Bevacizumab and Erlotinib: A Promising New Approach to the Treatment of Advanced NSCLC

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ABSTRACT

Biologic agents that target molecules involved in tumor growth, progression, and pathological angiogenesis—such as the human epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF)—have demonstrated efficacy in patients with non-small cell lung cancer (NSCLC). Erlotinib (Tarceva®; OSI Pharmaceuticals, Inc., Melville, NY, Genentech, Inc., South San Francisco, CA, and F. Hoffmann-La Roche Ltd, Basel, Switzerland), a highly selective tyrosine kinase inhibitor that inhibits EGFR, and bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA, and F. Hoffmann-La Roche Ltd, Basel, Switzerland), a VEGF-targeted recombinant humanized monoclonal antibody, have displayed very encouraging activity in a randomized phase II trial in patients with previously treated NSCLC. Because erlotinib and bevacizumab act on two different pathways critical to tumor growth and dissemination, administering these drugs concomitantly may confer additional clinical benefits to cancer patients with advanced disease, by virtue of their complementary (or additive) antitumor activity. The combination of bevacizumab plus erlotinib may prove to be a viable second-line alternative to chemotherapy or erlotinib monotherapy in patients with NSCLC. The benefits of the combination may be further enhanced by selecting for patients who are likely to respond to this therapy. While a number of potential predictive markers have been identified for erlotinib, their value remains to be confirmed in prospective trials. In addition, the application of such personalized therapy will also depend on the availability of validated screening methods. The Oncologist 2008;13:000–000
INTRODUCTION

Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all cases of lung cancer [1], and >60% of patients with NSCLC present with locally advanced or metastatic (stage III/IV) disease at initial diagnosis [2].

Historically, first-line treatment for patients with advanced NSCLC has been platinum-based doublet chemotherapy, in combination with a third-generation cytotoxic compound such as gemcitabine (Gemzar®; Eli Lilly and Company, Indianapolis, IN), paclitaxel (Taxol®; Bristol-Myers Squibb, Princeton, NJ), or docetaxel (Taxotere®; Sanofi-Aventis, Bridgewater, NJ) [3]. Clinical trials of a platinum in combination with any of these agents demonstrated comparable efficacy, and meta-analyses showed that these regimens offered superior survival and symptom palliation versus best supportive care (BSC) [4–6]. However, response to first-line chemotherapy is generally short lived, with progression occurring, on average, 4–6 months after treatment is discontinued [7] and a median survival duration of only 8–11 months [8]. The benefit of these first-line chemotherapy regimens for patients with advanced NSCLC would therefore appear to have reached a plateau, and more effective treatments are clearly needed.

Second-line treatment for advanced NSCLC is traditionally single-agent chemotherapy based, with both docetaxel and pemetrexed (Alimta®; Eli Lilly and Company, Indianapolis, IN) approved in this setting [9, 10]. However, biologic agents that target molecules involved in tumor growth and progression represent a promising new therapeutic alternative to chemotherapy for advanced NSCLC treatment [11]. In particular, agents that target the human epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) have demonstrated efficacy in patients with NSCLC as first- and/or second-line therapies [12, 13].

The clinical practice guidelines from the National Comprehensive Cancer Network now recommend that bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA, and F. Hoffmann-La Roche Ltd, Basel, Switzerland), a VEGF-targeted monoclonal antibody, be given in combination with carboplatin and paclitaxel as first-line therapy for patients with nonsquamous advanced NSCLC, and erlotinib (Tarceva®; OSI Pharmaceuticals, Inc., Melville, NY, Genentech, Inc., South San Francisco, CA, and F. Hoffmann-La Roche Ltd, Basel, Switzerland), an EGFR inhibitor, is recommended as a second-line option for these patients [3].

Recently, the combination of erlotinib and bevacizumab has displayed very encouraging activity in a randomized phase II trial in patients with previously treated NSCLC [14].

BEVACIZUMAB

VEGF is another key target for new antitumor therapies, because its expression is upregulated in a range of solid tumors [15]. VEGF is a major regulator of angiogenesis, the growth of new vessels from pre-existing vessels [16]. This process is fundamental to the growth of solid tumors, which rely on the formation of new blood vessels [17], and it plays a significant role in NSCLC; microvessel count is an independent predictor of poor prognosis in patients with NSCLC [18].

Unlike EGFR-targeted agents, which directly impact cell proliferation, VEGF receptor–targeted agents indirectly block tumor growth, through the inhibition of new vessel formation. The VEGF-targeted recombinant humanized monoclonal antibody bevacizumab has demonstrated efficacy in NSCLC [13]. Of the new biologics, bevacizumab is notable in showing clear therapeutic potential in combination with chemotherapy. This is in contrast to the findings of phase III trials of erlotinib and of gefitinib, with standard first-line chemotherapy, which failed to show superior survival compared with chemotherapy alone [19–22]. A phase II trial compared carboplatin (area under the concentration–time curve of 6) and paclitaxel (200 mg/m²), given every 3 weeks for six cycles, with carboplatin and paclitaxel followed by bevacizumab (7.5 or 15 mg/kg), given until disease progression, in patients with advanced or recurrent NSCLC. Compared with the control arm, treatment with carboplatin and paclitaxel plus bevacizumab (15 mg/kg) resulted in a higher response rate (31.5% versus 18.8%), longer median time to progression (TTP) (7.4 versus 4.2 months), and modestly longer survival time (17.7 versus 14.9 months). Bleeding (minor mucocutaneous hemorrhage or major hemoptysis) was the predominant adverse event (AE), occurring in six of 66 (9%) bevacizumab-treated patients (five of the six events were observed in the 7.5-mg/m² bevacizumab arm) [23]. Squamous cell histology was identified as a risk factor for pulmonary hemorrhage, leading to the exclusion of patients with squamous cell histology from future bevacizumab trials.

In a subsequent randomized phase III trial in 878 patients with stage IIIb/IV nonsquamous NSCLC [13], in which patients were treated with carboplatin and paclitaxel, with or without bevacizumab (15 mg/kg), every 3 weeks for up to six cycles, followed by bevacizumab until disease progression, the median survival time in the chemotherapy plus bevacizumab arm was 12.3 months, versus 10.3 months in the chemotherapy-alone group (hazard ratio [HR] for death, 0.79; \( p = .003 \)). The median progression-free survival (PFS) times in the two groups were 6.2 and 4.5 months, respectively (HR for disease progression, 0.66; \( p < .001 \)), with corresponding response rates of 35% and
15% ($p < .001$). Rates of clinically significant bleeding were 4.4% and 0.7%, respectively ($p < .001$). Restricting the patient population to nonsquamous histology resulted in a lower incidence of grade $\geq 3$ pulmonary hemorrhage (1.9% in the bevacizumab arm).

Another phase III trial, enrolled outside the U.S., evaluated two different doses of bevacizumab (15 mg/kg or 7.5 mg/kg every 3 weeks until disease progression) in combination with gemcitabine and cisplatin in 1,043 patients with previously untreated, advanced nonsquamous NSCLC. That trial met its primary endpoint of a longer PFS duration, with the demonstration of a significantly longer PFS time in those patients randomized to receive bevacizumab therapy; the response rate, a secondary endpoint, was also significantly higher in patients randomized to the treatment arms compared with the control arm (PFS, 6.1, 6.7, and 6.5 months; response rate, 20%, 34%, and 30%, in the control, 7.5 mg/kg, and 15 mg/kg bevacizumab arms, respectively) [24]. That study also analyzed overall survival (OS) as a secondary endpoint. While the longer OS time, a secondary endpoint, with bevacizumab was not statistically significant compared with chemotherapy alone, the median survival time of patients in all arms of the study was $>13$ months, longer than the previously reported survival times of patients with advanced NSCLC [25]. It is likely that the unprecedented high use of multiple second-line therapies in this trial is the main reason why the PFS benefit did not translate into an OS benefit.

**ERLOTINIB**

One of the most promising targets for antineoplastic biologic agents is the EGFR, because it is dysregulated in many human tumors [26–28]. EGFR is a member of the human EGFR (HER) family, which consists of four known transmembrane receptors (EGFR, HER-2/neu, HER-3, and HER-4) [29]. Binding of an appropriate ligand, such as EGF, to EGFR results in receptor homo- or heterodimerization (either with another EGFR or with a member of the HER family), and the activation of intrinsic tyrosine kinase activity [30], which initiates downstream signaling pathways, including the mitogen-activated protein kinase and the phosphatidylinositol-3-OH kinase pathways [31].

Preclinical studies show that EGFR activation influences cell migration, proliferation, adhesion, invasion, angiogenesis, and inhibition of apoptosis [30, 32], and its overexpression has been correlated with disease progression, poor prognosis, and lower sensitivity to chemotherapy [33]. EGFR expression is a strong prognostic factor in bladder, ovarian, and cervical cancer [33]. Although this association with prognosis is less defined in NSCLC [33], 50%–90% of NSCLC tumors express high levels of EGFR [26, 34], and amplification and mutation of EGFR have been implicated as a major mechanism in the pathogenesis of lung tumors [35, 36].

A number of EGFR-targeted agents are in clinical development for NSCLC, including the monoclonal antibody cetuximab (Eributix®; ImClone Systems, Inc., New York) [37]. In a phase III study of patients with advanced NSCLC, cetuximab combined with vinorelbine plus cisplatin was reported to result in a longer OS time than with chemotherapy alone [38]. However, another phase III study demonstrated that a combination of cetuximab plus a taxane and carboplatin as first-line treatment of metastatic NSCLC did not produce a longer PFS duration [39]. Cetuximab monotherapy has also been investigated in relapsed disease, but with modest results [40]. It will be important to review the data when formally presented. Currently, the small-molecule EGFR tyrosine kinase inhibitors (TKIs) remain the most well studied for NSCLC.

Erlotinib is a highly selective TKI that is approved by the U.S. Food and Drug Administration and European regulators for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen [41, 42]. It is also approved in combination with gemcitabine for the first-line treatment of patients with locally advanced, unresectable, or metastatic pancreatic cancer [41, 42].

Another TKI, gefitinib (Iressa®; AstraZeneca Pharmaceuticals, Wilmington, DE), was also approved as a third-line option for patients with NSCLC. However, its approval was based on the results of a randomized phase II trial [43], and data from the phase III confirmatory trial failed to show a survival benefit [44]. The use of gefitinib is now restricted to patients currently or previously benefiting from it, and to patients enrolled in clinical studies in the U.S. [45], although it remains approved for the treatment of inoperable or recurrent NSCLC in Japan and several other Asian countries.

Two recent phase III studies have compared gefitinib with docetaxel in patients who have been previously treated for advanced NSCLC using an endpoint of noninferiority [46, 47]. The Japanese trial did not demonstrate noninferiority for gefitinib when compared with docetaxel based on OS [46]. Additionally, there was no significant difference between the treatments in OS and PFS. In contrast, the Iressa Non-small cell lung cancer Trial Evaluating Response and Survival against Taxotere (INTEREST trial) did demonstrate that gefitinib was noninferior to docetaxel with respect to OS [47].

Regulatory approval for erlotinib in NSCLC was granted based on the results of a randomized phase III trial (BR.21), in which 731 patients with advanced NSCLC were...
treated with erlotinib monotherapy or BSC [12]. Patient eligibility included two prior chemotherapy regimens or one prior platinum-based regimen in patients who were deemed unfit for second-line docetaxel. A significant survival benefit was observed versus BSC; the median OS times were 6.7 months and 4.7 months, respectively [12]. The survival advantage observed with second- or third-line erlotinib monotherapy in patients with advanced NSCLC would appear to compare favorably with those observed for both docetaxel and pemetrexed and the other chemotherapeutic options approved for second-line therapy (Table 1) [12, 48–50].

Although a direct comparison of erlotinib efficacy with that of docetaxel and pemetrexed will be possible only when data are available from comparative trials, the efficacy of erlotinib appears to be comparable to those of the cytotoxic chemotherapies. However, the different toxicity profiles associated with these agents should be taken into account. Whereas both docetaxel and pemetrexed are associated with hematological toxicity [9, 10], the most common AEs associated with erlotinib are rash and diarrhea, which are generally manageable [41, 51]. Such a favorable toxicity profile is particularly relevant for NSCLC, for which hematologic toxicity may deter oncologists from using cytotoxic chemotherapy in elderly patients and those with a poor performance status (PS). As many as 40% of patients with advanced NSCLC are estimated to have a poor PS [52], and the median age of newly diagnosed lung cancer patients in developed countries is 68 years [53]. Erlotinib may also represent a foundation on which to build rationally designed combinations of biologically targeted agents for advanced NSCLC.

### Table 1. Efficacy data for docetaxel, pemetrexed, and erlotinib

<table>
<thead>
<tr>
<th></th>
<th>Docetaxel (75 mg/m²) versus BSC&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Docetaxel (75 mg/m²) versus pemetrexed&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Erlotinib versus BSC&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Docetaxel (n = 55) Best supportive care (n = 100)</td>
<td>Docetaxel (n = 288) Pemetrexed (n = 283)</td>
<td>Erlotinib (n = 488) BSC (n = 243)</td>
</tr>
<tr>
<td>Response rate (%)</td>
<td>5.5</td>
<td>9.1</td>
<td>8.9&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Median survival (mos)</td>
<td>7.5&lt;sup&gt;d&lt;/sup&gt;</td>
<td>7.9</td>
<td>29.7</td>
</tr>
<tr>
<td>1-year survival (%)</td>
<td>7.9</td>
<td>9.1</td>
<td>31.2</td>
</tr>
<tr>
<td>Median survival (mos) for PS 0/1, second-line patients</td>
<td>6.3</td>
<td>9.4</td>
<td>21.5</td>
</tr>
</tbody>
</table>

<sup>a</sup>Patients with a PS score ≤2 and who had received one or two prior chemotherapy regimens were eligible for inclusion.

<sup>b</sup>Patients with a PS score ≤2 and who had received one prior chemotherapy regimen were eligible for inclusion.

<sup>c</sup>Patients with a PS score ≤3 and who had received one or two prior chemotherapy regimens were eligible for inclusion.

<sup>d</sup>p = 0.010.

<sup>e</sup>p < 0.001.

Abbreviations: BSC, best supportive care; PS, performance status.


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**BEVACIZUMAB PLUS ERLOTINIB FOR THE TREATMENT OF NSCLC**

Because bevacizumab and erlotinib act on two different pathways, one critical to tumor growth and the other regulating angiogenesis, administering both drugs together may confer additional clinical benefit to cancer patients with advanced disease. There is also evidence to suggest that these pathways are intimately associated and that coadministration of these agents may result in synergistic antitumor activity (Fig. 1).

Preclinical studies, in a number of tumor cell lines, show that upregulation of the EGFR signaling pathway results in the production of a number of angiogenic factors (including VEGF), suggesting that some of the antitumor effect of EGFR inhibitors may be mediated through inhibition of angiogenesis [54]. Other preclinical data suggest that upregulation of VEGF and other angiogenic factors may result in resistance to EGFR-targeted therapies such as cetuximab [55], providing a strong rationale for combining EGFR- and VEGF-targeted agents.

Initial preclinical studies demonstrated that dual blockade of VEGF and EGFR result in additive antitumor activity [56–59], and clinical data with bevacizumab and erlotinib have also been encouraging, suggesting additive benefits to patients with advanced NSCLC.

In a phase I/II trial [11] involving 40 patients with nonsquamous stage IIIb/IV NSCLC with one or more prior chemotherapies, administration of bevacizumab (15 mg/kg i.v.) every 3 weeks plus erlotinib (150 mg/day orally) until disease progression resulted in partial responses for eight patients (20%); 26 patients (65%) had stable disease as their best response. The median OS time was 12.6 months, with...
a PFS interval of 6.2 months. The most common AEs were mild-to-moderate rash, diarrhea, and proteinuria [11, 60].

In a recently reported phase II trial, 120 patients were randomized to receive erlotinib plus bevacizumab, bevacizumab plus chemotherapy (docetaxel or pemetrexed), or chemotherapy alone for recurrent or metastatic nonsquamous NSCLC after failure of one prior platinum-containing regimen [14]. The results from that trial were particularly encouraging. When compared with the PFS time with chemotherapy alone, the adjusted HR for the bevacizumab plus chemotherapy arm was 0.66, and for the bevacizumab plus erlotinib arm it was 0.72, demonstrating a trend toward significance (Fig. 2A) [14]. Patients receiving bevacizumab also survived longer than patients receiving chemotherapy alone; the median OS times were 8.6, 12.6, and 13.7 months for chemotherapy alone, bevacizumab plus chemotherapy, and erlotinib plus bevacizumab, respectively. Bevacizumab plus erlotinib was also associated with a higher response rate and similar disease control rate in patients with advanced NSCLC compared with the other study arms; the 1-year survival rate reached 57.4% in the bevacizumab plus erlotinib arm and was 53.8% in the bevacizumab plus chemotherapy arm, compared with 33.1% for patients who received chemotherapy alone (Fig. 2B) [14].

No unexpected AEs were encountered, and the rate of fatal pulmonary hemorrhage was consistent with previous bevacizumab trials in NSCLC patients. Additionally, the toxicity profile of the bevacizumab plus erlotinib combination was favorable compared with either of the chemother-apy-based regimens. Drug discontinuation due to AEs and severe AEs was greater in the chemotherapy-containing arms than in the bevacizumab plus erlotinib arm (Table 2).

Similar results were recently reported for a phase II trial of bevacizumab plus erlotinib in patients with advanced nonsquamous NSCLC who had received no prior chemotherapy [61]. In total, 38 patients were treated, the median TTP was 5.5 months, and at the time of the analysis 17 patients remained progression free. The regimen was well tolerated, with a low rate of grade 3 or 4 AEs and no unexpected toxicities [61].

These studies suggest that the combination of bevacizumab plus erlotinib may prove to be a viable second-line alternative to chemotherapy or erlotinib monotherapy in patients with NSCLC. Although results of the randomized phase II study did not demonstrate a statistically significant PFS benefit for the bevacizumab and erlotinib arm compared with the chemotherapy arm, the HRs were favorable, supporting further study of this combination as second-line therapy in phase III clinical trials.

Ongoing randomized studies are examining bevacizumab and erlotinib as both a first-line and second-line regimen for advanced NSCLC. In one phase III study [A study comparing bevacizumab therapy with or without erlotinib for first-line treatment of NSCLC (ATLAS)], the safety and efficacy of bevacizumab plus erlotinib versus bevacizumab plus placebo as a maintenance therapy are being evaluated in nonsquamous NSCLC patients (following first-line treatment with chemotherapy plus bevacizumab). In another

Figure 1. Key signaling pathways involved in tumor growth and progression.

Abbreviations: MW, molecular weight; T1/2, half-life; TGF-α, transforming growth factor α; VEGF, vascular endothelial growth factor.

A study evaluating the efficacy of bevacizumab in combination with Tarceva for advanced NSCLC after failure of standard first-line therapy (BeTA Lung) erlotinib plus bevacizumab (versus erlotinib plus placebo) is being studied as a second-line option for NSCLC.

**Figure 2.** Efficacy results. Kaplan–Meier estimated progression-free survival (A) and overall survival (B) from a phase II study of bevacizumab in combination with chemotherapy or erlotinib compared with chemotherapy alone for the treatment of recurrent or refractory nonsquamous non-small cell lung cancer.

Abbreviations: CI, confidence interval; HR, hazard ratio.


**The Value of Predictive Markers for Patients with NSCLC**

The utility of both bevacizumab and erlotinib (and other targeted agents) may be maximized through the identification of predictive markers of clinical response. Such markers may allow for the selection of patients who are most likely to benefit from a given targeted regime, effectively “personalizing” their medication.

To date there are no biomarkers that predict the efficacy of bevacizumab in patients with advanced NSCLC. However, a correlative study was carried out in NSCLC patients enrolled in a randomized phase II/III trial of paclitaxel plus carboplatin with or without bevacizumab [62, 63]. Levels of VEGF, basic fibroblast growth factor, and soluble intercellular adhesion molecule-1 (ICAM) were examined. Only baseline ICAM levels appeared to be a prognostic factor, being strongly prognostic for survival and response to chemotherapy. In addition, a longer PFS time with the ad-
dition of bevacizumab occurred mainly in patients with low baseline ICAM levels: a 53% lower PFS hazard rate was observed in patients with low baseline ICAM levels, whereas no benefit was observed for those with high levels [63]. However, no diagnostic test for ICAM has been validated for clinical use, limiting the clinical utility of these data. Further prospective analyses of ICAM in clinical trials are required to define cutoff levels that sensitively identify patients likely to respond to therapy.

For erlotinib, a number of potential biomarkers have been identified, although their value remains to be confirmed in prospective, randomized trials.

The relationship between EGFR expression and response to erlotinib is still unclear. A correlation between high EGFR protein levels and a higher response rate, but not longer survival, was demonstrated in the BR.21 trial [36]. However, in phase III studies of erlotinib combined with chemotherapy, no link between EGFR expression (as assessed through immunohistochemistry and fluorescence in situ hybridization) and response was observed [64, 65]. Data from the BR.21 trial do suggest that patients treated with erlotinib have a higher likelihood of response and extended survival if they have amplification or high gene copy numbers of the \( \text{HER}-\text{I/EGFR} \) gene [12].

The use of \( \text{KRAS} \) mutations as a predictive biomarker of response to EGFR therapy is under active investigation. While some studies indicate that patients with \( \text{KRAS} \) mutations would not benefit from TKI treatment [66-68], other published reports suggest that patients with \( \text{KRAS} \) mutations derive benefit from TKI treatment of NSCLC [47].

Certain physical characteristics of NSCLC patients have been linked to better outcome after treatment with erlotinib and gefitinib, another EGFR-targeted TKI. These characteristics include having no history of smoking (<100 cigarettes smoked in a lifetime), being female, having adenocarcinoma and/or bronchioalveolar histology, and Asian ethnicity [69-72].

Such characteristics may be related to underlying mutations occurring on exons 19 and 21 of the \( \text{EGFR} \) gene, resulting in amino acid deletions or substitutions in the TK domain [35, 73, 74]. These mutations are more common in adenocarcinomas, tumors from never smokers, and females [73-76], and their incidence also appears higher in Japanese and other Asians than in whites [73, 77]. Retrospective

Table 2. Selected AEs from a phase II study of bevacizumab in combination with chemotherapy or erlotinib compared with chemotherapy alone for treatment of recurrent or refractory nonsquamous non-small cell lung cancer [14]

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy alone (n = 42)</th>
<th>Bevacizumab + chemotherapy (n = 39)</th>
<th>Bevacizumab + erlotinib (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3, 4</td>
<td>Grade 5</td>
<td>Grade 3, 4</td>
</tr>
<tr>
<td>Any AE</td>
<td>30</td>
<td>7</td>
<td>26</td>
</tr>
<tr>
<td>Drug-related AEs</td>
<td>10</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>AEs of special interest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Hemorrhage, pulmonary</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hemorrhage, GI(^a)</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hemorrhage, other</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia(^a)</td>
<td>7</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>GI perforation</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Arterial thrombosis event</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Venous thrombosis event</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Wound dehiscence(^a)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Unexplained death</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

As-treated population.
\(^a\)One patient required surgery for GI hemorrhage and subsequently died of wound dehiscence.
\(^a\)Includes febrile neutropenia.
Abbreviations: AE, adverse event; GI, gastrointestinal.

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analyses of clinical data suggest that many patients who respond to treatment with erlotinib and gefitinib have these mutations [35, 64, 73, 74, 78–80], and another mutation in the **EGFR** TK domain, at position 790, may be associated with acquisition of erlotinib or gefitinib resistance [81, 82]. However, it is important to note that in the BR.21 trial, erlotinib demonstrated a beneficial effect on survival across the whole study population [41].

Despite these interesting subgroup findings, there is currently insufficient evidence upon which to base clinical decisions relating to the use of erlotinib in these patient populations. However, it is hoped that ongoing studies—SATURN (Sequential Tarceva in unresectable NSCLC, erlotinib versus placebo maintenance therapy), MERIT (Marker identification trial, open-label erlotinib), MARVEL (Marker validation of erlotinib in lung cancer, pemetrexed versus erlotinib), and TITAN (Tarceva in treatment of advanced NSCLC, erlotinib versus pemetrexed or docetaxel second-line) trials—will yield useful information on the prognostic value of patient **EGFR** status.

The appearance of a skin rash may be useful as a surrogate marker of efficacy for erlotinib (and other **EGFR**-targeted agents). A relationship between the severity of the rash and erlotinib treatment efficacy was observed in studies in a range of solid tumors, and was also noted in a retrospective analysis of the pivotal phase III trial of erlotinib in previously treated NSCLC patients [23, 54, 55]. In the retrospective analysis, patients who developed a rash had a significantly longer survival time than those who did not: 8.5 months for patients with grade 1 rash, 19.6 months for patients with grade 2 or 3 rash, and 1.5 months for patients with no rash (p < .0001) [54].

However, this correlation remains to be validated in prospective trials, and it should not be assumed that erlotinib is only effective in patients who do develop a rash. Ongoing erlotinib dose-escalation studies are attempting to elicit characteristic target rashes in patients, which may correlate with better response.

In the randomized phase II trial of bevacizumab plus erlotinib in NSCLC, **EGFR** gene amplification status was not observed to correlate with patient outcome [14]. Interestingly, among patients who did not display any **EGFR** gene amplification (as detected by fluorescence in situ hybridization), the longest PFS time was observed in those randomized to the erlotinib plus bevacizumab arm [14]. This is important because it suggests that by combining these agents, erlotinib may be active in patients without gene amplification, against predictions from the BR.21 trial analyses [12]. This combination may therefore be useful in other NSCLC settings.

### DISCUSSION

Combining agents that selectively target the VEGF and **EGFR** pathways represents a novel and exciting approach to the treatment of NSCLC and other forms of cancer, as shown by the erlotinib and bevacizumab data previously presented. It is hoped that ongoing phase III trials will validate this approach and offer new hope for patients with advanced NSCLC.

The benefits of this combination may be further enhanced by selecting for patients who are likely to respond to this therapy (although if the addition of bevacizumab markedly increases the effectiveness of erlotinib, this may reduce the necessity for selection). Although a number of potential predictive markers have been identified for erlotinib, their value remains to be confirmed in prospective trials. The application of such personalized therapy will also depend on the availability of validated screening methods.

An alternative strategy for targeting these two critical pathways is also currently being investigated. Vandetanib (ZD6474) is a TKI that targets both the **EGFR** and VEGF receptor simultaneously. Preclinical data indicate that vandetanib has activity against NSCLC cell lines and against xenograft models resistant to treatment with gefitinib [39]. Furthermore, in phase II trials, it has been demonstrated to have second-line activity against NSCLC, both as a monotherapy and in combination with docetaxel [16, 83].

It remains to be seen whether combinations of single-targeted agents (such as bevacizumab plus erlotinib) or single multitargeted agents (such as vandetanib) will prove to be more effective in the treatment of NSCLC and other cancers. A large number of trials are currently under way that are combining different targeted agents, and there are also numerous multitargeted compounds under development. Most notable among this latter group are sorafenib (Nexavar®; Bayer Pharmaceuticals Corporation, West Haven, CT) and sunitinib (Sutent®; Pfizer, Inc., New York), multitargeted VEGF receptor TKIs, both of which have been demonstrated to have single-agent activity in phase II trials in NSCLC [17, 18]. The value of each approach will become clear only when data from comparative trials are available. However, ongoing studies in the front-line setting in combination with chemotherapy have demonstrated excessive toxicities and challenges related to optimal dose combinations [84, 85]. While these agents are still under development in NSCLC, multitargeted agents may ultimately prove less effective or tolerable than using optimal doses of specific inhibitors to target each pathway separately.
AUTHOR CONTRIBUTIONS
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Data analysis: Roy S. Herbst, Alan Sandler
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