Grupo Español de Tumores Neuroendocrinos

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)

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DISCLOSURES

- **Advisory board and honoraria**
  - Novartis Oncology
  - Pfizer Oncology
  - IPSEN Pharma
- **Research support**
  - GSK Oncology
- **I will discuss the following off label use and/or investigational use in my presentation:**
  - Pazopanib

Pazopanib is not approved for the treatment of neuroendocrine tumors

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BACKGROUND

- Well to moderately differentiated neuroendocrine tumors (NETs) comprise a heterogeneous group of malignancies for which a range of therapeutic options have been used.[1]
- Overexpression of VEGF and VEFG-R is known to correlate with metastases and reduced progression free survival (PFS). [2]
- Randomized, placebo-controlled studies have recently demonstrated that treatment with sunitinib (multi-targeted tyrosine kinase inhibitor) or everolimus (mTOR inhibitor) is associated with improved PFS in pancreatic NETs. [3,4]
- Pazopanib is a multi-targeted agent that has already shown clinical activity in patients with advanced NETs and also decreases blood flow and permeability surface on functional CT scans.[5]

1 Yao et al. J Clin Oncol 2008;26:3063-72
2 Phan et al. J Clin Oncol 24:18s, 2006 (suppl; abstr 4091)
3. Raymond, N Engl J Med 2011;364(6):501-13
4. Yao et al. N Engl J Med 2011;364(6):514-23
5. Phan et al. ASCO 2010

STUDY DESIGN

A phase II, single arm, non-randomized, multicenter clinical trial

INCLUSION CRITERIA:

- **Well- and moderately-differentiated carcinoid or pancreatic islet cell metastatic tumors with documented progression of the disease within 12 months prior baseline.**
- **ECOG performance status of 0 or 1.**
- **Disease that is not amenable to surgery, radiation or combined modality therapy with curative intent.**
- **Presence of at least one dimensionally measurable target lesion (RECIST v1.0).**
- **Previous treatment with somatostatin analogues, chemotherapy, antiangiogenics, or mTOR inhibitors were permitted.**

PAZOPANIB 800 mg qd

- **Disease progression**
- **Intolerance**
- **Patient withdrawal**

Sample size: 44 patients (Simon's Minimax design)

Stage 1: 22 patients → **Stage 2:** 22 patients

If 12 or more experience clinical benefit

This design would allow to reject the null hypothesis of CBR = 50% in favour of CBR = 70% if a total of 28 or more subjects out of 44 experience clinical benefit

CBR: Clinical Benefit Rate

ENDPOINTS

Primary endpoint: Clinical Benefit Rate (CBR) defined as Complete Response (CR) plus Partial Response (PR) plus Stable Disease (SD) **at 6 months** by RECIST v1.0.

Secondary endpoints: **Progression Free Survival** (PFS), **safety**, **duration of response**, and **biomarker** studies.

- *Biomarkers:* Circulating Tumor Cells (CTCs), Circulating Endothelial Cells (CECs), Circulating Endothelial Progenitor Cells (CEPCs), immunohistochemistry tumor markers, metabolic polymorphisms and soluble angiogenic markers.

DEMOGRAPHIC AND BASELINE CHARACTERISTICS

- Between January 2011 and March 2012, the 44 planned patients were enrolled in 10 Spanish sites within GETNE.
- At the data cut-off, July 2012, a total of 42 patients were evaluable for response per protocol.

		N (%)
Gender	Male	22 (52.4)
	Female	20 (47.6)
Age (Median)		61 (38-79)
ECOG	0	16 (38.1)
	1	26 (61.9)
Tumor Type		
	Pancreatic islet cell tumors	17 (40.4)
	Gastrointestinal neuroendocrine tumors	15 (35.7)
	Pulmonary carcinoid tumors	4 (9.5)
	Thymic carcinoid tumors	3 (7.2)
	Unknown primary origin tumors	3 (7.2)
Tumor Grade		
	Well-differentiated (Ki 67<2%)	27 (84.4)
	Moderately-differentiated (Ki 67 2%-20%)	5 (15.7)
Previous Treatments		
Without prior novel target agents		
	Treatment naive	2 (4.8)
	Chemotherapy and SSA	7 (16.6)
Prior mTOR without multitarget		10 (23.8)
Prior multitarget without mTOR		15 (35.7)
Prior antiangiogenic and mTOR inhibitors		8 (23.8)
Number of previous systemic treatments (Median)		2 (0-7)

SSA: Somatostatin analogs

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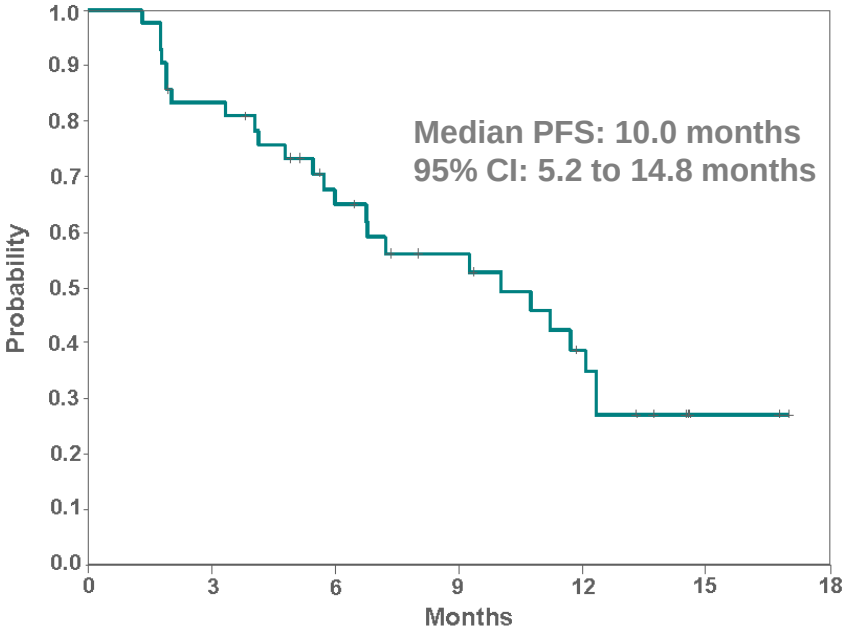
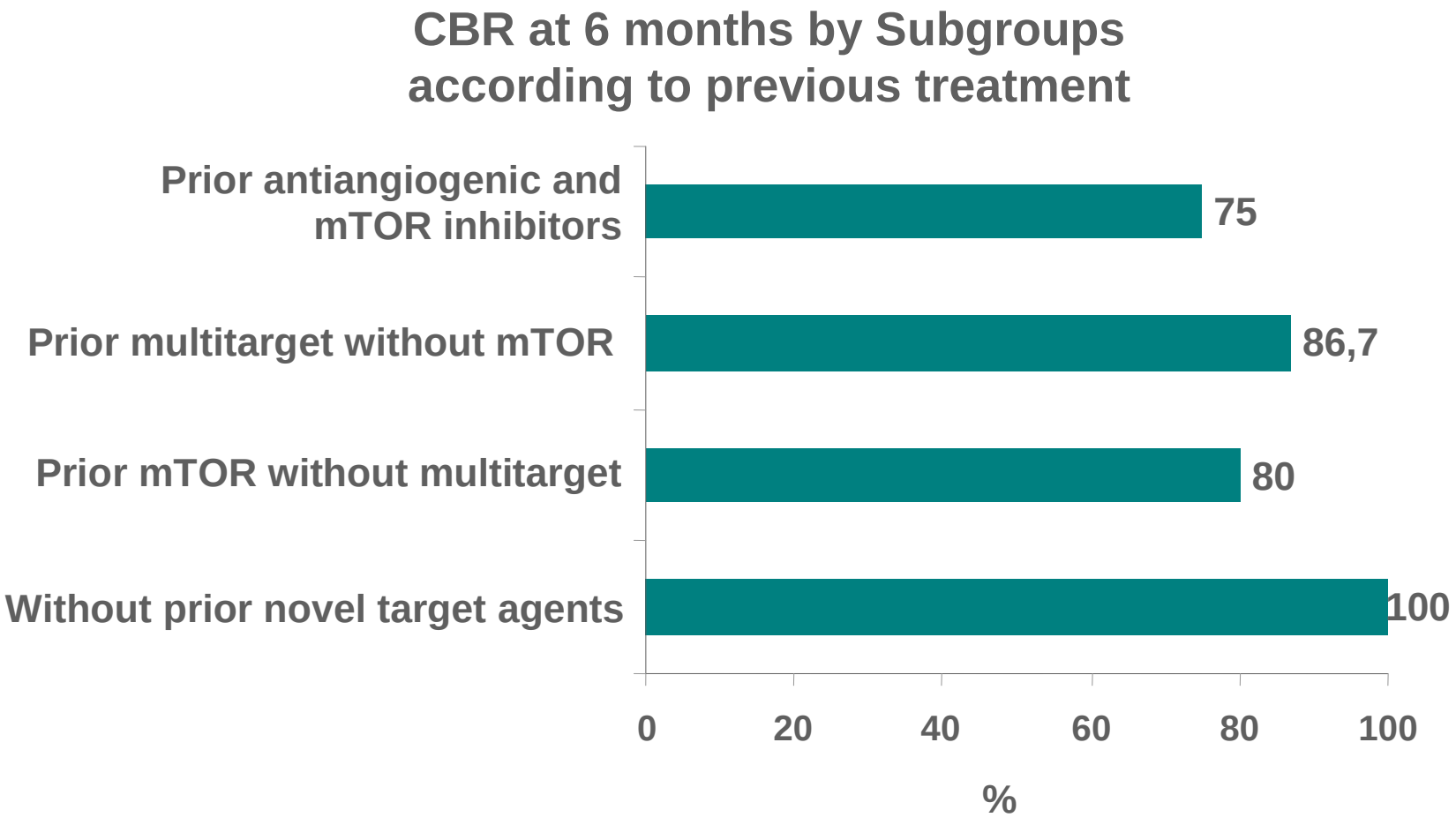
RESULTS

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)**

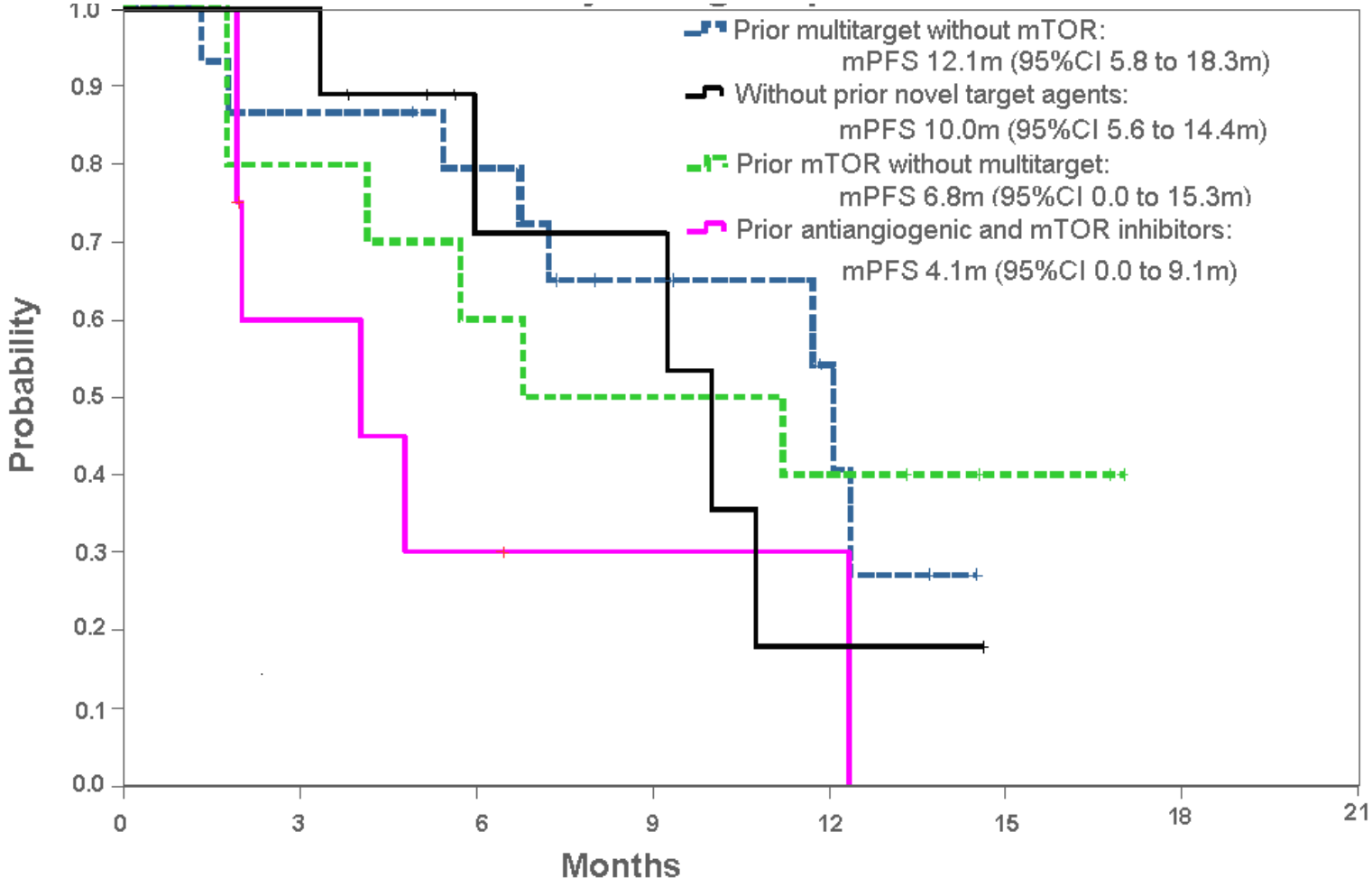


Data cut off July 2012

RESULTS


CBR at 6 months by Subgroups according to previous treatment
Prior antiangiogenic and mTOR inhibitors
75
Prior multitarget without mTOR
86,7
Prior mTOR without multitarget
80
Without prior novel target agents
100
0
20
40
60
80
100
%

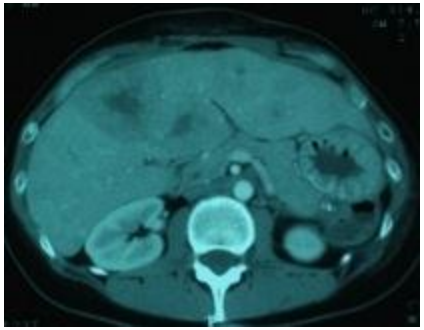
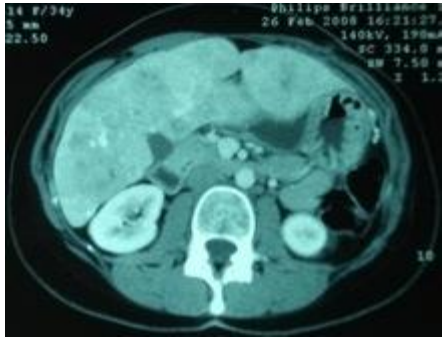
PROGRESSION-FREE SURVIVAL BY SUBGROUPS

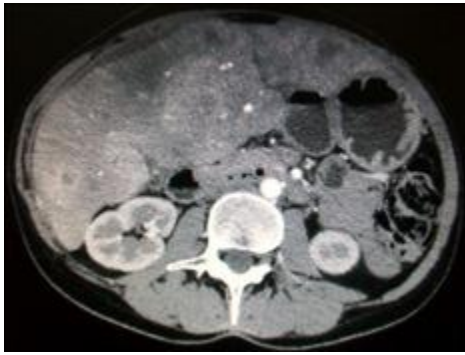


EVIDENCE OF ANTITUMOR AND HORMONE SECRETION CONTROL

Gastrin production (transforming) Ectopic-ACTH production

Ascites



10-2007 01-2008 02-2008 7-2010 10-2010 12-2011

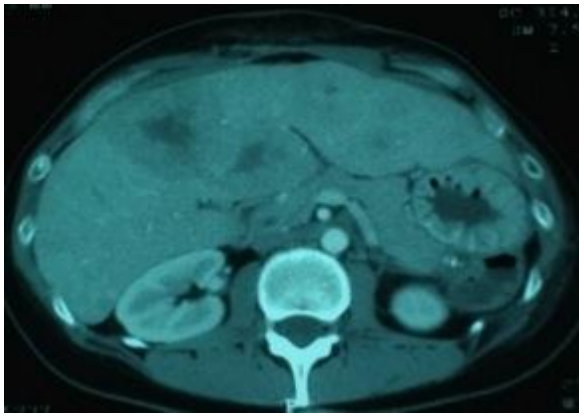
Octreotide LAR 30mg/m 4 mo

Sunitinib 37.5 mg/d 29 mo

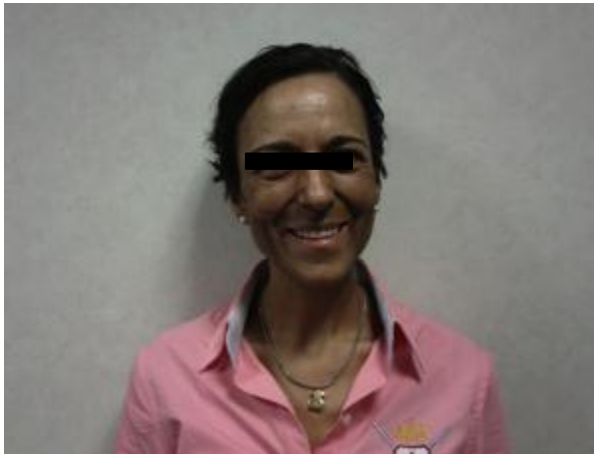
Everolimus 10 mg/d 15 mo

Symptoms control *Tumor shrinking* *Tumor shrinking*

EVIDENCE OF ANTITUMOR AND HORMONE SECRETION CONTROL

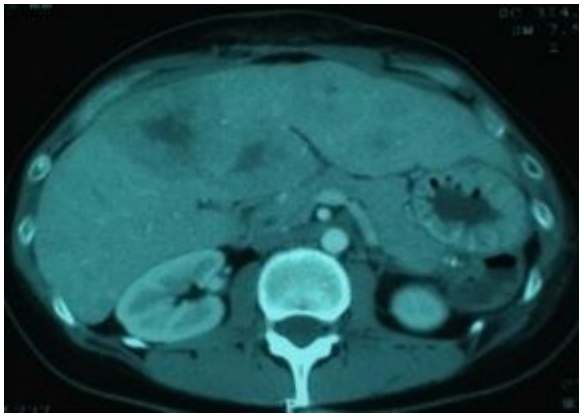


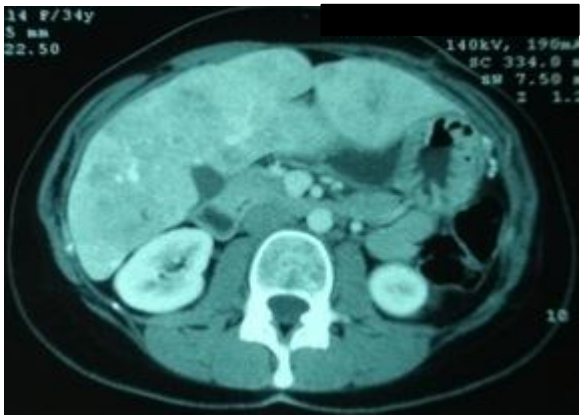
12-2011 Ectopic-ACTH production



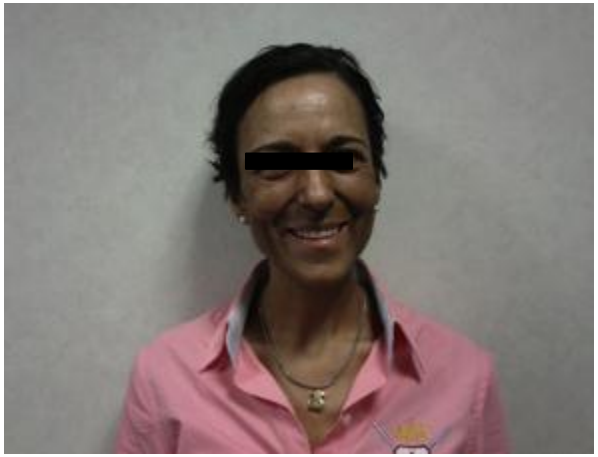
Pazopanib (PAZONET trial)

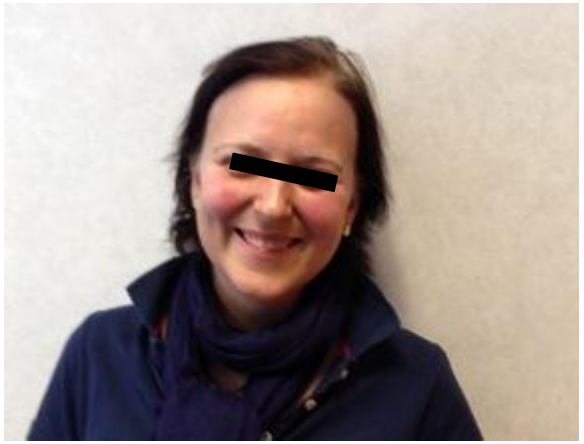
EVIDENCE OF ANTITUMOR AND HORMONE SECRETION CONTROL





12-2011 Ectopic-ACTH production **9-2012**





Pazopanib (PAZONET trial) **9 + mo**

Tumor shrinking

OS 59+ months (5 years)

VIENNA 2012 ESMO congress

www.esmo2012.org

Courtesy by Dr. Daniel Castellano

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TOXICITY

Toxicity	Grade I	Grade II	Grade III	Grade IV	Total	%
Asthenia	14	16	7	1	38	86,4
Diarrhoea	12	13	4	0	29	65,9
Hypertension	10	5	3	1	19	43,2
Nausea	10	7	0	0	17	38,6
Mucositis	12	2	0	0	14	31,8
Abdominal Pain	8	4	1	0	13	29,5
Hand-foot syndrome	10	2	0	0	12	27,3
Anorexia	7	4	1	0	12	27,3
Transaminase elevation	3	3	4	1	11	25,0
Vomiting	9	0	0	0	9	20,5
Hair depigmentation	7	2	0	0	9	20,5
Hyporexia	5	2	1	0	8	18,2
Edema	6	2	0	0	8	18,2
Hyperglycaemia	2	2	2	1	7	15,9

SUMMARY

- Pazopanib is the first drug to show clinical activity in patients with NETs who have failed to at least one previous systemic treatment based on mTOR inhibition or other multi-targeted agents.
- Pazopanib toxicity profile was similar to previous reports in other solid tumor studies.
- Pazopanib introduces the concept of ‘sequencing strategy’ in the treatment of patients with metastatic/advanced NETs.
- Biomarker analysis using CTCs, CECs, CEPCs, tumor markers, metabolic polymorphisms and soluble angiogenic markers are ongoing.

ACKNOWLEDGMENTS

- The patients and their families.
- The investigators, nurses and study coordinators.
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