X SIMPOSIO INTERNACIONAL GETNE

Current and future role of multitargeted agents in NETs

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GETNE
Grupo Español de Tumores Neuroendocrinos

Disclosures

Honoraria:

Novartis, Ipsen, Pfizer, Keocyt, SIRTex, Celgene

Grant Funding:

Novartis, AstraZeneca

Overview

- **Sunitinib**
- Sorafenib
- Axitinib
- Cabozantinib

Sunitinib – a new treatment option in 2011

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Sunitinib Malate for the Treatment of Pancreatic Neuroendocrine Tumors

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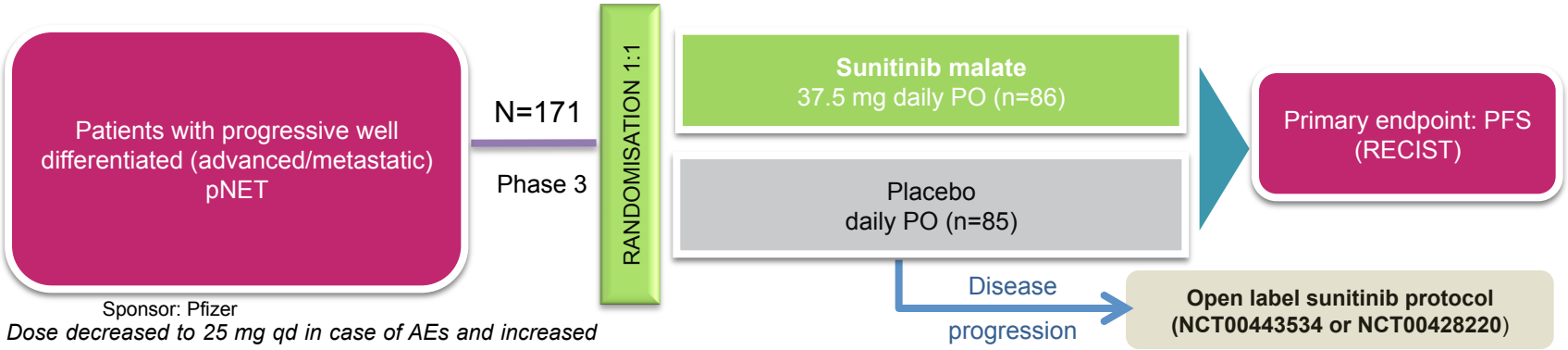
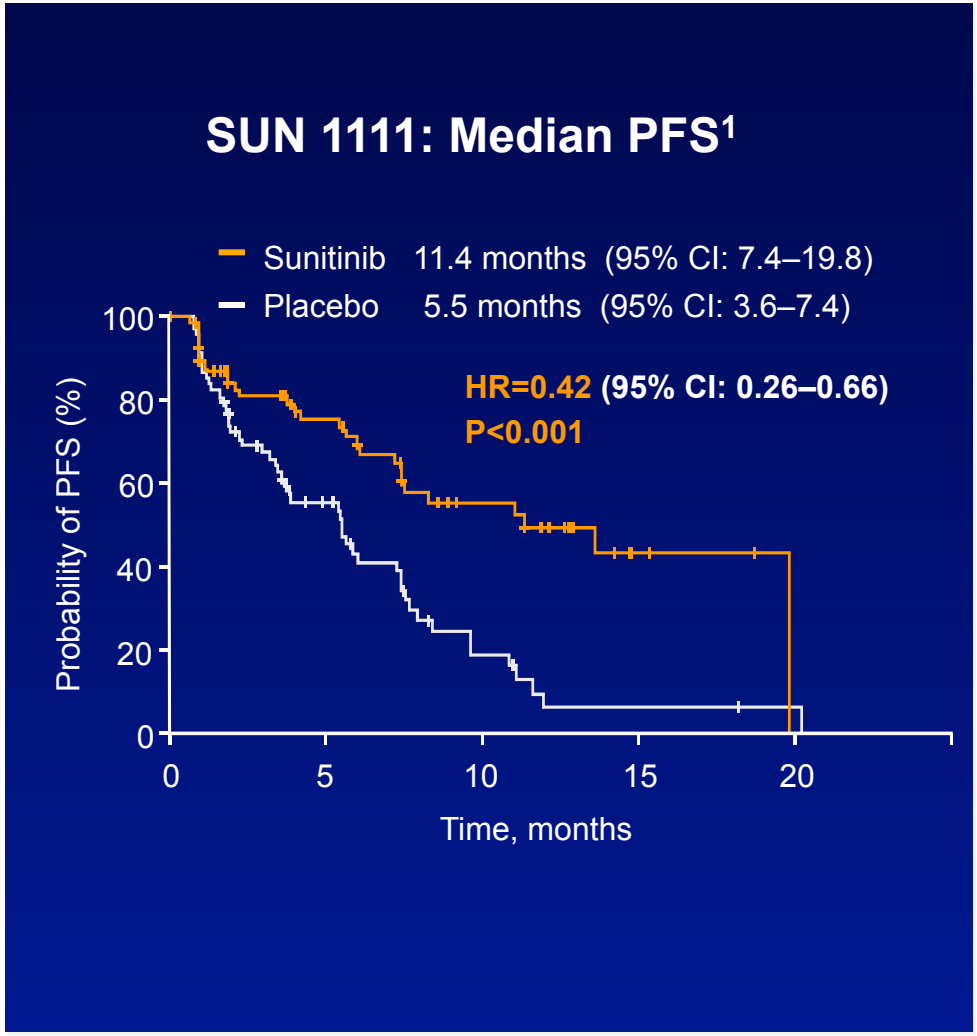
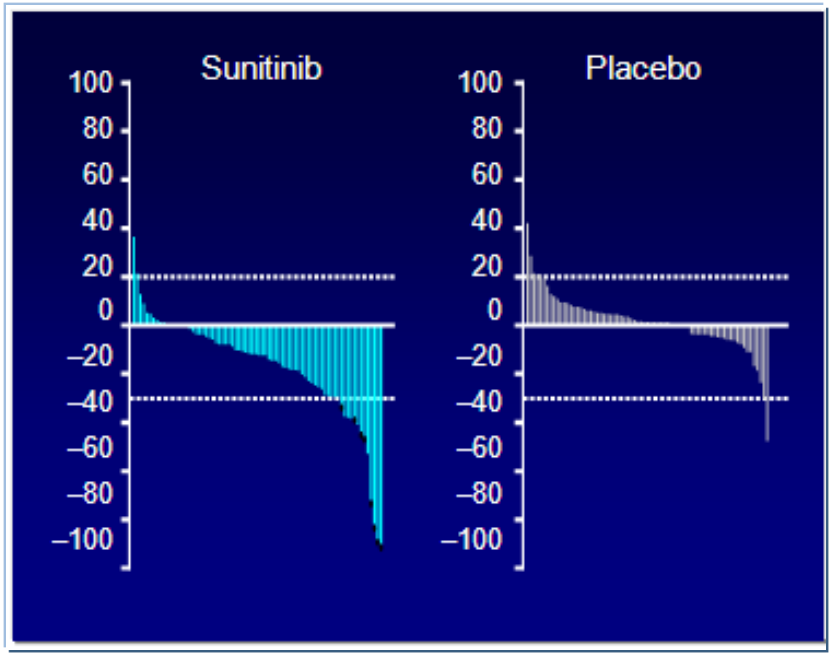


Sponsor: Pfizer

Dose decreased to 25 mg qd in case of AEs and increased to 50 mg qd if no response seen after 8 weeks

Sunitinib – a new treatment option in 2011





- Improved PFS
- Effect is mainly cytostatic
- Quality of life data
  - Good at baseline
  - Only diarrhoea increased with sunitinib

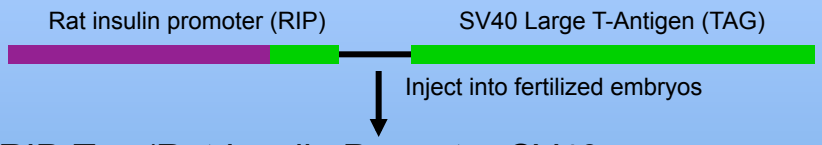
1. Raymond E et al. *N Engl J Med* 2011;364:501–1

Experience with Sunitinib in NET: Moving from the Laboratory to the Clinic

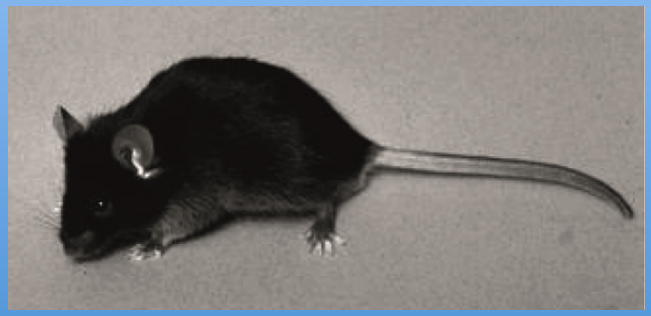
Preclinical 2005–2007

- 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]

Schematic on generating RIP-Tag model



RIP-Tag (Rat Insulin Promoter-SV40 Large T-Antigen) mouse



Vehicle

anti-VEGF therapy

1. Pietras K , Hanahan D. *J Clin Oncol* 2005;23:939–52
2. Yao V, et al. EORTC-NCI-AACR, Prague, 2007, Abstract 78; 3. Faivre S, et al. *J Clin Oncol* 2006;24:25–35
4. Kulke MH, et al. *J Clin Oncol* 2008;26:3403–410 ; 5. Raymond et al. *N Eng J Med* 2011;364:501–513

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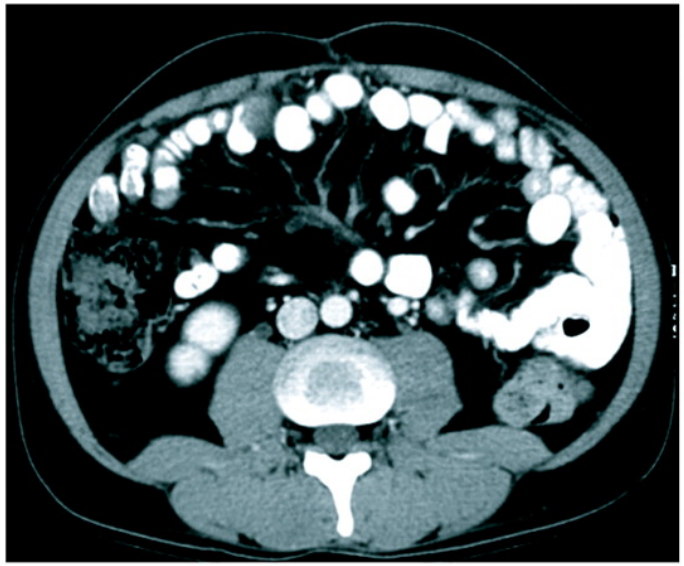
Phase I	2006	▪ A study of sunitinib in solid tumours including 4 patients with non-pancreatic NET,[3] induced 1 confirmed partial response and 1 stable disease



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Phase III	2011	▪ A phase III, randomised, double-blind trial of **sunitinib 37.5 mg CDD** 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 K , Hanahan D. *J Clin Oncol* 2005;23:939–52
2. Yao V, et al. EORTC-NCI-AACR, Prague, 2007, Abstract 78; 3. Faivre S, et al. *J Clin Oncol* 2006;24:25–35
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Sunitinib Following Hepatic Artery Embolisation in Metastatic NET: Results

Sunitinib days 1–28 in a 42-day cycle, starting 7 days after each HAE and ending 7 days before subsequent HAE (6-weekly)

Amongst 39 treated patients:

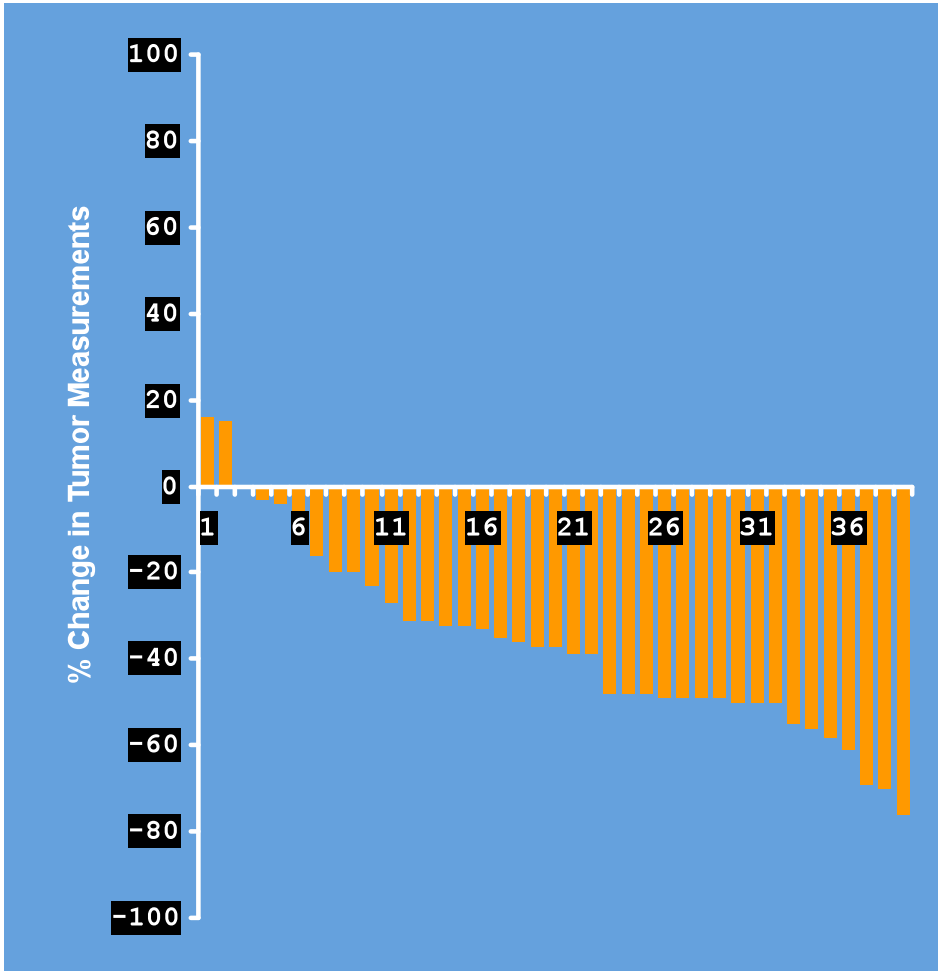
- PR: 28 patients (72%)
- SD: 8 patients (20%)
- PD: 3 patients (8%)

Median PFS, 18 months

2-year OS, 78%

Serum VEGF levels increased by an average of 34% (51 pg/mL)

Sunitinib 37.5 mg/day by CDD could be administered safely following HAE



Strosberg J, et al. Annals of Oncology 2013;23:2335–2341

Other ongoing studies with sunitinib

A Randomized Phase II Double-Blind Trial of Sunitinib vs. placebo **in combination with Lanreotide** in Patients with Progressive Advanced / Metastatic Midgut Carcinoid Tumours - NCT01731925

Antitumor Efficacy of **Peptide Receptor Radionuclide Therapy With ^{177}Lutetium -Octreotate** Randomized vs. Sunitinib in Unresectable Progressive Well-differentiated Neuroendocrine Pancreatic Carcinoma: First Randomized Phase II - NCT02230176

Specific/selective tyrosine kinase inhibitors (TKIs)

Name	Selective Target	Cancer (Examples)
Afatinib	HER2, EGFR	NSCLC, squamous cell carcinoma of the head and neck, breast cancer
Canertinib	EGFR, HER2, 4	Head and neck, breast, and NSCLC, ovarian cancer
Cediranib	VEGFRs	NSCLC, kidney and colorectal cancer
CP-673451	PDGFRs	NSCLC, colon carcinomas, glioblastoma
Crizotinib	MET	NSCLC, anaplastic large cell lymphoma, neuroblastoma
Dacomitinib	EGFR	NSCLC, gastric, head and neck cancer, glioma
Erlotinib	EGFR	NSCLC, pancreatic cancer
EMD1214063	MET	NSCLC
EMD1204831	MET	NSCLC
Gefitinib	EGFR	NSCLC, AML
Icotinib	EGFR	NSCLC
Lapatinib	HER-2, EGFR	Breast cancer
Lenvatinib	VEGFR2, 3	Approved for thyroid cancer in Japan
LY2801653	Met, RON	NSCLC
Neratinib	EGFR, HER2	NSCLC, breast cancer
PD-173074	FGFRs	NSCLC, gastric carcinoma, breast cancer
Tandutinib	FLT3	RCC, CML
Tivantinib	MET	RCC, breast cancer
Tivozanib	VEGFR1, 2, 3	RCC, breast cancer
Vatalanib	VEGFR2	NSCLC, DLBCL, colorectal adenocarcinoma

Adapted from Hojjat-Farsangi M. Int J Mol Sci. 2014 Aug 8;15(8):13768-801

Multi-targeted tyrosine kinase inhibitors (TKIs)

Name	Target Molecules (Examples)	Cancer (Examples)
Amuvatinib	ALK, MER, KIT, RET, PDGFRs, FLT3, RAD 51	NSCLC
Axitinib	VEGFRs, PDGFRs, KIT	RCC
Cabozantinib (XL184)	VEGF, RET, MET, NTRKB, TIE2, AXL	Medullary thyroid cancer
Dasatinib	BCR-ABL, SRC, KIT, PDGFRs, EPH, CSK	CML, ALL
Foretinib	VEGFR2, MET	NSCLC, breast, gastric, papillary renal cancer
Golvatinib	VEGFR2, MET	Gastric cancer, HCC, glioblastoma, melanoma
Imatinib	ABL, KIT, PDGFRs	GIST, leukemias
MGCD-265	MET, VEGFRs, TIE2, RON	NSCLC
Nilotinib	BCR-ABL, KIT, LCK, EPHA3, 8, DDR1, 2	CML
Pazopanib	PDGFRs, VEGFRs	Advanced RCC, advanced soft tissue sarcoma
Ponatinib	BCR-ABL, PDGFRα, SRC, KIT, FGFR, VEGFRs	CML, philadelphia chromosome positive ALL
Regorafenib	TIE2, PDGFRs, RET, KIT, B-RAF	Metastatic colon cancer
Sorafenib	VEGFRs, PDGFRs, B-RAF, MEK, ERK	Advanced RCC, hepatocellular carcinoma
Sunitinib	VEGFR2, PDGFRβ, KIT, RET, CSF1R, FLT3	RCC, GIST, **pNET**
Vandetanib	EGFR, VEGFRs, RET, Tie-2, FGFR1	Metastatic medullary thyroid cancer

Adapted from Hojjat-Farsangi M. Int J Mol Sci. 2014 Aug 8;15(8):13768-801

SORAFENIB

Sorafenib: inhibits several tyrosine protein kinase receptors (VEGFR and PDGFR) and Raf Kinases (CRaf)

A phase II trial of sorafenib in patients (pts) with metastatic neuroendocrine tumors (NET): A Phase II Consortium (P2C) study

- ECOG PS 0-2
- ≤1 prior chemotherapy
- Prior interferon and prior/concurrent octreotide at a stable dose allowed.

sorafenib 400 mg po BID

Primary endpoint: response RECIST
Two cohorts (i.e. Carcinoid and pNET) (separate 2-stage phase II designs).

Results:

N= 93 pts (50 Carcinoid, 43 pNET)

Response Rates:
Carcinoid: 4/41 (10%); pNET: 4/41 (10%)
6-month PFS:
Carcinoid: 8/20 (40%); pNET: 14/23 (61%)
Toxicity:
Grade 3–4 toxicity occurred in 43%
- skin (20%); GI (7%); fatigue (9%)

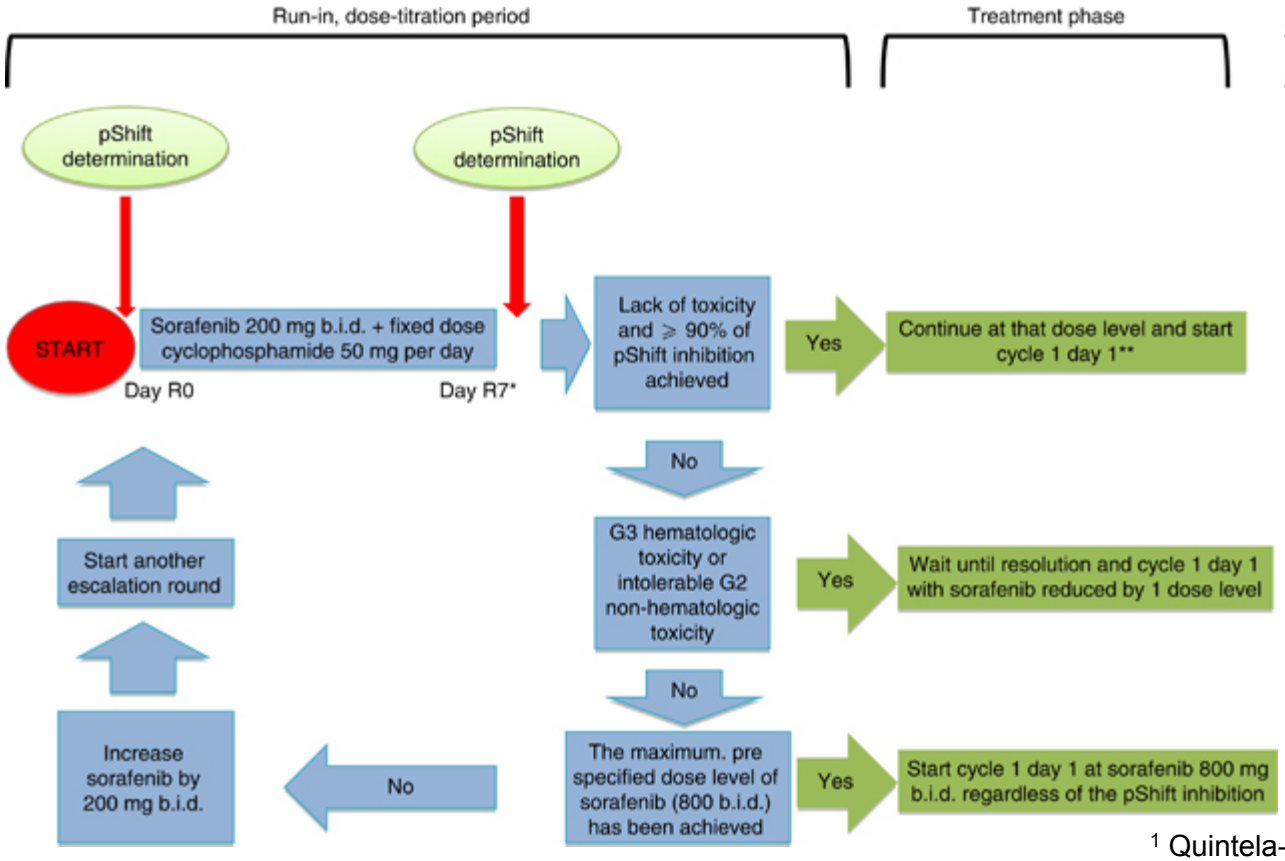
Conclusions: Sorafenib at 400 mg po BID has *modest activity* in metastatic neuroendocrine tumors, with frequent grade 3-4 toxicity.

T. J. Hobday et al, ASCO JCO 2007;25:18S (abstr 4504)

Sorafenib:

SORNET: Efficacy study of Sorafenib and cyclophosphamide to treat NETs[1] NCT00605566

N=22 patients



Phosphoshift **measures activation of RAF signal transduction** by detecting the phosphorylation of MEK1/2 in cells unstimulated or stimulated using IL3, a specific activator of the RAF signalling pathway in normal monocytes[2]

- Median PFS: 3 mo (95%CI 2–10.7); RR: 1/22 (5%)
- Improved PFS in five patients with an increase in pShift after 7 days of sorafenib vs. those who did not (14.9 months vs 2.8 months; p=0.047).

However, pShift did not add value to toxicity-based dose-titration.

[1] Quintela-Fandino M et al. BJC 2013;108(6):1298-305)
2 Yagisawa et al Exp Hematol 27: 1063–1076.

Sorafenib:

Sorafenib and bevacizumab combination targeted therapy in advanced NET: A phase II study of Spanish Neuroendocrine Tumour Group (GETNE0801)

N=44 patients
- Histologically-confirmed
- Measurable advanced NETs
- Moderately or well-differentiated NET
- GEP or lung
- ECOG PS 0-2
- ≤1 prior chemo

6 mo

sorafenib 200 mg bid D1-5 qw
bevacizumab 5 mg/kg q2w

Contd. (discretionary)

1º endpoint: 6-mo PFS
2º endpoints: PFS, TTP, OS

Median PFS: 12.4 mo
Median TTP: 14.5 mo
ORR: 9.4%
DCR: 95%.

All: 91%
Carcinoid: 92%
pNET: 89%

Tumour description (n, %[1])	
Carcinoid tumour	31
Foregut tumours (mainly bronchial, $n = 7$)	9
Midgut tumours	18
Hindgut tumours	2
Others tumours	2
Pancreatic tumour	13
Non-functioning	10
Functioning	3

Toxicity was an issue:
- Grade 3-4 adverse events: 64%
- Dose adjustments:
  - sorafenib (64%)
  - BVZ (36%)
- 6 patients (15%) withdrew due to adverse events

Castellano et al Eur J Cancer (2013) 49, 3780–3787

PAZOPANIB

Pazopanib: small molecule inhibitor of the VEGFR-1, -2, and -3, PDGF-α, PDGF-β, and c-kit tyrosine kinases

A prospective, multi-institutional phase II study of GW786034 (pazopanib) and depot octreotide (sandostatin LAR) in advanced low-grade neuroendocrine carcinoma (LGNEC)

Eligibility criteria

- Patients with either carcinoid or pNET
- G1-G2
- ECOG PS 0-1
- Stable dose of depot octreotide (LAR) for ≥2 months
- No prior VEGF pathway inhibitor treatment
- ≤1 prior cytotoxic
- 2-cohort, 2-stage design

N=51
Stratified by cohort
Carcinoid: n=20
Pancreatic: n=31

→ Pazopanib 800 mg PO QD + Octreotide at their prior dose level

Efficacy variables: tumour response, toxicity, and survival

Adverse Events

- Grade 3–4 toxicities were relatively rare and included (%): hypertension (14), fatigue (10), neutropenia (8), diarrhoea (6), elevated ALT (6), elevated AST (6), hypertriglyceridaemia (6), nausea (4)

Phan AT, et al. *J Clin Oncol* 2010;28:15S[Abstract 4001]

Pazopanib:

A prospective, multi-institutional phase II study of GW786034 (pazopanib) and depot octreotide (sandostatin LAR) in advanced low-grade neuroendocrine carcinoma (LGNEC)

RECIST best protocol response: ITT population			
Parameter	**Overall (N=51)***	**Carcinoid (n=20)**	**Pancreatic NET (n=31)**
PR, n (%)	**6 (12%)**	**0 (0%)**	**6 (19%)**
SD, n (%)	35 (69%)	14 (70%)	21 (68%)
PD, n (%)	6 (12%)	3 (15%)	3 (10%)
Unknown	4 (8%)	3 (15%)	1 (3%)
PFS		**12.7 mo**	**11.7 mo**

- Treatment with pazopanib and octreotide is feasible
- Tumor regression in patients with pNET
- Encouraging PFS durations in both carcinoid and pNET patients

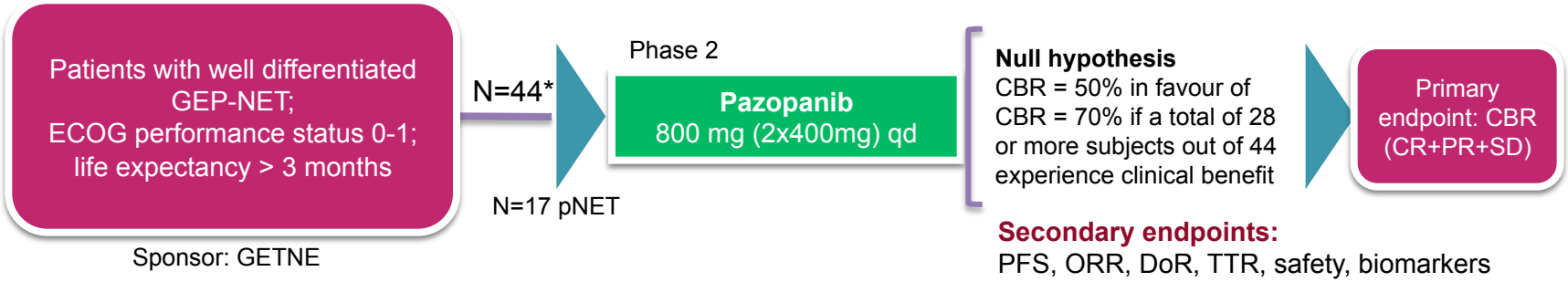
Phan AT, et al. *J Clin Oncol* 2010;28:15S[Abstract 4001]

Pazopanib:

PAZONET – Pazopanib as single agent in advanced/metastatic GEP NETs

Design:

Multicentre, open-label study evaluating pazopanib as a single agent in progressive advanced/metastatic GEP NETs patients **who have failed chemotherapy, SSA or molecular targeted therapies**



Sponsor: GETNE

- Open to pNET and non-pNET
- Heterogeneous prior therapies

Secondary endpoints:
PFS, ORR, DoR, TTR, safety, biomarkers assessment

Key Implications:

- Single-arm study exploring the activity of pazopanib (an oral, potent multi-target tyrosine kinase inhibitor VEGFR-1, -2, and -3, PDGFR-α and –β, and c-KIT)
- **The threshold of activity was reached to warrant further investigation; efficacy needs to be confirmed in a prospective phase 3 study**

Pazopanib:

PAZONET – Pazopanib as single agent in advanced/metastatic GEP NETs

Key Results:

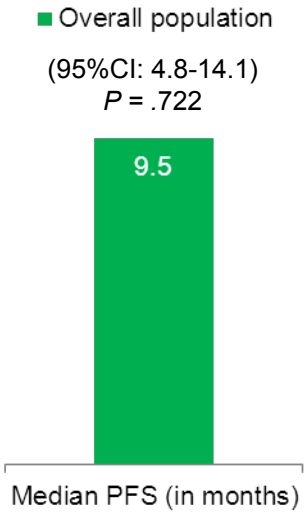
Clinical benefit (6-mo PFS) was achieved among 36 patients (SD 33 patients, PR 3 patients) = 85.4%

No patient achieved CR, while 6 patients were found to have PD

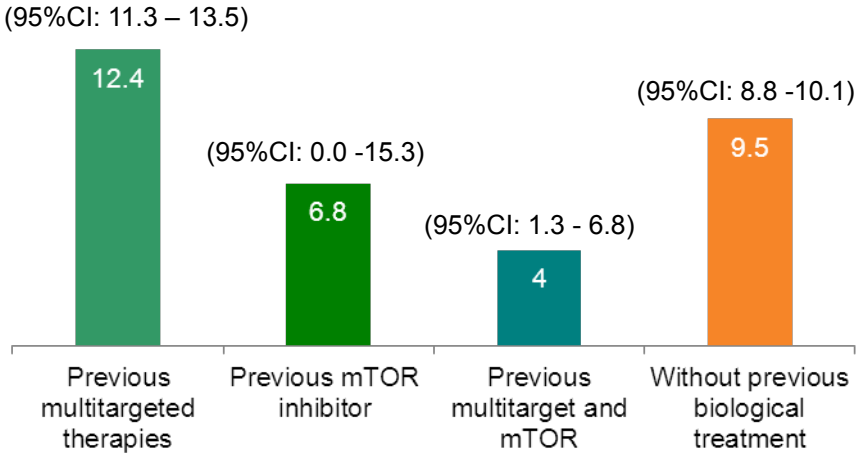
Median PFS: 10 months[1]

Pazopanib might be efficacious in patients with refractory NETs

Sum of the longest diameter of target lesions decreased over 10% among 32.5% of patients[2]



Progression free survival in months [3]



Progression free survival (in months) by subgroups (*P* = .040) [3]

1. Grande E. Poster presented at: European Society for Medical Oncology (ESMO); September 28-October 02, 2012; Vienna, Austria.
2. Pulido EG., et al. Poster presented at: American Society of Clinical Oncology (ASCO); June 1-5, 2012; Chicago; IL, USA
3. Capdevila J., et al. Poster presented at: European Cancer Congress (ECC); September 27–October 1, 2013; Amsterdam, Netherlands

Korean study

Phase II
N=37
(Pancreas 12)
(CRC 8)
(others 17)

G1 (8)
G2 (16)
G3 (13)

Primary end-point:
response rate 18.9%
(24.3% by independent review)

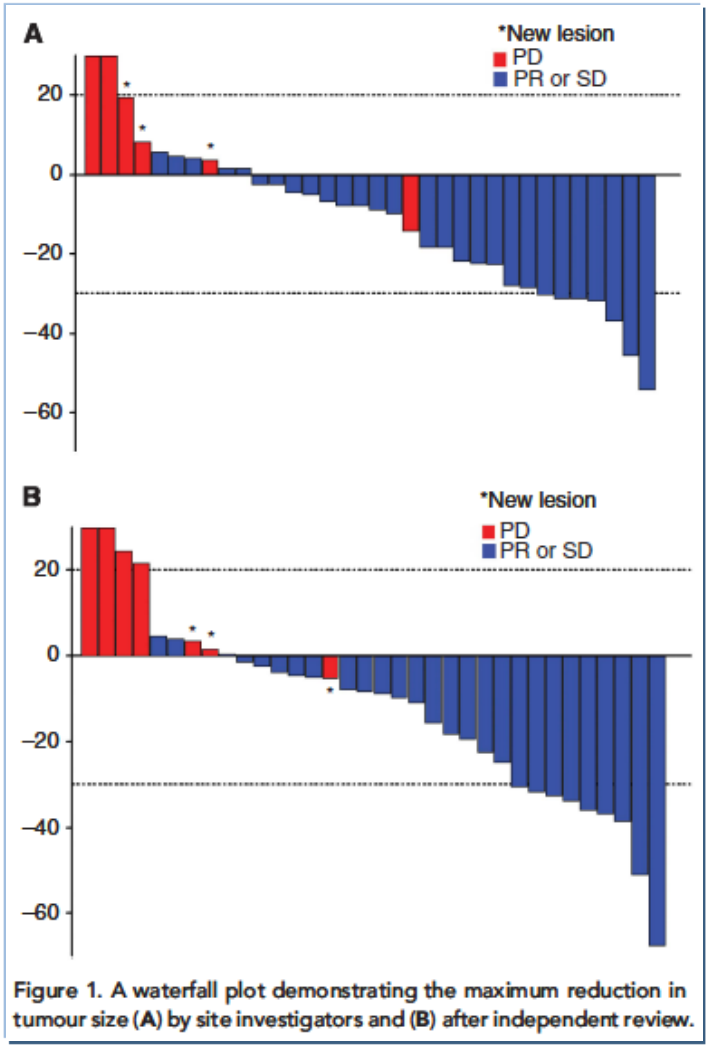


Figure 1. A waterfall plot demonstrating the maximum reduction in tumour size (A) by site investigators and (B) after independent review.

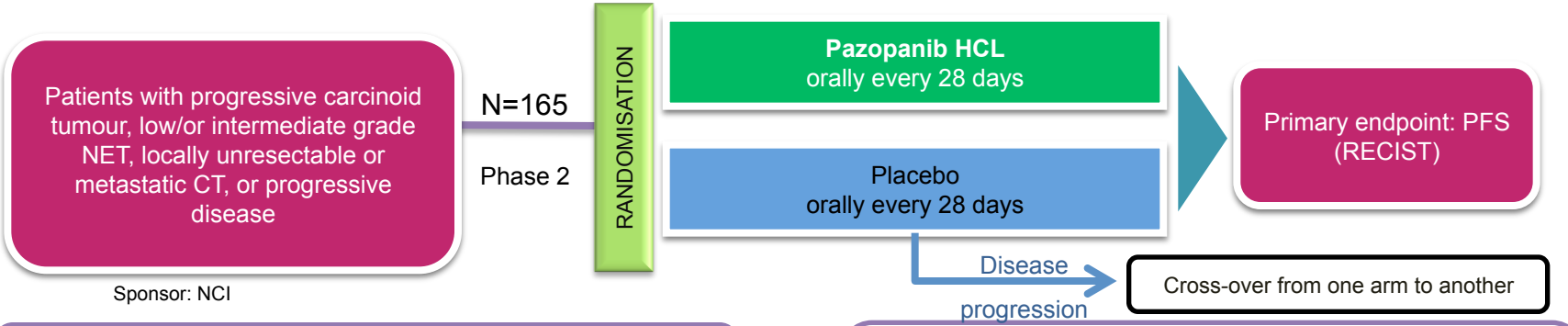
Ahn et al BJC 2013;109, 1414–1419

Pazopanib: ongoing study

Pazopanib in progressive carcinoid tumours

Design:

Randomised, double-blind, placebo-controlled, crossover study assessing the efficacy of pazopanib



Sponsor: NCI

Secondary endpoints:
OS, OR, QoL, DoR, TTR

Key Exclusion Criteria:

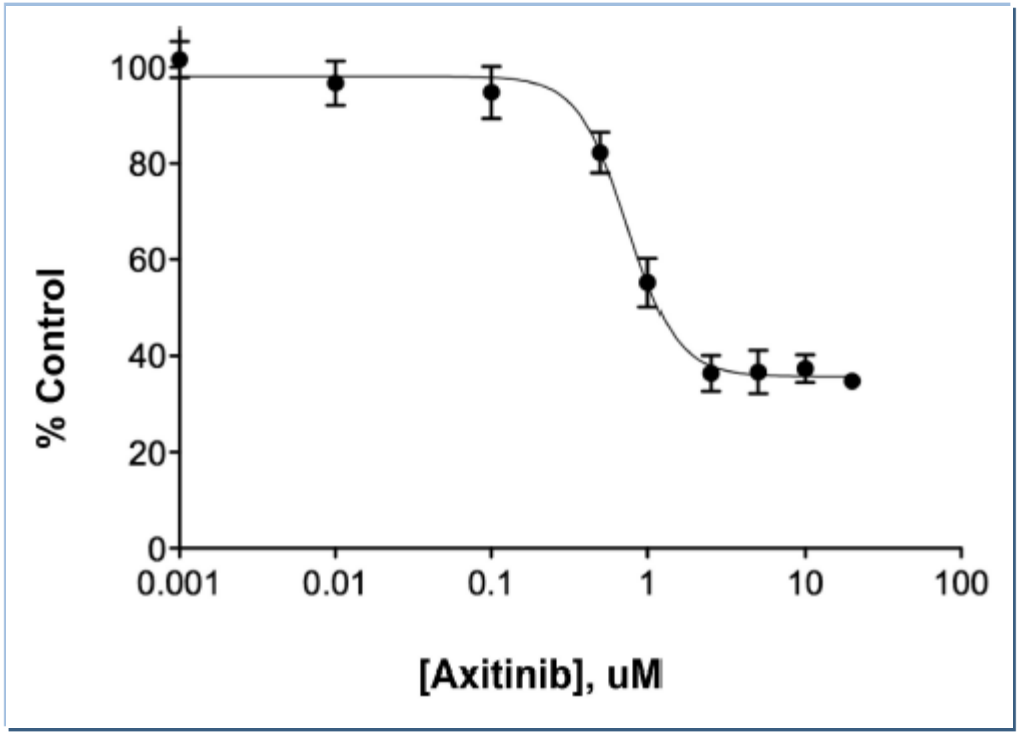
- Prior treatment with an inhibitor of VEGF or VEGFR
- Concurrent condition resulting in immune compromise, CNS metastases, GI abnormalities, uncontrolled BP, symptomatic congestive heart failure

Pazopanib hydrochloride in treating patients with progressive carcinoid tumours. Available at: http://clinicaltrials.gov/ct2/show/NCT01841736

Study Status: Ongoing (recruiting)
Estimated Primary Completion: Dec, 2016

AXITINIB

Pre-clinical



Effect of increasing concentrations of anticancer therapeutic axitinib (targeting VEGFR1–3, PDGFRA-B, and KIT) on QGP-1 Pancreatic Endocrine Tumour cell growth

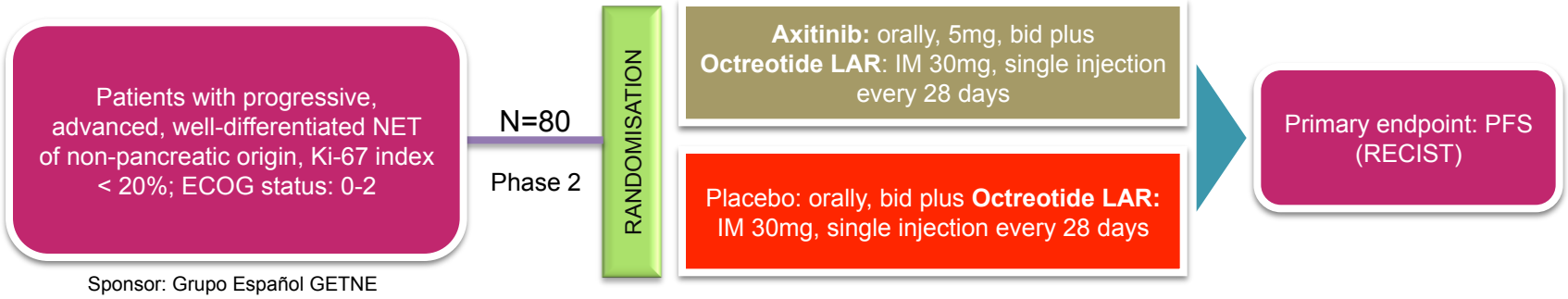
Gilbert et al Pancreas. 2013 April ; 42(3): 411–421.

Axitinib

Octreotide LAR plus axitinib vs. placebo in non-pancreatic NET

Design:

Randomised, double-blind, efficacy study to compare octreotide LAR in combination with axitinib vs. placebo



Sponsor: Grupo Español GETNE

Secondary endpoints:
OS, ORR, Safety

Key Exclusion Criteria:

- Prior VEGF or VEGFR-targeted therapy
- Major surgery in <4 weeks or radiation therapy <2 weeks
- Concomitant CYP3A4 inhibitors/inducers, or oral vitamin K antagonists

Key Implications:

- NETs are known to be highly vascular; this randomised phase 2 study will explore the activity of axitinib (a potent and selective tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR)-1, VEGFR-2 and VEGFR-3) in non-pancreatic, well-differentiated NETs

Available at: http://clinicaltrials.gov/ct2/show/NCT01744249

Axitinib:

A Phase II Study of Axitinib in Advanced Carcinoid Tumors
Strosberg, Lee Moffitt Cancer Centre

Eligibility criteria

- G1-G2 non-pNET aerodigestive NET, UKP and rare subtypes
- Measurable disease
- PD within 12 months
- Prior SSA mandated in mid-gut patients
- ECOG PS 0-2

N=30

Axitinib 5mg bd

Primary endpoint: PFS (RECIST)
Secondary endpoints: RR, OS, TTF, AEs

Clinicaltrials.gov NCT01435122

Pre-clinical

In RIP-Tag2 model[1], XL184

•Eliminated approximately 80% of the tumour vasculature

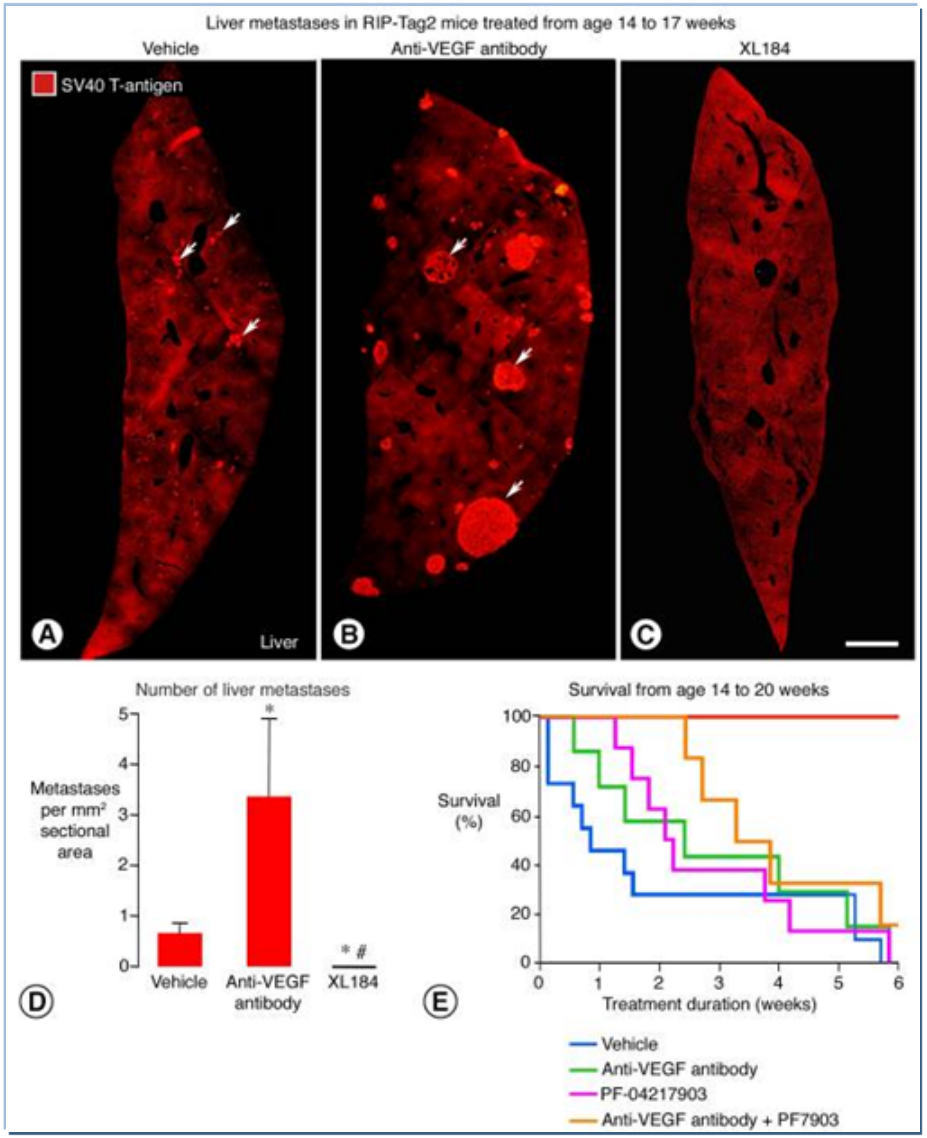
•reduced pericytes and empty basement membrane sleeves

•caused widespread intra-tumoural hypoxia and tumour cell apoptosis

•slowed regrowth of the tumour vasculature after drug withdrawal.

•decreased invasiveness of primary tumours and reduced metastasis

Effect of VEGR-blockade amplified[1,2]



1. You et al Cancer Res; 71(14); 4758–68
2. Sennino et al Cancer Discov. Mar 2012; 2(3): 270–287

Cabozantinib: inhibits VEGFRs, MET, RET and c-KIT

An Open-Label, Phase II Study of Cabozantinib (XL184) in Advanced Pancreatic Neuroendocrine and Carcinoid Tumors
Massachusetts General

Eligibility criteria

- Well- Mod-differentiated
- Measurable disease (RECIST)
- PD within previous 12 months
- SSA allowed (if stable ≥2 months
- ECOG PS 0-1

N=70, parallel cohorts, non-randomised

pNET

carcinoid

→ Cabozantinib (XL184) 60mg qd

Primary endpoint: RR (RECIST)
Secondary endpoints: OS, AEs, correlates of response

Faris et al ASCO 2014 abstr TPS4157
Clinicaltrials.gov NCT01466036

At a glance…

	Carcinoid		pNET	
	6mo-PFS	ORR	6mo-PFS	ORR
Sunitinib (phase III)	-	-	71%	9%
Sunitinib (phase II)	73%	2%	70%	11%
Pazopanib	68%	0%	81%	19%
Sorafenib	40%	10%	61%	10%
Axitinib	?	?	?	?
Cabozantinib	?	?	?	?

Summary

NETs are known to be vascular tumours

Pre-clinical data supports angiogenesis-targeted therapies

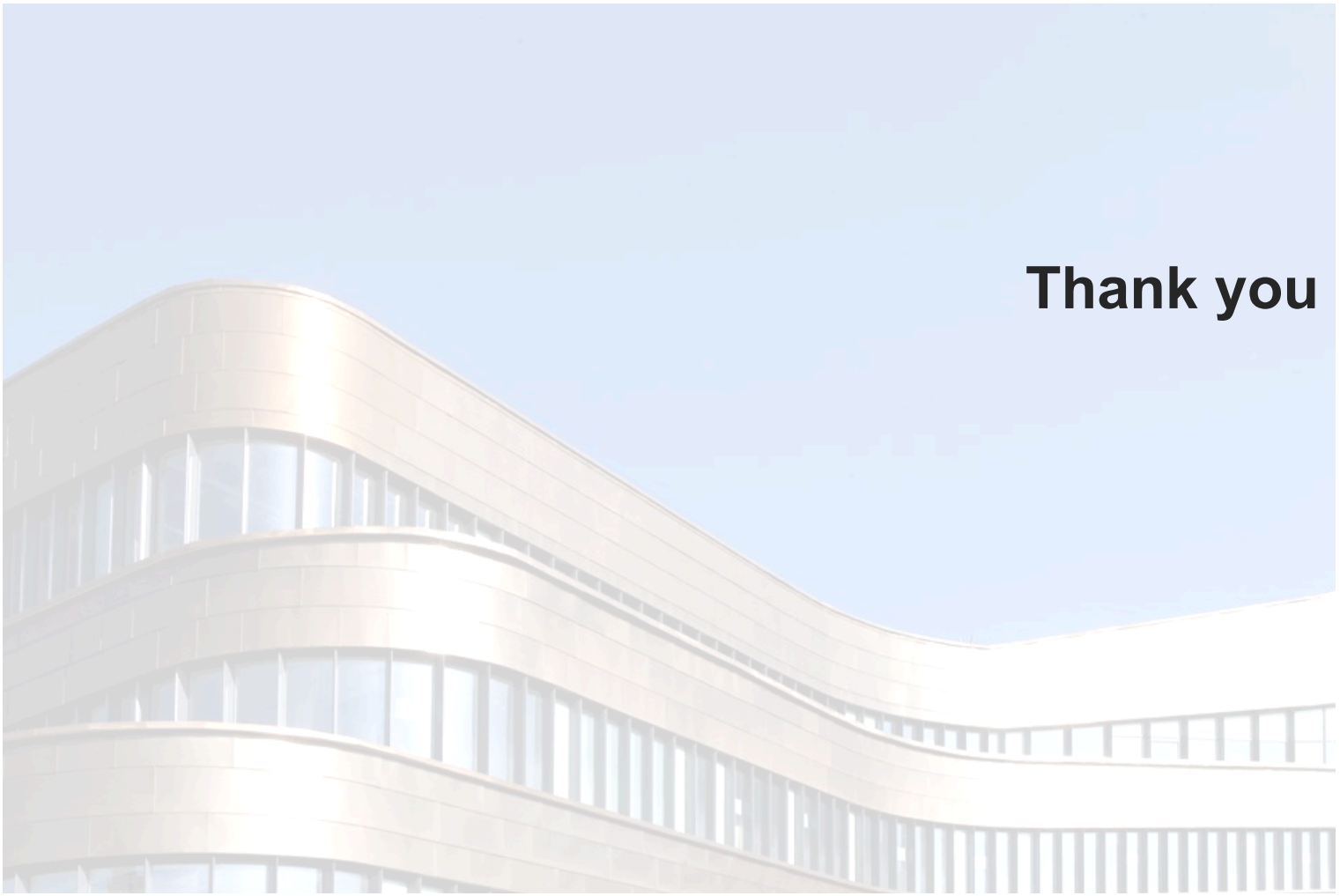
Sunitinib is the only VEGF-directed licensed therapy for pNETS

Effectiveness of sorafenib, axitinib, cabozantinib awaited

Combination studies need confirmation of safety

- YES: hepatic arterial embolisation, somatostatin analogues
- NO: bevacizumab (with sorafenib)

The paradigm has changed – ongoing research will change it further



Worldwide NET Cancer Awareness Day November 10

If you don't suspect it, you can't detect it.