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MEDICAL TREATMENT OF LUNG NET

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LUNG NET CLASSIFICATION

Typical carcinoid **G 1**

A tumour with carcinoid morpho[illegible]ss lacking necrosis and 0.5cm or larger

Well differenziated tumors

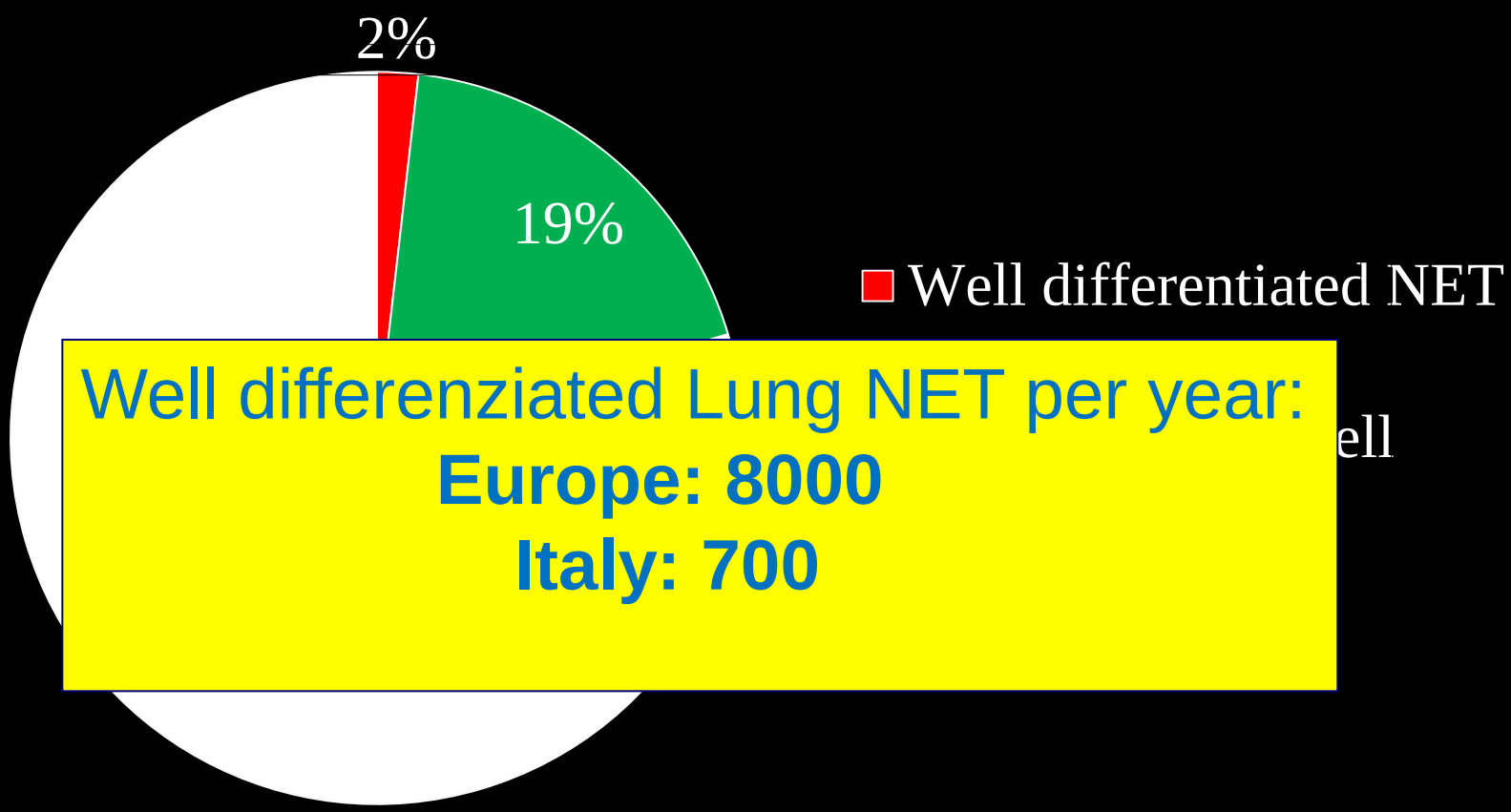
Atypical carcinoid **G 2**

A tumour with carcinoid morphology with 2-10 mitoses per $2mm^2$ (10 HPF), OR necrosis (often punctate)

Large cell neuroendocrine carcinoma **G 3**

1. A tumour with a neuroendocrine morphology (organoid nesting, palisading, rosettes, trabeculae)
2. High mitotic rate: 11 or greater per $2mm^2$ (10 HPF), median of 70 per $2mm^2$ (10 HPF)
3. Necrosis (often large zones)
4. Cytologic features of a non-small carcinoma (NSCLC): large cell size, low nuclear to cytoplasmic ratio, vesicular, coarse or fene chromatic, and/or frequent nucleoli. Some tumours have fine nuclear chromatin and lack nucleolo, but quality as NSCLC because of large cell size and abundant cytoplasm
5. Positive immunohistochemical staining for one or more NE markers (other than neuron specific enolase) and /or NE granules by electron microscopy.

Lung cancer in the United States (SEER)



Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence – SEER Regs Research Data, Nov 2011 Sub (1973-2009) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2010 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2012, based on the November 2011 submission

AIOT GUIDELINES

LINEA GUIDA PER LA GESTIONE INTEGRATA
DEL PAZIENTE CON TUMORE POLMONARE

FREE download from www.oncologiatoracica.it

CHEMOTHERAPY

Chemotherapy for advanced G1-G2 NET (including lung)

Author	Schedule (n. pts)	Response
Walter T, et al. Clin Colorectal Cancer 2010 (retrospective)	5FU+EDX+DTIC (n=39)	PR 44 %
Bajetta E et al. Cancer Chem Pharmacol 2007	XELOX (n=27)	SD 30 %
Fine RL et al. Cancer Chemother Pharmacol 2013	CAPE+TMZ (n=15)	PR 61 % PFS 14 months
Kulke MH et al. J Clin Oncol 2006	TMZ + THAL (n=21)	RP 25 % MDR 13.5 months
Eklebad S et al. Clin Cancer Res 2007 (retrospective)	TMZ (n=21)	PR 14 % PFS 7 months
Chong CR et al, Lung Cancer, 2014 (retriospective)	CDDP+VP-16 (n=13)	PR 23% PFS 7months

Chemotherapy for advanced large cells neuroendocrine lung carcinoma (G3)

Author	Schedule (n. pts)	Response
Igawa S et al. Lung Cancer 2010 (retrospective)	DDP-based CT or VNR or CPT-11 or TXT alone (n=14)	PR 50 %
Nakano K et al. Jpn J Clin Oncol 2010 (retrospective)	CDDP+CPT-11 (n=44)	PR 50 %
Fujiwara Y et al. Jpn J Clin Oncol 2007 (retrospective)	DDP+VP-16 or CPT-11 or VNR or TAX or TXT (n=22)	PR 59.1 %
Sun JM et al. Lung Cancer 2012 (retrospective)	DDP-based CT (n=34)	RP 50 % PFS 4.9 months MST 9.2 months
Le Treut Jet al. Ann Oncol 2013	CCDP+VP-16 (n=42)	PR 38 % PFS 5.2 months MST 7.7 months

1-LINE CHEMOTHERAPY IN ADVANCED DISEASE

- 1-LINE CHEMOTHERAPY CAN BE CONSIDERED IN TYPICAL (G1) AND ATYPICAL (G2) CARCINOIDS IF NO OTHER TREATMENT AVAILABLE

- 1-LINE CHEMOTHERAPY IS RECOMMENDED IN LARGE CELLS NEUROENDOCRINE CARCINOMA (G3)

- THERE IS NO STANDARD REGIMEN (USUALLY USED CIS or CARBO + VP-16)

IS THERE A ROLE FOR ADJUVANT CHEMOTHERAPY ?

- NO ROLE FOR ADJUVANT CHEMOTHERAPY IN TYPICAL (G1) AND ATYPICAL (G2) CARCINOIDS

- ADJUVANT CHEMOTHERAPY WITH CIS or CARBO+VP-16 CAN BE CONSIDERED IN STAGE II-III LARGE CELLS NEUROENDOCRINE CARCINOMA (G3)

SOMATOSTATIN ANALOGS (SSA)

Antiproliferative effect of octeotride in GEP-NET

Author	Schedule	Response
Saltz L, et al. Cancer 1993	Octreotide sc 250 µg tid (n=34)	SD 50% (duration 2-27 months)
Arnold R, et al. Gut 1996	Octreotide sc 200 µg tid (n=52)	SD 36,5% (duration 3-36 months)
Arnold R, et al. Clin Gastroenterol Hepatol 2005	Octreotide sc 200 µg tid (n=51) *or* Octreotide sc 200 µg tid + alpha interferon 4.5 x 10^6 IU 3 times /week (n=54)	No statistically difference SD o RP : • 44,8% lasting 3 months • 27,6% lasting 6 months • 15,2% lasting12 months
Bajetta E, et al. Ann Oncol 2005	Octreotide LAR 30 mg/28 days (n=31)	SD 52% lasting ≥6 mesi in 95% of cases; RP 6%
Butturini G, et al. Endocr Relat Cancer 2006	Octreotide LAR 20 mg/28 days (n=21)	SD 38% (median duration time 49,5 months)

VOLUME 27 · NUMBER 28 · OCTOBER 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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

Anja Rinke, Hans-Helge Müller, Carmen Schade-Brittinger, Klaus-Jochen Klose, Peter Barth, Matthias Wied, Christina Mayer, Behnaz Aminossadati, Ulrich-Frank Pape, Michael Bläker, Jan Harder, Christian Arnold, Thomas Gress, and Rudolf Arnold

Symptomatic Response

Ten and 12 patients had ≥ one flushing episodes per week at random assignment in the octreotide LAR and placebo groups, respectively. At 6 months, seven octreotide LAR recipients and three placebo recipients had less than one flushing episode per week. Of the six octreotide LAR and seven placebo recipients with diarrhea ≥ four times a day at random assignment, two patients and one patient, respectively, experienced a reduction in diarrhea frequency (Table 4).

Biochemical Response

At random assignment, CgA was elevated in 26 of 41 octreotide LAR recipients and 30 of 42 placebo recipients; at 6 months, normalization of elevated CgA levels was observed in nine and four recipients, respectively (Table 4).

WHO Response

Tumor progression 6 months after random assignment occurred in 10 of 42 octreotide LAR recipients and 23 of 43 placebo recipients. Stable disease was observed in 28 of 42 and 16 of 43 octreotide LAR and placebo recipients, respectively. Only one partial remission was seen in either group. No complete response occurred. In six of 85 patients, tumor response was unknown. Comparison by the Wilcoxon-Mann-Whitney test showed a difference in favor of octreotide LAR ($P = .0079$).

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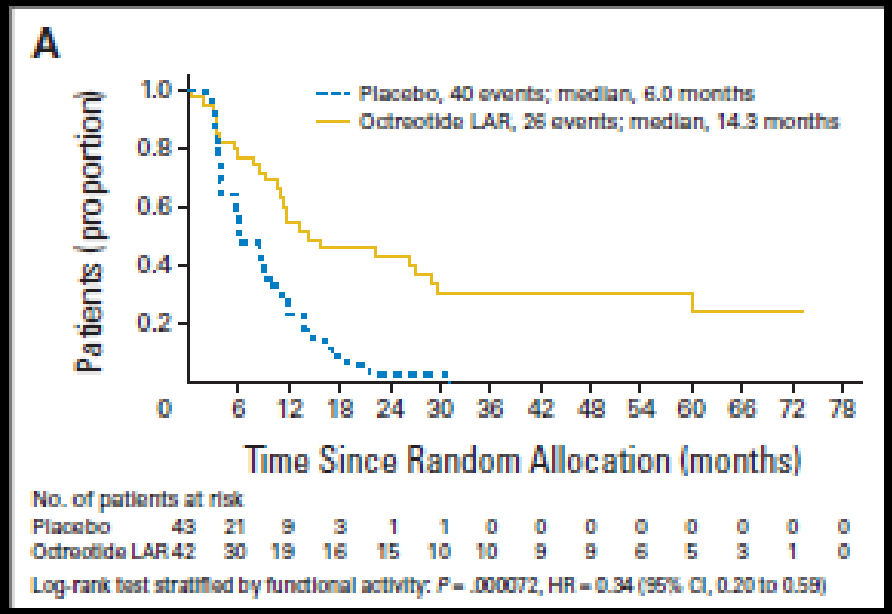
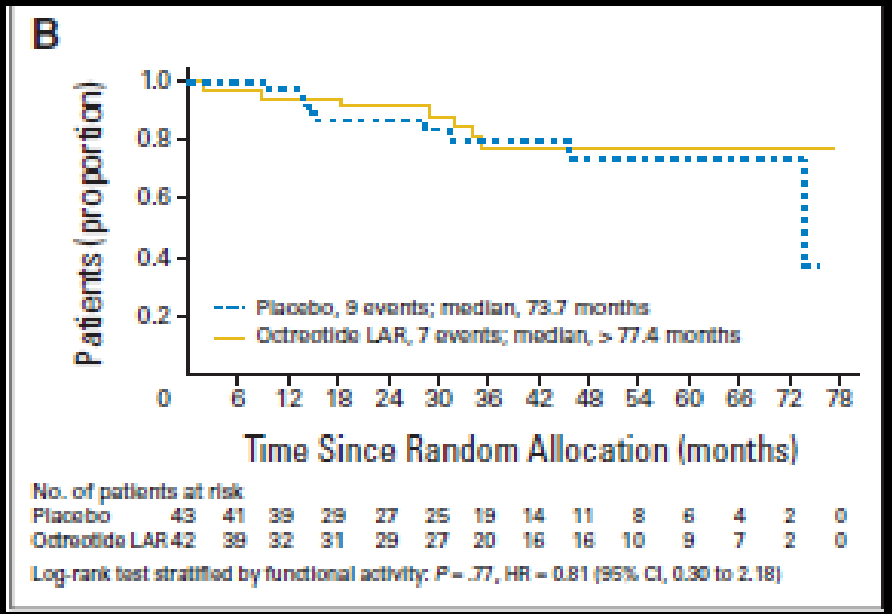




Conclusion
Octreotide LAR significantly lengthens time to tumor progression compared with placebo in patients with functionally active and inactive metastatic midgut NETs. Because of the low number of observed deaths, survival analysis was not confirmatory.

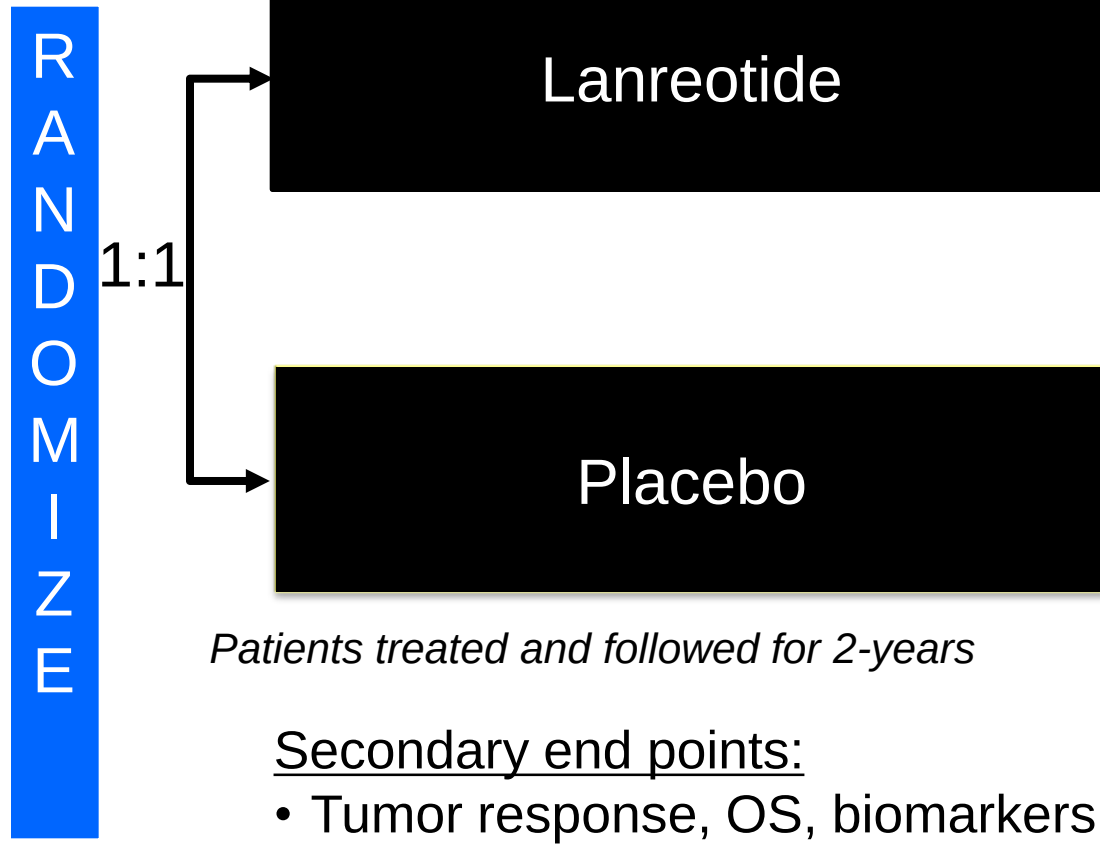
Clarinet: Lanreotide vs Placebo

Phase III, Double-Blind, Placebo-Controlled Trial

Non-functional advanced **GEP NET**

Stratified by progression status during 3 month observation period

(N=200)



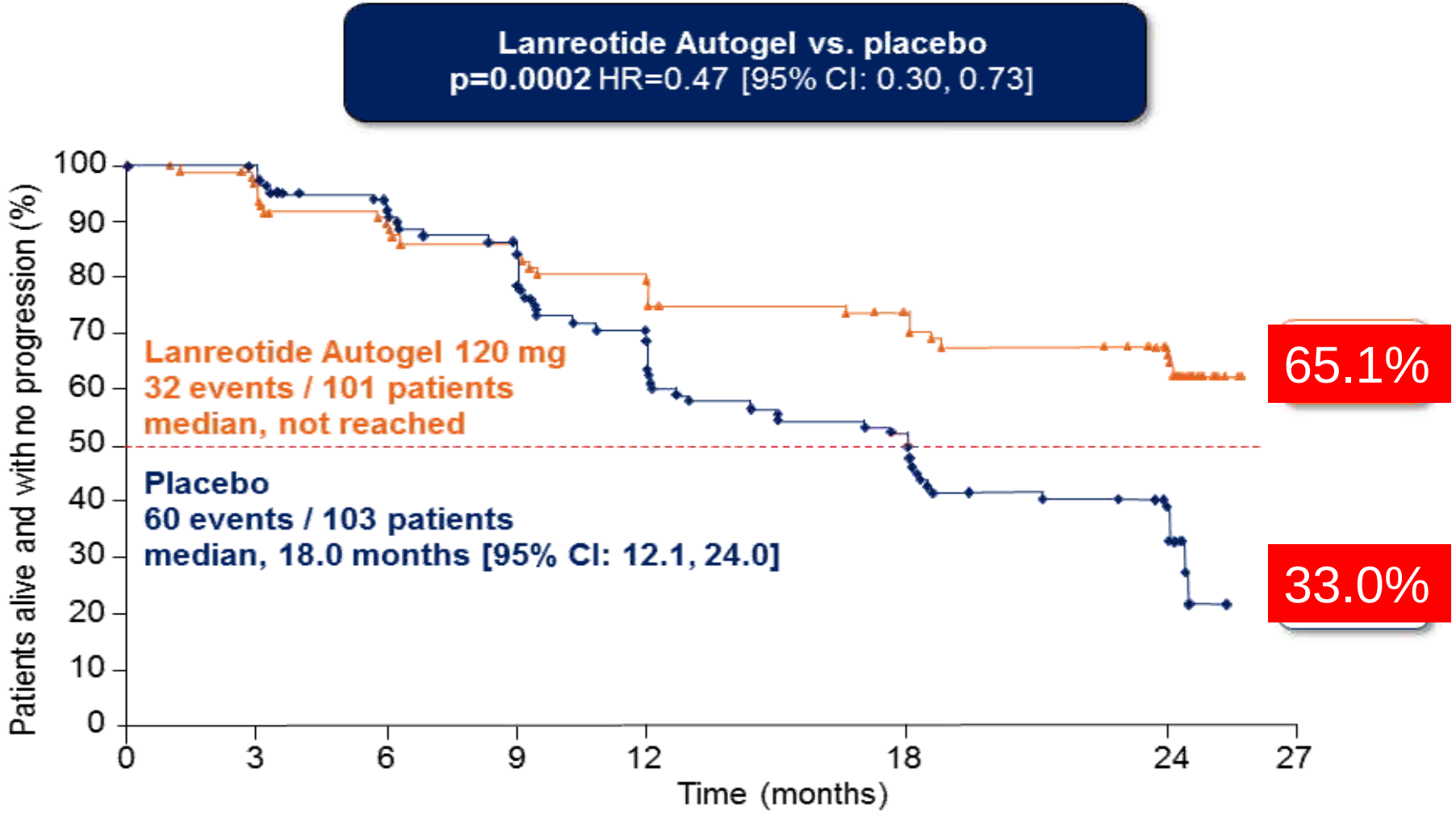
Patients treated and followed for 2-years

Primary end point:
- PFS (RECIST)

Secondary end points:
- Tumor response, OS, biomarkers, safety

Kaplin ME et al. NEJM 2014

Primary endpoint: PFS (ITT population, N=204)

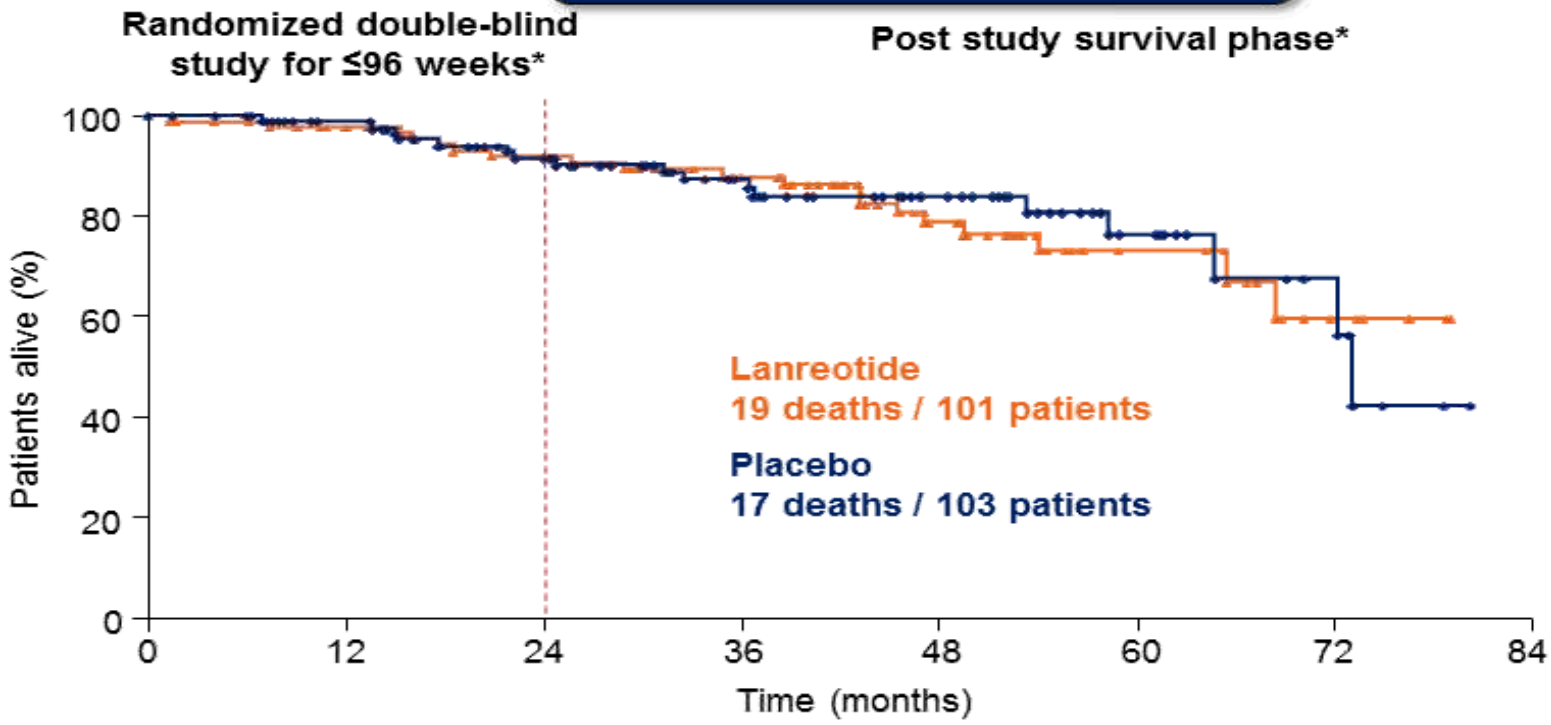


P-value derived from stratified log-rank test; HR derived from Cox proportional hazard model.
HR, hazard ratio; ITT, intention-to-treat.

Kaplin ME et al. NEJM 2014

Overall survival (ITT)

Lanreotide Autogel 120 mg vs. placebo
p=0.8791



Lanreotide, n	101	89	78	59	37	14	5	0
Placebo, n	103	88	73	51	35	16	6	0

P-value derived from log-rank test.
* Survival was followed throughout the randomized study for patients on study medication for up to 96 weeks or until early withdrawal / PD , and then continued to be followed during the post-study survival phase (when the patient may or may not have continued or switched to lanreotide).

Kaplin ME et al. NEJM 2014

ROLE OF SSA IN ADVANCED DISEASE

- IN CARCINOID SYNDROME FROM LUNG NET SSA ARE RECOMMENDED

- IN NON-FUNCTIONAL TYPICAL (G1) AND ATYPICAL (G2) CARCINOIDS SSA ARE RECOMMENDED

- IN LARGE CELLS NEUROENDOCRINE CARCINOMA (G3) SSA ARE NOT RECOMMENDED

IS THERE A ROLE FOR ADJUVANT SSA ?

- NO ROLE FOR ADJUVANT SSA IN LUNG NET

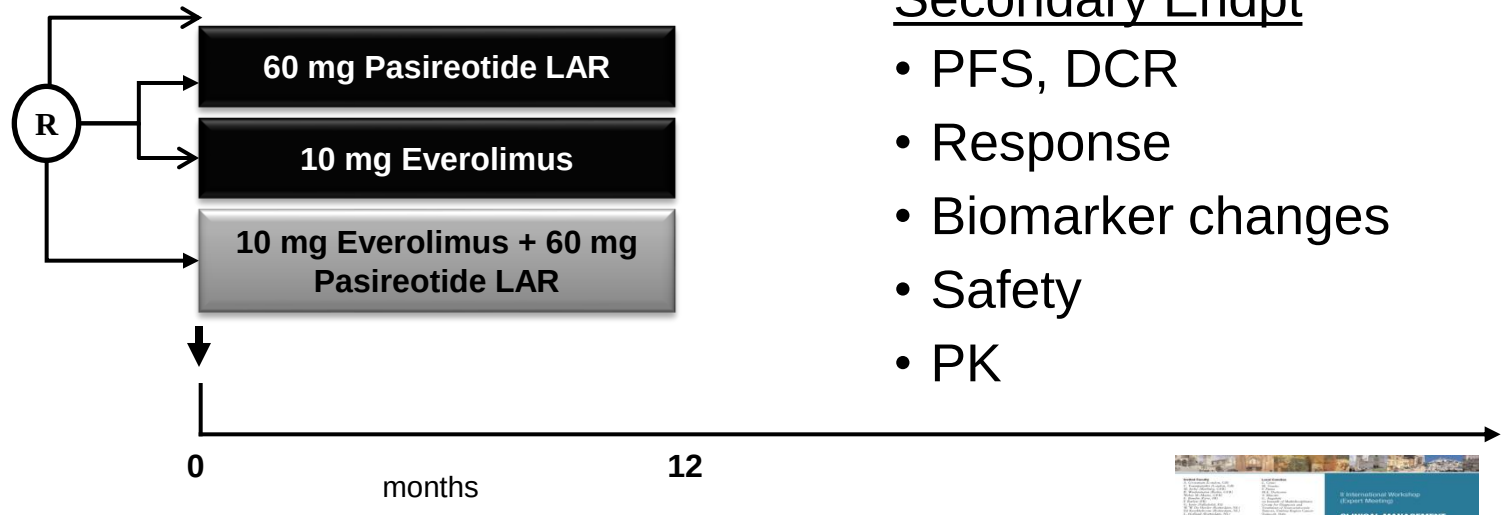
IS THERE ANY DIFFERENCE IN OUTCOME AMONG SSA ?

- OCTEOTRIDE AND LANREOTIDE ARE BOTH RECOMMENDED WITH NO COMPARATIVE TRIAL BETWEEN THE TWO DRUGS

LUNA: Phase II Study in lung NET

- Advanced metastatic or inoperable lung or thymic NET Randomized multicenter phase II study
- 112 patients in 3 arms (28/arm)

Progressive lung NET



Primary EndPt

- Proportion of pts. progression free at 12 months

Secondary Endpt

- PFS, DCR
- Response
- Biomarker changes
- Safety
- PK

EVEROLIMUS

(PI3KA pathway inhibitor)

RADIANT-3: Study Design Pancreatic NETs

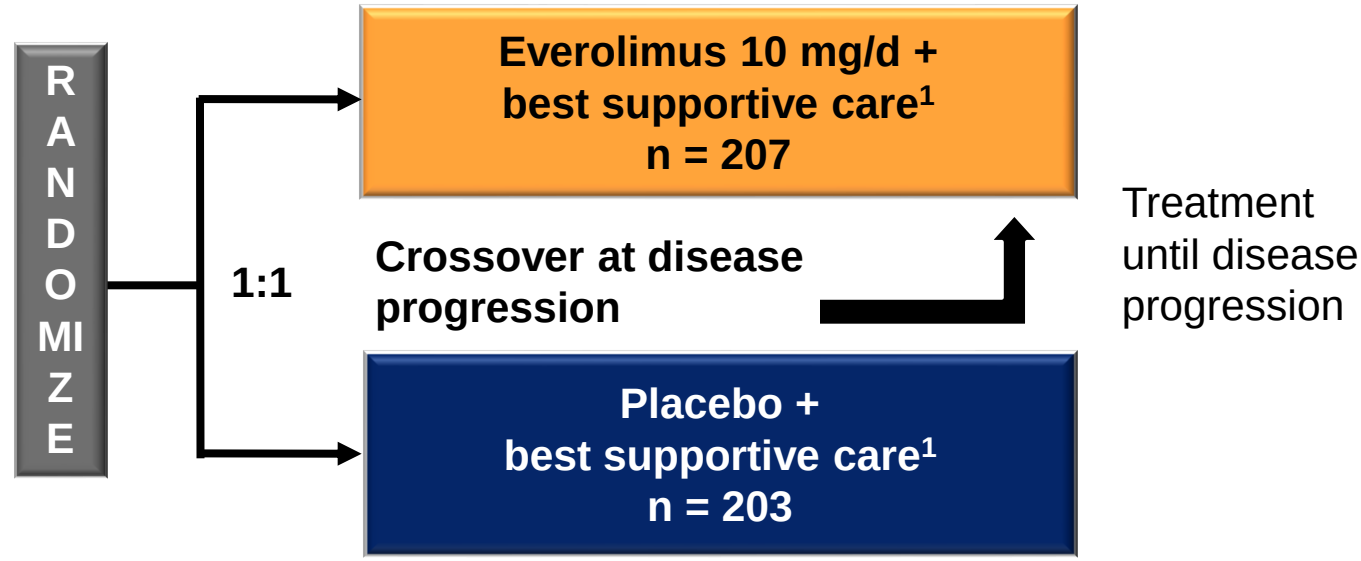
Phase III, Double-Blind, Placebo-Controlled Trial

Patients with advanced pancreatic NET (N = 410)

- Advanced well or moderately differentiated
- Radiologic progression with SSA ≤12 months
- Prior antitumour therapy allowed
- WHO PS ≤2

Stratified by:

- WHO PS
- Prior chemotherapy

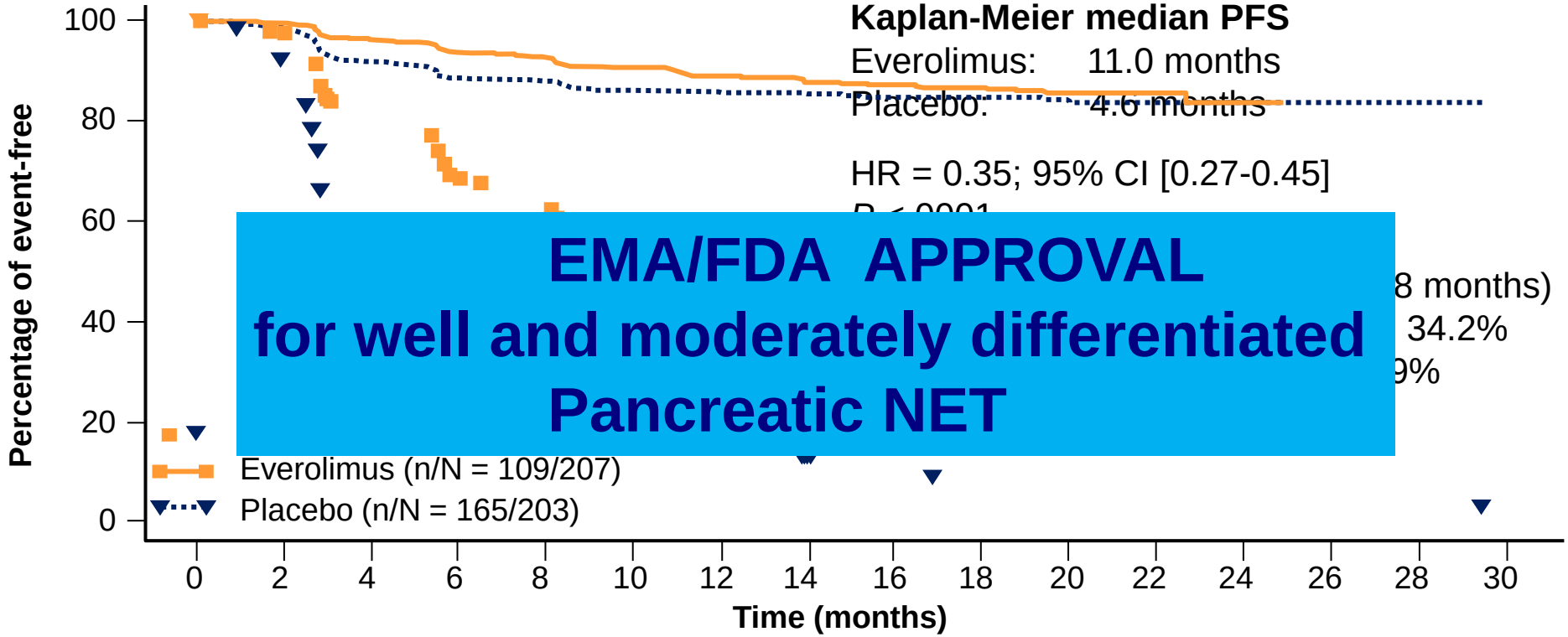


Primary Endpoint: Progression-free survival By investigator review
Secondary Endpoints: OS, ORR, biomarkers, safety, pharmacokinetics (PK)

[1]Concurrent somatostatin analogues allowed

Yao JC, et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med. 2011 Feb 10;364(6):514-23.

RADIANT-3:
PFS by Investigator Review



Number 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 is obtained from stratified one-sided log-rank test
Hazard ratio is obtained from stratified unadjusted Cox model

Yao JC, et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med. 2011 Feb 10;364(6):514-23.

RADIANT-2 Study Design
Advanced NETs with history of carcinoid syndrome

Phase III, Double-Blind, Placebo-Controlled Trial

Patients with advanced NET and a history of symptoms attributed to carcinoid syndrome (N=429)

PD with SSA within 12 mo

RANDOMIZE

1:1

Everolimus 10 mg/d + octreotide LAR 30 mg/28 d
n = 216

Placebo + octreotide LAR 30 mg/28 d
n = 213

Crossover

Treatment until disease progression

Multiphasic CT or MRI performed every 12 wk

Primary end point:
- PFS (RECIST)

Secondary end points:
- Tumor response, OS, biomarkers, safety, PK

Pavel ME, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. Lancet. 2011;378(9808):2005-12.

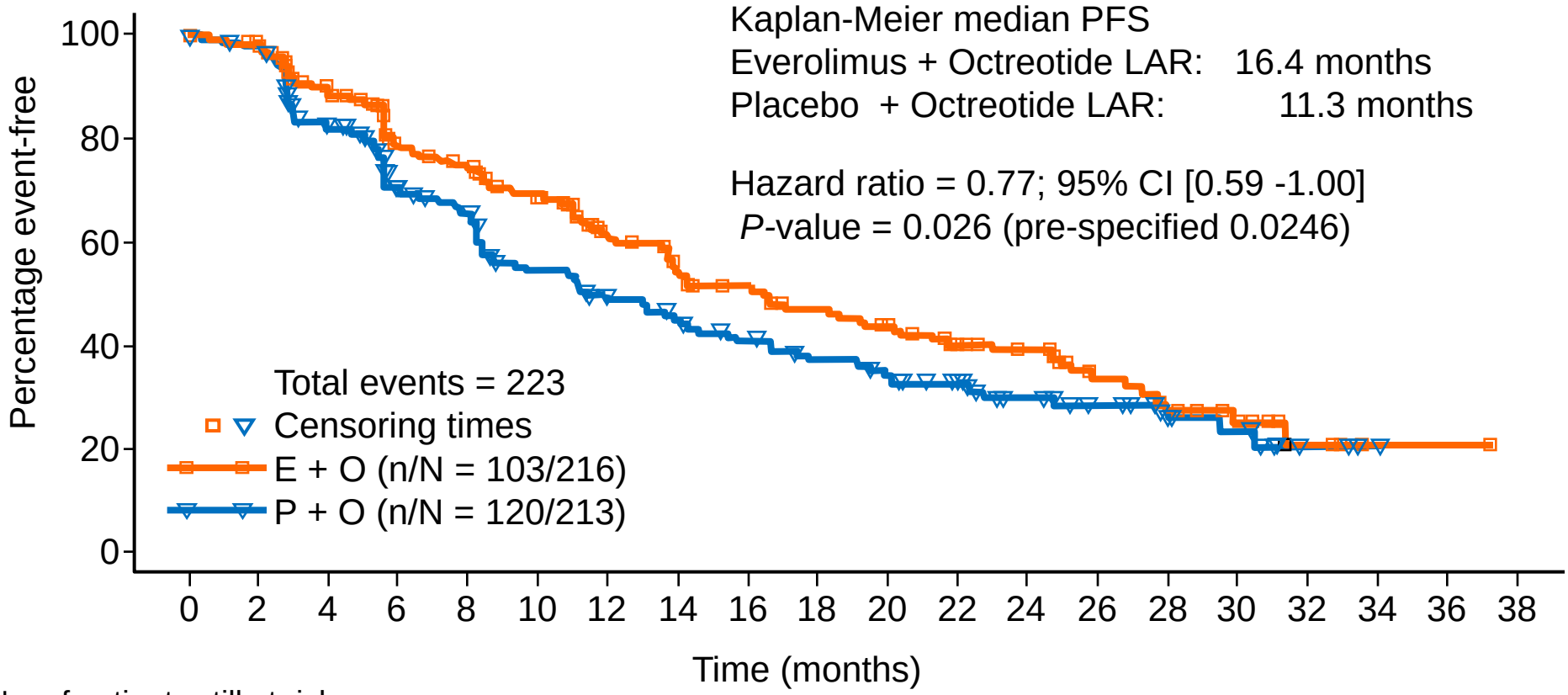
Baseline Characteristics

	Everolimus + octreotide LAR (n=216)	Placebo + octreotide LAR (n=213)
Median age, yr (range)	60 (22–83)	60 (27–81)
Male	45%	58%
Female	55%	42%
WHO PS		
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, $P<0.05$.
1 missing PS in placebo arm.

Pavel M, et al. Lancet 2011

RADIANT-2: 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

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

Pavel M, et al. Lancet 2011

CHEST

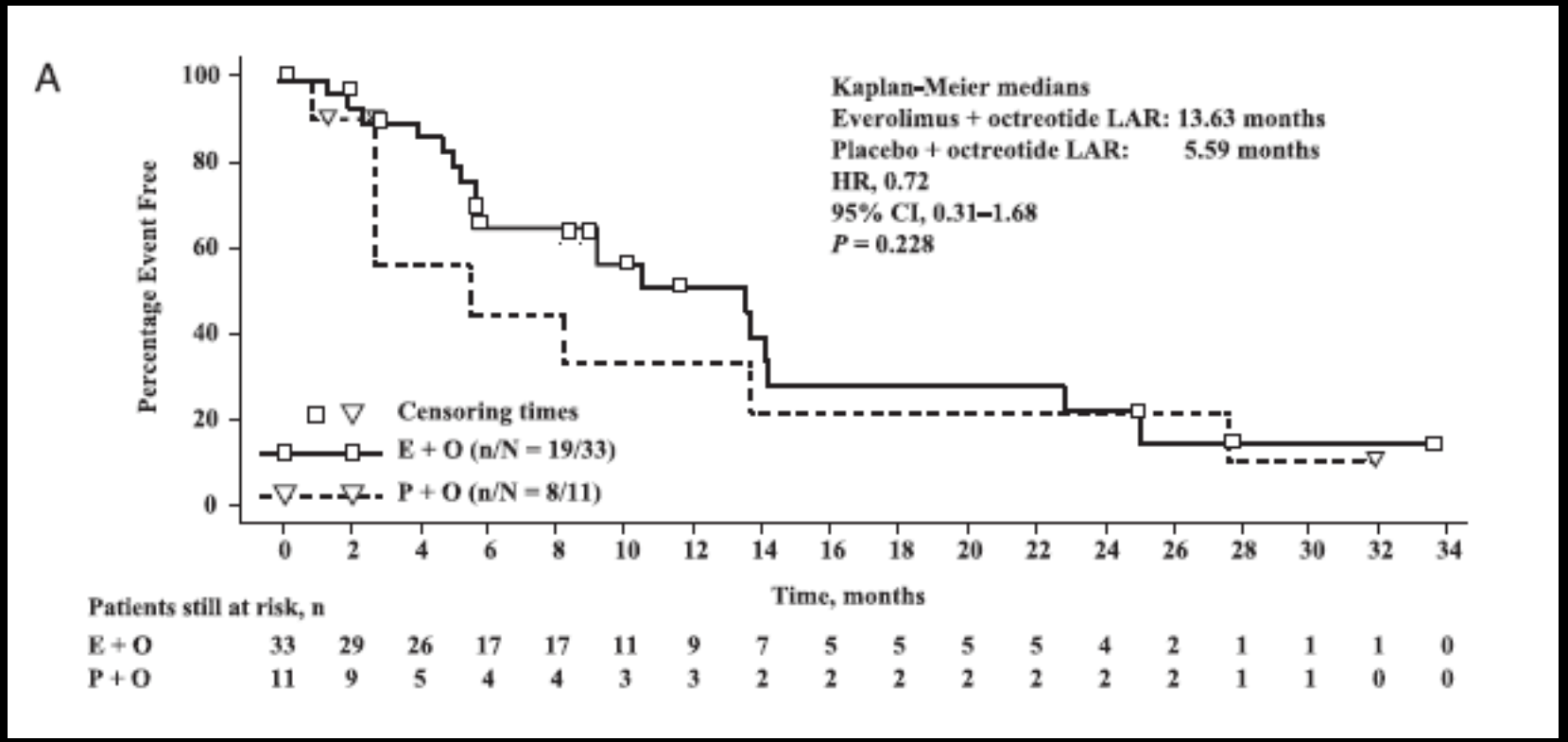
Original Research

LUNG CANCER

Everolimus Plus Octreotide Long-Acting Repeatable in Patients With Advanced Lung Neuroendocrine Tumors

Analysis of the Phase 3, Randomized, Placebo-Controlled RADIANT-2 Study

Nicola Fazio, MD; Dan Granberg, MD, PhD; Ashley Grossman, MD; Stephen Saletan, MD; Judith Klimovsky, MD; Ashok Panneerselvam, PhD; and Edward M. Wolin, MD



CHEST

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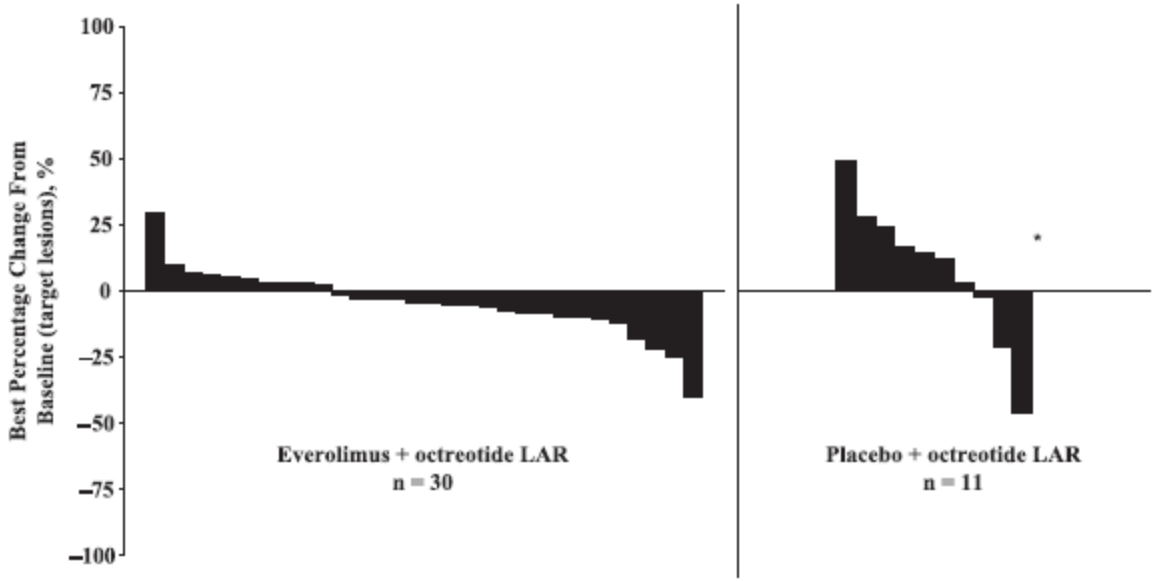


FIGURE 2. Best percentage change from baseline in tumor response. * denotes change in size of target lesion contradicted by lesion response of progressive disease (see Table 2). See Figure 1 legend for expansion of abbreviation.

In addition, more patients treated with the combination of everolimus plus octreotide LAR (67%) experienced tumor shrinkage than did those treated with placebo plus octreotide LAR (27%) (Fig 2, Table 2). The decrease in tumor size did not meet RECIST criteria for partial response.

1156O

RAMSETE: A SINGLE-ARM, MULTICENTER, SINGLE-STAGE PHASE II TRIAL OF RAD001 (EVEROLIMUS) IN ADVANCED AND METASTATIC SILENT NEURO-ENDOCRINE TUMOURS IN EUROPE: ANALYSIS BY TUMOR ORIGIN

M. Pavel[1], B. Wiedenmann[1], J. Capdevila[2], J.W. Valle[3], W.W. De Herder[4], C. Metzer[5], R. Salazar[6], D. Horsch[7], K. Oberg[8]

Ann Oncol 2012 (ESMO)

Characteristic and Endpoint	Lung, thymic, bronchial, mediastinal (n = 22)	Other than lung (n = 34)	Unknown (n = 17)
Well differentiated, %	40.9	97.0	82.3
Moderately differentiated, %	59.0	2.9	17.6
Ki67 >10%, %	62.5	42.8	50.0
Stable disease, %	63.2	42.9	69.2
Progressive disease, %	36.8	57.1	30.8
Median PFS, days (95% CI)	189 (84–321)	174 (118–245)	316 (126–337)

Conclusions: These results provide evidence that everolimus may be effective in nonsyndromic, nonpancreatic NET with diverse tumor origin sites and in pts with high tumor grade. These data support previous results from phase III trials that indicate everolimus is effective in pancreatic NET (RADIANT-3) and in NET associated with carcinoid syndrome (RADIANT-2).

Everolimus in Combination with Octreotide Long-Acting Repeatable in a First-Line Setting for Patients with Neuroendocrine Tumors

Emilio Bajetta, MD[1]; Laura Catena, MD[1]; Nicola Fazio, MD[2]; Sara Pusceddu, MD[3]; Pamela Biondani, MD[3]; Giusi Blanco, MD[4]; Sergio Ricci, MD[5]; Michele Aieta, MD[6]; Francesca Pucci, MD[7]; Monica Valente, MD[8]; Nadia Bianco, MD[1]; Chiara Maria Mauri, MD[1]; and Francesca Spada, MD[2]

An ITMO Group Study

Cancer Month 00, 2014

Characteristic		Patients, no. (%)
Sex	Female	21 (42)
	Male	29 (58)
Ethnic group	Caucasian	50 (100)
	Other	–
Age (years)	Median	58.4
	Range	25-76
ECOG performance status	0	50 (100)
	1	–
	2	–
Primary tumor site	Pancreas	14 (28)
	Lung	11 (22)
	Ileum	9 (18)
	Duodenum/jejunum	2 (4)
	Unknown	14 (28)
Octreoscan	Positive	42 (84)
	Negative	8 (16)
Serum CgA concentration	Above ULN	38 (76)
	Normal	12 (24)
Prior surgery	Yes	25 (50)
	No	25 (50)
Carcinoid syndrome	Yes	13 (26)
	No	37 (74)

The ORR was 18.0% (95% CI = 9.5%-31.0%)

CR+PR+SD, was 92%.

The CR and all PRs as well as 91.7% of SDs had a duration $\geq$ 6 months.

Time to Progression and Overall Survival

After a median follow-up of 277 days, median TTP was not reached (Fig. 1), as in the case of median OS (Fig. 2). There were no significant differences in TTP and OS with respect to the primary tumor site.

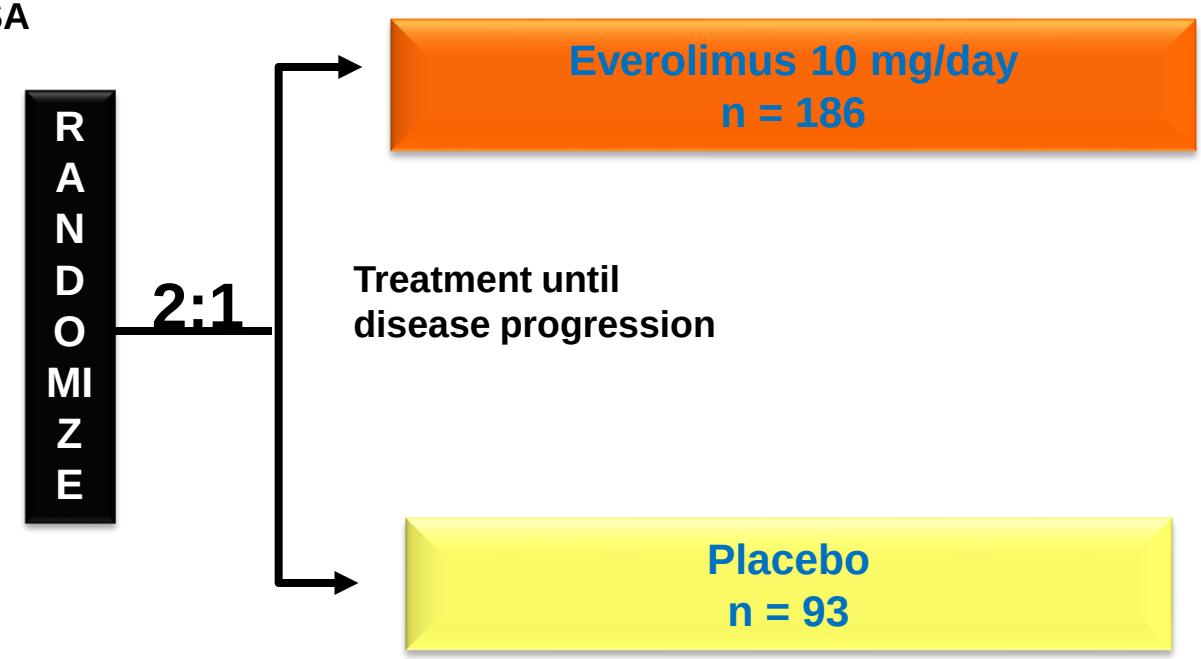
RADIANT-4

Phase III study of everolimus versus placebo in nonfunctional NET

A randomized, double-blind, multicenter, phase III study of everolimus plus best supportive care versus placebo plus best supportive care in the treatment of patients **with advanced NET of gastrointestinal or lung origin progressing with SSA**

Patients with advanced NET and no history of secretory symptoms
(N = 279)

- Advanced low- or intermediate-grade NET
- Radiologic progression
- Absence of carcinoid syndrome (flushing, diarrhea, or both)
- Presence of measurable disease (RECIST v1.0)
- Previous antitumor therapy allowed
- WHO PS ≤1



Primary endpoint: PFS (real-time central radiology review)

IS THERE A ROLE FOR EVEROLIMUS IN LUNG NET ?

- EVEROLIMUS COMBINED TO SSA COULD BE CONSIDERED IN TYPICAL (G1) AND ATYPICAL (G2) CARCINOIDS WITH CARCINOID SYNDROME PROGRESSING AFTER SSA
  (Lung NET included in RADIANT-2 trial)

- EVEROLIMUS IN TYPICAL (G1) AND ATYPICAL (G2) NON-FUCTIONAL CARCINOIDS PROGRESSING AFTER SSA IS NOT RECOMMENDED
  (Lung NET not included in RADIANT-3 trial enrolling only well or moderately differentiated pancreatic NET)

ANTIANGIOGENETICS

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

Study A6181111

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

RANDOMIZATION

1:1

Arm A

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

Arm B

Placebo*

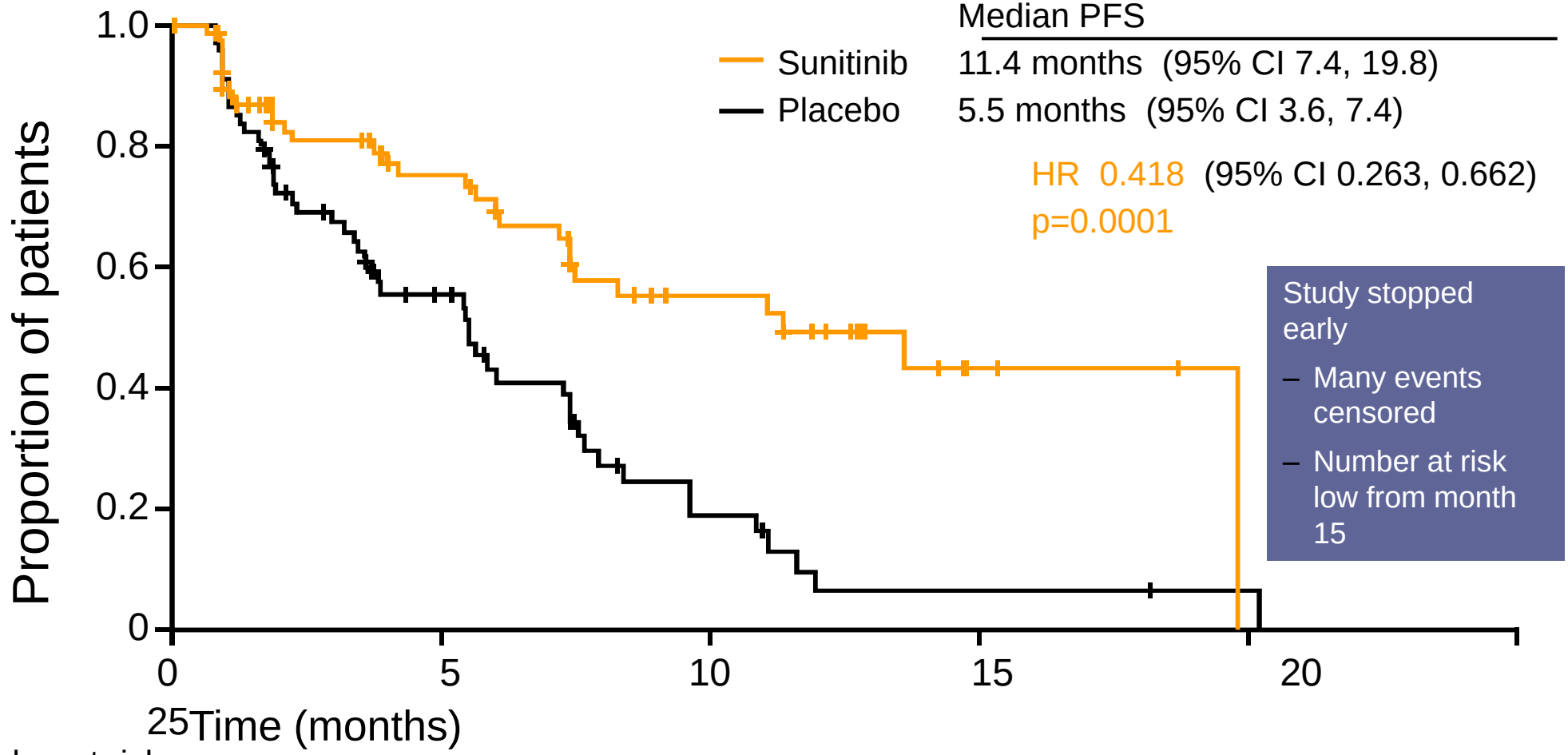
Primary endpoint: PFS

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

*With best supportive care

Somatostatin analogs were permitted

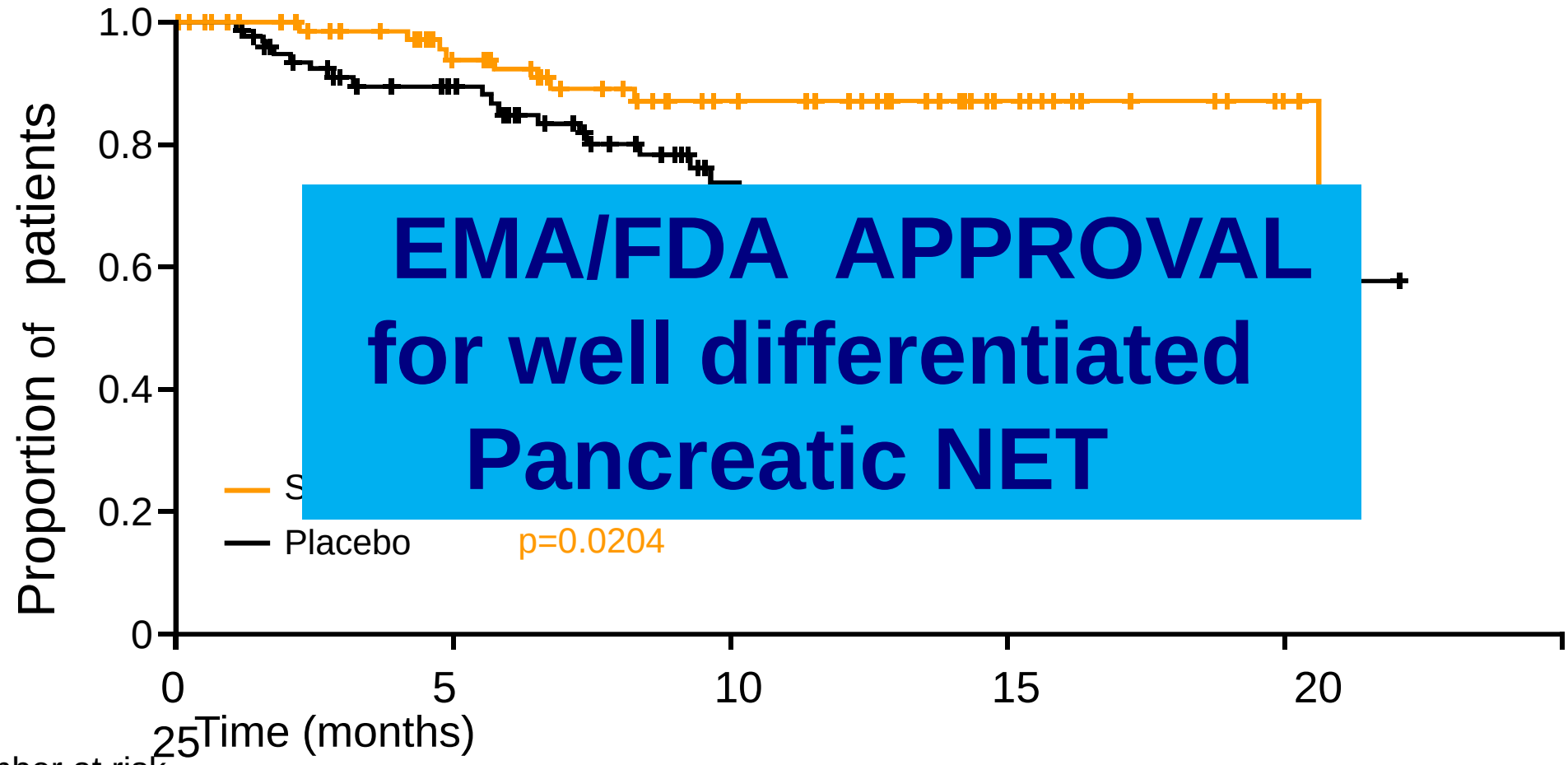
Progression-Free Survival
(Primary Endpoint)



Number at risk

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

Overall Survival



EMA/FDA APPROVAL for well differentiated Pancreatic NET

Number at risk

Sunitinib	86	60	38	16	3	0
Placebo	85	61	33	12	3	0

IS THERE A ROLE FOR SUNITINIB IN LUNG NET ?

- **SUNITINIB IN TYPICAL (G1) AND ATYPICAL (G2) CARCINOIDS PROGRESSING AFTER SSA IS NOT RECOMMENDED**

  (Lung NET not included in A6181111 trial enrolling only well differentiated pancreatic NET)