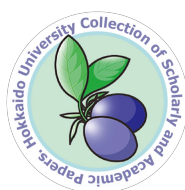




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A randomized phase II trial of erlotinib versus S-1 as a third- or fourth-line therapy for patients with wild-type *EGFR* non-small cell lung cancer (HOT1002)

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☆ Clinical trial registration no. UMIN000005308

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Abstract

Purpose: A high proportion of patients with wild-type *EGFR* non-small cell lung cancer (NSCLC) receive third-line therapy and beyond, with no prospective randomized trials addressing the issue. This study aimed to select the most suitable regimen as a third- or fourth-line therapy for wild-type *EGFR* NSCLC.

Methods: This multicenter, randomized phase II study in Japan included patients with recurrent or advanced NSCLC with wild-type or unknown *EGFR*, who progressed after two or three previous chemotherapies. The patients were randomly assigned to erlotinib (150 mg/day, days 1-21) or S-1 (80-120 mg/day, days 1-14) every 3 weeks until disease progression or unacceptable toxicity. The primary endpoint was disease control rate (DCR). The secondary endpoints included overall survival (OS), progression-free survival (PFS), objective response rate (ORR), toxicity, and quality of life (QOL).

Results: From 2011 to 2016, 37 patients were randomly assigned to receive erlotinib (E arm, n = 19) and S-1 (S arm, n = 18). This study was terminated prematurely because of poor patient accrual. DCR/ORR were 42.1%/15.8% in the E arm and 66.7%/16.7% in the S arm. Median PFS/OS were 1.6 months/8.0 months in the E arm and 3.3 months/12.2 months in the S arm. In both groups, the most commonly reported grade 3-4 toxicities were fatigue, anorexia, and nausea. One grade 5 pneumonitis occurred in the S arm. No significant difference was seen in QOL.

Conclusions: S-1 as a third- or fourth-line therapy for wild-type *EGFR* NSCLC showed numerically better clinical outcomes than erlotinib.

Clinical trial registration no. UMIN000005308.

Keywords: Erlotinib; S-1; Non-small cell lung cancer; Third-line therapy; Fourth-line therapy

Introduction

Lung cancer has a high incidence and is the most common cause of cancer-related death worldwide [1]. Non-small cell lung cancer (NSCLC) comprises >80% of all lung cancers, and two-thirds of NSCLC are diagnosed at an advanced stage. Platinum-based doublet chemotherapy, the standard first-line therapy for advanced NSCLC with no driver mutations, has a response rate of approximately 30%, and the response usually lasts about 6 months [2]. Furthermore, maintenance therapy has been reported to significantly improve survival for patients with non-squamous NSCLC [3]. Currently, docetaxel, pemetrexed, erlotinib, nivolumab, pembrolizumab, and Atezolizumab are considered the standard second-line therapy based on several randomized controlled trials [4-10]. Most patients experience disease progression, and a high proportion (30-70%) receive a third-line therapy as a subsequent treatment after failure of the standard first- and second-line therapies for NSCLC [4-6, 11, 12]. Hence, there is an unmet need for establishing the standard third- and fourth-line therapies.

When this study was planned, erlotinib, an *EGFR* tyrosine kinase inhibitor, was recommended as the standard second-line therapy, irrespective of *EGFR* status, based on the results of the BR.21 study [13]. Erlotinib might have also been recommended as third-line in the 2009 ASCO guidelines based on the subgroup analysis of the BR.21 study, which showed equivalent efficacy in patients who received erlotinib as third-line compared with those who received erlotinib as second-line [13, 14]. Thus, erlotinib is a candidate of the standard third- or fourth-line therapy for wild-type *EGFR* NSCLC.

S-1, which is an oral fluoropyrimidine formulation of tegafur, 5-chloro-2,4-dihydroxypyridine (CDHP), and potassium oxonate in a molar ratio of 1:0.4:1, has been reported to show high antitumor activity for NSCLC with low intestinal toxicity [15, 16]. Nokihara et al. conducted a prospective phase II trial of S-1 for NSCLC as a second-, third-, or fourth-line therapy and reported an objective response rate (ORR) of 19%, a median progression-free survival (PFS) of 3.4 months, and a median overall survival (OS) of 10.2 months [17]. Meanwhile, Ono et al. reported the retrospective analysis of S-1 as a third- or fourth-line therapy, which showed an ORR of 5.7%, a median OS of 208 days, and a 1-year survival rate of 37.8% with a favorable toxicity profile [18]. From the results of these studies, S-1 is also a candidate of the standard third- or fourth-line therapy for wild-type *EGFR* NSCLC.

Currently, there are no prospective randomized controlled trials aiming to establish the standard third- or fourth-line therapy [19]. Although several studies using intravenous chemotherapy such as irinotecan or amrubicin have reported moderate efficacy of these drugs as a third- or fourth-line therapy, frequent hospital visits might impair the quality of life (QOL) of patients with a limited survival estimate [20, 21]. Hence, we conducted this prospective randomized phase II study of S-1 vs. erlotinib, Hokkaido Oncology Trial (HOT) 1002, to select which was more suitable as a third- or fourth-line therapy for wild-type *EGFR* NSCLC for a future phase III study.

Patients and Methods

Patients

Eligible patients met the following criteria: age of 20-74 years, histologically or cytologically confirmed NSCLC, and recurrent or refractory disease after two or three previous regimens including platinum-based chemotherapy. Patients were also required to have a measurable disease, an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-2, adequate bone marrow function (absolute neutrophil count $>1500/\text{mm}^3$, platelet count $>100,000/\text{mm}^3$, and hemoglobin $>9.0 \text{ g/dL}$), adequate hepatic function (AST and ALT $<100 \text{ IU/L}$, total bilirubin level $<1.5 \text{ mg/dL}$), adequate renal function (serum creatinine level $\leq 1.2 \text{ mg/dL}$), and arterial oxygen pressure $\geq 60 \text{ Torr}$. Ineligible patients included those with severe allergic history, with an active infection, using corticosteroid or immunosuppressive agents, with serious medical complications, with radiographic signs of interstitial pneumonia or pulmonary fibrosis, with third-space fluid collection requiring drainage, who were lactating or pregnant, with symptomatic brain metastasis, or with active concomitant malignancy. The protocol was approved by the institutional review boards of all participating institutions (clinical trial registration no. UMIN000005308). Informed consent was obtained from all individual participants included in this study.

Treatment schedule

Enrolled patients were randomly assigned (1:1) to receive either erlotinib or S-1 using a dynamic allocation method. Central randomization was conducted by a data center in Hokkaido University

Hospital. Stratification factors were ECOG PS (0-1 vs. 2), *EGFR* mutation status (wild-type vs. unknown), smoking history (current or ex-smoker vs. never-smoker), and treatment line (third vs. fourth). All patients and investigators were unmasked to treatment allocation.

Erlotinib (150 mg/day) was given orally on days 1-21 of every 21-day cycle. In case of grade (Gr) 2 toxicities, treatment was withheld until the toxicity had recovered to Gr 0 or 1. In case of Gr 3 toxicities other than rash, treatment was withheld until the toxicity had recovered to Gr 0 or 1, and dosage was reduced to 100 mg/day. In case of Gr 3 rash, treatment was withheld until the toxicity had recovered to Gr 0-2, and dosage was reduced to 100 mg/day. If these toxicities occurred after the reduction of erlotinib dosage to 100 mg/day, the dosage was further reduced to 50 mg/day. If the toxicities occurred further, a third reduction was not permitted and the protocol treatment was terminated. In case of any Gr 4 toxicities, any grade of interstitial pneumonia, or a continuous uncontrollable toxicity >21 days, the protocol treatment was also terminated.

S-1 was administered orally for 14 consecutive days, followed by a 7-day drug-free period of every 21-day cycle. The drug was administered at three dosages: 80 mg/day for patients with a body surface area (BSA) $<1.25 \text{ m}^2$, 100 mg/day with BSA of $1.25\text{-}1.5 \text{ m}^2$, and 120 mg/day with $\text{BSA} \geq 1.5 \text{ m}^2$. A dosage reduction of 20 mg/day was recommended if a hematologic or non-hematologic toxicity of Gr 3 or more occurred. If these toxicities occurred at an 80 mg/day dosage, the protocol treatment was terminated. All patients continued assigned treatment until disease progression, unacceptable toxicity, the

patient's refusal, or the physician's decision of discontinuing protocol treatment.

Patient assessment

Patient assessment, which included physical examination, complete blood counts, and biochemistry, was conducted once a week during the first treatment cycle and then at least once for every subsequent cycle.

Tumors were measured during baseline assessment using chest radiography, computed tomography, or magnetic resonance imaging. Tumor response was assessed at baseline and every 6 weeks using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. If a patient was documented as having a complete response (CR) or partial response (PR), a confirmatory evaluation was performed after an interval of at least 4 weeks. A stable disease (SD) required a period of at least 6 weeks from the enrollment to the study. Clinical response data were confirmed by extramural review. Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. QOL was assessed using the Functional Assessment of Cancer Therapy - Lung (FACT-L) questionnaire, which was administered at baseline and every other cycle. The FACT-L questionnaire is a validated self-report questionnaire comprising physical, functional, social/family, and emotional well-being subscales [22].

The primary endpoint was disease control rate (DCR), defined as the proportion of patients whose best response was a CR, PR, or SD among all per-protocol patients. Secondary endpoints were OS,

PFS, ORR, toxicity, and QOL. PFS was defined as the time from the date of enrollment to the date of the first occurrence of disease progression or death from any cause; patients who had not experienced progression or death at data cutoff were censored at the last tumor assessment. OS was assessed from the date of enrollment to the date of death from any cause, or data were censored at the last date when the patient was confirmed to be alive.

Statistical analysis

We assumed that a DCR of 50% for eligible patients would indicate potential usefulness, while a DCR of 30% would constitute the lower limit of interest (with $\alpha = 0.1$ and $\beta = 0.2$). The estimated accrual was 26 patients in each arm. With an assumed dropout rate of 15%, we planned on enrolling 30 patients per arm in this study. Survival estimation was performed using the Kaplan-Meier method and log-rank test.

Results

This multicenter, open-label, randomized phase II study was conducted in nine institutions in Japan. From May 2011 to March 2016, a total of 37 patients were enrolled and randomly assigned to the erlotinib (E) group (19 patients) and S-1 (S) group (18 patients), as shown in Supplementary Fig. 1. Patient characteristics are summarized in Table 1. No significant differences in demographic characteristics were

found between the two groups. The median age was 64 years (range, 39-74 years), 56.7% of patients were male, and most patients (94.6%) had a good ECOG PS of 0-1. Thirty-one patients (83.8%) had an adenocarcinoma histology. Twenty-eight patients (75.7%) received the study treatment as a third-line therapy, and nine patients (24.3%) received it as fourth-line. Supplementary Table 1 shows the components of prior therapeutic regimens. Platinum-containing doublets were administered in 36 patients (97.3%) as first-line and in 8 patients (21.6%) as second-line.

The median number of treatment cycles was 3 (range, 1-10) in the E group and 4 (range, 1-11) in the S group. A dosage reduction was required only in three patients (15.8%) of the E group. A treatment delay was observed in two patients (11%) of the E group and four patients (22%) of the S group. The reasons for treatment discontinuation were as follows: disease progression (16 patients [84%] in the E group vs. 9 patients [50%] in the S group), adverse events (2 patients [11%] in the E group vs. 5 patients [28%] in the S group), and others (1 patient [5%] in the E group vs. 4 patients [22%] in the S group).

Among the 37 assessable patients, 3 patients had a PR and 5 an SD in the E group and 3 had a PR and 9 an SD in the S group (Table 2). The primary endpoint, DCR, was 42.1% in the E group and 66.7% in the S group ($p = 0.19$). The ORR was 15.8% in the E group and 16.7% in the S group ($p = 1.0$). With a median follow-up time of 10.5 months (range, 1.8-62.4), the median PFS was 1.6 months (95% confidence interval [CI], 0.8-3.7) in the E group and 3.3 months (95% CI, 1.5-5.8) in the S group ($p = 0.093$) (Fig. 1A). The median OS was 8.0 months (95% CI, 4.3-13.4) in the E group and 12.2 months

(95% CI, 5.5-16.5) in the S group ($p = 0.42$) (Fig. 1B). In patients who were enrolled under a third-line therapy, the median PFS/OS was 1.5/7.0 months in the E group and 2.7/11.0 months in the S group, respectively (Supplementary Fig. 2). In patients who were enrolled under a fourth-line therapy, the median PFS/OS was 3.3 months/not reached in the E group and 5.9/29.0 months in the S group, respectively (Supplementary Fig. 3).

Adverse events observed in each group are listed in Table 3. Grade 3-4 hematologic toxicities comprised neutropenia in one patient and thrombocytopenia in another in the S group only. Regarding non-hematologic toxicities, Gr 3-4 diarrhea, pruritus, pain, blepharitis, weight loss, and rash acneiform occurred in the E group. On the other hand, Gr 3-4 drug eruption, oral mucositis, increased ALT, increased creatinine, and increased AST were observed in the S group. Additionally, one patient in the S group died from treatment-related pneumonitis and alveolar hemorrhage. There was no statistically significant difference between both groups regarding QOL score of the FACT-L.

A 65-year-old man was diagnosed with stage IV lung adenocarcinoma with wild-type *EGFR* detected by a peptide nucleic acid/locked nucleic acid polymerase chain reaction (PNA-LNA PCR) clamp assay in May 2014. After his two lines of chemotherapy failed (first: cisplatin, pemetrexed, and bevacizumab; second: docetaxel), he was enrolled in this study in March 2015 and began receiving erlotinib. On day 50, his computed tomography scan revealed shrinkage of multiple metastatic lymph nodes (#2R, #4R, and #7), and on day 82, a PR was confirmed (Fig. 2). On day 93, his disease progressed

rapidly, and he died of lung cancer on day 111. An autopsy was performed, and genomic DNA was extracted from the autopsy sample of lung tumor for next-generation sequencing. The Human Clinically Relevant Tumor Panel (Qiagen), which allows detection of hot spots in 24 genes implicated in lung cancers, was used. The libraries were sequenced using MiSeq (Illumina). Mutation identification was performed using the GeneRead DNaseq variant analysis (Qiagen). There were no *EGFR* mutations including minor ones (data not shown).

Discussion

In this study, the DCR/ORR were 42.1%/15.8% in the E group and 66.7%/16.7% in the S group, and the median PFS/OS was 1.6/8.0 months in the E group and 3.3/12.2 months in the S group, respectively. After this study was initiated, the TAILOR study showed the superiority of docetaxel compared with erlotinib as a second-line treatment. The median OS was 8.2 months (95% CI, 5.8-10.9) with docetaxel vs. 5.4 months (95% CI, 4.5-6.8) with erlotinib (adjusted hazard ratio [HR], 0.73; 95% CI, 0.53-1.00; $p = 0.05$) [23]. Moreover, a subset analysis of wild-type *EGFR* NSCLC in the DELTA study showed that the median PFS of erlotinib vs. docetaxel was 1.3 vs. 2.9 months (HR, 1.45; 95% CI, 1.09-1.94; $p = 0.01$), and the median OS was 9.0 vs. 10.1 months (HR, 0.98; 95% CI, 0.69-1.39; $p = 0.91$), respectively [24]. These results suggest the superior efficacy of chemotherapy for patients with wild-type *EGFR* NSCLC. Furthermore, the EAST-LC study showed the non-inferiority of S-1 to docetaxel for patients with both

wild-type and mutated *EGFR* NSCLC in second-, third-, and fourth-line therapy settings [25]. Miyoshi et al. reported the results of a phase II trial of S-1 as a third-line therapy or beyond. Forty-five patients were enrolled. Four patients (8.9%) had a PR, and 24 patients (53.3%) had an SD, so the DCR was 62.2%. The median PFS/OS was 71/205 days, respectively. However, the results of a subset of 27 patients with wild-type *EGFR* NSCLC were not clarified [26]. Wada et al. reported the results of a phase II study of S-1 as a second-line therapy and beyond. Thirty patients were enrolled and 20 of them were treated with a third-line therapy and beyond. The ORR was 26.7% (8/30), the DCR was 70% (21/30), and the median PFS/OS was 3.1/11.2 months, respectively. The overall efficacy was good, presumably because this trial included many patients with a second-line therapy. In their study, patients with *EGFR* mutations showed better ORR/DCR (50%/90% vs. 11.8%/58.8%) and median PFS (4.8 months vs. 2.5 months), compared with those with wild-type *EGFR*. Subset analyses regarding PFS/OS of patients with third- and fourth-line therapies have not been reported in the literature [27]. Although our study had a small sample size and different settings, the S group showed a similar efficacy with previous studies of second-line therapy and beyond [18, 24-27]. Based on these findings, S-1 may be preferred as the third- and fourth-line treatment for wild-type *EGFR* NSCLC.

Erlotinib for patients with wild-type *EGFR* NSCLC has been reported to have an ORR of 3.0-5.6%, median PFS of 1.3-2.4 months, and median OS of 5.4-9.2 months in previous studies [23, 24, 28-30]. Our study showed a better ORR and equivalent median PFS/OS of erlotinib compared with those

results. The better ORR may be explained by tumor heterogeneity or the quality of *EGFR* sequence methods, which might not have been able to detect the minor sensitizing *EGFR* mutations. Additionally, the *EGFR* mutation analysis of this study was conducted by the local laboratory, which might have led to false-negative results of *EGFR* mutation status in some patients. However, as shown in Fig. 2, we experienced a case whose best response was a PR to erlotinib, and DNA sequencing of this patient's tumor specimen using next-generation sequencing showed no activating *EGFR* mutations including minor ones. Though the frequency is small, novel sensitizing *EGFR* alteration could be found in some patients with "wild-type *EGFR*" [31]. Taking these into consideration, although not being recommended in the second-line therapy for wild-type *EGFR* NSCLC in current guidelines, erlotinib can still be an option in the fourth-line settings and beyond.

Recently, the approval of new molecularly targeted agents such as *EGFR* tyrosine kinase inhibitors, anaplastic lymphoma kinase (*ALK*), and *ROS1*, or immune checkpoint inhibitors, has markedly improved the treatment outcomes of molecularly selected patients of advanced NSCLC. On the other hand, patients without these specific molecular abnormalities can also maintain a performance status, even after failure of the first- and second-line treatment, thanks to the introduction of less toxic chemotherapy such as pemetrexed [32]. Thus, several retrospective or prospective studies have been conducted to evaluate the efficacy and safety of chemotherapy in the third-line setting and beyond [20, 33, 34]. However, when we started this study, there were no prospective randomized controlled trials

addressing this issue other than the BR.21 study. This present study showed limited but important data on S-1 vs. erlotinib as a third- or fourth-line therapy for patients with wild-type *EGFR* NSCLC.

This study has some limitations. First, it was terminated prematurely due to poor patient accrual. This might have been affected by the results of the TAILOR and DELTA studies [23, 24], or the fact that before these reports, cytotoxic chemotherapy has been widely used as a third-line therapy or beyond for patients with a maintained performance status in Japan [20, 21]. Second, the sample size was too small. Finally, due to advancement in immunotherapy, targeted agents, and other cytotoxic chemotherapy regimens, the whole strategy of treating wild-type *EGFR* NSCLC has been rapidly changing and these situations have made it difficult to interpret the results of this study.

Conclusions

Although this trial had no statistical power to draw any conclusion, S-1 as a third- or fourth-line therapy showed numerically better clinical outcomes compared with erlotinib. The growing availability of new agents in the first- and second-line therapy settings has led to the increasing demand for establishing the standard third-line therapy and beyond.

Abbreviations: NSCLC, non-small cell lung cancer; DCR, disease control rate; OS, overall survival; PFS, progression-free survival; ORR, objective response rate; QOL, quality of life; HOT, Hokkaido Oncology

Trial; ECOG PS, Eastern Cooperative Oncology Group performance status; Gr, grade; BSA, body surface area; FACT-L, Functional Assessment of Cancer Therapy - Lung; CR, complete response; PR, partial response; SD, stable disease; CI, confidence interval; HR, hazard ratio

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Conflict of interest

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

Ethical approval

All procedures performed were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This study was approved by the Institutional Review Board of all participating institutions (clinical trial registration no. UMIN000005308).

Informed consent

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

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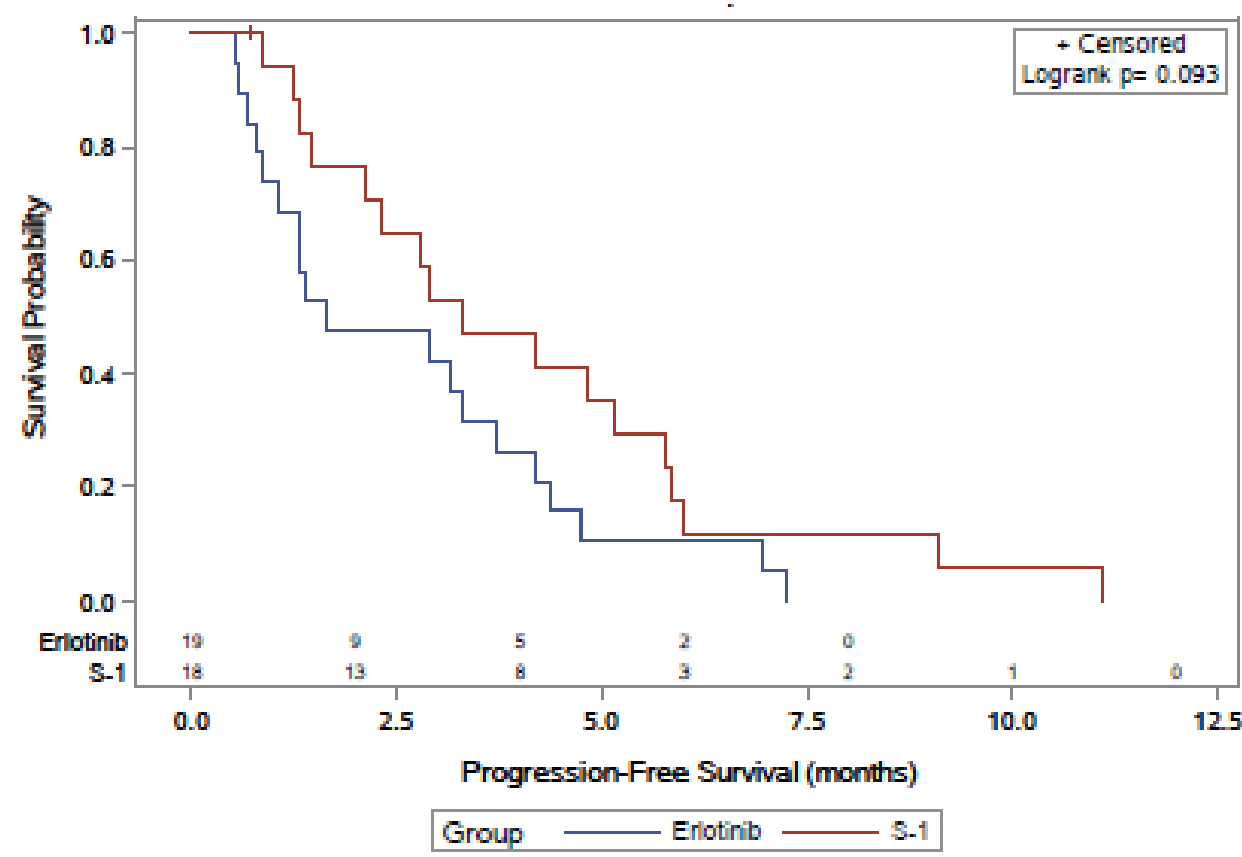
Figure legends

Fig. 1. Kaplan-Meier curves for (A) progression-free survival and (B) overall survival of both groups. CI, confidence interval.

Fig. 2. A representative case of the erlotinib arm. A 65-year-old man was enrolled in this study in March 2015 and began receiving erlotinib. On day 50, a computed tomography scan revealed a reduction in size of multiple metastatic lymph nodes (#2R and #7), and on day 82, a partial response (PR) was confirmed.

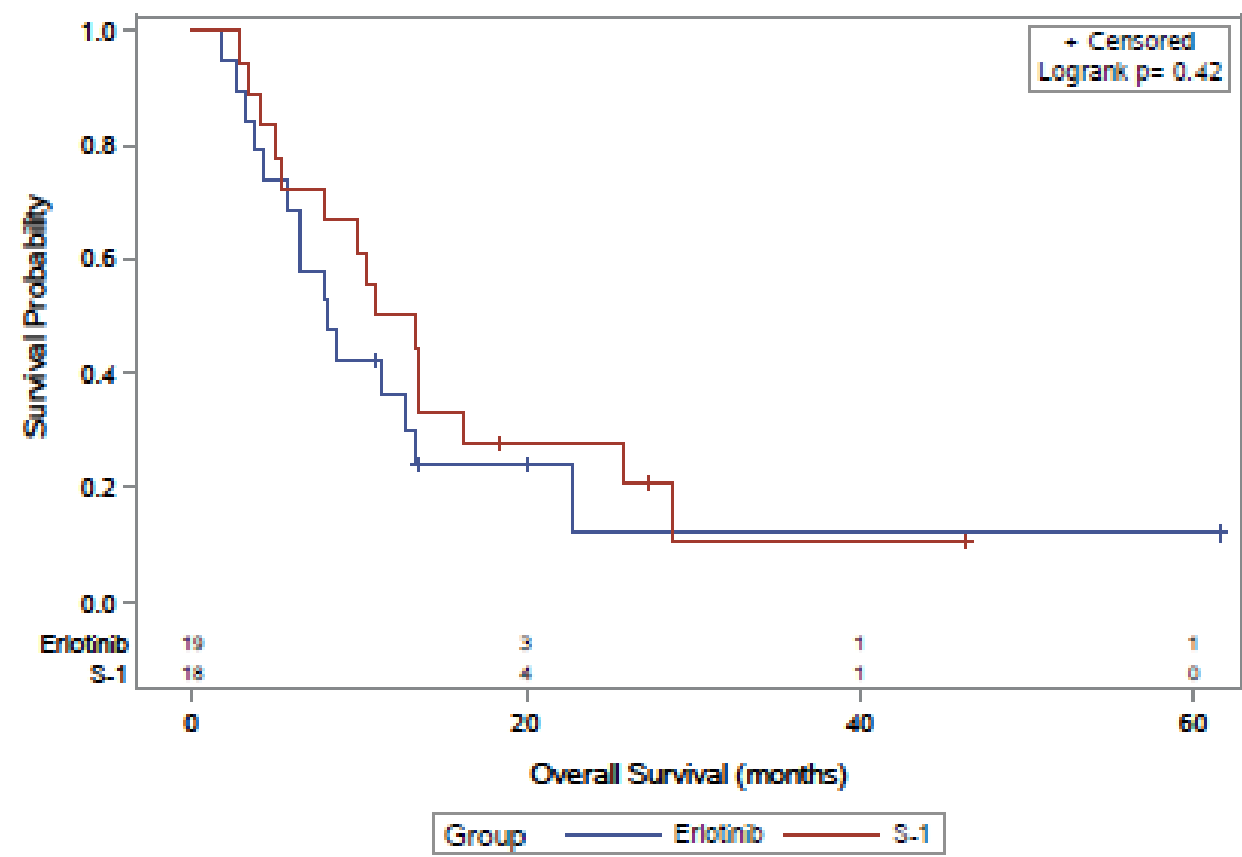
Figure 1

A



Erlotinib	1.6 mos. (95% CI, 0.8-3.7)
S-1	3.3 mos. (95% CI, 1.5-5.8)

B



Erlotinib	8.0 mos. (95% CI, 4.3-13.4)
S-1	12.2 mos. (95% CI, 5.5-16.5)

Figure 2

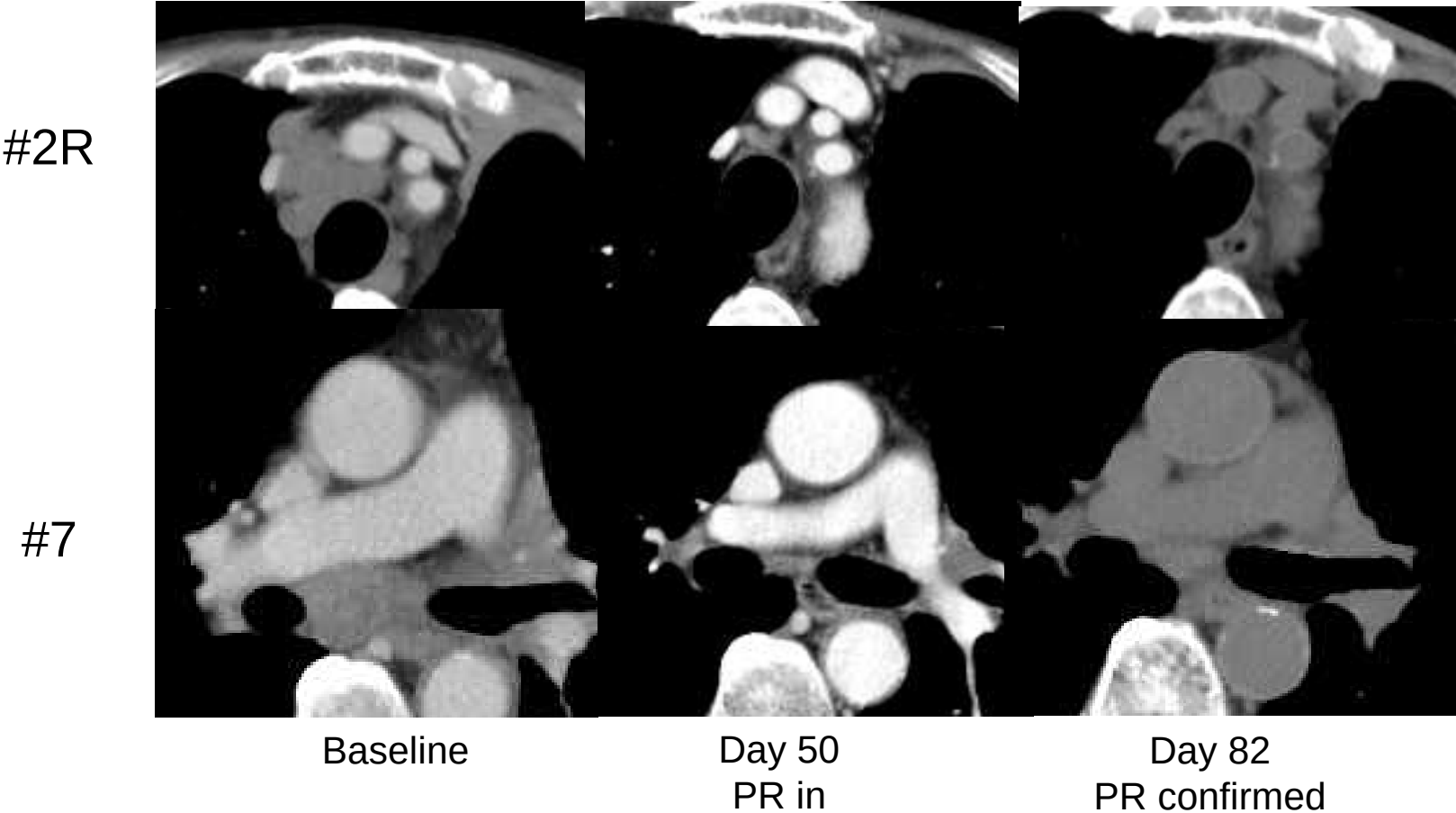


Table 1. Patient characteristics.

Characteristics	Erlotinib (n = 19)		S-1 (n = 18)	
	No. of patients	(%)	No. of patients	(%)
Sex				
Male/female	13/6	(68/32)	8/10	(44/56)
Age (years)				
Median (range)	65 (39-74)		64 (41-72)	
Stage				
III/IV/recurrent	2/13/4	(11/68/21)	0/10/8	(0/56/44)
Performance status				
0/1/2	5/13/1	(26/68/6)	4/13/1	(22/72/6)
Smoking status				
Never/ever	3/16	(16/84)	4/14	(22/78)
Histology				
Adeno/Sq/NSCLC	14/3/2	(74/16/10)	17/1/0	(94/6)
Regimen lines				
3rd/4th	16/3	(84/16)	13/5	(67/33)
<i>EGFR</i> status				
Wild-type/unknown	18/1	(94/6)	18/0	(100/0)

Adeno, adenocarcinoma; Sq, squamous cell carcinoma; NSCLC, non-small cell lung carcinoma.

Table 2. Tumor response according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

	Erlotinib group (n = 19)	S-1 group (n = 18)
Partial response	3	3
Stable disease	5	9
Progressive disease	11	4
Not evaluable	0	2
Overall response rate (%)	15.8	16.7
Disease control rate (%)	42.1	66.7

Table 3. Toxicity (>10% incidence or $\geq$ G3 incidence in either group) according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Toxicity	Erlotinib						S-1					
	G1	G2	G3	G4	G5	$\geq$ G3 (%)	G1	G2	G3	G4	G5	$\geq$ G3 (%)
Hematologic												
Leukopenia	0	2	0	0	0	0	4	2	1	0	0	5.6
Neutropenia	0	2	0	0	0	0	2	4	1	0	0	5.6
Anemia	1	0	0	0	0	0	3	2	0	0	0	0
Thrombocytopenia	0	0	0	0	0	0	4	0	1	0	0	5.6
Non-hematologic												
Hypoalbuminemia	4	0	0	0	0	0	2	2	0	0	0	0
Increased bilirubin	1	2	0	0	0	0	2	0	0	0	0	0
Increased AST	3	0	0	0	0	0	1	0	0	1	0	5.6
Increased ALT	2	0	0	0	0	0	2	1	0	0	0	0
Hyponatremia	2	0	0	0	0	0	4	0	0	0	0	0
Increased ALP	1	0	0	0	0	0	3	0	0	0	0	0
Increased creatinine	4	0	0	0	0	0	0	1	0	0	0	0
Fatigue	1	1	1	0	0	5.3	5	1	1	0	0	5.6
Anorexia	4	2	1	0	0	5.3	4	3	1	0	0	5.6
Nausea	1	1	1	0	0	5.3	4	0	0	0	0	0
Diarrhea	1	0	1	0	0	5.3	3	1	0	0	0	0
Chromatosis	1	0	0	0	0	0	2	1	0	0	0	0
Pruritus	4	0	0	0	0	0	2	1	0	0	0	0
Rash acneiform	3	4	0	0	0	0	1	0	0	0	0	0
Pain	0	1	1	0	0	5.3	0	0	0	0	0	0
Pneumonitis	0	0	0	0	0	0	0	0	0	0	1	5.6
Oral mucositis	2	1	0	0	0	0	2	1	0	0	0	0
Drug eruption	0	0	1	0	0	5.3	0	0	1	0	0	5.6
Alveolar hemorrhage	0	0	0	0	0	0	0	0	0	0	1	5.6
Blepharitis	0	0	1	0	0	5.3	0	0	0	0	0	0

G, grade; AST, aspartate aminotransferase; ALT, alanine aminotransaminase; ALP, alkaline phosphatase.