

# Neuroendocrine Tumor

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# Disclosure slide

- Honoraria from Novartis, IPSEN, Pfizer, Lexicon
- Consultancy fee from Novartis, IPSEN, Pfizer, Lexicon
- Research support from Novartis and IPSEN

# Neuroendocrine Neoplasms (NEN)

## Classifications of NEN



### 1963 Williams & Sandler

#### Foregut (~40%)

- Lungs
- Thymus
- Stomach
- Pancreas
- First part of

subgroup

#### Pancreatic NETs (~6%)

- Gastrinoma
- Insulinoma
- Glucagonoma
- Somatostatinoma
- VIPoma
- Pancreatic polypeptidoma
- Non-functioning tumours

**Carcinoid  
Syndrome**

	Grading	Mitosis (10HPF) <sup>a</sup>	Ki-67 Index (%) <sup>b</sup>
NET G1	G1	< 2	≤ 2
NET G2	G2	2 – 20	>2 – 20
NEC	G3	> 20	> 20

<sup>a</sup>10 HPF: high power field = 2cm<sup>2</sup>, at least 40 Fields (40x magnification, areas of highest mitotic density)

<sup>b</sup>MIB-1 Antibody in % of 2000 Tumor cells in “hot spot” – areas

Factors with impact on prognosis:  
Proliferation activity, Primary tumor site etc.

**1980 First WHO-Classification :  
Carcinoid**



**WHO 2000  
WHO 2010**

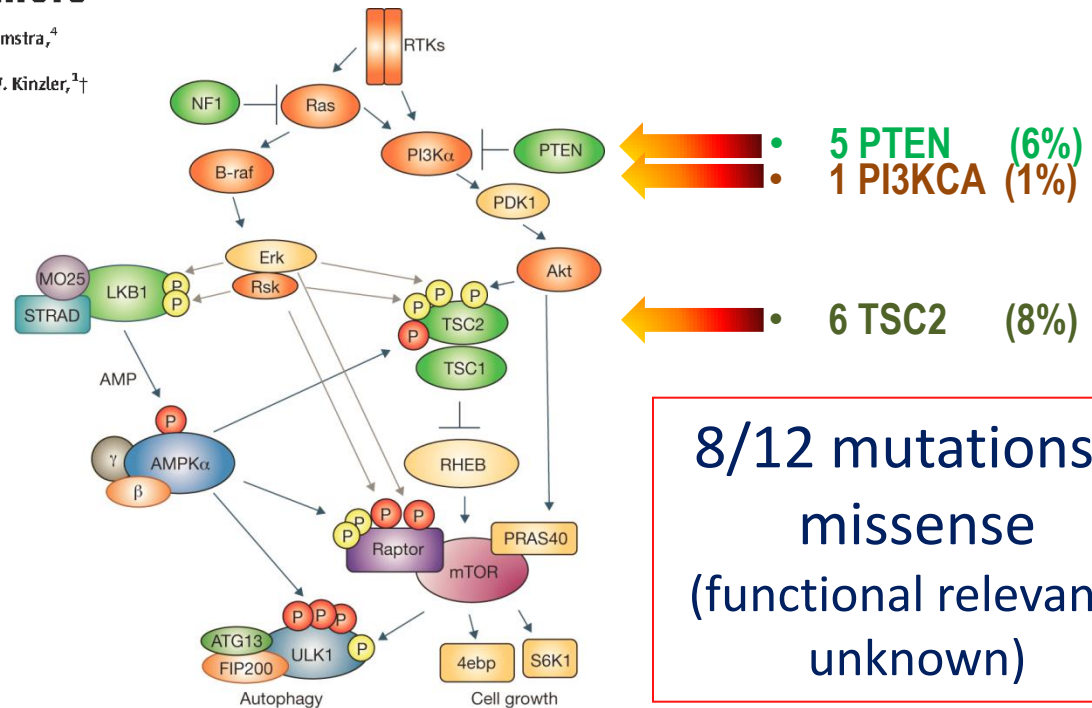
# Somatic Mutations in pNET vs. Adenocarcinoma of the pancreas

www.sciencemag.org SCIENCE VOL 331 4 MARCH 2011

## DAXX/ATRAX, MEN1, and mTOR Pathway Genes Are Frequently Altered in Pancreatic Neuroendocrine Tumors

Yuchen Jiao,<sup>1\*</sup> Chanjuan Shi,<sup>2\*</sup> Barish H. Edil,<sup>3</sup> Roeland F. de Wilde,<sup>2</sup> David S. Klimstra,<sup>4</sup> Anirban Maitra,<sup>5</sup> Richard D. Schulick,<sup>3</sup> Laura H. Tang,<sup>4</sup> Christopher L. Wolfgang,<sup>3</sup> Michael A. Choti,<sup>3</sup> Victor E. Velculescu,<sup>1</sup> Luis A. Diaz Jr.,<sup>1,6</sup> Bert Vogelstein,<sup>1</sup> Kenneth W. Kinzler,<sup>1†</sup> Ralph H. Hruban,<sup>5†</sup> Nickolas Papadopoulos<sup>1†</sup>

Genes <sup>a</sup>	PanNET	PDAC <sup>b</sup>
<i>MEN1</i>	44%	0%
<i>DAXX, ATRX</i>	43%	0%
Genes in mTOR pathway	15%	0.80%
<i>TP53</i>	3%	85%
<i>KRAS</i>	0%	100%
<i>CDKN2A</i>	0%	25%
<i>TGFBR1, SMAD3, SMAD4</i>	0%	38%

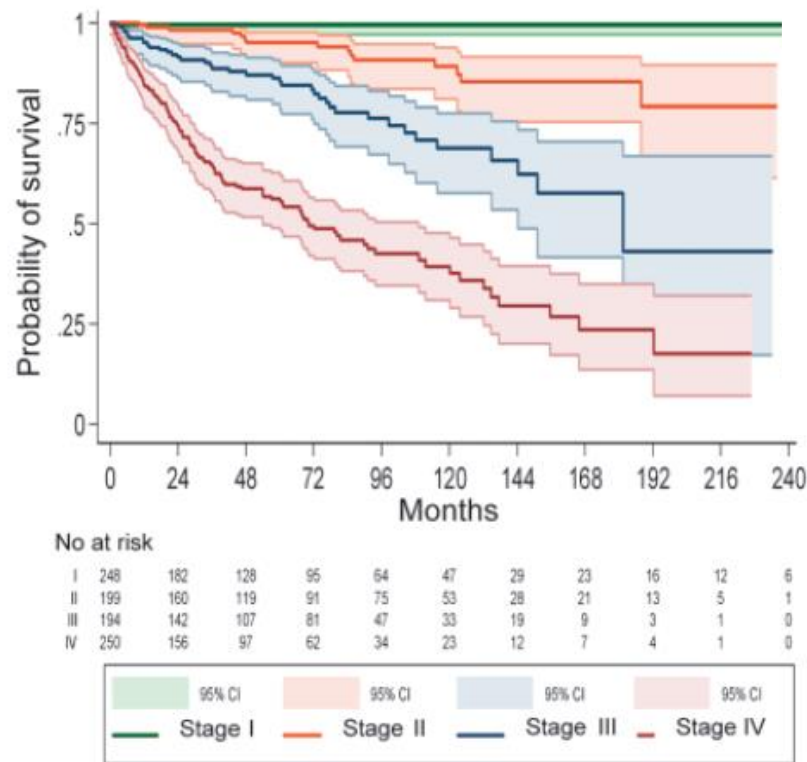
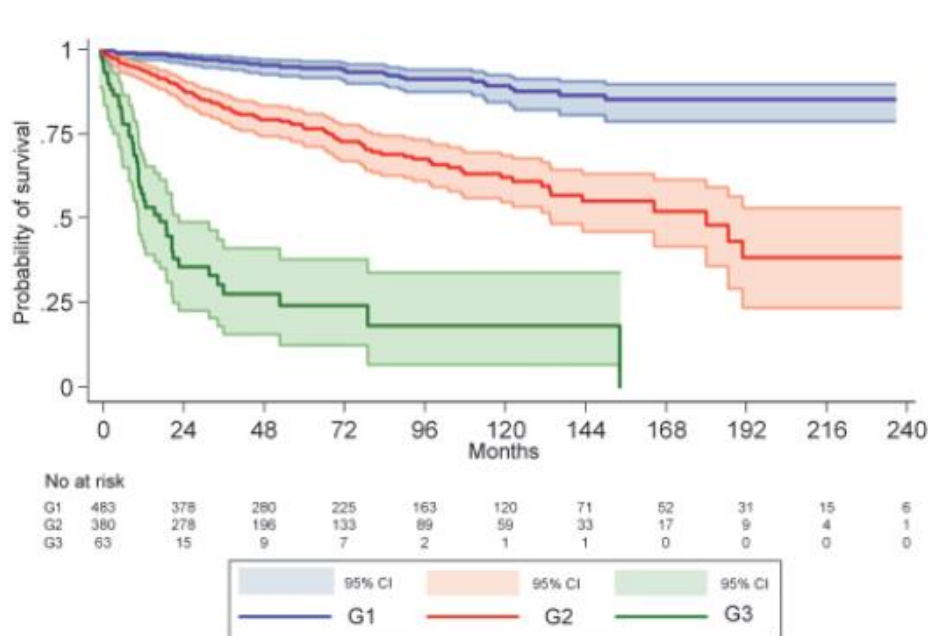


mTOR Pathway Mutations- no Genotype/ Phenotype Correlations

# Prognostic impact of grading & staging (n=926 Patients)

## TNM Staging of Neoplasms of the Endocrine Pancreas: Results From a Large International Cohort Study

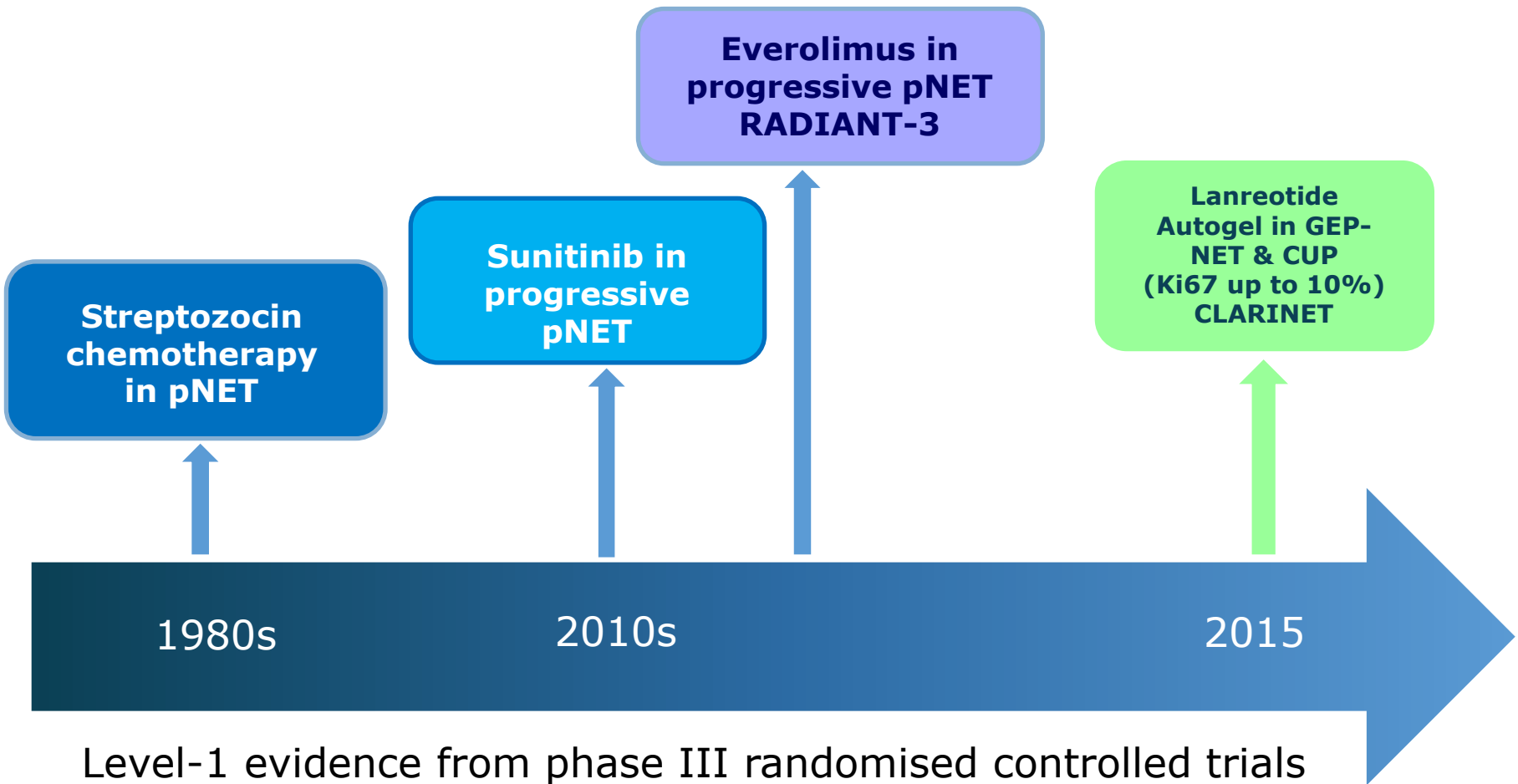
G. Rindi, M. Falconi, C. Klersy, L. Albarello, L. Boninsegna, M. W. Buchler, C. Capella, M. Caplin, A. Couvelard, C. Doglioni, G. Delle Fave, L. Fischer, G. Fusai, W. W. de Herder, H. Jann, P. Komminoth, R. R. de Krijger, S. La Rosa, T. V. Luong, U. Pape, A. Perren, P. Ruszniewski, A. Scarpa, A. Schmitt, E. Solcia, B. Wiedenmann



# Therapeutic options in advanced NET

- Loco-regional and ablative procedures incl. liver surgery
- **Somatostatin analogs**
- Interferon-alpha
- Systemic chemotherapy
- **Molecular-targeted therapies**
- Peptide-Receptor Radionuclide Therapy (PRRT)

# Evidence-based antiproliferative drug treatment in pancreatic NET



Caplin M et al., NEJM 2014, Rinke A et al., J Clin Oncol 2009, Blumenthal G, et al. Oncologist 2012, Yao et al., NEJM 2011, Raymond et al. NEJM 2011

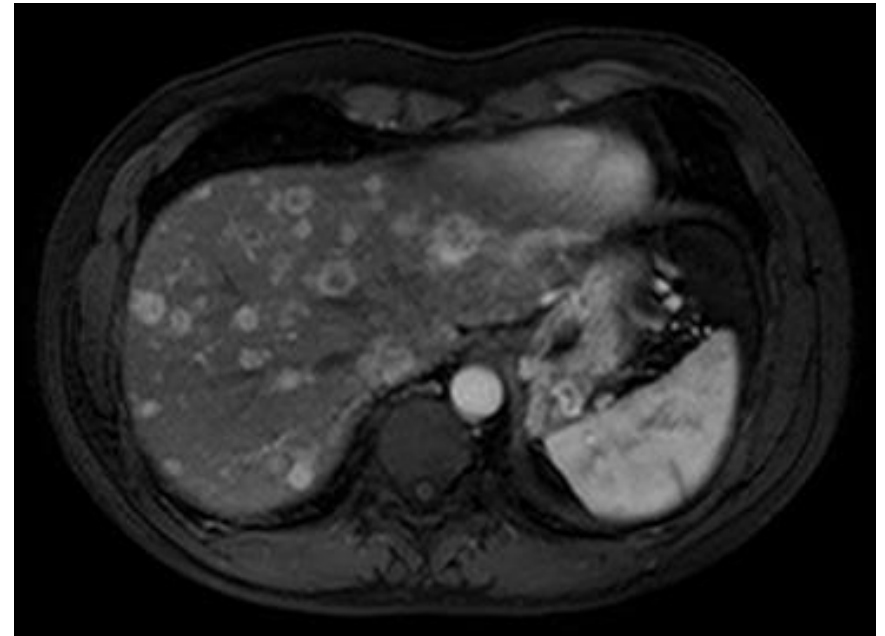
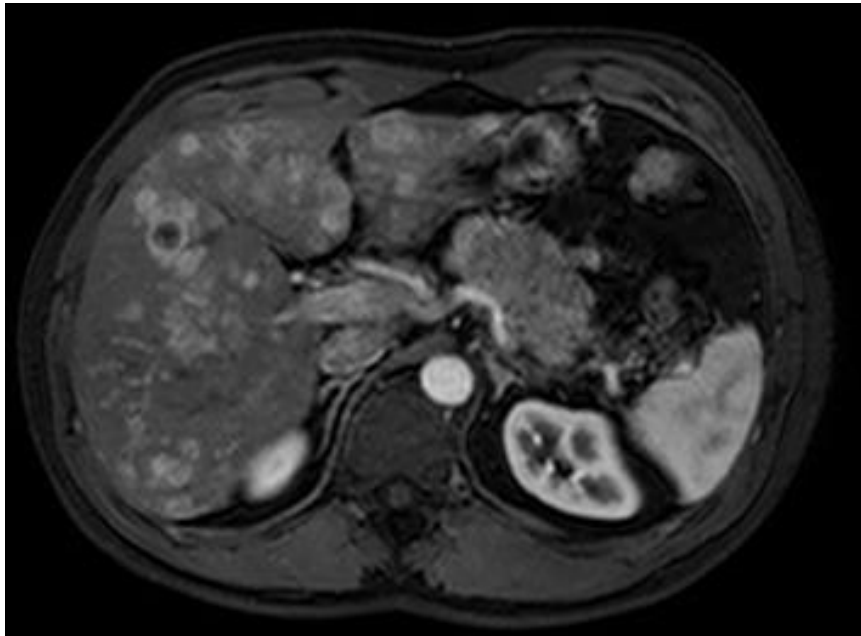
# 51 yr old patient

- Surgeon, active
- 02/13 first consultation at Charité University Clinic
- **Medical history:** increasing abdominal pain for several months, dark stools, no weight loss
- **Ultrasonography:** multiple liver lesions
- **Liver biopsy:** Well differentiated Neuroendocrine Tumor
  - Immunohistochemistry: **Synaptophysin +++**, **CgA+**, Panzytokeratin +, Zytokeratin 8+, VMAT 2 +, Serotonin +, **SSTR-2A >90%**, ISLET-1+; **MiB-1 15-20% (NET G2)**.
  - Negative: Gastrin, Glucagon, Somatostatin, Pancreatic Polypeptide, Calcitonin
- **Therapy:** none



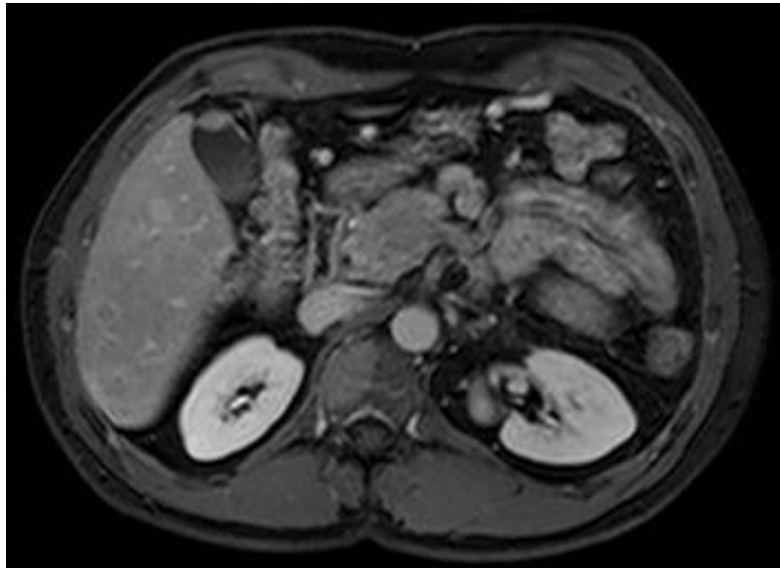
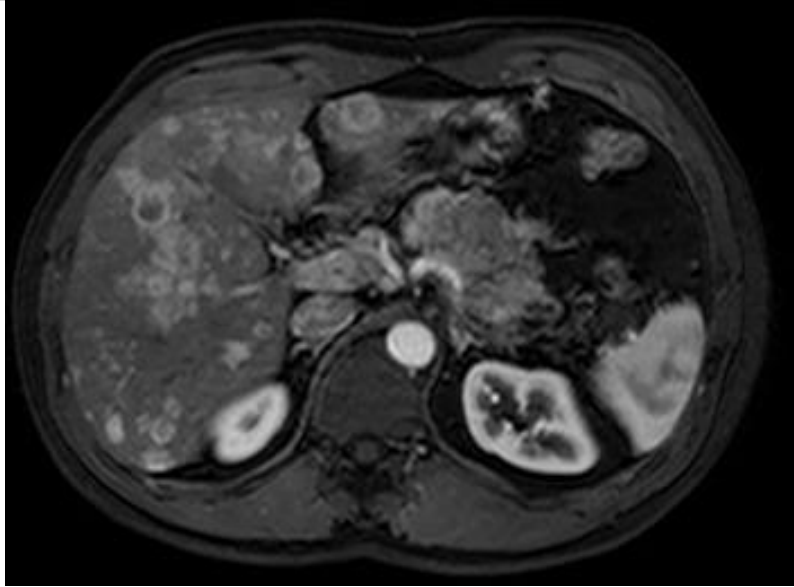
# 51 year old patient with pancreatic NET

02/13



# Pancreatic NET G2

**Tumor infiltration  
in the portal vein**



# How would you treat this patient?

- Surgery of the primary tumor +/- Transarterial embolisation
- Somatostatin analogs
- Everolimus
- Sunitinib
- Systemic chemotherapy
- Peptide receptor radionuclide therapy (PRRT)

# Additional diagnostics

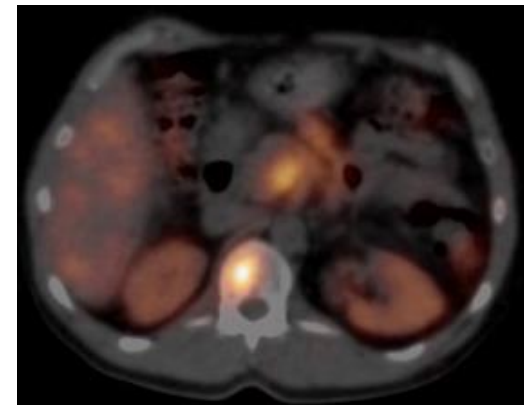
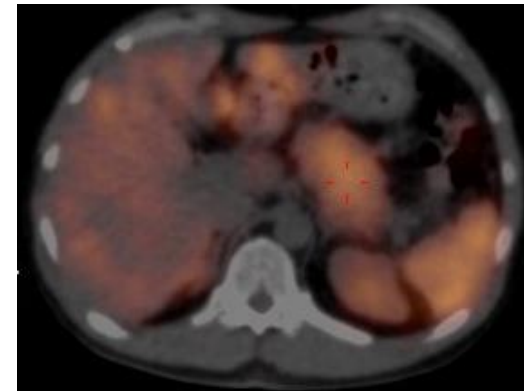
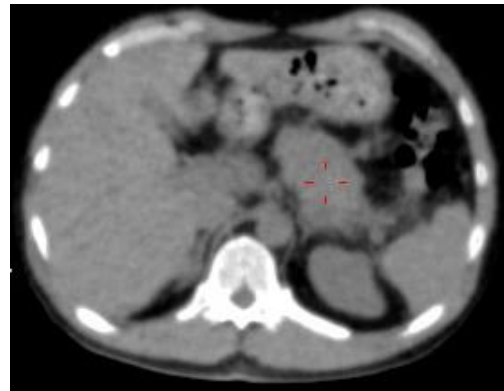
## Laboratory values

ALT 60 U/l (<40)  
AST 56 U/l (<50)  
gGT 91 (<60)

NSE 92 ug/l (<15.2)

Chromogranin A 345 ug/l (NR<150)

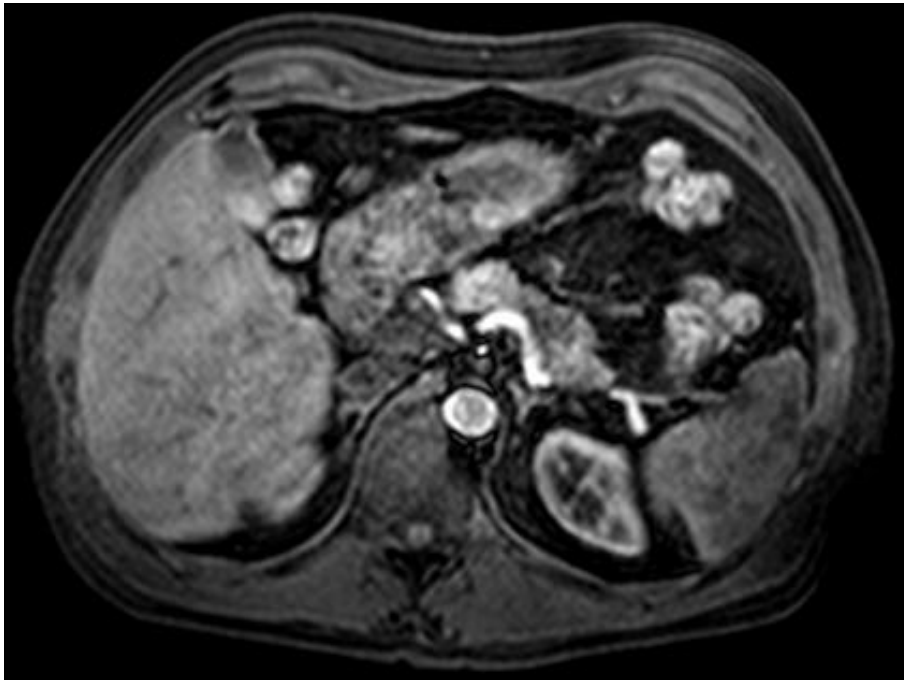
## <sup>111</sup>In Octreoscan



# Streptozocin based chemotherapy

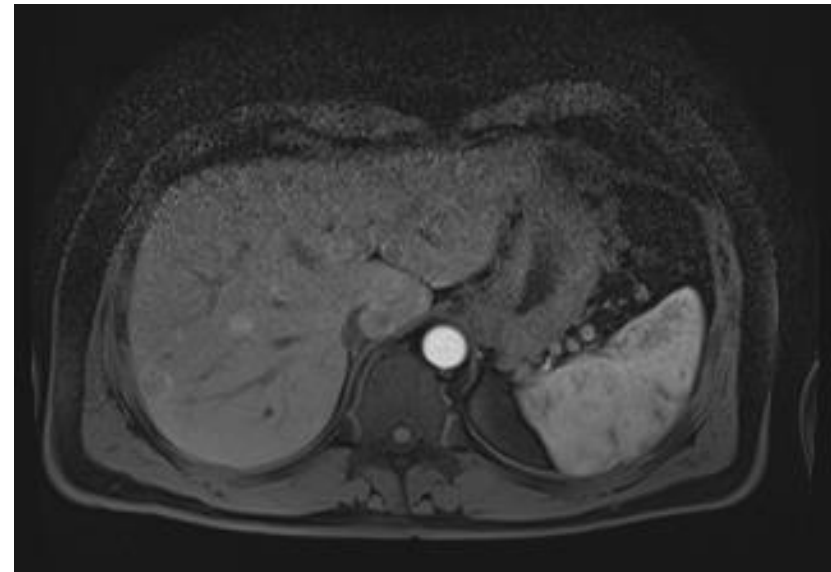
## 02/13 - 01/14

01/14



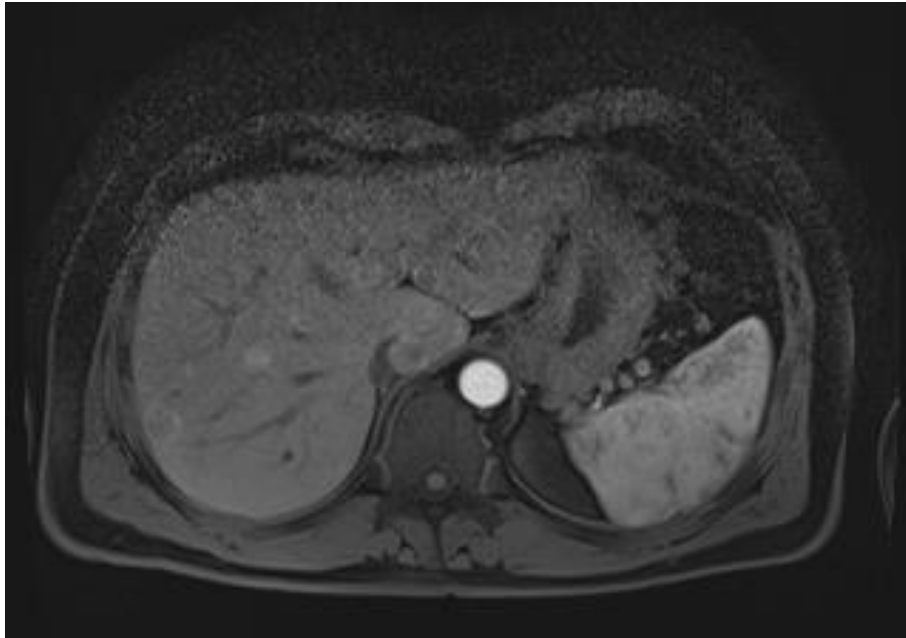
STZ 0.5 g/m<sup>2</sup> days 1–5  
5-FU 400 mg/m<sup>2</sup> days 1–5 q 6 weeks  
(Moertel)

Partial Remission of primary + LM

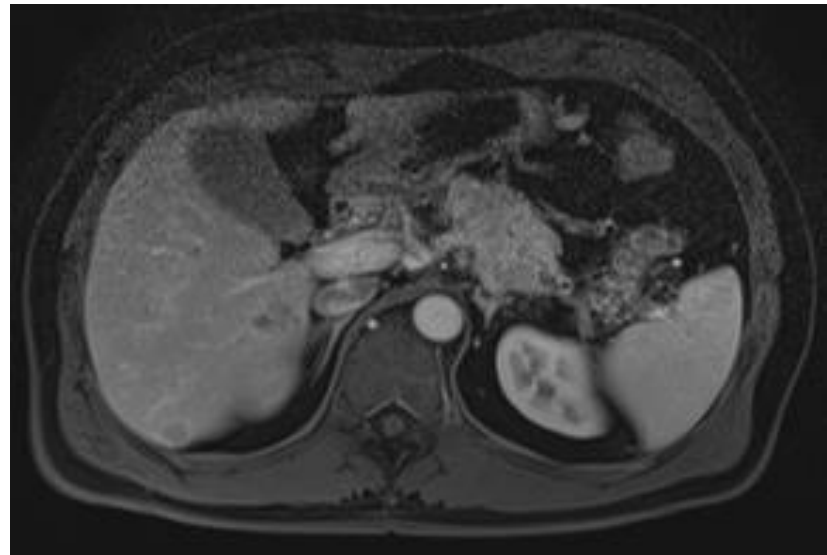
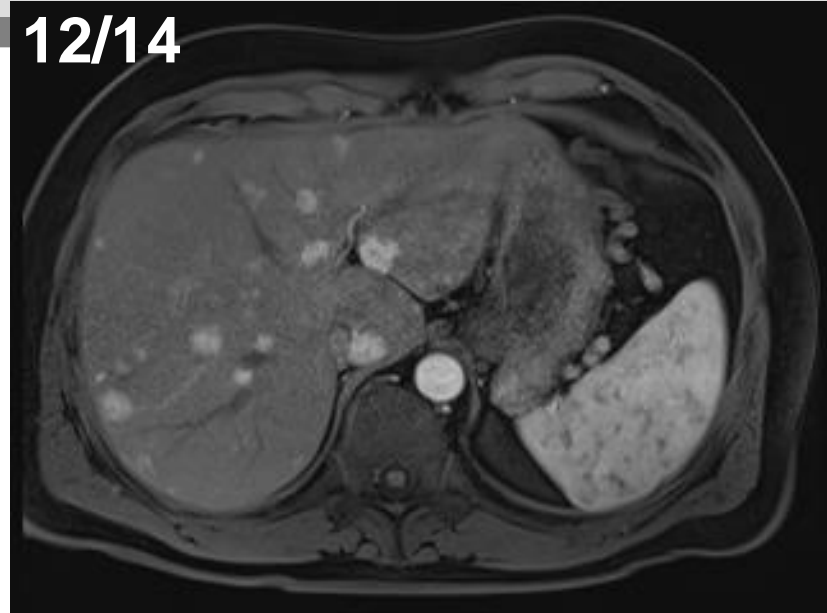


# Pancreatic NET - Follow-up

05/14



12/14



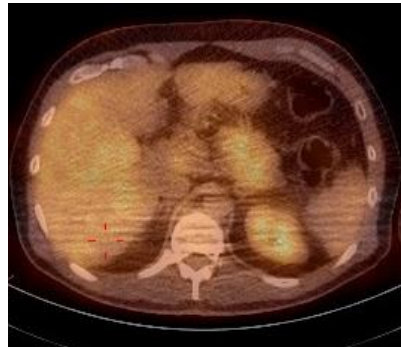
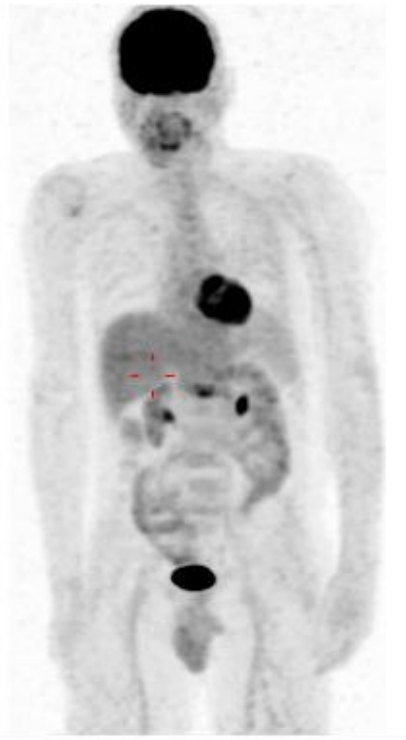
**What is your 2nd line therapy?**

- Temozolomide/Capecitabine ?
- Rechallenge STZ/ 5-FU ?
- Everolimus or Sunitinib?

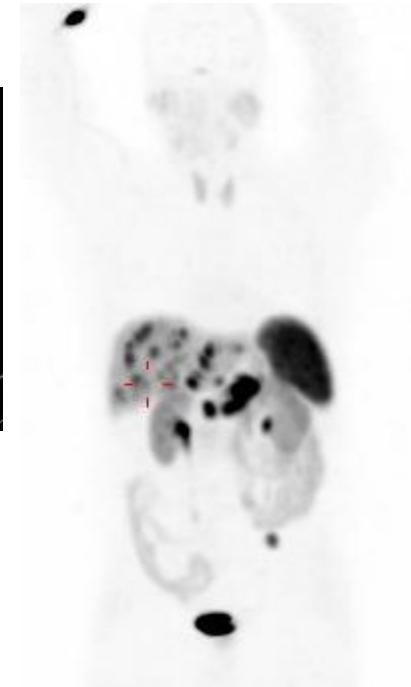
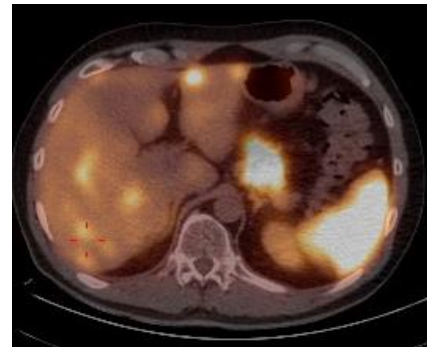


# Pancreatic NET - Follow-up 12/14

**FDG PET**

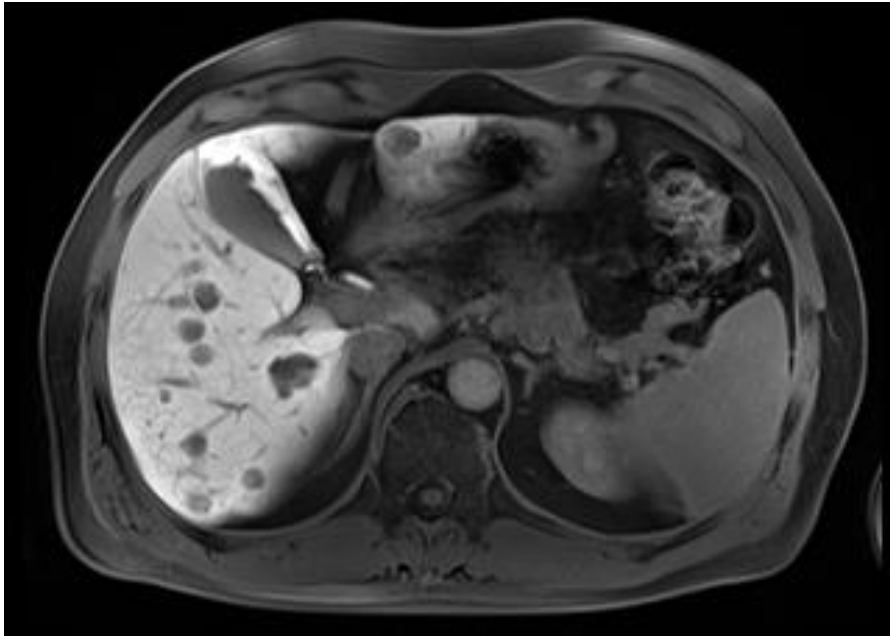


**Ga-68 DOTATOC  
PET/CT**



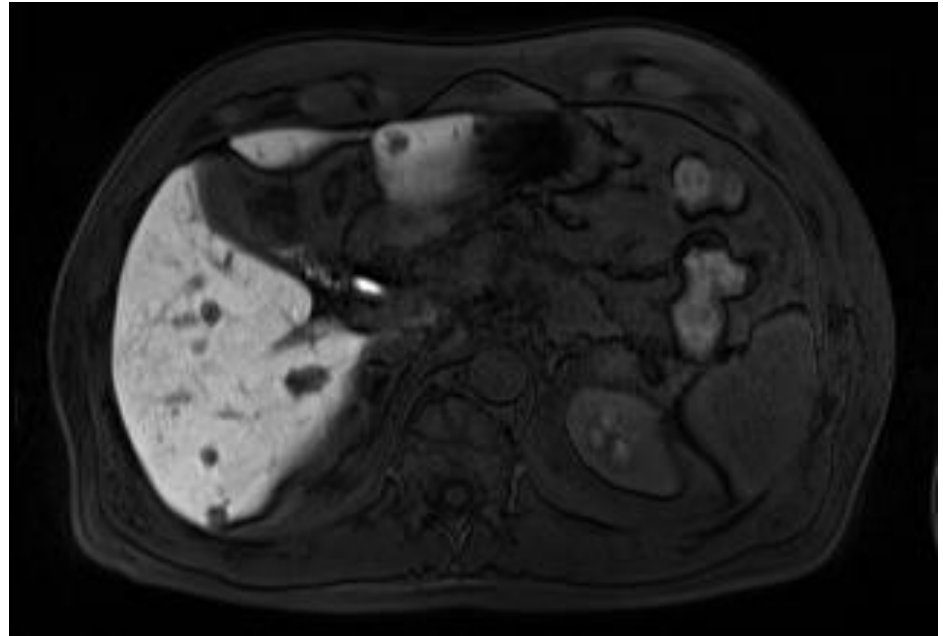
# Pancreatic NET - Follow-up

07/15



Everolimus 10 mg/ d

10/15



ongoing





# Everolimus side effects

- Sudden fatigue + severe Hypophosphataemia  
10 weeks after onset of EVE  
Phosphate supplementation
- Diabetes mellitus  
3 wks after onset of EVE;  
started on metformin,
- Hypercholesterolemia  
350-400 mg/dl  
3-4 weeks after onset of EVE  
Statin started

# Impact of PCT with SSA on treatment Guidelines (NCCN 2015)

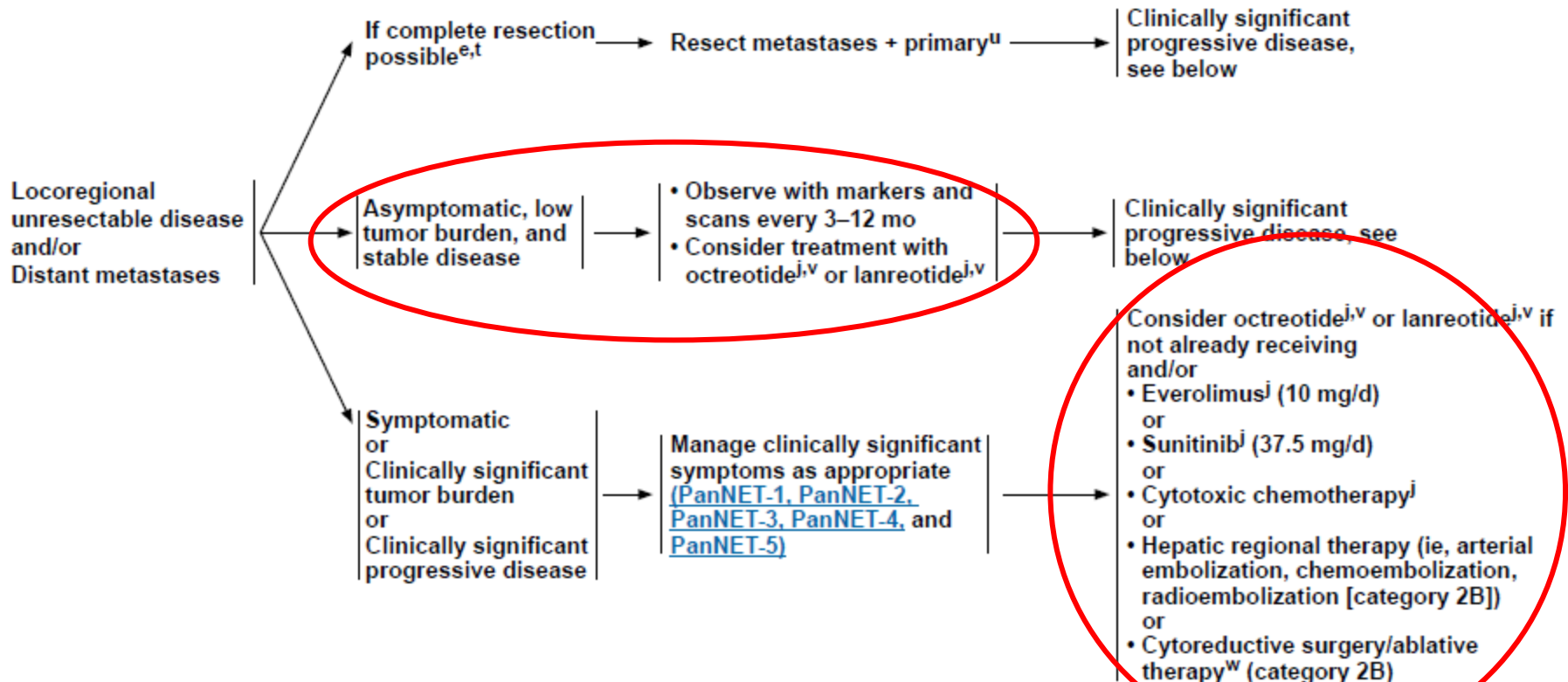


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## NCCN Guidelines Version 1.2015 Neuroendocrine Tumors of the Pancreas

[NCCN Guidelines Index](#)  
[Neuroendocrine TOC](#)  
[Discussion](#)

### MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES<sup>e</sup>



<sup>e</sup>See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).

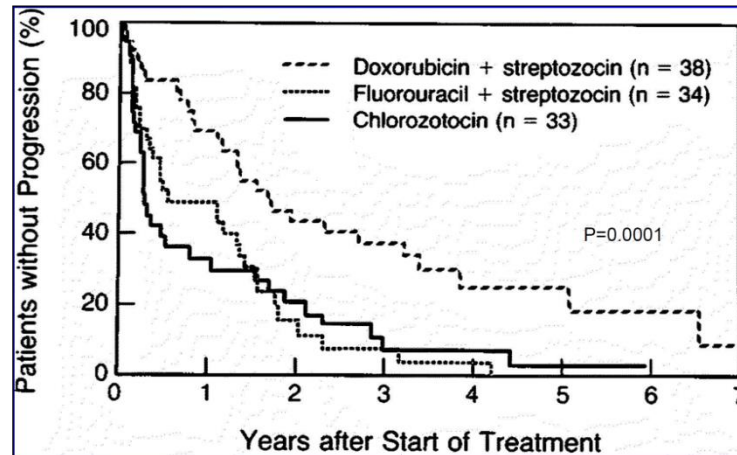
<sup>j</sup>See Principles of Systemic Anti-Tumor Therapy (NE-D).

Pan-NET-7

# Antiproliferative therapies in pNET

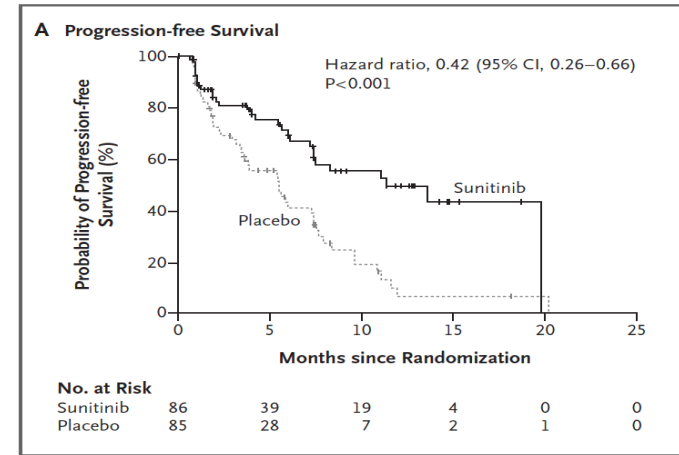
## Results from prospective randomized trials

### STREPTOZOTOCIN-BASED CT



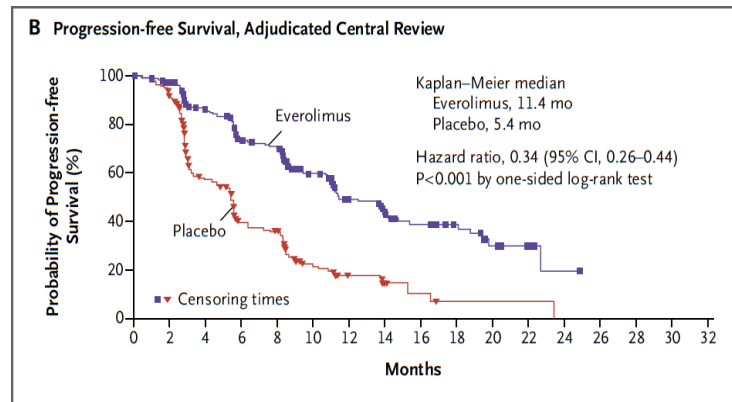
69% ORR  
45% ORR

### SUNITINIB



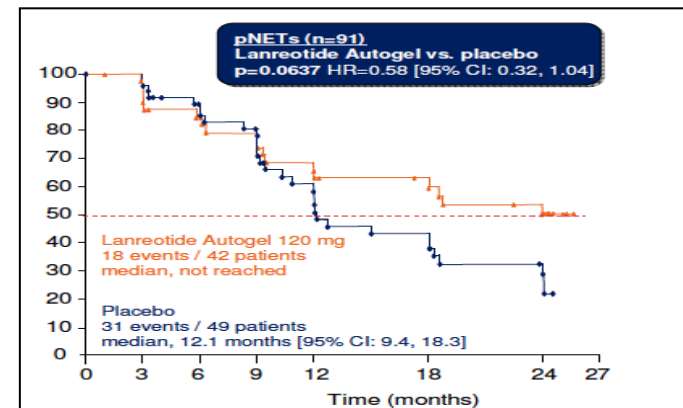
9% ORR

### EVEROLIMUS



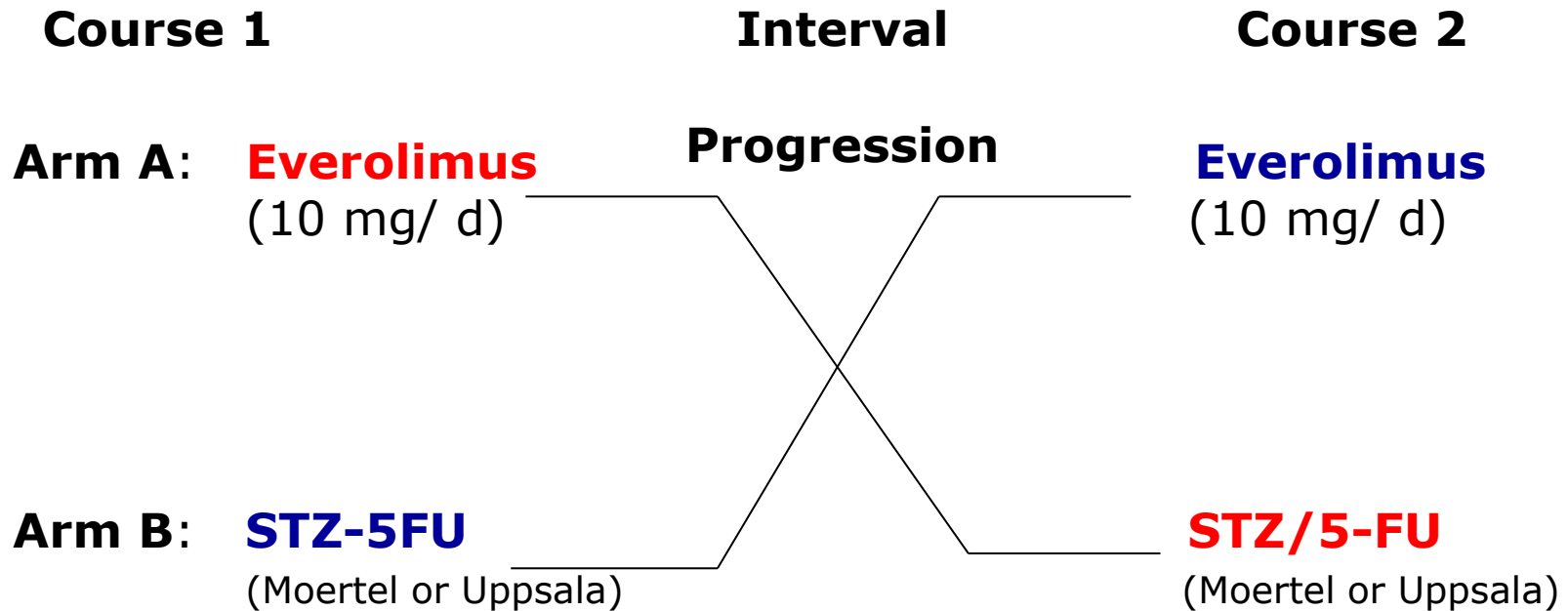
5% ORR

### LANREOTIDE



1% ORR

# Sequencing mTORi (SEQTOR) Everolimus – STZ/5-FU (ENETS)



Spanish GTE; supported by ENETS;  
Study Lead: Ramon Salazar, Barcelona

# Temozolomide based chemotherapy in advanced pancreatic NEN

Study	Type of study	Regimen	Number of patients with pNENs/ number of total NEN patients	Patients pretreated with chemotherapy, %	CR/PR, %	SD, %	TTP or PFS, months
Kulke et al. [45], 2006	phase II	TMZ 150 mg/m <sup>2</sup> /d, d1–7 and d15–21 thalidomide 50–400 mg/d, d1–30, q4wk	11/29	45	4/21	68	NA
Ekeblad et al. [34], 2007	retrospective	TMZ monotherapy 200 mg/m <sup>2</sup> , d1–5, q4wk	12/36	94	0/14	54	TTP: 7
Strosberg et al. [15], 2011					0/70	27	PFS: 18
Welin et al. [16], 2011					29	38	PFS: 6
Koumarianou et al. [46], 2012					57	21	TTP: 36
Chan et al. [47], 2012					15	65	PFS: 14
Claringbold et al. [60], 2012					5/38	38	PFS: 31
Chan et al. [51], 2013					7/40	53	PFS: 15
Fine et al. [53], 2013	retrospective	CAP 600 mg ×2/d, d1–14 TMZ 150–200 mg/m <sup>2</sup> :2/d, d10–14, q4wk	10/18	61	5/55	22	PFS: 14
Saif et al. [56], 2013	retrospective	CAP 1,000 mg ×2/d, d1–14 TMZ 200 mg/m <sup>2</sup> :2/d, d10–14, q4wk	7/7	57	0/42	28	PFS: 12
Peixoto et al. [59], 2014	retrospective	CAP 1,500 mg/m <sup>2</sup> /d, d1–14 TMZ 200 mg/m <sup>2</sup> /d, d10–14, q4wk	14/29	48	NA	NA	PFS: 5

Most studies are retrospective

TEM +/- CAP or BEV ...

ORR 14-70%

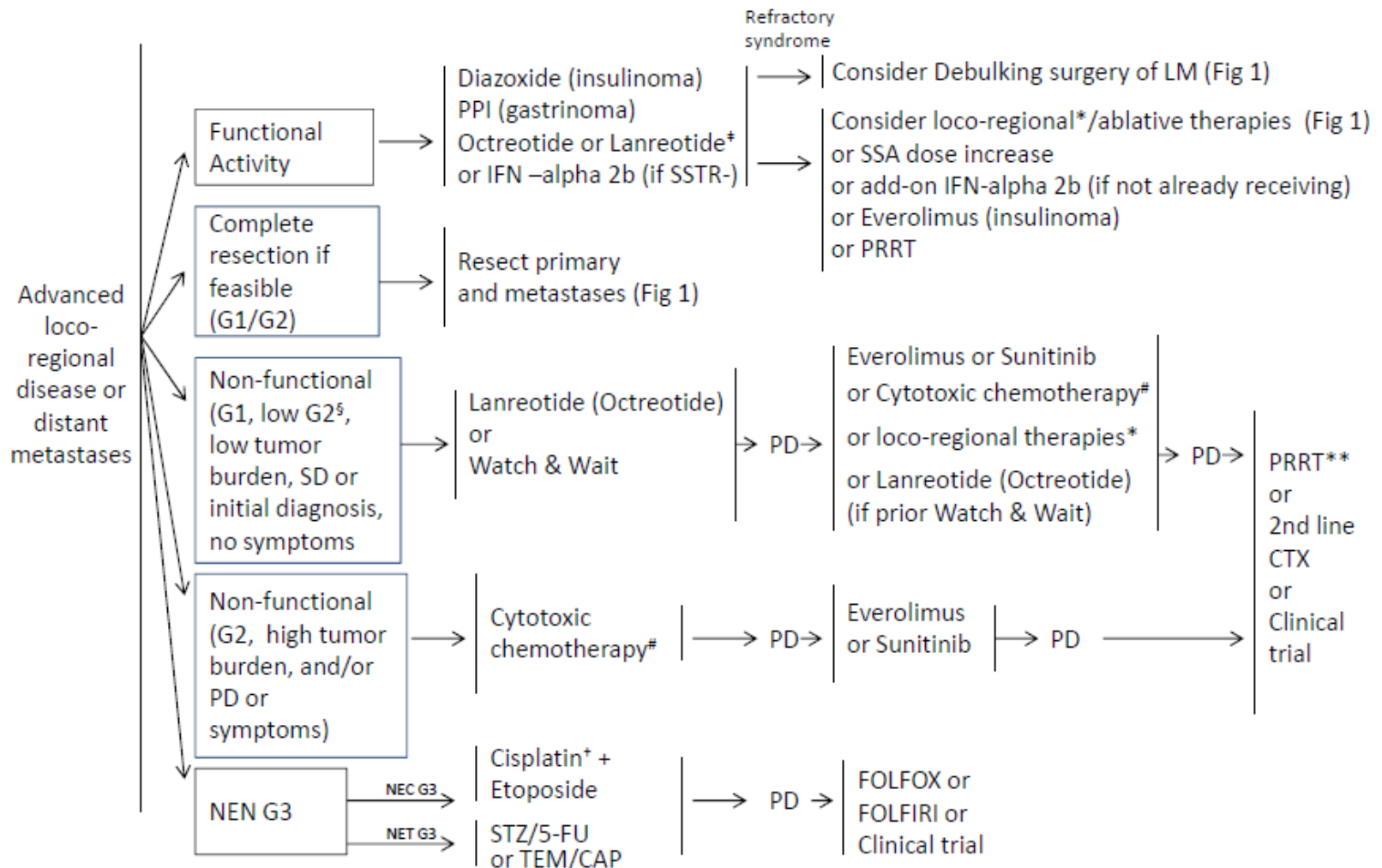
PFS or TTP: 5-36 mo.

# Parameters with impact on decision making

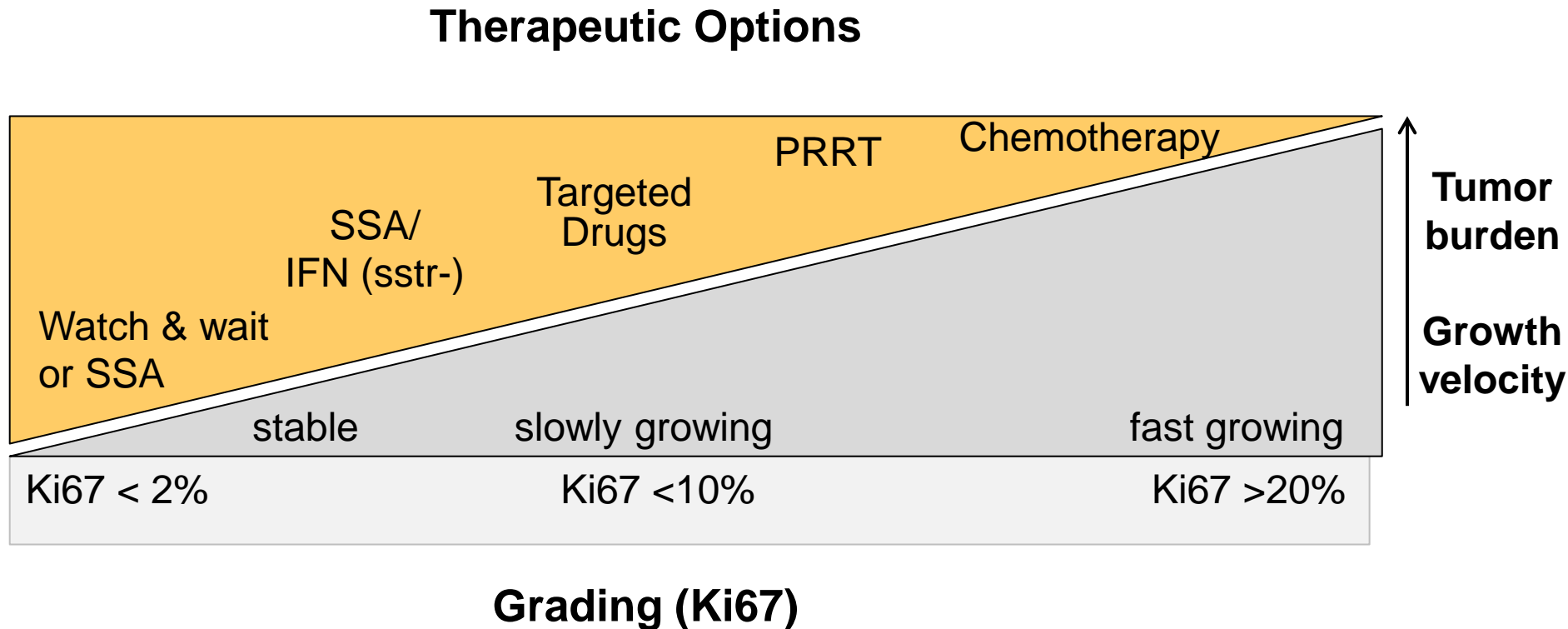
- SSTR status
- Growth velocity
- Grading
- Tumor burden
- Functionality
- Extrahepatic disease

# Updated ENETS Guidelines 2016

## Advanced pancreatic NET



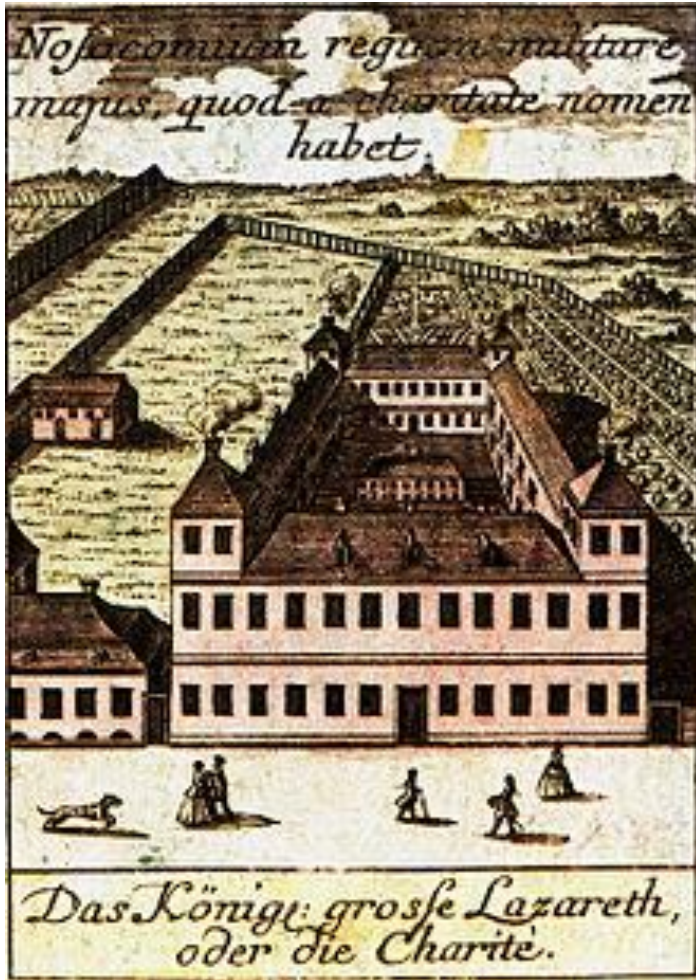
# Natural tumor biology of advanced NET: Factors with impact on decision making



Others: Functionality, Symptoms, SSTR expression profiles, side effects, safety, accessibility/ approval of drugs, primary site



# Thank You !



founded 1710

