

La terapia farmacologica dei NET, stato dell'arte e prospettive

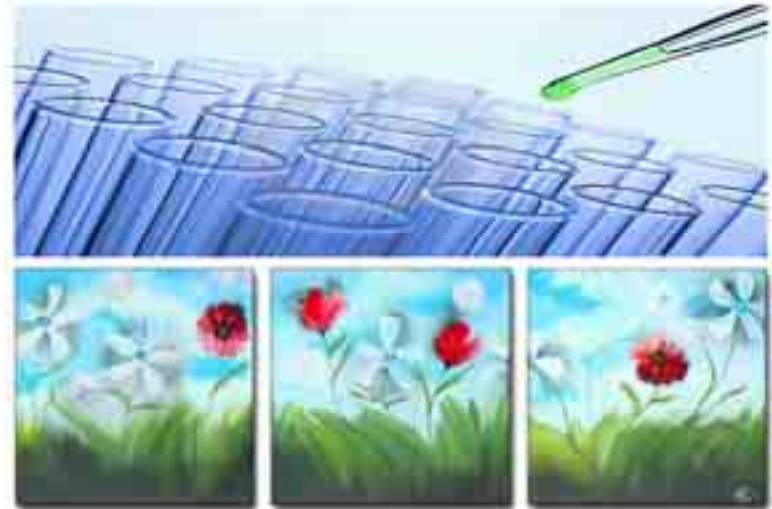
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Orbassano



Dipartimento Rete Oncologia del Piemonte
e della Valle d'Aosta

Incontro del GIC
Tumori rari
G.I.S.T. e N.E.T.



Torino, 15 novembre 2011

Aula Infermotti - AOU San Giovanni Battista Torino
Presidio San Giovanni Antica Sede
Via Cavot 31

Coordinatori: Dott. Oscar Berfatto e Dott.ssa Mirca Viale

Tumori neuroendocrini: 2009-2011 una svolta!!

Studi randomizzati possibili

Dimostrazione di efficacia di vecchi farmaci
(analoghi della Somatostatina)

Nuovi farmaci entreranno nell'armamentario
terapeutico

Placebo-Controlled, Double-Blind, Prospective,
Randomized Study on the Effect of Octreotide LAR in the
Control of Tumor Growth in Patients With Metastatic
Neuroendocrine Midgut Tumors: A Report From the
PROMID Study Group

*Arja Rinke, Hans-Helge Müllet, Carmen Schade-Brittinger, Klaus-Jochen Klase, Peter Borth, Matthias Wied,
Christina Mayer, Behnaz Aminossadati, Ulrich-Frank Pape, Michael Bläker, Jan Harder, Christian Arnold,
Thomas Gress, and Jüldolf Arnold*

Randomized, double-blind, placebo-controlled Phase IIb
18 Centers in Germany from 2001 to 2008
85 patients treated from a planned 162

Planned interim analysis

Based on 67 tumor progression and 16 deaths
Log rank test, planned group sequential analysis
at p level of 0.0122

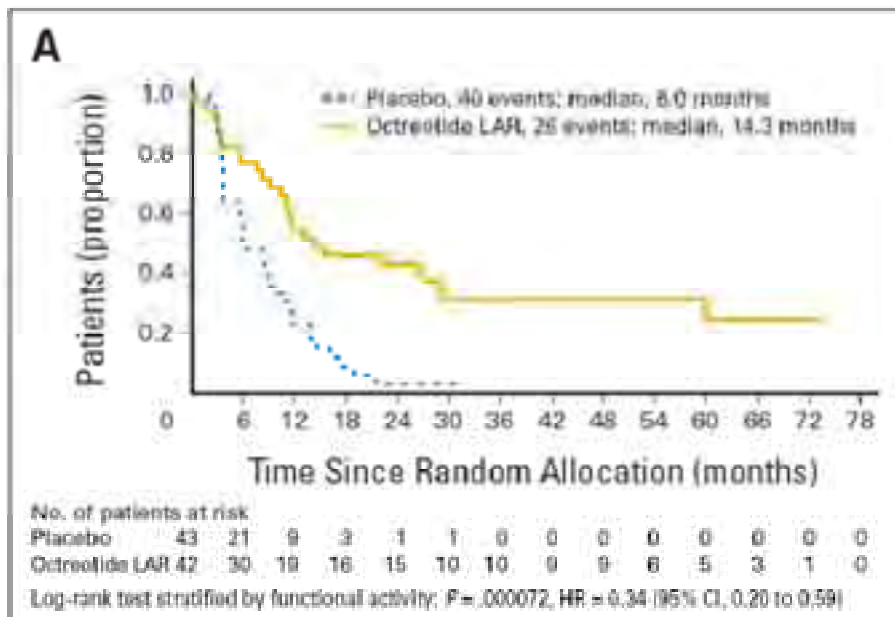
J Clin Oncol 27:4656-4663, 2009.

Octreotide LAR Achieved Superior Tumor Response at 6 Months (WHO)

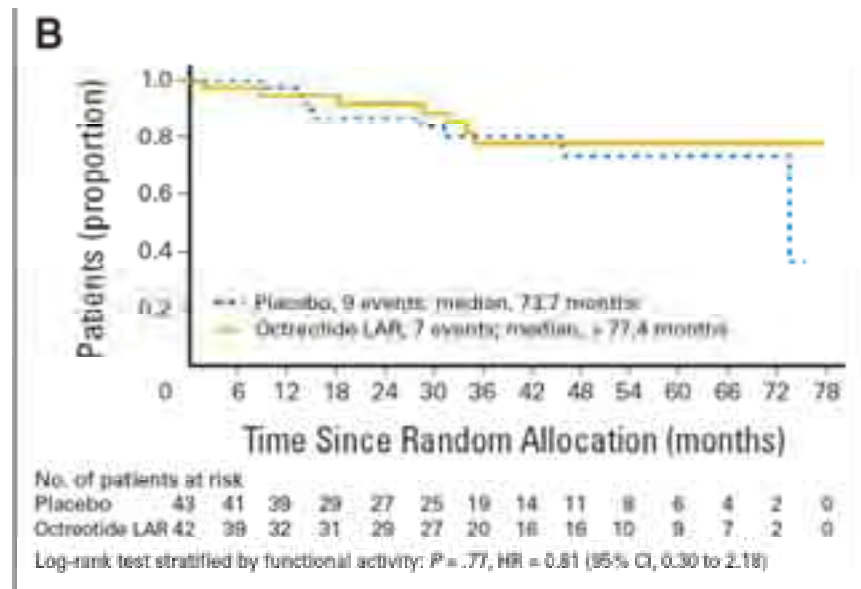
	Octreotide LAR (n=42)	Placebo (n=43)
Complete response (n)	0	0
Partial response (n)	1	1
Stable disease (n)	28	16
Progressive disease (n)	10	23
Unknown (n)	3	3

Wilcoxon-Mann-Whitney: $P=0.0079$

Time to progression

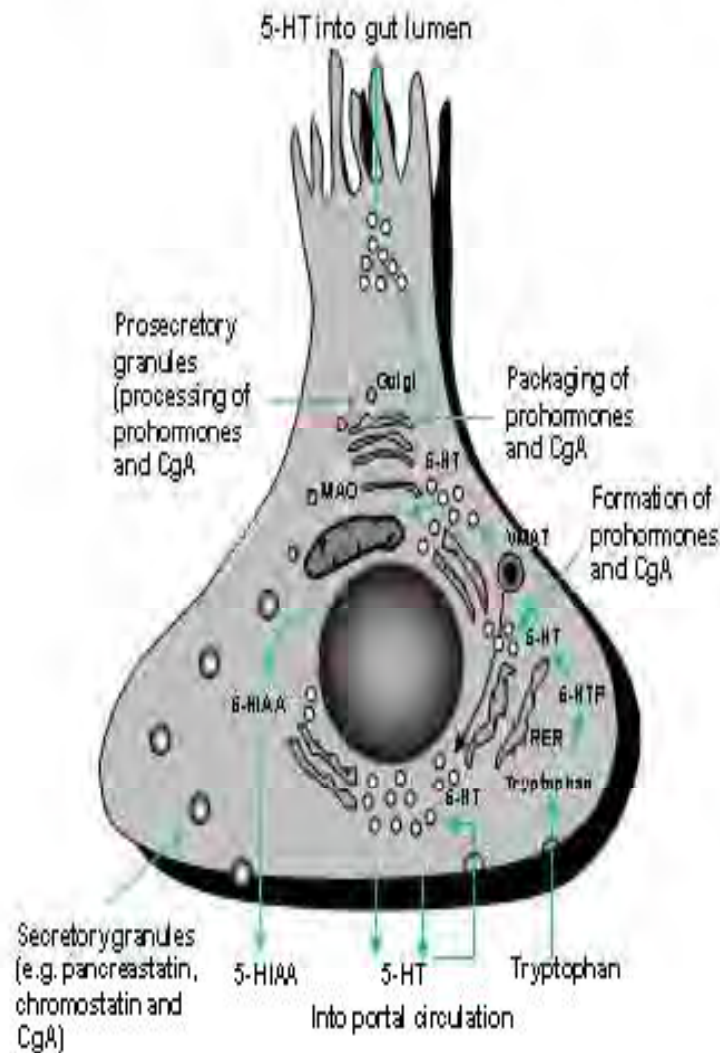


Overall Survival



Rinke A et al J Clin Oncol 27:4656-4663, 2009.

The neuroendocrine cell



Molecular targets in neuroendocrine cells

PDGFRa

bFGF

PDGFRβ

IGF-1

C-kit

TGFa

EGFR

VEGF

HIF-1a

HIF-2a

CA9

CD34

Met

SCF

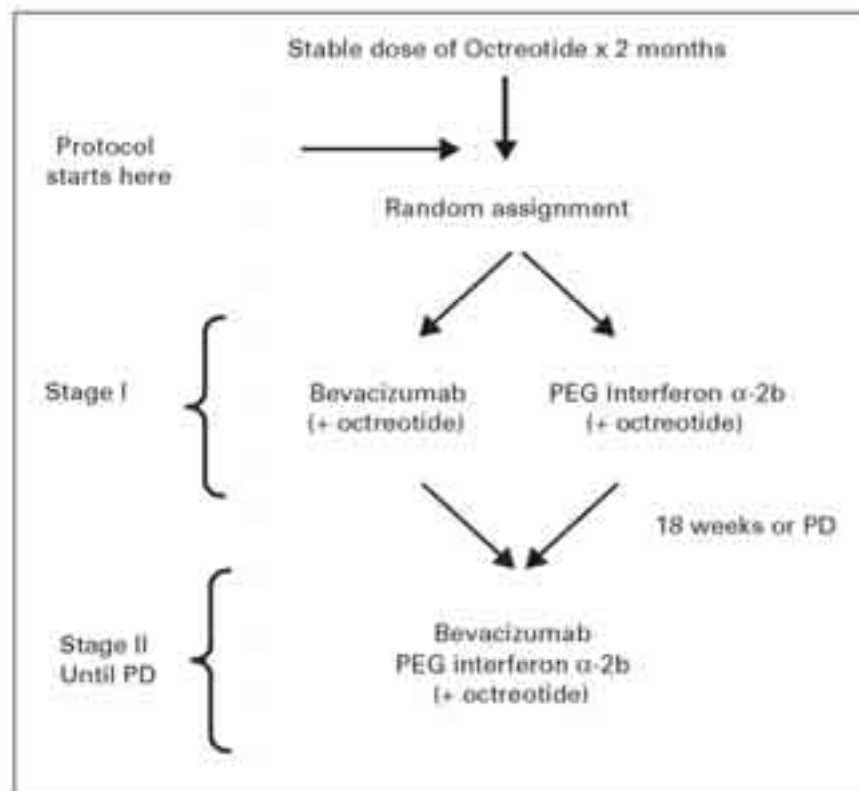
mTOR

aFGF

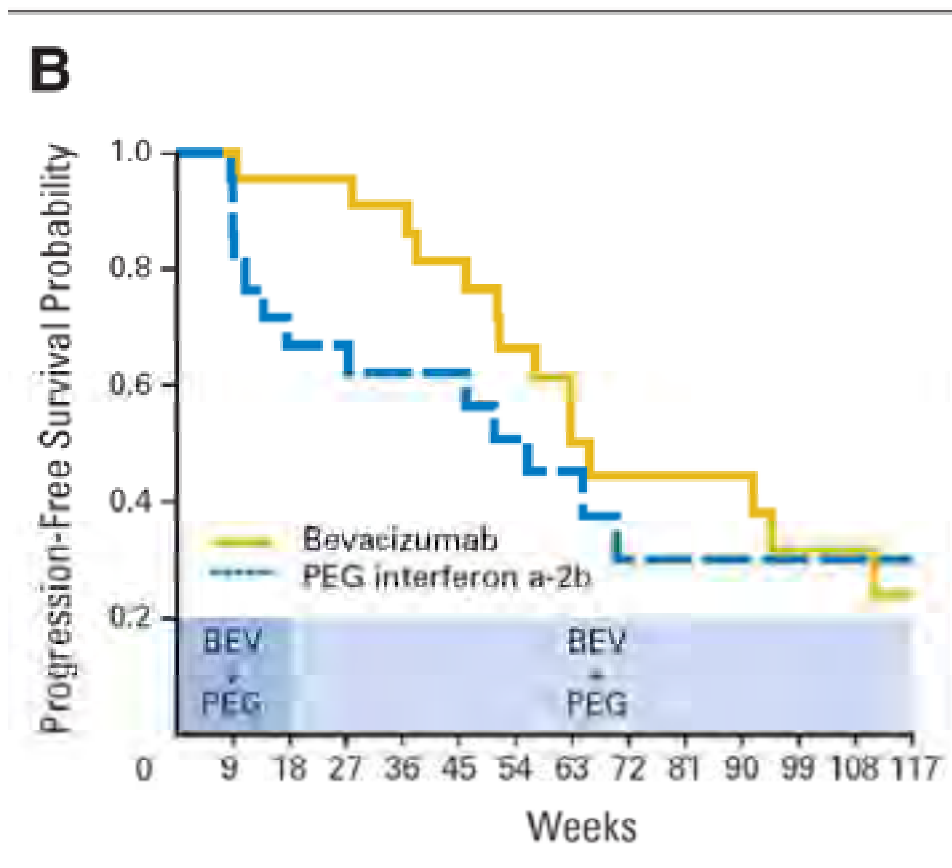
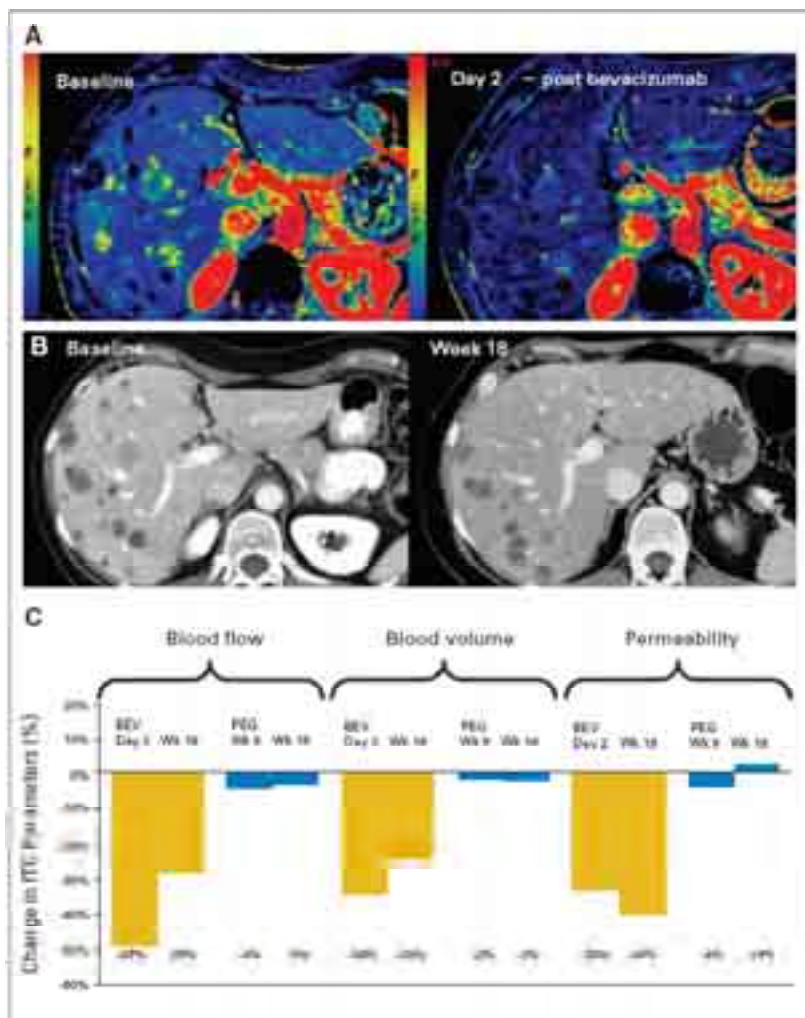
Targeting Vascular Endothelial Growth Factor in Advanced Carcinoid Tumor: A Random Assignment Phase II Study of Depot Octreotide With Bevacizumab and Pegylated Interferon Alfa-2b

James C. Yao, Alexandra Phan, Paulo M. Hoff, Helen X. Chen, Chun-P. Charnungorn, Sai-Ching J. Yung, Kenneth Heis, Chuan Ng, James L. Abbruzzese, and Jaffer A. Ajani

J Clin Oncol 26:1316-1323, 2008.



	Beva 22 pts	IFN 22 pts
RP	4 (18%)	0 (0%)
SD	17 (77%)	15 (68%)
PD	1 (5%)	6 (27%)



Yao J et al J Clin Oncol 26:1316-1323, 2008.

The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

FEBRUARY 10, 2011

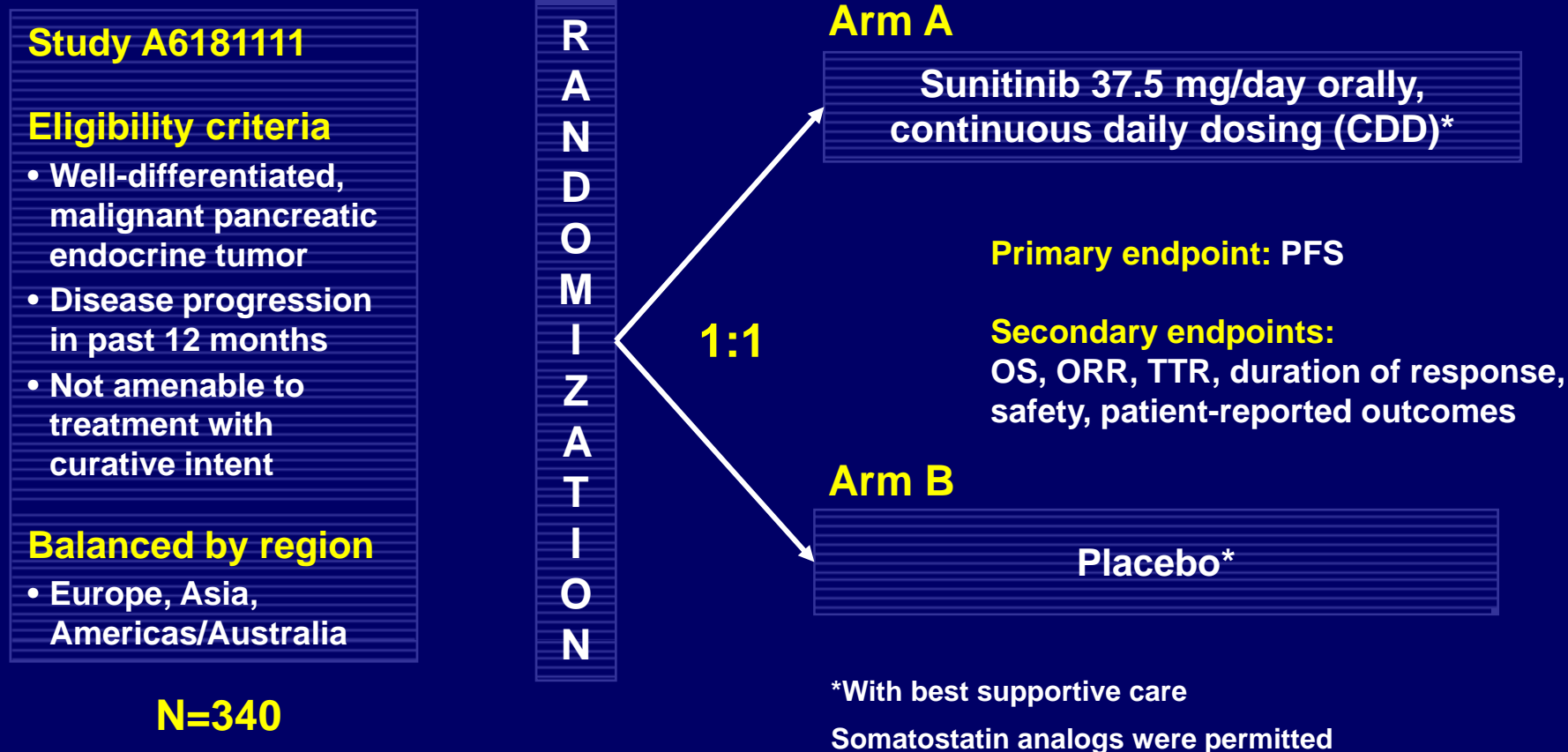
VOL. 364 501-5

Sunitinib Malate for the Treatment of Pancreatic Neuroendocrine Tumors

Eric Raymond, M.D., Ph.D., Laetitia Dahan, M.D., Ph.D., Jean-Luc Raoul, M.D., Ph.D., Yung-Jue Bang, M.D.,
Ivan Borbath, M.D., Ph.D., Catherine Lombard-Bohas, M.D., Juan Valle, M.D., Peter Metrakos, M.D., C.M.,
Denis Smith, M.D., Aaron Vinik, M.D., Ph.D., Jen-Shi Chen, M.D., Dieter Horsch, M.D.,
Pascal Hammel, M.D., Ph.D., Bertram Wiedenmann, M.D., Ph.D., Eric Van Cutsem, M.D., Ph.D.,
Shen Patyna, Ph.D., Dongrui Ray Lu, M.Sc., Carolyn Blanckmeister, Ph.D., Richard Chao, M.D.,
and Philippe Ruszniewski, M.D.

N Engl J Med 2011;364:501-13.

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



Previous experience with sunitinib daily dosing:

1. Escudier B, et al. *J Clin Oncol* 2009;27:4068–75;
2. George S, et al. *Eur J Cancer* 2009;45:1959–68
3. Barrios CH, et al. *Eur J Cancer Suppl* 2009;7:429

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

RADIANT-3 Study Design

Phase III Double Blind Placebo Controlled Trial

**Patients with
advanced pNET,
N = 410**

Stratified by:

- *WHO PS*
- *Prior
Chemotherapy*

**R
A
N
D
O
M
I
Z
E**

1:1

**Everolimus 10 mg/d +
best supportive care*
n = 207**

Crossover



**Placebo +
best supportive care*
n = 203**

**Treatment
until disease
progression**

Multi-phasic CT or MRI performed every 12 weeks

Primary endpoint:

- PFS (RECIST)

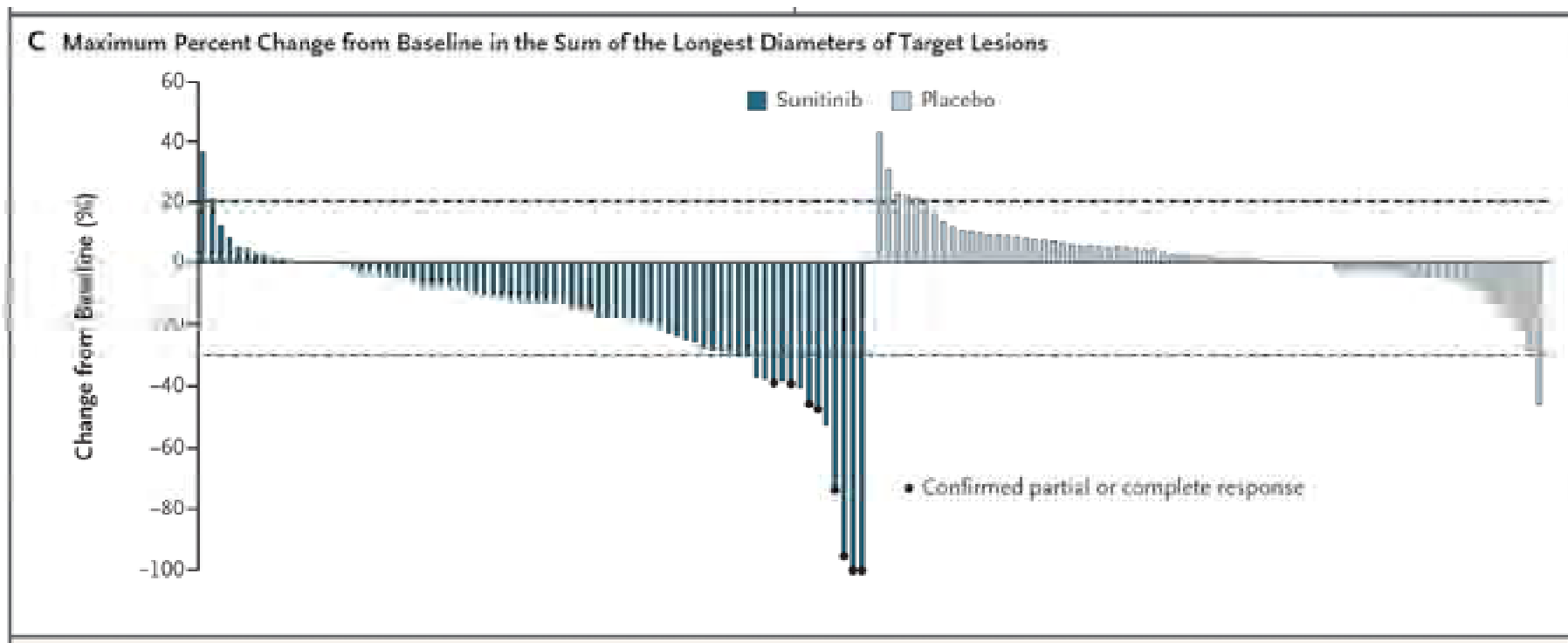
Secondary endpoints:

- Response, OS, biomarkers, safety, and PK

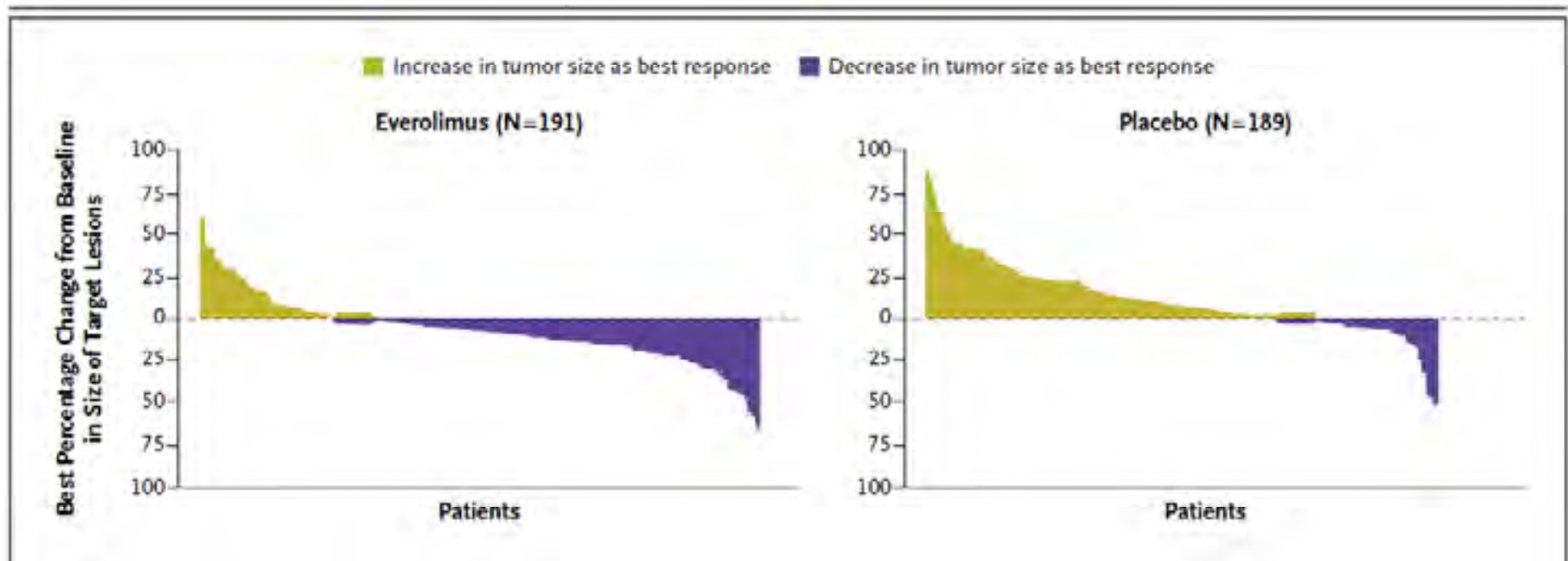
* Concurrent somatostatin analogs allowed

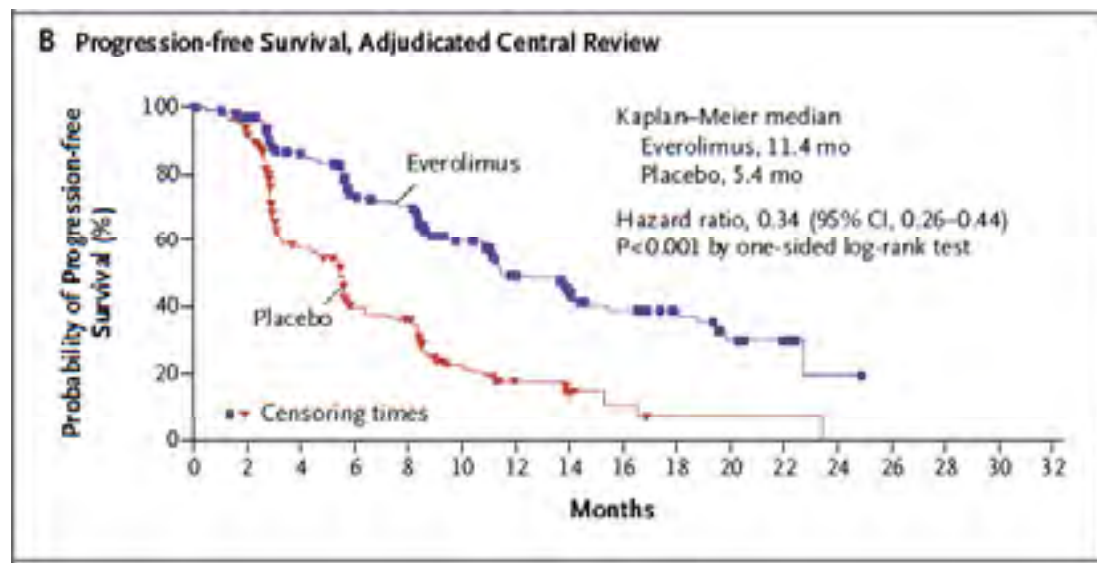
Randomization August 2007 - May 2009

Sunitinib activity

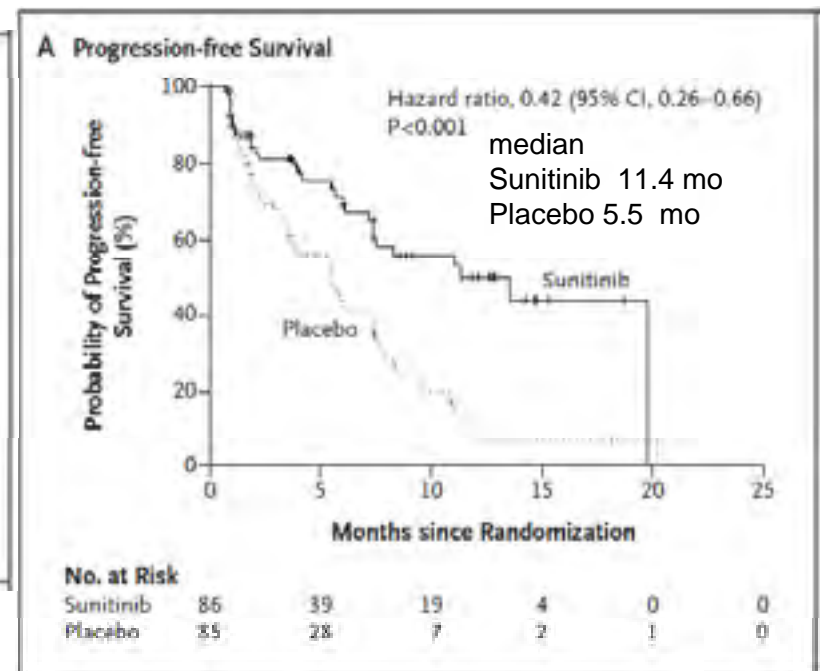


Everolimus activity



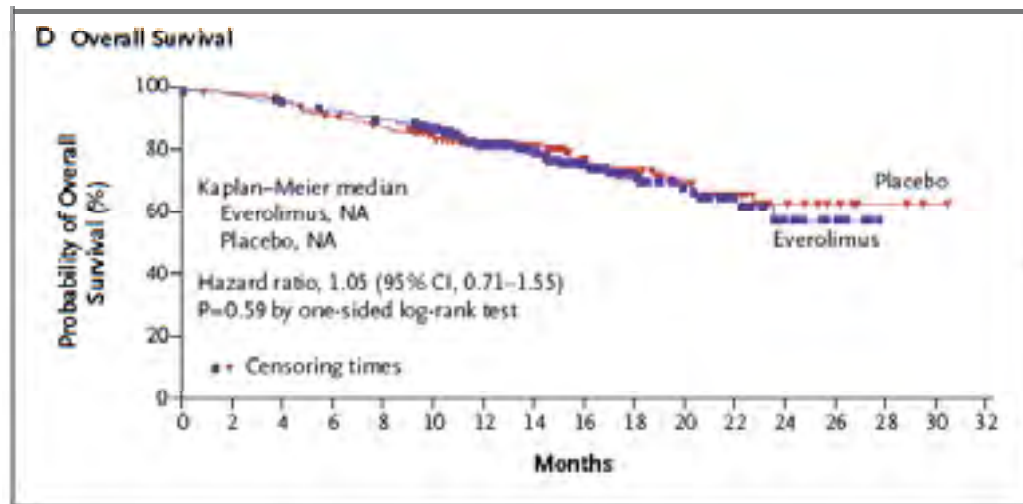


Everolimus

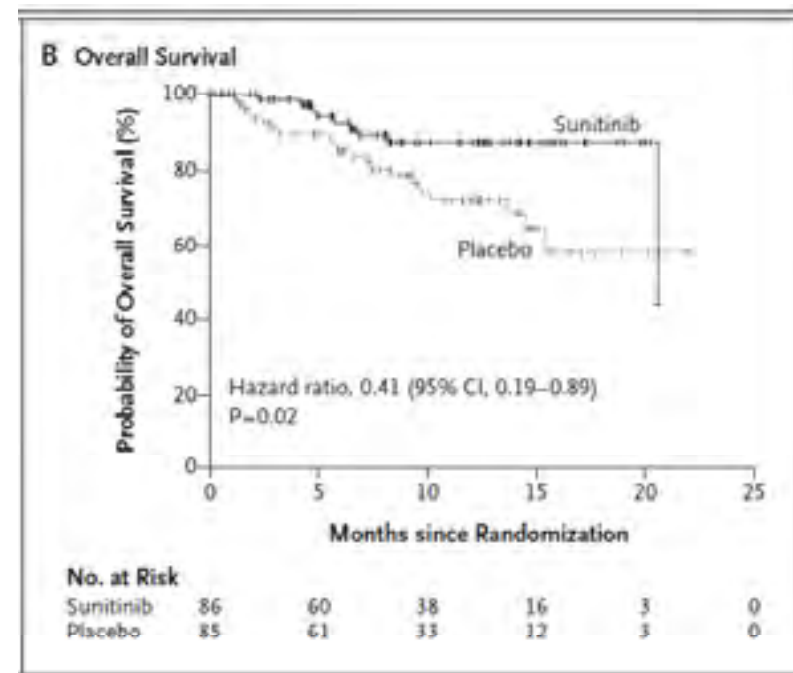


Sunitinib

OVERALL SURVIVAL



Everolimus



Sunitinib

NET PANCREATICI

Everolimus o Sunitinib?

Carcinoma NE del pancreas: quale target therapy?

Insulinoma → Everolimus

Glucagonoma → Sunitinib?

Carcinoma NE del pancreas quesiti aperti

Sunitinib ed everolimus quale sequenza?

E la combinazione?

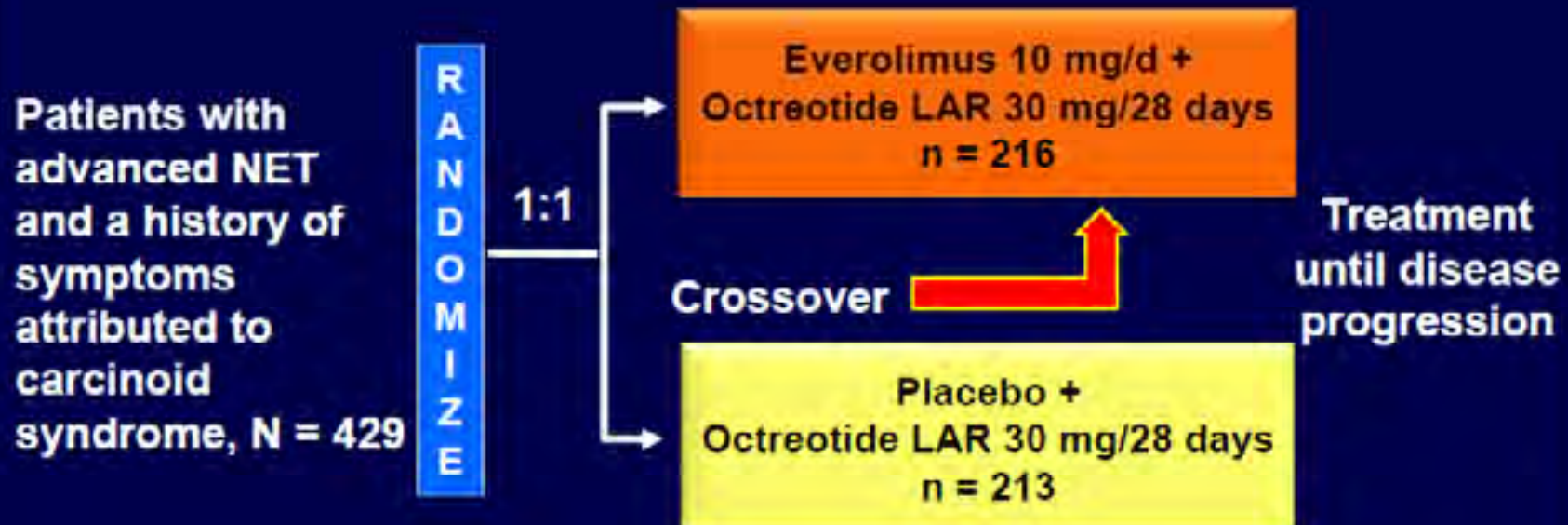
Randomized, Phase III Trial of Everolimus + Octreotide LAR vs Placebo + Octreotide LAR in Patients with Advanced Neuroendocrine Tumours (NET) (RADIANT-2)

Marianne Pavel¹, John Hainsworth²,
Eric Baudin³, Marc Peeters⁴, Dieter Hoersch⁵,
Lowell Anthony⁶, Sakina Hoosen⁷, Jessica St Peter⁷,
Valentine Jehl⁸, and James Yao⁹
for the RADIANT-2 Study Group

¹Charité-Universitätsmedizin Berlin/Campus Virchow Klinikum, Berlin, Germany; ²Sarah Cannon Cancer Center, Nashville, TN, USA; ³Oncologie Endocrinienne et Médecine Nucléaire, Institut Gustave Roussy, Villejuif, France; ⁴Department of Oncology, Antwerp University Hospital, Edegem, Belgium; ⁵Klinik für Innere Medizin, Gastroenterologie und Endokrinologie, Zentralklinik Bad Berka GmbH, Bad Berka, Germany; ⁶Ochsner Kenner Medical Center, Kenner, LA, USA; ⁷Novartis Oncology, Florham Park, NJ, USA; ⁸Novartis Pharma, Basel, Switzerland; ⁹M. D. Anderson Cancer Center, Houston, TX, USA

RADIANT-2 Study Design

Phase III Double Blind Placebo Controlled Trial



Multi-phasic CT or MRI performed every 12 weeks

Primary endpoint:

- PFS (RECIST)

Secondary endpoints:

- Tumour response, OS, biomarkers, safety, PK

Enrollment January 2007 - March 2008

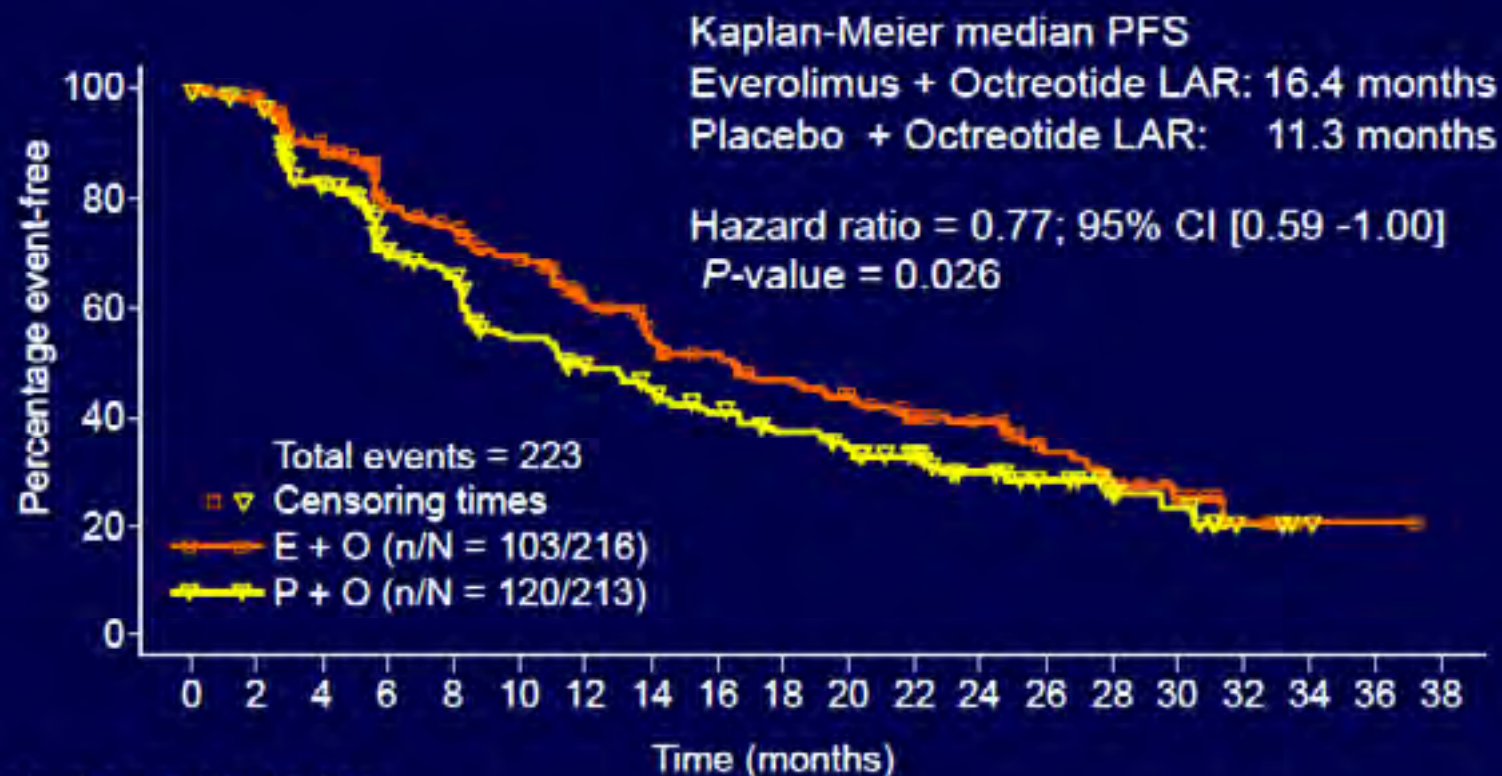
Baseline Characteristics

	Everolimus + Oct LAR N = 216, %	Placebo + Oct LAR N = 213, %
Median age, years (range)	60 (22-83)	60 (27-81)
Male	45	58
Female	55	42
WHO Performance Status		
0	55	66
1 / 2*	39 / 6	29 / 5
Primary site		
Small intestine	51	53
Lung*	15	5
Colon	7	7
Pancreas	5	7
Liver	3	5

***Statistically significant for imbalance, $P < 0.05$**

*One missing PS in placebo arm
Oct LAR= Octreotide LAR

PFS by Central Review*



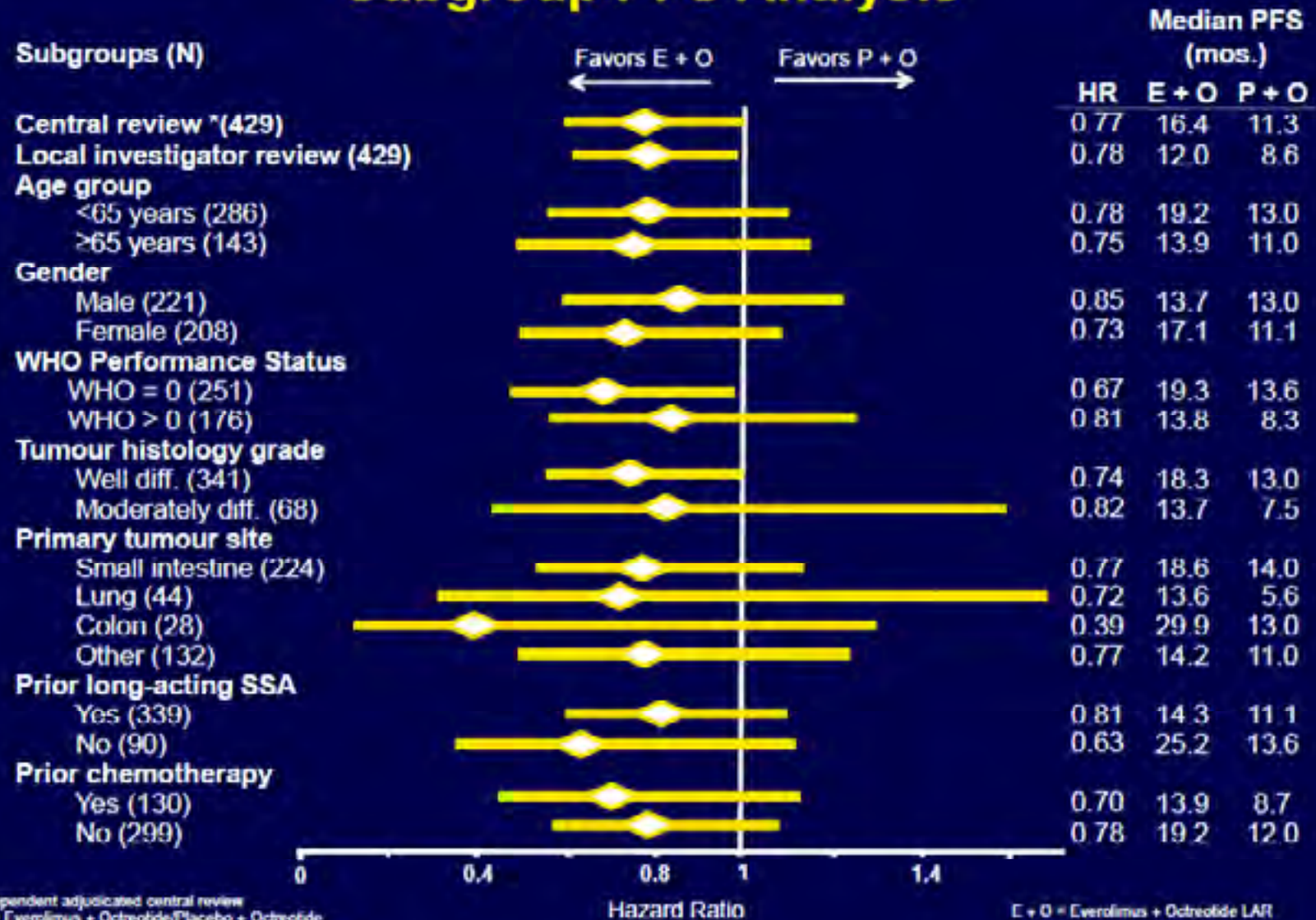
No. of patients still at risk

E + O	216	202	167	129	120	102	81	69	63	56	50	42	33	22	17	11	4	1	1	0
P + O	213	202	155	117	106	84	72	65	57	50	42	35	24	18	11	9	3	1	0	0

- * Independent adjudicated central review committee
- P-value is obtained from the one-sided log rank test
- Hazard ratio is obtained from unadjusted Cox model

E + O = Everolimus + Octreotide LAR
 P + O = Placebo + Octreotide LAR

Subgroup PFS Analysis



Prospettive future

Quale ruolo della radioterapia metabolica?

Quale integrazione con i nuovi farmaci?

Quale sequenza ottimale dei farmaci registrati?

E la chemioterapia metronomica?

Come attrarre nuovi farmaci sperimentali?