Phase II Study of Triplet Chemotherapy Using Tegafur-Uracil, Vinorelbine, Gemcitabine for Advanced Non-small Cell Lung Cancer

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Abstract. *Aim: To evaluate the efficacy and toxicity of triplet chemotherapy using tegafur-uracil (UFT), vinorelbine, and gemcitabine for patients with stage IIIB or IV non-small cell lung cancer. Patients and Methods: A total of 32 patients were enrolled in this study. The patients were subjected to a treatment regimen consisting of intravenous vinorelbine and gemcitabine on days 6 and 13, and oral UFT on days 1-5 and 8-12. This treatment was repeated every three weeks. Results: All patients had an initial performance status of 0 to 1. The objective response rate was 21.9%, median survival time was 13.9 months, and the one-year survival rate was 56.7%. Grade 3/4 toxicities (% of patients) consisted of leukocytopenia (40.6%), neutropenia (56.3%), thrombocytopenia (3.1%), infection (9.4%), hypoxia (6.3%) and dyspnea (3.1%). Conclusion: Triplet chemotherapy using UFT, vinorelbine, and gemcitabine was well-tolerated, with an acceptable toxicity profile. However, the response rate and median survival did not encourage for additional investigation.*

Lung cancer is a major cause of mortality worldwide, with an estimated annual incidence of 1.6 million cases and mortality of 1.4 million cases (1). Non-small cell lung cancer (NSCLC) accounts for at least 80% of all lung tumors, and approximately three-quarters of patients initially present with inoperable NSCLC (2-3). Chemotherapy is the mainstay of management for advanced NSCLC. Based on clinical data, the American Society of Clinical Oncology's (ASCO) clinical guidelines state that chemotherapy is appropriate for selected patients who have a good performance status (PS) with unresectable, locally advanced, and metastatic NSCLC. For these patients, the current standard of care is platinum-based doublet chemotherapy (4). The median survival and 1-year survival rates associated with platinum-based doublet chemotherapy are 8-10 months and 30%-35%, respectively (5). The recommendations in the guidelines of ASCO also stated that non-platinum regimens may be used as alternatives to platinum-based regimens as first-line treatment. Vinorelbine plus gemcitabine is an active and well-tolerated non-platinum-based chemotherapy regimen for the treatment of patients with advanced NSCLC (6-7). Tegafur-uracil (UFT) is an oral anticancer agent, which is composed of uracil and tegafur in a molar ratio of 4:1. Uracil is an inhibitor of dihydropyrimidine dehydrogenase (DPD), which is a metabolic product of 5-fluorouracil (5-FU), and tegafur is a pro-drug of 5-FU (8). It was found that prolonged administration of UFT results in a similar to or higher maximum concentration (Cmax) as well as an area under the curve (AUC) for 5-FU comparable to those associated with continuous infusion of 5-FU (9). Direct antitumor effects of UFT are minimal for most malignant tumor types, including NSCLC (10,11). However, a meta-analysis showed that postoperative adjuvant chemotherapy with UFT was associated with improved survival of patients with stage I adenocarcinoma (12). Sequential exposure to 5-FU followed by gemcitabine has been reported to achieve additive effects in vitro (13). The combination of gemcitabine and UFT would be more effective than either treatment alone because of the additive and synergistic activity of gemcitabine and 5-FU derived from UFT. Therefore, we anticipated that triplet chemotherapy using UFT, vinorelbine, and gemcitabine would be more effective than the doublet combination of vinorelbine and gemcitabine. To assess whether triplet

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Table I. *Treatment schedule*.

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
UFT 300 mg/m^2	↓	↓	↓	↓	↓			↓	↓	↓	↓	↓		
VNR 25 mg/m^2						↓							↓	
GEM 1000 mg/m^2						↓							↓	

BSA	UFT
<1.34	300 mg/body
1.34-1.66	400 mg/body
1.67-2.00	500 mg/body
>2.00	600 mg/body

chemotherapy is more effective than non-platinum doublet chemotherapy, we conducted this multicenter, prospective, open-label, phase II study of triplet chemotherapy.

Patients and Methods

Patient selection. Patients with histologically, or cytologically-confirmed stage IIIB (malignant pleural effusion and/or metastasis in the same lobe) or IV NSCLC were recruited for this study. Patients with recurrences after surgical resection were also recruited. Other inclusion criteria were age <75 years; Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; at least one measurable lesion; no previous chemotherapy or thoracic radiotherapy; life expectancy ≥3 months; adequate organ function (*i.e.* white blood cell count ≥4,000/mm^3, neutrophil count ≥2,000/mm^3, platelet count ≥100,000/mm^3, hemoglobin level ≥9.5 g/dl, blood urea nitrogen level ≤25 mg/dl, serum creatinine level≤1.5 mg/dl, total bilirubin level ≤the normal upper limit, and aspartate aminotransferase (AST)/alanine aminotransferase (ALT) level≤100 IU/l); no interstitial pneumonia or pulmonary fibrosis, as determined by chest radiography; no coexisting severe complications that would prevent compliance with the study protocol or expose the patients to unnecessary risk; no pregnancy or breast-feeding; no severe allergy to drugs; and no active concomitant malignancy. All patients were required to provide written informed consent, and the protocol was approved by the Institutional Review board of each of the participating institutions.

Treatment schedule. This was an open-label, multicenter, single-arm phase II study. The drug administration schedule is shown in Table I. UFT was administered orally twice daily after a meal on days 1-5 and 8-12. Four doses of UFT were selected according to the body surface area (BSA) such that they would be approximately equivalent to 300 mg/m^2/day: BSA <1.34 m^2, 300 mg/day (a.m. 100 mg, p.m. 200 mg); BSA 1.34-1.66 m^2, 400 mg/day (a.m. 200 mg, p.m. 200 mg); BSA 1.67-1.99 m^2, 500 mg/day (a.m. 200 mg, p.m. 300 mg); and BSA ≥2.00 m^2, 600 mg/day (a.m. 300 mg, p.m. 200 mg). UFT was discontinued in the following cases: leukocyte count <1,000/mm^3, neutrophil count <500/mm^3, platelet count <50,000/mm^3, and adverse reaction of grade 3 or higher. Patients received vinorelbine (25 mg/m^2) and gemcitabine (1,000 mg/m^2) intravenously on days 6 and 13. On the day that vinorelbine and gemcitabine was to be administered, a complete blood count test was performed, and these drugs were administered only when the following conditions were met: leucocyte count >2,000/mm^3, neutrophil count >1,000/mm^3, platelet count >75,000/mm^3, and AST/ALT level <100 IU/l. Vinorelbine and gemcitabine were not administered until the aforementioned conditions were met. That is, the next course of treatment was administered only when the leucocyte count recovered to >2,000/mm^3, neutrophil count to >1,000/mm^3, platelet count to >75,000/mm^3, and the AST/ALT level to <100 IU/l.

The doses of vinorelbine and gemcitabine were reduced by 5 mg/m^2 and 200 mg/m^2 in patients for whom the scheduled treatment was skipped on day 13 of the previous cycle. If patients experienced grade 4 hematological toxicity, the UFT dose was reduced by 100 mg/day in the subsequent cycle. The cycle was repeated every 21 days and at least two cycles were administered to each patient, unless disease progression or unacceptable toxicity occurred.

Evaluation. Intention-to-treat analysis was performed in this study. Response, survival, and toxicity were assessed in all patients who received any part of the treatment. Complete blood cell counts and blood chemistry parameters were measured on a weekly basis. The response was assessed based on the findings of chest radiography or computed tomography, which was initially used to define tumor extent. The response was evaluated according to the criteria of response evaluation criteria in solid tumors (RECIST 1.0) (14). A complete response (CR) was defined as the complete disappearance of all clinically detectable tumors for at least four weeks. A partial response (PR) was defined as an at least 30% decrease in the sum of the longest diameters of the target lesions for more than four weeks, with no new area of malignant disease. Progressive disease (PD) indicated at least a 20% increase in the sum of the longest diameters of the target lesions or a new malignant lesion. Stable disease (SD) was defined as insufficient shrinkage to qualify for PR and insufficient increase to qualify for PD. The best response achieved during the treatment course was recorded. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria version 2.0 (15).

Study design and statistical analysis. The primary end-point of this study was to determine the tumor response rate achieved by using the triplet chemotherapy protocol. The sample size was calculated

Table II. *Patients' characteristics*.

No. of enrolled patients	32
Median age, years (range)	65 (46-74)
Gender	
Male	20
Female	12
Performance statu s (ECOG)	
0	11
1	21
Stage	
III B	5
IV	27
Histology	
Adenocarcinoma	28
Squamous cell carcinoma	2
Large cell carcinoma	2
Pre-treatment	
Surgical resection	1
Radiotherapy	1
γ-Knife	1

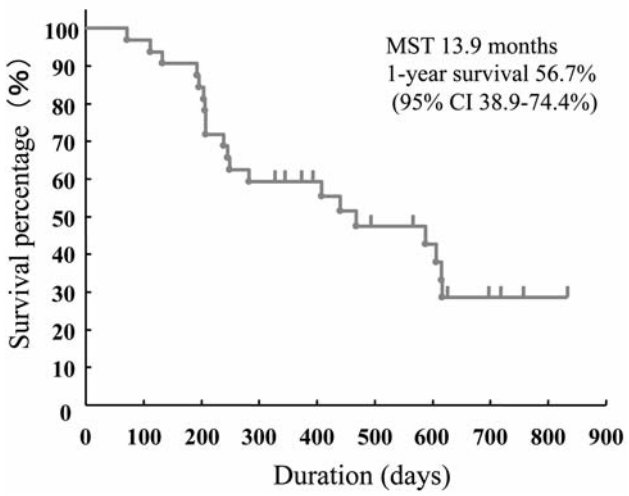

Figure 1. *Kaplan–Meier estimates of the overall survival of 32 patients with advanced non-small cell lung cancer receiving triplet chemotherapy treatment*.

according to the Simon minimax two-stage design (16). Based on the assumption that a response rate >40% would warrant a further investigation of this combination chemotherapy, and a rate of below 20% would make such an investigation unnecessary, a sample size of 33 patients was required with an alpha error of 0.05 and a beta error of 0.2. Overall survival was defined as the interval between enrollment in this study and death or the final follow-up visit. Median overall survival was estimated by the Kaplan–Meier method.

Results

Between September 2002 and November 2004, 32 eligible patients (20 men and 12 women) were enrolled in this study, in which one eligible patient mistakenly had not been included. Patients' characteristics are listed in Table II. The median age of the patients was 65 years (age range=46-74 years). Eleven patients had ECOG PS 0, and 21 patients had PS 1. Five patients had clinical stage IIIB disease, and 27 patients had stage IV disease. Histologically, adenocarcinoma was diagnosed in 28 patients, squamous cell carcinoma in two, and large-cell carcinoma in two. There were no early deaths during the first cycle of treatment.

Response and survival. Out of the 32 patients assessable for response, none of the patients achieved a CR, seven (21.9%) achieved a PR with an overall response rate of 21.9% (95% confidence interval=7.6%-36.2%), 14 (43.7%) had SD, 10 (31.2%) had PD, and one (3.1%) had no evaluable indication. As shown in Figure 1, the median survival time for all patients was 13.9 months, and the one-year survival rate was 56.7% (95% confidence interval=38.9%-74.4%).

Table III. *Hematological and non-hematological toxicity*.

	Grade				
	1	2	3	4	≥G3 (%)
Leukocytopenia	6	6	12	1	40.6
Neutropenia	5	3	10	8	56.3
Thrombocytepenia	14	1	1	0	3.1
Nausea	8	0	0	0	0
Constipation	5	0	0	0	0
Diarrhea	3	1	0	0	0
Fever	7	1	0	0	0
Rash	0	6	0	0	0
Fatigue	1	0	0	0	0
Allergy	0	1	0	0	0
Myositis	1	0	0	0	0
Dyspnea	1	1	1	0	3.1
Infection	2	1	3	0	9.4
Pneumonia	2	1	0	0	0
Hypoxemia	0	0	2	0	6.3
Phlebitis/dermopathy	2	1	0	0	0
Peripheral neuropathy	1	1	0	0	0
Liver	0	0	1	0	3.1

Toxicity of treatment. Hematological toxicity and non-hematological toxicity were analyzed during the treatment and follow-up periods. The major toxicities observed during the study period are shown in Table III. The incidence of toxicities was evaluated in all 32 patients. Grade 3 or 4 leukopenia was observed in 13 patients (40.6%), grade 3 or 4 neutropenia was observed in 18 patients (56.3%), and

grade 3 or 4 thrombocytopenia was observed one patient (3.1%). Non-hematological toxicity was relatively mild. Grade 3 infection was seen in three patients. Other toxicities included grade 3 dyspnea in one patient (3.1%), and grade 3 liver dysfunction in one patient (3.1%). There were no treatment-related deaths.

Treatment delivery. The median number of treatment cycles administered to all patients was two. Overall, 20 (62.5%) patients received at least two cycles of treatment. In the remaining 12 patients, chemotherapy was terminated before the second treatment cycle for the following reasons: disease progression in eight patients, and adverse events, including grade 3 infection, grade 2 diarrhea, and grade 2 rash, in four patients.

Discussion

Vinorelbine and gemcitabine are two of the most extensively evaluated newer cytotoxic agents. This combination regimen has been well-tolerated, with reported response rates of 25%-72.5% and median survival times of 8-11 months (17-19). These clinical trials also showed a more favorable toxicity profile. Because the effectiveness of these two drugs is fairly well-established, we added a third drug, UFT, to this doublet regimen to assess the effectiveness of a triplet chemotherapy regimen. In general, UFT is administered on a daily basis. Sadahiro *et al*. conducted a pharmacological study of the weekday-on/weekend-off oral UFT schedule in patients with colorectal cancer (20). In their study, UFT was administered for five consecutive days, followed by a two-day period off the drug. The 5-FU concentration in the tumor was maintained at a much higher level than that in the serum throughout these periods. Therefore, this schedule may be associated with better tolerance than the conventional daily administration schedule, without compromising on the antitumor effect of the drug. Based on their report, we adopted the weekday-on/weekend-off UFT schedule in this study. In this study, the triplet chemotherapy regimen of UFT, vinorelbine, and gemcitabine resulted in an objective response rate of 21.9%, disease control rate of 65.6%, and median survival time of 13.9 months in patients with advanced NSCLC. The principal toxicities were neutropenia and infection, with no treatment-related death. In 12 (37.5%) patients, chemotherapy was discontinued after one cycle: in eight patients, treatment was discontinued because of disease progression; in four patients (33.3%), treatment was discontinued due to adverse events, including two cases of grade 3 infection and one case each of grade 2 diarrhea and rash, which led the patients to terminate the treatment. Thus, triplet chemotherapy was found to be feasible as a first-line treatment. Cisplatin is an effective cytotoxic agent that is currently used as the standard treatment for lung cancer (21). Cisplatin, despite being considered the 'key drug' in NSCLC, is associated with several distressing toxicities in a subset of patients (22). It has been reported that platinum-based triplet chemotherapy generally results in increased toxicity, without significant gains in efficacy, compared with doublet chemotherapy (23). The German and Swiss Lung Cancer Study Group has examined the effectiveness of the gemcitabine plus vinorelbine regimen with and without the addition of cisplatin. They found that the cisplatin-based gemcitabine plus vinorelbine (GVP) regimen showed no survival benefit as first-line chemotherapy compared with the cisplatin-free gemcitabine plus vinorelbine regimen. Moreover, the latter regimen was better-tolerated than the GVP regimen (24). Similarly, the non-platinum-based triplet chemotherapy regimen examined in this study was found to be an effective first-line treatment. Recently, advances in the molecular understanding of lung cancer have led to changes in the treatment protocol for the disease. The treatment of patients with epithelial growth factor receptor (EGFR)-mutant NSCLC with tyrosine kinase inhibitor (TKI) has led to a superior response rate, a prolonged progression-free survival, and an improved quality of life compared to cytotoxic chemotherapy (25). In patients with echinoderm microtubule-associated protein-like-4 anaplastic lymphoma kinase (ALK) NSCLC, an ALK inhibitor was effective (26). The patients treated with the triplet chemotherapy regimen in this study, however, could not benefit from these molecular therapies, since such somatic mutations were not routinely examined at that time. In conclusion the combination chemotherapy of UFT, vinorelubine, and gemcitabine was well-tolerated, with an acceptable toxicity profile, in patients with advanced NSCLC. The efficacy and toxicity of this triplet chemotherapy was similar to those of other commonly used doublet regimens. The response rate and median survival, however, did not encourage for additional investigation.

Conflicts of Interest

No Author has any conflicts of interest.

Acknowledgements

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References

1 Jemal A, Bray F, Center MM, Ferlay J, Ward E and Forman D: Global cancer statistics. CA Cancer J Clin pp. 69-90, 2011.

2 Fu JB, Kau TY, Severson RK and Kalemkerian GP. Lung cancer in women: analysis of the national Surveillance, Epidemiology, and End Results database. Chest *127*: 768-77, 2005.

3 Swisher SG. Surgical treatment of locally advanced non-small cell lung cancer. *In*: Fossella FV, Komaki R and Putnam JB Jr., eds. Lung Cancer. New York, NY: Springer, pp. 118-141, 2002.
4 Azzoli CG, Temin S and Giaccone G: Focused update of 2009 American Society of Clinical Oncology clinical practice guideline update on chemotherapy for stage IV non-small cell lung cancer. J Clin Oncol *29*: 3825-3831, 2011.
5 Schiller J, Harrington D, Belani C, Langer C, Sandler A, Krook J, Zhu J and Johnson D: Comparison of four chemo-therapy regimens for advanced non-small cell lung cancer. N Engl J Med *346*: 92-98, 2002.
6 Palmeri S, Leonardi V, Gebbia V, De Bella MT, Ferraù F, Faillú G, Spatafora M, Valenza R, Di Vita G, Vitello S, Carroccio R, Sciortino G, Vaglica M, Accurso V, Agostara B and Licata G: Gemcitabine plus vinorelbine in stage IIIB or IV non-small cell lung cancer (NSCLC): A multicentre phase II clinical trial. Lung Cancer *34*: 115-123, 2001.
7 Frasci G, Lorusso V, Panza N, Comella P, Nicolella G, Bianco A, De Cataldis G, Iannelli A, Bilancia D, Belli M, Massidda B, Piantedosi F, Comella G and De Lena M: Gemcitabine plus vinorelbine *versus* vinorelbine alone in elderly patients with advanced non-small cell lung cancer. J Clin Oncol *18*: 2529-2536, 2000.
8 Diasio RB: Clinical implications of dihydropyrimidine dehydrogenase inhibition. Oncology *13*: 17-21, 1999.
9 Yonekura K, Basaki Y, Chikahisa L, Okabe S, Hashimoto A, Miyadera K, Wierzba K and Yamada Y: UFT and its metabolites inhibit the angiogenesis induced by murine renal cell carcinoma, as determined by a dorsal air sac assay in mice. Clin Cancer Res *5*: 2185-2191, 1999.
10 Keicho N, Saijo N, Shinkai T, Eguchi K, Sasaki Y, Tamura T, Sakurai M, Sano T and Hoshi A: Phase II study of UFT in patients with advanced non-small cell lung cancer. Jpn J Clin Oncol *16*: 143-146, 1986.
11 Shimizu E, Kimura K, Sone S, Inoue I, Nakamura Y, Noda Y, Hojo F, Yagi M, Nakanishi S and Yamasaki K: A phase II study of UFT in non-small cell lung cancer. Gan To Kagaku Ryoho *13*: 2970-2973, 1986, (in Japanese).
12 Tanaka F, Miyahara R, Ohtake Y, Yanagihara K, Fukuse T, Hitomi S and Wada H: Advantage of post-operative oral administration of UFT (tegafur and uracil) for completely resected p-stage I-IIIa non-small cell lung cancer (NSCLC). Eur J Cardiothracic Surg *14*: 256-262, 1998.
13 Rauchwerger DR, Firby PS, Hedley DW and Moore MJ: Equilibrative-sensitive nucleoside transporter and its role in gemcitabine sensitivity. Cancer Res *60*: 6075-6079, 2000.
14 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC and Gwyther SG: New guidelines to evaluate the response to treatment in solid tumors (RECIST Guidelines). J Natl Cancer Inst *92*: 205-216, 2000.
15 National Cancer Institute-Common Toxicity Criteria. (NCI-CTCVersion2.0April30,1999)http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcv20_4-30-992.pdf
16 Simon R: Optimal two-stage designs for phase II clinical trials. Control Clin Trials *10*: 1-10, 1989.
17 Chen YM, Perng RP, Yang KY, Liu TW, Tsai CM, Ming-Liu J and Whang-Peng J: A multicenter phase II trial of vinorelbine plus gemcitabine in previously untreated inoperable (stage IIIB/IV) non-small cell lung cancer. Chest *117*: 1583-1589, 2000.
18 Isokangas OP, Knuuttila A, Halme M, Mäntylä M, Lindström I, Nikkanen V, Viren M, Joensuu H and Mattson K: Phase II study of vinorelbine and gemcitabine for inoperable stage IIIB-IV non-small-cell lung cancer. Annals of Oncology *10*: 1059-1063,1999.
19 Lilenbaum R, Cano R, Schwartz M, Siegel L, Lutzky J, Lewis M, Krill E, Barreras L and Davila E: Gemcitabine and vinorelbine in advanced non-small cell lung carcinoma: A phase II study. Cancer *88*: 557-562, 2000.
20 Sadahiro S, Suzuki T, Kameya T, Iwase H, Tajima T and Makuuchi H: A pharmacological study of the weekday-on/weekend-off oral UFT schedule in colorectal cancer patients. Cancer Chemother Pharmacol *47*: 457-460, 2001.
21 American Society of Clinical Oncology: Clinical practice guidelines for the treatment of unresectable non-small cell lung cancer. J Clin Oncol *15*: 2996-3018, 1997.
22 Gridelli C, Gallo C, Shepherd FA, Illiano A, Piantedosi F, Robbiati SF, Manzione L, Barbera S, Frontini L, Veltri E, Findlay B, Cigolari S, Myers R, Ianniello GP, Gebbia V, Gasparini G, Fava S, Hirsh V, Bezjak A, Seymour L and Perrone F: Gemcitabine plus vinorelbine compared with cisplatin plus vinorelbine or cisplatin plus gemcitabine for advanced non-small cell lung cancer: A phase III trial of the Italian GEMVIN Investigators and the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol *21*: 3025-3034, 2003.
23 Delbaldo C, Michiels S, Syz N, Soria JC, Le Chevalier T and Pignon JP: Benefits of adding a drug to a single-agent or a two-agent chemotherapy regimen in advanced non-small-cell lung cancer: A meta-analysis. JAMA *292*: 470-484, 2004.
24 Laack E, Dickgreber N, Müller T, Knuth A, Benk J, Lorenz C, Gieseler F, Dürk H, Engel-Riedel W, Dalhoff K, Kortsik C, Graeven U, Burk M, Dierlamm T, Welte T, Burkholder I, Edler L and Hossfeld DK: Randomized phase III study of gemcitabine and vinorelbine *versus* gemcitabine, vinorelbine, and cisplatin in the treatment of advanced non-small cell lung cancer: from the German and Swiss Lung Cancer Study Group. J Clin Oncol *22*: 2348-2356, 2004.
25 Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, Sunpaweravong P, Han B, Margono B, Ichinose Y, Nishiwaki Y, Ohe Y, Yang JJ, Chewaskulyong B, Jiang H, Duffield EL, Watkins CL, Armour AA and Fukuoka M: Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med *361*: 947-957, 2009.
26 Kimura H, Nakajima T, Takeuchi K, Soda M, Mano H, Iizasa T, Matsui Y, Yoshino M, Shingyoji M, Itakura M, Itami M, Ikebe D, Yokoi S, Kageyama H, Ohira M and Nakagawara A: ALK fusion gene positive lung cancer and three cases treated with an inhibitor for ALK kinase activity. Lung Cancer *75*: 66-72, 2012.

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