Epidermal Growth Factor Receptor Inhibitors and Antiangiogenic Agents for the Treatment of Non-Small Cell Lung Cancer

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Abstract
Non-small cell lung cancer (NSCLC) is a major global health problem and represents the leading cause of cancer-related deaths worldwide. The majority of patients with NSCLC are diagnosed with advanced-stage disease, and the prognosis for such patients is poor. The currently approved cytotoxic chemotherapy is associated with substantial limitations in both efficacy and safety. The availability of agents targeted against the epidermal growth factor receptor (EGFR), as well as the antiangiogenic agent bevacizumab, have provided some clinical benefit. Nonetheless, the efficacy of these agents is also inadequate, and resistance has emerged as a clinical problem. Numerous novel targeted therapies are now in clinical development and may have potential for overcoming the limitations associated with currently available agents. In this article we review clinical data for molecular-targeted therapies in NSCLC, with emphasis on EGFR inhibitors and antiangiogenic agents. (Clin Cancer Res 2009;15(16): 5040–8)

In 2008, it is estimated that non-small cell lung cancer (NSCLC) will account for 80% of the anticipated 214,990 new cases and 161,890 deaths from lung cancer in the United States (1). Two thirds of patients with NSCLC present with advanced disease and have an average survival of 8 to 10 months when treated with standard chemotherapy (2). Novel strategies are thus required to improve patient outcomes. In this article we discuss the current status of the clinical testing of molecularly targeted therapies, focusing on epidermal growth factor receptor (EGFR) inhibitors and antiangiogenic agents for the treatment of patients with NSCLC.

Inhibition of the EGFR Pathway

The EGFR is a receptor tyrosine kinase (TK) of the ErbB/HER family. Ligand binding to EGFR induces receptor homo- or hetero-dimerization with other ErbB family members or with other extracellular receptors (e.g., insulin-like growth factor-1 receptor or MET; ref. 3). Receptor activation signals key downstream pathways that regulate cell proliferation, differentiation, and survival (4–6). EGFR overexpression has been reported in 50% to 80% of NSCLCs (7–10). Aberrant EGFR expression can lead to tumor development. Agents targeting the EGFR pathway have shown activity and continue to be evaluated in patients with NSCLC.

Monoclonal antibodies to the EGFR pathway. Cetuximab is a human murine chimeric immunoglobulin G (IgG)1 antibody that binds to EGFR and affects ligand-induced phosphorylation and receptor degradation (11). IgG1 antibodies also activate the complement pathway and mediate antibody-dependent cellular cytotoxicity. In a phase II trial of previously treated NSCLC patients, single agent cetuximab had activity similar to that reported with pemetrexed, erlotinib, or docetaxel (Table 1; refs. 12–25).

Phase II trials evaluating the addition of cetuximab to platinum-based chemotherapy in patients with advanced NSCLC have yielded favorable results (14, 16, 26, 27). In one phase II trial (LUCAS), patients with chemotherapy-naïve advanced NSCLC who had 1% EGFR positive cells as measured by immunohistochemistry (IHC) were randomized to receive chemotherapy with cisplatin-vinorelbine plus cetuximab or chemotherapy alone. A higher response rate (RR) and a nonsignificant trend toward improved progression-free survival (PFS) and overall survival (OS) was associated with the patients who received cetuximab (16). These findings led to a randomized phase III trial (FLEX) evaluating cisplatin-vinorelbine with or without cetuximab in 1,125 patients with advanced NSCLC and at least one EGFR positive cell by IHC (17). The low requirement for EGFR positivity allowed 85% (1,442 of 1,688) of screened patients to be eligible. There was no difference in PFS but a significant improvement in RR and OS (primary end point) in the patients receiving cetuximab compared with placebo, 11.3 versus 10.1 months [hazard ratio (HR), 0.871; P = 0.044]. A prespecified subgroup analysis showed no improvement in OS among Asian patients. However, fewer patients receiving cetuximab received poststudy treatment with EGFR TK
**Translational Relevance**

Lung cancer is the leading cause of cancer-related mortality in North America. NSCLC accounts for 80% to 85% of all new cases. Two thirds of patients are diagnosed with advanced disease at the time of diagnosis. These patients have a median survival of approximately 8 to 10 months when treated with standard platinum based chemotherapy. There has been considerable interest in developing novel therapeutic agents that target aberrant pathways involved in cell growth and metastases. The well-established role of angiogenesis and the epidermal growth factor receptor (EGFR) pathway in the pathogenesis of lung cancer has led to the rationale development of agents that selectively target these pathways. There are a few agents currently approved for the treatment of NSCLC and a multitude of new agents in clinical development. In this article we review these agents with an emphasis on their mechanism of action, clinical activity and mechanisms of resistance.

inhibitors (TKIs). Further, there was a significant improvement in OS among Caucasian patients receiving cetuximab (HR, 0.803; P = 0.003).

In a second phase III trial, BMS-099, 676 advanced NSCLC patients with no required EGFR testing were randomized to carboplatin-paclitaxel or docetaxel with or without cetuximab. This study did not meet its primary end point of PFS by an independent review committee (IRCC) (HR 0.90; P = 0.23), although there was a significant improvement in response as determined by an IRCC (16% versus 17%) and PFS as determined by investigators (28). OS was 9.7 months for cetuximab-treated patients compared with 8.4 months for chemotherapy alone [HR 0.89, 95% confidence interval (CI) = 0.75–1.05, P = 0.17] (29).

Two other monoclonal antibodies to the EGFR, panitumumab, a fully human monoclonal IgG2 antibody to the EGFR (25), and matuzumab, a humanized IgG1 monoclonal antibody to the EGFR (19), have shown limited success in patients with NSCLC. This latter agent has recently been halted in development following disappointing results in colon cancer patients.

Currently, cetuximab seems to be the only monoclonal antibody to EGFR that has shown benefit (albeit modest) in a subset of patients with NSCLC. Hirsch and colleagues reported a preferential benefit for treatment with cetuximab in patients who were EGFR positive as determined by fluorescence in situ hybridization (FISH; ref. 30). In addition colorectal cancer patients, with tumors that harbor the KRAS mutation do not benefit from treatment with cetuximab (31). Prospective studies are needed to further define the use of cetuximab in biomarker-enriched NSCLC patients, although a retrospective analysis of tissue samples from FLEX and BMS-099 may also provide useful information.

**Reversible EGFR TKIs.** Erlotinib and gefitinib inhibit EGFR signaling by binding to the intracellular TK domain, suppressing receptor phosphorylation and downstream signaling (32, 33). These agents were the first EGFR-targeted therapies to be approved for the second- or third-line treatment of patients with advanced NSCLC (Table 2; refs. 34–36). Two randomized phase III trials evaluated monotherapy with EGFR TKIs in patients with previously treated NSCLC (37, 38). Trial BR.21 found a significant improvement in OS among patients who were given erlotinib compared with placebo (P < 0.001; ref. 37), whereas the ISEL trial found no difference in OS between patients who received gefitinib compared with placebo (P = 0.087; ref. 38).

Clinical features known to correlate with response to EGFR TKI treatment include gender, smoking status, adenocarcinoma histology, and Asian ethnicity (34–37, 39). Molecular predictors of response have also been identified, and comprehensive reviews that focus on EGFR mutations in lung cancer are available (40, 41). Mutations in the kinase domain of EGFR correlate with response and improved survival with EGFR TKI treatment (8, 42–46). The point mutation in exon 21 (L858R) and the deletion at exon 19 account for 80% to 95% of EGFR mutations in NSCLC (47). High EGFR gene copy number as detected by FISH, and protein overexpression as determined by IHC, has also been associated with improved RRs and survival (48–50). KRAS mutations are a negative predictor of benefit from TKIs (51). In addition, most patients on EGFR TKIs eventually develop resistance, most commonly due to an exon 20-point mutation (T790M; refs. 52, 53). Recently reported results from an open label, first-line, phase III study of gefitinib versus carboplatin-paclitaxel in East Asian patients who were never or light smokers with advanced NSCLC (IPASS), indicated that gefitinib was favored over chemotherapy in patients testing positive for EGFR mutations (HR 0.48, 95% CI 0.36–0.64; P = 0.0001), whereas chemotherapy was favored in patients testing negative (HR 2.85, 95% CI 2.05–3.98; P < 0.0001; ref. 54).

Four randomized phase III trials evaluated erlotinib or gefitinib in combination with standard chemotherapy with disappointing results (55–58). Subgroup analyses from the TRIBUTE trial identified a benefit in nonsmokers treated with erlotinib and chemotherapy compared with placebo (57). These results led to the RADIANT trial, which is evaluating adjuvant chemotherapy with or without erlotinib in nonsmokers with EGFR-positive NSCLC. Lapatinib, a dual reversible inhibitor with a high affinity for EGFR and HER2 (59), has been investigated in patients with NSCLC and also produced disappointing results (60–62).

**Irreversible dual EGFR/HER2 receptor TKIs.** A new generation of dual irreversible EGFR/HER2 inhibitors that may be effective in patients with resistance to reversible EGFR TKIs are under development. These agents form a covalent bond with CYS-733 in EGFR (63). In preclinical studies, several such agents showed activity against tumors overexpressing EGFR or harboring the T790M mutation (64, 65). Resistance may also develop less frequently with irreversible EGFR TKIs than with reversible inhibitors (66). An additional advantage may be the dual inhibition of EGFR and HER2, which blocks cooperative signaling between these two receptors and has been shown to result in improved antitumor activity in preclinical models (67, 68). The clinical goals for patients treated with irreversible TKIs include activity after failure with reversible TKI therapy and a more prolonged PFS compared with reversible TKIs in therapy-naïve patients.
BIBW 2992 is an irreversible dual inhibitor of EGFR and HER2. Preliminary results of a phase I trial showed two partial responses (PRs) among 26 women with lung adenocarcinomas (69). The agent was well tolerated, with primary toxicities being rash and diarrhea. A phase II trial of previously treated patients with NSCLC with known activating EGFR mutations is currently ongoing (70). Additionally, a randomized phase III trial is underway comparing BIBW 2992 to placebo in patients with NSCLC with acquired resistance to gefitinib or erlotinib.

HKI-272 is an irreversible inhibitor of EGFR and HER2 that has been shown to inhibit the growth of cells that express EGFR or HER2, including cells with the T790 mutation (65). In a phase I trial involving 73 patients with tumors expressing EGFR or HER2, stable disease (SD) was reported in 42% of 16 NSCLC patients all of whom had initially responded to erlotinib or gefitinib. However, phase II studies in NSCLC patients are not planned at this time.

PF299804 is an irreversible inhibitor of EGFR, HER2, and HER4. Preclinical studies showed growth inhibition of cell lines expressing EGFR activating mutations and T790 mutations supporting further development of the compound for patients who develop acquired resistance to gefitinib or erlotinib (71). Phase I trials of PF299804 in patients with NSCLC are underway.

### Angiogenesis Inhibitors

Angiogenesis is a fundamental step in tumor growth and metastases (72, 73). Vascular endothelial growth factor (VEGF) is the central mediator of angiogenesis and its expression has been found to correlate with new vessel formation, disease-free survival, and OS in NSCLC patients (74–76). Given its important role in tumor development, angiogenesis is a rationale therapeutic target in NSCLC patients (77, 78).

### Table 1. Summary of trials with antibodies directed against EGFR and HER2

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Treatment</th>
<th>N</th>
<th>RR, %</th>
<th>OS, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hanna et al. (12)</td>
<td>II</td>
<td>Cetuximab 400 mg/m² week 1 then 250 mg/m² per week</td>
<td>66</td>
<td>5</td>
<td>8.9</td>
</tr>
<tr>
<td>Thienelt et al. (14)</td>
<td>I-II</td>
<td>Cetuximab 400 mg/m² then carboplatin AUC 6 day 1 + paclitaxel 200 mg/m² day 1 every 3 wk + cetuximab 250 mg/m² per week</td>
<td>31</td>
<td>26</td>
<td>11</td>
</tr>
<tr>
<td>Blumenschien et al. (15)</td>
<td>II</td>
<td>Carboplatin AUC 6 + paclitaxel 200 mg/m² day 1 gemcitabine 1,000 mg/m² days 1 and 8 every 3 wk + cetuximab 400 mg/m² week 1 then 250 mg/m² per week</td>
<td>35</td>
<td>29</td>
<td>10.2</td>
</tr>
<tr>
<td>Rosell (LUCAS) et al. (16)</td>
<td>II</td>
<td>Cisplatin 80 mg/m² day 1 + vinorelbine 25 mg/m² days 1 and 8 every 3 weeks</td>
<td>43</td>
<td>28</td>
<td>7.3</td>
</tr>
<tr>
<td>Pirker et al. (17) (FLEX)</td>
<td>III</td>
<td>Cisplatin 80 mg/m² day 1 + vinorelbine 25 mg/m² days 1 and 8 + cetuximab 400 mg/m² then 250 mg/m² per week</td>
<td>568</td>
<td>29</td>
<td>10.1</td>
</tr>
<tr>
<td>Rosell (LUCAS) et al. (16)</td>
<td>II</td>
<td>Cisplatin 80 mg/m² day 1 + vinorelbine 25 mg/m² days 1 and 8 + cetuximab 400 mg/m² then 250 mg/m² per week</td>
<td>557</td>
<td>36</td>
<td>11.3</td>
</tr>
<tr>
<td>Lynch (BMS 099) et al. (29)</td>
<td>III</td>
<td>Carboplatin AUC 6 + Paclitaxel 225 mg/m² or docetaxel 75 mg/m² day 1 every 3 wk Carboplatin AUC 6 + Paclitaxel 225 mg/m² or docetaxel 75 mg/m² day 1 every 3 wk + cetuximab 400 mg/m² then 250 mg/m² per week</td>
<td>338</td>
<td>17</td>
<td>8.4</td>
</tr>
<tr>
<td>Herbst et al. (18)</td>
<td>II</td>
<td>Pertuzumab 940 mg/m² then 420 mg/m² every 3 wk</td>
<td>43</td>
<td>0</td>
<td>NR</td>
</tr>
<tr>
<td>Kollmannsberger et al. (19)</td>
<td>I</td>
<td>Matuzumab 100-800 mg/m² + paclitaxel 175 mg/m² every 3 wk</td>
<td>18</td>
<td>22</td>
<td>NR</td>
</tr>
<tr>
<td>Clamon et al. (20)</td>
<td>II</td>
<td>Trastuzumab 4 mg/m² then 2 mg/m² every 3 wk</td>
<td>22</td>
<td>5</td>
<td>~5</td>
</tr>
<tr>
<td>Zinner et al. (23)</td>
<td>II</td>
<td>Cisplatin 75 mg/m² day 1 + gemcitabine 1,250 mg/m² days 1 and 8 every 3 wk + trastuzumab 4 mg/m² then 2 mg/m² per week Cisplatin 75 mg/m² day 1 + gemcitabine 1,250 mg/m² days 1 and 8 every 3 wk + trastuzumab 4 mg/m² then 2 mg/m² per week</td>
<td>21</td>
<td>38</td>
<td>Not reached at follow up (&gt;16.2)</td>
</tr>
<tr>
<td>Langer et al. (22)</td>
<td>II</td>
<td>Carboplatin AUC 6 + Paclitaxel 225 mg/m² + trastuzumab 4 mg/m² then 2 mg/m² per week</td>
<td>53</td>
<td>25</td>
<td>10.1</td>
</tr>
<tr>
<td>Crawford et al. (25)</td>
<td>II</td>
<td>Carboplatin AUC 6 + Paclitaxel 225 mg/m² + panitumumab 1-2.5 mg/m² every 3 wk</td>
<td>19</td>
<td>26</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviations: AUC, area under the curve; NR, not reported.
Bevacizumab. Bevacizumab is a monoclonal antibody with a high affinity for VEGF (79, 80). A randomized phase II trial found the addition of bevacizumab to carboplatin-paclitaxel improved RR and time to progression compared with chemotherapy alone in patients with advanced NSCLC (Table 3; ref. 81). There was also a nonsignificant improvement in OS. In this trial, patients whose tumors were squamous cell histology were found to be at greater risk for developing hemoptysis. On the basis of the results of this trial, the Eastern Cooperative Oncology Group (ECOG) conducted a phase III trial (E4599) comparing carboplatin-paclitaxel with and without bevacizumab in 878 patients with advanced nonsquamous NSCLC (82). The results indicated a significant improvement in RR (\( P < 0.001 \)), PFS (HR, 0.66; \( P < 0.001 \)), and OS (HR, 0.79; \( P = 0.003 \)) among bevacizumab-treated patients.

A second randomized phase III trial (AVAiL), compared cisplatin-gemcitabine with or without bevacizumab, 7.5 or 15 mg/kg, in 1,043 patients with advanced nonsquamous NSCLC (82). The results indicated a significant improvement in RR (\( P < 0.001 \)), PFS (HR, 0.66; \( P < 0.001 \)), and OS (HR, 0.79; \( P = 0.003 \)) among bevacizumab-treated patients.

Patients with brain metastases were initially excluded from trials with bevacizumab because of the catastrophic potential associated with intracranial hemorrhage. Several large trials, ATLAS, ARIES, and PASSPORT have included patients with brain metastases and have not found them to be at increased risk of central nervous system hemorrhage (86, 87). However, these trials are ongoing and more mature data are required.

### Table 2. Summary of trials with EGFR TKIs

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Treatment</th>
<th>N</th>
<th>RR, %</th>
<th>OS, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fukuoka et al. (34)</td>
<td>II</td>
<td>Gefitinib 250 mg/day</td>
<td>104</td>
<td>18</td>
<td>7.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gefitinib 500 mg/day</td>
<td>105</td>
<td>19</td>
<td>8.0</td>
</tr>
<tr>
<td>Kris et al. (35)</td>
<td>II</td>
<td>Gefitinib 250 mg/day</td>
<td>102</td>
<td>12</td>
<td>7.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gefitinib 500 mg/day</td>
<td>115</td>
<td>9</td>
<td>6.0</td>
</tr>
<tr>
<td>Perez-Soler et al. (36)</td>
<td>II</td>
<td>Erlotinib 150 mg/day</td>
<td>57</td>
<td>12</td>
<td>8.4</td>
</tr>
<tr>
<td>Thatcher et al. (38)</td>
<td>III</td>
<td>Placebo</td>
<td>563</td>
<td>1</td>
<td>5.1</td>
</tr>
<tr>
<td>Shepherd et al. (37)</td>
<td>III</td>
<td>Gefitinib 250 mg/day</td>
<td>1129</td>
<td>8</td>
<td>5.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>243</td>
<td>&lt;1</td>
<td>4.7</td>
</tr>
<tr>
<td>Giaccone et al. (55)</td>
<td>III</td>
<td>Cisplatin 80 mg/m(^2) day 1 + gemcitabine 1,250 mg/m(^2) days 1 and 8 every 3 wk</td>
<td>363</td>
<td>45</td>
<td>10.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cisplatin 80 mg/m(^2) + gemcitabine 1,250 mg/m(^2) + gefitinib 250 mg/day</td>
<td>365</td>
<td>50</td>
<td>9.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cisplatin 80 mg/m(^2) + gemcitabine 1,250 mg/m(^2) + gefitinib 500 mg/day</td>
<td>365</td>
<td>50</td>
<td>9.9</td>
</tr>
<tr>
<td>Herbst et al. (56)</td>
<td>III</td>
<td>Carboplatin AUC 6 + paclitaxel 225 mg/m(^3) every 3 wk</td>
<td>345</td>
<td>29</td>
<td>9.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carboplatin AUC 6 + paclitaxel 225 mg/m(^3) + gefitinib 250 mg/day</td>
<td>345</td>
<td>30</td>
<td>9.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carboplatin AUC 6 + paclitaxel 225 mg/m(^3) + gefitinib 500 mg/day</td>
<td>347</td>
<td>30</td>
<td>8.7</td>
</tr>
<tr>
<td>Herbst et al. (57)</td>
<td>III</td>
<td>Carboplatin AUC 6 + paclitaxel 225 mg/m(^3) every 3 wk</td>
<td>533</td>
<td>19</td>
<td>10.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carboplatin AUC 6 + paclitaxel 225 mg/m(^3) + erlotinib 150 mg/day</td>
<td>526</td>
<td>22</td>
<td>10.6</td>
</tr>
<tr>
<td>Gatzemeier et al. (58)</td>
<td>III</td>
<td>Cisplatin 80 mg/m(^2) day 1 + gemcitabine 1,250 mg/m(^2) days 1 and 8 every 3 wk</td>
<td>579</td>
<td>30</td>
<td>10.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cisplatin 80 mg/m(^2) + gemcitabine 1,250 mg/m(^2) + erlotinib 150 mg/day</td>
<td>580</td>
<td>32</td>
<td>10.0</td>
</tr>
<tr>
<td>Smylie et al. (61)</td>
<td>II</td>
<td>Lapatinib 1,500 mg/day or 500 mg twice daily</td>
<td>131</td>
<td>1.5</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviations: AUC, area under the curve; NR, not reported.

### Table 3. Summary of key trials with bevacizumab

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Treatment</th>
<th>N</th>
<th>RR, %</th>
<th>OS, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson et al. (81)</td>
<td>II</td>
<td>Carboplatin AUC 6 + paclitaxel 200 mg/m(^2) every 3 wk</td>
<td>32</td>
<td>19</td>
<td>14.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carboplatin AUC 6 + paclitaxel 200 mg/m(^2) + bevacizumab 7.5 mg/kg</td>
<td>35</td>
<td>28</td>
<td>11.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carboplatin AUC 6 + paclitaxel 200 mg/m(^2) + bevacizumab 15 mg/kg</td>
<td>32</td>
<td>35</td>
<td>17.7</td>
</tr>
<tr>
<td>Sandler et al. (82)</td>
<td>III</td>
<td>Carboplatin AUC 6 + paclitaxel 200 mg/m(^3)</td>
<td>427</td>
<td>35</td>
<td>10.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carboplatin AUC 6 + paclitaxel 200 mg/m(^3) + bevacizumab 15 mg/kg</td>
<td>440</td>
<td>15</td>
<td>12.3</td>
</tr>
<tr>
<td>Manegold et al. (83)</td>
<td>III</td>
<td>Cisplatin 80 mg/m(^2) day 1 + gemcitabine 1250 mg/m(^2) days 1 and 8 every 3 wk</td>
<td>347</td>
<td>20</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cisplatin 80 mg/m(^2) day 1 + gemcitabine 1250 mg/m(^2) + bevacizumab 7.5 mg/kg</td>
<td>345</td>
<td>34</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cisplatin 80 mg/m(^2) day 1 + gemcitabine 1250 mg/m(^2) + bevacizumab 15 mg/kg</td>
<td>351</td>
<td>30</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviations: AUC, area under the curve; NR, not reported.
Small-molecule inhibitors of angiogenic growth factors and their receptors. Sorafenib is an oral multi-kinase inhibitor that targets VEGFR2 and 3, platelet-derived growth factor-β (PDGFR-β) RAF, stem cell factor receptor (c-KIT), and fms-like TK-3 (FLT3; refs. 88–91). Of note, it has been suggested that the combined blockade of PDGFR- and VEGFR2-mediated signaling may induce greater inhibition of angiogenesis (91).

ECOG conducted the largest trial of single agent sorafenib in patients with previously treated NSCLC (E2501) (Table 4; ref. 92). In this trial, patients received two cycles of sorafenib with those patients who responded continuing on treatment whereas those patients who had SD were randomized to sorafenib or placebo. The primary end point of the study was the proportion of patients with disease control [SD, PR, complete response (CR)] 2 months following randomization. A total of 107 patients with SD were randomized and 83 were assessable for response. A significantly higher number of sorafenib-treated patients had disease control as compared with placebo (P = 0.01). Median PFS was also significantly longer (P = 0.009), and there was a trend toward improvement in OS.

Sorafenib has also been evaluated in combination with chemotherapy (Table 4; refs. 93, 94). The phase III ESCAPE trial, which randomized 926 untreated patients with advanced NSCLC to receive carboplatin-paclitaxel with or without sorafenib, found no difference in RR, PFS (HR, 1.0; P = 0.514), or OS (HR, 1.16; P = 0.930) between treatment groups. In a subset analysis, patients with squamous cell histology seemed to do poorly when treated with sorafenib (94). The NExUS study, a second phase III trial, is currently under way to evaluate cisplatin-gemcitabine with sorafenib. Based on the data from the ESCAPE trial, patients with squamous cell histology are no longer eligible for enrollment in NExUS.

Sunitinib (SU11248) is a multitargeted, small-molecule inhibitor of VEGFR1, 2, and 3; PDGFR-α and -β, FLT3, c-KIT, and the receptor encoded by the ret proto-oncogene (RET, rearranged during transfection; ref. 95). Phase II trials of single-agent sunitinib yielded favorable results (Table 4; refs. 96, 97). Sunitinib in combination with cisplatin-gemcitabine was evaluated in a phase I study in untreated patients with advanced NSCLC (Table 4) and 37.5 mg was recommended with this chemotherapy regimen (98). Further combination studies are ongoing.

BIBF 1120 is an oral angiokinase inhibitor targeting VEGFR1, 2, and 3, PDGFR-α and -β, and fibroblast growth factor receptor (FGFR) 1, 2, and 3. Casanova and colleagues showed that resistance to anti-VEGF treatment can arise through the secretion of alternative ligands, in particular, FGF (99). Thus, it has been postulated that the triple VEGF/PDGF/FGF inhibitory properties of BIBF 1120 may overcome such resistance and afford prolonged response to treatment (100). A randomized phase II trial compared two doses of BIBF 1120 (150 and 250 mg twice daily) in previously treated NSCLC patients (Table 4; ref. 101). Preliminary results showed no objective responses and similar SD and PFS rates between treatment groups. In a phase I trial of BIBF 1120 combined with pemetrexed, all previously treated NSCLC patients had a CR and two PRs and eight SD among 20 evaluable patients (Table 4; ref. 102). Phase III trials evaluating BIBF 1120 in combination with chemotherapy for patients with advanced NSCLC are ongoing.

Several other antiangiogenic TKIs are also in early clinical development, including cediranib, axitinib, and AE-941. Results from clinical trials with these agents are summarized in Table 4 (103–105). Of note, the National Cancer Institute of Canada recently closed a trial of carboplatin-paclitaxel with or without cediranib because of excess toxicities in the cediranib treatment group.

### Dual EGFR and VEGFR Inhibition

VEGFR and EGFR share common downstream signaling pathways (106). The inhibition of VEGFR is believed to contribute to the mechanism of action of agents targeting EGFR (107). Increased VEGFR activity is one mechanism via which tumors develop resistance to EGFR inhibitors (108). Dual EGFR-VEGFR inhibition has been shown to have additive effects and may help overcome resistance to EGFR inhibition (106).

### Table 4. Summary of trials with antiangiogenic TKIs

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Treatment</th>
<th>N</th>
<th>RR, %</th>
<th>OS, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schiller et al. (92)</td>
<td>II</td>
<td>Sorafenib 400 mg twice daily</td>
<td>51</td>
<td>2</td>
<td>11.9</td>
</tr>
<tr>
<td>Schiller et al. (93)</td>
<td>I-II</td>
<td>Carboplatin AUC 6 + paclitaxel 225 mg/m² day 1 + sorafenib 400 mg twice daily</td>
<td>15</td>
<td>29</td>
<td>NR</td>
</tr>
<tr>
<td>Scagliotti et al. (94)</td>
<td>III</td>
<td>Carboplatin AUC 6 + paclitaxel 225 mg/m² day 1 + sorafenib 400 mg twice daily</td>
<td>462</td>
<td>24</td>
<td>10.7</td>
</tr>
<tr>
<td>Hanna et al. (102)</td>
<td>I</td>
<td>Pemetrexed 500 mg/m² + BIBF 1120 100-200 mg twice daily</td>
<td>26</td>
<td>15</td>
<td>NR</td>
</tr>
<tr>
<td>von Pawel et al. (101)</td>
<td>II</td>
<td>BIBF 1120 150 or 250 mg twice daily</td>
<td>73</td>
<td>0</td>
<td>NR</td>
</tr>
<tr>
<td>Socinski et al. (96)</td>
<td>II</td>
<td>Sunitinib 50 mg/day</td>
<td>63</td>
<td>11</td>
<td>5.4</td>
</tr>
<tr>
<td>Brahmer et al. (97)</td>
<td>II</td>
<td>Sunitinib 37.5 mg/day</td>
<td>47</td>
<td>2</td>
<td>8.6</td>
</tr>
<tr>
<td>Reck et al. (98)</td>
<td>I</td>
<td>Cisplatin 80 mg/m² day 1 + gemcitabine 1000 or 1250 mg/m² days 1 and 8</td>
<td>13</td>
<td>23</td>
<td>NR</td>
</tr>
<tr>
<td>Laurie et al. (103)</td>
<td>I</td>
<td>Carboplatin AUC 6 + paclitaxel 200 mg/m² day 1 + sorafenib 400 mg twice daily</td>
<td>20</td>
<td>45</td>
<td>NR</td>
</tr>
<tr>
<td>Schiller et al. (104)</td>
<td>II</td>
<td>Axitinib 5 mg twice daily</td>
<td>32</td>
<td>9</td>
<td>12.8</td>
</tr>
<tr>
<td>Latreille et al. (105)</td>
<td>I</td>
<td>AE-941 30, 60, 120, or 240 mL/day</td>
<td>80</td>
<td>0</td>
<td>≤2.6 mL/kg per day: 4.6, &gt;2.6 mL/kg per day: 6.1</td>
</tr>
</tbody>
</table>

Abbreviations: AUC, area under the curve; NR, not reported.
Several studies have evaluated the combination of bevacizumab and erlotinib (Table 5; refs. 109–111). A promising phase I-II trial of bevacizumab plus erlotinib in advanced NSCLC patients (109) led to a randomized phase II trial in 120 patients with recurrent or refractory NSCLC in which chemotherapy alone (docetaxel or pemetrexed) was compared with chemotherapy plus bevacizumab or bevacizumab plus erlotinib (110). The RR was highest for patients who received bevacizumab plus erlotinib. The median PFS, OS, and 1-year survival rates were lowest in the patients who received chemotherapy alone and comparable in the two groups who received bevacizumab. Available tissue samples (<10% of patients) were tested for EGFR by IHC and FISH, as well as EGFR and k-Ras mutations. FISH-negative patients treated with erlotinib-bevacizumab had prolonged PFS (110). A phase III trial compared erlotinib plus bevacizumab to gefitinib and found a higher RR and PFS for vandetanib (Table 5; ref. 118). However, OS did not differ significantly between treatment arms. Two randomized phase III trials comparing vandetanib with erlotinib (ZEST) or placebo (ZEPHIR) in previously treated NSCLC are currently accruing.

Several studies have also evaluated vandetanib in combination with chemotherapy in patients with advanced NSCLC (Table 5; refs. 119, 120). A phase II randomized trial reported a higher RR but no difference in OS times when docetaxel combined with vandetanib was compared with docetaxel alone (119). The results of this study led to two phase III trials comparing chemotherapy with docetaxel (ZODIAC) or pemetrexed (ZEAL) with or without vandetanib in the same patient population. ZODIAC met its primary endpoint, improvement in PFS and both trials reported an improvement in RR with a trend toward improvement in OS when vandetanib was combined with chemotherapy compared with chemotherapy alone. A phase II trial randomized 181 untreated patients with advanced NSCLC to one of three treatments: vandetanib alone, pemetrexed and carboplatin, or vandetanib plus pemetrexed and carboplatin and reported no difference in RR, PFS, or OS between treatment arms (120, 121).

XL647 targets EGFR, HER2, VEGFR2, and EphB4. Two phase I studies of XL647 reported SD in an approximately two thirds of patients (122, 123). Preliminary results of a trial involving 23 patients with NSCLC treated with XL647 who relapsed after achieving an initial benefit from erlotinib or gefitinib showed one patient with a PR and seven patients with SD (Table 5; ref. 124). A second trial administered XL647 to 41 chemotherapy-naïve patients with NSCLC meeting at least one of the several criteria for inclusion (Table 5).

**Table 5. Summary of trials of dual EGFR/Antiangiogenic therapy**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Treatment</th>
<th>N</th>
<th>RR, %</th>
<th>OS, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heymach et al. (119)</td>
<td>II</td>
<td>Docetaxel 75 mg/m² every 3 wk</td>
<td>41</td>
<td>13</td>
<td>13.4</td>
</tr>
<tr>
<td>Heymach et al. (120)</td>
<td>II</td>
<td>Carboplatin AUC 6 + paclitaxel 225 mg/m² every 3 wk + vandetanib 200 mg/day</td>
<td>44</td>
<td>26</td>
<td>13.1</td>
</tr>
<tr>
<td>Miller et al. (124)</td>
<td>II</td>
<td>XL647 300 mg/day</td>
<td>23</td>
<td>4</td>
<td>NR</td>
</tr>
<tr>
<td>Rizvi et al. (125)</td>
<td>II</td>
<td>XL647 350 mg/day on an intermittent regimen (days 1-5 of each 14-day cycle)</td>
<td>41</td>
<td>28</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviations: AUC, area under the curve; NR, not reported.

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eligibility criteria: Asian ethnicity, female gender, and minimal (<15 pack-years) or no smoking history (Table 5; ref. 125). Among assessable patients, the PR rate was 28%, and 36% of patients had SD for ≥3 months. EGFR mutations were detected in 70% of patients who had a PR. Phase II studies with XL647 in patients with NSCLC are ongoing.

AEE788 is dual EGFR-VEGFR inhibitor with activity against EGFR, HER2, and VEGFR2 (126). It was found to inhibit the growth of NSCLCs in vivo with similar efficacy to a two-drug combination of an ErbB and VEGFR inhibitor. This agent has recently entered phase I clinical testing.

**Conclusion**

Despite advances in our knowledge of tumor biology and our ability to develop therapies that more precisely affect the target of interest, only modest improvements have been made in the treatment of patients with NSCLC. Agents that inhibit the EGFR, VEGF pathway, or both, have shown benefit in the treatment of patients with NSCLC in phase III trials. These agents are particularly appealing given their unique toxicity profile compared with that of chemotherapeutic agents in patients with comorbid illnesses. There are no proven biomarkers of anti-angiogenic therapy in patients with NSCLC. Despite EGFR overexpression in a large number of NSCLC patients, only approximately 10% of patients respond to anti-EGFR therapy. This may in part be due to limitations in study designs or methods currently employed to measure EGFR. As previously discussed, patients with EGFR amplification and/or mutations have prolonged PFS when treated with EGFR-directed therapy. It will be important to ensure that future studies are designed appropriately, and that consistent, reproducible mechanisms for measuring EGFR expression/mutations are identified. To achieve this goal, larger randomized phase III studies are needed. The increased sophistication of preclinical models and the enrollment of patients in clinical trials that include measurements of biomarkers will help identify patients who are likely to benefit from therapy, as well as further define mechanisms of resistance to therapy.

**Disclosure of Potential Conflicts of Interest**

A. Sandler: speakers’ bureau, Genentech; consultant, Genentech, BMS, Eli Lilly, Sanofi Aventis, OSI, Pfizer, Bayer, Astra Zeneca, and Amgen.

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**References**


91. Cabebe E, Wakelee H. Role of anti-angiogene-
sis agents in treating NSCLC: focus on bevacizu-
92. Schiller JH, Lee JW, Hanna NH, et al. A ran-
domized discontinuation phase II study of sora-
96. Socinski MA, Novello S, Brahmer JR, et al. Multicenter, phase II trial of sunitinib in previ-
97. Brahmer JR, Govindan R, Novello S, et al. Ef-
100. van Pawel J, Kaiser R, Eschbach C, et al. A double-blind, placebo controlled trial of 1,120 in pa-
tients suffering from relapsed advanced non-
101. Hanna N, Ellis P, Stopfer P, et al. A phase I study of continuous oral treatment with the tri-
ple angiogenesis inhibitor BIBF 1120 together with pemetrexed in previously treated patients with non-small cell lung cancer: P3–91. J Thor-
104. Latrellie J, Batist G, Laberge F, et al. Phase III trial of the safety and efficacy of AE-941 (Neova-
stat) in the treatment of non-small-cell lung can-
107. Herbst RS, Johnson DH, Mininberg E, et al. Phase II trial evaluating the anti-endothelial growth factor monoclonal antibody beva-
108. Herbst RS, O’Neill VJ, Fehrenbacher L, et al. Phase II study of efficacy and safety of bevacizu-
109. Fischbach N, Cohen EE, Gowinov R, et al. Phase II trial of sequential bevacizumab (B), erlotinib (E) and chemotherapy for first line treatment of clin-
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Leora Horn and Alan Sandler

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