Phase I trial of nedaplatin and S-1 in patients with advanced squamous cell lung cancer

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Abstract. The platinum doublet is considered to be the standard cytotoxic chemotherapy for advanced lung cancer. It has been previously reported that nedaplatin and S-1 have clinical efficacy against squamous cell lung cancer. As the combination of nedaplatin and S-1 has never been studied for advanced squamous cell lung cancer, a phase I trial of this combination in the first-line setting was conducted. Patients who had not received chemotherapy previously, aged ≥75 years and with advanced squamous cell lung cancer were recruited. Nedaplatin was administered intravenously (day 1), and S-1 was orally administered (days 1-14) at a fixed dose based on the body surface area (BSA) <1.25 m², 80 mg/day; BSA=1.25-1.5 m², 100 mg/day; and BSA ≥1.5 m², 120 mg/day. A total of 9 patients were enrolled. The maximum tolerated dose was 80 mg/m² for nedaplatin. At this dosage, dose-limiting toxicity was observed in 2 of the 6 patients. A total of one patient experienced grade 3 thrombocytopenia, and the other toxicity was observed in 2 of the 6 patients. A total of one patient experienced grade 3 thrombocytopenia, and the other patient experienced grade 3 anorexia and grade 3 nausea. The recommended dose for phase II studies was determined as being 70 mg/m² for nedaplatin (clinical trial registration no. UMIN-CTR UMIN000036387).

Introduction

Several lines of evidence have revealed that the combination of a platinum agent and another anticancer agent is suitable as the first-line therapeutic regimen for non-small cell lung cancer (NSCLC) (1,2). Squamous cell lung cancer is a major histologic subtype of NSCLC, accounting for 15-26% of all cases (3,4). S-1 is an oral fluoropyrimidine anticancer agent composed of tegafur, 5-chloro-2,4-dihydroxypyridine, and oteracil potassium. In a phase II study of S-1 monotherapy targeting patients with previously untreated advanced NSCLC, partial responses (PRs) were observed in 13 of 59 patients (22.0%) (5). In a subset analysis of the LETS study of patients with squamous cell lung cancer, the median overall survival (OS) was 14.0 months in the carboplatin and S-1 arm, vs. 10.6 months in the carboplatin and paclitaxel arm (6).

Nedaplatin is a second-generation platinum agent that was developed to have less renal toxicity than cisplatin. In a dose-finding and pharmacokinetic study of nedaplatin, 39 chemotherapy-naïve patients with advanced NSCLC (≥70 years old) received nedaplatin monotherapy at 60 or 80 mg/m² as the initial dose, and the recommended doses were determined as 80 and 100 mg/m² (7). PRs were observed in 13 patients (33%), and the histology of 12 of the responders was squamous cell carcinoma (7).

A phase I study of nedaplatin and S-1 for head and neck cancer has been conducted. The recommended doses were 80 mg/m² for both nedaplatin and S-1 (days 1-14). Responses were observed in 3 of 9 patients (33%) (8). In another phase I study of nedaplatin and S-1 (a fixed dose for 14 days) for head and neck cancer, the maximum tolerated dose of nedaplatin was determined to be 90 mg/m². Responses were observed in 8 of 14 patients (57.1%) (9).

Thus, several studies have revealed the efficacy of both nedaplatin and S-1 for squamous cell cancer. Combination chemotherapy featuring a platinum agent is considered the standard first-line regimen for advanced NSCLC, and the combination of nedaplatin and S-1 could be feasible for the treatment of squamous cell lung cancer. Therefore, we conducted a phase I trial of this combination for patients...
with advanced squamous cell lung cancer (trial registration: UMIN-CTR UMIN000036387).

Materials and methods

Eligibility. This study was approved by the Institutional Review Board of Kagawa University (No. 2012CS023) and all participating institutes. Patients who were diagnosed with advanced or relapsed squamous cell lung cancer between November 2012 and March 2017 were enrolled in this trial. Written informed consent was obtained from each patient before enrollment. The inclusion criteria were as follows: i) histologically or cytologically confirmed squamous cell lung cancer; ii) stage III or IV cancer without an indication for curable radiotherapy and surgery or relapse after surgery; iii) age ≤75 years; iv) Eastern Cooperative Oncology Group performance status of 0 to 1; v) adequate hematopoietic function (white blood cell count ≥4,000/mm³; neutrophil count ≥1,500/mm³; platelet count ≥100,000/mm³; hemoglobin level ≥9.0 g/dl); vi) adequate hepatic function (total bilirubin level <1.5 mg/dl; transaminase level <100 U/I); vii) no respiratory failure (PaO2 ≥60 Torr or SpO2 ≥90%); and viii) adequate renal function (creatinine clearance ≥60 ml/min). The exclusion criteria were as follows: i) previous treatment with chemotherapy and/or radiotherapy for lung cancer; ii) serious concomitant systemic disorders including severe heart failure, active ulcer, ileus, uncontrolled diabetes mellitus, severe diarrhea, and active infection; iii) interstitial lung diseases; iv) positivity for hepatitis B antigen; v) brain metastasis requiring emergency treatment; vi) pleural effusion, ascites, or pericardial effusion necessitating drainage; vii) pregnancy; and viii) other concomitant malignancies or the receipt of anticancer drugs.

Treatment schedule and dose escalation. S-1 (Taiho Pharmaceutical Co., Ltd.) was administered at a fixed dose based on the body surface area (BSA) of the patient as follows: BSA <1.25 m², 80 mg/day (40 mg twice a day); BSA=1.25-1.5 m², 100 mg/day; and BSA ≥1.5 m², 120 mg/day. S-1 was administered orally for 14 days, followed by 14 days of rest. Nedaplatin (Nichi-Iko Pharmaceutical Co., Ltd.) was administered at a fixed dose based on the body surface area (BSA) of the patient as follows: BSA <1.25 m², 100 mg/m²; BSA=1.25-1.5 m², 80 mg/m²; and BSA ≥1.5 m², 100 mg/m². The starting dose of nedaplatin was 70 mg/m² (level 1). Additional increases by 10 mg/m² up to 100 mg/m² were permitted to identify the maximum tolerated dose (MTD). The treatment schedule was repeated every 28 days until disease progression, unacceptable toxicities, or patient refusal.

Chemotherapy was temporarily stopped for any of the following occurrences: i) grade 3 or more leukocytopenia, neutropenia, or thrombocytopenia; ii) grade 3 febrile neutropenia; iii) elevated total bilirubin ≥1.5 mg/dl; iv) elevated transaminase ≥100 IU/I; v) elevated serum creatinine ≥1.5 mg/dl; and iv) grade 2 non-hematological toxicities. Chemotherapy was restarted after recovery from these criteria. At least three patients were treated at each dose level. Toxicities were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Dose-limiting toxicities (DLTs) were defined as follows: i) grade 4 neutropenia; ii) grade 3 febrile neutropenia; iii) grade 3 thrombocytopenia; vi) grade 3 non-hematological toxicities; v) less than 70% (20/28) doses of S-1 could be administered; and v) a >15-day delay in the start of the second cycle. When a DLT appeared, three patients were added at the same dose level. If DLTs occurred in zero of three or one of six patients, then the dose was increased to the next level. If a DLT was observed in two of six patients at the same dose level, the dose was defined as MTD, and the study was stopped. The previous dose level was considered the recommended dose.

Evaluation and follow-up. The baseline evaluation included medical history, physical examination, blood cell counts, serum chemistry, chest X-ray and computed tomography, enhanced brain magnetic resonance imaging, and either positron emission tomography or bone scintigraphy. Clinical response was evaluated for each cycle of chemotherapy. A complete response (CR) was defined as the disappearance of all clinically evident tumors and no new disease. A PR was defined as a >30% reduction of the sum of the longer diameter of the tumor and no new disease. Progressive disease (PD) was defined as a >20% increase in the sum of the longer diameter of tumors or the appearance of a new lesion. Stable disease (SD) was defined as disease regression that did not qualify as a PR or disease progression that did not qualify as PD and no new disease. Progression-free survival (PFS) was defined as the time from the start of chemotherapy to that of PD or death. OS was defined as the time from the date of diagnosis to that of death from any cause. PFS and OS curves were constructed, and median survival was estimated via the Kaplan-Meier method using Ekuseru-Toukei 2015 software (Social Survey Research Information).

Results

Characteristics of patients. Nine patients were enrolled in this trial, including three patients treated at dose level 1 and six patients treated at dose level 2. The details of patient characteristics are shown in Table I. All nine patients were men. Three patients were diagnosed with clinical stage III cancer, and

### Table I. Patient characteristics.

| Parameter | Value |
|-----------|-------|
| Number of patients enrolled | 9 |
| Sex | Male 9 Female 0 |
| Age | 60-74 |
| ECOG performance status | 0 4 1 5 |
| Histology | Squamous cell carcinoma 9 |
| Clinical stage | IIIA 1 IIIB 2 IV 6 |
| ECOG, Eastern Cooperative Oncology Group. |

This study was approved by the Institutional Review Board of Kagawa University (No. 2012CS023) and all participating institutes. Patients who were diagnosed with advanced or relapsed squamous cell lung cancer between November 2012 and March 2017 were enrolled in this trial. Written informed consent was obtained from each patient before enrollment. The inclusion criteria were as follows: i) histologically or cytologically confirmed squamous cell lung cancer; ii) stage III or IV cancer without an indication for curable radiotherapy and surgery or relapse after surgery; iii) age ≤75 years; iv) Eastern Cooperative Oncology Group performance status of 0 to 1; v) adequate hematopoietic function (white blood cell count ≥4,000/mm³; neutrophil count ≥1,500/mm³; platelet count ≥100,000/mm³; hemoglobin level ≥9.0 g/dl); vi) adequate hepatic function (total bilirubin level <1.5 mg/dl; transaminase level <100 U/I); vii) no respiratory failure (PaO2 ≥60 Torr or SpO2 ≥90%); and viii) adequate renal function (creatinine clearance ≥60 ml/min). The exclusion criteria were as follows: i) previous treatment with chemotherapy and/or radiotherapy for lung cancer; ii) serious concomitant systemic disorders including severe heart failure, active ulcer, ileus, uncontrolled diabetes mellitus, severe diarrhea, and active infection; iii) interstitial lung diseases; iv) positivity for hepatitis B antigen; v) brain metastasis requiring emergency treatment; vi) pleural effusion, ascites, or pericardial effusion necessitating drainage; vii) pregnancy; and viii) other concomitant malignancies or the receipt of anticancer drugs.

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six were diagnosed with stage IV cancer, including one patient whose tumor had relapsed with distant metastasis after surgery.

Toxicity. Table II presents the data for hematological and non-hematological toxicity. Three patients completed the first cycle at dose level 1 without DLTs. Then, six patients were enrolled at dose level 2 because one of the first three patients experienced CTCAE grade 3 thrombocytopenia. Anorexia was the most common toxicity of any grade, being observed in all nine patients. Other toxicities of any grade included nausea (7 cases; 78%), anemia (6 cases; 67%), neutropenia (6 cases; 67%), and thrombocytopenia (5 cases; 56%). No patients experienced vomiting. Grade 3 anorexia and grade 3 nausea occurred in one of the added patients. Thus, DLTs developed in two of six patients at dose level 2. Therefore, the MTD was dose level 2, the study was terminated, and dose level 1 was selected as the recommended dose.

Response and status. The number of cycle numbers of nedaplatin and S-1 therapy administered to the patients ranged 2-6 (mean, 3.4). No patients achieved CRs. Four, three, and two patients achieved PRs, SDs, and PDs, respectively. The response rate was 44%. However, all nine patients eventually experienced disease progression, and the median PFS was 6.0 months. All patients died of disease progression, and the median OS was 12.0 months.

Discussion

To the best of our knowledge, this phase I trial of the combination of nedaplatin and S-1 for patients with advanced squamous cell lung cancer is the first report of this combination in the treatment of lung cancer in this setting. As a result, the MTD and recommended dose were determined. Regarding efficacy, the response rate was 44%, and the median PFS was 6.0 months. Although the number of patients was too small to clarify efficacy; which is a limitation as a phase I trial, antitumor effects were certainly observed in some patients. A phase II trial of this combination regimen is warranted to further evaluate its feasibility.

Several studies have reported the efficacy of combination regimens including S-1 or nedaplatin for advanced squamous cell lung cancer (6,10,11). A subset analysis of the LETS study suggested that S-1 plus carboplatin tended to more strongly prolong OS than paclitaxel plus carboplatin in patients with squamous cell lung cancer (6). A phase II study of S-1 plus carboplatin followed by maintenance S-1 was conducted in patients with chemotherapy-naïve advanced squamous cell lung cancer. Patients received carboplatin on day 1 and S-1 on days 1-14 every 21 days. In the 33 analyzed patients, the response rate was 30.3%, and the disease control rate was 75.8%. The median PFS and OS were 3.5 and 11.3 months, respectively (10). A randomized phase III trial revealed that the OS was significantly longer in the nedaplatin plus docetaxel arm than in the cisplatin plus docetaxel arm (median OS: 13.6 months vs. 11.4 months) (11). Although the combination of nedaplatin and S-1 for squamous cell lung cancer has not been reported previously, the efficacy of this combination in advanced lung adenocarcinoma after the failure of first line chemotherapy has been evaluated (12). The response rate of nedaplatin and S-1 was 33.0%, which exceeded that of standard therapy consisting of docetaxel or pemetrexed.

Table II. Toxicity.

| Parameter                  | Level 1 (n=3), 70 mg/m² N, 80, 100 and 120 mg/m² S-1 based on BSA | Level 2 (n=6), 80 mg/m² N, 80, 100 and 120 mg/m² S-1 based on BSA |
|----------------------------|-------------------------------------------------------------------|-------------------------------------------------------------------|
| Hematological toxicity     |                                                                   |                                                                   |
| Anemia                     | 3  0  0  0  0                                                      | 2  2  0  0  0                                                     |
| Leukopenia                 | 3  0  0  0  0                                                      | 3  0  1  0  0                                                     |
| Neutropenia                | 1  2  0  0  0                                                      | 2  0  1  0  0                                                     |
| Thrombocytopenia           | 2  0  0  0  0                                                      | 2  0  1  0  0                                                     |
| AST                        | 1  0  0  0  0                                                      | 0  0  0  0  0                                                     |
| Non-hematological toxicity |                                                                   |                                                                   |
| Anorexia                   | 3  0  0  0  0                                                      | 2  3  1  0  0                                                     |
| Nausea                     | 3  0  0  0  0                                                      | 1  2  1  0  0                                                     |
| Fatigue                    | 0  0  0  0  0                                                      | 3  0  0  0  0                                                     |
| Diarrhea                   | 0  0  0  0  0                                                      | 1  1  0  0  0                                                     |
| Stomatitis                 | 0  0  0  0  0                                                      | 0  1  0  0  0                                                     |
| Fever                      | 0  0  0  0  0                                                      | 1  0  0  0  0                                                     |
| Heartburn                  | 1  0  0  0  0                                                      | 0  0  0  0  0                                                     |
| Sleeplessness              | 1  0  0  0  0                                                      | 0  0  0  0  0                                                     |

BSA, body surface area; CTCAE, Common Terminology Criteria for Adverse Events; AST, aspartate aminotransferase; N, nedaplatin.
monotherapy (19.3%). The response rate was not correlated with gender, age, performance status, or the first-line chemotherapeutic regimen. The median PFS of nedaplatin and S-1 was 3.34 months, which was also longer than that of standard therapy (12).

In addition to the use of combination chemotherapeutic regimens, therapeutic strategies for squamous cell lung cancer have been improved by the development of attractive drugs with new antitumor mechanisms. The addition of necitumumab, a second-generation epidermal growth factor receptor antibody, to gemcitabine and cisplatin chemotherapy improved OS in patients with advanced squamous cell lung cancer (SQUIRE phase III trial) (13). The median OS was significantly longer in the necitumumab plus gemcitabine and cisplatin arm than in the gemcitabine and cisplatin arm (11.5 months vs. 9.9 months) (13). An additional phase II trial in Japan also reported longer OS in the necitumumab plus gemcitabine and cisplatin arm than in the gemcitabine and cisplatin arm (14.9 months vs. 10.8 months) (14).

Furthermore, the usefulness of immune checkpoint inhibitors has been reported for a variety of malignancies including squamous cell lung cancer. In patients with previously treated squamous cell lung cancer, OS and PFS were significantly better for nivolumab than for docetaxel (CheckMate 017) (15). This surprising report proved the effectiveness of immuno-oncology. Subsequently, first-line pembrolizumab monotherapy improved PFS and OS in patients with NSCLC positive for programmed cell death ligand 1 (KEYNOTE-024 and -042) (16,17). The addition of pembrolizumab to carboplatin plus paclitaxel or nab-paclitaxel resulted in significantly longer PFS and OS than chemotherapy alone in patients with squamous cell lung cancer (KEYNOTE-407, median PFS: 6.4 months vs. 4.8 months; median OS: 15.9 months vs. 11.3 months) (18). The addition of pembrolizumab to chemotherapy also improved health-related quality of life scores compared with the effects of chemotherapy alone (19).

Based on these findings, the addition of an immune checkpoint inhibitor to nedaplatin plus S-1 could further improve the efficacy of the regimen for treating advanced squamous cell lung cancer, and we are planning a clinical trial of this combination strategy.

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Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Authors’ contributions

N Kan designed the study, enrolled the patients, collected the data, and prepared and revised the manuscript. TI, YU, HI and NKi designed the study, enrolled the patients, collected the data, and revised the manuscript. NKad designed the study and revised the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The current study was approved by the Institutional Review Board of Kagawa University (approval no. 2012CS023) and all participating institutes. All procedures performed in the study involving human participants were conducted in accordance with the ethical standards of the institutional research committee and the Declaration of Helsinki. Written informed consent for participation of this study was obtained from all individual participants.

Patient consent for publication

Written informed consent for publication of patient data was obtained from all individual participants.

Competing interests

The authors declare that they have no competing interests.

References

1. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, Zhu J and Johnson DH: Eastern Cooperative Oncology Group: Comparison of four chemotherapy regimens for advanced Non-small-cell lung cancer. N Engl J Med 346: 92-98, 2002.
2. Ohe Y, Ohashi Y, Kubota K, Tamura T, Nakagawa K, Negoro S, Nishiwaki Y, Saito N, Ariyoshi Y and Fukuoka M: Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced Non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. Ann Oncol 18: 317-323, 2007.
3. Kanaji N, Mizoguchi H, Inoue T, Tadokoro A, Watanabe N, Ishii T, Tojo Y, Yamaguchi M and Kadowaki N: Clinical features of patients with lung cancer accompanied by thromboembolism or disseminated intravascular coagulation. Ther Clin Risk Manag 14: 1361-1368, 2018.
4. Van de Ven M, Retél VP, Koffijberg H, van Harten WH and IJzerman MJ: Variation in the time to treatment for stage III and IV non-small cell lung cancer patients for hospitals in the Netherlands. Lung Cancer 154: 34-41, 2019.
5. Kawahara M, Furuze K, Segawa Y, Yoshimori K, Matsu K, Kudoh S, Hasegawa K and Niitani H: S-1 Cooperative Study Group (Lung Cancer Working Group): Phase II study of S-1, a novel oral fluorouracil, in advanced non-small-cell lung cancer. Br J Cancer 85: 939-943, 2001.
6. Yoshinka H, Okamato I, Morita S, Ando M, Takeda K, Seto T, Yamamoto N, Saka H, Atagi S, Hirashima T, et al: Efficacy and safety analysis according to histology for S-1 in combination with carboplatin as First-line chemotherapy in patients with advanced Non-small-cell lung cancer: Updated results of the West Japan Oncology Group LETS study. Ann Oncol 24: 1326-1331, 2013.
7. Yamamoto N, Tamura T, Kurata T, Yamamoto N, Sekine I, Kunitoh H, Ohe Y and Saito N: A dose-finding and pharmacokinetic study of nedaplatin in elderly patients with advanced non-small cell lung cancer. Cancer Chemother Pharmacol 65: 79-88, 2009.
8. Kodaira T, Fuwa N, Tachibana H and Hidano S: Phase I study of S-1 and nedaplatin for patients with recurrence of head and neck cancer. Anticancer Res 26: 2265-2268, 2006.
9. Kogashiwa Y, Yamauchi K, Nagafuji H, Matsuda T, Tsubosaka T, Kanaza T, Maruyama T and Kohno N: Phase I study of S-1 plus nedaplatin in patients with advanced/recurrent head and neck cancer. Chemotherapy 56: 453-458, 2010.
10. Yokoi T, Minami S, Shiroyama T, Koba T, Torii Y, Sugimoto H, Niki M, Mori M, Morimura O, Hirashima T, et al: A Phase II study of Tailored-dose S-1 plus carboplatin followed by maintenance S-1 for advanced squamous cell lung cancer: OSAKA-LCSG 1102. Intern Med 58: 1405-1410, 2019.

11. Shukuya T, Yamanaka T, Seto T, Daga H, Goto K, Saka H, Sugawara S, Takahashi T, Yokota S, Kaneda H, et al: Nedaplatin plus docetaxel versus cisplatin plus docetaxel for advanced or relapsed squamous cell carcinoma of the lung (WJOG5208L): A randomised, open-label, phase 3 trial. Lancet Oncol 16: 1630-1638, 2015.

12. Tang Y, Wang W, Teng XZ and Shi L: Efficacy of S-1 plus nedaplatin compared to standard second-line chemotherapy in EGFR-negative lung adenocarcinoma after failure of first-line chemotherapy. Tumour Biol 35: 8945-8951, 2014.

13. Thatcher N, Hirsch FR, Luft AV, Szczesna A, Ciuleanu TE, Dediu M, Ramlau R, Galiulin RK, Bálint B, Losonczy G, et al: Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small-cell lung cancer (SQUIRE): An open-label, randomised, controlled phase 3 trial. Lancet Oncol 16: 763-774, 2015.

14. Watanabe S, Yoshioka H, Sakai H, Hotta K, Takenoyama M, Yamada K, Sugawara S, Takiguchi Y, Hosomi Y, Tomii K, et al: Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line treatment for stage IV squamous non-small cell lung cancer: A phase 1b and randomized, open-label, multicenter, phase 2 trial in Japan. Lung Cancer 129: 55-62, 2019.

15. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, Antonia S, Pluzanski A, Vokes EE, Holgado E, et al: Nivolumab versus Docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 373: 123-135, 2015.

16. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, et al: Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 375: 1823-1833, 2016.

17. Mok TS, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, Castro G Jr, Srimuninnimit V, Laktionov KK, Bondarenko I, et al: Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): A randomised, open-label, controlled, phase 3 trial. Lancet 393: 1819-1830, 2019.

18. Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gümiş M, Mazieres J, Hermes B, Çay Şenler F, Csőszi T, Fülöp A, et al: Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. N Engl J Med 379: 2040-2051, 2018.

19. Mazieres J, Kowalski D, Luft A, Vicente D, Tafreshi A, Gümiş M, Laktionov K, Hermes B, Cicin I, Rodríguez-Cid J, et al: Health-related quality of life with carboplatin-paclitaxel or nab-Paclitaxel with or without pembrolizumab in patients with metastatic squamous non-small-cell lung cancer. J Clin Oncol 38: 271-280, 2020.