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
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 VEGF-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)
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

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**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.
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.

<table>
<thead>
<tr>
<th>N (%)</th>
<th>Gender</th>
<th>Male 22 (52.4)</th>
<th>Female 20 (47.6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Median)</td>
<td>61 (38-79)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG</td>
<td>0 16 (38.1)</td>
<td>1 26 (61.9)</td>
<td></td>
</tr>
<tr>
<td>Tumor Type</td>
<td>Pancreatic islet cell tumors 17 (40.4)</td>
<td>Gastrointestinal neuroendocrine tumors 15 (35.7)</td>
<td>Pulmonary carcinoid tumors 4 (9.5)</td>
</tr>
<tr>
<td>Tumor Grade</td>
<td>Well-differentiated (Ki 67&lt;2%) 27 (84.4)</td>
<td>Moderately-differentiated (Ki 67 2%-20%) 5 (15.7)</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Treatment naive 2 (4.8)</td>
<td>Chemotherapy and SSA 7 (16.6)</td>
<td>Prior mTOR without multitarget 10 (23.8)</td>
</tr>
<tr>
<td>Number of previous systemic treatments (Median)</td>
<td>2 (0-7)</td>
<td></td>
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</tbody>
</table>

SSA: Somatostatin analogs
## RESULTS

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

Median PFS: 10.0 months  
95% CI: 5.2 to 14.8 months

Data cut off July 2012

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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%
PROGRESSION-FREE SURVIVAL BY SUBGROUPS

- Prior multitarget without mTOR:
  mPFS 12.1m (95% CI 5.8 to 18.3m)

- Without prior novel target agents:
  mPFS 10.0m (95% CI 5.6 to 14.4m)

- Prior mTOR without multitarget:
  mPFS 6.8m (95% CI 0.0 to 15.3m)

- Prior antiangiogenic and mTOR inhibitors:
  mPFS 4.1m (95% CI 0.0 to 9.1m)
EVIDENCE OF ANTITUMOR AND HORMONE SECRETION CONTROL

Gastrin production  (transforming)  Ectopic-ACTH production

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

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Courtesy by Dr. Daniel Castellano
EVIDENCE OF ANTITUMOR AND HORMONE SECRETION CONTROL

12-2011  Ectopic-ACTH production

Pazopanib (PAZONET trial)

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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)

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Courtesy by Dr. Daniel Castellano
## TOXICITY

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
<th>Grade IV</th>
<th>Total</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>Asthenia</td>
<td>14</td>
<td>16</td>
<td>7</td>
<td>1</td>
<td>38</td>
<td>86,4</td>
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<tr>
<td>Diarrhoea</td>
<td>12</td>
<td>13</td>
<td>4</td>
<td>0</td>
<td>29</td>
<td>65,9</td>
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<tr>
<td>Hypertension</td>
<td>10</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>19</td>
<td>43,2</td>
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<tr>
<td>Nausea</td>
<td>10</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>17</td>
<td>38,6</td>
</tr>
<tr>
<td>Mucositis</td>
<td>12</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>14</td>
<td>31,8</td>
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<tr>
<td>Abdominal Pain</td>
<td>8</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>13</td>
<td>29,5</td>
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<tr>
<td>Hand-foot syndrome</td>
<td>10</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>12</td>
<td>27,3</td>
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<tr>
<td>Anorexia</td>
<td>7</td>
<td>4</td>
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<td>0</td>
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<td>Transaminase elevation</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>11</td>
<td>25,0</td>
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<tr>
<td>Vomiting</td>
<td>9</td>
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<td>0</td>
<td>9</td>
<td>20,5</td>
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<td>Hair depigmentation</td>
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<td>0</td>
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<td>Edema</td>
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<tr>
<td>Hyperglycaemia</td>
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<td>2</td>
<td>2</td>
<td>1</td>
<td>7</td>
<td>15,9</td>
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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.
• GETNE team support.
• GSK medical team: Natalia de la Fuente, Mauro Filori, Araceli Lopez and Linda Pronk.
• MFAR for the monitoring, data management, and statistical support.
• All study staff at each site specially Sara Lavin, Elena Ruiz and Gloria Carrascosa.