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PHASE II STUDIES

Switch maintenance therapy with S-1 after induction therapy with carboplatin and nanoparticle albumin-bound paclitaxel in advanced lung squamous cell carcinoma

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Summary

Background Optimal maintenance therapy for lung squamous cell carcinoma (SCC) has not been established. The aim of this study was to evaluate the efficacy and safety of switch maintenance therapy with S-1, an oral fluoropyrimidine, after induction therapy with carboplatin and nanoparticle albumin-bound paclitaxel (*nab*-paclitaxel) in chemotherapy-naïve patients with advanced SCC. *Methods* Chemotherapy-naïve patients with advanced SCC received induction therapy with four cycles of carboplatin (at an area under the curve of 6, day 1 of a 28-day cycle) and *nab*-paclitaxel (100 mg/kg, days 1, 8, and 15). Patients who achieved disease control after induction therapy received maintenance therapy with S-1 (80 mg/m^2, days 1–14 of a 21-day cycle) until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS) from the start of maintenance therapy. *Results* Seventy-two patients with SCC were enrolled to the study. After four cycles of induction therapy, 35 (48.6%) patients achieved disease control, and 31 (43.1%) of these patients received maintenance therapy. Median PFS from the start of maintenance therapy was 3.0 months (95% confidence interval: 2.1–3.8 months). The most common toxicities of grade 3 or higher during maintenance therapy were nausea (13.3%), neutropenia (10.0%), and diarrhea (6.7%). *Conclusions* Switch maintenance therapy with S-1 after induction therapy with carboplatin and *nab*-paclitaxel was associated with moderate efficacy and acceptable safety and may represent a feasible treatment option for patients with advanced SCC.

Keywords Lung squamous cell carcinoma · Maintenance therapy · S-1 · Carboplatin · *nab*-paclitaxel

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Abbreviations

AUC	Area under the curve
CBDCA	Carboplatin
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
nab-PTX	Nanoparticle albumin-bound paclitaxel
NSCLC	Non-small-cell lung cancer
OS	Overall survival
PFS	Progression-free survival
RECIST	Response Evaluation Criteria in Solid Tumors
SCC	Lung squamous cell carcinoma

Introduction

Maintenance therapy, defined as the continuation of chemotherapy immediately after first-line chemotherapy, is a standard treatment option for advanced non-squamous non-small-cell lung cancer (NSCLC) [1, 2]. In the pre-maintenance therapy era, up to 50% of patients with lung cancer did not receive second-line chemotherapy, mainly because of deterioration in health status during drug holidays after first-line chemotherapy [3, 4]. An advantage of maintenance therapy is the efficient delivery of subsequent chemotherapy to patients at risk of missing the opportunity to receive second-line treatment.

Several maintenance strategies have demonstrated clinical benefits in NSCLC. Maintenance therapy that continues one or more agents used in induction therapy is termed "continuation" maintenance therapy. Continuation maintenance therapy with pemetrexed after induction therapy with pemetrexed plus a platinum agent has been shown to improve overall survival, and is now widely used in clinical practice [5]. Maintenance therapy that delivers agents not used in induction therapy is termed "switch" maintenance therapy. Switch maintenance therapy with pemetrexed or erlotinib is recommended in patients receiving platinum-based therapy without pemetrexed as induction therapy [1, 2, 6, 7].

However, patients with lung squamous cell carcinoma (SCC) receive little benefit from these maintenance strategies. Switch maintenance therapy with pemetrexed has not been shown to confer a survival benefit on patients with SCC [6], because pemetrexed has reduced antitumor activity against SCC compared with non-squamous NSCLC [8]. Thus, patients with SCC were excluded in the PARAMOUNT study that evaluated the efficacy of continuation maintenance with pemetrexed [5]. Switch maintenance therapy with erlotinib has also been shown to be ineffective for SCC [7]. The optimal maintenance therapy for SCC therefore remains unknown.

S-1 (Taiho Pharmaceutical Co Ltd., Tokyo, Japan), an oral fluoropyrimidine agent, is widely used in cancer therapy [9–11]. In lung cancer, S-1 has demonstrated clinical efficacy and safety as a single agent or in combination with a platinum agent [12–17]. In addition to this efficacy, S-1 has demonstrated favorable safety and ease of administration as an oral tablet therapy, and therefore has a potential therapeutic advantage in maintenance therapy in SCC. We previously reported the efficacy and safety of continuation maintenance therapy with S-1 after induction therapy with carboplatin (CBDCA) and S-1 in SCC [18]. In that study, the proportion of patients who responded to induction therapy and received maintenance therapy with S-1 was 35.3%, which was not completely satisfactory, mainly because of the low efficacy of induction therapy with CBDCA and S-1. Combination therapy with CBDCA and nanoparticle albumin-bound paclitaxel (*nab*-PTX; Taiho Pharmaceutical Co Ltd., Tokyo, Japan) is has shown favorable efficacy in NSCLC, especially in SCC [19]. The aim of this phase II study was to evaluate the efficacy and safety of switch maintenance therapy with S-1 after induction therapy with carboplatin plus *nab*-paclitaxel in chemotherapy-naïve patients with advanced SCC.

Patients and methods

Study design

This study was a multicenter, open-label, single-arm phase II trial. The protocol was approved by the Institutional Review Board of each participating medical institution and was conducted in accordance with the principles of the Declaration of Helsinki. The trial was registered at the University Hospital Trial Registry (UMIN ID 0000006983).

Patients

The key inclusion criteria for the study were as follows: chemotherapy-naïve patients aged 20 years or older; histologically or cytologically confirmed SCC; nonresectable stage IIIB, stage IV, or recurrent disease; measurable lesions according to the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1; Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1; and life expectancy of more than 3 months. Additional eligibility criteria included oral intake ability; and adequate hematopoietic, hepatic, and renal function. Patients were excluded from this study if they had uncontrolled brain metastasis; uncontrolled pleural effusion, ascites, or pericardial effusion; watery diarrhea, digestive obstruction, ileus, digestive ulcer, interstitial lung disease, concomitant malignancy, or other uncontrolled complications. The use of antiemetic agents, granulocyte colony-stimulating factor, bisphosphonates, denosumab, and extra-thoracic palliative radiotherapy was permitted in this study.

Treatment schedule

Eligible patients received induction chemotherapy with 100 mg/m^2 of intravenous *nab*-PTX on days 1, 8, and 15, and intravenous CBDCA at an area under the curve (AUC) of 6 (Calvert formula) on day 1 of a 28-day cycle. After four cycles of induction therapy, patients who did not demonstrate progressive disease received switch maintenance therapy with oral S-1 at 80 mg/m^2 on days 1–14 of a 21-day cycle. Maintenance therapy was continued until disease progression or unacceptable toxicity. During induction therapy, two-stage dose reductions were permitted for CBDCA (AUC 4.5 and AUC 3) and *nab*-PTX (80 mg/m^2 and 50 mg/m^2). During maintenance therapy, a 20% reduction in dose was permitted for S-1. Patients were withdrawn from the study if they showed disease progression, had a treatment delay of >21 days, or had a dose reduction beyond the permitted range.

Assessment of efficacy and safety

The primary endpoint was progression-free survival (PFS) measured from the start date of maintenance therapy. Evaluation of tumor response was performed every two cycles during induction and maintenance therapy. Secondary endpoints were overall survival (OS) from the enrollment date, PFS from the enrollment date, overall response rate (ORR) and disease control rate (DCR) of induction therapy, and safety. Toxicities were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Statistical analyses

In the maintenance therapy phase, 32 patients were required to achieve 80% statistical power, assuming an expected PFS of 4.0 months [15, 20] and threshold PFS of 2.6 months [6] with a one-sided type I error of 0.1, based on the Southwest Oncology Group (SWOG) single-arm survival design [21]. It was assumed that approximately 50% of patients would demonstrate disease control in the induction therapy phase and thus receive maintenance therapy [15]. It was therefore calculated that enrollment of 70 patients was required, after taking the potential for dropouts into account. PFS and OS were analyzed using Kaplan–Meier methods. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). Values of $P < 0.05$ were considered statistically significant.

Results

Patient characteristics

Between April 2015 and December 2017, 72 patients were enrolled in this study. Patient characteristics are shown in Table 1. The median age (range) was 70 years (43–85 years), 60 (83.3%) patients were male, and 25 (34.7%) patients were aged >75 years. Fifty-eight (80.6%) patients had an ECOG performance status of 0, and 56 (77.8%) patients had stage IV disease. All patients had histologic diagnoses of squamous cell carcinoma. The median follow-up time was 10.6 months (range, 2.0–33.6 months).

Treatment

In the induction therapy phase, a median of four cycles (range, 1–4) was delivered and 53 (73.6%) patients completed four cycles of induction therapy. Dose reductions and delays were required in 41 (56.9%) and 20 (27.8%) patients, respectively. Forty-one (56.9) patients did not receive maintenance therapy because of disease progression ($n = 30$), adverse events ($n = 4$), patient decision ($n = 3$), physician decision ($n = 2$), or a treatment delay of >21 days ($n = 2$, Fig. 1). As a result, 31 (43.1%) patients received maintenance therapy, which comprised a median of three cycles (range, 2–17). Dose reductions and delays in the maintenance phase were required in four (12.9%) and five (16.1%) patients, respectively. Twenty-nine patients (93.3%) discontinued maintenance therapy because

Table 1 Patient characteristics

	All patients ($n = 72$)
Age, years	70 (43–85)
Sex, male	60 (83.3)
Smoking status	
Never smoker	8 (11.1)
Former smoker	43 (59.7)
Current smoker	21 (29.2)
ECOG performance status	
0/1	58 (80.6) / 14 (19.4)
Stage, IIIB/IV	16 (22.2) / 56 (77.8)
Histology, squamous cell carcinoma	72 (100)
Metastasis	
Brain	10 (13.9)
Bone	11 (15.3)
Carcinomatous pleurisy	15 (20.8)
Liver	11 (15.3)

Data are expressed as numbers (percentage) or the median (range)

ECOG Eastern Cooperative Oncology Group

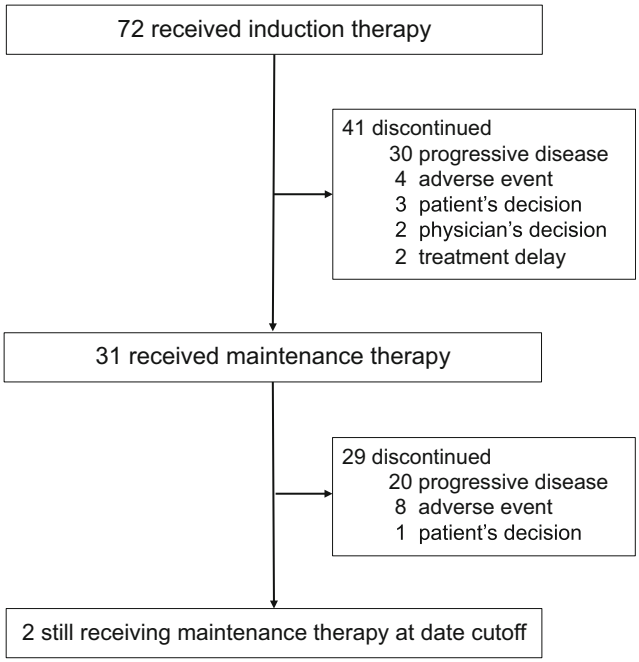

Fig. 1 Study profile

of disease progression ($n = 20$), adverse events ($n = 8$), or patient decision ($n = 1$). Two patients were still receiving maintenance therapy on the data cutoff date.

Efficacy

The median PFS from the start of maintenance therapy was 3.0 months (95% confidence interval [CI]: 2.1–3.8 months; Fig. 2). When measured from the study enrollment date, median PFS was 5.4 months (95% CI: 4.3–6.1 months). After induction therapy, 22 patients (30.6%) had a partial response and 13 (18.1%) had stable disease, yielding an ORR of 30.6% (95% CI: 20.2–42.5%) and a DCR of 48.6% (95% CI: 36.7–60.7%). The median OS from enrollment was 15.8 months (95% CI: 9.8–19.8 months). When measured from the start of maintenance therapy, median OS was 14.8 months (95% CI: 12.0 months–not estimable).

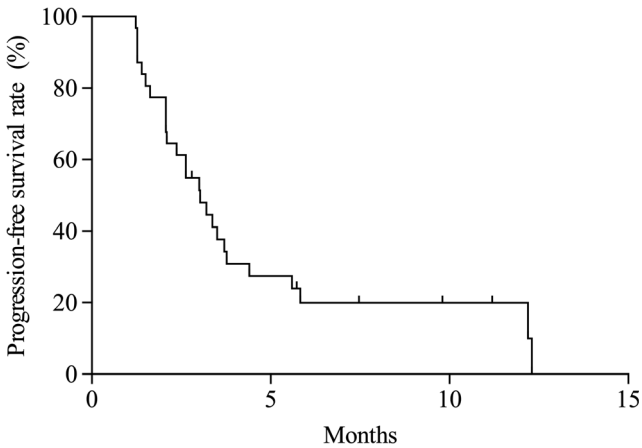

Fig. 2 Progression-free survival. Progression-free survival of patients who received maintenance therapy was estimated from the date of administration of maintenance therapy using the Kaplan–Meier method. Median progression-free survival was 3.0 months (95% confidence interval: 2.1–3.8 months)

Safety

Major adverse events are listed in Table 2. In the induction therapy phase, the most common toxicities were neutropenia, anemia, leukopenia, and nausea. Grade 3 or higher neutropenia and febrile neutropenia occurred in 33 (45.8%) and 4 (5.6%) patients, respectively. Twenty (27.7%) patients required the administration of granulocyte colony-stimulating factor (G-CSF), and blood transfusions were required in 12 (16.7%) patients. Eight (11.1%) patients required hospitalization (febrile neutropenia, $n = 4$; pneumonia, $n = 2$; empyema, $n = 1$; and ileus, n = 1). In the maintenance therapy phase, the most common toxicities were anemia, nausea, neutropenia, and thrombocytopenia.

Table 2 Adverse events

	Induction therapy ($n = 72$)		Maintenance therapy ($n = 30$)	
	Grade 1–4	Grade 3–4	Grade 1–4	Grade 3–4
Hematologic toxicity				
Leukopenia	39 (54.2)	23 (31.9)	6 (20.0)	0
Neutropenia	45 (62.5)	33 (45.8)	8 (26.7)	3 (10.0)
Anemia	45 (62.5)	13 (18.1)	15 (50.0)	0
Thrombocytopenia	22 (30.6)	4 (5.6)	7 (23.3)	0
Non-hematologic toxicity				
ALT/AST increased	9 (12.5)	2 (2.8)	3 (10.0)	0
Nephrotoxicity	3 (4.2)	0	2 (6.7)	0
Nausea	30 (41.2)	4 (5.6)	11 (36.7)	4 (13.3)
Vomiting	8 (11.1)	1 (1.4)	0	0
Constipation	16 (22.2)	0	3 (10.0)	0
Diarrhea	4 (5.6)	1 (1.4)	3 (10.0)	2 (6.7)
Fatigue	17 (23.6)	1 (1.4)	3 (10.0)	0
Infection	8 (11.1)	8 (11.1)	1 (3.3)	1 (3.3)
Febrile neutropenia	4 (5.6)	4 (5.6)	0	0
Alopecia	20 (27.8)	0	3 (10.0)	0
Rash	1 (1.4)	0	0	0
Allergy	0	0	0	0
Oral mucositis	0	0	1 (3.3)	0
Pneumonitis	4 (5.6)	3 (4.2)	1 (3.3)	1 (3.3)
Taste disorder	7 (9.7)	0	2 (6.7)	0
Peripheral neuropathy	11 (15.3)	0	1 (3.3)	0

Data are expressed as numbers (percentages)

ALT alanine aminotransferase, *AST* aspartate aminotransferase

Grade 3 or higher neutropenia occurred in three (10.0%) patients. No administration of G-CSF was required, and one (3.3%) patient required a blood transfusion. There were no treatment-related deaths during the study period.

Post-study therapy

Among the 70 patients who discontinued study treatment, 43 (61.4%) received post-study chemotherapy: 25 received nivolumab, 4 pembrolizmab, and 8 docetaxel.

Discussion

Switch maintenance therapy with S-1 following induction therapy with carboplatin plus *nab*-paclitaxel demonstrated moderate efficacy in patients with advanced SCC. Although the median PFS of 3.0 months did not reach the expected level of 4.0 months, it did exceed the preplanned lower threshold level of 2.6 months. Additionally, maintenance therapy with S-1 demonstrated acceptable safety, alongside the convenience of oral administration. Induction therapy with CBDCA and *nab*-PTX demonstrated favorable efficacy, which enabled a considerable proportion of patients to progress to maintenance therapy. Switch maintenance therapy with S-1 after induction therapy with CBDCA and *nab*-PTX may therefore represent a feasible treatment strategy for patients with SCC.

S-1 has been shown to demonstrate clinical efficacy, regardless of NSCLC histology. In a phase III study of first-line CBDCA and S-1, the treatment efficacy was comparable between patients with SCC and those with non-squamous NSCLC [12, 13]. In another phase III study of S-1 monotherapy for previously treated NSCLC, treatment efficacy did not differ according to histological type [16]. The median PFS of S-1 maintenance therapy observed in the current study was equivalent to that reported in a phase III study of S-1 monotherapy for previously treated NSCLC including both SCC and non-squamous histology (2.86 months) [16]. In addition, continuation maintenance therapy with S-1 after induction therapy with CBDCA and S-1 in SCC demonstrated an equivalent median PFS of 3.0 months [18]. Previous studies of maintenance therapy have resulted in little clinical benefit for SCC because of selective efficacy for non-squamous NSCLC (e.g. pemetrexed or erlotinib); however, S-1 may have a potential role in maintenance therapy for SCC.

When considering maintenance therapy, the efficacy of induction therapy may be of importance. First-line treatment with CBDCA and *nab*-PTX has the potential for superior efficacy, particularly in SCC rather than in non-squamous NSCLC [19]. Previously, we evaluated continuation maintenance with S-1 after induction therapy with CBDCA and S-1 in patients with SCC. In that study, induction therapy was associated with a numerically lower ORR (19.6%) and DCR (35.3%), and fewer patients therefore received maintenance therapy (35.3%) compared with those in the current study (30.6%, 48.6%, and 43.1%, respectively). The median PFS from the start of S-1 continuation maintenance therapy was 3 months, which was comparable with in the data from the current study. However, the median PFS from induction therapy was numerically longer in the current study compared with that observed for induction therapy with CBDCA and S-1 (4.4 months) [18]. The difference in overall PFS between these studies, which included identical maintenance therapy with S-1, may be attributable to differences in the efficacy of induction therapy.

No conclusive evidence for an optimal maintenance strategy has been reported to date. Continuation maintenance therapy has the advantage of continuing chemotherapeutic agents that have already demonstrated efficacy in induction therapy, therefore maximizing the potential efficacy of these agents. Indeed, a phase II trial of continuation maintenance therapy with *nab-PTX* following induction therapy with CBDCA and *nab*-PTX demonstrated a median PFS of 6.5 months for the maintenance therapy [22], which was numerically superior to that observed in the current study. However, in the previous study, grade 3 or higher neutropenia, anemia, and all hematological toxicities occurred at a rate of 25%, 6.3%, and 31.3%, respectively, which was more frequent than the rates observed in the current study. Furthermore, frequent hospital visits are required for maintenance therapy with *nab*-PTX (days 1, 8, 15 for every 28-day cycle). Tolerability and convenience are particularly important during maintenance therapy for SCC, because patients with SCC typically have the characteristics of older age, advanced disease, and high incidence of comorbidities [23–25]. For patients with SCC receiving induction therapy with CBDCA and *nab*-PTX who are unsuitable for maintenance therapy with *nab*-PTX, switch maintenance therapy with S-1 may represent a feasible treatment option.

The current study had some limitations. S-1 has the advantages of convenience and safety but demonstrates only moderate efficacy. In studies evaluating the efficacy of S-1 as second-line therapy or maintenance therapy, PFS was approximately 3 months, and this might be the therapeutic limit of S-1 monotherapy [15–18]. Combination maintenance therapy with S-1 and bevacizumab has demonstrated improved efficacy compared with maintenance S-1 monotherapy (median PFS of 4.6 months and 2.6 months, respectively) in non-squamous NSCLC [17]. Anti-antiangiogenic agents are known to increase the efficacy of chemotherapy [26–29]. Bevacizumab is not approved for use in SCC, but ramucirumab, another antiangiogenic agent, has demonstrated clinical efficacy in combination with docetaxel, regardless of NSCLC histology [30]. Combination maintenance therapy of S-1 and an antiangiogenic agent may therefore have potential benefits in SCC. Immune checkpoint inhibitors (ICIs) represent a novel treatment option for NSCLC, and biomarker-

based treatment strategies for ICIs (e.g. programmed death-ligand 1 and tumor mutation burden) are important [31–34]. Furthermore, combination therapy with cytotoxic chemotherapy and ICIs has demonstrated clinical efficacy [35, 36]. In a new era of complicated therapeutic strategies, further studies are required for the repositioning of cytotoxic chemotherapy and maintenance therapy for SCC.

Conclusion

Switch maintenance therapy with S-1 after induction therapy with CBDCA and *nab*-PTX demonstrated modest efficacy and acceptable safety and may therefore represent a feasible treatment option for patients with advanced SCC.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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References

1. Novello S, Barlesi F, Califano R, Cufer T, Ekman S, Levra MG, Kerr K, Popat S, Reck M, Senan S, Simo GV, Vansteenkiste J, Peters S (2016) Metastatic non-small-cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 27:v1–v27. https://doi.org/10.1093/annonc/mdw326
2. Hanna N, Johnson D, Temin S, Baker S Jr, Brahmer J, Ellis PM, Giaccone G, Hesketh PJ, Jaiyesimi I, Leighl NB, Riely GJ, Schiller JH, Schneider BJ, Smith TJ, Tashbar J, Biermann WA, Masters G (2017) Systemic therapy for stage IV non–small-cell lung cancer: american society of clinical oncology clinical practice guideline update. J Clin Oncol 35:3484–3515. https://doi.org/10.1200/JCO.2017.74.6065
3. Sun JM, Park JO, Won YW, Kim JH, Yun J, Lee J, Park YH, Ahn JS, Ahn MJ, Park K (2010) Who are less likely to receive subsequent chemotherapy beyond first-line therapy for advanced non-small cell lung cancer? Implications for selection of patients for maintenance therapy. J Thorac Oncol 5:540–545. https://doi.org/10.1097/JTO.0b013e3181d3504d
4. Gerber DE, Rasco DW, Le P, Yan J, Dowell JE, Xie Y et al (2011) Predictors and impact of second-line chemotherapy for advanced non-small cell lung cancer in the United States: real-world considerations for maintenance therapy. J Thorac Oncol 6:365–371. https://doi.org/10.1097/JTO.0b013e3181fff142
5. Paz-Ares LG, de Marinis F, Dediu M, Thomas M, Pujol JL, Bidoli P, Molinier O, Sahoo TP, Laack E, Reck M, Corral J, Melemed S, John W, Chouaki N, Zimmermann AH, Visseren-Grul C, Gridelli C (2013) PARAMOUNT: final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non–small-cell lung cancer. J Clin Oncol 31:2895–2902. https://doi.org/10.1200/JCO.2012.47.1102
6. Ciuleanu T, Brodowicz T, Zielinski C, Kim JH, Krzakowski M, Laack E, Wu YL, Bover I, Begbie S, Tzekova V, Cucevic B, Pereira JR, Yang SH, Madhavan J, Sugarman KP, Peterson P, John WJ, Krejcy K, Belani CP (2009) Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet 374:1432–1440. https://doi.org/10.1016/S0140-6736(09)61497-5
7. Cappuzzo F, Ciuleanu T, Stelmakh L, Cicenas S, Szczésna A, Juhász E et al (2010) Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol 11:521–529. https://doi.org/10.1016/S1470-2045(10)70112-1
8. Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, Serwatowski P, Gatzemeier U, Digumarti R, Zukin M, Lee JS, Mellemgaard A, Park K, Patil S, Rolski J, Goksel T, de Marinis F, Simms L, Sugarman KP, Gandara D (2008) Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 20:3543–3551. https://doi.org/10.1200/JCO.2007.15.0375
9. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, Furukawa H, Nakajima T, Ohashi Y, Imamura H, Higashino M, Yamamura Y, Kurita A, Arai K (2007) Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 357:1810–1820. https://doi.org/10.1056/NEJMoa072252
10. Uesaka K, Boku N, Fukutomi A, Okamura Y, Konishi M, Matsumoto I, Kaneoka Y, Shimizu Y, Nakamori S, Sakamoto H, Morinaga S, Kainuma O, Imai K, Sata N, Hishinuma S, Ojima H, Yamaguchi R, Hirano S, Sudo T, Ohashi Y (2016) Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer:a phase 3, open-label, randomised, non-inferiority trial (JASPAC01). Lancet 388:248–257. https://doi.org/10.1016/S0140-6736(16)30583-9
11. Oki E, Murata A, Yoshida K, Maeda K, Ikejiri K, Munemoto Y, Sasaki K, Matsuda C, Kotake M, Suenaga T, Matsuda H, Emi Y, Kakeji Y, Baba H, Hamada C, Saji S, Maehara Y (2016) A randomized phase III trial comparing S-1 versus UFT as adjuvant chemotherapy for stage II/III rectal cancer (JFMC35-C1: ACTS-RC). Ann Oncol 27:1266–1272. https://doi.org/10.1093/annonc/mdw162
12. Okamoto I, Yoshioka H, Morita S, Ando M, Takeda K, Seto T, Yamamoto N, Saka H, Asami K, Hirashima T, Kudoh S, Satouchi M, Ikeda N, Iwamoto Y, Sawa T, Miyazaki M, Tamura K, Kurata T, Fukuoka M, Nakagawa K (2010) Phase III trial comparing oral S-1 plus carboplatin with paclitaxel plus carboplatin in chemotherapy-naïve patients with advanced non-small-cell lung cancer: results of a West Japan oncology group study. J Clin Oncol 20:5240–5246. https://doi.org/10.1200/JCO.2010.31.0326
13. Yoshioka H, Okamoto I, Morita S, Ando M, Takeda K, Seto T, Yamamoto N, Saka H, Atagi S, Hirashima T, Kudoh S, Satouchi M, Ikeda N, Iwamoto Y, Sawa T, Nakanishi Y, Nakagawa K (2013) 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. https://doi.org/10.1093/annonc/mds629
14. Kubota K, Sakai H, Katakami N, Nishio M, Inoue A, Okamoto H, Isobe H, Kunitoh H, Takiguchi Y, Kobayashi K, Nakamura Y, Ohmatsu H, Sugawara S, Minato K, Fukuda M, Yokoyama A, Takeuchi M, Michimae H, Gemma A, Kudoh S (2015) A randomized phase III trial of oral S-1 plus cisplatin versus docetaxel plus cisplatin in Japanese patients with advanced non-small-cell lung cancer: TCOG0701 CATS trial. Ann Oncol 26:1401–1408. https://doi.org/10.1093/annonc/mdv190
15. Wada M, Yamamoto M, Ryuge S, Nagashima Y, Hayashi N, Maki S, Otani S, Katono K, Takakura A, Yanaihara T, Igawa S, Yokoba M, Mitsufuji H, Kubota M, Katagiri M, Masuda N (2012) Phase II study of S-1 monotherapy in patients with previously treated, advanced non-small-cell lung cancer. Cancer Chemother Pharmacol 69:1005–1011. https://doi.org/10.1007/s00280-011-1795-5
16. Nokihara H, Lu S, Mok TSK, Nakagawa K, Yamamoto N, Shi YK, Zhang L, Soo RA, Yang JC, Sugawara S, Nishio M, Takahashi T, Goto K, Chang J, Maemondo M, Ichinose Y, Cheng Y, Lim WT, Morita S, Tamura T (2017) Randomized controlled trial of S-1 versus docetaxel in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy (East Asia S-1 trial in lung cancer). Ann Oncol 28:2698–2706. https://doi.org/10.1093/annoc/mdx419
17. Niho S, Ohe Y, Ohmatsu H, Umemura S, Matsumoto S, Yoh K, Goto K (2017) Switch maintenance chemotherapy using S-1 with or without bevacizumab in patients with advanced non-small cell lung cancer: a phase II study. Lung Cancer 108:66–71. https://doi.org/10.1016/j.lungcan.2017.02.018
18. Suzuki S, Karayama M, Inui N, Kuroishi S, Yokomura K, Toyoshima M, Suda T et al (2016) Continuation maintenance therapy with S-1 in chemotherapy-naïve patients with advanced squamous cell lung cancer. Investig New Drugs 34:490–496. https://doi.org/10.1007/S10637-016-0365-4
19. Socinski MA, Bondarenko I, Karaseva NA, Makhson AM, Vynnychenko I, Okamoto I, Hon JK, Hirsh V, Bhar P, Zhang H, Iglesias JL, Renschler MF (2012) Weekly *nab*-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. J Clin Oncol 30:2055–2062. https://doi.org/10.1200/JCO.2011.39.5848
20. Shiroyama T, Komuta K, Imamura F, Hirashima T, Kijima T, Tachibana I, Kawase I (2011) Phase II study of S-1 monotherapy in platinum-refractory, advanced non-small cell lung cancer. Lung Cancer 74:85–88. https://doi.org/10.1016/j.lungcan.2011.01.017
21. Cancer researcch and biostatics: statistical tools https://stattools.crab.org/. Accessed 12 Jan 2015
22. Nakao A, Uchino J, Igata F, On R, Ikeda T, Yatsugi H, Hirano R, Sasaki T, Tanimura K, Imabayashi T, Tamiya N, Kaneko Y, Yamada T, Nagata N, Watanabe K, Kishimoto J, Takayama K, Fujita M (2018) Nab-paclitaxel maintenance therapy following carboplatin and *nab*-paclitaxel combination therapy in chemotherapy naïve patients with advanced non-small cell lung cancer: multicenter, open-label, single-arm phase II trial. Investig New Drugs 36:903–910. https://doi.org/10.1007/s10637-018-0617-6
23. Janssen-Heijnen ML, Schipper RM, Razenberg PP, Crommelin MA, Coebergh JW et al (1998) Prevalence of comorbodity in lung cancer patients and its relationship with treatment:population-based study. Lung Cancer 21:105–113
24. Papi A, Casoni G, Caramori G, Guzzinati I, Boschetto P, Ravenna F et al (2004) COPD increases the risk of squamous histological subtype in smokers who develop non-small cell lung carcinoma. Thorax 59:679–681. https://doi.org/10.1136/thx.2003.018291
25. Socinski MA, Obasaju C, Gandara D, Hirsch FR, Bonomi P, Bunn P, Kim ES, Langer CJ, Natale RB, Novello S, Paz-Ares L, Pérol M, Reck M, Ramalingam SS, Reynolds CH, Spigel DR, Stinchcombe TE, Wakelee H, Mayo C, Thatcher N (2016) Clinicopathologic features of advanced squamous NSCLC. J Thorac Oncol 11:1411–1422. https://doi.org/10.1016/j.jtho.2016.05.024
26. Ferrara N, Hillan KJ, Gerber HP, Novotny W et al (2004) Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. Nat Rev Drug Discov 3:391–400. https://doi.org/10.1038/nrd1381
27. Ma J, Waxman DJ et al (2008) Combination of antiangiogenesis with chemotherapy for more effective cancer treatment. Mol Cancer Ther 7:3670–3685. https://doi.org/10.1158/1535-7163.MCT-08-0715
28. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, Lilenbaum R, Johnson DH (2006) Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 355:2542–2550. https://doi.org/10.1056/NEJMoa061884
29. Barlesi F, Scherpereel A, Rittmeyer A, Pazzola A, Tur NF, Kim JH et al (2013) Randomized phase III trial of maintenance bevacizumab with or without pemetrexed after first-line induction with bevacizumab, cisplatin, and pemetrexed in advanced nonsquamous non–small-cell lung cancer: AVAPERL (MO22089). J Clin Oncol 31:3004–3011. https://doi.org/10.1200/JCO.2012.42.3749
30. Garon EB, Ciuleanu TE, Arrieta O, Prabhash K, Syrigos KN, Goksel T, Park K, Gorbunova V, Kowalyszyn RD, Pikiel J, Czyzewicz G, Orlov SV, Lewanski CR, Thomas M, Bidoli P, Dakhil S, Gans S, Kim JH, Grigorescu A, Karaseva N, Reck M, Cappuzzo F, Alexandris E, Sashegyi A, Yurasov S, Pérol M (2014) Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet 384:665–673. https://doi.org/10.1016/S0140-6736(14)60845-X
31. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E et al (2015) Nivolmab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 373:123–135. https://doi.org/10.1056/NEJMoa1504627
32. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, O'Brien M, Rao S, Hotta K, Leiby MA, Lubiniecki GM, Shentu Y, Rangwala R, Brahmer JR (2016) Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung Cancer. N Engl J Med 375:1823–1833. https://doi.org/10.1056/NEJMoa1606774
33. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, Gadgeel SM, Hida T, Kowalski DM, Dols MC, Cortinovis DL, Leach J, Polikoff J, Barrios C, Kabbinavar F, Frontera OA, de Marinis F, Turna H, Lee JS, Ballinger M, Kowanetz M, He P, Chen DS, Sandler A, Gandara DR (2017) Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): phase 3, open-label, multicentre randomised controlled trial. Lancet 389:255–265. https://doi.org/10.1016/S0140-6736(16)32517-X
34. Hellmann MD, Ciuleanu TE, Pluzanski A, Lee JS, Otterson GA, Audigier-Valette C et al (2018) Nivolumab plus Ipilimumab in lung cancer with a high tumor mutational burden. N Engl J Med 378:2093–2104. https://doi.org/10.1056/NEJMoa1801946
35. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F et al (2018) Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 378:2078–2092. https://doi.org/10.1056/NEJMoa1801005
36. Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gümüş M, Mazières J, Hermes B, Çay Şenler F, Csőszi T, Fülöp A, Rodríguez-Cid J, Wilson J, Sugawara S, Kato T, Lee KH, Cheng Y, Novello S, Halmos B, Li X, Lubiniecki GM, Piperdi B, Kowalski DM (2018) Pembrolizumab plus chemotherapy for squamous non-small-cell lung Cancer. N Engl J Med 379:2040–2051. https://doi.org/10.1056/NEJMoa1810865