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Vandetanib (ZD6474), a Dual Inhibitor of Vascular Endothelial Growth Factor Receptor (VEGFR) and Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinases: Current Status and Future Directions

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The article discusses unlabeled, investigational, or alternative uses of vandetanib (manufactured by AstraZeneca) in clinical trials in solid tumors. The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias.

LEARNING OBJECTIVES

1. Evaluate the mechanism of action of vandetanib in the care of patients with thyroid cancer.
2. Analyze the current status of clinical development and early clinical results observed with vandetanib.
3. Determine appropriate dose and schedule of administration, safety, and identification of molecular biomarkers predictive of response.

ABSTRACT

Vandetanib is a novel, orally available inhibitor of different intracellular signaling pathways involved in tumor growth, progression, and angiogenesis: vascular endothelial growth factor receptor-2, epidermal growth factor receptor, and REarranged during Transfection tyrosine kinase activity. Phase I clinical trials have shown that vandetanib is well tolerated as a single agent at daily doses ≤300 mg. In the phase II setting, nega-

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tive results were observed with vandetanib in small cell lung cancer, metastatic breast cancer, and multiple myeloma. In contrast, three randomized phase II studies showed that vandetanib prolonged the progression-free survival (PFS) time of patients with non-small cell lung cancer (NSCLC) as a single agent when compared with gefitinib or when added to chemotherapy. Rash, diarrhea, hypertension, fatigue, and asymptomatic QTc prolongation were the most common adverse events. Antitumor activity was also observed in medullary thyroid cancer. Four randomized phase III clinical trials in NSCLC are exploring the efficacy of vandetanib in combination with docetaxel, the Zactima in cOmbination with Docetaxel In non-small cell lung Cancer (ZODIAC) trial, or with pemetrexed, the Zactima Efficacy with Alimta in Lung cancer (ZEAL) trial, or as a single agent, the Zactima Efficacy when Studied versus Tarceva (ZEST) and the Zactima Efficacy trial for NSCLC Patients with History of EGFR-TKI chemo-Resistance (ZEPHYR) trials. Based on a press release by the sponsor of these trials, the PFS time was longer with vandetanib in the ZODIAC and ZEAL trials; the ZEST trial was negative for its primary superiority analysis, but was successful according to a preplanned noninferiority analysis of PFS. Ongoing phase II and III clinical trials will better define the appropriate schedule, the optimal setting of evaluation, and the safety of long-term use of vandetanib.
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INTRODUCTION

Vandetanib (ZD6474) (N-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(1-methyl-4-piperidinyl) methoxy]-4-quinazolinamine) is a novel, orally available, ATP mimetic small molecule (Fig. 1) that inhibits vascular endothelial growth factor receptor (VEGFR)-2, epidermal growth factor receptor (EGFR), and REarranged during Transfection (RET) tyrosine kinases [1, 2]. Inhibition of these tyrosine kinases blocks multiple intracellular signaling pathways involved in tumor growth, progression, and angiogenesis (Fig. 2) [3].

The VEGF signaling pathway is critical for endothelial cell proliferation, migration, and survival, and for the induction of vascular permeability [4, 5]. There are three associated transmembrane receptors for VEGF family ligands, Flt-1 (VEGFR-1), KDR (VEGFR-2), and Flt-4 (VEGFR-3), which are related to the platelet-derived growth factor receptor (PDGFR) family [6]. Each receptor possesses intrinsic tyrosine kinase activity that is stimulated after ligand binding and receptor dimerization, and is crucial for transmission of a cytoplasmic signaling response. VEGF-A (henceforth, VEGF) is the main mediator of physiological and tumor-associated angiogenesis [5]. VEGF belongs to a family of peptide growth factors that includes VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placenta-derived growth factor. VEGF exists in different isoforms that are generated through alternative splicing of VEGF mRNA. VEGFR-1 and VEGFR-2 have different binding specificities for the separate isoforms of VEGF and for additional VEGF family members (PDGF and VEGF-B, VEGF-C, and VEGF-D). VEGFR-3 only binds VEGF-C and VEGF-D and is largely located on lymphatic endothelium [7–9]. Despite the apparent complexity in VEGFR signaling, activation of VEGFR-2 alone is sufficient to promote all the major phenotypic responses to VEGF, including endothelial cell proliferation, migration, and survival, and the induction of vascular permeability [10–12].

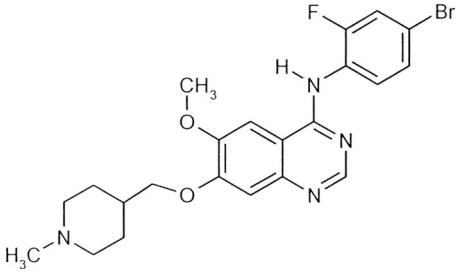

Figure 1. Chemical structure of vandetanib.

Vandetanib might produce a more significant inhibition of neoangiogenesis than other selective anti-VEGFR agents because it also has an "indirect" effect on angiogenesis, interfering with EGFR-induced production of angiogenic growth factors [13]. The EGFR family includes four different tyrosine kinase receptors: EGFR (ErbB-1), ErbB-2, ErbB-3, and ErbB-4 [14]. Each of these proteins has an extracellular ligand-binding domain, a single hydrophobic transmembrane domain, and a cytoplasmic tyrosine kinase–containing domain. The receptors of the ErbB family are activated following binding to peptide growth factors of the EGF family. Upon ligand binding, the ErbB receptors form either homo- or heterodimers. Following dimerization, auto- and transphosphorylation in tyrosine residues of the ErbB receptors occurs [15]. EGFR signaling plays a key role in promoting the growth and survival of various types of solid tumors, including non-small cell lung cancer (NSCLC) and breast, gastric, prostate, and colorectal cancer [16]. Antitumor activity of EGFR tyrosine kinase inhibitors was shown in different preclinical and clinical studies that led to the approval of these drugs for the treatment of NSCLC and pancreatic cancer. In addition, expression of

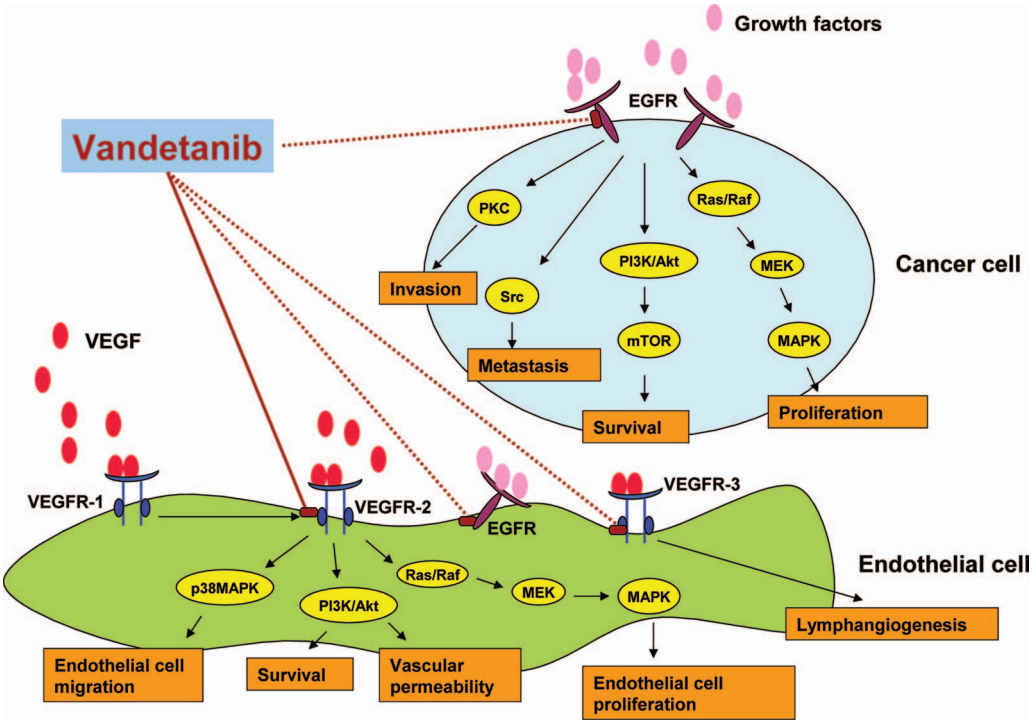

Figure 2. Intracellular signaling pathways blocked by vandetanib that are involved in tumor growth, progression, and angiogenesis. Vandetanib is a potent inhibitor (solid line) of VEGFR-2 (IC_{50}, 40 nM) and also has been shown to inhibit, with lower affinity (dashed lines), the kinase activity of VEGFR-3 (IC_{50}, 108 nM) and EGFR (IC_{50}, 500 nM).

Abbreviations: EGFR, epidermal growth factor receptor; IC_{50}, 50% inhibitory concentration; MAPK, mitogen-activated protein kinase; MEK, MAPK/extracellular signal–related kinase kinase; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3′ kinase; PKC, protein kinase C; VEGFR, vascular endothelial growth factor receptor.

EGFR in tumor-associated endothelial cells has been demonstrated [17]. In this respect, anti-EGFR agents have been shown to block proliferation and migration of endothelial cells. Therefore, the anti-EGFR activity of vandetanib might also result in an additional direct antiangiogenic mechanism.

The role of the *RET* oncogene in the development of medullary thyroid cancer (MTC) has been well characterized [18]. The *RET* gene encodes a transmembrane tyrosine kinase that binds glial cell line–derived neurotrophic factor family ligands [19]. RET signaling leads to activation of the RAS/mitogen-activated protein kinase and the phosphatidylinositol 3′ kinase/Akt pathways, having a key role in cell growth, differentiation, and survival. The activation of *RET* germline mutations has been identified as the primary cause of hereditary MTC syndromes, whereas somatic *RET* mutations account for one quarter to one half of all sporadic MTC cases [20].

Preclinical studies have suggested that the contemporary blockade of different mechanisms that are involved in tumor growth might result in more significant tumor growth inhibition than with blockade of a single pathway [21]. Tumor cells use different mechanisms to escape the activity of cytotoxic and biological agents, and the blockade of two distinct mechanisms that contribute to tumor growth, such as VEGFR-sustained angiogenesis and EGFR-induced proliferation, has a strong rationale for clinical development.

Preclinical Studies

In vitro studies have demonstrated that vandetanib is a selective inhibitor of VEGF- and EGF-stimulated cell proliferation. Studies with recombinant enzyme assays have shown that vandetanib is a potent inhibitor of VEGFR-2 tyrosine kinase activity (50% inhibitory concentration [IC_{50}], 40 nM) and a submicromolar inhibitor of EGFR tyrosine kinase (IC_{50}, 500 nM). This compound also inhibits the kinase activity of VEGFR-3 (IC_{50}, 108 nM), but has less activity versus VEGFR-1 (IC_{50}, 1,600 nM) [13]. Consistently, vandetanib potently inhibits VEGF-stimulated human umbilical vein endothelial cell (HUVEC) proliferation (IC_{50}, 60 nM) and threefold less potently inhibits EGF-stimulated HUVEC proliferation (IC_{50}, 170 nM), whereas much higher doses are required to inhibit basic fibroblast growth factor–stimulated or basal HUVEC proliferation [13]. Furthermore, Carlomagno et al. [2] showed that vandetanib inhibits the oncogenic RET kinase (IC_{50}, 100 nM) and RET-dependent thyroid tumor cell growth in vitro.

In vivo studies demonstrated the ability of vandetanib to

Table 1. Phase I clinical trials with vandetanib

Study	Treatment	*n* of patients	Recommended dose	Dose-limiting toxicity	Toxicity at recommended dose
Holden et al. (2005) [35]	Vandetanib single agent	77	300 mg/day	Diarrhea, hypertension, rash	Rash, diarrhea, hypertension, asymptomatic QTc prolongation
Tamura et al. (2006) [36]	Vandetanib single agent	18	100–300 mg/day	Grade 3 ALT elevation, hypertension	Rash, diarrhea, proteinuria, hypertension, asymptomatic QTc prolongation
De Boer et al. (2009) [37]	Vandetanib + pemetrexed	21	100–300 mg/day	Not reached	Rash, anorexia, fatigue, diarrhea, asymptomatic QTc prolongation
Saunders et al. (2009) [38]	Vandetanib + FOLFIRI	21	100–300 mg/day	Not reached	Diarrhea, nausea, fatigue, alopecia
Michael et al. (2009) [39]	Vandetanib + FOLFOX6	17	100–300 mg/day	Not reached	Diarrhea, nausea, lethargy, neutropenia, peripheral neuropathy

Abbreviations: ALT, alanine aminotransferase; FOLFIRI, 5-fluorouracil, leucovorin, and irinotecan; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin.

inhibit tumor-induced neovascularization and growth of human tumor models. The administration of vandetanib at different doses (12.5, 25, 50, or 100 mg/kg/day) produced a significant, dose-dependent inhibition of tumor growth in a panel of human tumor xenograft models, despite their different histological origins (breast, lung, prostate, colon, ovary, and vulva), growth rates, and sensitivities to the selective EGFR tyrosine kinase inhibitor gefitinib [13]. Vandetanib treatment was well tolerated, with only small effects on body weight (particularly at doses $\leq$50 mg/kg per day) and no adverse effects on clinical condition (even at 100 mg/kg per day for up to 5 weeks). Angiogenesis plays an important role in the antitumor effect of vandetanib. In fact, vandetanib significantly inhibited the ability of human NSCLC cells to induce new vessel formation when injected into athymic mice [13]. In addition, treatment with vandetanib produced a significant reduction in tumor microvessel density in a range of orthotopically implanted tumors, including gastric [22], pancreatic [23], renal [24], and lung [25] carcinoma models. Dynamic contrast-enhanced magnetic resonance imaging analysis showed a dose-dependent reduction in contrast agent uptake by tumors 24 hours after starting vandetanib treatment in mouse models of human prostate [26] and colon [27] cancer. Furthermore, vandetanib inhibited the growth of human GEO colon cancer xenografts with acquired resistance to treatment with EGFR-signaling inhibitors [28]. These studies confirm that vandetanib antitumor activity is a result of angiogenesis inhibition rather than a direct antiproliferative effect on tumor cells. Nevertheless, in both in vitro and in vivo studies in a PC-9 lung cancer model, harboring activating mutations of the *EGFR* gene, vandetanib induced robust tumor regression at all doses [29], showing the ability to inhibit EGFR-dependent tumor growth. Several studies have suggested that the combination of vandetanib with other anticancer therapies may produce additional therapeutic benefit. Ciardiello et al. [30] demonstrated that, in a xenograft model of colon cancer, vandetanib combined with paclitaxel yielded greater tumor growth inhibition than that obtained with each agent alone. Synergistic antiproliferative activity was demonstrated with vandetanib and oxaliplatin in human colorectal cancer cell lines, although only when oxaliplatin was administered before vandetanib [31]. The efficacy of combining vandetanib with radiation therapy was evaluated in xenograft models of lung cancer. Hoang et al. [32] showed that the concurrent administration of vandetanib and radiotherapy achieved greater antitumor effects than radiotherapy alone. Moreover, Williams et al. [33] investigated the impact of different scheduling of the combination and demonstrated that administration of vandetanib after radiotherapy is more effective than concurrent treatment. Finally, in vitro and in vivo studies on human pancreatic tumor models showed that vandetanib enhanced the antitumor activity of both gemcitabine and radiotherapy and that the combination of all three modalities produced a greater inhibition of tumor growth than gemcitabine alone [34].

Clinical Experience with Vandetanib

Phase I Clinical Studies

Vandetanib was evaluated as a single agent in two phase I clinical trials including patients with advanced refractory

solid tumors (Table 1). The first study enrolled 77 patients in U.S. and Australia, most having colorectal cancer [35]. The first administration of vandetanib, at doses in the range of 50–600 mg, was followed by a 7-day observation period to evaluate single-dose pharmacokinetics. Thereafter, patients began a once-daily treatment at the same dose they had previously received, with no intrapatient dose escalation. The mean duration of treatment was 11 weeks. The most common treatment-related adverse events were diarrhea and skin rash, which appeared to be dose related. Hypertension and asymptomatic QTc prolongation were also reported, but did not seem to be dose related. Doses of 500–600 mg were considered to exceed the maximum-tolerated dose (MTD); consequently, 300 mg was the recommended dose. Pharmacokinetic parameters showed that vandetanib has a large volume of distribution, slow absorption, and low clearance, with a half-life >100 hours and a minimum of 28 days of continuous dosing being required to achieve a steady-state plasma concentration. Moreover, the once-daily 300-mg dose achieved concentrations greater than the half maximal inhibitory concentration for in vitro inhibition of VEGFR-2 tyrosine kinase activity. Anti-VEGF activity was suggested clinically by delayed dermal wound angiogenesis. No objective response was achieved in this trial, although the stable disease rate was in the range of 12.5%–50% across all dose levels.

The second study recruited 18 Japanese patients [36]. They received vandetanib at doses in the range of 100–400 mg in 28-day cycles. The most common adverse events were diarrhea, skin rash, hypertension, and asymptomatic QTc prolongation, and the recommended daily dose was 300 mg. Pharmacokinetic parameters confirmed the findings of the previous trial, thus not differing between the western and Japanese populations. It is noteworthy that, in this trial, four of nine patients with NSCLC achieved an objective response according to the Response Evaluation Criteria in Solid Tumors at doses of either 200 mg or 300 mg.

Three further phase I trials of vandetanib in combination with chemotherapy were published recently. In the first trial, vandetanib was evaluated at a dose of 100 or 300 mg in combination with pemetrexed as second-line treatment for advanced NSCLC patients [37]. The MTD was not reached and no overlapping toxicity or pharmacokinetic interaction was shown; treatment was generally well tolerated. Moreover, among 21 treated patients, one partial response and 13 disease stabilizations were observed. In the other two studies, vandetanib was combined at a dose of 100 or 300 mg with 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI) and 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX)6 as first- or second-line treatment of advanced colorectal cancer patients [38, 39]. Both combinations were well tolerated, with no overlapping toxicity and without pharmacokinetic interaction reported. Two of the 14 assessable patients achieved a partial response with FOLFIRI plus vandetanib (100 mg) in first-line therapy and nine experienced stable disease of long duration (seven with the 100-mg dose and two with 300-mg dose). Preliminary efficacy results described with FOLFOX6 plus vandetanib as second-line therapy included one complete response and three confirmed partial responses.

In conclusion, phase I studies showed that once-daily administration of vandetanib at doses up to 300 mg is well tolerated, both as a single agent and in combination with chemotherapy, with mild adverse events, manageable with dose adjustment or appropriate therapy. Moreover, antitumor activity was encouraging for further clinical evaluation.

Phase II Clinical Studies

Published phase II clinical studies with vandetanib as a single agent or in combination with chemotherapy were conducted in a variety of tumor types, including NSCLC, small cell lung cancer (SCLC), MTC, breast cancer, and multiple myeloma (Table 2).

NSCLC

A randomized, double-blind, phase II dose-finding study of vandetanib monotherapy at 100, 200, and 300 mg was conducted by Kiura et al. [40] in advanced or metastatic refractory NSCLC patients. The objective response rate (RR) was the primary endpoint. Among 53 enrolled patients, seven partial responses (13%) and 27 cases of stable disease for ≥8 weeks (51%) were observed, with evidence of antitumor activity at all three doses. The safety profile was consistent with results of previous trials. A further trial is ongoing to evaluate vandetanib in NSCLC patients who failed at least one chemotherapy regimen, with the progression-free survival (PFS) rate at 8 weeks as the primary objective.

Vandetanib (300 mg) as a single agent was compared with gefitinib in a randomized double-blind study in 168 previously treated NSCLC patients [41]. The study had a crossover design to assess the activity of vandetanib in patients who failed treatment with gefitinib. The primary objectives were PFS and safety in both parts of the study. Secondary endpoints were the RR and overall survival (OS). The first part of the study (before the crossover) met its primary endpoint: the median PFS times were 11.0 weeks for vandetanib and 8.1 weeks for gefitinib (hazard ratio [HR], 0.69; 95% confidence interval, 0.50–0.96; $p = .025$). No objective responses were observed, but stable disease for >8 weeks was achieved in 37 of 83 (45%) patients receiving vandetanib and in 29 of 85 (34%) patients receiv-

Table 2. Published phase II clinical trials with vandetanib

Study	Setting	Design	*n* of patients	Treatment	Primary endpoint	Toxicity
Kiura et al. (2008) [40]	Pretreated NSCLC	Randomized, phase II	53	Vandetanib (100, 200, or 300 mg) single agent	RR, 13%	Rash, diarrhea, hypertension, asymptomatic QTc prolongation
Natale et al. (2006) [41]	Pretreated NSCLC	Randomized, phase II with crossover	168	Vandetanib (300 mg) versus gefitinib (250 mg)	PFS, 11 wks versus 8.1 wks	Diarrhea, rash, asymptomatic QTc prolongation
Heymach et al. (2007) [42]	Pretreated NSCLC	Randomized, phase II with a run-in part	127	Docetaxel + vandetanib (100 mg) or docetaxel + vandetanib (300 mg) or docetaxel + placebo	PFS, 18.7 wks (HR, 0.64; $p = 0.037$) versus 17 wks versus 12 wks	Diarrhea, fatigue, neutropenia, nausea
Heymach et al. (2008) [43]	Naïve NSCLC	Randomized, phase II	181	Vandetanib (300 mg) + carboplatin and paclitaxel versus carboplatin and paclitaxel versus vandetanib (300 mg)	PFS, 24 wks versus 23 wks ($p = .098$)[a]	Rash, diarrhea, hypertension, asymptomatic QTc prolongation
Arnold et al. (2007) [46]	Responsive SCLC	Randomized, phase II	107	Vandetanib (300 mg) versus placebo as maintenance therapy	PFS, 2.7 mos versus 2.8 mos	QTc prolongation, diarrhea, rash
Wells et al. (2007) [47]	Hereditary MTC	Phase II	30	Vandetanib (300 mg)	RR: 20%	Rash, diarrhea, fatigue, nausea
Haddad et al. (2008) [48]	Hereditary MTC	Phase II	19	Vandetanib (100 mg)	RR: 16%	Diarrhea, fatigue, rash
Miller et al. (2005) [49]	Pretreated metastatic breast cancer	Phase II	46	Vandetanib (100 and 300 mg)	RR: none	Diarrhea, rash, asymptomatic QTc prolongation
Boer et al. (2007) [50]	Pretreated metastatic breast cancer	Randomized, phase II	64	Docetaxel + vandetanib (100 mg) or docetaxel + placebo	*n* of progression events: HR, 1.19	Neutropenia, stomatitis, diarrhea, fatigue
Kovacs et al. (2006) [51]	Pretreated relapsed multiple myeloma	Phase II	18	Vandetanib (100 mg)	RR, none	Nausea, vomiting, fatigue, rash, itch, headache, diarrhea, dizziness, sensory neuropathy

[a]Statistically significant on the basis of study design.
Abbreviations: HR, hazard ratio; MTC, medullary thyroid cancer; NSCLC, non-small cell lung cancer; PFS, progression-free survival; RR, response rate; SCLC, small-cell lung cancer.

ing gefitinib. The most common side effects of vandetanib were diarrhea (grade 3–4 in 8.4% of patients), rash (grade 3–4 in 4.8% of patients), and asymptomatic QTc prolongation (all grade 1 in 20.5% of patients). In the second part of the study, disease control for >8 weeks was achieved in 16 of 37 patients (43%) who switched to vandetanib and in seven of 29 (24%) patients who switched to gefitinib. There were no unexpected safety findings with vandetanib or gefitinib. PFS prolongation did not translate into an OS advantage (median OS, 6.1 months and 7.4 months for patients initially randomized to vandetanib and gefitinib, respectively), but the crossover design might confound survival assessment.

A two-part, randomized, phase II study evaluated the efficacy of vandetanib in combination with docetaxel as second-line treatment for advanced or metastatic NSCLC patients [42]. The study design provided for a first open-label run-in part focused on treatment safety, in which patients received docetaxel at 75 mg/m^2 3-weekly plus daily vandetanib (100 or 300 mg), followed by a randomized phase with the inclusion of a docetaxel plus placebo group in a double-blind fashion. The primary objective was PFS;

secondary endpoints were safety and pharmacokinetics. The run-in phase recruited 15 patients and demonstrated that the combination of vandetanib and docetaxel did not result in greater toxicity or in changes in exposure to either drug. Half of the patients experienced stable disease for ≥12 weeks, and two partial responses were achieved in the 300-mg cohort. The median PFS times were 15.1 weeks and 19.8 weeks in the 100- and 300-mg cohorts, respectively. These findings supported advancement to the second phase of the study, enrolling a total of 127 patients. The primary endpoint was met, with the low-dose combination demonstrating a significantly longer PFS duration than with docetaxel alone: the median PFS times were 18.7 weeks for the vandetanib (100 mg) plus docetaxel (HR, 0.64; $p = .037$), 17 weeks for the vandetanib (300 mg) plus docetaxel (HR, 0.83; $p = .231$), and 12 weeks for the docetaxel plus placebo groups, respectively. Therefore, a better result than in the control arm was observed with the lower dose of vandetanib (100 mg), but not with the higher dose (300 mg). Overall, the most common adverse events were diarrhea, fatigue, neutropenia, and nausea. No clinically symptomatic changes in the electrocardiogram (ECG) were observed. The incidence of protocol-defined QTc prolongation was higher in the arm with vandetanib at 300 mg (five patients) than in the arm with vandetanib at 100 mg (two patients); no patients in the docetaxel alone arm experienced QTc prolongation.

Vandetanib was then evaluated in combination with carboplatin (area under the concentration–time curve, 6) plus paclitaxel (200 mg/m^2) as first-line treatment of advanced or metastatic NSCLC patients [43]. The appropriate dose of vandetanib was defined in a preliminary safety run-in phase, in which 10 subjects per cohort received daily doses of vandetanib of 200 mg (first cohort) and 300 mg (second cohort). The combination was generally well tolerated. A pharmacokinetic analysis showed no apparent difference in exposure to vandetanib when given with chemotherapy. It is noteworthy that seven of 18 evaluable patients in both cohorts achieved a partial response and two further patients experienced stable disease for ≥12 weeks. These results established 300 mg of vandetanib as an appropriate dose to be administered with chemotherapy in the randomized phase of the study. The primary objective was to determine whether vandetanib alone was noninferior to carboplatin and paclitaxel and whether vandetanib, carboplatin, and paclitaxel could result in a longer PFS duration than with carboplatin and paclitaxel alone (75% power to detect a 30% longer PFS time; one-sided $p = .2$). The vandetanib single-agent arm was stopped early, after a planned interim analysis showed that the PFS time was shorter with vandetanib monotherapy. The primary objective of the study was met, although the addition of vandetanib to chemotherapy achieved only a modestly longer PFS time (24 weeks versus 23 weeks; HR, 0.76; one-sided $p = .098$). OS was not significantly different between the two groups of patients. There was a higher incidence of some adverse events with vandetanib plus chemotherapy than with chemotherapy alone, including rash (64% versus 33%), diarrhea (53% versus 32%), asymptomatic QTc-related events (22% versus 4%), and hypertension (32% versus 4%). A biomarker analysis, including circulating endothelial cells and 35 plasma angiogenic factors and cytokines, suggested several potential markers predictive of clinical outcome [44]. Gender differences in the PFS benefit from vandetanib and in the plasma cytokine/angiogenic factor profile were found, suggesting advantages for females. Several cytokine/angiogenic factors were shown to be of prognostic value: high baseline E-selectin, interleukin (IL)-6, and IL-2R were adverse prognostic indicators for PFS; low levels of hepatocyte growth factor and IL-2R were associated with a longer PFS duration in the vandetanib monotherapy arm only. These gender differences and markers warrant further investigation.

An analysis of the potential relationship between baseline plasma VEGF levels and PFS was conducted in patients from the three randomized vandetanib studies in NSCLC patients [45]. The preliminary results of this analysis, reported at the 2008 American Society of Clinical Oncology Annual Meeting and not yet published as an extended paper, suggest that low baseline levels of circulating VEGF may be predictive of a PFS advantage in patients with NSCLC receiving vandetanib monotherapy (300 mg), versus gefitinib or paclitaxel and carboplatin, or vandetanib (100 mg) in combination with docetaxel versus docetaxel alone.

SCLC

A randomized phase II study evaluated vandetanib versus placebo as maintenance therapy in SCLC patients with complete or partial responses to induction chemotherapy with or without radiotherapy [46]. That trial failed its primary objective, because patients in the two arms obtained a superimposable median PFS duration (2.7 months versus 2.8 months for vandetanib and placebo, respectively). No significant difference in OS was observed. There was a higher incidence of adverse events with vandetanib than with placebo, including QTc prolongation (15.4% versus 0%; $p = .003$), diarrhea (78.8% versus 39%; $p = .001$), and rash (71.1% versus 49%; $p = .001$).

MTC

Promising data have been reported with vandetanib in MTC. Wells et al. [47] studied the drug in locally advanced or metastatic hereditary MTC patients, for whom *RET* activation is the main oncogenic event. The primary endpoint

was objective tumor response; secondary endpoints included evaluation of biochemical response (determined by changes in plasma levels of calcitonin) and safety/tolerability. Based on site investigator assessments, 20% (6 of 30) of patients experienced a partial response and another 30% (9 of 30) experienced long-lasting stabilization of disease. Moreover, a considerable reduction in plasma levels of calcitonin was observed in most patients. Adverse events occurring in >50% of patients were rash (73%), diarrhea (67%), fatigue (57%), and nausea (53%). Grade 3 adverse events included asymptomatic QTc prolongation (16.7%), rash, and diarrhea (both 10%), all of which were manageable. An additional phase II trial of vandetanib (100 mg) was conducted in the same population, with objective response as the primary endpoint [48]. Among 19 patients, three (16%) achieved a partial response and six experienced long-lasting (≥24 weeks) disease stabilization.

Metastatic Breast Cancer

Vandetanib as a single agent was studied in 46 patients with previously treated metastatic breast cancer who were enrolled sequentially in one of two dose cohorts (100 or 300 mg daily) on 28-days cycles [49]. The agent was generally well tolerated, with no unexpected toxicity: diarrhea was the most commonly reported toxicity and seemed dose related (grade 2, 4.5% and 37.5% in the 100-mg and 300-mg cohorts, respectively). Rash was reported by 26% of patients, and asymptomatic grade 1 prolongation of the QTc interval was observed in 29% of patients in the 300-mg cohort. However, the drug showed limited activity in this setting, because no objective response was observed and only one patient experienced stable disease for ≥24 weeks.

A randomized, double-blind, placebo-controlled study, presented at the 2007 San Antonio Breast Cancer Symposium, evaluated the activity and safety of vandetanib (100 mg) plus docetaxel (100 mg/m^2) as second-line treatment for metastatic breast cancer patients [50]. The combination revealed no unexpected toxicities, but no benefit was demonstrated for vandetanib plus docetaxel versus docetaxel plus placebo (HR, 1.19; $p = .59$). However, methodological limits of the trial were an imbalance in the number of patients randomized to the vandetanib arm at the study start and the choice, as primary endpoint, of the number of progression events at a cutoff date that was the same for all patients. A longer observation period prior to the cutoff for the vandetanib-treated patients may have influenced the final outcome, leading to results that should be cautiously interpreted. Longer follow-up and peer-reviewed publication are expected.

Other Cancers

A phase II trial of vandetanib (100 mg) as a single agent was conducted in 18 patients with pretreated relapsed multiple myeloma, in which angiogenesis is postulated to be a relevant target for therapy [51]. The primary endpoint was objective response, as assessed by a reduction in M protein. The most common treatment-related adverse events were nausea, vomiting, fatigue, rash, itching, headache, diarrhea, dizziness, and sensory neuropathy, all of which were not serious. No significant QTc interval changes were reported. Vandetanib achieved plasma levels that in preclinical study were predicted to inhibit VEGF signaling. However, this did not reflect the clinical benefit because no objective response was observed.

Vandetanib is currently being evaluated, as a single agent or in combination with chemotherapy or radiotherapy in several other tumor types, including gastrointestinal, head–neck, and genitourinary cancer (Table 3).

Phase III clinical studies

Two randomized, double-blind, placebo-controlled clinical trials are investigating the efficacy of the addition of vandetanib to chemotherapy as second-line treatment of patients with locally advanced or metastatic NSCLC—the Zactima in cOmbination with Docetaxel In non-small cell lung Cancer (ZODIAC) trial, comparing vandetanib (100 mg) plus docetaxel with docetaxel monotherapy in 1,391 patients, and the Zactima Efficacy with Alimta in Lung cancer (ZEAL) trial, comparing vandetanib (100 mg) and pemetrexed with pemetrexed monotherapy in 534 patients previously treated with one prior anticancer therapy for advanced NSCLC. Two further randomized, double-blind trials are evaluating the efficacy of vandetanib as a single agent—the Zactima Efficacy trial for NSCLC Patients with History of EGFR-TKI chemo-Resistance (ZEPHYR) trial, which is testing vandetanib (300 mg) versus placebo in a refractory population who failed chemotherapy and anti-EGFR therapy, and the Zactima Efficacy when Studied versus Tarceva (ZEST) trial, which is comparing vandetanib (300 mg) with erlotinib in 1,240 patients with locally advanced or metastatic NSCLC after failure of at least one prior anticancer therapy. In November 2008, the company producing vandetanib released to the press the preliminary results of the ZODIAC, ZEAL, and ZEST trials and reported that, in the first two studies, the addition of vandetanib to chemotherapy resulted in a longer PFS duration at a degree that was statistically significant in the ZODIAC but not in the smaller ZEAL study. Overall, some advantages for vandetanib were also announced for secondary endpoints (RR and symptom control). The ZEST trial did not meet its primary objective of demonstrating a statistically significant longer PFS time with vandetanib than with erlo-

Table 3. Ongoing randomized clinical trials with vandetanib

Tumor type	Study phase	Line of treatment	Treatment plan	Primary endpoint
NSCLC	II	First	Carboplatin + paclitaxel + vandetanib followed by vandetanib versus carboplatin + paclitaxel + vandetanib followed by placebo	Progression-free survival
	II	First	Carboplatin + docetaxel + vandetanib followed by placebo or vandetanib	Progression-free survival
	II	First (elderly)	Gemcitabine + vandetanib versus gemcitabine + placebo	Progression-free survival
	II	Second or third	Vandetanib versus gefitinib	Time to progression
	III	Second or third	Vandetanib versus erlotinib	Progression-free survival
	III	Second	Docetaxel + vandetanib versus docetaxel	Progression-free survival
	III	Second	Pemetrexed + vandetanib versus pemetrexed	Progression-free survival
	III	Third	Vandetanib + BSC versus BSC in patients who have failed anti-EGFR therapy	Progression-free survival
SCLC	II	First	Cisplatin + etoposide + vandetanib versus cisplatin + etoposide + placebo	Time to progression
Mesothelioma	II	Second	Vandetanib versus vinorelbine	Disease control rate
Medullary TC	II	First or second	Vandetanib (300 mg) versus placebo	Progression-free survival
Papillary/follicular TC	II	First	Vandetanib (300 mg) versus placebo	Progression-free survival
MBC	II	First or second	Fulvestrant + vandetanib (100 or 300 mg) versus fulvestrant + placebo	Event-free rate
Head and neck cancer	II	First or second	Docetaxel + vandetanib versus docetaxel	Response rate
	II	First	Cisplatin + RT versus cisplatin + RT + vandetanib	Progression-free survival
Metastatic CRC	II	Second	FOLFIRI + vandetanib (100 or 300 mg) versus FOLFIRI + placebo	Efficacy
	II	Second	FOLFOX + vandetanib (100 or 300 mg) versus FOLFOX + placebo	Efficacy
HCC	II	First	Vandetanib (100 or 300 mg) + BSC versus placebo + BSC	Disease control rate
Gastric cancer	II	First or second	Docetaxel + vandetanib (100 or 300 mg) versus docetaxel	Response rate
Biliary tract cancer	II	First	Vandetanib versus gemcitabine + vandetanib versus gemcitabine + placebo	Progression-free survival

(continued)

Table 3. (continued)

Tumor type	Study phase	Line of treatment	Treatment plan	Primary endpoint
Prostate cancer	II	First	Docetaxel + prednisolone + vandetanib versus docetaxel + prednisolone + placebo	PSA response
	II	Hormone sensitive	Vandetanib versus placebo during intermittent hormonal therapy	PSA response
	II	Hormone refractory	Bicalutamide + vandetanib versus bicalutamide	PSA response
	II	Hormone refractory	Bicalutamide + vandetanib versus bicalutamide + placebo	Biological progression-free rate
Transitional cell cancer	II	Second to fourth	Docetaxel + vandetanib versus docetaxel + placebo	Progression-free survival
	II	Second	Docetaxel + vandetanib (100 or 300 mg) versus docetaxel + placebo	Progression-free survival

Abbreviations: BSC, best supportive care; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; FOLFIRI, 5-fluorouracil, leucovorin, and irinotecan; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; HCC, hepatocellular carcinoma; MBC, metastatic breast cancer; NSCLC, non-small cell lung cancer; PSA, prostate-specific antigen; RT, radiotherapy; SCLC, small cell lung cancer; TC, thyroid cancer.

tinib. However, in a preplanned noninferiority analysis, vandetanib was not inferior to erlotinib in terms of PFS and OS. The observed safety profile in these three phase III studies was consistent with previous studies with vandetanib in NSCLC. The most common adverse events associated with vandetanib included rash, diarrhea, and hypertension.

Full results of these studies should be presented during 2009 and might lead to the approval of vandetanib in combination with chemotherapy (docetaxel or pemetrexed) or as a single agent for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior anticancer therapy.

Open Questions and Future Perspectives

With the increased understanding of the EGFR and VEGFR network and the preliminary information on phase III trials with vandetanib it is likely that, in the near future, this new agent will be another option for the treatment of patients affected by NSCLC. However, there are several questions that need to be addressed regarding the contrasting antitumor activity observed in clinical studies, the appropriate schedule (single agent versus combination) and dose (100 mg versus 300 mg) of the drug, the optimal setting of evaluation (pretreated or naïve patients), the safety of long-term administration, and the identification of molecular biomarkers defining groups of patients potentially benefiting from therapy.

The lack of antitumor activity observed with vandetanib as maintenance therapy in SCLC and in patients with heavily pretreated metastatic breast cancer could be explained by different expressions of the molecular targets of the drug, and also by the development of different adaptive mechanisms by cancer cells that lead to activation of alternative pathways involved in the proliferation and survival of tumor cells as well as in neoangiogenesis. In particular, activation of multiple signaling pathways has been shown to occur early in breast cancer cells, and this phenomenon might be significantly altered by treatment with anticancer agents, including target-based agents and endocrine therapies [52]. Evidence suggests that during tumor progression the number of angiogenic cytokines that cancer cells are able to produce increases [53]. On this basis, in patients with endocrine-responsive metastatic breast cancer, the early combination of hormonal treatment with a signal transduction inhibitor, targeting pathways alternative to those controlled by the estrogen receptor that are involved in mechanisms of resistance to endocrine treatments, might prove effective in preventing the occurrence of resistance and improving the efficacy of endocrine therapy [54]. Similarly, anti-VEGF therapies might be more effective in the early phase of tumor development, when angiogenesis is mainly dependent on VEGF. This hypothesis will be tested within a randomized, double-blind, Italian multicentre phase II study (the ZACtima FASlodex Trial; ClinicalTrials.gov identifier, NCT00752986), comparing two doses of vandetanib (100 mg and 300 mg) with placebo in combination with fulvestrant, an estrogen receptor antagonist with

no estrogen agonist effects, in postmenopausal patients with endocrine-responsive metastatic breast cancer.

Identifying the optimal dosing and scheduling of vandetanib is another significant challenge. In combination schedules, enhanced activity of docetaxel has been unexpectedly observed at lower doses of vandetanib (100 mg), but not at higher doses (300 mg), in advanced NSCLC. Intriguingly, this kinase inhibitor has higher affinity for VEGFR-2 than for EGFR. Therefore, we might assume that, at lower doses, the drug efficiently inhibits only VEGFR-2 and in this way enhances the efficacy of cytotoxic agents, as observed with bevacizumab and chemotherapy [55]. At higher doses, which are likely to block both VEGFRs and EGFRs, the synergism with docetaxel is no longer seen, and this observation is in agreement with the negative results reported with the combination of EGFR inhibitors and chemotherapy [56]. However, vandetanib was not evaluated at 100 mg in combination with carboplatin and paclitaxel in a subsequent randomized phase II study that demonstrated only a slight benefit in terms of PFS for vandetanib at 300 mg with paclitaxel and carboplatin. When vandetanib is used as a single agent, it has been hypothesized that the contemporary blockade of both EGFR and VEGFR signaling with an adequate dose of the drug (300 mg) should result in a more significant inhibition of tumor growth. However, the negative results recently announced for the ZEST trial make it difficult to predict whether such a hypothesis will be confirmed by clinical trials. Moreover, approximately 8%–10% of NSCLC patients respond to anti-EGFR agents—patients with mutations in the *EGFR* tyrosine kinase domain are likely to respond, whereas patients carrying mutations in *KRAS* are resistant to EGFR tyrosine kinase inhibitors. In this regard, it will be interesting to compare the activity of vandetanib and erlotinib in these subsets of patients.

Another issue is the long-term toxicity of this agent, taking into account the lack of adequate knowledge in this matter and the possibility of prolonged periods of therapy in nonprogressive patients. Rash, diarrhea, hypertension, and fatigue are common, but usually manageable with medical treatments or dose reductions. Diarrhea and rash appear to be dose related and are more frequent and severe in patients receiving higher doses of vandetanib (300 mg). They are likely related to the EGFR inhibitory effects of vandetanib, having also been observed with other EGFR inhibitors, such as gefitinib, erlotinib, and cetuximab. In contrast, hypertension does not appear to be dose related and it is likely to be a class effect of VEGF inhibitors, observed in studies of bevacizumab as well as with several other VEGF inhibitors [57]. Left ventricular dysfunction, which is the main cardiac side effect of sunitinib and is also observed with bevacizumab, has not been reported to date in studies with vandetanib. A characteristic cardiac adverse effect of vandetanib is asymptomatic QTc prolongation, which has been observed rarely with sunitinib (<1%). Asymptomatic QTc prolongation has garnered attention because of its risk for malignant cardiac arrhythmia with torsade de pointes and sudden cardiac death [58]. A defined mechanism to explain the QTc prolongation effects of vandetanib is at present unknown: both direct mechanisms, through interaction with potassium ion channels, and indirect mechanisms, involving age, comorbidities, intrinsic cardiac abnormalities, concomitant medications, and electrolyte disturbances resulting from vomiting, diarrhea, and decreased oral intake, have been hypothesized [59]. Based on the currently available data, several recommendations for QTc assessment can be made: a baseline ECG and cardiac history, including concomitant medications, should be obtained for all patients before initiating therapy; the ECG should be repeated weekly for the first month of therapy and, thereafter, every month for the first 6 months; drugs that are known to cause QTc prolongation, such as amiodarone, amitriptyline, erythromycin, levofloxacin, domperidone, octreotide, ondansetron, etc., should not be combined with vandetanib; and electrolytes should be closely monitored and replaced.

Another intriguing issue is the identification of molecular biomarkers predictive of response with vandetanib. The preliminary results of an exploratory analysis conducted on patients included in three randomized phase II studies suggest that low baseline plasma levels of circulating VEGF may be predictive of a PFS advantage in patients with NSCLC receiving vandetanib. However, this finding and the role of tissue or blood angiogenic factors, cytokines, and circulating endothelial cells should be confirmed in prospective studies.

Several unanswered questions also remain regarding the optimal clinical setting for evaluation. The preferred setting could be in patients having a small tumor burden for which the cytostatic effects of a target-based agent may result in maximum benefit [60]. In addition, the lower level of redundancy of angiogenic mechanisms in the early phase of tumor development might result in higher antitumor activity of anti-VEGF signaling agents. In untreated patients with advanced NSCLC, vandetanib will be evaluated in combination with carboplatin plus docetaxel, with carboplatin plus paclitaxel followed or not by maintenance therapy, or with gemcitabine in elderly patients (Table 3). Furthermore, randomized phase II studies are ongoing with vandetanib in SCLC (in combination with cisplatin and etoposide), in colon cancer (in combination with chemotherapy), in gastric cancer (in combination with docetaxel), in transitional cell cancer (in combination with do-

cetaxel), in head-neck tumor (in combination with radiotherapy, docetaxel, or cisplatin), in prostate cancer (as a single agent or in combination with docetaxel and prednisolone), in mesothelioma, and in thyroid cancer (medullary and papillary/follicular) and hepatocellular carcinoma (both as a single agent). The final results of these trials will better define the efficacy spectrum and the toxicity profile of vandetanib in the treatment of solid tumors.

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