Take home messages

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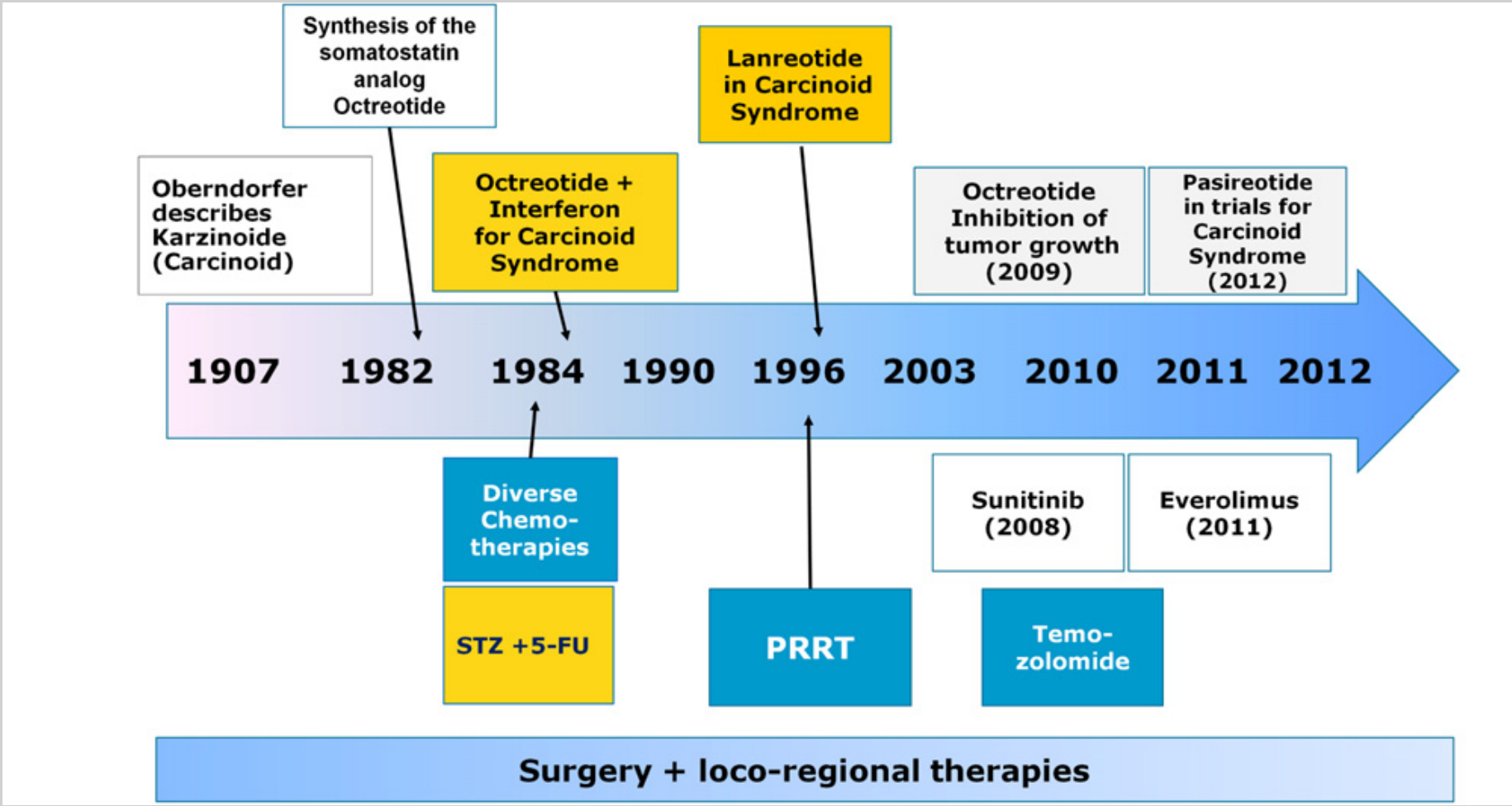
Systemic Therapeutic Options for Carcinoid

Marianne Pavel, Mark Kidd, and Irvin Modlin

Semin Oncol . 2013; 40: 84-99

Bari,
7-10 novembre 2013

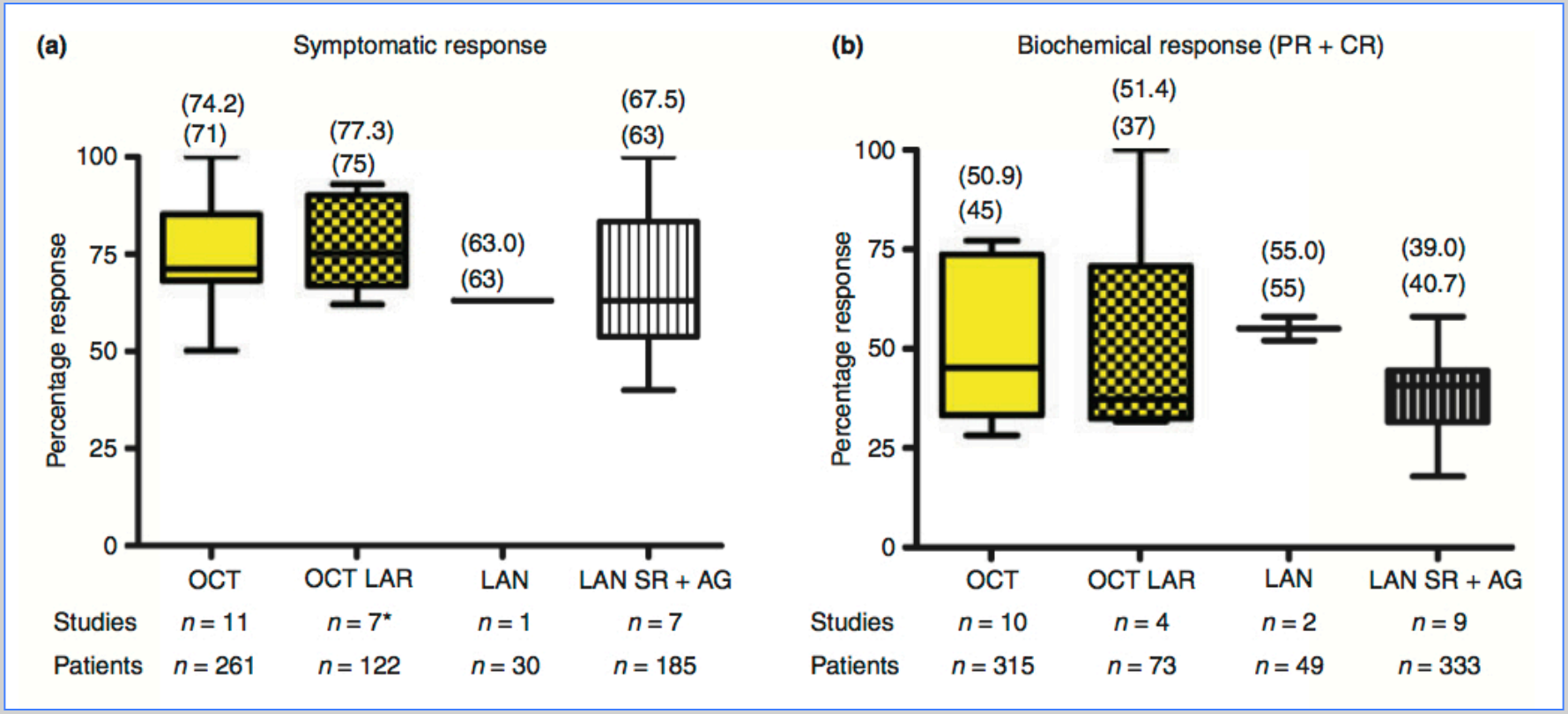


Review article: somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine (carcinoid) tumours

I. M. MODLIN*, M. PAVEL†, M. KIDD* & B. I. GUSTAFSSON‡,§

Aliment Pharmacol Ther **31**, 169–188 2010

Circa 481 pazienti in 15 studi 1972-2009



Promid and Clarinet

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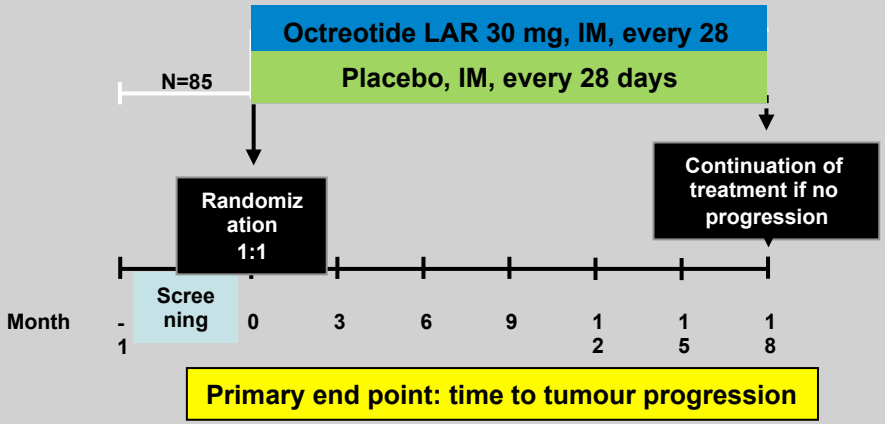
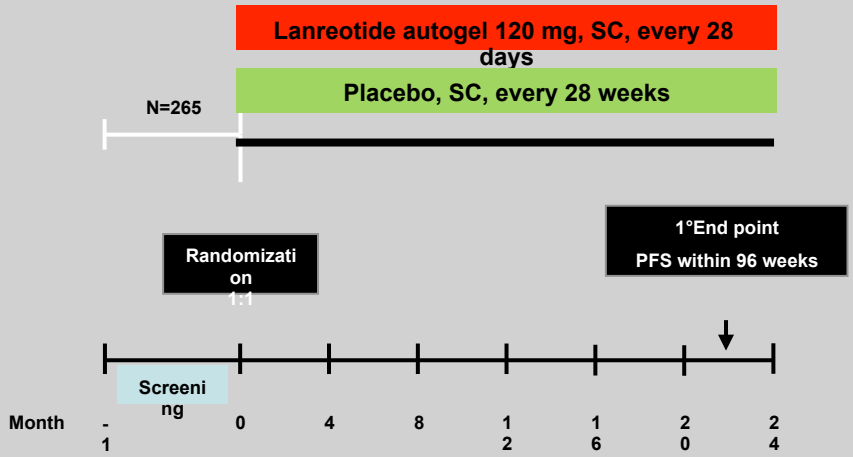
PROMID



- **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.

CLARINET



- **Treatment continued until tumor progression or death**
- **Estimated study completion June 2013**

ClinicalTrials.gov Identifier: NCT00353496. At: http://clinicaltrials.gov/ct2/show/NCT00353496?term=CLARINET&rank=3.

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clinical practice guidelines

Annals of Oncology 23 (Supplement 7): vii124–vii130, 2012
doi:10.1093/annonc/mds295

Neuroendocrine gastro-entero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

K. Öberg[1], U. Knigge[2], D. Kwekkeboom[3] & A. Perren[4] on behalf of the ESMO Guidelines Working Group*

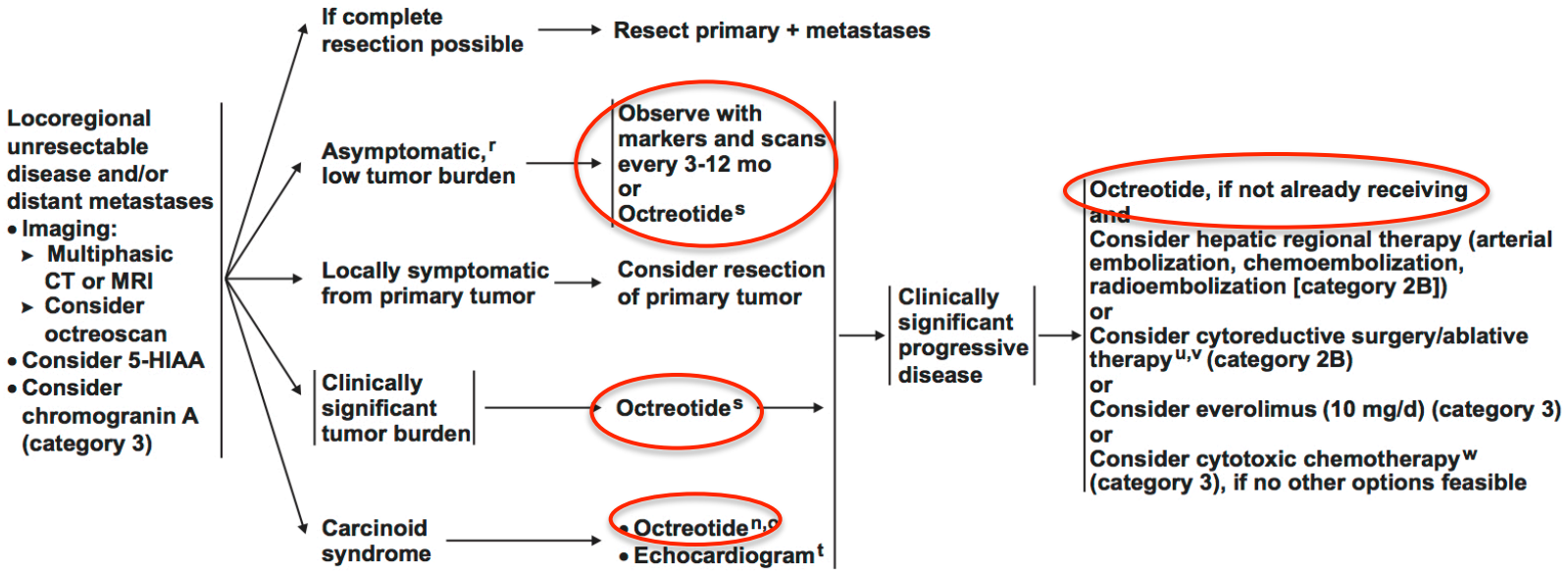
Table 10. Summary of recommendations

- The diagnosis of NET should be confirmed by histopathology (CgA, synaptophysin Ki-67).
- The current classification and staging systems should be applied in the clinic.
- Somatostatin receptor imaging besides standard imaging (CT and MRI) is part of standard of care.
- Resection of locoregional disease in patients with small intestinal NET (carcinoids) is recommended.
- Somatostatin analog therapy is first-line therapy in all functional NET and small intestinal NET G1/G2.
- Everolimus and sunitinib are registered for pancreatic NETs based on two phase III randomized trials.
- Temozolomide alone or in combination with capecitabine is promising for treatment of pancreatic NETs.

NCCN Guidelines Version 2.2013
Carcinoid Tumors

NCCN Guidelines Index
Neuroendocrine TOC
Discussion

MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES[c]



[c] See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).

[n] For symptom control, octreotide 150-250 mcg SC TID or octreotide LAR 20-30 mg IM every 4 weeks. Dose and frequency may be further increased for symptom control as needed. Therapeutic levels of octreotide would not be expected to be reached for 10-14 d after LAR injection. Short-acting octreotide can be added to octreotide LAR for rapid relief of symptoms or for breakthrough symptoms.

[o] Lanreotide is approved for symptom control in Europe. Lanreotide has a similar mechanism of action as octreotide and may be preferable in patients who have difficulty tolerating an IM versus SC injection.

[r] Resection of a small asymptomatic (relatively stable) primary in the presence of unresectable metastatic disease is not indicated.

[s] For tumor control, the PROMID study (J Clin Oncol 2009;27:4656-4663) used octreotide LAR 30 mg IM every 4 weeks.

[t] If signs and symptoms of heart disease or planning major surgery.

[u] Includes ablative techniques such as radiofrequency, microwave, and cryotherapy. There are no randomized clinical trials and prospective data for these interventions are limited. However, data on the use of these interventions are emerging.

[v] Only if near complete resection can be achieved.

[w] Anticancer agents such as capecitabine, dacarbazine, 5-FU, interferon, oxaliplatin, and temozolomide can be used in patients with progressive metastases for whom there are no other treatment options. See Discussion for details.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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A Multicenter, Randomized, Blinded, Phase 3 Study of Pasireotide LAR vs Octreotide LAR in Patients with Metastatic NET with Disease-Related Symptoms Inadequately Controlled by Somatostatin Analogs

Wolin (Abs#4031)

Objective:

- Determine effect of pasireotide LAR (PAS) vs octreotide LAR (OCT) on symptoms in NET

Methods:

- PAS (60 mg) or OCT (40 mg) q28d; stratified by main baseline symptoms (diarrhea/flushing)
- Objectives: primary, symptom response (SR) at 6 mo; secondary, tumor response (TR) & safety; exploratory PFS analysis

Results:

- N=110; PAS=53 & OCT=57 pts at interim analysis suggesting futility for SR (study halted)
- At 6 mo, symptom response was similar for PAS & OCT
- Most common G3/4 AEs: hyperglycemia, diarrhea, abd. Pain
- Investigator-assessed median PFS: 11.8 mo (PAS) & 6.8 mo (OCT), HR=0.46; *P*=0.045

ASCO 2013

Poster Discussion

PAS Significantly Prolonged PFS by 5 months

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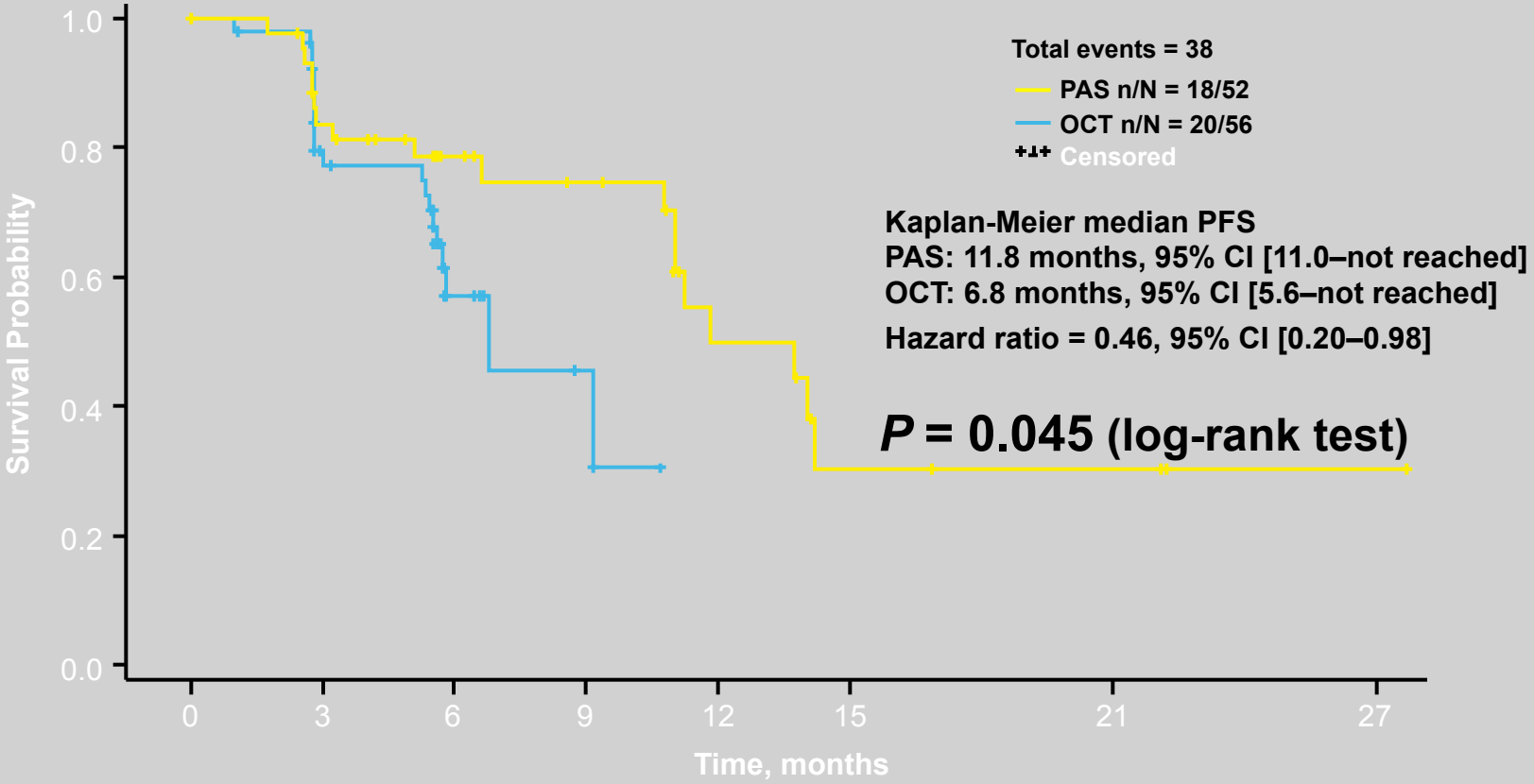

Time (months)	0	3	6	9	12	15	21	27
PAS	52	35	22	18	9	4	3	1
OCT	56	34	10	3	0	-	-	-

CI, confidence interval; OCT, octreotide LAR; PAS, pasireotide LAR; PFS, progression-free survival.
Presented during the ASCO Annual Meeting 2013 as a poster discussion on Monday, June 3rd, McCormick Center. Abstract #4031.

RADIANT- 4 Study

Advanced (unresectable or metastatic) well differentiated non functioning progressive GI and lung NETs

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- Primary Endpoint: PFS by central radiological assessment, (local supportive)
  - HR target value/ PFS median: 0.59/ 5 to 8.5 months
- Interim analysis at 60% of PFS events
- Stratification by tumor site, WHO and prior SSA

ClinicalTrials.gov identifier: NCT01524783

- Treatment with somatostatin analogs and alpha interferon might be an option for functional tumors with clinical symptoms (III,B) (PR in 5-10%, SD in 30-50%, symptomatic improvement in 40-60%).

- In non-functioning tumors the use of somatostatin analogs is still controversial, but after the PROMID study indicating antitumor efficacy by octreotide LAR in small intestinal NETs it is now widely accepted also for non-functioning tumors of other origins (III,B).

Volendo delineare una ipotetica sequenza terapeutica ideale sceglierei per i pazienti con pNET metastatico non resecabile

Bari,
7-10 novembre 2013

	1	2	3	4	5	Tot
	1	4	5	5	10	25
SSA -> Targeted Therapy -> CT -> PRRT	20%		80%			100%
	1	2	3	4	5	Tot
	3	5	6	9	2	25
SSA -> CT -> Targeted Therapy -> PRRT	32%		68%			100%
	1	2	3	4	5	Tot
	5	9	8	2	1	25
SSA -> PRRT -> CT -> Targeted Therapy	56%		44%			100%
	1	2	3	4	5	Tot
	3	6	7	7	2	25
SSA -> PRRT -> Targeted Therapy -> CT	36%		64%			100%
	1	2	3	4	5	Tot
	0	6	6	10	3	25
SSA -> Targeted Therapy -> PRRT -> CT	24%		76%			100%

ETRIS Project
Raccomandazioni sulla gestione dei NET

1 = massimo disaccordo; 2 = disaccordo; 3 = accordo; 4 = più che d'accordo; 5 = accordo assoluto

Grazie dell'attenzione