Neuroendocrine tumors overview of treatment

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NET

- Neuroendocrine tumors (NETs), sometimes referred to as carcinoids, are abnormal growths that begin in the neuroendocrine cells, which are distributed widely throughout the body.
- Neuroendocrine cells have roles both in the endoc rine system and the nervous system.
- They produce and secrete a variety of regulatory hormones (neuropeptides): neurotransmitters and growth factors.

- **NETs** = **Carcinoid tumours** - heterogeneous group of tumours arising from distinct neuroendocrine cells located throughout the body.
- **Neuroendocrine cells** **-** peptide hormone-producing cells that share a neural-endocrine phenotype (**DNES** = diffuse-neuroendocrine system)
- May produce peptides that lead to their syndromes (**APUD** = Amine Precursor Uptake and Decarboxylation)

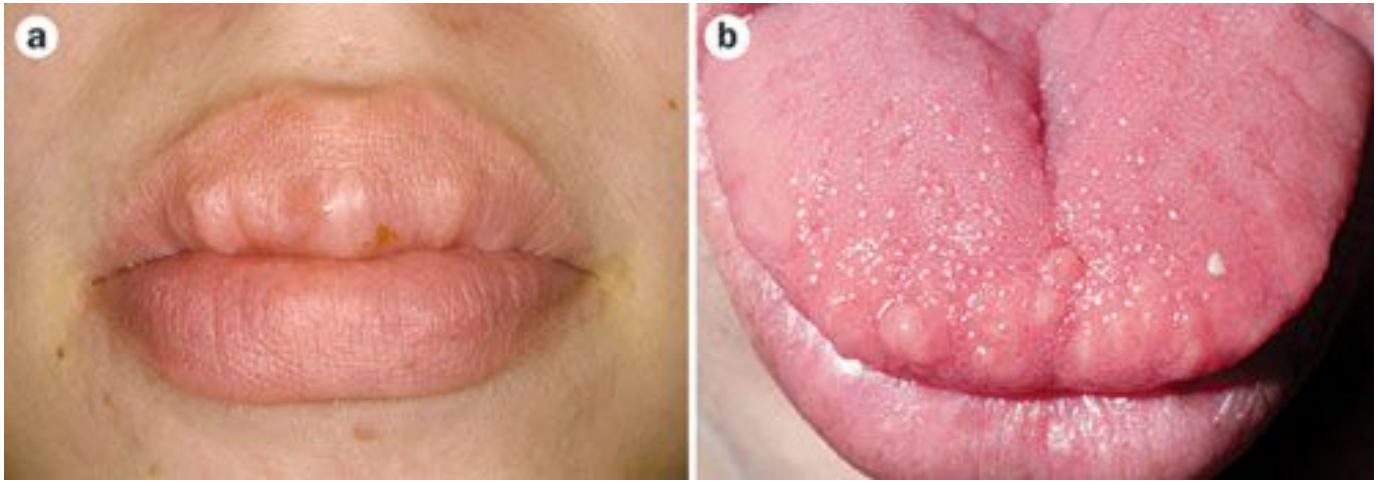
Cell Type	Localisation	Products
D cells	GI tract	Somatostatin
Enterochromaffin	GI tract	Serotonin, Substance P
Enterochromaffin -like	GI Tract	Histamine
G cells	Stomach & duodenum	Gastrin
VIP cells	GI Tract	VIP
A cells	Pancreas	Glucagon
B cells	Pancreas	Insulin
Chromaffin	Adrenals	Catecholamines
C cells	Thyroid	Calcitonin

NETs: An Overview

- Tumours may be sporadic or hereditary (rare)
- When hereditary, they may be associated with different genetic syndromes such as:
  - Multiple endocrine neoplasia type 1 (MEN1)
  - Multiple endocrine neoplasia type 2 (MEN2)
  - Von Hippel Lindau (vHL)
  - Neurofibromatosis type 1 (NF1) – duodenal somatostatinoma
  - TSC

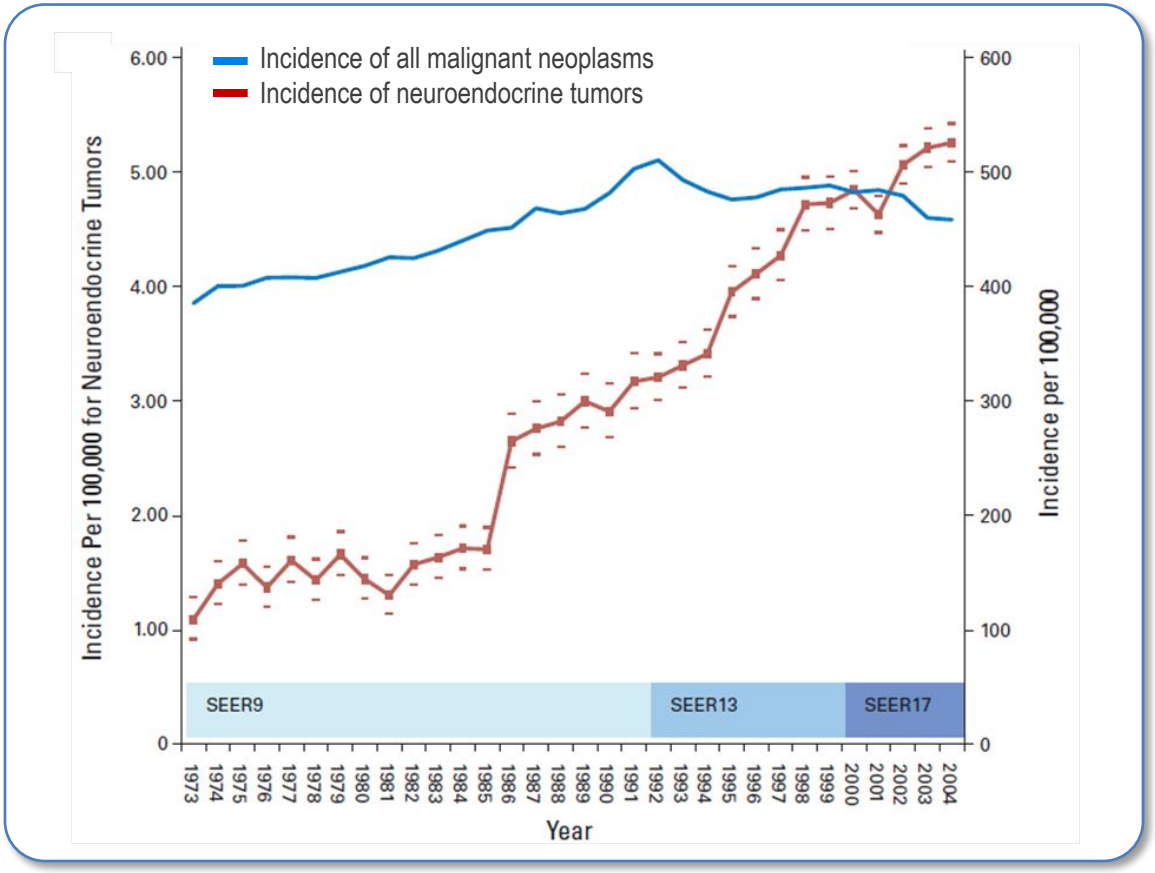
MEN 1	MEN2	
	2A	2B
Wermer syndrome	**Sipple syndrome**	**(multiple)**
Men 1 gene	**RET**	**RET**
Parathyroid hyperplasia (hypercalcemia) – 90%	Parathyroid hyperplasia (hypercalcemia) – 25%	Marfanoid body habitus
Pituitary adenoma	Medullary Thyroid Ca	Medullary Thyroid Ca
Pancreatic NET's	Pheochromocytoma 50%	Pheochromocytoma 50%
		Mucosal neuroma

Mucosal neuroma



Tuberous sclerosis	Renal-cell carcinoma Angiomyolipomas Astrocytoma	Pancreatic neuroendocrine tumors	TSC1 (9q34) TSC2 (16p13)
VHL s-m	hemangioblastomas of the brain, spinal cord, and retina; renal cysts and RCC; epididymal and broad ligament cysts	Pancreatic neuroendocrine tumors, Pheochromocytoma	VHL gene
Neurofibromatosis type 1	Optic gliomas Meningioma Astrocytoma Neurofibrosarcoma Rhabdomyosarcoma	Somatostatin/ insulin producing NET, duodenal NET, Pheochromocytoma	NF2 (17q11.2)

Increase in NET Incidence Compared with All Malignant Neoplasms*

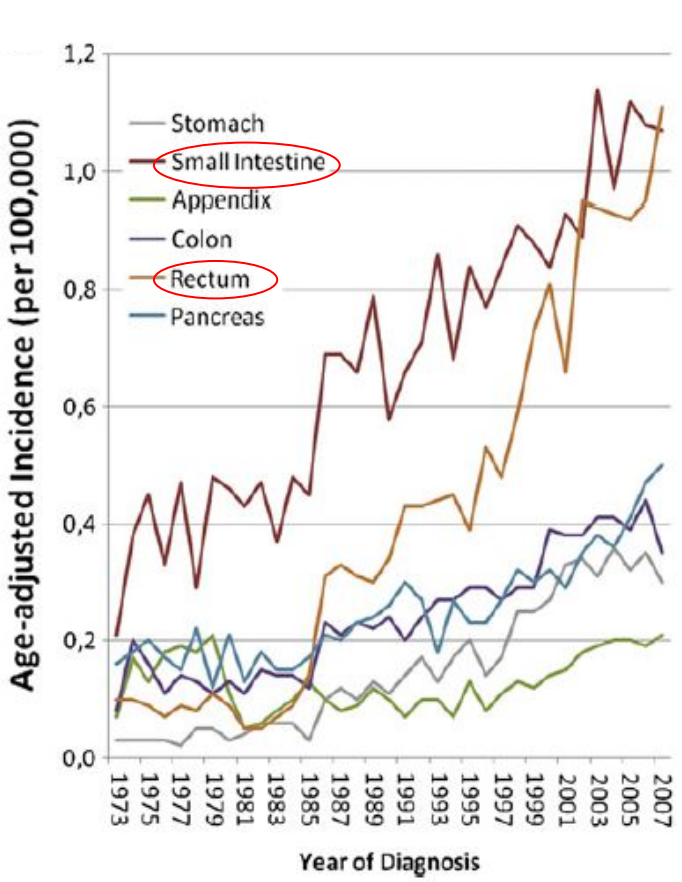


NETs, neuroendocrine tumors; SEER, Surveillance, Epidemiology, and End Results.
*Based on SEER data from 1973-2004.

Yao JC, et al. *J Clin Oncol.* 2008;26(18):3063-3072.

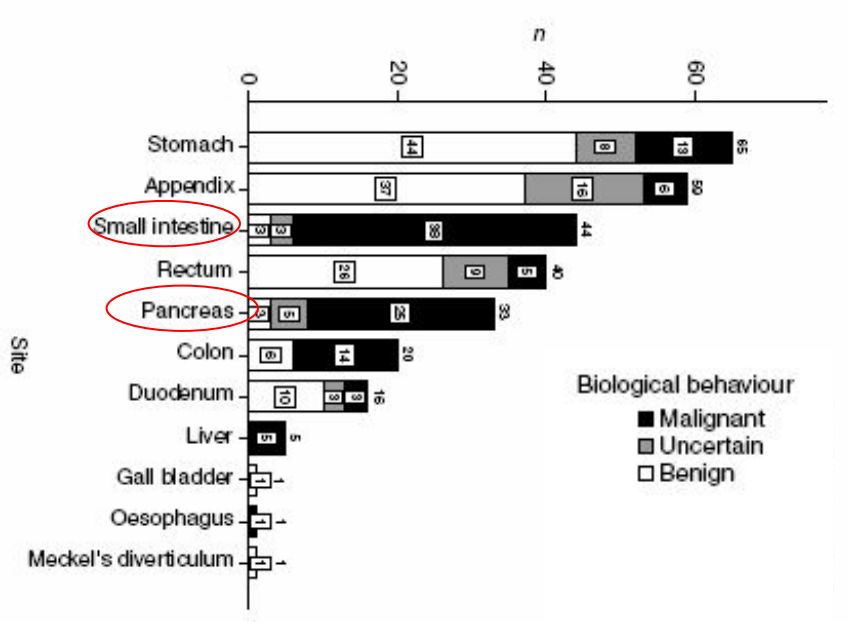
GEP-NETs: Rare But Increasing, particularly for small intestine and rectal tumors

SEER 9 Registry, 1973-2007



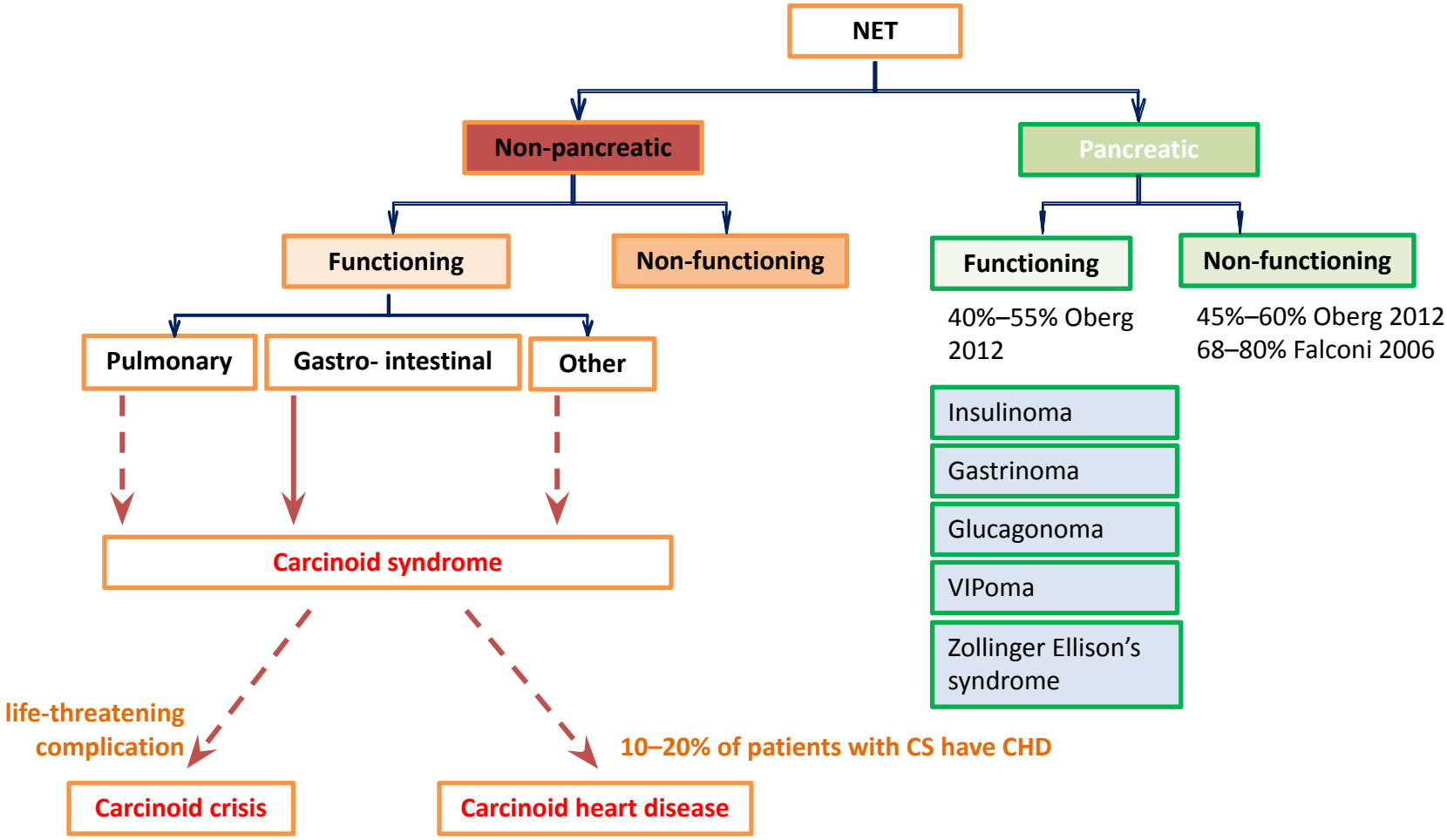
The most substantial change in incidence over time occurred in small intestinal and rectal NETs, and these are now the most common GEP-NETs according to SEER 9 Registry

Prospective Registry, Austria

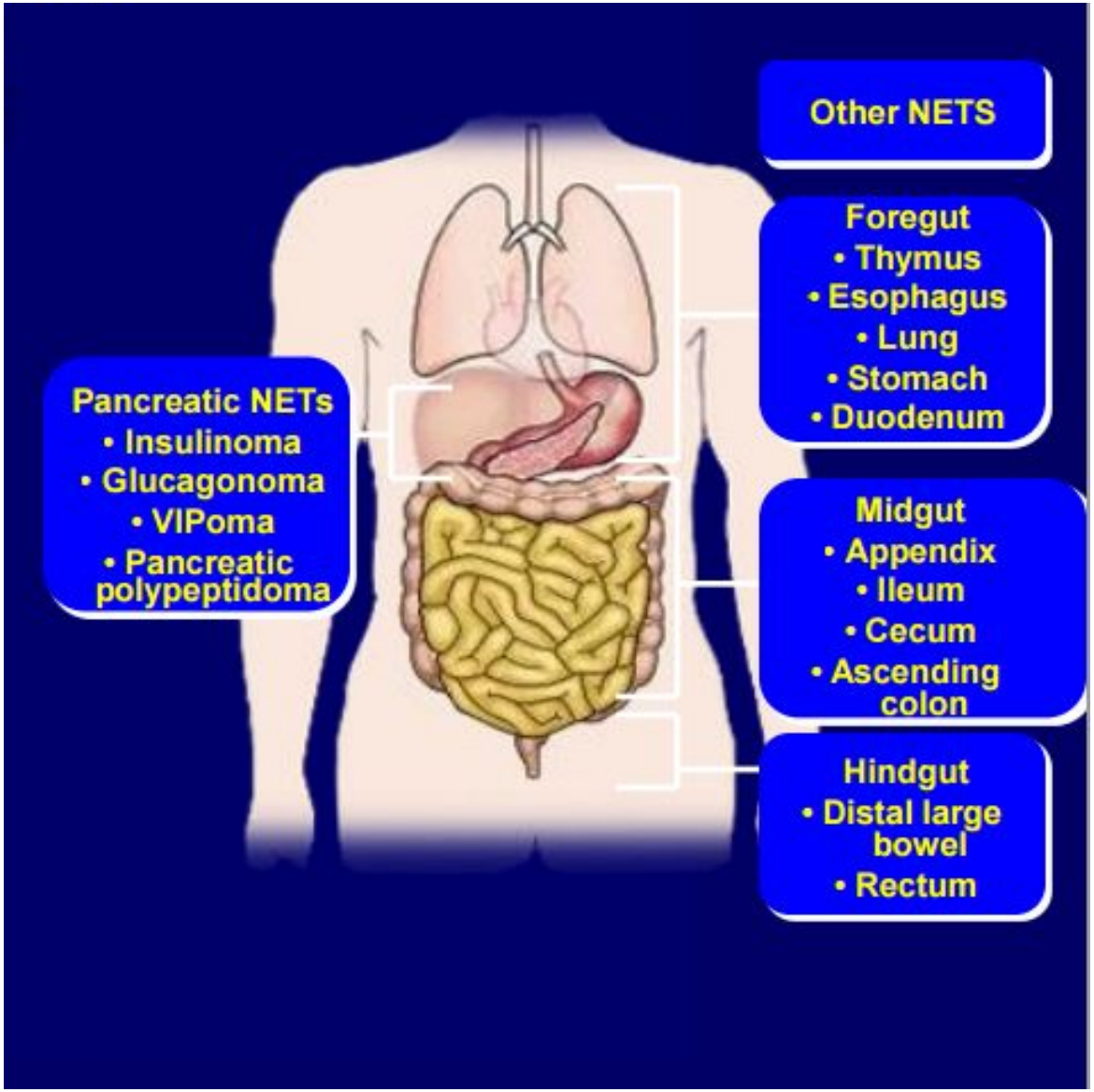


Small intestine and pancreatic tumors are the most malignant NETS

Lawrence B et al., Endocrinol Metab Clin North Am 40:1-18, 2011; Niederle et al. Endocrine Relat Cancer 17:909-918, 2010


NET
Non-pancreatic
Pancreatic
Functioning
Non-functioning
Functioning
Non-functioning
40%–55% Oberg 2012
45%–60% Oberg 2012
68–80% Falconi 2006
Pulmonary
Gastro- intestinal
Other
Insulinoma
Gastrinoma
Glucagonoma
VIPoma
Zollinger Ellison's syndrome
Carcinoid syndrome
life-threatening complication
10–20% of patients with CS have CHD
Carcinoid crisis
Carcinoid heart disease

Classification by embryonic origin



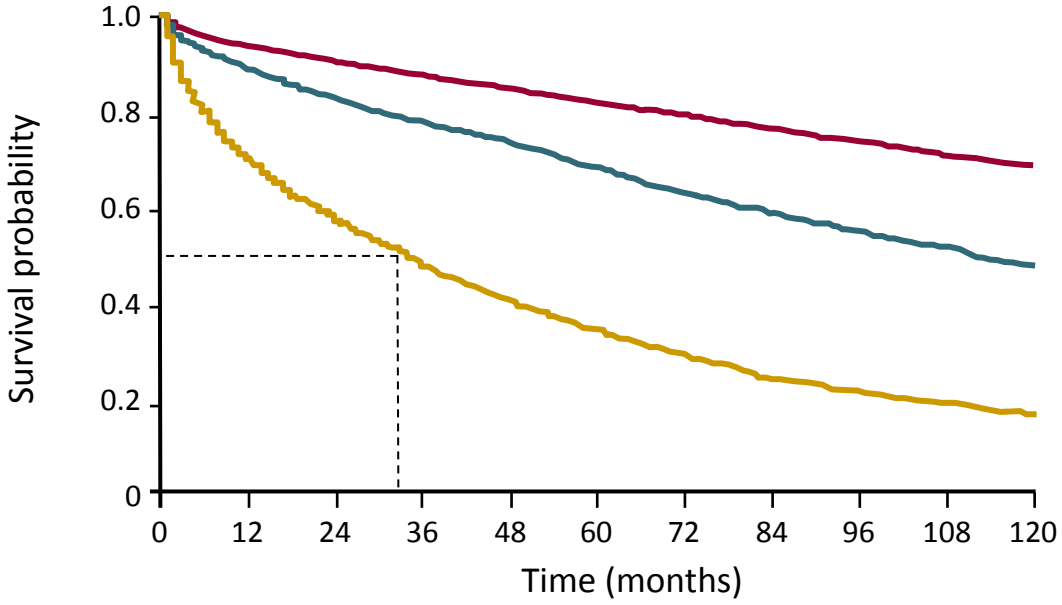
NETs: An Overview

- Over 60% of NETs are metastatic at the time of diagnosis
- Most NETs are non-secretory (non-functional), but some cause symptoms
- 80-90% of GI NETs express somatostatin receptors (sstr 2,5)[2]

1. Yao JC, et al. *J Clin Oncol.* 2008; 26: 3063-3072; 2. Hofland LJ & Lamberts SW, *Endocrine Reviews.* 2003. 24(1): 28-47.

Median Survival for Patients with Localised and Metastatic NET

Tumours with well- and moderately differentiated histology[1]

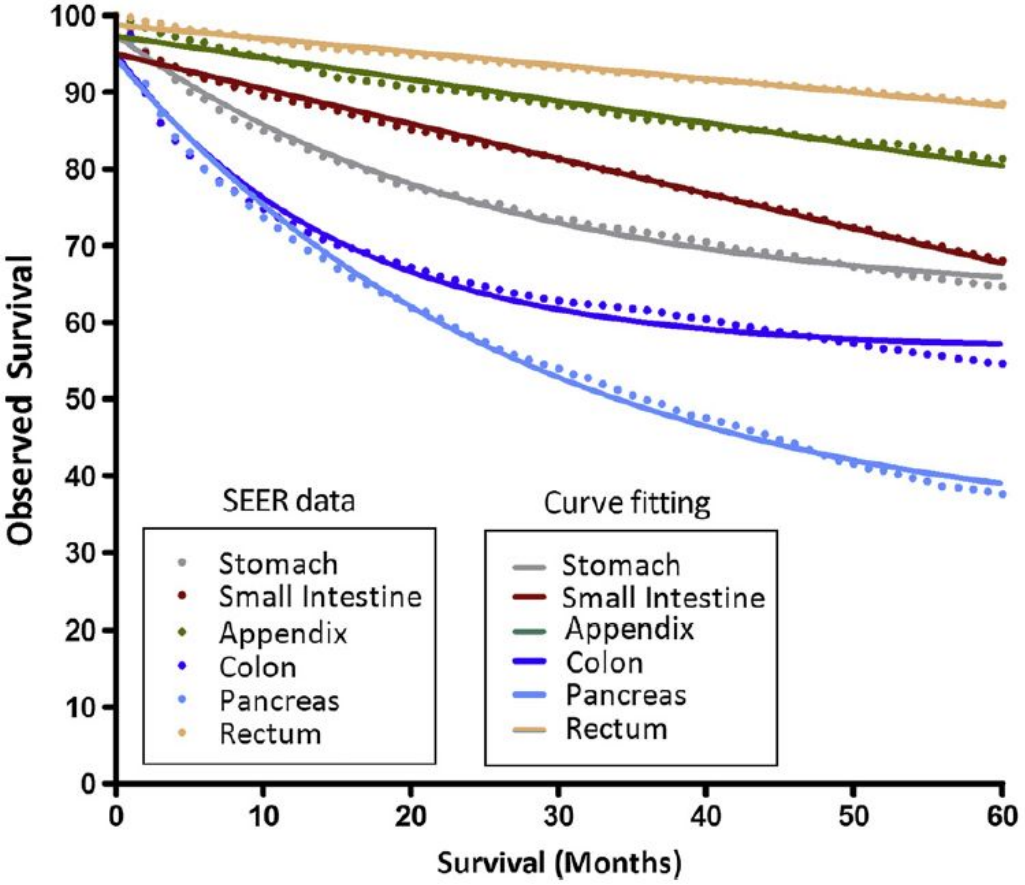


Stage	Median survival	
	Month	95% CI
Localised	223	208-238
Regional	111	104-118
Distant	33	31-35

CI = confidence interval

[1]Yao J, et al. *J Clin Oncol*. 2008; 26: 3063-3072; [2]Jemal A, et al. *CA Cancer J Clin.* 2010; 60: 277-300.

Observed 5-Year Survival for GEP-NET Primary Sites*



*SEER 17 registry, 1973 - 2007

5-year survival rate for GEP-NET: 68.1%

Pancreas:	**37.6%**
Colon:	54.6%
Stomach:	64.1%
Small intestine:	**68.1%**
Appendix:	81.3%
Rectum:	88.5%

50% of patients have died at:

10.3 mo (colonic NETs)

16.7 mo (gastric NETs)

18.9 mo (pancreatic NETs)

Source: US SEER database. Lawrence et al. *Endocrinol Metab Clin North Am*. 2011; 40(1): 1-18, vii

How Well Do They Resemble Their Normal Cell Counterpart?[1,2]

WHO 2010 Classification

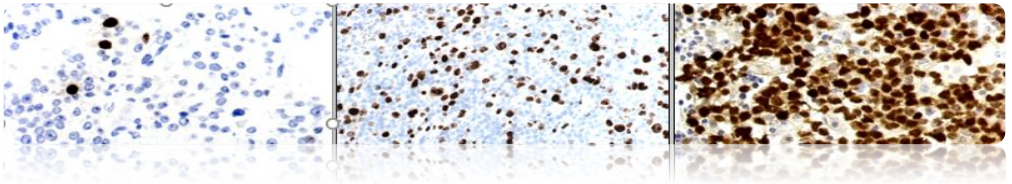
The proliferative rate can be assessed by:

- **Mitotic rate:** number of mitoses per unit area of tumor (mitoses/10 HPFs or mitoses/2 mm^2)
- **Ki-67 index:** percentage of cells that stain positive for the proliferation marker Ki-67

Prognosis of patients with NETs

Good → Poor

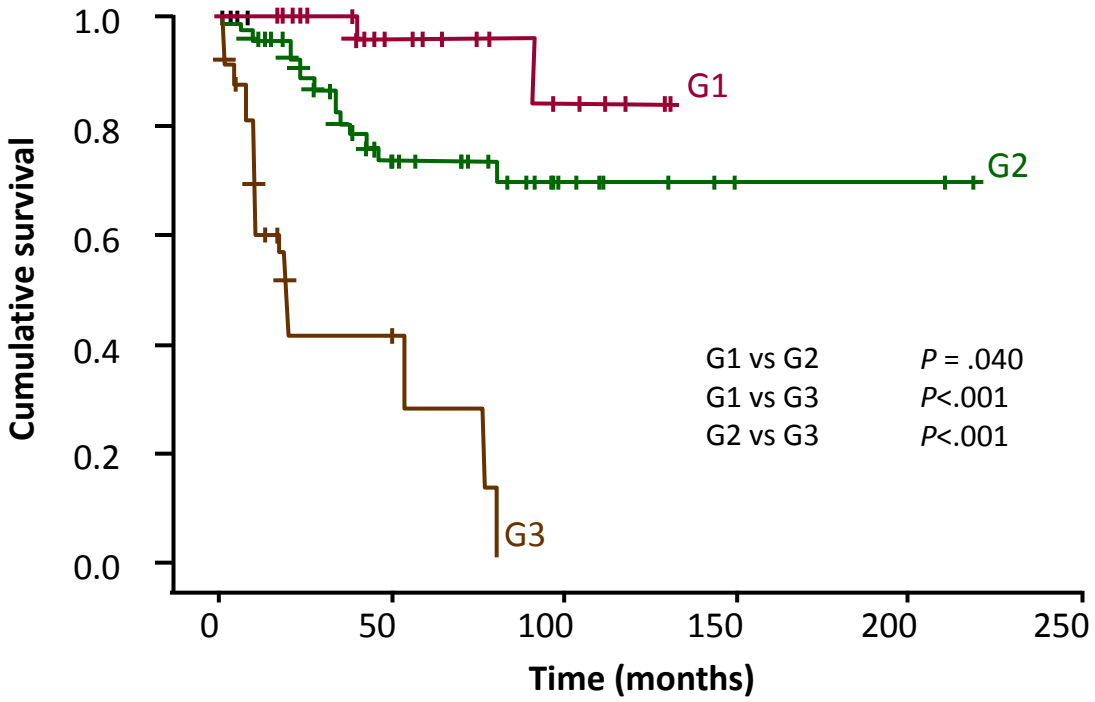
GI tract and pancreas	Neuroendocrine Neoplasm (or carcinoid)	Neuroendocrine Neoplasm	Neuroendocrine Carcinoma
Histological classification	Well-differentiated	Moderately and well-differentiated	Poorly differentiated
Grade	G1 (low grade)	G2 (intermediate grade)	G3 (high grade)
Mitotic rate (mitoses/10 HPF*)	<2	2-20	>20
Ki-67 index (%)	<3	3-20	>20



- HPF, high-power field; NETs, neuroendocrine tumors; WHO, World Health Organization.

1. Klimstra DS, et al. *Pancreas*. 2010;39(6):707-712.
2. Lawrence B, et al. *Endocrinol Metab Clin North Am*. 2011;40(1):1-18.

Correlation of Tumour Grade and Cumulative Survival



Grade[1]	Mitotic count (10 HPF)[2]	Ki-67 index (%)[3]
G1	<2	≤2
G2	2-20	3-20
G3	>20	>20

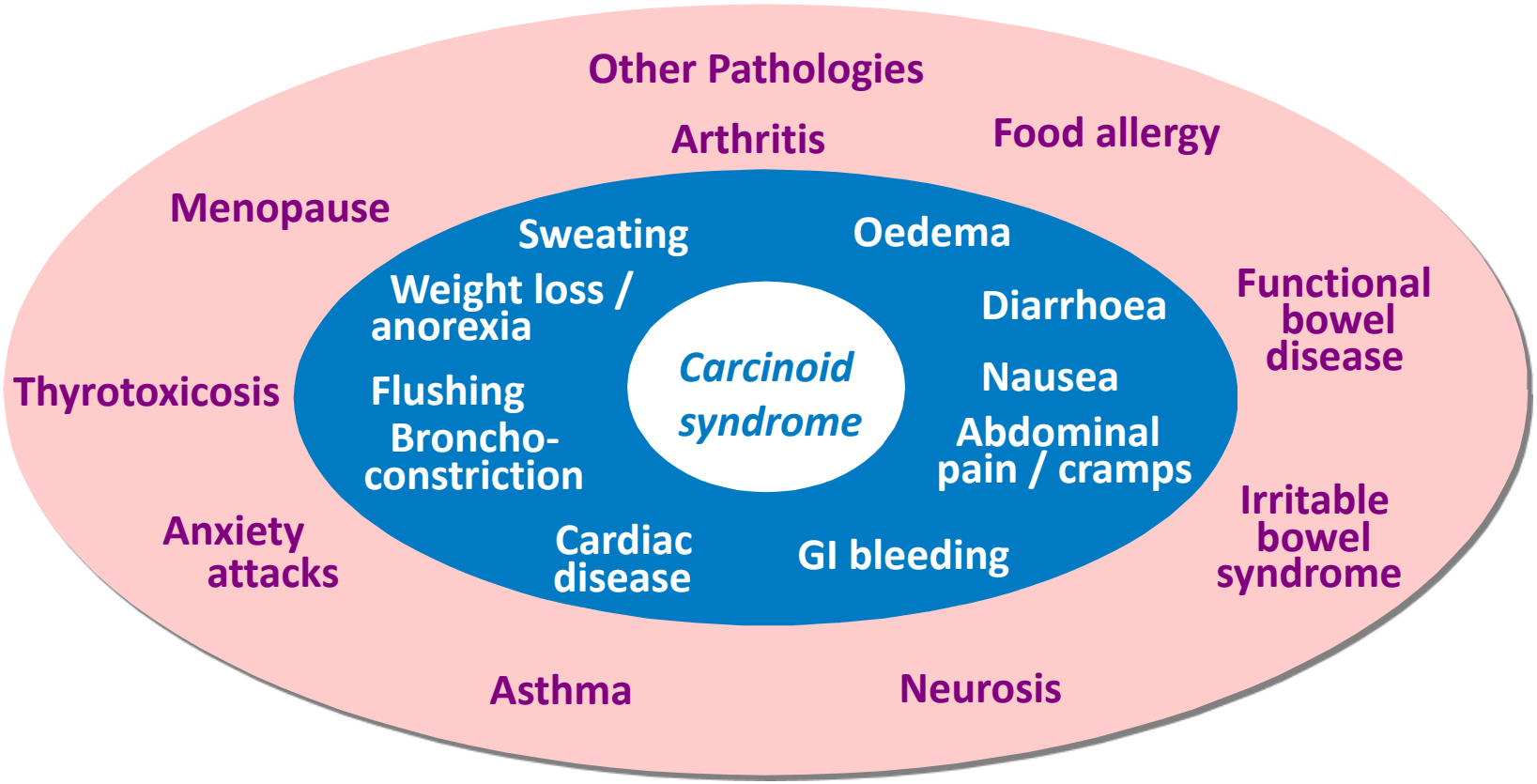
1 ENETS grading system.

2 10 HPF = 2 mm^2 at least 40 fields (40 × magnification) evaluated in areas of highest mitotic density.

3 Percentage of 2,000 tumour cells in areas of highest nuclear labelling with MIB1 antibody.

Pape UF, et al. *Cancer.* 2008; 113: 256-265.

Clinical Presentation



Adapted from Vinik A, et al. *Pancreas*. 2009; 38(8): 876-89.

Карциноидный синдром

- 10% случаев
- опухоли ***Midgut*** (около 70%).
- при метастазах в печени
- не характерен для легочный карциноидов

Клиника

- **приливы** (90%),
- **поносы** (80%),
- **боли в животе** (40%),
- поражение клапанов сердца и Сердечная недостаточность (**Carcinoid heart disease**) (40%)
- Характерен очень высокий уровень 5HIAA в моче
- **бронхообструкция** (астматичнские приступы – кинины, гистамин) –(10%)
- **пеллагра** (5%) - понос, деменция, дерматит (недостаточность ниацина – вит РР – при недостаточности триптофана, который расходуется карциноидной опухолью для выработки серотонина)

- Лечение: аналоги соматостатина

Карциноидный криз

- Во время операции резкий выход серотонина в кровь
- Бронхообструкция, гипотензия, аритмии
- Профилактика: аналоги соматостатина в предоперационный период

Диагностика

- CT
- MRI
- Radiolabeled somatostatin receptor scintigraphy
- DOTATATE (better)
- 5HIAA (5-Hydroxyindoleacetic acid - главный метаболит серотонина)
- CgA (PPI’s тоже повышают)

Ф: прекурсор многих активных протеинов и отвечает за генерацию секреторных гранул (например с инсулином)

Карциноид Тимуса

- 2% - 7% DS при наличии передней медиастинальной массы
- Кушинг
- 25% ассоциированы с MEN1

- Лечение- хирургическое (G1-2)
  CMT (G3)
  palliative RT

Легочный карциноид

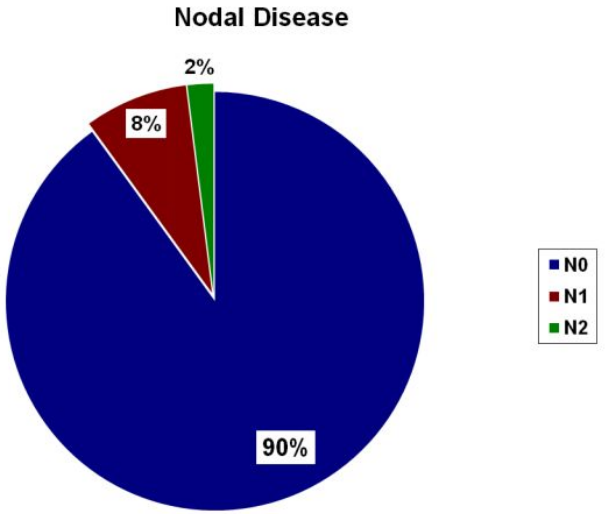
- 25%
- Typical (low grade)
- Atypical (intermediate grade)
- SCLC – KI67% > 30-40

- Diffuse idiopathic pulmonary cell hyperplasia

--- Tumorlets (очень маленькие карциноиды, меньше 0,5 cm , могут развиваться во множественные опухоли)

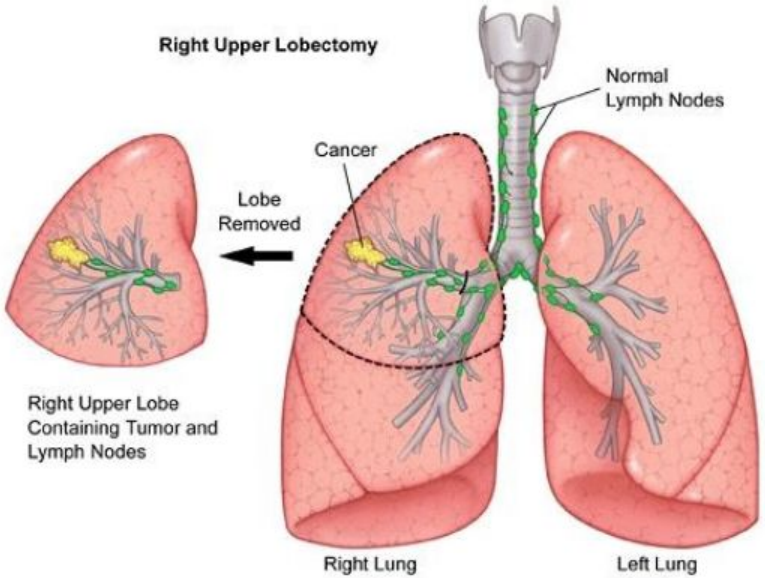
- Карциноидный синдром – редко
- АКТГ - Кушинг
- Акромегалия – редко, но самое частое место эктопической секреции GHRH

Лечение



Хирургическое

Лобэктомия с диссекцией л.у.



Карциноид желудка

	I тип (70-80%)	II тип	III тип
Локализация	Фундальный отдел желудка		Антральный или фундальный отделы желудка
Характер опухоли	Много узлов		Единичный узел
Размеры	Менее 1-2 см	Менее 1-2 см	2-5 см, invasion
	Аутоиммунный хронический атрофический гастрит (АТ к обкладочным клеткам - ахлоргидрия - гастрин - пролиферация)	**MEN1** (гастринома - гастрин - синдром Золингера Элисона)	нормальная слизистая оболочка
Биологические свойства	Медленный рост, иногда метастазирование		Относительно агрессивные опухоли, метастазируют в печень и другие органы (55%)
гастрин в плазме	Повышение		Норма
Кислотность желудочного сока	Пониженная	Повышенная	Нормальная, пониженная

Лечение карциноидных опухолей желудка

- **I тип**

- эндоскопическое иссечение одиночных опухолей

- частичная резекция желудка при множественных карциноидах

- ? аналоги соматостатина

- **II и III типы**

- резекция желудка

Карциноид кишечника

- лечение хирургическое
- Аппендикс - <2 cm – simple apedectomy

  > 2 cm – RT hemicolectomy
- Rectum - <2 cm – transanal/ endoscopic excision

  > 2 cm – APR, LAR

Нейроэндокринные опухоли поджелудочной железы

Инсулиномы

- Самые частые
- растет из бета клеток
- Только 5-10% злокачественные
- Основной симптом – гипогликемия, связан с гиперсекрецией инсулина.
- 4-5%имеют отношение к синдрому MEN1

Гастриномы (синдром Золлингера – Эллисона)

- Второе место среди эндокринных опухолей поджелудочной железы
- 70% - в двенадцатиперстной кишке

25% – в головке поджелудочной железы

5% – в других органах (желудке, тонкой кишке)

- Метастазирование
- Множественные пептические язвы

Випомы (синдром Вернера – Моррисона)

- Секреция вазоактивного интестинального пептида (VIP)
- MEN1 - 6%
- Метастазирование
- Поносы

Глюкагономы

- В α - клетках поджелудочной железы
- Глюкагон стимулирует распад гликогена, глюконеогенез, кетогенез, секрецию инсулина, липолиз, тормозит желудочную и поджелудочную секреции.
- Метастазирование
- MEN1 - 15%
- Клинические проявления :

  потеря массы тела (70–80%),

  диабет (75%),

  дерматит (65– 80%)

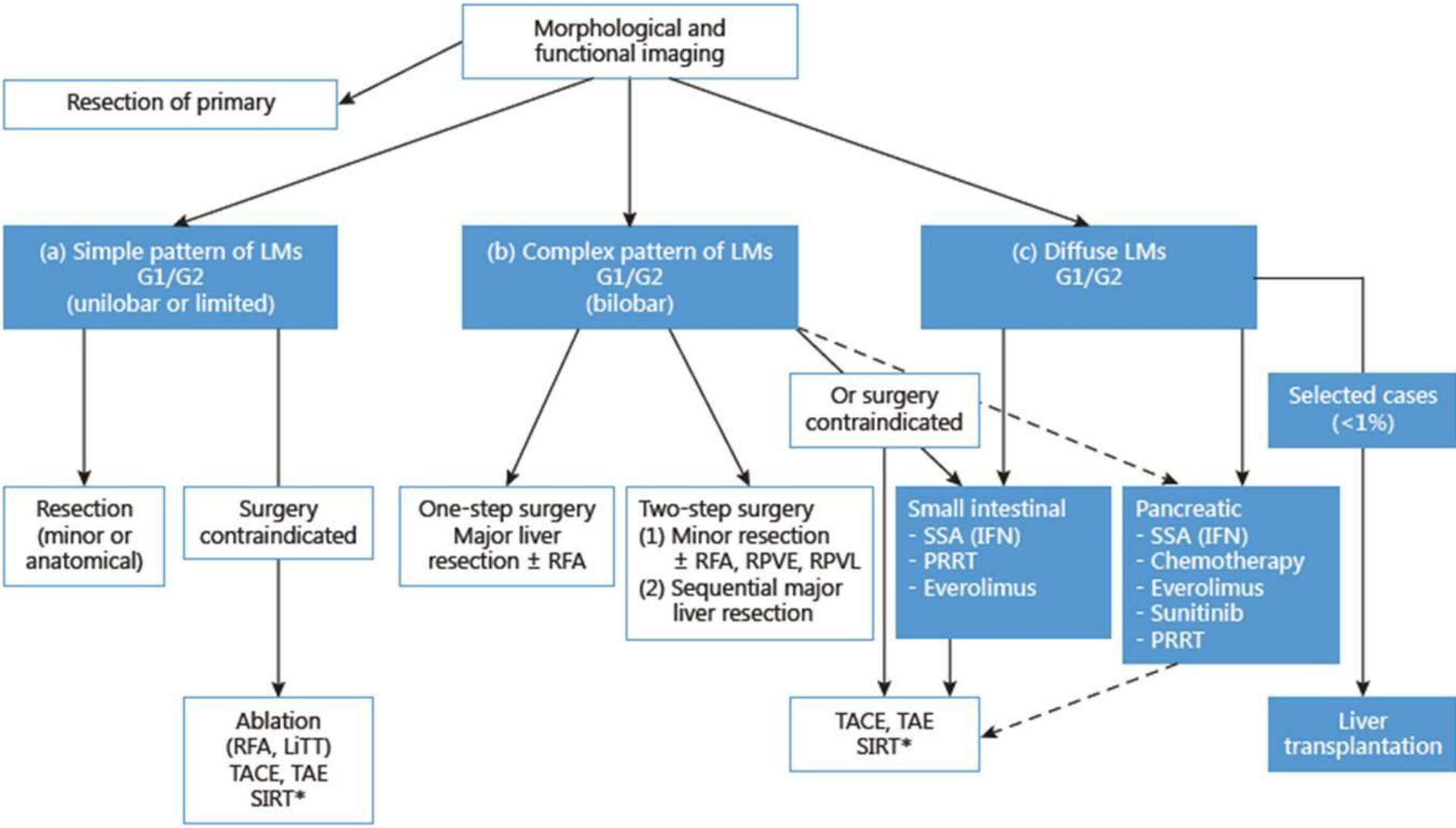
  стоматит (30–40%)

  диарея (15–30%).
- Necrolytic migratory erythema эритема, папулы и пустулы на лице, животе

Pancreatic polypeptidoma

- Относится к нефункционирующим опухолям ПЖЖ
- Как правило Дз в поздних стадиях
- Клиника обусловлена массой и метастазами (не гормональными симптомами)

Therapeutic Options NETs



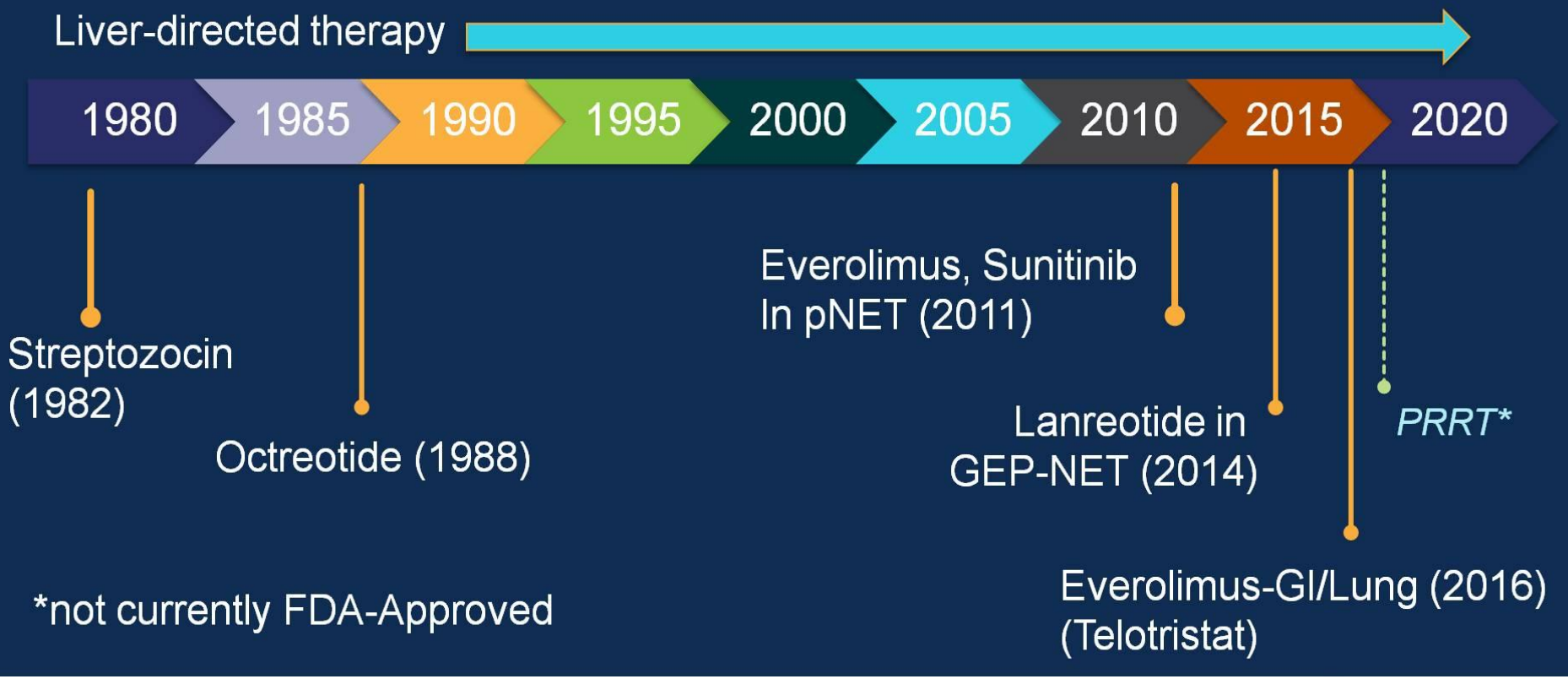
Общие принципы лечения локальной болезни в зависимости от GRADE

- G1-2 – хирургическое

- G3 – химиотерапия (экстраполяция из протоколов SCLC:

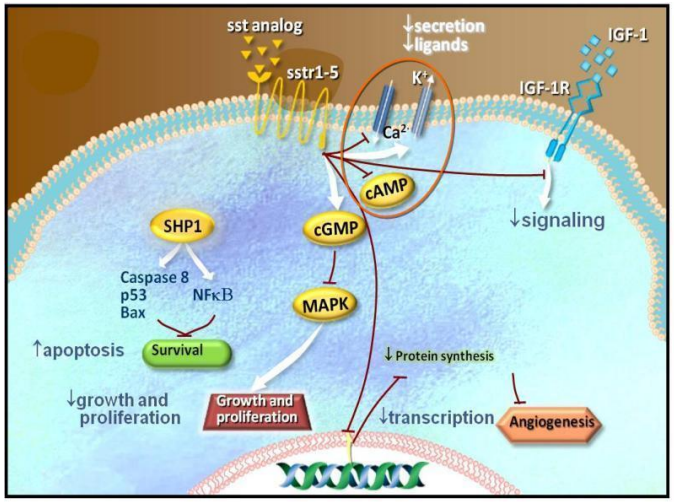
- cisplatin
- VP 16 (Etoposide)
- + RT? + surgery?

Drug Approvals for NET



Somatostatin Signalling in NETs

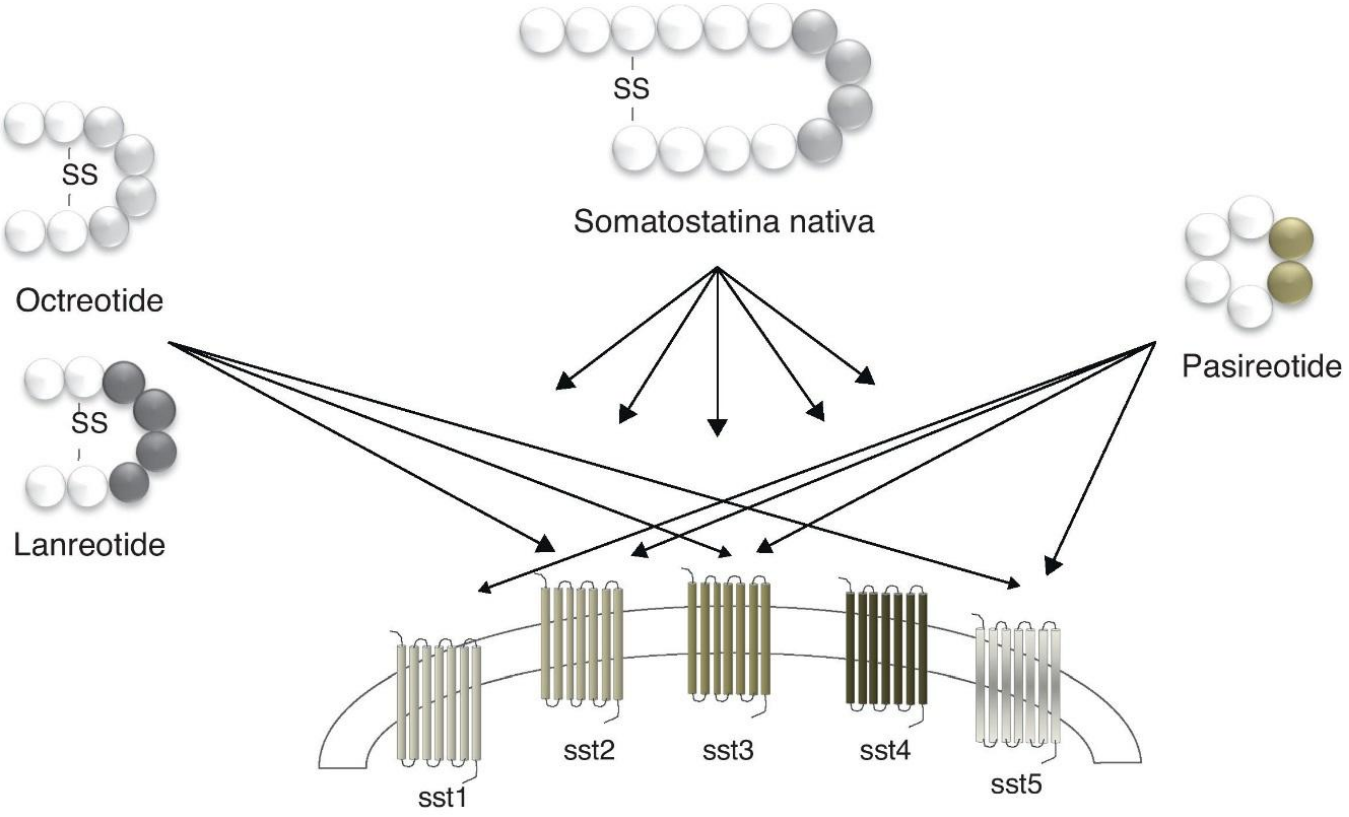
- More than 90% of NET express somatostatin receptors[3-5]



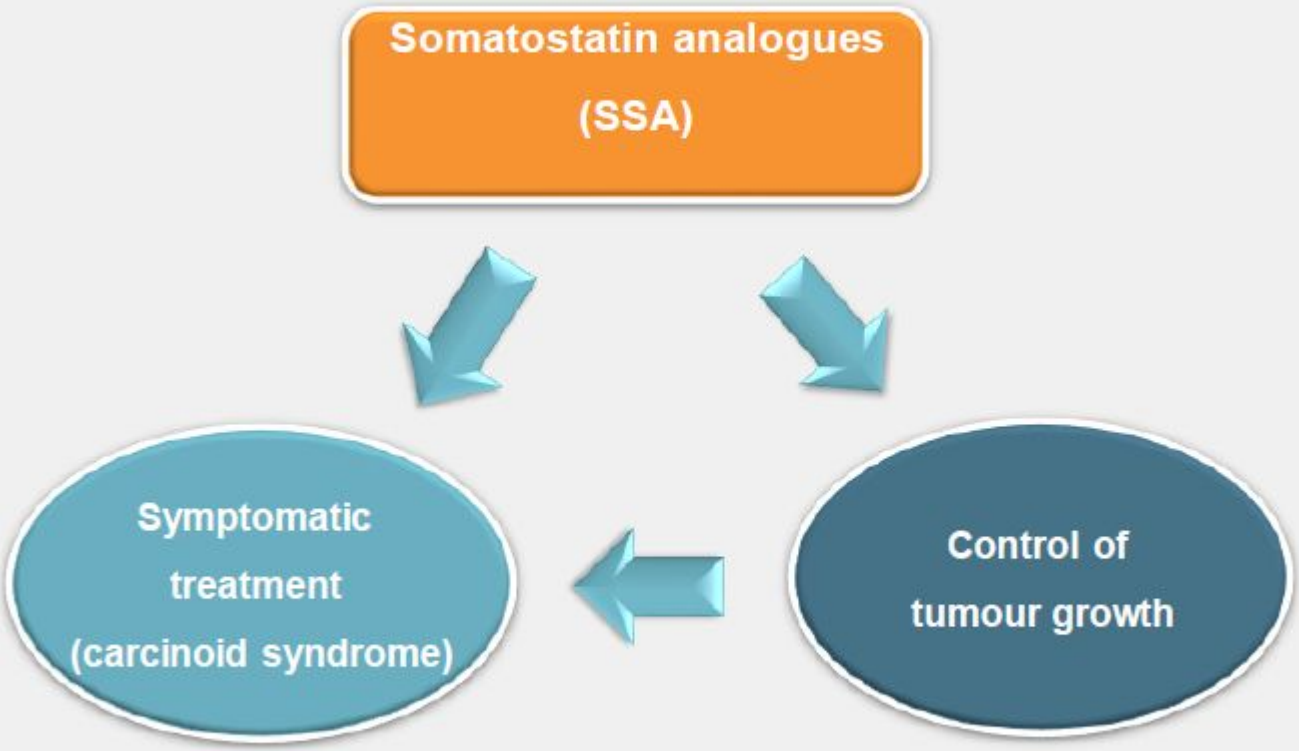
High prevalence in NET types across sstr with $sstr_2$ being the most prevalent

Prevalence on NET type[1]:	sst_1	sst_2	sst_3	sst_4	sst_5
Carcinoid	76%	80%	43%	68%	77%
Gastrinoma	79%	93%	36%	61%	93%
Insulinoma	76%	81%	38%	58%	57%
Non-functioning islet cell tumour	58%	88%	42%	48%	50%
Inhibitory effect[2,3]:					
Hormone secretion	+	+			+
Proliferation	+	+	+		+
Induction of apoptosis		+	+		

Somatostatin analogs



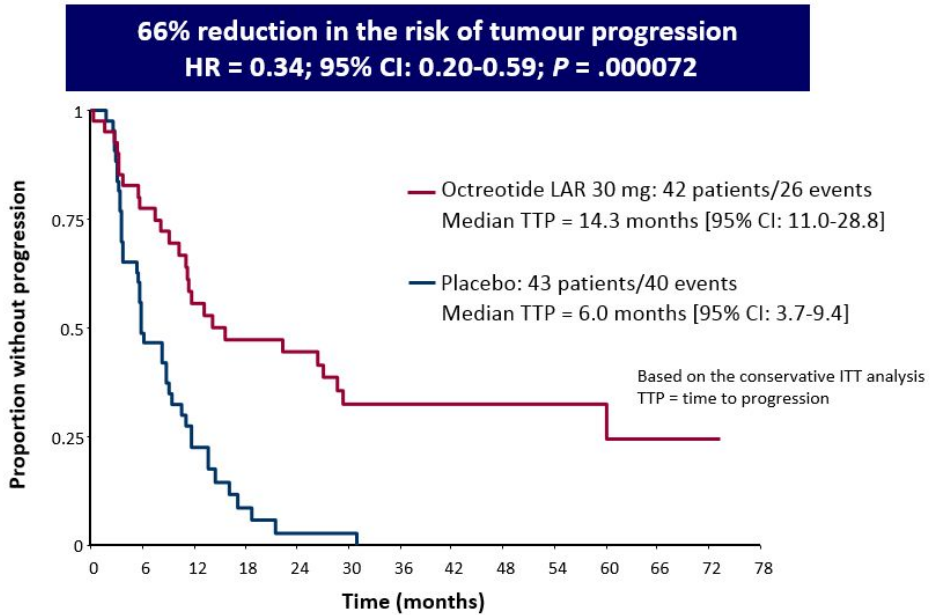
Importance of somatostatin analogues in NETs

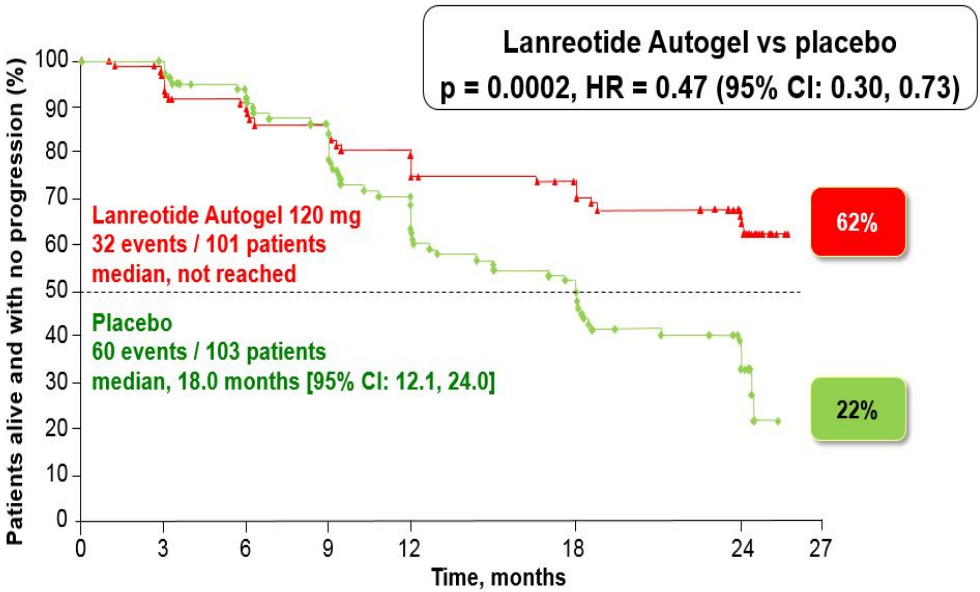


Somatostatin analogs

- **Octreotide LAR**
  - N=85
  - TTP
  - Midgut
  - Functional 39%
  - Octreoscan pos 75%
  - Live involvement up to 10% - 75%

- **Lanreotide autogel 120 mg**
  - N=204
  - PFS
  - Midgut, hingut, pancreatic
  - Non-functional
  - Octreoscan POS 100%
  - Live involvement up to 10% - 52%
  - Progression confirmed by two scans (12-24 week interval)





Tolerability of Somatostatin Analogues

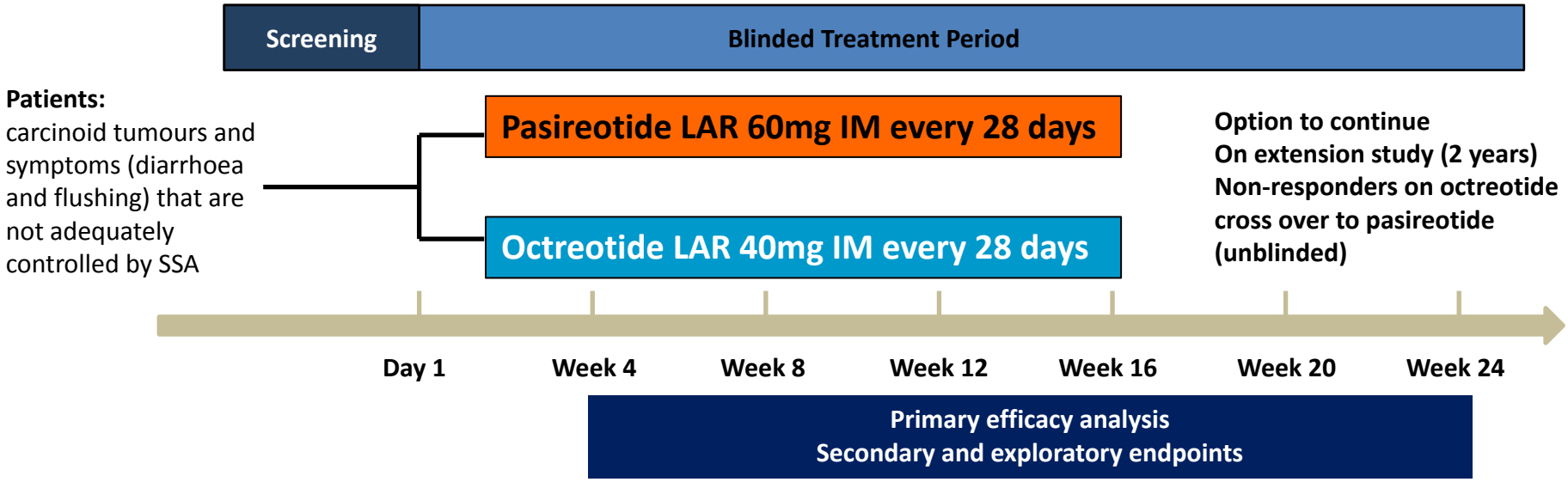
Diarrhoea	**37.3%**
Steatorrhoea	**28.6%**
Flatulence	**28.1%**
Pain at injection site	**28.1%**
Gallstones	**17.9%**
Emesis	**11.5%**
Hyperglycaemia	**10.8%**
Bradycardia	**4.3%**
Cholangitis	**4.3%**
Septicaemia	**< 1%**

- **Most side effects are transient**
- **Very good long-term tolerability**

Shah T & Caplin ME, *Best Pract Res Clin Gastroenterol*. 2005; 19(4): 617-36.
Original data from Arnold R, et al. *Gut* 1996, Öberg K, et al, *Acta Oncol.* 1991, Trendle MC, et al, *Cancer* 1997.

PASPORT Carcinoid (C2303)

Phase III Randomised, Double-Blind Clinical Trial to evaluate pasireotide for the treatment of carcinoid syndrome



[a] Double-blind SC injections, as required to achieve/maintain control.
Temporary dose reductions allowed, if needed for tolerability
Targeted enrollment: 216 patients

Primary endpoint:

- Reduction in bowel movements and/or flushing episodes at 24 weeks

ClinicalTrials.gov Identifier:NCT00690430

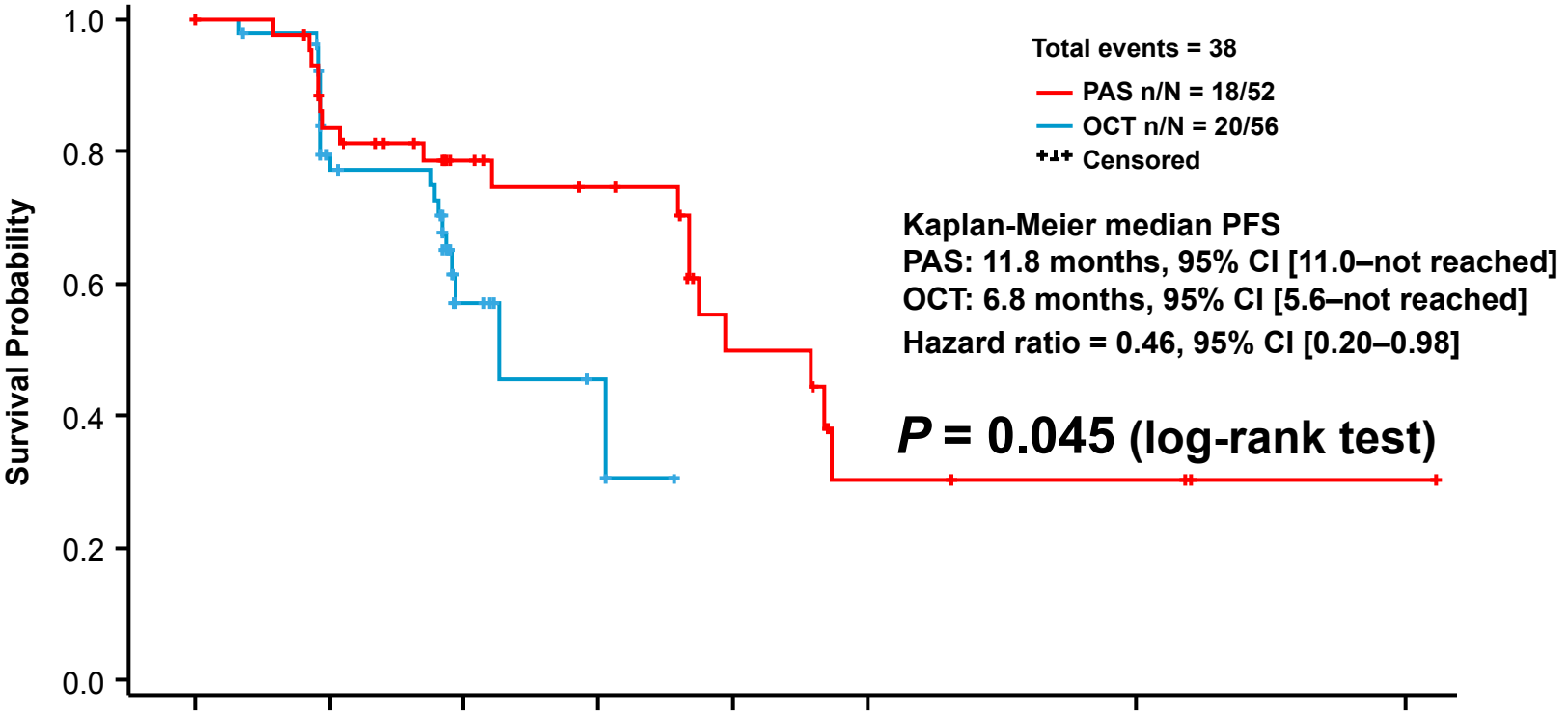
Secondary endpoints:

- Objective tumour response
- Disease control rate
- Quality of Life
- Biochemical markers

Trial was terminated early based on interim analysis demonstrating futility for primary end point
Overall response rates for symptom control at month 6 were similar in both treatment arms

Rate of grade **3/4 hyperglycemia** higher in the PAS arm (13.2% vs 1.8%)

PAS Significantly Prolonged PFS by 5 months



Time (months)	0	3	6	9	12	15	21	27
PAS	52	35	22	18	9	4	3	1
OCT	56	34	10	3	0	-	-	-

CI, confidence interval; OCT, octreotide LAR; PAS, pasireotide LAR; PFS, progression-free survival

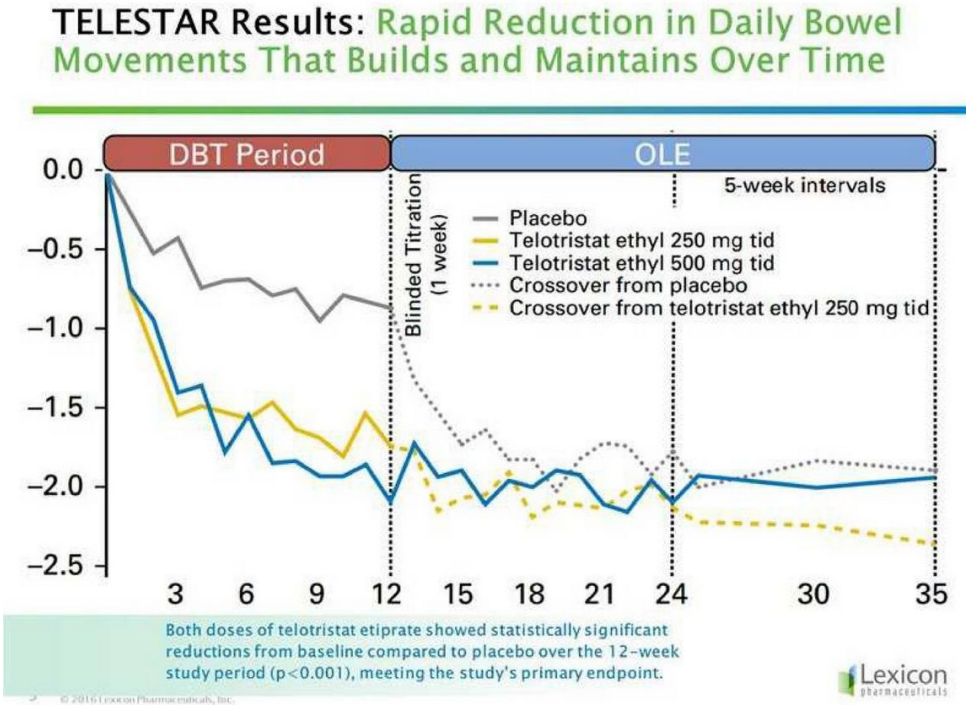
Wolin, EM. et al. *J Clin Oncol*. 2013; 31 (suppl.) Abstract #4031.

High doses of SSA

Retrospective trials	Primary/ number	Prior SSA?	Intervention	Reason for dose escalation	Symptoms	DCR	ORR
Shen 2016 (R)	Metastatic NET (59)	NA	Octreotide >30mg/28d	NR	NR	NR	NR
Al efraij 2015 (R)	Metastatic NET (37)	Y	Octreotide 40-60mg	Diarrhoea 43%, flushing 30%, progression 27%, increased markers 22%	Diarrhoea 63%, flushing 91%, bronchoconstriction 25%, abdominal pain 53%	30%	0%
Modica 2015(R)	Metastatic NET (21)	Y	Octreotide LAR (15), lanreotide (6)		63% improved	53%	5%
Faggiano 2015 (R)	Metastatic NET (14)	Y	Lanreotide 120mg/21d (4), Lanreotide 120mg/14d (4), Octreotide LAR 30mg/21d (4), Octreotide LAR 30mg/14d (2)*	9 PD, 5 uncontrolled syndromes	80% improved (4/5)	85%	14%
Strosberg 2014 (R)	Metastatic NET (239)	Y	Octreotide 40-133mg/month	28% PD, 62% uncontrolled syndromes	70-80% reported improvement in flushing/diarrhoea		NA
Anthony 2011 (R)	Metastatic NET (136)	NA	Octreotide 40-60mg/month	Lack of efficacy (in 65%)*	NA (by dose)	60% (72/120)	7% (8/120)
Chadha 2009 (R)	Metastatic NET (54)	Y	Octreotide LAR 40-90mg/28d	Diarrhoea 83%, abdominal pain 33%, flushing 21%, palpitations 6%	NA	NA	NA

SSA refractory Carcinoid Syndrome TELESTAR

- Telotristat etiprate is a novel oral inhibitor of Tryptophan
- Two early-stage clinical studies of telotristat etiprate demonstrated a favorable safety profile and evidence of clinical activity in carcinoid syndrome2,3
- Both preclinical and clinical studies suggested that telotristat etiprate is associated with minimal CNS activity1-3
- Approved in the United States, in combination with SSA, for the treatment diarrhea related to carcinoid syndrome that is inadequately controlled by somatostatin analog therapy alone

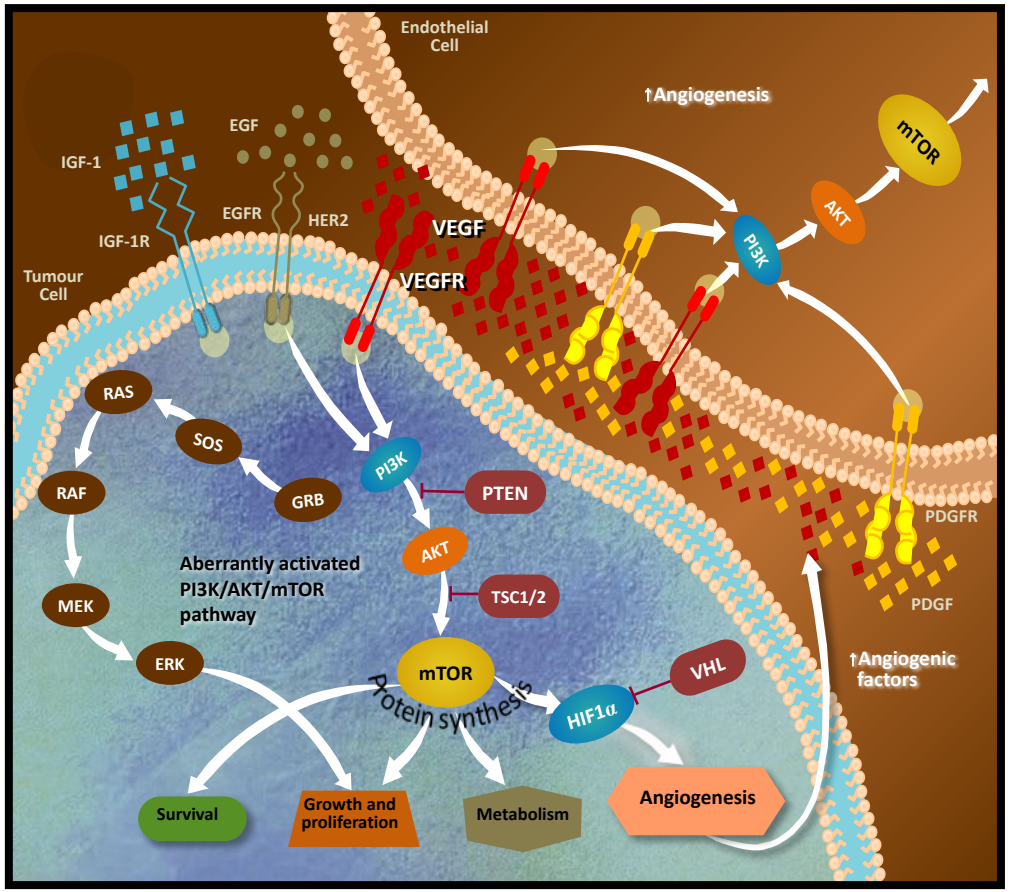


The recommended dose is 250 mg three times daily

1. Liu Q, Yang Q, Sun W, *et al. J Pharmacol Exp Ther* 2008; 325:47–55. 2. Kulke MH, O'Dorisio T, Phan A, *et al. Endocr Relat Cancer* 2014;21:705–714. 3. Pavel M, Horsch D, Caplin M, *et al. J Clin Endocrinol Metab* 2015;100:1511–1519

Targeting the mTOR and Pathways in NETs

- Everolimus (m-TOR inhibitor)
- Sunitinib (Inhibition of PDGF + VEGF Receptors)



The RADIANT Study Programme

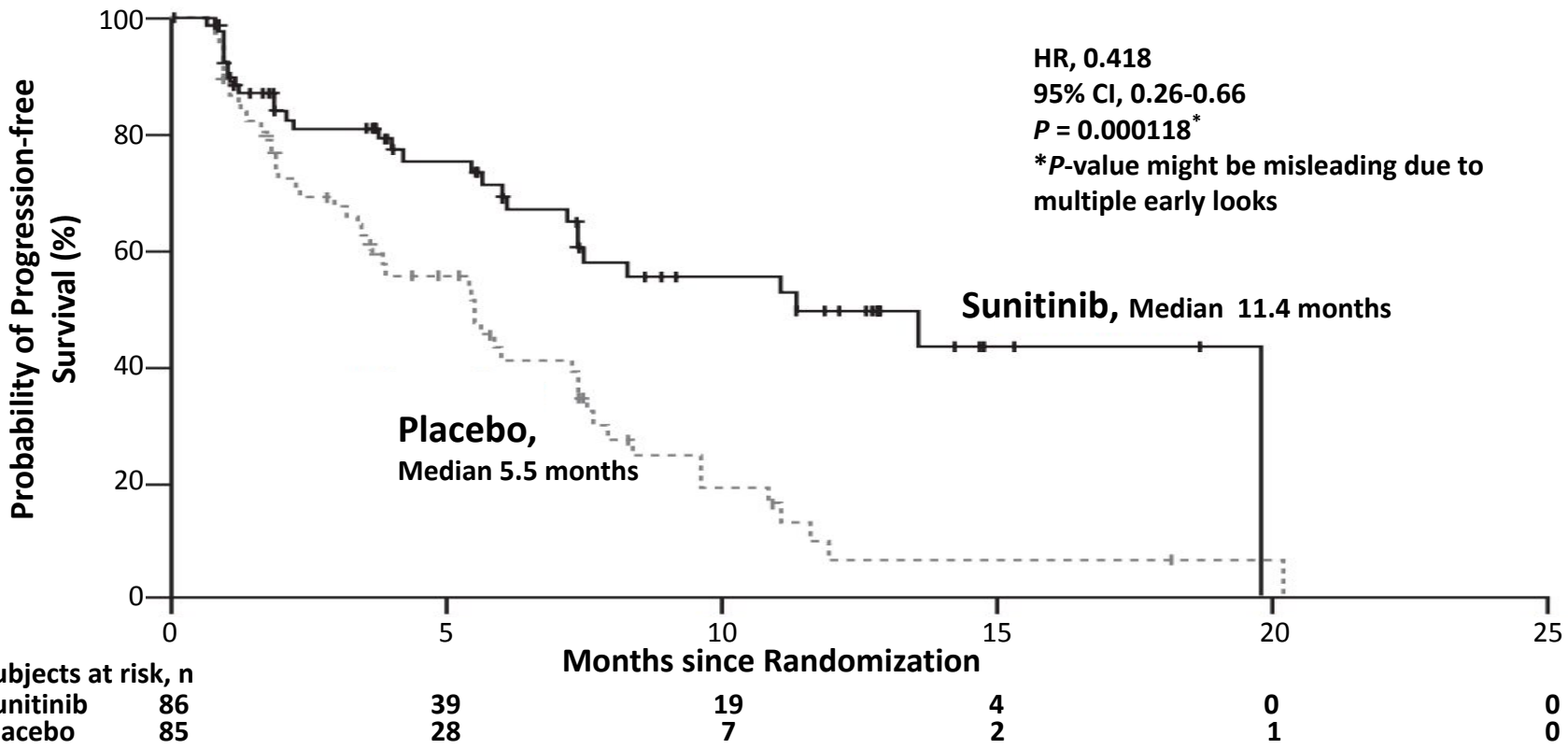
(RAD001 In Advanced Neuroendocrine Tumors) ***EVEROLIMUS***

Study	Phase	Patients	Treatment Arms	Primary Endpoints	Secondary Endpoints
RADIANT-1	II	Patients with advanced pNETs progressing during or after chemotherapy *N=160*	Everolimus; Everolimus + Octreotide LAR (2 Strata)	Objective Response Rate with Everolimus monotherapy (Stratum 1)	Objective Response Rate with combination therapy (Stratum 2), PFS, Response duration, OS and safety and pharmacokinetics in both strata
RADIANT-2	III	Patients with advanced NET and a history of secretory symptoms *N = 429*	Everolimus + Octreotide LAR vs. Placebo + Octreotide LAR	PFS +5.1 months (16.4 vs 11.3) P=0.026; *Statistical boundary:* *p ≤0.0246*	OS ORR Biomarkers Safety PK
RADIANT-3	III	Patients with progressive advanced pNET Prior anti-tumour therapy allowed *N=410*	Everolimus + best supportive care vs. Placebo + best supportive care	PFS **+6.4 m** (11 vs 4.6) Hazard ratio = 0.35; 95% CI 0.27-0.45 *P* value: <.0001 *Statistical boundary* *≤0.025*	OS - NS (crossover) ORR (5vs 2%) Biomarkers Safety PK
RADIANT-4	III	Patients with advanced, nonfunctional, progressive lung or GI NET *N=302*	Everolimus vs. Placebo	PFS **+7.1 m** (11 vs 3.9) Hazard ratio = 0.48; 95% CI 0.27-0.45 *P* value: <.0001	interim OS analysis favored everolimus / HR = 0.64, statistically not significant ORR 2vs 1%

Sunitinib Phase III Trial:

Well differentiated advanced pNET patients
(N = 171 enrolled / 340 planned)

ORR 9.3 vs 0%



(Somatostatin analogues were permitted)

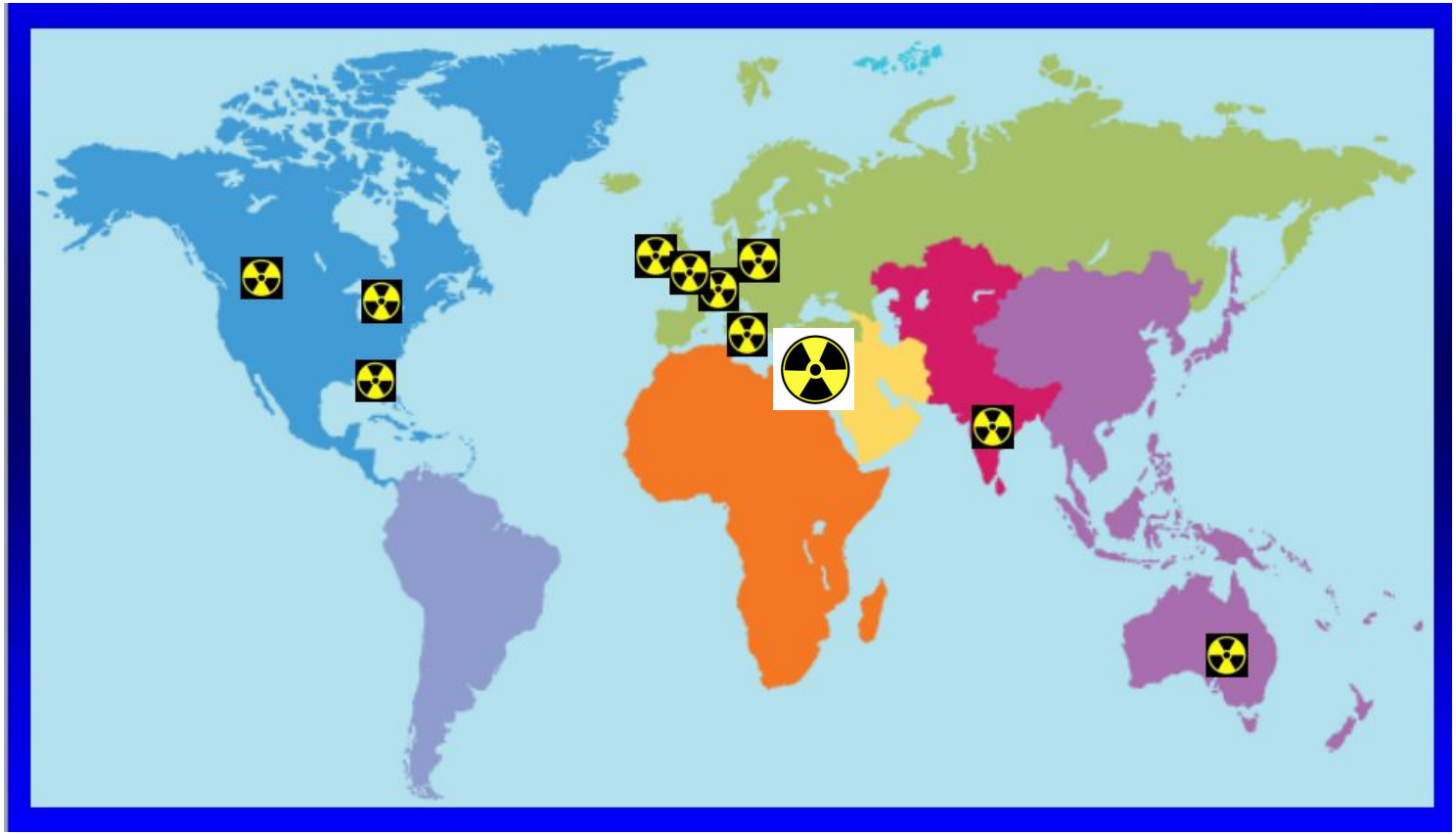
Raymond E, et al. *N Engl J Med*. 2011;364:501-513. Blumenthal GM, et al. *The Oncologist*. 2012;17(8):1108-13.

Everolimus vs Sunitinib

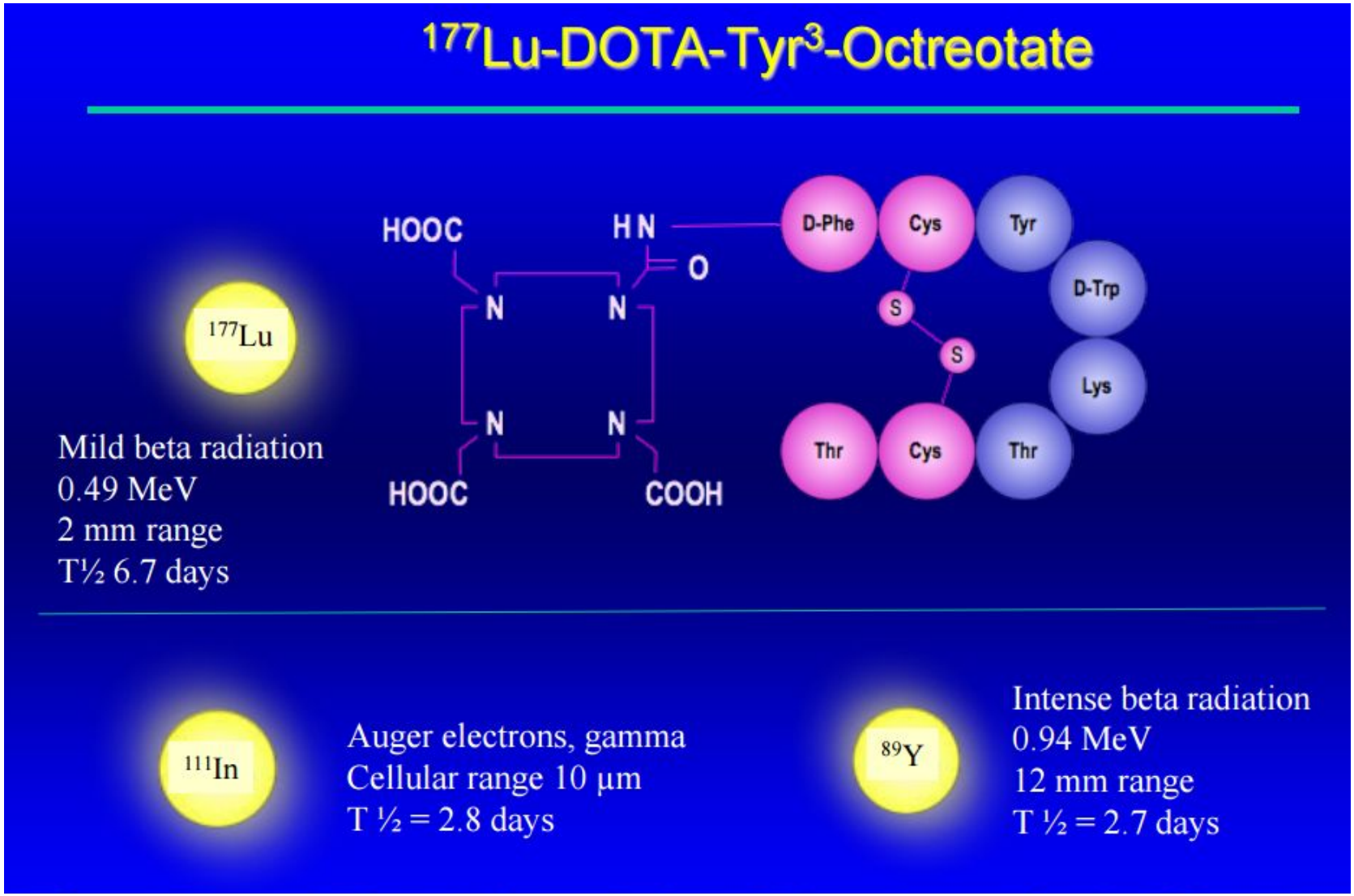
- GI & Lung NET
- A/E: stomatitis, pneumonitis, hypeglycemia (good for functional insulinoma)

- pNET
- A/E: hypertension, proteinuria, arterial thromboembolism, heart failure, thyroid dysfunction, bleeding, myelosuppression, hand-foot syndrome, hepatotoxicity

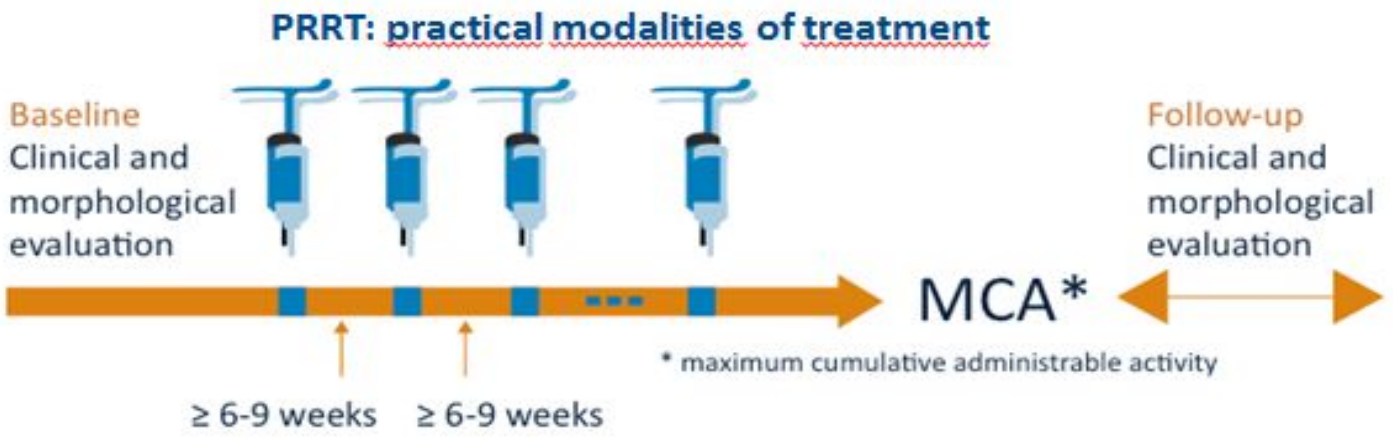
PRRT



PRRT


177Lu-DOTA-Tyr3-Octreotate
HOOC
HN
O
N
N
N
N
HOOC
COOH
D-Phe
Cys
Tyr
D-Trp
S
S
Lys
Thr
Cys
Thr
177Lu
Mild beta radiation
0.49 MeV
2 mm range
T½ 6.7 days
111In
Auger electrons, gamma
Cellular range 10 µm
T ½ = 2.8 days
89Y
Intense beta radiation
0.94 MeV
12 mm range
T ½ = 2.7 days

- Studies showed efficacy in tumor shrinkage, symptoms relief, QOL and possible impact on survival
- However, there are no RCT and evidence comes from individual cohort studies
- Survival with ^{177}L can be estimated at 40 – 72 months after diagnosis and 12 to 21 months from therapy start
- Short-term tolerance is good but long-term toxicity can be severe (kidney or bone marrow impairment)



The NEW ENGLAND JOURNAL of MEDICINE
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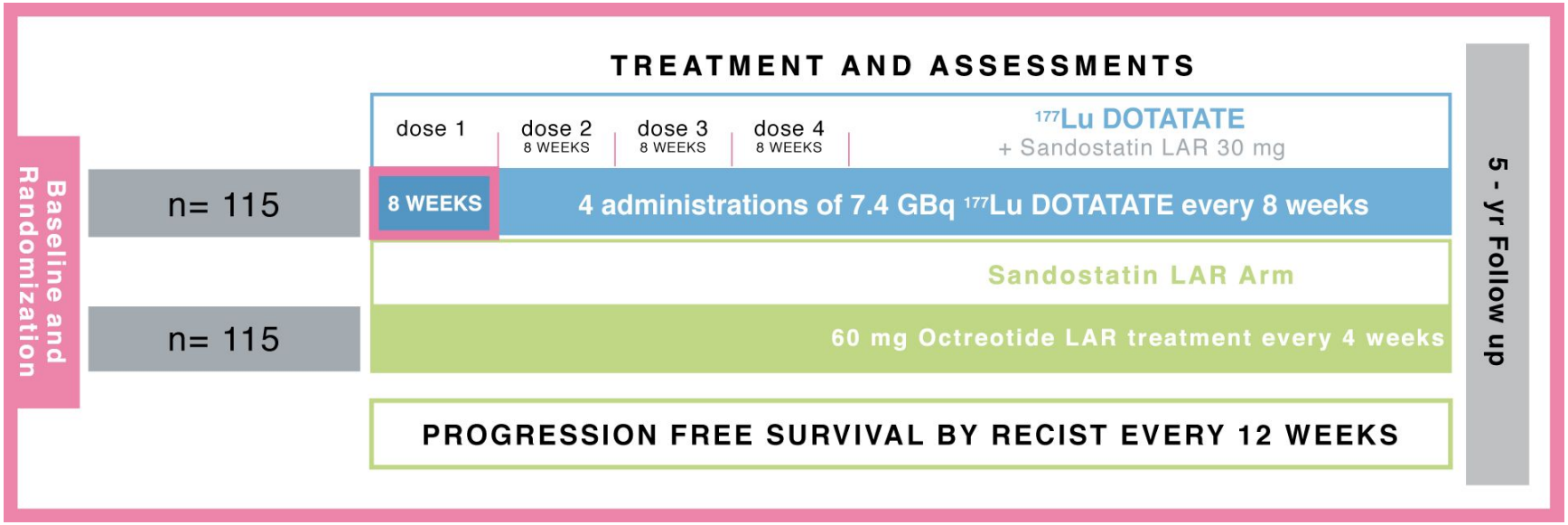
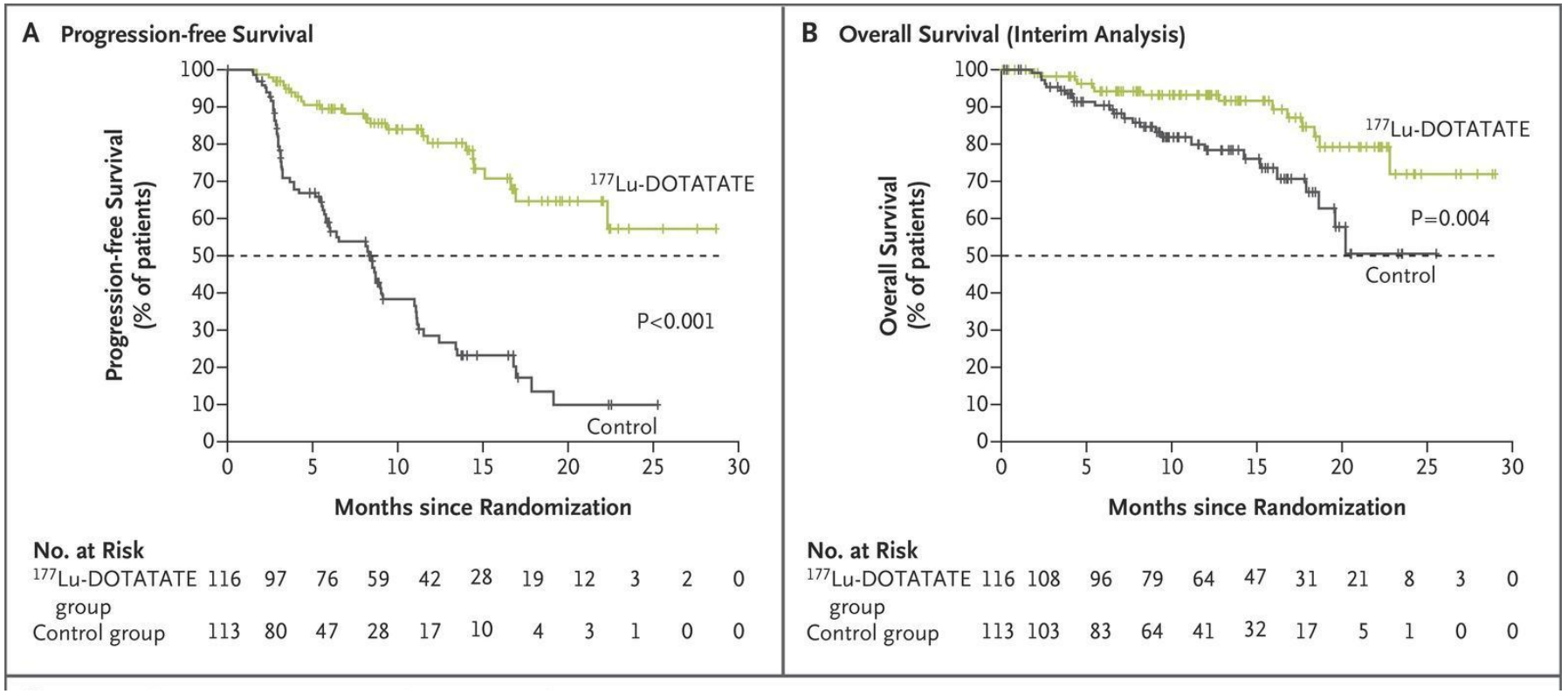
January 12, 2017

Netter-1 trial



PFS & OS



- In patients with midgut neuroendocrine tumors that progressed during octreotide analogue therapy, the addition of ^{177}Lu-Dotatate to octreotide resulted in an 18% response rate (vs 3%)
- The median PFS has not yet been reached in the ^{177}Lu-DOTATATE group but was 8.4 months on high-dose octreotide.
- In the planned interim analysis of overall survival, 14 deaths occurred in the ^{177}Lu-Dotatate group and 26 in the control group (P=0.004).

Chemotherapy in NET

- Well-differentiated NET do not exhibit high sensitivity to chemotherapy because:
  - of their low mitotic rates
  - of high levels of anti-apoptotic protein bcl-2
  - of increased expression of the multi-drug resistant (MDR) gene
- Well-differentiated midgut NETs show low response rates (10-15%) to traditional chemotherapeutic agents
  - streptozotocin in combination with 5-fluorouracil (FU) or doxorubicin
- Low-to-moderately differentiated pNET trials with streptozotocin plus 5FU/doxorubicin or dacarbazine showed objective response rates (RR) of 39% and 33%, respectively, and an improved overall survival (OS)

Reviewed ini Demirkan, B. & Eriksson, B. Turk J Gastroenterol 2012; 23 (5): 427-437

Chemotherapy in NET (cont'd)

Reference	Type of tumour	Regimen	No of patients	Objective response (%)	Response duration (months)	Median survival (months)
Moertel C. et al. (1980)	Pancreatic	STZ STZ + 5-FU	42 42	36 63	17 17	16.5 26
Eriksson B. et al. (1990)	Pancreatic	STZ + 5-FU or DOX	44	45	27.5	-
Moertel C. et al. (1992)	Pancreatic	STZ + DOX STZ + 5-FU	36 33	69 45	18 14	26 18
Cheng P. & Saltz L. (1999)	Pancreatic	STZ + DOX	16	6	18	-
McCollum A. et al. (2004)	Pancreatic	STZ + DOX	16	6	3.9	20.2
Kouvaraki M. et al. (2004)	Pancreatic	STZ + DOX + 5-FU	84	39	9.3	40
Turner N.et al. (2010)	Pancreatic	Cisplatin + 5-FU + STZ	49	38	9	30
Moertel C. & Hanley J. (1979)	Carcinoids	5-FU + cyclophosphamide STZ + 5-FU	47 42	33 33	- -	- -
Engstrom P. et al. (1984)	Carcinoids	STZ + 5-FU DOX	80 81	22 21	8 6.5	16 12
Bukowski R. et al. (1987)	Carcinoids	STZ + DOX + 5-FU + cyclophosphamide STZ + 5-FU + cyclophosphamide	56 9	31 22	- -	- 10.8
Sun W. et al. (2005)	Carcinoids	DOX + 5-FU STZ + 5-FU	25 27	15.9 16	4.5 5.3	15.7 24.3
Moertel C. et al. (1991)	Poorly differentiated	Cisplatin + etoposide	18	67	8	19
Mitry E. & Rougier P. (2001)	Poorly differentiated	Cisplatin + etoposide	41	42	9	15
Fjaellskog M. et al. (2001)	Poorly differentiated	Cisplatin + etoposide	36	47	9	-

Temozolomide

- Retrospective analysis of temozolomide alone suggests efficacy in treating bronchial and pancreatic NET (pNET), however, these were not controlled trials[1]
- Absence of methyl guanine methyl transferase expression appears to be key to realizing benefit with temozolomide

Study	Agent	Response
Kulke; 2006[2]	Temozolomide + bevacizumab	• pNET; RR 24% • GI NET; RR 0% • PFS; 8.6 months
Kulke; 2007[3] (retrospective)	Temozolomide + bevacizumab or thalidomide	• pNET; RR 31% • GI NET; RR 0%
Strosberg; 2011[4] (retrospective)	Temozolomide + capecitabine	• pNET; PR 70% (RECIST) • PFS; 18 months

RR = response rate; GI = gastrointestinal; PFS = progression-free survival; RECIST = Response Evaluation Criteria In Solid Tumours

1. Ekeblad, et al. *Clin Cancer Res.* 2007;13(10):2986-91. 2. Kulke, et al. *J Clin Oncol.* 2006;24(18S)(June 20 suppl.):4044.
3. Kulke, et al. *J Clin Oncol.* 2006;24(18S)(June 20 supplement):4505. 4. Strosberg JR, et al. *Cancer.* 2011;117:268-275


Thank you!