ESMO discussant abstracts 11560, 11570

E Baudin

Endocrine oncology

Disclosures

- HRA
- Ipsen
- Novartis
- Pfizer
- Sanofi

Antitumor strategy in advanced G1-G2 well differentiated GEP NETs

Other primaries	Pancreas (pNET)
Wait and see	(Wait and see)
Locoregional therapies	Locoregional therapies
Octreotide LAR*	Somatostatin analogs
(Interferon)	(Interferon)
-	Steptozotocin-based chemo.
Peptide Rc Radionucleide Therapy	PRRT
Everolimus	Everolimus
-	Sunitinib

Recommandations or, **Approvals**

*some countries, ileum NET

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

Marianne E. Pavel,[1] Bertram Wiedenmann,[1]
Jaume Capdevila,[2] Nicholas Reed,[3] Juan Valle,[4]
W. W. de Herder,[5] Cornelia Metzner,[6] Ramon Salazar,[7]
Dieter Hörsch,[8] and Kjell E. Öberg[9]

[1]Charité Universitätsmedizin Berlin/Campus Virchow Klinikum, Berlin, Germany; [2]Hospital Vall d'Hebron, Barcelona, Spain; [3]Gartnavel General Hospital, Glasgow, United Kingdom; [4]The Christie Hospital, Manchester, United Kingdom; [5]Erasmus University Medical Center, Rotterdam, Netherlands; [6]Ruprecht-Karls-Universität Heidelberg Medizinische Klinik und Poliklinik, Heidelberg, Germany; [7]ICO L'Hospitalet (Hospital Duran i Reynals), Barcelona, Spain; [8]Zentralklinik Bad Berka GmbH, Bad Berka, Germany; [9]Uppsala University Hospital, Uppsala, Sweden

VIENNA 2012 ESMO congress

RAMSETE : population

- Inclusion criteria

  - Non functioning
  - Well differentiated (moderately)
  - Progressive within 12 months
  - Various primaries except the pancreas
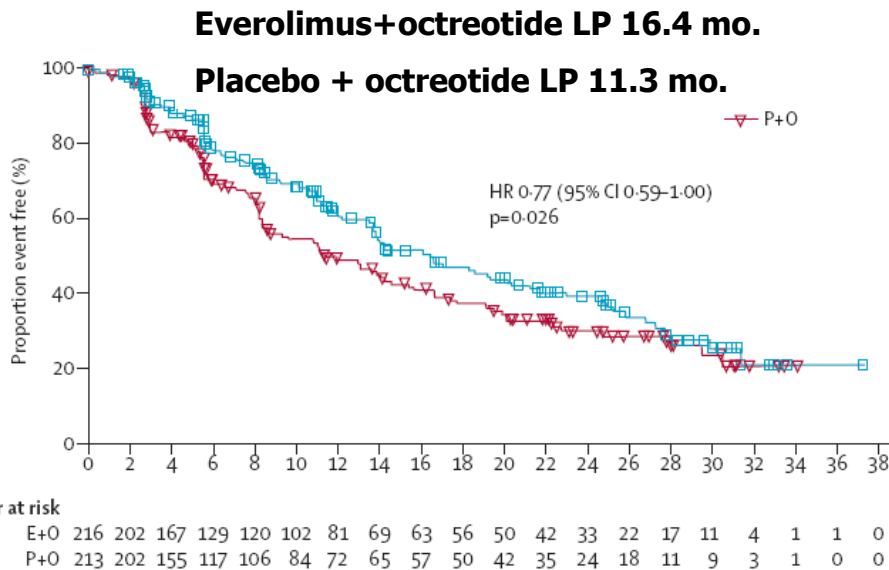   - 35% foregut, 35% midgut, 7% hindgut, 23% CUP

Functioning NET are defined by hormone-related symptoms : dedicated management required

Somatostatin analogs improved hormone-related symptoms but are also antitumor agents
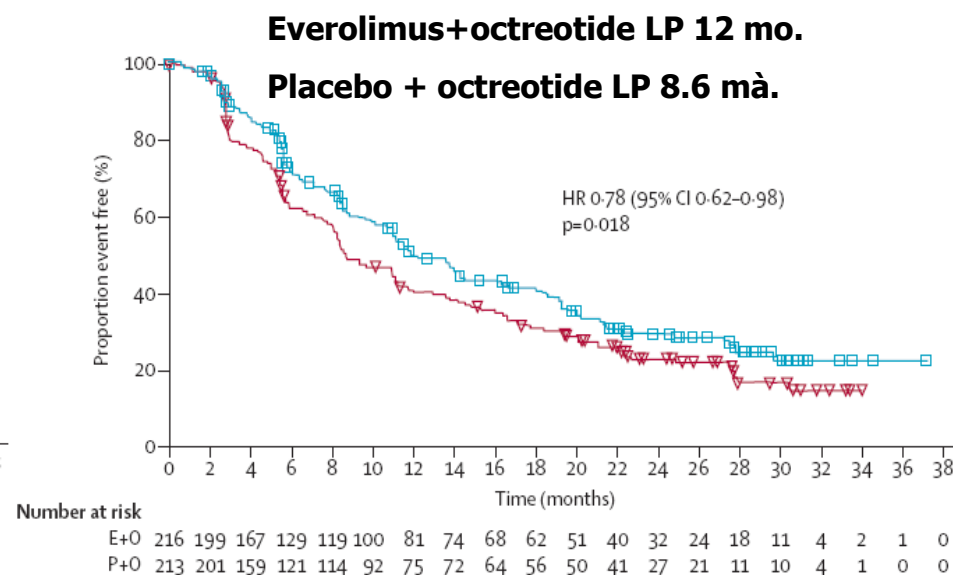
RADIANT-2 antitumor effect of everolimus in 429 progressive advanced well differentiated "functioning" NET : phase III double blind placebo controlled trial

| 1. PFS per-central review | 2. PFS per-local review |

Everolimus+octreotide LP 16.4 mo.

Placebo + octreotide LP 11.3 mo.

Everolimus+octreotide LP 12 mo.

Placebo + octreotide LP 8.6 mà.

Difference in median PFSs : 5.1 months   Difference in median PFSs : 3.4 months

Midgut 51% / Foregut 20% /Others 29%

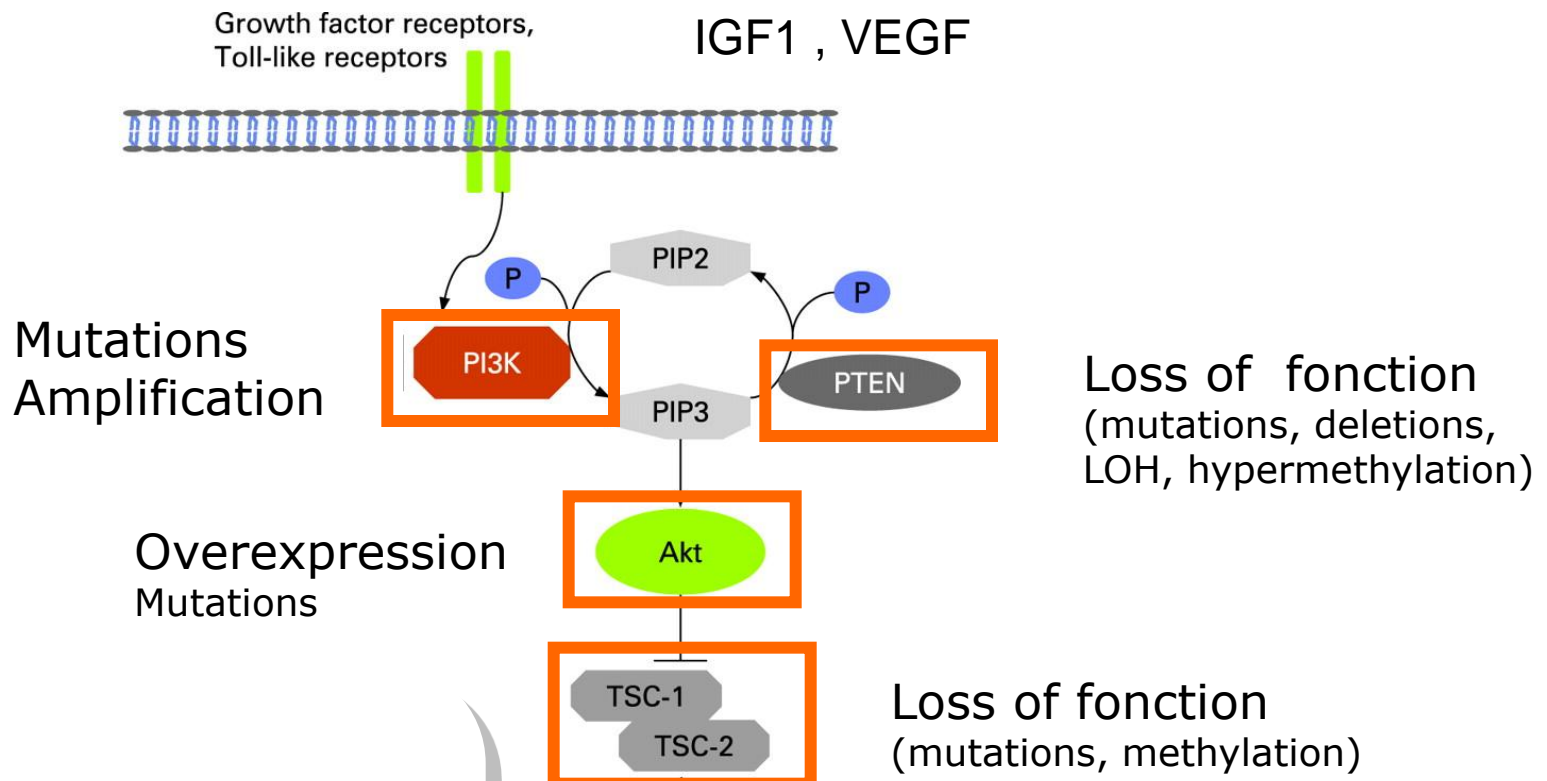Pavel M *et al*. The lancet nov 2011

mTOR inhibitors in advanced well differentiated NET : phase II trials

	OCT LAR	N patients /Primary	Progression at study entry	ORR*	PFS months
Duran 2006 Temsirolimus	?	36/Various (42% pNET)	100% 6 months	5%	6 mo.: 46%
Yao 2008 Everolimus	+/-	60/Various (48% pNET)	65%	22%	14
Yao 2009 Everolimus	-	115/Pancreas	100%	9.6%	9.7
Everolimus	+	45/Pancreas	100%	4.4%	16.7
Pavel M 2012 Everolimus	-	60/Various (No pNET)	100% 12 months	0%	6

*RECIST per-central review except Yao 2008 (local)

RAMSETE : Design

- Secondary exploratory post hoc analysis of the RAMSETE trial by primary tumor origin
- Not designed to detect statistical difference
- Central and local reviews of the primary endpoint, PFS, were performed

Growth factor receptors,
Toll-like receptors

IGF1 , VEGF

PIP2

P   P

Mutations
Amplification

PI3K

PTEN

Loss of fonction
(mutations, deletions,
LOH, hypermethylation)

PIP3

Overexpression
Mutations

Akt

TSC-1

TSC-2

Loss of fonction
(mutations, methylation)

Panreas : prognostic role of reduced PTEN or
TSC2 expression

Missaglia E et al. JCO 2010

mTOR pathway is
activated in NET

Pancreas : 0-14% mutations in mTOR pathway

Jorbo et al Ann Oncol 2011 ; Jiao Y et al Science 2011

Foregut : increased mTOR expession

Kasajima A et al. ERC 2011

Cingarlini S et al Target Oncol 2012 for review

4E-BP   p70S6K

RAMSETE
Primary origins : 2 comparable subroups ?

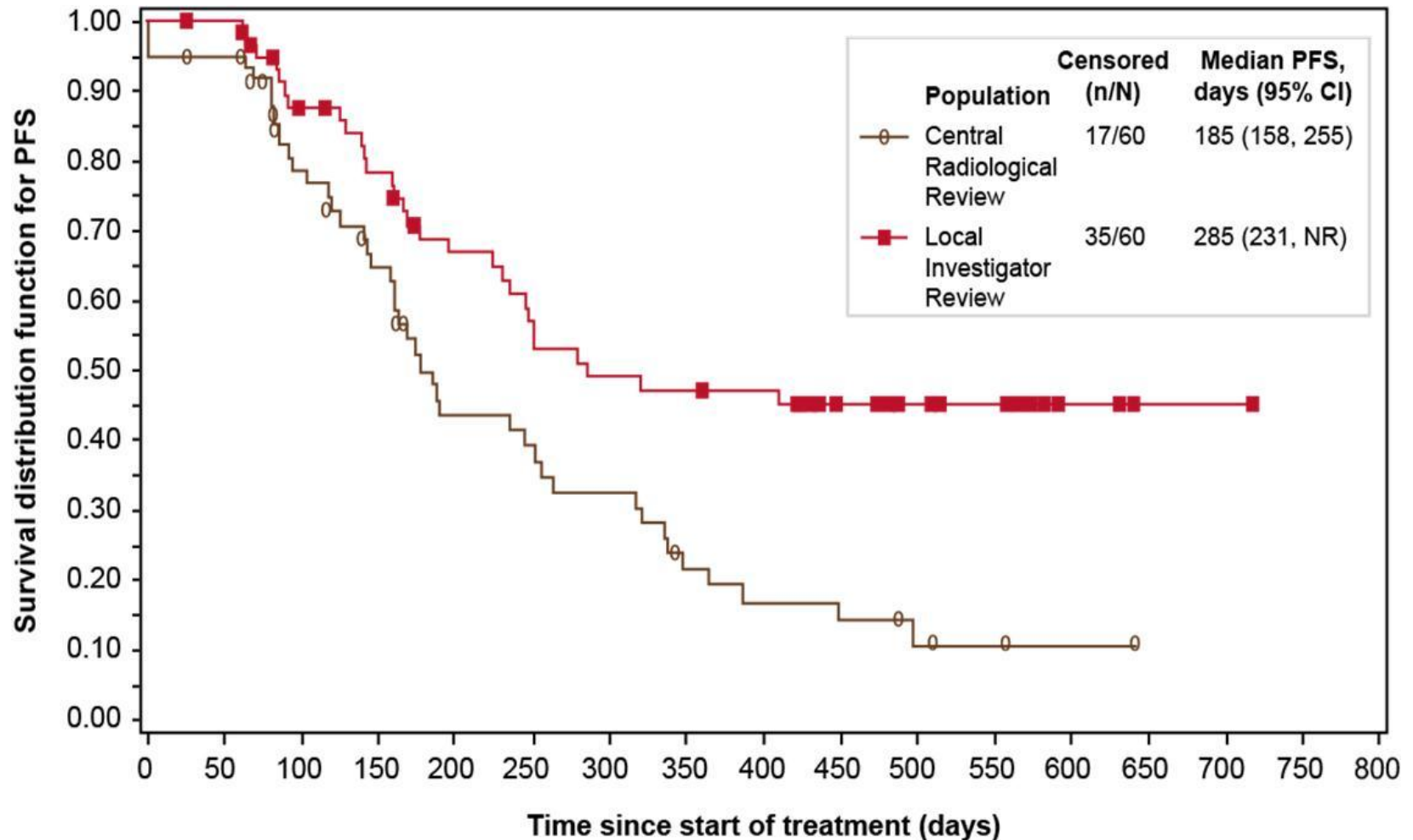|	Lung, Thymic, Bronchial, or Mediastinal n = 22	Small Bowel, Rectum, and Others n = 34	Unknown n = 17
Median age, years (range)	56.5 (30.0-75.0)	62.5 (33.0-79.0)	63.0 (31.0-81.0)
Male/female sex, n (%)	7 (32)/15 (68)	26 (76)/8 (24)	7 (41)/10 (59)
Histologic grade, n (%)			
Well differentiated	9 (41)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

Tumor burden ?

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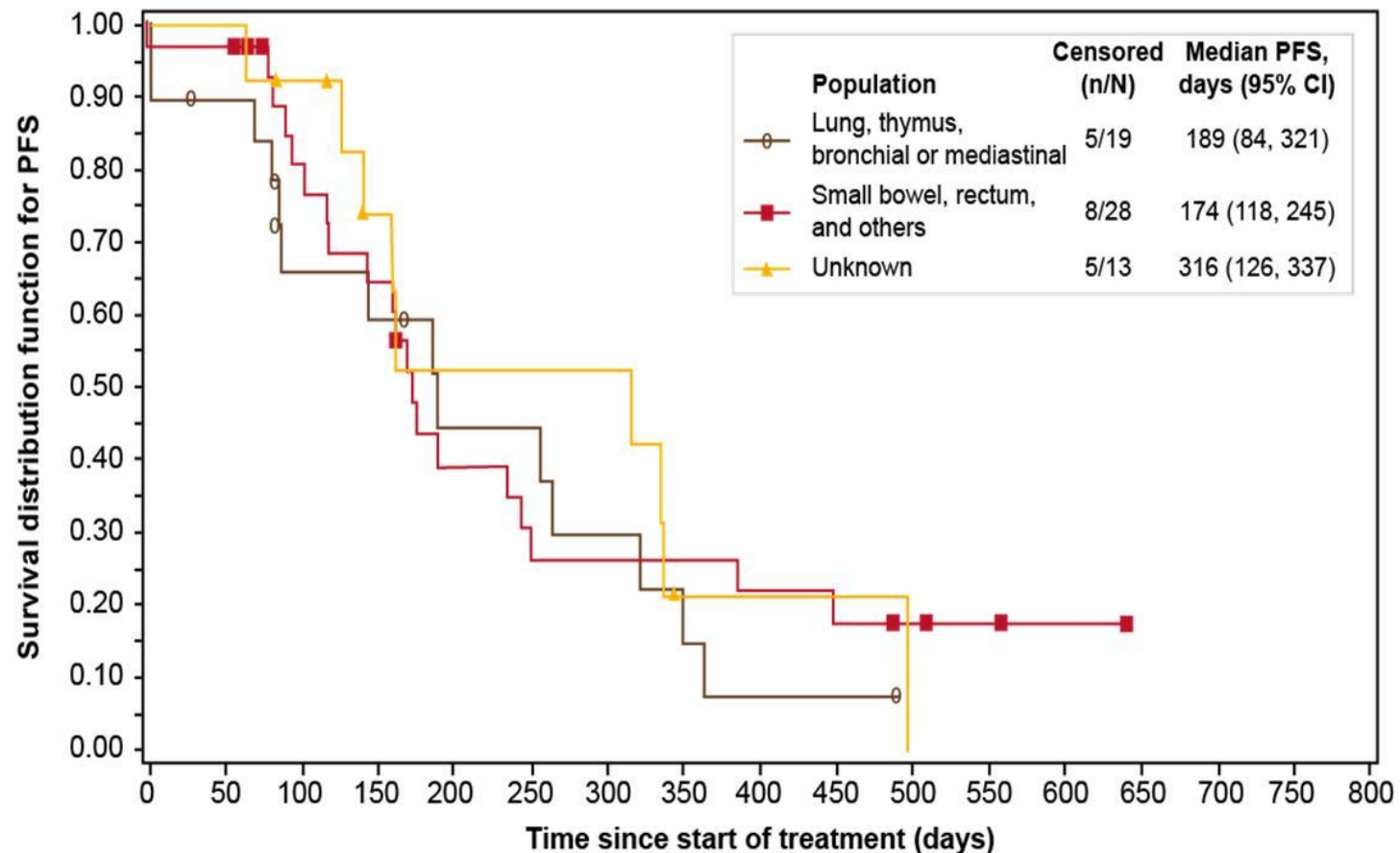
RAMSETE :
Progression-Free Survival
in Per Protocol Population

RAMSETE : 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)

Hypothesis: higher rate of discrepancy between central of local investigator in small bowel (midgut) primaries : slowest rate of progression

What I learn

- No major difference in terms of disease control rate and progression free survival of two subroups of NET primaries which differ for Ki67 index measurements

- Discrepancies observed in assessments of progression according to central and local reviews mainly in slowly progressive NET : best methodology to determine PFS ? stratification for midgut primary?

PAZONET: A phase II trial of pazopanib as a sequencing treatment in progressive metastatic neuroendocrine tumors (NETs) patients (pts), on behalf of the Spanish Task Force for NETs (GETNE)

Enrique Grande[1], Daniel Castellano[2], Rocío García-Carbonero[3], Alex Teulé[4], Ignacio Durán[5], José Fuster[6], Isabel Sevilla[7], Pilar Escudero[8], Javier Sastre[9], Oriol Casanovas[10], Luis Ortega[11], Julie Earl[12], Juan José Díez[13], Guillermo de Velasco[2], Federico Longo[1], Alejandro Navarro[14], Vanessa Pachón[1], Alfredo Carrato[1], Ramón Salazar[4], Jaume Capdevila[14]

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GEP NET and antiangiogenic

Carcinoid (n=41)

Pancreas (n=66)
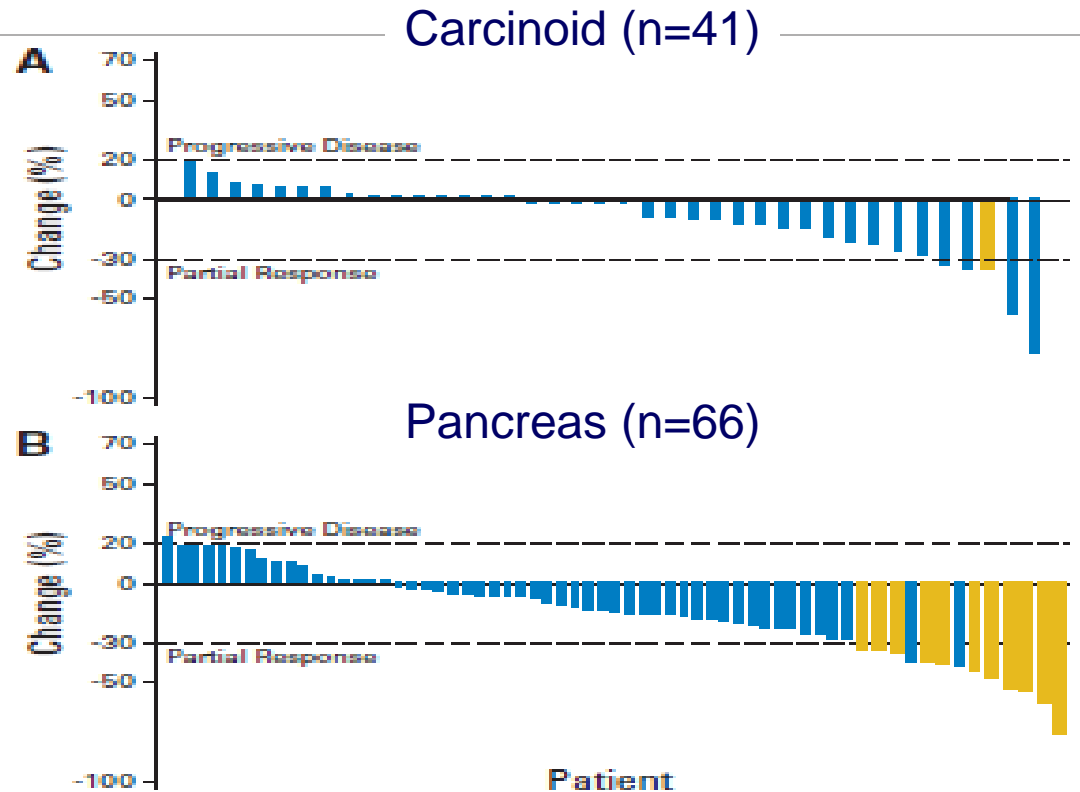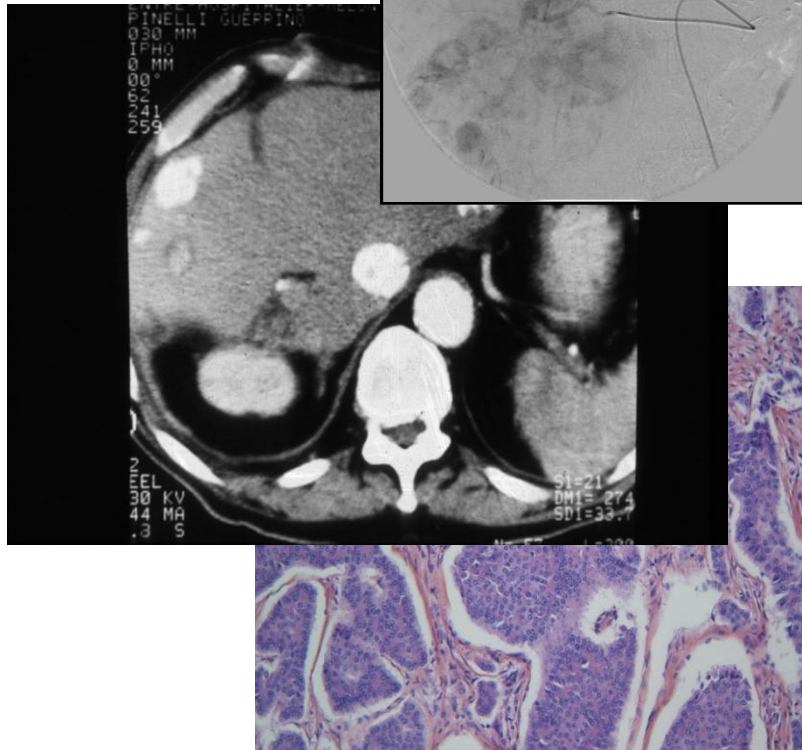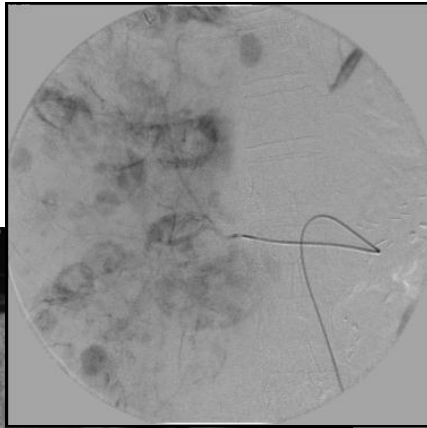
NET are hypervascularized

Courtesy C Dromain, C Caramella, T de Baere

Kulke M JCO 2008 Sunitinb phase II

16.7% of ORR in pancreatic NET

vs 2.4% in other NET primaries

PAZONET : population

- **Inclusion criteria**
  - ◆ Advanced
  - ◆ Various primaries including pancreas
  - ◆ Progressive within 12 months
  - ◆ Well differentiated (moderately)
  - ◆ Prior therapies allowed

PAZONET : Design

- Single arm multicenter phase II trial

- Primary endpoint : clinical benefit rate (CBR = CR+PR+S) at 6 months

- RECIST 1.0 per-local imaging review

- Secondary exploratory post hoc analysis by type of prior therapy

  - 79% received previous treatment with TKI and or mTOR inhibitors

  - No typical sequencing design

- Not designed to compare CBR by prior lines

PAZONET : RESULTS

Responses by RECIST v1.0 (N=42)	N	% (CI95%)
Complete Responses (CR)	0	0
Partial Responses (PR)	3	7.1 (3.3-14.9)
Stable Disease (SD)	33	78.6 (66.2-91.0)
Progressive Disease (PD)	6	14.3 (3.7-24.9)
Clinical Benefit Rate (CR + PR + SD) at 6 months	36	85.7 (71.1-96.3)

Median PFS: 10.0 months
95% CI: 5.2 to 14.6 months
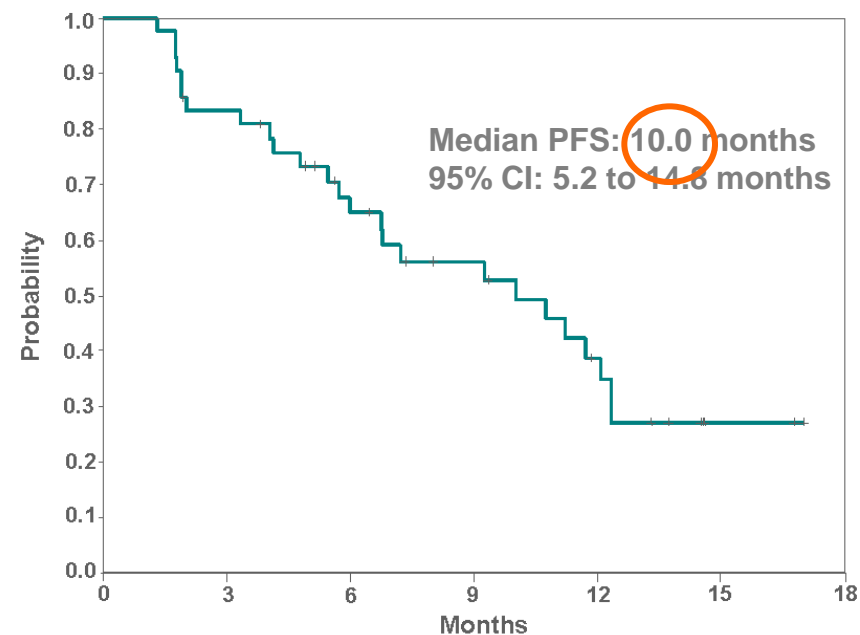
Data cut off July 2012

Pancreas vs others ?

Antiangiogenic in advanced well differentiated NET phase II trials

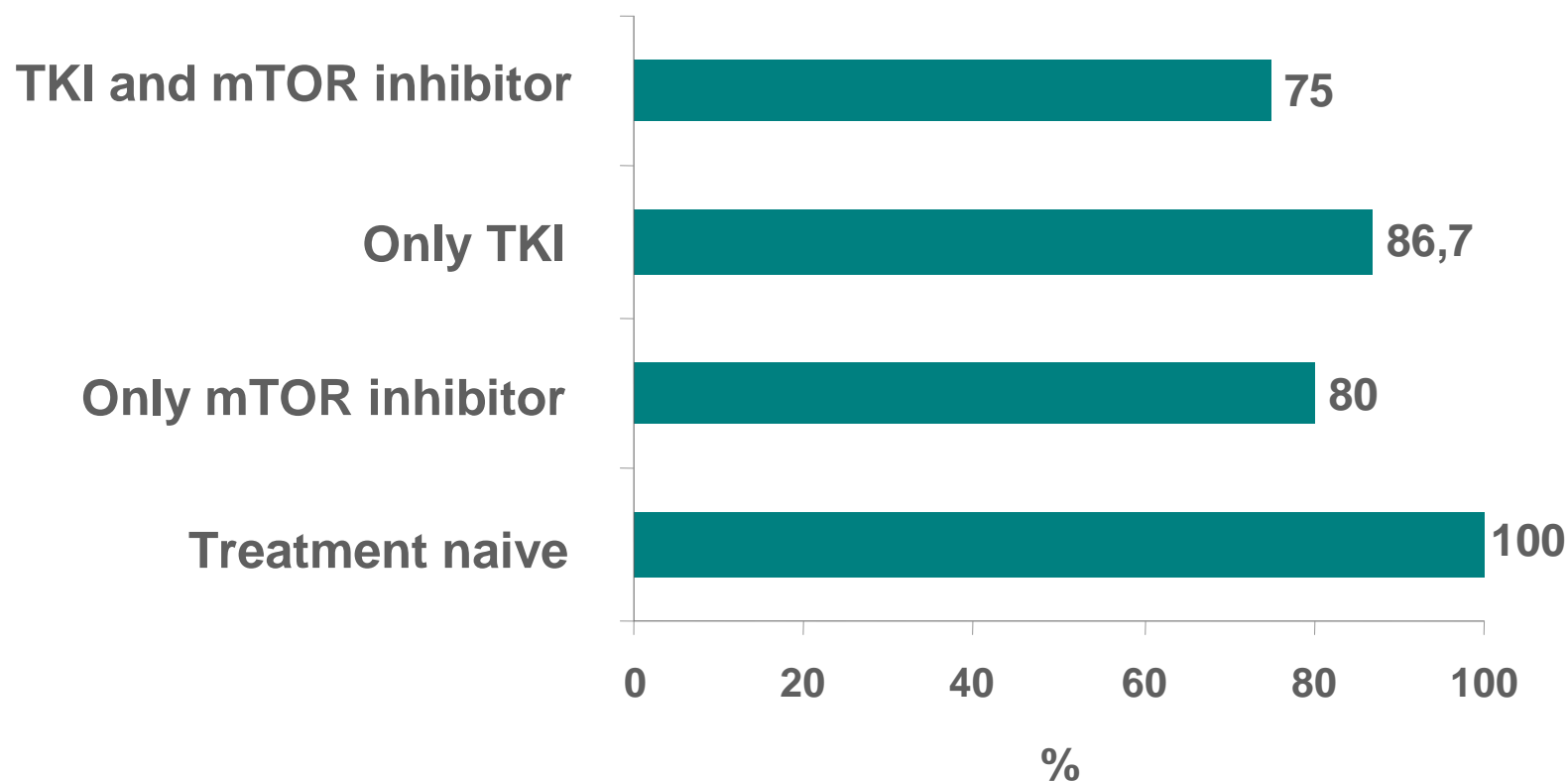| Trials	N patients	Agent	ORR Pancreas	ORR Other NETs
Hobday ASCO 2007	41	Sorafenib*	10%	10%
Yao JCO 2008	22	Bevacizumab + OC LAR	-	18%
Kulke JCO 2008	107	Sunitinib*	16.7%	2.4%
Phan ASCO 2010	50	Pazopanib*	17%	0%
Okusaka ASCO GI 2012	12	Sunitinib	42%	-

7%

*SSA therapy or not

Slope not standardized prior enrolment

PAZONET : RESULTS

CBR by Subgroups
according to previous treatment

TKI and mTOR inhibitor — 75

Only TKI — 86,7

Only mTOR inhibitor — 80

Treatment naive — 100

%

PROGRESSION-FREE SURVIVAL BY SUBGROUPS

PFS by Subgroups

- Only TKI: mPFS 12.1m (95%CI 5.8 to 18.3m)
- Treatment naive: mPFS 10.0m (95%CI 5.6 to 14.4m)
- Only mTOR inhibitor: mPFS 6.8m (95%CI 0.0 to 15.3m)
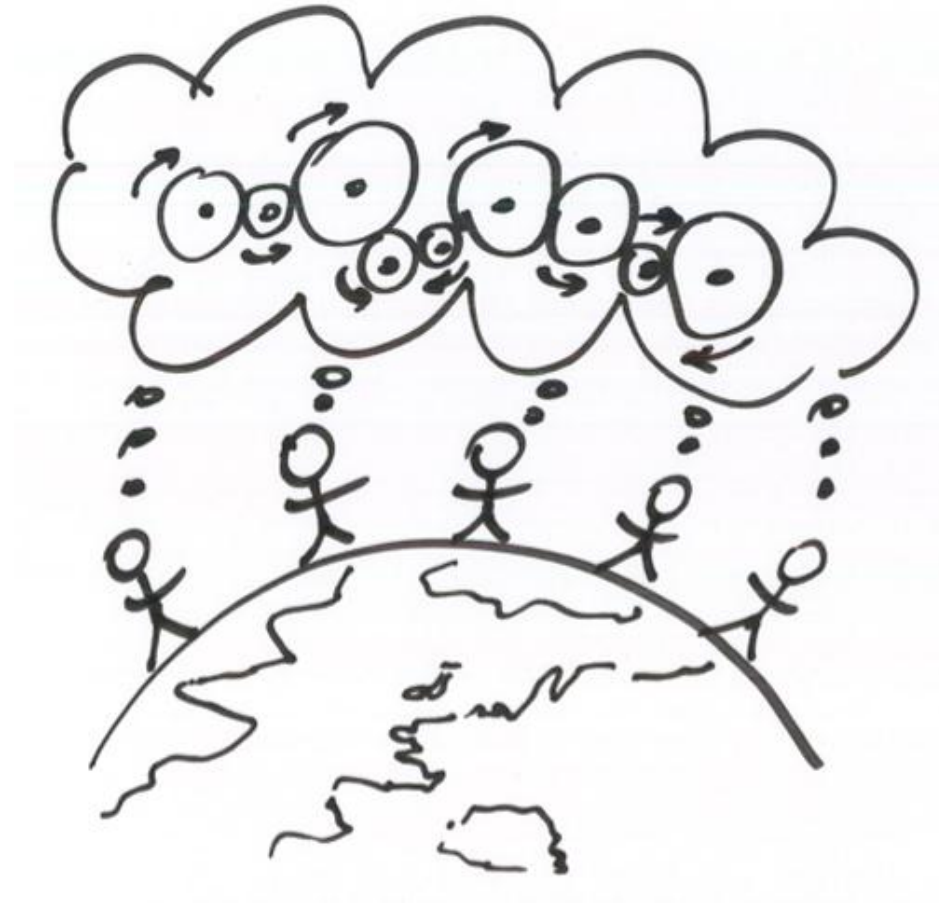- TKI and mTOR inhibitor: mPFS 4.1m (95%CI 0.0 to 9.1m)
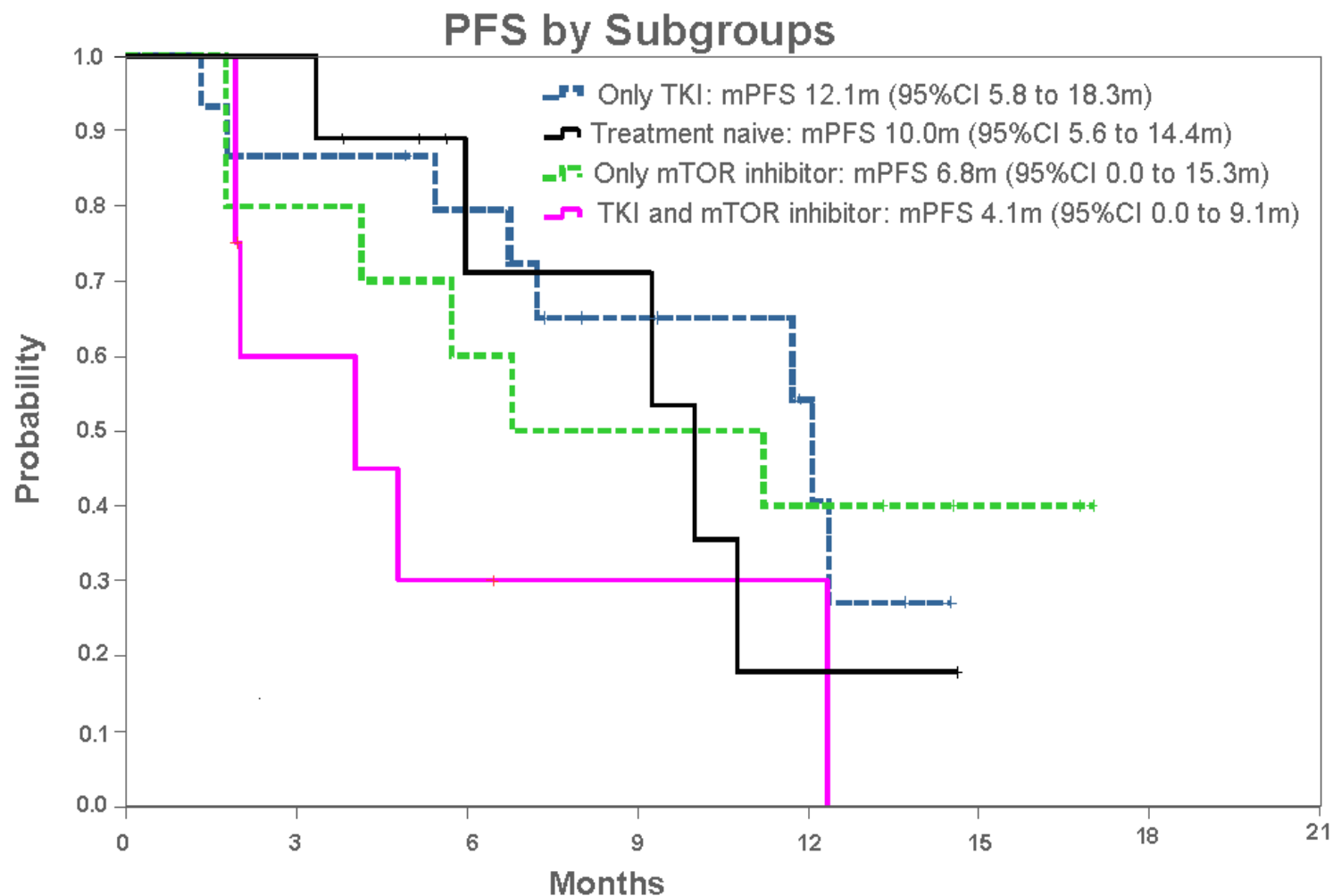
Approach of the best sequence in porgressive well differentiated NET : post first-line chemotherapy results?

Study	Patients	Agent	ORR	Median PFS
Sun et al 2005	Various (no pNET)	Dacarbazine	8%	-
Yao et al 2009	Pancreas	Everolimus	9.6%	9.7
Grande et al 2012	Various (pNET)	Pazopanib	7%	10

What I learn

- This study suggests antitumor activity of Pazopanib in a mixed population of well differentiated NET pretreated with multiple options including TKI and or mTOR inhibitors in 80% of cases

- Safety : preliminary results encouraging, more details expected

- Sequencing of targeted molecular therapies could be considered an option in futur protocol analyzing best sequencing strategy in NET

Thank you

Think NET=Think multidsciplinary