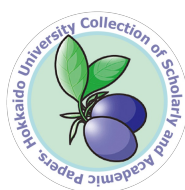




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A phase II study of carboplatin, pemetrexed, and bevacizumab followed by erlotinib and bevacizumab maintenance for non-squamous non-small cell lung cancer with wild-type *EGFR* (HOT1101)

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Abstract

Background: This study evaluated the efficacy and safety of switch maintenance erlotinib and bevacizumab after induction therapy with carboplatin/pemetrexed/bevacizumab for non-squamous non-small cell lung cancer (NSCLC) with wild-type *EGFR*.

Methods: Enrolled patients had treatment-naïve, advanced non-squamous NSCLC with wild-type *EGFR*. Carboplatin (area under the curve [AUC] 5.0), pemetrexed (500 mg/m²) and bevacizumab (15 mg/kg) were administered on day 1 every 3 weeks for 4-6 cycles. Maintenance therapy with erlotinib (150 mg/body) on day 1 through 21 plus bevacizumab on day 1 every 3 weeks were continued until disease progression or unacceptable toxicity. The primary endpoint was 6-month progression-free survival (PFS); secondary endpoints included overall survival (OS), overall response rate (ORR), toxicity, and quality of life (QOL).

Results: Fifty-one patients were enrolled between September 2011 and June 2014. The median number of cycles for induction and maintenance therapy were 4 (range: 1-6) and 4 (range: 1-20). Twenty-nine patients (58%) received maintenance therapy. The 6-month PFS rate was 59.5% (95% confidence interval [CI]: 45.0-72.6%). The ORR was 48.0% (95% CI: 34.8-61.5%), and disease control rate was 86.0% (95% CI: 73.8-93.0%). The median PFS and OS were 6.5 months (95% CI: 5.8-7.2 months) and **21.4 months (95% CI: 15.9-26.9 months)**, respectively. Although grades ≥ 3 adverse events were observed in 33 patients (66.0%), most were hematologic; there was no febrile neutropenia. QOL was maintained throughout treatment.

Conclusions: Carboplatin/pemetrexed/bevacizumab followed by erlotinib and bevacizumab maintenance showed modest efficacy and was well tolerated in non-squamous NSCLC patients with wild-type *EGFR*.

Keywords: maintenance therapy, pemetrexed, bevacizumab, erlotinib, non-small cell lung cancer

1 Introduction

2 Lung cancer is the leading cause of cancer-related death worldwide, and non-small cell lung
3 cancer (NSCLC) accounts for more than 80% of all lung cancer cases [1,2]. Non-squamous (non-Sq)
4 histology, mainly adenocarcinoma, is the predominant subtype of NSCLC. Nowadays, agents that target
5 specific molecular abnormalities within the tumor, such as *EGFR* mutation, *ALK* rearrangement, and
6 *ROS1* rearrangement, are the preferred first-line therapies [3-5]. Immune checkpoint inhibitors (ICIs) are
7 also effective for subgroups of patients with NSCLC; pembrolizumab has shown superiority over
8 platinum-based doublet therapy, leading to its approval as a first-line therapy for patients with NSCLC
9 exhibiting programmed death-ligand 1 (PD-L1) overexpression [6]. However, chemotherapy remains the
10 standard of care for the majority of patients without a defined molecular abnormality for which an
11 approved targeted therapy is available.

12 Second-line therapy significantly improves overall survival (OS) of patients with NSCLC. As
13 rapid deterioration after progression to first-line therapy might render patient ineligible for subsequent
14 treatment, only two-thirds of patients receive second-line therapy in current clinical practice [7,8].
15 Maintenance therapy can increase the proportion of patients who receive additional therapy beyond first-
16 line platinum-based chemotherapy [9,10]. Decades ago, prolonging first-line platinum doublet therapy led
17 to cumulative toxicity issues that precluded the use of this strategy [11]. The availability of better-
18 tolerated drugs (pemetrexed, epidermal growth factor receptor [EGFR]-tyrosine kinase inhibitors [TKIs],
19 and bevacizumab) has produced maintenance therapy as a feasible option [12-14].

20 There are two effective maintenance strategies: continuation maintenance and switch
21 maintenance. The former is the practice of discontinuing the platinum agent after 4–6 cycles and then
22 resuming one or more of the drugs used in the induction regimen; the latter involves switching to non-
23 cross-resistant agents immediately following first-line therapy [15]. Single agents such as pemetrexed and
24 erlotinib administered as maintenance therapy have shown significant improvements in OS compared
25 with placebo [12,13,16], while gemcitabine showed improvement in progression-free survival (PFS) over
26 placebo [10]. Combination therapies using bevacizumab plus either pemetrexed or erlotinib as
27 continuation or switch maintenance have also been investigated in several phase 3 trials [17-20], and
28 some have shown improved PFS over single-agent comparators [17,18,19].

29 Despite low objective response rates, some patients with wild-type *EGFR* NSCLC received a

modest survival benefit with EGFR-TKIs in certain clinical settings [13,21]. Moreover, potential crosstalk exists in vascular endothelial growth factor (VEGF) and EGFR pathways during tumor growth, metastasis, and angiogenesis in NSCLC, and the dual inhibition of these pathways using bevacizumab and EGFR-TKI showed efficacy in preclinical models, including in wild-type *EGFR* NSCLC [22,23]. Both the BeTA and ATLAS phase 3 trials, which investigated the efficacy of combination bevacizumab and erlotinib, showed improved PFS in Western patients with a lower prevalence of *EGFR* mutations [17,24]. These 2 trials used induction therapies consisting of several combinations of platinum-based doublets other than platinum plus pemetrexed, which is currently the most frequently used regimen for the induction treatment. These data suggest that better tolerability to carboplatin and pemetrexed plus bevacizumab as an induction treatment might increase the efficacy of switch maintenance that comprises erlotinib and bevacizumab.

Based on this background, we conducted this prospective phase 2 trial to evaluate the efficacy and safety of combination carboplatin, pemetrexed, and bevacizumab followed by switch maintenance erlotinib and bevacizumab in patients with non-Sq NSCLC carrying wild-type *EGFR*.

Patients and Methods

Eligibility

Eligible patients were those of ages 20–74 years old with histologically or cytologically confirmed stage IIIB, stage IV, or postoperative recurrent non-Sq NSCLC carrying wild-type *EGFR*. Patients who received prior systemic therapy for lung cancer were excluded, but patients who experienced postoperative recurrence after at least 1 year had elapsed from the last administration of adjuvant chemotherapy were allowed. The following were also required for eligibility: an Eastern Cooperative Oncology Group performance status of 0 or 1; adequate organ function including of the bone marrow, liver, kidneys (creatinine clearance ≥ 60 mL/min and proteinuria $\leq 1+$), and lungs (alveolar O_2 pressure ≥ 60 Torr); and at least 1 measurable lesion as defined by the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1).

The exclusion criteria included: a history of hemoptysis (≥ 2.5 mL); regular use of aspirin (≥ 325 mg/day) or anticoagulants; a tumor in close proximity to a major vessel or with cavitation; symptomatic central nervous system metastasis; uncontrollable hypertension, presence of severe pleural,

1 abdominal, or cardiac effusion; unstable comorbidities including cardiovascular disease, stroke, gastric
2 ulcer, and interstitial pneumonitis; a history of active double cancer; or ineligibility as deemed by an
3 investigator. This study protocol was approved by the institutional review board at each participating
4 institution. All patients were required to provide written informed consent before enrollment. This trial
5 was registered under the University Medical Hospital Information Network (UMIN) Clinical Trials
6 Registry Identifier UMIN000005872.

8 **Study design and treatment**

9 This study was designed as a prospective, multicenter, single-arm phase 2 trial. The primary
10 endpoint was treatment efficacy measured as PFS rate at 6 months. Secondary endpoints were OS, overall
11 response rate (ORR), safety, proportion of patients receiving maintenance treatment, and quality of life
12 (QOL).

13 Eligible patients received pemetrexed 500 mg/m² through a 10-min intravenous infusion
14 followed by intravenous infusion of carboplatin at a dose corresponding to an area under the curve (AUC)
15 equal to 5 mg/mL/min (AUC=5) over 30 min, as well as bevacizumab 15 mg/kg for at least 30 min
16 intravenously on day 1 of every 21-day cycle, for 4–6 cycles during the induction therapy. We used an
17 AUC=5 of carboplatin based on the results of our previous trial instead of AUC=6 [25]. Afterwards,
18 patients with complete response (CR), partial response (PR), or stable disease (SD) received maintenance
19 therapy with erlotinib 150 mg/body on days 1–21 and bevacizumab 15 mg/kg on day 1 of every 21-day
20 cycle until evidence of disease progression or unacceptable toxicity manifested. The period between the
21 last dosage of induction therapy and the first dosage of maintenance therapy was required to be 3–6
22 weeks. All patients received oral folic acid (0.5 mg) daily and a vitamin B12 (1 mg) injection every 9
23 weeks, beginning at least 1 week before the first dose and continuing until 3 weeks after the last dose of
24 pemetrexed.

25 In the event of severe toxicities during a given cycle, the doses of carboplatin and/or
26 pemetrexed were reduced in subsequent cycles. Such toxicities included grade 4 thrombocytopenia, grade
27 ≥ 3 febrile neutropenia, or other grade ≥ 3 nonhematological toxicities. Dose reduction comprised of a
28 decrease in carboplatin to an AUC of 4 mg/mL/min and a decrease in pemetrexed to 400 mg/m².
29 Subsequent dose increases were not permitted after a reduction in the chemotherapy dose. In the event of

recurrent severe toxicities following dose reduction, the protocol treatment was terminated.

Administration of erlotinib during the maintenance phase was interrupted if patients developed grade 3 neutropenia, grade 2 thrombocytopenia, a putative infection with a fever of $\geq 38^{\circ}\text{C}$, grade 1 hemoptysis or interstitial lung disease, intolerable grade 2 rash, or other grade 3 nonhematological toxicities until the toxicity had recovered to grade 0 or 1. Erlotinib dose was reduced to 100 mg/day (level -1) and 50 mg/day (level -2); the protocol treatment was terminated in the event of a third severe toxicity.

Bevacizumab administration was delayed in the presence of bevacizumab-related severe toxicities, such as grade ≥ 3 thrombotic events, bleeding events, hypertension, or proteinuria. Bevacizumab dose reductions were not permitted. If patients required a treatment delay of ≥ 2 weeks during both induction and maintenance phase, the protocol treatment was terminated.

Baseline and treatment assessments

Patient assessment, which included physical examination, complete blood counts, and biochemistry, was conducted once a week during the first cycle of treatment and then at least once for every subsequent cycle. Chest radiography, computed tomography (CT) scans of the chest and abdomen, magnetic resonance imaging studies of the brain, and bone scintigraphy or positron emission tomography-CT studies were performed for baseline tumor assessment within 28 days before initiation of the protocol treatment. Tumor response was assessed at baseline and every 2 cycles using the RECIST version 1.1. If a patient was documented as having a CR or PR, confirmatory evaluation was performed after an interval of at least 4 weeks. SD required a minimum 6-week period from enrollment in the study. Clinical response data were confirmed by extramural review. Toxicities were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). The quality of life was assessed with the Functional Assessment of Cancer Therapy-General (FACT-G) and FACT-Lung (FACT-L) questionnaires completed at baseline and after every other cycle. 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 the data cutoff time were censored at the last tumor assessment. OS was calculated from the date of enrollment to the date of death of any cause; data were censored at the date of last follow-up if the patient was confirmed to be alive.

Statistical methods

At the time of trial planning in 2010, only the E4599 trial had shown superior OS with the PacCBeV (induction therapy with carboplatin, paclitaxel, and bevacizumab followed by bevacizumab continuation) regimen [14]. The median PFS of PacCBeV in the E4599 trial was 6.2 months. Assuming a hazard constant exponential distribution in the survival time distribution, the 6-month PFS rate of E4599 was calculated as 51.3%. Assuming that a 6-month PFS rate of 70% in eligible patients would indicate potential treatment efficacy while a 6-month PFS rate of 50% would be the lower limit of interest, with $\alpha = 0.05$ and $\beta = 0.20$, the estimated accrual number was 47 patients. Hence, the accrual goal was 51 patients to allow for potential dropouts. Efficacy and safety analyses were planned for patients who received at least 1 cycle of the treatment. Survival estimation was performed using the Kaplan-Meier method.

Results

Patient characteristics

Between September 2011 and January 2014, a total of 51 patients were enrolled at 10 institutions of the Hokkaido lung cancer clinical study group Trial (HOT) in Japan. Of these patients, 50 were eligible for analysis and received the induction therapy; 1 patient developed cardiac tamponade rapidly before starting protocol treatment and was excluded from further analysis. Table 1 shows the baseline characteristics of the 50 patients. An *EGFR* mutation test for each patient was conducted at the local laboratory and not confirmed centrally. Highly sensitive methods such as PNA-LNA PCR clamp or Scorpion ARMS assay was covered by health insurance and widely used in Japan during the study period.

Treatment delivery

The CONSORT diagram of the study is shown in Fig. 1. Overall, the 50 eligible patients received a median of 4 cycles (range: 1–6 cycles) of induction therapy; 43 patients (86%) completed at least 4 cycles of induction therapy. Twenty-nine patients (58%) switched to the maintenance therapy and received a median of 4 cycles (range: 1–20 cycles). Of 29 patients, 6 (20.7%) and 3 (10.3%) received ≥ 8 and ≥ 10 cycles of maintenance treatment, respectively. Twenty-one patients (42%) did not receive maintenance therapy because of disease progression during or after the completion of induction therapy

(n=10), toxicity (n=7), or patient choice (n=4). In the induction phase, 10 patients (20%) experienced dose reductions of chemotherapy. Of 29 patients who received maintenance therapy, 8 (28%) experienced erlotinib dose reductions. The reasons for discontinuing maintenance therapy were disease progression (n=16), toxicity (n=9), or patient choice (n=3). Rash acneiform was the most frequent reason for discontinuing maintenance treatment (5/9 patients) despite erlotinib dose reduction. One patient was still on treatment by the cutoff date.

Efficacy

Fifty patients were deemed eligible for evaluation of efficacy. No patient achieved a CR while 24 (48%) had a PR; the ORR was 48% (95% confidence interval [CI]: 34.8–61.5%) (Table 2). All 24 patients with PR achieved an objective response during the induction phase. Nineteen patients (38%) maintained an SD, yielding a disease control rate of 86% (95% CI: 73.8–93.0%). Seven patients (14%) experienced PD. After a median follow-up period of 14.3 months (range: 1.1–30.7 months), the median PFS (mPFS) and OS (mOS) were 6.5 months (95% CI: 5.8–7.2 months) and 21.4 months (95% CI: 15.9–26.9 months), respectively (Fig. 2). The 6-months PFS rate (the primary endpoint) was 59.5% (95% CI: 45.0–72.6%). The mPFS of the maintenance phase only (n=29) was 4.2 months (95% CI: 2.1–6.0 months). At the time of data collection cutoff, which was 1 year and 8 months after the last patient enrolled, 17 patients (34%) were still alive.

Safety

The major adverse events of all eligible patients in each treatment phase (induction and maintenance phase) are summarized in Table 3. Although grade ≥ 3 adverse events were observed in 33 patients (66.0%), most were hematologic, and no febrile neutropenia was detected. One patient experienced grade 4 intestinal perforation and was salvaged by emergency surgery on day 5 in the first cycle of induction therapy. The operative pathology reported a metastasis at the perforation site. It is possible that bevacizumab caused intestinal perforation. One patient (3.4%) died due to ventricular fibrillation on day 15 in the first cycle of maintenance therapy, which was considered a treatment-related event.

Quality of life

Thirty-nine patients (78%) completed the QOL questionnaire at baseline. The number of patients with evaluable QOL was lower than expected owing to the low questionnaire completion rate at some institutions. Fig. 3 showed the mean FACT-L and FACT-G scores, trial outcome index (TOI), and Lung Cancer Subscale (LCS) at baseline, at the beginning of third cycle in the induction phase, at the beginning of maintenance therapy, and at the third, fifth, and seventh cycles in the maintenance phase. Although the number of evaluable patients was relatively low in the latter course of treatment, there was no significant decline in the FACT-L, FACT-G, TOI and LCS scores during treatment.

Second-line therapy

Thirty-seven patients (74%) underwent second-line therapy. The regimens of second-line therapy are shown in Table 4. No patients who progressed during induction phase were administered erlotinib or erlotinib plus bevacizumab as second-line therapy. Three patients (8%) achieved PR, 23 patients (62%) had SD, 7 patients (19%) had PD, and 4 patients (11%) were not evaluable, judged by each investigator.

Discussion

To our knowledge, this is the first multicenter phase 2 study to evaluate the efficacy and safety of switch maintenance erlotinib and bevacizumab after the induction therapy with carboplatin/pemetrexed/bevacizumab for non-Sq NSCLC with wild-type *EGFR*. Switch maintenance is considered an “early second-line” therapy. Docetaxel is the standard second-line treatment and has been previously tested as “early second-line” therapy; therefore, we tested another hypothesis and selected erlotinib in this trial [26]. This combination therapy achieved an ORR of 48%, mPFS of 6.5 months, and mOS of 21.4 months. The lower limit of the one-sided 95% CI of the 6-month PFS rate, the primary endpoint, was 45.0%; this did not exceed the prior assumption of 50%. Although 1 patient (2%) died due to ventricular fibrillation in the maintenance phase, 43 patients (86%) completed ≥ 4 cycles of induction therapy without experiencing febrile neutropenia, and 29 (58%) received a median of 4 cycles of maintenance therapy.

1 In the PointBreak study, the PemCBeV (induction therapy with carboplatin, pemetrexed, and
2 bevacizumab followed by continuation maintenance therapy with pemetrexed and bevacizumab) and the
3 PacCBeV treatment groups showed identical efficacy, with ORRs of 34.1% and 33.0%, DCRs of 65.9%
4 and 69.8%, mPFS of 6.0 months and 5.6 months, and mOS of 12.0 months and 13.4 months from the start
5 of induction therapy, respectively. Additionally, 66.0% of patients in the PemCBeV arm and 67.3% of
6 those in the PacCBeV arm received maintenance therapy [19]. In the ATLAS study, induction therapy
7 with any platinum-doublet (other than pemetrexed) plus bevacizumab followed by switch maintenance
8 therapy with bevacizumab and erlotinib or placebo improved PFS over placebo to 4.8 months vs. 3.7
9 months (hazard ratio [HR], 0.71; 95% CI, 0.58–0.86; $p < .001$) without improving OS (14.4 months vs.
10 13.3 months; HR, 0.92; 95% CI, 0.70–1.21; $p = .5341$) from the start of maintenance therapy [17].
11 Considering that only patients with *EGFR* wild-type NSCLC were eligible for our study, mOS of 21.4
12 months was favorable. In addition, our findings of an ORR of 48% without febrile neutropenia by using
13 an AUC=5 of carboplatin are also noteworthy.

14 On the other hand, the favorable OS in our study might be attributable to the strict eligibility
15 criteria. Several retrospective studies showed that eligibility for bevacizumab is an independent favorable
16 prognostic factor in NSCLC [27,28]. Additionally, erlotinib eligibility was required in our study, which
17 might have increased the proportion of patients with never or light smoking status and contributed to the
18 favorable OS outcome. Weiss et al. conducted a phase 2 trial of PemCBeV in patients with NSCLC with
19 never or former/light smoking status, and showed similar efficacy with an ORR of 47%, mPFS of 12.6
20 months, and mOS of 20.3 months from the start of induction therapy [28]. Two other Japanese phase 2
21 studies of PemCBeV also reported similar favorable outcomes [29,30]. The additional benefits of adding
22 bevacizumab to carboplatin and pemetrexed in Non-Sq NSCLC patients should be verified in other
23 contexts.

24 Despite the statistically superior efficacy of EGFR-TKIs in the initial randomized clinical
25 trial [21], the indication of such agents in patients with wild-type *EGFR* NSCLC has been limited
26 [3,32,33]. However, even when using the “sensitive” *EGFR* mutation analysis method, a substantial
27 number of patients who might benefit from EGFR-TKIs may be unable to take advantage of them
28 because of their limited indication [34]. Therefore, in addition to the dual blockade of the EGFR and
29 VEGF pathways in wild-type *EGFR* NSCLC, our protocol using EGFR-TKIs as a maintenance strategy

1 would therefore treat those patients who would have otherwise missed such therapies because of a false-
2 negative *EGFR* mutation status test. Considering the modest clinical efficacy of EGFR-TKI and
3 bevacizumab for wild-type EGFR, which is the most likely explanation for not achieving the primary
4 endpoint, it is difficult to justify the routine use of this regimen for EGFR wild-type NSCLC. However,
5 the fact that 10% of patients received ≥ 10 cycles of maintenance therapy suggests that a subpopulation of
6 patients can derive a benefit from this switch maintenance strategy. The increased QOL in the latter
7 course of treatment may also reflect the treatment's efficacy in such subpopulations.

8 Seventeen patients (34%) survived for over 2 years. After undergoing protocol treatment, 2
9 patients were diagnosed as ALK positive and 1 patient was diagnosed as ROS1 positive. One case has
10 recently been identified as an EGFR false negative case. After 20 cycles of maintenance therapy, the
11 patient relapsed with pleural effusion, which contained EGFR mutation positive NSCLC cells. However,
12 driver mutations were not found in the remaining 14/17 patients in whom survival exceeded 2 years.
13 There was no association between baseline characteristics and longer survival and we did not collect any
14 pretreatment tumor specimens. Therefore, we could not identify the specific subgroup with a favorable
15 outcome, which is the greatest limitation of the present study.

16 In the United States (US), pembrolizumab was recently approved as a first-line combination
17 therapy with carboplatin and pemetrexed for patients with advanced NSCLC irrespective of their PD-L1
18 expression status, based on the result of a randomized phase 2 study, recently corroborated by a
19 subsequent phase 3 trial [35,36]. Although this combination therapy has not yet been approved outside the
20 US, most patients without activating driver mutations might be good candidates for this ICI combination
21 therapy. Identifying patients who should be treated with a bevacizumab combination regimen and/or an
22 ICI combination remains an important issue.

23 In conclusion, although carboplatin/pemetrexed/bevacizumab followed by erlotinib and
24 bevacizumab maintenance showed modest efficacy and was well tolerated in non-squamous NSCLC
25 patients with wild-type *EGFR*, this is a negative phase 2 trial. Considering a subpopulation of patients
26 might be able to derive a long-time survival benefit from this switch maintenance strategy, further
27 exploration of identifying useful biomarkers are warranted.

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9

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Figure Captions

Fig. 1

CONSORT diagram of the study.

Fig. 2

Kaplan-Meier curves of (A) progression-free survival (PFS) and (B) overall survival (OS). CI, confidence interval.

Fig. 3

Functional Assessment of Cancer Therapy (FACT)-Lung (FACT-L), FACT-General (FACT-G), trial outcome index (TOI), and lung cancer subscale (LCS) scores at baseline and during treatment. (i), induction therapy; (m), maintenance therapy.

Table 1. Patient characteristics

Characteristics	n	(%)
Age (years)		
Median	64	
Range	36–74	
Sex		
Male	27	(54)
Female	23	(46)
ECOG Performance Status		
0	28	(56)
1	22	(44)
Disease Stage		
IIIB	5	(10)
IV	41	(82)
Recurrence	5	(8)
Histology		
Adenocarcinoma	48	(96)
Non-small cell carcinoma	2	(4)
Smoking status		
Never	13	(26)
Ever	34	(68)
Unknown	3	(6)

ECOG, Eastern Cooperative Oncology Group.

Table 2. Treatment outcomes

Outcome	n	(%)
CR	0	(0)
PR	24	(48)
SD	19	(38)
PD	7	(14)
ORR	24	(48)
DCR	43	(86)

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; DCR, disease control rate

Table 3. Safety profiles

Adverse Event	Induction phase, n=50						Maintenance phase, n=29							
	Any Grade		Grade 3		Grade 4		Any Grade		Grade 3		Grade 4		Grade 5	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Hematologic														
Leukopenia	38	(76.0)	12	(24.0)	2	(4.0)	7	(24.1)	0	(0)	0	(0)	0	(0)
Neutropenia	41	(82.0)	17	(34.0)	7	(14.0)	3	(10.3)	1	(3.4)	0	(0)	0	(0)
Anemia	43	(86.0)	9	(18.0)	0	(0)	19	(65.5)	1	(3.4)	0	(0)	0	(0)
Thrombocytopenia	38	(76.0)	8	(16.0)	3	(6.0)	4	(13.8)	0	(0)	0	(0)	0	(0)
Nonhematologic														
Fatigue	31	(62.0)	3	(6.0)	0	(0)	12	(41.4)	1	(3.4)	0	(0)	0	(0)
Anorexia	31	(62.0)	7	(14.0)	0	(0)	10	(34.5)	1	(3.4)	0	(0)	0	(0)
Nausea	26	(52.0)	3	(6.0)	0	(0)	6	(20.7)	0	(0)	0	(0)	0	(0)
Vomiting	6	(12.0)	0	(0)	0	(0)	2	(6.9)	0	(0)	0	(0)	0	(0)
Diarrhea	6	(12.0)	0	(0)	0	(0)	10	(34.5)	2	(6.9)	0	(0)	0	(0)
Constipation	18	(36.0)	0	(0)	0	(0)	7	(24.1)	0	(0)	0	(0)	0	(0)
Mucositis	7	(14.0)	0	(0)	0	(0)	8	(27.6)	1	(3.4)	0	(0)	0	(0)
Hypertension	19	(38.0)	5	(10.0)	0	(0)	10	(34.5)	1	(3.4)	0	(0)	0	(0)
Proteinuria	7	(14.0)	0	(0)	0	(0)	11	(37.9)	1	(3.4)	0	(0)	0	(0)
Localized edema	0	(0)	0	(0)	0	(0)	1	(3.4)	1	(3.4)	0	(0)	0	(0)
Epistaxis	8	(16.0)	0	(0)	0	(0)	2	(6.9)	0	(0)	0	(0)	0	(0)

Intestinal perforation	1	(2.0)	0	(0)	1	(2.0)	0	(0)	0	(0)	0	(0)	0	(0)
Rash acneiform	2	(4.0)	1	(2.0)	0	(0)	18	(62.0)	3	(10.3)	0	(0)	0	(0)
Pruritus	3	(6.0)	0	(0)	0	(0)	9	(31.0)	0	(0)	0	(0)	0	(0)
Alopecia	4	(8.0)	0	(0)	0	(0)	2	(6.9)	0	(0)	0	(0)	0	(0)
Pneumonitis	1	(2.0)	0	(0)	0	(0)	1	(3.4)	0	(0)	0	(0)	0	(0)
Infection	4	(8.0)	1	(2.0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
AST increased	26	(52.0)	1	(2.0)	0	(0)	11	(37.9)	0	(0)	0	(0)	0	(0)
ALT increased	24	(48.0)	0	(0)	0	(0)	9	(31.0)	0	(0)	0	(0)	0	(0)
Cre increased	14	(28.0)	0	(0)	0	(0)	12	(41.4)	0	(0)	0	(0)	0	(0)
Hyperkalemia	12	(24.0)	0	(0)	0	(0)	2	(7.0)	0	(0)	0	(0)	0	(0)
Ventricular fibrillation	0	(0)	0	(0)	0	(0)	1	(3.4)	0	(0)	0	(0)	1	(3.4)

Abbreviations: AST, aspartate transaminase; ALT, alanine transaminase; Cre, creatinine.

Table 4. Second-line therapy

Regimen	n	(%)
docetaxel	15	(41)
S-1	4	(11)
pemetrexed/bevacizumab	3	(8)
carboplatin/pemetrexed	2	(5)
pemetrexed	2	(5)
carboplatin/docetaxel	1	(3)
carboplatin/nab-paclitaxel	1	(3)
carboplatin/pemetrexed/bevacizumab	1	(3)
cisplatin/S-1	1	(3)
cisplatin/vinorelbine	1	(3)
amrubicin	1	(3)
gemcitabine	1	(3)
bevacizumab	1	(3)
alectinib	1	(3)
crizotinib	1	(3)
nivolumab	1	(3)
Total	37	(100)

Fig. 1

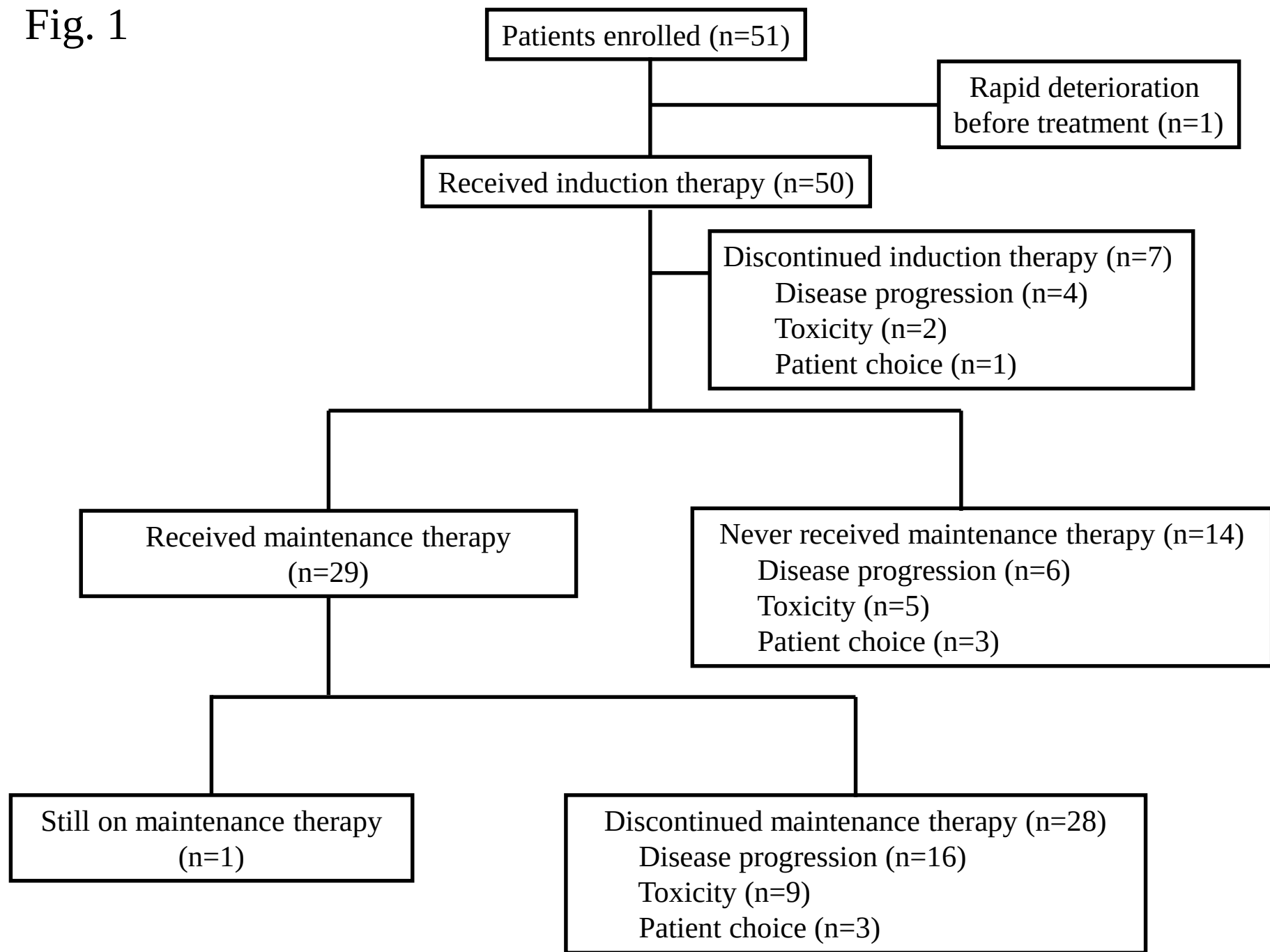
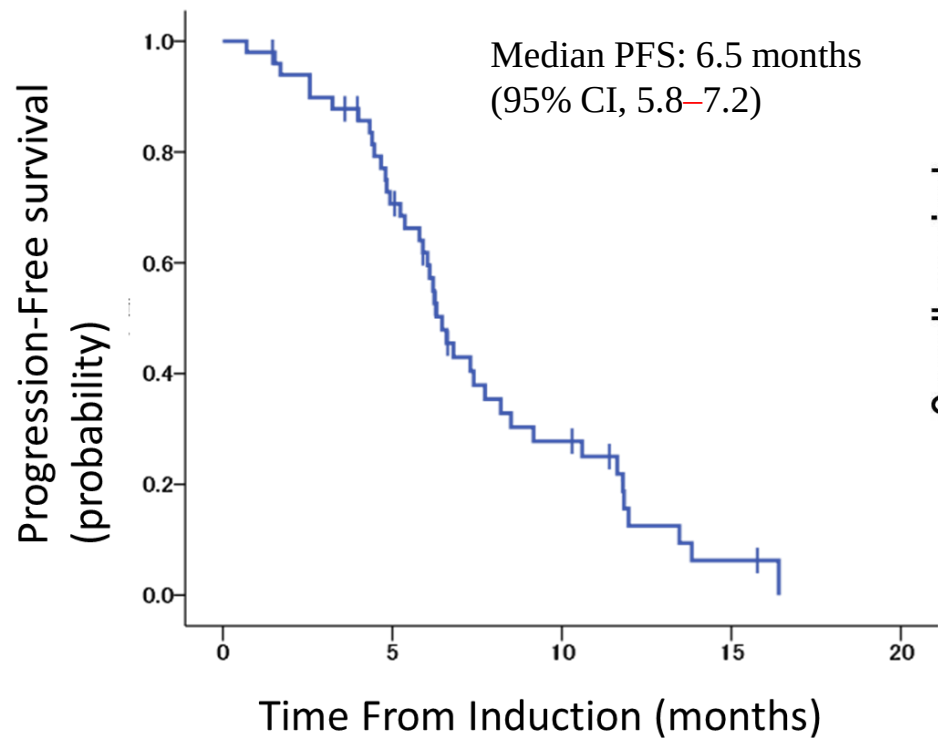


Fig. 2

A



B

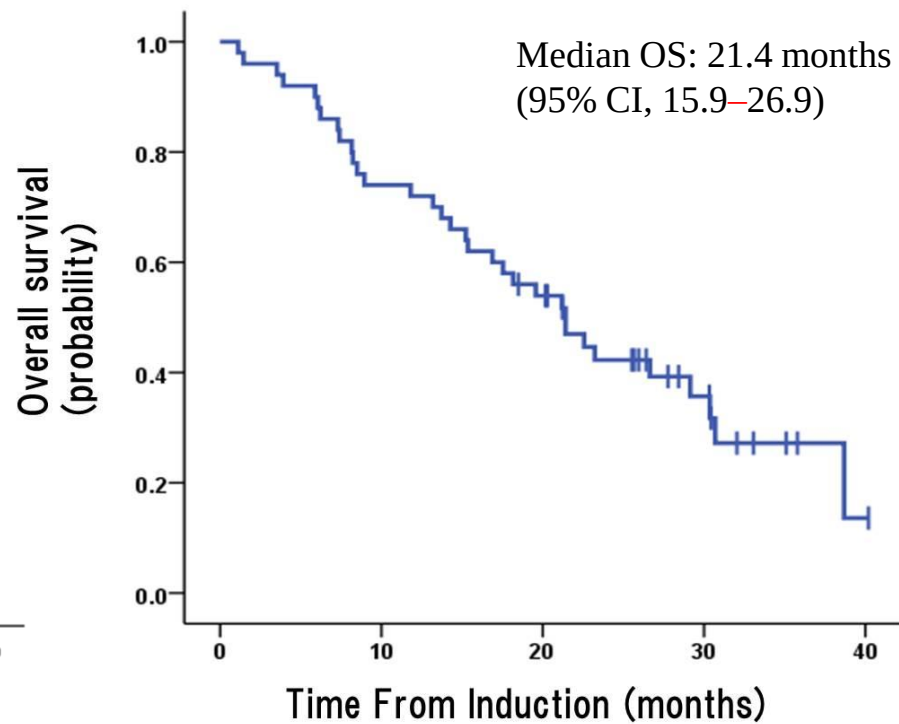


Fig. 3

