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

R. Dienstmann, F. Andrè, J.C. Soria, J. Tabernero, F. De Braud, R. Cereda, R. Bahleda, A. Hollebecque, A. Delmonte, M.G. Camboni

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.**

Turner N. & Grose R. **Fibroblast growth factor signalling: from development to cancer.** Nature Rev Cancer 2010

Turner N., et al. **FGFR1 amplification drives endocrine therapy resistance and is a therapeutic target in breast cancer.** Cancer Res 2010

E-3810 Preclinical Features

- **Novel small molecule [1,2], equipotent inhibitor of FGFR1 and VEGFR 1-3 kinase activity**
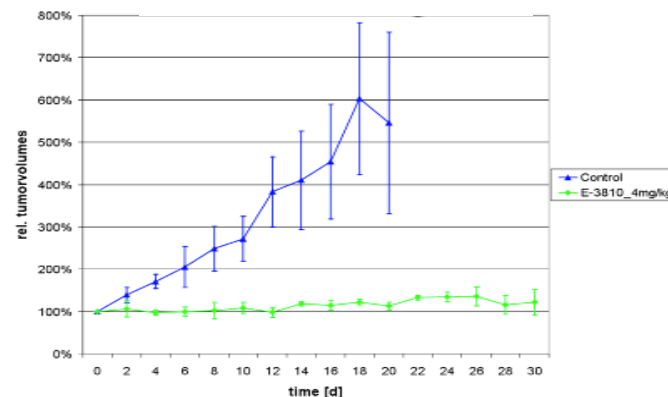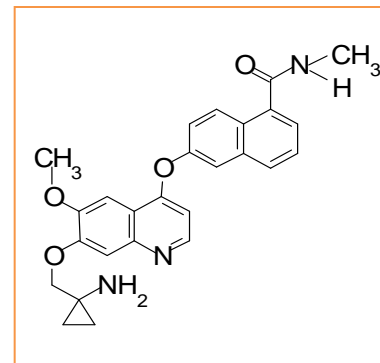
In vitro **kinase inhibition**

   - **IC50 FGFR1 17 nM, VEGFR1-3 7-25 nM**
   - FGFR2 82 nM, FGFR3 238 nM

Antiproliferative IC$_{50}$

   - **Sub micromolar range in HUVEC and tumour cells with *FGFR1* amplification**
   - 10-30 µM in non-amplified tumour lines

- **Strong antitumor activity *in vivo*, especially in models with *FGFR1* amplification or high expression of FGFR1 or FGF2**

H1581 lung xenograft FGFR-1 amplification [3]

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

Study Design

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

Dose-escalation → | **Expansion Basket design at recommended dose** →

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

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, PlGF), 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)**

> **MTD over first cycle → 30 mg/day**
>> **DLTs: 2 grade 4 proteinuria (thrombotic microangiopathy – TMA)**
>>> **1 grade 3 somnolence (reversible encephalopathy)**
>> **Recommended dose over first cycle → 20 mg/day**

- 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.

E-3810 Pharmacokinetic Profile

Day 1
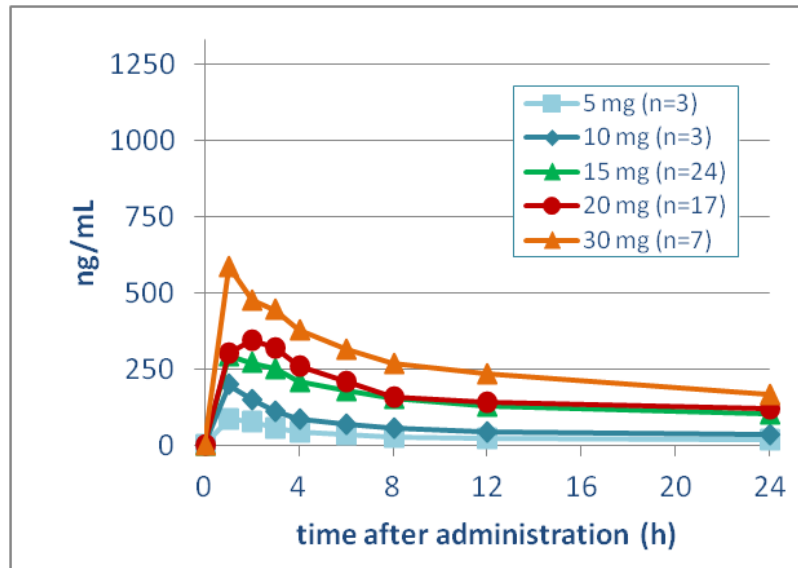
Pre-dose
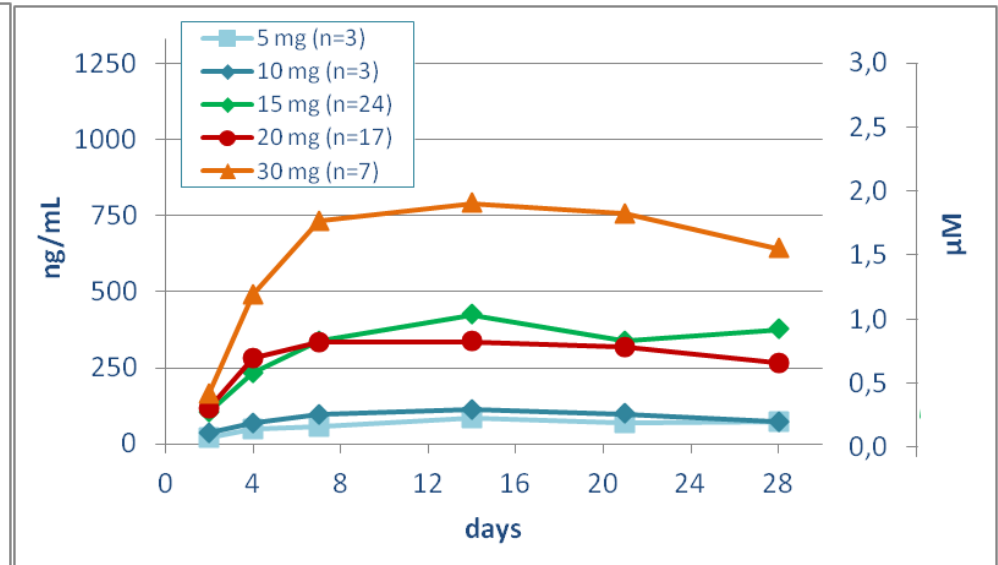
- Linear kinetics in the dose range explored despite large individual variability.
- Half life 18-36 h with about two-fold accumulation at steady state (reached within 7 days).

Expansion Cohorts
Patients Characteristics

		FGF+ (n=18)	Antiangiogenic sensitive (n= 33)	All (n=51)
Sex	M/F	3/15	18/15	21/30
Age (years)	*median (range)*	56 (34-74)	56 (38-80)	56 (34-77)
Prior therapy		18	30	48
Treatment lines	*median (range)*	4 (1-15)	3 (0-11)	3 (0-15)
Antiangiogenics	*any* *as last line*	12 6	27 20	39 26

Expansion Cohorts - Overall Safety

		FGF+		Antiangiogenic Sensitive	
		20 mg (n=3)	15 mg (n=15)	20 mg (n=10)	15 mg (n=23)
Off for toxicity	Any Cy	-	2* (13%)	4** (40%)	4*** (17%)
	@ C1	-	1 (7%)	3 (30%)	2 (9%)
Dose decreased	Any Cy	3 (100%)	8 (53%)	7 (70%)	12 (52%)
	@ C1-2	2 (67%)	5 (33%)	6 (60%)	10 (43%)
Treatment interruption		3 (100%)	8 (53%)	7 (70%)	15 (65%)

* 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

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

* 6 pts

Breast Cancer Patients Best Overall Response

	FGF+				Antiangiogenic sensitive			
	Evaluable	PR	SD	PD	Evaluable	PR	SD	PD
Breast cancer	10	7*@	1	2	2		1	1
ER+/PR+, HER2-	4	3		1	1			1
ER+/PR-, HER2-	3	2	1					
ER+/PR+, HER2+					1		1**	
ER+/PR-, HER2+	1			1				
TNBC	2	2						

* 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
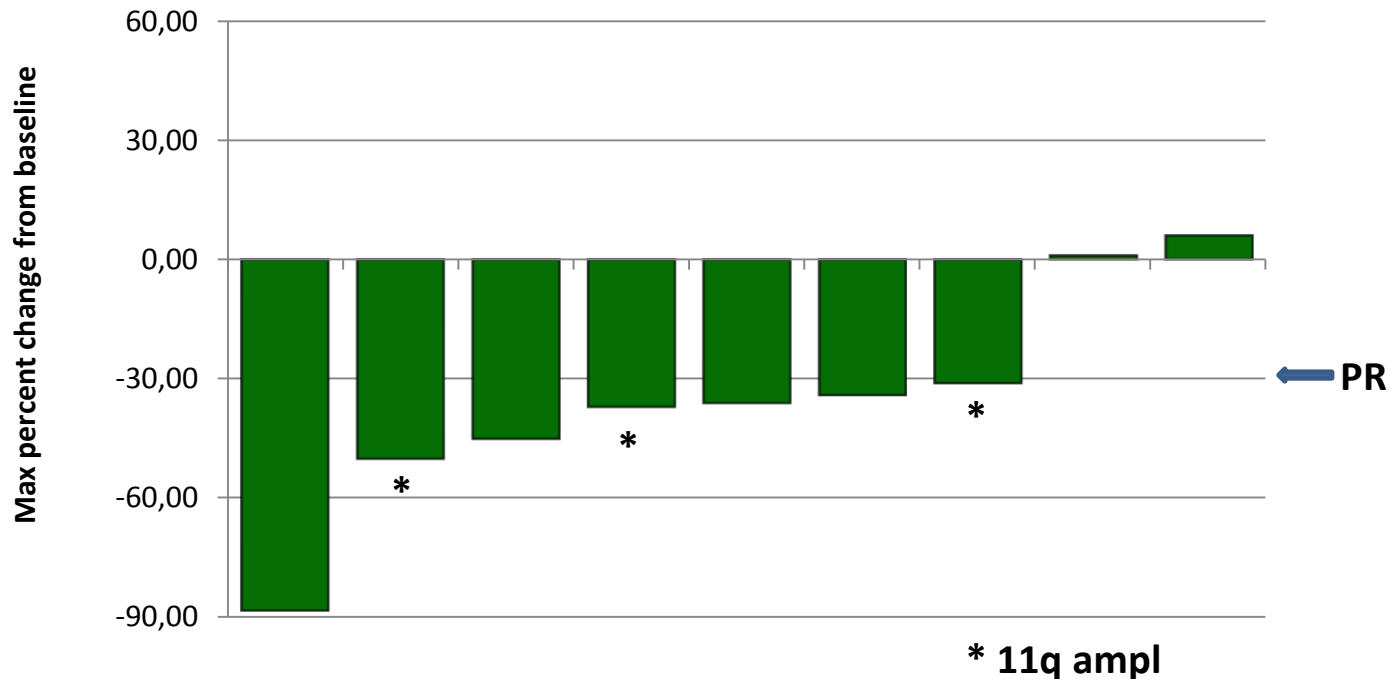
One patient with non-measurable target lesions and off study for PD not shown.

Time on study of FGF+ Breast Patients

Time on study (weeks)

Best response

PR

SD

PD

Not evaluable

* ongoing

AEs

AEs

*
*
*

20 mg   15 mg   10 mg
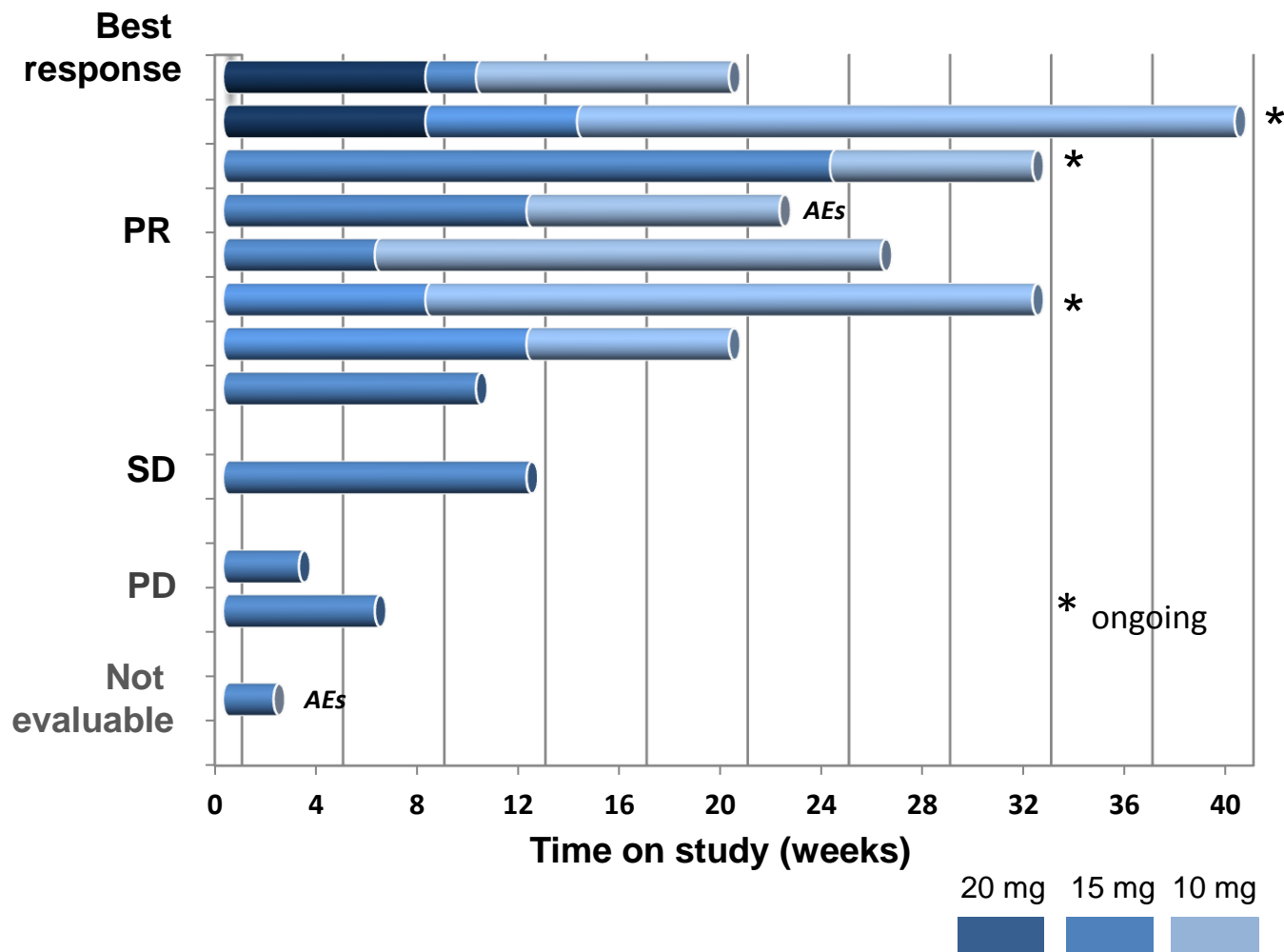
Patient 18028 (VHIO)

Baseline
Aug. 29, 2011

C1D14
Sept. 12, 2011

C2D1
Sept. 26, 2011

C3D1
Oct. 21, 2011

- **TNBC**, *FGFR1* **ampl (ratio 3.62)**
- Locally advanced disease, lymph node metastasis
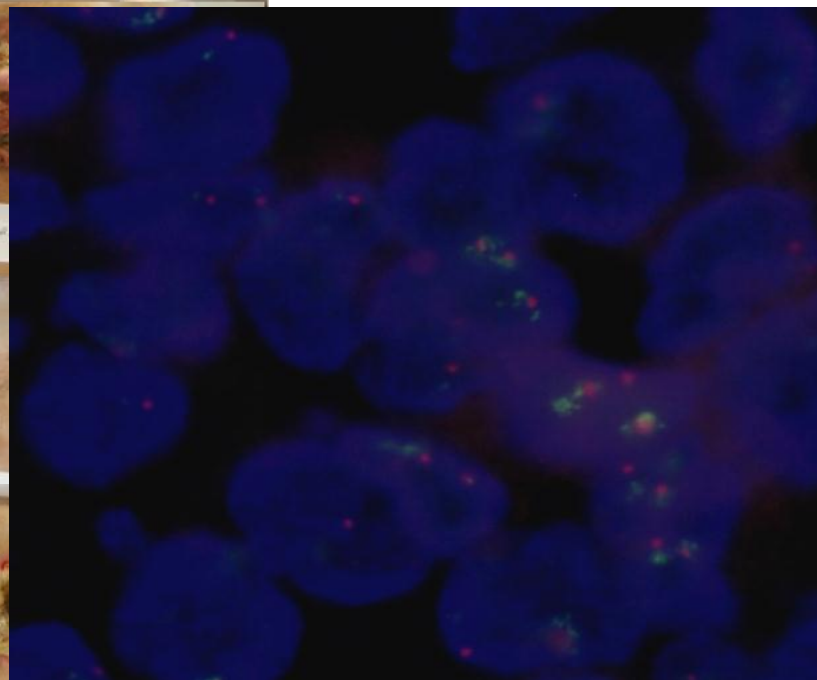
Patient 18032 (VHIO)

Baseline
Sept. 20, 2011
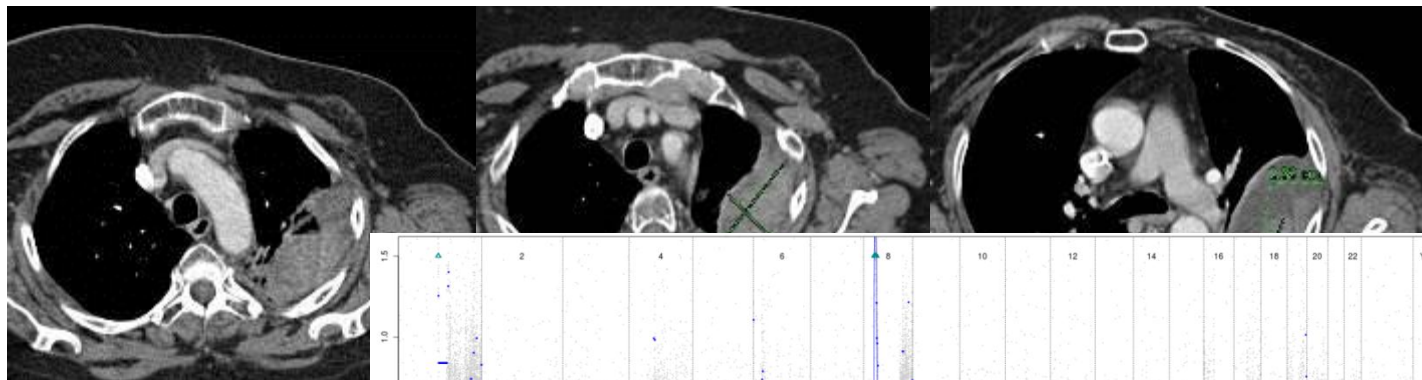
C3D1
Nov. 18, 2011
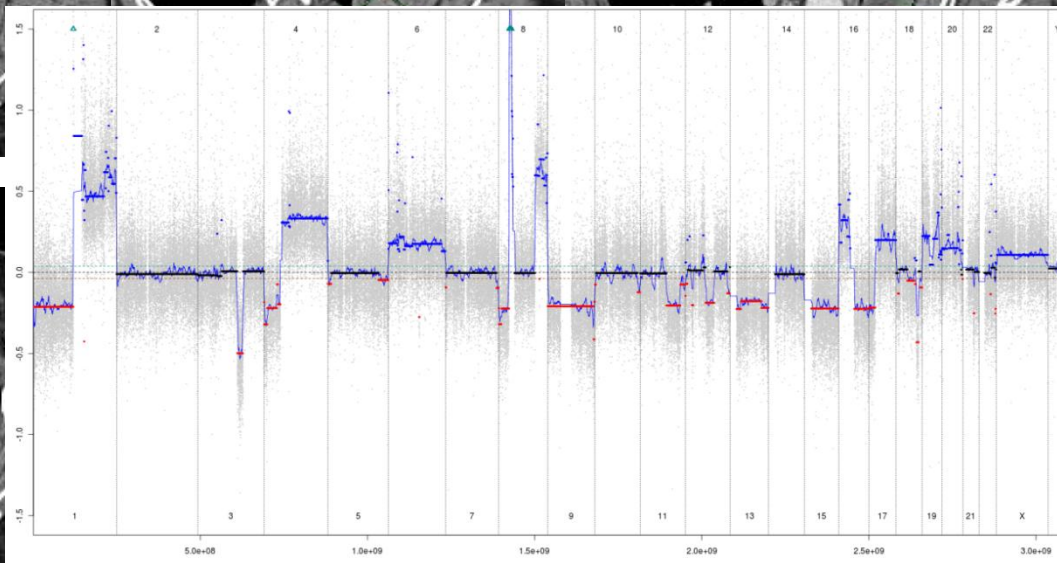
- **HR+/HER2-, *FGFR1* ampl (ratio 2.21) and CGH**
- Bone, lung and pleura metastases
- 14 prior treatment lines, including 5 Phase 1 trials
- E-3810 at 20 mg/day

Patient 61046 (IGR)

Baseline
Dec. 14, 2011
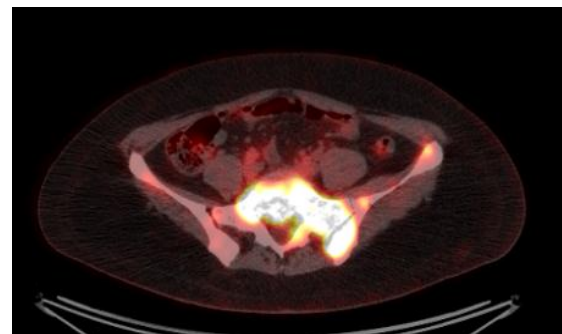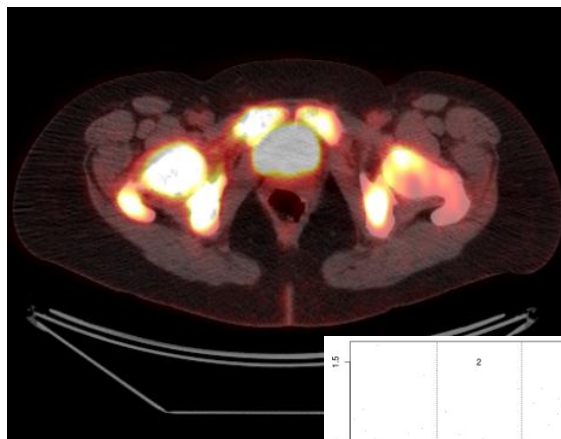
C3D1
Feb. 15, 2012
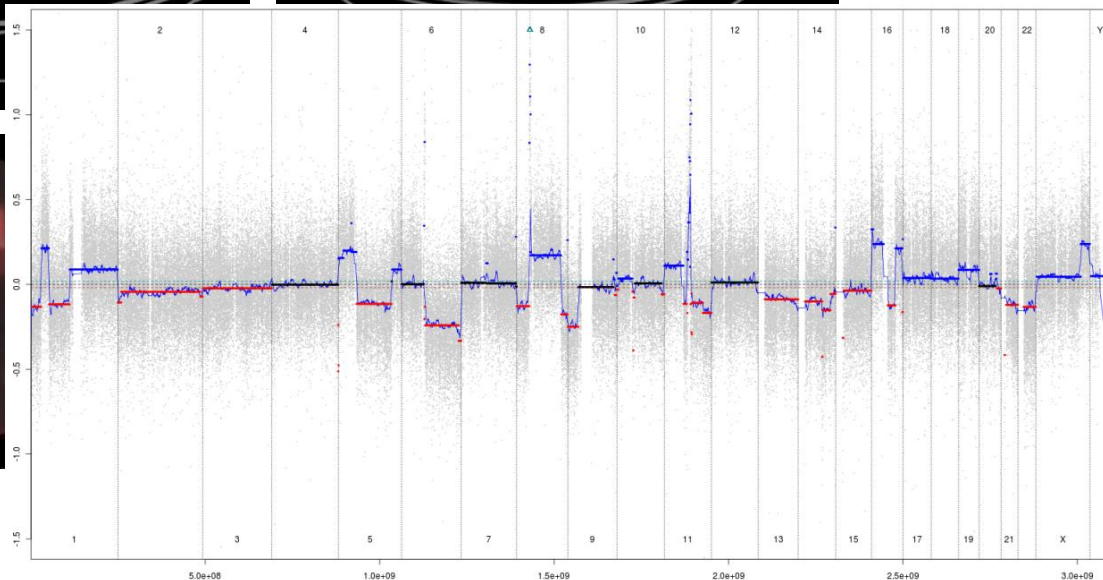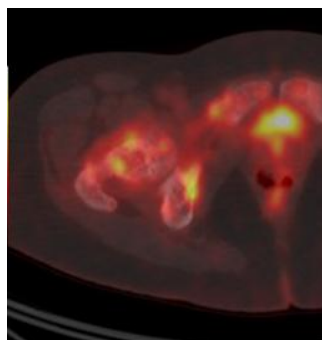
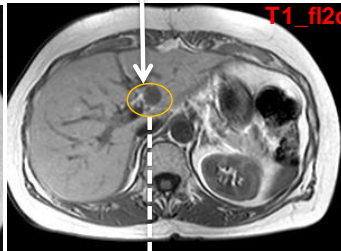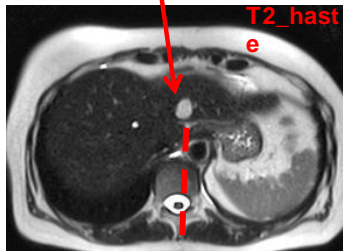- **HR+/HER2-, *FGFR1* ampl (ratio 7)**
- Liver and bone metastasis
- E-3810 at 15 mg/day

Patient 18042 (VHIO)

HEMANGIOMA

29-NOV-11

T2_haste

10-FEB-12

T2_haste

T1_fl2d — 17x15mm

T1_fl2d — 9x7mm

METASTASIS

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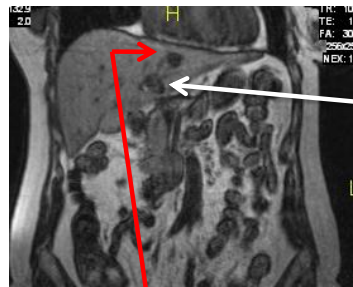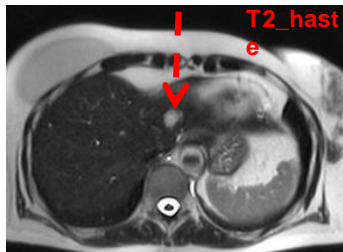
Expansion Cohort
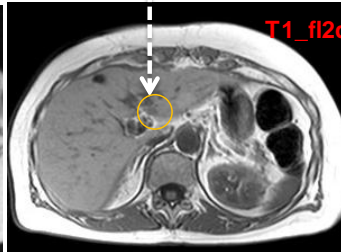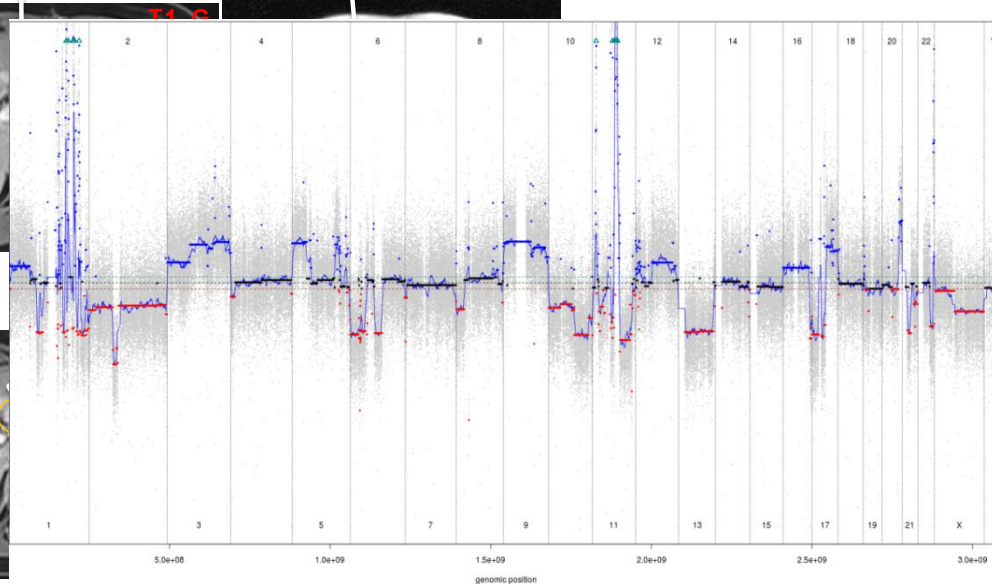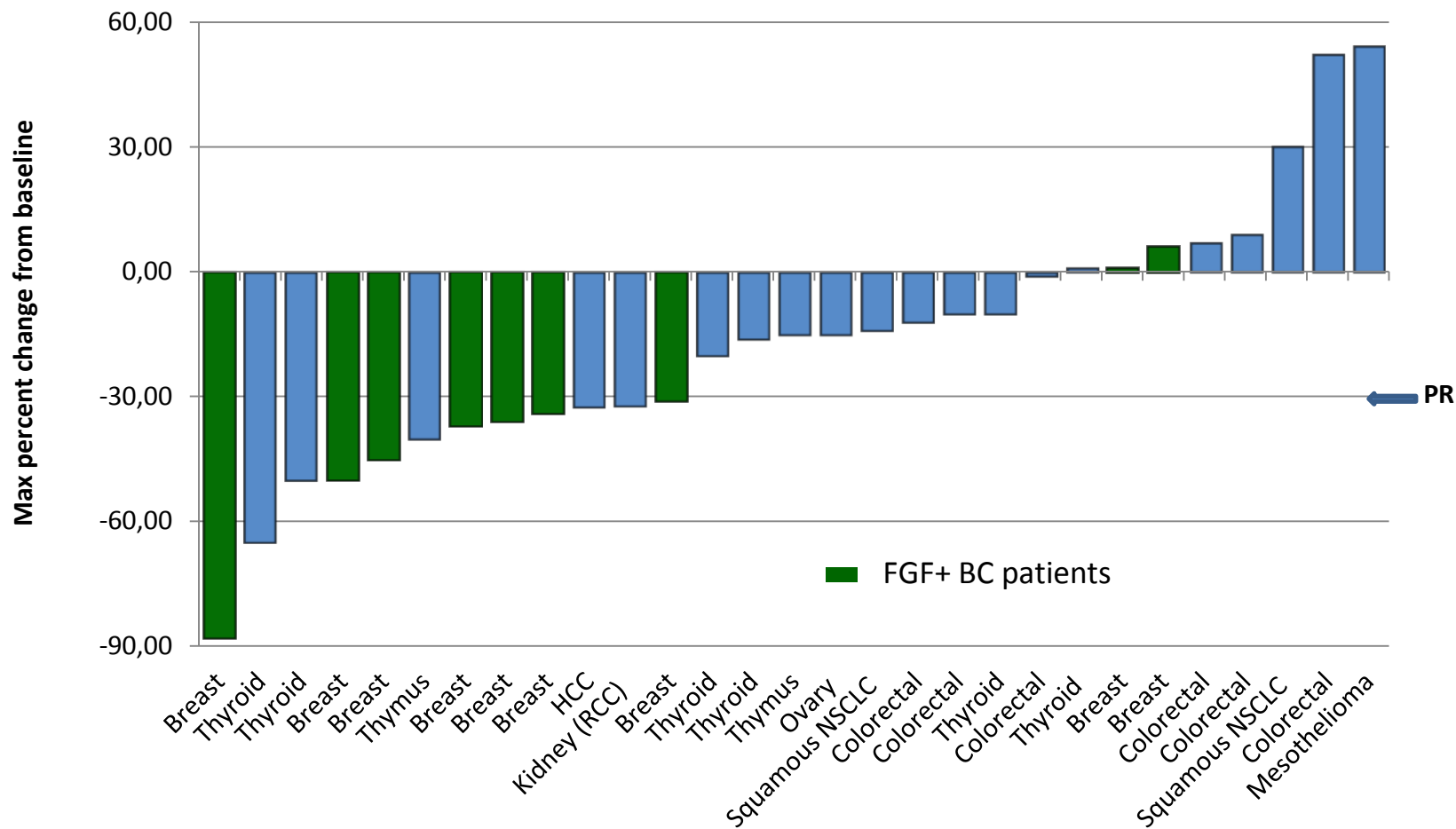# Patients with Measurable Disease

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