

Anti-vascular endothelial growth factor therapies at the crossroads: linifanib for non-small cell lung cancer

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Abstract: Activated vascular endothelial growth factor receptors (VEGFR) 1, 2 and 3, and platelet-derived growth factor receptor (PDGFR) work together to guide the microvasculature into tumor lesions, and have been shown to be involved in tumor growth, invasion and metastasis. In non-small cell lung cancer (NSCLC), tumor angiogenesis mediated by vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) is known to be associated with a poor disease free survival and poor overall survival. A randomized phase II trial was carried out to compare the efficacy/safety of three doses of linifanib with that of CBDCE + paclitaxel (PTX), as the largest and first placebo-controlled trial of linifanib for NSCLC. The result revealed modest, but not robust improvement of the progression-free and overall survival. A number of negative results and number of positive results without robust clinical benefit have been reported from trials of treatments targeting tumor angiogenesis, and anti-angiogenesis therapies seem to be at the crossroads between a prosperous future and a downhill path. Appropriate predictive markers to select right the drugs for the right patients need to be developed to obtain clinical benefit from anti-VEGF therapies.

Keywords: Linifanib; anti-VEGF therapy; non-small cell lung cancer (NSCLC); predictive marker

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Solid tumors are dependent on the vascular system for growth, invasion and metastasis. Tumor angiogenesis has been shown to support solid tumors mainly by supplying energy and providing the means to the formation of metastases (1). A number of growth factors, proteases and cytokines have been reported to have pro-angiogenic effects and to induce tumor angiogenesis. Among these vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), transforming growth factor- α , platelet-derived growth factor (PDGF) and the receptors for these factors are the best recognized pro-angiogenic substances (2).

Three subtypes of vascular endothelial growth factor receptors (VEGFR) that play distinct roles in the growth of tumor vasculatures have been recognized. VEGFR 1 and 2 are considered to activate endothelial cells and to induce growth of the tumor microvasculature, thereby aiding in tumor progression and formation of metastases (3).

Expression of VEGFR 3 on the lymphatic vasculature is reported to be associated with tumor lymphangiogenesis in a variety of solid tumors (4). PDGF and platelet-derived growth factor receptor (PDGFR) activate pericytes which cover new microvasculature, and promote tumor angiogenesis (5,6). Activated VEGFR 1, 2 and 3 and PDGFR work together to guide the microvasculature into tumor lesions, and are reported to be involved in tumor growth, invasion and metastasis (7).

In non-small cell lung cancer (NSCLC), tumor angiogenesis mediated by VEGF and PDGF is known to be associated with a poor disease-free survival and poor overall survival. Fontanini *et al.* reported, based on univariate and multivariate analyses carried out after adjustments for various prognostic factors, that VEGF expression had a significant influence on new vessel formation and the prognosis in resected NSCLC patients (8). O'Byrne

et al. investigated the association of VEGF and PDGF expressions with tumor angiogenesis, and revealed that the expressions of these pro-angiogenic factors have significant indicators of a poor prognosis (9).

Several agents targeting VEGF and PDGF activity have been introduced for the treatment of such cancers as renal cell carcinoma, hepatocellular carcinoma and NSCLC. Sorafenib, a multikinase inhibitor that inhibits the tyrosine kinases of VEGFR 1, 2 and 3, PDGFR, c-kit, RET and serin-threonine kinase of the Raf family has been shown to offer significant survival benefit (prolongation by 3 months) as compared to best supportive care in patients with refractory hepatocellular carcinoma (10). Sunitinib, a multi-targeted kinase that blocks VEGFR 1, 2 and 3, PDGFR, c-kit and RET, was shown to be superior, in terms of the response rate and progression-free survival, to the previously used standard therapy (interferon alpha) in cases of renal cell carcinoma (11). Axitinib is a second-generation multikinase inhibitor of VEGFR 1, 2 and 3, c-kit, FLT-3 and B-Raf with a 50–450 times higher potency than that of the first generation VEGFR inhibitors. In a randomized phase III trial conducted in patients with relapsed renal cell carcinoma, axitinib yielded a significantly longer progression-free survival as compared to sorafenib, a first-generation VEGFR inhibitor (12). Pazopanib is also an inhibitor of VEGFR 1, 2 and 3, PDGFR and c-kit and was shown in a phase III non-inferiority trial conducted in patients with metastatic renal cell carcinoma, to show similar activity to sunitinib, while being better tolerated (13). However, no multikinase inhibitors targeting the VEGF and/or PDGF pathway that offer robust survival benefit in NSCLC patients have been identified.

Linifanib (ABT-869), 1-[4-(3-amino-1H-indazol-4-yl)phenyl]-3-(2-fluoro-5-methylphenyl) urea, is an inhibitor that blocks adenosine triphosphate (ATP) binding to the receptor tyrosine kinases. Linifanib has been demonstrated by enzyme assays to exert activity against VEGFR-1 [half-maximal inhibitory concentration (IC₅₀) = 30 nmol/L], VEGFR-2 (IC₅₀ = 8.5 nmol/L), VEGFR-3 (IC₅₀ = 40 nmol/L), PDGFR (IC₅₀ = 25 nmol/L) and Flt3 kinase (IC₅₀ = 9.5 nmol/L) (14). Therefore, it was expected that linifanib would show a potent anti-tumor angiogenetic effect by synergistically inhibiting endothelial cells (VEGFR 1, 2 and 3) and pericytes (PDGFR).

In a phase I dose-finding study, linifanib was administered as a single daily dose, and a dose of up to 0.25 mg/kg/day was found to be well-tolerated (15,16). Similar to those associated with other VEGFR inhibitors, the common

adverse hypertension, proteinuria, fatigue, hand and foot rashes and myalgia, all of which could generally be managed by routine supportive measures (15,16). A randomized phase II trial of linifanib monotherapy (0.1 or 0.25 mg/kg) was conducted in patients with refractory NSCLC who had previously received one or two lines of chemotherapies. The response rate was 5.1% and the median progression-free survival and overall survival were 3.6 and 9.0 months, respectively (17). Based on the safety and efficacy data in the monotherapy setting, a phase I trial of linifanib in combination with carboplatin (CBDCA) plus paclitaxel (PTX) was planned (18). In this dose finding study, concurrent administration of CBDCA (AUC = 6 mg/mL/min) + PTX (200 mg/m²) and linifanib at a fixed dose of 7.5 or 12.5 mg/body/day was evaluated in patients with advanced NSCLC. The recommended dose of linifanib for administration in combination with CBDCA + PTX was determined to be 12.5 mg/body/day (18). The overall response rate was 75% and the median progression free survival was 7.2 months.

In 2015, Ramalingam *et al.* reported the result of a randomized phase II trial carried out to compare two doses of linifanib [placebo (arm A), 7.5 mg (arm B) and 12.5 mg (arm C)] administered in combination with CBDCA + PTX (19). This was the largest and first placebo-controlled trial of linifanib in patients with NSCLC. The results revealed modest, but not robust improvement of the progression-free survival and overall survival. The median progression free survival times in arm A, B and C were 5.4, 8.3 and 7.3 months, respectively. The overall survival times in arm A, B and C were 11.3, 11.4 and 13.0 months, respectively. In a planned biomarker analysis, plasma samples of patients were profiled by the levels of carcinoembryonic antigen (CEA) and soluble cytokeratin 19 fragments (CYFRA 21-1) using ARCHITECT enzyme-linked immunosorbent assays (Abbott Diagnostics, Abbott Park, IL, USA). A positive profile (CEA 3 ng/mL; CYFRA 21-1 7 ng/mL) in pretreatment plasma samples significantly predicted better progression free survival in the linifanib treatment arms (arm B: HR 0.49; arm C: HR 0.38), although no statistically significant correlation with the overall survival was detected. Although these results had a modest impact, there had been no information on subsequent clinical trials as at the time of publication of this trial.

The two anti-VEGF targeted drugs for which phase III trials have provided significantly favorable results are bevacizumab and ramucirumab. Bevacizumab is a monoclonal antibody directed against VEGF-A, which was

shown to successfully improve the progression-free and overall survivals in patients with non-squamous NSCLC when administered in combination with CBDCA + PTX (20). Ramucirumab administered in combination with docetaxel yielded statistically significant prolongation of the overall survival in comparison with docetaxel alone in patients with NSCLC who had received prior systemic chemotherapy (21). Based on these data, the FDA, as also the regulatory agencies in other countries, has approved the use of bevacizumab and ramucirumab for NSCLC. Although it was statistically significant, the impact of these agents on the overall survival was modest (bevacizumab: prolongation by 2 months, ramucirumab: prolongation by 1.4 months). No predictive markers applicable for clinical use have been identified for selecting patients suitable for these anti-VEGF therapies.

To identify predictors of the efficacy of anti-VEGF therapy, a number of proangiogenic factors (VEGF, PIGF, SDF-1 α , SCF, IL-6, PDGF, EPO, G-CSF etc.) and other biomarkers have been evaluated in translational analyses (22-24). Of these, measurement of circulating endothelial cells (CECs) and circulating endothelial cell progenitors (CEPs) were reported to be associated with angiogenesis and to be correlated with the efficacy of anti-VEGF treatment in solid tumors (22,23). As previously described, the classical tumor markers (CEA and CYFRA 21-1) may be useful as predictive biomarkers in NSCLC patients receiving linifanib (19). This finding about predictive biomarkers could be as important as the results on the efficacy in this randomized phase II trial (19).

Recently, Cainap *et al.* reported a phase III trial comparing linifanib and sorafenib in patients with advanced hepatocellular carcinoma. Although linifanib yielded better results in terms of the overall response and time to progression, it failed to show any statistically significant superiority or non-inferiority as compared to sorafenib (25). Based on the number of negative results and number of positive results without robust clinical benefits reported from trials of treatments targeting tumor angiogenesis, anti-angiogenesis therapies seem to be at the crossroads between a prosperous future and a downhill path. Just like other driver-oncogene driven therapeutics, predictive markers needed to develop to select the right drugs for the right patients even in relation to anti-VEGF therapies.

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Footnote

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