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Dual Inhibition of EGFR with Afatinib and Cetuximab in Kinase Inhibitor-Resistant *EGFR*-Mutant Lung Cancer With and Without *T790M* Mutations

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Abstract

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EGFR-mutant lung cancers responsive to reversible EGFR inhibitors (gefitinib/erlotinib) develop acquired resistance, mediated by second-site *EGFR T790M* mutation in >50% cases. Preclinically, afatinib (irreversible ErbB family blocker) plus cetuximab (anti-EGFR monoclonal antibody) overcomes *T790M*-mediated resistance. This phase Ib study combining afatinib and cetuximab enrolled heavily pretreated patients with advanced *EGFR*-mutant lung cancer and acquired resistance to erlotinib/gefitinib. Patients provided post-acquired-resistance tumor samples for profiling *EGFR* mutations. Among 126 patients, objective response rate (overall 29%) was comparable in *T790M*-positive and *T790M*-negative tumors (32% vs. 25%; $P = 0.341$). Median progression-free survival was 4.7 months (95% confidence interval, 4.3–6.4); median duration of confirmed objective response was 5.7 months (range, 1.8–24.4). Therapy-related grade 3/4 adverse events occurred in 44%/2% of patients. Afatinib/cetuximab demonstrated robust clinical activity and a manageable safety profile in *EGFR*-mutant lung cancers with acquired resistance to gefitinib or erlotinib, both with and without *T790M* mutations, warranting further investigation.

Keywords

afatinib; cetuximab; acquired resistance

INTRODUCTION

Lung cancers with activating epidermal growth factor receptor (*EGFR)* mutations (e.g., exon 19 deletions, L858R) are sensitive to the small-molecule EGFR tyrosine kinase inhibitors (TKIs), erlotinib and gefitinib. Patients with *EGFR* mutant, non-small cell lung cancer (NSCLC) who receive these drugs experience dramatic tumor regression and derive a progression-free survival (PFS) advantage over chemotherapy (1–5). However, acquired resistance to erlotinib or gefitinib eventually develops in most patients (4, 6, 7). Currently, there are no targeted therapies approved for the treatment of patients with acquired resistance to erlotinib or gefitinib (8).

At the time of acquired resistance to erlotinib or gefitinib, a second-site *EGFR T790M* mutation, which alters binding of first generation EGFR TKIs to EGFR can be identified in more than half of tumors (6, 9–11). In preclinical models, *EGFR*-mutant tumor cells with *T790M*-mediated acquired resistance remain dependent upon EGFR signaling, suggesting that inhibition of EGFR may still be a therapeutic option (9, 10). Another 5–10% of patients display *MET* amplification (12, 13), with or without *T790M* mutations (14). Efforts to overcome acquired resistance in the clinic utilizing more potent irreversible EGFR TKIs, combination therapy with EGFR and MET TKIs, and other targeted strategies have had limited success to date (7, 15, 16).

Afatinib is an ErbB family blocker that irreversibly blocks signaling from EGFR (ErbB1), HER2 (ErbB2), HER4 (ErbB4), and all relevant ErbB family dimers (17, 18). Afatinib was recently approved for first-line treatment of patients with metastatic NSCLC whose tumors harbor activating *EGFR* mutations (19, 20). In the LUX-Lung 1 trial, conducted in patients with 1 or 2 lines of previous chemotherapy and acquired resistance to gefitinib/erlotinib, median PFS was 3 times longer in the afatinib-treated group than in the placebo-treated

group (3.3 months with afatinib vs. 1.1 months with placebo; $P < 0{\cdot}0001$). Although approximately half of afatinib-treated patients had tumor burden decreases below baseline, the objective response (OR) rate was 7% (21). Cetuximab, approved for the treatment of colorectal cancer (CRC) and head and neck cancer, is a chimeric, human-murine monoclonal antibody that binds the extracellular domain of EGFR competitively and with high affinity (22, 23). Experiments in mice with *L858R/T790M* erlotinib-resistant tumors showed that the combination of afatinib with cetuximab, but not the individual drugs, induced near complete tumor regression by depleting phosphorylated EGFR and total EGFR in tumors (24). Moreover, animals treated with both drugs appeared to tolerate the regimen without difficulty. On the basis of these preclinical observations, we conducted a study to determine the maximum tolerated dose (MTD) and to investigate the safety and preliminary efficacy of combined EGFR blockade with afatinib and cetuximab in patients with *EGFR*-mutant tumors and acquired resistance to erlotinib or gefitinib. Studies conducted in patients with advanced CRC indicated that bi-weekly cetuximab was a convenient, effective and well-tolerated regimen (25, 26). Based on this evidence we selected the bi-weekly dosing regimen for cetuximab, with no expectation of differences in toxicity between weekly and bi-weekly dosing of cetuximab.

A cohort of 126 patients with *EGFR*-mutant lung cancer was treated with the MTD of afatinib (40 mg oral daily) plus cetuximab (500 mg/m^2 intravenously every 2 weeks). Efficacy and safety outcomes in these patients are reported.

METHODS

Patients

Eligible patients were at least 18 years old and had a diagnosis of stage IIIB/IV lung cancer harboring an *EGFR* mutation known to be associated with drug sensitivity. Other eligibility criteria included disease progression while on continuous treatment with erlotinib or gefitinib within 30 days of starting this study with no intervening systemic therapy (thus meeting the consensus definition of acquired resistance; ref. (27); an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 (asymptomatic), 1 (ambulatory but restricted in strenuous activity), or 2 (capable of all self care but unable to work); and adequate organ function. Exclusion criteria included symptomatic or untreated brain metastases, and prior treatment with EGFR-targeting antibodies. Patients were allowed to continue their previous EGFR TKI following progression in order to minimize risk of disease flare (28) prior to enrollment in the current study. Patients were required to discontinue their previous EGFR TKI before initiating study therapy; the EGFR TKI-free interval prior to enrollment was limited to 3 days.

EGFR-Mutation Assessment

Fresh or archived tumor tissues, after disease progression on erlotinib or gefitinib within the previous 30 days and prior to study start, was required for *EGFR*-mutation analysis. All patients (except those enrolled only in the dose-finding phase) had a known status of *EGFR* mutations (including exon 18 [G719X], exon 19 deletion, exon 20 insertion, exon 20

T790M, and exon 21 [L858R and L861Q]) after developing acquired resistance to erlotinib/gefitinib.

Study Design and Cohort Expansion

This was a phase Ib, open-label, uncontrolled, multicenter study comprising 3 phases, a dose-finding phase (identification of the MTD of afatinib plus cetuximab), an expansion phase (patients treated with the MTD of afatinib plus cetuximab until disease progression), and a sequential therapy phase (patients treated with afatinib monotherapy until disease progression and afatinib plus cetuximab thereafter; Fig. 1). Afatinib was administered daily as oral medication, while cetuximab was administered intravenously. Initially, 10 patients were enrolled in the dose-finding phase: 4 patients received afatinib 40 mg daily plus cetuximab 250 mg/m^2 every 2 weeks and 6 received the prespecified maximum dose of afatinib 40 mg daily plus cetuximab 500 mg/m^2 every 2 weeks. The MTD was rapidly identified as afatinib 40 mg daily plus cetuximab 500 mg/m^2 every 2 weeks. Based on preliminary efficacy signals at the MTD, the protocol was amended to permit treatment of additional patients to further evaluate safety and to incorporate a statistical design to detect efficacy at this dose. An additional 134 patients (total 140) with *EGFR*-mutant lung cancers, including at least 40 patients with *T790M*-positive and 40 patients with *T790M*-negative tumors, were planned to be treated at the MTD. The target of 140 patients was based on an assumed response rate of at least 23%, and a 95% probability of observing a 15% response (11 responses in each 70 patient *T790M* subgroup). Robust efficacy results from the combination phase prompted incorporation of a sequential design to investigate the safety and efficacy of the afatinib/cetuximab combination in *EGFR*-mutant NSCLC patients who had developed acquired resistance to afatinib monotherapy. The dose-finding and sequential therapy phases will be reported subsequently in a separate manuscript.

Treatment continued until documented disease progression according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (29); intolerable adverse events; withdrawal from the study; or death. Patients could continue treatment beyond RECIST-defined progression based on continued clinical benefit at the discretion of the principal investigator. A dose-reduction scheme for the management of toxicity was specified in the study protocol. Briefly, on first occurrence of ≥grade 3 adverse events (other than hypomagnesemia where only cetuximab was to be reduced), cetuximab was to be reduced by 100 mg (from 500 mg to 400 mg, and with second occurrence, afatinib and cetuximab were both to be reduced (by 10 mg from 40 mg to 30 mg for afatinib and by 100 mg from 400 mg to 300 mg for cetuximab).

Study Endpoints

Efficacy endpoints included OR, defined as a best response to treatment of complete response (CR) or partial response (PR), as assessed by investigators according to RECIST; PFS, defined as the duration of time from start of treatment until progressive disease (PD) according to RECIST or death; duration of disease control, defined as the duration of time from the start of treatment until progression or death; and duration of response, defined as duration of time from first recorded CR/PR until recurrent or PD according to RECIST.

Adverse events were assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (30).

Tumor Assessments

Tumor assessments took place at week 4, 8, and 12, and every 8 weeks thereafter according to RECIST using computed tomography. Best overall responses were derived from tumor measurements provided by the study-site radiologists and investigators according to RECIST version 1.1, which specifies confirmation of stable disease (SD) in 6 to 8 weeks. (29)

Statistical Analysis

All patients who had received the combination regimen at the MTD were included in the description of baseline characteristics, efficacy, and safety analysis. All patients were evaluable for response. All evaluable patients had one of the following: at least 1 tumor evaluation during treatment, clinical progression of disease, or death before the first tumor evaluation during treatment.

Descriptive statistics were calculated and tabulated for endpoints relating to antitumor activity. Within each treatment arm, antitumor activity was further summarized by *EGFR*-mutation status based on tumor tissue testing results after manifestation of acquired resistance (including drug-sensitizing *EGFR* mutations and the presence or absence of *T790M* mutation). No formal statistical tests and multiplicity adjustments were to be performed for the differences between groups with respect to response rate or other efficacy measures. PFS was analyzed using Kaplan-Meier methodology. Greenwood's variance estimate was used to form confidence intervals (CIs).

Study Conduct

The study protocol was approved by the institutional review boards/ethics committees at the participating centers. All patients provided written informed consent. The study was designed by senior academic authors and the sponsor, Boehringer Ingelheim Pharmaceuticals Inc. Study medications were provided by the sponsor. The first author wrote all drafts of the manuscript, with editorial support provided by a medical writer and funded by the sponsor.

RESULTS

Patients and Treatment

Between March 2010 and April 2013, a total of 201 patients were enrolled into the 3 phases of the trial (Fig. 1). Overall, the trial enrolled patients across six centers in The Netherlands and the United States; 164 patients from the United States and 37 from The Netherlands. Of these, 126 patients were treated with the MTD of afatinib plus cetuximab (40 mg daily; 500 mg/m^2 every 2 weeks) in the combination phase. Overall baseline patient demographics and disease characteristics are shown in Table 1. Tumor status for *EGFR*-sensitizing mutations was known for all patients. Exon 19 deletion, found in 62% of patients, was the most frequent *EGFR* mutation detected. *T790M* mutation status was known for 124 patients; 57%

were *T790M*-positive (baseline demographics and disease characteristics by *T790M* mutation status are also shown in Table 1). In the overall population, the median time since diagnosis of any lung cancer was 2 years (range, 4.5 months to 11 years). All patients had received prior erlotinib or gefitinib; 79% of patients had been treated with cytotoxic chemotherapy in addition to erlotinib or gefitinib, and 52% had received 2 or more lines of prior chemotherapy. Patients had been treated with an EGFR TKI for a median of 1 year (range, 1 month to 7 years) prior to study entry. The median duration of prior TKI treatment was 2 years for those with *T790M* versus 1 year for those without, consistent with *T790M*-positive disease being associated with a more favorable prognosis (31).

Efficacy

Of the 126 patients treated with the MTD of afatinib and cetuximab, 37 (29%) had a confirmed OR (all PRs; Table 2), 22 (18%) of whom had ≥50% tumor shrinkage from baseline (Fig. 2). There was no significant difference in OR rate between patients harboring *T790M*-positive and *T790M*-negative tumors (32% [95% CI, 21.8–44.5] vs. 25% [95% CI, 13.8–38.3]; $P = 0.341$; Table 2). ORs were observed in 25 (20%) patients by treatment week 4. There was a trend towards improved OR rate with respect to duration of treatment with prior EGFR TKIs, although comparisons between groups were not statistically significant (<11 months: 26%; ≥11– <22 months: 28%; ≥22–<33 months: 29%; 33+ months: 38%). The OR rate to afatinib and cetuximab was 80%, 31% and 21% in patients who achieved CR, PR or SD, respectively, on a prior EGFR TKI. The overall median duration of confirmed OR was 5.7 months (range, 1.8 to 24.4); patients with *T790M*-positive and *T790M*-negative tumors had median durations of confirmed OR of 5.6 months (range, 1.8 to 24.4) and 9.5 months (range, 2.9 to 14.8), respectively. Fifty-two (41%) patients had SD as confirmed best OR, including 5 (4%) patients with an unconfirmed PR (Table 2). Eighty percent of patients suffered disease progression or died during the study, and the median PFS was 4.7 months (95% CI, 4.3–6.4; Fig. 3). PFS was similar for *T790M*-negative and *T790M*-positive patients (4.6 vs. 4.8 months; $P = 0.643$). Duration of PFS for individual patients with respect to best response and T790M status is shown in Fig. 4. A summary of censoring for PFS showed that 23 patients (19%) were alive and non-PD according to the available imaging results at the time of database lock. Two additional patients (2%) were censored as a result of starting a new anti-cancer medication before progression or death, when the interval between the start of new medication and subsequent PD was >7 days. Thirteen percent of patients treated at the MTD were continued on study treatment for clinical benefit following radiographic disease progression for a median period of 3 months (range, 1.8–7).

Tolerability and Adverse Event Profile

The median duration of treatment was 4.8 months (range, <1 to 29.1). Treatment-related adverse events were observed in 99% of patients, with the most common being rash (90%), diarrhea (71%), nail effects (57%), stomatitis (56%), fatigue (47%), and nausea (42%; Table 3). Grade 3 and 4 treatment-related adverse events were noted in 44% and 2% of patients, respectively. The most common grade 3 events were rash (20%) and diarrhea (6%; Table 3). Grade 4 events (fatigue, pneumonitis, and lung infiltration) occurred in 2 patients. Two patients died due to treatment-related adverse events (dyspnea and pneumonitis). Adverse events of any causality were experienced by all patients (Supplementary Table S1A).

Serious adverse events related to treatment were reported in 14% of patients (Supplementary Table S1B). The most common of these were drug hypersensitivity (2%) and dehydration (2%). Overall, 13% of patients discontinued therapy due to treatment-related adverse events. The majority of patients (64%) did not require a dose reduction. Median time to a first-dose reduction of either afatinib or cetuximab was 3.1 months (range, <1 to 14.1). The median duration of treatment following a first-dose reduction was 4.4 months (range, <1 to 25.6).

DISCUSSION

To our knowledge, this trial is the first study to demonstrate robust and durable clinical activity of a targeted treatment regimen in *EGFR*-mutant lung cancers with acquired resistance to erlotinib or gefitinib. The confirmed OR rate of 29%, with median duration of response of 5.7 months, is particularly meaningful considering the majority of patients were heavily pretreated, i.e., 52% had failed 2 or more lines of standard cytotoxic chemotherapy in addition to a reversible EGFR TKI prior to enrollment. This study demonstrates that a significant proportion of tumors in patients with acquired resistance to gefitinib/erlotinib remain dependent upon EGFR signaling for survival and confirms the preclinical hypothesis that dual EGFR inhibition is particularly meaningful in this patient population.

Combination therapy with afatinib and cetuximab also demonstrated a manageable safety profile, with rash and diarrhea as the most frequent treatment-related adverse events and 64% of patients remaining on the full treatment dose throughout the study. Despite the occurrence of grade 3 adverse events in nearly half of the patient population, the dose reduction and interruption scheme led to a discontinuation rate due to treatment-related adverse events of only 13%.

Although the combination of afatinib and cetuximab was developed to overcome *T790M*-mediated resistance in preclinical models, response rates and PFS were similar in patients with and without *T790M* mutations. These data suggest that even tumor cells without *T790M* remain dependent upon the ErbB signaling axis for survival. Such dependence may be due to *EGFR* amplification, alone or in conjunction with *T790M*, which has been reported in cases of acquired resistance (6, 32). Since afatinib also inhibits HER2, another possibility is that such tumors harbored *HER2* amplification, which can occur in patients with acquired resistance in the absence of *T790M* mutations (13, 33). Studies are ongoing to determine if responses are correlated with EGFR or HER2 copy number as well as other reported rarer mechanisms of resistance to gefitinib/erlotinib (e.g., *PIK3CA* mutation, *BRAF* mutation, fibroblast growth factor receptor [FGFR] activation, AXL upregulation, small cell lung cancer transformation, epithelial mesenchymal transition, etc.; ref. (7).

The OR rate with afatinib and cetuximab in combination in the current study was 29%. In the LUX-Lung 1 and LUX-Lung 4 studies, conducted in patients with NSCLC and prior chemotherapy and progression on gefitinib/erlotinib, afatinib monotherapy demonstrated response rates of 7% and 8%, respectively (21, 34). Similarly, cetuximab alone has demonstrated OR rates of 4.5% in patients with NSCLC previously treated with chemotherapy and 0% in patients heavily pretreated with chemotherapy and TKIs (35, 36). Of note, no ORs were observed in trials of cetuximab in combination with erlotinib or

gefitinib in patients with acquired resistance (37, 38). Although cross-trial comparisons are not possible due to different study parameters, these results suggest that the factors specific to afatinib's mechanism of action, namely irreversible inhibition of EGFR and more complete inhibition of ErbB-family members, are key elements of the mechanism of action of the combination of afatinib plus cetuximab. The antibody (cetuximab) blocks ligand binding and induces receptor degradation but is insufficient alone to inhibit the ligand-independent activity of the mutant receptors. The kinase inhibitor (afatinib) inhibits phospho-EGFR activity but only incompletely at the doses administered. Only the combination of both agents together induces depletion of both phosphorylated and total EGFR, lowering the amount of signaling from mutant EGFRs below a certain threshold needed for cell survival. Multiple mechanisms could explain this observation. One possibility is that afatinib increases binding of cetuximab to the cell surface. As a consequence of increased binding, EGFR could be degraded more efficiently. A second possibility is that cetuximab and afatinib target different receptor pools. We had previously speculated that a third possibility was that cetuximab binding leads to enhanced antibody-dependent cellular cytotoxicity (24); however, since afatinib plus panitumumab (anti anti-EGFR antibody IgG4 that cannot mediate antibody-dependent cellular cytotoxicity is also effective against T790M-driven tumors (33), this scenario is less likely.

At present, treatment options for patients with acquired resistance to first generation EGFR TKIs are limited. Trials of investigational agents/regimens such as neratinib (39), XL-647 (40), everolimus plus erlotinib (41), and dasatinib plus erlotinib (42) have failed to produce OR rates above 5% in this setting. Recently, third generation EGFR mutant-specific TKIs (CO-1686 and AZD9291) have shown some promise in early phase trials (43, 44). These TKIs specifically inhibit mutant EGFRs, including T790M, sparing the wild-type receptor and thus limiting toxicity due to wild-type EGFR inhibition. Since these agents were designed to overcome *T790M*-mediated resistance, whether or not they will have activity comparable to afatinib and cetuximab in *T790M*-negative cases remains to be seen. Nevertheless, eventually, patients will be treated with multiple lines of EGFR-targeted therapies with increasing frequency. A patient with *EGFR*-mutant lung cancer may receive erlotinib or afatinib as first-line therapy, followed by additional EGFR-targeted therapies such as either afatinib and cetuximab or third-generation TKIs. Patients could eventually receive a third-generation TKI in the first or second-line setting, but whether acquired resistance will be more aggressive and amenable or refractory to targeted therapies remains unknown. The effects of sequential treatment with various anti-EGFR agents on tumor evolution and drug resistance in *EGFR*-mutant lung cancer are currently under investigation and will need to be understood to optimize sequential anti-EGFR treatment for patients.

In summary, this study showed that dual blockade of EGFR with afatinib and cetuximab, combined with afatinib's inhibition of all ErbB family members in patients with EGFR-mutant NSCLC and acquired resistance to gefitinib or erlotinib, conferred robust and durable clinical responses irrespective of *T790M* status combined with a manageable safety profile. As this activity was demonstrable in a heavily pretreated cohort of patients, its evaluation is also of particular interest in an earlier line setting. Thus, 2 randomized trials are planned to evaluate this combination in *EGFR*-mutant NSCLC. The first intends to enroll

TKI-naïve patients, while the second will study patients with acquired resistance but only 1 prior line of standard platinum-based doublet chemotherapy. Molecular correlative studies are ongoing to determine which tumors are most sensitive to dual inhibition of EGFR.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SIGNIFICANCE

This article reports the results of a trial combining afatinib and cetuximab in patients with acquired resistance and details the first clinical proof-of-concept for the preclinical hypothesis that a significant proportion of tumors in patients with acquired resistance to gefitinib/erlotinib remain dependent on EGFR signaling for survival.

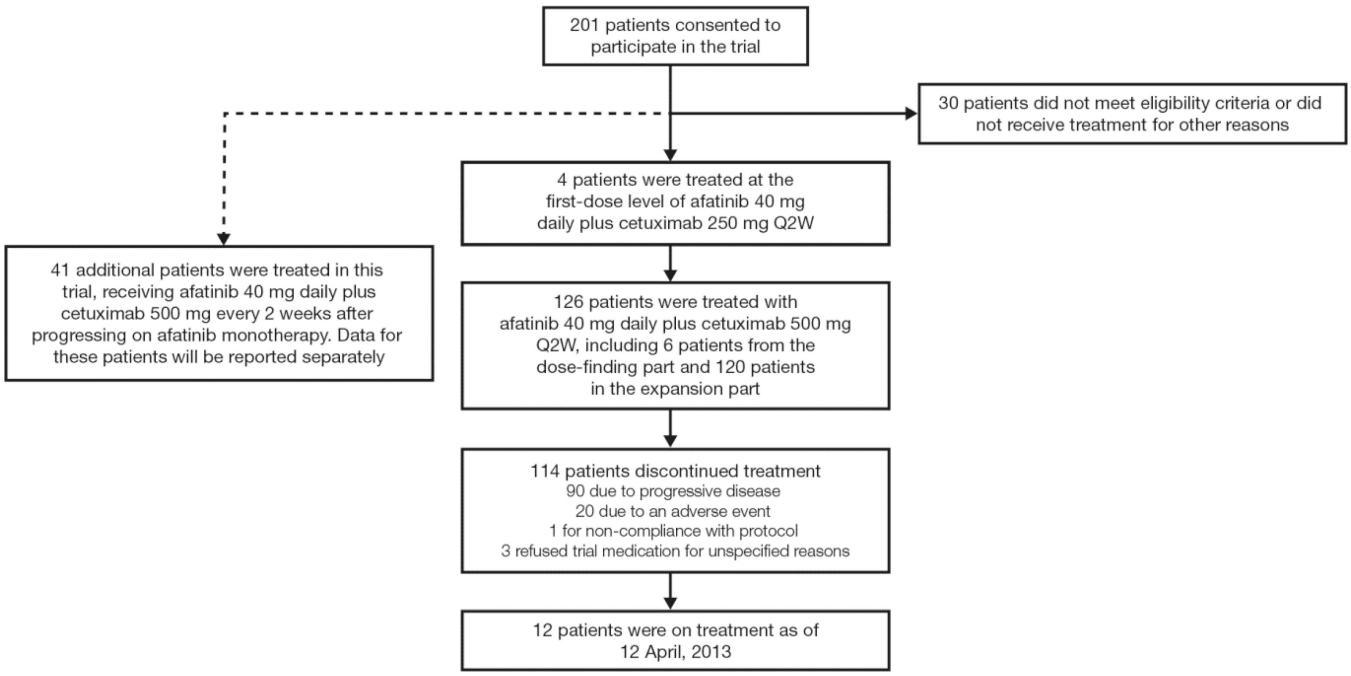

Figure 1.
Study design and patient disposition.

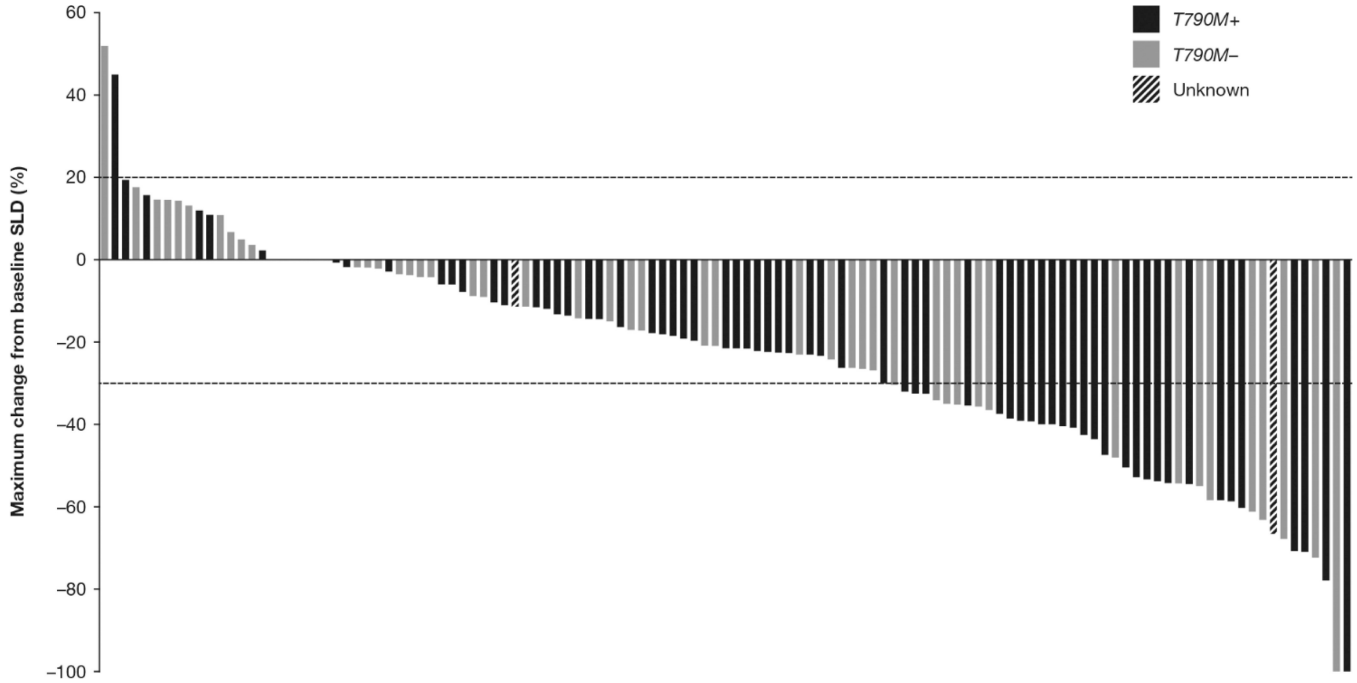

Figure 2.

Waterfall plot showing maximum percentage change from baseline in size of tumors in patients who received the concurrent regimen of afatinib and cetuximab. Data available for 119 patients. [a]Tumor tissue from 2 patients was uninformative as to *T790M* status. Abbreviation: SLD, sum of the longest diameter.

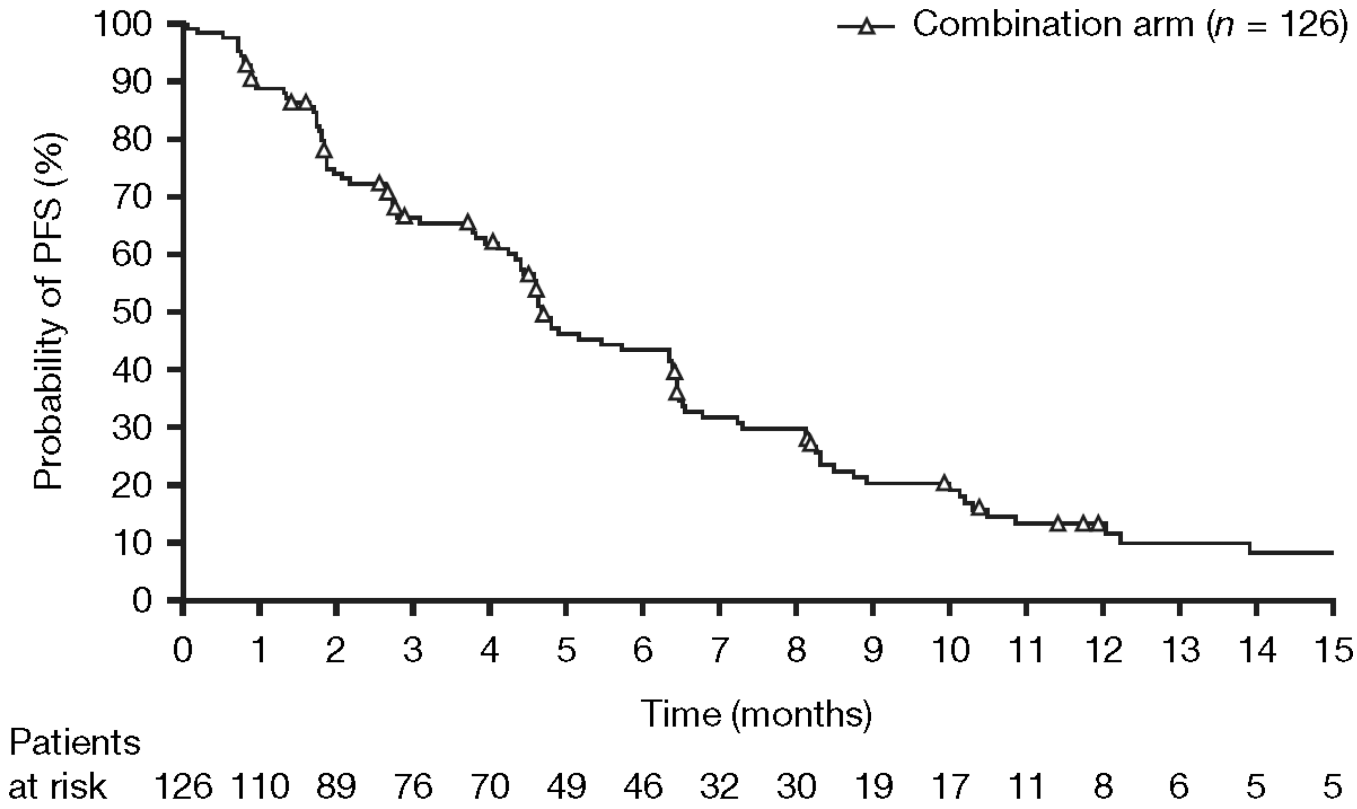

Figure 3.
Kaplan-Meier curve showing PFS in patients who received the concurrent regimen of afatinib and cetuximab.

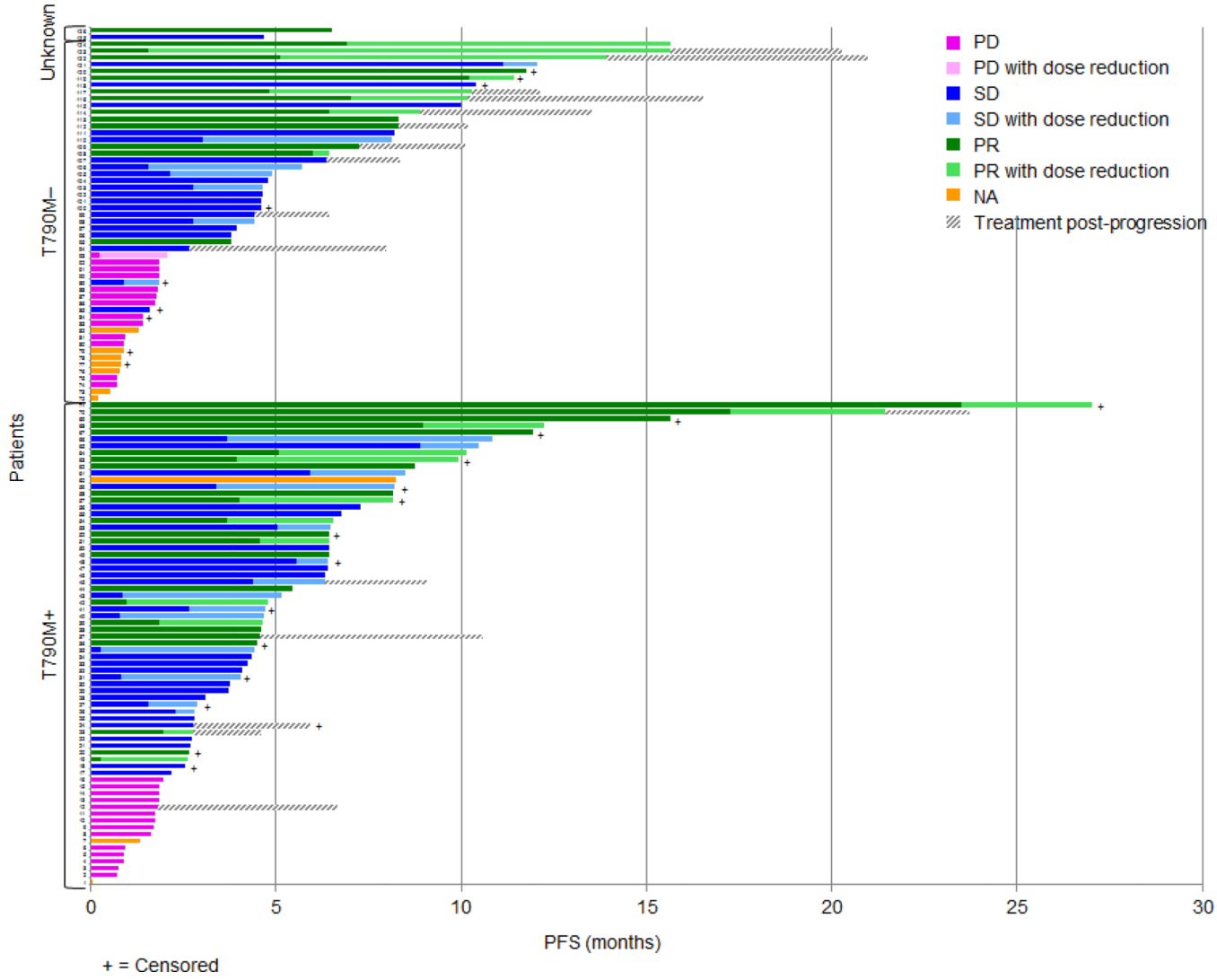

Figure 4.

Duration of PFS for individual patients with respect to best response and T790M status. For patients who required a dose reduction prior to disease progression, timing of implementation and duration of dose reductions is indicated by paler shading of the individual bars. Sixteen patients continued on study treatment after disease progression, duration of treatment post-progression is indicated by an extended patient timeline in cross-hatched pale grey after the progression event. Abbreviation: NA, not available

Table 1

Baseline characteristics of patients treated with afatinib and cetuximab concurrently

		***T790M* Mutation status (available for 124 patients)**	
	Total	***T790M+***	***T790M−***
Patients, *n* (%)	126 (100)	71 (100)	53 (100)
Median age at baseline, years (range)	59 (31–82)	58 (31–82)	60 (40–79)
Gender, *n* (%)			
Male	33 (26)	20 (28)	12 (23)
Female	93 (74)	51 (72)	41 (77)
Race, *n* (%)			
American Indian/Alaska Native	2 (2)	1 (1)	1 (2)
Asian	19 (15)	12 (17)	7 (13)
Black/African American	10 (8)	7 (10)	3 (6)
White	95 (75)	51 (72)	42 (79)
Baseline ECOG PS, *n* (%)			
0	27 (21)	17 (24)	10 (19)
≥1	99 (79)	54 (76)	43 (81)
Median time since diagnosis[a], years (range)	2 (0.5[b]–11)	2 (0.5[b]–11)	2 (1–7)
Median duration of prior EGFR TKI treatment[c], years (range)	1(0–7)	2 (0–7)	1(0–6)
Prior chemotherapy, *n* (%)			
0–1 line	61 (48)	32 (45)	28 (53)
≥2 lines	65 (52)	39 (55)	25 (47)
EGFR-mutation status, *n*			
Del 19+	78	44	34
L858R+	41	24	15
Other[d]	4	2	2
EGFR wild-type[e]	3	1	2

[a] Data available for 121, 69, and 50 patients, respectively.

[b] 4.5 months.

[c] Maximum duration if patients received more than 1 prior EGFR TKI regimen.

[d] Includes: G719S, G719A, G719C, S768I, and L861Q.

[e] Patients enrolled into the dose-finding phase were not required to be *EGFR* mutation-positive; patients enrolled following identification of the MTD were required to be *EGFR* mutation-positive.

Table 2

Confirmed response per RECIST tumor assessments for all patients and by mutation status: concurrent regimen

		Cohort			
n	**All Patients**[a]	***T790M+***[b]	***T790M–***[b]	***Del 19***	***L858R***
Total treated	126	71	53	78	41
RECIST response	89	54	33	48	34
OR[c] (CR/PR)	37	23	13	23	14
SD	52	31	20	25	20
Unconfirmed OR	5	4	1	3	1
PD	27	14	13	23	4
CR/PR <35 days followed by PD	3	1	2	3	0
SD <35 days followed by PD	15	8	7	14	1

[a] Includes 2 patients for whom *T790M* status was unknown due to tissue samples insufficient for testing.

[b] Available for 124 of 126 treated patients.

[c] All ORs were PRs; no CRs were observed.

Table 3

Drug-related adverse events occurring in >20% of patients by grouped and preferred term and by highest CTCAE grade

	All Grades *n* (%)	**Grade 3 *n* (%)**	**Grade 4 *n* (%)**
Total patients treated	126 (100)	126 (100)	126 (100)
Total patients with related adverse events	125 (99)	56 (44)	2 (2)
Rash[a]	114 (90)	25 (20)	0 (0)
Diarrhea	89 (71)	8 (6)	0 (0)
Nail effects[a]	72 (57)	0 (0)	0 (0)
Stomatitis[a]	71 (56)	1 (1)	0 (0)
Fatigue[a]	59 (47)	2 (2)	1 (1)
Nausea	53 (42)	3 (2)	0 (0)
Xerosis	53 (42)	3 (2)	0 (0)
Pruritus	50 (39)	2 (2)	0 (0)
Headache	46 (37)	4 (3)	0 (0)
Ocular effects[a]	38 (30)	0 (0)	0 (0)
Dry skin	37 (29)	1 (1)	0 (0)
Vomiting	33 (26)	1 (1)	0 (0)
Hypomagnesemia	29 (23)	3 (2)	0 (0)

[a]Grouped terms.