POWERED BY COR2ED

NET CONNECT
EXPERTS KNOWLEDGE SHARE

with

Prof Marianne Pavel
Dr Jaume Capdevila
Dr Louis de Mestier
Dr Angela Lamarca

TREATMENT SEQUENCING IN ADVANCED DIGESTIVE NET

Barcelona, Spain

Saturday 28th September

20:30–22:00

DISCLOSURE

NET CONNECT

is supported by an Independent Educational Grant from IPSEN

The views expressed within this presentation are the personal opinions of the author. They do not necessarily represent the views of the author's academic institution or the rest of the NET CONNECT group

NET CONNECT
EXPERTS KNOWLEDGE SHARE 2019

NET connect
POWERED BY COR2ED

THE SCIENTIFIC COMMITTEE

- Prof. Marianne Pavel
- Dr. Jaume Capdevila
- Dr. Angela Lamarca
- Dr. Louis de Mestier




THE DISCUSSION

Treatment sequencing in advanced digestive NET: Challenges in clinical practice

BACKGROUND AND APPROACHES CONSIDERED

- Overview of available treatment options and key trials - *Dr. Capdevila*
- Treatment choices for Metastatic low grade SI-NET- *Dr. de Mestier*
- Treatment choices for Metastatic grade 2 pNET- *Dr. Lamarca*
- Summary of discussion – *Prof. Pavel*

SCIENTIFIC COMMITTEE DISCLOSURES

NET connect
POWERED BY COR2ED

- Prof Marianne Pavel has received financial research support from IPSEN and Novartis (former institution) , and consultation or speaker fees from the following companies: IPSEN, Novartis, Pfizer, Lexicon, Prime Oncology

- Dr Jaume Capdevila has received financial support/sponsorship for research support, consultation or speaker fees from the following companies: Bayer, Eisai, Advanced Accelerator Applications, Novartis, IPSEN, Pfizer, Merck, Sanofi, Amgen

- Dr Louis de Mestier has received financial support/sponsorship for research support, consultation or speaker fees from the following companies: IPSEN, Novartis, Pfizer

- Dr Angela Lamarca has received honoraria or consultation fees: Eisai, Nutricia, IPSEN; Participation in company sponsored speaker bureau: Pfizer, IPSEN, Merck, Incyte; Travel, education funding: IPSEN, Pfizer, Bayer, AAA, Sirtex, Novartis, Mylan, Delcath

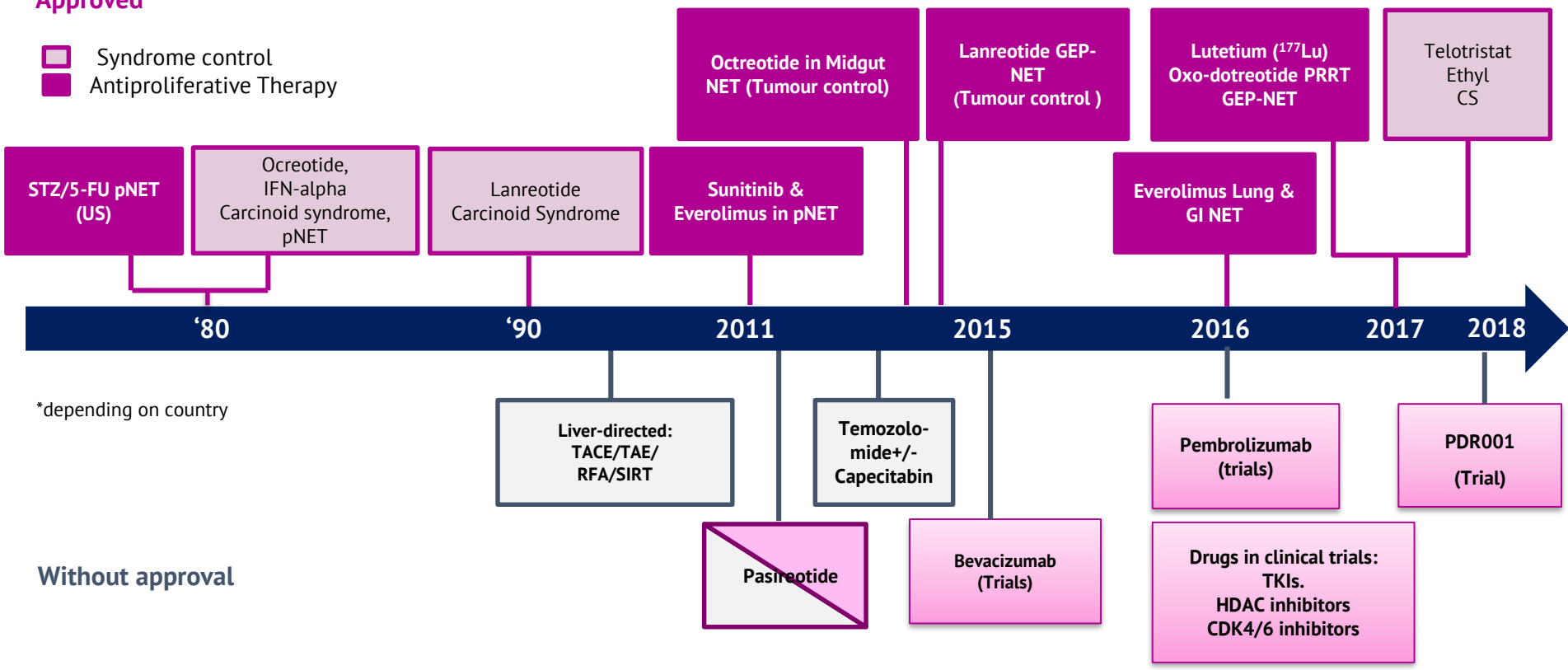
OVERVIEW

Dr Jaume Capdevila, MD, PhD

Gastrointestinal and Endocrine Tumours Group, Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

THERAPEUTIC OPTIONS IN NEUROENDOCRINE TUMOURS

NET connect
POWERED BY COR2ED



CDK4/6, Cyclin-dependent kinase 4/6; CS, carcinoid syndrome; GEP-NET, gastroenteropancreatic neuroendocrine tumours; GI NET, gastrointestinal neuroendocrine tumour; HDAC, histone deacetylase; IFN, interferon; pNET, pancreatic neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; RFA, radiofrequency ablation; SIRT, selective internal radiation therapy; STZ/5-FU, streptozotocin/ fluorouracil; TACE, transarterial chemoembolization; TAE, transarterial embolization; TKI, tyrosine kinase inhibitors; TMZ, Temozolomide . Slide provided by Prof. Marianne Pavel

NOVEL AGENTS FOR NEUROENDOCRINE TUMOURS

- In the past 10 years, a number of key trials reported resulting in the availability of new treatments for NETs:-
  - **PROMID:** Octreotide
  - **RADIANT-3 & RADIANT-4:** Everolimus
  - **CLARINET:** Lanreotide
  - **NETTER-1:** ^{177}Lu-DOTATATE
  - **TELESTAR/ TELECAST:** Telotristat Ethyl
  - **Study A6181111:** Sunitinib
  - **ECOG-ACRIN study E2211:** Temozolomide

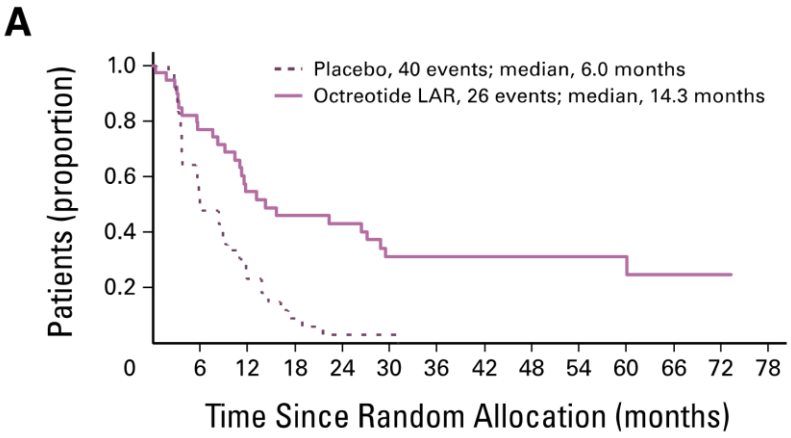
- These trials have contributed to the current treatment recommendations and therapeutic algorithm.

Rinke, et al. J Clin Oncol 2009;27:4656-63; Yao, et al. N Engl J Med 2011;364:514-23; Yao, et al. Lancet 2016;387:968–77; Caplin, et al. N Engl J Med 2014;371:224-33; Strosberg, et al. N Engl J Med 2017;376:125-35 ; Kulke M et al. Journal of Clinical Oncology 2017; 35 (1): 14-23

PROMID STUDY

OCTREOTIDE VS PLACEBO IN MIDGUT-NET

PRIMARY ENDPOINT: TTP

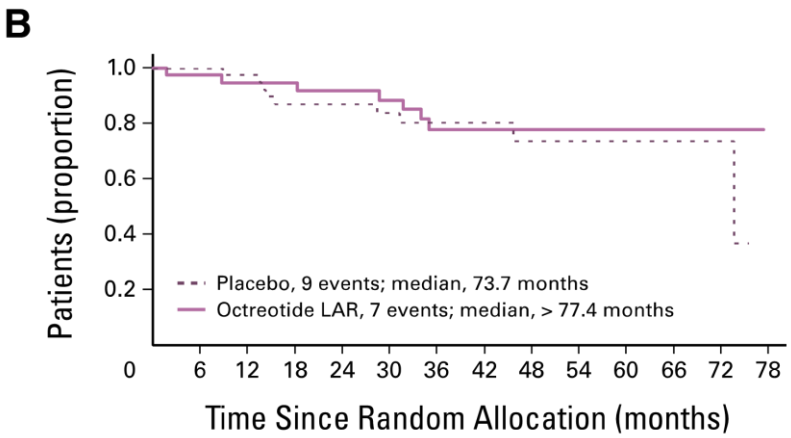


No. of patients at risk

Placebo	43	21	9	3	1	1	0	0	0	0	0	0	0	0
Octreotide LAR	42	30	19	16	15	10	10	9	9	6	5	3	1	0

Log-rank test stratified by functional activity: $P = .000072$, HR = 0.34 (95% CI, 0.20 to 0.59)

SECONDARY ENDPOINT: OS



No. of patients at risk

Placebo	43	41	39	29	27	25	19	14	11	8	6	4	2	0
Octreotide LAR	42	39	32	31	29	27	20	16	16	10	9	7	2	0

Log-rank test stratified by functional activity: $P = .77$, HR = 0.81 (95% CI, 0.30 to 2.18)

CI, confidence interval; HR, hazard ratio; LAR, long acting release; OS; overall survival; SI-NET, small intestine neuroendocrine tumour; TTP, time to tumour progression.

Rinke, et al. J Clin Oncol 2009;27:4656-63.

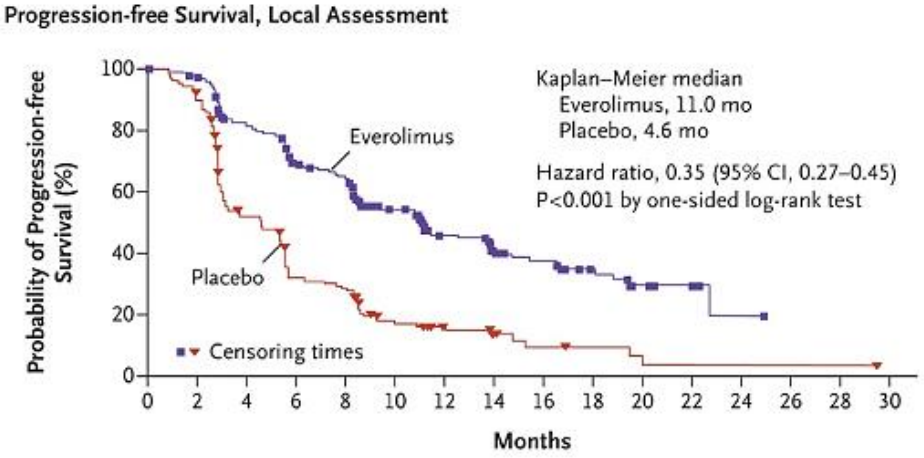
RADIANT-3 STUDY

EVEROLIMUS VS PLACEBO IN PAN-NET

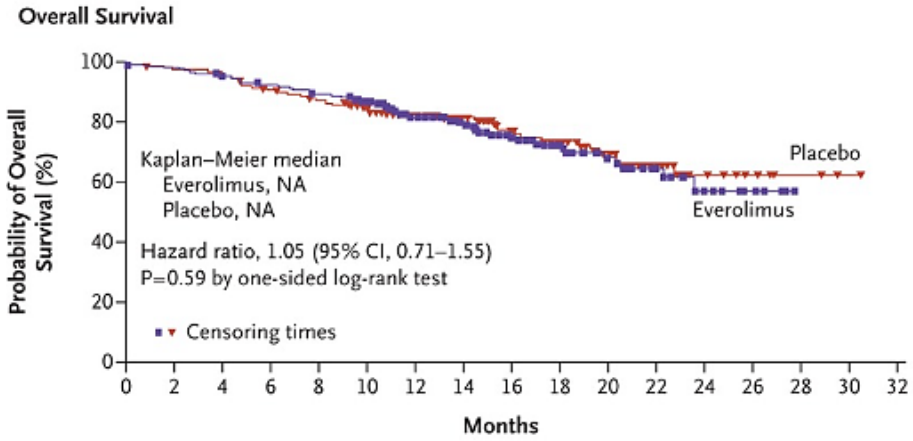
NET connect
POWERED BY COR2ED

PRIMARY ENDPOINT: PFS

N = 410
Everolimus: 207
Placebo: 203



SECONDARY ENDPOINT: OS



CI, confidence interval; mo, months; NA, not available; OS, overall survival; PFS, progression-free survival.

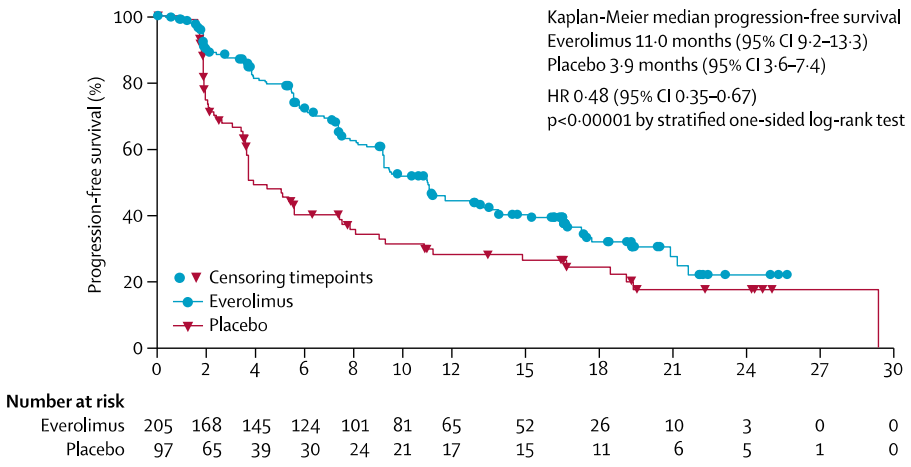
Yao, et al. N Engl J Med 2011;364:514-23.

RADIANT-4 STUDY

EVEROLIMUS VS PLACEBO IN LUNG, INTESTINAL NET AND NET OF UNKNOWN ORIGIN

NET connect
POWERED BY COR2ED

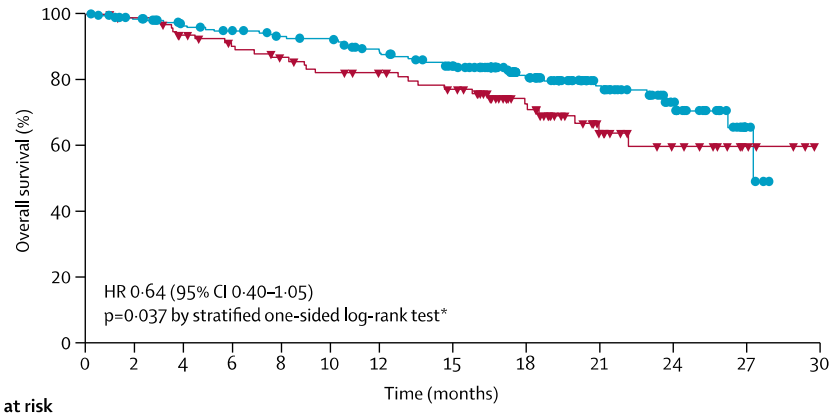
PRIMARY ENDPOINT: PFS



Number at risk

Everolimus	205	168	145	124	101	81	65	52	26	10	3	0	0
Placebo	97	65	39	30	24	21	17	15	11	6	5	1	0

SECONDARY ENDPOINT: OS (premature)



Number at risk

Everolimus	205	195	184	179	172	170	158	143	100	59	31	5	0
Placebo	97	94	86	80	75	70	67	61	42	21	13	5	0

OS accordingly to interim analysis.

CI, confidence interval; HR, hazard ratio; NA, not available; OS, overall survival, PFS, progression-free survival.

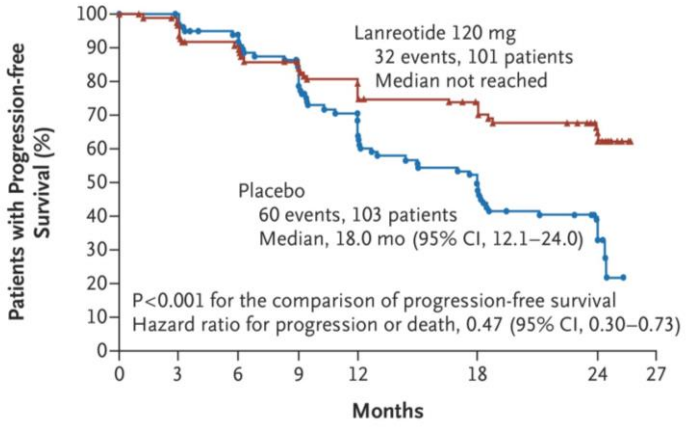
Yao, et al. Lancet 2016;387:968–77.

CLARINET STUDY

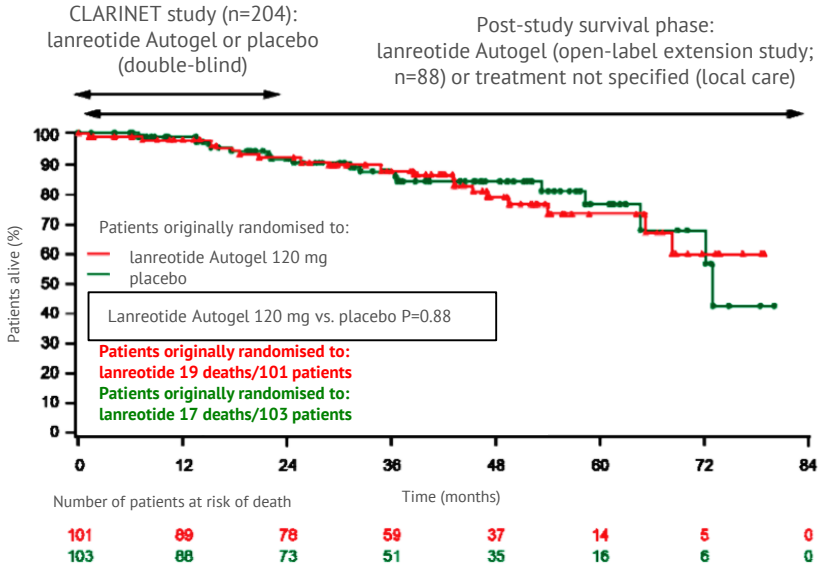
LANREOTIDE VS PLACEBO IN GEP-NET

NET connect
POWERED BY COR2ED

PRIMARY ENDPOINT: PFS



SECONDARY ENDPOINT: OS (premature)



PFS accordingly to central investigation

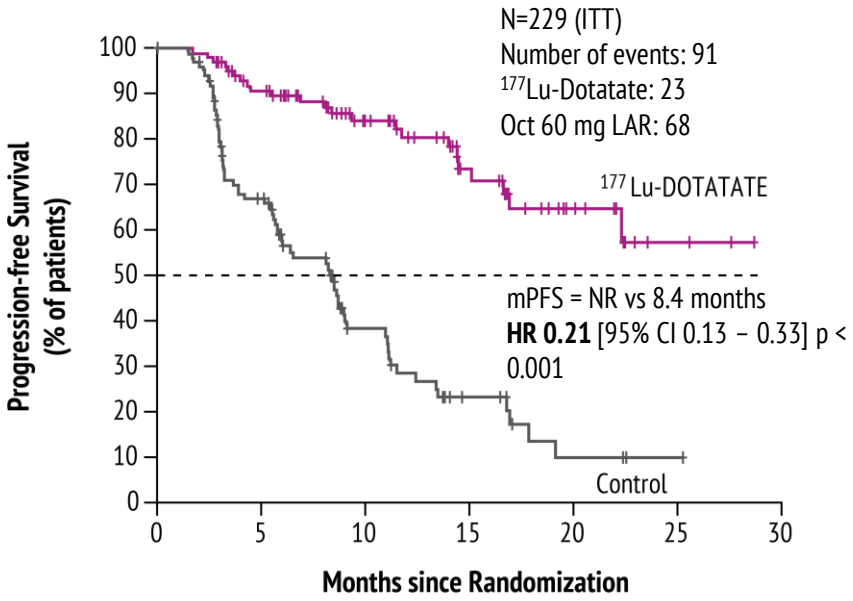
CI, confidence interval; GEP-NET, gastroenteropancreatic- neuroendocrine tumour; OS, overall survival; PFS, progression-free survival.

Caplin, et al. N Engl J Med 2014;371:224-33.

NETTER-1 STUDY

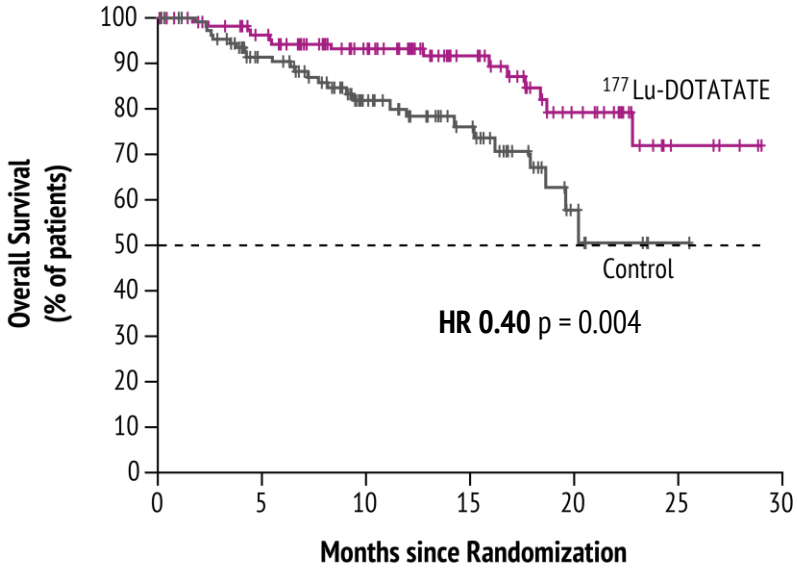
^{177}LU-DOTATATE VS HIGH DOSE OCTREOTIDE IN MIDGUT NET

PRIMARY ENDPOINT: PFS



No. at Risk											
^{177}Lu-DOTATATE group	116	97	76	59	42	28	19	12	3	2	0
Control group	113	80	47	28	17	10	4	3	1	0	0

SECONDARY ENDPOINT: OS (premature)



No. at Risk											
^{177}Lu-DOTATATE group	116	108	96	79	64	47	31	21	8	3	0
Control group	113	103	83	64	41	32	17	5	1	0	0

Primary analysis of NETTER-1 with interim analysis of overall survival. CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mPFS, median progression free survival; NR, not reached; LAR, long acting release; Lu, lutetium; Oct, octreotide, OS, overall survival.

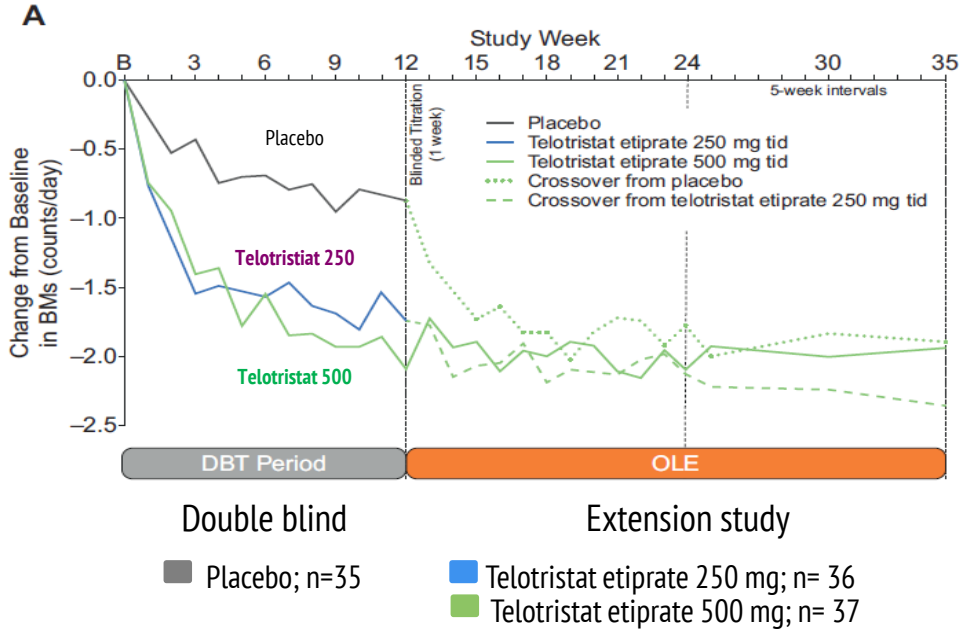
Strosberg, et al. N Engl J Med 2017;376:125-35.

TELESTAR STUDY

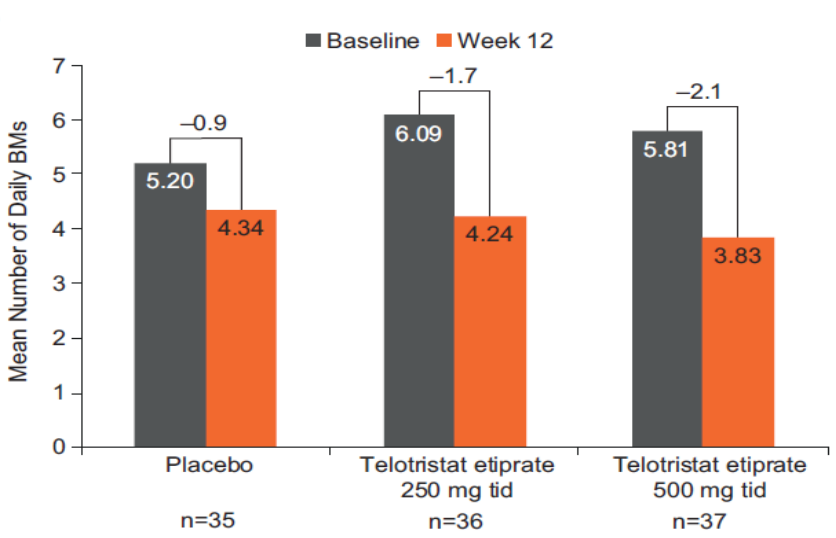
TELOTRISTAT ETHYL VS PLACEBO

SYMPTOM CONTROL IN REFRACTORY CARCINOID SYNDROME (PHASE 3)

Bowel movements/day



Bowel movements/day



44 and 42% patients treated with Telotristat (250 mg and 500 mg respectively) had a durable benefit

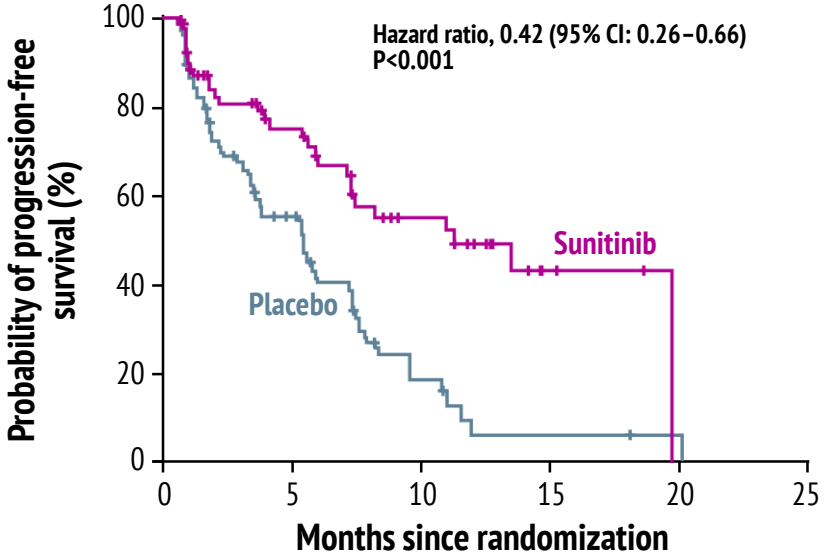
(≥30% Reduction of diarrhea for ≥50% of the double-blind study period)

Kulke M et al. Journal of Clinical Oncology 2017; 35 (1): 14-23

STUDY A6181111

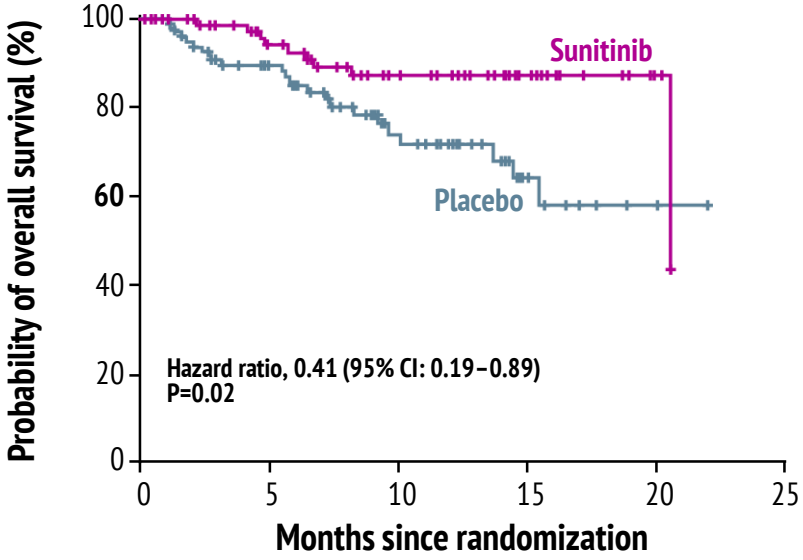
SUNITINIB VS PLACEBO IN PANCREATIC NET

PRIMARY ENDPOINT: PFS



No. at risk						
Sunitinib	86	39	19	4	0	0
Placebo	85	28	7	2	1	0

SECONDARY ENDPOINT: OS



No. at risk						
Sunitinib	86	60	38	16	3	0
Placebo	85	61	33	12	3	0

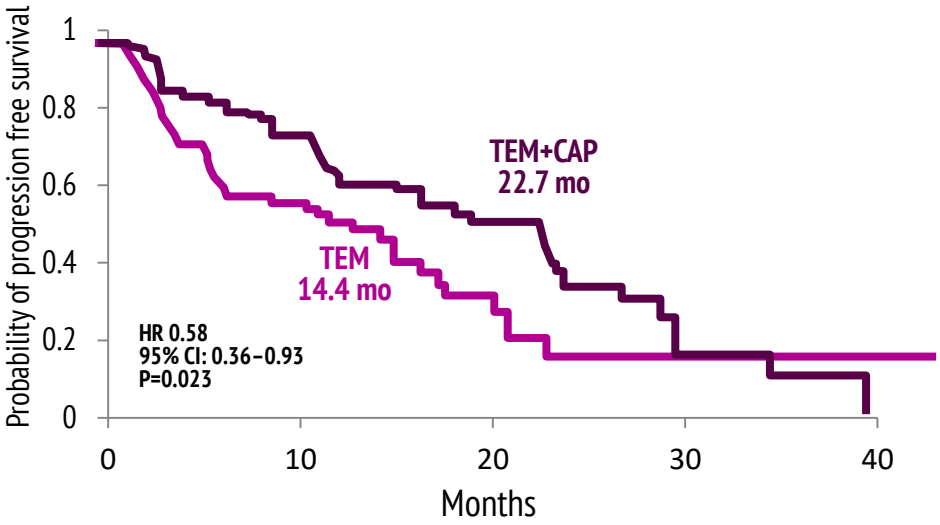
CI, confidence interval; PFS, progression free survival; OS, overall survival.

Raymond, E et al. N Engl J Med 2011;364(6):501-13.

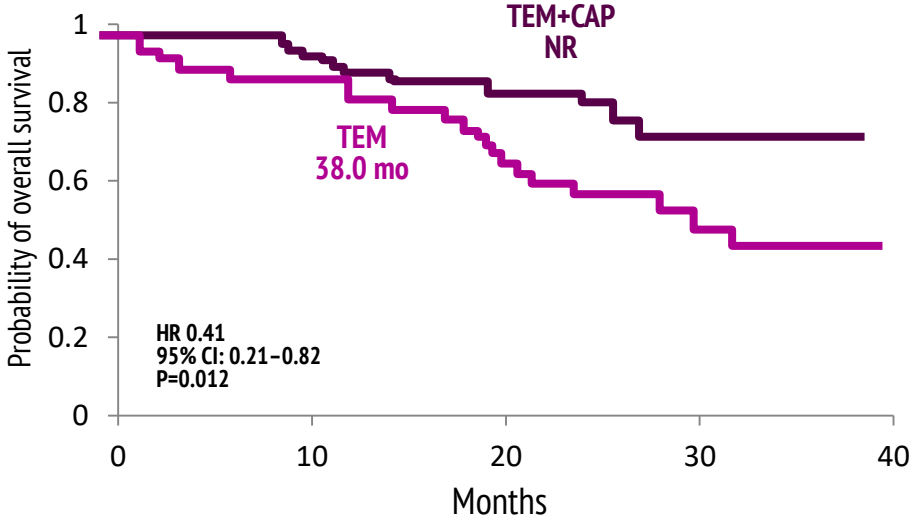
ECOG-ACRIN STUDY (E2211)

TEMOZOLOMIDE VS TEMOZOLOMIDE + CAPECITABINE IN PANCREATIC NET

PRIMARY ENDPOINT: PFS



SECONDARY ENDPOINT: OS



CAP, capecitabine; CI, confidence interval; NR, not reached; OS, overall survival.; PFS, progression free survival; TEM, temozolomide

Kunz, PL et al. ASCO 2018 Abstract #4004

ENETS CONSENSUS GUIDELINES

ENETS Consensus Guidelines

Neuro endocrinology

Neuroendocrinology 2016;103:172–185 Published online: January 5, 2016
DOI: 10.1159/000443167

ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site

M. Pavel[a] D. O'Toole[b] F. Costa[c] J. Capdevila[d] D. Gross[e] R. Kianmanesh[f]
E. Krenning[g] U. Knigge[h] R. Salazar[i] U.-F. Pape[a] K. Öberg[j]
all other Vienna Consensus Conference participants

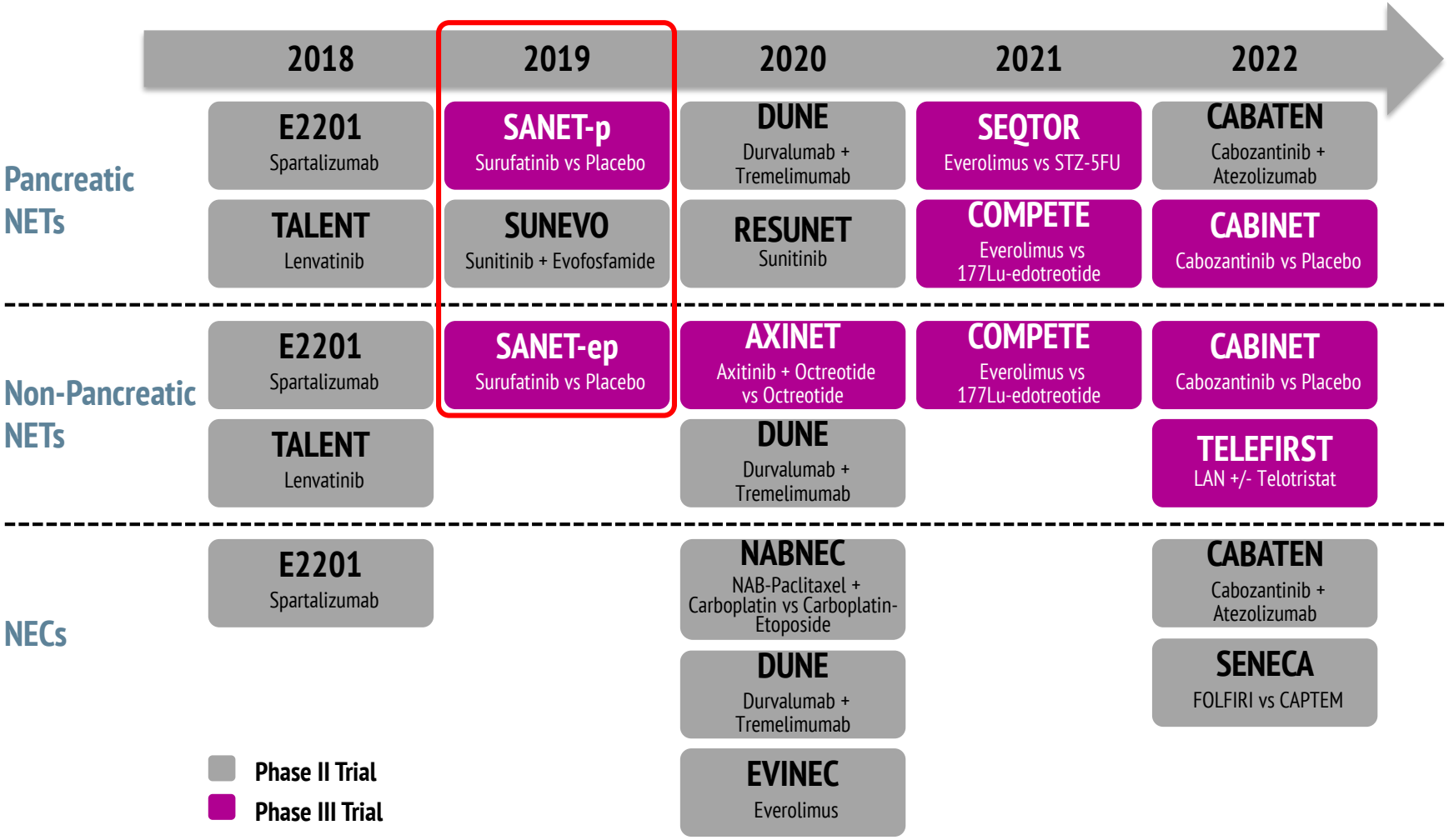
Therapeutic options and conditions for preferential use as first-line therapy in advanced NEN

Drug	Functionality	Grading	Primary site	SSTR status	Special considerations
Octreotide	+/–	GI	Midgut	+	Lower tumor burden
Lanreotide	+/–	G1/G2 (–10%)	Midgut, pancreas	+	Low and high (>25%) liver tumor burden
IFN-alpha 2b	+/–	G1/G2	Midgut		If SSTR negative
STZ/5-FU	+/–	G1/G2	Pancreas		Progressive in short-term* or high tumor burden or symptomatic
TEM/CAP	+/–	G2	Pancreas		Progressive in short-term* or high tumor burden or symptomatic; if STZ is contraindicated or not available
Everolimus	+/–	G1/G2	Lung		Atypical carcinoid and/or SSTR negative
			Pancreas		Insulinoma or contraindication for CTX
			Midgut		If SSTR negative
Sunitinib	+/–	G1/G2	Pancreas		Contraindication for CTX
PRRT	+/–	G1/G2	Midgut	+ (required)	Extended disease; extrahepatic disease, e.g. bone metastasis
Cisplatin[§]/ etoposide	+/–	G3	Any		All poorly differentiated NEC

* ⩽6–12 months; [§]Cisplatin can be replaced by carboplatin.

CAP, capecitabine; TEM, temozolomide.
Pavel, et al. Neuroendocrinology. 2016;103:172-85.

OVERVIEW OF KEY ON-GOING CLINICAL TRIALS IN NETS



Presented by Dr. Enrique Grande, ESMO 2019

DOES ONE SIZE FIT ALL?

The following patient case studies will help answer this question.

PATIENT CASE 1: METASTATIC LOW G2 (ki67 5%) SMALL INTESTINE NET

Dr Louis de Mestier, MD
Dept Gastroenterology-Pancreatology
ENETS Centre of Excellence
Beaujon Hospital, University of Paris
Clichy, France

THERAPEUTIC OPTIONS FOR ADVANCED SI NET

- Watch and wait
- Long-acting somatostatin analogs
- Resection ablation of metastases
- Liver transarterial embolization
- ^{177}Lu-DOTATATE PRRT
- Everolimus
- Interferon-alpha
- Chemotherapy
- Clinical trials

There is no unique adequate sequence

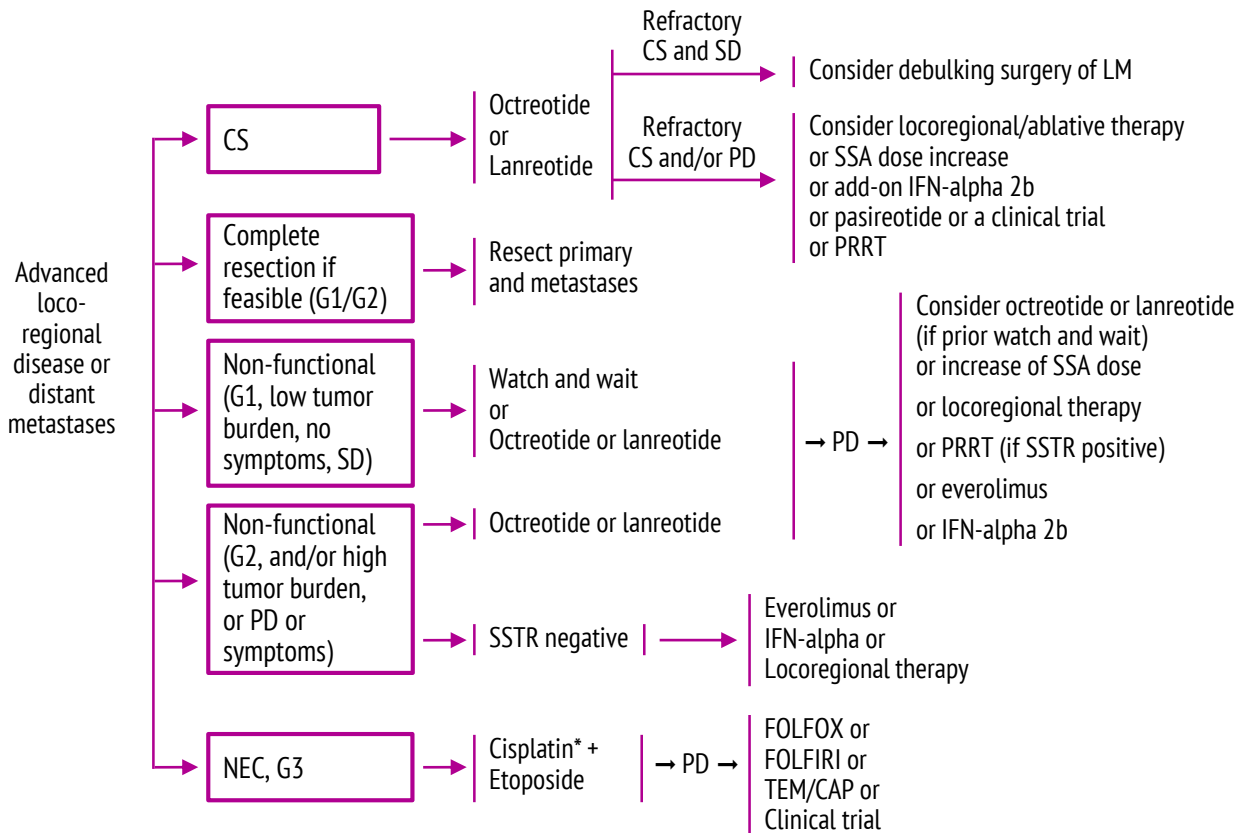
Treatment must be individualized

Lu, Lutetium; SI NET, small intestine neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy.

THERAPEUTIC DECISION MUST BE PERSONALIZED

NET connect
POWERED BY COR2ED

MANAGEMENT OF INTESTINAL (MIDGUT) NEN



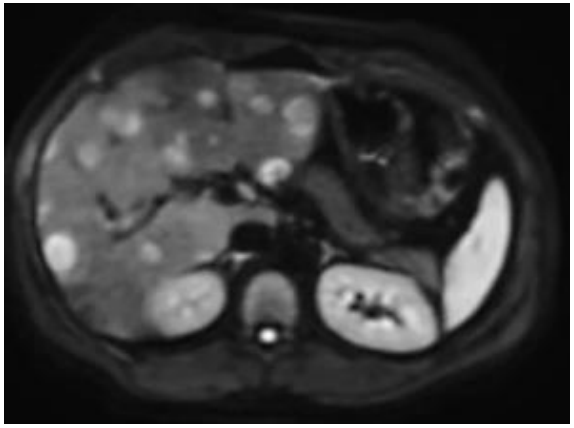
*Cisplatin may be replaced by carboplatin

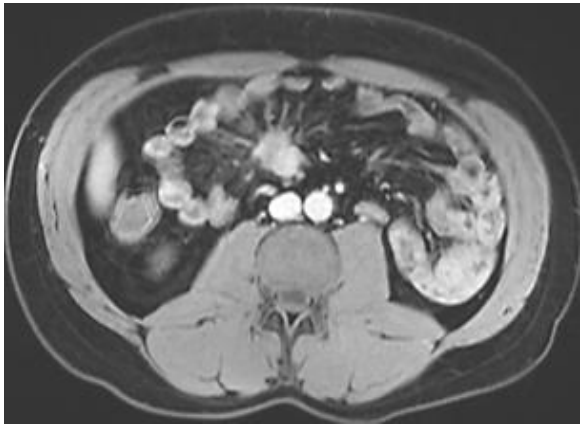
CS, carcinoid syndrome; FOLFIRI, folinic acid, fluorouracil and irinotecan; FOLFOX, folinic acid, fluorouracil and oxaliplatin; IFN, interferon; LM, liver metastasis; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; PD, progressive disease; PRRT, peptide receptor radionuclide therapy; SD, stable disease; SSA, somatostatin analogues; SSTR, somatostatin receptor; TEM/CAP, temozolomide-capecitabine.

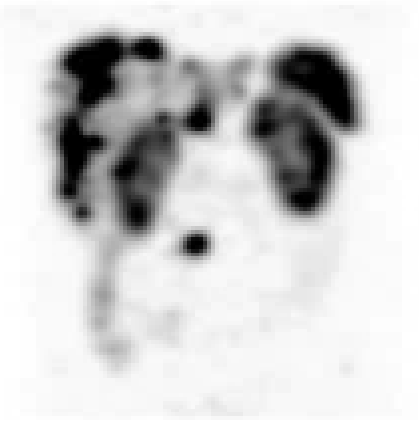
Pavel, et al. Neuroendocrinology. 2016;103:172-85.

CASE 1: MR. D. O.

- 42 years old
- No particular history
- June 2014: abdominal pain and postprandial flushing. WHO-PS = ~~0~~
- CT-scan and MRI : multiple liver mets, mesenteric lymph-node complex
- Liver biopsy: well-diff NET, Ki67 = 5%
- Positive SST-receptor scintigraphy
- 5-HIAA = 4xN, Echocardiography: no sign of carcinoid heart disease







5-HIAA, 5-hydroxyindoleacetic acid; CT, computed tomography; MRI, magnetic resonance imaging; NET, neuroendocrine tumour; SST, somatostatin; WHO-PS, world health organisation performance status.

WHAT TREATMENT SHOULD WE CONSIDER FIRST ?

- SST analogs with antisecretory intent?
- Surgery of the primary tumour(s) and associated LN metastases?
- Treatment of the metastatic disease:
  - Watch and wait ?
  - SST analogs ?
  - Liver transarterial embolization ?
  - Everolimus ?
  - ^{177}Lu-DOTATATE PRRT ?
  - Chemotherapy ?

- **Small-intestine NET**
- **Carcinoid syndrome**
- **G2**
- **Liver involvement 30-50%**
- **Metastases non-resectable**

LN, lymph node; Lu, Lutetium; NET, neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; SST, somatostatin.

WHAT TREATMENT SHOULD WE CONSIDER FIRST ?

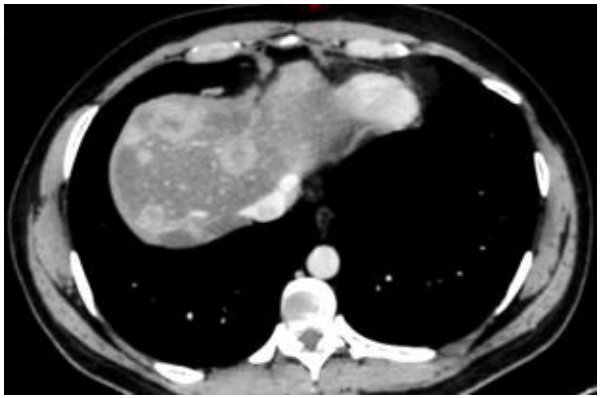
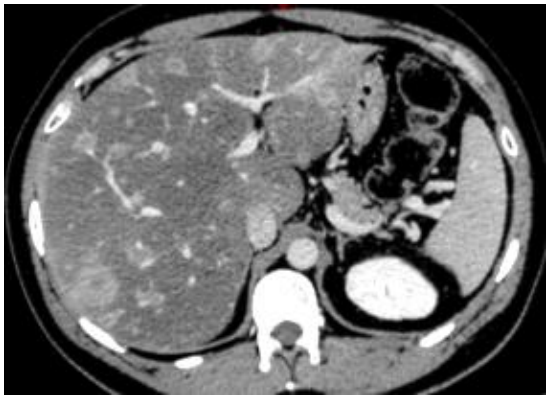
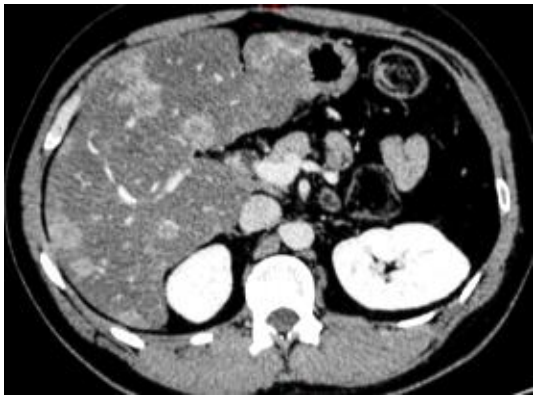
- **SST analogs with antisecretory intent**
- **Surgery of the primary tumour(s) and associated LN metastases**
- Treatment of the metastatic disease:
  - Watch and wait ?
  - **SST analogs**
  - Liver transarterial embolization ?
  - Everolimus ?
  - ^{177}Lu-DOTATATE PRRT ?
  - Chemotherapy ?

- **Small-intestine NET**
- **Carcinoid syndrome**
- **G2**
- **Liver involvement 30-50%**
- **Metastases non-resectable**

LN, lymph node; Lu, Lutetium; PRRT, peptide receptor radionuclide therapy; SST, somatostatin.

WHAT TREATMENT SHOULD WE CONSIDER FIRST ?

- July 2014:
  - Right ileocolectomy, mesenteric lymphadenectomy, cholecystectomy
  - 6 siNETs, max 2 cm, pT4N+M+, Ki67 = 5%
- July 2014: lanreotide AG 120 mg
- December 2015: carcinoid syndrome not completely controlled
- CT: Hepatic progression, increase in size and new lesions, no new lesions elsewhere

AG, autogel; CT, computed tomography; siNETs, small intestine neuroendocrine tumour.

WHAT SECOND-LINE TREATMENT ?

- Double-dose SST analogs ?
- Liver transarterial embolization ?
- Everolimus ?
- ^{177}Lu-DOTATATE PRRT ?
- Chemotherapy ?

- **G2, liver involvement 30-50 %**
- **Fast progression under SST analogs**
- **Uncontrolled functioning syndrome**
- **Disease restricted to the liver**
- **Positive SST-receptor imaging**

Lu, Lutetium; PRRT, peptide receptor radionuclide therapy; SST, somatostatin.

WHAT SECOND-LINE TREATMENT ?

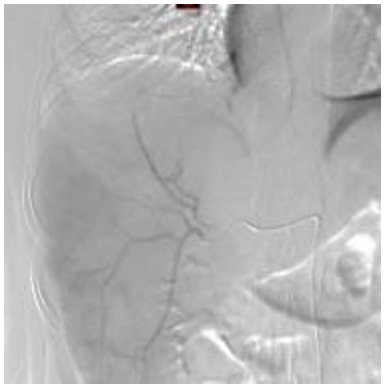
- Double-dose SST analogs ?
- **Liver transarterial embolization**
- Everolimus ?
- ^{177}Lu-DOTATATE PRRT ?
- Chemotherapy ?

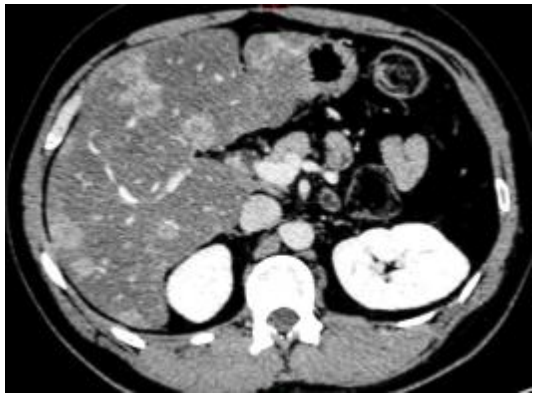
- **G2, liver involvement 30-50 %**
- **Fast progression under SST analogs**
- **Uncontrolled functioning syndrome**
- **Disease restricted to the liver**
- **Positive SST-receptor imaging**

Lu, Lutetium; PRRT, peptide receptor radionuclide therapy; SST, somatostatin.

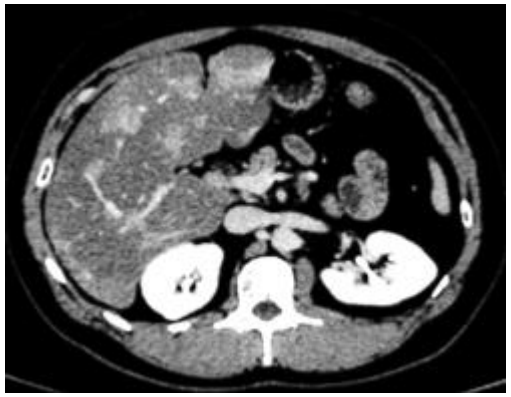
WHAT SECOND-LINE TREATMENT ?

- January 2016 and April 2016:
  - 2 procedures of liver transarterial embolization + continuation of lanreotide AG 120 mg / 28 days
  - Good symptomatic response
  - Prolonged morphological control

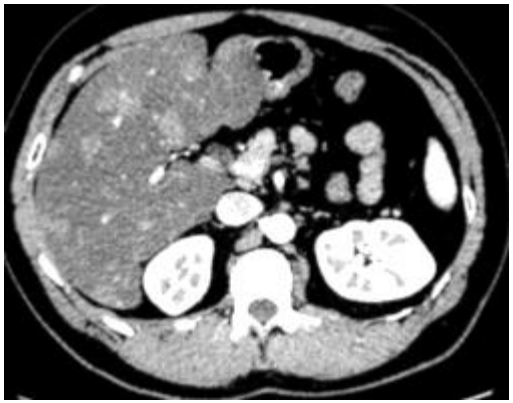




December 2015



July 2016

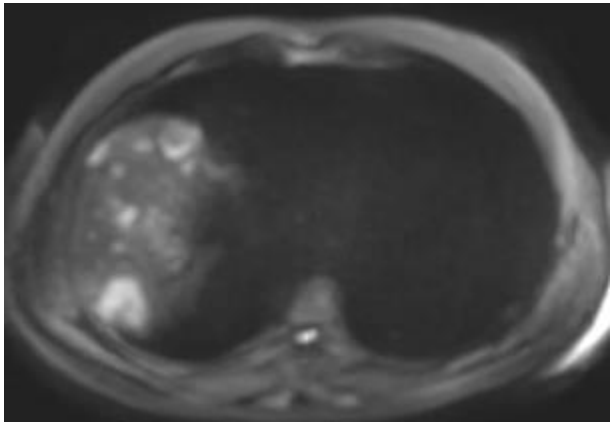


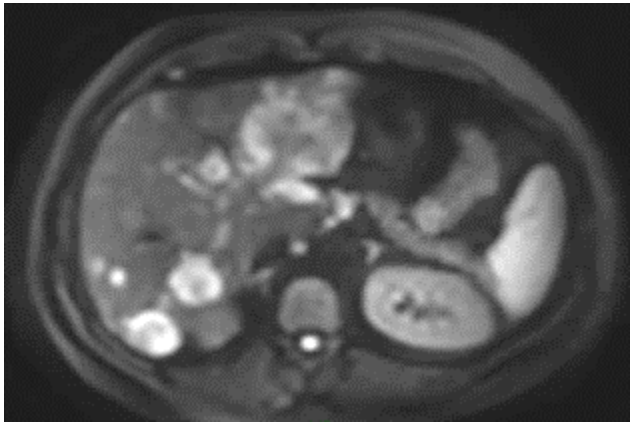
July 2017

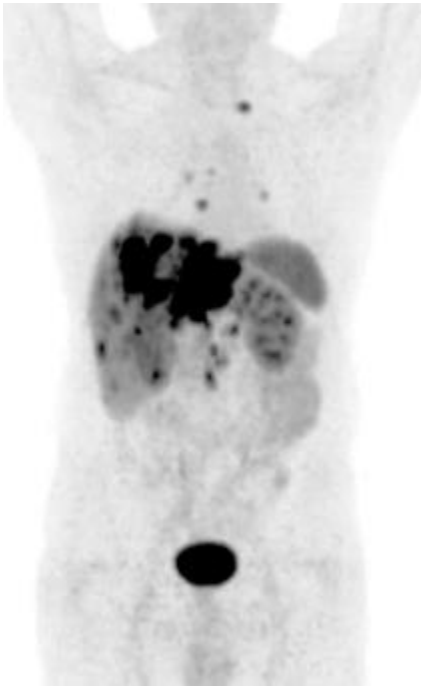
lanreotide AG, lanreotide auto gel

WHAT HAPPENED NEXT

- The patient remained stable until April 2018
- Mild carcinoid syndrome under SST analogue
- Recent weight loss and abdominal pain, flushing (3 per day) and diarrhea (5 BM per day)
- 5-HIAA 8N and CgA 10N
- CT, MRI and DOTATOC-PET: liver and extrahepatic progression







5-HIAA, 5-hydroxyindoleacetic acid; BM, bowel movements; CgA, chromogranin A; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; SST, somatostatin.

WHAT THIRD-LINE TREATMENT ?

- Liver transarterial embolization ?
- Everolimus ?
- ^{177}Lu-DOTATATE PRRT ?
- Chemotherapy ?

- **G2, liver involvement 30-50 %**
- **Progression**
- **Uncontrolled functioning syndrome**
- **Extra-hepatic disease**
- **Positive SST-receptor imaging**

Lu, Lutetium; PRRT, peptide receptor radionuclide therapy; SST, somatostatin.

WHAT THIRD-LINE TREATMENT ?

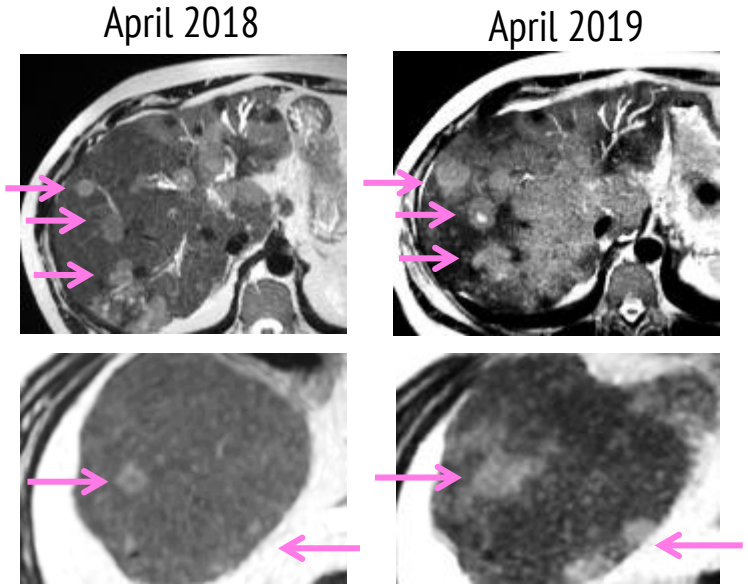
- Liver transarterial embolization ?
- Everolimus ?
- **^{177}Lu-DOTATATE PRRT**
- Chemotherapy ?

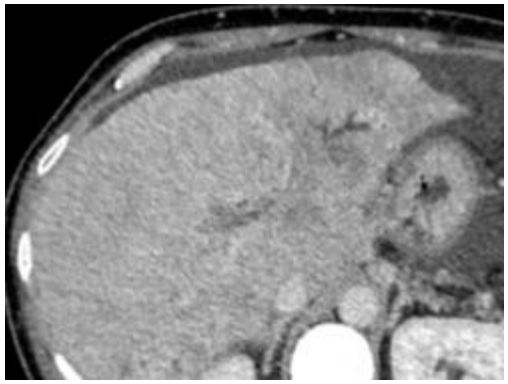
- **G2, liver involvement 30-50 %**
- **Progression**
- **Uncontrolled functioning syndrome**
- **Extra-hepatic disease**
- **Positive SST-receptor imaging**

Lu, Lutetium; PRRT, peptide receptor radionuclide therapy; SST, somatostatin.

WHAT THIRD-LINE TREATMENT ?

- May 2018 to January 2019 : 4 cycles of 177Lu-DOTATATE, yielded tumour control
- April 2019: clinical worsening: WHO-PS 1-2, weight loss, abdominal pain, carcinoid syndrome
- MRI : progression, increase in size and new lesions (liver and lymph nodes)





- Liver deterioration related to diffuse infiltration of the left lobe
- Ascites
- Segmental biliary dilatation
- Mild perturbations of the liver tests

Lu, lutetium; MRI, magnetic resonance imaging; WHO-PS, world health organisation performance status.

WHAT FOURTH-LINE TREATMENT ?

- Liver transarterial embolization ?
- Everolimus ?
- Chemotherapy ?
- Best supportive care ?

- **G2, liver involvement 50 %**
- **Fast progression**
- **Uncontrolled functioning syndrome**
- **Extra-hepatic disease**
- **Signs of liver deterioration**

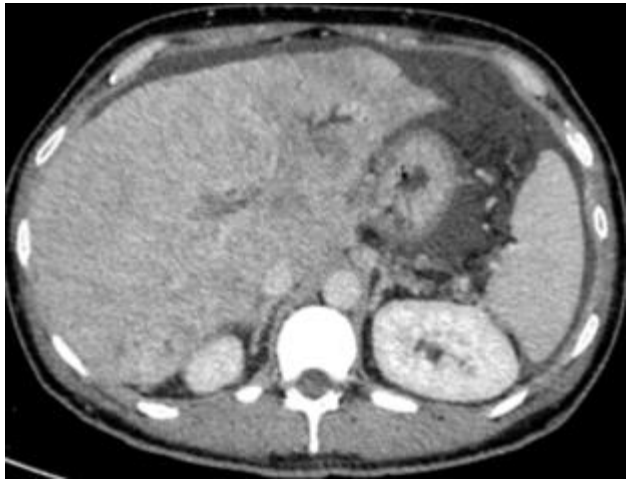
WHAT FOURTH-LINE TREATMENT ?

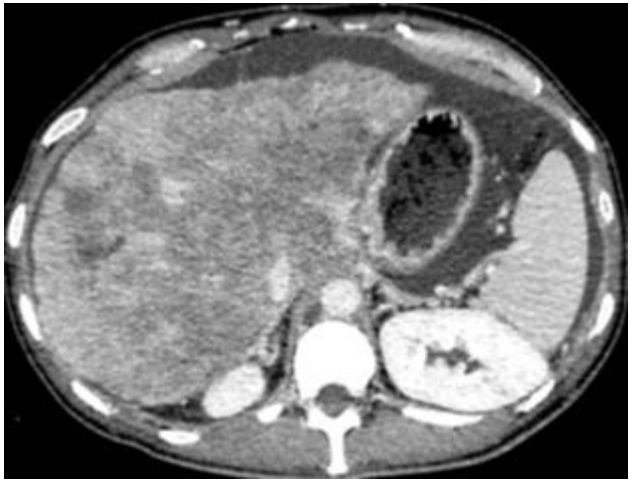
- Liver transarterial embolization ?
- Everolimus ?
- **Chemotherapy**
- Best supportive care ?

- **G2, liver involvement 50 %**
- **Fast progression**
- **Uncontrolled functioning syndrome**
- **Extra-hepatic disease**
- **Signs of liver deterioration**

WHAT FOURTH-LINE TREATMENT ?

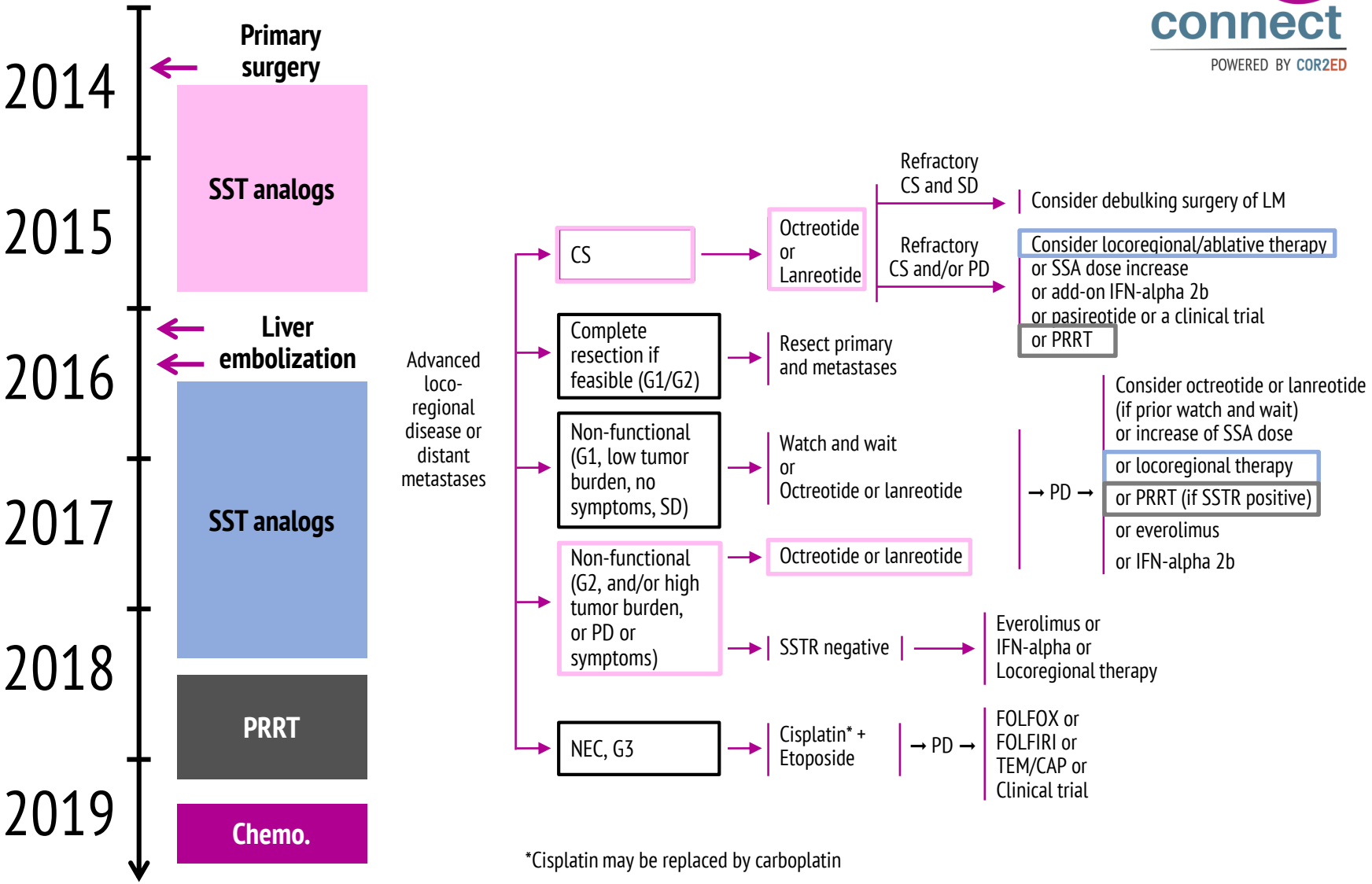
- May 2019 to September 2019 : 5 cycles of FOLFOX-bevacizumab
- Clinical worsening: WHO-PS 3, abdominal pain, carcinoid syndrome
- CT-scan: progression
- Decision of palliative care





CT, computed tomography; FOLFOX, folinic acid, fluorouracil and oxaliplatin; WHO-PS, world health organisation performance status.

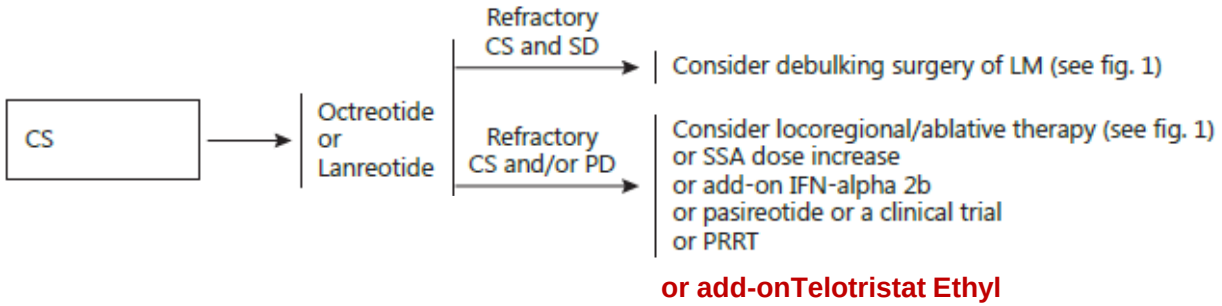
SUMMARY – CASE 1



Chemo, chemotherapy; CS, carcinoid syndrome; FOLFIRI, folinic acid, fluorouracil and irinotecan; FOLFOX, folinic acid, fluorouracil and oxaliplatin; IFN, interferon; LM, liver metastasis; NEC, neuroendocrine carcinoma; PD, progressive disease; PRRT, peptide receptor radionuclide therapy; SD, stable disease; SSA, somatostatin analogues; SST, somatostatin; SSTR, somatostatin receptor; TEM/CAP, temozolomide-capecitabine.

Pavel, et al. Neuroendocrinology. 2016;103:172-85.

ENETS CONSENSUS GUIDELINES 2016



Dose escalation of SSA is still a considerable approach,

particularly if not only diarrhea is present but also flushing symptoms.

Pasireotide can be considered (off-label) if all other options failed

CS, carcinoid syndrome; IFN, interferon; LM, liver metastasis; PD, progressive disease; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogue; SD, stable disease

Pavel, et al. Neuroendocrinology. 2016;103:172-85.

PATIENT CASE 2:
METASTATIC GRADE 2 Pan-NET, ki67 15%

Dr Angela Lamarca MD, PhD, MSc

Department of Medical Oncology
The Christie NHS Foundation Trust
University of Manchester
United Kingdom

POTENTIAL OPTIONS OF TREATMENT FOR Pan-NETS

1. Chemotherapy (TemCap; STZ/5-FU)
2. Clinical trials
3. Everolimus
4. IFN-alpha
5. Liver-directed therapies
6. PRRT
7. SSA
8. Sunitinib
9. Surgery
10. Watch and wait

Could you order them by preference to be used in patients with Pan-NETs?

If all patients received all options of therapy: 3,628,800 possible sequences

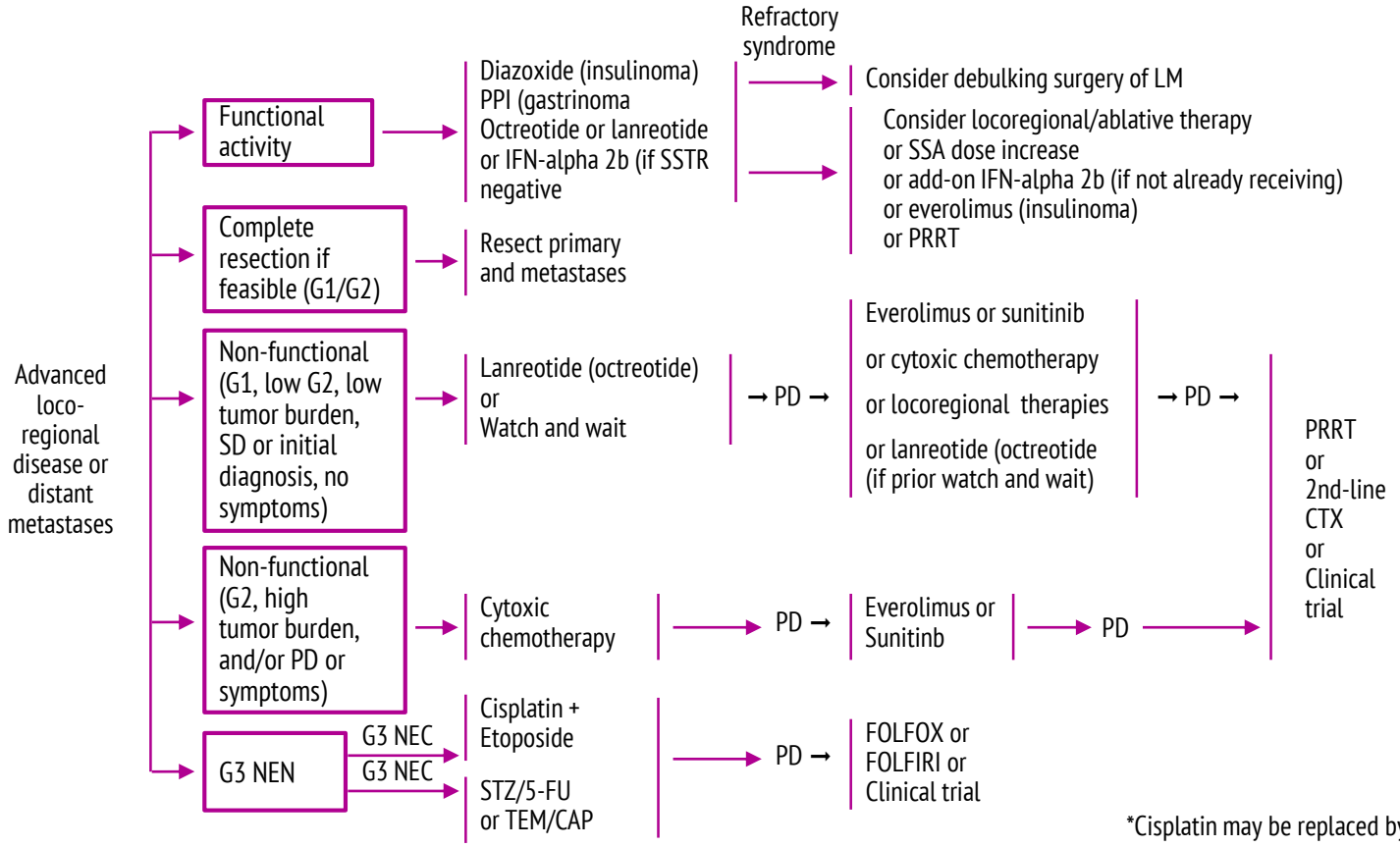
Is there only 1 correct answer?

IFN, interferon; Pan-NETs, pancreatic neuroendocrine tumours; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogues; STZ/5-FU, streptozotocin/ fluorouracil; TemCap, temozolomide-capecitabine.

CURRENT GUIDELINES

MANAGEMENT OF PANCREATIC NEN

- **Individualised** therapeutic plan based on evidence and patient's characteristics (discussion in **NET MDT)**



CS, carcinoid syndrome; CTX, chemotherapy; FOLFIRI, folinic acid, fluorouracil and irinotecan; FOLFOX, folinic acid, fluorouracil and oxaliplatin; IFN, interferon; LM, liver metastasis; MDT, multidisciplinary team; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumour; PD, progressive disease; PPI, proton pump inhibitor; PRRT, peptide receptor radionuclide therapy; SD, stable disease; SSA, somatostatin analogues; STZ/5-FU, streptozotocin/5-Fluorouracil; TEM/CAP, temozolomide-capecitabine.

Pavel, et al. Neuroendocrinology. 2016;103:172-85.

CASE 2: MR XX

- 69 years old male
- PMH: hypertension
- FMH: nil
- SH: retired, non-smoker, moderated alcohol

- Presented with abdominal pain and tiredness. Performance status 1
- January 2016: CT 7x4cm mass in the uncinate process of the pancreas; indeterminate liver lesions.
- February 2016: EUS-FNA well differentiated neuroendocrine tumour, Ki-67 = 15% (grade 2)

CT, computed tomography; EUS-FNA, endoscopic ultrasound-fine needle aspiration; FMH, family medical history; PMH, past medical history; SH, social history.

CASE 2: MR XX

- March 2016: further staging:
  - MRI liver: multiple innumerable liver metastases
  - 68 Gallium SR- PET: Receptor positive disease within bone, liver (some uptake is heterogeneous), nodal metastases, and pancreatic mass (primary). Evidence of progression compared with previous imaging

MRI, magnetic resonance imaging; SR-PET, somatostatin receptor positron emission tomography

CASE 2: MR XX

Grade 2
Metastatic Pan-NET
Widespread disease
Progressing
High tumour burden
Ga-SR PET +ve

Options:

- SSA
- Sunitinib
- Everolimus
- TemCap
- STZ/5-FU
- PRRT

Ga-SR PET, gallium somatostatin receptor positron emission tomography; Pan-NET, pancreatic neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogues; STZ/5-FU, streptozotocin/ fluorouracil; TemCap, temozolomide-capecitabine.

CASE 2: MR XX

Grade 2
Metastatic Pan-NET
Widespread disease
Progressing
High tumour burden
Ga-SR PET +ve

Options:

- SSA
- Sunitinib
- Everolimus
- **TemCap**
- **STZ/5-FU**
- PRRT

Ga-SR PET, gallium somatostatin receptor positron emission tomography; Pan-NET, pancreatic neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogues; STZ/5-FU, streptozotocin/ fluorouracil; TemCap, temozolomide-capecitabine.

CASE 2: MR XX

- Zoledronic acid (widespread bone metastases)
- April-September 2016: TemCap
  - Partial response after 3 months: -32.6% RECIST 1.1
  - Maintained response after 6 months; treatment break
  - 3-monthly imaging until October 2017: stable
- December 2017: one of lesions within the liver increased in size; otherwise stable disease (1.4cm→3.2cm)
  - **MDT**: considered radiotherapy to liver lesion
    - Not possible due to size and further progression
    - TemCap restarted → new progression after 3 months
  - **MDT**: New biopsy confirmed G2 NET with areas of G3 NEC
    - Mitotic index is 22 per 10 high power fields; Ki-67 not available

MDT, multidisciplinary team; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumour; RECIST, response evaluation criteria in solid tumours; TemCap, temozolomide-capecitabine.

CASE 2: MR XX

Grade 2; **areas of G3-NEC**
Metastatic Pan-NET
Widespread disease
Progressing
High tumour burden
Ga-SR PET +ve

Options:

- Everolimus
- SSA
- Sunitinib
- Platinum-Etoposide
- Other chemotherapy
- PRRT

Ga-SR PET, gallium somatostatin receptor positron emission tomography; NEC, neuroendocrine carcinoma; Pan-NET, pancreatic neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogues.

CASE 2: MR XX

Grade 2; **areas of G3-NEC**
Metastatic Pan-NET
Widespread disease
Progressing
High tumour burden
Ga-SR PET +ve

Options:

- Everolimus
- SSA
- Sunitinib
- **Platinum-Etoposide**
- **Other chemotherapy**
- PRRT

Ga-SR PET, gallium somatostatin receptor positron emission tomography; NEC, neuroendocrine carcinoma; Pan-NET, pancreatic neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogues.

CASE 2: MR XX

- March 2018: started Platinum-Etoposide
- New progression after 3 months

CASE 2: MR XX

Grade 2; areas of G3-NEC
Metastatic Pan-NET
Widespread disease
Progressing
High tumour burden
Ga-SR PET +ve

Options:

- Everolimus
- Best supportive care
- PRRT
- Sunitinib
- Other

Ga-SR PET, gallium somatostatin receptor positron emission tomography; NEC, neuroendocrine carcinoma; Pan-NET, pancreatic neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogues.

CASE 2: MR XX

Grade 2; areas of G3-NEC
Metastatic Pan-NET
Widespread disease
Progressing
High tumour burden
Ga-SR PET +ve

Options:

- Everolimus
- Best supportive care
- **PRRT**
- Sunitinib
- Other

Ga-SR PET, gallium somatostatin receptor positron emission tomography; NEC, neuroendocrine carcinoma; Pan-NET, pancreatic neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogues.

CASE 2: MR XX

- Ga-SR PET repeated: +ve disease confirmed
- PRRT:
  - #1 Sept 2018; #2 Oct 2018
  - CT scan: Stable disease → planned for #3 (cancelled)
  - Drop platelets after #2: further PRRT could not proceed

- **MDT**: Everolimus vs FOLFIRI
  - Feb 2019: favoured everolimus (due to myelosuppression following PRRT)
- Mar 2019: clinical deterioration
  - Best supportive care (passed away April 2019)

CT, computed tomography; FOLFIRI, folinic acid, fluorouracil and irinotecan; Ga-SR PET, gallium somatostatin receptor positron emission tomography; PRRT, peptide receptor radionuclide therapy.

TAKE HOME MESSAGE

- Every patient diagnosed with Pan-NETs requires an **individualised plan of treatment** based on:
  - Grade
  - Disease spread / tumour burden
  - Localisation of disease
  - Symptoms
  - Performance status

- Discussion in NET MDT is warranted

MDT, multidisciplinary team; NET, neuroendocrine tumours; Pan-NETs, pancreatic neuroendocrine tumours.

SUMMARY

Prof Marianne Pavel, MD

Gastroenterology, Pulmonology and Endocrinology Department of Medicine 1,
University of Erlangen, Germany

TUMOUR FEATURES IMPACT ON TREATMENT CHOICES

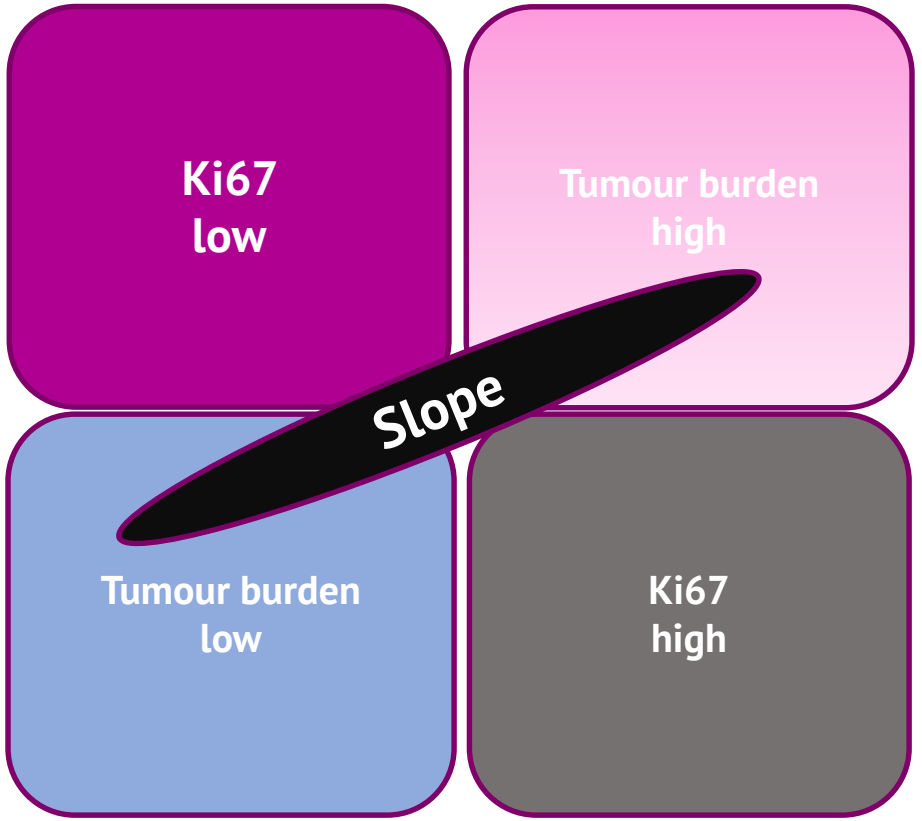
NET connect
POWERED BY COR2ED

	Well differentiated			Poorly differentiated
ENETS Grade	Low (G1)	Intermediate (G2)	High (G3)	High (G3)
Ki67 (%)	< 2%	3-20	>20	>20
Growth (Imaging)	No/ slowly	moderate	more rapid	rapid
Functional imaging	SRI +ve			FDG PET +ve
Prognosis	Indolent			Poor
Therapy	Surgery			Chemotherapy
	SSA	PRRT, Targeted drugs		?
Adjuvant therapy	No			Yes

PARAMETERS WITH IMPACT ON DECISION MAKING

- Age
- ECOG PS
- Functional activity
- Elevated biomarkers
- Comorbidities

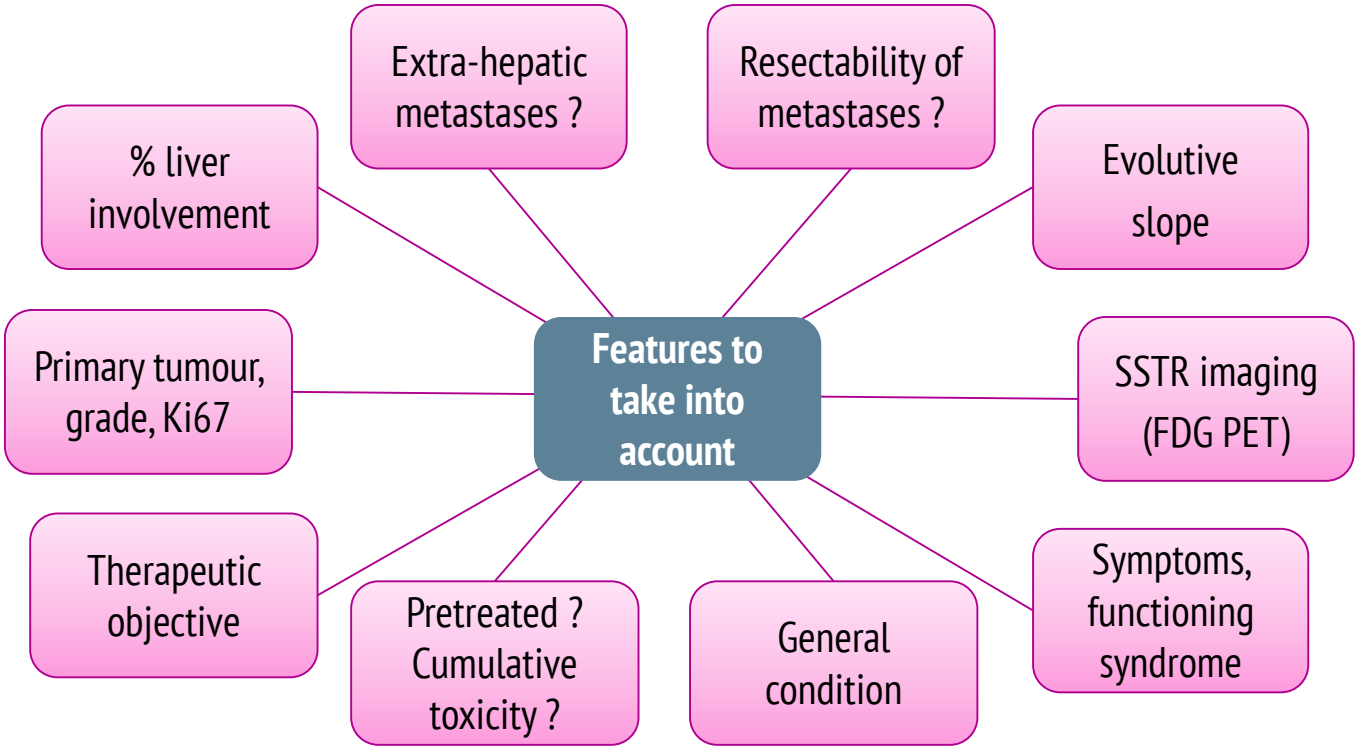
Nomograms for
NET G1/2 and NEC



Panzuto F et al, The Oncologist 2017; 22(4): 409-415; Lamarca A et al, JNCI 2017; 109 (5): https://doi.org/10.1093/jnci/djw277; Modlin IM et al, Neuroendocrinology 2010; 92(3): 143-157

THERE IS NO SINGLE APPROACH TO TREAT PATIENTS WITH METASTATIC NEN

ALL CASES TO BE DISCUSSED IN EXPERT MDT MEETING



FDG PET, fluorodeoxyglucose-positron emission tomography; SSTR, somatostatin receptor

REACH NET CONNECT VIA TWITTER, LINKEDIN, VIMEO AND EMAIL OR VISIT THE GROUP'S WEBSITE

http://www.net-connect.info

Follow us on Twitter
@net_connectinfo

Join the
NET CONNECT
group on LinkedIn

Watch us on the
Vimeo Channel
NET CONNECT

Email
antoine.lacombe@cor2ed.com

NET CONNECT
Bodenackerstrasse 17
4103 Bottmingen
SWITZERLAND

Dr. Antoine Lacombe
Pharm D, MBA
Phone: +41 79 529 42 79
antoine.lacombe@cor2ed.com

Dr. Froukje Sosef
MD
Phone: +31 6 2324 3636
froukje.sosef@cor2ed.com