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# Phase I/IIa study evaluating the safety, efficacy, pharmacokinetics, and pharmacodynamics of lucitanib in advanced solid tumors

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**Background:** Lucitanib is a potent, oral inhibitor fibroblast growth factor receptor types 1 and 2 (FGFR), vascular endothelial growth factor receptor types 1, 2, and 3 (VEGFR), platelet-derived growth factor receptor types α and β (PGFRα/β), which are essential kinases for tumor growth, survival, migration, and angiogenesis. Several tumor types, including breast carcinoma, demonstrate amplification of fibroblast growth factor (FGF)-related genes. There are no approved drugs for molecularly defined FGF-aberrant (*FGFR1*- or *FGF3/4/19*-amplified) tumors.

**Methods:** This open-label phase I/IIa study involved a dose-escalation phase to determine maximum tolerated dose (MTD), recommended dose (RD), and pharmacokinetics of lucitanib in patients with advanced solid tumors, followed by a dose-expansion phase to obtain preliminary evidence of efficacy in patients who could potentially benefit from treatment (i.e. with tumors harboring FGF-aberrant pathway or considered angiogenesis-sensitive).

**Results:** Doses from 5 to 30 mg were evaluated with dose-limiting toxic effects dominated by vascular endothelial growth factor (VEGF) inhibition-related toxic effects at the 30 mg dose level (one case of grade 4 depressed level of consciousness and two cases of grade 3 thrombotic microangiopathy). The most common adverse events (all grades, all cohorts) were hypertension (91%), asthenia (42%), and proteinuria (57%). Exposure increased with dose and $t_{½}$ was 31–40 h, suitable for once daily administration. Seventy-six patients were included. All but one had stage IV; 42% had >3 lines of previous chemotherapy. Sixty-four patients were assessable for response; 58 had measurable disease. Clinical activity was observed at all doses tested with durable Response Evaluation Criteria In Solid Tumors (RECIST) partial responses in a variety of tumor types. In the angiogenesis-sensitive group, objective RECIST response rate (complete response + partial response) was 26% (7 of 27) and progression-free survival (PFS) was 25 weeks. In assessable FGF-aberrant breast cancer patients, 50% (6 of 12) achieved RECIST partial response with a median PFS of 40.4 weeks for all treated patients.

**Conclusion:** Lucitanib has promising efficacy and a manageable side-effect profile. The spectrum of activity observed demonstrates clinical benefit in both FGF-aberrant and angiogenesis-sensitive populations. A comprehensive phase II program is planned.

**Key words:** FGFR1 amplification, Phase I trial, kinase inhibitor, breast cancer, lung cancer

## introduction

Tumor angiogenesis is a complex process by which new blood vessels are formed from the pre-existing vasculature. Several growth factors are key to promoting tumor angiogenesis, including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF). Aberrant FGF signaling promotes tumor development by driving cancer cell proliferation and survival [1, 2]; FGF may also contribute to the acquired resistance to anti-VEGF therapy [3]. Activation of the VEGF/vascular endothelial growth factor receptor types 1, 2, and 3 (VEGFR) receptor pathway promotes endothelial cell growth, migration, and survival. This pathway also

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mediates vessel permeability and mobilizes endothelial progenitor cells [4, 5]. Activation of PDGF/platelet-derived growth factor receptor (PGFR) pathways promotes cellular proliferation, survival and migration, pericyte recruitment, and vessel stabilization.

Fibroblast growth factor receptor type 1 (FGFR1) amplification has been reported in a variety of cancers, such as breast cancer [10%, predominantly estrogen receptor positive (ER+)], ovarian cancer (5%), bladder cancer (3%), rhabdomyosarcoma (3%), lung cancer (21% of squamous cell carcinomas and 3% of adenocarcinomas), and oral squamous carcinoma (9%) [6–8]. Moreover, ~15% of breast cancers harbor amplification of the 11q 12–14 region, which carries genes critical to the FGF axis (*FGF3*, *4*, and *19*). These aberrations were shown to be associated with poor prognosis [8–13]. Overexpression of FGFR1 is associated with luminal B-type breast cancer (16%–27%) [14]. The potential role of the FGFR pathway in the targeted therapy of solid tumors has recently been reviewed [2, 6].

Lucitanib is a potent, highly selective inhibitor of the tyrosine kinase activity of FGFR types 1 and 2, VEGFR types 1–3, and PDGFR types α and β, with a preclinical profile supporting clinical investigation in cancer patients [15]. Here, we describe the results of the first-in-human phase I/IIa study of lucitanib in patients with advanced solid tumors.

## patients and methods

### patients

Eligible patients were aged ≥18 years and had histologically or cytologically confirmed locally advanced metastatic solid tumors, relapsed or refractory to standard therapy. Patients recruited during the dose-expansion phase had to be either (i) FGF aberrant, i.e. they suffered from a tumor harboring *FGFR1* or *FGF3/4/19* amplification (assessed locally by fluorescence *in situ* hybridization, comparative genomic hybridization , or chromogenic *in situ* hybridization on the most recent archived sample or biopsy of a current lesion); or (ii) angiogenesis-sensitive, i.e. they had a tumor that was newly progressing following response or stable disease for at least 6 months to an antiangiogenic-based treatment, or was of a histological type known to be potentially sensitive to antiangiogenic therapy. For all patients, other main eligibility criteria included Eastern Cooperative Oncology Group performance status ≤1, and adequate bone marrow, hepatic, and renal function. Patients with any clinically significant concomitant condition were excluded, notably those with active central nervous system metastases, uncompensated hypothyroidism, and cardiovascular disease including uncontrolled hypertension (defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg with optimized antihypertensive therapy) or left ventricular ejection fraction (LVEF) <50%. Patients of childbearing potential not willing to employ effective contraception were also excluded.

The trial was conducted in three centers in accordance with the ethical principles of the Declaration of Helsinki (6th revision, 2008). Ethics committee approval was obtained before the start of the study. Patients provided written informed consent before enrollment. The trial is registered (EU Clinical Trials Register, EudraCT No 2010-019121-34 and Clinicaltrials.gov, NCT01283945).

### study design and treatment

This was an open-label phase I/IIa study with a dose-escalation phase to determine the maximum tolerated dose (MTD) and the recommended dose (RD) defined according to the European Guideline [16], as well as the pharmacokinetics of lucitanib in patients with advanced solid tumors. The dose escalation was followed by a dose-expansion phase to characterize the safety profile over multiple courses and obtain preliminary evidence of efficacy in patients that could potentially benefit from treatment. Lucitanib was administered orally once daily in fasting conditions. Dosing continued uninterrupted for 28 days; for assessment purposes, 4-week (28-day) cycles were conventionally defined. Patients were allowed to continue treatment if they were receiving clinical benefit, and unless there was unacceptable toxic effect, progressive disease, or consent withdrawal.

The starting dose was 5 mg. The dose-escalation procedure and the definition of the MTD were based on toxic effects appearing in the initial 4-week treatment period and followed a classical 3 + 3 design [17]. Toxic effects were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0 [18]. Doses were escalated by doubling until the first drug-related grade 2 toxic effect occurred, with smaller increments thereafter. In case of a dose-limiting toxic effect (DLT), the dose was withheld until recovery to grade 2 for hematological or grade 1 for nonhematological toxic effects, and then the patient continued on the next lower dose level.

### assessments

Medical history, demographic features, disease characteristics, and amplification status (if applicable) were collected at inclusion. Visits were scheduled on days 1, 2, 4, 7, 11, 14, 21, and 28, then monthly thereafter. Safety assessments included adverse events (AEs), serial blood chemistry and hematology, proteinuria, and blood pressure monitoring. Of note, blood pressure was also self-monitored every other day (three separate measurements) and a renal biopsy was mandatory in case of laboratory abnormalities that might suggest a potential thrombotic microangiopathy (e.g. unremitting proteinuria). Cardiac safety was closely monitored by serial ECG and Holter recordings, echocardiography or MUGA scan for LVEF, and specific laboratory tests (troponin and brain natriuretic peptide). Thyroid function was assessed by measuring thyroid stimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4). Clinical efficacy was evaluated, when applicable, as tumor response according to the revised Response Evaluation Criteria In Solid Tumors (RECIST) [19].

### pharmacokinetic analysis

Blood samples (5 ml each) were collected on day 1 before treatment intake, and then 1, 2, 3, 4, 6, 8, 12, and 24 h after, on days 4, 7, 14, 21 before treatment, and on day 28 day before treatment and 1, 2, and 4 h after. The samples were analyzed centrally (Istituto Mario Negri, Milan, Italy); plasma concentrations were measured with a validated high-performance liquid chromatography-tandem mass spectrometry method [20]. The pharmacokinetic analysis was carried out by the Department of Clinical Pharmacokinetics, Institut de Recherche International Servier (IRIS).

### statistical methods

Baseline characteristics and the results on safety and efficacy are presented as descriptive statistics and were carried out on the safety set (patients who took at least one dose of lucitanib) and the evaluable for response set (patients who took at least one dose and had baseline and one postbaseline tumor evaluation). Exact binomial 95% confidence intervals estimated by the Wilson method are reported for objective response rate (ORR, defined as rate of complete plus partial response). Median time to response (time from treatment initiation to first response) and duration of response (time from first response to progressive disease or death) are reported among responders. Progression-free survival (PFS) was measured from treatment initiation to time of progressive disease or death for any cause. Duration of response and PFS were censored at the date patients were last known to be event-free or alive, respectively. All analyses were carried out by IRIS using SAS®, version 9.2.

## results

Seventy-six patients were included between June 2010 and September 2012, 17 in the dose-escalation and 59 in the dose-expansion phase. The date of cutoff for analysis was 25 April 2014. The baseline characteristics are presented in Table 1; mean age was 55.6 ± 10.7 years and 45% were male. Nineteen patients had breast cancer (25%), 11 colon cancer (14%), 9 thyroid cancer (12%), and 7 lung cancer (9%); all but one had stage IV and 42% had >3 lines of previous chemotherapy.

During the dose escalation, 17 patients received at least one dose of lucitanib and were assessable for safety. Four dose levels (i.e. 5, 10, 20, and 30 mg daily) were tested. No DLTs were observed at the first three levels; at 30 mg once daily, three DLTs were observed in the six patients assessable for DLT out of seven treated (one case of grade 4 depressed level of consciousness and two cases of grade 3 thrombotic microangiopathy confirmed by renal biopsy in one patient), which were reversible upon treatment withdrawal. The MTD was therefore defined as 30 mg lucitanib once daily and the RD for the next phase was 20 mg once daily.

The dose-expansion phase was initiated at 20 mg once daily, although subsequently this was reduced to 15 because more than half of patients required dose reductions with 20 mg, and then for some patients to 10 mg (Table 2). Median treatment duration was 3.2 months (range 0.5–42.8 months) and 30 patients (39%) received more than four cycles of treatment. At study cutoff, 70 patients (92%) had withdrawn mostly for progressive disease (49 patients, 64.5%) or drug-related AEs (12 patients, 15.8%), mainly proteinuria and/or thrombotic microangiopathy; one due to death related to progressive disease.

**Table 1.** Demographic and disease characteristics at baseline

| Characteristics | All patients ($N = 76$) |
|---|---|
| Age (years) | 55.6 ± 10.7 |
| Median (range) | 56.5 (34–80) |
| Male, *n* (%) | 34 (45%) |
| ECOG performance status, *n* (%) | |
| 0/1 | 26 (34%)/50 (66%) |
| Primary tumor, *n* (%) | |
| Breast cancer | 19 (25%) |
| Colon cancer | 11 (14%) |
| Thyroid cancer | 9 (12%) |
| Nonsmall-cell lung cancer | 7 (9%) |
| Rectal cancer | 6 (7%) |
| Thymoma and thymic carcinoma | 3 (4%) |
| Other | 21 (28%) |
| Time from first diagnosis (months) | 66.6 ± 62.4 |
| Median (range) | 48.2 (3–311) |
| Stage, *n* (%) | |
| Stage III | 1 (1%) |
| Stage IV | 75 (98.7%) |
| Prior lines of therapy | |
| None[a]/1–3 lines/>3 lines | 8/36/32 |

[a]Among eight patients: two patients have missing data; six patients participated in expansion phase and were included based on antiangiogenic sensitive tumor (five patients) and FGF-aberrant (one patient) status.
ECOG, Eastern Cooperative Oncology Group.

Drug-related AEs were reported in 76 patients (Table 3); 21% of patients had grade 2 and 76% grade 3 as the worst grade. There was no grade 5 treatment-related AE. Fifteen patients (48.4%) had a serious AE considered to be related to lucitanib. The most frequent AEs were hypertension in 69 patients (91%; 58% grade 3) and proteinuria in 43 patients (57%; 16% grade 3). Eleven patients (6 having received antiangiogenic treatment before) had grade 3 thrombotic microangiopathy, but only 4 discontinued as a result. Otherwise, these events were managed through dose reduction/temporary hold. Grade 4 treatment-related AEs were reported in two patients: one patient had increased lipase and one had increased blood uric acid and depressed level of consciousness. Other drug-related AEs included asthenia (28 patients grade 2; 4 grade 3), hypothyroidism (30 patients, grade 2 only), diarrhea (15 patients grade 2; 4 grade 3), anorexia (17 patients grade 2; 2 grade 3), weight decreased (12 patients grade 2; 3 grade 3), thrombocytopenia (7 patients grade 2; 3 grade 3), and nausea (9 patients grade 2; 1 grade 3). Decreases in LVEF were reported in 5 patients (3 of grade 2 and 2 of grade 3), and 2 patients had grade 2 or 3 ECG QTC prolongations, but only one case was considered clinically significant and reported as an AE.

In general, events were reversible and managed with dose reduction or temporary treatment discontinuation (57 of 76 patients, 75%, had at least one cycle delayed or dose interrupted due to drug-related AE). Hypertension, though common, was managed aggressively through a prespecified treatment algorithm and was not a reason for withdrawal. Patients with increase in TSH were given supplemental levothyroxine to prevent clinically evident hypothyroidism. In the 12 patients who permanently discontinued treatment because of toxic effects, the predominant reasons were proteinuria and/or thrombotic microangiopathy.

Sixty-four of 76 patients were assessable for response and 58 had measurable disease. Figure 1 shows 3D waterfall plot of these 58 patients in terms of RECIST response versus time on treatment; 10 patients maintained a significant benefit for over 1 year of treatment. Figure 2 shows 3D waterfall plot in the breast cancer patients. Table 4 summarizes clinical activity in the 50 assessable patients of the expansion cohort with FGF-aberrant ($n = 23$) or angiogenesis-sensitive tumors ($n = 27$). In the angiogenesis-sensitive group, ORR was 26%; PFS was 25 weeks (range 5–120 weeks); median time to response was 24.1 weeks (range 8–56 weeks) and duration of response was 31.9 weeks (range 4–96 weeks). The ORR in patients with measurable FGF-aberrant breast cancer was 50% with a PFS of 40.4 weeks (range 7–128 weeks); median time to first response was 7.5 weeks (range 7–8 weeks) and duration of response 48.7 weeks (range 3–120 weeks); an example of response in a patient with *FGFR1*-amplified ER+/HER2− metastatic breast cancer is shown in Figure 3.

Lucitanib was rapidly absorbed with $T_{max}$ of 1–3 h; its apparent terminal half-life ($t_{½}$) was long (31–40 h), consistently with low apparent clearance and high apparent volume of

**Table 2.** Treatment exposure and dose modifications

| | Lucitanib dosage[a] | | | | | All ($N = 76$) |
|---|---|---|---|---|---|---|
| | 5 mg/day ($N = 3$) | 10 mg/day ($N = 11$) | 15 mg/day ($N = 38$) | 20 mg/day ($N = 17$) | 30 mg/day ($N = 7$) | |
| Participation in study | | | | | | |
| Dose-escalation phase | 3 (100%) | 3 (27%) | 0 | 4 (24%) | 7 (100%) | 17 (22%) |
| Dose-expansion phase | 0 | 8 (73%) | 38 (100%) | 13 (76%) | 0 | 59 (78%) |
| Treatment duration (months), mean ± SD | 24.6 ± 0.2 | 4.2 ± 3.7 | 7.6 ± 8.4 | 7.0 ± 9.7 | 1.9 ± 1.4 | 7.1 ± 9.2 |
| Median (range) | 28.9 (2.1–42.8) | 2.4 (1.4–13.2) | 4.0 (0.7–28.4) | 2.8 (0.5–31.7) | 1.4 (0.7–4.5) | 3.2 (0.5–42.8) |
| Number of cycles, mean ± SD | 26.3 ± 21.4 | 4.8 ± 3.9 | 8.0 ± 8.8 | 7.7 ± 10.3 | 2.0 ± 1.2 | 7.7 ± 9.7 |
| Median (range) | 31.0 (3–45) | 3.0 (2–14) | 4.0 (1–30) | 3.0 (1–34) | 2.0 (1–4) | 3.5 (1–45) |
| >4 cycles | 2 (67%) | 3 (27%) | 18 (47%) | 7 (41%) | 0 | 30 (39%) |
| Patients with ≥1 cycle delayed or dose interrupted[a] | 2 (67%) | 9 (82%) | 35 (92%) | 15 (88%) | 5 (71%) | 66 (87%) |
| Drug-related adverse event | 2 | 6 | 30 | 15 | 4 | 57 |
| Nondrug-related adverse event | 1 | 3 | 15 | 4 | 1 | 24 |
| Other reason | 2 | 1 | 15 | 4 | 1 | 23 |
| Patients with ≥1 dose reduction[b] | 0 | 1 (9%) | 14 (37%) | 10 (59%) | 2 (29%) | 27 (36%) |
| Drug-related adverse event | 0 | 1 | 9 | 9 | 1 | 20 |
| Non-drug-related adverse event | 0 | 0 | 2 | 0 | 0 | 2 |
| Other reason | 0 | 0 | 4 | 1 | 1 | 6 |
| Patients withdrawn | 3 (100%) | 11 (100%) | 33 (87%) | 16 (94%) | 7 (100%) | 70 (92%) |
| Death related to progressive disease | 0 | 0 | 1 | 0 | 0 | 1 |
| Drug-related adverse event | 0 | 0 | 7 | 1 | 4 | 12 |
| Nondrug-related adverse event | 0 | 1 | 1 | 2 | 0 | 4 |
| Patients request (subjective intolerance) | 0 | 1 | 1 | 2 | 0 | 4 |
| Progressive disease | 3 | 9 | 23 | 11 | 3 | 49 |

[a]The analysis is done according to the dose assigned at the study entry.
[b]Patients could have more than one reason. Values are numbers (%), unless otherwise stated.

**Table 3.** Incidence of treatment-related adverse events by worse grade events occurring in >10% of patients or at grade 4 in any patient

| Preferred term | Grade 2 | Grade 3 | Grade 4 | Any grade |
|---|---|---|---|---|
| All | 16 (21.1%) | 58 (76.3%) | 2 (2.6%) | 76 (100.0%) |
| Hypertension | 25 (32.9%) | 44 (57.9%) | 0 | 69 (90.8%) |
| Proteinuria | 31 (40.8%) | 12 (15.8%) | 0 | 43 (56.6%) |
| Asthenia | 28 (36.8%) | 4 (5.3%) | 0 | 32 (42.1%) |
| Hypothyroidism | 30 (39.5%) | 0 | 0 | 30 (39.5%) |
| Anorexia | 17 (22.4%) | 2 (2.6%) | 0 | 19 (25%) |
| Diarrhea | 15 (19.7%) | 4 (5.3%) | 0 | 19 (25%) |
| Weight decreased | 12 (15.8%) | 3 (3.9%) | 0 | 15 (19.7%) |
| Thrombotic microangiopathy[a] | 0 | 11 (14.5%) | 0 | 11 (14.5%) |
| Platelet count decreased | 7 (9.2%) | 3 (3.9%) | 0 | 10 (13.2%) |
| Nausea | 9 (11.8%) | 1 (1.3%) | 0 | 10 (13.2%) |
| Lipase increased | 0 | 3 (3.9%) | 1 (1.3%) | 4 (5.3%) |
| Blood uric acid increased | 0 | 0 | 1 (1.3%) | 1 (1.3%) |
| Depressed level of consciousness | 0 | 0 | 1 (1.3%) | 1 (1.3%) |

Values are numbers (%).
[a]Diagnosed by renal biopsy in five patients.

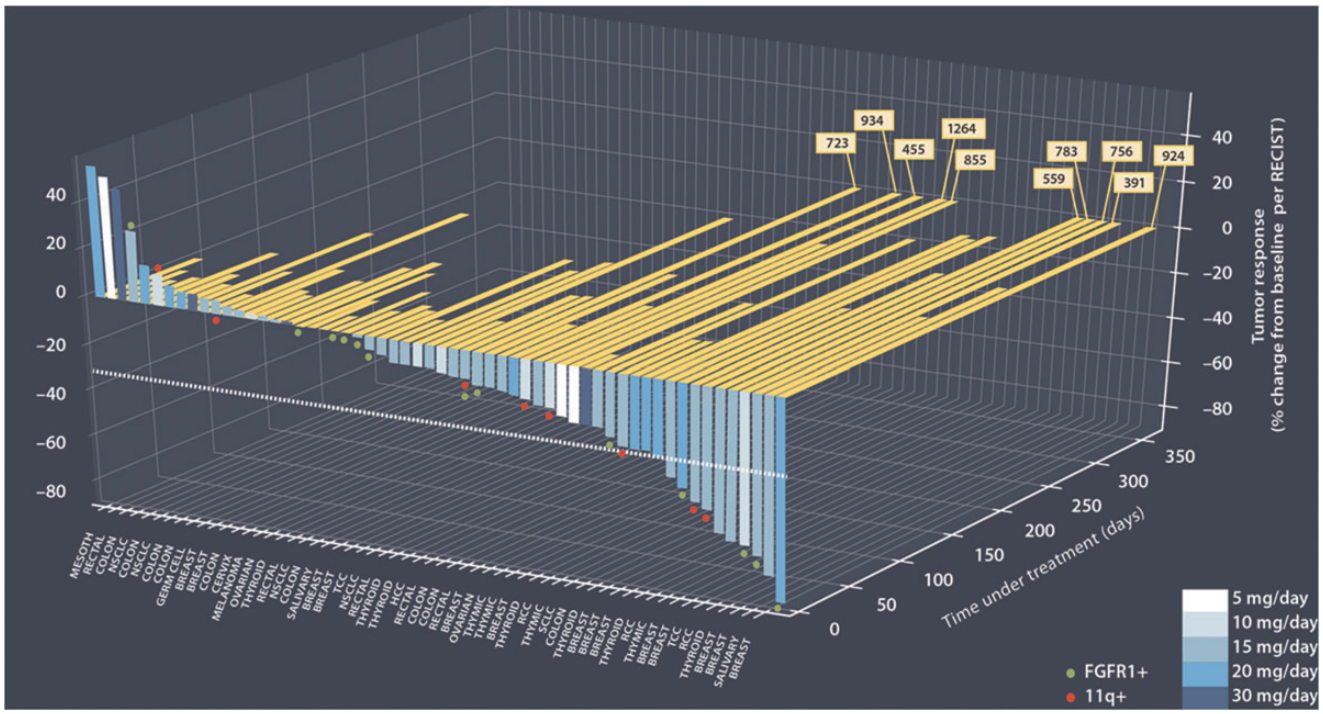


**Figure 1.** Tumor response to treatment (RECIST) in 58 assessable patients with measurable lesions and time on treatment (days). The five dosages (5, 10, 15, 20, and 30 mg/day) are graded from white (5 mg/day) to dark blue (30 mg/day).

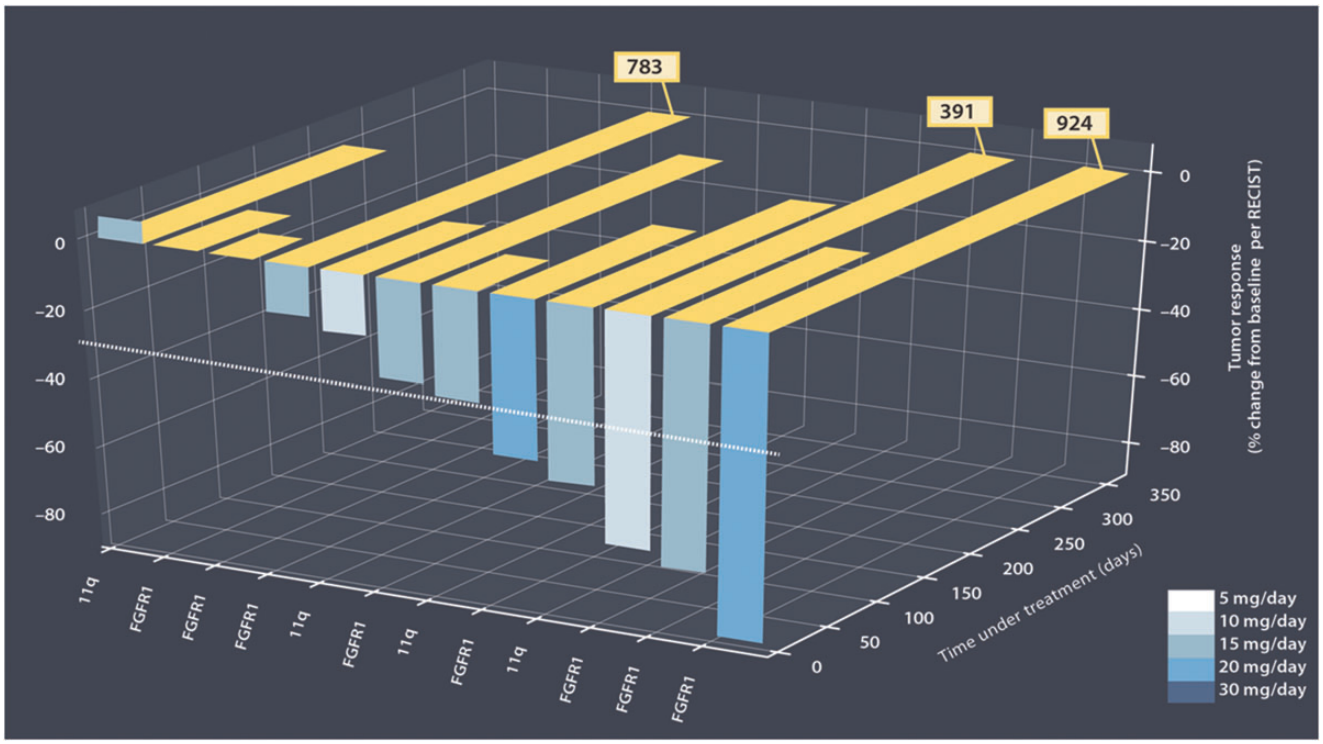


**Figure 2.** Tumor response to treatment (RECIST) in 12 breast cancer patients with measurable lesions and time on treatment (days). The five dosages (5, 10, 15, 20, and 30 mg/day) are graded from white (5 mg/day) to dark blue (30 mg/day).

distribution. The observed trough levels suggest that during continuous daily administration steady state is reached by day 8 (Figure 4). At steady state, the $AUC_{(0-24)}$ was approximately double that on day 1. As expected, there was high interpatient variability in exposure and no evidence of nonlinearity within the dose range tested.

**Table 4.** Antitumor activity in patients enrolled in the expansion phase and assessable for efficacy

| | FGF aberrant ($N = 23$) | | Angiogenesis-sensitive ($N = 27$) | All ($N = 50$) |
|---|---|---|---|---|
| | Total ($N = 23$) | Breast FGF-aberrant ($N = 12$)[a] | | |
| Best overall response, *n* (%) | | | | |
| Complete response[b] | 0 | 0 | 3 (11.1%) | 3 (6.0%) |
| Partial response[c] | 7 (30.4%) | 6 (50.0%) | 4 (14.8%) | 11 (22.0%) |
| Stable disease | 11 (47.8%) | 6 (50.0%) | 15 (55.6%) | 26 (52.0%) |
| Progressive disease | 5 (21.7%) | 0 | 5 (18.5%) | 10 (20.0%) |
| Objective response rate,[d] *n* (%) | 7 (30.4%) | 6 (50.0%) | 7 (25.9%) | 14 (28.0%) |
| 95% CI[e] | (15.60–50.87) | (25.38–74.62) | (13.17–44.68) | (17.47–41.67) |
| Progression-free survival (weeks), median | 32.1 | 40.4 | 24.9 | 31.6 |
| 95% CI[e] | (9.7–56.1) | (9.7 to –)[f] | (15.7–40.0) | (16.1–39.6) |
| Range | 6.7–127.6 | 6.7–127.6 | 5.0–120.0 | 5.0–127.6 |
| Time to first response (weeks), median | 7.6 | 7.5 | 24.1 | 8.3 |
| Range | 7.14–31.14 | 7.14–8.29 | 8.0–56.0 | 7.1–56.0 |
| Duration of response (weeks), median | 48.7 | 48.7 | 31.9 | 39.0 |
| Range | 2.7–120.1 | 2.7–120.1 | 4.0–96.3 | 2.7–120.1 |

[a]Twelve patients of 23 assessable FGF-aberrant patients had measurable (according to RECIST) breast cancer.
[b]Type of tumors: two patients with thyroid cancer, one patient with renal cell carcinoma.
[c]Type of tumors: one patient with kidney cancer and six patients with breast cancer in the FGF-aberrant cohort, and two patients with thyroid cancer, one patient with thymic carcinoma and one patient with hepatocellular carcinoma in the angiogenesis-sensitive cohort.
[d]Objective response rate (best overall response = complete response or partial response).
[e]95% confidence interval of the estimate using Wilsons' method.
[f]The upper limit of the 95% CI not calculated due to limited number of values.

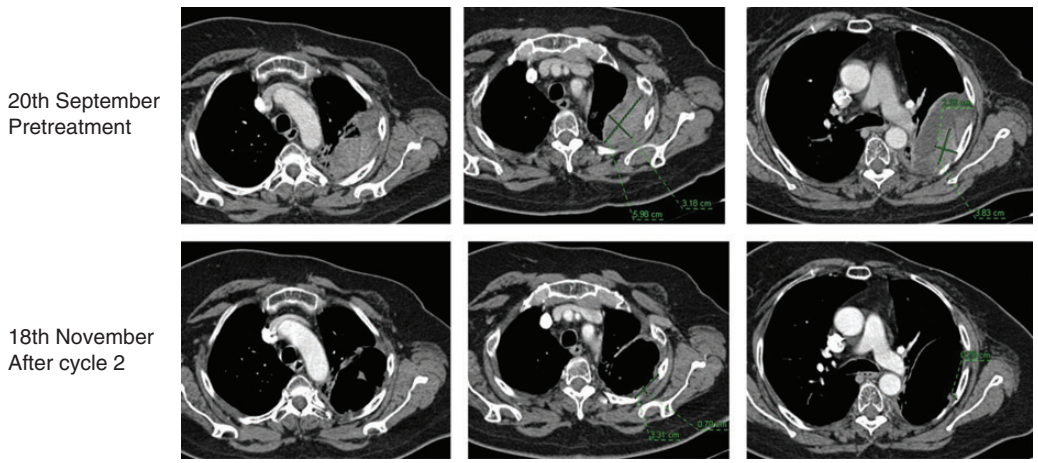


**Figure 3.** Radiological response to two cycles of lucitanib 20 mg/day in a patient with HR+/HER2–, *FGFR-1* amplified (ratio 2.21) metastatic breast cancer with bone, lung, and pleural metastases, with 14 prior treatment lines (including five phase I trials). The patient is still on study after 35 cycles of treatment with lucitanib.

## discussion

In this first-in-human study, the MTD of oral lucitanib in patients with advanced solid tumors was 30 mg once daily based on the toxic effect profile observed over the first 4 weeks of treatment. The recommended dose was therefore initially defined as 20 mg once daily; however, this proved difficult to sustain over multiple cycles with DLTs observed beyond cycle 1, and the RD for further development has been adjusted to 15 mg daily. For targeted therapeutics, there is increasing evidence to suggest that the dose for phase II should be established based on information acquired over multiple cycles, rather than relying on cycle 1 data, as toxic effects may accumulate with prolonged therapy [21]. Lucitanib exhibited a long $t_{½}$, suitable for once-a-day dosing with a steady state reached after 8 days.

Lucitanib is a potent inhibitor of FGFR1/2, VEGFR 1–3, and PDGFRα/β. Overall, the observed toxic effect profile is consistent with the expected effects of a potent inhibitor of the VEGF axis, with hypertension and proteinuria frequently observed as markers of on-target activity. Other common treatment-related

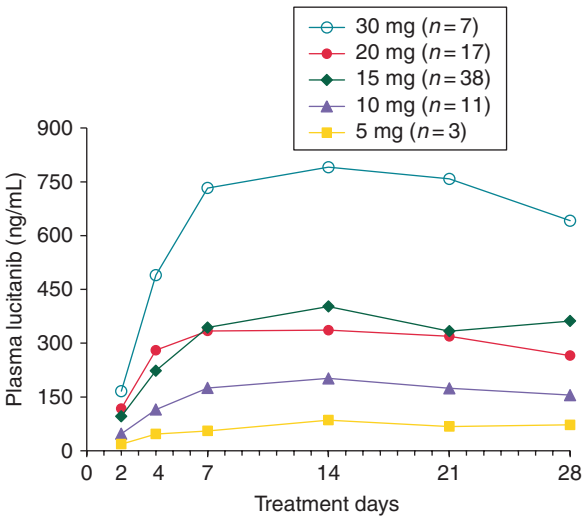


**Figure 4.** Mean plasma levels of lucitanib at trough in patients on a continuous dosing schedule.

events include subclinical hypothyroidism, asthenia, and gastrointestinal symptoms (diarrhea, abdominal pain, nausea, and vomiting). These events have been observed in various combinations with other oral kinase inhibitors, with differences in frequency/severity likely related to their different selectivity profile, as well as unique off-target effects. Unlike other agents targeting the FGF axis, hyperphosphatemia has not been associated with lucitanib treatment. This may be explained by the low affinity of lucitanib for FGFR4 [22, 23].

The adverse effects of lucitanib appear to be manageable with appropriate supportive treatments, dose reduction, and/or temporary treatment discontinuation. In particular, aggressive hypertension management prevented treatment withdrawal. Dose reduction to address toxic effects is common during long-term treatment with oral kinase inhibitors; a rate of 75% was recently reported for lenvatinib [24]. Whether a lower starting dose or preplanned treatment breaks can further improve tolerability is currently under investigation; a randomized phase II study comparing two doses of lucitanib in patients with FGF-aberrant advanced breast cancer is planned.

Lucitanib has been demonstrated to have meaningful clinical activity in a variety of tumor types, with an objective RECIST response rate of 28% (Table 4). The disease control rate reached 80% with several durable responses and long-lasting disease stabilizations, generally maintained when dose or schedule adjustment was required. Two complete responses were seen in patients with advanced medullary thyroid cancer not previously treated with tyrosine kinase inhibitors. At the time of writing, these patients are still on treatment, with maintained response at 31 and 28 months. One patient with renal cancer, previously treated with tyrosine kinase inhibitors, was assessed as complete response and is still on study treatment after 28 months.

The activity of lucitanib was particularly pronounced in the subgroup of patients with FGF-aberrant breast cancer: the disease control rate reached 100% with 6 patients achieving partial response and 6 patients with stable disease; the PFS was close to 10 months. Responses were observed at the first restaging (at the end of the second cycle) and their median duration was 11.5 months. These patients were heavily pretreated, and had failed three to nine prior lines.

Although lucitanib shows potent inhibition of FGF and VEGF, the relative contribution of blocking these two receptors cannot yet be determined, and was not specifically explored in this study, but both may be important for the notable efficacy of lucitanib in patients with FGF-aberrant breast cancer. In support of the hypothesis that dual VEGF/FGFR inhibition is relevant for efficacy in FGF-aberrant breast cancer, other VEGFR-targeted small molecules that lack notable FGFR inhibition activity, such as sunitinib, have shown limited activity in nonselected breast cancer patients [25]. In addition, the early results reported for FGFR selective inhibitors in *FGFR1*-amplified breast cancer have been modest [26, 27].

In conclusion, the spectrum of activity observed appears consistent with the hypothesized mechanism of action of lucitanib, with clinical benefit in both FGF-aberrant and angiogenesis-sensitive populations. The very promising efficacy in patients with metastatic breast cancer-bearing FGF-pathway aberrations prompted a comprehensive phase II program to clarify the molecular determinants of activity in these patients.

## disclosure

Following authors have indicated conflicts of interest: JCS (consultancy fees from EOS, Servier and Clovis); MGC (Former employee and stock holder of EOS, stock holder of Clovis); FD, CS and RR (Servier employees); RC (Clovis employee); AA, JI, JL (stock holder and employee of Clovis Oncology, Inc.). All other authors have declared no conflicts of interest.

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# Long-term survival, prevalence, and cure of cancer: a population-based estimation for 818 902 Italian patients and 26 cancer types

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**Background:** Persons living after a cancer diagnosis represent 4% of the whole population in high-income countries. The aim of the study was to provide estimates of indicators of long-term survival and cure for 26 cancer types, presently lacking.
**Patients and methods:** Data on 818 902 Italian cancer patients diagnosed at age 15–74 years in 1985–2005 were included. Proportions of patients with the same death rates of the general population (cure fractions) and those of prevalent

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