Final results of the STEM trial: SFX-01 in the Treatment and Evaluation of Metastatic breast cancer

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BACKGROUND

Estrogen receptor (ER) positive metastatic breast cancer (mBC) is frequently sensitive to endocrine manipulation. However, almost all tumours will eventually become resistant to therapy. Multiple mechanisms of resistance have been identified including induction of cancer stem-like cell (CSC) activity[1].

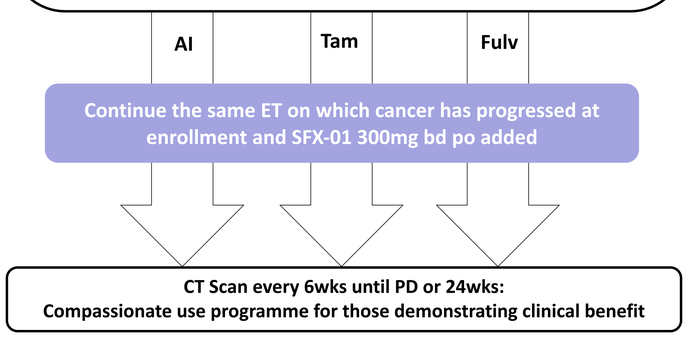
Sulforaphane is an isothiocyanate derived from plant glucoraphanin through myrosinase activity. Sulforaphane has been shown to inhibit breast CSCs in vitro[2] but it's instability has hitherto rendered it impractical for drug development. SFX-01 is a proprietary synthetic pharmaceutical based upon a stabilised sulforaphane. In preclinical models *in vivo* SFX-01 inhibits the activity of CSCs and reverses resistance to the endocrine therapies tamoxifen (Tam) and fulvestrant (Fulv)[3].

The STEM study is an open label parallel arm exploratory phase II trial designed to investigate the potential of SFX-01 to reverse acquired resistance to Tam, Fulv and third generation aromatase inhibitor (AI) therapy.

TRIAL DESIGN

Key Eligibility Criteria

- Women/men aged ≥18yrs with histologically confirmed ER +ve Her2-ve MBC or locally advanced BC not amenable to surgical resection
- Currently receiving AI, Tam or Fulv with either:
  - relapse on adjuvant ET (AI or Tam) after more than 2 years or
  - progression on ET (AI, Tam or Fulv) for mBC after stable disease ≥6 months or prior objective response (clinical benefit)
- Maximum 3 line ET and 1 line chemotherapy for MBC
- Measurable disease
- No rapidly progressive disease
- Anticipated life expectancy of at least 12 weeks
- ECOG PS 0,1 or 2



Primary objectives:

- To determine the safety & tolerability of SFX-01 in combination with ET
- To determine the clinical benefit rate (CBR) at 24wks using RECIST 1.1

Key secondary objectives:

- To determine the objective response rate (ORR) using RECIST 1.1
- To determine the median duration of clinical benefit

The sample size of 20 patients in each treatment cohort is such that if the observed CBR on any arm is 15%, it will provide a 90% exact binomial confidence interval (CI) for the true CBR of 4.2% to 34.4%.

RESULTS

PATIENT CHARACTERISTICS

- 46 patients were treated across 10 centres in the UK, Belgium, France and Spain
- Median age 63 (range 43-82)
- 35/46 (76%) had visceral involvement
- Prior lines of ET for MBC were 1 =32/46 (69.6%); 2 =9/46 (19.6%) and 3 =5/46 (10.9%)
- 4/46 patients had prior chemotherapy for advanced disease
- Only 1 patient had prior CDK4/6 inhibitor and 7 prior mTor inhibitor (everolimus) therapy.

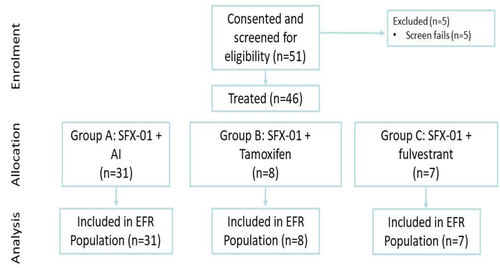


Figure 1. Study Consort Flow Diagram

EFR = Evaluable for Response: eligible subjects who received study drug and had either had at least one post-baseline disease assessment or were withdrawn prior to this due to clinical progression or death.

SAFETY

- 45 /46 patients had an adverse event (AE; see table) which were almost all low grade
- Gastrointestinal toxicity predominated
- 3/46 (6.5%) patients discontinued therapy due to GI toxicity
- 10/46 patients had a serious adverse event (SAE) of which only 1 was considered by the local PI to be possibly drug related (pleuritic chest pain)
- There were no deaths reported on study

Table: Most Common Adverse Events ≥10% with any causality

Adverse Event	Number with any grade AE	Number with grade 3/4 AE
Nausea	25 (54.3%)	0
Dyspepsia	15 (32.6%)	0
Diarrhoea	12 (26.1%)	0
Abdominal Pain	11 (23.9%)	0
Back Pain	10 (21.7)	0
Vomiting	10 (21.7%)	0
Fatigue	9 (19.6%)	1 (2.2%)
Asthenia	8 (17.4%)	0
Blood alkaline phosphatase increased	6 (13%)	0
Decreased appetite	6 (13%)	0
Alanine aminotransferase increased	5 (10.9%)	1 (2.2%)
Arthralgia	5 (10.9%)	0
Pain in extremity	5 (10.9%)	0

EFFICACY

- The clinical benefit rate (CBR) was 26% (12/46)
- The objective response rate 4.3% (2/46)
- CBR by type of ET:
  - 7/28 (25%) with AI + SFX-01
  - 4/8 (50%) with Tamoxifen + SFX-01
  - 1/7 (14%) with fulvestrant + SFX-01
- The median duration of CB was 9.0 months (range 5.9 – 17.0 months)
- 2 patients remain on combination therapy at 441 and 479 days – both with SFX-01 and tamoxifen

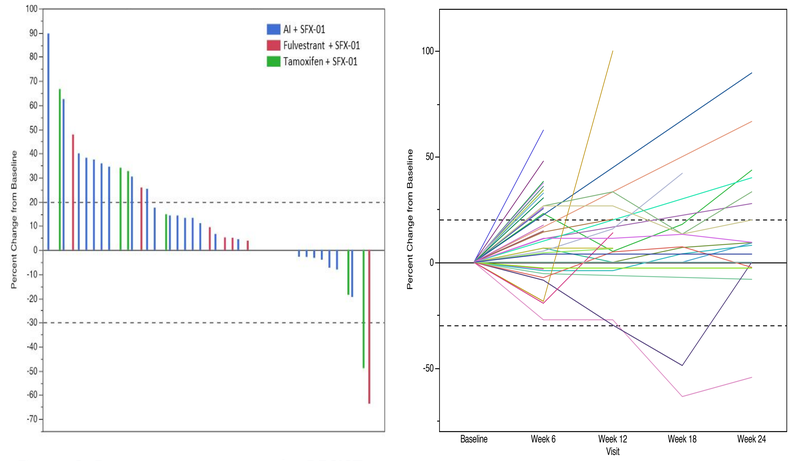


Figure 2. Response assessment by RECIST

Waterfall plot of best percentage change from baseline in target lesion measurements (left panel) and spider diagram showing individual patient summed target lesion measurements at each imaging assessment to 24 weeks (right panel)

CONCLUSIONS

- **SFX-01 300mg BD po is a generally well tolerated treatment with no significant safety concerns when combined with endocrine therapies (ET).**
- **SFX-01 demonstrated objective responses and meaningful stabilisation of disease when added to ET on which cancers were actively progressing.**
- **Further development of SFX-01 in mBC is warranted**

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Disclosures

Ross SJ and Morris T declare whole or part time employment with the study sponsor Evgen Pharma plc
None of the other authors have any conflicts of interest to disclose
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References: 1. Simoes et al. Cell Reports 2015;12:1968-77

2. Li *et al*, Clin Cancer Res 2010;16:2580-2590

3. Howell et al; SABCS 2016 PD2-02

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