ORIGINAL ARTICLE

Afatinib and Necitumumab in *EGFR*-Mutant NSCLC with Acquired Resistance to Tyrosine Kinase Inhibitors

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ABSTRACT

Introduction: Although tyrosine kinase inhibitors (TKIs) are effective against NSCLC harboring sensitizing *EGFR* gene mutations, acquired resistance is inevitable. Preclinical studies suggest that combining EGFR TKI and monoclonal antibody therapies may have activity in *EGFR*-mutated NSCLC that has progressed on TKI therapy alone. Therefore, we prospectively evaluated afatinib plus necitumumab in patients with *EGFR*-mutated NSCLC.

Methods: This was a phase 1, dose-escalation, dose-expansion trial assessing the safety and efficacy of afatinib plus necitumumab. Patients had advanced or metastatic *EGFR*-mutated NSCLC with progression after (1) first-generation TKI if T790M negative, (2) subsequent line third-generation TKI if T790M positive, or (3) third-generation TKI in the first-line setting. Dose-escalation followed a 3+3 design. The primary end point of dose-expansion was objective response rate.

Results: A total of 22 patients with *EGFR*-mutated NSCLC were enrolled. The maximum tolerated dose was afatinib 40 mg oral daily plus necitumumab 600 mg intravenous on days 1 and 15 every 28 days. There were no grade 4 to 5 adverse events observed, and seven patients (32%) experienced grade 3 treatment-related adverse events (three rash; one each oral mucositis, diarrhea, headache, ventricular arrhythmia, and tachycardia). In the entire cohort, there were no responses observed, the median progression-free survival was 1.8 months, and the disease control rate was 36% but varied between the subgroups.

Conclusions: Afatinib plus necitumumab was safe but had limited activity in patients with *EGFR*-mutated NSCLC. Biomarker studies may identify patient subgroups that are more likely to benefit.

Keywords: Dual EGFR inhibition; Phase I trial; Lung cancer; *EGFR*-mutated

Introduction

Oncogenic alterations in the *EGFR* gene (e.g., exon 19 deletions, L858R point mutations) are identified in approximately 20% of newly diagnosed NSCLCs, with predominance in patients who never smoked and those with adenocarcinoma.[1,2] Multiple tyrosine kinase

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inhibitors (TKIs) targeting EGFR are now available including third-generation osimertinib, which is standard frontline therapy in untreated, metastatic *EGFR*-mutated NSCLC due to its improved progression-free survival (PFS) and overall survival (OS) compared with first-generation erlotinib and gefitinib.[3,4]

Although highly effective, osimertinib and other EGFR TKIs are associated with eventual resistance and disease progression. Before the adoption of osimertinib as frontline therapy, the most common mechanism of acquired resistance to first-generation TKIs was an on-target *EGFR* T790M mutation occurring in approximately 50% of tumors.[5] T790M mutations result in steric hindrance that limits the binding of erlotinib and gefitinib but retains sensitivity to osimertinib.[6,7] Mechanisms of acquired resistance to osimertinib, however, are varied and include on-target *EGFR* mutations (e.g., C797S) and *EGFR* amplification, off-target tyrosine kinase alterations (e.g., *BRAF* V600E, *PIK3CA* mutations, *MET* amplification), and histologic transformation.[8] Despite overlap, some mechanisms of resistance also differ when osimertinib is used as first-line versus later-line therapy. For example, loss of T790M occurs frequently as a mechanism of resistance to subsequent-line osimertinib and is associated with faster time to treatment failure.[9] In the case of acquired resistance to first-line osimertinib, T790M is not observed whereas other *EGFR* mutations (C797S, L718Q) are uncommon, and off-target resistance mechanism of *MET* amplification and histologic transformation are also found.[8,10,11] Many patients with acquired resistance to first-line osimertinib will have more than one mechanism detected.[12] For those patients with on-target mechanisms of resistance to osimertinib involving *EGFR*, there has been suggestion that dual mechanisms of EGFR inhibition may be effective.[13,14] Nevertheless, as of now, there are no approved oral targeted therapies for refractory *EGFR*-mutated NSCLC after osimertinib, leaving platinum-doublet chemotherapy and more recently, in combination with amivantamab, as the usual next-line option outside of a clinical trial.

An additional class of therapies targeting EGFR are monoclonal antibodies, which include cetuximab, panitumumab, and necitumumab. Compared with TKIs that bind to the intracellular kinase domain of EGFR, monoclonal antibodies block the extracellular binding pocket, leading to decreased downstream signaling, impaired receptor dimerization, and increased receptor internalization and degradation.[15] As monotherapy, the efficacy of EGFR antibodies in *EGFR*-mutated NSCLC is limited with no responses observed and median PFS of 1.8 months in patients receiving cetuximab after erlotinib or geftinib.[16] Preclinical studies, however, suggest potential activity for monoclonal antibodies in combination with EGFR TKIs in the post-TKI setting. Afatinib, a second-generation TKI, irreversibly inhibits pan-ERBB receptors that include classic *EGFR* mutations and is the only TKI approved for uncommon *EGFR* mutations (e.g., G719X), thereby offering potentially broader applications.[17–19] In a mouse model of *EGFR* L858R/T790M-mutated lung cancer, Regales et al.[20] observed complete tumor responses in mice treated with afatinib plus cetuximab but not in those mice treated with afatinib or cetuximab alone or erlotinib plus cetuximab. In the clinical setting, a phase 1b trial reported a response rate of 29% in patients with *EGFR*-mutated NSCLC receiving afatinib plus cetuximab after disease progression on erlotinib or gefitinib,[21] with responses similar in T790M-positive versus -negative disease (32% versus 25%; $p = 0.341$).

Although these preclinical and clinical findings are notable, the potential of dual EGFR inhibition remains incompletely realized, and its efficacy after progression on first-line osimertinib has not been well studied. In addition, compared with cetuximab, the fully human recombinant EGFR monoclonal antibody, necitumumab, may be better tolerated given its lower theoretical risk of infusion reactions.[22] With this in mind, we report here the results of a prospective phase 1, dose-escalation, dose-expansion trial evaluating the safety and activity of afatinib plus necitumumab in patients with advanced or metastatic *EGFR*-mutated NSCLC after progression on first-generation or third-generation TKI therapy.

Materials and Methods

This is an open-label, multisite, nonrandomized, phase 1, dose-escalation, and dose-expansion study of afatinib plus necitumumab in *EGFR*-mutated NSCLC. The clinical trial was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the Investigational Review Boards at each participating institution. In addition, each participant provided written informed consent before joining the study.

Eligibility Criteria

Adult ($\geq$18 y of age) participants with advanced or metastatic NSCLC harboring an activating *EGFR* mutation were enrolled. Eligible *EGFR* mutations included exon 19 deletions, L858R point mutations, and other rare sensitizing mutations (e.g., G719X). Central testing for *EGFR* mutations was not performed; sites used local institutional protocols for *EGFR* testing. In addition, the study did not specify required specimen type (tissue or blood) for *EGFR* testing. Participants must have progressed on a first-generation EGFR TKI (and be T790M negative), first-line osimertinib, or subsequent-line osimertinib (if T790M positive at time of progression on first- or second-generation TKI). Participants were excluded if they had already received an EGFR monoclonal antibody

or previous treatment with afatinib; however, patients who had received an intervening third-generation EGFR TKI after concluding previous afatinib were eligible. Patients with treated, asymptomatic brain metastases were eligible if no clinical change in brain disease status for at least 2 weeks before starting study treatment. A complete list of eligibility criteria is included in the Supplementary Material.

Study Design and End Points

Dose escalation followed a standard 3+3 design with four dose levels (DLs) planned and one de-escalation DL if needed (Table 1). The starting DL was 30 mg daily of afatinib (oral) with 400 mg necitumumab (intravenous infusion) on days 1 and 15 of a 28-day cycle. The primary end point of dose escalation was the maximum tolerated dose (MTD). Dose expansion included the following three subcohorts of 15 patients each that were treated at the MTD: (1) participants without a T790M mutation who had progressed on a first-generation EGFR TKI (e.g., erlotinib, gefitinib); (2) participants who had progressed on first-line osimertinib; and (3) participants who progressed on subsequent-line osimertinib (if T790M positive at time of progression on first- or second-generation TKI; hereafter, referred to as subsequent-line osimertinib). Presence or absence of T790M mutation in above-mentioned contexts was tested locally using tissue or circulating tumor DNA and not confirmed centrally before study entry. Of note, patients who were positive for T790M at the time of initiation of subsequent-line osimertinib were not retested for T790M before study enrollment, and therefore, it is not known whether patients had retained or lost T790M mutation at the time of starting study treatment.

The primary end point of dose expansion was the objective response rate in each of the subcohorts, defined as the percentage of patients having a confirmed complete response or partial response to therapy according to Response Evaluation Criteria in Solid Tumors (RECIST) version (v.) 1.1.[23] Patients with missing or no response assessments were classified as nonresponders.

Table 1. Planned Dose Levels

Dose Level	Afatinib (Oral Daily), mg	Necitumumab (IV on D 1 and 15 of 28-D Cycle), mg
−1	20	300
1 (starting dose level)	30	400
2	40	400
3	40	600
4	40	800

IV, intravenous.

Secondary end points included PFS, OS, disease control rate (DCR), duration of response, and safety. PFS was defined from time of study treatment initiation to the first occurrence of documented disease progression (per RECIST v.1.1) or death from any cause during the study, whichever occurs first. For patients who do not have documented progressive disease or death during the study, PFS was censored at the date of the last tumor assessment. Tumor assessments were performed at baseline and every 8 weeks using RECIST v.1.1.

Statistical Analysis

For dose escalation, at least three patients were studied at each DL following the standard 3+3. If more than or equal to two of three or more than or equal to two of six patients experienced a dose-limiting toxicity (DLT), the MTD was exceeded. A DLT was defined as any of the following adverse events occurring during the first treatment cycle (i.e., 28 d) that were classified by the investigator to be possibly, probably, or definitely related to treatment: grade more than or equal to 3 nonhematologic toxicity (except grade 3 asymptomatic rash); grade more than or equal to 4 neutropenia for more than 5 days; febrile neutropenia; grade more than or equal to 4 thrombocytopenia or grade 3 with bleeding; or inability to initiate cycle 2 within 4 weeks of scheduled treatment due to slow recovery from treatment-related adverse events (TRAEs).

Due to the small sample size and nature of the dose-escalation study, no formal hypothesis testing was performed. In dose expansion, if at least three responses were observed in any of the three 15-patient subcohorts described, then the combination therapy would be considered active in that population and further testing warranted. The probability of observing three or more responses in 15 patients is approximately 85% if the true response rate is 30%.

Demographic information, such as age, race or ethnicity, and sex, was tabulated. Descriptive statistics, including means with SDs and medians with ranges for continuous parameters and percentages and frequencies for categorical parameters, were estimated. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, v. 4.03, dated June 14, 2010, and presented as a summary statistic. The Kaplan-Meier method was used to estimate survival outcomes (PFS, OS) with 95% confidence intervals (CIs).

Results

Participants

Between August 2017 and August 2021, 22 participants with *EGFR*-mutated NSCLC were enrolled to the

study, 14 in dose escalation and eight across the predefined dose-expansion cohorts. Because of slow accrual, the study was closed early at all sites before dose expansion was completed. Baseline demographics are listed in Table 2; most patients were female (82%), white (66%), and never smokers (68%) with a median age of 59 (range: 38–62) years. All participants except one had nonsquamous NSCLC. In total, four participants were T790M negative and had progressed on first-generation TKI, 13 had progressed on subsequent-line osimertinib, and five had progressed on first-line osimertinib. The median duration of follow-up was 9.1 (range: 1–21.9) months.

MTD Identified in Dose Escalation

Two DLTs were observed in DL4 (Table 1; afatinib 40 mg, necitumumab 800 mg), including grade 3 diarrhea and symptomatic grade 3 rash (recorded as a delayed DLT given occurrence beyond the first 28 d during cycle 4). No DLTs were observed at other DLs. Thus, the MTD was exceeded, and the recommended

Table 2. Baseline Demographics and Disease Characteristics

Variables	Total (N = 22)	Dose Escalation (n = 14)	Dose Expansion (n = 8)
Median age, y (range)	60 (38-82)	61 (38-82)	59 (47-70)
Sex			
Male	4 (18)	3 (21)	1 (12)
Female	18 (82)	11 (79)	7 (88)
Race			
White	14 (64)	10 (71)	4 (50)
Asian	4 (18)	2 (15)	2 (25)
Native Hawaiian	1 (4)	1 (7)	0
Not reported	3 (14)	1 (7)	2 (25)
Ethnicity			
Non-Hispanic or Latino	19 (86)	12 (86)	7 (88)
Hispanic or Latino	2 (9)	2 (14)	0
Not reported	1 (5)	0	1 (12)
Smoking status			
Never smoker	15 (68)	10 (71)	5 (62)
Current or previous smoker	7 (32)	4 (29)	3 (38)
ECOG performance status			
0	3 (14)	1 (7)	2 (25)
1	16 (72)	12 (86)	4 (50)
2	3 (14)	1 (7)	2 (25)
Median previous lines of treatment (range)[a]	3 (1-8)	3 (1-8)	2 (1-5)
Previous platinum chemotherapy			
Yes	17 (77)	11 (79)	6 (75)
No	5 (23)	3 (21)	2 (25)
DL			
DL1	3 (14)	3 (21)	-
DL2	3 (14)	3 (21)	-
DL3 (expansion dose)	12 (55)	4 (28)	8 (100)
DL4	4 (17)	4 (28)	-
T790M negative and progressed on first-generation TKI	4 (18)	4 (28)	-
Progressed on first-line osimertinib	5 (23)	1 (7)	4 (50)
Progressed on subsequent-line osimertinib	13 (59)	9 (64)	4 (50)
Primary *EGFR* mutation			
Exon 21 L858R	6 (27)	2 (14)	4 (50)
Exon 19 del	15 (68)	12 (86)	3 (38)
G719X	1 (5)	0 (0)	1 (12)
Brain metastasis			
Yes	5 (23)	2 (14)	3 (38)
No	17 (77)	12 (86)	5 (62)

Note: All values are n (%) unless otherwise specified.
[a]All but one patient had previous osimertinib, 11 had previous erlotinib, two had erlotinib and afatinib, one had gefitinib, and one had afatinib.
DL, dose level; ECOG, Eastern Cooperative Oncology Group; TKI, tyrosine kinase inhibitor.

dose for expansion was determined to be 40 mg afatinib once daily and 600 mg necitumumab on days 1 and 15 of a 28-day cycle.

Safety

Across dose escalation and expansion, all 22 participants experienced at least one TRAE and most (74%) were grade 1 (Table 3). The most frequently observed TRAEs were rash and other skin conditions, including fissures, dermatitis, and paronychia. Other frequently observed TRAEs included diarrhea, mucositis, nausea, vomiting, fatigue, and headache. No grade 4 or 5 TRAEs were observed. Nine (41%) patients required at least one dose reduction, with seven requiring at least two reductions. Three of the four patients enrolled in DL4 had dose reductions, and levels of both drugs were reduced. Three of the eight patients enrolled in dose expansion required dose reductions, with two requiring two dose reductions. The other three patients with dose reductions were enrolled in DL2 (n = 2) and DL3 (n = 1). Seven (32%) patients had at least one dose interruption. Two patients discontinued treatment due to a TRAE. One patient, who was on therapy for 6 months, discontinued study treatment due to grade 2 rash that persisted at 30 days after treatment interruption. The other patient withdrew from the study due to grade 2 fatigue and vomiting after approximately 3 months of treatment. The only treatment-related serious adverse event was in a patient enrolled in dose expansion who required hospitalization after experiencing grade 3 ventricular tachycardia that was related to necitumumab and grade 3 ventricular arrhythmia that was related to both afatinib and necitumumab.

Preliminary Efficacy

No participants enrolled on this trial had a complete or partial response (objective response rate = 0%). Eight had stable disease for a DCR of 36% (eight of 22; 95% CI: 0.18–0.59). Fourteen were categorized as having progressive disease (PD) as best response including three participants not represented in Figure 1: two with clinical progression and one who died, each before the first post-baseline imaging response assessment (Fig. 1). The median PFS was 1.8 months (95% CI: 1.8–3.9), and the median OS was 9.8 months (95% CI: 7.2–not available).

In the subgroup of patients who were T790M negative and progressed on a first-generation TKI (n = 4; two treated at MTD), all had disease control with a median duration of treatment of 3.6 (range 3.2–5.5) months, suggesting there may be a role for dual EGFR inhibition in this patient population. In the subgroup of patients who had progressed on first-line osimertinib (n = 5; all treated at the MTD), three had best response of PD radiographically and one each clinically progressed and died, respectively, before repeat post-baseline imaging assessment. The patient who died before cycle 2 was hospitalized due to an infection that was unrelated to the study treatment. In the subgroup of patients that progressed on subsequent-line osimertinib (n = 13), DCR was 31% (four of 13; 95% CI: 0.1–0.61) with all patients experiencing stable disease treated at either the MTD (n = 2) or DL4 (n = 2; higher than MTD) for a median duration of treatment lasting 4.6 (range 3.7–5.5) months. Of note, an analysis of best response according to time from last EGFR TKI therapy revealed no association, suggesting that resensitization to EGFR-directed therapy after a period of intervening chemotherapy did not account for some patients having stable versus progressive disease (data not shown).

Table 3. Most Frequently (>10%) Observed Treatment-Related AEs

Toxicity	Grade 1	Grade 2	Grade 3[a]	Total[b]
Rash	9 (41)	3 (13.7)	3 (13.7)	15 (68.2)
Diarrhea	6 (27.3)	3 (13.7)	1 (4.6)	10 (45.5)
Other skin or subcutaneous tissue disorder[c]	5 (22.8)	3 (13.7)	0 (0)	8 (36.4)
Vomiting	5 (22.8)	2 (9.1)	0 (0)	7 (31.9)
Fatigue	5 (22.8)	1 (4.6)	0 (0)	6 (27.3)
Headache	4 (18.2)	1 (4.6)	1 (4.6)	6 (27.3)
Mucositis oral	5 (22.8)	0 (0)	1 (4.6)	6 (27.3)
Nausea	3 (13.7)	3 (13.7)	0 (0)	6 (27.3)
Paronychia	8 (36.4)	0 (0)	0 (0)	8 (36.4)
Dry skin	3 (13.7)	2 (9.1)	0 (0)	5 (22.8)
Fever	4 (18.2)	0 (0)	0 (0)	4 (18.2)
Pruritus	2 (9.1)	1 (4.6)	0 (0)	3 (13.7)

Note: All values are n (%).
[a]Other grade 3 AEs: ventricular arrhythmia and ventricular tachycardia.
[b]Highest grade per toxicity per patient is listed; no grade 4 or 5 treatment-related AEs observed.
[c]Other skin or subcutaneous tissue disorders beyond the terms rash, paronychia, dry skin, and pruritus: skin fissures, peeling hands, dermatitis, erythema, xerosis, cracking of the skin, and scalp tenderness.
AE, adverse event.

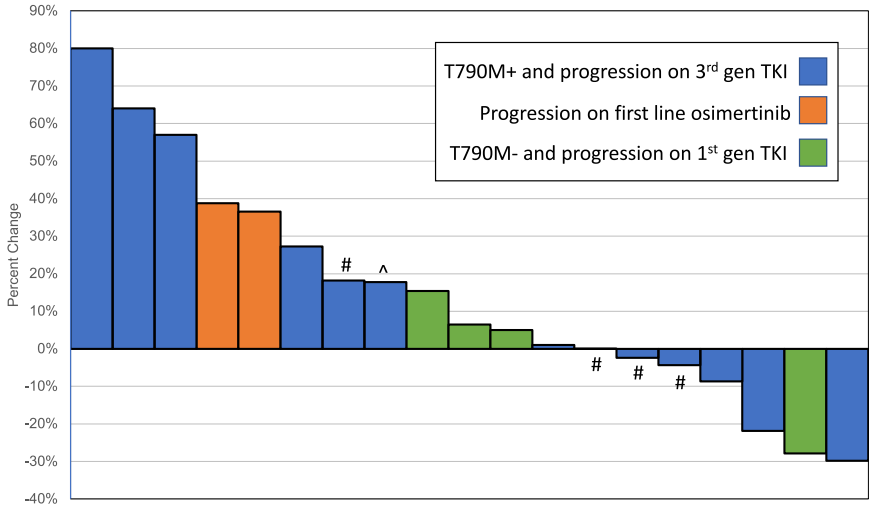

Figure 1. Waterfall plot depicting best response in target lesion sum of diameters categorized by subgroup. Three patients are not found in the figure: two patients (n = 1, progression on first-line osimertinib; n = 1, progression on subsequent-line osimertinib) had clinical progression before the first post-baseline response assessment and one patient (progression on first-line osimertinib) died before the first post-baseline response assessment. ^Site recorded clinical progression as off-treatment reason. #Best response of progressive disease due to development of new nontarget lesions that were not present at baseline. gen, generation; TKI, tyrosine kinase inhibitor.

Discussion

In this phase 1 trial, afatinib plus necitumumab had limited activity in patients with *EGFR*-mutated NSCLC after progression on first-line first-generation EGFR TKI with T790M-negative disease or first- or subsequent-line third-generation EGFR TKI. Although the number of patients in each subgroup was small, stable disease was only observed among patients who had progressed on either subsequent-line osimertinib that was prescribed in the context of T790M-positive NSCLC (four of 13 patients) or first-generation EGFR TKI with T790M-negative NSCLC (four of four patients). Nevertheless, all patients who had received osimertinib for EGFR TKI-naive, metastatic, *EGFR*-mutated NSCLC had primary progression on afatinib plus necitumumab, suggesting a limited role for this combination in the current treatment era.

The MTD for the treatment combination was afatinib 40 mg daily plus necitumumab 600 mg on days 1 and 15 every 28 days (DL3). Further dose escalation was limited, as two DLTs were noted at DL4 of grade 3 rash and diarrhea, both of which are well-described toxicities of EGFR-directed therapies.[24] At the MTD, grade 3 rash and diarrhea were not observed in any patients, whereas grade 4 and 5 toxicities were not found at any DL, suggesting that the therapy combination was safe. Nevertheless, despite most toxicities being limited to grades 1 to 2, dose reductions (41%) and dose interruptions (32%) were common, suggesting the potential for increased symptom burden. Overall, the range of side effects was similar to that described in afatinib plus cetuximab clinical trial, with dose reductions required for 36% of patients and common toxicities of all-grade diarrhea (71%) and grade 3 rash (20%).[21]

The lack of responses and median PFS of 1.8 months of afatinib plus necitumumab in our trial were lower than those reported in several previous studies of EGFR TKI–antibody combinations. It is important to note the precise EGFR TKI generation-antibody combination, previous type and line of therapy, and available data from any molecular testing that preceded study treatment to interpret the results relative to our study. Most notably, a phase 1 study from Janjigian et al.[21] reported a response rate of 29% and a median PFS of 4.7 months in 126 patients with *EGFR*-mutated NSCLC who received second-generation afatinib plus cetuximab after disease progression on first-generation erlotinib or gefitinib, with activity noted irrespective of T790M resistance status. Another phase 1,2 trial evaluated 19 patients with progression after first-generation EGFR TKI (nine known T790M positive and three known T790M negative) using combination of erlotinib plus cetuximab with zero responses.[11] Another phase 1 trial from Riess et al.[25] evaluated third-generation osimertinib plus necitumumab across multiple cohorts of patients with metastatic *EGFR*-mutated NSCLC. Among 18 participants with T790M-negative disease after first- or second-generation EGFR TKI therapy, the response rate to osimertinib plus necitumumab was 22% with median PFS of 3.9 months.[25] In 18 patients who received first-line osimertinib, next-line osimertinib plus necitumumab resulted in a response rate of 22%, although the median PFS was limited at 2.3 months.[25]

The heterogeneity of our study cohort and the small number of patients enrolled may account in part for the lack of responses found. Most notably, our trial of afatinib plus necitumumab included 23% of patients who had received osimertinib in the first-line setting whereas the study of afatinib plus cetuximab enrolled only patients with disease progression on first-line erlotinib or gefitinib.[21] Although in our study there was a proportion of disease control observed in patients with progression on subsequent-line osimertinib (in the context of T790M-positive disease) or first-line erlotinib or gefitinib with T790M-negative disease, nearly all patients previously treated with first-line osimertinib had PD as best response to afatinib plus necitumumab. It is known that *EGFR*-mutated lung cancer exposed to first-generation TKI therapies may maintain greater ongoing dependence on EGFR signaling in the post-progression setting, with approximately 50% acquiring a second-site T790M resistance mutation in *EGFR*.[5] Nevertheless, secondary *EGFR* mutations when osimertinib is used both as first-line and subsequent-line therapy are observed less frequently.[8,10,12] In patients with T790M mutations receiving second-line osimertinib on the AURA3 trial, for example, the incidence of acquired *EGFR* mutations at the time of progression was only 22%, including 18% with C797X mutations.[10] In the FLAURA trial of first-line osimertinib, only 10% developed acquired *EGFR* mutations at the time of progression, including 6% with C797S mutations.[12] Furthermore, the incidence of *EGFR* C797X mutations seems to differ in patients receiving second-line osimertinib depending on whether the T790M mutation is retained or lost at the time of progression.[9] Although these factors could potentially account for the results in our study, biomarker assessment is limited given that repeat molecular testing for the continued retention of T790M and presence or absence of other secondary *EGFR* mutations was not collected immediately before study therapy.

The findings of this study are consistent with real-world analyses that have revealed limited activity for afatinib with or without EGFR antibody therapy in the post-osimertinib setting. In a single-center retrospective study of 15 patients with metastatic, *EGFR*-mutated NSCLC receiving afatinib after previous osimertinib in the first- or subsequent-line setting, the response rate and median PFS were 6.7% and 2.5 months, respectively.[26] Those patients who received afatinib in combination with cetuximab had similar outcomes compared with the overall cohort, with a median PFS of 1.9 months.[26] A study of dacomitinib, another second-generation TKI that irreversibly inhibits pan-ERBB receptors, similarly reported minimal activity after progression on first-line osimertinib with a response rate of 17% and a median PFS of 1.8 months.[27] In addition, although EGFR monoclonal antibody therapy in combination with TKI therapy may increase inhibition of EGFR in vivo, an additive or synergistic effect has not been found clinically.[28,29] In the SWOG S1403 trial, for example, patients with treatment-naive, *EGFR*-mutated NSCLC who were randomized to receive afatinib alone versus afatinib plus cetuximab had similar response rates (74% versus 67%; $p = 0.38$) and median PFS (13.4 versus 11.9 mo; $p = 0.94$).[28] This suggests that dual inhibition of EGFR is not by itself sufficient to lead to deeper or durable responses in *EGFR*-mutated NSCLC. In addition, the emerging efficacy of alternative therapies such as bispecific EGFR and MET antibody amivantamab plus lazertinib or HER3 antibody–drug conjugate patritumumab deruxtecan suggests that targeting other receptor kinases such as MET or HER3 may be a more effective approach than dual targeting of EGFR alone in an unselected post-TKI setting.[30,31]

The limited efficacy of afatinib plus necitumumab in our study suggests that this combination does not have a role in clinical practice. Nevertheless, further study of other EGFR TKI–antibody combinations or particular patient subgroups may be warranted to determine if a role can be defined. First, osimertinib compared with afatinib more effectively inhibits tumor growth in vivo and may be a preferred TKI partner in combination with monoclonal antibodies.[32] Second, although efficacy was overall low, the different rates of disease control of afatinib plus necitumumab between the three cohorts in this study may be due to differing resistance patterns that were not interrogated before the study treatment. In addition to on-target *EGFR* resistance, EGFR expression and *EGFR* copy number have been suggested to be predictive biomarkers in patients with unselected NSCLC receiving EGFR antibodies with chemotherapy, although results have been mixed overall.[33–35] Finally, afatinib has been studied in NSCLC harboring atypical *EGFR* mutations such as G719X and therefore may be better suited for this patient subgroup.[19] Nevertheless, only one patient in this study had a G719X mutation, whereas all others harbored exon 19 deletion or L858R mutations. Therefore, conclusions cannot be made regarding the activity of this treatment combination for atypical *EGFR* mutations.

Overall, the results of this phase 1 trial do not support further analysis of afatinib plus necitumumab in unselected *EGFR*-mutated NSCLC after TKI therapy. As we now understand that mechanisms of resistance to EGFR TKI therapy are heterogeneous, future studies of EGFR TKI–antibody combinations should focus on identifying resistance patterns or biomarkers that predict greater likelihood of response to combination therapy.

CRediT Authorship Contribution Statement

Nathaniel J. Myall: Investigation, Data curation, Formal analysis, Writing – original draft, Review, and Editing.

Jennifer G. Whisenant: Data curation, Formal analysis, Writing – original draft, Review, and Editing.

Joel W. Neal: Investigation, Writing – review and editing.

Wade T. Iams: Investigation, Writing – review and editing.

Karen L. Reckamp: Investigation, Writing – review and editing.

Sally York: Investigation, Writing – review and editing.

Lynne D. Berry: Methodology, Formal analysis, Writing – review and editing.

Yu Shyr: Supervision, Methodology, Writing – review and editing.

Leora Horn: Conceptualization, Funding acquisition, Investigation, Project administration, Writing – review and editing.

Heather A. Wakelee: Conceptualization, Investigation, Writing – review and editing.

Sukhmani K. Padda: Investigation, Project administration, Data curation, Formal analysis, Writing – Original draft, Review, and Editing.

Disclosure

Dr. Neal reports receiving research support to institution from Genentech/Roche, Merck, Novartis, Boehringer Ingelheim, Exelixis, Nektar Therapeutics, Takeda Pharmaceuticals, Adaptimmune, GlaxoSmithKline, Janssen, AbbVie, and Novocure; receiving royalty payments from UpToDate; serving as a consultant for AstraZeneca, Genentech/Roche, Exelixis, Takeda Pharmaceuticals, Eli Lilly and Company, Amgen, Iovance Biotherapeutics, Blueprint Pharmaceuticals, Natera, Sanofi/Regeneron, D2G Oncology, Surface Oncology, Turning Point Therapeutics, Mirati Therapeutics, Gilead Sciences, AbbVie, Summit Therapeutics, Novartis, Novocure, Janssen Oncology, Anheart Therapeutics, and Bristol Myers Squibb; and receiving honoraria from CME Matters, Clinical Care Options, Research to Practice, Medscape, Biomedical Learning Institute, MLI PeerView, Prime Oncology, Projects in Knowledge, Rockpointe, MJH Life Sciences, Medical Educator Consortium, and HMP Education. Dr. Iams reports serving as a consultant for AstraZeneca, Sanofi, Genentech, Jazz Pharma, G1 Therapeutics, Mirati, Takeda, Janssen, Amgen, Bristol Myers Squibb, OncLive, Clinical Care Options, Chardan, Outcomes Insights, Cello Health, and Curio Science; Dr. Iams is an employee of Tennessee Oncology at the time of publication Dr. Reckamp reports serving as a consultant with honoraria to self for Amgen, AstraZeneca, Blueprint, Daiichi Sankyo, EMD Serono, Genentech, GlaxoSmithKline, Janssen, Eli Lilly, Novartis, and Mirati; receiving research funding to institution from Genentech, Blueprint, Calithera, Daiichi Sankyo, Elevation Oncology, and Janssen. Dr. Horn is an AstraZeneca employee; was a faculty member at Vanderbilt during the study. Dr. Wakelee reports serving as an advisory board participant for IOBiotech (September 2023), Mirati (ended December 2022), OncoC4 (April 2024–ongoing), Beigene (April 2024); serving as an unpaid consultant for Bristol Myers Squibb (October 2024), Genentech/Roche (ongoing), Merck (ongoing), and AstraZeneca (ongoing); receiving clinical trial support provided to institution from AstraZeneca /Medimmune, Bayer, Bristol Myers Squibb, Genentech/Roche, Helsinn, Merck, SeaGen, and Xcovery. Dr. Padda reports serving on the advisory board or as a consultant for Takeda, AstraZeneca, Bayer, Amgen, Sanofi Genzyme, Rayze Biotech, Mirati, Janssen, Regeneron, Jazz Pharma, Genentech, Nanobiotix, Jazz Pharma (to 2021), before 2021, G1 Therapeutic, Blueprint, Pfizer, and AbbVie; receiving CME support from PER, Curio Science LLC, MECC Global Meetings, and CME Solutions; and receiving research support provided to institution from EpicentRx, Bayer, Boehringer Ingelheim, Bioalta, Takeda, and Amgen. The remaining authors declare no conflict of interest.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2024.100757.

References

1. Shigematsu H, Lin L, Takahashi T, et al. Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. *J Natl Cancer Inst*. 2005;97:339–346.

2. Aisner DL, Sholl LM, Berry LD, et al. The impact of smoking and TP53 mutations in lung adenocarcinoma patients with targetable mutations-the lung cancer mutation consortium (LCMC2). *Clin Cancer Res*. 2018;24:1038–1047.
3. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med*. 2018;378:113–125.
4. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. *N Engl J Med*. 2020;382:41–50.
5. Sequist LV, Waltman BA, Dias-Santagata D, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci Transl Med*. 2011;3:75ra26.
6. Kobayashi S, Boggon TJ, Dayaram T, et al. EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. *N Engl J Med*. 2005;352:786–792.
7. Cross DA, Ashton SE, Ghiorghiu S, et al. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. *Cancer Discov*. 2014;4:1046–1061.
8. Leonetti A, Sharma S, Minari R, Perego P, Giovannetti E, Tiseo M. Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer. *Br J Cancer*. 2019;121:725–737.
9. Oxnard GR, Hu Y, Mileham KF, et al. Assessment of resistance mechanisms and clinical implications in patients with EGFR T790M-positive lung cancer and acquired resistance to osimertinib. *JAMA Oncol*. 2018;4:1527–1534.
10. Chmielecki J, Mok T, Wu YL, et al. Analysis of acquired resistance mechanisms to osimertinib in patients with EGFR-mutated advanced non-small cell lung cancer from the AURA3 trial. *Nat Commun*. 2023;14:1071.
11. Janjigian YY, Azzoli CG, Krug LM, et al. Phase I/II trial of cetuximab and erlotinib in patients with lung adenocarcinoma and acquired resistance to erlotinib. *Clin Cancer Res*. 2011;17:2521–2527.
12. Chmielecki J, Gray JE, Cheng Y, et al. Candidate mechanisms of acquired resistance to first-line osimertinib in EGFR-mutated advanced non-small cell lung cancer. *Nat Commun*. 2023;14:1070.
13. Uchibori K, Inase N, Araki M, et al. Brigatinib combined with anti-EGFR antibody overcomes osimertinib resistance in EGFR-mutated non-small-cell lung cancer. *Nat Commun*. 2017;8:14768.
14. Wang Y, Yang N, Zhang Y, et al. Effective treatment of lung adenocarcinoma harboring EGFR-activating mutation, T790M, and cis-C797S triple mutations by brigatinib and cetuximab combination therapy. *J Thorac Oncol*. 2020;15:1369–1375.
15. Herbst RS, Shin DM. Monoclonal antibodies to target epidermal growth factor receptor-positive tumors: a new paradigm for cancer therapy. *Cancer*. 2002;94:1593–1611.
16. Neal JW, Heist RS, Fidias P, et al. Cetuximab monotherapy in patients with advanced non-small cell lung cancer after prior epidermal growth factor receptor tyrosine kinase inhibitor therapy. *J Thorac Oncol*. 2010;5:1855–1858.
17. Li D, Ambrogio L, Shimamura T, et al. BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. *Oncogene*. 2008;27:4702–4711.
18. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol*. 2013;31:3327–3334.
19. Yang JC, Sequist LV, Geater SL, et al. Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. *Lancet Oncol*. 2015;16:830–838.
20. Regales L, Gong Y, Shen R, et al. Dual targeting of EGFR can overcome a major drug resistance mutation in mouse models of EGFR mutant lung cancer. *J Clin Invest*. 2009;119:3000–3010.
21. Janjigian YY, Smit EF, Groen HJ, et al. Dual inhibition of EGFR with afatinib and cetuximab in kinase inhibitor-resistant EGFR-mutant lung cancer with and without T790M mutations. *Cancer Discov*. 2014;4:1036–1045.
22. Kuenen B, Witteveen PO, Ruijter R, et al. A phase I pharmacologic study of necitumumab (IMC-11F8), a fully human IgG1 monoclonal antibody directed against EGFR in patients with advanced solid malignancies. *Clin Cancer Res*. 2010;16:1915–1923.
23. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline, version 1.1. *Eur J Cancer*. 2009;45:228–247.
24. Ding PN, Lord SJ, Gebski V, et al. Risk of treatment-related toxicities from EGFR tyrosine kinase inhibitors: a meta-analysis of clinical trials of gefitinib, erlotinib, and afatinib in advanced EGFR-mutated non-small cell lung cancer. *J Thorac Oncol*. 2017;12:633–643.
25. Riess JW, Krailo MD, Padda SK, et al. Osimertinib plus necitumumab in EGFR-mutant NSCLC: final results from an ETCTN California Cancer Consortium phase I study. *J Clin Oncol*. 2022;40:9014–9014.
26. Aredo JV, Wakelee HA, Neal JW, Padda SK. Afatinib after progression on osimertinib in EGFR-mutated non-small cell lung cancer. *Cancer Treat Res Commun*. 2022;30:100497.
27. Choudhury NJ, Makhnin A, Tobi YY, et al. Pilot study of dacomitinib for patients with metastatic EGFR-mutant lung cancers with disease progression after initial treatment with osimertinib. *JCO Precis Oncol*. 2021;5. PO.21.00005.
28. Goldberg SB, Redman MW, Lilenbaum R, et al. Randomized trial of afatinib plus cetuximab versus afatinib alone for first-line treatment of EGFR-mutant non-small-cell lung cancer: final results from SWOG S1403. *J Clin Oncol*. 2020;38:4076–4085.
29. Cortot AB, Madroszyk A, Giroux-Leprieur E, et al. First-line afatinib plus cetuximab for EGFR-mutant non-small cell lung cancer: results from the randomized Phase II IFCT-1503 ACE-lung study. *Clin Cancer Res*. 2021;27:4168–4176.
30. Bauml J, Cho BC, Park K, et al. Amivantamab in combination with lazertinib for the treatment of osimertinib-relapsed, chemotherapy-naïve EGFR mutant (EGFRm) non-small cell lung cancer (NSCLC) and potential biomarkers for response. *J Clin Oncol*. 2021;39(suppl 15): 9006–9006.

31. Janne PA, Baik C, Su WC, et al. Efficacy and safety of patritumab deruxtecan (HER3-DXd) in EGFR inhibitor-resistant, EGFR-mutated non-small cell lung cancer. *Cancer Discov*. 2022;12:74–89.
32. Finlay MR, Anderton M, Ashton S, et al. Discovery of a potent and selective EGFR inhibitor (AZD9291) of both sensitizing and T790M resistance mutations that spares the wild type form of the receptor. *J Med Chem*. 2014;57:8249–8267.
33. Hirsch FR, Herbst RS, Olsen C, et al. Increased EGFR gene copy number detected by fluorescent in situ hybridization predicts outcome in non-small-cell lung cancer patients treated with cetuximab and chemotherapy. *J Clin Oncol*. 2008;26:3351–3357.
34. O'Byrne KJ, Gatzemeier U, Bondarenko I, et al. Molecular biomarkers in non-small-cell lung cancer: a retrospective analysis of data from the phase 3 FLEX study. *Lancet Oncol*. 2011;12:795–805.
35. Pirker R, Pereira JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. *Lancet*. 2009;373:1525–1531.