Efficacy of Lenvatinib in Patients With Advanced Pancreatic (panNETs) and Gastrointestinal (giNETs) WHO Grade 1/2 (G1/G2) Neuroendocrine Tumors: Results of the International Phase II TALENT Trial (GETNE 1509)

Abstract 1307O

Capdevila J, Fazio N, Lopez C, Teulé A, Valle JW, Tafuto S, Custodio A, Reed N, Raderer M, Grande E, Garcia-Carbonero R, Jimenez-Fonseca P, Alonso V, Antonuzzo L, Spallanzani A, Berruti A, Sevilla I, La Casta A, Hernando J, and Ibrahim T

Background

- **Patients with advanced neuroendocrine tumors (NETs) have limited therapeutic approaches with overall survival (OS) ranging from 3.6 years for pancreatic NETs (pNETs) to 5.8 years for small intestine NETs[1]**
- **Approved treatments for pNETs include somatostatin analogues, chemotherapy, everolimus, sunitinib, and peptide receptor radionucleotide therapy (PRRT); for gastrointestinal (GI NETs), somatostatin analogues (SSAs), everolimus, and PRRT**
- **Main symptoms of patients with advanced NETs are related to hormone-release and tumor burden**

1. Dasari A, et al. *JAMA Oncol.* 2017;3(10):1335-1342.
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Background: Phase III Evidence-Based

Treatment Schedule	Primary Site	Progression Prior Inclusion	PFS, Months	ORR (%)
Streptozotocin-based	Pancreas	NA	NR	63*
Octreotide	GI	No	14.3	<5
Lanreotide	Pancreas and GI	No	32.8	<5
Everolimus	Pancreas, GI, and lung	Yes (12 months)	11	2-5
Sunitinib	Pancreas	Yes (12 months)	11.4	9
^{177}Lu-Dotatate	GI	Yes (36 months)	28.4	19

*Old trials with nonstandard evaluation of radiological tumor response

ORR, overall response rate; PFS, progression-free survival

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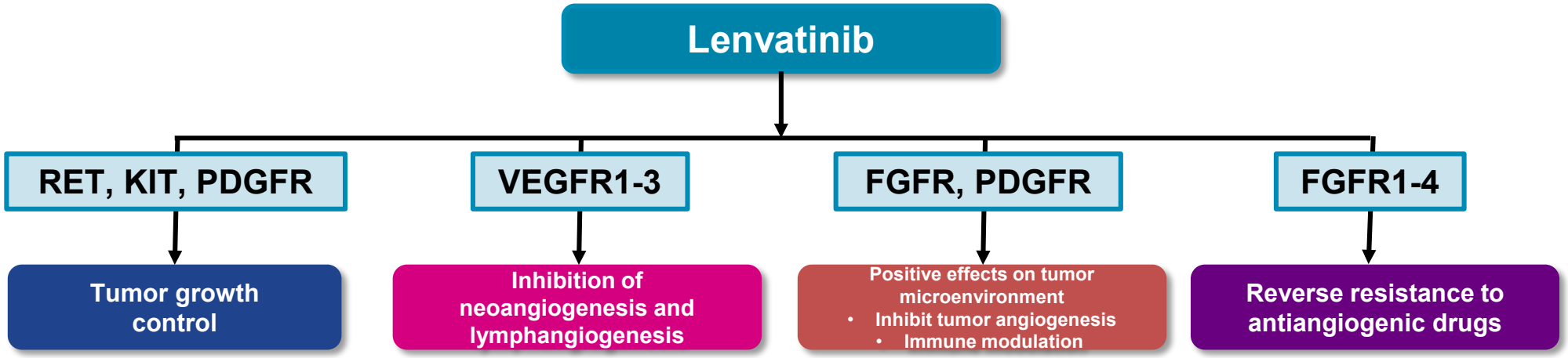
Background: Lenvatinib Mechanism of Action



Lenvatinib binds to VEGFR2 through type V binding mode:

- **Binds both allosteric and ATP sites, producing high selectivity and residence time**
- **Exhibits high potency as the first type V kinase inhibitor evaluated in clinical trials**

VEGFR1	1.3 nM	FGFR1	22 nM
VEGFR2	0.74 nM	FGFR2	8.2 nM
VEGFR3	0.71 nM	FGFR3	15 nM

1. Capdevila J, et al. *Eur J Endocrinol*. 2017;177(4):309-317. 2. Stjepanovic N, et al. *Biologics*. 2014;8:129-139. 3. Lenvatinib [product labelling]. Hudson, Ohio, United States; Lexi-Drugs; 2018. 4. Matsuki M, et al. *Cancer Med.* 2018;7(6):2641-2653. 5. Cabanillas ME, et al. *Cancer Treat Rev.* 2016;42:47-55. 6. Okamoto K, et al. *ACS Med Chem Lett.* 2015;6:89-94. 7. Wu P, *et al. Drug Discov Today.* 2016;21:5-10. Ichikawa K, *et al.* Cancer Res., 2018;78(Suppl): Abstract 11. 11. Kato Y, et al. Presented at: AACR Annual Meeting; 4-7 December 2015: Boston, Massachusetts, United States. Abstract A92. 12. Kato Y, et al. AACR Annual Meeting; 1-5 April 2017: Washington, DC, United States. Abstract 4614.

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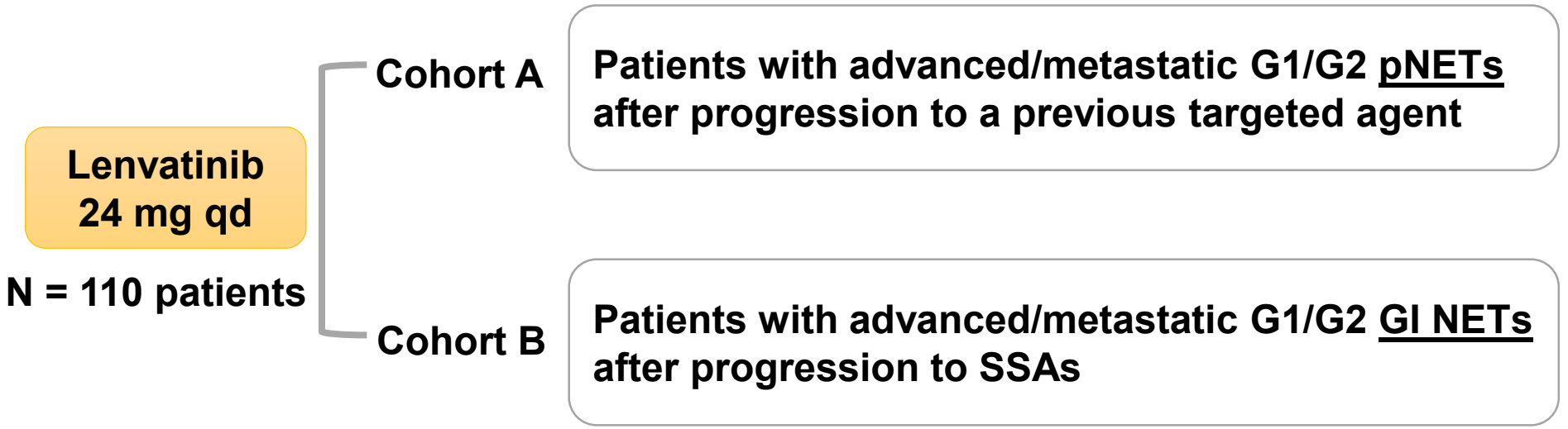
Study Design

TALENT Trial: A phase II trial to assess the efficacy of lenvatinib in metastatic NETs (GETNE 1509)



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Study Design

- **Hypothesis**
  - ORR with targeted agents in NETs are between 2% to 9%
  - We expected to increase the probability of ORR with lenvatinib up to 25%
  - With a 90% power and α-error of 5, 55 patients per arm are needed to demonstrate the primary hypothesis

- **Study objectives**
  - Primary endpoint: ORR by RECIST v 1.1 upon independent central radiological assessment
  - Secondary endpoints: Safety, PFS, OS, biomarkers

RECIST, Response Evaluation Criteria in Solid Tumors

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Main Inclusion Criteria

- Advanced NETs WHO G1/G2 (Ki67<20% and mitotic count ≤20 mitosis x 10 HPF)
- Measurable lesions by RECIST v1.1 were mandatory
- Documented disease progression during the last 12 months of follow-up
- Cohort A:
  - pNETs after progression to prior targeted agent (including mTOR inhibitors and multikinase inhibitors). Prior PRRT, interferon or chemotherapy were allowed
- Cohort B:
  - GI NETs after progression to SSAs. Prior interferon or PRRT was allowed
- Locoregional liver therapies were allowed if performed >6 months before starting lenvatinib

WHO, World Health Organization

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Baseline Characteristics (1)

Patient Characteristics	pNETs (n = 55)	GI NETs (n = 56)
Gender, % female	56	41
Age, median, years	58	61
ECOG PS 0/1 (%)	72/23	61/39
WHO grade, n (%)		
1	11 (20)	19 (34)
2	39 (71)	33 (59)
3	0	0
Total	50 (91)	52 (93)
Not available	5 (9)	4 (7)
Ki67 index		
Mean, % (SD)	9.24 (6.52)	5.73 (4.91)

ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation

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Baseline Characteristics (2)

Prior Therapies	pNETs (n = 55)	GI NETs (n = 56)
Time from initial diagnosis, years	4.8	4.11
Surgery of primary tumor, n (%)	27 (49)	36 (64)
Surgery of metastases, n (%)	9 (16)	16 (28)
SSAs, n (%)	46 (84)	55 (98)
Chemotherapy, n (%)	17 (31)	0
Everolimus, n (%)	35 (64)	0
Sunitinib, n (%)	15 (27)	0
Other targeted agent, n (%)	1 (2)	0
Not available, n (%)	4 (7)	1 (2)

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Primary Endpoint: ORR (Central Radiology Review)

	pNETs (n = 55)	GI NETs (n = 56)	Total (N = 111)
Patients with tumor assessments	52	54	106*
Best overall response, n(%)			
Complete response (CR)	0	0	0
Partial response (PR)	21 (40.4)	10 (18.5)	31 (29.2)
Stable disease (SD)	29 (55.8)	41 (76)	70 (66)
Progressive disease (PD)	2 (3.8)	0	2 (2)
Not evaluable	0	3** (5.5)	3 (2.8)

*Five patients withdrew the informed consent before the first postbasal tumor assessment.
**Central radiologist confirms that 3 patients did not have evaluable target lesions; they have been considered as not evaluable.

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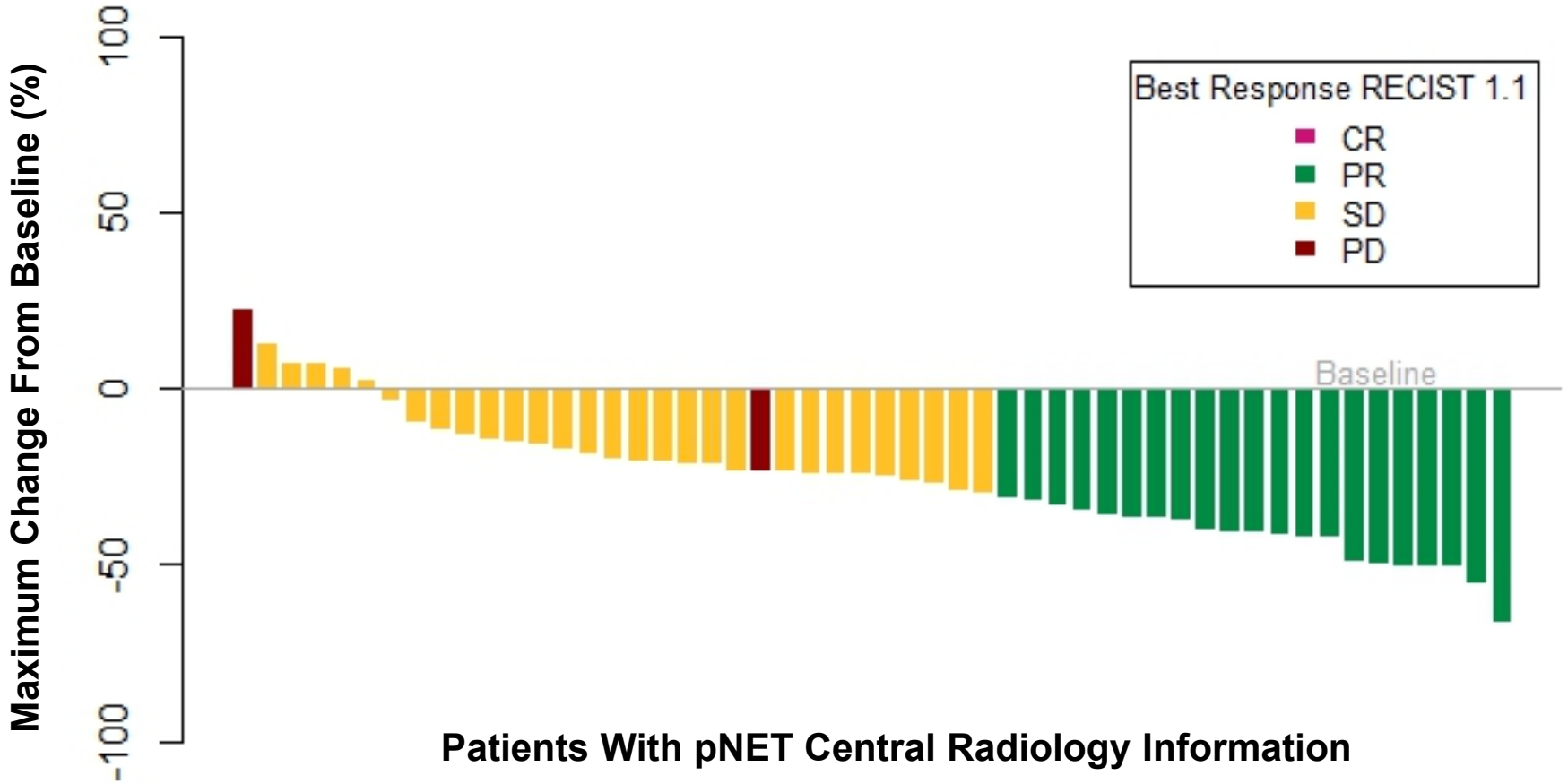
ORR: pNETs (Central Radiology Review)



ORR (95% CI): 40.4% (27.3-54.9)

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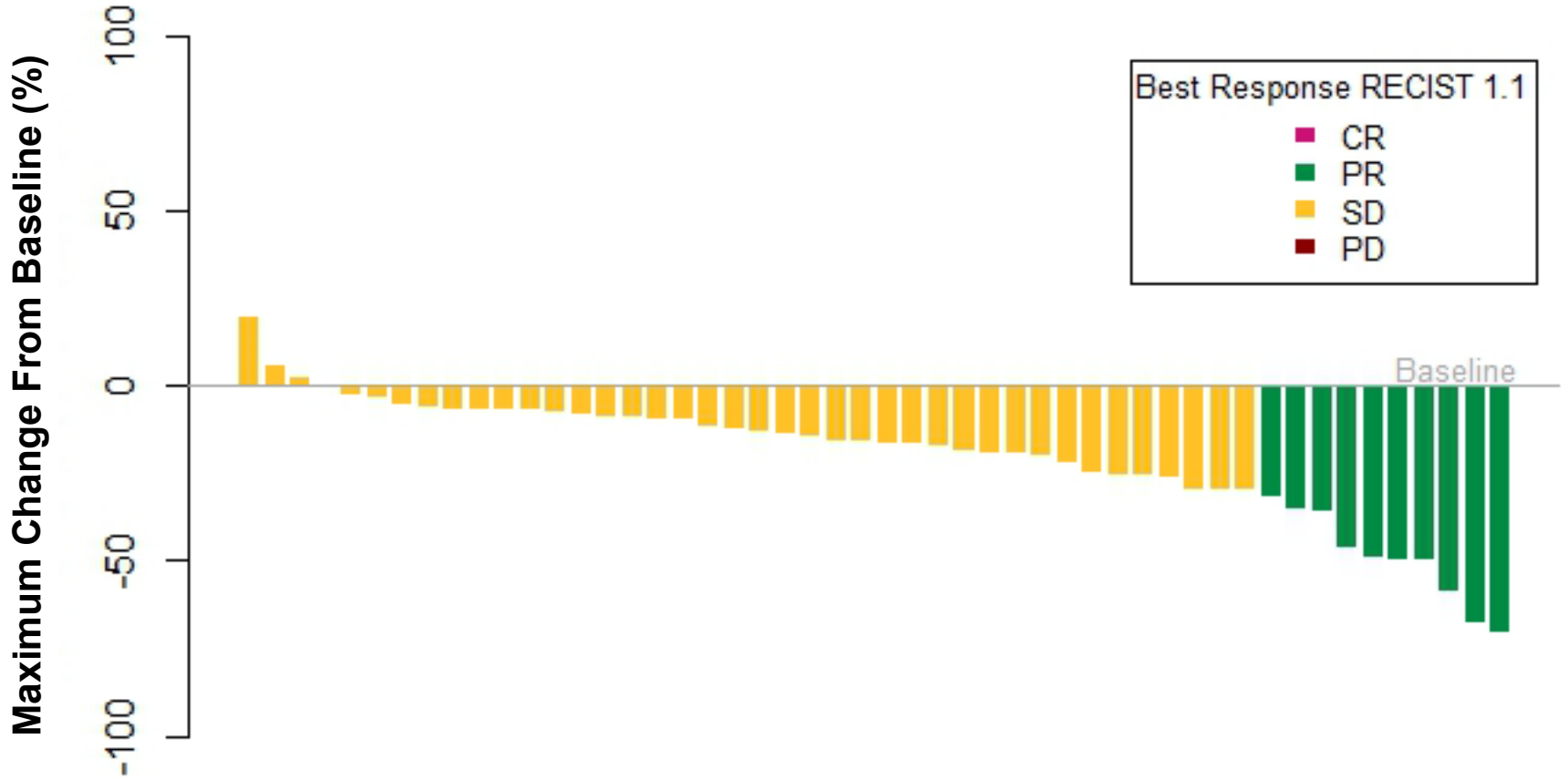
ORR: GI NETs (Central Radiology Review)



Patients With GI NET Central Radiology Information

ORR (95% CI): 18.5% (9.7-31.9)

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Overall Response Rate (Investigator Assessment)

	pNETs (n = 55)	GI NETs (n = 56)	Total (N = 111)
Patients with tumor assessments	**52**	**54**	**106***
Best overall response n (%)			
CR	**0**	**0**	**0**
PR	**18 (34.6)**	**11 (20.3)**	**29 (27.3)**
SD	**30 (57.7)**	**43 (79.6)**	**73 (68.8)**
PD	**4 (7.7)**	**0**	**4 (3.7)**
Not evaluable	**0**	**0**	**0**

*Five patients withdrew the Informed Consent before the first post-basal tumor assessment.

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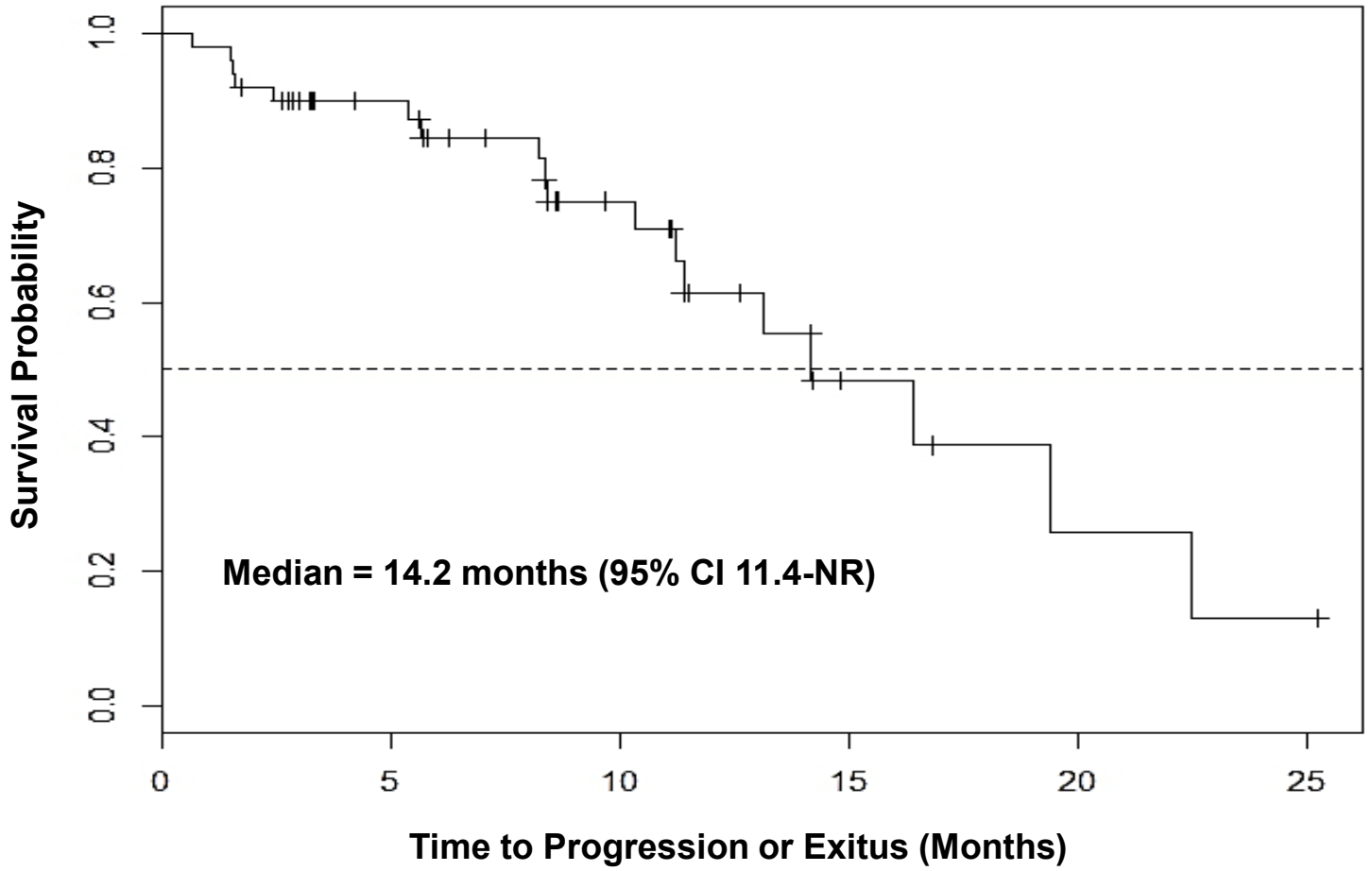
Progression-Free Survival: pNETs



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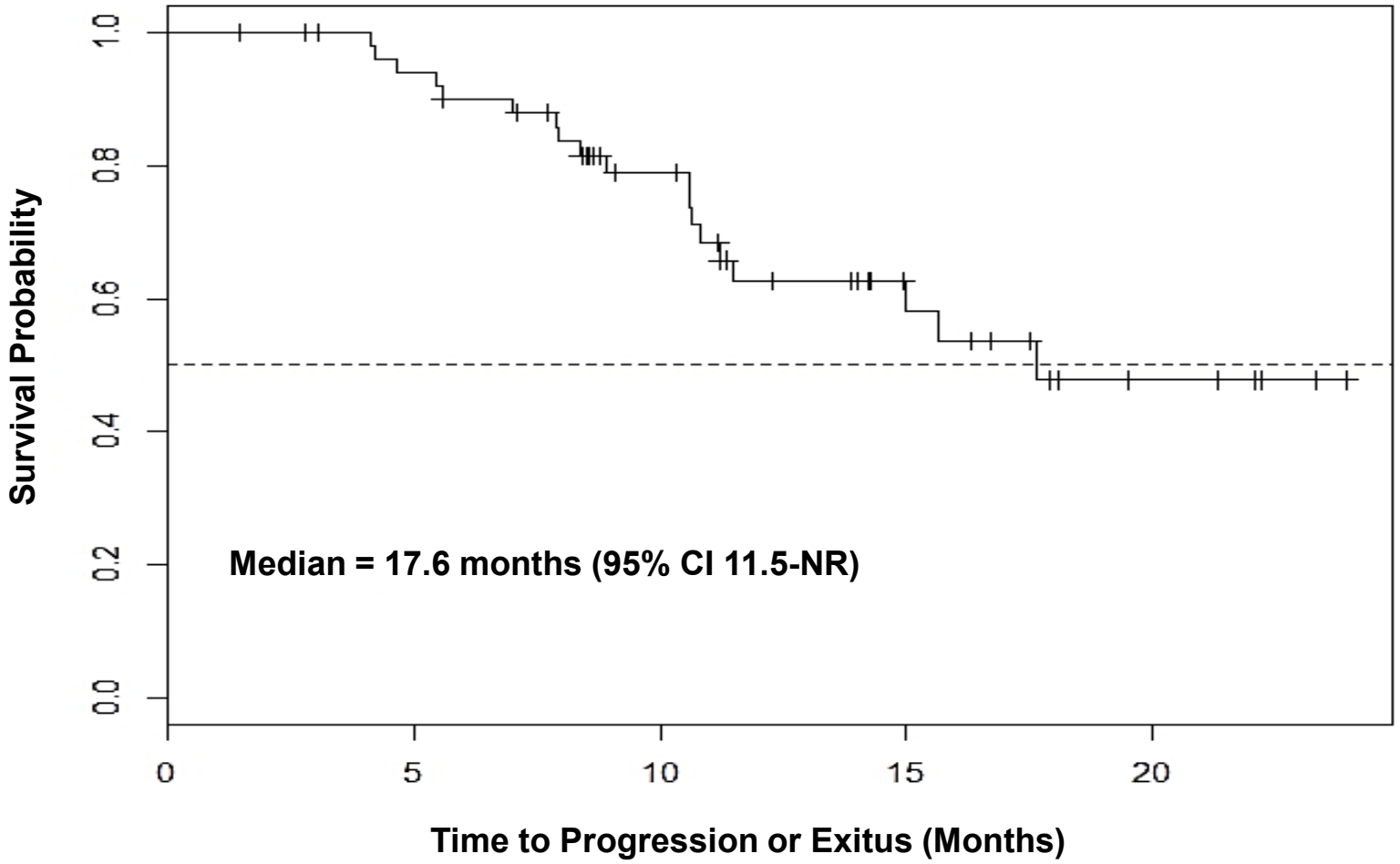
Progression-Free Survival: GI NETs



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Dose Modifications and Adverse Events

	pNETs (n = 55)	GI NETs (n = 56)
Dose modifications Patients (%)		
Dose reduction/interruption, n (%)	47 (88.6)	51 (91.1)
Definitive drug interruption due to side effects, n (%)	6 (10.9)	10 (17.8)
Total number of adverse events, n (%)		
Grade 1/2	894 (90.7)	862 (89.8)
Grade 3	85 (8.6)	92 (9.6)
Grade 4	5 (0.5)	6 (0.6)
Grade 5*	1 (0.1)	0

*1 patient presented grade 5 toxicity: Acute renal insufficiency

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Safety Profile

Adverse Event	pNETs (n = 55)		GI NETs (n = 56)	
	Grade 1/2, n (%)	Grade 3/4, n (%)	Grade 1/2, n (%)	Grade 3/4, n (%)
Asthenia/fatigue	32 (58.1)	3 (5.4)	26 (46.4)	12 (21.4)
Hypertension	24 (43.6)	11 (20)	25 (44.6)	12 (21.4)
Diarrhea	19 (34.5)	4 (7.2)	30 (53.5)	4 (7.1)
Nausea	17 (30.9)	1 (1.8)	12 (21.4)	-
Mucosal inflammation	16 (29)	1 (1.8)	10 (17.8)	-
Hypothyroidism	16 (29)	-	15 (26.7)	-
Headache	14 (25.4)	-	12 (21.4)	-
Vomiting	13 (23.6)	4 (7.2)	8 (14.2)	1 (1.8)
Abdominal pain	10 (18.1)	2 (3.6)	17 (30.3)	3 (5.3)
Anorexia	11 (20)	-	17 (30.3)	2 (3.5)
Arthralgia	11 (20)	-	6 (10.7)	-
Rash	8 (14.5)	1 (1.8)	6 (10.7)	-
Proteinuria	7 (12.7)	-	9 (16)	2 (3.5)
HFS	6 (10.9)	2 (3.6)	7 (12.5)	2 (3.5)

HFS, hand-foot syndrome

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Conclusions

- **Lenvatinib showed the highest reported ORR by central radiology assessment with a targeted agent in advanced NETs: 29.2%**
  - **pNETs: 40.4% (95% CI 27.3-54.9)**
  - **GI NETs: 18.5% (95% CI 9.7-31.9)**
- **Efficacy has been demonstrated in pretreated population showing a promising PFS in both cohorts (pNETs & GI NETs)**
- **Safety profile was consistent to prior studies with lenvatinib**
- **Biomarker studies are currently ongoing**

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