New Tyrosine Kinase Inhibitors in NENs

Jaume Capdevila, MD, PhD

GI and Endocrine Tumor Unit
Vall d'Hebron University Hospital
Developmental Therapeutics Unit
Vall d'Hebron Institute of Oncology (VHIO)

VHIO
VALL D'HEBRON
Institute of Oncology

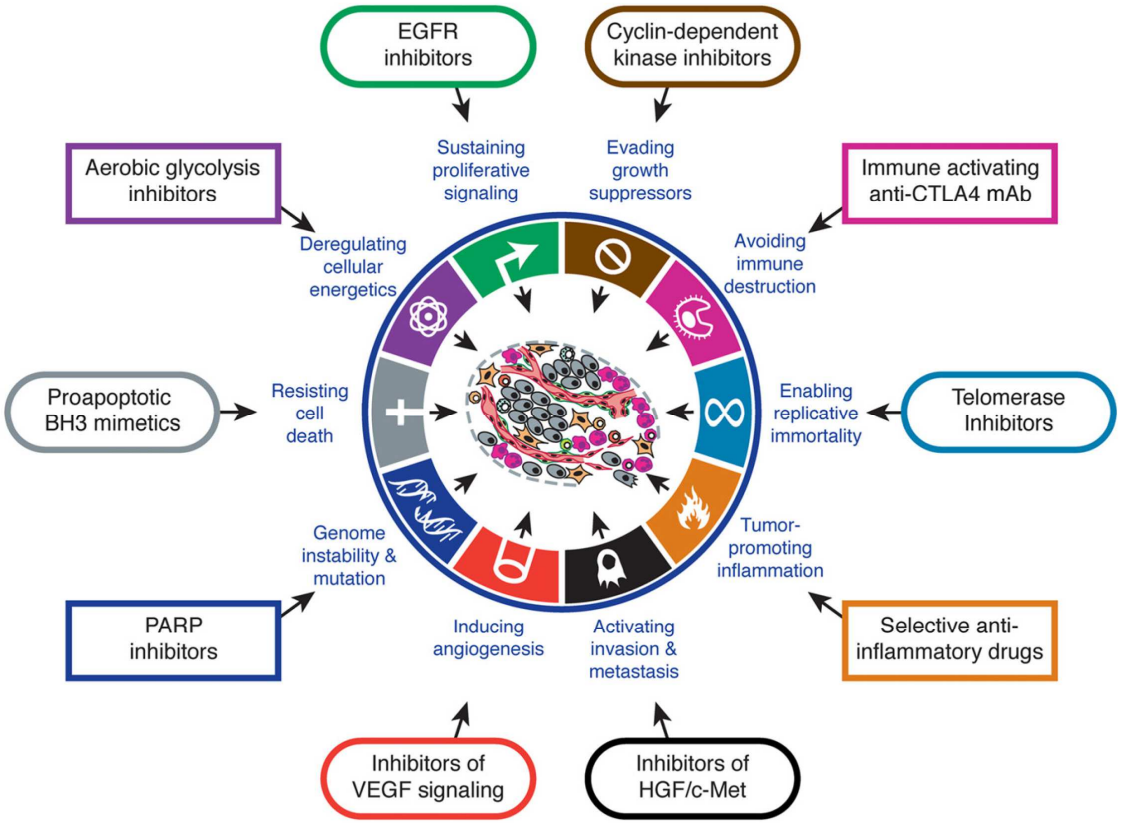
Disclosure slide

- Personal conflicts of interest: Scientific consultancy role (speaker and advisory roles) from Novartis, Pfizer, Ipsen, Exelixis, Bayer, Eisai, Advanced Accelerator Applications, Amgen, Sanofi and Merck Serono.

- Research support : Research grants from Novartis, Pfizer, Astrazeneca, Advanced Accelerator Applications, Eisai and Bayer.

NEOANGIOGENESIS AND NETS

NEOANGIOGENESIS AS ONE OF THE FIRST HALLMARKS OF CANCER DESCRIBED



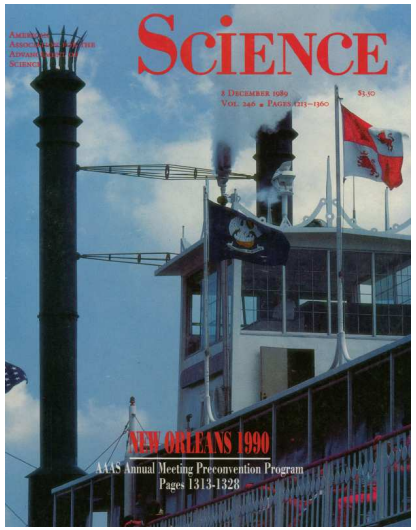
Hanahan D & Weinberg RA. *Cell* 2011

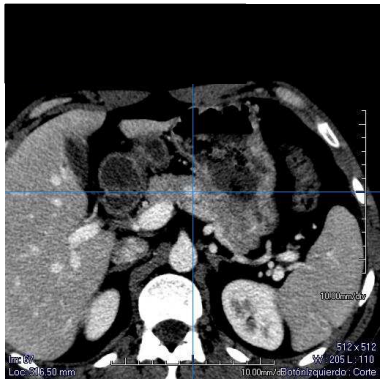
Vall d'Hebron Hospital

VHIO VALL D'HEBRON Institute of Oncology

Transgenic Mice as Probes into Complex Systems

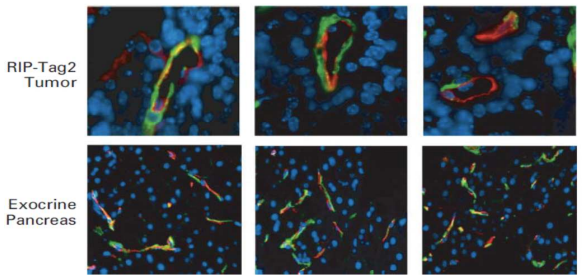
DOUGLAS HANAHAN

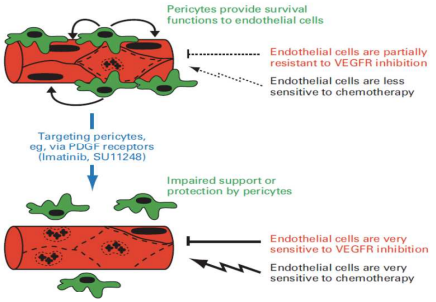


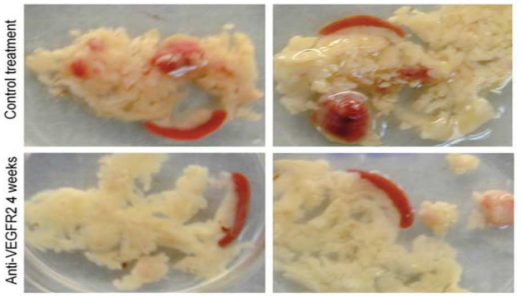


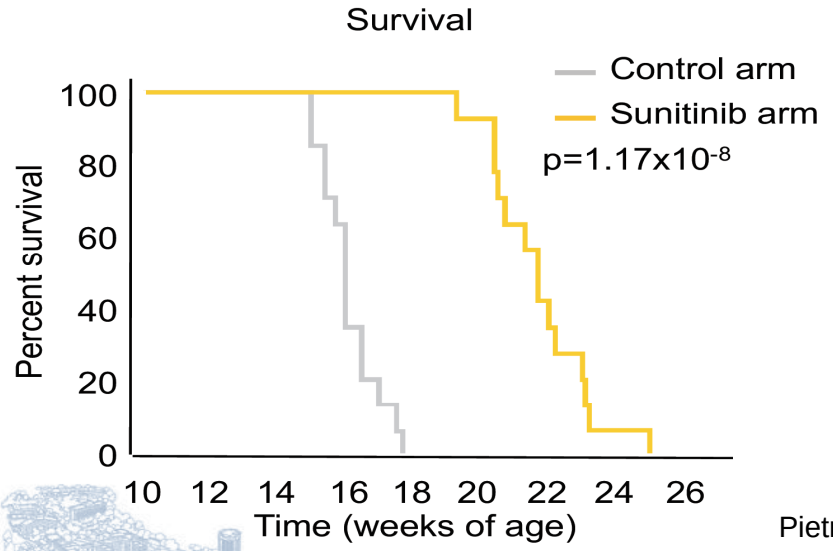
Hanahan D. *Science 1989*

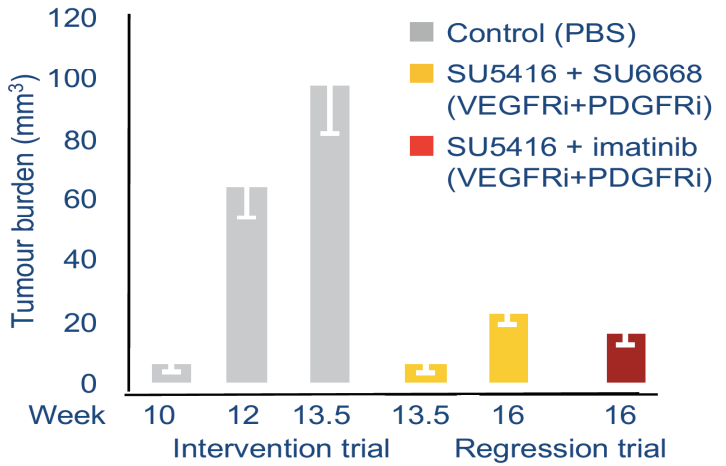
ANTIANGIOGENESIS IN NETS: TARGETING PERICYTES AND ENDOTHELIAL CELLS











Pietras K & Hanahan D. *J Clin Oncol* 2005; Casanovas O, et al. *Cancer Cell* 2005

QUICK DEVELOPMENT OF A MULTIKINASE INHIBITOR IN NETs

Preclinical	2005–2007	▪ In the RIP-Tag transgenic mouse model of pancreatic islet cell carcinoma, sunitinib: ◆ reduced tumour burden and increased survival[1] ◆ reduced endothelial cell population (VEGFR inhibition)[2] ◆ reduced pericyte coverage (PDGFR inhibition)[2]
Phase I	2006	▪ A study of sunitinib in solid tumours including 4 patients with non-pancreatic NET,[3] induced 1 confirmed partial response and 1 stable disease
Phase II	2008	▪ An open-label, multicentre study of sunitinib (50 mg/day on Schedule 4/2) in 66 patients with advanced pancreatic NET[4] yielded 16.7% partial response, 56.1% stable disease ≥6 months and median time to progression of 7.7 months
Phase III	2011	▪ A phase III, randomised, double-blind trial of sunitinib vs placebo in patients with progressive, well-differentiated pancreatic NET yielded longer PFS (11.4 vs. 5.5 months), OS (HR 0.409) and greater response rate (9.3% vs 0%)[5]

1. Pietras *J Clin Oncol* 2005; 2. Yao EORTC-NCI-AACR 2007. 3. Faivre *J Clin Oncol* 2006; 4. Kulke *J Clin Oncol* 2008; 5. Raymond *N Eng J Med* 2011

SEVERAL MECHANISMS OF RESISTANCE OF MKIs

Angiogenesis is a vital, multi-step process that causes proliferation of new blood vessels from pre-existing capillaries, via...

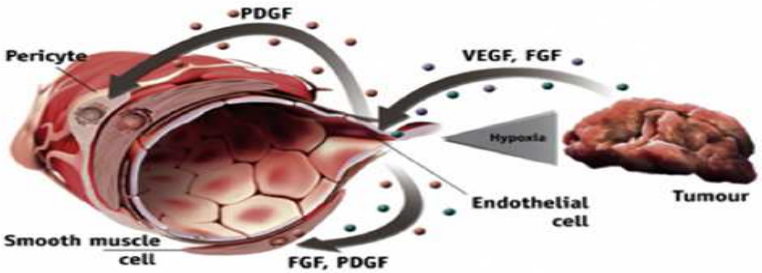
- Proliferation of activated endothelial cells
- Migration and assembly of endothelial cells into new capilliary tubes
- Synthesis of new basement membrane
- Maturation of new vessels with formation of vascular lumen

A variety of solid tumour cells, including CRC, exploit this process, leading to:

- Aberrant architectural and functional traits
- Increased permeability
- Abnormal levels of proliferation and apoptosis
- High intratumoral pressure
- Paradoxical hypoxia

VEGF pathway

- Most extensively characterized angiogenic pathway
- VEGF is the central mediator of angiogenesis
- **VEGF ligands:** VEGF-A, VEGF-B, VEGF-C, VEGF-D, PlGF
- **VEGF receptor TKs:** VEGFR-1 (Flt-1), VEGFR-2 (KDR), VEGFR-3



PDGF pathway

- **PDGF ligands:** PDGF-A, PDGF-B, PDGF-C, PDGF-D
- **PDGF receptors:** PDGFRα, PDGFRβ
- All four ligands form homodimers, and PDGF-A and PDGF-B form heterodimers

FGF pathway

- FGF family consists of 18 ligands
- **FGF receptors:** FGFR-1–4, FGFR-5 (does not contain intracellular TK domain)
- Acts synergistically with VEGF in inducing angiogenesis
- Acts synergistically with PDGF-BB to promote tumor angiogenesis and metastasis

Capdevila J, et al. *Crit Rev Hematol Oncol* 2014

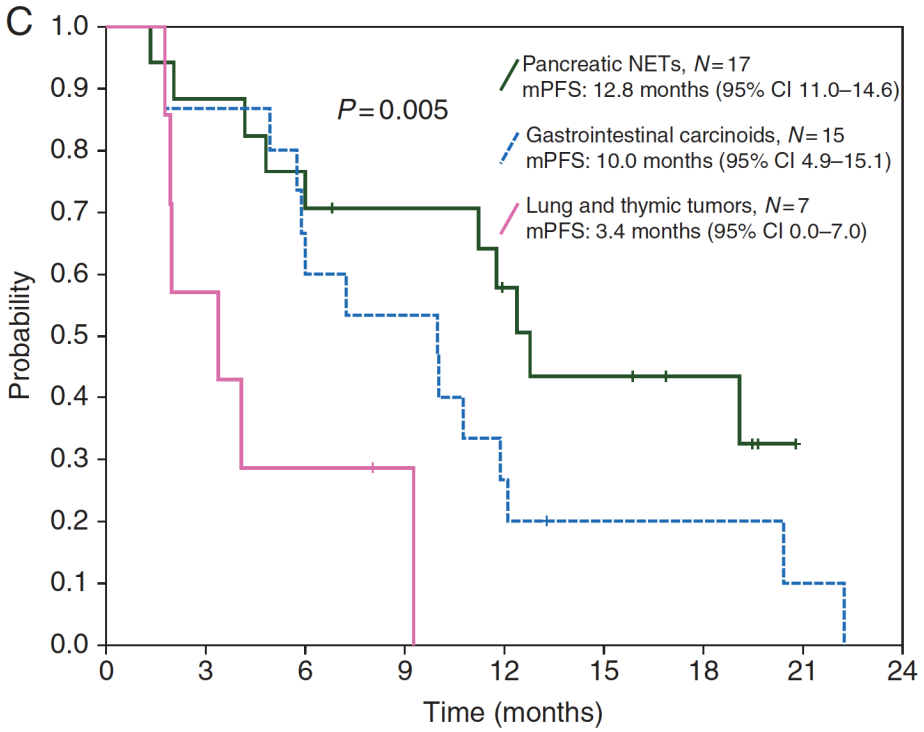
IF WE TRY SIMILAR MKIs, WE OBTAIN SIMILAR RESULTS…

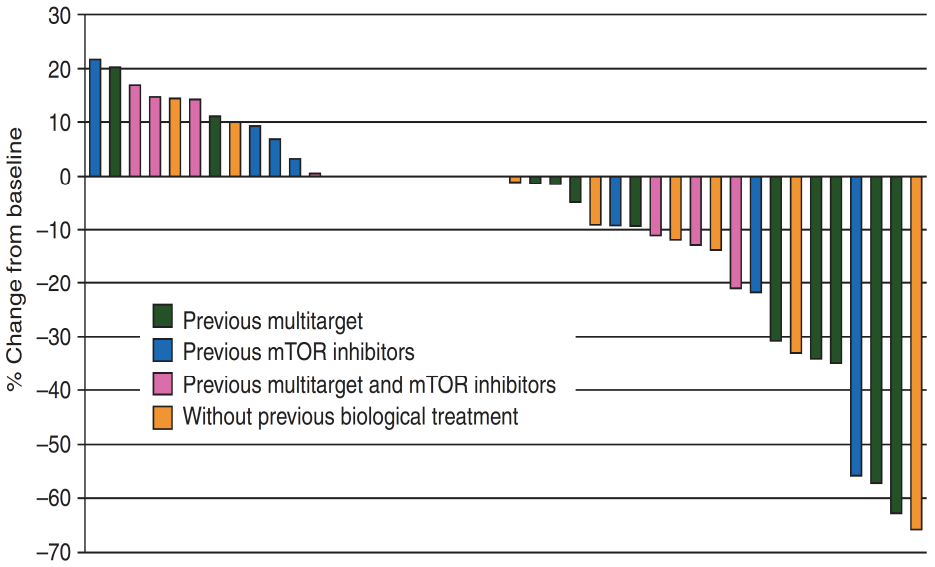
Table 2 Profile of tyrosine kinase inhibitors in development[57]

TKR	IC_{50} (nmol/L)							
	Motesanib	**Axitinib**	**Sorafenib**	**Sunitinib**	**Pazopanib**	**Vandetanib**	**Cabozantinib**	**Lenvatinib**
VEGFR-1	2	0.1	26	10	10	–	–	22
VEGFR-2	3	0.2	90	10	30	40	0.035	4
VEGFR-3	6	0.29	20	10	47	110	–	5.2
PDGFRβ	84	2	57	39	84	–	–	39
c-KIT	8	1.7	68	1-10	74	–	–	–
RET	59	1.2	47	10	–	130	4	35
RET/PTC	–	–	50	224	–	100	–	–
BRAF	–	–	25	–	–	–	–	–
Others (IC_{50})	–	–	–	–	–	EGFR (500)	c-MET (1.8)	FGFR-1 (1.8)

Capdevila J, et al. Eur J Endocrinol 2017

PHASE II DATA OF PAZOPANIB IN NETS



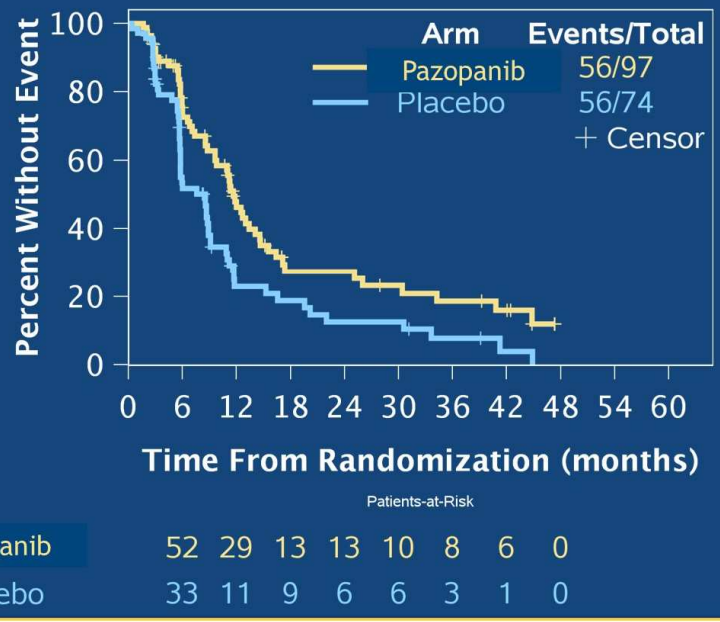


ORR: 4%

Grande E, et al. Ann Oncol 2015

RANDOMIZED PHASE II STUDY WITH NO IMPRESSIVE RESULTS…

Progression Free Survival (Central Review, ITT)



	Pazopanib (N=97)	Placebo (N=74)
No. of events	56	56
12 mo. PFS, % (90% UCB*)	46.4 (54.7)	22.9 (31.4)
Median PFS, mo. (90% UCB)	**11.6 (13.0)**	**8.5 (8.9)**
HR (90% UCB)	**0.53 (0.69)**	**REF**
Stratified Log-Rank P-value = 0.0005		
Adj. HR** (90% UCB)	0.57 (0.74)	REF
Adjusted Log-Rank P-value = 0.0020		

**Gender, functional tumor, age, and stratification factors (concurrent SSA, site of primary)

*UCB=Upper Confidence Bound

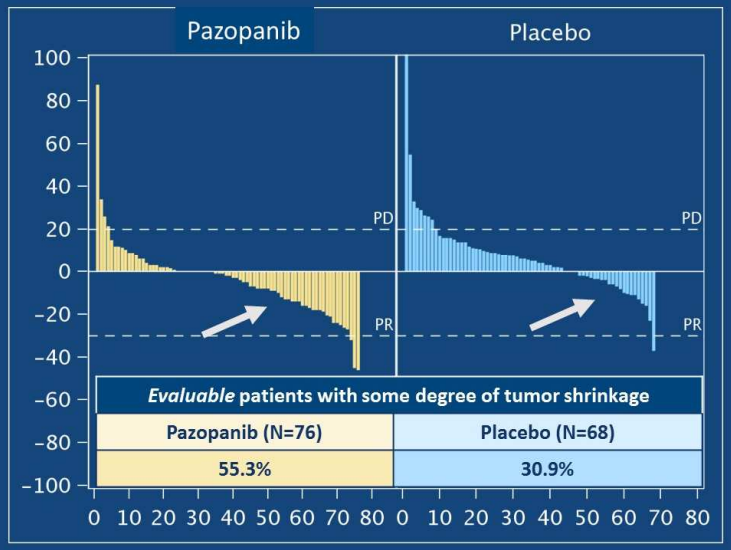
PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19 Slides are the property of the author, permission required for reuse.

PRESENTED BY: Emily Bergsland, MD Abstract #4005

Bergsland E, et al. ASCO 2019

RANDOMIZED PHASE II STUDY WITH NO IMPRESSIVE RESULTS…

Best Response & Waterfall Plots for RECIST Measurements (Central Review)



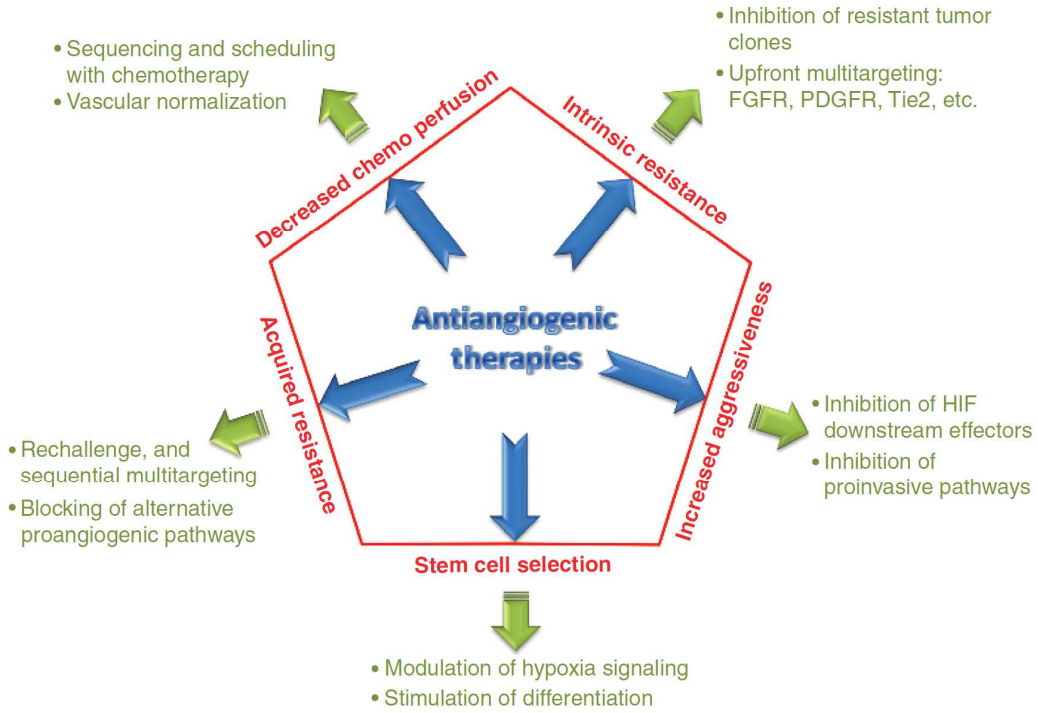
Best Response (ITT) by RECIST 1.1	Pazopanib (N=97)	Placebo (N=74)
Partial Response*, N (%)	2 (2.1)	0
Stable Disease , N (%)	70 (72.2)	54 (73.0)
Progressive Disease, N (%)	4 (4.1)	14 (18.9)
Not Evaluable, N (%)	21 (21.6)	6 (8.1)
No treatment	*8*	*2*
Did not reach 1st re-staging	*8*	*3*
Pending receipt/review	*5*	*1*
P-value	0.0010	

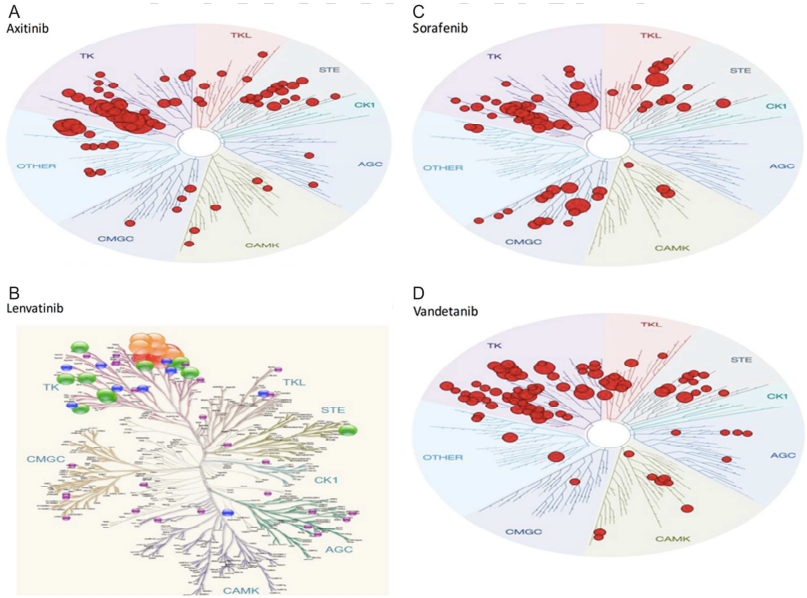
* Confirmed PR; No complete responses observed.

Slides are the property of the author, permission required for reuse.

Bergsland E, et al. ASCO 2019

CAN WE REVERT RESISTANCE TO ANTIANGIOGENICS WITH NEW MKIs ?



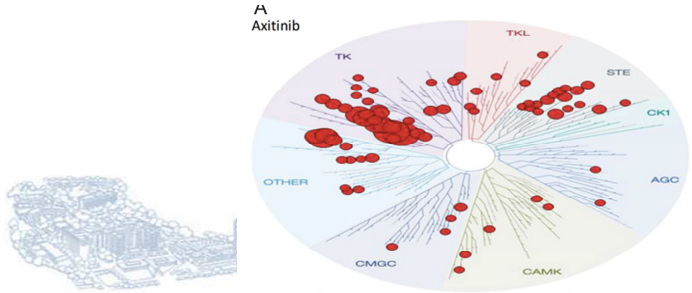


Moserle L, et al. *Cancer Discovery* 2014; Capdevila J, et al. Eur J Endocrinol 2017

CAN WE FOCUS MORE ON VEGFR?

Table 2 Profile of tyrosine kinase inhibitors in development[57]

TKR	IC_{50} (nmol/L)							
	Motesanib	**Axitinib**	**Sorafenib**	**Sunitinib**	**Pazopanib**	**Vandetanib**	**Cabozantinib**	**Lenvatinib**
VEGFR-1	2	0.1	26	10	10	–	–	22
VEGFR-2	3	0.2	90	10	30	40	0.035	4
VEGFR-3	6	0.29	20	10	47	110	–	5.2
PDGFRβ	84	2	57	39	84	–	–	39
c-KIT	8	1.7	68	1-10	74	–	–	–
RET	59	1.2	47	100	–	130	4	35
RET/PTC	–	–	50	224	–	100	–	–
BRAF	–	–	25	–	–	–	–	–
Others (IC_{50})	–	–	–	–	–	EGFR (500)	c-MET (1.8)	FGFR-1 (1.8)

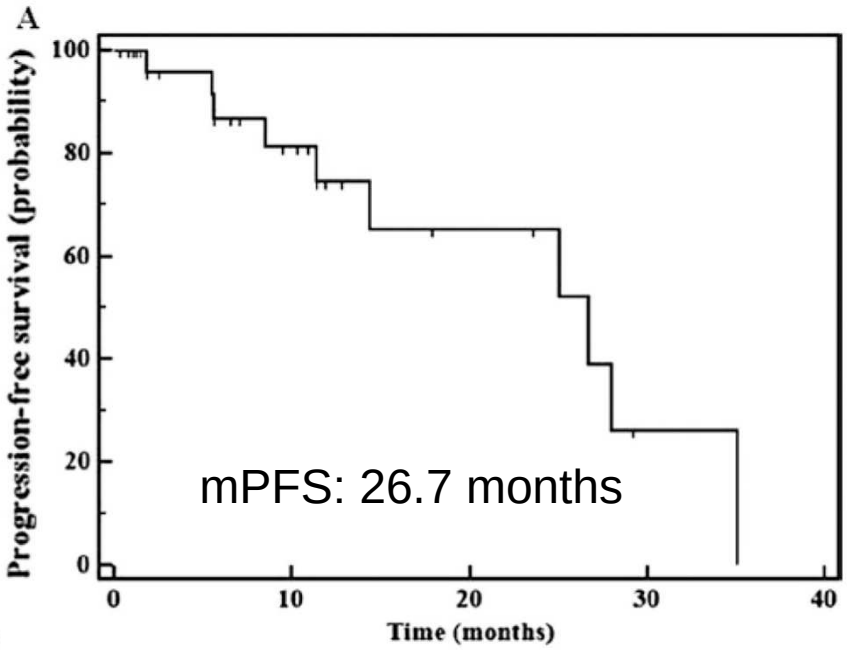


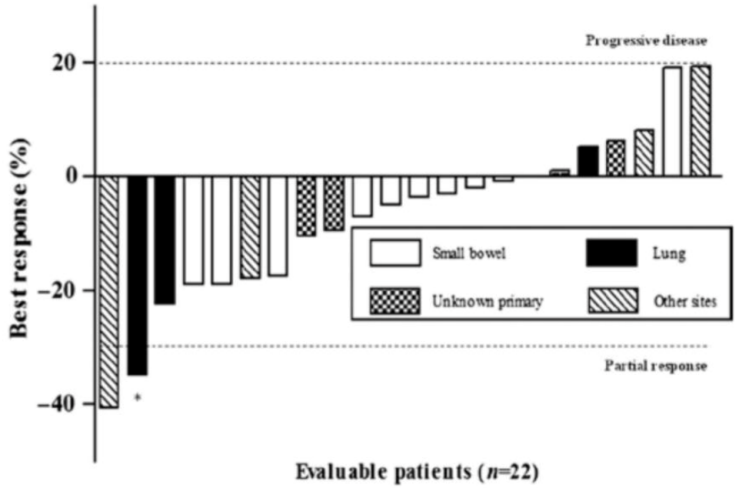
Capdevila J, et al. Eur J Endocrinol 2017

Stepanovich & Capdevila Biologics: Targets and Therapy 2014

INCREASED ANTIANGIOGENIC EFFECT

AXITINIB





ORR: 3%

Grade 3/4 AEs: 63% HT

Strosberg JR, et al. Endocr Relat Cancer 2016

AXITINIB PHASE III TRIAL IN NON-PANCREATIC NETS

GETNE
Grupo Español de Tumores Neuroendocrinos y Endocrinos

AXINET TRIAL: Double-blind randomized phase II-III study of Axitinib and octreotide vs Placebo and octreotide in advanced G1-2 EP-NETs

- Well- or moderately-differentiated G1-2 NETs of non-pancreatic origin
- Functioning or non-functioning. ECOG PS 0-1.
- Disease progression in the prior 12 months
- Up to 2 prior lines of systemic therapy
- Prior SSA, IFN, PRRT, Everolimus allowed
- Prior VEGF/VEGFR-targeted therapy not permited

N = 253

R

1:1

Axitinib 5 mg bid + Octreotide LAR 30/4w

Placebo bid + Octreotide LAR 30/4w

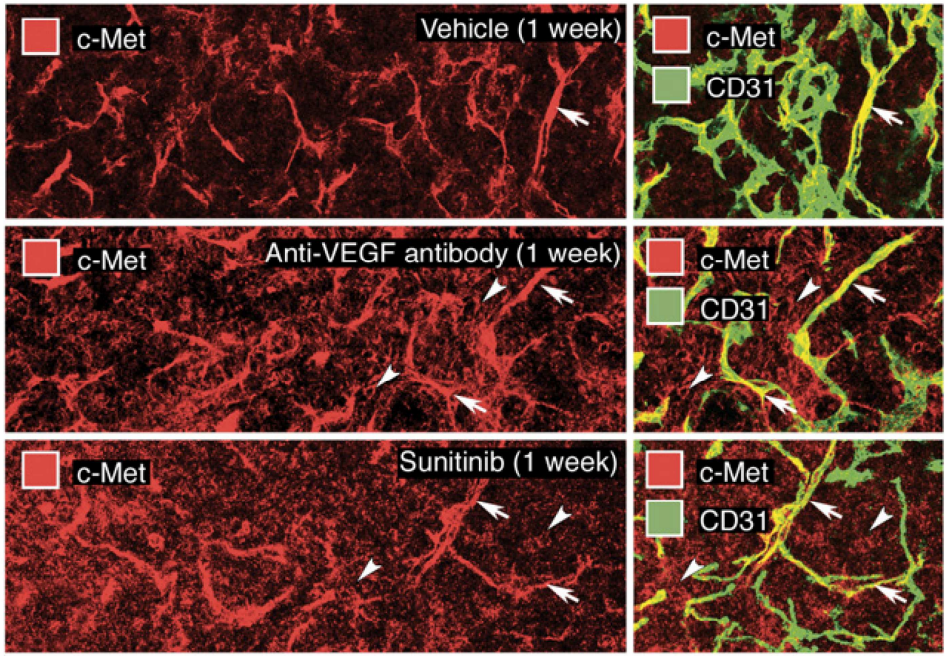
Primary endpoint: PFS

Estimated accrual completion: June 2019

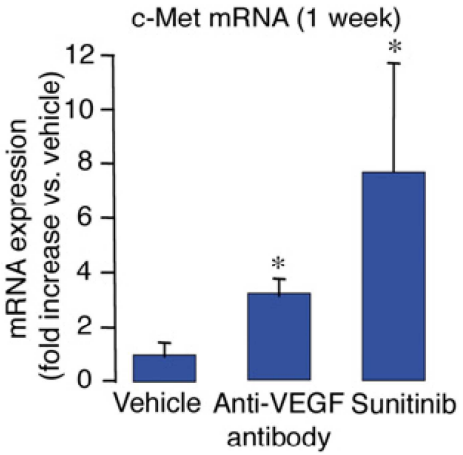
Stratification Factors:
- Time from diagnosis to study entry (greater or lower than 12 months),
- Site of primary tumor (GI vs non-GI)
- Ki-67 (≤ 5% vs >5%).

C-MET OVEREXPRESSION AS MECHANISMS OF RESISTANCE TO ANTIANGIOGENIC THERAPY

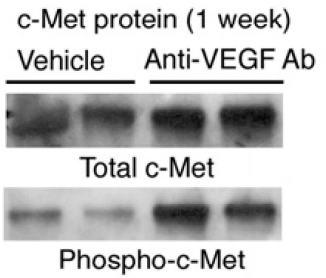
F



G

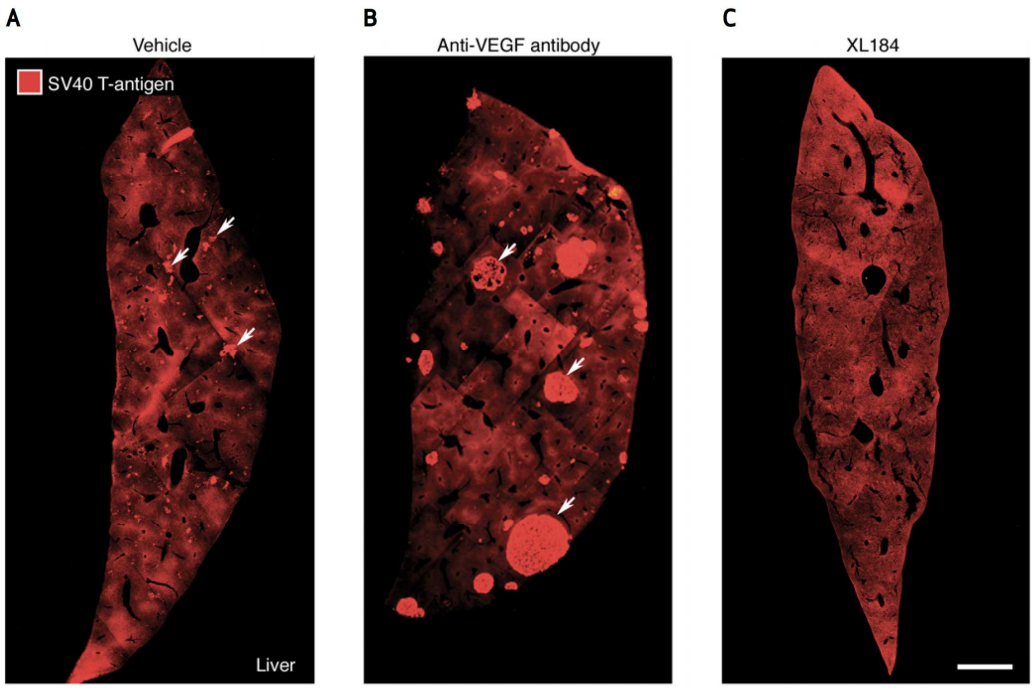


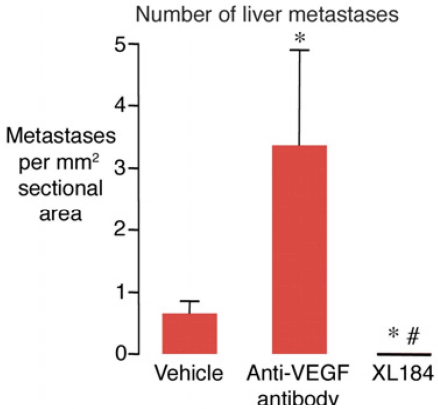
H

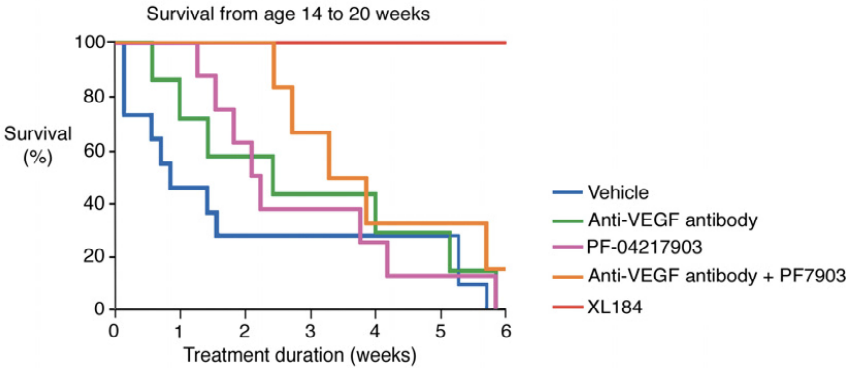


Sennino, et al. *Cancer Discovery* 2012

C-MET OVEREXPRESSION AS MECHANISMS OF RESISTANCE TO ANTIANGIOGENIC THERAPY





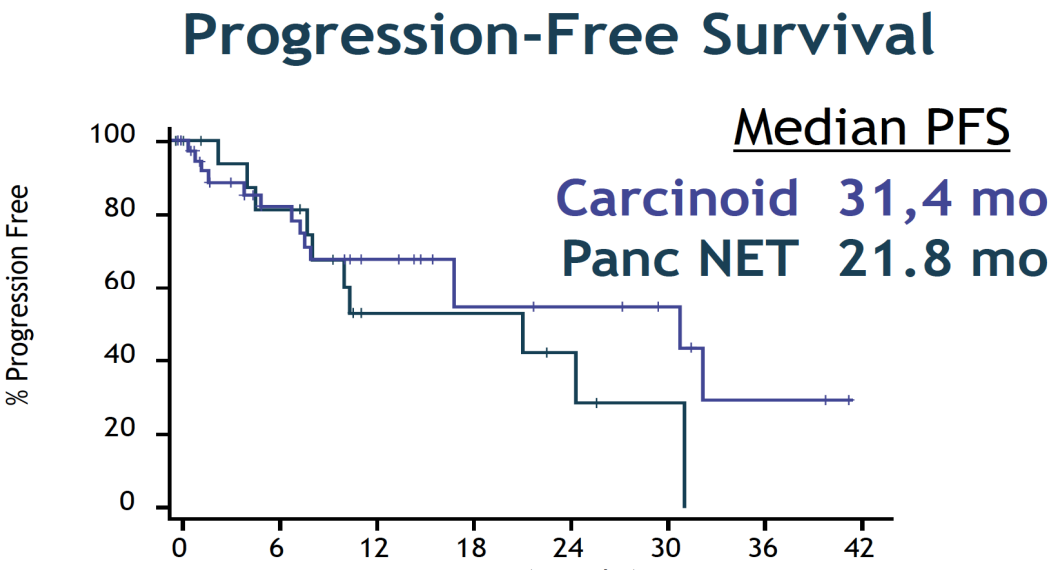


Sennino, et al. *Cancer Discovery* 2012

INCREASE THE SPECTRUM OF TARGETS TO REVERT/PREVENT RESISTANCE: c-MET

CABOZANTINIB

Response	Pancreatic NET (n = 20) n, %	Carcinoid (n = 41) n, %
PR	3, **15%**	6, **15%**
SD	15, 75%	26, 63%
PD	-	2, 5%
Unknown*	2, 10%	7, 17%

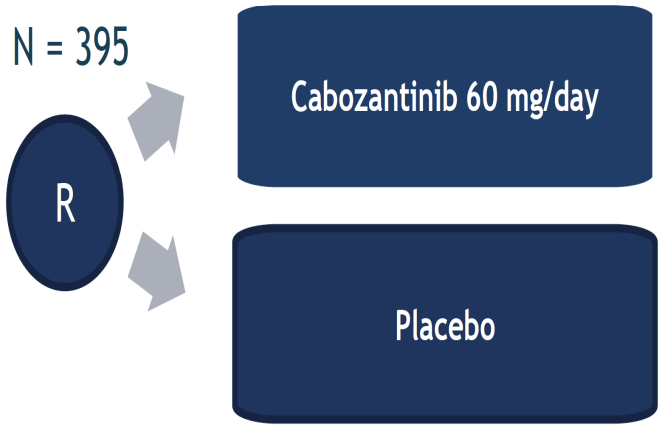


Chan JA, et al. ASCO GI 2018

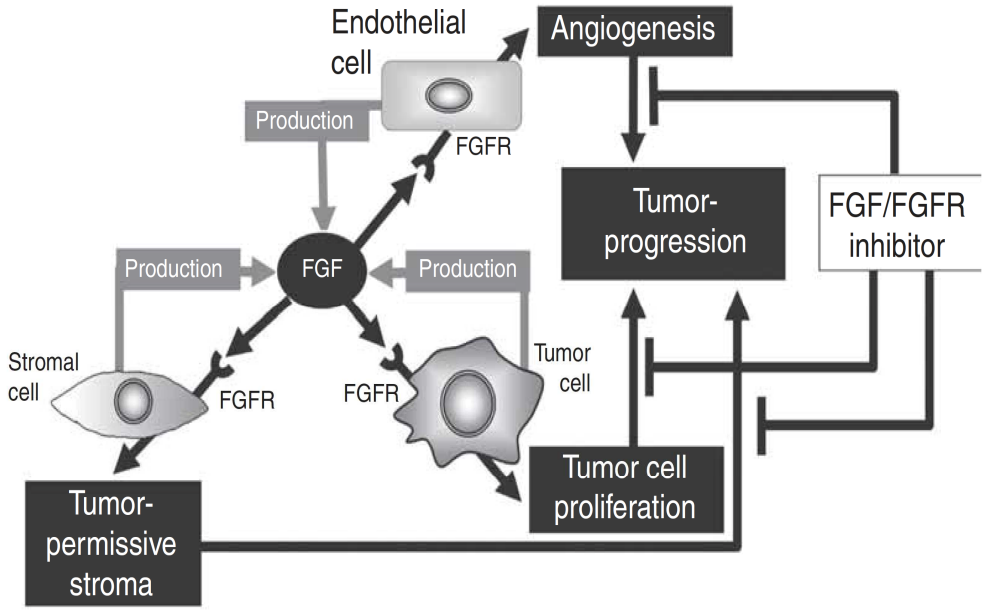
PHASE III STUDY OF CABOZANTINIB IN ALL NETS

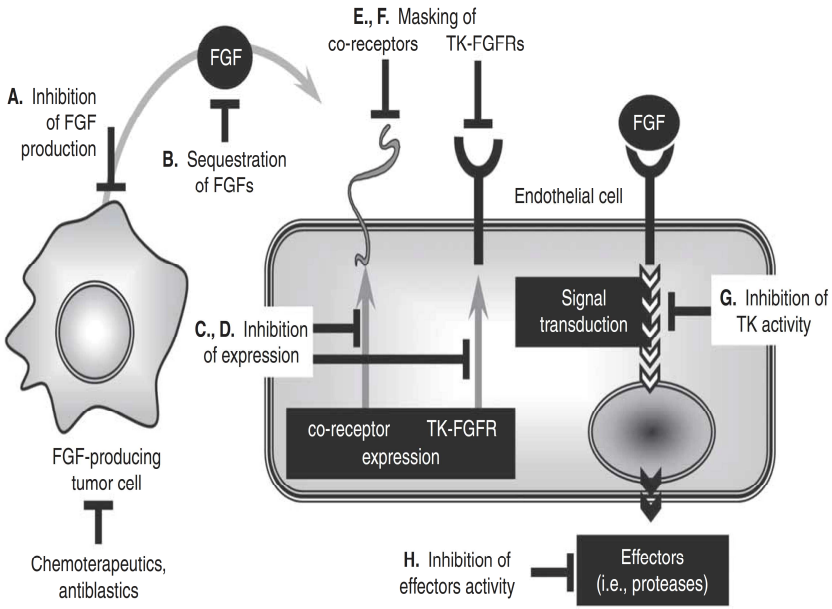
CABINET TRIAL: Double-blinded phase III study of Cabozantinib vs placebo in patients with advanced NETs after progression on everolimus

- Well- or moderately-differentiated neuroendocrine tumours of pancreatic and non-pancreatic origin
- Target lesions must have shown disease progression within **6 months**
- Patient must have failed **at least 1 prior systemic therapy that included everolimus**



FOCUSING ON FGFR PATHWAY. CAN WE INCREASE ANTIANGIOGENIC EFFECT?

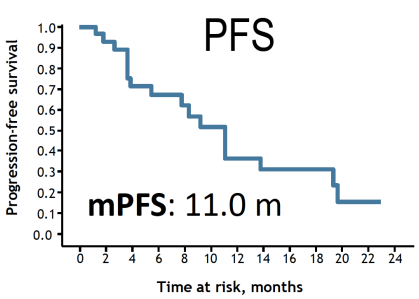


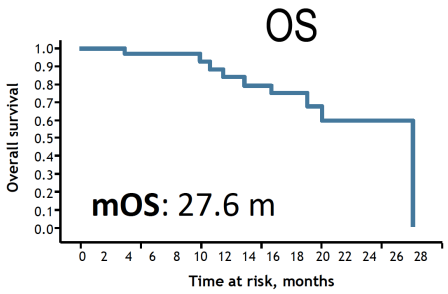


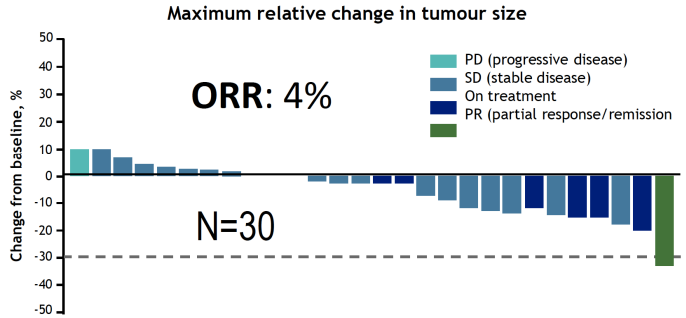
Ronca et al. Expert Opin Ther Targets 2015

NOT ALWAYS WHAT WE SEE IN THE LAB TRANSLATES TO THE CLINICS

NINDETANIB



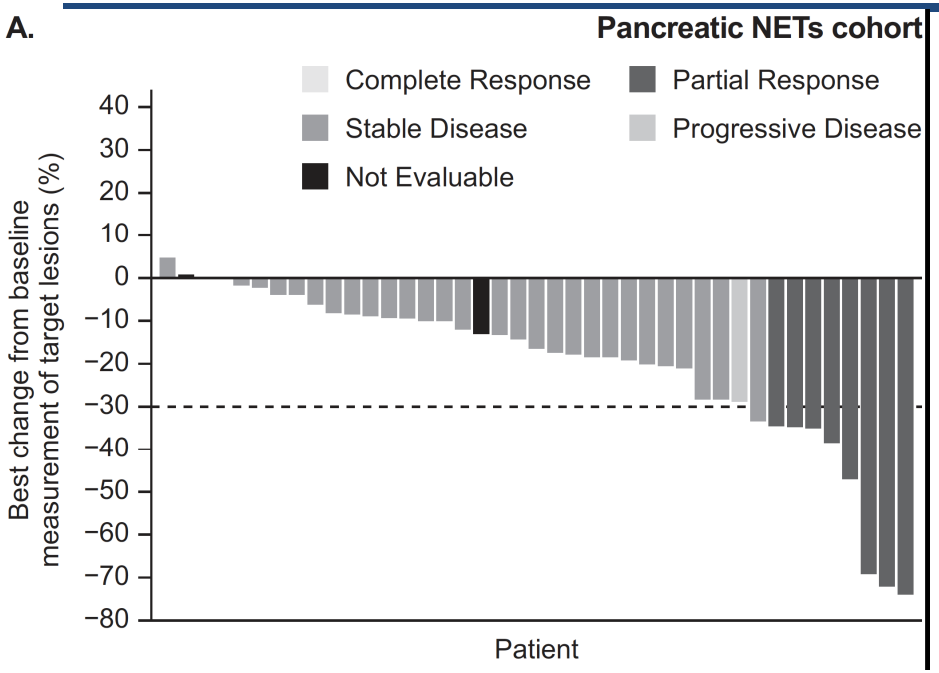


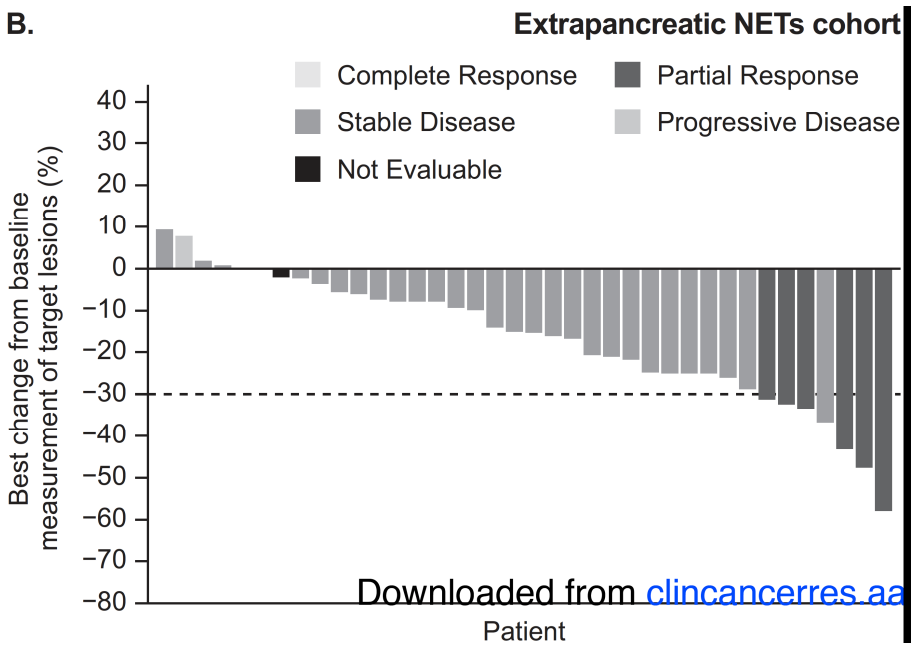


Adverse event	Grade 2	Grade 3
Neutropenia	1 (3%)	
Lymphopenia	4 (13%)	
Leucopenia	3 (10%)	
Nausea	2 (7%)	
Diarrhoea	3 (10%)	
Vomiting	1 (3%)	
Abdominal pain	4 (13%)	
Fatigue	2 (7%)	1 (3%)
Liver function ABN	3 (10%)	
Decreased appetite	2 (7%)	2 (7%)
Dysgeusia	1 (3%)	
Confusion	1 (3%)	
Renal failure	1 (3%)	
Hypertension	3 (10%)	**6 (20%)**
Troponin elevation		1 (3%)

Iyer R, et al. ASCO 2018

SURUFATINIB: A NEW VEGFR/FGFR MKI





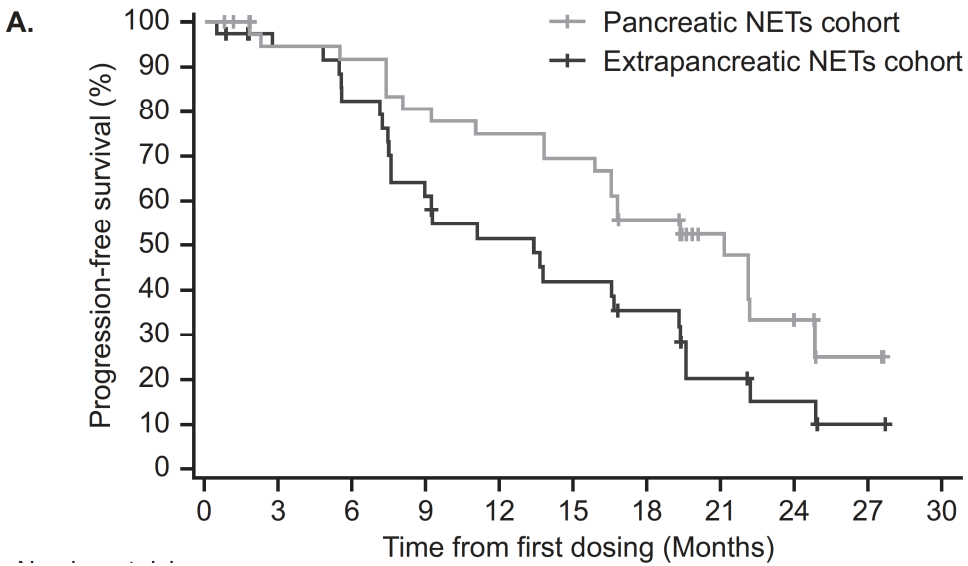
Downloaded from clincancerres.aa

Investigator: 19%
Central assessment: 12%

Investigator: 15%
Central assessment: 10%

Xu et al, Clin Cancer Res 2019

SURUFATINIB: A NEW VEGFR/FGFR MKI



PFS pan: 21.2 m

PFS extrapan: 13.4 m

Toxicity

Preferred Term	Grade 1–2 N (%)	Grade 3 N (%)	Grade 4 N (%)
Proteinuria	56 (69)	10 (12)	0
Diarrhea	53 (65)	5 (6)	0
Hypertension	22 (27)	27 (33)	0
Blood thyroid-stimulating hormone increased	42 (52)	0	0
Asthenia	34 (42)	2 (2)	0
Aspartate aminotransferase increased	31 (38)	1 (1)	1 (1)
Hypertriglyceridemia	26 (32)	5 (6)	0
Alanine aminotransferase increased	22 (27)	4 (5)	0
Hypoalbuminemia	25 (31)	0	0
Hyperbilirubinemia	23 (28)	2 (2)	0
Blood bilirubin increased	23 (28)	1 (1)	0
Edema peripheral	21 (26)	3 (4)	0
Face edema	21 (26)	2 (2)	0
Hyperuricemia	13 (16)	1 (1)	7 (9)

Xu et al, Clin Cancer Res 2019

SURUFATINIB IN CHINA ALREADY RECRUITED AND READY TO GO WORLDWIDE

SANET-ep

- G1 or G2 advanced extrapancreatic NETS incl. lung, thymus, GI and unknown origin
- No more than 2 prior systemic treatments
- Radiological documentation of PD within 12 month prior to randomization

N = 273

R

- Sulfatinib 300 mg/day
- Placebo

Primary endpoint: progression-free survival (PFS)
Estimated primary completion date: March 2018

ClinicalTrials.gov ID: NCT02589821

SANET-p

- G1 or G2 advanced pancreatic NETS
- No more than 2 prior systemic treatments, incl. SSA, INF, PRRT, chemo, or mTOR
- Radiological documentation of PD within 12 month prior to randomization

N = 195

R

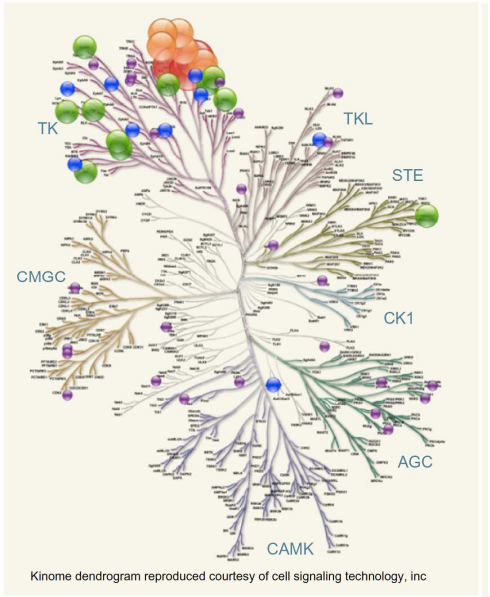
- Sulfatinib 300 mg/day
- Placebo

Primary endpoint: progression-free survival (PFS)
Estimated primary completion date: March 2018

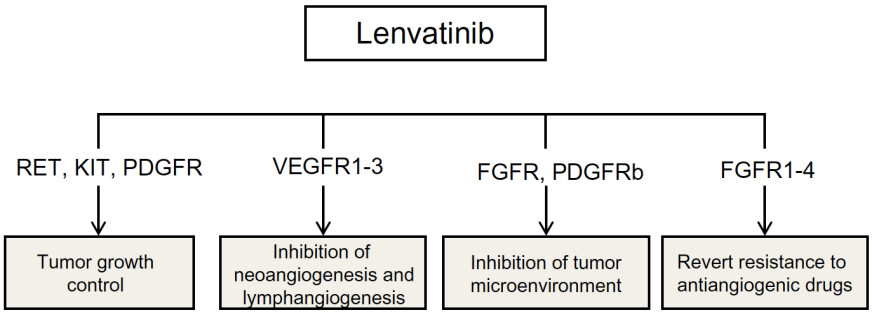
ClinicalTrials.gov ID: NCT02588170

LENVATINIB:
THE MOST POTENT VEGFR/FGFR IN CURRENT DEVELOPMENT

Lenvatinib



Kinome dendrogram reproduced courtesy of cell signaling technology, inc



METHODS

TALENT Trial: A phase II Trial to Assess the efficacy of LENvatinib in metastatic neuroendocrine Tumors (GETNE 1509)

Lenvatinib 24 mg qd

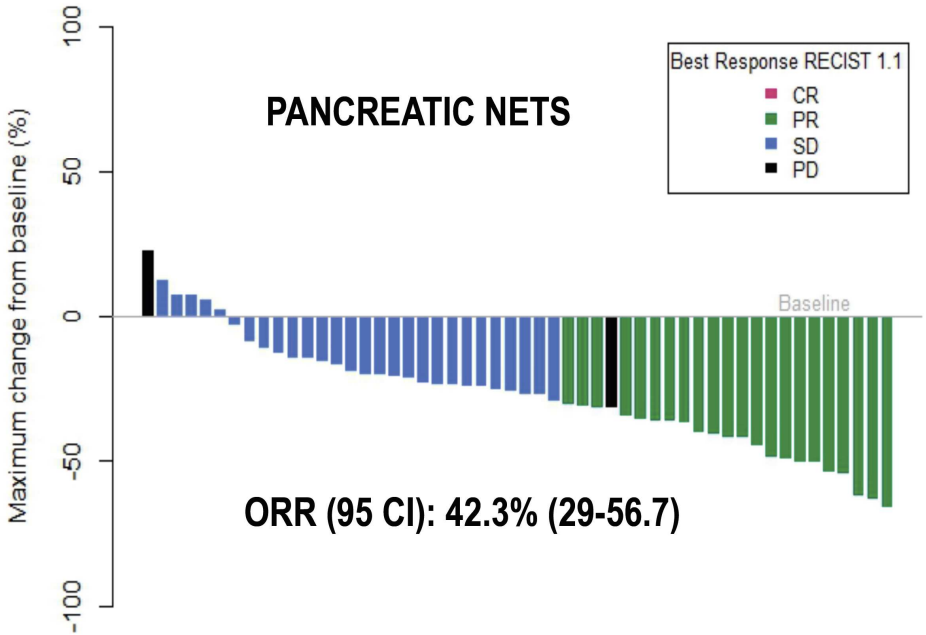
N = 110 pts

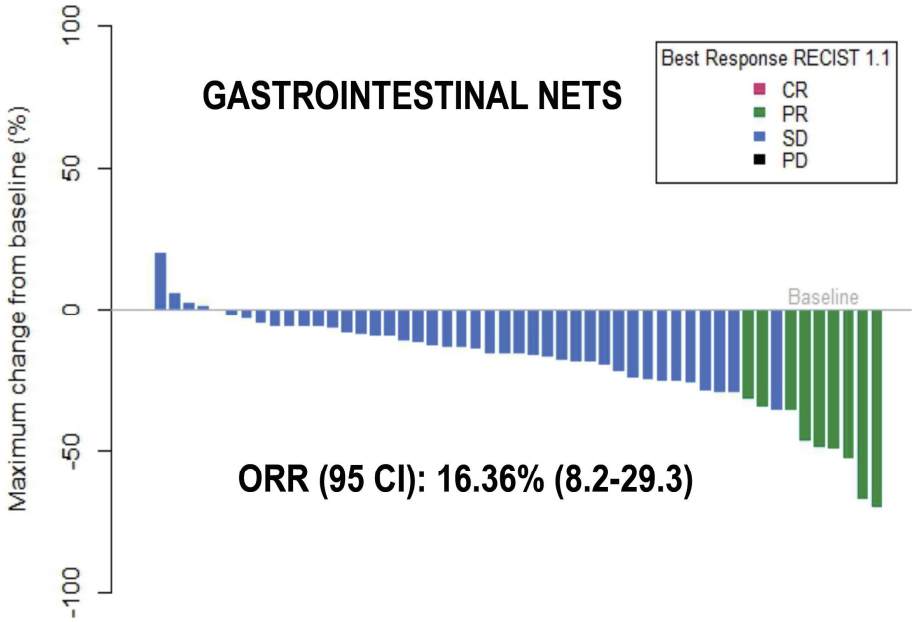
Cohort A: Patients with advanced/metastatic G1/G2 **neuroendocrine tumors of the pancreas** after progression to a previous targeted agent

Cohort B: Patients with advanced/metastatic G1/G2 **neuroendocrine tumors of the gastrointestinal tract** after progression to somatostatin analogs

Capdevila J, et al. ASCO 2019; Stepanovich & Capdevila Biologics: Targets and Therapy 2014

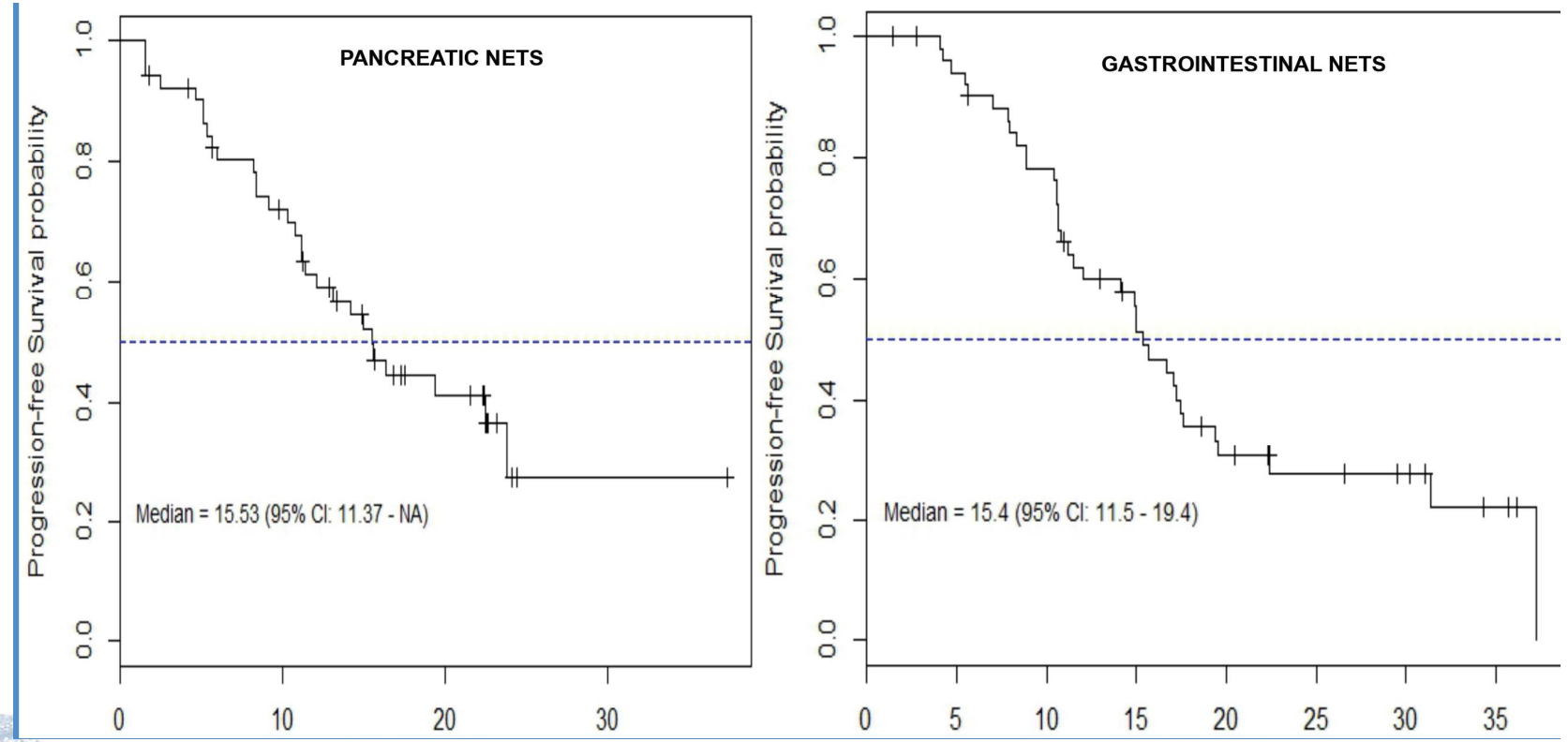
THE HIGHEST ORR EVER REPORTED BY CENTRAL RADIOLOGY ASSESSMENT IN NETs





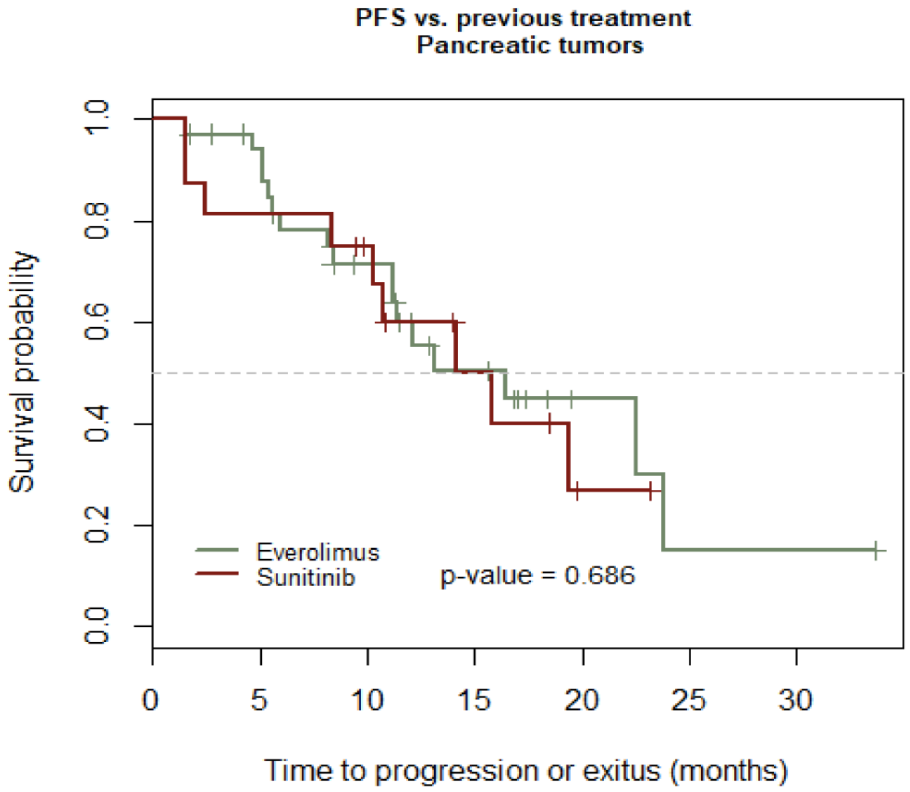
Capdevila J, et al. ASCO 2019

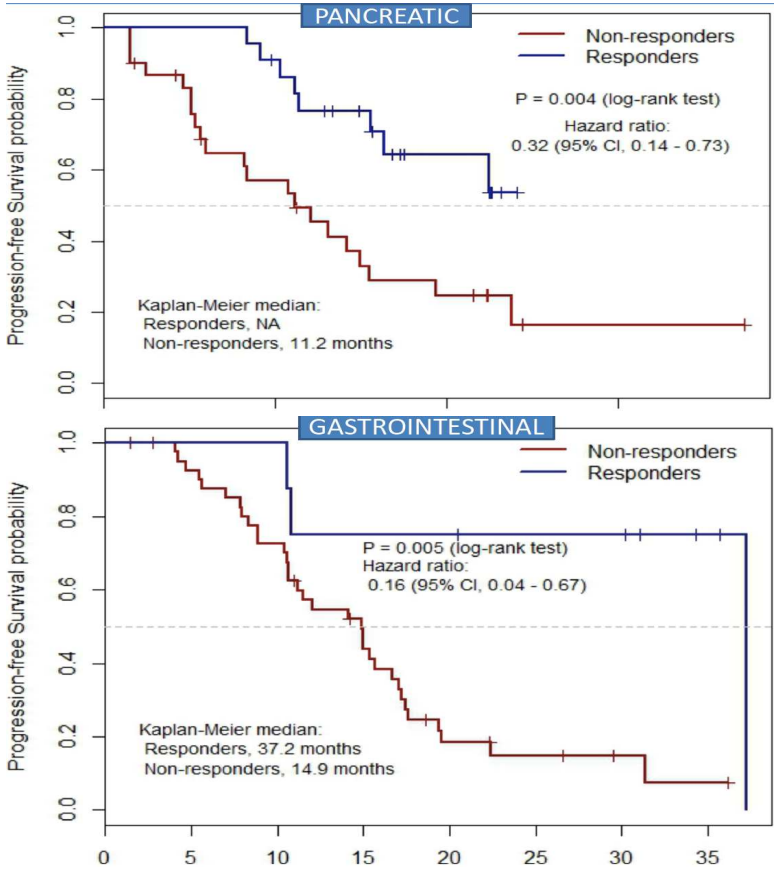
WITH PROMISING PFS AFTER FAILURE TO PRIOR TARGETED AGENTS



Capdevila J, et al. ASCO 2019

AND BEING ABLE TO REVERT RESISTANCE





Capdevila J, et al. ASCO 2019

WITH KNOWN TOXICITY PROFILE

Safety profile

Dose reductions/interruptions were needed in 91.8% with a median dose of lenvatinib 20 mg qd.

	Pancreatic NETs (n=55)		Gastrointestinal NETs (n=55)	
Description **MedDRA Preferred Term (PT). CTCAE.**	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Asthenia	28 (50.91%)	3 (5.45%)	22 (39.29%)	9 (16.07%)
Hypertension	27 (49.09%)	12 (21.82%)	30 (53.57%)	13 (23.21%)
Diarrhoea	24 (43.64%)	4 (7.27%)	27 (48.21%)	8 (14.29%)
Dysphonia	21 (38.18%)	0 (0%)	16 (28.57%)	0 (0%)
Hypothyroidism	20 (36.36%)	0 (0%)	18 (32.14%)	0 (0%)
Nausea	20 (36.36%)	1 (1.82%)	13 (23.21%)	0 (0%)
Mucosal inflammation	17 (30.91%)	2 (3.64%)	11 (19.64%)	0 (0%)
Headache	15 (27.27%)	0 (0%)	14 (25%)	0 (0%)
Pyrexia	15 (27.27%)	0 (0%)	5 (8.93%)	1 (1.79%)
Abdominal pain	14 (25.45%)	3 (5.45%)	20 (35.71%)	2 (3.57%)
Vomiting	13 (23.64%)	5 (9.09%)	9 (16.07%)	1 (1.79%)

Capdevila J, et al. ASCO 2019

OTHER MKIs OUT OF ANTIANGIOGENESIS FOCUS?

- Bruton's tyrosine kinase
  - ORR: 0%
  - PFS: 3.1 months

- No NENs in NTRK trials…

- RET inh for MTC and MPPGs, but anectodical in GI-NENs…

Al-Toubah T, et al. ASCO GI 2019;

MKIs IN COMBINATION…¿?

*Exploratory basket trial of **CAB**ozantinib plus **AT**ezolizumab in advanced and progressive neoplasms of the **EN**docrine system – The **CABATEN** study*

GETNE
Grupo Español de Tumores Neuroendocrinos y Endocrinos

Cabozantinib 60 mg PO
+
Atezolizumab 1200 mg Q3W

Cohort 1	**Well-differentiated neuroendocrine tumors of lung origin** (WHO grade 1 and 2, typical and atypical carcinoids)	N = 9 + 15 pts
Cohort 2	**Anaplastic thyroid cancer**	N = 9 + 15 pts
Cohort 3	**Adrenocortical carcinoma**	N = 9 + 15 pts
Cohort 4	**Pheochromocytoma and paraganglioma**	N = 9 + 15 pts
Cohort 5	**Well-differentiated neuroendocrine tumors of gastroenteropancreatic and origin** (WHO grade 1 and 2)	N = 9 + 15 pts
Cohort 6	**Poorly differentiated neuroendocrine tumors** (WHO grade 3), excluding small cell lung cancer	N = 9 + 15 pts

Primary endpoint: Overall Objective Response Rate
Estimated Primary Completion Date: June 2020

PI: Dr. Jaume Capdevila
Dr. Enrique Grande

HOW I SEE THE FUTURE FOR MKIs IN NENs?

panNETs

Sunitinib	Surufatinib/Lenvatinib	Cabozantinib
2019	>2023	>2025

siNETs/lungNETs

∅	Axitinib	Surufatinib*/Lenvatinib	Cabozantinib*
2019	2021	>2023	>2025

*Only siNETs