Vascular Endothelial Growth Factor Receptor Tyrosine Kinase Inhibitors Vandetanib (ZD6474) and AZD2171 in Lung Cancer

Emer O. Hanrahan1 and John V. Heymach1,2

Abstract  Vascular endothelial growth factor (VEGF) is a rational target for advanced non–small cell lung cancer (NSCLC), a hypothesis validated by the recent Eastern Cooperative Oncology Group E4599 trial showing that the addition of the VEGF monoclonal antibody bevacizumab to chemotherapy prolongs overall survival. Several new tyrosine kinase inhibitors targeting the VEGF pathway are currently in advanced clinical development for NSCLC and offer several possible advantages compared with monoclonal antibodies, including oral administration, more flexible dosing, a broader spectrum of target inhibition, and different toxicity profiles. Among these agents, vandetanib (ZD6474), an inhibitor of the VEGF receptor (VEGFR)-2 and epidermal growth factor receptor tyrosine kinase, has been the most extensively studied. In a randomized phase II study of patients with platinum-refractory NSCLC, including squamous histology, vandetanib prolonged progression-free survival compared with gefitinib. In another phase II trial, an improvement in progression-free survival was observed for vandetanib in combination with docetaxel compared with docetaxel alone. AZD2171 is an inhibitor of VEGFR-1, VEGFR-2, and VEGFR-3 and other tyrosine kinases that has shown clinical activity in NSCLC in combination with carboplatin and paclitaxel. Several phase III trials are under way testing these agents either as monotherapy or in combination with chemotherapy in patients with lung cancer. Early results with these agents, and others being tested, raise the possibility that there will eventually be multiple VEGF–targeted therapies available in the clinic that can potentially benefit a broader range of patients with advanced-stage NSCLC.

Non–small cell lung cancer (NSCLC) is the leading cause of cancer-related mortality in the United States (1). The median survival with modern chemotherapy doublet regimens for stage IV disease is only 8 to 10 months (2, 3), a figure that has not changed appreciably despite the intensive testing of different chemotherapy agents and combinations (4). Consequently, there has been great interest in the development of novel agents for the treatment of this disease.

Much of this research has focused on targeting epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR) signaling. Bevacizumab, a monoclonal antibody directed against VEGF, has recently been approved by the Food and Drug Administration for use in combination with first-line paclitaxel/carboplatin chemotherapy for stage IIIB/IV nonsquamous NSCLC based on a 2-month improvement in median survival in the landmark Eastern Cooperative Oncology Group E4599 trial (3). In patients receiving second- or third-line treatment, erlotinib was shown to improve median survival by 2 months compared with best supportive care, although gefitinib in a similar trial yielded no survival advantage (6, 7). Clearly, agents that inhibit a single target in NSCLC have limited long-term benefits. The molecular pathways involved in the proliferation of cancer cells and the regulation of tumor angiogenesis are highly complex, and prolonged inhibition of one target may lead to up-regulation of other signaling pathways, resulting in the development of an escape mechanism that allows continued tumor progression. Therefore, the ongoing evaluation of multitargeted agents in NSCLC represents a rational therapeutic approach that may yield more prolonged antitumor effects.

Several new agents targeting multiple cell signaling pathways, including the VEGF and EGFR pathways, are currently in advanced clinical development, including tyrosine kinase inhibitors (TKI), targeting both pathways simultaneously (reviewed in refs. 8–10). This review will discuss two VEGFR TKIs in development for NSCLC: vandetanib (ZD6474) and AZD2171.

Angiogenesis Inhibitors in NSCLC

Angiogenesis is essential for the growth and metastatic spread of tumors. Retrospective and prospective studies have shown that increased tumor microvessel density correlates with advanced disease stage and inferior patient outcome in NSCLC (11–14). In addition, increased tumor expression of proangiogenic factors, such as VEGF, basic fibroblast growth factor, and...
interleukin-8, has been found to correlate with inferior prognosis in this disease (14–19). Among these proangiogenic factors, VEGF is thought to play a central role (20) and is the target of intense preclinical and clinical investigation.

Inhibition of VEGF using bevacizumab, an i.v. administered monoclonal antibody that binds VEGF and prevents it from interacting with its receptors, has shown clinical benefit for several diseases, including colorectal cancer and NSCLC (5, 21). In the randomized phase II/III E4599 trial, patients who received bevacizumab in combination with standard paclitaxel and carboplatin chemotherapy had an improved survival compared with the chemotherapy doublet alone. Despite this progress, however, it is worth noting that the absolute improvement in median survival was a modest 2 months; an unplanned subgroup analysis found that the survival benefit was confined to male patients; and patients with squamous cell carcinoma were excluded from the trial and from the Food and Drug Administration approval of bevacizumab due to an excessive risk of life-threatening hemoptysis associated with squamous histology in the phase II evaluation of this regimen (22). Clearly, there remains a great need for improved treatment options for all histologic subtypes of NSCLC. Several multitargeted receptor TKIs (RTKI) with anti-VEGFR activity are currently being evaluated in NSCLC and may help address this need.

Potential Benefits of Using Multitargeted RTKIs to Inhibit VEGFR Signaling

Several multitargeted RTKIs that inhibit VEGF receptors are in advanced clinical evaluation in NSCLC, including vandetanib, AZD2171, sorafenib, axitinib, and sunitinib (Table 1). It is not known if these agents will be comparable or superior with monoclonal antibodies or other approaches directed against the VEGF ligand. They do, however, offer several potential advantages. First, these agents are orally bioavailable, which may provide greater convenience. Second, they have shorter half-lives ranging from hours to days, which provide more flexible dosing and the potential to stop or reduce dosing in the case of toxicities; bevacizumab, in contrast, has a half-life of ~3 weeks (23). There is, however, a potential disadvantage of this shorter half-life as it is thought that consistent blockade of the VEGF pathway may produce improved antiangiogenic activity. Third, these agents are designed to target the ATP-binding site, which is relatively well conserved in many receptor tyrosine kinases. Therefore, RTKIs typically have a broader spectrum of activity than monoclonal antibodies (Table 1; ref. 24). These “off-target” effects may include inhibition of therapeutically relevant targets, such as EGFR, platelet-derived growth factor receptor (PDGFR), c-Kit, and VEGFR-3, a receptor thought to be critical for lymphangiogenesis. This broader spectrum of activity may, at least in part, explain why several of these agents have shown considerable single-agent activity in NSCLC (25, 26).

<table>
<thead>
<tr>
<th>Table 1. Multitargeted RTKIs under evaluation in NSCLC</th>
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<tbody>
<tr>
<td><strong>RTKI</strong></td>
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<tr>
<td>---</td>
</tr>
<tr>
<td>Vandetanib</td>
</tr>
<tr>
<td>AZD2171</td>
</tr>
<tr>
<td>Sorafenib</td>
</tr>
<tr>
<td>Sunitinib</td>
</tr>
<tr>
<td>Axitinib</td>
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<td>AMG 706</td>
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</table>

*Current phase of clinical trial development in NSCLC.

Vandetanib: Combined Targeting of VEGFR and EGFR Signaling

Vandetanib is an orally bioavailable, small-molecule TKI of VEGFR-2, EGFR, and RET. It is suitable for once-daily administration due to its long half-life of >120 h. By simultaneously targeting the VEGFR and EGFR signaling pathways, vandetanib may produce greater clinical benefits than targeting either pathway alone.

EGFR inhibition has a direct effect on tumor proliferation and survival, whereas the inhibition of VEGF signaling in tumor endothelial cells has indirect antitumor effects through inhibition of tumor angiogenesis. Furthermore, EGFR is also expressed on endothelial cells and EGFR plays a role in the regulation of angiogenesis (27). EGFR inhibition down-regulates the production of proangiogenic factors, such as VEGF and interleukin-8 (28–30). Preclinical studies have shown that dual blockade of these molecular targets produces additive or synergistic antitumor effects (31, 32). Early clinical results also suggest that dual blockade of these pathways may have activity greater than blockade of either pathway alone. In a phase I/II trial assessing the safety and efficacy of bevacizumab and erlotinib in patients with metastatic, nonsquamous NSCLC and at least one prior therapy, an objective response rate of 20% and a median survival of 12.6 months were observed (33). In a randomized, three-arm, phase II trial, this combination showed a higher response rate and a trend to greater progression-free survival (PFS) and overall survival than standard chemotherapy alone (34).

Clinical Trials of Vandetanib in Lung Cancer

Vandetanib was initially evaluated in two phase I clinical trials among patients with advanced solid tumors refractory to standard therapy (35, 36). One of these studies involved a Western population of 77 patients with a variety of solid tumors, mostly colorectal cancer, and only 1 patient had NSCLC (37). The second study recruited 18 patients in Japan, most of whom had NSCLC or colorectal cancer (9 and 4 cases, respectively). In these studies, vandetanib was shown to be well tolerated at daily oral doses of ≤300 mg, and observed adverse effects were generally mild and manageable. They included rash and diarrhea, which were both dose dependent, proteinuria, hypertension, and asymptomatic QTc prolongation. In the Western population, there were no patients with objective responses, but >40% of patients had stable disease of at least 8 weeks of duration. In the Japanese population, four of the nine patients with NSCLC exhibited an objective response by Response Evaluation Criteria in Solid Tumors (36).
Single-agent vandetanib showed significant antitumor activity in a randomized phase II trial involving 168 patients with locally advanced or metastatic NSCLC who had progressed despite first- or second-line platinum-based therapy. Patients received either vandetanib (300 mg once daily) or gefitinib (250 mg once daily) until disease progression or limiting toxicity, with PFS as the primary end point (part A; ref. 25). Squamous histology was allowed. There was a statistically significant improvement in median PFS with vandetanib compared with gefitinib (11 versus 8.1 weeks; \( P = 0.025 \)). On progression, patients had the option to cross over to the alternative therapy (part B). In part B, stable disease for >8 weeks was achieved in 16 of 37 patients (43%) who switched from gefitinib to vandetanib and in 7 of 29 (24%) who switched from vandetanib to gefitinib. Based on these results, an international randomized phase III trial is planned to compare vandetanib with erlotinib as second- or third-line therapy for patients with advanced NSCLC (Table 2). Another international randomized phase III trial will be opening to accrual in the near future and will evaluate whether vandetanib offers a survival advantage over best supportive care in patients with disease that has progressed on an EGFR TKI and for whom no standard treatment options are available.

Vandetanib has also been assessed in combination with chemotherapy in two randomized phase II trials, both of which allowed patients with squamous histology. One trial evaluated vandetanib in combination with second-line docetaxel in 127 patients with progressive stage IIIB/IV NSCLC after first-line platinum-based chemotherapy (38). There were three treatment arms: docetaxel (75 mg/m\(^2\)) iv. every 21 days with either placebo, vandetanib (100 mg), or vandetanib (300 mg). This study met its primary end point of prolonged median PFS in the docetaxel plus vandetanib 100 mg arm (18.7 versus 12 weeks for the control arm; hazard ratio, 0.64). PFS was not significantly improved with the 300 mg dose of vandetanib (17 weeks; hazard ratio, 0.83) relative to placebo, and no overall survival benefit (secondary end point) was shown with either dose of vandetanib in this trial. Toxicities associated with vandetanib use in combination with docetaxel were generally mild and manageable. The most common reported toxicities were diarrhea (grade 3-4 events: one in the placebo arm, none in vandetanib 100 mg arm, and six in the vandetanib 300 mg arm), rash (grade 3 events: eight in vandetanib 300 mg arm and none in the other two arms), nausea and vomiting (grade 3 events: one in the vandetanib 100 and 300 mg arms and two in the placebo arm), hypertension (grade 3 events: one in the vandetanib 300 mg arm).

### Table 2. Randomized clinical trials of vandetanib for advanced-stage NSCLC and for SCLC

<table>
<thead>
<tr>
<th>Disease (reference)</th>
<th>Treatment arms</th>
<th>Phase</th>
<th>n</th>
<th>Status</th>
<th>Results*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second- to third-line NSCLC (25)</td>
<td>Gefitinib (250 mg) Vandetanib (300 mg)</td>
<td>II</td>
<td>168</td>
<td>Completed</td>
<td>Improved PFS with vandetanib (HR, 0.63)</td>
</tr>
<tr>
<td>Second- to third-line NSCLC</td>
<td>Erlotinib (150 mg) Vandetanib (300 mg)</td>
<td>III</td>
<td>1,150</td>
<td>Ongoing</td>
<td>NA</td>
</tr>
<tr>
<td>NSCLC after EGFR TKI</td>
<td>BSC Vandetanib (300 mg)</td>
<td>III</td>
<td>790</td>
<td>Planned</td>
<td>NA</td>
</tr>
<tr>
<td>First-line NSCLC</td>
<td>PC Vandetanib (300 mg) PC + vandetanib (300 mg)</td>
<td>II</td>
<td>200</td>
<td>Completed</td>
<td>Awaited</td>
</tr>
<tr>
<td>Second- to third-line NSCLC (38)</td>
<td>Docetaxel (75 mg/m(^2)) Docetaxel (75 mg/m(^2)) + vandetanib (100 mg) Docetaxel (75 mg/m(^2)) + vandetanib (300 mg)</td>
<td>II</td>
<td>127</td>
<td>Completed</td>
<td>Improved PFS with 75 mg/m(^2) docetaxel + 100 mg vandetanib (HR, 0.64)</td>
</tr>
<tr>
<td>Second-line NSCLC</td>
<td>Docetaxel (75 mg/m(^2)) Docetaxel (75 mg/m(^2)) + vandetanib (100 mg)</td>
<td>III</td>
<td>1,240</td>
<td>Ongoing</td>
<td>NA</td>
</tr>
<tr>
<td>Second-line NSCLC</td>
<td>Pemetrexed (500 mg/m(^2)) Pemetrexed (500 mg/m(^2)) + vandetanib (100 mg)</td>
<td>III</td>
<td>418</td>
<td>Planned</td>
<td>NA</td>
</tr>
<tr>
<td>SCLC maintenance</td>
<td>Placebo Vandetanib</td>
<td>II</td>
<td>100</td>
<td>Completed</td>
<td>Awaited</td>
</tr>
</tbody>
</table>

Abbreviations: BSC, best supportive care; n, number of enrolled or planned participants; NA, not applicable; PC, paclitaxel (200 mg/m\(^2\)) and carboplatin area under the curve = 6; HR, hazard ratio.

*Primary end point for all studies is PFS, except for the vandetanib versus best supportive care trial, in which overall survival is the primary end point.

† Patients with refractory NSCLC that has progressed on an EGFR TKI and for whom no standard treatment options are available.

‡ Patients with limited or extensive stage SCLC that has responded to standard first-line treatment with chemotherapy ± radiotherapy are randomized to 2 y of placebo or vandetanib.
each of the placebo and vandetanib 100 mg arms and two in the vandetanib 300 mg arm), and asymptomatic prolongation of QTc interval (one grade 3 event in the placebo arm and no grade 3-4 events in the vandetanib arms). There were no cases of intracranial hemorrhage or fatal hemoptysis among the 127 patients in the randomized phase of this study.

It is not clear why the addition of the lower 100 mg dose of vandetanib to docetaxel seems to be more effective that the addition of the higher 300 mg dose in this trial. One possible explanation is that the anti-EGFR activity of vandetanib at higher doses may predominate over its antiangiogenic effects, and it has already been shown in multiple phase III clinical trials that the addition of EGFR inhibitors (gefitinib or erlotinib) to chemotherapy yields no therapeutic advantage (39–42). It has been hypothesized that EGFR blockade may slow proliferation and cause G1 cell cycle arrest in tumor cells, thereby reducing the sensitivity of tumors to the cell cycle phase-dependent activity of chemotherapy (43). An international randomized phase III trial of docetaxel combined with 100 mg vandetanib or placebo as second-line therapy for locally advanced or metastatic NSCLC has been initiated (Table 2) and will confirm whether 100 mg vandetanib added to docetaxel confers a true PFS advantage in advanced NSCLC. Another interesting observation in this phase II trial was a trend toward greater benefit from vandetanib in females than in males, which is the converse of the greater survival benefit seen among males with the addition of bevacizumab to chemotherapy in the E4599 trial. This suggests that NSCLC angiogenesis in females may be more dependent on EGFR signaling. In fact, the ongoing phase III study has a preplanned subset analysis by gender and is powered to detect an advantage with vandetanib in females only.

In a second randomized, phase II trial, standard carboplatin/paclitaxel chemotherapy, vandetanib monotherapy, and carboplatin/paclitaxel in combination with vandetanib were compared in patients with chemotherapy-naive, locally advanced, metastatic, or recurrent NSCLC. In the run-in phase of this trial, the combination was found to be active and with an acceptable toxicity profile (44). The trial has completed accrual and results will be available at the 2007 American Society of Clinical Oncology annual meeting.

Vandetanib is also being evaluated in SCLC. The National Cancer Institute of Canada Clinical Trials Group has recently completed a phase II randomized trial of “maintenance” vandetanib or placebo in patients with either limited or extensive stage SCLC who had a confirmed response (complete or partial) to standard treatment with chemotherapy or chemoradiation. Results from this trial have not yet been reported.

Clinical Trials of AZD2171 in Lung Cancer

AZD2171 is another orally bioavailable, multitargeted RTKI. It has potent activity against VEGFR-1, VEGFR-2, and VEGFR-3 and lesser activity against PDGFR-β and c-Kit. AZD2171 has not been as well studied in lung cancer as vandetanib, but it is showing encouraging early results. As well as inhibiting new tumor vessel formation, AZD2171 theoretically may also reduce lymphatic spread of cancer cells due to inhibition of VEGFR-3. The expression of VEGFR-3 and its ligands (VEGF-C and VEGF-D) in tumors, including NSCLC, has been associated with dissemination to regional lymph nodes (45, 46).

As a single agent and in combination with various chemotherapy regimens, AZD2171 has been the subject of several phase I trials in solid tumors, which found it to be well tolerated at doses ≤45 mg/d (47–49). The safety, tolerability, and antitumor activity of AZD2171 in combination with standard doses of paclitaxel/carboplatin chemotherapy have recently been assessed in a phase I trial involving 20 patients with stage IIB/IV NSCLC, including squamous histology, and no prior chemotherapy for metastatic disease (49). AZD2171 was administered once daily at 30 mg in 9 patients and 45 mg in 11 patients. There did not seem to be an increase in hematologic toxicity with the addition of AZD2171 to paclitaxel/carboplatin. Common toxicities were manageable and included hypertension, fatigue, anorexia, and mucositis. There were no reports of hemoptysis. Among 15 patients evaluable for response, there were 6 partial responses and 8 patients with stable disease. Several patients with stable disease by Response Evaluation Criteria in Solid Tumors criteria had evidence of tumor response, with some shrinkage and/or central cavitation. The National Cancer Institute of Canada Clinical Trials Group is now conducting a phase II/III trial of carboplatin/paclitaxel in combination with 45 mg/d AZD2171 or placebo for first-line treatment for stage IIB/IV NSCLC. Similar to the vandetanib trials, all NSCLC histologic subtypes are allowed, but patients with a central thoracic lesion with cavitation or clinically relevant hemoptysis within the preceding 4 weeks are ineligible.

A recently presented phase I trial evaluated AZD2171 (20-45 mg/d) in combination with gefitinib (250-500 mg/d) in 83 patients with solid tumors, 11 of whom had lung cancer (50). Overall, there were 6 reported partial responses and 31 patients with stable disease. Although there were no responses in the lung cancer patients, four experienced stable disease.

Up to 70% of SCLC tumors express c-Kit, a proto-oncogene protein product (51). Although results with imatinib, a c-Kit inhibitor, have been disappointing in SCLC, the antiangiogenic properties of AZD2171, in addition to its activity against c-Kit, make it an interesting agent for evaluation in SCLC (52, 53). A multicenter, single-arm, phase II trial in the United States is currently evaluating AZD2171 monotherapy in patients with recurrent SCLC. In addition, a phase I trial of AZD2171 in combination with etoposide and cisplatin for the first-line treatment of SCLC is planned.

Conclusions

The recent success of bevacizumab in combination with paclitaxel/carboplatin chemotherapy for first-line treatment of stage IIB/IV, nonsquamous NSCLC in the E4599 trial confirms that antiangiogenic strategies are a rational therapeutic approach for NSCLC. However, the clinical use of bevacizumab is restricted to patients with nonsquamous histology without central nervous system metastases, and the absolute improvement in median survival from the addition of bevacizumab to standard chemotherapy is modest. Multitargeted small-molecule RTKIs that incorporate both direct antitumor and toxicities of RTKIs in NSCLC. It has shown encouraging results in randomized phase II trials as monotherapy and in combination...
with chemotherapy in the second- and later-line settings (25, 38), and three large international phase III trials are now ongoing or planned (Table 2). The results of another randomized phase II trial that considered this agent in combination with first-line paclitaxel/carboplatin for stage IIIIB/IV NSCLC will be available at the American Society of Clinical Oncology 2007 annual meeting. AZD2171 and sorafenib are also being assessed in combination with first-line paclitaxel/carboplatin in phase II/III trials for advanced-stage NSCLC. The results of these phase III trials, and other ongoing trials of VEGFR TKIs, are eagerly anticipated.

Hopefully, these novel agents will lead to an expanded clinical repertoire of effective targeted therapies for all patients with advanced-stage NSCLC. Although these agents all target VEGF signaling and share many common toxicities, there are some differences in their spectra of activity, which may translate into different efficacies in lung cancer, and several of these agents may not be entirely cross-resistant. However, these considerations are not yet being addressed in clinical studies, and a further generation of clinical trials will likely be required to determine the optimal sequencing of these agents.

Open Discussion

Dr. Thomas Lynch: There is a general perception that AZD2171 is more active than ZD6474. Why do we perceive that? Are we all off-base?

Dr. Heymach: I believe the monotherapy activity of ZD6474 will be greater than that of a pure VEGF inhibitor, such as bevacizumab, because it has enough EGFR activity to achieve synergy in getting the sensitive mutation-bearing tumors. In terms of combinations with chemotherapy, it wouldn’t surprise me if 2171 would work better.

Dr. Roy Herbst: I am always surprised that people are more excited by 2171. It is perhaps a more specific agent, but the positive phase II data already exist for 6474, similar data to what existed for bevacizumab when it went forward to phase III.

Dr. Lynch: Do you think these agents will be safe for squamous cell?

Dr. Heymach: So far, we have treated a substantial number of squamous cell patients with 6474. Thus far, we have not run into an increase in hemoptysis above that of chemotherapy alone, but the question is: have we just not treated sufficient numbers to see it? Out of 40-odd patients per arm, out of which approximately 30% had squamous histology, there were two with grade 2 hemoptysis in the control arm and one in the 100 mg arm. If it is happening, it isn’t happening frequently.

Dr. Mark Socinski: The Canadian trial of 2171 is not excluding squamous cell patients. In our sunsitinib study, we did have two fatal pulmonary hemorrhages in squamous cell patients. I am not sure that we have enough data to say yet that squamous cell is not an issue with all of these agents.

Dr. Charles Butts: The problem that we have had with 2171 is the overall toxicity profile, primarily myelosuppression and sepsis, that we are mostly seeing after cycle 3. The phase I trials that look for the MTD are usually one or two cycles and then they stop.

Dr. Lynch: In his presentation, Dr. Heymach alluded to the fact that the outcome in the Eastern European population was worse. For the clinical investigators here, when you are designing trials of novel agents, how hesitant are you to think about including Eastern European populations?

Dr. Kwok-Kin Wong: We don’t know what the mutational profile is. There is not as much information from Eastern Europe as we have for Far East Asian countries.

Dr. Angela Davies: I think the issue is more practical—differences in supportive care and how patients are diagnosed.

Dr. Ramaswamy Govindan: The infrastructure to conduct clinical trials does not exist in many parts of the world. More than the biology, I worry about the logistics. Use of homeopathic medicines is very prevalent in many parts of the world. The potential for interactions is an issue that we sometimes forget or overlook.

Dr. Heymach: For the patients from Eastern Europe, there were certainly imbalances in poststudy treatment that could have impacted the results, and there were questions about the appropriateness of some patients. For example, there were a number of patients who came off study in the first couple of weeks who either died or became ill. An expected life span at least 12 weeks was required for the patient to be entered.

References


Clinical Cancer Research

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