RAMSETE: A Single-Arm, Multicenter, Single-Stage Phase II Trial of RAD001 (Everolimus) in Advanced and Metastatic Silent Neuro-Endocrine Tumors in Europe: Analysis by Tumor Origin

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Disclosures

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Background

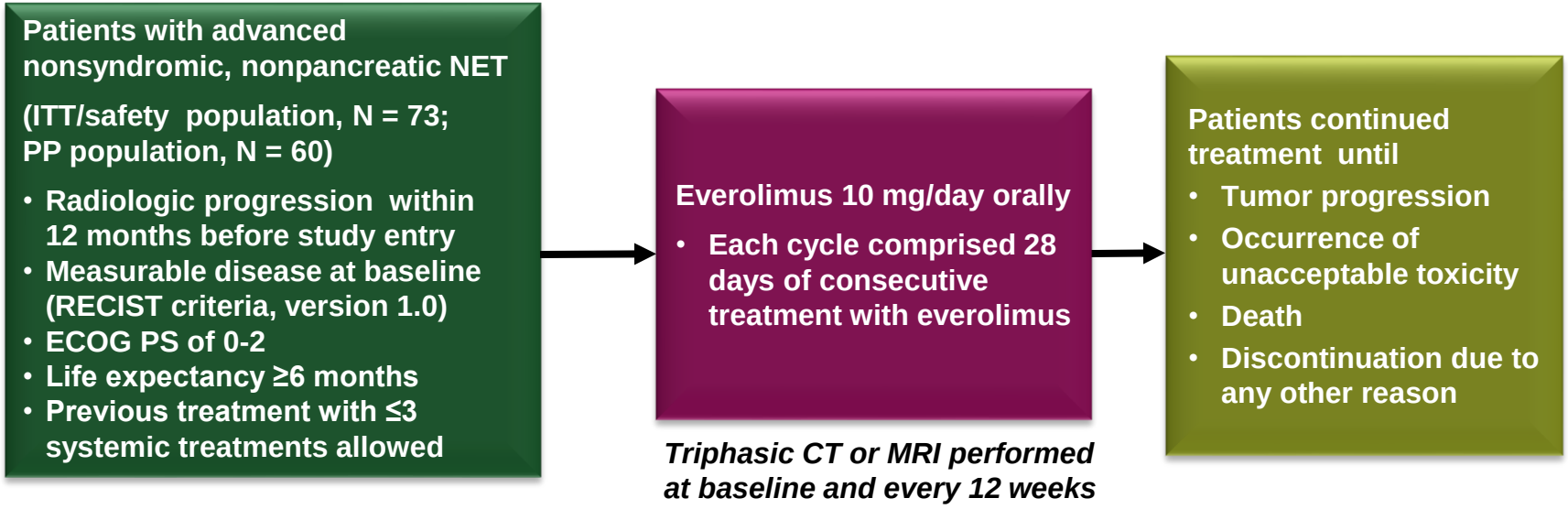
- More than 60% of NET are nonfunctioning[1-3]
- Everolimus, an oral mTOR inhibitor, demonstrated efficacy in patients with advanced pancreatic NET (RADIANT-3)[4] and advanced NET associated with carcinoid syndrome (RADIANT-2)[5]
- The RAMSETE trial was designed to evaluate the efficacy of everolimus in patients with advanced nonsyndromic, nonpancreatic NET
- Primary analysis revealed a high rate of disease stabilization and good tolerability, comparable to the known safety profile of everolimus[6]
- Here we report a secondary exploratory post hoc analysis of the RAMSETE trial by primary tumor origin

RAMSETE, RAD001 in Advanced and Metastatic Silent Neuro-Endocrine Tumors in Europe.

1. Falconi M et al. *Neuroendocrinology*. 2012;95:120-134. 2. Jensen RT et al. *Neuroendocrinology*. 2012;95:98-119. 3. Pape UF et al. *Neuroendocrinology*. 2012;95:135-156. 4. Yao JC et al. *N Engl J Med*. 2011;364:514-523. 5. Pavel ME et al. *Lancet*. 2011;378:2005-2012. 6. Pavel M et al. ASCO Annual Meeting; June 1-5, 2012; Chicago, IL, USA.

RAMSETE Study Design

An open-label, single-arm, multicenter, phase II study conducted in 16 European sites (ClinicalTrials.gov number NCT00688623)



Primary Endpoint
- ORR as per RECIST by central radiologic review

Secondary Endpoints
- Disease control rate, PFS, OS, Safety

Follow-up: Every 28 days (after the last dose of everolimus) for AEs and SAEs; every 12 weeks for radiologic assessment

AE, adverse event; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; MRI, magnetic resonance imaging; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PP, per protocol; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event.

Baseline Characteristics by Primary Tumor Origin in ITT/Safety Population

	Lung, Thymic, Bronchial, or Mediastinal n = 22	Small Bowel, Rectum, and Others n = 34	Unknown n = 17
Median age, years (range)	56.5 (30.0-75.0)	62.5 (33.0-79.0)	63.0 (31.0-81.0)
Male/female sex, n (%)	7 (32)/15 (68)	26 (76)/8 (24)	7 (41)/10 (59)
Histologic grade, n (%)			
Well differentiated	9 (41)	33 (97)	14 (82)
Moderately differentiated	13 (59)	1 (3)	3 (18)
Ki67 ≥10%, n (%)	10 (63)	9 (43)	5 (50)

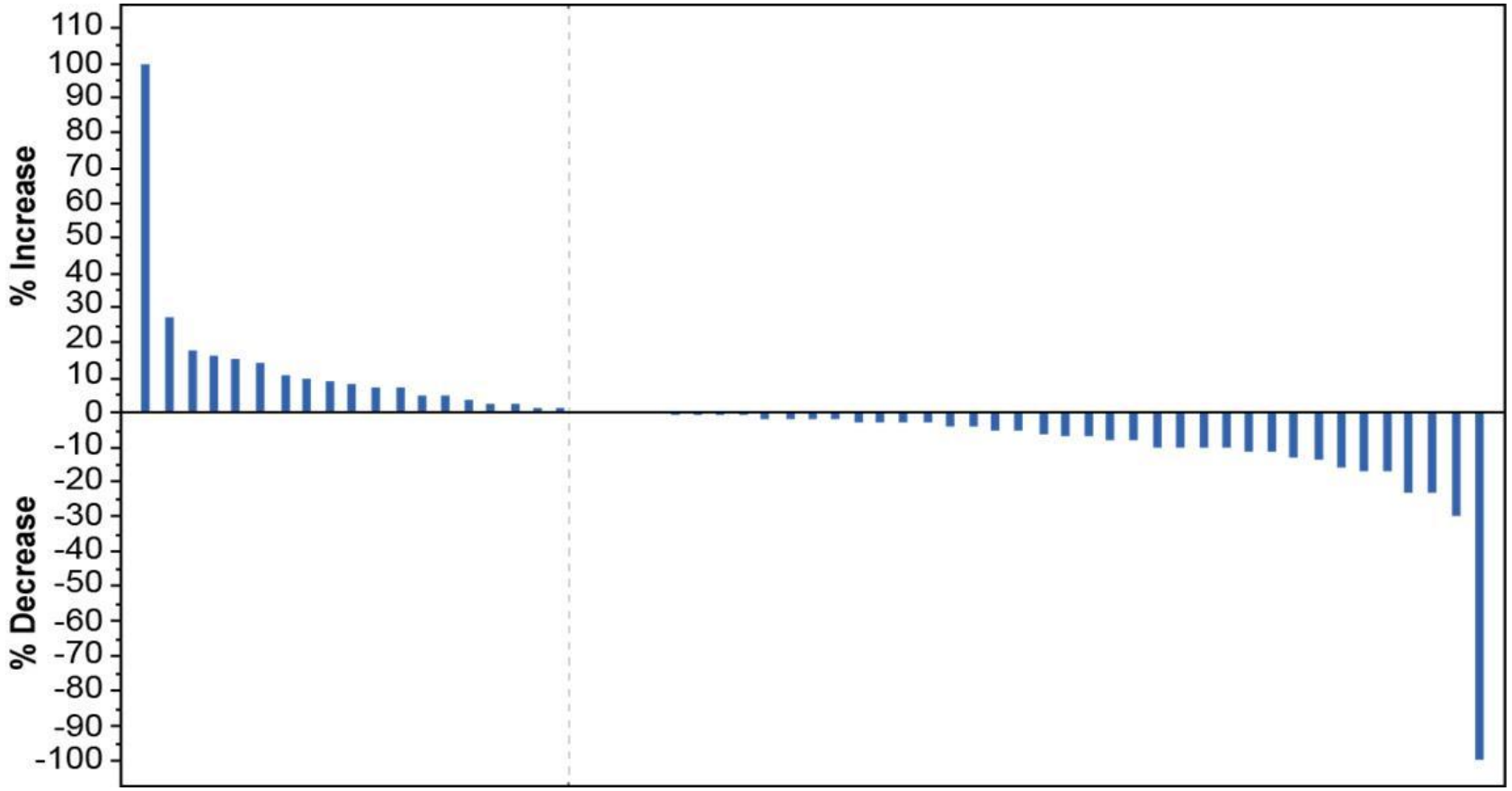
- Database lock date: December 1, 2011
- Median duration of treatment, including days of treatment interruption: 225 days

Best Overall Response in Per Protocol Population (primary endpoint)

	Central Radiologic Review N = 60	Local Investigator Review N = 60
CR, n (%)	0 (0)	0 (0)
PR, n (%)	0 (0)	3 (5)
SD, n (%)	33 (55)	39 (65)
PD, n (%)	27 (45)	16 (27)
Unknown, n (%)	0 (0)	2 (3)
ORR, n (%)	0 (0)	3 (5)
DCR (CR+PR+SD), n (%)	33 (55)	42 (70)

CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PP, per protocol; PR, partial response; SD, stable disease.

Best Overall Response in Per Protocol Population (Central Radiologic Review)

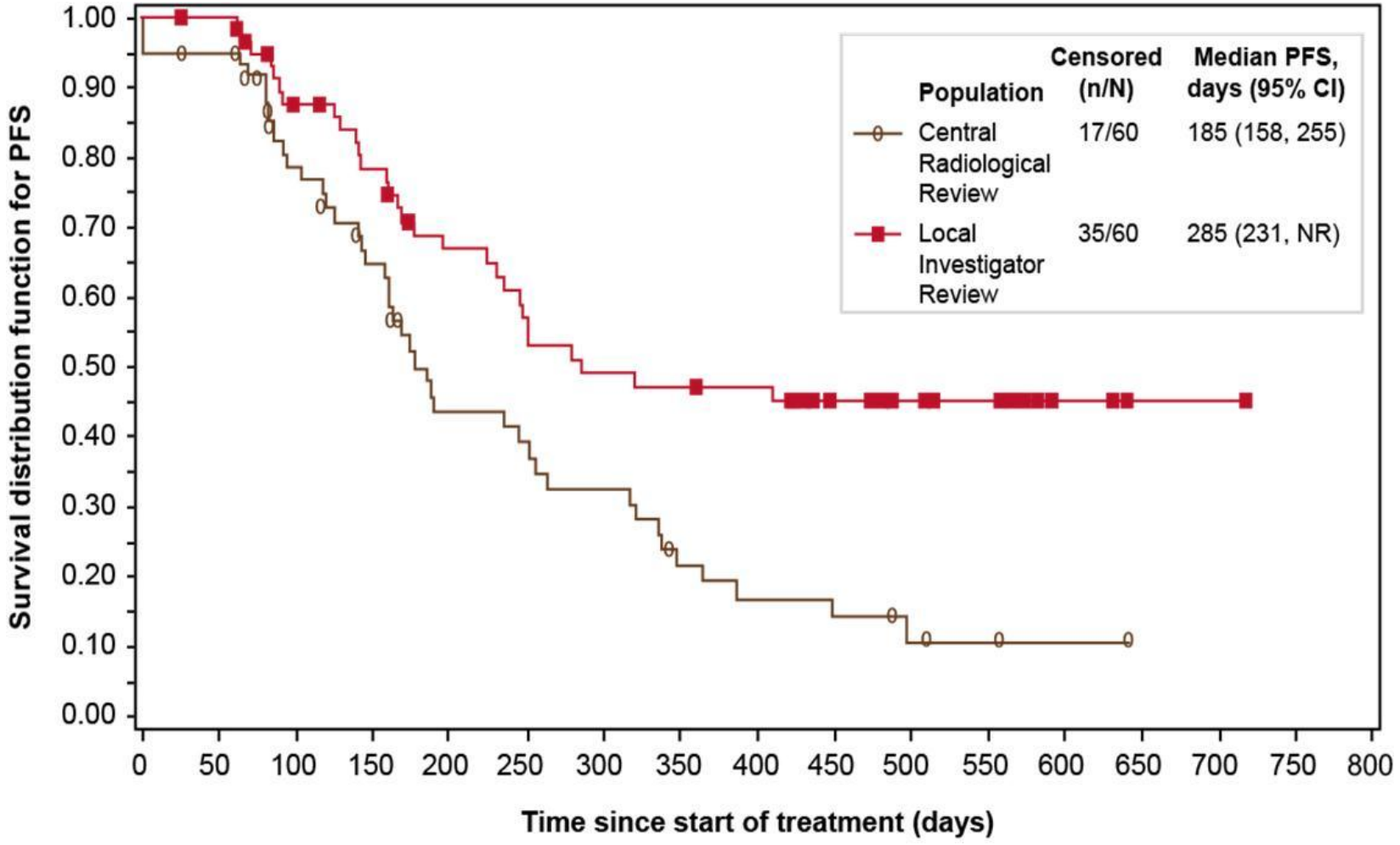


Patients for whom the best percentage changes in target lesions were not available are excluded. And measurements that contradicted the measurement for target lesion response were excluded. One patient experienced CR on target lesions, but a new lesion appeared

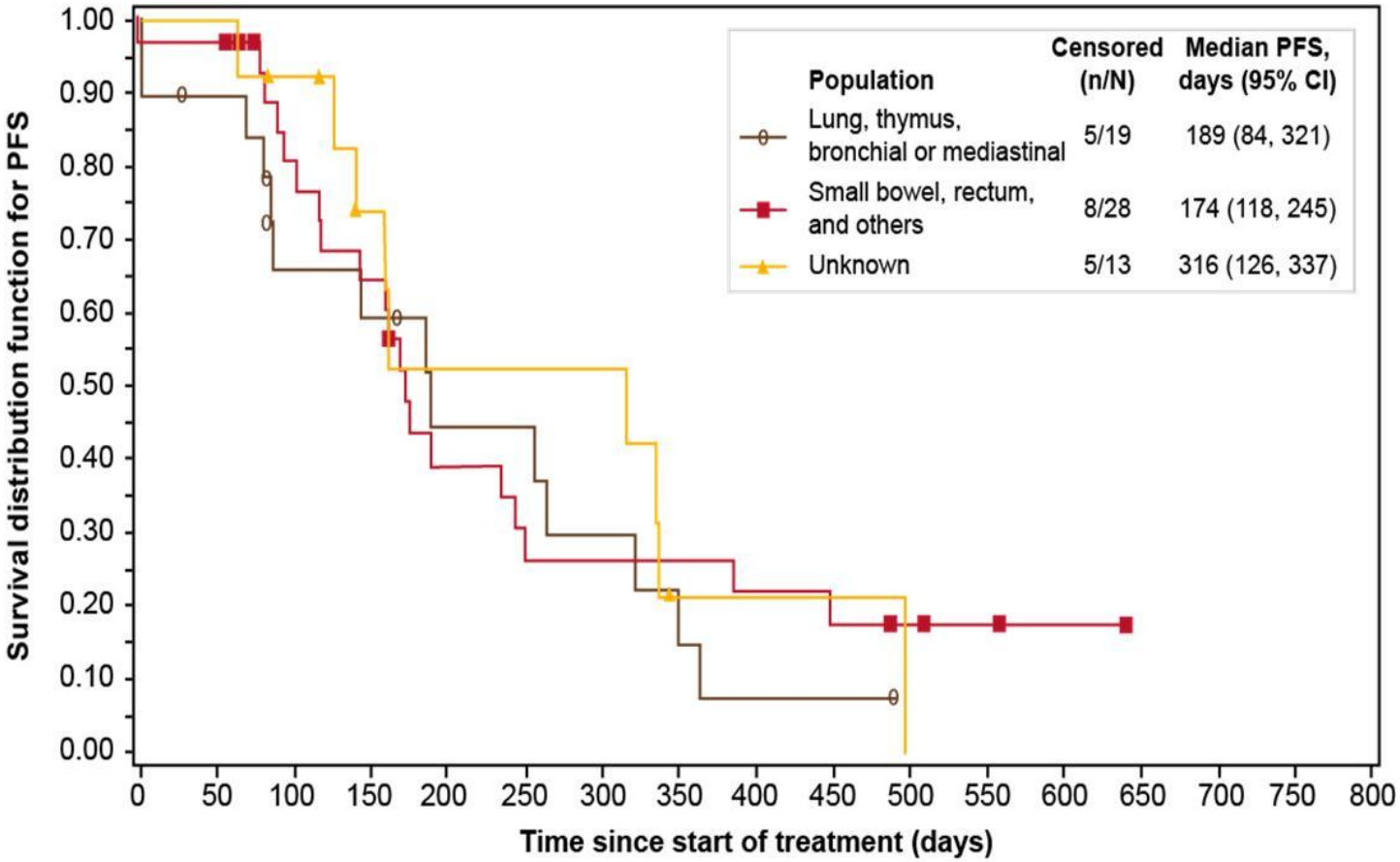
Best Overall Response by Primary Tumor Origin in Per Protocol Population

	Lung, Thymic, Bronchial, or Mediastinal n = 19		Small Bowel, Rectum, and Others n = 28		Unknown n = 13	
	Central Radiologic Review	Local Investigator Review	Central Radiologic Review	Local Investigator Review	Central Radiologic Review	Local Investigator Review
CR, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
PR, n (%)	0 (0)	0 (0)	0 (0)	2 (7)	0 (0)	1 (8)
SD, n (%)	12 (63)	12 (63)	12 (43)	18 (64)	9 (69)	9 (69)
PD, n (%)	7 (37)	6 (32)	16 (57)	7 (25)	4 (31)	3 (23)
Unknown, n (%)	0 (0)	1 (5)	0 (0)	1 (4)	0 (0)	0 (0)
ORR, n (%)	0 (0)	0 (0)	0 (0)	2 (7)	0 (0)	1 (8)
DCR (CR+PR+SD), n (%)	12 (63)	12 (63)	12 (43)	20 (71)	9 (69)	10 (77)

Progression-Free Survival in Per Protocol Population



Progression-Free Survival by Primary Tumor Origin in Per Protocol Population (Central Radiologic Review)



Patients With Ki67>20%

Gender/Age	Number of Prior Antineoplastic Therapies	Tumor Origin	Histologic Grade	Ki67 (%) (type of tissue)	Days on Treatment
M/63	2	Gastric	Well differentiated	50 (primary tumor)	91
F/46	2	Cecum	Moderately differentiated	30 (primary tumor)	On active treatment (since Dec 2009)
M/30	0-1	Lung	Moderately differentiated	30 (other)	232
M/57	0-1	CUP	Well differentiated	40 (liver met)	169

M, male; F, female; CUP, cancer of unknown primary

Adverse Events Occuring in ≥15% of Patients in Safety Population (N = 73)

Preferred Term	All Grades		Grade 3/4	
	Patients, n	%	Patients, n	%
Rash	33	45	1	1
Diarrhea	31	42	4	5
Abdominal pain	22	30	7	10
Decreased appetite	22	30	1	1
Nausea	20	27	0	0
Dyspnea	20	27	5	7
Vomiting	19	26	2	3
Asthenia	19	26	6	8
Fatigue	18	25	2	3
Mucosal inflammation	18	25	2	3
Cough	18	25	1	1
Edema peripheral	16	22	2	3
Weight decreased	15	21	1	1
Stomatitis	14	19	0	0
Anemia	13	18	3	4
Mouth ulceration	12	16	0	0
Hypercholesterolemia	12	16	1	1
Back pain	12	16	1	1
Abdominal pain upper	11	15	0	0
Urinary tract infection	11	15	2	3

Pneumonitis: all grades: 7 (9.6%) – G3/4: 2 (2.7%)
Hyperglycemia: all grades: 7 (9.6%) – G3/4: 1 (1.4%)

Conclusions

- Everolimus (10 mg/day) was associated with a high proportion of SD along with an encouraging PFS in patients with advanced nonsyndromic, nonpancreatic NET
- Efficacy was independent of primary tumor site (foregut, midgut, and hindgut origin)
- Efficacy was also seen in individual patients wither higher proliferative activity (NET G3)
- The safety profile of everolimus was consistent with that of previous everolimus oncology studies. Further, most of the AEs reported in this study were grade 1/2
- This study confirms the safety and efficacy of everolimus in NET types other than those studied in RADIANT-3 (pancreatic NET)[1] and RADIANT-2 (NET associated with carcinoid syndrome)[2]

1. Yao JC et al. *N Engl J Med*. 2011;364:514-523.
2. Pavel ME et al. *Lancet*. 2011;378:2005-2012.

RADIANT-4 Study Design

Patients with advanced, well-differentiated, nonfunctional GI or lung NET (N = 285)

- Patients with absence of secretory-related carcinoid symptoms
- Radiologic documentation of disease progression within 6 months before randomization
- Measurable disease according to RECIST 1.0 determined by CT or MRI

RANDOMIZE

2:1

Everolimus 10 mg/day + best supportive care n = 195

Placebo + best supportive care n = 90

Crossover to open-label everolimus only after IA and DMC recommendation

<u>Primary endpoint</u>:
PFS assessment as determined by central radiology review

<u>Secondary endpoints:</u>
Assessments of OS, safety, tolerability, ORR, DCR, CgA, NSE, time to definitive deterioration in WHO PS or in FACT-G total score

CgA, chromogranin A; FACT-G, functional assessment of cancer therapy-general; GI, gastrointestinal; NSE, neuron-specific enolase; WHO, World Health Organization