Significant antitumor activity of E-3810, a novel FGFR and VEGFR inhibitor, in patients with *FGFR1* amplified breast cancer

Disclosure

No conflicts of interest to disclose.
Rationale for FGFR targeting
Focus on Breast Cancer

- Aberrant FGF signalling can promote tumour development by directly driving cancer cell proliferation and survival, and by supporting tumour angiogenesis.
- *FGFR1* amplification (8p 11-12) in 10% of breast tumours (predominantly luminal).
  - Resistance to endocrine treatment, poor prognosis.
- 11q 12-14 amplification (including *FGF3*) in 15%-30% of breast tumours.
  - Increased aggressiveness.
- Functional preclinical data demonstrate that *FGFR1* signalling is required for the survival of breast cancer cells harbouring *FGFR1* amplification.
- *FGFR1* is a potential therapeutic target in breast cancer.

E-3810 Preclinical Features

• Novel small molecule \(^{(1,2)}\), equipotent inhibitor of FGFR1 and VEGFR 1-3 kinase activity

\textit{In vitro} kinase inhibition
- IC\textsubscript{50} FGFR1 17 nM, VEGFR1-3 7-25 nM
- FGFR2 82 nM, FGFR3 238 nM

\textbf{Antiproliferative IC\textsubscript{50}}
- Sub micromolar range in HUVEC and tumour cells with \textit{FGFR1} amplification
- 10-30 μM in non-amplified tumour lines

• Strong antitumor activity \textit{in vivo}, especially in models with \textit{FGFR1} amplification or high expression of FGFR1 or FGF2

1. E-3810 Is a Potent Dual Inhibitor of VEGFR and FGFR that Exerts Anti-Tumor Activity in Multiple Preclinical Models. Cancer Res 2011, 71(4)::1396-140
2. E-3810 Anti-Tumor Activity in Human Xenografts Expressing Different Levels of FGFR-1. AACR Meeting, 2011 (abstr 594)
3. Courtesy of MPI – Dr Roman Thomas

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Study Design

Open-label non comparative expansion of the First-in-Man dose escalation trial

**Dose-escalation**
- **Standard 3 + 3 design**
- **Patients:** advanced solid tumours
- **MTD** = dose level with DLTs in ≥ 2/6 pts at first cycle (4 weeks)

**Expansion Basket design at recommended dose**

**Assessment of sustained tolerability and preliminary efficacy**
- **Patients:**
  - FGF+ → tumours with *FGFR1* or 11q amplification
  - Antiangiogenic sensitive → tumours potentially sensitive to anti-VEGFR therapy (based on prior response or tumour type)
- **Efficacy threshold for *FGFR1* ampl. subset:** 3/14 confirmed RECIST responses or non-progressive disease ≥6 cycles (restaging every 2 cycles). One-stage Fleming design: H0 5%, H1 30%, power 80%

**Cycle 1:**
- Serial blood sampling for PK on D1, D7 and D28 – pre-dose on D4, D14 and D21
- PD (baseline, D7 and D28)
  - Tumor perfusion/permeability by imaging technique (DCE-MRI and DCE-US)
  - Circulating markers of angiogenesis (VEGFR1/2, VEGF, bFGF, Collagen IV, PIGF), FGF23, CEC/CEP/CTC
FGF+ definition

- **Fluorescent in situ hybridization (FISH) cutoff:**
  - *FGFR1*
    - ≥ 6 gene copies/nucleus (*Kreatech Poseidon FGFR1 (8p12) Break Probe*); or
    - FGFR1/CEN8 > 2.2 (*ZytoLight Dual color probe*).

- **Comparative Genomic Hybridization (CGH) array - Agilent platform**
  - *FGF3*
    - 11q 12-14 amplification log2 ratio > 0.9
  - *FGFR1*
    - 8p 11-12 amplification log2 ratio > 0.9
Dose Escalation Summary

- 17 patients over 4 dose levels (5, 10, 20 and 30 mg/day)

<table>
<thead>
<tr>
<th>MTD over first cycle</th>
<th>30 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLTs: 2 grade 4 proteinuria (thrombotic microangiopathy – TMA)</td>
<td></td>
</tr>
<tr>
<td>1 grade 3 somnolence (reversible encephalopathy)</td>
<td></td>
</tr>
<tr>
<td>Recommended dose over first cycle</td>
<td>20 mg/day</td>
</tr>
</tbody>
</table>

- Noteworthy dose-related AEs:
  - **Proteinuria** seen in all patients at 30 mg over cycle 1
  - **Hypertension** common, onset at cycle 1 but not a DLT
  - **Increase in TSH** after 1-2 cycles, treatment with levothyroxine in most patients
  - **Asthenia, anorexia and diarrhoea** common after 2 cycles

- No consistent hyperphosphatemia.
- No major cardiovascular toxic events.
• Linear kinetics in the dose range explored despite large individual variability.
• Half life 18-36 h with about two-fold accumulation at steady state (reached within 7 days).
## Expansion Cohorts
### Patients Characteristics

<table>
<thead>
<tr>
<th></th>
<th>FGF+ (n=18)</th>
<th>Antiangiogenic sensitive (n= 33)</th>
<th>All (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td>M/F</td>
<td>3/15</td>
<td>18/15</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>median (range)</td>
<td>56 (34-74)</td>
<td>56 (38-80)</td>
</tr>
<tr>
<td><strong>Prior therapy</strong></td>
<td></td>
<td>18</td>
<td>30</td>
</tr>
<tr>
<td><strong>Treatment lines</strong></td>
<td>median (range)</td>
<td>4 (1-15)</td>
<td>3 (0-11)</td>
</tr>
<tr>
<td><strong>Antiangiogenics</strong></td>
<td>any as last line</td>
<td>12/6</td>
<td>27/20</td>
</tr>
</tbody>
</table>
## Expansion Cohorts - Overall Safety

<table>
<thead>
<tr>
<th></th>
<th>FGF+</th>
<th>Antiangiogenic Sensitive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20 mg (n=3)</td>
<td>15 mg (n=15)</td>
</tr>
<tr>
<td>Off for toxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Cy</td>
<td>-</td>
<td>2* (13%)</td>
</tr>
<tr>
<td>@ C1</td>
<td>-</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Dose decreased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Cy</td>
<td>3 (100%)</td>
<td>8 (53%)</td>
</tr>
<tr>
<td>@ C1-2</td>
<td>2 (67%)</td>
<td>5 (33%)</td>
</tr>
<tr>
<td>Treatment interruption</td>
<td>3 (100%)</td>
<td>8 (53%)</td>
</tr>
</tbody>
</table>

* Proteinuria G3 and TMA @ C1 (1 pt); nausea, vomiting and asthenia G2 @ C6 (1 pt)

** HTN and proteinuria G3 @ C1 (2 pts); depression, headache and vomiting G2 @ C1 (1 pt); Vaso-vagal episode with headache and vomiting @ C1 → off @ C2 (1 pt)

*** Proteinuria G3 and TMA @ C1 (1 pt) and @ C3-4 (2 pts); G4 increase amylase-lipase @ C1 (1 pt)

**Reasons for interruption/dose decrease:** GI toxicity and asthenia (14 pts), proteinuria (10 pts), HTN (8 pts).

**Other significant events:** LVEF decrease (2 pts), asymptomatic amylase-lipase increase (2 pts), anorectal infection due to pelvic abscess (1 pt)
# Breast Cancer Patients Characteristics

<table>
<thead>
<tr>
<th></th>
<th>FGF+ (n=12)</th>
<th>Antiangiogenic sensitive (n=3)</th>
<th>All (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median (range)</td>
<td>52 (34-63)</td>
<td>47 (42-58)</td>
<td>51 (34-63)</td>
</tr>
<tr>
<td><strong>Prior therapies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment lines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median (range)</td>
<td>12</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>5 (3-15)</td>
<td>3 (2-11)</td>
<td>4 (2-15)</td>
</tr>
<tr>
<td><strong>Endocrine therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td><strong>Antiangiogenics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>any as last line</td>
<td>11</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td><strong>Receptor status</strong></td>
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<td></td>
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</tr>
<tr>
<td>ER+/PR+, HER2-</td>
<td>4</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>ER+/PR-, HER2-</td>
<td>3</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>ER+/PR+, HER2+</td>
<td>1</td>
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<td>1</td>
</tr>
<tr>
<td>ER+/PR-, HER2+</td>
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</tr>
<tr>
<td>ER-/PR+, HER2-</td>
<td>3</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>TNBC</td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td><strong>FGFR1 ampl (FISH)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amplification Ratio*</td>
<td>median (range)</td>
<td>9 (7.5 (2.21-13.6))</td>
<td>-</td>
</tr>
<tr>
<td><strong>11q ampl (CGH)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>--</td>
<td></td>
</tr>
</tbody>
</table>

* 6 pts
## Breast Cancer Patients
### Best Overall Response

<table>
<thead>
<tr>
<th></th>
<th>FGF+</th>
<th>Antiangiogenic sensitive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Evaluable</td>
<td>PR</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>10</td>
<td>7* @</td>
</tr>
<tr>
<td>ER+/PR+, HER2-</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>ER+/PR-, HER2-</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>ER+/PR+, HER2+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+/PR-, HER2+</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>TNBC</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

* 1 additional patient with PET response (bone lesions)
@ 4 patients with *FGFR1* ampl and 3 patients with 11q ampl
** SD > 6 months
FGF+ Breast Cancer Patients with Measurable Disease

One patient with non-measurable target lesions and off study for PD not shown.
Time on study of FGF+ Breast Patients

- Best response
- PR
- SD
- PD
- Not evaluable

AEs

Time on study (weeks)

20 mg 15 mg 10 mg

ongoing
Patient 18028 (VHIO)

- TNBC, FGFR1 ampl (ratio 3.62)
- Locally advanced disease, lymph node metastasis

Baseline
Aug. 29, 2011

C1D14
Sept. 12, 2011

C2D1
Sept. 26, 2011

C3D1
Oct. 21, 2011

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Patient 18032 (VHIO)

- **HR+/HER2-, FGFR1 ampl (ratio 2.21) and CGH**
- Bone, lung and pleura metastases
- 14 prior treatment lines, including 5 Phase 1 trials
- E-3810 at 20 mg/day

Baseline
Sept. 20, 2011

C3D1
Nov. 18, 2011
Patient 61046 (IGR)

Baseline
Dec. 14, 2011

C3D1
Feb. 15, 2012

- HR+/HER2-, FGFR1 ampl (ratio 7)
- Liver and bone metastasis
- E-3810 at 15 mg/day
Patient 18042 (VHIO)

- HR+/HER2-, no FGFR1 ampl FISH
- 11q ampl CGH
- Liver metastasis
- 7 prior treatment lines
- E-3810 at 15 mg/day

CEA levels: 52 ng/mL
CEA levels: 28 ng/mL

- HR+/HER2-, no FGFR1 ampl FISH
- 11q ampl CGH
- Liver metastasis
- 7 prior treatment lines
- E-3810 at 15 mg/day
Expansion Cohort
Patients with Measurable Disease

Max percent change from baseline

-90,00 -60,00 -30,00 0,00 30,00 60,00

FGF+ BC patients

Breast Thyroid Breast Breast Thymus Breast Breast Kidney (RCC) Breast Thyroid Thymus Ovary NSCLC Colorectal Thyroid Colorectal Breast Colorectal Squamous NSCLC Colorectal Mesothelioma

PR
Conclusions

• E-3810 has shown significant activity in heavily pretreated breast cancer with FGF aberrations, with durable responses.

  **New subcategory of breast cancer with a targetable aberration.**

• Toxicity profile was mostly related to antiangiogenic effects.
  – Manageable and reversible upon dose reduction

• Pharmacodynamic analyses are ongoing.

• Further studies are planned in order to validate predictive biomarkers and clinical efficacy.
Acknowledgements

• Patients and their families
• Investigators, Co-Investigators and Study Teams at IGR, IEO and VHIO
  – Jean-Charles Soria, Rastilav Bahleda, Antoine Hollebecque, Elodie Zedouard
  – Filippo De Braud, Cristina Noberasco, Angelo Delmonte, Fabio Vecchio
  – Josep Tabernero, Marta Beltran and Breast Cancer Unit
• Maurizio D’Incalci and the Pharmacokinetics team of the IRFMN
• Fabrice André, Monica Arnedos, Benjamin Besse (IGR)
• The Sponsor EOS S.p.A, Milan, Italy