Neuroendocrine Tumors. A Medical Oncologists Perspective

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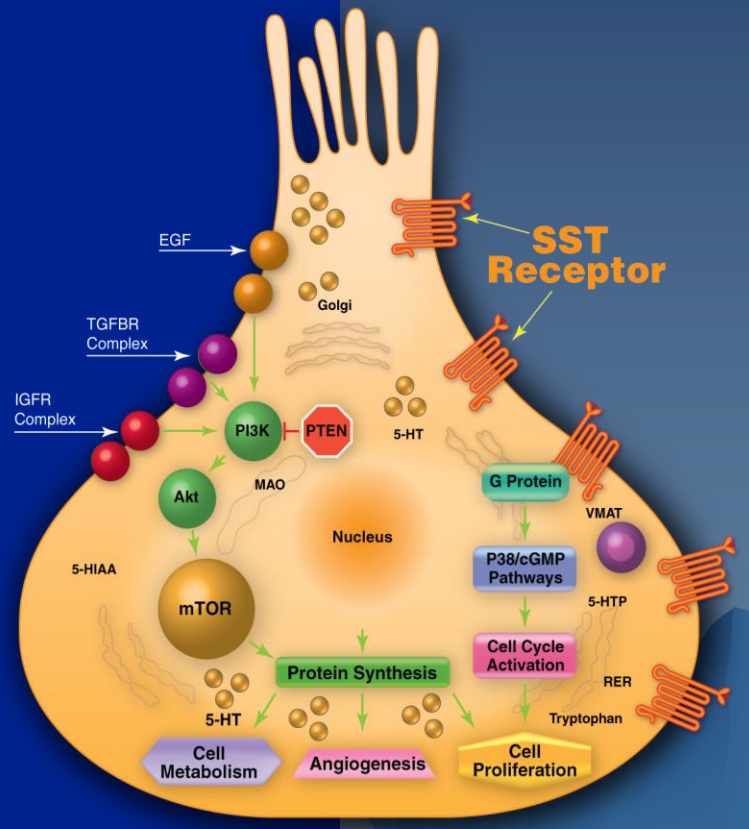
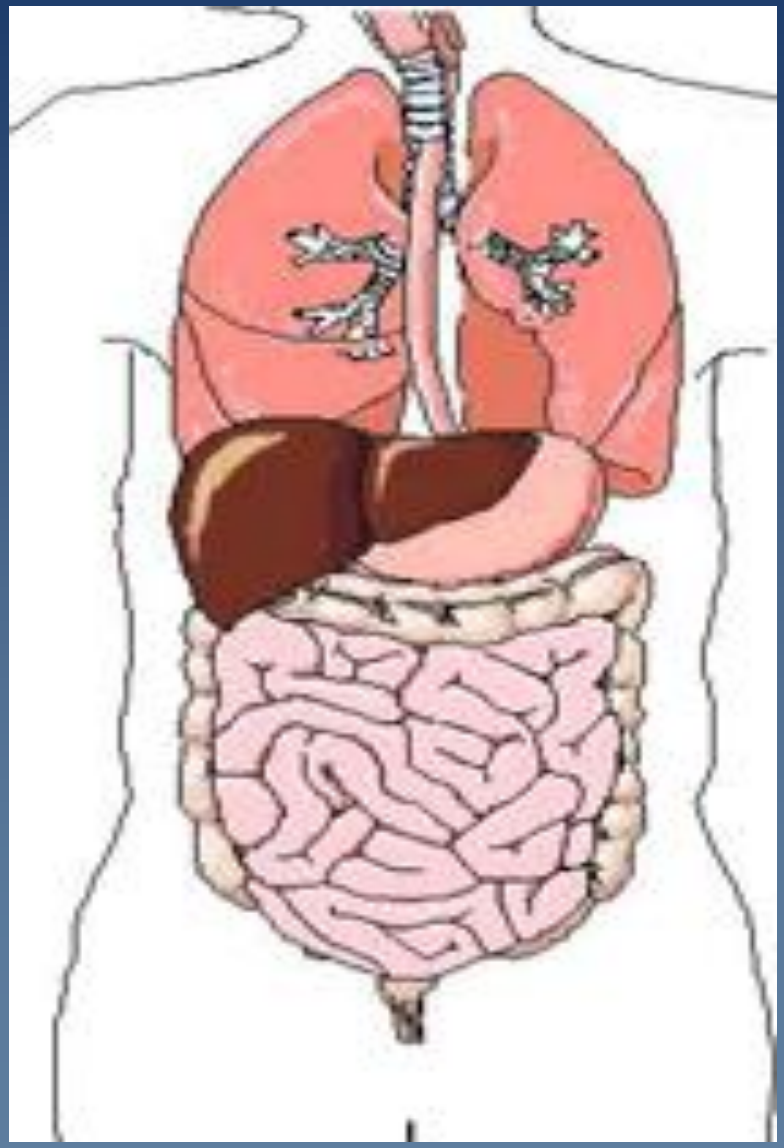
Neuroendocrine Tumors

- NETS are a "mixed bag" of neoplasm's.
  - PNETS & ENET'S
  - Pheochromocytomas/ Paragangliomas
  - Lung and Thymic tumors
    - including small cell lung ca
  - Medullary thyroid cancer
  - Merkel's cell carcinoma
  - Others



The Diffuse Neuroendocrine System (DES)



Embryologic Derivation*

Foregut (33%):
lungs, thymus, thyroid, esophagus, stomach, duodenum, pancreas

Midgut (34%):
jejunum, ileum, appendix, cecum, ascending colon

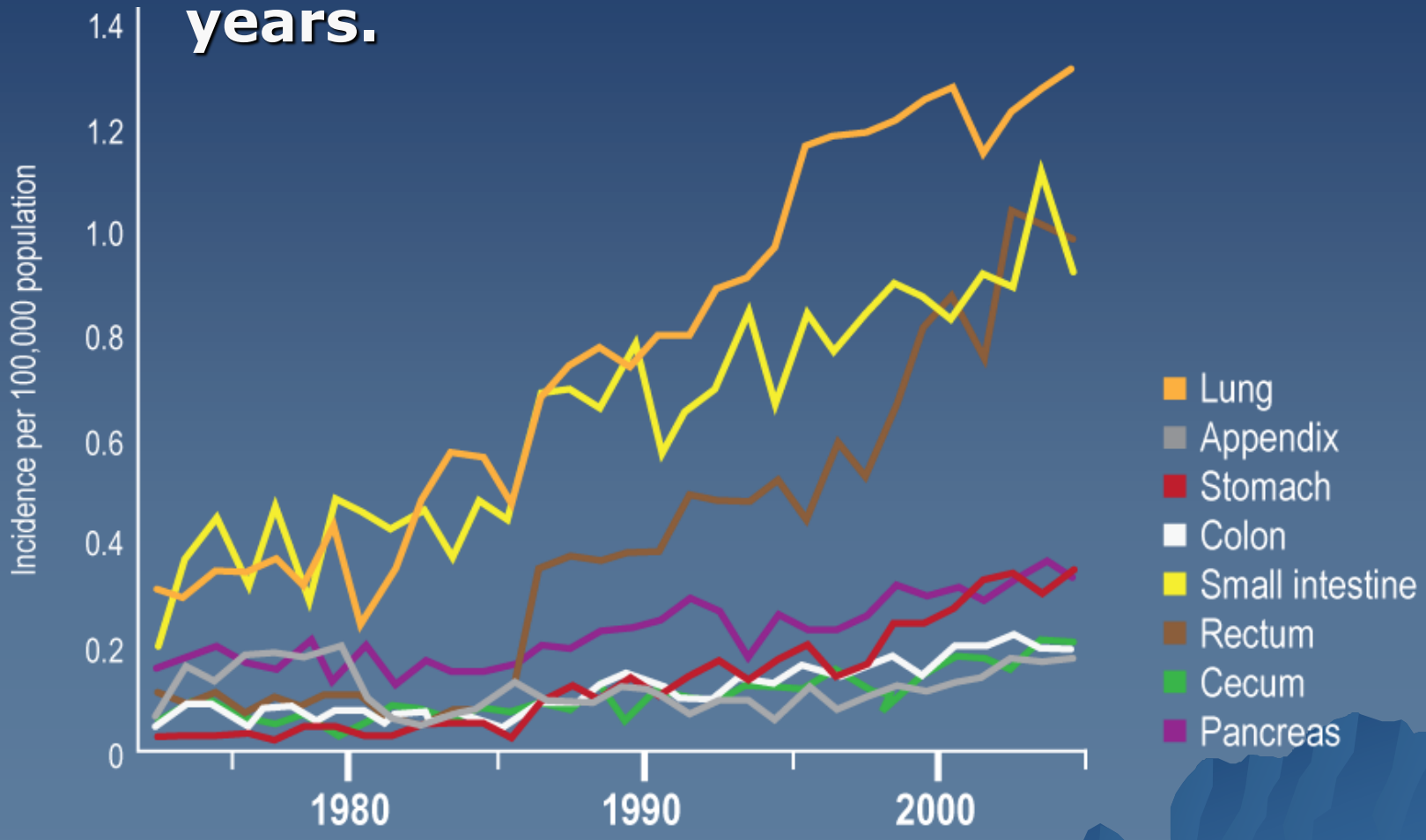
Hindgut (14%):
Descending colon, rectum

Adrenal gland, Skin,

* Endodermal tissue

NETS. Incidence.

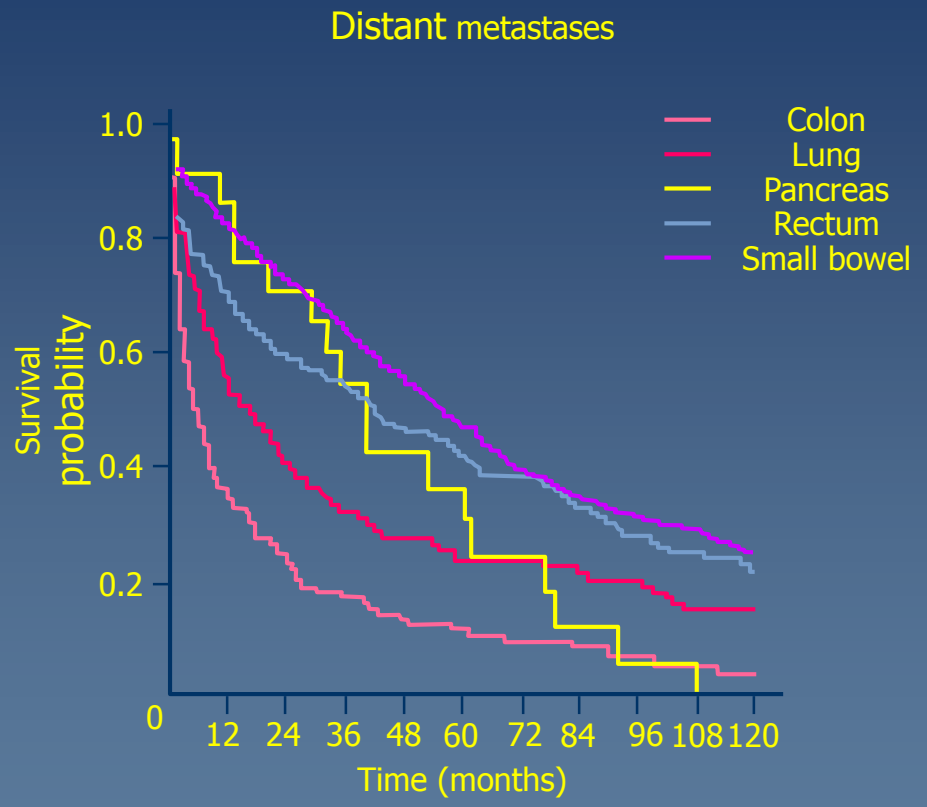
US SEER data. 5-fold increase in 30 years.



SEER = Surveillance, Epidemiology and End Results.
Adapted with permission from Yao JC, Hassan M, Phan A, et al. *J Clin Oncol*. 2008;26(18):3063-3072

NETS. Similarities and Differences.

- Prognostic factors:
  - Location of primary
  - Extent of disease
  - Stage
  - Degree of differentiation/ proliferative index (PI)
  - Grade
  - Patient age (60)
  - Performance status



65% of patients with advanced NET will not be alive in 5 years

Yao JC, et al. *J Clin Oncol.* 2008;26:3063–3072.

NETS. Patient Challenges

- "Rare" diseases
  - 2% of cancers dx in the Western World
- Misdiagnosed or unrecognized (for years).
- Often advanced and incurable at presentation.
  - Relative to other epithelial malignancies behave indolently but often become more aggressive over time.

NETS. Patient Challenges

- The challenges of living with a chronic illness.
- Access to good educational material and peer support.
- Most patients will die of their disease.
  - 5yr survival for patients:
    - with nodal metastases 50- 75%.
    - with distant metastatic disease 25-40%.

NETS. Patient Challenges

- COORDINATION OF CARE.
  - Interactions with multiple health care providers and many components of the health care system.
- Many treatment options along the disease trajectory.
  - Which treatment?
  - When?
  - In What sequence?
  - Access

Systemic Treatment In NETS

Systemic Treatment In NETS

- NET's vary not only in their biological and clinical characteristics and behavior, but also in their response to therapy.
- Other than surgical resection with curative intent where appropriate, the optimum treatment strategy for this diverse group of diseases is not clear, ESPECIALLY in the metastatic setting.

Systemic Treatment In NETS

- Surgery
  - The only potentially curative treatment.
  - An EFFECTIVE palliative treatment in many patients that MAY impact survival.
  - Always ask the question
    - Is there a role for surgery in this patient?

Systemic Treatment In NETS

- Loco-Regional Treatment
  - Effective palliative treatment.
  - No RCT data.
    - Radiofrequency ablation
    - Bland embolization
    - TACE
    - Cryosurgery
    - Alcohol injection
    - Radioactive microsphere embolization
  - MAY impact survival.
  - Always ask the question
    - Is there a role for loco-regional therapy in this patients care?

Systemic Treatment In NETS

- In developing a (systemic) treatment strategy for a patient consider:
  - Hormonal activity (functional VS not).
  - Location of primary.
  - Extent of disease and prognosis.
  - (Potential) growth behaviour –KI 67, mitotic index and clinical behaviour.
  - Patient preferences.
  - Toxicities of treatment, QOL.

Systemic Treatment In NETS

- Goals
  - Inhibit hormone secretion (symptomatic relief).
  - Maintain (Improve) quality of life.
  - Inhibit tumor growth.
  - Prevent complications (heart disease, GI bleeding, bowel obstruction).
  - Prolong survival.
  - Minimize impact of treatment.

Systemic Treatment In NETS

- The evidence base for systemic treatment is historically poor, but improving.
- Clinical trials have been a challenge to complete. Much published data is criticized:
  - Single institution.
  - Retrospective.
  - Derived from heterogeneous populations.

Systemic Treatment In NETS: The Importance of the Somatostatin Receptor

- 70-90% of NET's express Somatostatin Receptors (5 Subtypes).
  - An important feature of the disease:
    - Imaging
    - PRRT
    - Drugs
  - Not well expressed in poorly differentiated NETS.

Role for Somatostatin Analogues

- Octreotide (SSR 2 & 5)
- Lanreotide (SSR 2 & 5)
- Pasireotide (SSR 1,2,3 & 5)

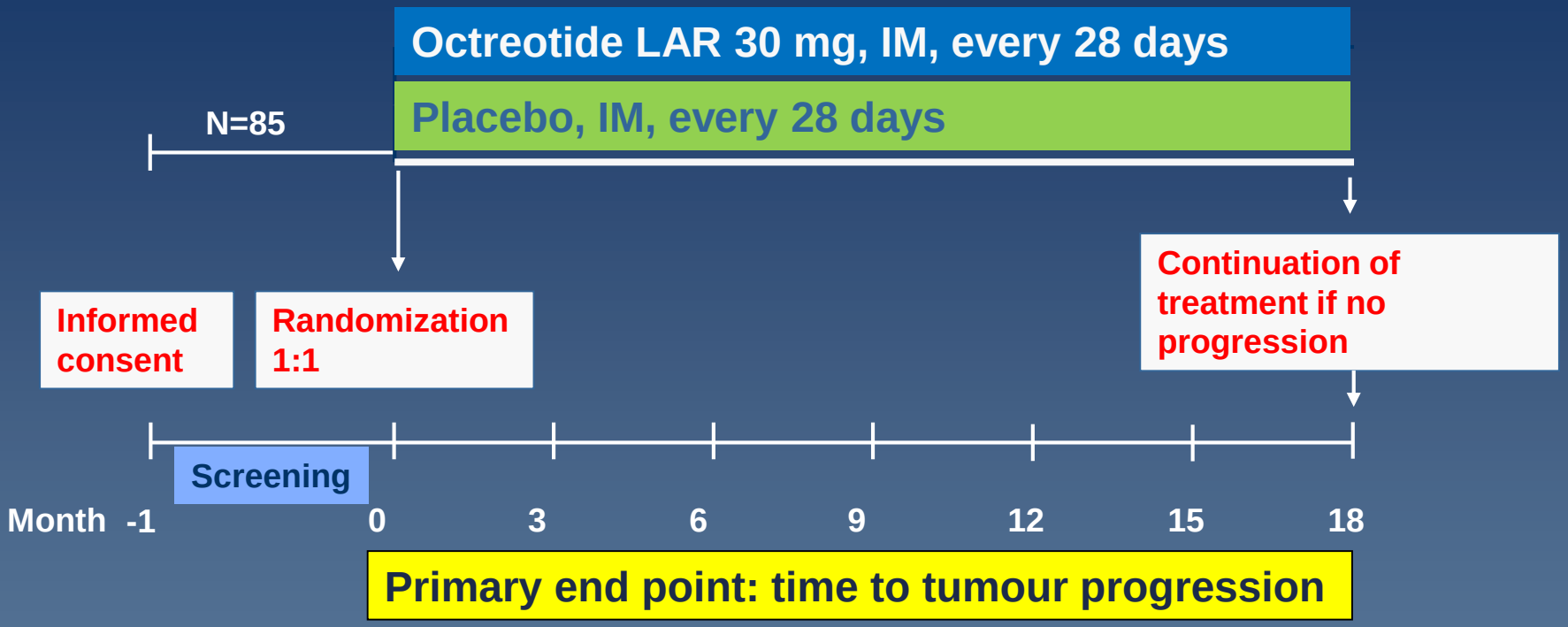
- Dramatic impact on:
  - QOL in patients with functional tumors.
  - The natural history of the disease.
  - Survival.
- SOC in managing functional tumors.

NETS: The Importance of the Somatostatin Receptor

- Do the SSA's have an anti-proliferative effect?
  - Retrospective and small prospective trials have suggested 8% RR & disease stabilization in 28 -87% of patients.
  - Prospective data
    - PROMID
    - CLARINET

- PROMID
  - Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients with Metastatic Neuroendocrine MID-gut Tumors
- CLARINET
  - Controlled study of Lanreotide Anti-proliferative Response In NET

PROMID Study Design



- Histologically confirmed, newly diagnosed and treatment naïve, locally inoperable or metastatic midgut NET
- Treatment was continued until CT or MRI documented tumor progression
- Follow-up until death
- CT and/or MRI was evaluated by a blinded central reader

Rinke et al. *J Clin Oncol.* 2009; 27:4656-4663.

PROMID: Methods - Design & Entry Criteria

Parameter	PROMID
Phase/Design	• Phase IIIb, randomized, double-blind, placebo-controlled • 18 centers in Germany • Conducted 2001 to 2008 • 85 patients treated from a planned 162
Key Inclusion Criteria	• Histologically confirmed, locally inoperable or metastatic **midgut NET** • Well-differentiated histology confirmed by pathology • Newly diagnosed and **treatment naive** • Measurable tumor by CT or MRI • **Functional** (hormone secreting and symptomatic) and **nonfunctional** (asymptomatic) tumors • Karnofsky performance status >60% • No curative therapeutic option available
Key Exclusion Criteria	• Pretreatment with SSA for ≥4 weeks • Previous treatment with interferon alfa, chemotherapy, or chemoembolization • If functional tumors, only patients tolerating flushing without intervention or responding to treatment with loperamide or cholestyramine in case of diarrhea

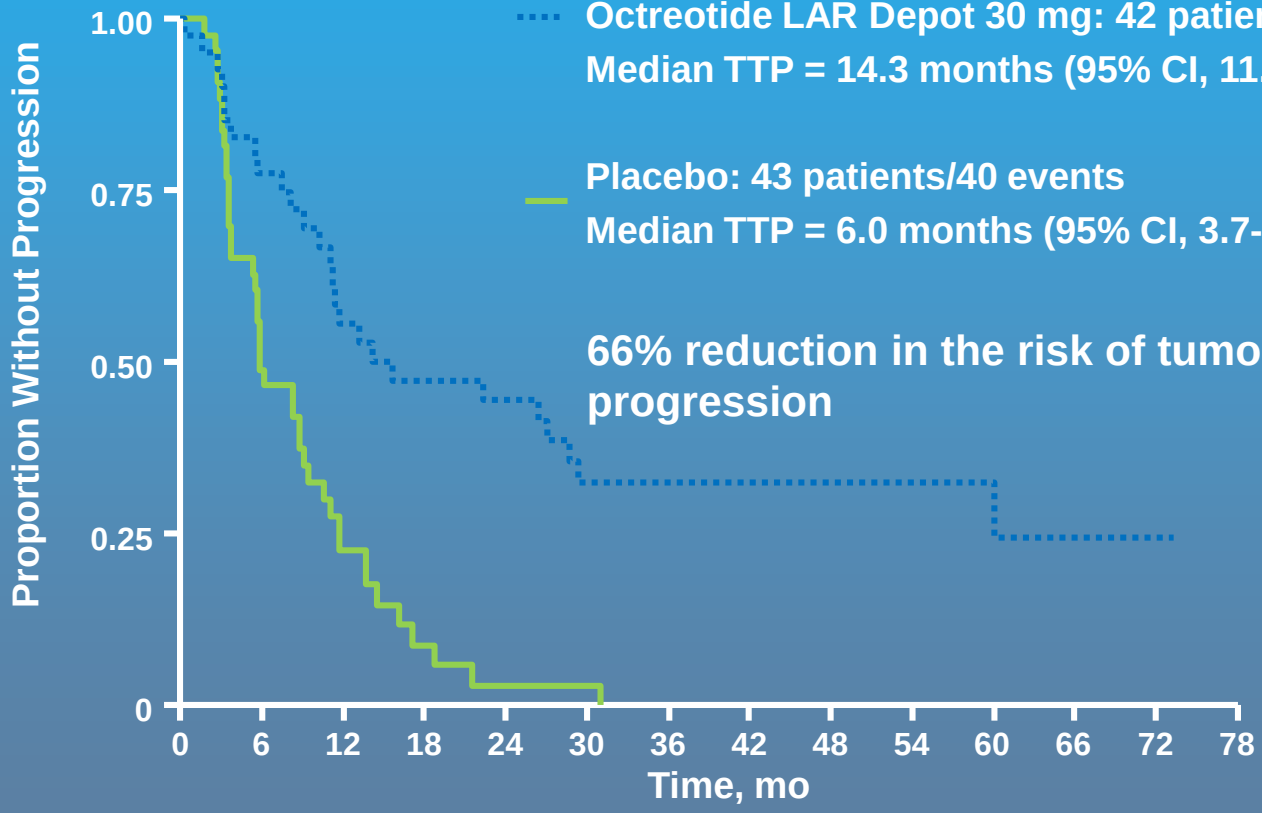
CT, computed tomography; MRI, magnetic resonance imaging; RECIST, Response Evaluation Criteria In Solid Tumors

(ID 13SOL008E)

Rinke et al. *J Clin Oncol.* 2009; 27:4656-4663.

Octreotide LAR 30 mg Significantly Prolonged TTP

Primary End Point	Octreotide LAR (n=42)	Placebo (n=43)	Statistical Analysis
Median TTP (95% CI)	14.3 months (11.0-28.8)	6.0 months (3.7-9.4)	HR, 0.34 (95% CI: 0.20-0.59) *p*=0.000072



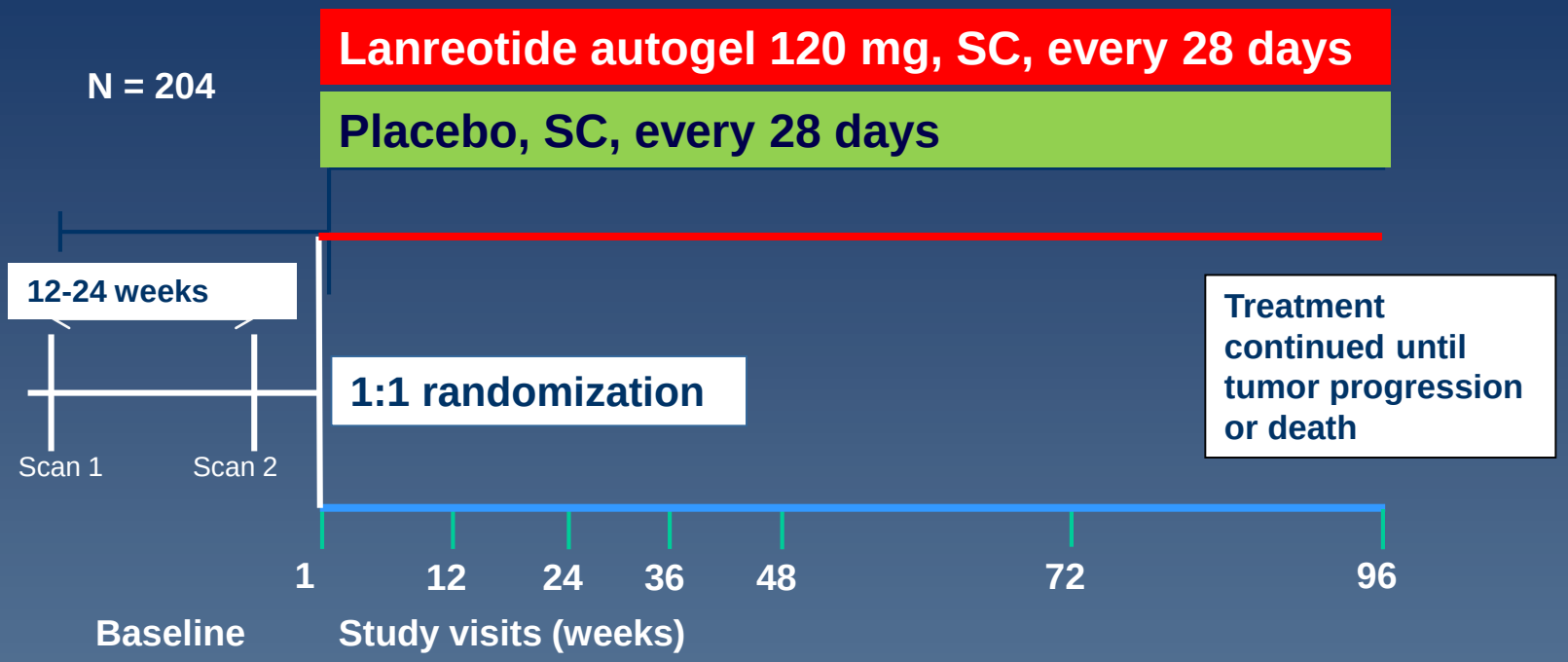
CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; LAR, long-acting repeatable; TTP, time to progression. Based on conservative ITT analysis.

Rinke et al. *J Clin Oncol.* 2009; 27:4656-4663.

PROMID- Summary

- Octreotide LAR significantly improved TTP in patients with metastatic WD midgut NETS.
  - The most favorable effect was tumor stabilization.
  - Octreotide LAR effective in functioning and nonfunctioning NETS.

CLARINET Study Design



- **Well-/moderately differentiated non-functioning GEP NET**

GEP NET, gastroenteropancreatic neuroendocrine tumors; SC, subcutaneous administration

Caplin M, et al. LBA3 *Eur J Cancer* 2013;49 (supp 3). Presented at ECCO-ESMO 2013

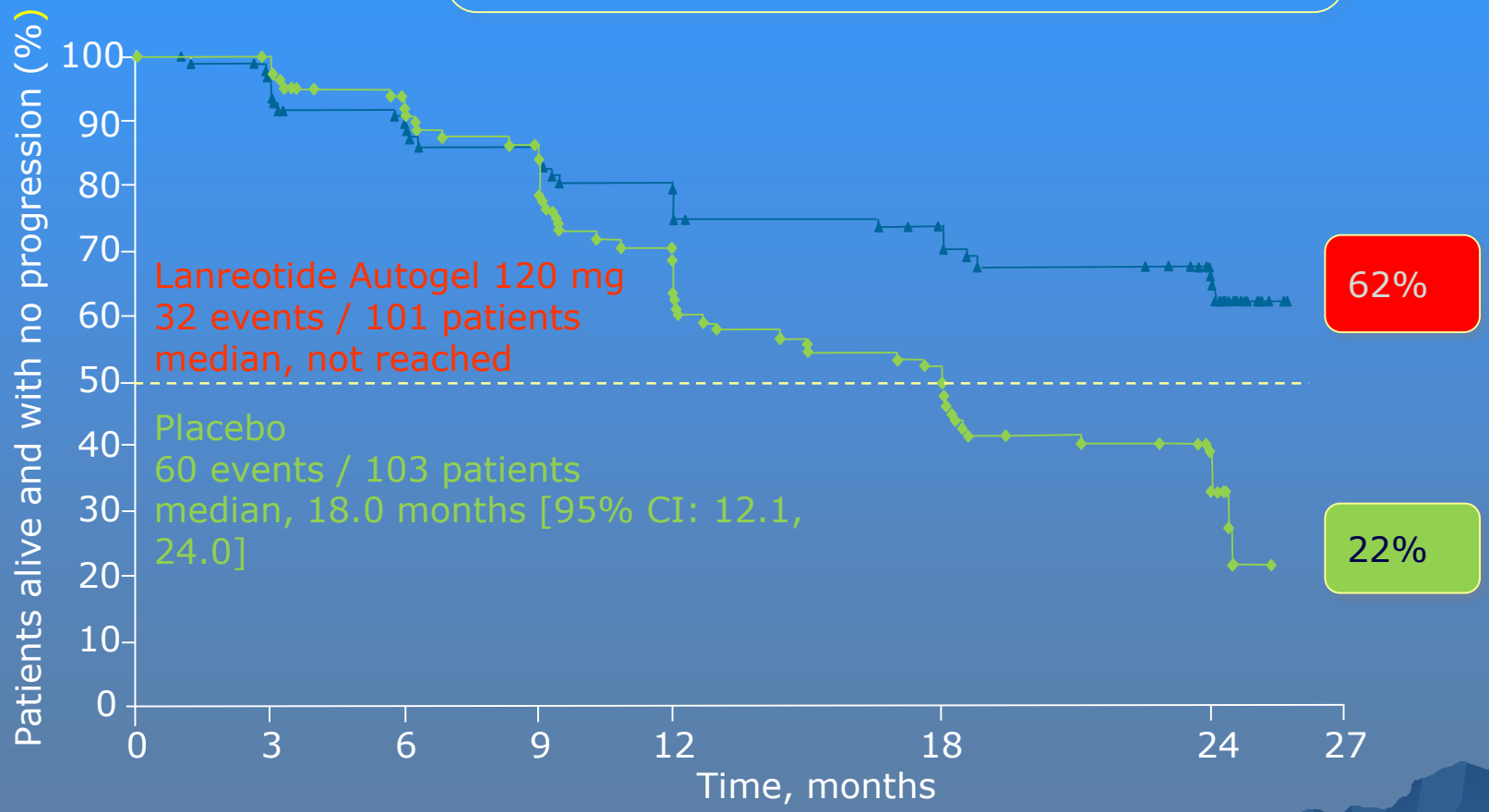
CLARINET: Methods - Design & Entry Criteria

Parameter	CLARINET
Phase, design	• Phase III, randomized, double-blind, placebo-controlled • 44 centers in 14 countries • Study duration: 2006 to 2013
Key inclusion criteria	• Histologically confirmed, locally inoperable (or patient refused surgery) or **metastatic GI NET or pancreatic NET (pNET)** • **Well-/moderately-differentiated** tumors with a low proliferation index (Ki-67% <10%) • **Prior therapy allowed** • Tumor measurable according to RECIST criteria • **Non-functioning** tumors • Grade ≥2 on Somatostatin receptor scintigraphy (Krenning scale)
Key exclusion criteria	• Prior treatment with SSA unless >6 months elapsed and given for no more than 15 days • Treatment within prior 6 months with interferon, chemoembolization or chemotherapy or at any time with a radionuclide

Caplin M, et al. LBA3 *Eur J Cancer* 2013;49 (supp 3). Presented at ECCO-ESMO 2013

CLARINET: PFS

Lanreotide Autogel vs placebo
p = 0.0002, HR = 0.47 (95% CI: 0.30, 0.73)



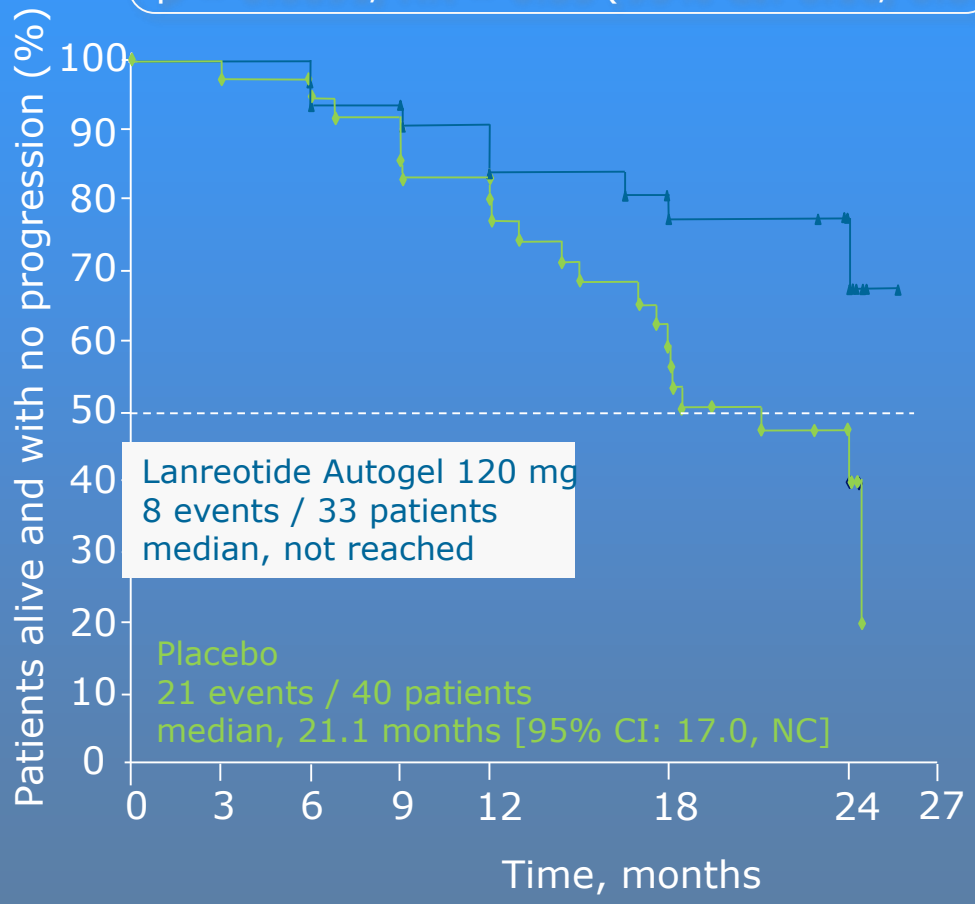
HR, hazard ratio; ITT, intention-to-treat; PFS, progression-free survival. p value derived from stratified log-rank test, HR derived from Cox proportional hazard model

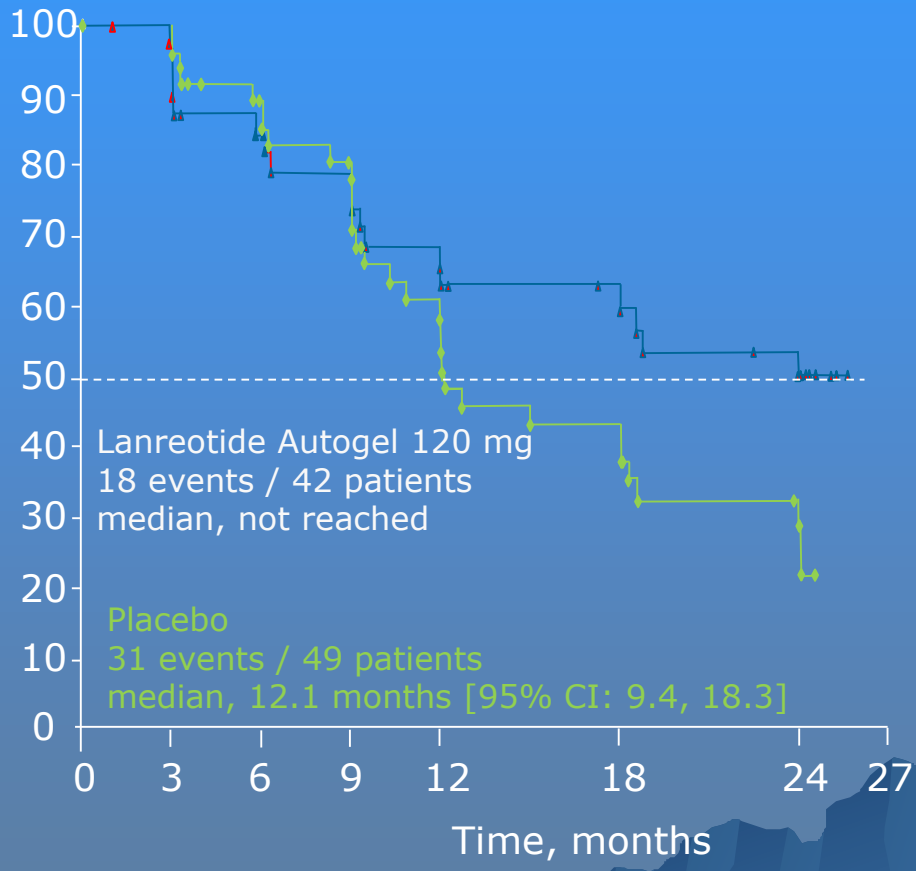
Caplin M, et al. LBA3 *Eur J Cancer* 2013;49 (supp 3). Presented at ECCO-ESMO 2013

Subgroup Analysis (ITT): Midgut vs. pNET

Midgut NETs (n = 73)
Lanreotide Autogel vs. placebo
p = 0.0091, HR = 0.35 (95% CI: 0.16, 0.80)

pNET (n = 91)
Lanreotide Autogel vs. placebo
p = 0.0637, HR = 0.58 (95% CI: 0.32, 1.0





HR, hazard ratio; ITT, intention-to-treat; NC, not calculable. p value derived from log-rank test, HR derived from Cox proportional hazard model

Caplin M, et al. LBA3 *Eur J Cancer* 2013;49 (supp 3). Presented at ECCO-ESMO 2013

Comparison: PROMID and CLARINET Key Differences Baseline Characteristics

Parameter	PROMID	CLARINET
Tumor locations [a]	• Midgut primary tumor – (or NET of unknown origin believed to be of midgut origin)	• Entero-pancreatic NET – (includes pNET and midgut, hindgut, gastrinoma [adequately controlled], and NET of unknown origin)
Tumor functionality	• 39% of patients had functional tumors	• Functional tumors are excluded from trial
Tumor Grade	• Well-differentiated	• Well or moderately differentiated
Assessment of tumor progression	• WHO	• RECIST
Ki67 cut off	• Not prespecified • 95% of pts ≤ 2%	• < 10%
Prior treatment	• Treatment-naive	• Previous treatment permitted
Baseline disease progression status	• Unknown	• Confirmed as stable disease in majority of patients

[a] The reported distribution of GI tumors in CLARINET is: small intestine (n=69), colon (n=9), appendix (n=2), rectum (n=5)

Rinke et al. *J Clin Oncol.* 2009; 27:4656-4663.

Comparison: PROMID and CLARINET Key Differences

Parameter	PROMID	CLARINET
Primary end point	• Time to tumor progression – (calculated from date of random assignment until date of first progressive disease [CT- or MRI-documented] or tumor-related death)	• Time to either disease progression (using RECIST criteria) or death from any cause
Symptom control	• Sub-analyses performed	• Only patients with nonfunctional NET
Prior treatment/ Baseline disease progression status		• Patients stratified by prior tumor progression status and presence/absence of previous therapies
Statistical analyses of primary end point	• Interim analysis performed per prespecified number of events	• No interim analysis is planned – Would incur statistical penalty
Primary end point	• Time to tumor progression – (calculated from date of random assignment until date of first progressive disease or tumor-related death)	• Time to either disease progression or death (PFS)

PROMID and CLARINET: Key Learning Points

PROMID

- The first randomized study to demonstrate an anti-proliferative effect of an SSA (Octreotide LAR).
- Beneficial effect of Octreotide LAR in patients with functional & nonfunctional NETS.
- PROMID led to changes in international guideline recommendations (including Canadian) and treatment algorithms for NETS.

CLARINET

- The largest phase III study evaluating antiproliferative activity of SSA's.
- Findings support the antiproliferative activity of SSA in patients with midgut NET and the results of PROMID.
- Demonstrated a beneficial effect for lanreotide in patients with pNETS.

PROMID and CLARINET Summary

- Results from these trials should not be compared side by side.
- Patient populations in these trials are different (Patients in the PROMID trial had more advanced disease).
- How the data will be implemented into clinical practice and guidelines?

Systemic Treatment In NETS: SSA's

- The role these agents play in the systemic management of patients with NETS will expand and evolve.
- Still lots of unanswered questions
  - Dose?
  - When to start? Is early treatment better than later?
  - In combination with other systemic treatments?

Systemic Treatment In NETS: PRRT

- (This) medical oncologists perspective.
- PRRT is SYSTEMIC Therapy
  - Intuitively attractive
  - Effective palliation
  - Responses occur
  - Resource intensive and expensive
  - Confined to specialist centers

Systemic Treatment In NETS: PRRT

- Questions
  - When should it be considered?
  - Where does it fit in the treatment algorithm (sequence)?
  - How does it compare to other systemic therapies?
  - Can it be combined with other systemic therapies?

Systemic Treatment In NETS: Interferon

- Retrospective series of low dose IFN show:
  - Reduce symptoms associated with hormonal hyper-secretion (70%).
  - PR & DS in up to 15%).
  - Not as well tolerated as the SSA's. Challenging S/E profile.
  - Not gained wide spread acceptance.
  - Still in clinical trials.

Systemic Treatment In NETS: "Targeted Therapy"

- mTOR
  - RADIANT Trials (1,2, 3)
    - PR <10%. Significant disease stabilization (65+%). PFS benefit 6 months in PNETS.
    - Ongoing trials in other NET patient populations.
    - Side effects manageable in most patients.
  - Everolimus funded for mPNETS.

Systemic Treatment In NETS: "Targeted Therapy"

- Tyrosine Kinase Inhibitors
  - Activity demonstrated in phase 2 & 3 CT with similar RR and rates of disease stabilization to mTOR trials.
    - 6 month PFS improvement with Sunitinib in mPNETS.
    - Ongoing clinical trials with TKI's in other NET populations.
    - Side effects a challenge but manageable in most patients.
  - Sunitinib funded for mPNETS.

Systemic Treatment In NETS: Chemotherapy in G3 disease.

- Chemotherapy has a limited, but definite role in the treatment of NETS.
- Platinum based.
  - Grade 3, KI67>20%, clinically aggressive disease.
- Reasonable RR (40-70%), but duration often short.
- Other options needed.

Systemic Treatment In NETS: Chemotherapy in G1/G2 disease.

- Streptozocin based combinations (5 FU/ Adriamycin) considered the SOC. More accurate radiologic assessment of tumor response in recent trials suggest RR < 40%.
  - Difficult treatment with significant side effects and toxicity.
  - Resource intensive.
  - Access problematic (SAP).

Systemic Treatment In NETS: Chemotherapy in G1/G2 disease.

- DTIC single agent or combined with Epirubicin & 5 FU
  - RR 18-26%.
  - Challenging for patients.
- Temozolomide (oral DTIC)
  - Single agent.
  - Combined with Bevacizumab, Capecitabine, Thalidomide.

Temozolomide & Capecitabine

- RR of 71% in treatment naive patients with m PNET's (Strosberg, 2008).
  - Convenient for patients.
  - Oral administration.
  - Well tolerated.
  - Low cost.

Systemic Therapy Clinical Trials In NETS

- Chemotherapy
- Immune modulators
- Monoclonal Antibodies
- "Targeted" Therapy

- Alone and in Combinations

Systemic Treatment In NETS

- General Principles
  - Optimal surgical treatment
    - Curative and Palliative Intent.
  - Optimal Loco-regional control.
  - Aggressive use of Somatostatin targeted therapy.
    - For symptom control.
    - To delay/ prevent disease related complications.
    - To delay disease progression.

Systemic Treatment In NETS

- General Principles
  - Multidisciplinary assessment and discussion to ensure that patients have access to as many therapeutic options at appropriate time over the course of their disease.

Systemic Treatment In NETS

- General Principles
  - Period of observation to assess the clinical behavior and rate of progression of disease is reasonable in many patients.
  - Re-biopsy progressing/ new sites of disease, especially if clinical behavior suggests it.

Systemic Treatment in NETS: Sequencing?

TKI	mTOR	Chemo	PRRT
mTOR	TKI	PRRT	Chemo
Chemo	PRRT	TKI	mTOR
PRRT	Chemo	mTOR	TKI

SSA's?

Systemic Treatment In NETS

- Other NET patient populations:
  - Medullary Thyroid Cancer
  - Pheochromocytomas & Paragangliomas
- Clinical trial opportunities must be part of our day to day business to improve treatment options for patients with NETS.
- LOTS of questions!

Systemic Treatment In NETS

- We have to be smarter about how we evaluate intervention and treatment and how we learn from what our patients can teach us.
  - Registries and data bases
  - Sequential cohorts of patients?
  - Better, faster ways of assessing the pros and cons of treatment.

Thank You