Table 2 Hematologic Toxicities of Grade ≥ 3

	Arm A (n = 32) (AMR)				Arm B (n = 30) (C + E)				
	3	4	≥3	(%)	3	4	≥3	(%)	*P*[a]
Leukopenia	15	10	25	(78)	10	4	14	(47)	.017
Neutropenia	8	21	29	(91)	9	15	24	(80)	.294
Febrile Neutropenia	11	0	11	(34)	1	0	1	(3)	.003
Lymphopenia	11	0	11	(34)	4	0	4	(13)	.076
Thrombocytopenia	5	1	6	(19)	4	3	7	(23)	.759
Anemia	7	1	8	(25)	7	0	7	(23)	1.000

Abbreviations: AMR = amrubicin; C + E = carboplatin/etoposide.
[a]Fisher exact test.

60 evaluable patients per arm were needed to obtain 90% power. Thus, the sample size was determined to be 130 patients (65 per arm).

QOL was evaluated using the score on the LCS of the FACT-L and the EQ-5D utility index. The changes in QOL scores from baseline to each time point were compared between arms A and B using analysis of covariance (ANCOVA). A repeated-measures analysis of variance (ANOVA) was used to evaluate the difference in QOL score curves between the 2 arms. The quality-adjusted life-year (QALY) value was calculated from the area under a line drawn with survival time on the horizontal axis and the EQ-5D utility index on the vertical axis. QALYs in the 2 arms were compared by log-rank test and generalized Wilcoxon test.

Results

Enrollment

Between July 4, 2006, and September 5, 2007, 21 and 22 patients were enrolled in arms A and B, respectively. Two patients in arm A treated with amrubicin at 45 mg/m^2/d died from severe infection associated with grade 4 neutropenia (sepsis in the first cycle in one patient and pneumonia in the third cycle in the other). There were no treatment-related deaths in arm B. The dose of amrubicin was reduced to 40 mg/m^2/d in subsequent cycles in 4 of 8 patients who started at 45 mg/m^2/d. After a recommendation from the Data Monitoring Committee (DMC), the protocol was amended and amrubicin was administered at 40 mg/m^2/d in all patients registered in arm A thereafter. From December 2007 to April 2008, 11 and 8 patients were added to arms A and B, respectively. Of these patients, one in arm A died of amrubicin-induced pneumonitis. Enrollment of patients was then terminated early after a DMC recommendation. Thus, 32 and 30 patients were enrolled in arms A and B, respectively (Fig. 1). Patient characteristics were well-balanced between the arms (Table 1). No patients had received palliative radiotherapy before the study registration except for one patient in arm B, who had received whole-brain irradiation for brain metastases.

Table 3 Nonhematologic Toxicities of grade ≥ 3

	Arm A (n = 32) (AMR)					Arm B (n = 30) (C + E)			
	3	4	5	≥3	(%)	3	≥3	(%)	*P*[a]
Fatigue	0	1	0	1	(3)	1	1	(3)	1.000
Nausea	0	0	0	0	(0)	1	1	(3)	.484
Anorexia	3	0	0	3	(9)	3	3	(10)	1.000
Paralytic Ileus	0	1	0	1	(3)	0	0	(0)	1.000
Bacterial Pneumonia	3	0	1	4	(13)	3	3	(10)	1.000
Sepsis	0	0	1	1	(3)	0	0	(0)	1.000
Other Neutropenic Infection	1	0	0	1	(3)	1	1	(3)	1.000
Other Nonneutropenic Infection	0	0	0	0	(0)	3	3	(10)	.107
Interstitial Lung Disease	3	0	1	4	(13)	0	0	(0)	.114
Cardiotoxicity	0	0	0	0	(0)	1	1	(3)	.484
Cerebrovascular Stroke	1	0	0	1	(3)	0	0	(0)	1.000
Cholecystitis	0	1	0	1	(3)	0	0	(0)	1.000
Elevated ALT	0	0	0	0	(0)	1	1	(3)	.484
Hyperbilirubinemia	0	0	0	0	(0)	1	1	(3)	.484
Hypokalemia	0	0	0	0	(0)	1	1	(3)	.484
Hyponatremia	4	0	0	4	(13)	2	2	(7)	.672
Miscellaneous	4	0	0	4	(13)	2	2	(7)	.672

No grade 4 or 5 nonhematologic toxicity occurred in arm B.
Abbreviations: ALT = alanine aminotransferase; AMR = amrubicin; C + E = carboplatin/etoposide.
[a]Fisher exact test.

Figure 2 Time to Progression in Arm A (Amrubicin, n = 31; Pink) and Arm B (Carboplatin/Etoposide, n = 30; Blue). The Median Times to Progression Were 4.7 Months and 4.4 Months for Arms A and B, Respectively (P = .28 by log-Rank Test)

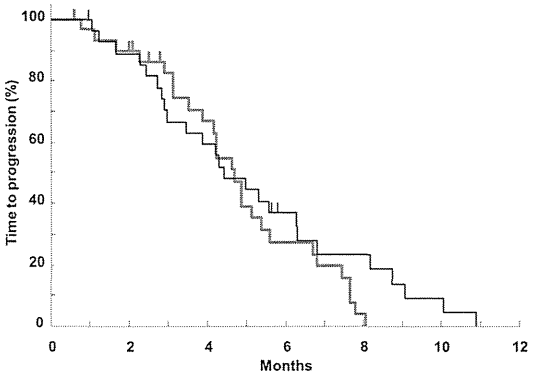
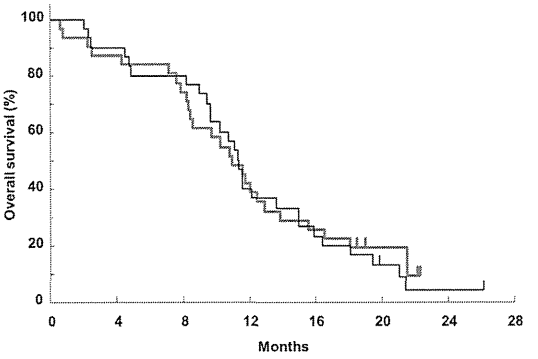


Figure 3 Overall Survival in Arm A (Amrubicin, n = 31; Pink) and Arm B (Carboplatin/Etoposide, n = 30; Blue). The Median Survival Times Were 10.9 Months and 11.3 Months for Arms A and B, Respectively (P = .74 by log-Rank Test)



Treatment Delivery

The median number of chemotherapy cycles per patient was 4 (range, 1-6) in both arms, and the total number of cycles was 130 in arm A and 120 in arm B. The dose of chemotherapy for subsequent cycles was reduced in 14 (44%) of 32 patients in arm A. Thus, the dose of amrubicin was 45 mg/m^2 in 23 cycles (18%), 40 mg/m^2 in 71 cycles (55%), and 35 mg/m^2 in 36 cycles (28%). Dose reduction was required in 12 (40%) of 30 patients in arm B. Full doses of carboplatin/etoposide were administered in 89 cycles (74%), but the doses were reduced to AUCs of 4 mg·min/mL for carboplatin and 60 mg/m^2 for etoposide in 31 cycles.

Although it was not provided in the protocol, 2 patients in arm B received prophylactic cranial irradiation before disease progression, but none in arm A did so.

Toxicity

Grade 3 febrile neutropenia occurred in 34% of patients in arm A but in only 3% of patients in arm B (P = .003) (Table 2). Bacterial pneumonia and sepsis developed during grade 4 neutropenia in one patient each in arm A, and they were fatal (grade 5). Another patient (a 78-year-old man) developed grade 5 interstitial lung disease and died from respiratory failure on the 23rd day of amrubicin chemotherapy. His underlying pulmonary diseases were emphysema and mild interstitial pneumonitis detected by chest CT scan before chemotherapy. In contrast, there was one case with grade 1 interstitial lung disease, but no grade 2 or severe cases, in arm B (Table 3).

Efficacy

One patient in arm A was excluded from the analysis of efficacy because of a violation of the exclusion criteria owing to drainage of pleural effusion before treatment (see Fig. 1). The median TTP was 4.7 months (CI, 3.9-5.4) in arm A and 4.4 months (CI, 3.0-6.3) in arm B (P = .279) (Fig. 2). The median OS was 10.9 months (CI, 8.4-12.9) in arm A and 11.3 months (CI, 9.6-14.9) in arm B (P = .735) (Fig. 3). The HR for OS was 0.87 (CI, 0.51-1.48). Thus, noninferiority of amrubicin compared with carboplatin/etoposide was not found in this study. There were 3 patients in arm A and 4 patients in arm B in whom response was not evaluable because they received only one cycle of chemotherapy owing to severe toxicity. The objective response rates were 74.2% (CI, 55.4-88.1) in arm A and 60.0% (CI, 40.6-77.3) in arm B (P = .283). The same tendency for the response was observed in patients who received amrubicin at doses of 45 mg/m^2 and 40 mg/m^2 (Table 4).

Postprotocol second-line chemotherapy was administered in 13 patients (50%) in arm A and in 19 patients (63%) in arm B (Table 5).

Quality of Life

The mean (± standard deviation) QOL scores at each time point for the 2 treatment arms are shown in Figure 4. The scores for the LCS of the FACT-L and the EQ-5D utility index in arm B indicated a better QOL than those in arm A at several time points; however, ANCOVA found no significant difference at any time

Table 4 Tumor Response

Treatment	CR	PR	SD	PD	NE	Response Rate (%) (95% CI)
Amrubicin (n = 31)	0	23	3	2	3	74.2 (55.4-88.1)
45 mg/m^2 (n = 8)	0	5	2	0	1	
40 mg/m^2 (n = 23)	0	18	1	2	2	
Carboplatin/Etoposide (n = 30)	0	18	4	4	4	60.0 (40.6-77.3)

Abbreviations: CR = complete response; NE = not evaluated; PD = progressive disease; PR = partial response; SD = stable disease.

Table 5 Second-Line Chemotherapy After Disease Progression

	Arm A (n = 32) (AMR)		Arm B (n = 30) (C + E)	
Chemotherapy Regimen	**n**	**(%)**	**n**	**(%)**
Carboplatin/Etoposide	13	(41)	6	(20)
Amrubicin	2	(6)	10	(33)
Irinotecan	1	(3)	1	(3)
Topotecan	0		2	(7)
None	16	(50)	11	(37)

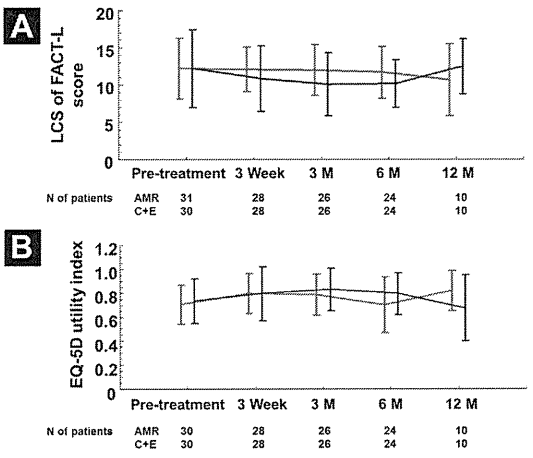
Abbreviations: AMR = amrubicin; C + E = carboplatin/etoposide.

point (LCS score: $P = .171$, .080, .112, and .371; EQ-5D utility index: $P = .171$, .080, .112, and .371 for 3 weeks and 3, 6, and 12 months after the start of chemotherapy, respectively). The repeated-measures ANOVA also found no significant difference between the arms for LCS scores ($P = .067$) and the EQ-5D utility index ($P = .865$). In the analysis of QALY, there was no significant difference between the arms by log-rank test ($P = .716$) and generalized Wilcoxon test ($P = .959$) (Table 6).

Discussion

This study was planned to test for the noninferiority of monotherapy with amrubicin compared with combination therapy with carboplatin/etoposide, in terms of overall survival. The toxicity of amrubicin was initially considered to be mild, because single-agent chemotherapy generally has toxicity milder than that of multiple-agent regimens and because a previous phase II study[7] of amrubicin monotherapy at a dose of 45 mg/m^2 for 3 days in patients with ED-SCLC found tolerable myelotoxicity. In this previous trial, 13 patients (39% of the study population) were ≥ 70 years old, and the oldest patient was 78 years old. Grade 3 to 4 leukopenia and neutropenia were noted in 52% and 85% of patients, respectively, with no febrile neutropenia or treatment-related death. One patient developed interstitial pneumonia after the second cycle, but this was resolved by steroid therapy and cessation of amrubicin treatment.[7]

Figure 4 Quality of Life (QOL) in Arm A (Amrubicin; Pink) and Arm B (Carboplatin/Etoposide; Blue) Based on the Lung Cancer Subscale (LCS) of the Functional Assessment of Cancer Therapy-Lung (FACT-L) (A) and Euro-QOL 5-Dimension (EQ-5D) Utility Index (B). The QOL Scores at Each Time Point are Shown as Mean ± Standard Deviation. A Lower LCS Score on the FACT-L and a Higher EQ-5D Utility Index Indicate a Better QOL



Abbreviations: AMR = amrubicin; C + E = carboplatin/etoposide.

For these reasons, the starting dose of 45 mg/m^2 on days 1 to 3 every 3 to 4 weeks for patients aged 70 to 74 years in the current study was considered reasonable. However, leukopenia and neutropenia in the amrubicin arm were severer than expected. The incidence of grade 3 to 4 leukopenia was as high as 80%; febrile neutropenia developed in 34% of patients; and treatment-related deaths from neutropenia-associated infection occurred in 2 patients who received amrubicin at 45 mg/m^2 for 3 days. A retrospective comparison of amrubicin chemotherapy at 30 to 40 mg/m^2 for 3 days between patients aged ≥ 70 and < 70 years found that the mean number of treatment cycles, mean dose, and mean interval of amrubicin administration, as well as hematologic toxicity, did not differ between the 2 age groups.[15] In another retrospective case series, amrubicin at 35 to 40 mg/m^2 for 3 days was also well tolerated in patients aged > 75 years, without treatment-related death.[16] Thus, the dose of amrubicin is critical for development of serious neutropenia.

In this study, 4 patients developed grade 3 to 5 interstitial lung disease in arm A, whereas no grade 3 or severe lung disease occurred in arm B. Yoh et al[17] recently summarized 7 cases of amrubicin-associated interstitial lung disease in a review of 100 cases of SCLC treated with amrubicin monotherapy. The incidences of interstitial lung disease were 3% and 33% in patients without and with pre-existing pulmonary fibrosis, respectively. These results are consistent with the present study's finding that a patient who developed fatal interstitial lung disease had pulmonary fibrosis before amrubicin chemotherapy. Preexisting pulmonary fibrosis is a risk factor for chemotherapy-associated interstitial lung disease, with odds ratios of approximately 5 and 25 for mild and severe preexisting pulmonary fibrosis, respectively.[18] Any type of anticancer agent can cause severe

Table 6 Quality-Adjusted Life-Years (QALY)

Arm	No. of Patients	QALY, Median	P^a	P^b
A (AMR)	30	0.745	–	–
B (C + E)	30	0.714	.716	.959

Abbreviations: AMR = amrubicin; C + E = carboplatin/etoposide.
[a]Log-rank test.
[b]Generalized Wilcoxon test.

interstitial lung disease in patients with preexisting pulmonary fibrosis, including platinum-containing drugs and etoposide.[19] Because pulmonary fibrosis is common among elderly people, the indication of chemotherapy with amrubicin and other chemotherapeutic agents may be limited in elderly patients with SCLC.

This study was performed as a registration-directed industry-sponsored clinical trial in Japan that meets Japanese Good Clinical Practice Guidelines and the Pharmaceutical Affairs Law. However, the trial failed to provide sufficient information on the efficacy and safety of amrubicin because of early termination due to excessive toxicity in the experimental arm (arm A). Similarly, a subset analysis of a phase III trial of carboplatin and paclitaxel with or without bevacizumab in patients with advanced non–small-cell lung cancer found that bevacizumab was significantly associated with grade 3 to 5 toxicities and no overall survival benefit in elderly patients.[20] Many of the elderly patients had preexisting comorbid conditions that may have adversely affected organ function and influenced functional status. Thus, it is important to exclude patients with poor general conditions to avoid trials with inappropriate populations for evaluation of the efficacy of new anticancer agents.

Conclusion

Amrubicin monotherapy at 40 to 45 mg/m^2 was toxic and intolerable in elderly Japanese patients with ED-SCLC.

Clinical Practice Points

- SCLC has an extremely poor prognosis, and elderly patients (≥ 70 years old) account for approximately 30% to 40% of SCLC at diagnosis.
- Amrubicin, a third-generation synthetic anthracycline, has shown promising efficacy in phase II studies with patients with ED-SCLC at 45 mg/m^2/d for 3 consecutive days every 3 weeks.
- In this study, the efficacy and safety of amrubicin were evaluated by comparison with carboplatin/etoposide combination therapy in elderly Japanese patients with ED-SCLC. The trial was prematurely closed owing to 3 treatment-related deaths in the amrubicin arm. Noninferiority of OS and TTP of amrubicin compared with carboplatin/etoposide was not found in this study.
- Amrubicin monotherapy at 40 to 45 mg/m^2 was toxic and intolerable for elderly patients with ED-SCLC. More attention should be paid to the elderly patients with preexisting pulmonary fibrosis in amrubicin-containing chemotherapy.

Acknowledgments

The authors thank all the patients, their families, and all investigators who participated in the trial.

Disclosure

The study was sponsored by Dainippon Sumitomo Pharma Co Ltd, Osaka, Japan. Dr Fukuoka received an advisory fee from Dainippon Sumitomo Pharma Co Ltd. All other authors state that they have no conflicts of interest.

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A randomized phase III study of cisplatin (CDDP), etoposide (ETOP) and irinotecan versus topotecan as second-line chemotherapy in patients with sensitive relapsed small-cell lung cancer (SCLC): Japan Clinical Oncology Group study JCOG0605

Subcategory:
Small Cell Lung Cancer

Category:
Lung Cancer - Non-Small Cell Local-Regional/Small Cell/Other Thoracic Cancers

Meeting:
2014 ASCO Annual Meeting

Session Type and Session Title:
Oral Abstract Session, Lung Cancer - Non-small Cell Local-regional/Small Cell/Other Thoracic Cancers

Abstract Number:
7504

Citation:
J Clin Oncol 32:5s, 2014 (suppl; abstr 7504)

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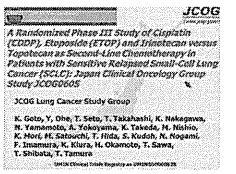

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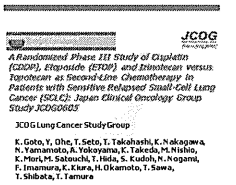

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Abstract:

Background: ETOP and irinotecan are drugs known to exert promising activity in SCLC. A phase II study of weekly chemotherapy using a combination of CDDP, ETOP and irinotecan (PEI), which are known to inhibit both topoisomerase I and II, showed quite favorable outcome in patients with sensitive relapsed SCLC. A phase III study confirming the superiority of PEI over topotecan as second-line chemotherapy in patients with sensitive relapsed SCLC was conducted. **Methods:** SCLC patients who responded to first-line treatment and relapsed/progressed more than 90 days after the completion of first-line treatment were eligible for this study. Additional eligibility criteria included age 20-75 years, PS of 0-2, and adequate organ functions. Patients were randomized 1:1 to PEI, which consisted of CDDP (25 mg/m^2) weekly for 10 weeks, ETOP (60 mg/m^2) for 3 days on weeks 1, 3, 5, 7, and 9, and irinotecan (90 mg/m^2) on weeks 2, 4, 6, 8 and 10 with granulocyte colony-stimulating factor support, or to topotecan (1.0 mg/m^2) on days 1-5, every 3 weeks for 4 courses. The primary endpoint was overall survival. The planned sample size was 180 patients, to attain 80% power with a one-sided alpha of 5%. **Results:** From Sep. 2007 to Nov. 2012, 180 patients were randomized to topotecan (n=90) and PEI (n=90): median age 64 (44-75) years; M/F 155/25; LD/ED 45/135; PS 0-1/2 175/5. The overall survival was significantly longer in the PEI arm than in the topotecan arm (HR 0.67; 90% CI 0.51-0.88; p=0.0079) with MST 18.2 months vs. 12.5 months. PFS was also significantly longer in the PEI arm (HR 0.50; 95% CI 0.37-0.68; p<0.0001) with the median PFS 5.7 months vs. 3.6 months. Grade 3/4 adverse events in PEI and topotecan arms, respectively, were: neutropenia 83.3% vs. 85.6%; anemia 84.4% vs. 27.8%; thrombocytopenia 41.1% vs. 27.8%; diarrhea 7.8% vs. 0%; febrile neutropenia 31.1% vs. 6.7%. There was 1 treatment-related death in the PEI arm, and 2 in the topotecan arm. **Conclusions:** The combination chemotherapy with CDDP, ETOP and irinotecan should be considered as the standard second-line chemotherapy for sensitive relapsed SCLC. Clinical trial information: 000000828.

Abstracts by Koichi Goto:

Tolerability study of adjuvant modified FOLFOX6 treatment in curatively resected stage II/III colon cancer (JFMC41-1001-C2: JOIN trial).

Meeting: 2014 Gastrointestinal Cancers Symposium | **Abstract No:** 530 | **First Author:** Katsunori Shinozaki

Category: Cancers of the Colon and Rectum - Multidisciplinary Treatment

A new nationwide genomic screening system in Japan for the development of targeted therapies against advanced non-small lung cancers with rare driver mutations.

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A prospective, multicenter phase II trial of low-dose erlotinib monotherapy for patients with previously treated non-small cell lung cancer (NSCLC) with activating mutation of epidermal growth factor receptor (EGFR): Thoracic Oncology Research Group (TORG) 0911.

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Lung Cancer - Non-Small Cell Metastatic

Category:
Lung Cancer - Non-Small Cell Metastatic

Meeting:
2014 ASCO Annual Meeting

Session Type and Session Title:
General Poster Session, Lung Cancer - Non-Small Cell Metastatic

Abstract Number:
8080

Citation:
J Clin Oncol 32:5s, 2014 (suppl; abstr 8080)

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Abstract Disclosures

Abstract:

Background: Erlotinib and gefitinib have been shown to have similar activity for EGFR mutation-positive (EGFRm+) NSCLC. Since the steady-state plasma trough concentration of erlotinib is approximately 3.5 times higher than that of gefitinib when administered at the respective approved dose, treatment with low-dose erlotinib may be as effective as full-dose therapy, with less toxicity and cost. **Methods:** Eligible patients had

advanced EGFRm+ NSCLC with 1 to 3 prior chemotherapy treatments. Erlotinib with the initial daily dosage of 50 mg was administered. Dose was escalated to 150 mg in case of not achieving CR or PR by RECIST criteria at the evaluation after the first 4 weeks of treatment. Erlotinib was continued until disease progression or unacceptable toxicities. The primary endpoint was independent committee-determined objective response rate (ORR) to the low-dose erlotinib, with target ORR of 70% and threshold of 50%. The sample size was calculated to be 40, and the primary endpoint was met if 26 or more patients responded. **Results:** Thirty-four patients were enrolled between Apr. 2010 and Nov. 2012. Males/females 20/14; median age 67 (range 38-81); PS 0/1 16/18; Ad/Sq 33/1. One patient was excluded from evaluation due to absence of active tumor. The study was closed early according to the protocol definition when 15 of 33 evaluable patients failed to achieve CR/PR, making it impossible to meet the primary endpoint. ORR was 54.5% (95% C.I.: 36.4% to 71.9%), with disease control rate of 84.8%. Median progression free survival and overall survival were 9.5 months and 28.5 months, respectively. Grade 3 toxicities were 2 cases with transient neutropenia, and 1 with reversible AST/ALT elevation. No grade 4 toxicity or treatment-related death was observed. **Conclusions:** This trial is the first prospective study evaluating low-dose erlotinib. Although it appeared to have a certain efficacy, the primary endpoint was not met. Because of its low toxicity, it may be worth further evaluation in elderly and/or frail patients. Trial registry UMIN #000003313.

Abstracts by Yoshiro Nakahara:

Key components of chemotherapy for thymoma and thymic carcinoma: Anthracycline-, carboplatin-, or cisplatin-based chemotherapy.

Meeting: 2014 ASCO Annual Meeting | **Abstract No:** e18556 | **First Author:** Yusuke Okuma

Category: Lung Cancer - Non-Small Cell Local-Regional/Small Cell/Other Thoracic Cancers - Thymic Malignancies

More

Event	ESMO 2014
Session	Poster Display session
Topics	**Anti-Cancer Agents & Biologic Therapy** **Small-Cell Lung Cancer** **Surgery and/or Radiotherapy of Cancer**
Presenter	Yuki Misumi
Citation	Annals of Oncology (2014) 25 (suppl_4): iv511-iv516. 10.1093/annonc/mdu355
Authors	Y. Misumi[1], H. Okamoto[1], K. Naoki[2], Y. Hosomi[3], Y. Takagi[4], T. Kato[5], N. Masuda[6], A. Takakura[7], K. Minato[8], Y. Miura[9], T. Yokoyama[10], S. Takata[11], K. Kishi[12], M. Nishikawa[13], F. Oshita[14], N. Seki[15], I. Goto[16], K. Watanabe[1] **Author Affiliations**

View Poster

Abstract

Aim

The effect of irinotecan in treatments for LD-SCLC in the elderly is unclear, and the optimal timing of TRT when combined with chemotherapy has not been fully evaluated. We report a phase I/II trial of induction chemotherapy with carboplatin and irinotecan followed by sequential TRT in this population?

Methods

Patients with untreated, measurable LD-SCLC >70 years with performance status (PS) 0 to 2 and adequate organ function were eligible. Treatment consisted of induction with carboplatin on day 1 and irinotecan on days 1 and 8 every 21 days for four cycles. TRT of 54Gy in 27 fractions was then administered sequentially. Carboplatin dose was escalated from AUC of 4 to 5 (Levels 1 and 2, respectively)?with a fixed dose of irinotecan at 50 mg/m^2. The primary objective of the phase II portion was evaluation of efficacy.

Results

A total of 41 patients were enrolled [median age 75 years, range 70-86 years; 31 male, 10 female; PS 0/1/2: 22/18/1]. At Level 1 (n=6), one patient experienced dose-limiting toxicity (DLT) as Grade 3 hypertension. At Level 2 (n=6), two patients experienced DLT as Grade 4 thrombocytopenia. Therefore, level 1 was chosen as the recommended dose. The phase II trial was then expanded by 35 patients in the level 1 based on the Simon minimax design. In all cohorts, the median chemotherapy cycle was 4 (1/2/3/4 courses administered as 4/2/2/33); median radiation dose was 54Gy (range 36-60). Toxicities were generally mild, as expected.?Gr 3/4 leukopenia and thrombocytopenia were both observed in six (15%) patients. No Gr 3/4 diarrhea or esophagitis was noted. Although Gr 3 febrile neutropenia and Gr 3 pneumonitis were seen in two patients each, no treatment-related deaths occurred. There were five complete responses and 32 partial responses, for a response rate of 90%. With

median follow-up of 80.4 months (n=41), median progression-free and overall survival times were 12.4 and 27.1 months, respectively.

Conclusions

Induction chemotherapy with carboplatin plus irinotecan followed by sequential TRT was well tolerated and highly active in elderly patients with LD-SCLC. Further confirmatory studies are warranted.

Disclosure

All authors have declared no conflicts of interest.

1236P - Amrubicin (AMR) versus docetaxel (DTX) as second- or third-line treatment for non-small cell lung cancer (NSCLC): A randomized phase III trial

Date 27 September 2014

Event	ESMO 2014
Session	Poster Display session
Topics	**Anti-Cancer Agents & Biologic Therapy** **Non-Small-Cell Lung Cancer, Metastatic**
Presenter	Nobuyuki Katakami
Citation	Annals of Oncology (2014) 25 (suppl_4): iv426-iv470. 10.1093/annonc/mdu349
Authors	N. Katakami[1], H. Yoshioka[2], H. Okamoto[3], Y. Iwamoto[4], T. Seto[5], T. Takahashi[6], N. Sunaga[7], S. Kudoh[8], K. Chikamori[9], M. Harada[10], H. Tanaka[11], H. Saka[12], K. Takeda[13], N. Nogami[14], N. Masuda[15], T. Harada[16], N. Yamamoto[17], K. Nakagawa[18] **Author Affiliations**

View Poster

Abstract

Aim

DTX is one of the standard drugs for patients (pts) with previously treated NSCLC. However, its efficacy seems insufficient. The efficacy of AMR for NSCLC has been previously reported. Thus, we conducted a randomized phase III trial comparing AMR to DTX, sponsored by Dainippon Sumitomo Pharma Co., Ltd.

Methods

We enrolled pts with NSCLC, Eastern Cooperative Oncology Group Performance Status 0-1, undergoing second- or third-line treatment, and aged 20–74 years. Pts were classified by histology, prior treatment, and institution into 2 groups and then randomly assigned (1:1 ratio) to treatment with AMR (35 mg/m^2/day i.v., on days 1–3, q3w) or DTX (60 mg/m^2/day i.v., on day 1, q3w). We planned a sample size of 100 patients per group, with a 2-sided alpha of 5% and power of 90%. We hypothesized a median progression-free survival (PFS) time of 3.3 and 2.0 months for AMR and DTX, respectively. The primary endpoint was PFS; secondary endpoints included overall survival (OS), overall response rate (ORR), disease control rate (DCR), and adverse events according to Common Terminology Criteria for Adverse Events v 4.03.

Results

From October 2010 to June 2012, 202 pts were enrolled from 32 institutions. Patient characteristics were well balanced between both groups. OS was measured after a median follow-up of 13.5 months. Median PFS was 3.6 and 3.0 months with AMR and DTX, respectively (adjusted Hazard Rate (HR) 0.96, 95% Confidence Interval (CI) 0.69–1.34, p = 0.831). Median OS was 14.6 and 13.5 months with AMR and DTX, respectively (adjusted HR 1.02, 95% CI 0.72–1.43, p = 0.933). ORR was 14.8% and 18.8% with AMR and DTX, respectively (p = 0.544). DCR was 55.7% for both AMR and DTX (p = 1.000). The most frequent adverse events (≥grade 3) for AMR and DTX were neutropenia (82.7% and 78.8%, respectively) and leukopenia (63.3% and 70.7%, respectively). Two

treatment-related deaths occurred in the DTX arm: a case of interstitial pneumonia and another of drowning in a bath.

Conclusions

We were not able to demonstrate superiority of AMR over DTX for PFS, despite the 20-day PFS prolongation. Our results suggest that AMR may become a treatment option for patients with previously treated NSCLC.

Disclosure

All authors have declared no conflicts of interest.

1470P - The effect of prophylactic cranial irradiation (PCI) in the patients with extensive-disease small-cell lung cancer (ED-SCLC): Results of a Japanese...

Date 29 September 2014

Event	ESMO 2014
Session	Poster Display session
Topics	**Small-Cell Lung Cancer** **Surgery and/or Radiotherapy of Cancer**
Presenter	Tateaki Naito
Citation	Annals of Oncology (2014) 25 (suppl_4): iv511-iv516. 10.1093/annonc/mdu355
Authors	T. Naito[1], T. Takahashi[1], T. Yamanaka[2], H. Harada[3], T. Seto[4], M. Satouchi[5], S. Oizumi[6], N. Katakami[7], K. Shibata[8], M. Maemondo[9], K. Kiura[10], H. Okamoto[11], K. Minato[12], N. Yamamoto[13] **Author Affiliations**

Abstract

Aim

A previous study has shown that PCI reduced the risk of brain metastases (BM) and prolonged the overall survival (OS) of patients with ED-SCLC (Slotman B et al, NEJM 2007). There were, however, several concerns that arose in association with that study, including the lack of magnetic resonance imaging (MRI) assessment to confirm the absence of BM before enrollment, the use of induction chemotherapy other than platinum, and variations in the radiation doses. The aim of this study is to assess the efficacy and safety of the PCI in the patients with ED-SCLC.

Methods

From March 2009, patients with ED-SCLC who had any response to first-line chemotherapy (platinum agent plus irinotecan or etoposide) were randomized to either PCI (25Gy/10 fractions) or observation (Obs) alone. The patients were required to prove the absence of BM by MRI prior to enrollment. The primary endpoint was OS and a planned sample size of 330 was determined to detect the hazard ratio (HR) of 0.75 at a significance level of 0.05 and a power of 80%. Secondary endpoints included time to BM, progression-free survival (PFS), and adverse effects (AEs).

Results

In July 2013, a preplanned interim analysis was conducted for the survival data of 163 pts from 41 centers. The study was terminated because of futility; with a median follow-up of 9.4 months and 111 observed deaths, the median OS was 10.1 and 15.1 months for PCI (n=84) and Obs (n=79), respectively (HR=1.38, 95%CI= 0.95-2.01; stratified log-rank test, P=0.091). Bayesian predictive probability of showing superiority of PCI over Obs was 0.01%. PCI significantly reduced the risk of BM as compared to Obs (32.4% vs 58.0% at 12 months; Gray's test, P<0.001), whereas PFS was comparable between the two arms (median, 2.2 vs. 2.4 months; HR=1.12, 95%CI=0.82-1.54). No significant difference in AEs greater than Grade 2 was observed between the two arms.

Conclusions

PCI after response to chemotherapy might have a negative impact on OS in pts with ED-SCLC. Updated safety data will be presented at the conference.

Disclosure

All authors have declared no conflicts of interest.

Int J Clin Oncol
DOI 10.1007/s10147-014-0761-8

ORIGINAL ARTICLE

The effect of gefitinib in patients with postoperative recurrent non-small cell lung cancer harboring mutations of the epidermal growth factor receptor

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Received: 14 August 2014 / Accepted: 6 October 2014

Abstract
Background It is unclear whether there is a difference in the effect of gefitinib treatment between patients with postoperative recurrent non-small cell lung cancer (NSCLC) and those with stage IV NSCLC harboring mutations in the epidermal growth factor receptor (EGFR).
Methods We retrospectively reviewed the medical records of consecutive patients with postoperative recurrent NSCLC (postoperative group) or stage IV NSCLC (stage IV group) harboring EGFR mutations who were treated with gefitinib at the Shizuoka Cancer Center between September 2002 and March 2012 to compare the effect of gefitinib on survival from treatment initiation.
Results A total of 168 patients were treated with gefitinib (postoperative group, 49 patients; stage IV group, 119 patients). The response rate of gefitinib treatment in the postoperative group was similar to that in the stage IV group (58 vs. 61 %, $p = 0.613$). In contrast, median progression-free survival (PFS; 15.8 vs. 9.8 months, $p < 0.001$) and median overall survival (OS; 51.1 vs. 22.2 months, $p < 0.001$) were significantly longer in the postoperative group. In addition, postoperative recurrent disease, performance status (0–1), and a single metastatic organ were independent favorable prognostic factors in the multivariate analysis of survival.
Conclusions PFS and OS were superior in patients with postoperative recurrent NSCLC harboring EGFR mutations treated by gefitinib than in those with stage IV disease. These results suggest that postoperative recurrent disease may be considered a stratification factor in clinical trials for NSCLC with EGFR mutations.

Keywords Non-small cell lung cancer · Epidermal growth factor receptor mutations · Postoperative recurrence · Stage IV · Gefitinib

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Introduction

Surgical resection is considered the most effective treatment for early stage non-small cell lung cancer (NSCLC), and can provide the best opportunity for cure and to improve survival. However, despite complete surgical resection, 50–60 % of patients with stage I–IIIA NSCLC relapse and die [1, 2]. Postoperative NSCLC relapse is seldom curable, and the median survival time after recurrence

Published online: 25 October 2014

is estimated at 8.1–17.7 months [3, 4]. An optimal treatment strategy for postoperative recurrence is designed for each patient to relieve clinical symptoms, maintain quality of life, and delay disease progression.

Gefitinib is an oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor with reported efficacy in limited populations, harboring EGFR mutations including activating mutations such as a deletion in exon 19 and the L858R point mutation in exon 21 [5]. Several clinical trials in patients with advanced NSCLC harboring EGFR mutations have demonstrated that as compared with chemotherapy, gefitinib results in significantly longer progression-free survival (PFS) and higher response rates [6, 7]. According to these results, gefitinib can be considered a standard therapy for patients with stage IV NSCLC harboring EGFR mutations.

Therefore, gefitinib is frequently used for treatment of patients with postoperative recurrent NSCLC harboring EGFR mutations in clinical practice, in accordance with treatment for patients with stage IV NSCLC. However, it remains unclear whether there is a difference in the effect of gefitinib treatment between patients with postoperative recurrent NSCLC and patients with stage IV NSCLC harboring EGFR mutations. The objectives of this retrospective study were to evaluate the effect of gefitinib on survival in these two patient groups.

Patients and methods

Patients

We retrospectively reviewed clinical data from the medical records of consecutive patients with postoperative recurrent or stage IV NSCLC harboring EGFR mutations, who were treated with gefitinib, at the Shizuoka Cancer Center between September 2002 and March 2012. Gefitinib was administered at 250 mg/day until disease progression or unacceptable toxicity. Treatment change such as dose reduction or skipping was based on the physician's decision. Patients were excluded if they had received other EGFR tyrosine kinase inhibitors before gefitinib administration.

Evaluation of patient characteristics

All pretreatment and treatment parameters were compared between the following two groups: one group with postoperative recurrent NSCLC (postoperative group) and a second group with stage IV NSCLC at diagnosis (stage IV group). All patients underwent systematic evaluation and standardized staging procedures before the start of systemic treatment. Clinical stage was assigned based on the results of physical examination, chest radiography, computed tomography scans of the chest and abdomen, computed tomography or magnetic resonance imaging of the brain, and bone scintigraphy or positron emission tomography. Patients were excluded if they had only postoperative local recurrence without distant metastases. Performance status (PS) was evaluated based on the Eastern Cooperative Oncology Group (ECOG) PS scale. EGFR mutations were examined by commercial clinical laboratories. Only one patient with a single brain metastasis was diagnosed as pathological stage IV NSCLC and was included in the postoperative group. Although both the primary lesion and brain metastasis were completely resected, the patient experienced postoperative disease recurrence. On the other hand, patients who had received only exploratory thoracotomy were included in the stage IV group. Adjuvant chemotherapy in the postoperative group was not considered as first-line chemotherapy in this study. If patients had symptomatic brain metastases, we selected stereotactic radiotherapy or whole brain radiotherapy before gefitinib treatment in our institution.

Evaluation of efficacy

The response to gefitinib treatment was evaluated according to the guidelines of the Response Evaluation Criteria in Solid Tumors version 1.1 [8]. After the start of gefitinib, chest radiography was performed at 1-monthly intervals. Also, computed tomography of the chest and abdomen was performed every 2–3 months. When patients had been treated with gefitinib longer than 1 year, the frequency of radiological examinations was suitably adjusted according to the physician's judgment. If disease progression was suspected by chest radiography, additional computed tomography was performed as necessary. When clinical signs and symptoms suspicious for brain and bone involvement were present, magnetic resonance imaging of the brain and positron emission tomography were performed based on the physician's decision. PFS was defined as the period between the start of gefitinib treatment and progressive disease or death from any cause. Overall survival (OS) was defined as the period between the start of gefitinib treatment and the date of death from any cause.

Statistical analyses

The chi-squared and Mann–Whitney U tests were used to evaluate differences in categorical and continuous variables between the two groups, respectively. OS and PFS were evaluated using the Kaplan–Meier method and compared using the log-rank test. Cox proportional hazards models were used to adjust for potential confounding factors. A p value of <0.05 was considered statistically significant. All

analyses were performed using JMP 10 for Windows statistical software (SAS Institute Japan Inc., Tokyo, Japan). This study was approved by the institutional review board of Shizuoka Cancer Center.

Results

Patient characteristics

A total of 168 patients with postoperative recurrent NSCLC (49 patients, 29.2 %) or stage IV NSCLC (119 patients, 70.8 %) were included in this study. In the postoperative group, pathological stages I, II, III, IV, and multiple primary sites were noted in 14 (28.6 %), 17 (34.7 %), 15 (30.6 %), 1 (2.0 %), and 2 (4.1 %) patients, respectively. The median interval from surgical resection for the primary disease to the start of cytotoxic chemotherapy or gefitinib was 17.0 months. The baseline characteristics stratified by the groups are summarized in Table 1. The distribution of gender and age were similar between the two groups.

Table 1 Patient characteristics at the start of gefitinib treatment

	Postoperative group ($n = 49$) *n* (%)	Stage IV group ($n = 119$) *n* (%)	*p*
Sex			0.951
Male	15 (30.6)	37 (31.1)	
Female	34 (69.4)	82 (68.9)	
Age median (range)	71 (42–85)	66 (31–92)	0.077
Performance status			0.049
0–1	43 (87.8)	88 (73.9)	
2–4	6 (12.2)	31 (26.1)	
Smoking status			0.479
Never	31 (63.3)	82 (68.9)	
Previous/current	18 (36.7)	37 (31.1)	
Histology			–
Adenocarcinoma	46 (93.9)	119 (100)	
Nonadenocarcinoma	3 (6.1)	0	
Type of EGFR mutation			0.970
Exon 19 deletion	25 (51.0)	59 (49.6)	
L858R	20 (40.8)	49 (41.2)	
Other	4 (8.2)	11 (9.2)	
Prior chemotherapy before gefitinib treatment			0.525
No	35 (71.4)	79 (66.4)	
Yes	14 (28.6)	40 (33.6)	

EGFR epidermal growth factor receptor

Patients in the postoperative group showed better PS than those in the stage IV group ($p = 0.049$). Almost all patients were pathologically diagnosed with adenocarcinoma. The type of EGFR mutation did not differ between the two groups. About 30 % patients in both groups received cytotoxic chemotherapy before gefitinib treatment.

Metastatic sites

Metastatic sites stratified by the groups are summarized in Table 2. At the start of gefitinib treatment, 20 (40.8 %) patients in the postoperative group and 71 (59.7 %) in the stage IV group had multiple metastatic organs. Patients in the stage IV group had significantly more metastatic organs than those in the postoperative group ($p = 0.033$). The predominant metastatic organs differed between the two groups: bone and liver metastases were more common in the stage IV group ($p < 0.001$ and $p = 0.034$, respectively), while pulmonary metastases were more common in the postoperative group ($p = 0.003$).

Responses and survival

The median follow-up period from the start of gefitinib treatment was 24.6 months. Of the 168 patients, 153 (91.1 %) were observed until disease progression and 103 (61.3 %) until death. The response rate (RR) of gefitinib treatment in the postoperative group was comparable with that in the stage IV group (57.1 vs. 61.3 %, $p = 0.613$). However, the median PFS was significantly longer in the postoperative group than in the stage IV group (15.8 vs. 9.8 months, $p < 0.001$) (Fig. 1). The median OS was also significantly superior in the postoperative group than in the stage IV group (51.1 vs. 22.2 months, $p < 0.001$) (Fig. 2).

Prognostic factors

The results of univariate and multivariate analyses for OS are shown in Table 3. In the univariate analysis for OS, postoperative group, PS (0–1), and a single metastatic organ were associated with favorable survival. Multivariate analysis showed that postoperative group (hazard ratio (HR) 0.389, 95 % confidence interval (CI) 0.220–0.657, $p < 0.001$), PS (0–1) (HR 0.461, 95 % CI 0.272–0.787, $p = 0.005$), and a single metastatic organ (HR 0.442, 95 % CI 0.279–0.690, $p < 0.001$) were independent favorable prognostic factors.

Discussion

In our study, the RR of gefitinib treatment was comparable between both groups, but PFS and OS were significantly

Table 2 Metastatic sites

	Postoperative group ($n = 49$) n (%)	Stage IV group ($n = 119$) n (%)	p
Number of metastatic organs			0.033
1	29 (59.2)	48 (40.3)	
>2	20 (40.8)	71 (59.7)	
Metastatic sites			
Brain			0.181
No	35 (71.4)	72 (60.5)	
Yes	14 (28.6)	47 (39.5)	
Bone			<0.001
No	34 (69.4)	49 (41.2)	
Yes	15 (30.6)	70 (58.8)	
Lung			0.003
No	27 (55.1)	93 (78.2)	
Yes	22 (44.9)	26 (21.8)	
Liver			0.034
No	48 (98.0)	104 (87.4)	
Yes	1 (2.0)	15 (12.6)	

superior in patients with postoperative recurrent NSCLC harboring EGFR mutations than in those with stage IV disease. To our knowledge, there are only two reports in the literature that have presented similar results. Mitsudomi et al. reported the results of a phase III study (WJTOG3405) that compared the effect of gefitinib with that of cisplatin plus docetaxel in patients with NSCLC harboring EGFR mutations. In this study, 71 of 172 (41.3 %) patients had postoperative recurrent disease. Exploratory analyses of PFS in this study showed that patients with postoperative recurrent disease had a significantly better prognosis than those with stage IIIB/IV disease (HR 0.433, 95 % CI 0.290–0.649, $p < 0.001$) [7]. Sekine et al. conducted a retrospective study to compare the effects of chemotherapy in postoperative recurrent NSCLC patients with those in stage IV NSCLC patients regardless of EGFR mutations. Although the RR of chemotherapy was comparable between postoperative recurrent NSCLC patients and stage IV NSCLC patients, PFS and OS were superior in the former (median PFS; 5.5 vs. 4.2 months, $p = 0.007$ and median OS; 21.3 vs. 13.3 months, $p < 0.001$). Multivariate analysis showed that patients with postoperative recurrent NSCLC had a better prognosis than those with stage IV NSCLC (HR 0.66, 95 % CI 0.540–0.810, $p < 0.001$) [9]. In our study, the HR of the postoperative group to the stage IV group for OS was 0.389 (95 % CI 0.220–0.657, $p < 0.001$). These results suggested that patients with postoperative recurrent NSCLC may have better prognosis than those with stage IV. These results were also confirmed in a report by ECOG [10].

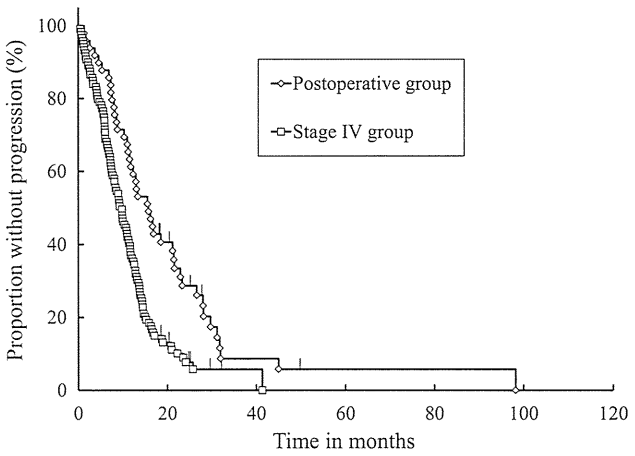

Fig. 1 Progression-free survival of patients in the postoperative ($n = 49$) and stage IV ($n = 119$) groups

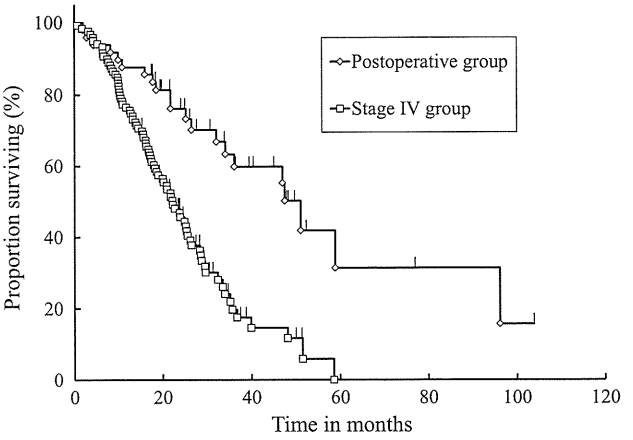

Fig. 2 Overall survival of patients in the postoperative ($n = 49$) and stage IV ($n = 119$) groups

Although the reasons for these results remain unclear, there are several hypotheses. These results may be related to tumor heterogeneity and burden because tumor heterogeneity may contribute to resistance, and small cell subpopulations may acquire or stochastically already possess some features that enable them to emerge under selective drug pressure [11–15]. Most patients with postoperative recurrent NSCLC received regular follow-ups after surgical resection; thus, the tumor burden may be lower than that in patients with stage IV NSCLC at diagnosis. These differences in tumor heterogeneity and burden may be associated with favorable PFS and OS in patients with postoperative recurrent NSCLC [12, 15–17]. In our study, patients in the postoperative group had fewer metastatic sites than those in the stage IV group. The results may support the difference in tumor burden between the two groups [16]. These results suggest that surgical reduction of tumor burden may improve the effectiveness of gefitinib treatment in patients with stage IV NSCLC