Vandetinib is a novel, selective dual inhibitor of the vascular endothelial growth factor receptor pathway and epidermal growth factor receptor pathway. Phase I studies have established that it is suitable for once-daily oral dosing at a dose of up to 300 mg. Vandetinib has been tested in multiple randomized controlled phase II clinical studies, which have established that this is a promising new targeted agent for the treatment of patients with advanced non-small cell lung cancer and which also support the potential role of vandetinib administered concurrently with chemotherapy. Further testing of its role in lung cancer is in ongoing.

Key Words: Angiogenesis, Dual kinase inhibitor, Lung cancer, T790, K-ras.

(J Thorac Oncol. 2008;3: Suppl 2, S128 –S130)
arm with a hazard ratio of 0.69 (95% confidence interval, 0.50–0.96) and a 2-sided p value of 0.025. In part B of the study, vandetinib achieved disease control in 16 of 37 patients (43%) who were initially treated with gefitinib. In contrast, gefitinib achieved disease control in only 7 of 29 patients (24%) initially treated with vandetinib.

Rash, diarrhea, and nausea were similar in the two arms of the study in part A and were generally mild. Headache, dizziness, hypertension, and QT-related events were more common in the vandetinib arm than in the gefitinib arm.

Trial 6 consisted of a run-in feasibility study of docetaxel combined with vandetinib followed by a 3-armed phase II randomized trial of docetaxel, 75 mg/m² every 3 weeks alone or combined with 100 mg per day or 300 mg per day of vandetinib⁵ (Figure 2). Eligibility criteria were similar to trial 3 except patients may have received only first-line platinum-based chemotherapy. Progression-free survival was again the primary study end point. One hundred twenty-seven patients were entered into the trial. Both vandetinib arms produced an improvement in progression-free survival compared with the docetaxel control arm, but only the 100-mg dose level of vandetinib combined with docetaxel achieved the study end point, with a hazard ratio of 0.64 (95% confidence interval, 0.38–1.05). Adverse effects, including rash, diarrhea, nausea or vomiting, hypertension, and QT-related events, were mildly increased in the 100 mg of vandetinib plus docetaxel arm compared with docetaxel alone (40% versus 24%, 38% versus 27%, 31% versus 24%, 7% versus 2%, and 12% versus 5%, respectively) and moderately to unacceptably increased in the 300 mg of vandetinib plus docetaxel arm (46%, 50%, 34%, 9%, and 16%, respectively).

These two trials establish that vandetinib is a promising new targeted agent for the treatment of patients with advanced NSCLC. Trial 3 confirms the single-agent activity of this agent and that its efficacy is at least partly mediated through its VEGFR inhibitory property. Combined EGFR and VEGFR inhibition with vandetinib produced a better progression-free survival compared with EGFR inhibition alone with gefitinib. The fact that the disease control rate in part B of the study was greater with vandetinib after gefitinib than it was with gefitinib after vandetinib suggests that the improved effectiveness of vandetinib in part A of the study derived, at least in part, from its VEGFR inhibition. The reduced activity of gefitinib after vandetinib in part B compared with gefitinib in vandetinib-naïve patients in part A strongly suggests that vandetinib is an effective EGFR inhibitor as well. These observations are currently under investigation in a definitive, prospective, randomized, double-blind, international clinical trial of vandetinib versus erlotinib.

Trial 6 strongly supports the potential role of vandetinib administered concurrently with chemotherapy. Not only was toxicity reduced at the 100-mg dose compared with the...
300-mg dose of vandetinib combined with docetaxel, but the response rate and progression-free survival were somewhat better as well. Although not proven by this study, this differential effect suggests that the reduced EGFR inhibition that occurred at the 100-mg dose compared with the 300-mg dose allowed beneficial interaction between vandetinib’s VEGFR inhibition and chemotherapy and that this beneficial interaction was partially overcome by increased EGFR inhibition at the 300-mg dose level. These observations are also currently under investigation in a definitive, prospective, randomized, double-blind, international clinical trial of docetaxel combined with vandetinib, 100 mg daily, versus docetaxel combined with placebo.

REFERENCES