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**

EGFR-mutant lung cancers responsive to reversible EGFR inhibitors (gefitinib/erlotinib) develop acquired resistance, mediated by second-site EGFR T790M mutation in >50% of 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), and the 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.

**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. Cancer Discov; 4(9); 1–10. ©2014 AACR.

**INTRODUCTION**

Lung cancers with activating EGFR mutations (e.g., exon 19 deletions, L858R) are sensitive to the small-molecule EGFR tyrosine kinase inhibitors (TKI) 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% to 10% of patients display MET amplification (12, 13), with or without T790M mutations (14). Efforts to overcome acquired resistance in the clinic using 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 one or two lines of previous chemotherapy and acquired resistance to gefitinib/erlotinib, median PFS was three times longer in the afatinib-treated group than in the placebo-treated group (3.3 months with afatinib vs. 1.1 months with placebo; $P < 0.0001$). 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 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 seemed to tolerate the regimen without difficulty. On the basis of these preclinical observations, we conducted a study to determine...

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**Note:** Supplementary data for this article are available at Cancer Discovery Online (http://cancerdiscovery.aacrjournals.org/).

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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 colorectal cancer indicated that biweekly cetuximab was a convenient, effective, and well-tolerated regimen (25, 26). On the basis of this evidence, we selected the biweekly dosing regimen for cetuximab, with no expectation of differences in toxicity between weekly and biweekly 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/m² intravenously every 2 weeks). Efficacy and safety outcomes in these patients are reported.

RESULTS

Patients and Treatment

Between March 2010 and April 2013, a total of 201 patients were enrolled into the three phases of the trial (Fig. 1). Overall, the trial enrolled patients across a total of 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 (40 mg oral daily) plus cetuximab (500 mg/m² 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–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 two or more lines of prior chemotherapy. Patients had been treated with an EGFR TKI for a median of 1 year (range, 1 month–7 years) before 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 (27).

Efficacy

Of the 126 patients treated with the MTD of afatinib and cetuximab, 37 (29%) had a confirmed OR [all partial responses (PR); 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% confidence interval, 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 toward improved OR rate with respect to the 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 complete response (CR), PR, or stable disease (SD), respectively, on a prior EGFR TKI. The overall median duration of confirmed OR was 5.7 months (range, 1.8–24.4), which included two patients with notably longer duration of OR than the rest of the population. Patients with T790M-positive and T790M-negative
tumors had median durations of confirmed OR of 5.6 months (range, 1.8–24.4; 8 patients censored without further imaging) and 9.5 months (range, 2.9–24.4; 2 patients censored without further imaging), 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; \( P = 0.643 \)). The 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 (18.3%) were alive and without progressive disease (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 anticancer 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, <1–29.1). 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 because of treatment-related adverse events (dyspnea and pneumonitis). Adverse events of any causality were experienced by all patients (Supplementary Table S1).

Serious adverse events related to treatment were reported in 14% of patients (Supplementary Table S2). 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, 1–14.1). The median duration of treatment following a first-dose reduction was 4.4 months (range, <1–25.6).

### 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 a median duration of response of 5.7 months, is particularly meaningful considering the majority of patients were heavily pretreated; that is, 52% had failed two or more lines of standard cytotoxic chemotherapy in addition to a reversible EGFR TKI before 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...
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. Tumor tissue from 2 patients was uninformative as to T790M status. SLD, sum of the longest diameter.

Table 2. Confirmed response per RECIST tumor assessments for all patients and by mutation status: concurrent regimen

<table>
<thead>
<tr>
<th>Cohort</th>
<th>All patients</th>
<th>T790M</th>
<th>T790M</th>
<th>Del 19</th>
<th>L858R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total treated</td>
<td>126</td>
<td>71</td>
<td>53</td>
<td>78</td>
<td>41</td>
</tr>
<tr>
<td>RECIST response</td>
<td>89</td>
<td>54</td>
<td>33</td>
<td>48</td>
<td>34</td>
</tr>
<tr>
<td>OR (CR/PR)</td>
<td>37</td>
<td>23</td>
<td>13</td>
<td>23</td>
<td>14</td>
</tr>
<tr>
<td>SD</td>
<td>52</td>
<td>31</td>
<td>20</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>Unconfirmed OR</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>PD</td>
<td>27</td>
<td>14</td>
<td>13</td>
<td>23</td>
<td>4</td>
</tr>
<tr>
<td>CR/PR &lt;35 d followed by PD</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>SD &lt;35 d followed by PD</td>
<td>15</td>
<td>8</td>
<td>7</td>
<td>14</td>
<td>1</td>
</tr>
</tbody>
</table>

*Includes 2 patients for whom T790M status was unknown due to tissue samples insufficient for testing.
†Available for 124 of 126 treated patients.
‡All ORs were PRs; no CRs were observed.
Abbreviation: d, days.
**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 before 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 postprogression is indicated by an extended patient timeline in cross-hatched pale gray after the progression event. NA, not available; +, censored.

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**Dual EGFR Inhibition in TKI-Resistant, EGFR-Mutant NSCLC**

**Rebecca A. MacDonald, Emanuele Petruzzelli, Olga Rojas, et al.**

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of resistance to gefitinib/erlotinib (e.g., PIK3CA mutation, BRAF mutation, FGFR activation, AXL upregulation, small-cell lung cancer transformation, and epithelial–mesenchymal transition; 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, 30). 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 (31, 32). Of note, no ORs were observed in trials of cetuximab in combination with erlotinib or gefitinib in patients with acquired resistance (33, 34). 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 alone is insufficient to inhibit the ligand-independent activity of the mutant receptors. The kinase inhibitor (afatinib) blocks tyrosine kinase activity of these receptors and resulting in reduced but incomplete inhibition of autophosphorylation and transphosphorylation of ErbB receptor dimers. 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, because afatinib plus panitumumab (anti-EGFR antibody IgG4 that cannot mediate antibody-dependent cellular cytotoxicity) is also effective against T790M-driven tumors (29), 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 (35), XL-647 (36), everolimus plus erlotinib (37), and dasatinib plus erlotinib (38) 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 (39, 40). These TKIs specifically inhibit mutant EGFRs, including T790M, sparing the wild-type receptor and thus limiting toxicity due to wild-type EGFR inhibition. Because these agents were designed to overcome T790M-mediated resistance, whether or not they will have activity comparable with afatinib and cetuximab in T790M-negative cases remains to be seen. As these patients continue to experience extended survival, incorporation of multiple lines of EGFR-directed therapies would likely increase in frequency. As an example, a patient with EGFR-mutant lung

### Table 3. Drug-related adverse events occurring in >20% of patients by grouped and preferred term and by highest CTCAE grade

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

*Grouped terms.

Abbreviation: CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.
cancer may receive erlotinib, gefitinib, or afatinib as first-line therapy followed by afatinib or afatinib plus cetuximab, or, once approved, a third-generation TKI. Whether acquired resistance will be more aggressive and amenable or refractory to targeted therapies if patients eventually receive a third-generation TKI in the first- or second-line setting 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, two randomized trials are planned to evaluate this combination in EGFR-mutant NSCLC. The first intends to enroll TKI-naive patients, whereas the second will study patients with acquired resistance but only one 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.

**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. 41); 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 use of EGFR-directed therapy. Molecular correlative studies are ongoing to determine which tumors are most sensitive to dual inhibition of EGFR.

**EGFR-Mutation Assessment**

Fresh or archived tumor tissues, after disease progression on erlotinib or gefitinib within the 30 days and before study start, were required for EGFR-mutation analysis. All patients (except those enrolled in only 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 gefitinib/erlotinib.

**Study Design and Cohort Expansion**

This was a phase Ib, open-label, uncontrolled, multicenter study comprising three 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, whereas cetuximab was administered intravenously. Initially, 10 patients were enrolled in the dose-finding phase: 4 patients received 40 mg of afatinib daily plus 250 mg/m² of cetuximab every 2 weeks, and 6 received the specified maximum dose of 40 mg of afatinib daily plus 500 mg/m² of cetuximab every 2 weeks. The MTD was rapidly identified as 40 mg of afatinib daily plus 500 mg/m² of cetuximab every 2 weeks. On the basis of 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 of the 2 arms) with 95% confidence. The dose-finding and sequential therapy phases will be reported subsequently in a separate article.

**Tumor Assessments**

Tumor assessments took place at weeks 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 SD in 6 to 8 weeks (43).

**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 one 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 variance estimate was used to form 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 article, with editorial support provided by a medical writer and funded by the sponsor.

**Disclosure of Potential Conflicts of Interest**

L. Horn is a consultant/advisory board member for Boehringer Ingelheim. G.J. Riely reports receiving commercial research grants from Novartis, Roche, Infinity, Pfizer, Millennium, and GlaxoSmithKline and is a consultant/advisory board member for Ariad, Merusana, Foundation Medicine, Abbott Molecular, and Celgene. V.A. Miller is CMO at Foundation Medicine and has ownership interest in Foundation Medicine and a T790M patent. W. Pao reports receiving a commercial research grant from Boehringer Ingelheim and has ownership interest in MolecularMD. No potential conflicts of interest were disclosed by the other authors.

**Disclaimer**

The authors were fully responsible for all content and editorial decisions and were involved at all stages of manuscript development and have approved the final version.

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**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** Y.Y. Janjigian, E.F. Smit, H.J.M. Groen, L. Horn, S.Gettinger, D.R. Camidge, G.J. Riely, Y. Fu, V.A. Miller, W. Pao

**Analysis and interpretation of data (e.g., statistical analysis, bioostatistics, computational analysis):** Y.Y. Janjigian, E.F. Smit, H.J.M. Groen, S. Gettinger, D.R. Camidge, G.J. Riely, B. Wang, Y. Fu, V.K. Chand, V.A. Miller, W. Pao

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**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** B. Wang, W. Pao

**Study supervision:** Y.Y. Janjigian, E.F. Smit, H.J.M. Groen, L. Horn, S. Gettinger, D.R. Camidge, G.J. Riely, Y. Fu, V.K. Chand, V.A. Miller, W. Pao

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**REFERENCES**


Dual EGFR Inhibition in TKI-Resistant, EGFR-Mutant NSCLC

RESEARCH ARTICLE


Dual Inhibition of EGFR with Afatinib and Cetuximab in Kinase Inhibitor-Resistant \textit{EGFR}-Mutant Lung Cancer with and without T790M Mutations


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