

Current status of vandetanib (ZD6474) in the treatment of non-small cell lung cancer

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Abstract: Vandetanib (ZD6474) is an oral small molecule inhibitor of multiple intracellular receptor kinases, including the vascular endothelial growth factor receptor (VEGFR) -2 and epidermal growth factor receptor (EGFR). Both VEGFR and EGFR pathways have emerged as instrumental in the growth and metastasis of multiple malignancies, including non-small cell lung cancer (NSCLC). Indeed, inhibitors of each pathway have been approved by the US Food and Drug Administration for use in advanced NSCLC. As there is considerable cross talk between these pathways, dual inhibition with such agents has become an attractive strategy, with encouraging Phase II clinical trial data to date. The convenience of one oral agent targeting both pathways is clear, and clinical trials have established the maximum tolerated daily dose of vandetanib, with data from randomized Phase III trials emerging. This report will review completed and ongoing NSCLC clinical trials evaluating vandetanib, and speculate on the future of this agent in NSCLC.

Keywords: Zactima, ZD6474, non-small cell lung cancer, vandetanib

Introduction

Lung cancer continues to be the leading cause of cancer related mortality worldwide, accounting for over one million deaths annually.¹ The majority of patients present with metastatic disease, with a median survival of six months.² Approximately 85% of lung cancers are classified as non-small cell lung cancer (NSCLC), which can be further subdivided in adenocarcinoma, squamous cell carcinoma and large cell carcinoma histology. Chemotherapy remains the cornerstone of treatment in advanced NSCLC; however, a plateau of effectiveness with such therapy has been reached. Molecularly targeted agents have further improved outcome over the last decade, and several additional targeted agents are being developed.

To date, three targeted agents have been approved by the US Food and Drug Administration (FDA) in advanced NSCLC. The first to receive FDA approval was gefitinib, a small molecule inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase, a transmembrane receptor whose activation leads to intracellular signaling involved in cancer cell proliferation and survival. Gefitinib was later restricted to use only in those who were previously benefiting, as a Phase III trial comparing gefitinib to best supportive care did not ultimately find a survival advantage.³ The second drug to be granted approval was erlotinib, another small molecule inhibitor of the EGFR tyrosine kinase, which is currently indicated as second or third line therapy in patients with advanced NSCLC. The last FDA-approved agent is bevacizumab, a humanized

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monoclonal antibody to the vascular endothelial growth factor (VEGF), a key mediator of angiogenesis required for growth and metastasis of cancer. A trial conducted by the Eastern Cooperative Oncology Group (ECOG) found that the addition of bevacizumab to first line chemotherapy with carboplatin and paclitaxel led to improved response and survival, with a landmark median survival of one year.⁴ Cetuximab is another promising monoclonal antibody which targets the extracellular ligand binding domain of EGFR, and a recent Phase III study found a modest improvement in survival when this agent was combined with cisplatin and vinorelbine in patients with chemo-naïve advanced NSCLC.⁵ The US FDA is currently considering approval of this drug.

Clearly, the EGFR and VEGF pathways have been clinically validated as important targets in the treatment of NSCLC. Preclinical studies further suggest that combined inhibition of both pathways may lead to synergistic effects on cancer cell growth, survival and metastases.^{6–8} The rationale for dual inhibition comes from our increased understanding of the redundancy of these pathways and their interconnectedness.

Vascular endothelial growth factor receptor (VEGFR) Pathway

Three transmembrane receptors mediate the angiogenic and lymphogenic effects of VEGF; VEGFR-1 (Flt-1), -2 (KDR), and -3 (Flt-4).⁹ Of these, VEGFR-2 is believed to play the primary role in endothelial cell proliferation, migration, survival and induction of vascular permeability characteristic of neo-vascularization required for tumor growth and metastasis.^{10,11} VEGFR-2 is activated by binding of VEGF elaborated by tumor cells, which leads to receptor dimerization and intracellular signaling initiated by the VEGFR tyrosine kinase.^{11,12} This ultimately results in the production of tumor vasculature that is highly permeable, dilated and tortuous, with increased tumor interstitial pressure that may impede delivery of cytotoxic agents.¹³ The resultant increasingly hypoxic microenvironment in turn upregulates expression of VEGF contributing to further neo-vascularization.

EGFR Pathway

Like the VEGFR, the EGFR is activated by ligand (ie, EGF, TGF- α) binding leading to receptor dimerization and autophosphorylation of its intracellular tyrosine kinase domain. This kinase in turn phosphorylates other proteins, initiating a cascade of signaling events responsible for cell proliferation, cell survival, metastasis and angiogenesis.¹⁴ EGFR is overexpressed in several solid tumors, including NSCLC.¹⁵ Activating mutations in the EGFR gene have additionally been

identified that lead to constitutive activity of the intracellular tyrosine kinase and predict for high response rates to the small molecule EGFR inhibitors, erlotinib and gefitinib.^{16–19} Although only approximately 10%–15% of NSCLCs harbor EGFR mutations, it is estimated that up to 50% of lifelong nonsmokers with NSCLC have EGFR mutant tumors.²⁰ The reliance of these mutant tumors on the EGFR pathway has led to the term oncogene addiction.

Crosstalk between VEGFR and EGFR Pathways

Both *in vitro* and *in vivo* data have established that activation of EGFR by its ligands can lead to increased VEGFR expression and neovascularization in cancer models.^{21,22} Indeed, both small molecule inhibitors and antibodies to EGFR (and downstream signaling mediators) have resulted in decreased VEGF expression and cell death in cancer cell lines and animal models.^{23–25} VEGF over expression may also mediate resistance to EGFR antagonists, with preclinical data supporting efforts to overcome acquired resistance with the addition of a VEGF inhibitor, and delaying emergence of resistance with upfront dual inhibition.²⁶ Combining bevacizumab and erlotinib in the clinic is a particularly appealing strategy, considering good tolerance of each agent alone, with lack of overlapping toxicities. This regimen has been well tolerated in a Phase II NSCLC clinical trial that showed promising activity, and the final results of two Phase III trials are awaited.^{27–29}

Vandetanib (ZD6474, Zactima™; AstraZeneca) (N-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-amine)

Vandetanib is an oral anilinoquinazoline that competes with ATP binding in the catalytic domain of several tyrosine kinases.³⁰ Recombinant enzyme assays have shown it to be a potent inhibitor of VEGFR-2 (50% inhibitory concentration [IC₅₀] of 40 nM), with additional activity against VEGFR-3 (IC₅₀ 110 nM), EGFR (IC₅₀ 500 nM) and the rearranged during transfection (RET; IC₅₀ 130 nM) kinase. Further studies on human umbilical vein endothelial cells (HUVEC) have found vandetanib to potently inhibit proliferation of VEGFR stimulated cells (IC₅₀ 60 nM) with higher doses necessary for EGFR stimulated HUVEC proliferation (IC₅₀ 170 nM). Additional *in vitro* and *in vivo* studies have also demonstrated that vandetanib inhibits cell growth of several human cancer cell

lines that have functional EGFR but are devoid of VEGFR-2, and further potentiates the anti-proliferative effects of docetaxel and paclitaxel.^{21,31} Xenograft models have in turn shown dose dependent inhibition of tumor growth with vandetanib, including NSCLC tumors resistant to gefitinib, and reduction in tumor microvessel density and inhibition of new blood vessel formation.^{30,32-34} Together, these and other preclinical studies suggest the effect of vandetanib on tumor growth and survival is mediated by both the EGFR and VEGFR pathways, and support further clinical evaluation.

Phase I studies

Two Phase I dose escalation studies evaluating daily vandetanib alone in advanced solid tumors have been completed. The first was conducted in the United States and Australia, enrolling 77 patients, with colon cancer being the most common tumor type.³⁵ Dose limiting toxicities included diarrhea, hypertension and rash. The recommended dose to evaluate in further studies was 300 mg daily. This dose was tolerated well, with the most common toxicities being rash and diarrhea. Asymptomatic QTc prolongation was also observed in 7 patients. Pharmacokinetic studies showed vandetanib to be extensively distributed, with a half life of approximately 120 hours and a minimum of 28 days continuous oral dosing required to achieve steady-state plasma concentrations. The second Phase I study was conducted in Japan, and enrolled 18 patients.³⁶ Again, 300 mg daily was determined to be the recommended dose with similar toxicity profile and pharmacokinetic findings. Of note, four of nine patients with advanced refractory NSCLC achieved a partial response per Response Evaluation Criteria in Solid Tumors (RECIST) criteria at doses of 200 or 300 mg daily.

A third Phase I trial further evaluated vandetanib in combination with pemetrexed, a newer anti-folate approved for use in advanced nonsquamous NSCLC.³⁷ Only patients with advanced NSCLC who failed first line chemotherapy were eligible. Two dose levels of vandetanib were evaluated, 100 mg and 300 mg daily, given with full doses of pemetrexed every three weeks. Both doses were well tolerated, without obvious pharmacokinetic interactions. Of the 21 patients enrolled, one achieved a partial response by RECIST criteria (from the vandetanib 100 mg cohort), and an additional 13 patients had stabilization of disease.

Phase II studies

Based on encouraging activity in Phase I studies with good tolerability of vandetanib up to 300 mg daily, four randomized Phase II trials evaluating vandetanib alone and in combination

with chemotherapy have been conducted in advanced NSCLC (Table 1).³⁸⁻⁴¹ These trials confirmed the good tolerability of vandetanib seen in Phase I studies, with modest activity supporting Phase III evaluations. The most common side effects experienced were rash, diarrhea, hypertension, and asymptomatic prolonged QTc interval. In the two studies where vandetanib was combined with chemotherapy, there were no pharmacokinetic interactions. Interestingly, the study evaluating two dose levels of vandetanib with standard docetaxel dosing suggested that a lower dose of vandetanib may be more beneficial when combined with chemotherapy. One hypothesis offered to explain this has been that with greater inhibition of EGFR achieved with higher doses of vandetanib, cancer cell proliferation is decreased with G1 cell cycle arrest compromising effectiveness of cell cycle phase-dependent activity of chemotherapy.⁴² Four Phase III trials evaluating the addition of a small molecule EGFR inhibitor (erlotinib or gefitinib) to standard first line chemotherapy support this, with no benefit appreciated.⁴³⁻⁴⁶

Correlative studies from the randomized Phase II studies included serum markers (ie, several cytokines and angiogenic factors including VEGF) and tumor tissue analysis for EGFR and KRAS mutational status, and EGFR gene copy number by FISH.^{38,41,47,48} Limited samples preclude any conclusions; however, there was a suggestion that circulating VEGF levels may be a potential biomarker, with lower values being more predictive of benefit. Additional biomarker studies are clearly needed, and such analyses from Phase III studies are awaited.

Phase III studies

Three Phase III clinical trials evaluating vandetanib were presented at the American Society of Clinical Oncology (ASCO) annual meeting in 2009 and are awaiting formal publication. Two of the studies investigated vandetanib in combination with standard second-line chemotherapy, and the third compared vandetanib to erlotinib.

ZEST

Based on the Phase II study by Natale et al³⁹ showing promising data for vandetanib versus gefitinib as monotherapy in previously treated NSCLC (Table 1), the ZEST (ZACTIMA Efficacy Study versus Tarceva) trial was designed with the primary objective to show superiority in progression-free survival (PFS) for vandetanib versus erlotinib.⁴⁹ A total of 1,240 patients with advanced lung cancer who had received previous therapy (all histologies permitted) were randomized in a 2:1 fashion to either vandetanib 300 mg/day (n = 623) or erlotinib 150 mg/day (n = 617).

Table I Randomized NSCLC clinical trials evaluating vandetanib

Study # Pts # prior chemo	Design	RR (%)	PFS*	OS (m)
Randomized Phase II Trials				
Kiura 2008 ³⁸ 53/1–2	All arms 1. V 100 mg 2. V 200 mg 3. V 300 mg	13 17.6 5.6 16.7	TTP 8.3 weeks 12.3 weeks 12.3 weeks	–
Natale 2009 ³⁹ 168/1–2	1. V 300 mg 2. Gefitinib 250 mg daily; crossover allowed	8 1	8.1 weeks 11.3 weeks HR .69; <i>P</i> = 0.013;	6.1 7.4 NS
Heymach 2007 ⁴⁰ 127/1	1. Docetaxel + V 100 mg 2. Docetaxel + V 300 mg 3. Docetaxel	26 18 12	18.7 weeks [^] 17 weeks 12 weeks [^] [^] HR 0.64; <i>P</i> = 0.037	13.1 7.9 13.4
Heymach 2008 ⁴¹ 181/chemonaive	1. Carboplatin/Paclitaxel + V 300 mg 2. Carboplatin/Paclitaxel 3. V 300 mg	32 25	24 weeks (1). 23 weeks (2) HR 0.76; <i>P</i> = 0.098 [V alone arm closed]	10.2 12.6 NS
Phase III Trials				
Natale 2009 ⁴⁹ ZEST 1240/1–2	1. V 300 mg 2. Erlotinib	12 12	11.3 weeks 8.9 weeks HR 0.98; <i>P</i> = 0.721	6.9 7.8 NS
De Boer 2009 ⁵⁰ ZEAL 534/1	1. Pemetrexed + V 100 mg 2. Pemetrexed	19 8	17.6 weeks 11.9 weeks HR 0.86; <i>P</i> = 0.108	10.5 9.2 NS
Herbst 2009 ⁵¹ ZODIAC 1391/1	1. Docetaxel + V 100 mg 2. Docetaxel	17 10	4 months 3.2 months HR 0.79; <i>P</i> < 0.001	10.6 10 NS

Note: *PFS primary endpoint of all trials except Kiura et al study³⁸ where RR was primary endpoint.

Abbreviations: RR, response rate; PFS, progression-free survival; OS, overall survival; m, months; TTP, time to progression; V, vandetanib (given once daily in all studies); NS, not statistically significant.

After a median duration of follow up of 14 months, this study failed to show any difference in PFS for patients treated with vandetanib (hazard ratio [HR] 0.98; 95.22% confidence interval [CI]: 0.87–1.10; *P* = 0.721). Secondary endpoints including overall survival, objective response rate, and time to deterioration of symptoms were similar in both groups. There was a higher incidence of adverse events in the vandetanib group, including diarrhea, hypertension, and rash.

ZEAL

The ZEAL (ZACTIMA Efficacy with Alimta in Lung cancer) trial evaluated the addition of vandetanib to pemetrexed.⁵⁰ The prior Phase I trial of this combination by De Boer et al³⁷ demonstrated the safety and tolerability of vandetanib when given with pemetrexed. Vandetanib doses of 100 mg/day were better tolerated than doses of 300 mg/day. This observation and the concern about theoretical antagonism with chemotherapy from greater EGFR inhibition achieved with the 300 mg dose led De Boer and colleagues to choose the

100 mg dose in the ZEAL study. Patients were randomized to vandetanib 100 mg/day plus pemetrexed 500 mg/m² every three weeks (*n* = 256) versus placebo plus pemetrexed (*n* = 278), with the primary endpoint of PFS. Secondary endpoints included overall survival, objective response rate, time to deterioration of symptoms, and safety. Patients received up to six cycles of chemotherapy. All patients had advanced NSCLC previously treated with first-line therapy and all histologies were included. After a median follow up duration of nine months, this study showed a trend for improved PFS (HR, 0.86; 97.58% CI: 0.69–1.06, *P* = 0.108) and OS (HR, 0.86; 97.54% CI: 0.65–1.13; *P* = 0.219); however, these results were not statistically significant. As demonstrated in other studies, the adverse events with vandetanib were most commonly rash (Grade 3+: 38% in vandetanib arm vs 26% in placebo arm), diarrhea (26% vs 18%), and hypertension (12% vs 3%). Interestingly, typical side effects of pemetrexed, such as anemia, fatigue, nausea, vomiting, were reduced in the arm receiving vandetanib.

ZODIAC

The Phase III ZODIAC (ZACTIMA in cOmbination with Docetaxel In non-smAll cell lung Cancer) trial randomized over one thousand patients with advanced NSCLC who had received first line chemotherapy to two groups: vandetanib 100 mg/day plus docetaxel 75 mg/m² every three weeks (n = 694) or to placebo plus docetaxel (n = 697).⁵¹ Patients were given up to 6 cycles of chemotherapy. This study had a median duration of follow up of 12.8 months. This study met its primary endpoint by demonstrating a statistically significant improvement in PFS for the arm treated with vandetanib plus docetaxel (HR, 0.79; 97.58% CI: 0.70–0.90; *P* < 0.001). Median PFS was 8.9 months in those receiving vandetanib and 4 months in those in the chemotherapy only arm. Difference in overall survival; however, was not statistically significant in those receiving

vandetanib (HR, 0.91; 97.52% CI: 0.78–1.07; *P* = 0.196). Not surprisingly, the adverse event profile was similar to that previously observed with vandetanib in NSCLC. Patients in the vandetanib arm experienced more diarrhea, rash, and neutropenia. The incidence of protocol-defined QTc prolongation was <2% in patients receiving vandetanib.

Conclusions

The future of vandetanib in NSCLC is uncertain. In late October 2009, Astra Zeneca announced that it was withdrawing regulatory submissions for use of vandetanib 100 mg in combination with docetaxel in patients with advanced NSCLC after initial application to the US FDA and the European Medicines Agency in June 2009. This was based on only modest PFS with no overall survival advantage with the addition of vandetanib to docetaxel

Table 2 Ongoing/pending trials of vandetanib in NSCLC

Sponsor/trial	Phase	Target N	Eligibility	Treatment	Primary endpoint
AstraZeneca ⁵² ZEPHYR NCT00404924	III	930	– Prior treatment with an EGFR TKI and up to 2 chemo regimens	1. BSC + V 300 2. BSC	OS
AstraZeneca ⁵³ NCT00753714	R II	122	– No prior chemo – ≥70 years of age	1. gemcitabine +V 100 2. gemcitabine	PFS
Pr-ECOG, LLC. ⁵⁴ NCT00687297	R II	160	– No prior therapy for advanced NSCLC	1. Docetaxel/carboplatin/ V 100 + maintenance V 300 2. Docetaxel/carboplatin/V 100	PFS
AstraZeneca ⁵⁵ NCT00777179	R II	126	– No POD after 4 cycles of gemcitabine/cisplatin for advanced NSCLC	1. Maintenance V 300 2. Placebo	PFS
MD Anderson ⁵⁶ NCT00745732	I/II	48	– Inoperable/unresectable NSCLC, not candidate for chemo	Escalating doses of V starting at 100 mg + thoracic irradiation	MTD
AstraZeneca ⁵⁷ NCT00807170	I	18	– Untreated brain metastases	V 100/200/300 + WBRT	MTD
MD Anderson ⁵⁸ BATTLE NCT00410189	II	72	– At least one prior chemo for advanced NSCLC	V 300 (biomarker directed)	PFS
MD Anderson ⁵⁹ NCT00402896	II	25	– Symptomatic recurrent pleural effusion	V 300	Time until removal of pleurex catheter
Simmons Cancer Center ⁶⁰ NCT00975260	R I/II	72	Stage IIIA/B NSCLC	1. Definitive CRT with carboplatin/paclitaxel + V followed by maintenance V 2. Definitive CRT with carboplatin/paclitaxel	OS
Karmanos Cancer Institute ⁶¹ NCT00459121	II	15	Clinical Stage IB, II, and T3N1 NSCLC	Neoadjuvant carboplatin/paclitaxel + V	Complete resection (R0) *trial completed, awaiting results
AstraZeneca ⁶² NCT00496275	I	17	Chemonaive advanced disease	Cisplatin/gemcitabine/V Cisplatin/vinorelbine/V	Safety *trial completed, awaiting results

Abbreviations: N, number of patients; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; BSC, best supportive care; V, vandetanib given once daily; R, randomized; POD, progression of disease; PFS, progression-free survival; MTD, maximum tolerated dose; WBRT, whole brain irradiation; CRT, chemoradiation; OS, overall survival.

in the ZODIAC trial. With negative results of the ZEAL and ZEST trial presented at the annual ASCO conference last year, further evaluation of vandetanib as monotherapy or with pemetrexed in unselected patients with NSCLC is unlikely. There are still several ongoing clinical trials evaluating vandetanib in various settings (see Table 2), and the results of these will help determine if an indication will be reached in NSCLC. Of particular importance will be the identification of clinical and molecular predictors of benefit from vandetanib, and correlative biomarkers from randomized trials are awaited. Without such predictors, further development of Zactima in NSCLC is unlikely.

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