Phase II Study of Docetaxel-plus-Bevacizumab Combination Therapy in Patients Previously Treated for Advanced Non-squamous Non-small Cell Lung Cancer

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Abstract. *Aim: This phase II study was conducted to evaluate the efficacy and safety of docetaxel and bevacizumab combination therapy in patients with previously-treated non-squamous non-small cell lung cancer (Nsq NSCLC). Patients and Methods: Patients with histologically- or cytologically-confirmed Nsq NSCLC, 20-74 years of age, who had performance status 0-2, and had undergone at least one prior chemotherapy course were eligible for the study. Patients were treated with docetaxel (60 mg/m^2) and bevacizumab (15 mg/kg) on day 1, which was repeated every three weeks until progressive disease or unacceptable toxicity occurred. The primary end-point was the response rate (RR) and the planned sample size was 28 patients. Results: Between May 2010 and July 2011, 28 patients were enrolled (16 males, 12 females; median age=65 years; performance status 0/1: 19/9; adenocarcinoma/other: 22/6; number of prior chemotherapy courses 1/2/3 or more: 16/5/7). Twenty-eight patients were included in the toxicity analysis, out of whom 27 were evaluable for response. Objective response was observed in 18 patients (partial response in 18, stable disease in 8, progressive disease in 1); the RR and disease control rates were 66.7% and 96.0%, respectively. The median follow-up was 23.9 months, median progression-free survival was 7.2 months, and median overall survival was 21.6 months. The main toxicity associated with this regimen was myelosuppression (grade 3/4 neutropenia: 82.1%; febrile neutropenia: 21%). Mild non-hematological toxicity was observed but there was no severe bleeding. Conclusion: The combination regimen of docetaxel-plus-bevacizumab is very active in patients with previously-treated Nsq NSCLC and warrants further research.*

Lung cancer remains the leading cause of cancer-related death worldwide. Non-small cell lung cancer (NSCLC) accounts for 80% of all cases of lung cancer, with a 65%-75% rate of locally advanced or metastatic disease (1).

Platinum-based doublet combination chemotherapy is regarded as the standard treatment for metastatic NSCLC, and it usually consists of a platinum compound (cisplatin or carboplatin) combined with a third-generation agent (gemcitabine, paclitaxel, docetaxel, vinorelbine, or pemetrexed). Although this regimen has significantly improved median survival and quality of life (2, 3), patients with advanced NSCLC who initially respond will eventually show disease progression. For patients with good performance status (PS) when the disease has progressed during or after first-line chemotherapy, second-line chemotherapy offers a modest survival advantage over best supportive care-alone (4).

On the basis of phase III trials, docetaxel (Taxotere®; Sanofi-Aventis) (4, 5), erlotinib (6), gefitinib (7), and pemetrexed (8) are regarded as second-line therapeutic agents for patients with advanced NSCLC. However, reference to the published data suggests that treatment options for NSCLC, especially in the second-line setting, remain poor. In view of these modest results, new agents with activity when administered alone are urgently needed for this patient population.

Vascular endothelial growth factor (VEGF) has been identified as a key molecular target for NSCLC therapy (9). Bevacizumab (Avastin®; Roche), a recombinant, humanized, monoclonal antibody against VEGF, has been shown to

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benefit patients in a variety of cancer settings. The addition of bevacuzimab to paclitaxel-plus-carboplatin in the treatment of selected patients with NSCLC has shown significant survival benefit in the first-line setting. Bevacuzimab is now regarded as the standard treatment for metastatic non-squamous (Nsq) NSCLC, and has recently received US Food and Drug Administration approval for use in combination with carboplatin and paclitaxel, followed by bevacuzimab alone until disease progression, for the first-line treatment of patients with recurrent or metastatic Nsq NSCLC (10).

Several lines of evidence lend support to the notion that combining taxane and bevacuzimab in the treatment of recurrent NSCLC might confer additional clinical benefits. Firstly, pre-clinical data in breast cancer cell lines demonstrate that the activity of docetaxel and bevacuzimab is at least additive and may be synergistic (11). Secondly, it had been proposed that a dual approach targeting both tumor and endothelial cells that would ultimately inhibit tumor growth (by inhibiting VEGF) might be more effective. Finally, a combination of docetaxel and bevacuzimab would potentially provide added benefit without increased toxicity.

We conducted a phase II study to assess the feasibility and efficacy of combination docetaxel-plus-bevacuzimab in patients with previously-treated Nsq NSCLC.

Patients and Methods

Eligibility criteria. Patients with histologically- or cytologically-confirmed Nsq NSCLC and who had received one or more lines of treatment were eligible for this study. Additional eligibility criteria were as follows: 20-74 years of age; Eastern Cooperative Oncology Group (ECOG) PS 0-2; measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria, version 1.1 (12); and adequate bone marrow, renal, and hepatic function.

Patients were excluded in case of the following: documented brain metastases on computed tomography (CT) scan at the time of study enrolment, hypertension not controlled by medication, history of hemoptysis (≥2.5 ml bright red blood), evidence of bleeding diathesis or coagulopathy, previous history of other malignancies, active infection, history of pulmonary thromboembolism, or prior administration of docetaxel or anti-angiogenic agents. The study was approved by the relevant Institutional Review Boards (No. 2009-1088). All patients provided written informed consent for participation prior to study enrolment.

Treatment schedule. Docetaxel (60 mg/m^2) was administered intravenously (*i.v.*) over 60 min on day 1 of a 21-day cycle, followed by bevacuzimab (15 mg/kg *i.v.*). The first dose of bevacuzimab was administered over 90 min. If no incident occurred, the second dose was administered over 60 min and subsequent doses over 30 min. Dexamethasone (3.3 mg *i.v.*) was administered immediately before docetaxel infusion. Treatment was discontinued in the event of progressive disease, unacceptable adverse events, or patient withdrawal of consent.

Dose adjustment. Criteria for discontinuation of the study included grade 3/4 drug-related toxicity requiring treatment delay of three weeks or more, progressive disease, withdrawal of consent, and change in patient's condition that made further treatment inappropriate. Patients with a nadir platelet count of <25,000/μl required a 25% dose reduction in docetaxel. When continuation of grade 4 neutropenia was seen for seven days or more of any cycle, docetaxel dose was reduced by 25%. Treatment was delayed when a patient presented with grade 3 or more non-hematological toxicity, and subsequent doses of docetaxel were reduced by 25%. Administration of granulocyte colony-stimulating factor was permitted in cases of leucopenia and/or neutropenia, but not on a prophylactic basis.

Reduction in bevacuzimab dose was not permitted. Bevacuzimab administration was delayed when patients experienced either grade 2 hemorrhage (until resolution of bleeding) or grade 3 proteinuria (until resolution to grade 2 or less). Bevacuzimab was permanently discontinued in the following cases: grade 3 hypertension not controlled by medication, or grade 4 hypertension; grade 2 or more pulmonary hemorrhage; symptomatic grade 4 venous thromboembolism; arterial thromboembolic event (any grade); gastrointestinal perforation (any grade); or wound dehiscence (any grade).

Study evaluation. Complete patient histories, physical examinations, complete blood cell counts, serum electrolytes and chemistry, prothrombin time/partial thromboplastin time, and urinalysis were performed at baseline and before each cycle of treatment. Blood pressure monitoring was performed to evaluate the incidence and severity of hypertension. Radiological studies, including CT, were performed at baseline and after every two cycles of therapy to assess tumor response.

Response criteria and toxicity. Patients received a minimum of two cycles of therapy unless unacceptable toxicity or early progression of disease occurred. Patients were evaluated for response according to RECIST criteria after two successive cycles.

RECIST criteria, ver. 1.1 (12) were used to evaluate tumor response. Toxicities were evaluated and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) ver. 4.0 (13).

Statistical analysis. The primary end-point of this phase II study was to evaluate the overall response rate (RR); secondary endpoints were the assessment of tolerance, progression-free survival (PFS), and overall survival (OS). A two-stage Simon's minimax design (14) was used to define sample size; assuming an expected overall RR of ≥30% and a minimum acceptable RR of 10%, a sample of 16 patients would be required as a first step. When a minimum of one response was observed, a total of 25 patients would be required. Therefore, if at least four responses occurred, the treatment would be declared sufficiently promising. OS was defined as the time from date of registration to date of death, and PFS as the time from registration to documented progression or death from any cause, whichever occurred first. Survival analyses were performed using the Kaplan–Meier method.

Results

Patients' characteristics. Twenty-eight patients were enrolled between May 2010 and July 2011. All patients were evaluable for toxicity and 27 patients were evaluable for response assessment. At study termination (September 2012),

Table I. *Patients' characteristics.*

	n=28
Age, years	
Median (range)	65 (39-74)
Gender	
Male/female	16/12
Performance status (ECOG)	
0/1	19/9
Histology	
Adenocarcinoma/other	22/6
Prior regimens	
1/2/3 or more	16/5/7
EGFR mutation status	
Positive/negative/unknown	6/13/9

ECOG, Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor.

Table II. *Response rates.*

Response	n=27
CR	0
PR	18
SD	8
PD	1
NE	1
RR	66.7%
DCR	96%

NE, Not evaluable; DCR, disease control rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; RR, response rate.

18 deaths had been recorded. Patients' characteristics are presented in Table I. Of note, 12 (43%) patients had received at least two prior courses of chemotherapy and all patients had PS 0-1. Six patients had *EGFR*-active mutation.

Treatment administration. Overall, a total of 219 cycles were delivered (median=6; range=1-23). Nine patients required dose reduction because of toxicity. Reasons for stopping treatment included disease progression (n=19), toxicity (n=6), and patient choice (n=2).

Treatment efficacy. Among the 27 evaluable patients, there was no complete response and 18 showed partial response, accounting for an overall RR of 66.7% [95% confidence interval (CI)=48.9%-84.5%; Table II]. Eight (29.6%) additional patients showed stable disease as their best response, resulting in an overall disease control rate (DCR) of 96% (95% CI=92.2%-99.8%).

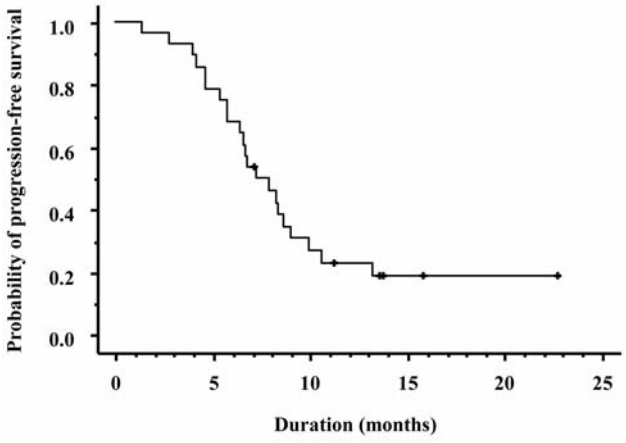

Figure 1. *Kaplan–Meier curves for progression free survival (N=28). Median progression-free survival was 7.2 months (95% confidence interval=5.4-10.6 months).*

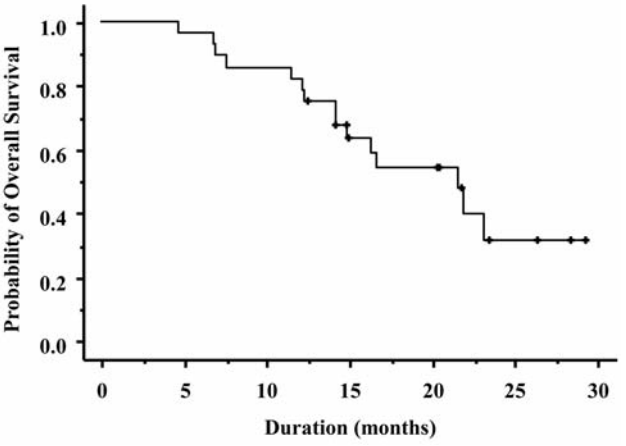

Figure 2. *Kaplan-Meier curves for overall survival (N=28). Median overall survival was 21.6 months (95% confidence interval=10.5-25.1 months).*

Table III. *Hematological toxicities (n=28).*

	Grade*				
Toxicity	1	2	3	4	% of ≥grade 3
Hematological toxicity					
Leucopenia	1	7	16	3	68
Neutropenia	0	4	7	16	82
Anemia	14	10	0	1	4
Thrombocytopenia	7	0	0	0	0

*By National Cancer Institute-Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (12).

Table IV. *Non-hematological toxicities (N=28).*

Non-hematological toxicity	Grade*				Grade 3 or more (%)
	1	2	3	4	
Bleeding	20	5	0	0	0
Anorexia	18	4	0	0	0
Increased aspartate aminotransferase level	15	2	0	0	0
Increased alanine aminotransferase level	8	1	0	0	0
Hand–foot syndrome	6	3	1	0	4
Nausea/vomiting	8/3	1/0	0/0	0/0	0
Diarrhea	7	2	0	0	0
Increased creatinine level	8	0	0	0	0
Febrile neutropenia	0	0	6	0	21
Hypertension	0	3	0	0	0
Infection	0	0	2	0	7
Pneumonitis	2	0	0	0	0
Proteinuria	0	1	0	0	0

*National Cancer Institute-Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (12). Data shown are the number of patients.

The Kaplan–Meier curve for PFS is shown in Figure 1; the estimated median PFS was 7.2 months (95% CI=5.3-10.9 months). Figure 2 shows the Kaplan–Meier curve for OS; the median overall OS was 21.6 months (95% CI=10.5–25.1 months) and the 1-year OS rate was 78.6%.

Treatment toxicity. All patients were evaluable for toxicity. Overall, treatment was well-tolerated despite the unfavorable characteristics of this heavily pre-treated population, and the adverse events recorded were anticipated considering the toxicity profiles of docetaxel and bevacuzimab. Hematological toxicities were common, with grade 3-4 neutropenia and leukopenia occurring in 82.1% and 68.0% of patients, respectively (Table III). The most common grade 3-4 non-hematological toxicities were febrile neutropenia (21%) and infection (6%) (Table IV). Bleeding episodes, although frequent, were usually mild and involved epistaxis in 25 patients. There were no grade 34 bevacuzimab-related adverse events such as thrombosis, hemorrhage, and bowel perforation; only grade 2 hypertension, proteinuria, and hemorrhagic events were observed.

Discussion

The combination of docetaxel and bevacuzimab, administered every three weeks, was relatively well-tolerated in this fragile population of heavily pre-treated patients with advanced Nsq NSCLC. Moreover, the regimen demonstrated clinical activity, yielding an RR of 66.7%, a median PFS of 7.2 months, and a median OS of 21.6 months.

The efficacy of docetaxel monotherapy, which is considered as a second-line standard therapy for NSCLC, yielded an RR of 6.7%-8.8%, a median PFS of 2-3 months, and a median OS of 5.7-7.9 months in previous phase III studies (4, 5, 8). Compared to these results, the efficacies of the combination therapy of docetaxel and bevacuzimab in our current study were impressive (10-fold higher RR and 3-4-fold longer PFS and OS than treatment with docetaxel alone).

One possible reason for the high RR and prolonged PFS and OS of the combination therapy may be the additional effects of bevacuzimab on chemotherapy. It has been confirmed that bevacuzimab enhances the efficacy of first-line chemotherapy with platinum doublet in terms of RR and PFS in phase III studies (10, 15). In particular, E4599, which compared the combination of bevacuzimab, paclitaxel and carboplatin with paclitaxel plus carboplatin, demonstrated that the bevacuzimab arm had a significantly prolonged OS.

However, a few studies that evaluated the additional effect of bevacuzimab on second-line chemotherapy for NSCLC have been reported. Herbst *et al.* conducted a randomized phase II study that evaluated the efficacy of bevacuzimab in combination with standard second-line chemotherapies that included pemetrexed, docetaxel, or erlotinib (16). Although the study showed that chemotherapy on the bevacuzimab arm demonstrated higher 1-year survival rates and prolonged median PFS and OS, the effect was not impressive when compared with our results (16). However, Herbst *et al.*'s study did not separately evaluate the combined efficacy of bevacuzimab with docetaxel or pemetrexed. It might have been different between the docetaxel and pemetrexed arm. E4599, which evaluated bevacuzimab with carboplatin-plus- paclitaxel, demonstrated that bevacuzimab significantly prolonged OS, but the AVAiL study, which evaluated bevacuzimab with gemcitabine/cisplatin, did not demonstrate prolonged OS (10, 15). In addition, a recent randomized phase III study

(PointBreak study), which compared carboplatin, pemetrexed and bevacuzimab with carboplatin, paclitaxel and bevacuzimab, was reported (17). Despite continuation/maintenance treatment of pemetrexed with bevacuzimab, carboplatin with pemetrexed and bevacuzimab this did not significantly prolong survival. These results suggest that the combined effects of bevacuzimab and chemotherapy are different for each drug, and a taxane with bevacuzimab may be a better combination. Combined effect of bevacuzimab and taxanes (paclitaxel or docetaxel) was well-evaluated in pre-clinical studies that demonstrated that because of the synergistic effect of BV and taxane, taxanes may good candidates for combination with bevacuzimab (11, 18). On the other hand, ethnic differences might have contributed to the good results of this phase II study. Several recent studies suggested that ethnic differences might influence the efficacy of chemotherapy; in particular, a major difference between Asian and Caucasian ethnicities might be observed (19, 20). In terms of the efficacy of bevacuzimab, a sub-group analysis in the AVAiL study demonstrated that the combination of bevacuzimab and cisplatin/gemcitabine prolonged PFS (8.5 *versus* 6.1 months) and OS (hazard ratio=0.46; 95% CI=0.22-0.97) more in the Asian subset than in other ethnicity (19). In addition, a Japanese randomized phase II study, which evaluated bevacuzimab with carboplatin and paclitaxel, (JO19907) demonstrated a higher RR (61%) and longer survival (median overall survival=22.8 months) compared to the results of the ECOG 4599 study (21). On the other hand, no major difference between Japanese and Caucasian ethnicities in terms of the efficacy of docetaxel was observed, because the results of the previous Japanese phase II and III studies of docetaxel were similar in other global studies (4, 5, 8, 22, 23).

In terms of toxicity, bevacuzimab slightly enhanced the toxicity of docetaxel, but it was manageable. During therapy, the bevacuzimab and docetaxel combination led to slightly higher incidences of grade 3/4 myelosuppression and grade 3 febrile neutropenia (21%). Although nine patients required dose reduction because of toxicity, these patients continued treatment without severe myelosuppression following dose reduction. On the other hand, this combination did not enhance the typical adverse events associated with bevacuzimab, such as hypertension, proteinuria, and bleeding. These results were almost similar to the previous studies of bevacuzimab combined with other agents (10, 16). A possible mechanism for increased myelotoxicity is that anti-VEGF treatment may delay leukocyte recovery through inhibition of VEGFR1- and VEGFR2-dependent bone marrow hematopoietic progenitor cell proliferation (24).

The greatest limitation of our study is that it was a single-Institution, single-treatment arm, phase II trial of only 28 patients. Nevertheless, the results of this study encouraged and promoted us to further confirm these results.

In conclusion, the combination of docetaxel and bevacuzimab is clinically feasible and exhibits high activity. Despite our relatively small sample size, the suggestion of benefits conferred by docetaxel and bevacuzimab to patients by this study warrants further research.

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