

Medical Treatments for Neuroendocrine Tumors (NETS) and The Carcinoid Syndrome

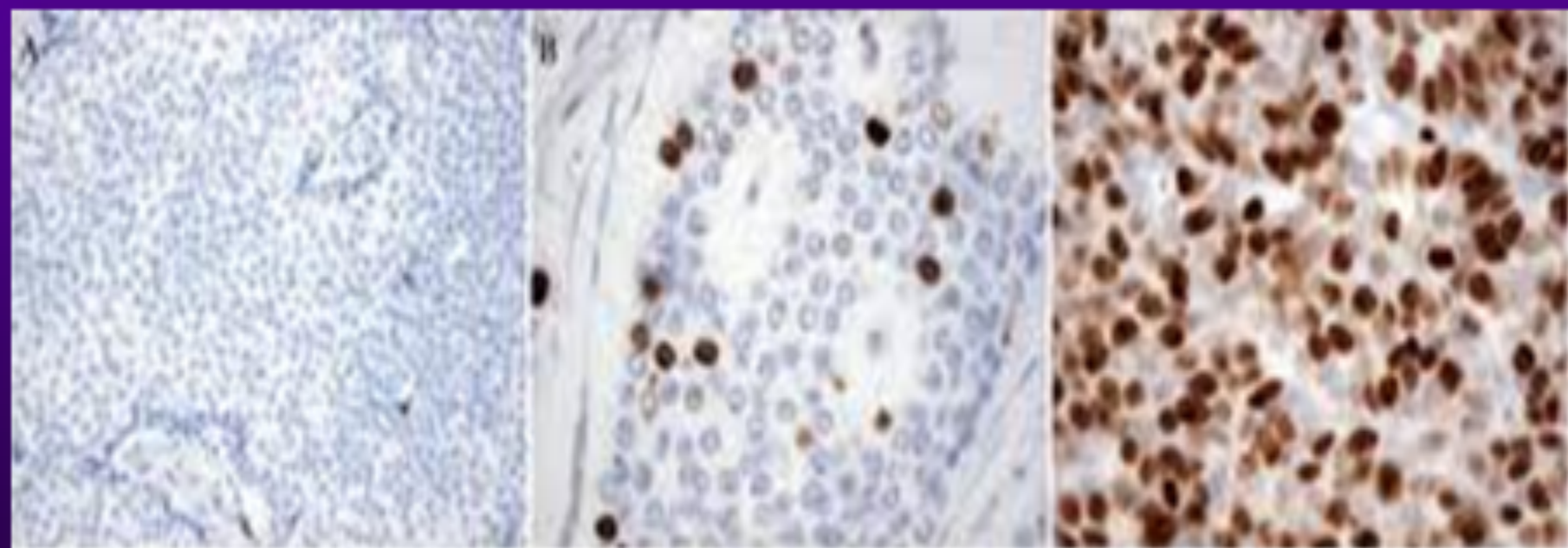
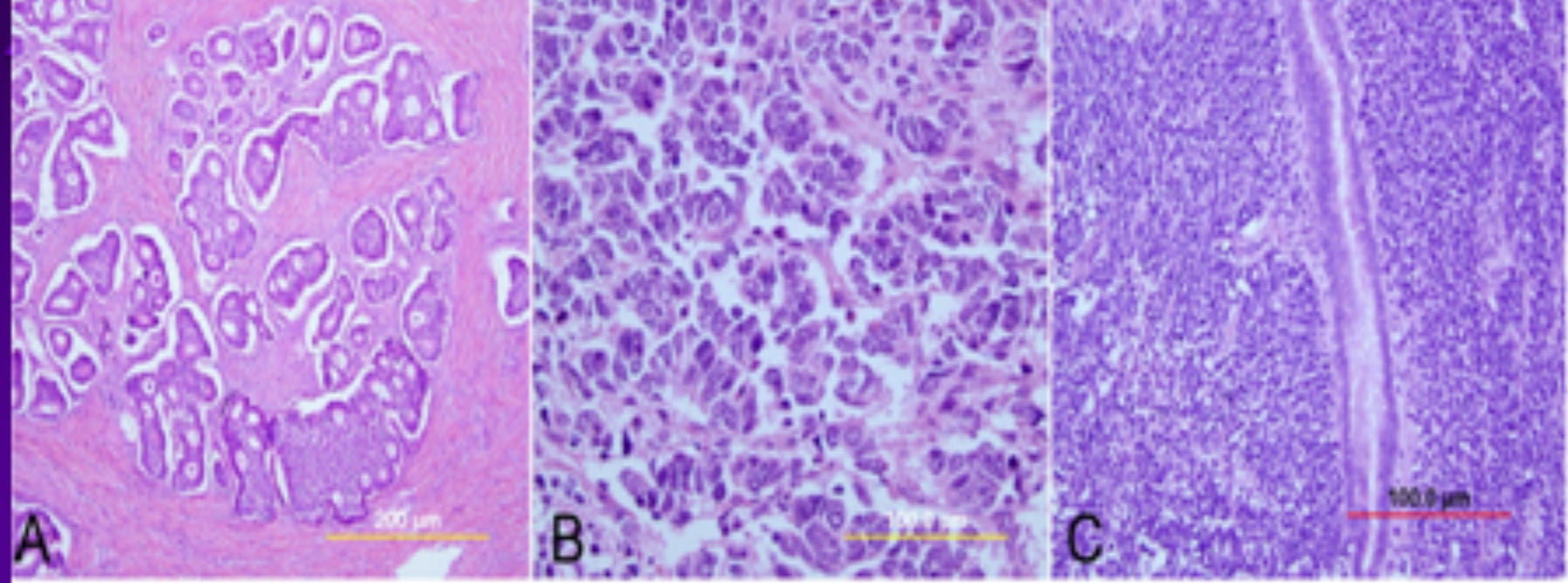


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**Halifax, NS
May 23/2015**



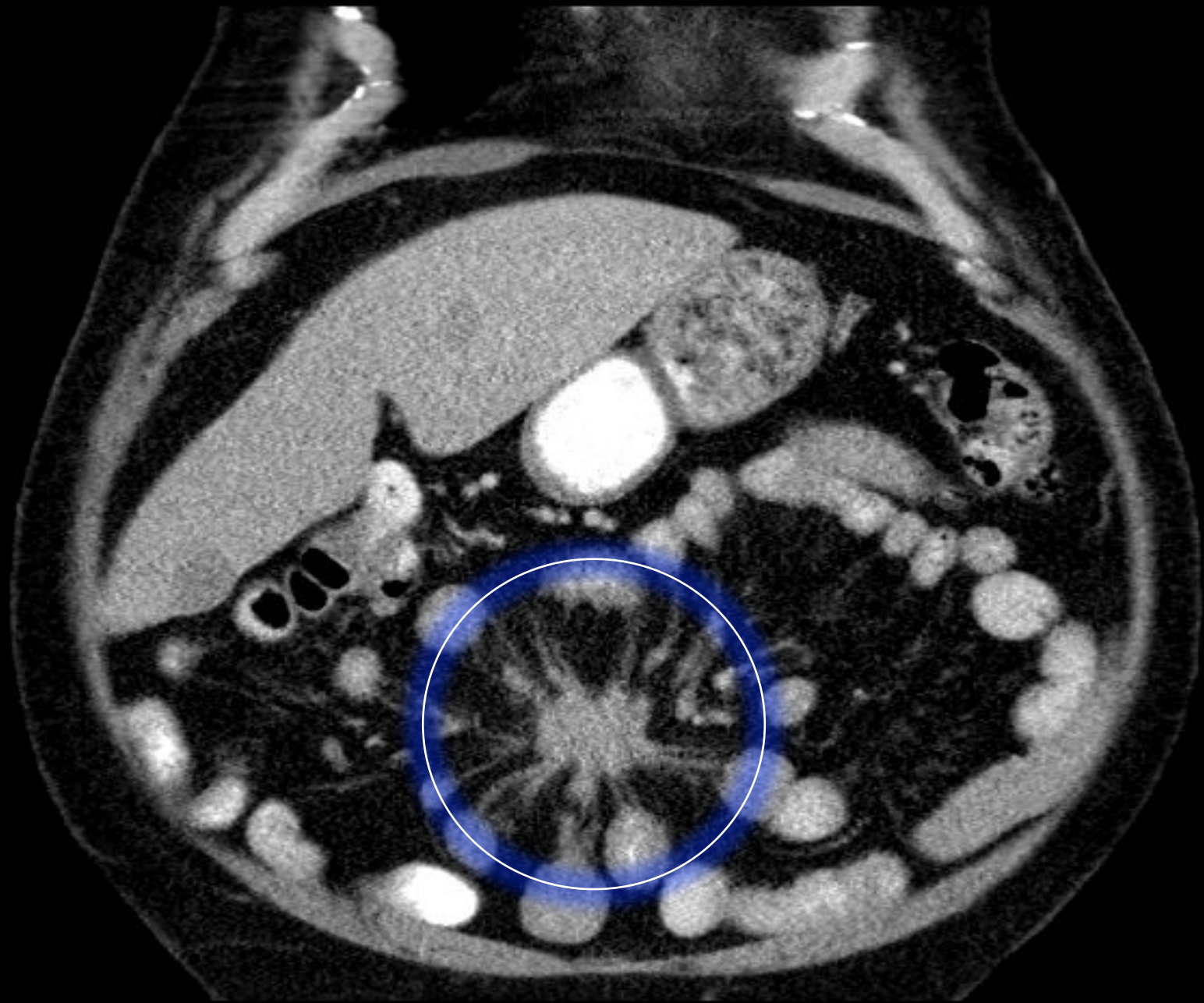
The Carcinoid Syndrome





Small Intestinal NETS and Carcinoid Syndrome

- ◆ **~ 30-40% develop carcinoid syndrome during the disease course, many have it for years before diagnosis**
- ◆ **Typical syndrome arises due to liver metastases and secretion of large amounts of serotonin into the systemic circulation through the portal system**
- ◆ **Classic symptoms: flushing and diarrhea**



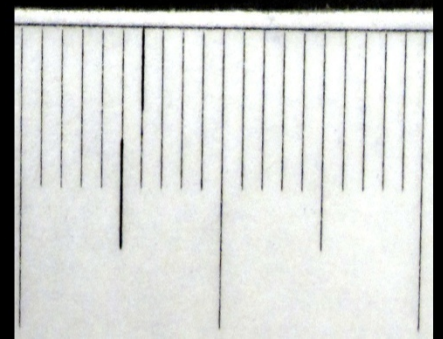


Diagnosis Often Delayed Due To ...

- ◆ **Rarity**
- ◆ **Insidious symptom onset**
- ◆ **Common symptoms overlapping common conditions such as menopausal hot flashes or irritable bowel syndrome**
- ◆ **Delay between symptoms and diagnosis often > 3-5y**
- ◆ **Many patients suffer for years on multiple medications and with multiple diagnostic procedures before diagnosis**







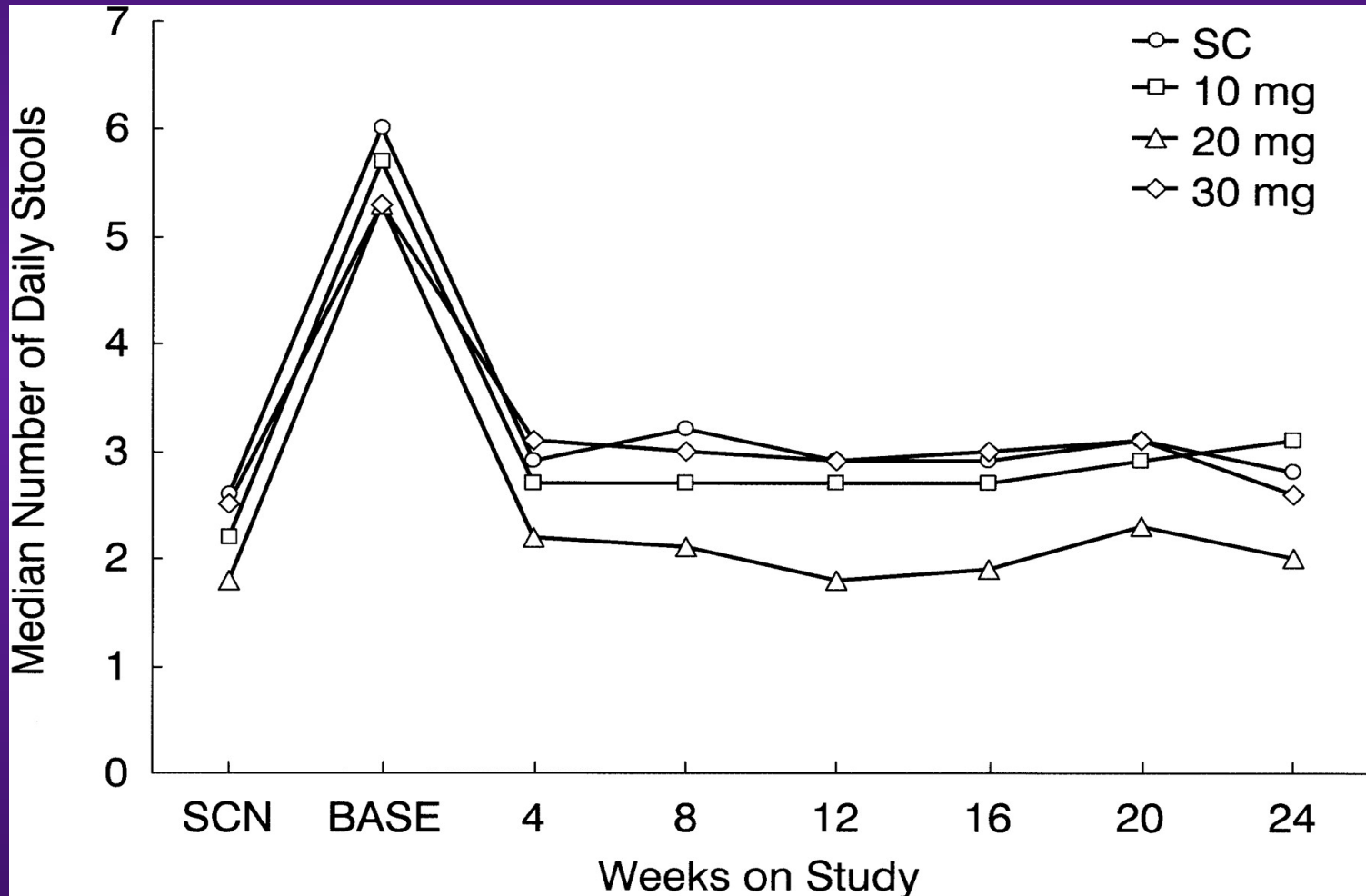


Approved Treatments for Carcinoid Syndrome

- ◆ **Octreotide (Sandostatin®) short acting**
Approved by Health Canada **June 13, 1989**
for treatment of the malignant carcinoid
syndrome based on Single Center Phase I Trial
(n=25)
- ◆ **Octreotide LAR (Sandostatin LAR®)**
Approved as monthly depot injection
by Health Canada **December 23 1998** based on
Multicentre Phase II Trial (n=93)

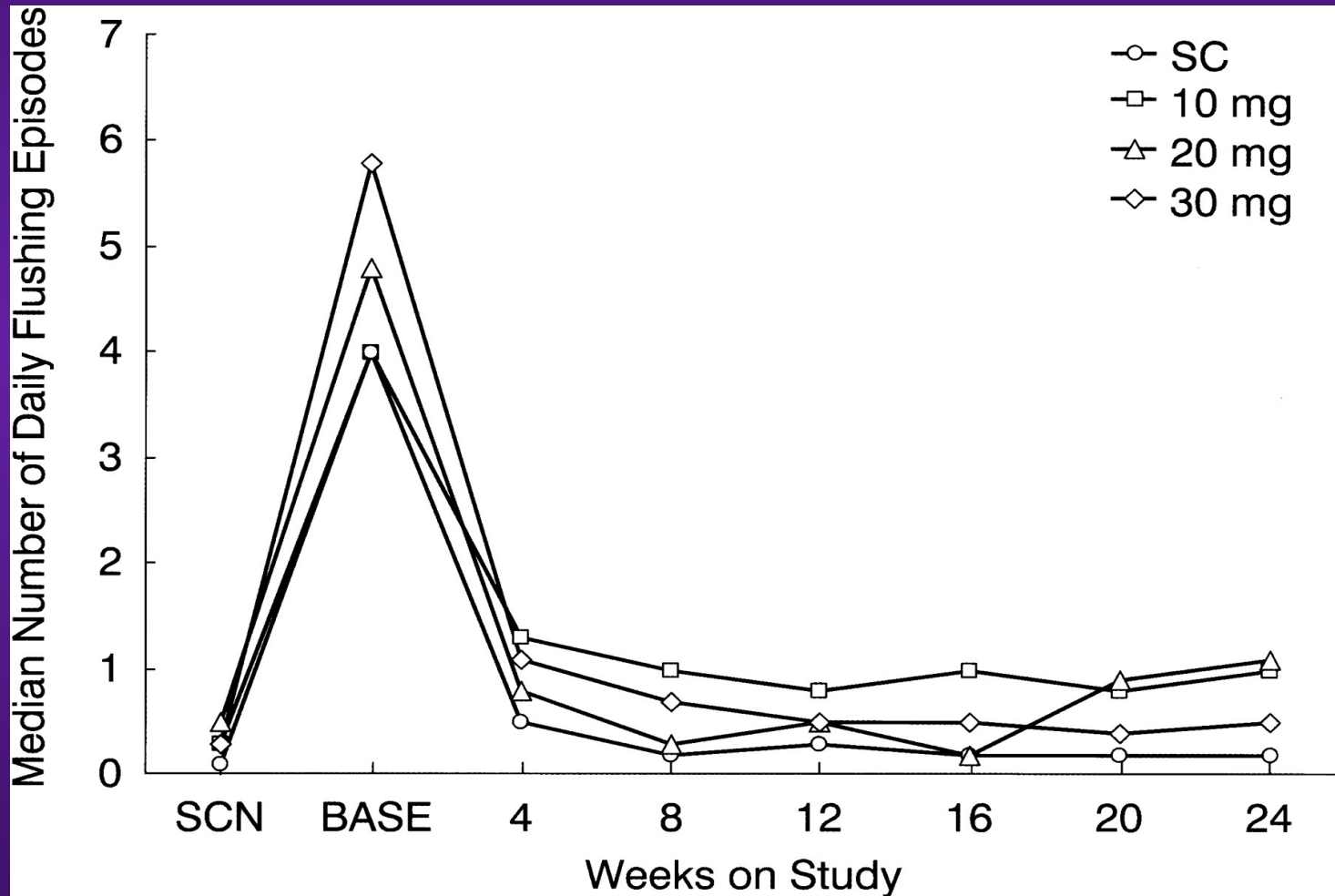


Octreotide LAR

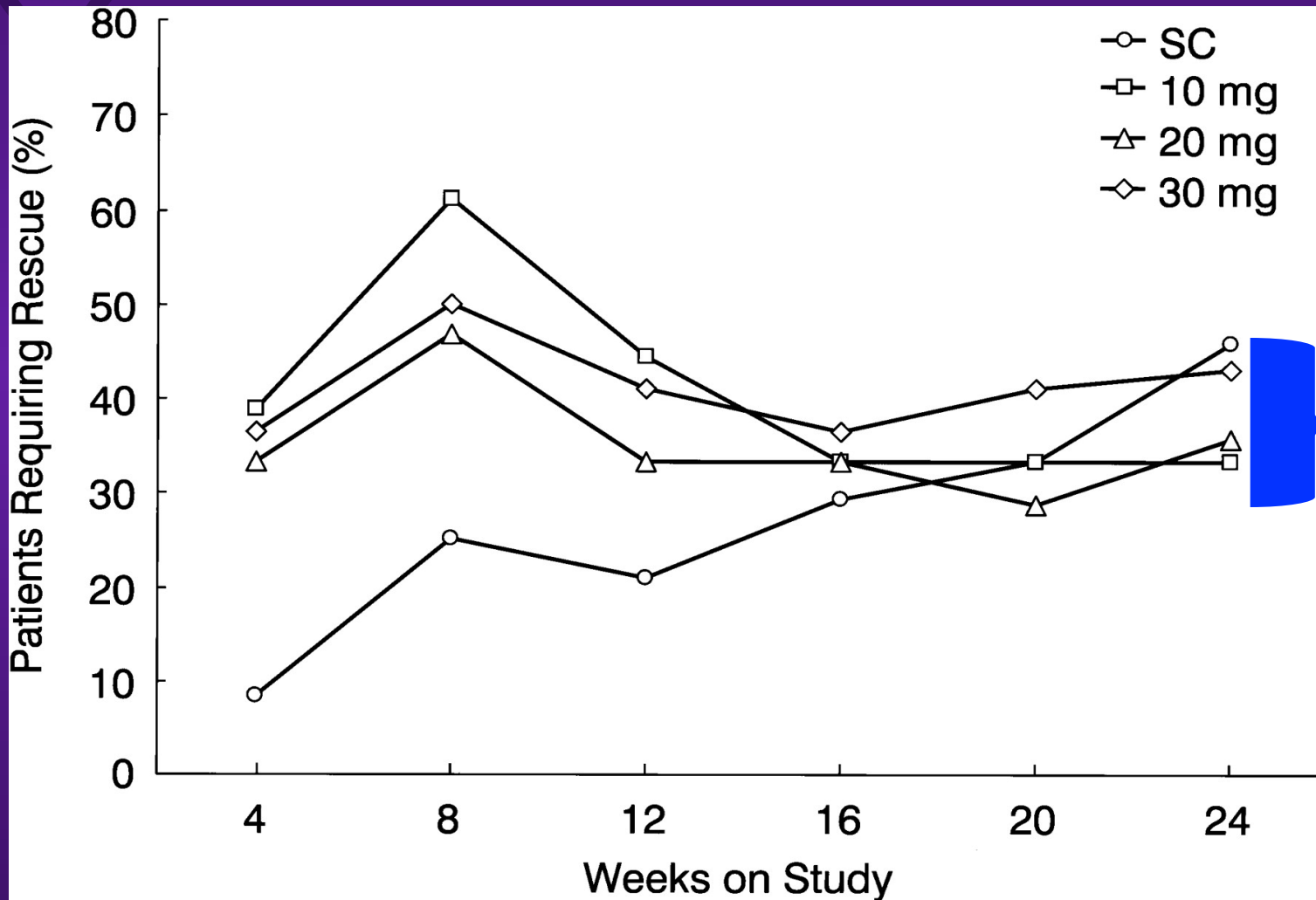




Octreotide LAR



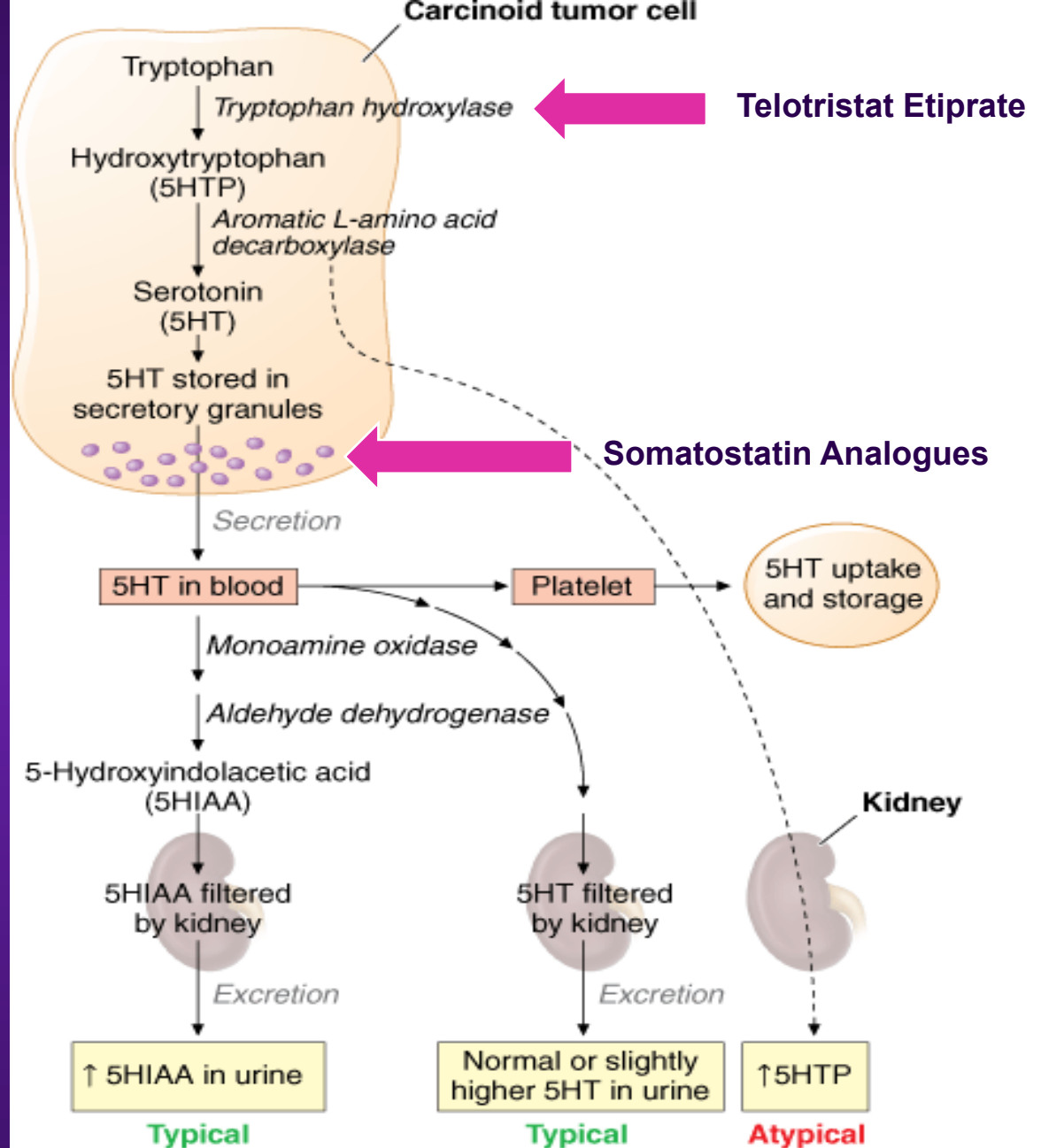
Need for Rescue Medication Observed on Phase II Trial



30-40 %
requiring
rescue
medication
for
symptom
control



Serotonin metabolism and Carcinoid syndrome



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J. *Harrison's Principles of Internal Medicine*, 17th Edition: <http://www.accessmedicine.com>

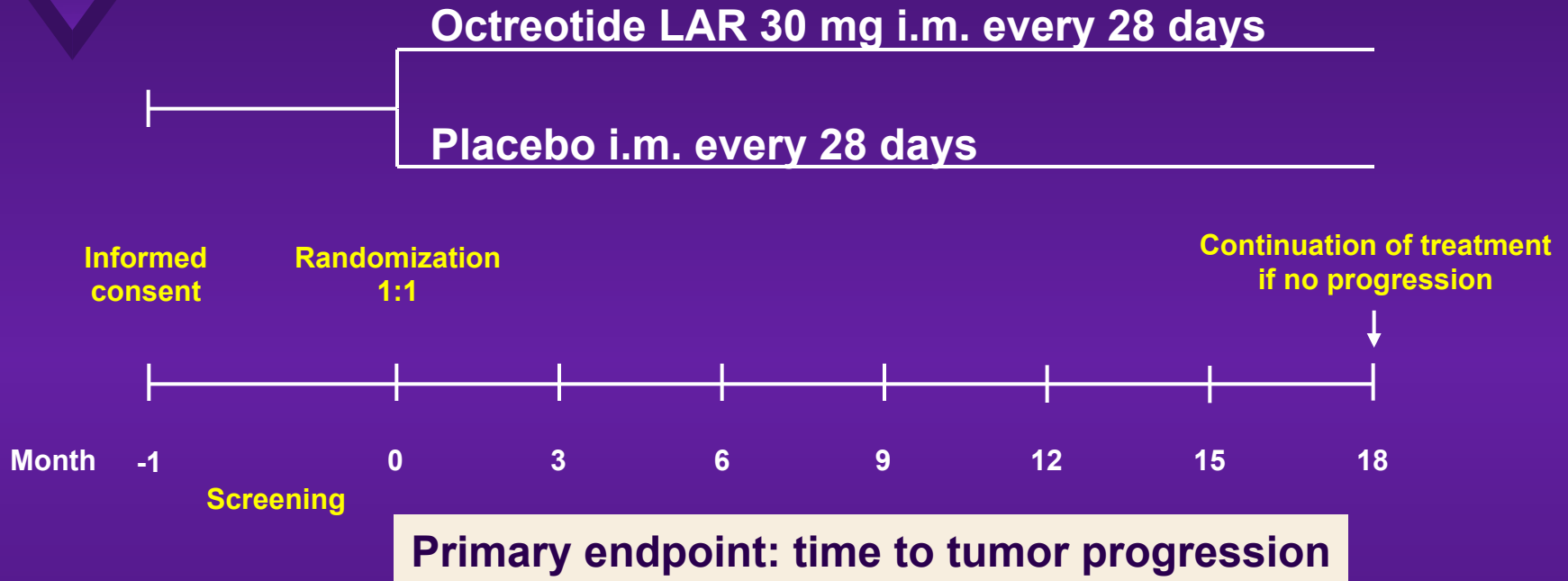
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**What about patients
without carcinoid
syndrome (~60-70%)?**

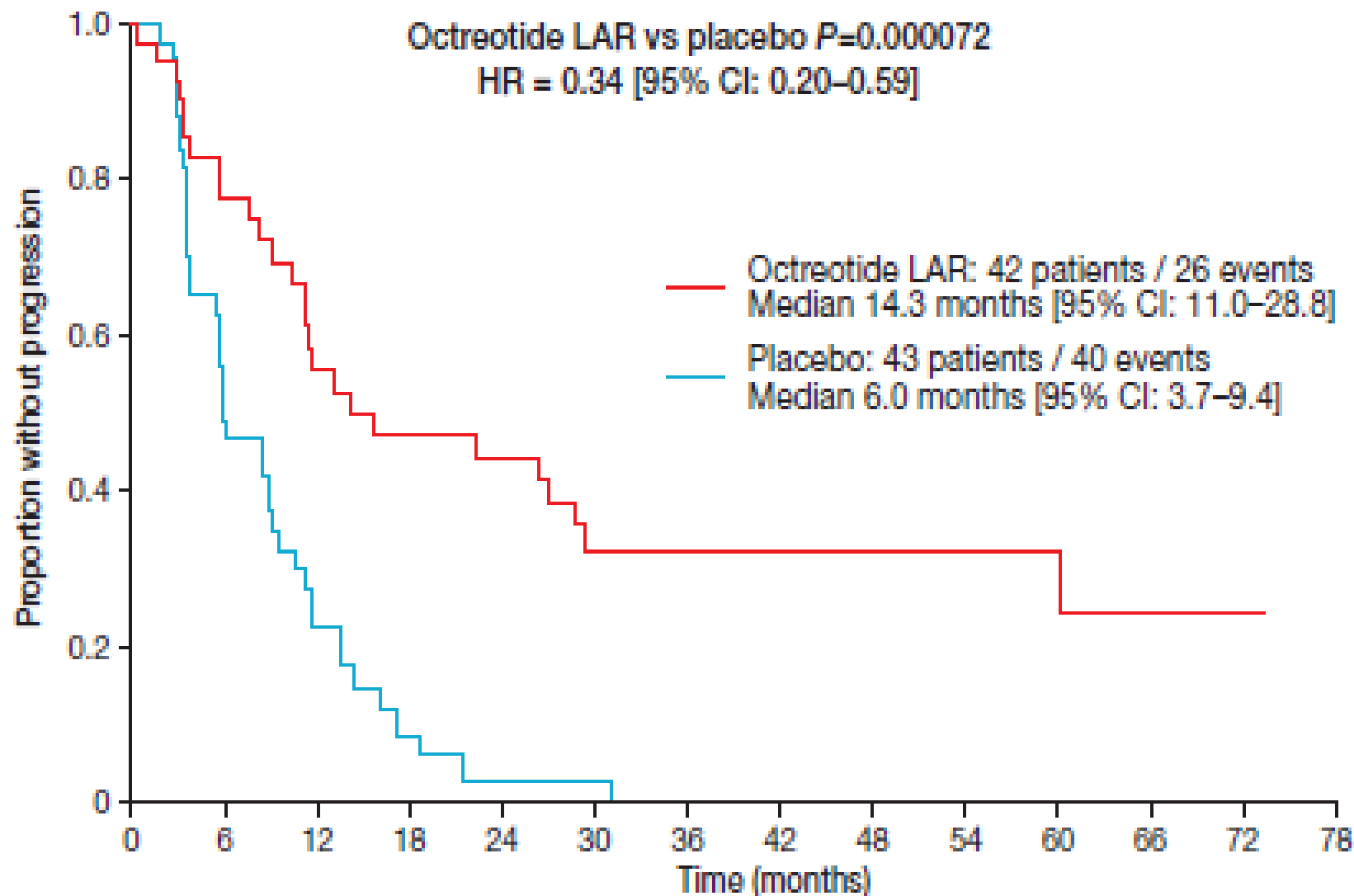


PROMID Study Design

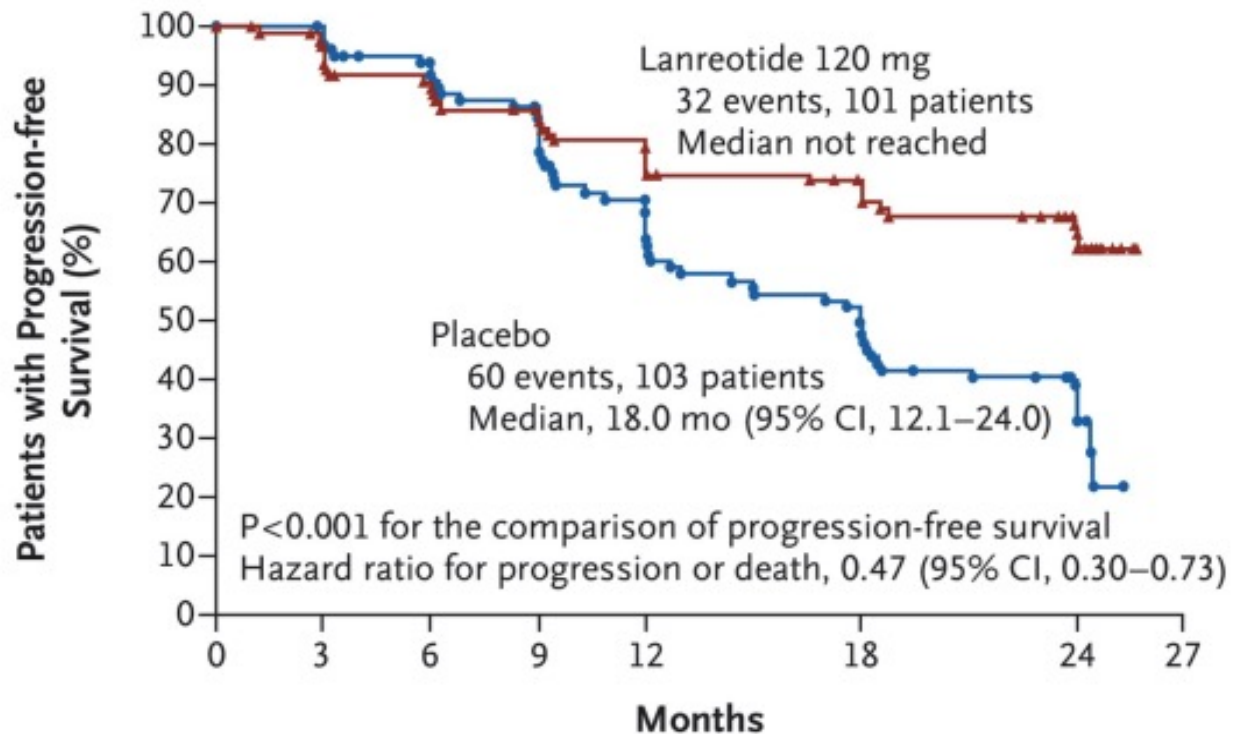


Patients received octreotide LAR 30 mg or placebo every 28 days until tumor progression, documented by CT or MRI, or death.

Figure 2. Time to tumor progression in patients with metastatic midgut NETs treated with octreotide LAR (red) or placebo (blue) every 28 days in the conservative intention-to-treat analysis



Progression-free Survival (Intention-to-Treat Population).



No. at Risk

Lanreotide	101	94	84	78	71	61	40	0
Placebo	103	101	87	76	59	43	26	0

Caplin ME et al. N Engl J Med 2014;371:224-233.



The NEW ENGLAND
JOURNAL of MEDICINE



Indications for Somatostatin Therapy

- ◆ **Carcinoid syndrome**
- ◆ **Treatment of refractory intra-operative hypotension**
- ◆ **Non-functioning but progressive disease**
- ◆ **??? To decrease risk of carcinoid heart disease in those with syndrome???**



New treatments for NETS of Pancreatic origin

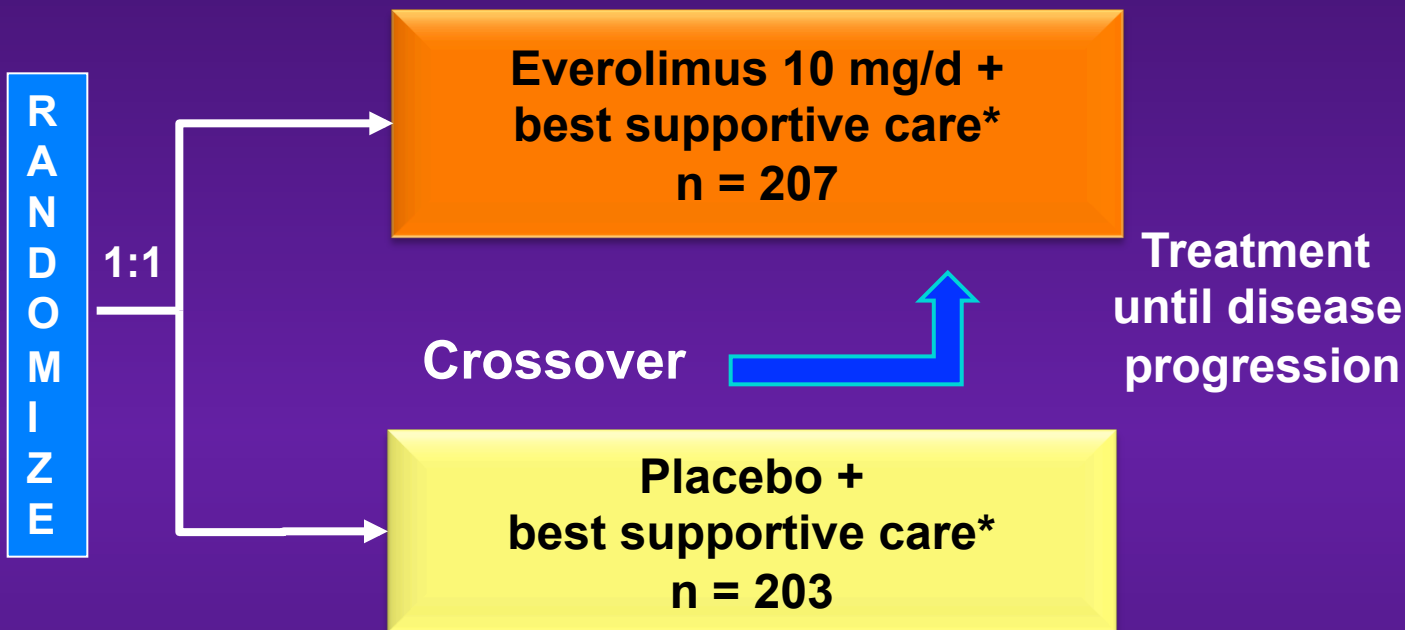
RADIANT-3 Study Design

Phase III Double Blind Placebo Controlled Trial

Patients with advanced pNET, N = 410

Stratified by:

- WHO PS
- Prior Chemotherapy



Primary endpoint:

- PFS (RECIST)

Secondary endpoints:

- Response, OS, biomarkers, safety, and PK

* Concurrent somatostatin analogs allowed

Randomization August 2007 - May 2009

Yao et al. NEJM 2011.

PFS by Central Review*

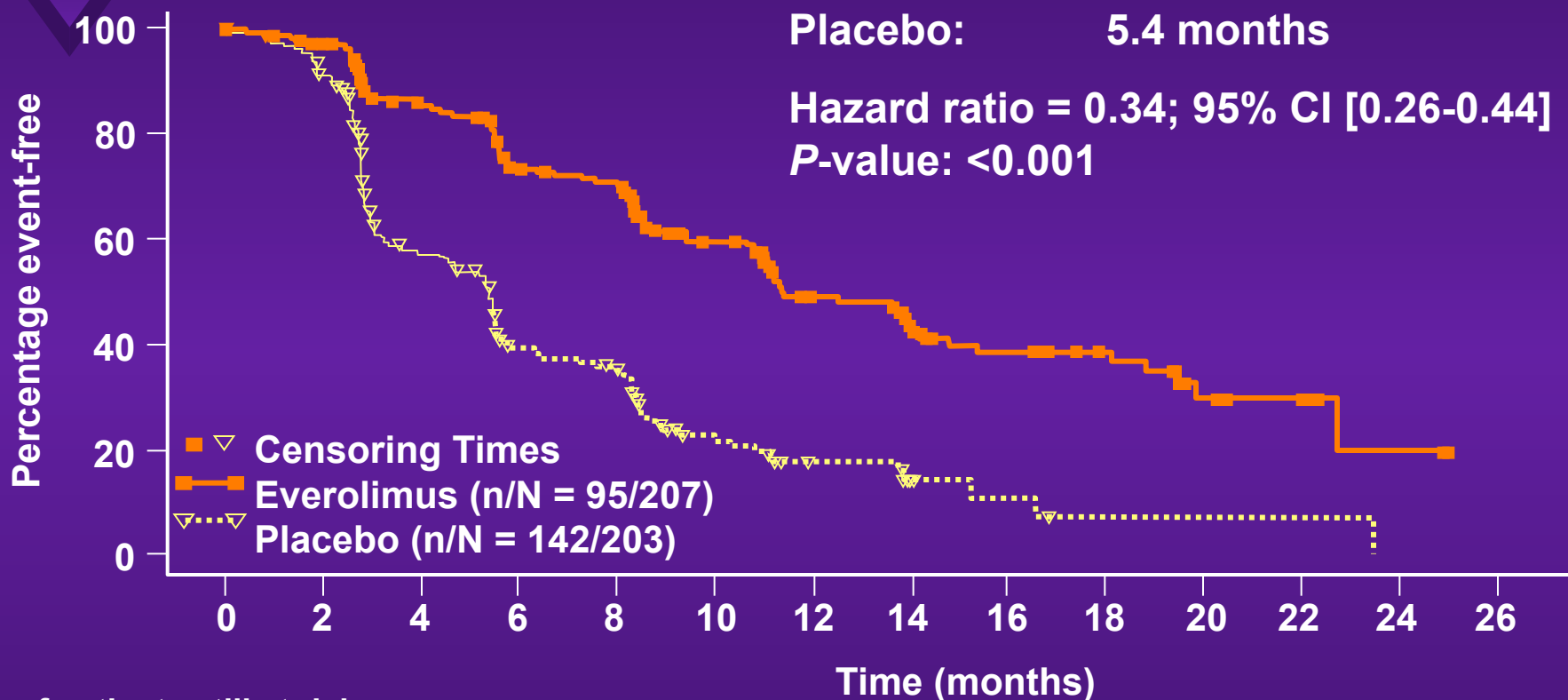
Kaplan-Meier medians PFS

Everolimus: 11.4 months

Placebo: 5.4 months

Hazard ratio = 0.34; 95% CI [0.26-0.44]

P-value: <0.001



No. of patients still at risk

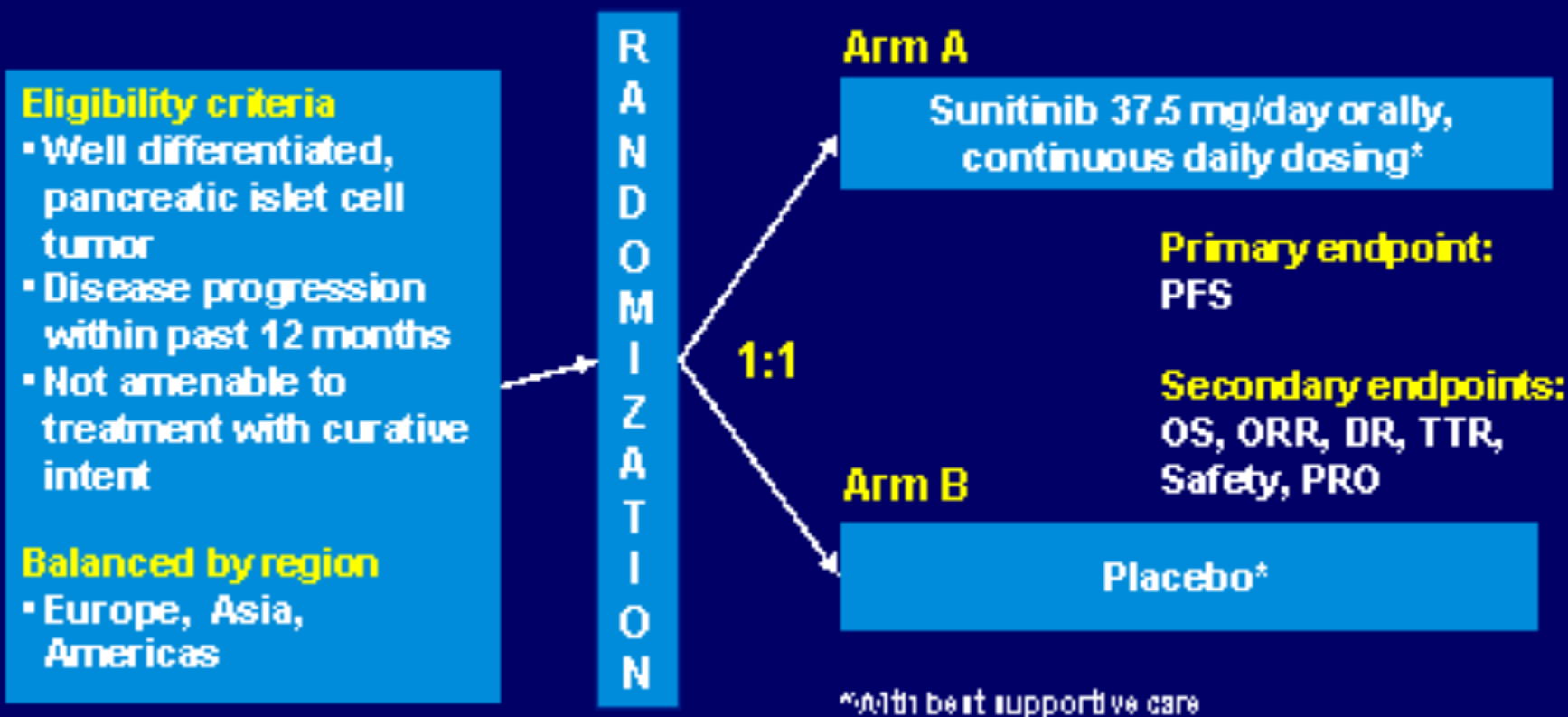
Everolimus	207	187	152	126	117	81	49	36	27	22	10	6	2	0
Placebo	203	180	99	60	52	22	12	5	3	1	1	1	0	0

* Independent adjudicated central review committee

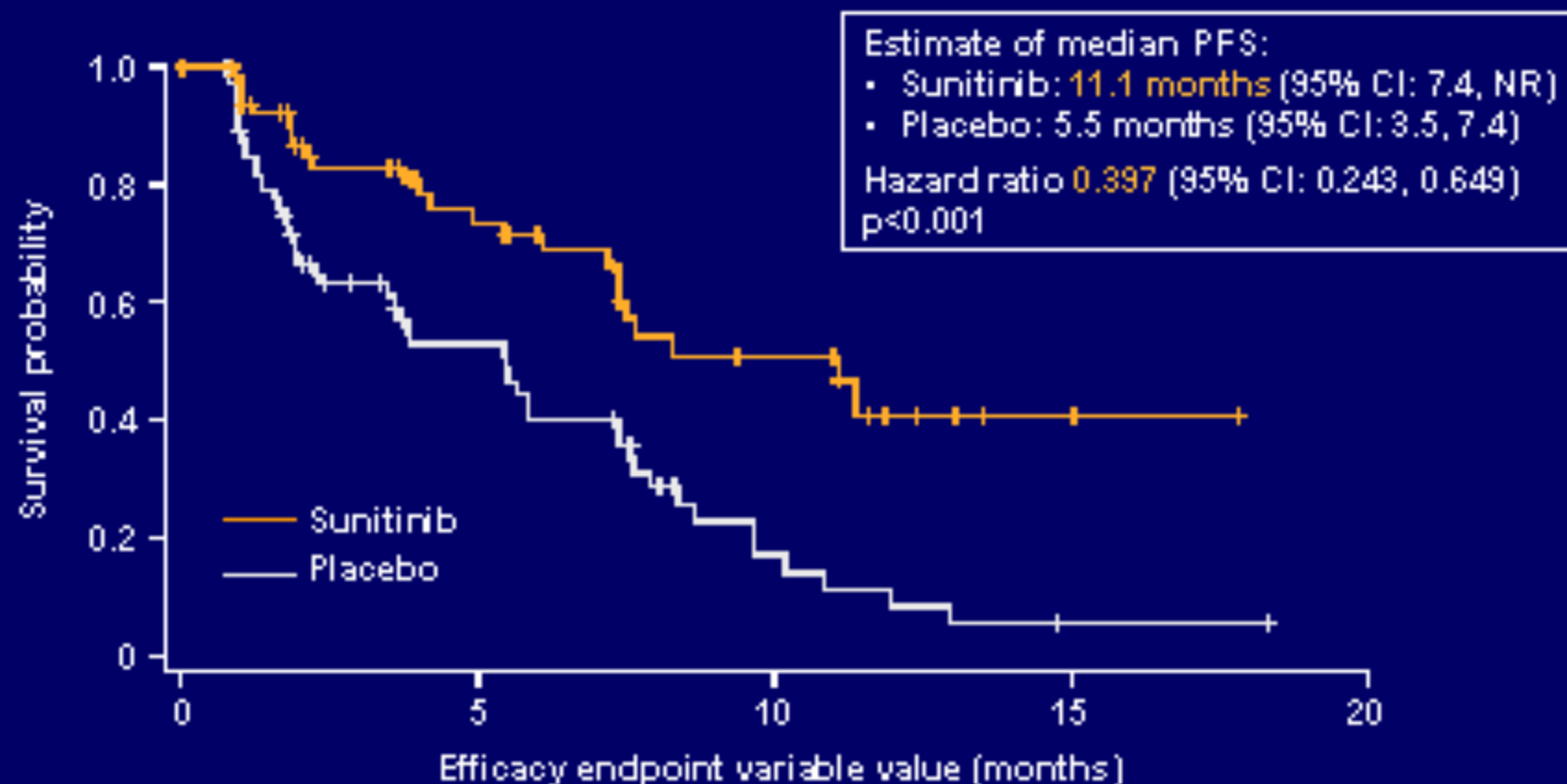
• P-value obtained from stratified one-sided log rank test

• Hazard ratio is obtained from stratified unadjusted Cox model

Study A6181111: A Phase 3, Randomized, Double-blind, Trial of Sunitinib vs. Placebo in Patients with Progressive, Well Differentiated, Malignant Pancreatic Islet Cell Tumors



Kaplan-Meier Analysis of PFS*



Placebo, n	79	25	6	1	0
Sunitinib, n	74	32	14	2	0

*Preliminary results, at time of DMC review.



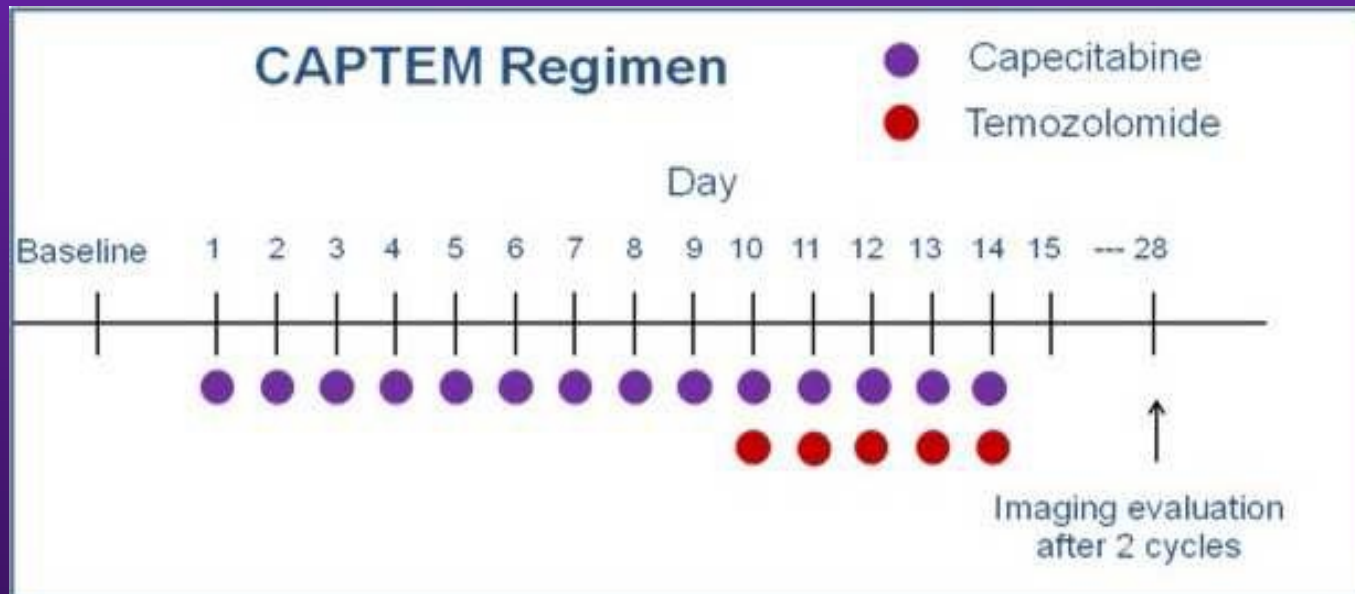
Selected Toxicities: Sunitinib ***(Grade 3/4 ≥ 3%)***

	Sunitinib (n = 83)		Placebo (n = 82)	
	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grades 3/4 (%)
Diarrhea	59	5	39	2
Asthenia	34	5	27	4
Fatigue	32	5	27	8
Abdominal Pain	28	5	32	10
Hypertension	26	10	5	1
PPE	23	6	2	0
Stomatitis	22	4	2	0
Thrombocytopenia	17	4	5	0
Neutropenia	29	12	4	0



CAPTEM

- ◆ Oral combination chemotherapy regimen
 - ◆ Capecitabine 750mg/m² BID
 - ◆ Temozolomide 150-200mg/m² daily



Original Article

First-Line Chemotherapy With Capecitabine and Temozolomide in Patients With Metastatic Pancreatic Endocrine Carcinomas

Jonathan R. Strosberg, MD¹; Robert L. Fine, MD²; Junsung Choi, MD¹; Aejaz Nasir, MD³; Domenico Coppola, MD³; Dung-Tsa Chen, PhD⁴; James Helm, MD¹; and Larry Kvolts, MD¹

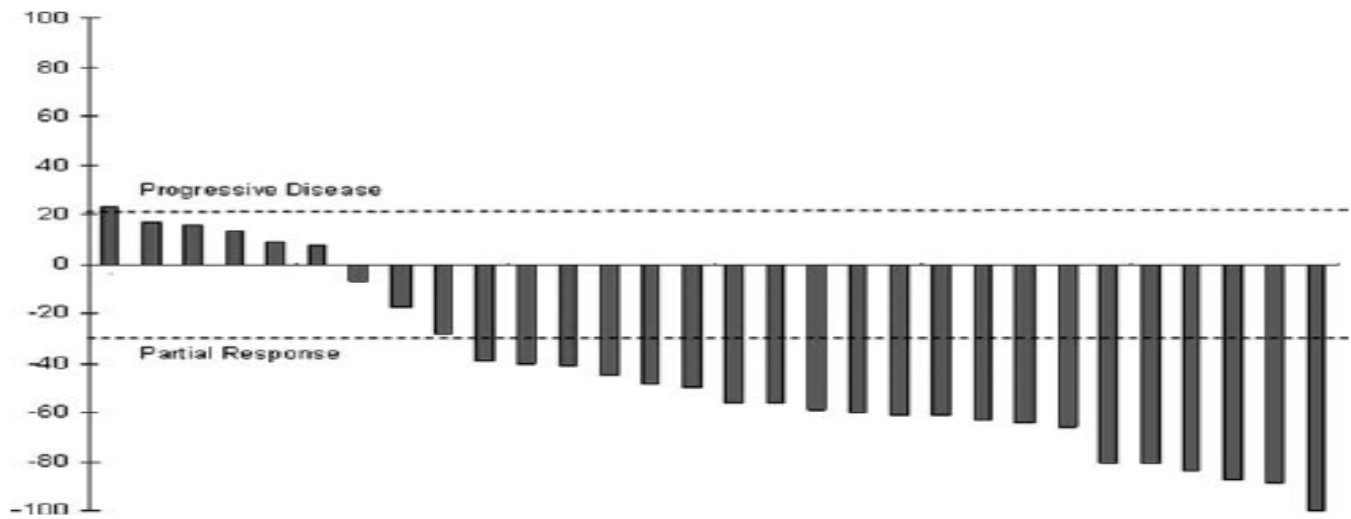
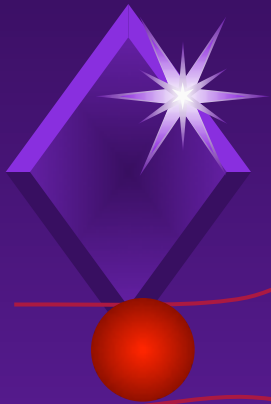


Figure 1. Waterfall plot illustrating best radiographic response (percent change) in each patient.



**What about targeting the
liver?**



ischemia

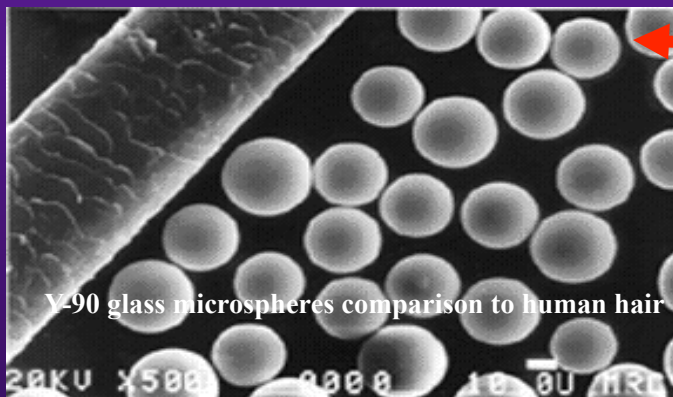
radiation

Radioembolization

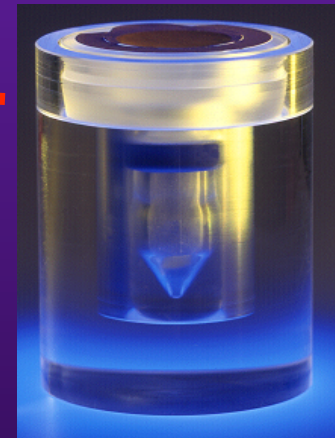
Source: Bilbao, JI. Interventional Radiologist, Pamplona, Spain

Y-90 TheraSphere®

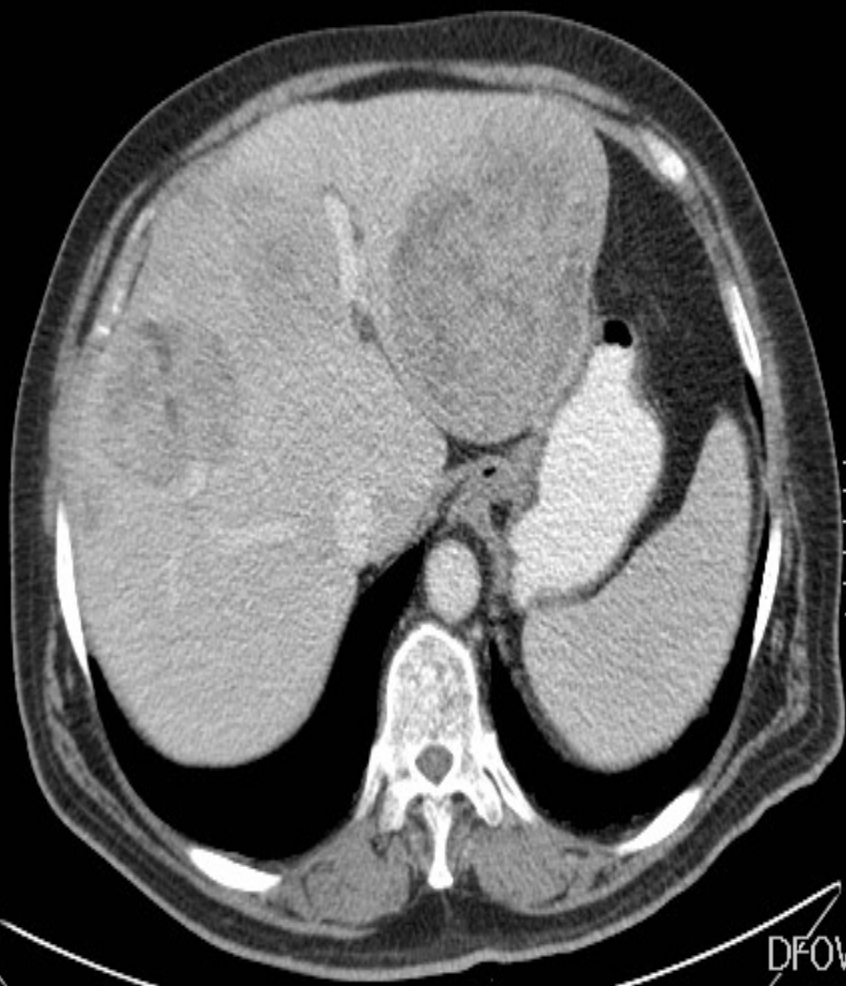
- ◆ Powerful, well-tolerated yttrium-90 glass microspheres therapy for transarterial radioembolization (TARE) in liver neoplasia including HCC with or without PVT
- ◆ Delivers high-dose radiation inside the liver tumor while minimizing exposure to normal liver parenchyma
- ◆ 20-30 μm glass microspheres
 - ◆ Y-90 is an integral constituent of the glass matrix



TheraSphere dose vial



R
2
3
2



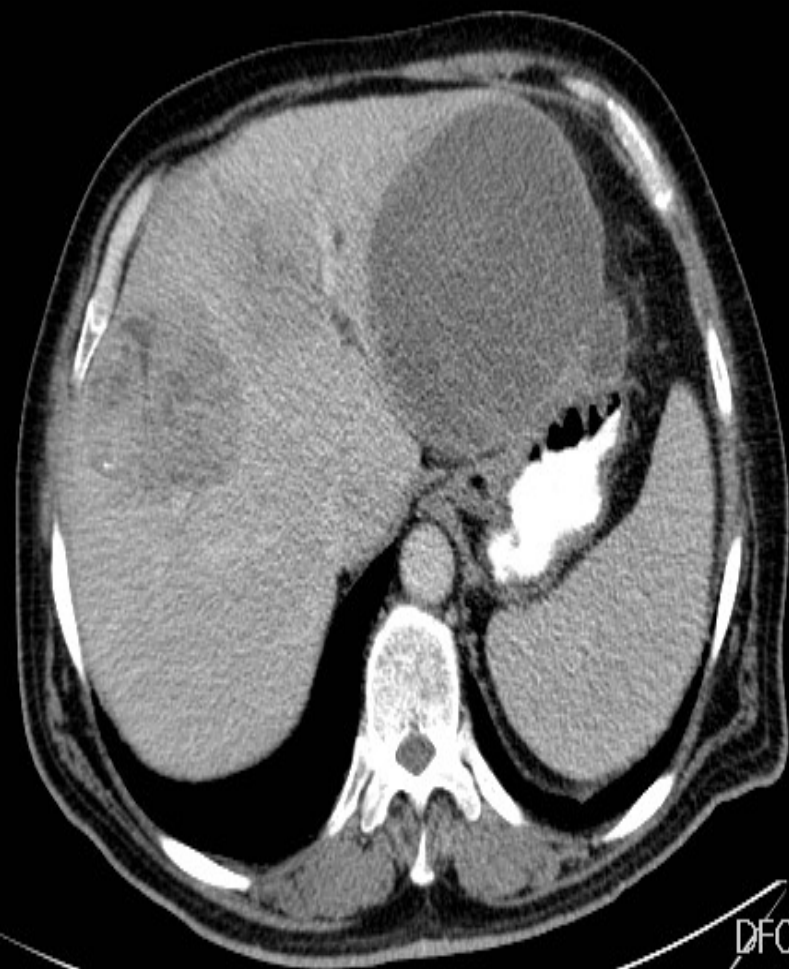
R
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DFOV4
TIL1
SE
390
01/06/2014
5m

09/10/2013

P382

L
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6



DFOV455
TILT:0
SE:3
283.2
5mm

P369

Some Key Points: I



➤ Although the ultimate goal is always cure, when that is not possible, the treatments should **NOT** be worse than the disease

➤ If disease is not progressing, a treatment cannot make it progress any slower: some patients can be monitored for years without needing any specific treatment, others need more urgent treatment

Some Key Points: II

➤ **All treatments are potentially helpful in different sequences depending on:**



the type of NET

the pace of progression

whether there is a hormonal syndrome

where the disease is located

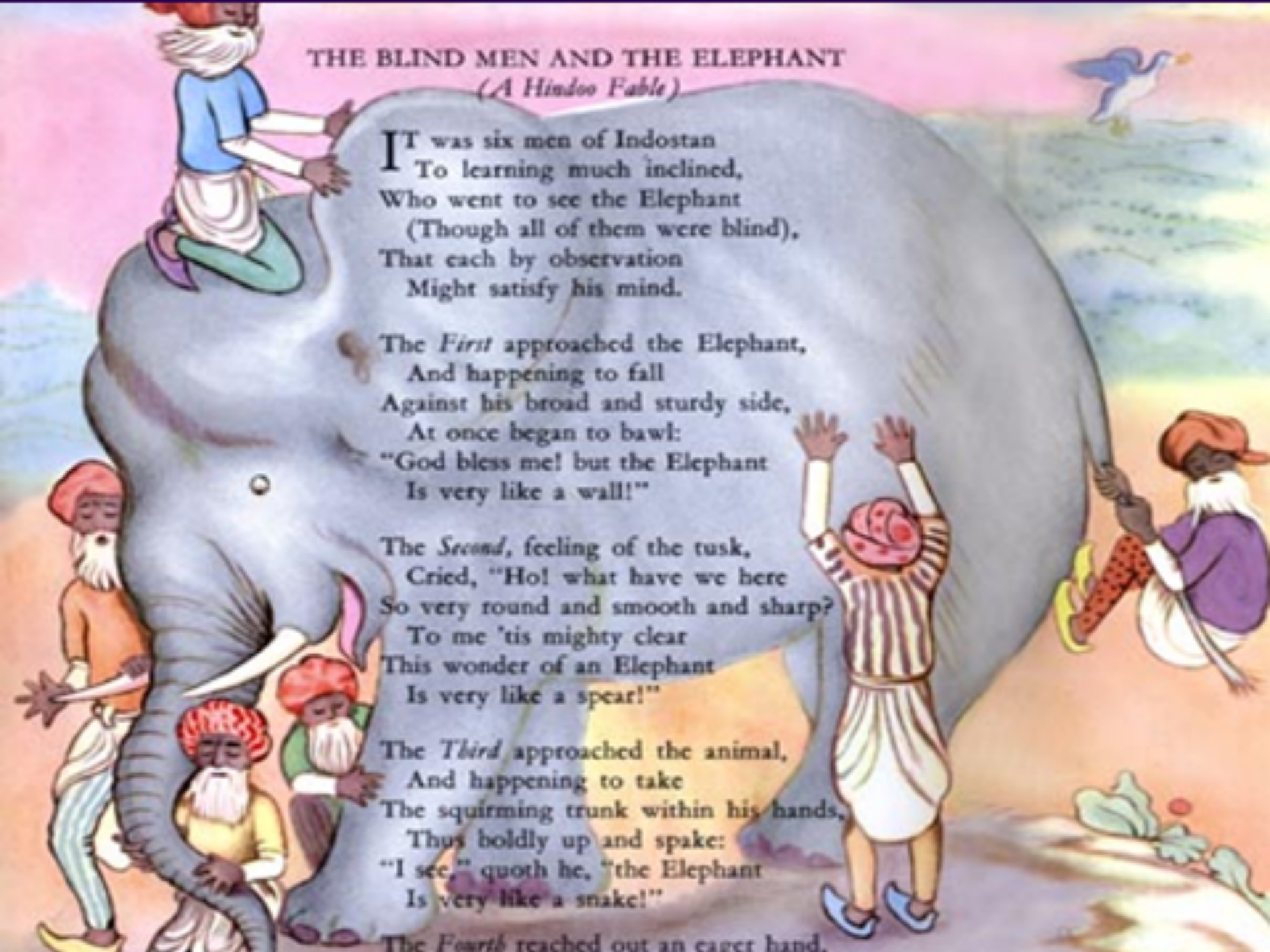
whether the cells take up radioisotopes

the age and health of the patient



Some Key Points: III

- ◆ **All NET patients benefit from, and deserve, monitoring and treatment from an experienced team that communicates with each other and works well together.**
- ◆ **The past 10 years have seen an explosion of interest and research in NETS.**
- ◆ **The future promises ongoing progress**

An illustration of the parable of the blind men and an elephant. A large grey elephant is the central focus. A man in a blue shirt and white dhoti is kneeling on its back, touching its side. Another man in a purple shirt and white dhoti is touching its side from the right. A man in a striped shirt and white dhoti is touching its side from the front. A man in an orange shirt and white dhoti is touching its trunk. A man in a yellow shirt and white dhoti is touching its trunk. A man in a green shirt and white dhoti is touching its trunk. The background shows a landscape with a blue sky, a white bird flying, and a body of water. The text is written in a serif font, with the first letter of the first paragraph being large and bold.

THE BLIND MEN AND THE ELEPHANT
(A Hindoo Fable)

IT WAS six men of Indostan
To learning much inclined,
Who went to see the Elephant
(Though all of them were blind),
That each by observation
Might satisfy his mind.

The *First* approached the Elephant,
And happening to fall
Against his broad and sturdy side,
At once began to bawl:
"God bless me! but the Elephant
Is very like a wall!"

The *Second*, feeling of the tusk,
Cried, "Ho! what have we here
So very round and smooth and sharp?
To me 'tis mighty clear
This wonder of an Elephant
Is very like a spear!"

The *Third* approached the animal,
And happening to take
The squirming trunk within his hands,
Thus boldly up and spake:
"I see," quoth he, "the Elephant
Is very like a snake!"

The *Fourth* reached out an eager hand,

TEAMWORK

