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

Introduction

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

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

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

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 ≤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,

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

Study design and treatment

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

Eligible patients received pemetrexed 500 mg/m^2 through a 10-min intravenous infusion followed by intravenous infusion of carboplatin at a dose corresponding to an area under the curve (AUC) equal to 5 mg/mL/min (AUC=5) over 30 min, as well as bevacizumab 15 mg/kg for at least 30 min intravenously on day 1 of every 21-day cycle, for 4–6 cycles during the induction therapy. We used an AUC=5 of carboplatin based on the results of our previous trial instead of AUC=6 [25]. Afterwards, patients with complete response (CR), partial response (PR), or stable disease (SD) received maintenance therapy with erlotinib 150 mg/body on days 1–21 and bevacizumab 15 mg/kg on day 1 of every 21-day cycle until evidence of disease progression or unacceptable toxicity manifested. The period between the last dosage of induction therapy and the first dosage of maintenance therapy was required to be 3–6 weeks. All patients received oral folic acid (0.5 mg) daily and a vitamin B12 (1 mg) injection every 9 weeks, beginning at least 1 week before the first dose and continuing until 3 weeks after the last dose of pemetrexed.

In the event of severe toxicities during a given cycle, the doses of carboplatin and/or pemetrexed were reduced in subsequent cycles. Such toxicities included grade 4 thrombocytopenia, grade ≥3 febrile neutropenia, or other grade ≥3 nonhematological toxicities. Dose reduction comprised of a decrease in carboplatin to an AUC of 4 mg/mL/min and a decrease in pemetrexed to 400 mg/m^2. 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 ≥38˚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.

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

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

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

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

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

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

In conclusion, although 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*, this is a negative phase 2 trial. Considering a subpopulation of patients might be able to derive a long-time survival benefit from this switch maintenance strategy, further exploration of identifying useful biomarkers are warranted.

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References

1. Jemal A, Siegel R, Xu J, et al. (2010) Cancer statistics, 2010. CA Cancer J Clin 60:277–300
2. Parkin DM. (2001) Global cancer statistics in the year 2000. Lancet Oncol 2:533–543.
3. Lee CK, Wu YL, Ding PN, et al. (2015) Impact of specific epidermal growth factor receptor (EGFR) mutations and clinical characteristics on outcomes after treatment with EGFR tyrosine kinase inhibitors versus chemotherapy in EGFR-mutant lung cancer: A meta-analysis. J Clin Oncol 33:1958–1965
4. Shaw AT, Kim DW, Nakagawa K, et al. (2013) Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 368:2385–2394
5. Facchinetti F, Rossi G, Bria E, et al. (2017) Oncogene addiction in non-small cell lung cancer: Focus on ROS1 inhibition. Cancer Treat Rev 55:83–95
6. Reck M, Rodríguez-Abreu D, Robinson AG, et al. (2016) Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 375:1823–1833
7. Sun JM, Park JO, Won YW, et al. (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
8. Gerber DE, Rasco DW, Le P, 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
9. Fidias PM, Dakhil SR, Lyss AP, et al. (2009) Phase III study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non-small-cell lung cancer. J Clin Oncol 27:591–598
10. Pérol M, Chouaid C, Pérol D, et al. (2012) Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol 30:3516–3524
11. Socinski MA, Schell MJ, Peterman A, et al. (2002) Phase III trial comparing a defined duration of therapy versus continuous therapy followed by second-line therapy in advanced-stage IIIB/IV non-

small-cell lung cancer. J Clin Oncol 20:1335–1343

12. Ciuleanu T, Brodowicz T, Zielinski C, et al. (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
13. Cappuzzo F, Ciuleanu T, Stelmakh L, 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
14. Sandler A, Gray R, Perry MC, et al. (2006) Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 355:2542–2550
15. Johnson ML, Patel JD. (2014) Chemotherapy and targeted therapeutics as maintenance of response in advanced non-small cell lung cancer. Semin Oncol 41:93–100
16. Paz-Ares LG, de Marinis F, Dediu M, et al. (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
17. Johnson BE, Kabbinavar F, Fehrenbacher L, et al. (2013) ATLAS: randomized, double-blind, placebo-controlled, phase IIIB trial comparing bevacizumab therapy with or without erlotinib, after completion of chemotherapy, with bevacizumab for first-line treatment of advanced non-small-cell lung cancer. J Clin Oncol 31:3926–3934
18. Barlesi F, Scherpereel A, Rittmeyer A, 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
19. Patel JD, Socinski MA, Garon EB, et al. (2013) PointBreak: a randomized phase III study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small-cell lung cancer. J Clin Oncol 31:4349–4357
20. Zinner RG, Obasaju CK, Spigel DR, et al. (2015) PRONOUNCE: randomized, open-label, phase III

study of first-line pemetrexed + carboplatin followed by maintenance pemetrexed versus paclitaxel + carboplatin + bevacizumab followed by maintenance bevacizumab in patients with advanced nonsquamous non-small-cell lung cancer. J Thorac Oncol 10:134–142

21. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. (2005) Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 353:123–132
22. Pennell NA, Lynch TJ. (2009) Combined inhibition of the VEGFR and EGFR signaling pathways in the treatment of NSCLC. Oncologist 14:399–411
23. Rolff J, Becker M, Merk J, et al. (2016) Preclinical study of a combination of erlotinib and bevacizumab in early stages of unselected non-small cell lung cancer patient-derived xenografts. Target Oncol 11:507–514
24. Herbst RS, Ansari R, Bustin F, et al. (2011) Efficacy of bevacizumab plus erlotinib versus erlotinib alone in advanced non-small-cell lung cancer after failure of standard first-line chemotherapy (BeTa): a double-blind, placebo-controlled, phase 3 trial. Lancet 377:1846–1854
25. Kanazawa K, Yokouchi H, Wang X, et al. (2014) Phase II trial of carboplatin and pemetrexed as first-line chemotherapy for non-squamous non-small cell lung cancer, and correlation between the efficacy/toxicity and genetic polymorphisms associated with pemetrexed metabolism: Hokkaido Lung Cancer Clinical Study Group Trial (HOT) 0902. Cancer Chemother. Pharmacol 74:1149–1157
26. Fidias PM, Dakhil SR, Lyss AP, et al. (2009) Phase III study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non-small-cell lung cancer. J Clin Oncol 27:591-598
27. Takagi Y, Toriihara A, Nakahara Y, et al. (2013) Eligibility for bevacizumab as an independent prognostic factor for patients with advanced non-squamous non-small cell lung cancer: a retrospective cohort study. PLoS One 8:e59700
28. Nakashima K, Murakami H, Omori S, et al. (2016) Doublet chemotherapy with cisplatin and pemetrexed is associated with a favorable outcome in patients with advanced non-squamous non-small-cell lung cancer who are eligible for bevacizumab and maintenance therapy. Mol Clin Oncol 5:575–578
29. Weiss JM, Villaruz LC, O'Brien J, et al. (2016) Results of a phase II trial of carboplatin, pemetrexed, and bevacizumab for the treatment of never or former/light smoking patients with stage IV non-small

cell lung cancer. Clin Lung Cancer 17:128–132

30. Yokoi T, Torii Y, Katashiba Y, et al. (2014) Phase II study of pemetrexed and carboplatin plus bevacizumab, followed by maintenance pemetrexed and bevacizumab in Japanese patients with non-squamous non-small cell lung cancer. Oncol Lett 8:2453–2457
31. Karayama M, Inui N, Fujisawa T, et al. (2016) Maintenance therapy with pemetrexed and bevacizumab versus pemetrexed monotherapy after induction therapy with carboplatin, pemetrexed, and bevacizumab in patients with advanced non-squamous non-small cell lung cancer. Eur J Cancer 58:30–37
32. Kawaguchi T, Ando M, Asami K, et al. (2014) Randomized phase III trial of erlotinib versus docetaxel as second- or third-line therapy in patients with advanced non-small-cell lung cancer: Docetaxel and Erlotinib Lung Cancer Trial (DELTA). J Clin Oncol 32:1902–1908
33. Garassino MC, Martelli O, Broggini M, et al. (2013) Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): a randomized controlled trial. Lancet Oncol 14:981–988
34. Morise M, Taniguchi H, Saka H, et al. (2014) Phase II study of erlotinib for previously treated patients with EGFR wild-type non-small-cell lung cancer, following EGFR mutation status reevaluation with the Scorpion Amplified Refractory Mutation System. Mol Clin Oncol 2:991–996
35. Langer CJ, Gadgeel SM, Borghaei H, et al. (2017) Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol 17:1497–1508
36. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. (2018) Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med 378:2078-2092

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

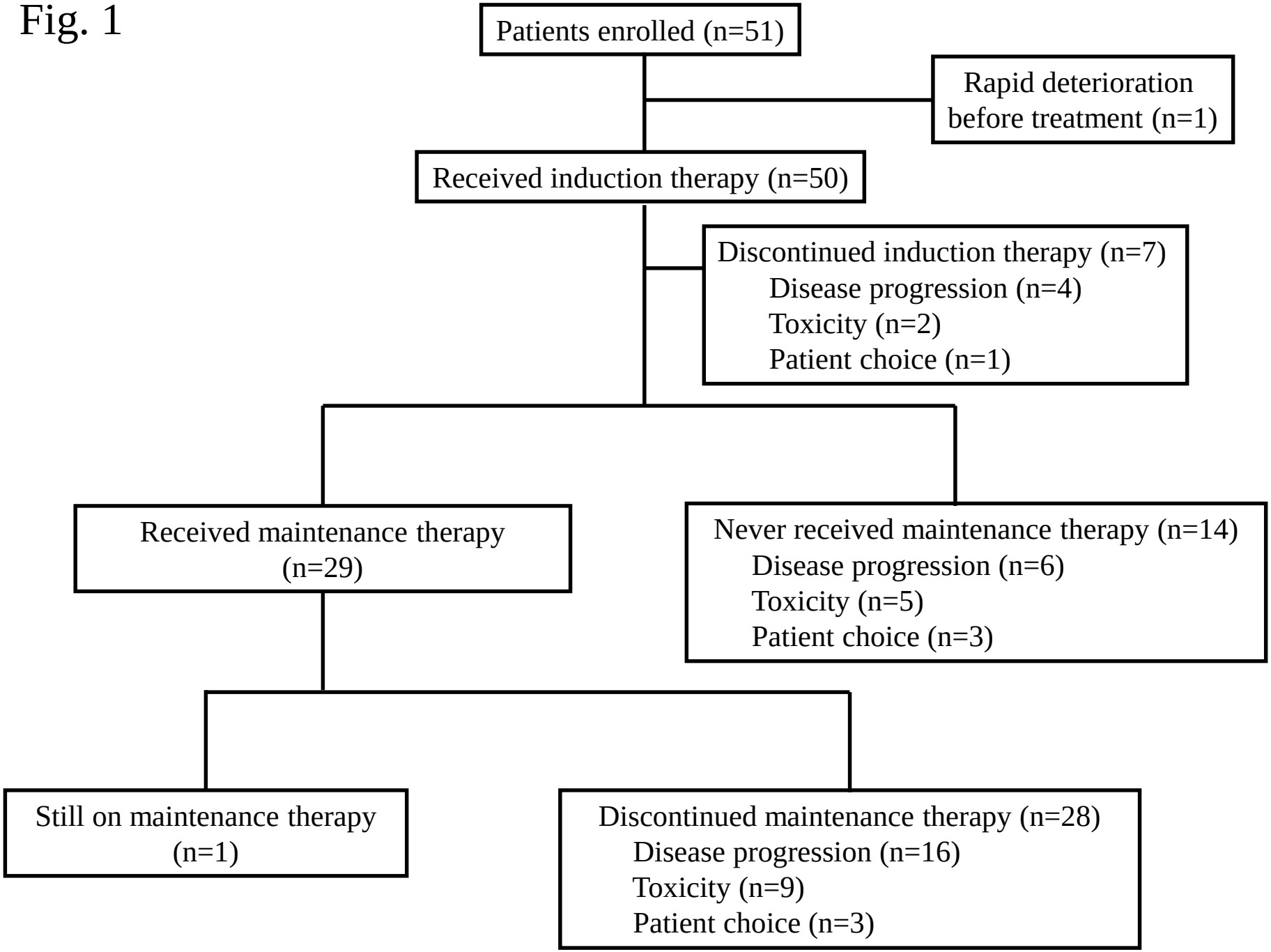

Patients enrolled (n=51)
Rapid deterioration before treatment (n=1)
Received induction therapy (n=50)
Discontinued induction therapy (n=7)
Disease progression (n=4)
Toxicity (n=2)
Patient choice (n=1)
Received maintenance therapy (n=29)
Never received maintenance therapy (n=14)
Disease progression (n=6)
Toxicity (n=5)
Patient choice (n=3)
Still on maintenance therapy (n=1)
Discontinued maintenance therapy (n=28)
Disease progression (n=16)
Toxicity (n=9)
Patient choice (n=3)

Fig. 2

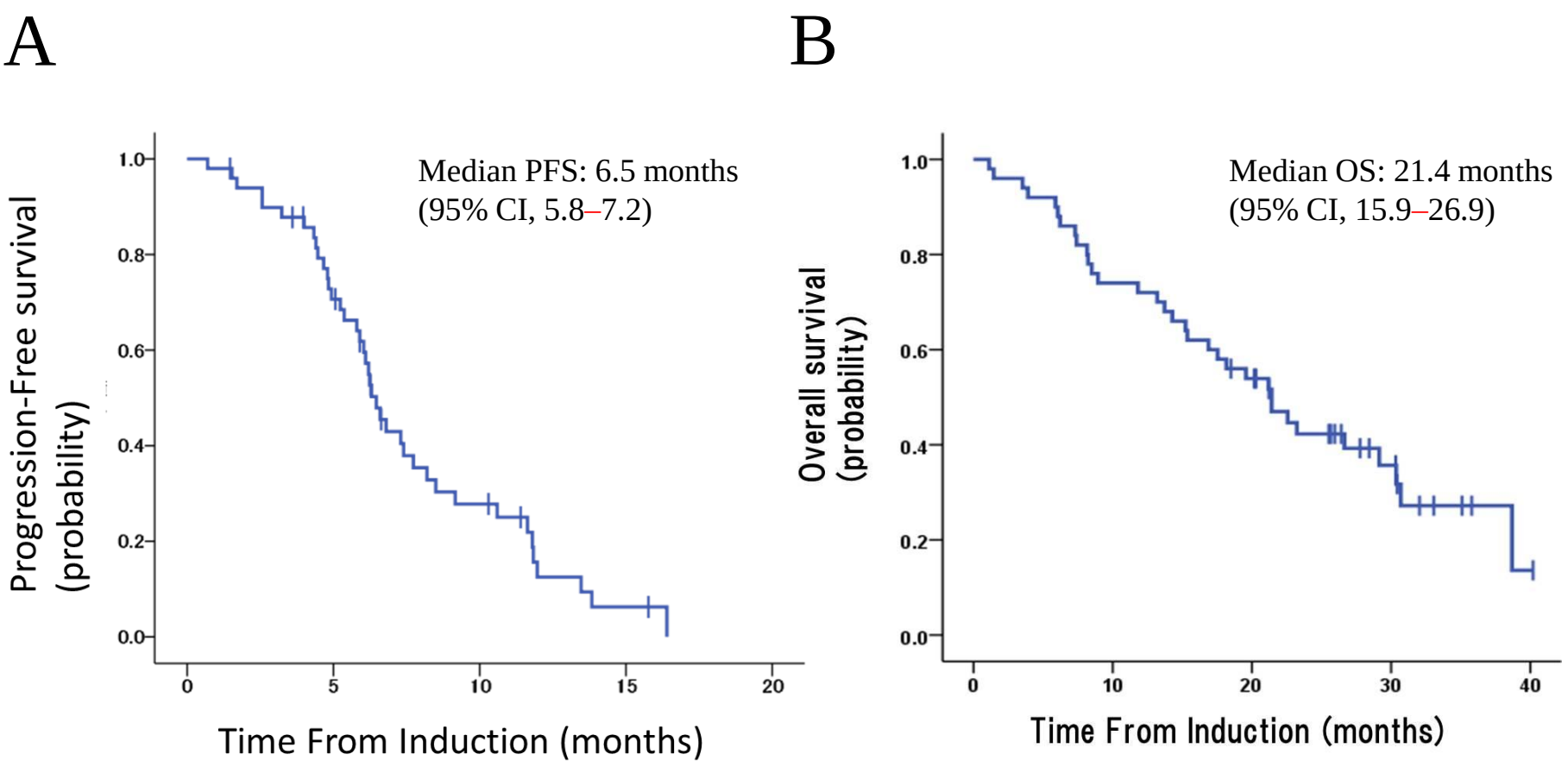
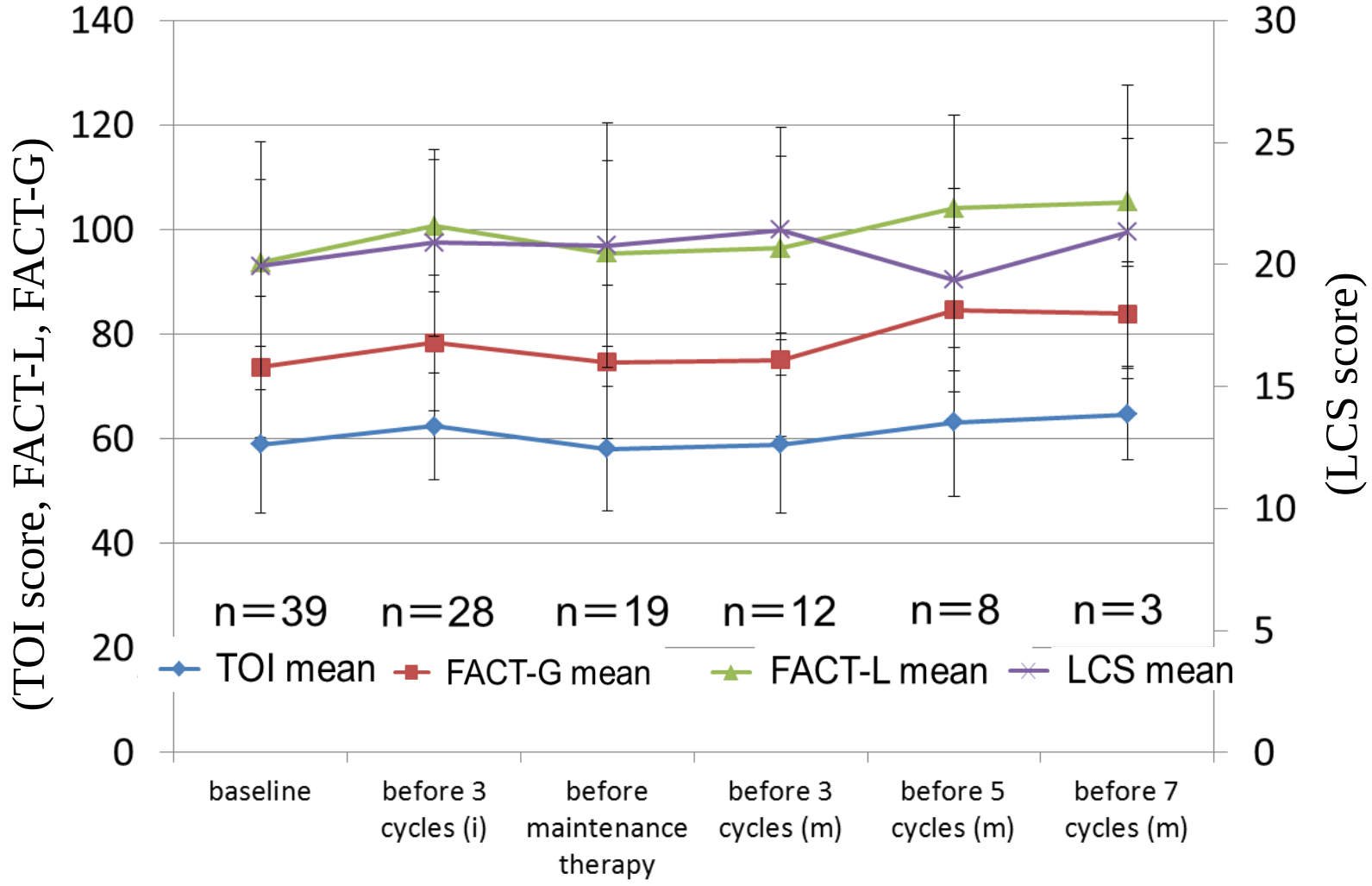

A
Progression-Free survival (probability)
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
20
Time From Induction (months)
Median PFS: 6.5 months
(95% CI, 5.8–7.2)
B
Overall survival (probability)
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
Time From Induction (months)
Median OS: 21.4 months
(95% CI, 15.9–26.9)

Fig. 3


(TOI score, FACT-L, FACT-G)
(LCS score)
140
120
100
80
60
40
20
0
30
25
20
15
10
5
0
n=39
n=28
n=19
n=12
n=8
n=3
TOI mean
FACT-G mean
FACT-L mean
LCS mean
baseline
before 3 cycles (i)
before maintenance therapy
before 3 cycles (m)
before 5 cycles (m)
before 7 cycles (m)