Multicenter Phase II Study of Nedaplatin and Irinotecan for Patients with Squamous Cell Carcinoma of the Lung: Thoracic Oncology Research Group 0910

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Abstract. *Squamous cell carcinoma (SCC) of the lung is moderately responsive to anticancer drugs, but no specific chemotherapy regimens have yet been established. We conducted a multicenter phase II study of nedaplatin (NP) and irinotecan (CPT) for SCC of the lung. Fifty patients underwent 4 to 6 cycles of chemotherapy comprising of NP at 100 mg/m^2 on day 1 and CPT at 60 mg/m^2 on days 1 and 8 every 4 weeks. Twenty-seven patients received 4 to 6 cycles of chemotherapy (median=4 cycles). Major toxicities included neutropenia (46.0%), grade 3 or 4 anorexia (22.0%), febrile neutropenia (16.0%), diarrhea (12.0%), hyponatremia (12.0%), grade 4 anemia (10.0%), thrombocytopenia (10.0%) and infection (10.0%). There were no treatment-related deaths. One patient achieved a complete response and 16 a partial response, with an overall response rate of 34.0%. The median survival time was 11.8 months (95% CI=8.3-15.8 months) and the 2-year survival rate was 22.0%. In conclusion, the NP and CPT regimen is not recommend for further evaluation for patients with advanced SCC of the lung.*

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Non-small cell lung cancer (NSCLC) has several types of pathology, including adenocarcinoma, squamous cell carcinoma (SCC), large cell carcinoma and others. All types of NSCLC are moderately responsive to anticancer drugs, and regimens based on combinations of anticancer agents such as vinorelbine, gemcitabine, docetaxel and paclitaxel with platinum compounds have emerged as a gold-standard for chemotherapy-naïve NSCLC (1).

Pemetrexed is a potent inhibitor of thymidylate synthase and other folate-dependent enzymes, currently approved as a first-line treatment for malignant pleural mesothelioma (2). A randomized phase III study has shown that a regimen comprising of cisplatin and pemetrexed provides similar efficacy with better tolerability and more convenient administration than cisplatin and gemcitabine as a first-line treatment for advanced NSCLC (3). That study also demonstrated that patients with adenocarcinoma and large cell carcinoma showed better overall survival when treated with cisplatin and pemetrexed. Therefore, it is suggested that uniform treatment for NSCLC may not be appropriate, and that treatment needs to be tailored according to histological or

genetic type. In particular, an effective chemotherapy specific for SCC is required.

Nedaplatin (NP) is an analogue of cisplatin, with relatively low neuro- and nephro-toxicity (4). A phase I study has demonstrated that 100 mg/m^2 NP was the recommended dose, and that the dose-limiting toxicity was thrombocytopenia (5). A phase II study of NP for NSCLC, in which the drug was administered at a dose of 100 mg/m^2 every 4 weeks, demonstrated a 14.7% objective response, and this included 4 of 9 patients with SCC (6). Three-dimensional analytical models have demonstrated marked synergistic interaction of concurrently administered NP and irinotecan (CPT) (7). A phase I/II study we conducted demonstrated high activity and low toxicity of NP and CPT when used in combination against NSCLC (8), and some other studies of NP and CPT chemotherapy for advanced NSCLC yielded similar results, with favorable patient survival (9-11). No differences in activity among histological types were evident, but NP was considered to be basically active against SCC. In a meta-analysis, we analyzed the outcomes of some studies using NP and CPT for chemotherapy-naïve patients with NSCLC and compared them between SCC and non-SCC. Twenty-seven of the 121 patients included in the analysis had SCC, and the response rates for SCC and non-SCC were 51.9% and 35.1%, respectively. Comparisons of survival for patients with SCC and non-SCC revealed that the median survival time, 1-year survival rate and 2-year survival rate were 14.5 and 9.1 months, 63.0% and 39.4%, and 29.6% and 19.1%, respectively. These results suggested that the NP and CPT regimen is more active against SCC of the lung (12). Therefore, we conducted a multicenter phase II study of NP and CPT for SCC of lung: the Thoracic Oncology Research Group (TORG) study.

Patients and Methods

This trial was designed as a multicenter, prospective, single-arm study and the study protocol was approved by the Committee of the TORG and the Institutional Review Board of each participating institution. All data of the study were managed by the TORG0910 data center at Yokohama City University of Medicine. The study was registered with the UMIN Clinical Trials Registry (number UMIN000003330).

Patients. Patients with histologically- or cytologically-proven SCC of the lung were registered. The eligibility criteria were: unresectable or contraindication for thoracic radiotherapy, clinical stage III or IV, an expected survival of at least 12 weeks, patient age >20 and <75 years, Eastern Cooperative Oncology Group PS score ≤1, leukocyte count ≥4,000/μl, neutrophil count ≥1,500/μl, hemoglobin ≥9.0 g/dl, platelet count ≥100,000/μl, total serum bilirubin ≤1.5 mg/dl, aspartate aminotransferase and alanine aminotransferase ≤100 IU/L, serum creatinine ≤1.5 mg/dl, $SatO_2$ >94% or PaO_2 >65 torr. Patients who had undergone radiotherapy for bone or brain metastasis, or surgical resection, were eligible, but a 2-week rest period was required. Patients with pleural or pericardial effusion were excluded. Written informed consent was obtained from every patient.

Table I. *Patients' characteristics*.

		No. of patients
Total		50
Age, years		
Median	67	
Range	(37-74)	
Gender		
Male		44
Female		6
PS(ECOG)		
0		19
1		31
Clinical stage		
IIIB		9
IV		40
Rec.		1

PS: Performance status; ECOG: Eastern Cooperative Oncology Group; Rec.: post-surgical recurrence.

Table II. *Delivered cycles of chemotherapy*.

No. of cycles	No. of patients
1	11
2	8
3	4
4	14
5	2
6	11

Before enrollment in the study, each patient provided a complete medical history and underwent physical examination, blood cell count determinations, biochemical laboratory examinations, chest X-ray, electrocardiography, chest computed tomography, whole-brain computed tomography or magnetic resonance imaging, abdominal computed tomography, and isotope bone scans or PET scans. Blood cell counts, differential white counts, and other laboratory data were obtained weekly during each course of chemotherapy. All patients were re-assessed at the end of treatment in the same manner as at the time of enrollment.

Chemotherapy. Patients exhibiting no disease progression were treated every four weeks with 60 mg/m^2 CPT on days 1 and 8 and with 100 mg/m^2 NP on day 1. Patients received 5-HT_3 receptor antagonist IV and 8 mg dexamethasone IV before administration of the anticancer drugs. Recombinant human granulocyte colony-stimulating factor (G-CSF), at 50μg /m^2/day or 2 μg/kg/day, was administered subcutaneously once a day when the patient's leukocyte or neutrophil count was below 1,000/μl and 500/μl, respectively. Subsequent cycles of chemotherapy were started when patients were able to satisfy the organ function eligibility criteria, with the exception of hemoglobin count, for entry into the study. The NP and

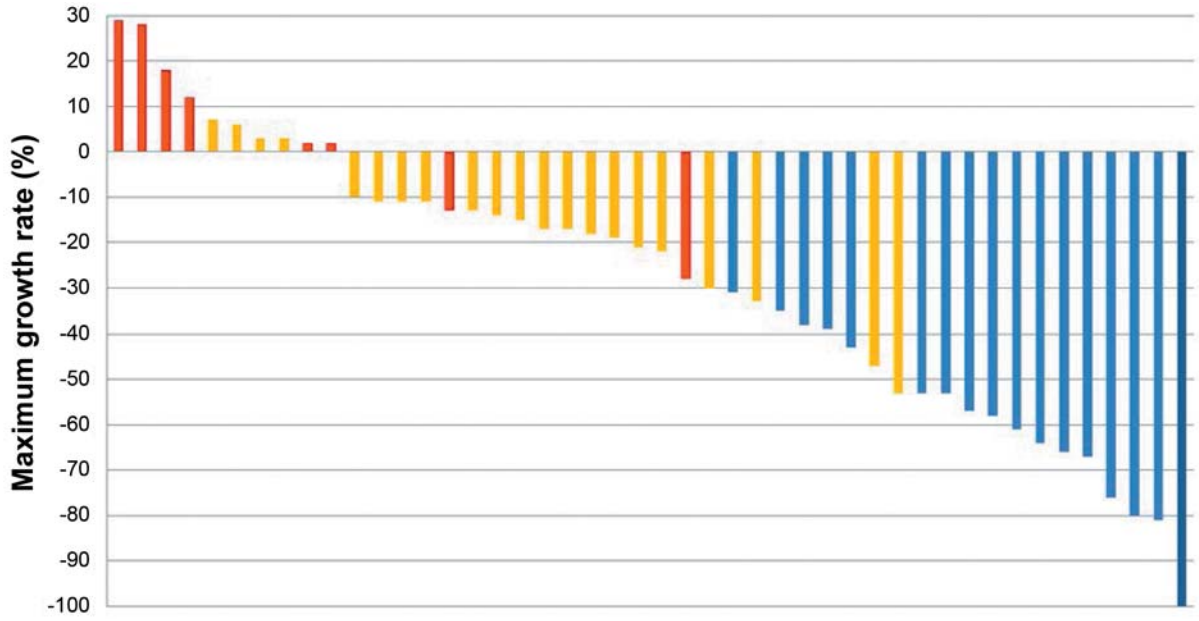

Figure 1. *Maximum change in target tumor from the baseline in evaluable patients. Patients with confirmed complete response (CR) or partial response (PR) are highlighted in blue; patients with confirmed stable disease (SD) are highlighted in yellow; patients with confirmed progression disease (PD) are highlighted in red. Twenty-one patients achieved PR or CR (42.0%) but only 17 of them were confirmed.*

CPT chemotherapy was repeated for a maximum of 6 cycles unless the disease progressed, or if severe toxicities developed.

Evaluation of response and toxicities. Tumor response was evaluated according to the RECIST 1.1 criteria (13). Complete response (CR) was defined as the complete disappearance of all evidence of tumor. Partial response (PR) was defined as at least a 30% reduction in the longest diameter of all indicator lesions with no appearance of new lesions or progression of any existing lesions. Progressive disease (PD) was defined as at least a 20% increase at the longest diameter of all indicator lesions or the appearance of new lesions. All other outcomes were classified as stable disease (SD). Toxicities were evaluated according to the CTCAE ver. 4 criteria (http://www.jcog.jp/SHIRYOU/ctcae.html).

Study design. We chose a 50% response rate as a desirable target level and considered a 30% response rate as uninteresting. The study design had power in excess of 90% and less than 10% error, and therefore 22 assessable patients in the first step and 24 in the second step were required according to the optimal design of Simon (14). We decided to stop the study if there were fewer than 8 responders in the first step. The regimen was defined as active if there were 18 or more responders out of the total of 46 patients. Overall survival was estimated by the Kaplan and Meier method.

Results

Patients' characteristics. Between May 2010 and January 2013 a total of 50 patients were registered in the study. Forty-four patients were males and 6 females, with a median age of 67 years (range=37-74 years). Nineteen patients had a PS of 0 and 31 had a PS of 1. Nine patients had clinical stage IIIB and 40 had stage IV. One patient had bone metastasis after surgical resection. Patients characteristics are summarized in Table I. All patients were assessed for toxicities, response to chemotherapy and survival.

Treatment delivery. Fifty patients received 1 to 6 cycles of the NP and CPT regimen (Table II). Twenty-seven of them received 4 to 6 cycles of chemotherapy, and the median number of chemotherapy cycles was four. Chemotherapy dose reduction was required in 20 patients. Eleven patients did not continue the second cycle of chemotherapy because of PD in 5, toxicity in 4 and patient refusal in 2, respectively. The reasons for discontinuing chemotherapy after 2 cycles were PD in 2 patients, toxicity in 4 and other reasons in 2. Seven out of 19 patients terminated chemotherapy after 1 or 2 cycles because of toxicities, including grade 3 pneumonia in 2, grade 4 diarrhea with grade 3 febrile neutropenia in one, grade 3 diarrhea with grade 2 totoxicity in one, grade 4 liver damage in one, grade 3 anaphylaxis in one, and grade 2 creatinine in one. CPT on day 8 was skipped in 29 cycles and the major reasons were diarrhea in 9 cycles, leukopenia in 6 and appetite loss in 5.

Toxicities. Adverse effects overall, and in every cycle of chemotherapy, are summarized in Table III. Hematological toxicities such as leukopenia, neutropenia, anemia and thrombocytopenia were observed in 72-98% of patients.

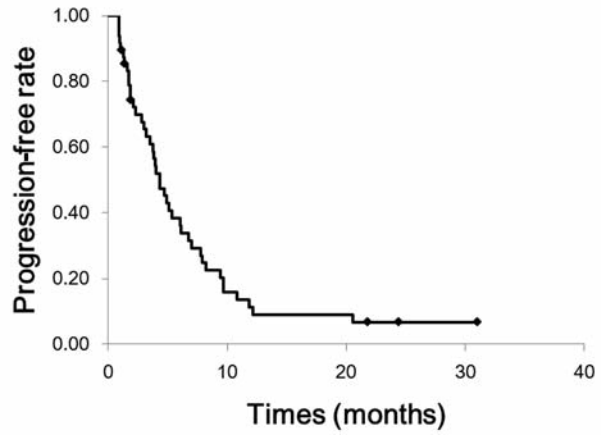

Figure 2. *Progression-free survival curve constructed using the Kaplan-Meier method. The median progression-free survival was 4.3 months (95% CI=3.2-6.1 months).*

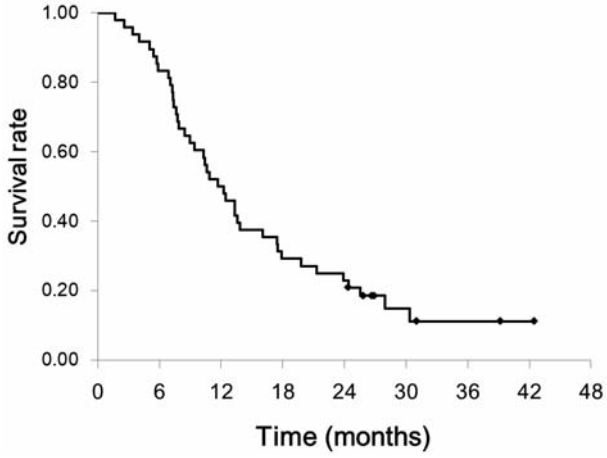

Figure 3. *Overall survival curve constructed using the Kaplan-Meier method. The median survival time (MST) was 11.8 months (95% CI 8.3-15.8 months). The 1- and 2-year survival rates were 50.0% and 22.0%, respectively*

Major gastrointestinal toxicities such as anorexia, nausea, diarrhea and constipation were observed in 64.0%, 58.0%, 58.0% and 50.0% of patients, respectively. Major laboratory disorders were increased bilirubin, increased creatinine, hyponatremia, hypocalcaemia and hyperkalemia. Moderate hematological toxicities included neutropenia in 46.0% of patients, leukopenia in 14.0%, grade 4 anemia in 10.0%, and thrombocytopenia in 10.0%. Major non-hematological toxicities included grade 3 or 4 anorexia in 22.0%, diarrhea in 12.0% and hyponatremia in 12.0%. Febrile neutropenia and grade 3 infection were observed in 16.0% and 10.0%, respectively. Severe liver damage with a grade 4 increase of serum bilirubin and AST occurred in one patient. Grade 3 serum creatinine elevation was observed in one patient. Bronchial hemorrhage, airway obstruction and pain were all due to disease progression. Each toxicity was manageable, and there were no treatment-related deaths.

Response and survival. Responses to the NP and CPT regimen in the 50 patients were confirmed as complete in 1 and partial in 16. Twenty and 9 patients showed SD and PD, respectively. Response was not evaluable in 4 patients. The overall response rate in this series was 34.0%, and the disease control rate (percentage of patients who achieved CR, PR or SD) was 74.0% (Table IV). Maximum regression rates in the patients overall are shown in Figure 1. Twenty-one and 13 patients (42.0% and 26%) achieved 30% and 50% tumor regression, respectively, and the median duration of >30% tumor regression was 6.0 months (range 2.3-24.7+months). The median progression-free survival period was 4.3 months (95% CI=3.2-6.1 months; Figure 2). The median survival time was 11.8 months (95% CI 8.3-15.8 months) and the 1- and 2-year survival rates were 50.0% and 22.0%, respectively (Figure 3).

Second treatments. Forty-seven patients suffered recurrences during follow-up. Forty-two patients received additional treatments after cessation of NP plus CPT, or tumor recurrence. Thirty-two patients received second-line chemotherapies, including docetaxel in 18, S-1 in 4, paclitaxel-based therapy in 4, and others in 6. Ten patients received radiation therapy directed at the primary tumor or metastatic sites. Two patients received both chemotherapy and radiation therapy.

Discussion

NP has been shown to have antitumor activity against SCC originating from various organs such as the lung, esophagus, head and neck, and uterine cervix. Not only CPT, but also other drugs such as docetaxel, paclitaxel and 5-FU have been combined with NP, and phase II studies of NP-based chemotherapy have demonstrated response rates of 41.7-100% for 39-52 previously untreated patients with SCC of the cervix, esophagus, or head and neck (15-17). These studies showed that some patients achieved CR, suggesting that NP is highly effective against SCC. A small single-institutional study has demonstrated that NP with docetaxel was active against SCC of the lung (18); however, no multicenter phase II study of NP combination chemotherapy for lung SCC has yet been reported. Although we were unable to find any differences in treatment outcome between SCC and non-SCC in each of

Table III. *Adverse effects and events in chemotherapy of NP plus irinotecan.*

	Grade (NCICTC ver.2)					
	0	1	2	3	4	% of G3 and 4
Leukocyte	9	6	21	7	7	28.0
Neutrophil	10	2	7	8	23	62.0
Hemoglobin	1	15	18	11	5	32.0
Platelet	14	17	7	7	5	24.0
Albumin	0	31	16	3	0	6.0
Alkaline phosphatase	49	0	0	1	0	2.0
ALT	21	26	2	1	0	2.0
AST	34	15	0	0	1	2.0
Bilirubin	40	5	4	0	1	2.0
Hypocalcemia	39	5	5	1	0	2.0
Hypercalcemia	49	0	0	0	1	2.0
Creatinine	35	11	3	1	0	2.0
γGTP	49	0	0	0	1	2.0
Hyperglycemia	49	0	0	0	1	2.0
Hyperkalemia	40	7	3	0	0	-
Hypokalemia	45	2	1	1	1	4.0
Hyponatremia	28	16	0	6	0	12.0
Allergy	48	0	1	1	0	2.0
Supraventricular arrythmia-atrial fibrillation	48	1	0	1	0	2.0
Hypotension	47	1	0	2	0	4.0
Fatigue	27	15	6	2	0	4.0
Fever	35	12	2	1	0	2.0
Weight loss	41	9	0	0	0	-
Alopecia	31	15	4	0	0	-
Urticaria	48	1	1	0	0	-
Anoxia	18	13	8	11	0	22.0
Constipation	25	23	2	0	0	-
Dehydration	48	0	1	1	0	2.0
Diarrhea	21	12	11	5	1	12.0
Esophagitis	49	1	0	0	0	-
Distension	49	0	0	1	0	2.0
Mucositis	46	3	1	0	0	-
Nausea	21	13	11	5	0	10.0
Vomiting	37	10	2	1	0	2.0
Hemorrhage, bronchoulmonary NOS	49	0	0	1	0	2.0
Colitis	48	0	1	1	0	2.0
Febrile neutropenia	42	0	0	8	0	16.0
Infectin(normal ANC)	49	0	1	0	0	-
Infection	40	1	4	5	0	10.0
Infection-skin	49	1	0	0	0	-
Edema: limb	48	2	0	0	0	-
Confusion	49	0	0	1	0	2.0
Neropathy: cranial-hearing	49	0	0	1	0	2.0
Neuropathy: motor	49	1	0	0	0	-
Neropathy: sensory	47	2	1	0	0	-
Pain-back	49	0	0	1	0	2.0
Pain-bone	45	2	1	1	1	4.0
Pain	49	0	0	1	0	2.0
Dyspnea	46	4	0	0	0	-
Hiccoughs	49	1	0	0	0	-
Airway obstruction: bronchus	49	0	0	1	0	2.0
Pneumonitis	48	0	2	0	0	-
Pneumothorax	49	0	0	1	0	2.0
Voice changes/hoarseness	49	1	0	0	0	-

Table III. *Continued*

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SGOT: Serum glutamic oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase.

the previous small studies (8-11), our meta-analysis of those studies suggested that NP and CPT elicited favorable responses and survival in patients with SCC (12). The present study yielded 17 confirmed responders. Although in some patients graphical confirmation of PR for 4 weeks was not possible, 21 patients (42.0%) showed tumor regression of 30% or more, indicating that NP and CPT is effective against SCC of the lung.

Eleven patients in the study received only one cycle of NP and CPT. The reason for treatment withdrawal was PD in 5 of them. Other reasons were toxicities or patient refusal related to such toxicities, including grade 3 pneumonia, grade 3 diarrhea, and grade 2 nausea with grade 2 appetite loss. Two of the 11 patients showed 40-50% tumor regression; therefore, the toxicities of this regimen are required to be better-managed. In the present study, anorexia, nausea, diarrhea and hyponatremia, as grade 3 or 4 non-hematological toxicities occurred at frequencies of 10-22%. Diarrhea is a specific toxicity of CPT, but the others were considered to be mostly related to NP. Gastrointestinal toxicities of NP are similar to those of cisplatin, not carboplatin. Like any cisplatin-based chemotherapy, the NP and CPT combination should be considered a high-risk emetic regimen, and therefore a full panel of prophylactic anti-emetic drugs such as the NK1 receptor antagonist aprepitant, 5-HT_3 receptor antagonist and dexamethasone should be used before and after administration of the anticancer drugs. Nineteen patients in the present study dropped-out after 1 or 2 cycles. Ten of them did so because of PD, and the other 9 because of chemotherapy-related toxicities such as diarrhea, infection and liver damage. One patient each dropped-out of the study because of renal toxicity and anaphylaxis, and 2 patients refused further chemotherapy because of anorexia or nausea. This chemotherapy regimen will also require prophylactic use of anti-allergic agents and fluid therapy.

Table IV. *Therapeutic outcome in phase II study*

Response	No. of patients	Rate (%)
CR	1	
PR	16	
SD	20	
PD	9	
NE	4	
Response		34.0%
Disease control		74.0%

A phase III trial comparing oral S-1 plus carboplatin with paclitaxel plus carboplatin in chemotherapy-naïve patients with advanced NSCLC demonstrated that oral S-1 with carboplatin yielded equally good survival (19). The overall response rate achieved with carboplatin and paclitaxel was superior to that obtained with carboplatin and S-1 (29.0% *vs*. 20.4%). The second report related to that study indicated that median overall survival was 14.0 months in the carboplatin and S-1 arm, and 10.6 months in the carboplatin and paclitaxel arm for patients with SCC (20). Therefore, the survival data for the present study demonstrated that the NP and CPT regimen had an efficacy comparable to that of carboplatin-S1 and carboplatin-paclitaxel. The above second report indicated that it was unclear whether the possible survival benefits conferred by carboplatin and S-1 in SCC patients was due to any intrinsic superiority of this drug combination in comparison with carboplatin and paclitaxel. In fact, during the first-line treatment period, the overall survival curves for SCC patients showed that those treated with carboplatin and paclitaxel had better survival than those treated with carboplatin and S-1. On the other hand, the curve for the S-1 group demonstrated better survival during the period of second-line treatment. Seventy-eight percent of patients in the S-1 group received second-line chemotherapy, compared with 66% of those in the paclitaxel group. Significantly more patients in the S-1 group received standard second-line chemotherapy with docetaxel than those in the paclitaxel group (58.2% *vs*. 30.5%, p=0.003) (20). Thus, in patients with SCC, the possible survival benefit seen in the S-1 group was considered to be due to the effects of docetaxel. In the present study, 32 patients received second-line chemotherapy, and 18 (36.0%) of them were treated with docetaxel. If more patients registered in the present study had been able to receive NP and CPT followed by docetaxel, overall survival might have been better.

Over the last decade, critical molecular and cellular mechanisms in NSCLC have led to the discovery of a variety of novel drug targets and the development of new treatment strategies. Already, the standard-of-care for patients with advanced NSCLC is shifting from selection of therapy based empirically on a patient's clinicopathological features to the use of biomarker-driven treatment algorithms based on the molecular profile of a patient's tumor. Genotype-based targeted therapies represent the first step toward personalization of NSCLC therapy. Recent technological advances in multiplex genotyping and high-throughput genomic profiling using next-generation sequencing technologies now offer the possibility of rapidly and comprehensively interrogating the cancer genome of individual patients from small tumor biopsies. Increasingly, practicing oncologists are facing the challenge of determining how to apply genotyping and genomic tests in therapeutic decision-making for NSCLC. In conclusion, the primary end-point was not met and combination chemotherapy with NP and CPT is not recommended for further evaluation of patients with SCC of the lung.

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Conflicts of Interest

Yuichi Takiguchi, Hiroaki Okamoto, Yukio Hosomi and Kazuma Kishi received research funding from Daiichi-Sankyo Co., Ltd. None of the other authors have any conflicts of interest to declare, including financial, personal or other relationships with other individuals or organizations within 3 years of beginning our submitted work that could have inappropriately influenced our findings.

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