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Lucitanib for the Treatment of HR$^+$/HER2$^-$ Metastatic Breast Cancer: Results from the Multicohort Phase II FINESSE Study

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ABSTRACT

Purpose: The *FGFR1* gene is amplified in 14% of patients with HR$^+$/HER2$^-$ breast cancer. Efficacy and safety of lucitanib, an inhibitor of VEGFR1-3, FGFR1-3, and PDGFRα/β, were assessed.

Patients and Methods: Patients with HR$^+$/HER2$^-$ metastatic breast cancer (MBC) received oral lucitanib in three centrally confirmed cohorts: (i) *FGFR1* amplified, (ii) *FGFR1* nonamplified, 11q13 amplified, and (iii) *FGFR1* and 11q13 nonamplified. Key inclusion criteria included Eastern Cooperative Oncology Group Performance Status ≤2, ≥1 line of anticancer therapy, but ≤2 lines of chemotherapy. Primary endpoint was overall response rates (ORR) by RECIST1.1. Simon's two-stage design was used: If ≥2 patients responded among 21 patients, 20 additional patients could be enrolled in each cohort. *FGFR1* copy-number variation (CNV) was determined by FISH and droplet digital PCR, whereas FGFR1 expression was determined by IHC.

Results: Seventy-six patients (32/18/26 in cohorts 1/2/3) from nine countries were enrolled. The prespecified primary endpoint was met in cohort 1 with ORR of 19% [95% confidence interval (CI), 9%–35%], but not in cohorts 2 and 3 with ORR of 0% (95% CI, 0%–18%) and 15% (95% CI, 6%–34%), respectively. Frequent adverse events included hypertension (87%), hypothyroidism (45%), nausea (33%), and proteinuria (32%). Exploratory biomarker analyses suggested higher ORR in patients with high *FGFR1* amplification (≥4 CNV) than those without high amplification (22% vs. 9%). ORR in patients with FGFR1-high tumors (IHC, H-score ≥50) was 25% versus 8% in FGFR1-low cancers.

Conclusions: Lucitanib had modest antitumor activity and significant hypertension-related toxicity in patients with HR$^+$/HER2$^-$ MBC. Although based on small sample sizes, exploratory biomarker analyses suggested that patients with high *FGFR1* amplification or expression might derive greater benefit.

Introduction

Metastatic breast cancer (MBC) remains incurable, with hormone receptor–positive (HR$^+$)/HER2$^-$ being the most common subtype, accounting for 70% of all breast cancers. Endocrine therapy is the cornerstone treatment for this subtype (1), but the development of endocrine resistance is unfortunately inevitable. Although patients can be offered chemotherapy, treatment response is short-lasting and with the exception of eribulin (2), there is little value of chemotherapy after three lines of therapy. There is an urgent need for the development of novel treatments.

FGFR 1–4 are a family of protein tyrosine kinase transmembrane receptors with roles in development, differentiation, and proliferation (3, 4). Genetic aberrations in *FGFR*s have been reported in a variety of cancers, including gastric, lung, and breast cancers (4–6). Genetic events activating the FGFR pathway include receptor amplification, receptor mutation, and generation of aberrant receptor fusions through genetic translocation (4). The *FGFR1* gene is amplified in about 14% of breast cancers and is associated with HR$^+$/HER2$^-$ disease (7, 8). The 11q13 amplicon contains genes for FGF3, FGF4, and FGF19 proteins that are ligands of FGFR1. Upon binding of FGFs to FGFRs, receptor dimerization activates downward cascade signaling

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Translational Relevance

FGFR1 amplification is associated with poor prognosis and endocrine resistance in patients with HR$^+$/HER2$^-$ breast cancer. Lucitanib is an oral multikinase inhibitor with selective activity against FGFR1–3 and VEGFR1–3. This phase II study of patients with lucitanib-treated HR$^+$/HER2$^-$ metastatic breast cancer with *FGFR1* amplification or 11q13 amplification or no amplification for either showed overall response rates (ORR) of 19% (95% CI, 9%–35%), 0% (0%–18%), and 15% (6%–34%), respectively. In exploratory biomarker analyses, patients with high-level *FGFR1* amplification ($\geq$4 copy-number variation) had higher ORR than those without high amplification (22% vs. 9%). Similarly, ORR in patients with high expression of FGFR1 (IHC, H-score $\geq$50) was 25% versus 8% in FGFR1-low cancers. Further exploration of FGFR1 as a biomarker for FGFR inhibitor therapy in this patient population is warranted.

pathways including the MAPK and PI3K–AKT pathways, ultimately regulating cell proliferation, differentiation, and survival (3, 9). FGFs also induce neoangiogenesis with a direct effect on both vessel assembly and sprouting (10). Amplification of *FGFR1* and 11q13 may lead to increased signaling in the FGF/FGFR pathway and mediation of resistance to targeted and endocrine therapies (6). Up to 25% of breast cancers have either *FGFR1* amplification or 11q13 amplification or both. The 11q13 amplicon also contains *CCND1,* which is a cell-cycle gene encoding cyclin D1. *CCND1* amplification, occurring in 15% of breast cancers, has been shown to be associated with estrogen receptor (ER) positivity and poor prognosis (11, 12).

Blocking the FGF/FGFR pathway with multitargeted inhibitors may enhance the antitumor activity by targeting proangiogenic and proliferative pathways. Several preclinical studies have suggested that targeting FGFR1 in *FGFR1*-amplified cell lines leads to antitumor effects (13, 14). Furthermore, FGFR1 knockdown was shown to decrease cell proliferation and reverse resistance to endocrine therapy in *FGFR1*-amplified breast cancer cell lines (15). Lucitanib is a potent inhibitor of vascular endothelial growth factor receptor (VEGFR) 1–3, FGFR1–3, and platelet derived growth factor receptor (PDGFR) α/β, with promising antitumor activity in xenograft models. Among the patients with heavily pretreated FGF-aberrant breast cancer in a phase I first-in-human study of lucitanib at daily doses of 5 to 20 mg, the overall response rate (ORR) was 50% (6/12 patients) with a median progression-free survival (PFS) of 40.4 weeks (16). This compelling clinical activity led to the initiation of this global multicenter phase II study of lucitanib in HR$^+$/HER2$^-$ MBC in three selected populations (*FGFR1* or 11q13 amplified or nonamplified) and to explore the role of *FGFR1* or 11q13 amplifications through translational analyses.

Patients and Methods

Study participants and design

FINESSE study (CL2-80881-001/BIG2-13/EudraCT 2013-000288-10/NCT02053636) was an open-label, multicenter, phase II, two-stage trial testing oral administration of single-agent lucitanib in three cohorts of patients with histologically confirmed HR$^+$/HER2$^-$ MBC: cohort 1, *FGFR1*-amplified irrespective of 11q amplification; cohort 2, *FGFR1*-nonamplified with 11q amplification; cohort 3, *FGFR1*-nonamplified without 11q amplification (Supplementary Fig. S1A). These patients had received at least 1 line of systemic anticancer therapy in the metastatic setting, but no more than two lines of chemotherapy. There was no limit to lines of prior endocrine therapy or targeted therapy. All patients had measurable disease at baseline and had demonstrated disease progression by radiologic or clinical assessment. Men and women of at least 18 years of age, Eastern Cooperative Oncology Group (ECOG) performance status (PS) $\leq$2, a life expectancy of over 3 months, and a left ventricular ejection fraction of at least 50% were eligible to enroll. Patients were ineligible if they received bevacizumab within 3 months of the first dose of lucitanib, had uncontrolled arterial hypertension requiring more than 2 antihypertensive agents, were at risk of developing hypertension-related complications, had a previous stroke, history of renal impairment, past history of thromboembolism in the last 6 months, uncontrolled thyroid function, uncontrolled diabetes mellitus, QTc prolongation or the use of medications with strong effect on CYP2C8 or CYP3A4 within 7 days of starting lucitanib. Central nervous system metastases without the requirement of high-dose steroid treatment were allowed if clinically stable for at least 4 weeks.

It was mandatory for all patients to submit adequate tumor tissue either obtained at the time of study or previously archived from a metastatic biopsy. For patients with nonamplification of both *FGFR1* and 11q assigned to cohort 3, if the initial submitted tissue was from archival material, a fresh biopsy from a metastatic site was required before starting study drug for subsequent confirmation of molecular status. Blood samples were collected on cycle 1 day 1, cycle 1 day 14, and end of treatment for soluble growth factor analyses.

The study protocol and amendments were approved by local or central ethics committees at each study centre. All patients provided written informed consent prior to participating in the study which was then performed in accordance with the International Conference on Harmonization Guidelines on Good Clinical Practice and the Declaration of Helsinki.

Treatments

Lucitanib was administered orally, once daily, on a continuous schedule in fasting conditions. A mandatory checklist for the optimal management of hypertension was completed by the investigator for each patient. All patients were trained to measure blood pressure daily using the provided equipment on the first cycle and at least twice a week thereafter. Patients were advised to immediately contact the hospital if blood pressure was abnormal. After each adverse event of hypertension, daily self-monitoring of blood pressure was recommended for the subsequent 4 weeks. The starting dose was reduced from 15 to 10 mg after protocol amendment 5 due to high rates of grade $\geq$3 hypertension. For patients who enrolled prior to this protocol amendment, the dose was reduced to 10 mg when starting the next 4-weekly cycle, unless the treating physician chose to continue treatment at 15 mg. Following an adverse event, dose reduction to 7.5 and 5 mg daily could be considered, but dosing below 5 mg was not allowed. Patients continued treatment until disease progression, intolerable toxicity, physician decision, or consent withdrawal (Supplementary Table S1).

Assessments

Each of the three cohorts was evaluated separately. The primary endpoint was objective response rate (ORR), defined as the proportion of patients with complete response (CR) or partial response (PR) as best overall response, evaluated by the investigator every 8 weeks by computed tomography or magnetic resonance imaging according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1. Secondary endpoints included clinical benefit rate (CBR),

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PFS, duration of response (DOR), safety and pharmacokinetics of lucitanib. CBR was defined as the proportion of patients for whom a confirmed CR or a confirmed PR or prolonged stable disease (SD; according to RECIST criteria for at least 24 weeks from inclusion) was observed during the treatment. Toxicity was graded according to the Common Terminology Criteria for Adverse Event (CTCAE) version 4.0. An independent data monitoring committee regularly reviewed activity and safety data during the course of the trial and made recommendations regarding changes or adjustments required to ensure patient safety and preserve study integrity. Exploratory endpoints were to characterize the biological activity of lucitanib on soluble growth factors of interest, on tumor cells and to explore biomarkers potentially predictive for lucitanib response in blood samples and in primary archived or metastatic tumors.

Statistical analysis

For each of the three cohorts, sample size was estimated to assess the antitumor activity of lucitanib, based on a Simon's optimal two-stage design (17) with the hypotheses H_0: $P \leq 5\%$ versus H_1: $P \geq 20\%$. With a type I error at 5% (one-sided) and a 90% statistical power, 21 patients were required for the first stage, with early termination if there were fewer than two confirmed responses in stage 1. Otherwise, 20 more patients (for a total of 41 patients in each cohort) were to be recruited. The null hypothesis would be rejected if there were at least 5 responders among all 41 patients in that cohort with responses. Therefore, the total sample size was between 63 patients (in case of early termination in each group of patients) and 123 patients (if no early termination).

The statistical analysis plan was finalized before the database lock on July 19, 2017. There was no statistical test intended to compare cohorts or dose levels. The statistical analyses were descriptive. The 95% Wilson's confidence interval for rates was computed based on inverting the normal test that uses the null proportion in the variance. The median duration and 95% confidence interval for time-dependent parameters, including PFS, DOR, and duration of clinical benefit were estimated using the Kaplan–Meier method.

Biomarker analysis

Determination of *FGFR1*, *CCND1*, and *FGF3,4,19* copy number by FISH

The FISH analyses were performed centrally at ZytoVision (Germany) GmbH using the Zyto*Light* SPEC *FGFR1*/CEN 8 Dual Color Probe (IVD-CE FISH probe, Z-2072-200), Zyto*Light* SPEC *CCND1*/CEN 11 Dual Color Probe (IVD-CE FISH probe, Z-2071-200), and Zyto*Light* SPEC FGF3,4,19/CEN 11 Dual Color Probe (IVD-CE FISH probe), all with the "Zyto*Light* FISH-Tissue Implementation Kit."

Evaluation of FISH was performed following adapted Schildhaus criteria (18). Copy-number ratio was calculated as the average number of target gene signals per cell divided by the average number of centromeric signals per cell.

For the purposes of recruitment, *FGFR1* was considered "amplified" if its gene/centromere ratio was $\geq$2 and/or if its average number of signals per tumor cell nucleus was $\geq$6. For exploratory biomarker analysis, samples were classified as high-amplified (*FGFR1*/centromere ratio $\geq$4), amplified (ratio $\geq$2 but <4 or average signal $\geq$6) or not/low amplified (ratio <2).

Similarly, for the purposes of recruitment, *CCND1* was used as a surrogate for 11q13 amplification. All samples identified as amplified for *CCND1* were also assessed for *FGF3/4/19* copy number. Samples were considered "amplified" for *CCND1* and *FGF3/4/19* if the gene/centromere ratio was $\geq$2 and/or if the average number of signals per tumor cell nucleus was $\geq$6. All samples identified as having *CCND1* amplification were also amplified for *FGF3/4/19* (Supplementary Fig. S2).

Serum FGF23 using ELISA

The concentration of FGF23 in serum and plasma samples was determined using the FGF23 ELISA kit from Kainos Laboratories, Inc (cat. #CY4000), according to the manufacturer's guidelines). Performance of the FGF23 ELISA is presented in Supplementary Table S2A and range of determined concentrations in Supplementary Table S2B.

FGFR1 CNV ddPCR

Tumor content of tissue sections was determined by a pathologist from the Breast Cancer Now Histopathology Core facility, Institute of Cancer Research, London, UK. Tissue sections were stained with nuclear fast red and the tumor-rich area was dissected. DNA and RNA were extracted using the AllPrep DNA/RNA FFPE extraction kit (QIAGEN 80234) according to the manufacturer's guidelines with an overnight digestion of the DNA containing pellet the only modification (19). DNA extracted from tumor samples was analyzed to determine *FGFR1* CNV using ddPCR following the method of Pearson and colleagues (19). Digital PCR was performed on a QX100 droplet PCR system (Bio-Rad). PCR reactions were prepared as previously described (20, 21). Briefly, emulsified PCR reactions were run on a 96-well plate on a G-Storm GS4 thermal cycler incubating the plates at 95°C for 10 minutes followed by 40 cycles of 95°C for 15 seconds, 60°C for 60 seconds, followed by 10-minute incubation at 98°C. Plates were read on a Bio-Rad QX100 droplet reader using QuantaSoft v1.6.6.0320 software. Copy-number variation was calculated as a ratio with multiplexed reference genes (Supplementary Table S2C). CNV assays were performed using 1–3 ng genomic DNA, to obtain a minimum of 300 reference droplets.

FGFR1 IHC

IHC for FGFR1 was performed using 3-μm tissue sections, probed with anti-human FGFR1 (Abcam ab76464). Chromogenic signal was developed using the ChromoMap DAB detection kit (Roche Diagnostics, 052666450010). Tissues sections were counterstained with hematoxylin, and coverslips were mounted using Pertex (Histolabs, 00811).

Scoring for protein expression was determined according to the hybrid scoring system (H-score) criteria by a pathologist. Specimens were scored based on the different cellular compartment (e.g., cytoplasmic, membranous, and total). Scoring was performed with the H-score based on the percentage of tumor cells staining at various intensities as follows: 0x (% tumor cells with no staining) + 1x (% with faint expression) + 2x (% with moderate expression) + 3x (% with strong expression).

Results

Patient characteristics and treatment

Between December 19, 2013, and August 4, 2016, among a total of 129 patients screened for the study, 76 patients were enrolled from nine countries. Thirty-two patients were recruited to cohort 1 with amplified *FGFR1* irrespective of 11q13 amplification, 18 to cohort 2 with 11q13 amplification but *FGFR1* nonamplified, and 26 to cohort 3 with both *FGFR1* and 11q13 nonamplified (Supplementary Fig. S1B). Fifty-nine patients received lucitanib at a starting dose of 15 mg daily and 17 patients at a lower starting dose of 10 mg after protocol amendment. The median age was 54 years (range, 26–78), 66% of patients had ECOG PS of 0, 86% were

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postmenopausal and the median time from the diagnosis of MBC was 2.4 years (range, 0.2–12.6). The majority (82%) of the tumors were ductal and 38% were grade 3. Of all the patients, 50% had bone metastases and 36% had liver metastases; 99% received prior endocrine therapy and 92% received at least one line of chemotherapy. The baseline characteristics were similar in the three cohorts (**Table 1**).

Outcome

In cohorts 1 and 3, two responses were observed during stage 1 of the study, thus additional patients were enrolled into stage 2 of the study. The ORR in the entire population was 13% (95% CI, 7%–23%; **Table 2**). The waterfall plot in **Fig. 1A** illustrating the best relative change in sum of the size of target lesions from baseline suggested antitumor activity of lucitanib in all cohorts, but partial

Table 1. Baseline characteristics of patients enrolled in the three cohorts.

Characteristics	Cohort 1 *FGFR1* amp *n* (%)	Cohort 2 11q13 amp *n* (%)	Cohort 3 Both nonamp *n* (%)	All *n* (%)
Female	32 (100%)	18 (100%)	26 (100%)	76 (100%)
Age (median, years)	53	52	57	54
Ethnicity				
White	24 (75%)	18 (100%)	21 (81%)	63 (83%)
Asian	2 (6%)	—	1 (4%)	3 (4%)
Other	4 (13%)	—	—	4 (5%)
Unknown	2 (6%)	—	4 (15%)	6 (8%)
ECOG				
0	21 (66%)	13 (72%)	16 (62%)	50 (66%)
1	8 (25%)	5 (28%)	9 (35%)	22 (29%)
Disease duration (median, years)	6.1 (1.4–20.1)	6.0 (1.3–20.0)	7.4 (1.8–19.4)	6.7 (1.3–20.1)
Time since diagnosis of MBC (median, years)	2.3 (0.3–7.3)	2.0 (0.7–5.7)	3.5 (0.2–12.6)	2.4 (0.2–12.6)
PFS of the last treatment received (median, days)	217 (20–1,181)	251 (13–1,884)	246 (40–1,105)	241 (13–1,884)
Histology type				
Ductal	29 (91%)	14 (78%)	19 (73%)	62 (82%)
Lobular	—	2 (11%)	3 (12%)	5 (7%)
Other	3 (9%)	2 (11%)	4 (15%)	9 (12%)
Histology grade				
Grade 1	1 (3%)	2 (11%)	7 (27%)	10 (13%)
Grade 2	15 (47%)	5 (28%)	10 (39%)	30 (40%)
Grade 3	15 (47%)	6 (33%)	8 (31%)	29 (38%)
Unknown	1 (3%)	5 (28%)	1 (4%)	7 (9%)
HER2 status				
Positive	2 (6%)	—	—	2 (3%)
Negative	30 (94%)	18 (100%)	26 (100%)	74 (97%)
ER status				
Positive	31[a] (97%)	17 (94%)	26[c] (100%)	75 (99%)
Negative	—	1[b] (6%)	—	1 (1%)
PR status				
Positive	11 (34%)	6 (33%)	10 (39%)	27 (36%)
Negative	4 (13%)	5 (28%)	7 (27%)	16 (21%)
Metastatic sites				
Bone	13 (41%)	12 (67%)	13 (50%)	38 (50%)
Liver	13 (41%)	7 (39%)	7 (27%)	27 (36%)
Brain	0 (0%)	0 (0%)	1 (4%)	1 (1%)
Previous treatment				
Endocrine therapy	32 (100%)	17 (94%)	26 (100%)	75 (99%)
Letrozole or anastrozole	27 (84%)	16 (89%)	23 (89%)	66 (87%)
Tamoxifen	24 (75%)	13 (72%)	23 (89%)	60 (79%)
Exemestane	13 (41%)	5 (28%)	15 (58%)	33 (43%)
Fulvestrant	6 (19%)	3 (17%)	5 (19%)	14 (18%)
Everolimus	7 (22%)	1 (6%)	7 (27%)	15 (20%)
Palbociclib	—	1 (6%)	—	1 (1%)
Chemotherapy	30 (94%)	17 (94%)	23 (89%)	70 (92%)
Bevacizumab	2 (6%)	2 (11%)	2 (8%)	6 (8%)

Note: *n*, Number of patients with at least one medical history of breast cancer. %: $(n/N) \times 100$.

[a]One value was missing.

[b]One patient was first found ER$^+$ based on an archived biopsy (before Amendment No. 4), but was found ER$^-$ on a new baseline biopsy (that was performed because no metastatic material was available for the inclusion in the study). A retest confirmed the tumor status of ER$^-$; however, the patient stayed in the study on investigator's request.

[c]For 1 patient, there were two observations: one on an archived biopsy + a new baseline biopsy for ER status.

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Table 2. Summary of antitumor activities of lucitanib.

	Cohort 1 *FGFR1* amp	Cohort 2 11q13 amp	Cohort 3 Both nonamp	All
ORR (*n*, %) (95% CI)	6 (19%) (9–35)	0 (0%)	4 (15%) (6–34)	10 (13%) (7–23)
TFR (median, days) (range)	90 (44–164)	—	82 (53–166)	90 (44–166)
DOR (median, days) (95% CI)	264 (106–337)	—	108 (88–392)	129 (88–337)
CBR[a] (*n*, %) (95% CI)	13 (41%) (26–58)	2 (11%) (3–33)	7 (27%) (14–46)	22 (29%) (20–40)
PFS (median, days) (95% CI)	148 (96–212)	108 (54–140)	141 (52–214)	113 (69–164)

Abbreviations: CBR, clinical benefit rate; CI, confidence interval; DOR, duration of response; ORR, objective response rate; PFS, progression-free survival; TFR, time to first response.
[a]Clinical benefit rate: CR + PR + SD for ≥24 weeks.

responses were only evident in cohorts 1 and 3, with no confirmed responses observed in cohort 2 per RECIST criteria. The ORR was 19% (95% CI, 9%–35%) and 15% (95% CI, 6%–34%) in cohorts 1 and 3, respectively. Clinical benefit rates (CR, PR, and SD ≥ 24 weeks) were 41% (95% CI, 26%–58%), 11% (95% CI, 3%–33%), 27% (95% CI, 14%–46%) in cohorts 1, 2, 3, respectively and 29% (95% CI, 20%–40%) in the entire population (**Table 2**). Among the patients who achieved PR, the median time to response was 90 days and the median DOR was 129 days (**Table 2**). The overall median PFS was 113 days (approximately 3.7 months; 95% CI, 69–164 days) and numerically shortest in cohort 2 (**Fig. 1B**).

Safety

Safety was assessed in all patients who received at least 1 dose of lucitanib. The most frequent treatment-related adverse event (AE) was hypertension with 88% of any grade and 66% of grade ≥3. The median time to onset of grade 3 to 4 hypertension was 7.5 days. Other common treatment-related AEs (all grades/grade 3–4) included hypothyroidism (45%/0%), nausea (33%/1%), proteinuria (32%/0%), diarrhea (30%/1%), and fatigue (30%/4%; **Table 3**). Due to difficulty to sustain more than three cycles of 15 mg daily lucitanib in the first 59 patients, mainly because of hypertension, the starting dose was reduced to 10 mg daily for the subsequent 17 patients enrolled. Despite the dose reduction to 10-mg daily lucitanib, 8 of 17 (47%) patients still experienced grade 3 to 4 hypertension. However, hypertension resolved in 77% patients after drug discontinuation, and proteinuria resolved in 68% at the end of the study. Most AEs were adequately managed with dose reductions, interruptions, and the use of appropriate supportive treatments. A case of Posterior Reversible Encephalopathy Syndrome at 15-mg daily lucitanib was observed in one patient, but all symptoms completely resolved after stopping the study drug. AEs led to treatment discontinuation in 16 patients (21%), of which 6 were due to hypertension and 1 was due to proteinuria. Treatment interruption and dose reduction occurred in 63% and 66% of patients, of whom 67% and 89%, respectively, were due to AE (Supplementary Table S1). One patient died of unknown causes.

The prespecified primary study objective of rejecting the null hypothesis if at least 5 responders among 41 patients was achieved in cohort 1 with *FGFR1*-amplified $HR^+/HER2^-$ MBC (PR in 6/32 patients). However, on the basis of a risk/benefit analysis run on all available data of the lucitanib breast cancer clinical development program showing that lucitanib was not likely to be superior to standard of care, the sponsor decided to terminate the study. Nonetheless, patients under treatment at that moment were offered the option to continue lucitanib following discussion with their treating physician.

Biomarker analyses

Evidence of drug activity

Serum FGF23 levels after 14 days of lucitanib were significantly increased from baseline (median increase by 45%, $P = 1.74e{-}06$), suggesting effective targeting of FGFR (5, 22–24). Increases in serum FGF23 were similar in all 3 cohorts and were regardless of treatment response. Similar findings were observed in plasma samples (**Fig. 2A**).

Relationship between FGFR amplification/expression and antitumor activity

Tissue was available from all 76 patients for analysis of *FGFR* amplification by FISH. Of these, 53 samples were available for *FGFR1* CNV ddPCR, and 59 were available for IHC to assess FGFR1 protein expression. Exploratory biomarker analyses suggested that patients classified as *FGFR1* highly amplified by FISH (*FGFR*1/centromere ratio ≥4, $n = 23$) presented higher ORR than those without high-level amplification (<4, $n = 53$): 22% (5/23) versus 9% (5/53; **Fig. 2B**). By contrast, 11q amplification might be associated with poor response (2/29 = 7% responders). FISH and ddPCR showed good agreement ($P = 0.79$) and assessment of *FGFR1* copy number using ddPCR gave similar results with ORR of 25% (4/16, ≥4) versus 8% (3/37, <4; **Fig. 2B**). A similar level of agreement was detected between *FGFR1* FISH signals or ddPCR copy numbers and FGFR1 IHC H-score ($P = 0.71$, data not shown). FGFR1 overexpression was mostly detected for patients with *FGFR1* amplification (24/27; 89%). Further, in patients with high FGFR1 expression (H-score ≥50), assessed by IHC, ORR was higher (25%, 5/20) than in patients with low FGFR1 expression (8%, 3/39; **Fig. 2B**). Interestingly, patients with *FGFR*1-high amplification (FISH ≥ 4) had 49 days [approximately 2 months; 158 (57–332) days vs. 109 (56–165) days] nominally longer median PFS than those with no amplification (<2; Supplementary Fig. S3A). Patients with higher FGFR1 expression (H-score ≥ 50) also had nominally longer median PFS than those with FGFR-low tumors (H-score < 50) by 103 days [approximately 3 months; 212 (165–NA) days vs. 109 (57–158) days; Supplementary Fig. S3B]. Endothelial expression of FGF2 or Ki67 was not different between cohorts (Supplementary Fig. S4). Similarly, no trend of association was observed between PFS and endothelial expression of either FGF2 or Ki67 (Supplementary Fig. S5A and S5B).

Discussion

Breast cancer is a heterogeneous disease with the largest proportion being $HR^+/HER2^-$. Despite recent advances with the addition of targeted therapy, including CDK4/6 inhibitors (palbociclib, ribociclib, and abemaciclib), mTOR inhibitor (everolimus), and PI3K inhibitor (alpelisib), to endocrine therapy (25–27), ultimate treatment resistance is unavoidable. Dysregulation of the FGFR/FGF pathway is often observed in human cancers, including 14% of breast cancers (28), and may act as a driver of tumor progression. In this study, 42% (32/76) of enrolled patients had *FGFR1*-amplified breast tumors, with 30% displaying high level of amplification (≥4 CNV). This higher prevalence of *FGFR1* amplification in this study is likely due to selection bias, as some patients might have already undergone prior local

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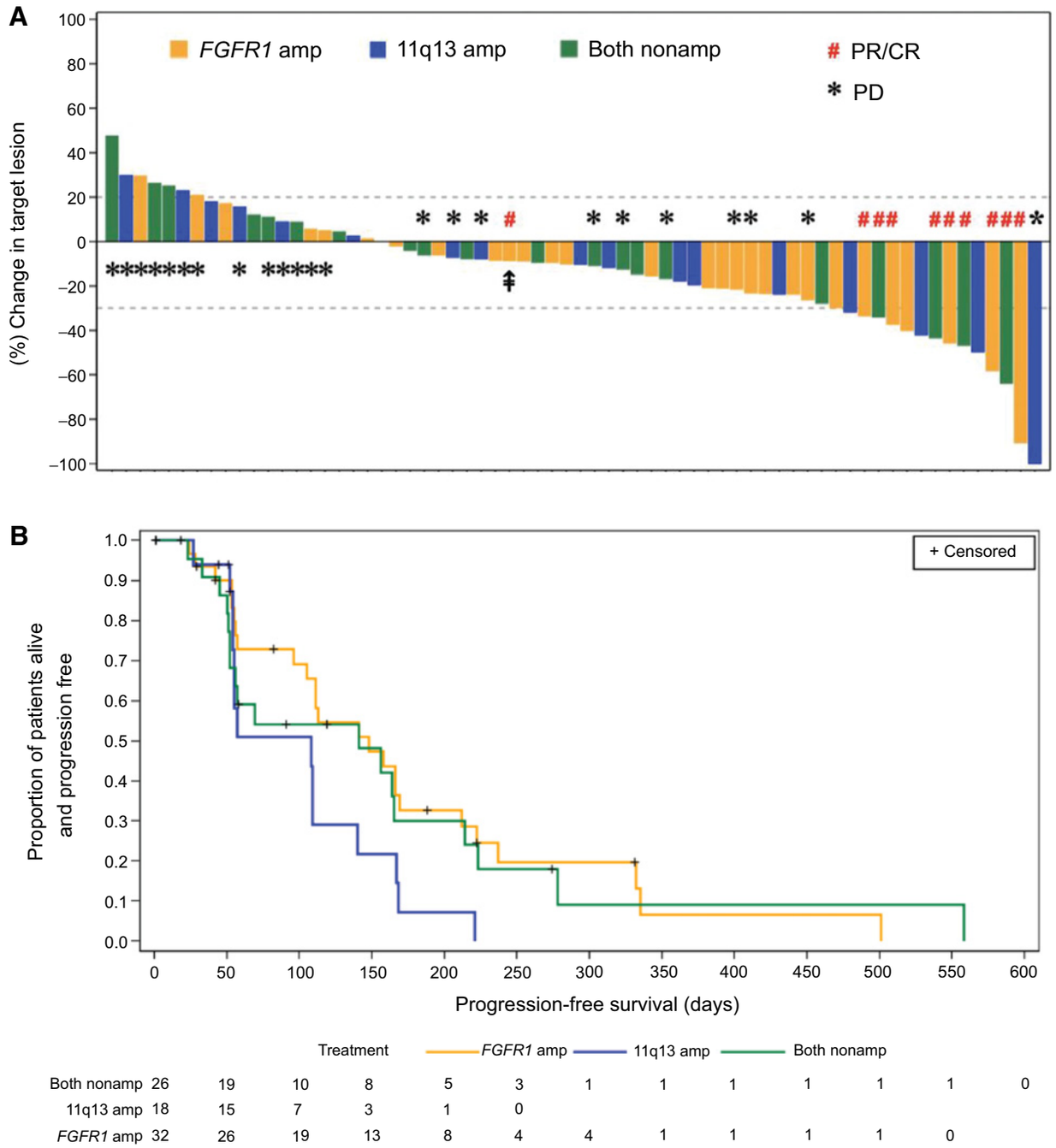

Figure 1.

Efficacy of lucitanib in metastatic HR$^+$/HER2$^-$ breast cancer by cohorts. **A,** Best relative change in sum of the size of target lesions from baseline; ǂ for this patient, partial response was defined after external review of the imaging. Of note, the reasons for the 10 patients who are not on the above graph showing 66/76 are as follows: 1 patient only had nontarget lesions; 8 patients had a BOR = NE; 1 patient had a BOR = PD but did not appear because, after baseline, there was no evaluation on target lesions, only a new nontarget lesion. **B,** Progression-free survival. CR, complete response; PD, progression of disease; PR, partial response.

molecular testing. Moreover, recruitment of patients without *FGFR1* amplification but with 11q13 amplification to cohort 2 was stopped early due to the lack of treatment response. Fifty-nine patients had adequate tissue for IHC assessment, and a third of the breast cancers overexpressed FGFR1 with H-score of ≥50.

FGFR1 amplification was previously shown to be associated with resistance to endocrine therapy, shorter time to distant metastasis (15) and shorter overall survival (7) in HR$^+$ breast cancer. Activation of the FGFR1/FGF pathway induces neoangiogenesis and mediates resistance to VEGFR inhibitors, highlighting the need for multitargeted

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Table 3. Most frequently reported treatment-related adverse events (at least 5 patients overall).

	Cohort 1 *FGFR1* amp ($n = 32$)	Cohort 2 11q13 amp ($n = 18$)	Cohort 3 Both nonamp ($n = 26$)	All ($n = 76$)	
	n (%)	*n* (%)	*n* (%)	*n* all grades (grades 3–4)	% all grades (grades 3–4)
Hypertension	28 (88)	14 (78)	24 (92)	66 (50)	87 (66)
Hypothyroidism	20 (63)	4 (22)	10 (39)	34 (0)	45 (0)
Nausea	14 (44)	2 (11)	9 (35)	25 (1)	33 (1)
Proteinuria	12 (38)	6 (33)	6 (23)	24 (0)	32 (0)
Fatigue	15 (47)	3 (17)	5 (19)	23 (3)	30 (4)
Diarrhea	12 (38)	4 (22)	7 (27)	23 (1)	30 (1)
Headache	9 (28)	2 (11)	7 (27)	18 (0)	24 (0)
Asthenia	7 (22)	3 (17)	6 (23)	16 (2)	21 (3)
AST increased	11 (34)	2 (11)	2 (8)	15 (1)	20 (1)
ALT increased	10 (31)	2 (11)	2 (8)	14 (2)	18 (3)
Vomiting	6 (19)	2 (11)	5 (19)	13 (0)	17 (0)
Thrombocytopenia	6 (19)	1 (6)	5 (19)	12 (2)	16 (3)
Reduced appetite	6 (19)	1 (6)	5 (19)	12 (0)	16 (0)
GGT increased	5 (16)	3 (17)	3 (12)	11 (6)	15 (8)
Abdominal pain	6 (19)	1 (6)	3 (12)	10 (0)	13 (0)
Abdominal pain upper	5 (16)	2 (11)	3 (12)	10 (0)	13 (0)
ALP increased	4 (13)	2 (11)	1 (4)	7 (1)	9 (1)
Myalgia	2 (6)	2 (11)	2 (8)	6 (1)	8 (1)

tyrosine kinase inhibitors (TKI) such as lucitanib (29, 30). The modest ORR of 13% (95% CI, 7%–23%) in the entire population of patients with metastatic $HR^+/HER2^-$ breast cancer in this study was higher than the ORR of the unselected patients with MBC in another lucitanib study which included triple-negative and HER2-positive subtypes (31). Furthermore, in cohort 1 patients with *FGFR1* amplification, the activity of lucitanib with an ORR of 19% and a CBR of 41% was similar to the single-agent CDK4/6 inhibitor abemaciclib (32) or chemotherapy, including eribulin and capecitabine (33), in previously treated MBC. Although CBR might be a less reliable endpoint in a small phase II study as it could be attributed by the natural history of indolent disease, the ORR of lucitanib was higher than monotherapy palbociclib (34) or everolimus (35). Exploratory biomarker analyses showed an apparent increased ORR with higher *FGFR1* amplification ($\geq$4 CNV) as assessed by either FISH or ddPCR as compared with low or no *FGFR1* amplification. This was consistent with the results from a phase II study of another FGFR1 multikinase inhibitor, dovitinib, which showed an ORR of 25% in patients with ER-positive breast cancer harboring *FGFR1* amplification (22). *FGFR1* amplification has been reported to correlate with FGFR1 overexpression and is associated with endocrine resistance (15). In our study, despite no definite correlation between *FGFR1* amplification and overexpression of FGFR1 protein, nominally higher ORR and longer PFS were observed in patients with high FGFR1 membrane H-score of $\geq$50 by IHC. FGFR1 expression has been shown to predict sensitivity to FGFR inhibitors in lung cancer as well as head and neck cancer (36, 37). To our knowledge, this is the first study to suggest FGFR overexpression may be a potential biomarker of response to FGFR1 TKI in breast cancer.

Unlike selective FGFR inhibitors, but similar to another multitarget TKI dovitinib, hyperphosphataemia was not reported in patients treated with lucitanib, which may suggest inadequate inhibition of the FGFR pathway (9, 22) or counteractive effect of the frequently observed hypophosphatemia with VEGFR inhibitors (38). However, the increase in serum FGF23 after 14 days of treatment with lucitanib in the pharmacodynamic assay suggested lucitanib was targeting FGFRs. The toxicity profile characterized by hypertension and proteinuria was consistent with the action of lucitanib as an inhibitor of VEGFR (39). The antitumor activity evident in cohort 3 with nonamplification of both *FGFR1* and 11q13 was likely due to the antiangiogenic effects of lucitanib.

Although 11q13 amplification with aberrations of the ligands (FGF3, 4, and 19) to FGFRs may lead to dysregulation of the FGFR/FGF pathway, no treatment response to lucitanib was observed in cohort 2 patients with their breast cancers harboring only 11q13 amplification without *FGFR*1 amplification. This suggests that the presence of FGF ligands in the 11q amplicon may have limited significance in breast cancer. In this study, 11q13 amplification was assessed by copy number of *CCND1*. Amplification of *CCND1* is associated with increased cyclin D1 expression and poor prognosis in ER^+ $HER2^-$ breast cancer (40–42). Cyclin D1 with its catalytic subunit CDK4/6 phosphorylates retinoblastoma protein, initiating G_1–S progression in the cell cycle. The key oncogenic driver of the breast cancers in the cohort 2 patients may be the cyclin D/CDK4/6 pathway instead of the FGFR/FGF pathway. Hypothetically, CDK4/6 inhibitors may be more effective than the FGFR1 inhibitor in this group of patients; however, studies thus far have shown that *CCND1* amplification is not a predictive biomarker of CDK4/6 inhibitors in breast cancer treatment (43).

Previous studies selected patients with *FGFR* amplification based on criteria used for assessment of *ERRB2* copy number (CNV $\geq$ 2; ref. 44). In gastric cancer, tumors with high levels of homogeneous amplification of *FGFR2* were found to have marked sensitivity to inhibition of FGFR (19). Consistent with this, patients in this study with higher FGFR1 expression and/or high-level copy number tended to have greater clinical benefit, suggesting that more stringent cutoffs should be applied when selecting patients based on *FGFR* status. Similarly, tumor heterogeneity, in terms of CNV and mutational burden, is recognized as a significant factor in the development of resistance by tumors in response to targeted therapies (19, 45, 46). Heterogeneity and active clonal dynamics have been characterized in the progression

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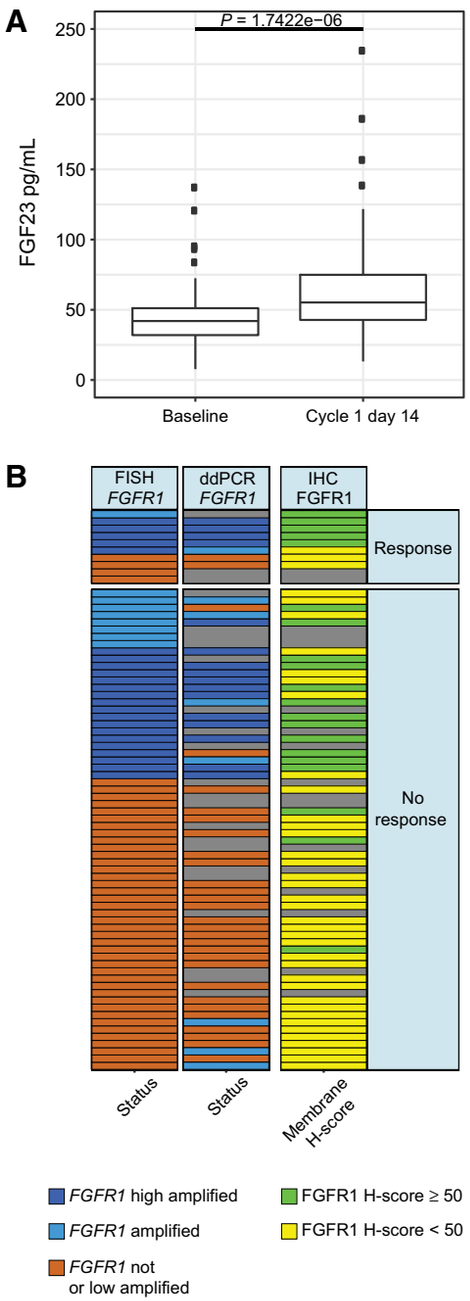

Figure 2.

A, Serum FGF23 levels at baseline and at cycle day 15. $P = 1.7422e{-}06$ Wilcoxon test. **B,** Association of biomarkers with objective response. No statistical analyses of association were performed due to small sample size.

of early breast cancer (47). The limited antitumor activity reported here may in part be explained by patients being recruited to this study by *FGFR1* amplification status, without addressing the degree of heterogeneity in *FGFR1* CNV among tumor cells. Furthermore, mutations in the FGFR downstream signaling pathways, including Ras/MAPK and PI3K, confer resistance to FGFR inhibitors *in vitro* (15, 19). Mutations in *PIK3CA* are among the most common in MBC (8) and thus preexisting genetic events may further limit the effectiveness of drugs such as lucitanib irrespective of *FGFR1* amplification status.

Preclinical studies in cell lines and xenografts have demonstrated more effective inhibition of tumor cell growth with combined blockade of FGFR1 and ER using both lucitanib and fulvestrant (28). The efficacy of lucitanib in combination with fulvestrant in a small study showing CBR of 55.6% in patients with metastatic HR$^+$/HER2$^-$ breast cancer with unselected *FGFR1* status appeared to be numerically higher than monotherapy lucitanib in our study (48). Given the role of *FGFR1* aberrations in the development of endocrine resistance, it may be useful to explore the combination of lucitanib and fulvestrant as a potential treatment for HR$^+$/HER2$^-$ *FGFR1*-amplified breast cancers after resistance to first-line endocrine therapy.

Based on the first-in-human study results, 15-mg daily lucitanib was initially selected as the recommended phase II dose for this study (16). However, 15-mg continuous daily dosing was difficult to sustain beyond three cycles, with the predominant side effect of arterial hypertension related to the antiangiogenic effect of lucitanib. Similar safety profiles across lucitanib clinical studies (16, 22, 31, 48) have been observed. Although reduction in the starting dose of lucitanib to 10 mg resulted in an improved safety profile with lower incidence of grade 3 hypertension, a substantial rate of hypertension still occurred. However, only 6 patients (8%) permanently discontinued treatment due to hypertension, as most patients could be managed with dose adjustment and supportive measures. Hypothyroidism was the second most common AE, consistent with the toxicity profile of other multitarget TKI such as sunitinib (49), but could be easily managed with thyroid hormone supplementation. Further exploration of biomarkers in selecting patients who may benefit from an FGFR inhibitor may also avoid unnecessary side effects.

In conclusion, single-agent lucitanib showed limited antitumor activity in HR$^+$/HER2$^-$ MBC and significant hypertension-related toxicity, but with a higher ORR and CBR in a subset of patients with *FGFR1* amplification. Exploratory biomarker analyses suggested that patients whose tumors had high *FGFR1* amplification or FGFR1 expression might derive greater benefit. Although the study was stopped prematurely based on a decision by the sponsor after evaluating risk and benefit of lucitanib monotherapy, the benefit of lucitanib treatment to patients with MBC with *FGFR1* amplification or overexpression deserves further exploration.

Disclosure of Potential Conflicts of Interest

R. Hui is an employee/paid consultant for MSD, Novartis, AstraZeneca, Bristol-Myers Squibb, Roche, and Eli Lilly. J. Cortes is an employee/paid consultant for Roche, Celgene, Cellestia, Biothera, AstraZeneca, Merus, Seattle Genetics, Daiichi Sankyo, Erytech, Athenex, Polyphor, Lilly, Servier, Merck Sharp & Dohme, and GlaxoSmith-Kline; holds ownership interest (including patents) in MedSIR; and reports receiving other remuneration from Roche, Novartis, Eisai, Celgene, Pfizer, Samsung Bioepis, Lilly, and Merck Sharp & Dohme. H.A. Azim Jr is an employee/paid consultant for Inaate Pharma and reports receiving speakers bureau honoraria from Roche. D. Fumagalli, A. Arahmani, and T. Goulioti report receiving commercial research grants from Servier. M. Lambertini reports receiving speakers bureau honoraria from Theramex and Takeda. J. Perez-Garcia is an advisory board member/unpaid consultant for Roche and Lilly. P. Aftimos is an employee/paid consultant for Servier, Amcure, Novartis, Roche, Macrogenics, Boehringer Ingleheim, Synthon, G1 Therapeutics, and Amgen, and reports receiving other remuneration from Amgen, MSD, Pfizer, and Roche. P.L. Bedard reports receiving commercial research grants from Pfizer; other commercial research support from Servier, Roche/Genentech, Bristol-Myers Squibb, GlaxoSmithKline, Novartis, Seattle Genetics, Nektar, Merck, Lilly, Mersana, Zymeworks, AstraZeneca, and Sanofi; and is an advisory board member/unpaid consultant for Bristol-Myers Squibb, Pfizer, Roche/Genentech, and Sanofi.

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