Diagnosis and Treatment of Neuroendocrine Tumors

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SON Fall Update
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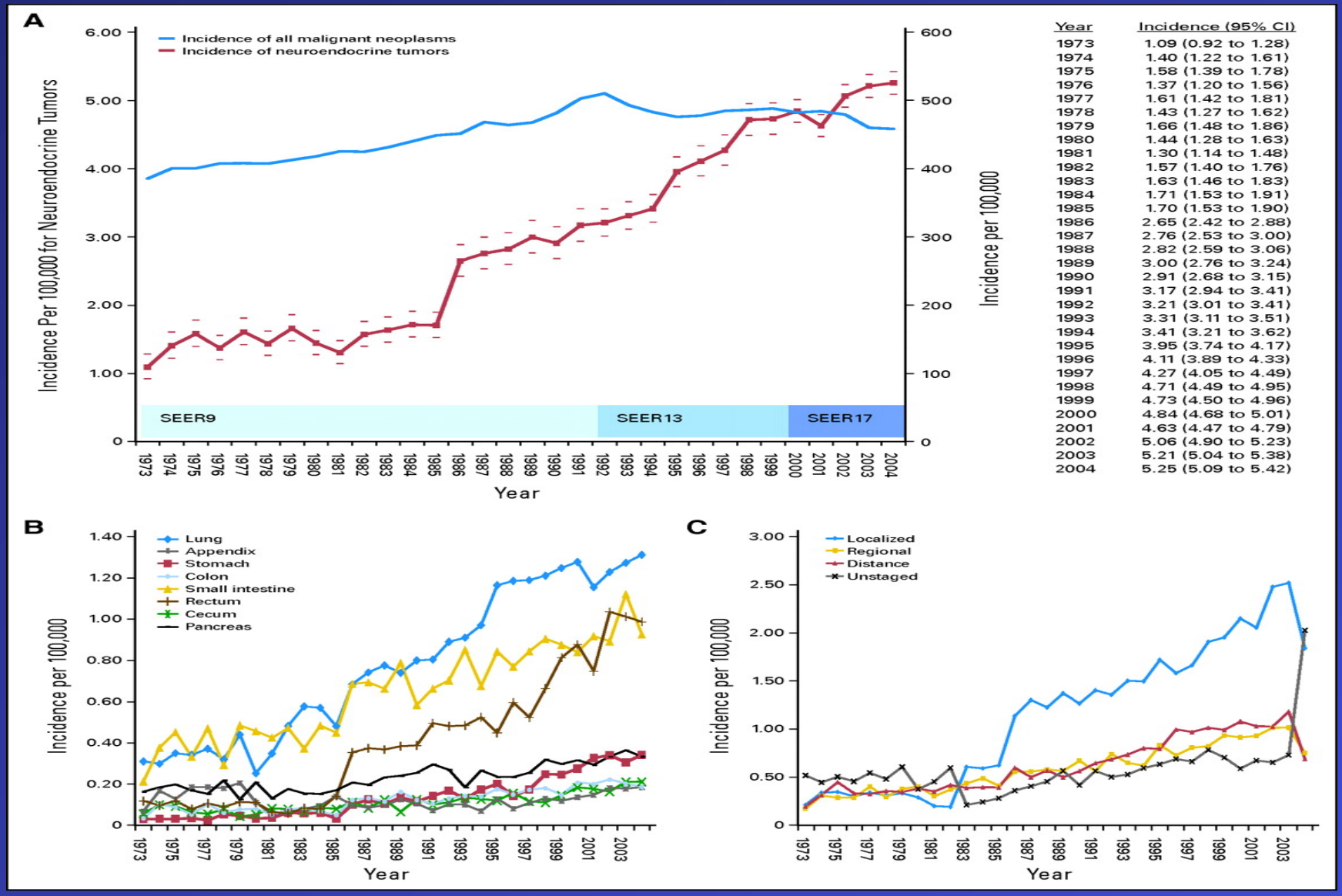
Objectives

- Review incidence and survival of NETs.
- Present new terminology and classification.
- Consider NET treatment 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

Diagnosis

- Pathological:
  - IHC: Synaptophysin, Chromogranin
- Active versus Inactive:
  - 30-50% hypersecretion syndromes
  - Foregut: peptides (insulin, glucagon, VIP, gastrin)
  - Midgut: biogenic amines (serotonin, tachykinins)
  - Not prognostic, but influence management

Confusing Terminology

Carcinoid

Neuroendocrine Carcinoma

Atypical carcinoids

Large Cell Neuroendocrine Carcinoma

Insulinoma

Islet cell tumor

ENTES Classification and Staging

WHO Classification

AJCC Staging

Convergence of Classification

- Use NET: Neuroendocrine Tumors
  - Foregut: Lung, Gastric, Pancreas
  - Midgut: Small bowel, Appendix
  - Hindgut: Large Bowel, Rectum

- Exclude NEC: Neuroendocrine CARCINOMAS.

NET vs NEC

Grade	Mitotic Count 40 fields at 40x	Ki-67 % of 2000 tumor cells
G1	<2	≤2
G2	2-20	3-20
G3	>20	>20

Therapeutic Options LOCAL and REGIONAL Disease

- RESECTION
- Adjuvant therapy is not currently indicated in completely resected NETs

Advanced NETs: Therapeutic Options

- RESECTION and ABLATION
- Radioparticle therapy
- Octreotide and Interferon therapy
- Chemotherapy
- Small molecule targeted therapy

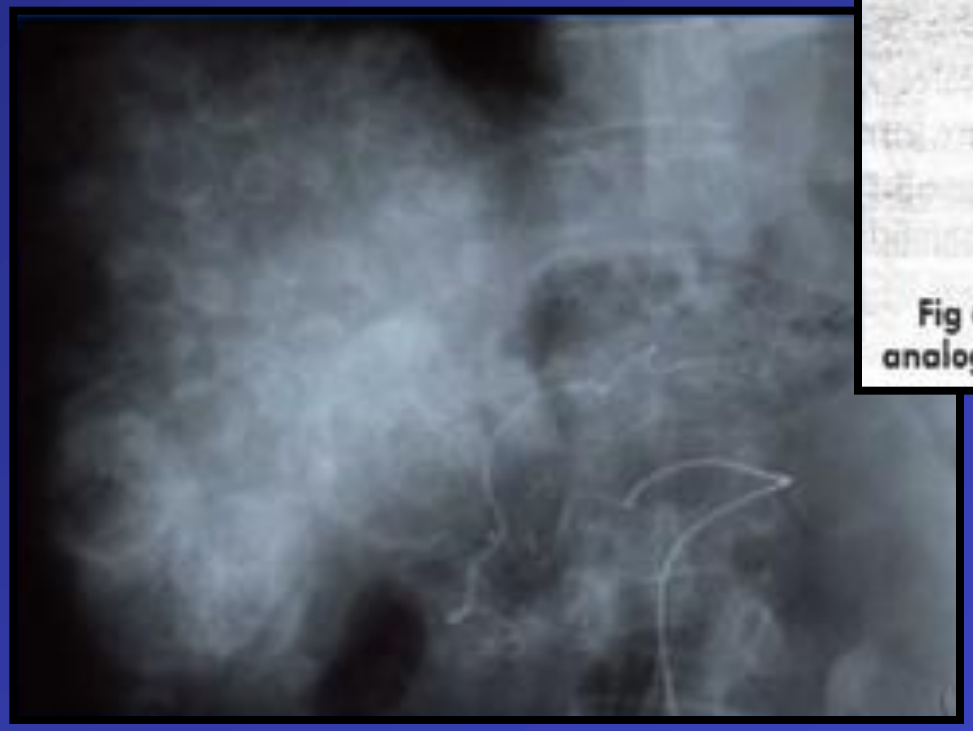
Hepatic SURGERY

- Resectable metastatic disease is treated with curative surgical intent
- Unresectable bulky or symptomatic tumors are treated with surgical DEBULKING ! ?
- Numerous case series report 5 year survival of 50-70% among resected patients

Non-Resectable Hepatic Disease

- If NOT resectable:
  - Ablate, Embolize, Radiate.
- No randomized trials evaluating these techniques

CAUTION: Carcinoid crisis and hepatic directed therapy!!!



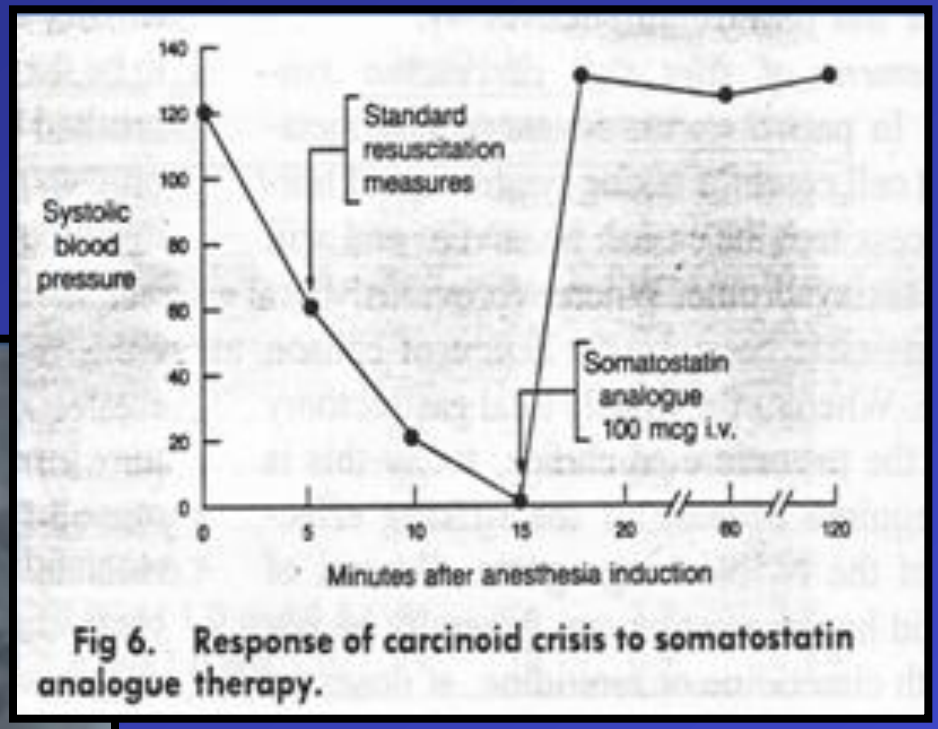
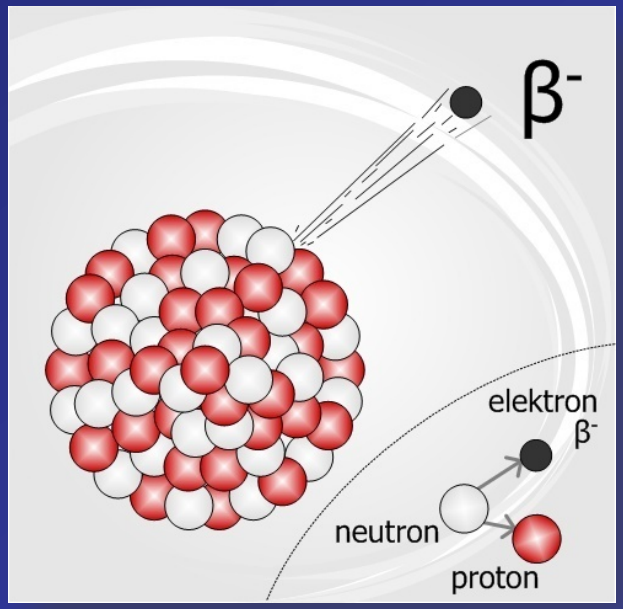


Fig 6. Response of carcinoid crisis to somatostatin analogue therapy.

Radiation Source: Yttrium-90



- 99.97% ß radiation (‘pure’)
- Penetration range = 11mm
- Half-life = 64.2 hours and decays to stable zirconium-90
- Intra-arterial administration – Not truly embolic.
- Response rates variable

Courtesy D Liu

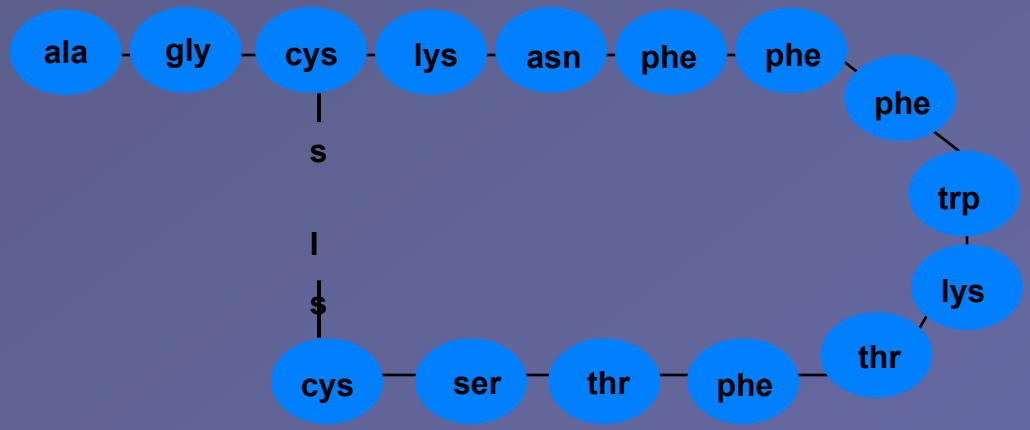
Peptide Receptor Radiotherapy

- Radioactive isotopes attached to octreotide: Lutetium, Indium, Yttrium
- LU-Octreotate among the best evidence:
  - Response Rate 30% in Single Institution
  - Now Available in CANADA!
- Octreoscan positivity (ie. positive Indium^{111}scintigraphy) is a requirement for therapy.

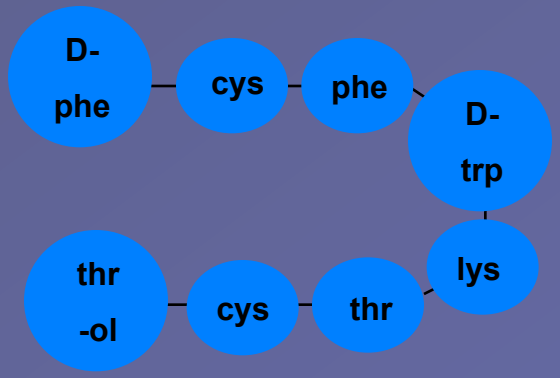
Kwekkeboom JCO 2008

Therapeutic Options

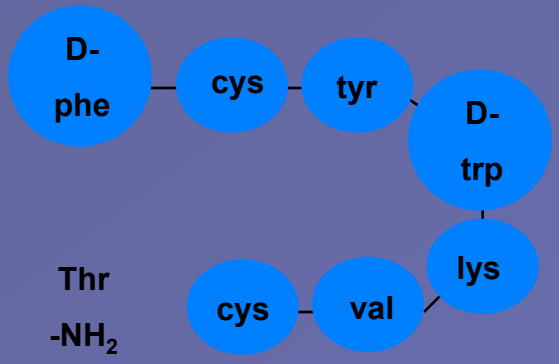
- Resection and Ablation
- Radioparticle therapy
- OCTREOTIDE AND INTERFERON
- Chemotherapy
- Small molecule targeted therapy



Human somatostatin



Octreotide acetate

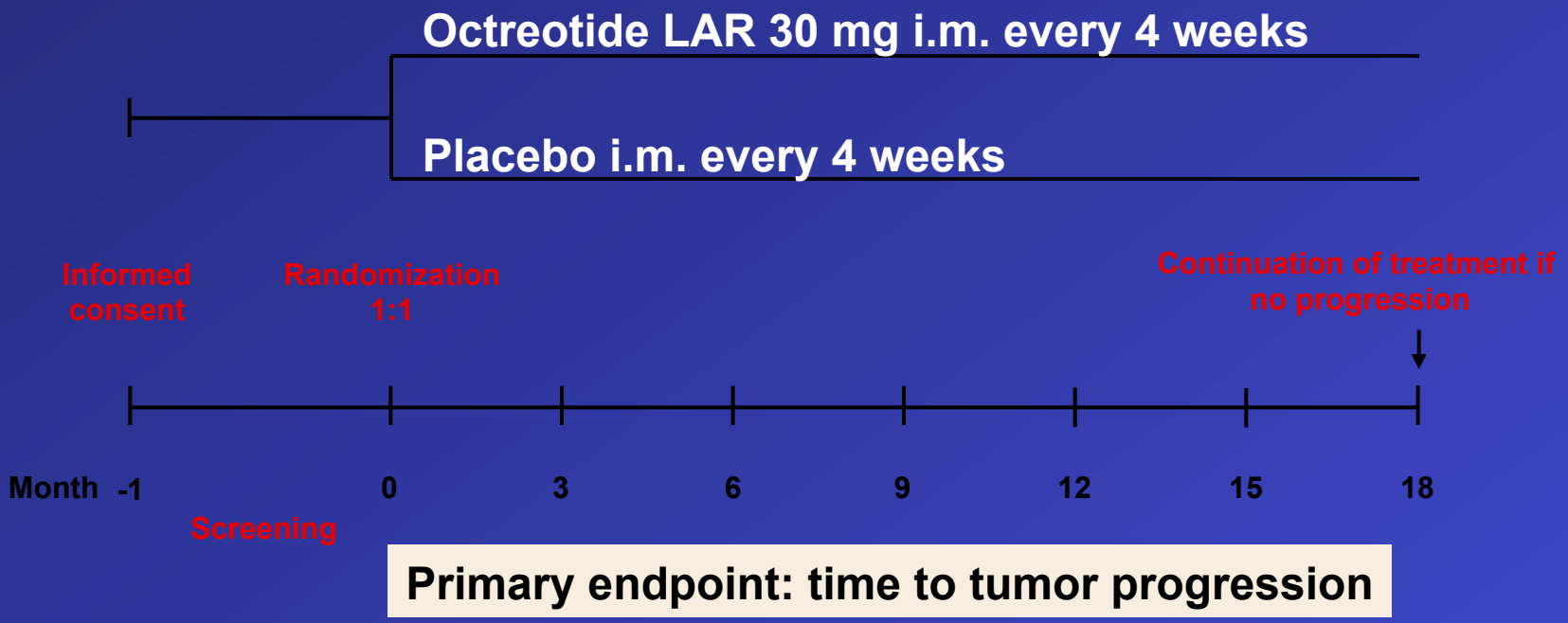


lanreotide

Somatostatin Analogs: SSA

- Somatostatin analogs bind to somatostatin receptors
- Current indication is for control of symptoms related to FUNCTIONAL neuroendocrine tumors.
- Biochemical responses > 70% and objective response < 5 %
- What about use to control disease?

PROMID: Phase III Study



Primary endpoint: time to tumor progression

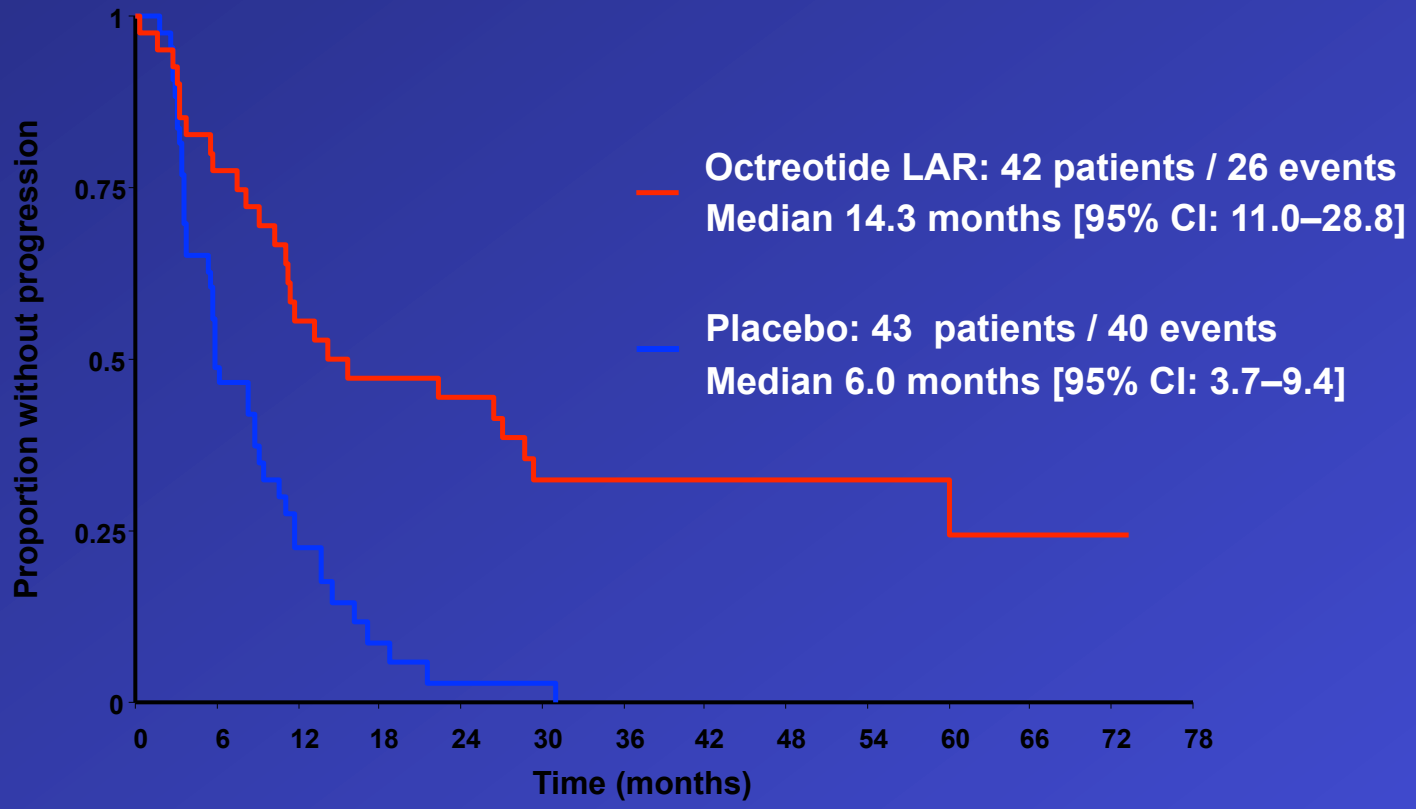
- **Treatment was continued until CT or MRI documented tumor progression.**
-

Patient population

- Newly diagnosed and treatment naïve
- Histologically confirmed, locally inoperable or metastatic well-differentiated midgut NETs.
- ACTIVE or INACTIVE

Octreotide LAR significantly increases time to tumor progression

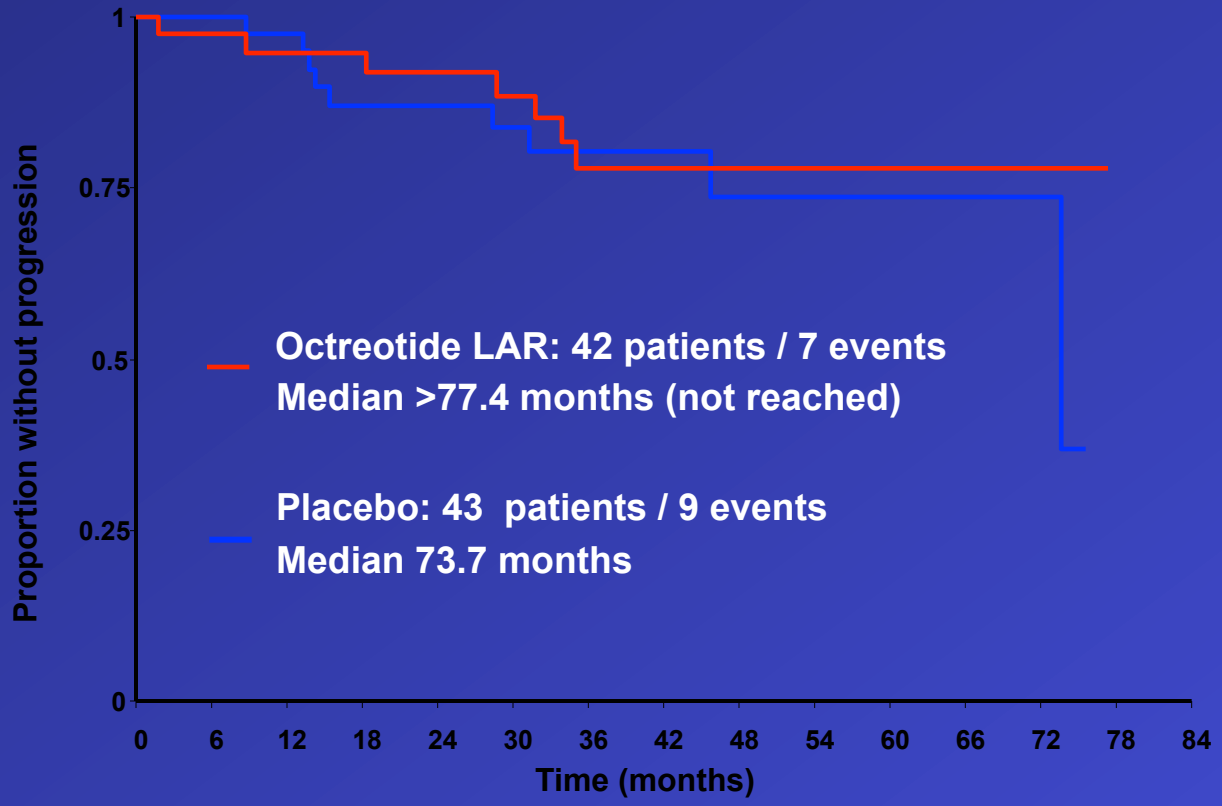
Octreotide LAR vs placebo *P*=0.000072
HR= 0.34 [95% CI: 0.20–0.59]



Based on the conservative ITT analysis

Overall survival

Octreotide LAR median survival duration not yet reached (>77.4 months)
Placebo: 73.7 months



Therapeutic Options

- Resection and Ablation
- Radioparticle therapy
- Octreotide
- CHEMOTHERAPY
- Small molecule targeted therapy

Chemotherapy

- PNETs are generally more chemosensitive than other NETs.
- Benefit hard to quantify as chemotherapy trials included non-PNETs and no phase III randomized trials.
- Alkylating agents are active in pancreatic NETs.

Therapeutic Options

- Resection and Ablation
- Radioparticle therapy
- Octreotride and IFN
- Chemotherapy
- SMALL MOLECULE TARGETED THERAPY

Targeted Therapy for NETs

- Sutent – Tyrosine Kinase inhibitor
- Everolimus – mTOR inhibitor
- Sutent and Everolimus developed in PNETs

- Phase III trial of Everolimus in NET did not demonstrate superiority over placebo

The NEW ENGLAND JOURNAL of MEDICINE

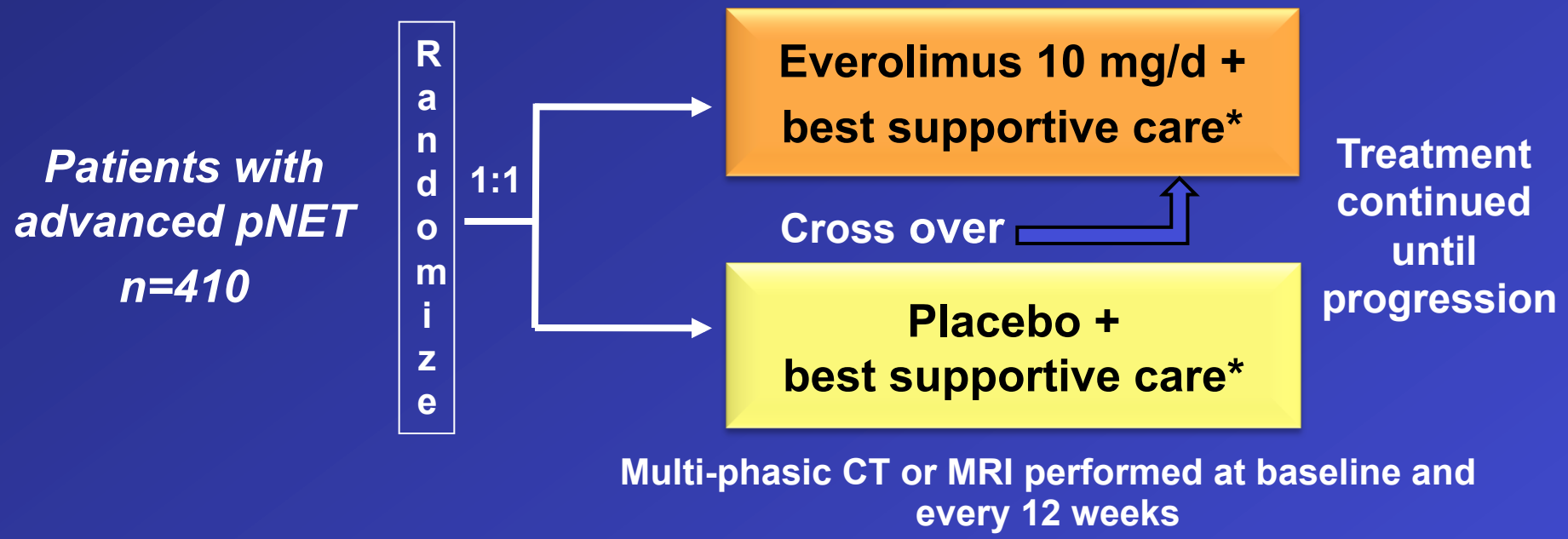
ORIGINAL ARTICLE

Everolimus for Advanced Pancreatic Neuroendocrine Tumors

James C. Yao, M.D., Manisha H. Shah, M.D., Tetsuhide Ito, M.D., Ph.D., Catherine Lombard Bohas, M.D., Edward M. Wolin, M.D., Eric Van Cutsem, M.D., Ph.D., Timothy J. Hobday, M.D., Takuji Okusaka, M.D., Jaume Capdevila, M.D., Elisabeth G.E. de Vries, M.D., Ph.D., Paola Tomassetti, M.D., Marianne E. Pavel, M.D., Sakina Hoosen, M.D., Tomas Haas, Ph.D., Jeremie Lincy, M.Sc., David Lebwohl, M.D., and Kjell Öberg, M.D., Ph.D., for the RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3) Study Group

ABSTRACT

RADIANT-3: Study Design



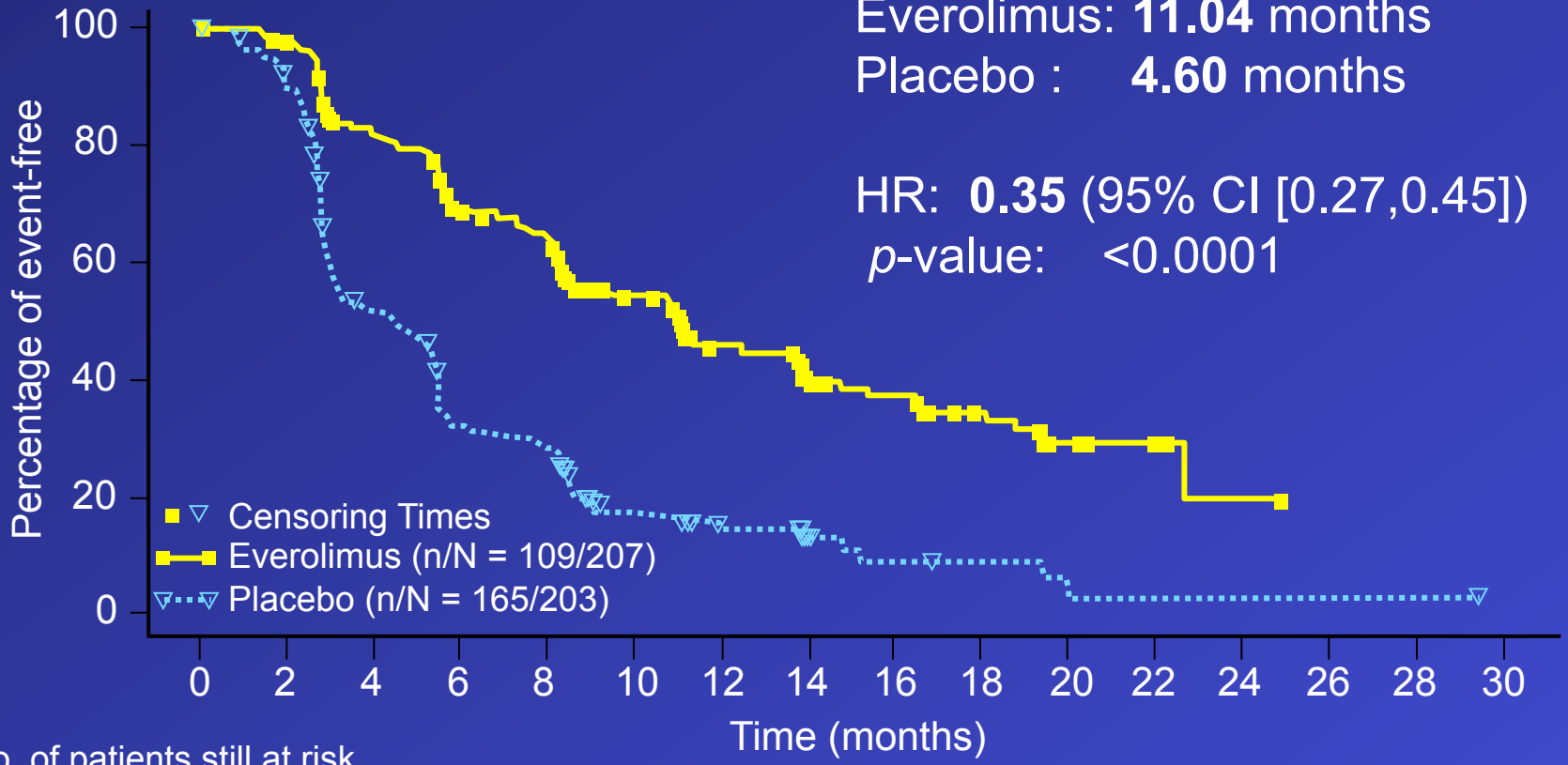
Randomization Aug. 2007 – May. 2009

*concurrent somatostatin analogs allowed

Primary Endpoint: PFS by Treatment

Kaplan Meier median PFS
Everolimus: **11.04** months
Placebo : **4.60** months

HR: **0.35** (95% CI [0.27,0.45])
p-value: <0.0001



No. of patients still at risk

Everolimus	207	189	153	126	114	80	49	36	28	21	10	6	2	0	0	0
Placebo	203	177	98	59	52	24	16	7	4	3	2	1	1	1	1	0

- *p*-value obtained from stratified one-sided log-rank test
- Hazard ratio is obtained from stratified unadjusted Cox model

Phase III, Randomized, Double-Blind Study of Sunitinib vs. Placebo in Patients with Progressive, Well-Differentiated Pancreatic NET

Eligibility criteria

- Well-differentiated, malignant pancreatic endocrine tumor
- Disease progression in past 12 months
- Not amenable to treatment with curative intent

Balanced by region

- Europe, Asia, Americas/Australia

N=340 planned

↓

N=171 randomized

RANDOMIZATION

1:1

Sunitinib 37.5 mg/day orally, continuous daily dosing (CDD)*

Placebo*

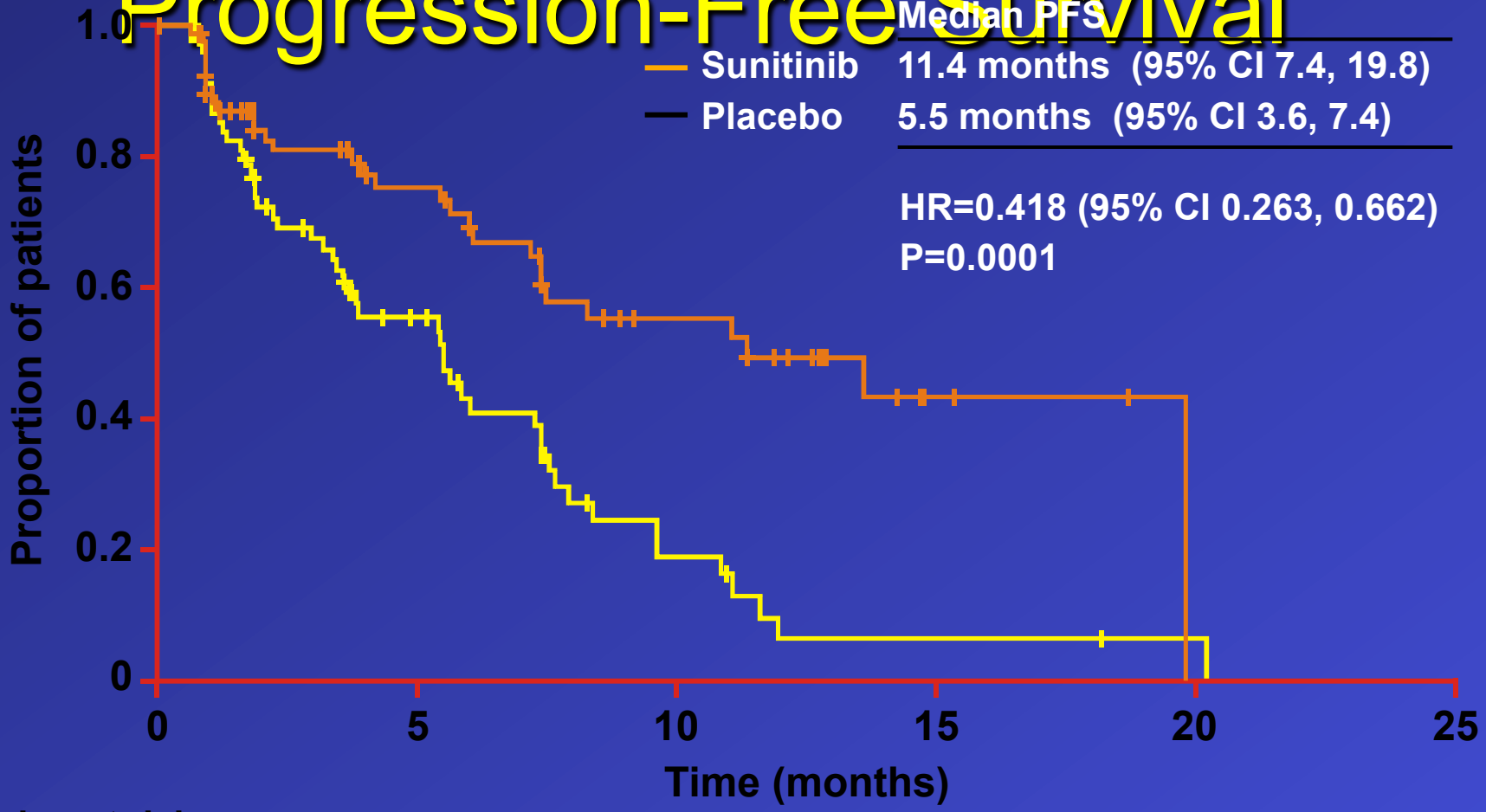
Primary endpoint: PFS

Secondary endpoints:
OS, ORR, TTR, duration of response, safety, patient-reported outcomes

*With best supportive care.
Somatostatin analogs were permitted

After trial closure (due to differences in deaths, serious AEs and PFS), patients became candidates for open-label sunitinib in trial NCT00443534 or NCT00428220

Progression-Free Survival



Number at risk

Sunitinib	86	39	19	4	0	0
Placebo	85	28	7	2	1	0

CONCLUSIONS

- NETs represent heterogeneous but distinct clinical group.
- Consider as biologically distinct tumors, regardless of site of origin
- Surgical resection is paramount
- For non-resectable disease, increasing number of hepatic directed options.

CONCLUSIONS

- Octreotide primarily for FUNCTIONAL tumors.
- Consider PNETS for systemic therapy (chemo, everolimus, sutent).
- Consider ablative therapies and clinical trials for NETs.