Editorial

Anti-angiogenic therapy in nonsquamous non-small cell lung cancer (NSCLC) with tyrosine kinase inhibition (TKI) that targets the VEGF receptor (VEGFR): perspective on phase III clinical trials

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Annually, there are over 200,000 lung cancer diagnoses in the United States (1). Only about 15% of patients are diagnosed with early stage disease (1). The prognosis of those with advanced disease, such as stage IIIB or stage IV, is dismal and less than 5% (1). The standard of care includes platinum based systemic therapy combinations. However, treatments are shifting toward newer targeted and small molecule therapies to improve outcomes among patients with advanced non-small cell lung cancer (NSCLC).

Angiogenesis is an integral process for growth of solid tumors dependent on endothelial cell proliferation and migration (2). The vascular endothelial growth factor (VEGF) pathway has been well studied and shown to play a critical role in angiogenesis (2). As a result, there are numerous studies that examined small-molecule inhibitors of VEGF receptors (VEGFR) and their ability to inhibit angiogenesis and tumor growth (2). There has been increased interest in anti-angiogenic agents to treat various malignancies including NSCLC.

Bevacizumab is a humanized monoclonal antibody to VEGF and thereby prevents its interaction with the VEGF receptor (3). It is approved for use in combination with chemotherapy for the treatment of patients with metastatic NSCLC. Two large phase III trials demonstrated the efficacy of combined bevacizumab to platinum based doublet therapy, the North American Eastern Cooperative Oncology Group (ECOG) 4599 (4) and the European AVAiL (5,6).

In ECOG 4599, previously untreated patients with advanced, nonsquamous NSCLC were randomized to paclitaxel/carboplatin plus bevacizumab or the same chemotherapy alone (4). The addition of bevacizumab to paclitaxel and carboplatin compared to chemotherapy alone had a significantly improved median PFS, ORR, and OS in patients that received bevacizumab (*Table 1*). In the AVAiL study, patients with nonsquamous NSCLC were randomly assigned to cisplatin and gemcitabine plus low dose bevacizumab, high dose bevacizumab, or placebo (5,6). The addition of bevacizumab resulted in significantly improved PFS and ORR (*Table 1*). However, OS was not significantly increased with bevacizumab (*Table 1*). The promising results of bevacizumab combined with chemotherapy contributed to the development of other anti-angiogenic drugs, such as tyrosine kinase inhibitors (TKIs) that target the VEGF receptor (VEGFR) with associated inhibition of multiple targets (7).

Motesanib (AMG706) is a potent oral nicotinamide that selectively inhibits VEGFR1, VEGFR2, VEGFR3, platelet derived growth factor receptor (PDGFR), and Kit receptors (2,8,9). In preclinical studies, motesanib demonstrated tumor regression and anti-tumor properties in multiple solid malignancies including breast cancer, lung cancer,

Table 1 Phase III trials ECOG 4599 (4) and AVAiL (5,6) evaluating efficacy of bevacizumab

Variable	ECOG 4599 (stage IIIB/IV)			AVAiL (stage IIIB/IV)			
	PCB	PC	P value	CGB-LD	CGB-HD	CG	P value
Number of patients (N)	434	444		345	351	347	–
Median PFS (month)	6.2	4.5	<0.05	6.7	6.5	6.1	<0.05
ORR (%)	35	15	<0.05	20.1	34.1	30.4	<0.05
Median OS (month)	12.3	10.3	<0.05	8.7		7.3	NS

PCB, paclitaxel-carboplatin-bevacizumab; PC, paclitaxel-carboplatin-placebo; CGB-LD, cisplatin-gemcitabine-bevacizumab low dose; CGB-HD, cisplatin-gemcitabine-bevacizumab high dose; CG, cisplatin-gemcitabine-placebo; PFS, progression free survival; ORR, objective response rate; OS, overall survival; NS, not significant (P>0.05).

Table 2 Phase III trials MONET1 (10,11) and Kubota *et al.* study (12) to evaluate efficacy of motesanib

Variable	MONET 1 (stage IIIB/IV)			Kubota *et al.* study (stage IV)		
	PCM	PC	P value	PCM	PC	P value
Number of patients (N)	541	549	–	197	204	–
Median PFS (month)	5.6	5.4	<0.05	6.1	5.6	NS
ORR (%)	40	26	<0.05	60.1	41.6	<0.05
Median OS (month)	13	11	NS	Not reached	21.6	NS

PCM, paclitaxel-carboplatin-motesanib; PC, paclitaxel-carboplatin-placebo; PFS, progression free survival; ORR, objective response rate; OS, overall survival; NS, not significant (P>0.05).

thyroid cancer, and colon cancer (2,8). Blumenschein *et al.* conducted a phase II trial that evaluated subjects with advanced nonsquamous NSCLC (stage IIIB and IV) that were randomized to receive paclitaxel and carboplatin with motesanib or the same chemotherapy with bevacizumab (1). The ORR, PFS, and OS were comparable between motesanib or bevacizumab plus chemotherapy (1). These promising results led to evaluating the efficacy of motesanib in the MONET1 (Motesanib NSCLC Efficacy and Tolerability) trial (10).

Scagliotti *et al.* reported on the findings of the phase III MONET 1 study where untreated patients with stage IIIB/IV nonsquamous NSCLC were randomized to chemotherapy (carboplatin and paclitaxel) with motesanib or the same chemotherapy alone (*Table 2*) (10). There was a higher incidence of grade ≥3 adverse incidents (73% and 59%, respectively) with motesanib therapy (10). The addition of motesanib to chemotherapy failed to show any significant improvement in OS with an attendant increased toxicity related to motesanib (*Table 2*).

Although the overall results from the MONET 1 trial failed show improved OS with motesanib, there was a preplanned, exploratory subgroup analysis of Asian subjects (N=227) compared to non-Asian patients (N=863) with nonsquamous NSCLC who were randomized to receive chemotherapy (carboplatin and paclitaxel) with motesanib or the same chemotherapy alone (10). There was a significant difference in ORR between Asian and non-Asian subjects (34.5% *vs.* 9.2%, respectively; P<0.05) receiving motesanib (11). Additionally, there was a significant difference in the median OS (20.9 *vs.* 10.9 months, respectively; P<0.05) and PFS (7 *vs.* 5.5 months, respectively; P<0.05) in Asians compared to non-Asian subjects receiving motesanib (11). There was an unclear understanding of what accounted for the differences in clinical outcomes in the subset analysis. These findings led to the development and need for a confirmatory trial designed with appropriate statistical power among Asian patients in an effort to validate and reproduce the findings from the subset analysis of the MONET1 trial.

Kubota *et al.* conducted a phase III trial of carboplatin and paclitaxel with motesanib compared to the same chemotherapy alone randomized to East Asian patients with stage IV nonsquamous NSCLC to evaluate the efficacy of motesanib (12). Given the known differences in incidence

of epidermal growth factor receptor (EGFR) mutations in Asian *vs.* non-Asian subjects, the study was stratified for EGFR mutational status. The addition of motesanib to chemotherapy led to no significant difference in median PFS or OS (*Table 2*). Similar to previous studies that have documented increased adverse events among patients on motesanib, side effects included gastrointestinal upset, hypertension and gallbladder pathology (12). Because the hypothesized improvement in PFS was not met, and increased AE with motesanib, the study was terminated and evaluation of OS and other secondary end points were not performed. Although this study was well designed and conducted appropriately, the findings are concordant with the results from the phase III MONET1 study and were not able to replicate the subgroup analysis of Asian subjects. Additionally, the MONET1 study and the current trial by Kubota *et al.* add to the existing body of evidence that demonstrate the lack of efficacy and increased toxicity with VEGFR TKIs combined with chemotherapy in unselected, nonsquamous NSCLC patients.

Translation of the preclinical promising findings into clinical practice has been challenging due to the insufficient understanding of mechanisms underlying resistance to anti-angiogenesis treatment and lack of validated biomarkers that predict efficacy, toxicity, and resistance to VEGF targeted therapy (7). There is an increasing body of studies that have revealed mechanisms of intrinsic or acquired resistance to anti-angiogenesis therapies directed at VEGF or VEGFR (7,13). Potential mechanisms of resistance to anti-angiogenic drugs have included amplification of pro-angiogenic genes, escape via different modes of vascularization, secretion of multiple pro-angiogenic factors from malignant cells and stromal cells, and recruitment of pro-angiogenic bone marrow derived cells (7,13). Additionally, anti-angiogenesis treatment induced hypoxia may mediate resistance to therapy at the interface between tumor and host (7). A number of additional non-VEGF angiogenic pathways have been described including hypoxia inducible factor (HIF), platelet derived growth factor (PDGF), fibroblast growth factor (FGF), angiopoietin (Ang), and Notch, along with various inflammatory mediators of angiogenesis (7,13).

In conclusion, angiogenesis has a critical role in carcinogenesis. The translation of anti-angiogenesis therapies from preclinical studies to clinical trials has been challenging in malignancies, such as lung cancer. There is a vital need to understand angiogenic biomarkers that predict efficacy and toxicity to anti-angiogenic therapies in order to select patients most likely to respond to treatment. The mechanisms of intrinsic (primary) and acquired resistance to anti-angiogenic therapies are inadequately understood. At the current time, further clinical trials to evaluate the efficacy of VEGFR TKI alone or in combination with chemotherapy in non-selected patients with nonsquamous NSCLC is unlikely to show positive findings in clinical primary and secondary endpoints.

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Footnote

Conflicts of Interest: JM Lee serves on the Steering Committee for Genentech and as Co-Chair of Thoracic Surgery on the Executive Committee for Lung Cancer Mutation Consortium (LCMC). SL Revels has no conflicts of interest to declare.

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