What Have We Learned from Recent Major Clinical Trials for the Management of GEP-NET?

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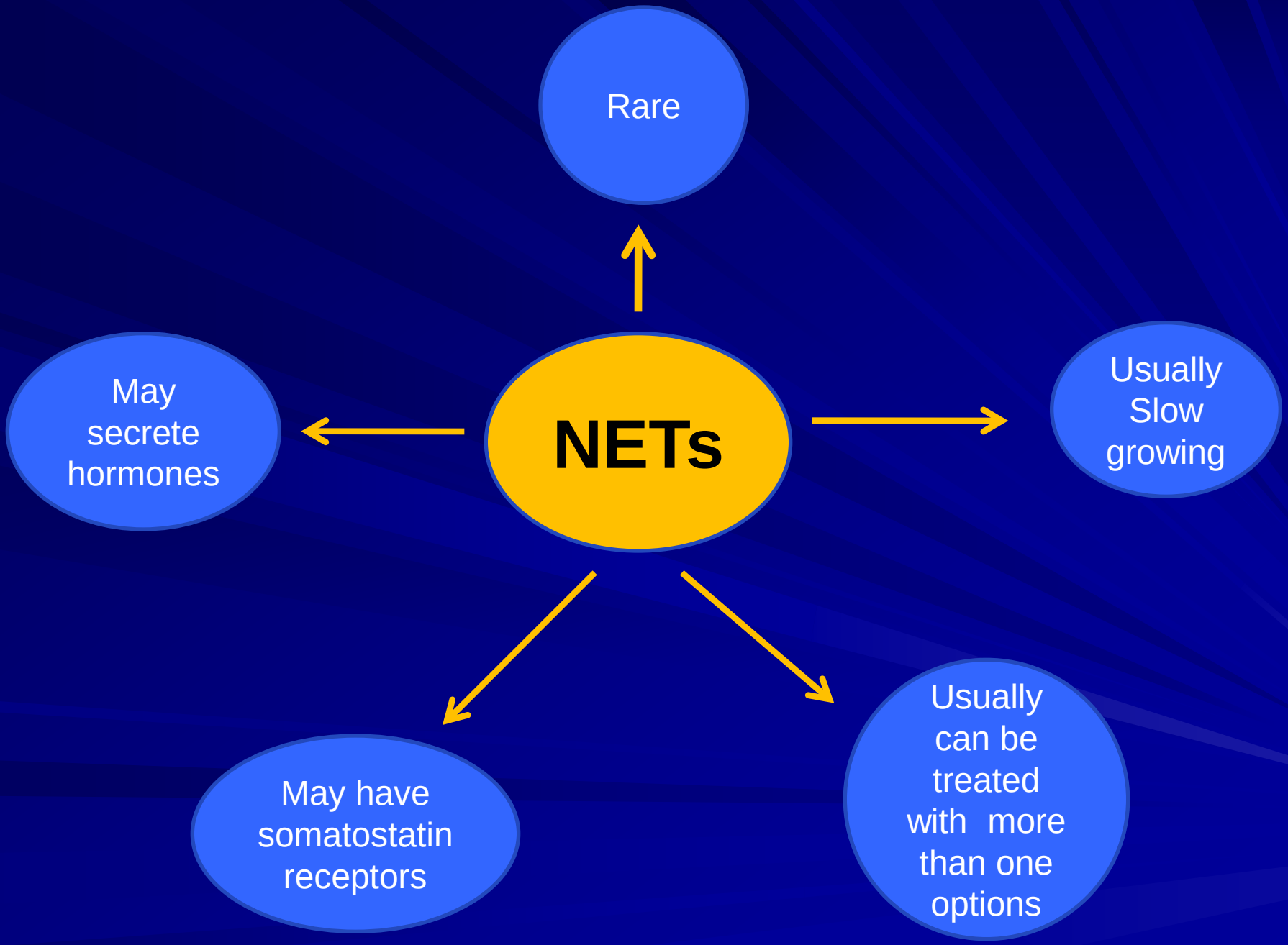
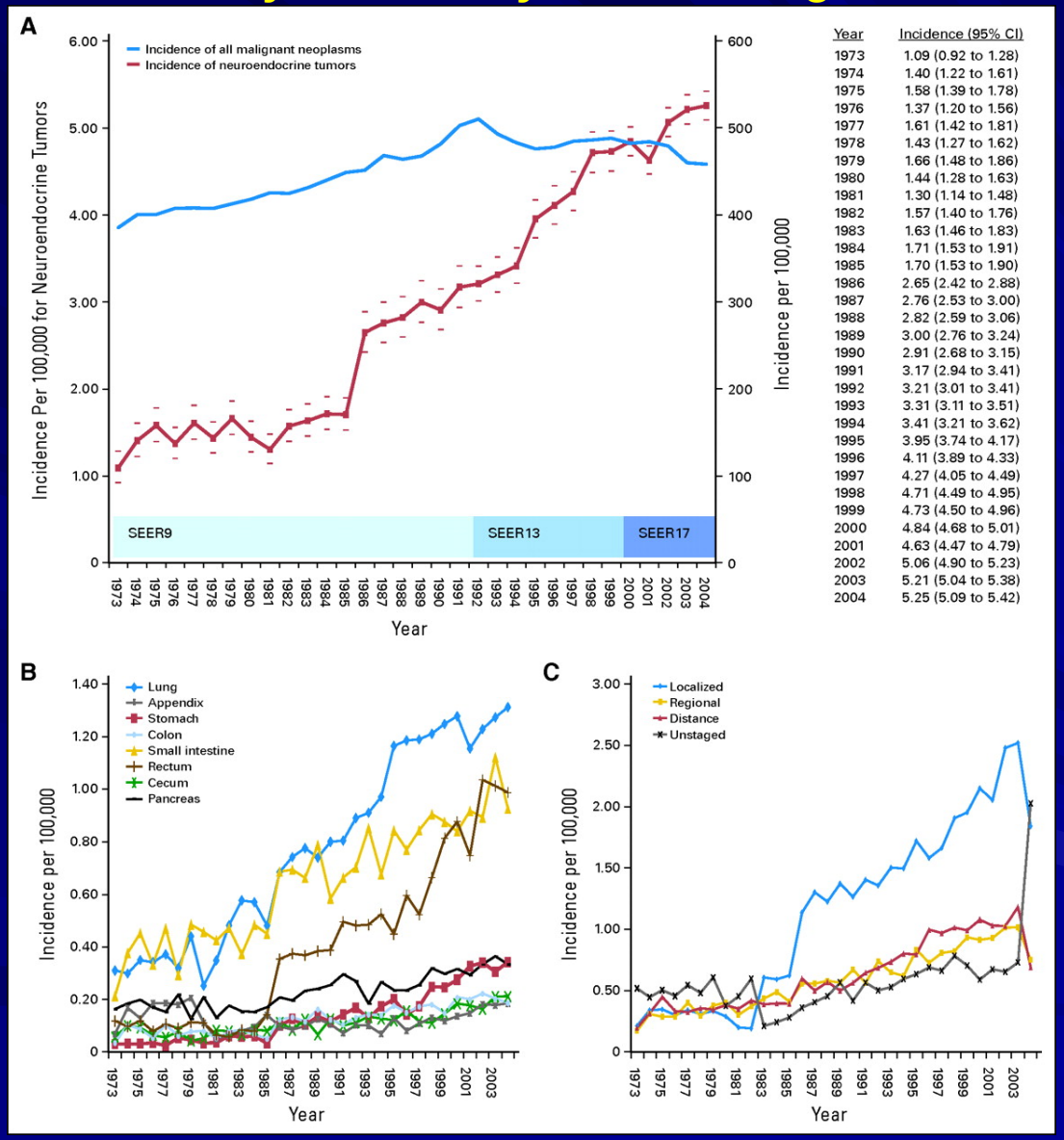
Contents

- Treatment targets in GEP NETs
- Large clinical trials in GEP-NETs for symptom control and control of tumour growth which resulted in approval of certain treatments
- New data for those treatments
- Position of those treatments in “Guidelines”


Rare
May secrete hormones
NETs
Usually Slow growing
May have somatostatin receptors
Usually can be treated with more than one options

Incidence of neuroendocrine tumors (NETs) over time, by site and by disease stage

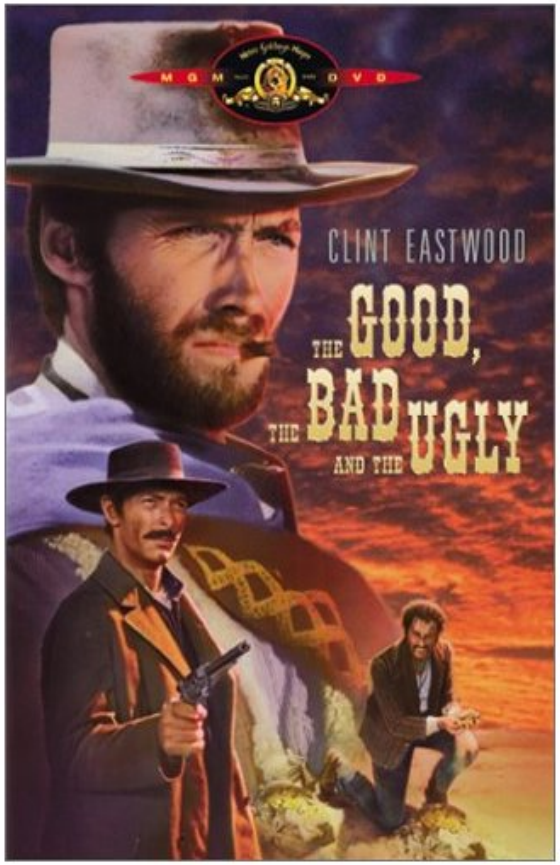


Year	Incidence (95% CI)
1973	1.09 (0.92 to 1.28)
1974	1.40 (1.22 to 1.61)
1975	1.58 (1.39 to 1.78)
1976	1.37 (1.20 to 1.56)
1977	1.61 (1.42 to 1.81)
1978	1.43 (1.27 to 1.62)
1979	1.66 (1.48 to 1.86)
1980	1.44 (1.28 to 1.63)
1981	1.30 (1.14 to 1.48)
1982	1.57 (1.40 to 1.76)
1983	1.63 (1.46 to 1.83)
1984	1.71 (1.53 to 1.91)
1985	1.70 (1.53 to 1.90)
1986	2.65 (2.42 to 2.88)
1987	2.76 (2.53 to 3.00)
1988	2.82 (2.59 to 3.06)
1989	3.00 (2.76 to 3.24)
1990	2.91 (2.68 to 3.15)
1991	3.17 (2.94 to 3.41)
1992	3.21 (3.01 to 3.41)
1993	3.31 (3.11 to 3.51)
1994	3.41 (3.21 to 3.62)
1995	3.95 (3.74 to 4.17)
1996	4.11 (3.89 to 4.33)
1997	4.27 (4.05 to 4.49)
1998	4.71 (4.49 to 4.95)
1999	4.73 (4.50 to 4.96)
2000	4.84 (4.68 to 5.01)
2001	4.63 (4.47 to 4.79)
2002	5.06 (4.90 to 5.23)
2003	5.21 (5.04 to 5.38)
2004	5.25 (5.09 to 5.42)

Yao, J. C. et al. J Clin Oncol; 26:3063-3072 2008 JOURNAL OF CLINICAL ONCOLOGY

Classification of NETS

WHO 2010 classification



(a) well- differentiated neuroendocrine tumours of G1-grade (Ki67≤ 2%)

(b) well-differentiated neuroendocrine tumours of G2-grade (Ki67 3-20%)

(c) poorly differentiated neuroendocrine carcinomas with high grade (G3, Ki67>20%) malignant behaviour.

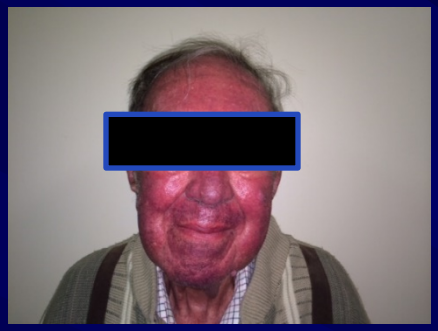
Treatment of GEP - NETs

A) Medical control of patient's hormonal symptoms.

B) Resection of tumor primary and if possible, metastatic lesions.

C) Control of tumor growth in cases of advanced disease.

D) Improvement and maintenance of patient's quality of life.



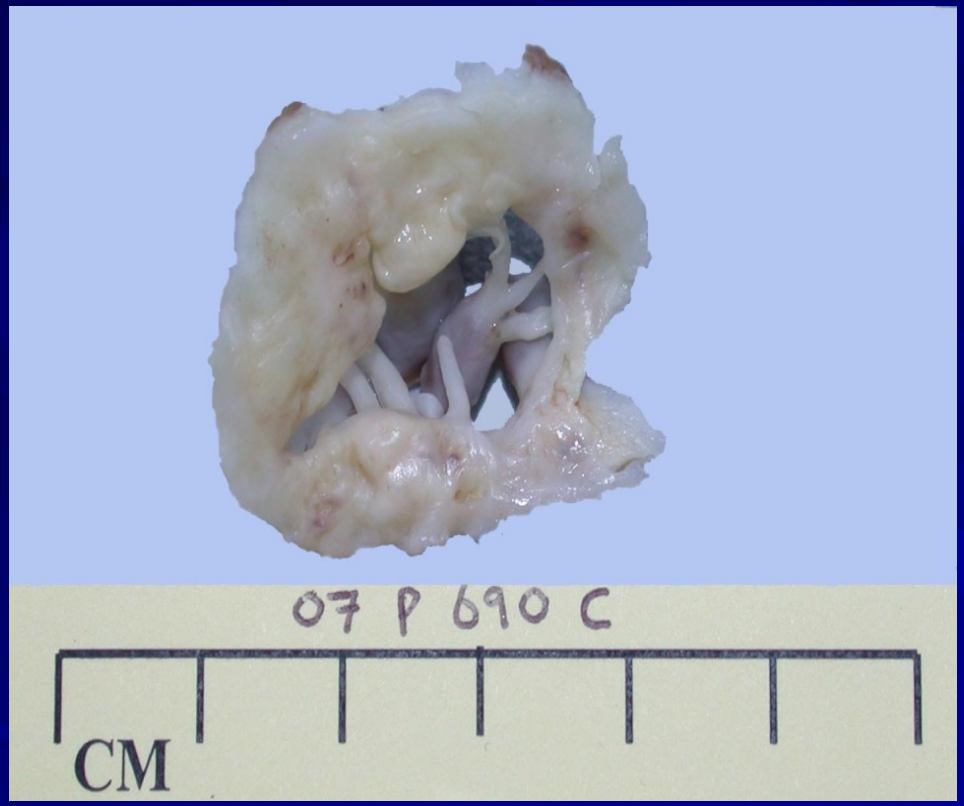
Carcinoid Syndrome

- **Associated with :**
  Serotonin, kallikrein and other tachykinins and bradykinins
- **In which NETs ?**
  In 20-40% of advanced small bowel NET, in 5% of bronchial and 1% of pancreatic NETs
- **Consists of:**
  Flushing, diarrhoea, bronchospasm, Carcinoid Heart Disease

- 20 – 30 % of patients with liver metastases
- 5% of patients with carcinoid syndrome do not have liver metastases

- **“Carcinoid crisis”**
  Severe symptoms of carcinoid syndrome + hypotension during procedures that involve GA, as well as in TAE, and when the patient is on inotropes

Carcinoid Heart Disease

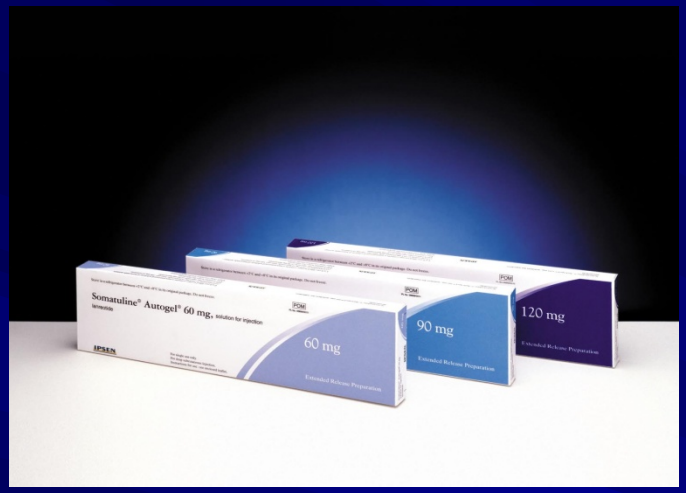


- May develop in 20 % of patients, with carcinoid syndrome.
- Main cause of death in 40-50% of patients.
- Involves mainly the right valves of the heart.
- May be present even in asymptomatic patients.
- Valve replacement in a selected group of patients.

Davar et al, JACC 2017

Somatostatin Analogues

Lanreotide Autogel



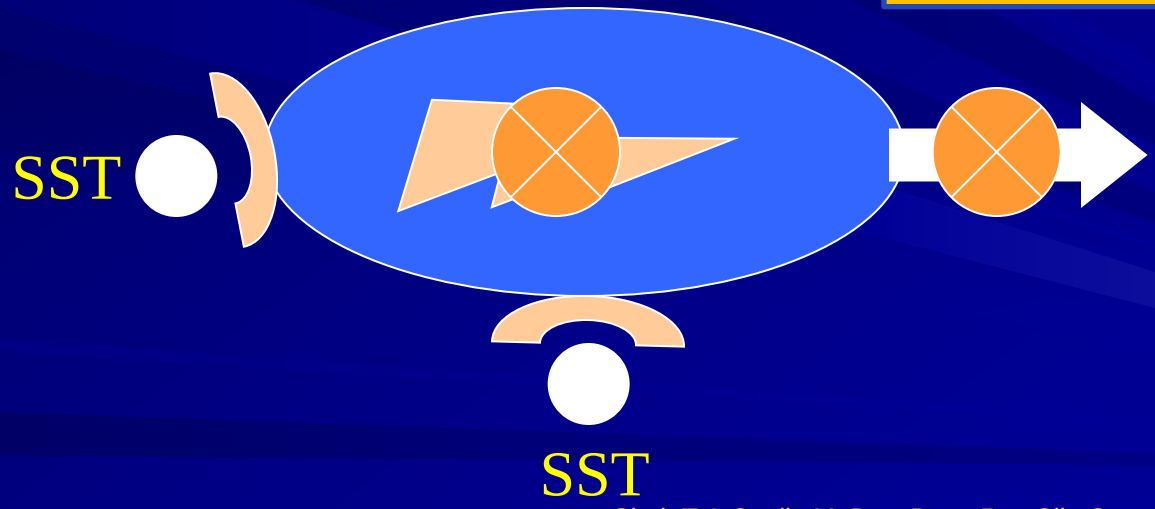
Octreotide LAR

Somatostatin analogues in “carcinoid syndrome”

- First & best choice medications
- Reduce flushing > 70%
- Reduce diarrhoea > 60%
- Biochemical response ~ 50%

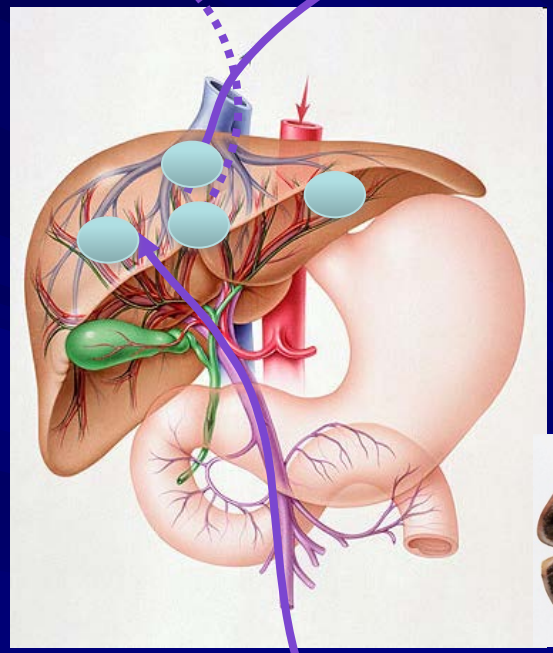
- Prospective cross over analysis of 33 patients
- No differences between octreotide and lanreotide in symptom control or biochemical response

O’Toole et al, Cancer 2000



Shah T & Caplin M, Best Pract Res Clin Gastroenterol. 2005
Plockinger U & Wiedenmann B, Best Pract Res Clin End Metab 2007

In addition to SSA, telotristat etiprate inhibits serotonin production and alleviates symptoms



Serotonin ↓

hormonal syndrome ↓

flushing, diarrhoea.....

5-HIAA ↓

Urine

NET-Cell

Tryptophan

Tryptophan-Hydroxylase

Telotristat etiprate

5-Hydroxytryptophan (5-HTP)

Serotonin (5-HT)

Serotonin ↓

SSTR

SSA

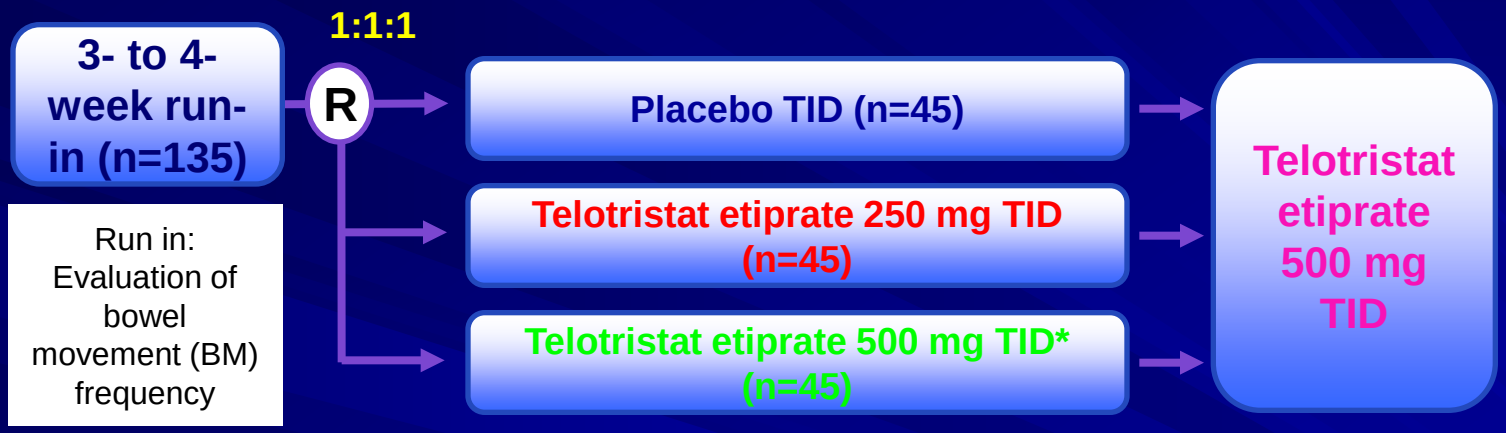
5-HIAA: 5-hydroxyindole acetic acid

SSA somatostatin analogue

SSTR somatostatin receptor

TELESTAR

Phase 3 Study – Refractrory diarrhoea due to carcinoid syndrome (> 4 bowel movements / day)

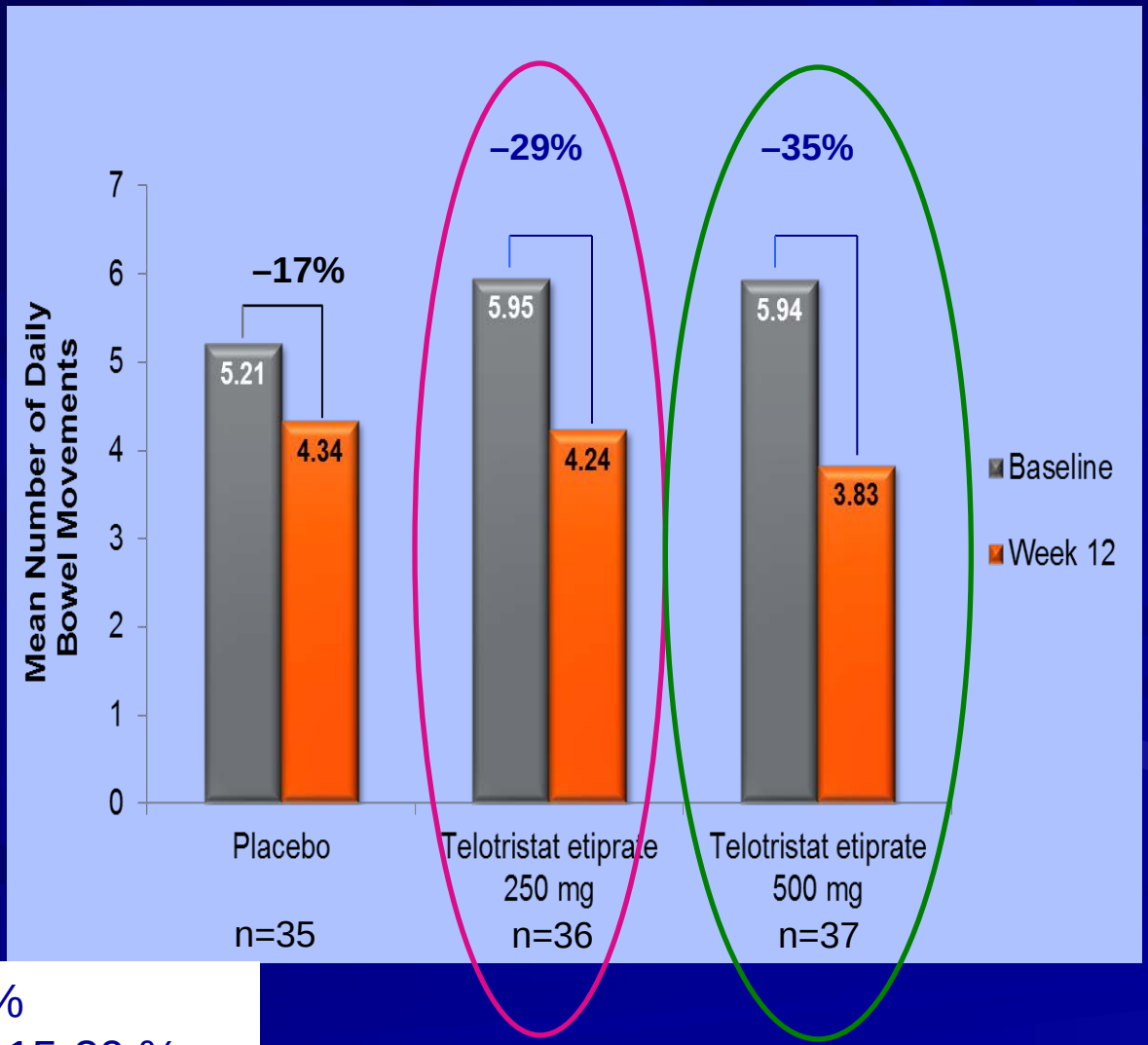


Evaluation of primary endpoint:

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

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

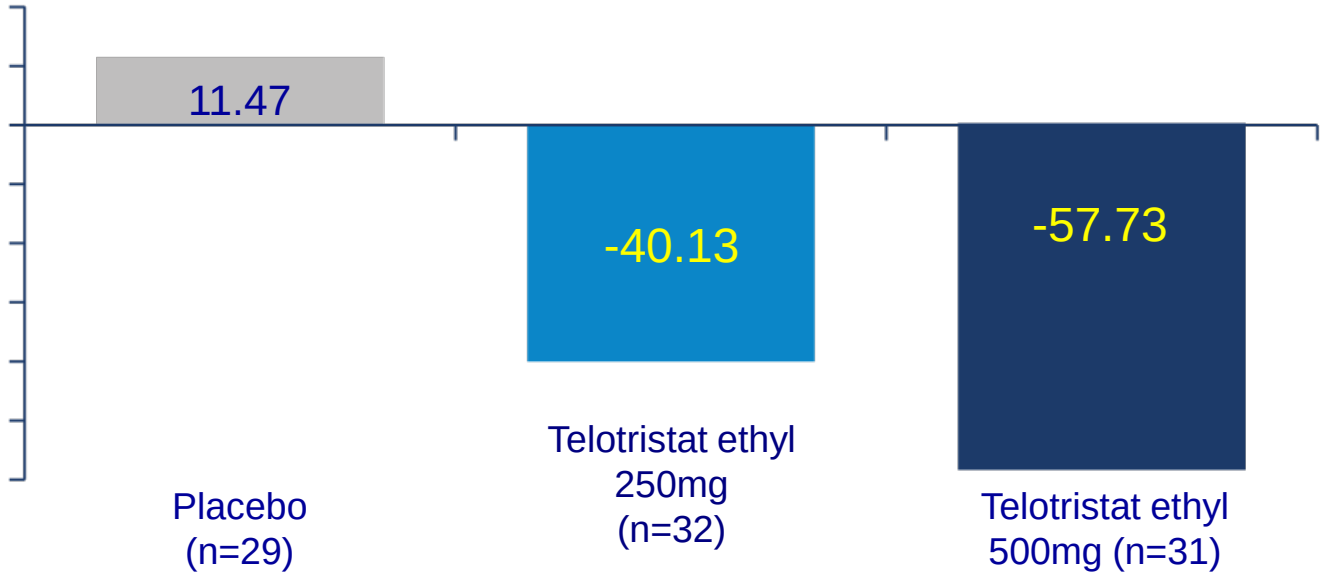
TELESTAR results : Reduction in Mean Daily Bowel Movement Frequency at Baseline and Week 12



Mild nausea: 15%
Mild depression: 15-20 %

Phase III TELESTAR

Mean change in u5-HIAA (mg/24 hours) from baseline to week 12[1]



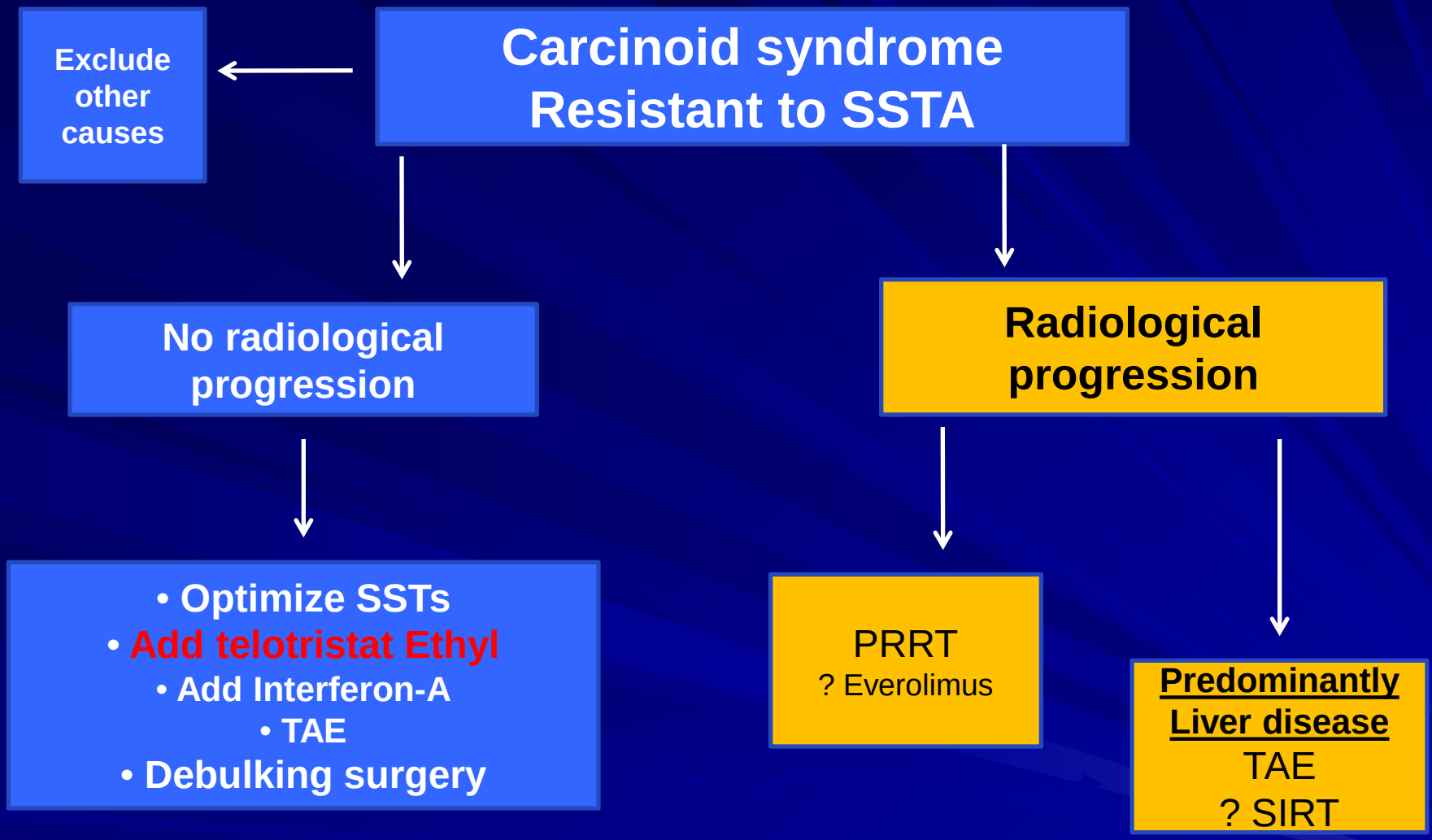
All patients continued SSA therapy throughout the study period.

Data include only patients for whom both baseline and week 12 assessments were available.

- *Wilcoxan rank-sum test showed significant differences for each telotristat ethyl dose vs placebo (P<0.001)*
- *Baseline 5-HIAA levels across treatment arms ranged from 80.96-92.65 mg/24 h*

Phase III TELESTAR:

- *Telotristat ethyl significantly reduced BM frequency in patients with carcinoid syndrome inadequately controlled with SSA therapy[1]*
- *Patients receiving telotristat ethyl demonstrated more durable responses compared with placebo and the difference was statistically significant[1]*
- *Telotristat ethyl significantly decreased 24-hour u5-HIAA in a dose-dependent manner in patients with inadequately controlled carcinoid syndrome[1]*
- *Inhibition of u-5HIAA is consistent with the proposed mechanism of action of telotristat ethyl*
- *Reductions in flushing and abdominal pain were greater on treatment with telotristat ethyl (not statistically significant)[1]*
- *Telotristat ethyl was well tolerated in the TELESTAR study[1]*


Carcinoid syndrome
Resistant to SSTA
Exclude other causes
No radiological progression
Radiological progression
• Optimize SSTs
• Add telotristat Ethyl
• Add Interferon-A
• TAE
• Debulking surgery
PRRT
? Everolimus
Predominantly Liver disease
TAE
? SIRT

Control of tumour growth for advanced GEP-NET

Locoregional therapy

- Radiofrequency ablation (RFA)
- Embolization / chemoembolization / radioembolization

Medical therapy

- Somatostatin analogs (SSAs)
- Interferon-α
- Molecular Targeted therapies
  - mTOR inhibitors
  - VEGFR inhibitors
  - other TKIs
- Systemic Chemotherapy

Nuclear medicine and Radiation

- Tumor-targeted, radioactive therapy: PRRT using e.g.
  - MIBG
  - ^{90}Y-DOTATOC
  - ^{177}Lu –DOTATATE
- External Radiation (for bone, brain-metastases)
- Brachytherapy (for liver metastases)

MIBG, meta iodobenzylguanidine; mTOR, mammalian target of rapamycin; PRRT, peptide-receptor radiotherapy; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

ENETS consensus guidelines for the management of NET. Neuroendocrinology. 2012;95:71-176. NCCN guidelines: Neuroendocrine tumors. V2.2013.

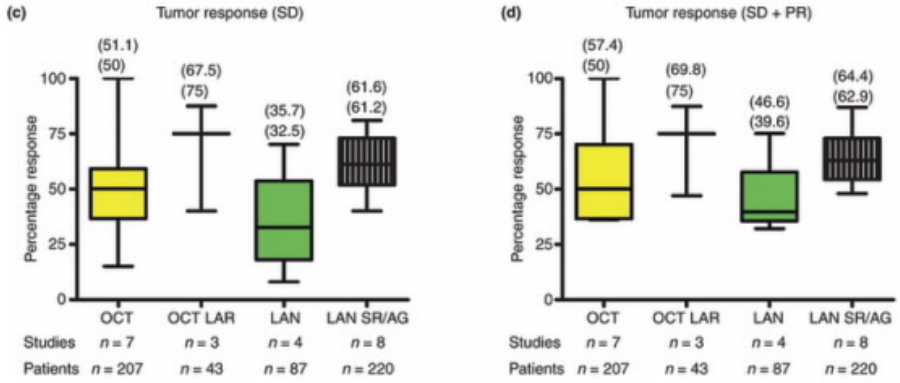
Somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine (carcinoid) tumours

- Number of studies : 7

-Number of patients : 207

- Tumour shrinkage: 3 – 8 %

- Overall tumour responses : 60 – 70%



Modlin et al, Aliment Pharmacol Ther, 2010

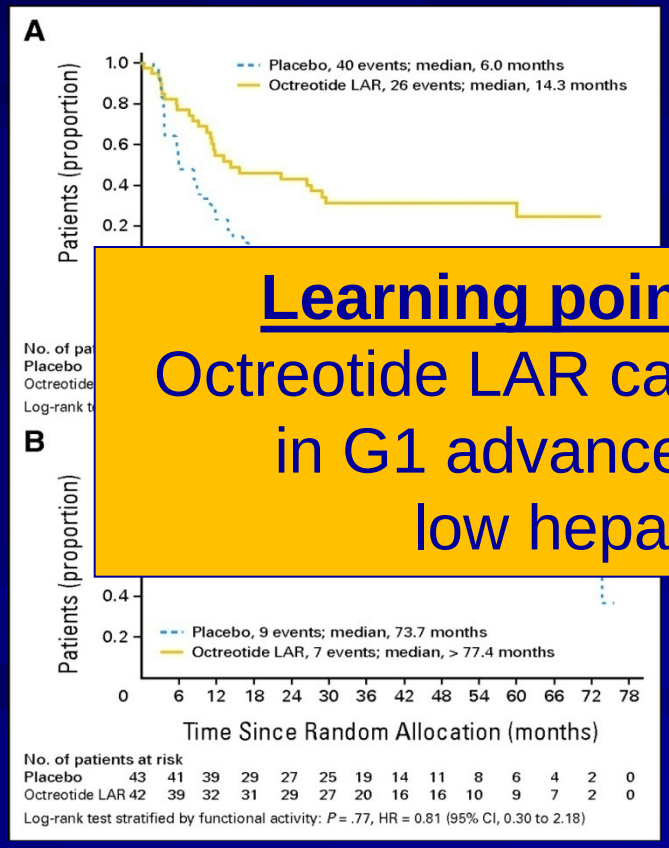
VOLUME 27 · NUMBER 28 · OCTOBER 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients With Metastatic Neuroendocrine Midgut Tumors: A Report From the PROMID Study Group

Anja Rinke, Hans-Helge Müller, Carmen Schade-Brittinger, Klaus-Jochen Klose, Peter Barth, Matthias Wied, Christina Mayer, Behnaz Aminossadati, Ulrich-Frank Pape, Michael Bläker, Jan Harder, Christian Arnold, Thomas Gress, and Rudolf Arnold



- Median time to progression in LAR group:
  14.3 m vs 6 months in placebo

of LAR

patients with low-hepatic tumour load and resected primary tumour

Learning point from PROMID trial

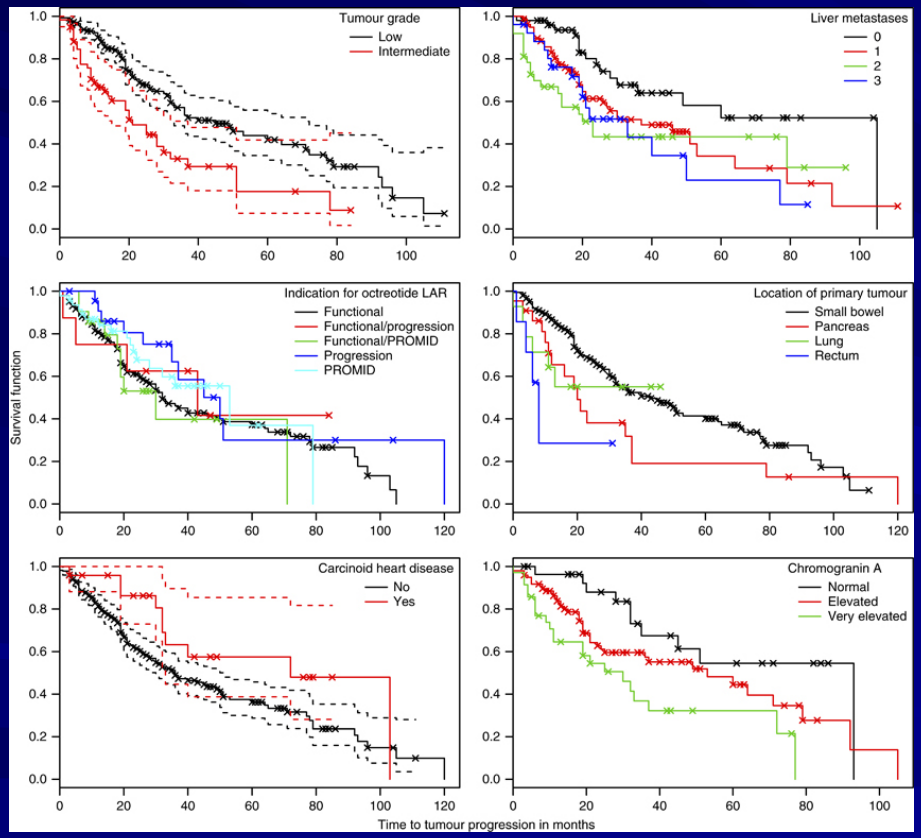
Octreotide LAR can control tumour growth in G1 advanced midgut NETs and low hepatic tumour load

Rinke A et al. JCO 2009;27:4656-4663

JOURNAL OF CLINICAL ONCOLOGY

Predictive factors of antiproliferative activity of octreotide LAR as first-line therapy for advanced neuroendocrine tumours

Laskaratos et al, British J Cancer 2016



- **204 patients**
- 5% Objective Response
- **Median TTRP was 37 months** (95% confidence interval, CI: 32–52 months).
- There was a statistically significant shorter TTRP in patients with pancreatic tumours, liver metastases and intermediate grade tumours.
- Extremely raised (>10 times the upper limit of normal) baseline Chromogranin A levels were associated with an unfavourable outcome.
- Male sex, carcinoid heart disease and **initiation of treatment in the presence of stable disease** were predictive of a better response.

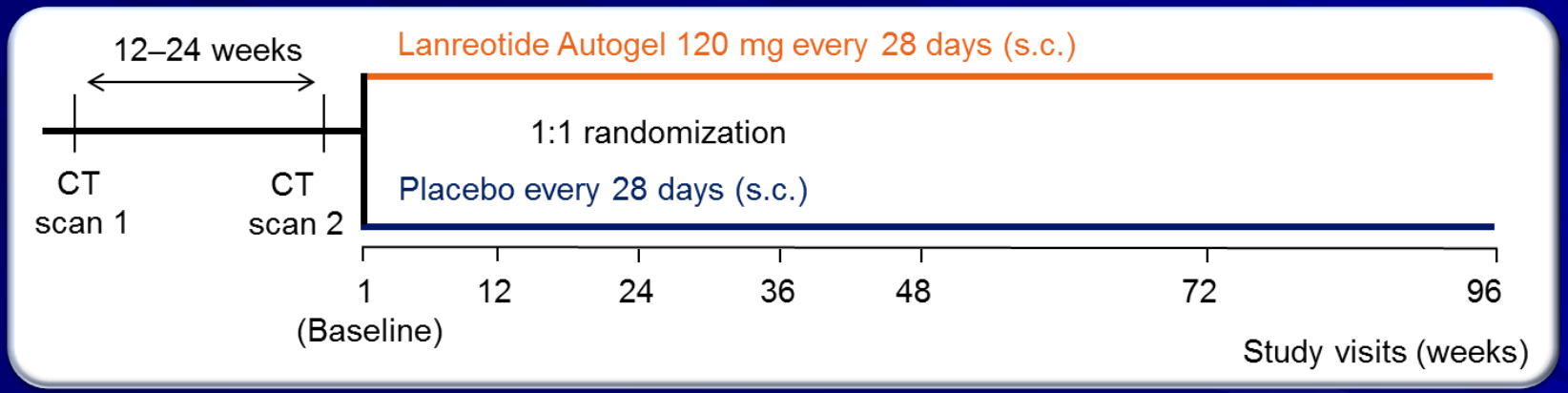
CLARINET
(Controlled study of Lanreotide Antiproliferative Response In NET)

Aim

- To compare effect of lanreotide Autogel 120 mg vs. placebo on PFS in well-/moderately differentiated non-functioning enteropancreatic NETs

Design

- International multicentre randomized double-blind placebo-controlled phase 3 study

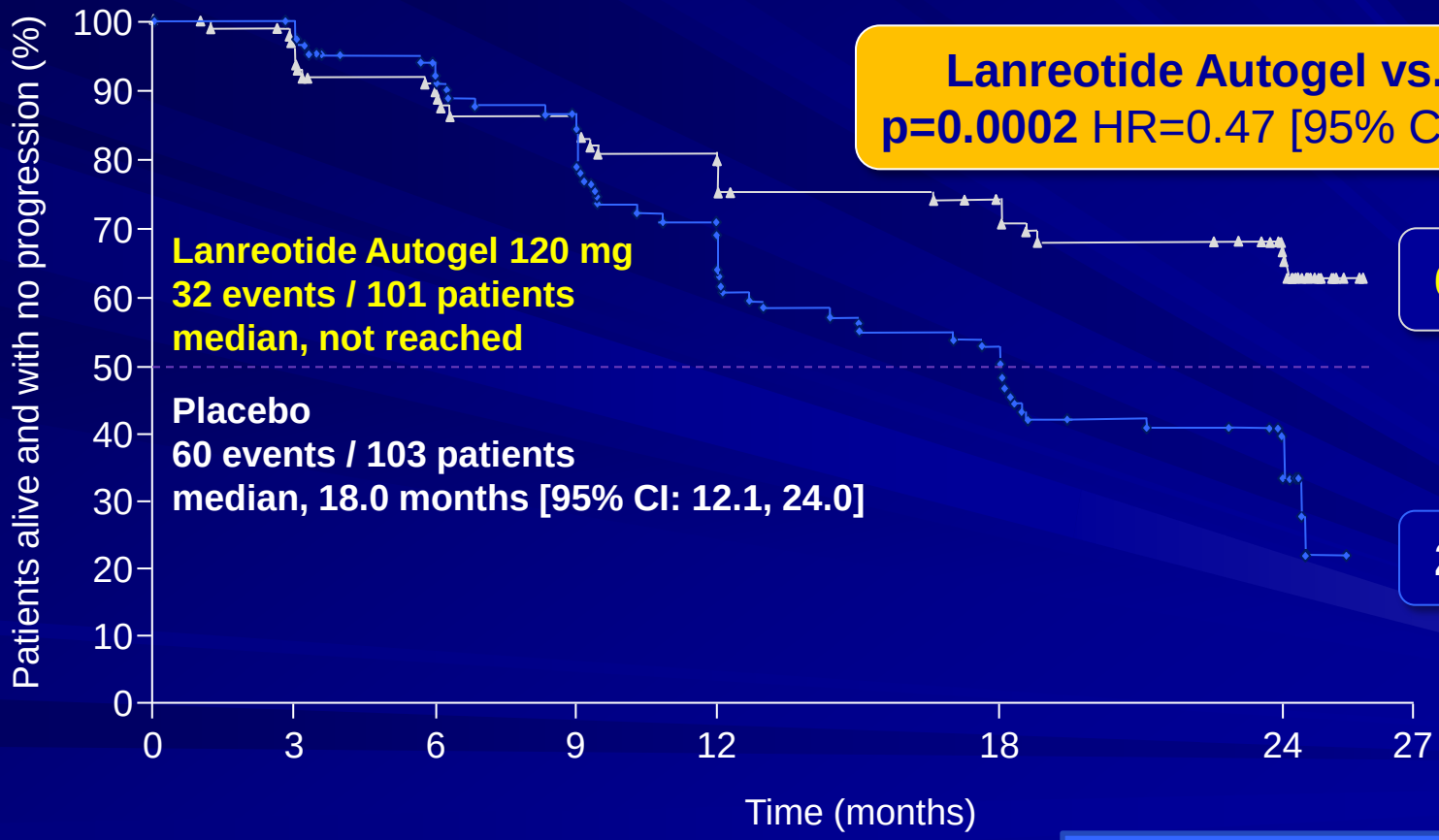


- Ki-67 <10%
- Tumours measurable according to RECIST 1.0 (centrally assessed)
- 96% had NO progression before randomization
- 33% had hepatic tumour volumes > 25%

Caplin M, et al. New Engl J Med 2014

Progression-free survival and tumor growth with Lanreotide Autogel in patients with enteropancreatic NETs: *Results from CLARINET, a randomized, double-blind, placebo-controlled study*

Primary endpoint: PFS (ITT, N=204)

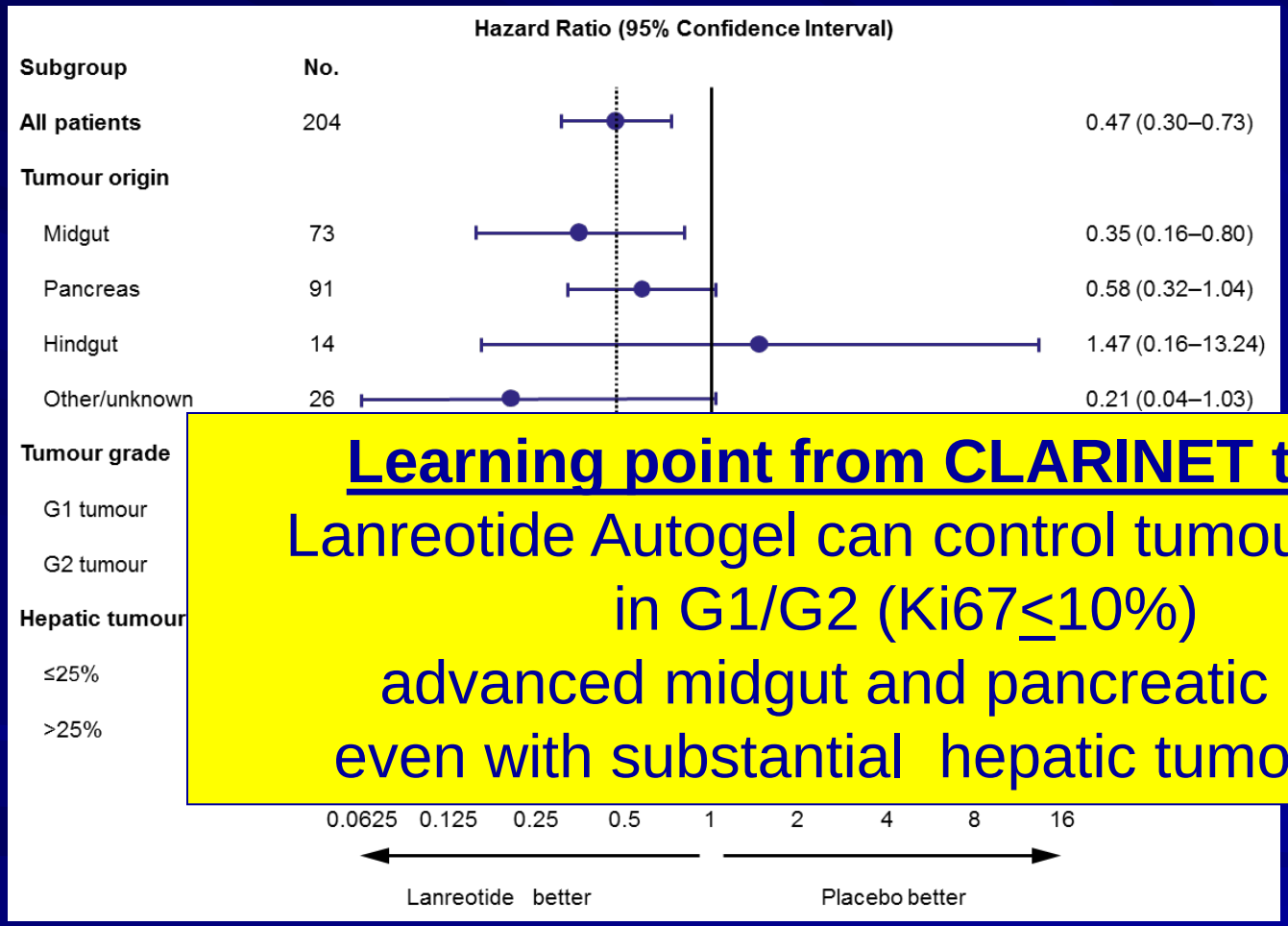


Lanreotide Autogel vs. placebo
p=0.0002 HR=0.47 [95% CI: 0.30, 0.73]

Caplin et al, NEJM 2014

P-value derived from stratified log-rank test; HR derived from Cox proportional hazard model.
HR, hazard ratio; ITT, intention-to-treat.

PFS: therapeutic effect in pre-defined subgroups generally consistent with overall population



PFS in p NETs
Lanreotide : not reached
Placebo: 12.1 months

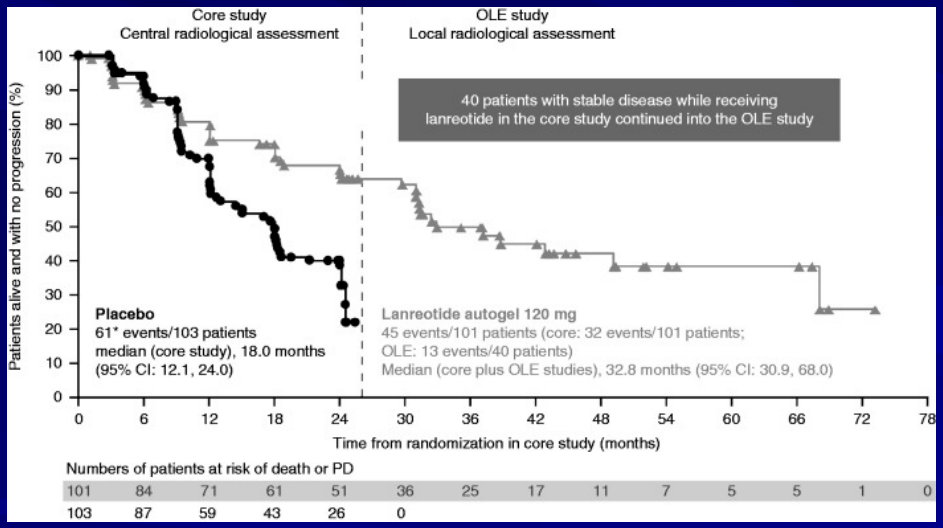
Learning point from CLARINET trial

Lanreotide Autogel can control tumour growth
in G1/G2 (Ki67≤10%)
advanced midgut and pancreatic NETs
even with substantial hepatic tumour load

Caplin M, et al. New Engl J Med 2014

Anti-tumour effects of lanreotide for pancreatic and intestinal neuroendocrine tumours: the CLARINET open-label extension study

Caplin et al, Endocr Rel Cancer 2016



- Patients with stable disease (SD) at core study end (lanreotide/placebo) or PD (placebo only) continued or switched to lanreotide in the OLE.
- In total, **88 patients** (previously: lanreotide, *n*=41; placebo, *n*=47) participated: 38% had pancreatic, 39% midgut and 23% other/unknown primary tumours.
- Median time to further PD after placebo-to-lanreotide switch (*n*=32) was **14.0 months.**

Tumour Growth Rate as an indicator of antitumour activity with lanreotide Autogel/Depot vs placebo in intestinal/pancreatic NET: post hoc analysis of CLARINET data

Caplin M et al, Abstract in 13th Annual ENETS Conference, 2016

- **Tumour Growth Rate (TGR)** : % variation of tumour volume per month
- Mean pre-treatment TGR
  - Lanreotide group: 4.1%
  - Placebo group: 3.3%
- At 12 weeks' treatment
  - Mean TGR Lanreotide : 1.2%
  - Mean TGR Placebo : 4.1%

- *ROC analysis : TGR > 4% resulted in 4-fold higher risk of progression than TGR ≤ 4%*
- *Regardless of pretreatment TGR, Lanreotide is more effective than Placebo in delaying progressive disease*

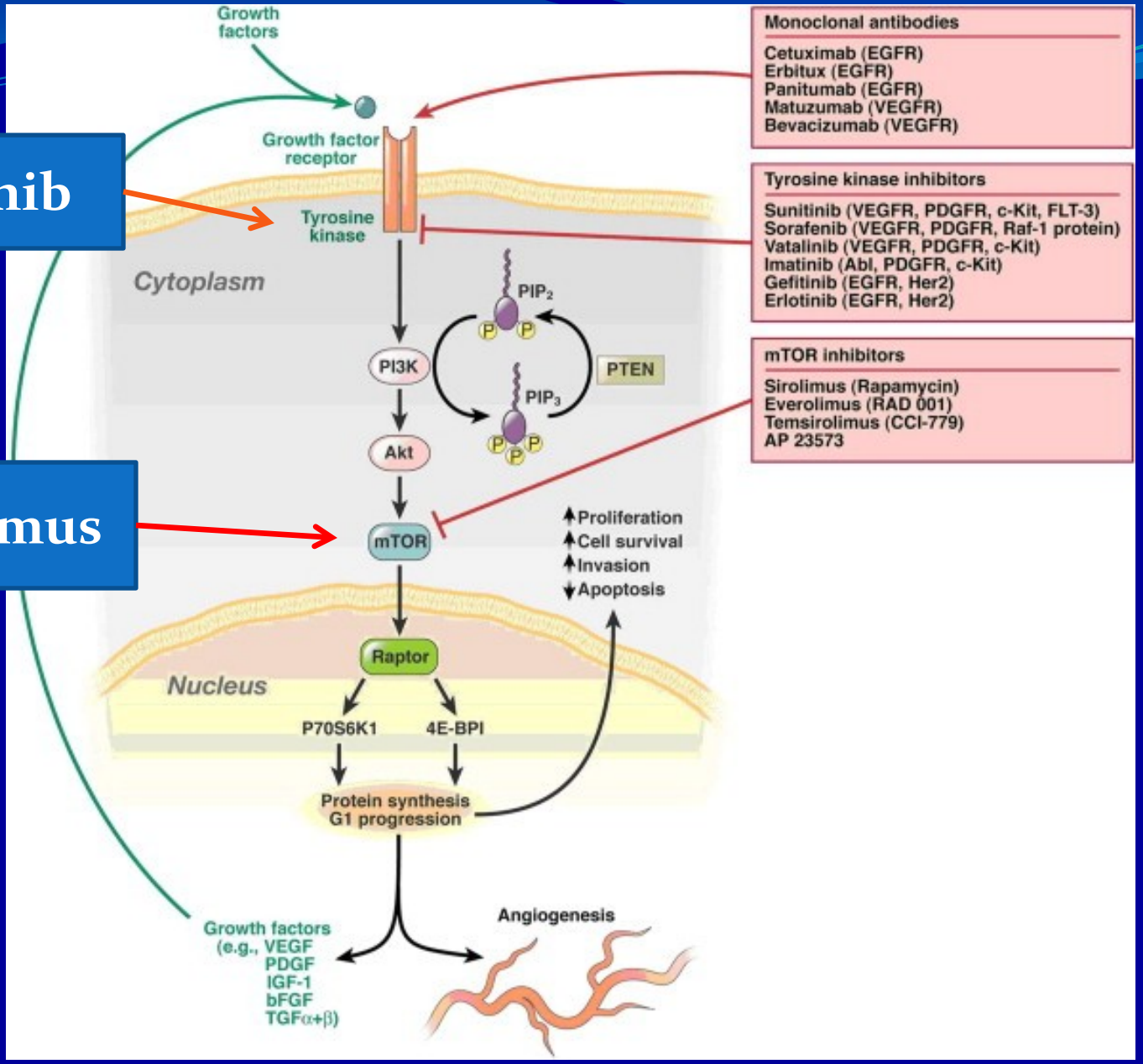
Prognostic factors for progression-free survival (PFS) in CLARINET study of lanreotide depot/autogel (LAN) vs placebo (PBO) in neuroendocrine tumors (NETs)

Wolin EM, et al. J Clin Oncol 2015; 33 (suppl.): e15180.

- **Risk of Progressive Disease (PD) /death** was increased in patients with:
  - *Hepatic tumor load (HTL) >25%*
  - *Primary tumor in pancreas*
  - *Below-median BMI*
- Effect of previous treatments was not significant.
- Adjusted for covariates, treatment with LAN vs PBO reduced the risk of PD/death by 60%.

Sunitinib

Everolimus



D.Metz & R.Jensen, Gastroenterology 2008

Sunitinib Malate for the Treatment of Pancreatic Neuroendocrine Tumors

Eric Raymond, M.D et al, *N ENGL J MED 2011; 364:501-513*

- Double blind randomized study
- 171 patients
- Progression within 12 months
- Ki67 ≤ 2
- 69% ha
- Sunitinib

	PFS	OR	Deaths
Sunitinib	11.4	9.3%	9 (10%)
			5%)

Learning point from Sunitinib trial

Oral Sunitinib can control tumour growth in G1/G2 advanced & progressive pancreatic NETs with potential favorable implications to OS

30% : diarrhoea, nausea, vomiting, fatigue
10-20% : Hypertension, neutropenia

hea, n
global HRQoL

Vinik A et al, Target Oncol 2016

Five years after study closure, **median OS was 38.6** (25.6-56.4) months for sunitinib and 29.1 (16.4-36.8) months for placebo (P = 0.094), with 69% of placebo patients having crossed over to sunitinib

Faivre et al, Ann Oncol 2016

Everolimus for Advanced Pancreatic Neuroendocrine Tumours (RADIANT-3)

James C. Yao et al, *N ENGL J MED 2011; 364:514-523*

- Double blind randomized trial
- 410 patients – 50% chemo-naive
- Ki
- Pr
- Ev

	PFS	OR
		%
		%

Learning point from RADIANT-3 trial

Oral Everolimus can control tumour growth
in G1/G2
advanced & progressive pancreatic NETs

➢ 10 – 30% : lower respiratory infections, interstitial pneumonitis
➢< 10% : cytopenias, hyperglycaemia

Everolimus prolonged PFS regardless of prior chemotherapy

Lombard-Bohas C et al, Pancreas 2015

RADIANT-4 Study Design

Patients with well-differentiated (G1/G2), advanced, progressive, nonfunctional NET of lung or GI origin (N = 302)

- Absence of active or any history of carcinoid syndrome
- Pathologically confirmed advanced disease
- Enrolled **within 6 months from radiologic progression**

RANDOMIZE

2:1

Everolimus 10 mg/day
N = 205

Placebo
N = 97

Treated until PD, intolerable AE, or consent withdrawal

Endpoints:

- **Primary:** PFS (central)
- **Key Secondary:** OS
- **Secondary:** ORR, DCR, safety, HRQoL (FACT-G), WHO PS, NSE/CgA, PK

Stratified by:

- Prior SSA treatment (yes vs. no)
- Tumor origin (stratum A vs. B)*
- WHO PS (0 vs. 1)

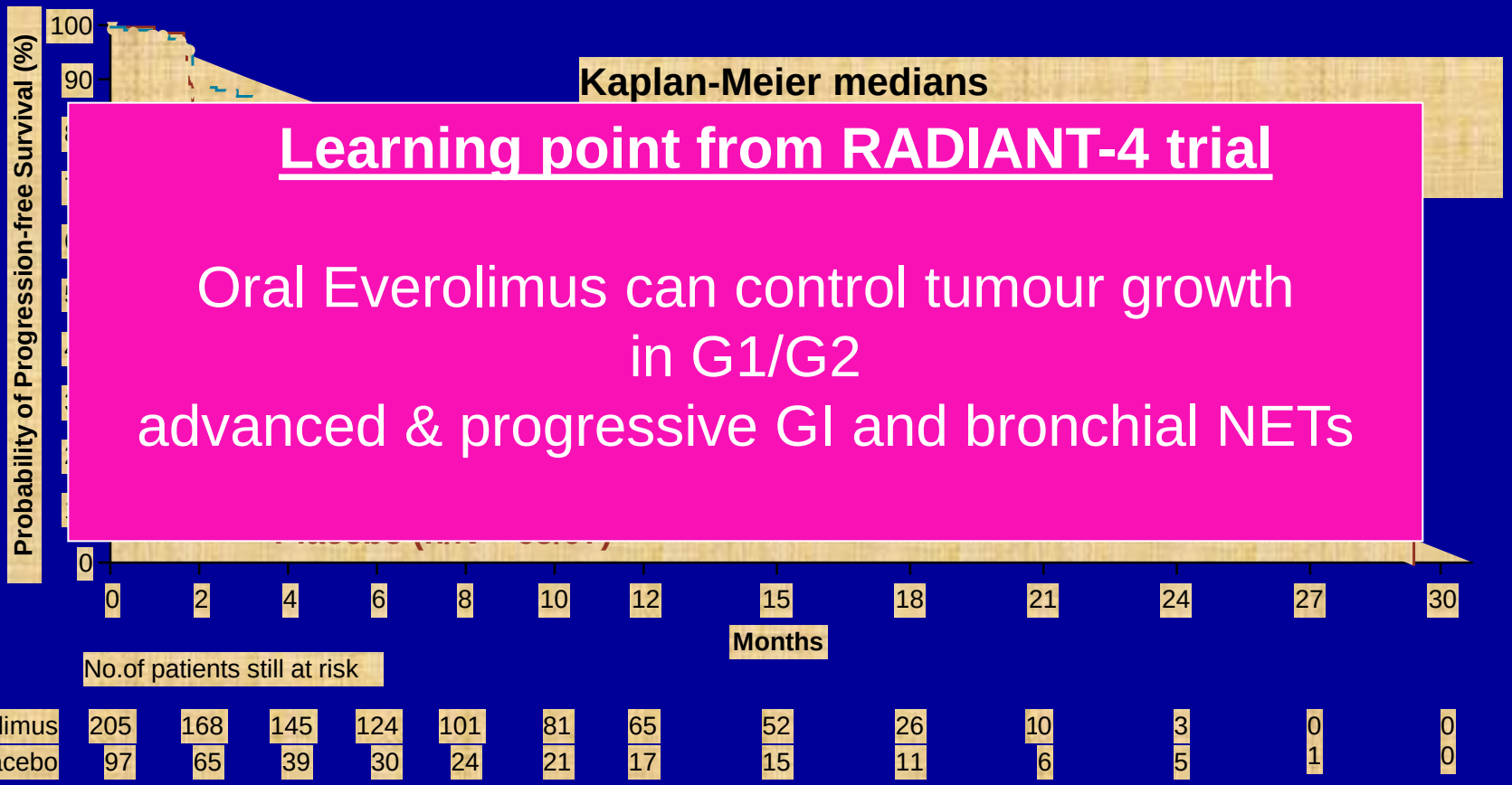
*Based on prognostic level, grouped as: **Stratum A (better prognosis)** – appendix, caecum, jejunum, ileum, duodenum, and NET of unknown primary. **Stratum B (worse prognosis)** – lung, stomach, rectum, and colon except caecum.

Crossover to open label everolimus after progression in the placebo arm was not allowed prior to the primary analysis.

Primary Endpoint: PFS by Central Review

52% reduction in the relative risk of progression or death with everolimus vs placebo

HR = 0.48 (95% CI, 0.35-0.67); *P* < 0.00001



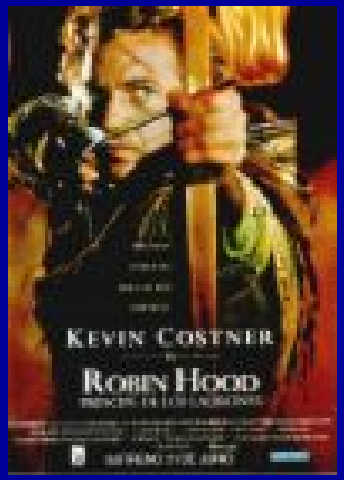
Learning point from RADIANT-4 trial

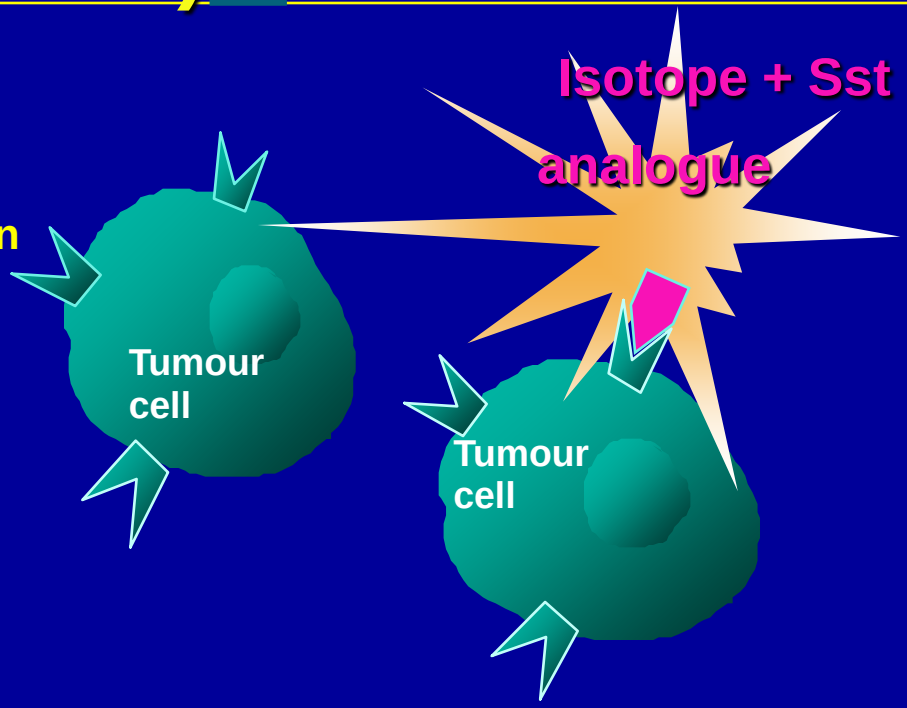
Oral Everolimus can control tumour growth
in G1/G2
advanced & progressive GI and bronchial NETs

Yao JC et al, LANCET 2016

Peptide Receptor Radionuclide Therapy (PRRT)

Mechanism of Action





The β^--emitter labelled somatostatin analogue delivers a lethal radiation dose to the tumour cell.

NETTER-1 trial (phase III trial)

- **In progressive** (over a maximum period of 3 years) **advanced midgut NETs**, despite the patients been on Octreotide LAR 30mg / 28 days :

- **Arm 1**: **PRRT with Lu-177 DOTATATE** + Octreotide LAR 30 mg / 28 days
- **Arm 2**: Octreotide LAR 60mg/28 days

Primary end point : progression-free-survival or death from any cause

Secondary end points : objective response rate, overall survival and safety profile

Progression-Free Survival in NETTER-1

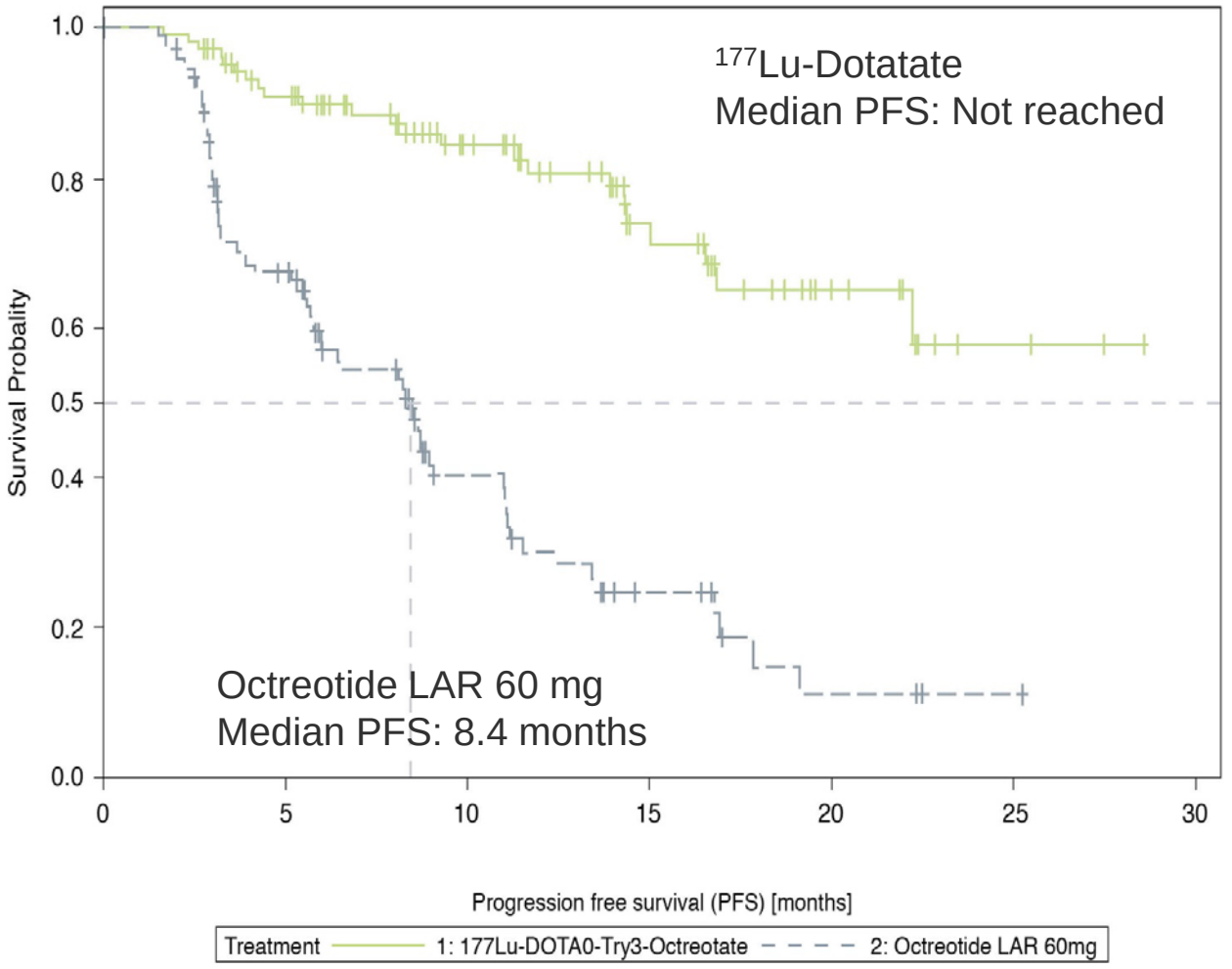
N = 229 (ITT)
Number of events: 90

- **^{177}Lu-Dotatate: 23**
- **Oct 60 mg LAR: 67**

Hazard ratio : **0.21** [0.129 – 0.338] **p < 0.0001**

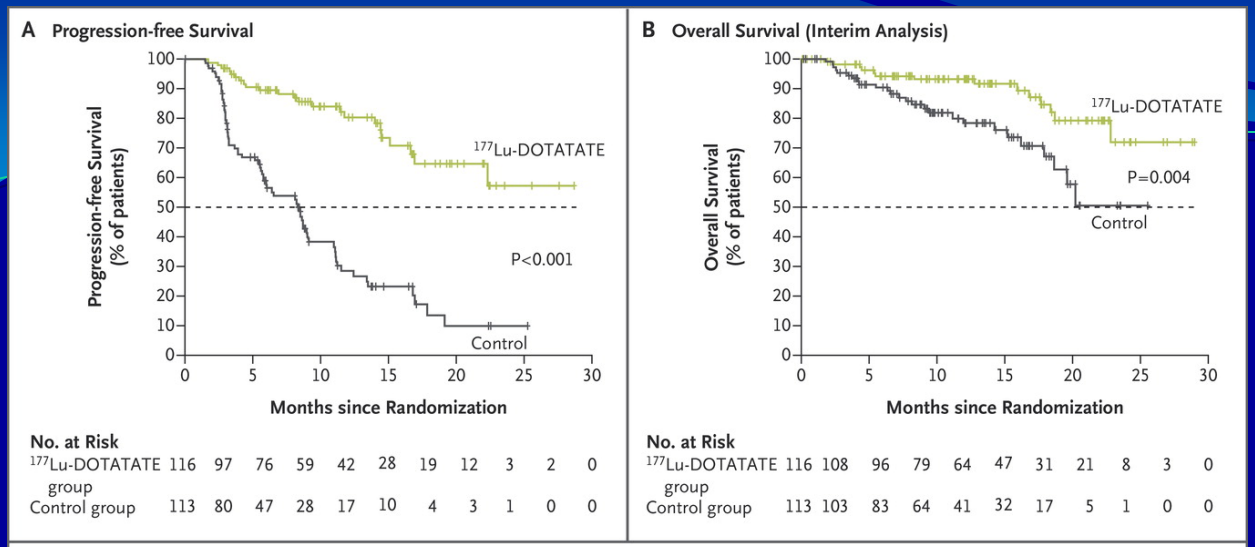
79% reduction in the risk of disease progression/death

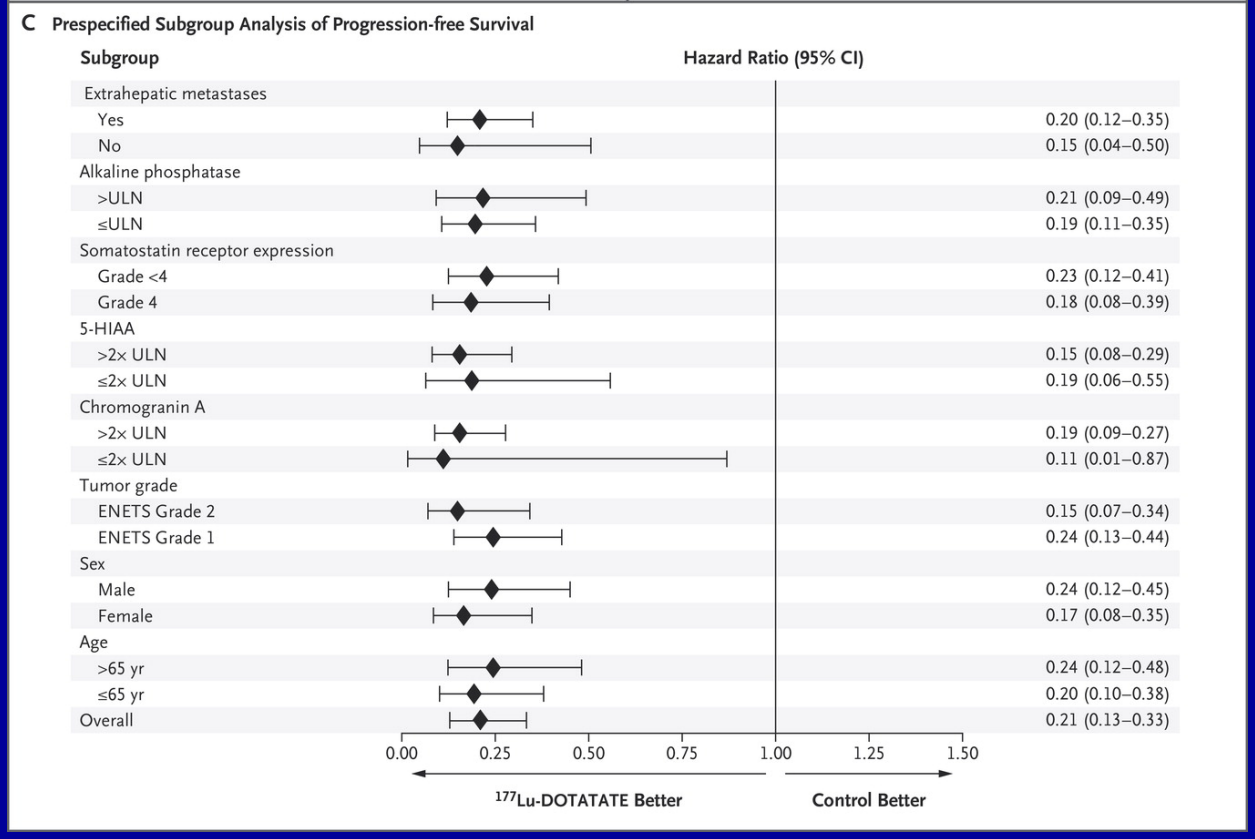
Estimated Median PFS in the ^{177}Lu-Dotatate arm **≈ 40 months**



All progressions centrally confirmed and independently reviewed for eligibility (SAP)

Strosberg et al, NEJM 2017





PFS, OS and subgroup analysis in NETTER - 1

Adverse effects

Nausea: 59%
Vomiting: 47%
Anemia:14%
Neutropenia: 6%
Thrombocytopenia: 25%
NO RENAL TOXICITY

Strosberg et al, NEJM 2017

Objective Response in NETTER-1

Table 2. Objective Tumor Response.*

Response Category	^{177}Lu-Dotatate Group (N=101)	Control Group (N=100)	P Value†
Complete response — no. (%)	1 (1)	0	
Partial respo			
Objective re			
No. with			
Rate — %			

Learning point from NETTER-1 trial

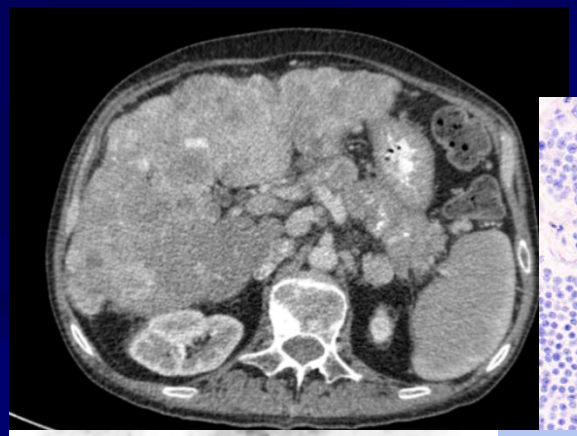
PRRT with Lu-177 DOTATATE
can control tumour growth in G1/G2
advanced & progressive midgut NETs
with quite good objective response rates

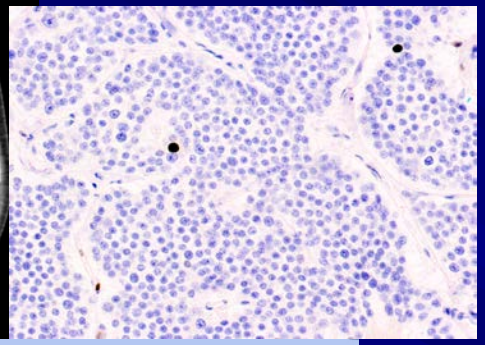
* The objectiv… se Evaluation C… whom no post-base… data were available (15 patients in the ^{177}Lu-Dotatate group and 13 patients in the control group) were excluded from this analysis (trial is still ongoing).

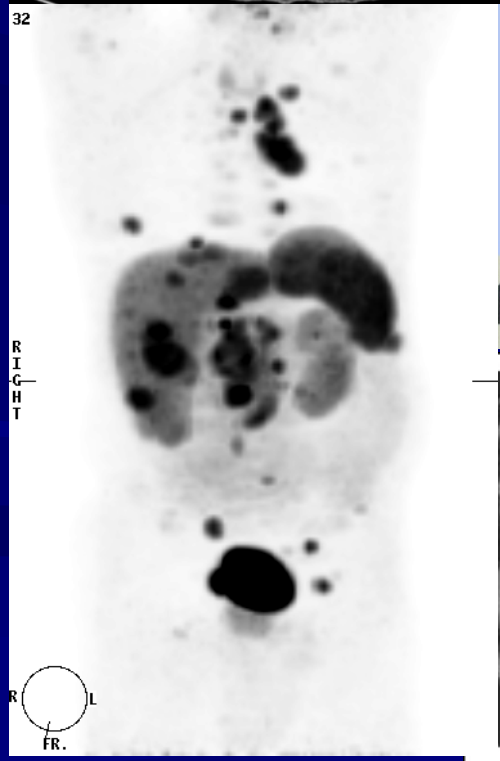
† The P value was calculated with the use of Fisher's exact text.

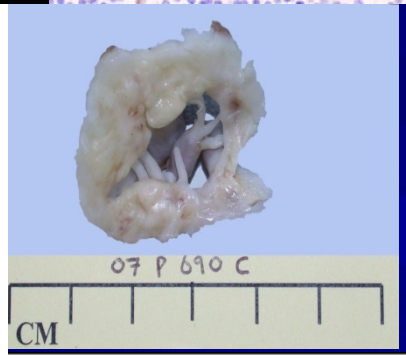
Strosberg et al, NEJM 2017

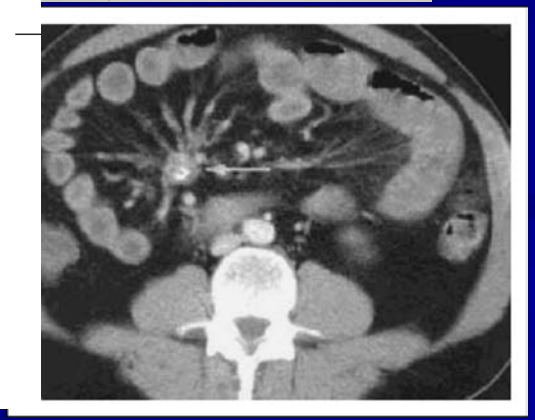
Which treatment and for Whom











- Patient's clinical status, co-morbidities and preferences
- Tumour Histology
- Location of primary
- Positive uptake in Octreoscan or Ga-68 PET
- Tumour burden
- Tumour status
- Presence of carcinoid heart disease and/or mesenteric fibrosis
- Predictive molecular markers ?
- Cost??

Control of tumour growth in G1/G2 small bowel NETs

Asymptomatic patient with stable disease and low-grade tumour

Octreotide LAR or Lanreotide Autogel
(PROMID CLARINET)

Active surveillance

Disease progression

Octreotide LAR or Lanreotide Autogel

Progression on somatostatin analogues

PRRT

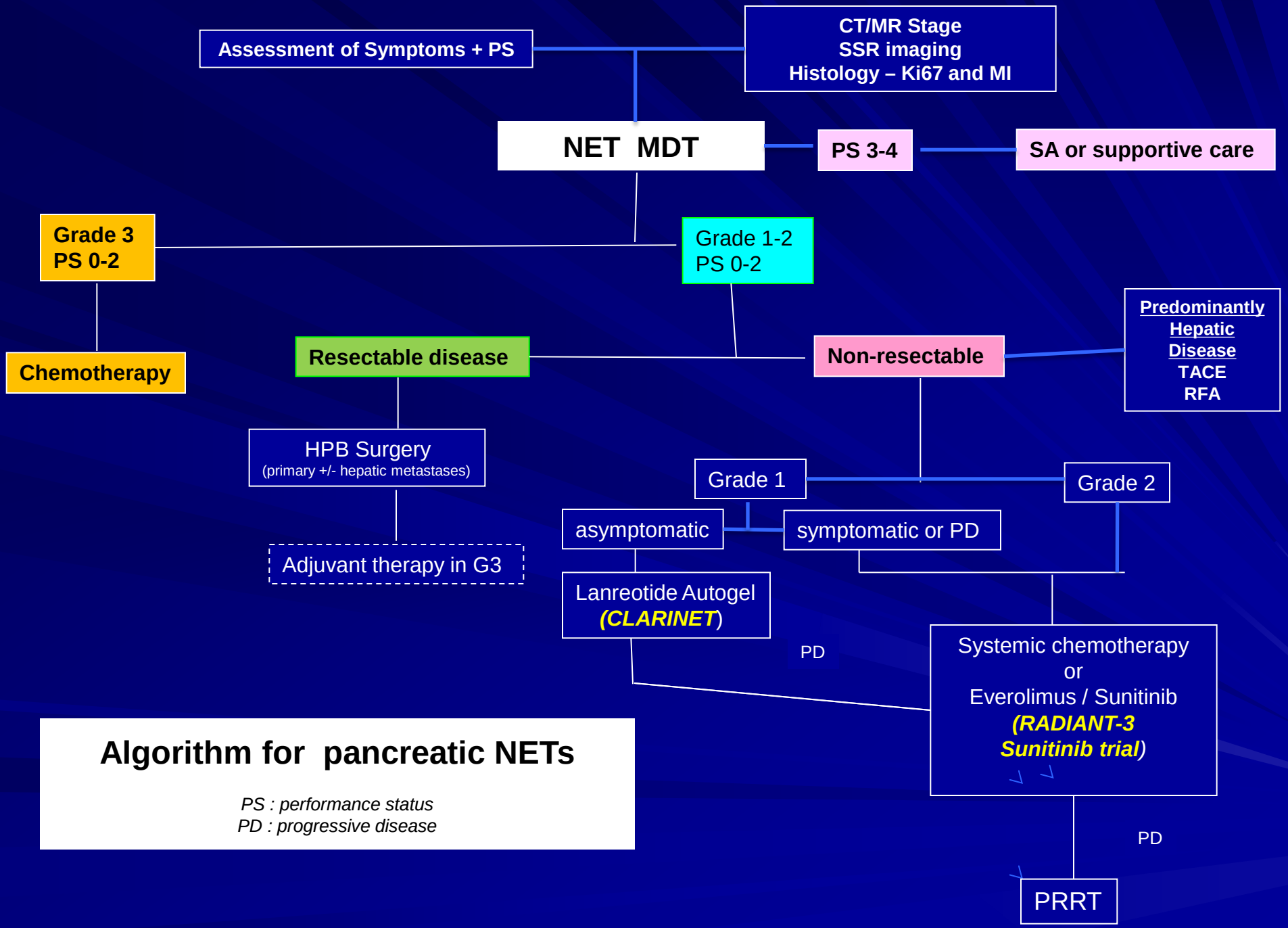
Lu-177 DOTATATE
(NETTER-1)

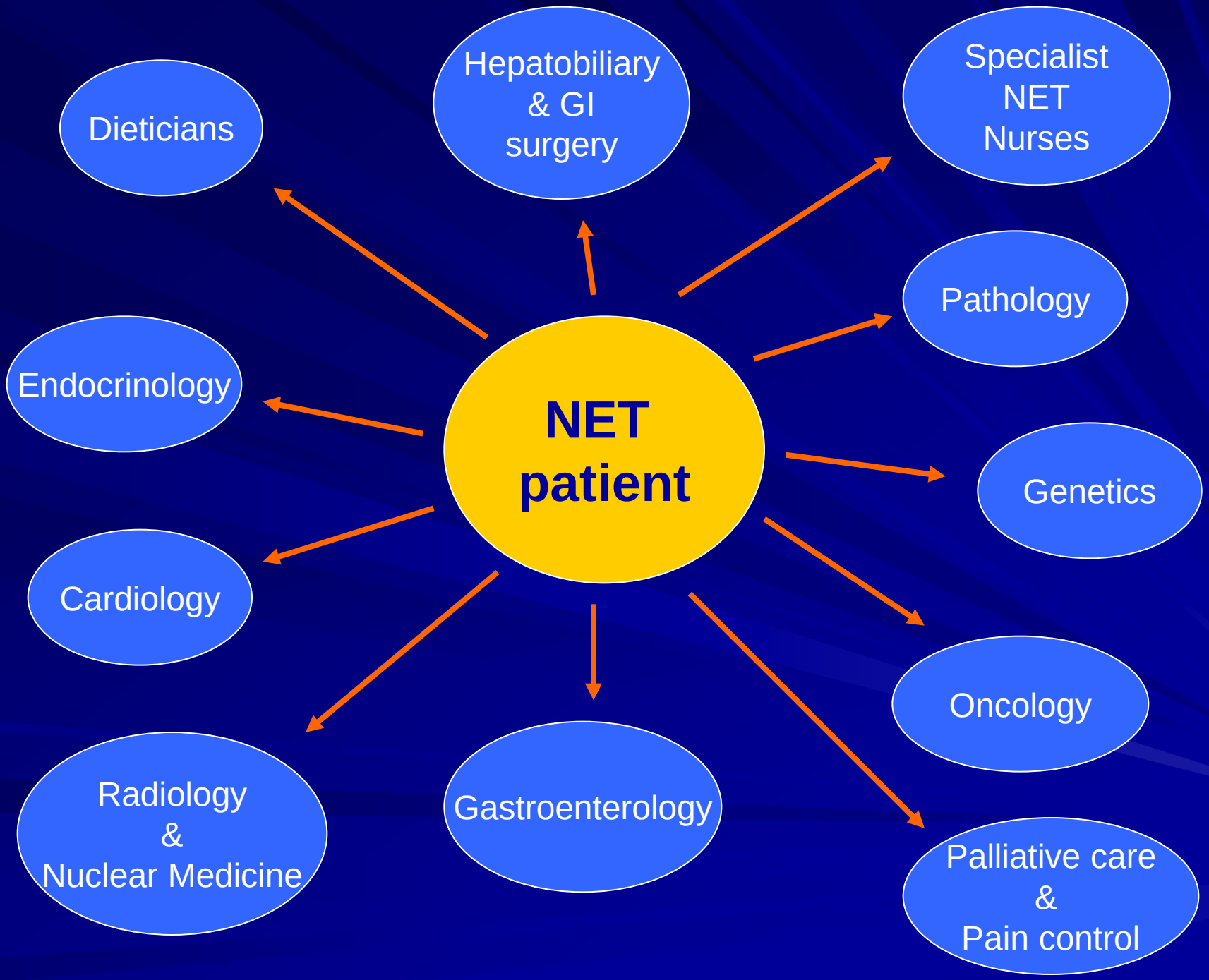
TAE

Portal vein patent
Good Performance status
No severe CHD

Combination with :

- **EVEROLIMUS**
  (RADIANT-4)
- Interferon-A


Assessment of Symptoms + PS
CT/MR Stage
SSR imaging
Histology – Ki67 and MI
NET MDT
PS 3-4
SA or supportive care
Grade 3
PS 0-2
Grade 1-2
PS 0-2
Chemotherapy
Resectable disease
Non-resectable
Predominantly
Hepatic
Disease
TACE
RFA
HPB Surgery
(primary +/- hepatic metastases)
Grade 1
Grade 2
asymptomatic
symptomatic or PD
Adjuvant therapy in G3
Lanreotide Autogel
(CLARINET)
PD
Systemic chemotherapy
or
Everolimus / Sunitinib
(RADIANT-3
Sunitinib trial)
PD
PRRT
Algorithm for pancreatic NETs
PS : performance status
PD : progressive disease


NET patient
Dieticians
Hepatobiliary & GI surgery
Specialist NET Nurses
Pathology
Endocrinology
Genetics
Cardiology
Oncology
Radiology & Nuclear Medicine
Gastroenterology
Palliative care & Pain control

Multi-Disciplinary Team (MDT) approach for NETs

- Accurate diagnosis & staging
- Evaluation of performance status & quality of life
- Consensus agreement on treatment plan
- Continuous reassessment, discussion and peer review of the individualized treatment plan

Take Home messages

- Somatostatin analogues are first line, established treatment for carcinoid syndrome.
- Telotristat ethyl is a promising new treatment for refractory diarrhoea, associated with carcinoid syndrome.
- Somatostatin analogues can also control tumour growth in advanced well-differentiated small bowel and pancreatic NETs.
- Everolimus can control tumour growth in progressing well-differentiated / non-functioning small bowel and pancreatic NETs.
- Sunitinib can control tumour growth in progressing well-differentiated pancreatic NETs.
- Peptide Receptor Radionuclide Treatment with Lu-177 DOTATATE can control tumour growth in progressing well-differentiated small bowel NETs.


Thank you