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Phase II study of gefitinib readministration in patients with advanced non-small cell lung cancer and previous response to gefitinib

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Short Title: Gefitinib readministration in NSCLC patients

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Key words: epidermal growth factor receptor (EGFR); EGFR-tyrosine kinase inhibitor (EGFR-TKI); gefitinib; non-small cell lung cancer (NSCLC); readministration; chemotherapy

ABSTRACT

Objective: Salvage treatment for acquired resistance to gefitinib has yet to be developed. We conducted the first prospective phase II study of gefitinib readministration in previous gefitinib responders. **Methods:** Gefitinib (250 mg/day) was readministered to patients with advanced/metastatic non-small cell lung cancer (NSCLC) who had achieved objective response to initial gefitinib and subsequently received cytotoxic chemotherapy after disease progression with initial gefitinib. The primary endpoint was the objective response rate with gefitinib readministration. Secondary endpoints were disease control rate, progression-free survival (PFS), overall survival (OS), quality of life (QOL), and toxicity. Changes in lung cancer-related symptoms were evaluated using the seven-item lung cancer subscale of the questionnaire. **Results:** Sixteen patients were enrolled between February 2005 and January 2008. Most had received ≥3 regimens of chemotherapy. Response and disease-control rates for all patients were 0% and 44%. Median PFS and OS were 2.5 months and 14.7 months, respectively. Four of 7 patients with stable disease experienced long duration≥6 months) of disease control without severe toxicity.

Symptom improvement was observed in 2 of 12 patients (17%) for whom QOL was evaluable. **Conclusion:** Gefitinib represents a useful therapeutic option for selected previous gefitinib responders.

INTRODUCTION

Gefitinib is the first commercially available epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) and is widely used for the treatment of advanced or recurrent non-small cell lung cancer (NSCLC). The Iressa Pan Asia Study (IPASS) demonstrated superior progression-free survival (PFS) in the gefitinib arm than in the carboplatin and paclitaxel (CP) arm for chemotherapy-naive patients with never-smoker or light smoking status [1]. For EGFR mutation-positive patients, gefitinib monotherapy can produce superior PFS than CP or cisplatin and docetaxel combinations in the first-line setting [2] [3]. As a second-line therapy, gefitinib showed significantly better overall survival (OS) than placebo for never-smokers and patients of Asian origin in the Iressa Survival Evaluation in Lung Cancer (ISEL) trial and non-inferiority of OS compared to docetaxel in the Iressa NSCLC Trial Evaluating REsponse and Survival versus Taxotere (INTEREST) study [4] [5].

Despite the initial efficacy of gefitinib monotherapy, acquired resistance appears almost inevitable and median PFS does not exceed 12 months [6]. Approximately 60-70% of cases with acquired resistance to EGFR-TKI can be explained by the

secondary resistance T790M mutation [7, 8], acquired amplification of the MET oncogene [9, 10], or a small number of other secondary mutations, such as L858R-D761Y [11], L858R-L747S [12] and L858R-T854A [13]. Details of resistance have yet to be completely clarified, but establishment of salvage treatment is an urgent issue.

Several case reports have described successful readministration of gefitinib to NSCLC patients who achieved objective response with the initial administration of gefitinib before eventual progression [14, 15]. The present study represents the first prospective phase II study to evaluate gefitinib readministration as a therapeutic option for heavily pretreated patients with NSCLC who responded to initial gefitinib treatment and received subsequent cytotoxic chemotherapy.

PATIENTS AND METHODS

Patient Eligibility

Subjects comprised patients with recurrent or metastatic NSCLC with documented progressive disease (PD) according to Response Evaluation Criteria in Solid Tumors

(RECIST) [16] after achieving objective response with initial gefitinib and then receiving at least one subsequent cytotoxic chemotherapy regimen. Other eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2, at least one unidimensionally measurable lesion, and adequate organ functions. Patients were excluded if they displayed unresolved chronic toxicity of prior therapy, other active malignancies, uncontrolled brain metastasis, or severe comorbidities. The institutional review board at each participating hospital approved all study protocols and the genetic analysis of tumours, and written informed consent was obtained from all patients prior to enrolment.

Treatment Plan

Patients received gefitinib at 250 mg/day. In the event of unacceptable toxicity defined as grade 3 or more, gefitinib was ceased until the toxicity resolved and improved to below grade 3 within 2 weeks. No dose reduction was permitted. Treatment was continued until disease progression, intolerable toxicity, or withdrawal of consent.

Evaluation of Response and Adverse Events

Evaluations of treatment response by computed tomography (CT) were repeated every 4 weeks according to RECIST. The minimum interval to qualify for stable disease (SD) was defined as 8 weeks. Responses were evaluated by the physician in charge and confirmed by extramural review. In addition, changes in lung cancer-related symptoms were evaluated using the seven-item lung cancer subscale (LCS) of the questionnaire [17]. The LCS is an independently validated tool that measures disease-related symptoms of lung cancer on a scale of 0 (most symptomatic) to 28 (asymptomatic). A change of $\geq$2 points in LCS score reportedly reflects a minimally important difference associated with PS, weight loss, objective tumour response, and time to progression [17]. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 (CTCAE v3.0).

Statistical Analysis

Objective response rate (RR) with gefitinib readministration was taken as the primary endpoint. Secondary endpoints were disease control rate (DCR), PFS, OS,

symptom improvement rate, time to symptom improvement, and toxicity. DCR was defined as the sum of the objective response rate plus the rate of SD. Simon's two-stage minimax design was used to determine the sample size and decision criteria for this phase II study. With a target activity level of 25% (P1) and the minimum response rate of interest set at 5% (P0), 14 evaluable patients were needed to accept the hypothesis and a 5% significance level to reject the hypothesis with 80% power. Assuming an inevaluability rate of≤15%, we projected an accrual of 16 patients. All patients who were enrolled and treated with gefitinib were included in both efficacy and toxicity analyses. OS was defined as the interval between enrolment in this study and death from any cause. PFS was defined as the interval between enrolment in this study and the date of documented PD or death from any cause. If a patient was lost to follow-up, that patient was censored at the last date of contact. Median OS and PFS were estimated using Kaplan-Meier analysis. Factors potentially associated with long SD were assessed as follows. Categorical variables were compared using Fisher's exact test or the chi-square test, while continuous variables were assessed using the Mann-Whitney nonparametric test. Relevant parameters for influence on long SD were studied by

univariate analysis using the log-rank test. Differences were considered to be significant at the level of $p<0.05$. Statistical analysis was performed using JMP 8 software (SAS Institute, Cary, NC, USA).

RESULTS

Patient Characteristics

Between February 2005 and January 2008, a total of 16 patients were enrolled in this study. Patient characteristics are described in Table 1. The major tumour histological type was adenocarcinoma in 14 patients (88%). Eleven patients (69%) were never-smokers. Three patients showed EGFR gene mutations (2 patients with exon 19 deletions; 1 patient with L861Q in exon 21), 3 had the wild-type gene, and the status of the remaining 10 patients was unknown. All mutational analyses were performed using biopsy specimens obtained before initial gefitinib treatment.

All patients had received various therapies before study entry (Table 2). Fourteen patients received gefitinib readministration as a fourth-line or later therapy.

Tumour Response and Survival

Responses were evaluable for 15 of the 16 enrolled patients. No patients achieved objective response, with an overall response rate of 0% (95% confidence interval (CI), 0-21%), while 7 patients (44%) showed SD and 8 patients (50%) had PD as the best response. DCR was 44% (95%CI, 20-70%). One patient experienced a transient reduction in diameter of the primary lesion. However, due to regrowth of other metastasis, the best response of this patient was SD (Figure 1). By the time of analysis, all patients had experienced disease progression and 14 patients had died. With a median follow-up of 14.7 months, median PFS and OS were 2.5 months (95%CI, 1.6-3.2 months) and 14.7 months (95%CI, 11.1-15.5 months), respectively (Figure 2). Four of 7 patients with SD experienced long duration (≥6 months) of disease control. When we compared baseline characteristics between patients with and without long SD (≥6 months), no significant differences were observed in age, sex, PS, histology, smoking history, number of previous treatment regimens, duration of initial gefitinib treatment, or interval between initial and rechallenge of gefitinib (Table 3). One of the 3 patients with EGFR gene mutations (L861Q) had SD with 6.7 months of PFS, while the

other 2 patients had PD as the best response.

Toxicity Profile

Toxicity was evaluated in all eligible patients. The most common adverse event was fatigue in 13 patients (81%), including 2 patients with grade 3. One patient experienced grade 4 central nervous system cerebrovascular ischaemia and terminated gefitinib treatment on day 47. Overall, toxicity appeared similar to the previously published trials of gefitinib monotherapy.

Symptom Improvement

LCS was evaluated in 12 of the 16 enrolled patients and compliance rate (ratio of the number of assessable weekly forms to the number of forms expected) was 70%. Median baseline LCS was 22 (range, 12-28). Symptom improvement was observed in 2 of 12 patients, providing a symptom improvement rate of 16.7% (95%CI, 2.1-48.4%). Time to symptom improvement in these 2 patients was 1 and 4 weeks [17].

DISCUSSION

To the best of our knowledge, this represents the first prospective phase II study to assess whether gefitinib readministration confers any clinical benefit in patients with advanced NSCLC who have previously achieved objective response with the initial administration of gefitinib. No patients exhibited objective response, the primary endpoint of this study, suggesting that gefitinib readministration has little effect with respect to tumour shrinkage. However, the fact that 4 patients achieved a long duration (≥6 months) of disease control without severe toxicity is noteworthy.

Several retrospective studies have described the clinical activity of one EGFR-TKI after the failure of another [18-24] or readministraion of the same drug [14, 15, 25]. Most such reports have noted favourable results, although Viswanathan et al. and Costa et al. reported no or only limited response to erlotinib after progression on gefitinib [19, 24]. Two prospective studies by Cho et al. [26] and Lee et al. [27] have shown similar results to our own, namely that RR/DCR were 9.5%/28.6% and 4.3%/8.7% each. In another prospective study, Riely et al. also reported that in patients who develop acquired resistance, stopping gefitinib or erlotinib results in symptomatic progression,

worsening of results on FDG-PET, and increased tumour size, while restarting EGFR-TKI results in a median 1% decrease in tumour diameter, 4% decrease in FDG-PET uptake and improvement of symptoms [28]. These results imply that some patients with clinically acquired resistance to EGFR-TKI possess some tumour cells that remain sensitive to EGFR blockade and may benefit from readministration of EGFR-TKI.

Identifying the predictive factors to distinguish those who might benefit from gefitinib re-administration is also an important issue. Tomizawa et al. mentioned the importance of the 'EGFR-TKI-free interval' [25]. That retrospective study of gefitinib readministration demonstrated a favourable result, with RR 25% and DCR 65%, accompanying a sufficient EGFR-TKI-free interval (median, 217 days) with 1-3 regimens of cytotoxic chemotherapy in all patients [25]. Conversely, Costa et al. reported that erlotinib was ineffective (RR, 6%; DCR, 22%) in 18 patients with resistance to gefitinib without any interval after resistance to gefitinib [24]. In the present study, due to the lack of a control group (i.e. cohort of patients who did not have any gefitinib readministration), we could only examine the prognostic factors for

patients re-treated with gefitinib. No significant differences were seen regarding baseline characteristics (including EGFR-TKI-free interval) between patients with long SD (n=4) and without long SD (n=12). This may, in part, be attributed to the small sample size.

Some authors have explained the usefulness of EGFR-TKI readministration by the hypothesis that cytotoxic chemotherapy subsequently administered after the initial EGFR-TKI might modify the proportion of sensitive or resistant cells or produce some genetic changes in the tumour [14, 15, 25]. We could not perform comparative molecular analysis of tissue specimens between before initial administration and readministration of gefitinib. Further investigations are required regarding this issue.

In conclusion, gefitinib readministration seems to represent a potential therapeutic option for some selected NSCLC patients who respond to initial gefitinib therapy. New approaches for identifying molecular markers are important to overcome the resistance to EGFR-TKIs seen with progression after initial response.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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Table 1. Patient characteristics (n=16)

Characteristic	n (%)
Age (years)	
Median	66.5
Range	53-79
Sex	
Male	3 (19)
Female	13 (81)
ECOG performance status	
0	5 (31)
1	9 (56)
2	2 (13)
Histology	
Adenocarcinoma	14 (88)
Squamous cell carcinoma	1 (6)
Large-cell carcinoma	1 (6)
Smoking history	
Current or ex-smoker	5 (31)
Never-smoker	11 (69)
Stage	
IIIB	1 (6)
IV	10 (63)
Recurrence	5 (31)
EGFR mutation	
Positive	3 (19)
Negative	3 (19)
Unknown	10 (63)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor.

Table 2. Summary of prior therapy for NSCLC (n=16)

Characteristic	n (%)
No. of prior chemotherapy regimens	
2	2 (13)
3	9 (56)
4	2 (13)
5	2 (13)
6	1 (6)
Best response to prior cytotoxic chemotherapy	
Partial response	6 (38)
Stable disease	7 (44)
Progressive disease	3 (19)
Time from first-line treatment to readministration of gefitinib	
≤12 months	2 (13)
12-24 months	4 (26)
≥12 months	10 (63)
Period of initial gefitinib administration	
≤6 months	1 (6)
6-12 months	7 (44)
≥12 months	8 (50)
Time from last day of initial gefitinib administration to first day of gefitinib readministration	
≤6 months	8 (50)
6-12 months	6 (38)
≥12 months	2 (13)

Table 3. Comparison between patients with or without long duration (≥6 months) of SD

Characteristics/groups	Pt with long SD (n=4)	Pt without long SD (n=12)	P
Age (years, mean±SD)	72.5±3.9	64.5±2.3	0.10
Sex (male/female)	3/1	10/2	1.00
ECOG PS (0/1/2)	2/1/1	3/8/1	0.33
Histology (Ad/Sq/La)	4/0/0	10/1/1	0.68
Smoking history (ever/never)	2/2	3/9	0.55
Stage (IIIB/IV/Rec)	0/1/3	1/9/2	0.09
No. of previous regimens (mean)	3.5	3.4	0.90
Duration of initial gefitinib treatment (median, months)	19.4	10.6	0.59
Interval between initial and rechallenge gefitinib administrations (median, months)	8.8	5.5	0.10
MST of gefitinib rechallenge (months)	NR	12.8	0.03

Abbreviations: SD, stable disease; Pt, patient; PS, performance status; Ad, adenocarcinoma; Sq, squamous cell carcinoma; La, large-cell carcinoma; Rec, recurrence; MST, median survival time; NR, not reached.

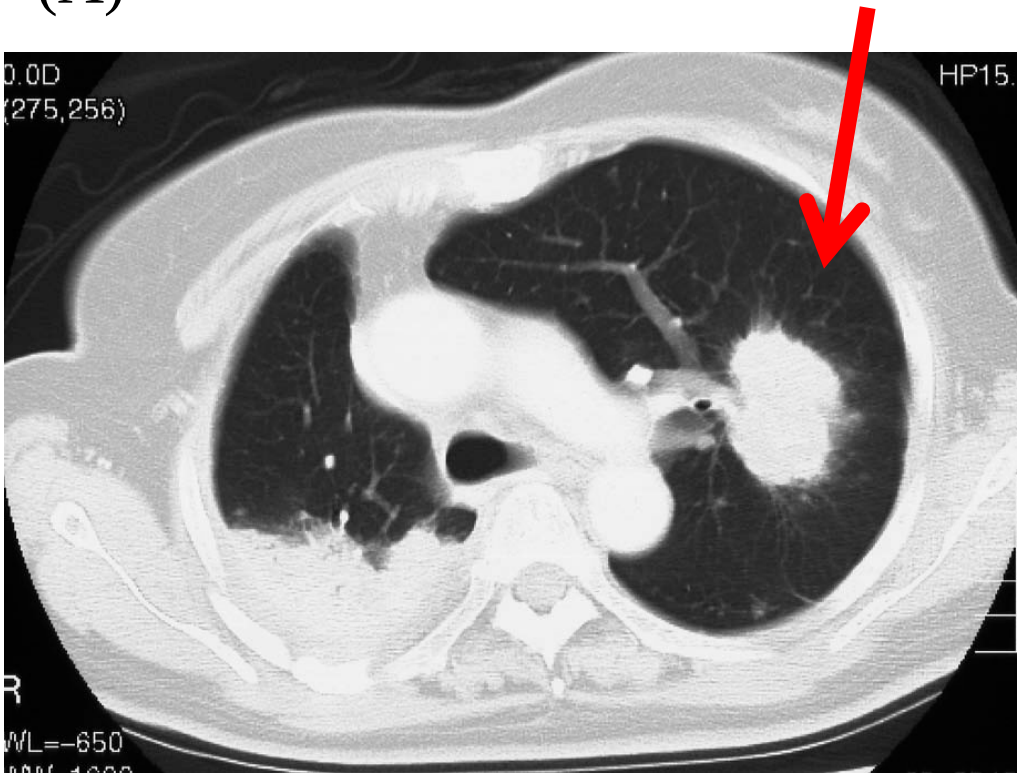
Figure Legends

Figure 1. Primary lesion in Patient 5 (Arrow). A) Before gefitinib readministration. B) After 45 days of gefitinib readministration.

Figure 2. Overall survival (A) and progression-free survival (B) for all eligible patients (n=16), calculated according to the Kaplan-Meier method. Median survival time was 14.7 months (95%CI, 11.1-15.5 months) and median progression-free survival was 2.5 months (95%CI, 1.6-3.2 months).

Figure 1

(A)



(B)

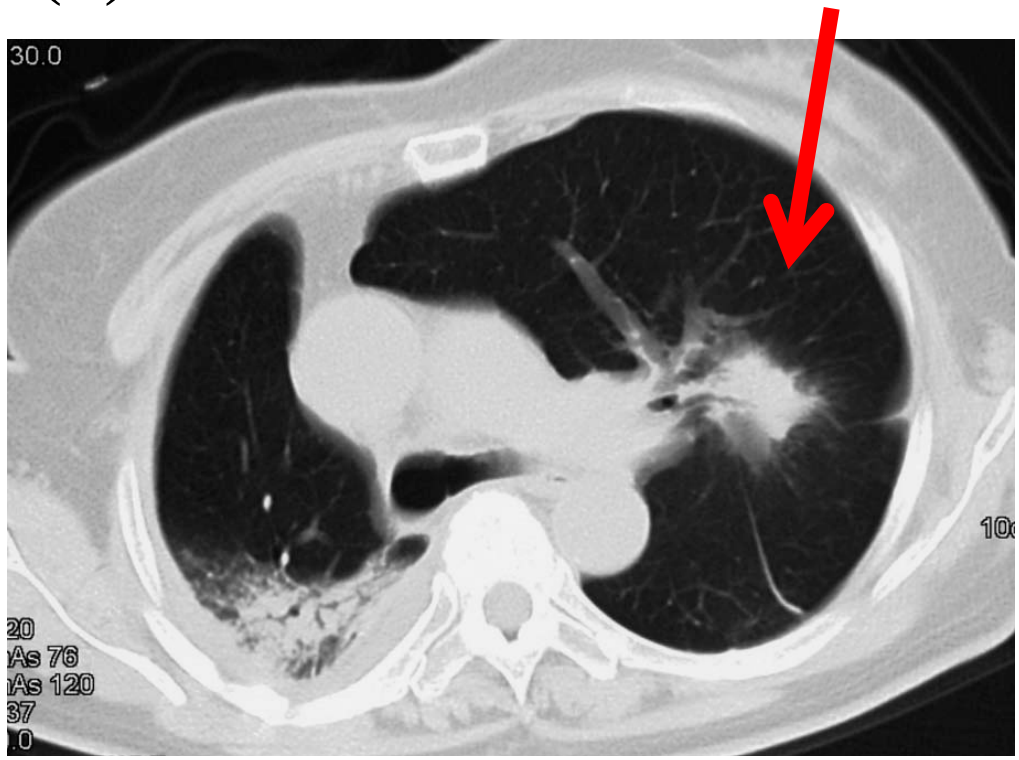
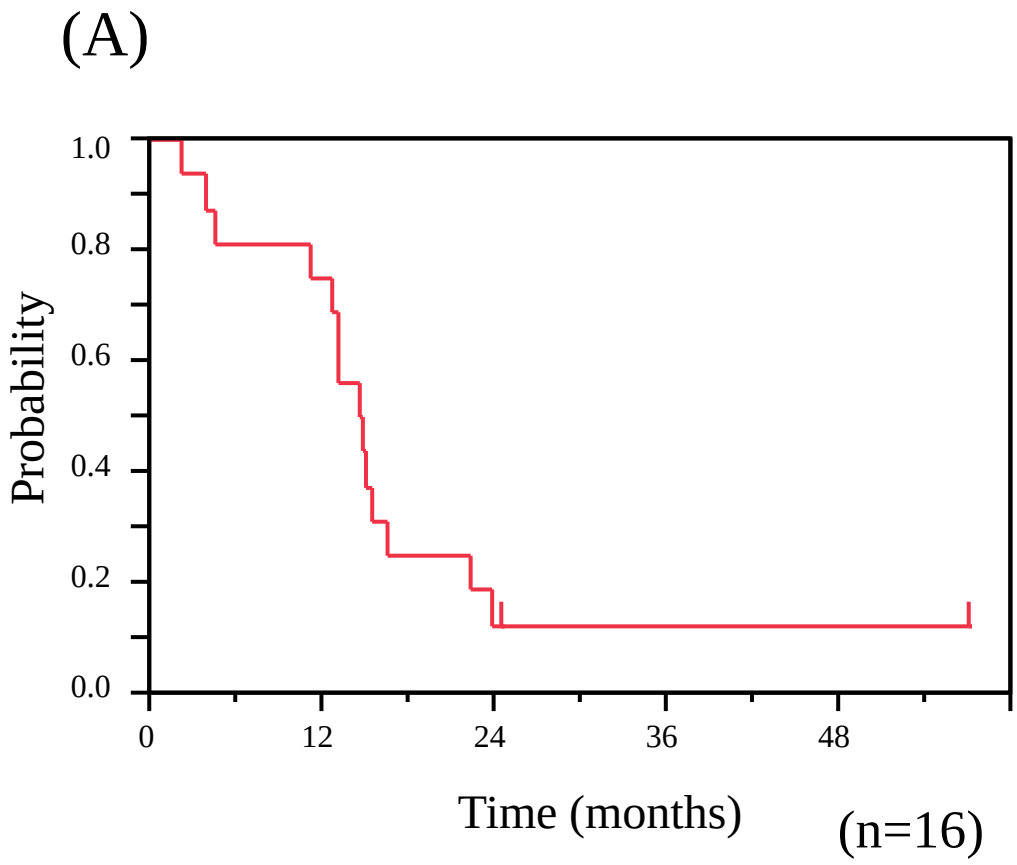
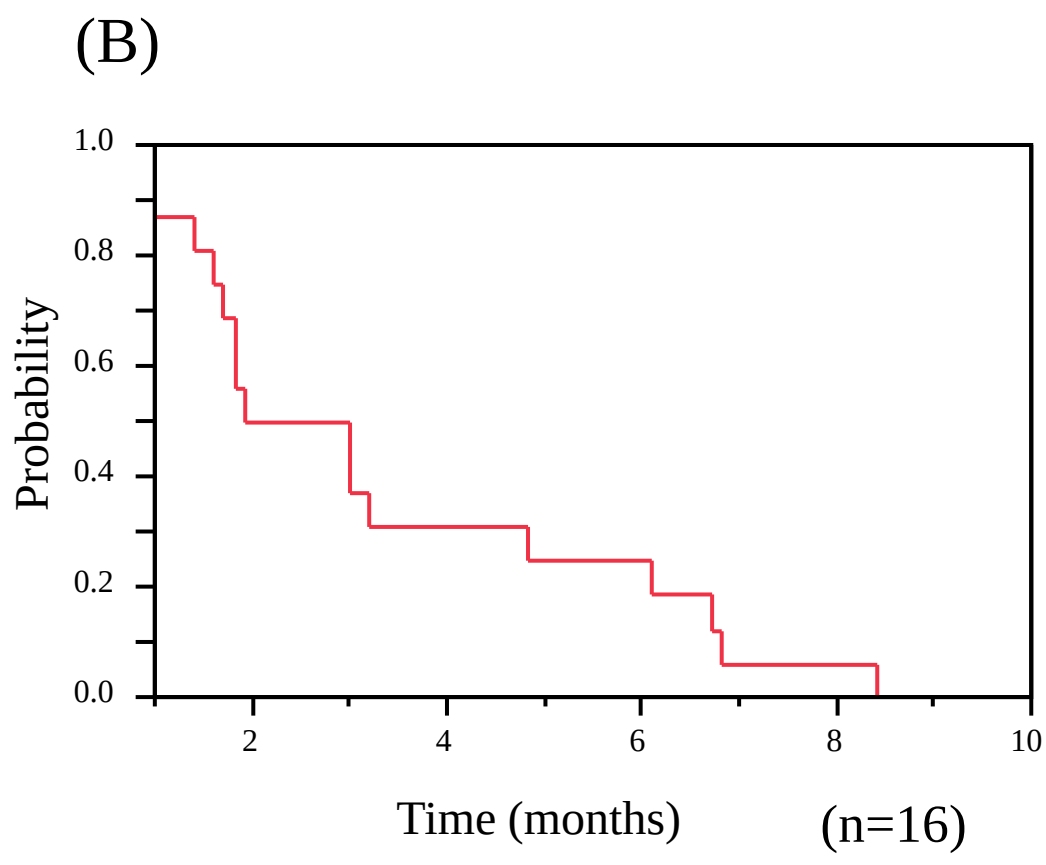


Figure 2


(A)
1.0
0.8
0.6
0.4
0.2
0.0
Probability
0
12
24
36
48
Time (months)
(n=16)


(B)
1.0
0.8
0.6
0.4
0.2
0.0
Probability
2
4
6
8
10
Time (months)
(n=16)