The potential role of bevacizumab in early stages and locally advanced non-small cell lung cancer

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***Abstract*:** Improving outcomes for early-stage non-small cell lung cancer (NSCLC) is a major research area considering that a significant percentage of such patients develop recurrent disease within 5 years of complete lung resection. Adjuvant chemotherapy prolongs survival, with an absolute improvement in 5-year overall survival of about 5% with drawbacks such as treatment toxicity. Approximately, one third of patients with newly diagnosed NSCLC have locally advanced disease not amenable for surgical resection – in this setting of patients concurrent chemoradiation is the standard of therapy. However, the treatment of locally advanced NSCLC is still controversial and clinical outcomes are disappointing, and so new approaches are required to improve the clinical benefit in this setting of patients. Vascular endothelial growth factor (VEGF) is a key angiogenic factor implicated in tumor blood vessels formation and permeability, and tumor VEGF overexpression in patients with early stage lung cancer has been associated with worse relapse free and overall survival. Several agents have been developed that inhibit VEGF or its receptor signalling system. Bevacizumab is the first recombinant humanized monoclonal antibody binding VEGF to demonstrate clinical benefit or rather a survival prolongation in combination with chemotherapy in the treatment of non-squamous advanced NSCLC patients. These positive results led to a large number of clinical trials to evaluate bevacizumab in combination with other targeted agents in advanced disease, and to define the role of this agent in early stage NSCLC such as the impact of bevacizumab integration in chemoradiotherapy strategy for locally advanced disease.

***Keywords*:** non-small cell lung cancer, angiogenesis, vascular endothelial growth factor, bevacizumab

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Introduction

Lung cancer accounts for the largest number of new cases of cancer worldwide and results in about 1 million deaths annually [Parkin *et al.* 2000]. For early-stage non-small cell lung cancer (NSCLC) surgical lung resection is the treatment of choice, however 5-year survival rates range from 30 to 60% [Ponn *et al.* 2005].

The role of adjuvant chemotherapy for resected early stage NSCLC was still an open question until a few years ago but currently it represents the standard treatment for patients with resected stages II–IIIA. Oncologists have tried for more than 30 years to improve cure rates in patients with surgically resectable NSCLC by treating them with adjuvant chemotherapy. These efforts culminated in some randomized clinical trials that demonstrate that postoperative cisplatin-based chemotherapy for patients with completely resected stages IB–IIIA NSCLC improves survival over surgery alone [Douillard *et al.* 2006; Winton *et al.* 2005; Arriagada *et al.* 2004]. The benefit of adjuvant chemotherapy is a 14–30% reduction in the risk of death, which translates into a 5–15% improvement in 5-year survival.

However, the first phase III studies failed to show a significant benefit with adjuvant chemotherapy, these trials included the Eastern Cooperative Oncology Group (ECOG) 3590 (Intergroup 0115) trial [Keller *et al.* 2000] and

the Big Lung Trial (BLT) [Waller *et al*. 2004], both of which were relatively small, but the Adjuvant Lung Project Italy (ALPI) [Scagliotti *et al*. 2003] enrolled over 1,000 patients and showed no survival advantage with the addition of adjuvant chemotherapy.

An individual patient meta-analysis (LACE) of the five largest, cisplatin-based studies (ALPI, BLT, IALT, JBR.10, and ANITA) has demonstrated a 5.3% absolute survival advantage at 5 years [Hazard Ratio (HR): 0.89; 95% CI 0.82–0.96; $p = 0.004$) for adjuvant cisplatin therapy; however, this benefit depends on stage and is statistically significant in patients with stages II and III (HR: 0.83; 95% CI 0.73–0.95) while a detriment for chemotherapy was suggested in stage IA patients (HR: 1.41; 95% CI 0.96–2.09) [Pignon *et al.* 2006].

The stage IB subset analysis trended toward benefit (HR: 0.92), but failed to reach statistical significance (95% CI: 0.78–1.10). This meta-analysis provides further validation that the benefit of platinum-based adjuvant chemotherapy, if it exists in stage IB, is small and would require a prohibitively large trial to be detected.

The Cancer and Leukemia Group B 9633 trial, the only trial to focus exclusively on stage IB patients, showed no statistically significant survival benefit from adjuvant chemotherapy in this population, however in an unplanned subset analysis, patients on CALGB 9633 with tumors of at least 4 cm did have an overall survival advantage, with an HR of 0.66 ($p = 0.04$) [Strauss *et al.* 2006]. The patients in each arm with tumors <4 cm did not differ in survival based on treatment, with an HR of 1.02 ($p = 0.51$). These results are not conclusive, but support further studies looking at patients with stage IB disease with larger tumors.

Despite the widespread acceptance of cisplatin-based treatment for patients with stages II and III, a number of questions have not yet been answered with regard to a possible role for regimens other than cisplatin, markers that might predict benefit from adjuvant therapy, and the possible advantage of the incorporation of biologic agents into the adjuvant regimen.

Nevertheless at diagnosis, locally advanced NSCLC patients are not eligible to surgical resection. The majority of these patients can be appropriately treated with a combination of chemotherapy and radiotherapy. At the present time for unresectable stage III NSCLC patients with good performance status (0–1) and with good pulmonary function tests, concomitant chemo-radiotherapy is the standard of care [Govindan *et al*. 2008]. However, among oncologists, the approach to locally advanced NSCLC and to chemoradiotherapy regimens is still heterogeneous. Thus, the search for new strategies is mandatory – progress in the treatment of locally advanced NSCLC will require the addition of further combination chemotherapy as induction or consolidation to concurrent chemoradiotherapy, the careful integration of new therapeutic agents, including target drugs that could also potentiate chemoradiotherapy treatment.

To date, several biological agents have been investigated in NSCLC treatment; however, only a few of these agents can offer hope of a substantial impact on the natural history of the disease, and negative results are more commonly reported than positive ones. One of the targeted approaches most widely studied in the treatment of NSCLC is the inhibition of angiogenesis. Bevacizumab, the anti-vascular endothelial growth factor (VEGF) monoclonal antibody (mAb), has shown clinical benefit in multiple cancers including NSCLC. This review will focus on the potential role of bevacizumab, in early and locally advanced NSCLC treatment.

Tumor angiogenesis in lung cancer

Lung cancer presents elevated vascularization levels, and high microvessel density is thought to be predictive of metastasis and poor prognosis [Meert *et al.* 2002]. Cancer cells express numerous angiogenic factors released in the extracellular matrix (ECM) before binding to endothelial cell receptors, inducing an angiogenesis specific signal. These factors lead to increased expression of α-v-β3 integrins on the endothelial cell surface, binding activated matrix metalloprotease-2 (MMP2), which causes breakdown of the basal endothelial membrane. The proliferation of endothelial cells supports vascular budding. The structure and functional mechanism of these tumor vessels are abnormal [Morgensztern and Govindan, 2006]. These abnormalities can result in an alteration of fluid, blood, and oxygen transfers leading to either chemo- or radio-resistance. The anarchy of this tumor vascularization is caused by the abnormal development, maturation and

remodelling of unexpected vessels related to a modification of the balance among biological factors. Of the factors that induce proliferation, improvement and survival of the endothelial cell, VEGF is the most potent and specific of the endothelial cell mitogens [Herbst *et al.* 2005; Hicklin and Ellis, 2005].

The VEGF-related gene family comprises six angiogenic and lymphangiogenic secreted glycoproteins growth factors referred to as VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placenta growth factor (PlGF)-1 and PlGF-2 [Ferrara *et al.* 2003; Houck K *et al.* 1991]. VEGF-A, commonly named as VEGF, is a 45-kDa homodimeric glycoprotein with a diverse range of angiogenic activities. VEGF has two identified receptors: fms-like tyrosine kinase-1 (Flt-1) and fetal liver kinase-1/kinase domain region (Flk-1/KDR) [Ferrara, 1999]. A tyrosine kinase receptor, VEGFR-3 – also referred to as fms-like tyrosine kinase 4 (Flt-4) – is activated by VEGF-C and VEGF-D and has been found to be primarily associated with lymphangiogenesis [Paavonen *et al.* 2000].

Vascular regression has been demonstrated to occur rapidly after initiation of anti-VEGF therapy in both preclinical models and cancer patients [Willet *et al.* 2004]. The morphology and the function of surviving tumour blood vessels are transiently normalized so that they more closely resemble the normal vasculature [Jain, 2005]. These changes reduce intratumoral pressure, facilitating the delivery of other anticancer therapies to the tumor [Jain, 2005; Ferrara *et al.* 2003]. Consequently, several therapeutic agents that inhibit the actions of VEGF or its receptors are currently in development for use in several solid tumors such as breast cancer, colorectal cancer and NSCLC.

The anti-VEGF agents currently investigated in NSCLC include mAbs that bind the VEGF or multi-targeted tyrosine kinase inhibitors (TKIs) that target the VEGF receptors (VEGFRs).

Bevacizumab in non-small cell lung cancer treatment

On October 11, 2006, the US Food and Drug Administration (FDA) granted approval for bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA), administered in combination with carboplatin and paclitaxel, for the initial treatment of patients with locally advanced, or metastatic, nonsquamous, NSCLC. The approval was based on the results of a randomized, multicenter phase III clinical trial, conducted by the ECOG; eligible patients were chemotherapy-naïve patients with stage IIIB/IV nonsquamous NSCLC and ECOG performance status score of 0 or 1; patients with gross hemoptysis (1/2 tsp red blood) and those receiving therapeutic anticoaugulation were excluded. This trial (ECOG 4599) evaluated bevacizumab plus carboplatin and paclitaxel (BV/CP, 434 patients) *versus* carboplatin and paclitaxel alone (CP, 444 patients). The overall survival (OS) was significantly longer in patients receiving BV/CP than in those receiving CP alone (median OS: 12.3 *versus* 10.3 months; HR: 0.80; $p = 0.013$, stratified log rank test). The median progression-free survival (PFS) times in the two groups were 6.2 and 4.5 months respectively (HR: 0.66; $p < 0.001$), with corresponding response rate (RR) of 35% and 15% ($p < 0.001$) [Sandler *et al.* 2006]. The restriction of the patient population to nonsquamous histology, based on life-threatening or fatal hemoptysis occurring in 4 of 13 patients with squamous histology who received a BV/CP regimen in a phase II study, have determined in this trial a lower incidence of grade 3 pulmonary hemorrhage [Johnson *et al.* 2004]. Another phase III trial, enrolled outside the US, has evaluated the combination of bevacizumab (15 mg/kg or 7.5 mg/kg every 3 weeks until disease progression) with gemcitabine and cisplatin *versus* the same chemotherapy regimen alone in 1,043 patients with previously untreated, advanced nonsquamous NSCLC. This trial was not powered to compare the two doses of bevacizumab directly. A significantly longer PFS time, the primary study endpoint, [6.1 months, 6.7 months (HR: 0.75; $p = 0.002$), and 6.5 months (HR: 0.82; $p = 0.03$), in the control, 7.5 mg/kg, and 15 mg/kg bevacizumab arms, respectively], and a higher RR (20%, 34%, and 30.4%, in the control, 7.5 mg/kg, and 15 mg/kg bevacizumab arms, respectively), were observed in patients randomized to receive bevacizumab therapy [Reck *et al.* 2009]. Median OS, the secondary endpoint of study, was 13.1 months for chemotherapy alone, 13.6 months for bevacizumab 7.5 mg/kg + chemotherapy (HR *versus* placebo 0.92, 95% CI 0.77–1.10) and 13.4 months for bevacizumab 15 mg/kg + chemotherapy (HR 1.02, 95% CI 0.85–1.22) [Manegold *et al.* 2008]. It is likely that the unprecedented high use of multiple second-line therapies in this trial is the main reason why the PFS benefit did not

translate into an OS benefit. These two clinical trials represent the first evidence of an improvement in treatment outcomes of chemotherapy with targeted therapies in the first-line treatment of advanced NSCLC – in contrast to phase III trials in which the combination of epidermal growth factor receptor (EGFR) TKIs such as erlotinib and gefitinib with standard first-line chemotherapy failed to show superior survival compared to chemotherapy alone [Gatzemeier *et al*. 2007; Herbst *et al.* 2005; Giaccone *et al.* 2004; Herbst *et al.* 2004]. Initially squamous cell histology was identified as a risk factor for pulmonary hemorrhage, leading the exclusion of patients with squamous cell histology from clinical trials with bevacizumab. However, pulmonary hemorrhage appeared to be associated with centrally located tumors, tumors closely adjacent to major blood vessels, and the presence or development of tumor cavitation. Because squamous cell tumors are more frequently centrally located and have a greater tendency to cavitate as compared to adenocarcinoma, it is not clear whether histology alone is the most important risk factor for bleeding, or simply a surrogate for other risk factors. Thus, there is interest in determining if patients with squamous histology and with brain metastases which represent another risk factor for bleeding, can be, at least partially, recandidated to this effective targeted therapy. Moreover, the risk related to these two conditions, although not negligible, is not completely clear for this reason several clinical trials are ongoing to investigate these arguments. In fact, in a phase II trial, the BRIDGE trial, patients with squamous cell histology will be treated with two cycles of carboplatin and paclitaxel, and then treatment initiated with carboplatin, paclitaxel, and bevacizumab for an additional four cycles. Another phase I/II AVASQ (Avastin in Squamous NSCLC) study will evaluate the safety of administering thoracic radiotherapy to central lung lesions before carboplatin and paclitaxel plus bevacizumab in the first- and second-line treatment of advanced squamous NSCLC. Based on the results reported in advanced disease, a major question is whether this advance can be translate into an improved cure rate for patients in adjuvant setting.

Bevacizumab in adjuvant and neoadjuvant setting

Several clinical studies have been planned and others are already ongoing aimed at extending the benefit of bevacizumab into the adjuvant and neoadjuvant settings.

An important issue is that in the adjuvant setting bevacizumab efficacy may be expected to be enhanced considering that the problems related to the squamous histology, central lesion or previous severe hemoptysis are solved by the primary tumor already being resected.

The US Intergroup phase III trial, ECOG 1505, has tested one of following chemotherapy options: cisplatin/vinorelbine, cisplatin/docetaxel, cisplatin/gemcitabine, cisplatin/pemetrexed (non-squamous histology only), with some chemotherapy regimens plus bevacizumab in patients with resected IB-IIIA NSCLC; however patients with stage IB disease must have tumors measuring 4 cm. The primary objective of this study is to evaluate overall survival with chemotherapy with or without bevacizumab in this set of patients.

A total of 1,500 patients will be selected for this study, and they will be randomized to receive bevacizumab starting with the first cycle of chemotherapy and continuing for up to 1 year, or chemotherapy without bevacizumab; chemotherapy will be administered for four cycles. Patients are stratified according to type of chemotherapy, stage [IB *versus* II *versus* IIIA (N2) *versus* IIIA (T3, N1)], histology (squamous cell *versus* other), and gender. In this trial, squamous cell histologies will be allowed as there will be no gross tumor and the risk of pulmonary hemorrage should be absent.

A further multicenter randomized phase II trial is ongoing to evaluate the safety and efficacy of carboplatin/docetaxel chemotherapy plus bevacizumab followed by maintenance bevacizumab and erlotinib therapy in completely resected Ib/II and selected stage III NSCLC patients.

A pharmacogenomic study, in completely resected stages IB–IIIA NSCLC patients unfit for cisplatin-based adjuvant chemotherapy treatment and with excision repair cross-complementing one (ERCC1) positive tumor, will evaluate the feasibility of docetaxel plus vinorelbine combination in the adjuvant setting. An additional purpose of this study is to establish whether a third drug, bevacizumab, may be delivered safely with docetaxel plus vinorelbine. The safety and feasibility of the addition of bevacizumab to radiotherapy and cisplatin-based chemotherapy (cisplatin/docetaxel or cisplatin/gemcitabine) in resected stage IIIA-N2 NSCLC

is being evaluated in a pilot trial. In this trial, bevacizumab is administered simultaneously with chemotherapy and with radiotherapy, and after as maintenance therapy for 1 year.

The Bevacizumab and Chemotherapy for Operable NSCLC (BEACON) is a single institution phase II trial for stage IB–IIIA resectable NSCLC patients. The primary goal of this study is to show that the addition of bevacizumab to a cisplatin-based chemotherapy in the neo-adjuvant setting for nonsquamous cell carcinomas improves the rate of pathologic downstaging. In this trial, patients with nonsquamous histology will receive neo-adjuvant cisplatin based chemotherapy plus bevacizumab, while patients with squamous cell carcinoma or nonsquamous cell large central tumor in proximity to blood vessels will be assigned to receive pre-operative chemotherapy alone. Postoperatively, all patients independently to histology receive maintenance bevacizumab treatment for 1 year; following surgical removal of the primary tumor lesion, patients with squamous tumors may be able to benefit from the use of the bevacizumab to attack microscopic residual disease remaining after surgery.

The activity and the tolerability profile of the combination cisplatin/docetaxel plus bevacizumab were tested in patients with resectable IB-IIIA stage NSCLC. Patients with adenocarcinoma (cohort 1) were treated with preoperative bevacizumab and docetaxel/cisplatin (DC); while patients with squamous histology, central location or recent hemoptysis received DC induction therapy without bevacizumab (cohort 2). Patients enrolled in cohort 1 received bevacizumab (15 mg/kg) followed by chemotherapy 2 weeks later to assess single-agent bevacizumab response. Cohort 2 patients were treated with chemotherapy alone followed by resection. All patients received adjuvant bevacizumab treatment for 1 year. Preliminary data of 19 enrolled patients (11 cohort 1 and 8 cohort 2) have been recently presented. After single agent bevacizumab (by bimensional measurement), >10% reduction in tumor size was observed after 2 weeks in 6/11 patients. After bevacizumab plus chemotherapy, there were reported 6/10 (60%) PR, 6/10 patients underwent R0 resection and no bevacizumab-related operative complications were observed. In this trial, bevacizumab administered in the neoadjuvant and adjuvant setting appear well tolerated and with more than 90% full-dose drug delivery [Rizvi *et al*. 2007]. Table 1 summarizes several clinical trials in early stage NSCLC.

Bevacizumab in locally advanced setting

The phase I/II Southern West Oncology Group (SWOG) S0533, has been planned to assess the frequency and severity of toxic effects of induction chemo- and radiotherapy with or without bevacizumab followed by consolidation chemotherapy plus bevacizumab in a total of 182 untreated unresectable stage III NSCLC patients. Patients are assigned to one of three of the following treatment groups: chemotherapy (cisplatin/etoposide) plus concurrent thoracic radiotherapy (cohort 1), or the same chemotherapy regimen and radiotherapy treatment plus bevacizumab administered on two different schedules (cohort 2 and cohort 3). All patients receive a consolidation therapy including docetaxel and bevacizumab for three cycles. Patients are stratified according to risk criteria: low-risk disease (nonsquamous NSCLC, no primary tumor with cavitation and/or tumor within 1 cm of a major vessel, and no hemoptysis in the past 28 days) or high-risk disease (squamous cell and/or tumor that has cavitation or is located within 1 cm of a major vessel and/or hemoptysis in the past 28 days).

Two single-arm open label, multicenter trials in locally advanced unresectable nonsquamous NSCLC will assess the feasibility of treatment and tolerability of bevacizumab in combination with concurrent thoracic radiation and chemotherapy. These trials will also establish the preferred dose of bevacizumab (7.5 or 15 mg/kg iv) in combination with cisplatin/vinorelbine (B021247 trial) or cisplatin/etoposide (B021563 trial) and explore the overall RR of these combinations.

An additional phase I/II study will evaluate concurrent radiotherapy and weekly carboplatin and paclitaxel chemotherapy plus tri-weekly bevacizumab followed by consolidation treatment with two cycles of tri-weekly carboplatin/paclitaxel plus bevacizumab.

Patients with lung cancer receiving bevacizumab plus chemotherapy and radiation may be at risk of developing trache-oesophageal (TE) fistula formation. Trache-oesophageal fistula has been seen in a study combining concurrent chemotherapy and radiation plus bevacizumab in patients with limited-stage small cell lung cancer (SCLC).

Table 1. Selected clinical trials of bevacizumab (bev) in early and locally advanced non-small cell lung cancer.

Trial	Phase	Stage	Setting	n pts	Treatment	Primary Endpoint
ECOG 1505	III	IB–IIIA	Adjuvant	1500	CDDP + TXT ± bev; CDDP + VNR ± bev; CDDP + GEM ± bev; CDDP + PEM* ± bev;	OS
BEACON	II	IB–IIIA	Neoadjuvant	–	cisplatin-based chemotherapy ± bevacizumab	Rate of downstaging
Rizvi *et al.* 2007	–	IB–IIIA	Neoadjuvant	70	bev CDDP + TXT + bev CDDP + TXT§	Response to single agent bev, rate of downstaging
			Adjuvant		bev for 1 year	
SWOG S0533	I–II	IIIA (N2)–IIIB	Locally advanced	182	Induction therapy: CDDP + ETO + RT ± bev Consolidation therapy: TXT + bev for 3 cycles	Frequency and severity of toxicity
B021247	I		Locally advanced	<100	Cohort 1:CDDP + VNR + RT + bev (7.5 mg/kg) for 5 cycles Bev for 4 cycles Cohort 2:CDDP + VNR + RT + bev (15 mg/kg) for 5 cycles bev for 4 cycles	Safety and tolerability, PfD of bev
B021563	I		Locally advanced	<100	Cohort 1:CDDP + ETO + RT + bev (7.5 mg/Kg) for 3 cycles Cohort 2:CDDP + ETO + RT + bev (15 mg/Kg) for 3 cycles Cohort 3: CDDP + ETO + RT + bev PfD bev for 6 cycles	Safety and tolerability, PfD of bev
UNC-LCCC-0511	I–II	IIIA/IIIB	Locally advanced	50	Induction therapy: CBDCA + PTX + bev Cohort 1:CBDCA + PTX + bev + RT Cohort 2:CBDCA + PTX + bev + RT + Er (100 mg/die) Cohort 3:CBDCA + PTX + bev + RT + Er (150 mg/die)	MTD of bev and Er; safety and toxicity; PFS

CBDCA, carboplatin; CDDP, cisplatin; Er, erlotinib; ETO, etoposide; GEM, gemcitabine; MTD, maximun tolerated dose; OS, overall survival; PEM, pemetrexed; PFS, progression free survival; PfD, preferred dose; pts, patients; PTX, paclitaxel; TXT, docetaxel; VNR, vinorelbine.
*(nonsquamous histology only); §(squamous histology; central location or recent hemoptysis).

In an investigator-sponsored multicenter, single-arm phase II trial, patients with limited-stage SCLC received four cycles of concurrent irinotecan, carboplatin, radiation therapy, and bevacizumab followed by maintenance bevacizumab for up to 6 months. There have been two confirmed serious adverse events of TE fistula (one fatal) reported in the first 29 patients enrolled in the study. A second and third fatal event (upper aerodigestive tract hemorrhage and death of unknown cause) was also reported, in which TE fistula was suspected but not confirmed. All three events occurred during the bevacizumab maintenance phase of the study in the context of persistent esophagitis. Potential mechanisms include enhanced regional tissue injury and impaired mucosal healing.

The rate of TE fistula in patients with limited-stage SCLC is estimated to be <1%.The incidence of TE fistula observed in this trial to date exceeds this rate. Due to the small number of patients treated in the setting of limited-stage SCLC and the nonrandomized nature of this trial, it is not possible to distinguish the toxicity observed in this trial from other risk factors for the development of TE fistula, such as intrathoracic organ sensitivity from chemotherapy and radiotherapy alone.

A direct cause and effect between bevacizumab and these events has not been established, but cannot be ruled out.

Combining targeted agents that block multiple signalling pathways may reveal a very useful therapeutic approach leading to better outcomes [Maione *et al.* 2006]. The University of North Caroline has coordinated a phase I/II trial to investigate the role of bevacizumab in unresectable IIIA/B NSCLC patients and its combination with erlotinib. Patients with squamous histology are elegible for this trial, while patients with the same histology but tumor adjacent or infiltrating major blood vessels are ineligible. Patients received an induction therapy with carboplatin/paclitaxel/bevacizumab for two cycles; patients with stable or responding disease proceed to chemoradiotherapy according to their assigned dose cohort (cohort 1: thoracic radiotherapy plus carbolatin/paclitaxel weekly and bevacizumab every 2 weeks; cohort 2: chemoradiotherapy/bevacizumab as in cohort 1 plus erlotinib at 100 mg; cohort 3: chemoradiotherapy/bevacizumab as in cohort 1 plus erlotinib at 150 mg). After completion of chemoradiotherapy, patients proceed to consolidation therapy with bevacizumab and erlotinib.

Eighteen out of 20 enrolled patients have completed induction therapy reporting one grade 3–4 nonhematologic toxicity (grade 3 hypertension), and no pulmonary hemorrhage has been seen. Eight of 18 patients (44.4%) have had objective responses and none have progressed during induction treatment. There was one grade 3 pulmonary hemorrhage requiring bevacizumab termination, one grade 3 interstitial pneumonitis and two grade 3 esophagitis with four out of five patients achieving the target dose of 74 Gy. Overall, 5/15 (33%) patients had grade 3 esophagitis. One grade 5 late hemorrhage occurred in a squamous patient.

Preliminarily, the incorporation of bevacizumab and erlotinib into this treatment paradigm appears feasible – esophagitis remains the primary toxicity and phase II expansion is ongoing with erlotinib at dose of 100 mg [Socinski *et al.* 2008].

Table 1 summarizes several clinical trials of bevacizumab in locally advanced NSCLC.

Conclusion

The VEGF-targeted recombinant humanized monoclonal antibody, bevacizumab, has demonstrated efficacy in advanced NSCLC. Among new biologic drugs, bevacizumab is the first agent to show clear therapeutic potential in combination with chemotherapy; in fact the addition of bevacizumab to first-line chemotherapy with carboplatin/paclitaxel improved RR and PFS and added 2 months to median OS. Also, when bevacizumab was added to cisplatin-based chemotherapy there was a significant increase of PFS and RR. However, about half of all advanced NSCLC patients, such as patients with brain metastases and/or squamous histology, are not candidates for bevacizumab treatment according to eligibility criteria from the landmark phase III trial. Several clinical studies are ongoing to explore the safety of bevacizumab in these patient populations, to assess the combination of bevacizumab with other cytotoxic chemotherapy regimens and new active biological drugs in the treatment of NSCLC.

Some studies are also planned to explore other applications of bevacizumab such as in the

adjuvant and neoadjuvant settings and into combined modality approaches for locally advanced disease these studies should further help to define the therapeutic strategies that could improve outcomes in early and locally advanced NSCLC patients.

Conflict of interest statement

None declared.

References

Arriagada, R., Bergman, B., Dunant, A., Le Chevalier, T., Pignon, J.P., Vansteenkiste, J. and International Adjuvant Lung Cancer Trial Collaborative Group (2004) Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med* 350: 351–360.

Douillard, Y., Rosell, R., De Lena, M., Carpagnano, F., Ramlau, R., Gonzáles-Larriba, J.L. *et al.* (2006) Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. *Lancet Oncol* 7: 719–727.

Ferrara, N. (1999) Molecular and biological properties of vascular endothelial growth factor. *J Mol Med* 77: 527–543.

Ferrara, N., Gerber, H.P. and LeCouter, J. (2003) The biology of VEGF and its receptors. *Nat Med* 9: 669–676.

Gatzemeier, U., Pluzanska, A., Szczesna, A., Kaukel, E., Roubec, J., De Rosa, F. *et al.* (2007) Phase III study of erlotinib in combination with cisplatin and gemcitabine in advanced non-small-cell lung cancer: The Tarceva Lung Cancer Investigation Trial. *J Clin Oncol* 25: 1545–1552.

Giaccone, G., Herbst, R.S., Manegold, C., Scagliotti, G., Rosell, R., Miller, V. *et al.* (2004) Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: A phase III trial—INTACT 1. *J Clin Oncol* 22: 777–784.

Govindan, R., Bogart, J. and Vokes, E.E. (2008) Locally advanced non-small cell lung cancer: the past, present, and future. *J Thorac Oncol* 3: 917–928.

Herbst, R.S., Giaccone, G., Schiller, J.H., Natale, R.B., Miller, V., Manegold, C. *et al.* (2004) Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: A phase III trial—INTACT 2. *J Clin Oncol* 22: 785–794.

Herbst, R.S., Onn, A. and Sandler, A. (2005) Angiogenesis and lung cancer: Prognostic and therapeutic implications. *J Clin Oncol* 23: 3243–3256.

Herbst, R.S., Prager, D., Hermann, R., Fehrenbacher, L., Johnson, B.E., Sandler, A. *et al.* (2005) TRIBUTE: A phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. *J Clin Oncol* 23: 5892–5899.

Hicklin, D.J. and Ellis, L.M. (2005) Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. *J Clin Oncol* 23: 1011–1027.

Houck, K., Ferrara, N., Winer, J., Cachianes, G., Li, B. and Leung, D.W. (1991) The vascular endothelial growth factor family: Identification of a fourth molecular species and characterization of alternative splicing of RNA. *Mol Endocrinol* 5: 1806–1814.

Jain, R.K. (2005) Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. *Science* 307: 58–62.

Johnson, D.H., Fehrenbacher, L., Novotny, W.F., Herbst, R.S., Nemunaitis, J.J., Jablons, D.M. *et al.* (2004) Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* 22: 2184–2191.

Keller, S.M., Adak, S., Wagner, H., Herskovic, A., Komaki, R., Brooks, B.J. *et al.* (2000) Eastern Cooperative Oncology Group. A randomized trial of postoperative adjuvant therapy in patients with completely resected stage II or IIIA non-small-cell lung cancer. *N Engl J Med* 343: 1217–1222.

Maione, P., Gridelli, C., Troiani, T. and Ciardiello, F. (2006) Combining target therapies and drugs with multiple target in the treatment of NSCLC. *The Oncologist* 11: 274–284.

Manegold, C., Von Pawel, J., Zatloukal, P., Ramlau, R., Gorbounova, V., Hirsh, V. *et al.* (2008) BO17704 (AVAIL): a phase III randomised study of first-line bevacizumab combined with cisplatin/gemcitabine (CG) in patients (pts) with advanced or recurrent non-squamous, non-small cell lung cancer (NSCLC). *Annal of Oncol* 19: LAB1 abstr.

Meert, A.P., Paesmans, M., Martin, B., Delmotte, P., Berghmans, T., Verdebout, J.M. *et al.* (2002) The role of microvessel density on the survival of patients with lung cancer: a systematic review of the literature with meta-analysis. *Br J Cancer* 87: 694–701.

Morgensztern, D. and Govindan, R. (2006) Clinical trials of antiangiogenic therapy in non-small cell lung cancer: focus on bevacizumab and ZD6474. *Expert Rev Anticancer Ther* 6: 545–551.

Paavonen, K., Puolakkainen, P., Jussila, L., Jahkola, T. and Alitalo, K. (2000) Vascular endothelial growth factor receptor-3 in lymphangiogenesis in wound healing. *Am J Pathol* 156: 1499–1504.

Parkin, D.M., Bray, F., Ferlay, J. and Pisani, P. (2000) Estimating the world cancer burden: Globocan. *Int J Cancer* 94: 153–156.

Pignon, J.P., Tribodet, H., Scagliotti, G.V., Douillard, J.Y., Shepherd, F.A., Stephens, R.J. *et al.* (2006) Lung Adjuvant Cisplatin Evaluation

(LACE): A pooled analysis of five randomized clinical trials including 4,584 patients. *J Clin Oncol* 24: 7008 abstr.

Ponn, R.B., Lo Cicero, J. III and Daly, B.D.T. (2005) Surgical treatment of non small cell lung cancer. In: Shields, T.W., Lo Cicero, J.III, Ponn, R., Rusch, V.W. (eds), *General thoracic surgery*, 6th edn. Philadelphia: Lippincot Williams and Wilkin, pp. 1548–1587.

Reck, M., von Pawel, J., Zatloukal, P., Ramlau, R., Gorbounova, V., Hirsh, V. *et al.* (2009) Phase III Trial of Cisplatin Plus Gemcitabine With Either Placebo or Bevacizumab As First-Line Therapy for Nonsquamous Non-Small-Cell Lung Cancer: AVAiL. *J Clin Oncol* 27: 1227–1234.

Rizvi, N.A., Rusch, V., Zhao, B., Senturk, E., Schwartz, L., Fury, M. *et al.* (2007) Single agent bevacizumab and bevacizumab in combination with docetaxel and cisplatin as induction therapy for resectable IB-IIIA non-small cell lung cancer. *J Clin Oncol* 25: 18045 abstr.

Sandler, A., Gray, R., Perry, M.C., Brahmer, J., Schiller, J.H., Dowlati, A. *et al.* (2006) Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 355: 2542–2550.

Scagliotti, G.V., Fossati, R., Torri, V., Crinò, L., Giaccone, G., Silvano, G. *et al.* (2003) Randomized study of adjuvant chemotherapy for completely resected stage I, II, or IIIA non-small-cell lung cancer. *J Natl Cancer Inst* 95: 1453–1461.

Socinski, M.A., Morris, D.E., Stinchcombe, T.E., Halle, J.S., Moore, D.T., Tynan, M.T. *et al.* (2008) Incorporation of bevacizumab (B) and erlotinib (Er) with induction (I) and concurrent (C) carboplatin (Cb)/paclitaxel (P) and 74 Gy of thoracic radiotherapy in stage III non-small cell lung cancer (NSCLC). *J Clin Oncol* 26: 7517 abstr.

Strauss, G.M., Herndon, J.E., Maddaus, M.A., Johnstone, D.W., Johnson, E.A., Watson, D.M. *et al.* (2006) Adjuvant chemotherapy in stage IB non-small cell lung cancer (NSCLC): Update on Cancer and Leukemia Group B (CALGB) protocol 9633. *J Clin Oncol* 24: 7007 abst.

Waller, D., Peake, M.D., Stephens, R.J., Gower, N.H., Milroy, R., Parmar, M.K. *et al.* (2004) Chemotherapy for patients with non-small cell lung cancer: The surgical setting of the Big Lung Trial. *Eur J Cardiothorac Surg* 26: 173–182.

Winton, T., Livingston, R., Johnson, D., Rigas, J., Johnston, M., Butts, C. *et al.* (2005) Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. *N Engl J Med* 352: 2589–2597.