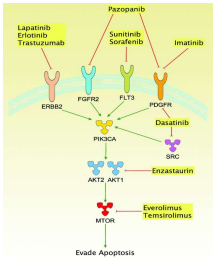
Exome sequencing in Small Intestine NETs (SI-NETs)

- 48 SI-NETs (70% G1, 30% G2)
- Integrated analysis: recurrent alterations (chromatin remodeling, DNA damage, apoptosis, RAS signaling, axon guidance)
- Most frequent alterations along mTOR pathway (33%)



Banck et al. (2013), J Clin Invest http://clicktoeditURL.com

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Multidisciplinary Treatment for Advanced NETs

Surgery

Nonsurgical Liver-Directed Therapy
- Embolization (+/- chemotherapy)

Medical Treatment
- SSAs
- IFN-α (carcinoid- toxic)
- Cytotoxic chemotherapy (pNET)
- Biologic targeted agents (pNET)
- PRRT (carcinoid)

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Role of Liver Directed Therapy

- Response rates similar across all embolization types (bland embolization, Y90 Radioembolization, Chemoembolization)
- No randomized controlled trials to know which is better
- Drug eluting beads have high rate of abscesses and bilomas
- Radioembolization for large bulky disease may be safer but could be risks with PRRT
- Largely dependent on the comfort level of Interventional Radiologist

Kennedy, et al American Journal of Clinical Oncology. 31(3):271-279, June 2008; Chamberlain et al Cancer, 2006; Gupta et al Cancer 2007

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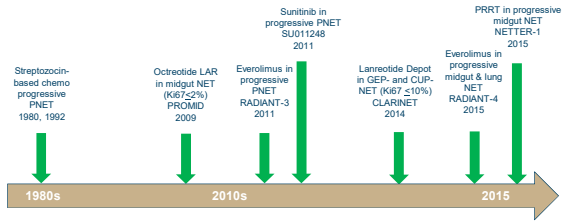
Systemic Treatment in Advanced NETs

NET Therapy: Key Advances through Level 1 Evidence



Moertel et al. (1980), N Engl J Med; Moertel et al. (1992), N Engl J Med; Rinke et al. (2009), J Clin Oncol; Yao et al. (2011), N Eng J Med; Raymond et al. (2011), N Eng J Med; Caplan et al. (2014) N Eng J Med; Yao et al. (2016), Lancet; Strosberg et al. (2015), ESMO Annual Meeting

Systemic Treatment Options for Advanced NETs

Pancreatic NET	Extra-Pancreatic NETs
Lanreotide	Lanreotide, Octreotide (GI)
Everolimus	Everolimus (non-functional GI, lung)
Sunitinib	^{177}Lu-Dotatate
Alkylating agents (streptozocin, temozolomide); platinum, 5FU	
^{177}Lu-Dotatate	

- Activity of sunitinib in pancreatic NET was established in patients without prior everolimus
- Activity of VEGF pathway inhibitors in advanced carcinoid tumors has not been established

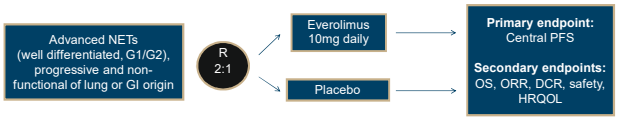
Somatostatin Analogs

What We Know

- No data to use a different somatostatin analog upon disease progression
- No data comparing octreotide and lanreotide
- No data to use beyond progression in nonfunctional patients

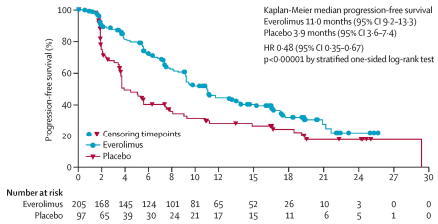
"Carcinoid" GI and Lung NETs: Targeted Trials

RADIANT-4



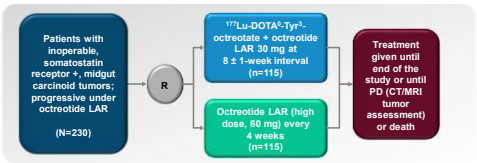
Yao et al. (2016), *Lancet*

RADIANT-4 Results: PFS (central review)



Yao et al. (2016), *Lancet*

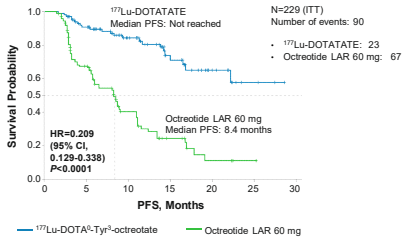
NETTER-1: Phase 3 Study Design Role of PRRT



Primary Endpoint	Secondary Endpoints
PFS according to RECIST criteria (objective tumor response)	Safety and tolerability

A study comparing treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-octreotate to octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive midgut carcinoid tumours (NETTER-1). ClinicalTrials.gov website. https://www.clinicaltrials.gov/ct2/show/NCT01578291?term=NETTER&rank=1. Accessed 10/2/2015.
Ruszniewski P, et al. ESMO 2015 (abstr 6LBA)

NETTER-1 Study Results: Progression-Free Survival



Ruszniewski P, et al. ESMO. 2015 (abstr 6LBA).

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Side Effects Lu177-DOTATATE

- Nausea
- Lymphopenia
- Anemia
- Hair loss
- MDS/leukemia 1-2% risk

Strosberg et al NEJM 2017, Bodei et al, Eur J Nuc Med, 2014

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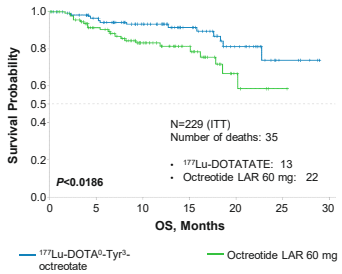
NETTER-1 Study Results: Interim OS Analysis



Ruszniewski P, et al. ESMO. 2015 (abstr 6LBA).

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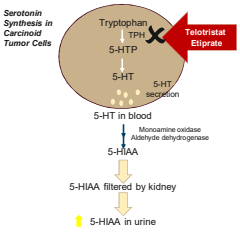
Carcinoid Syndrome

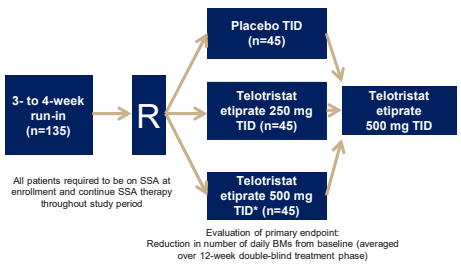
- Treat the disease!
  - Embolization and other systemic approaches
- Somatostatin Analogs

Telotristat Etiprate
A Tryptophan Hydroxylase (TPH) Inhibitor



- Telotristat etiprate is a novel oral inhibitor of TPH, the rate-limiting enzyme in serotonin biosynthesis
- Two early-stage clinical studies of telotristat etiprate demonstrated a favorable safety profile and evidence of clinical activity in carcinoid syndrome
- Both preclinical and clinical studies suggested that telotristat etiprate is associated with minimal CNS activity

Study Design Phase III Telestar

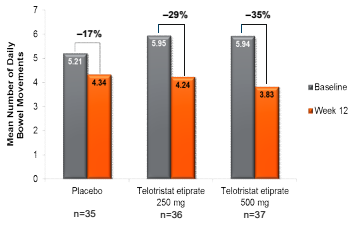


All patients required to be on SSA at enrollment and continue SSA therapy throughout study period

Evaluation of primary endpoint:
Reduction in number of daily BMs from baseline (averaged over 12-week double-blind treatment phase)

TELESTAR: Reduction in Mean Daily Bowel Movement Frequency at Baseline and Week 12

All patients continue SSA therapy throughout study period. Data include only patients for whom both baseline and Week 12 assessments were available.



SSA, somatostatin analog.

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Pancreatic NETs: Targeted and Cytotoxic Therapies

Summary

Parameter	Everolimus (RADIANT-3)	Sunitinib
No. of patients	410	171
	Low-intermediate grade	Low grade
Design	Phase III multicenter RCT	Phase III multicenter RCT
Intervention	10mg Everolimus QD	37.5mg Sunitinib QD
Control	Placebo	Placebo
Crossover	Yes	No
Primary outcome - PFS	**11 months vs. 4.6 months**	**11.4 months vs. 5.5 months**
Secondary - OS	NS	NS
CR/PR	5% vs 2%	9% vs 0%
SD	73% vs 51%	63% vs 60%

Raymond et al. (2011), N Engl J Med; Yao et al. (2011), N Engl J Med

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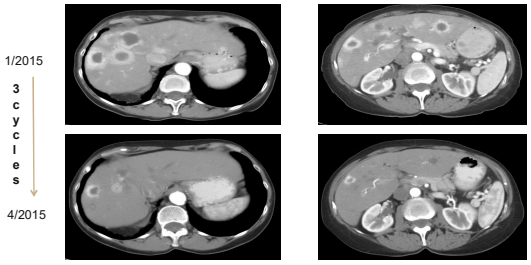
Cytotoxic Chemotherapy in Pancreatic NETs

- Streptozocin – very toxic
- ECOG randomized phase II cape/tem versus tem alone > Capecitabine + temodar greater PFS 22.7 months versus 14 months temodar alone
- Platinum drugs-higher grade tumors
- Sequencing of therapy needs to be addressed

Kunz et al 2018 ASCO

Well differentiated, high grade Pancreatic NET (Ki-67 30%) Tx with cape/tem



Biomarkers to Guide NET Therapy

Biomarkers in NETs: What we Know

- NCCN guidelines do not limit use of SSA to NETs that are SSTR positive
  - But it is likely that SSA treatment only benefits patients whose tumors harbor the SSTR
- To date, all studies have failed to identify a NET patient cohort more likely to benefit from everolimus
- SSTR expression on imaging studies predicts response to PRRT

Janson et al. (1994), *Eur J Endocrinol*; Mehta et al. (2015), *Medicine*; Qian et al. (2016), *Pancreas*; Zatelli et al. (2016), *Endocr Relat Cancer*

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A word on poorly differentiated NEC

- Poorly differentiated NEC are treated with platinum- based therapy
- Platinum/etop or platinum/irinotecan are reasonable first line treatment options
- A PET DOTATATE is NOT HELPFUL as it should not drive management – even if positive, PRRT is ONLY approved for well differentiated NET and not NEC

Walenkamp et al Cancer Treat Rev. 2009;35(3); Cancer Sci. 2014 Sep;105(9):1176-81. Epub 2014 Sep 6.

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Conclusions

- Pathologic and molecular (genetics) features are important to characterize NET biology
- Through Level 1 evidence, treatment landscape is broadening
- Many therapies to consider that were not available 10 years ago
  - Role for biomarkers in NETs remains limited
- Takes a team approach!

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