

Table 4. Toxicity for all cycles

Toxicity	Grade				Grade ≥ 3	
	1	2	3	4	n	%
Hematologic						
Leukopenia	7	5	17	5	22	53.7
Neutropenia	4	5	8	20	28	68.3
Anemia	23	6	4	1	5	12.2
Thrombocytopenia	6	3	4	1	5	12.2
Febrile neutropenia	0	0	7	0	7	17.1
Nonhematologic						
Nausea/vomiting	15	4	4	0	4	9.8
Anorexia	10	5	5	0	5	12.2
Diarrhea	2	0	1	0	1	2.4
Stomatitis	0	0	1	0	1	2.4
Pneumonitis	1	2	1	0	1	2.4
Infection	0	1	4	0	4	9.8
Fever	0	1	0	0	0	0
Fatigue	1	1	0	0	0	0
Liver dysfunction	7	0	0	0	0	0

fourth-line chemotherapy for patients with advanced NSCLC. Our study demonstrated the efficacy of amrubicin as shown by the ORR of 9.8%, DCR of 61.0%, median PFS of 3.0 months, median OS of 12.6 months, and 1-year survival rate of 53.7% in 41 patients. Although common, hematological toxicities were manageable and nonhematological toxicities were mild and reversible. Previous phase III trials for second- or third-line therapy of NSCLC patients have reported ORRs of 7.6%–9.1%, median OS of 6.7–8.3 months, and 1-year survival rates of 29.7%–34% [6–9, 21]. Amrubicin is a potent inhibitor of topoisomerase II, with a different mechanism of action from those of the currently available active cytotoxic agents for advanced NSCLC [15].

Several studies have evaluated the efficacy and safety of amrubicin for patients with advanced NSCLC. With regard to the dose of amrubicin, favorable results with tolerable toxicity were demonstrated with 45 mg/m² per day on three consecutive days every 3 weeks for first-line therapy [17, 22], 40 mg/m² for second-line therapy (West Japan Thoracic Oncology Group [WJTOG]0401 trial) [23], 35 mg/m² for primarily second-line therapy and for a small number of patients treated with third-line therapy [24], and 35 mg/m² or 40 mg/m² for third or subsequent lines of therapy [25]. Based upon these results, we conducted a prospective phase II trial of amrubicin at a dose of 35 mg/m² in NSCLC patients as a third- or fourth-line therapy.

The incidence of febrile neutropenia was certainly high in this study (17%, seven of 41 patients). Five patients developed febrile neutropenia in the first cycle, one patient developed this toxicity in the second cycle, and one patient developed this toxicity in the fourth cycle. A previous phase II study of amrubicin at 40 mg/m² for the second-line therapy of NSCLC patients (the WJTOG0401 trial) reported that 29.5% of the patients developed febrile neutropenia [23]. Thus, the possible reasons for the higher incidence of febrile neutropenia in our study are as follows: the 35-mg/m² dose of amrubicin

might be formidable in the third- or fourth-line setting and neither the prophylactic use of G-CSF nor the prophylactic use of antibiotics was allowed. In addition, an adverse event of particular concern related to amrubicin administration is cardiac toxicity, the incidence of which was 3.2% in previous trials [17, 22]. For safety reasons, this study allowed the enrollment of only patients with a left ventricular ejection fraction of 60% as determined by echocardiography. No cardiac toxicity was observed in our trial, and there were no treatment-related deaths in this study.

The number of patients who need third-line therapy is increasing, and third-line therapy represents a clinical problem for advanced NSCLC treatment. However, there is no standard definition for third-line therapy because the population of patients who could be grouped as potential candidates is heterogeneous [13] and clinical trial information regarding this population is sparse. Retrospective analyses from three institutions reported that 20.3%, 28.2%, and 38.4% of patients received third-line chemotherapy in clinical practice [11, 14, 26]. Those analyses showed that the ORR was 5.6%–17.0%, the DCR was 34.4%–44.4%, the median PFS was 2.4 months, and the median OS was 5.8–12.0 months. Patients who received third-line therapy benefited over those who did not.

In the second-line or later settings, the MST is not associated with the ORR, but is associated with the DCR [27]. Because amrubicin has a different mechanism of action from those of other anticancer agents and is associated with a high DCR with tolerable toxicity [15, 17], we conducted the present study in which the DCR was chosen as the primary endpoint. Based on a DCR of 33%–56% in previous phase III trials of second- and third-line therapy of NSCLC patients [7, 8, 28, 29] and the third- and fourth-line settings of this study, we assumed that a DCR of 50% was a desirable target and that a DCR of 30% was irrelevant. The lower end of the 95% CI in the present study was higher than the threshold DCR of 30%, and the primary endpoint was met. Single-agent chemotherapy and

EGFR TKI therapy had advantages over doublet chemotherapy in prolonging PFS and decreasing toxicity when used in third-line therapy [26]. In a BR.21 trial, erlotinib demonstrated survival benefits when administered as a second- or third-line therapy, compared with placebo (OS, 6.7 months vs. 4.7 months, respectively) [7]. That landmark trial included 49% of patients receiving third-line therapy; thus, treatment with erlotinib is recommended as a third-line therapy for patients with a PS of 0–3 who have not received prior EGFR TKIs. These data are not sufficient to make a recommendation for or against using a cytotoxic agent as a third-line therapy. However, there is no prospective trial of cytotoxic agents in that setting, which encouraged us to conduct the present study.

Similar to any phase II study, this analysis has several limitations. All patients enrolled in this study had an ECOG PS of 0–1, except for one patient with PS score of 2. Thus, these patients may not be representative of the population of patients with NSCLC who receive third- or fourth-line therapy in clinical practice. Additionally, seven (17%) patients harboring an EGFR mutation had an excellent prognosis (median OS, 16.7 months; range, 10.8–27.2 months). The survival outcome might have been influenced by the good health condition of these patients or by the indolent nature of the patients' disease. Therefore, further evaluation is warranted to implement this regimen into daily clinical practice as a third- or fourth-line therapy.

CONCLUSION

In conclusion, amrubicin is a promising agent associated with effective disease control and manageable toxicity as a third- or

fourth-line treatment for patients with advanced NSCLC. This study provides relevant data for routine practice and future prospective trials evaluating third- or fourth-line treatment strategies for patients with advanced NSCLC.

ACKNOWLEDGMENTS

This study is registered with University Hospital Medical Information Network Clinical Trial Registry (<http://www.umin.ac.jp/ctr/index.htm>; identification number, UMIN C000002306).

AUTHOR CONTRIBUTIONS

Conception/Design: Toshiyuki Harada, Satoshi Oizumi

Provision of study material or patients: Toshiyuki Harada, Satoshi Oizumi, Kenichiro Ito, Kei Takamura, Eiki Kikuchi, Tomoya Kuda, Shunichi Sugawara, Aya Suzuki, Makoto Maemondo, Yuka Fujita, Ichiro Kinoshita, Akira Inoue, Fumihiro Hommura, Yutaka Katsuura, Hirotochi Dosaka-Akita, Hiroshi Isobe, Masaharu Nishimura

Collection and/or assembly of data: Toshiyuki Harada, Satoshi Oizumi, Kenichiro Ito, Kei Takamura, Eiki Kikuchi, Tomoya Kuda, Shunichi Sugawara, Aya Suzuki, Makoto Maemondo, Yuka Fujita, Ichiro Kinoshita, Akira Inoue, Fumihiro Hommura, Yutaka Katsuura, Hirotochi Dosaka-Akita, Hiroshi Isobe, Masaharu Nishimura

Manuscript writing: Toshiyuki Harada, Satoshi Oizumi, Fumihiro Hommura, Yutaka Katsuura

Final approval of manuscript: Toshiyuki Harada, Satoshi Oizumi, Kenichiro Ito, Kei Takamura, Eiki Kikuchi, Tomoya Kuda, Shunichi Sugawara, Aya Suzuki, Makoto Maemondo, Yuka Fujita, Ichiro Kinoshita, Akira Inoue, Hirotochi Dosaka-Akita, Hiroshi Isobe, Masaharu Nishimura

DISCLOSURES

The author indicated no financial relationships.

REFERENCES

- Jemal A, Siegel R, Ward E et al. Cancer statistics, 2009. *CA Cancer J Clin* 2009;59:225–249.
- Pfister DG, Johnson DH, Azzoli CG et al.; American Society of Clinical Oncology. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: Update 2003. *J Clin Oncol* 2004;22:330–353.
- Schiller JH, Harrington D, Belani CP et al.; Eastern Cooperative Oncology Group. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002;346:92–98.
- NSCLC Meta-Analyses Collaborative Group. Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: A systematic review and meta-analysis of individual patient data from 16 randomized controlled trials. *J Clin Oncol* 2008;26:4617–4625.
- Oizumi S, Kobayashi K, Inoue A et al. Quality of life with gefitinib in patients with EGFR-mutated non-small cell lung cancer: Quality of life analysis of North East Japan Study Group 002 Trial. *The Oncologist* 2012;17:863–887.
- Shepherd FA, Dancey J, Ramlau R et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol* 2000;18:2095–2103.
- Shepherd FA, Rodrigues Pereira J, Ciuleanu T et al.; National Cancer Institute of Canada Clinical Trials Group. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005;353:123–132.
- Hanna N, Shepherd FA, Fossella FV et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 2004;22:1589–1597.
- Kim ES, Hirsh V, Mok T et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): A randomised phase III trial. *Lancet* 2008;372:1809–1818.
- Murillo JR Jr, Koeller J. Chemotherapy given near the end of life by community oncologists for advanced non-small cell lung cancer. *The Oncologist* 2006;11:1095–1099.
- Asahina H, Sekine I, Horinouchi H et al. Retrospective analysis of third-line and fourth-line chemotherapy for advanced non-small-cell lung cancer. *Clin Lung Cancer* 2012;13:39–43.
- de Marinis F, Grossi F. Clinical evidence for second- and third-line treatment options in advanced non-small cell lung cancer. *The Oncologist* 2008;13(suppl 1):14–20.
- Azzoli CG, Baker S Jr, Temin S et al.; American Society of Clinical Oncology. American Society of Clinical Oncology clinical practice guideline update on chemotherapy for stage IV non-small-cell lung cancer. *J Clin Oncol* 2009;27:6251–6266.
- Girard N, Jacoulet P, Gaiet M et al. Third-line chemotherapy in advanced non-small cell lung cancer: Identifying the candidates for routine practice. *J Thorac Oncol* 2009;4:1544–1549.
- Hanada M, Mizuno S, Fukushima A et al. A new antitumor agent amrubicin induces cell growth inhibition by stabilizing topoisomerase II-DNA complex. *Jpn J Cancer Res* 1998;89:1229–1238.
- Inoue A, Sugawara S, Yamazaki K et al. Randomized phase II trial comparing amrubicin with topotecan in patients with previously treated small-cell lung cancer: North Japan Lung Cancer Study Group Trial 0402. *J Clin Oncol* 2008;26:5401–5406.
- Sawa T, Yana T, Takada M et al. Multicenter phase II study of amrubicin, 9-amino-anthracycline, in patients with advanced non-small-cell lung cancer (study 1): West Japan Thoracic Oncology Group (WJTOG) trial. *Invest New Drugs* 2006;24:151–158.
- Okamoto I, Hamada A, Matsunaga Y et al. Phase I and pharmacokinetic study of amrubicin, a synthetic 9-aminoanthracycline, in patients with refractory or relapsed lung cancer. *Cancer Chemother Pharmacol* 2006;57:282–288.
- World Medical Association Declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. *JAMA* 1997;277:925–926.
- Therasse P, Arbuck SG, Eisenhauer EA et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–216.
- Fossella FV, DeVore R, Kerr RN et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. *J Clin Oncol* 2000;18:2354–2362.

22. Takeda K, Takifuji N, Negoro S et al. Phase II study of amrubicin, 9-amino-anthracycline, in patients with advanced non-small-cell lung cancer: A West Japan Thoracic Oncology Group (WJTOG) study. *Invest New Drugs* 2007;25:377–383.

23. Kaneda H, Okamoto I, Hayashi H et al. West Japan Thoracic Oncology Group. Phase II trial of amrubicin for second-line treatment of advanced non-small cell lung cancer: Results of the West Japan Thoracic Oncology Group trial (WJTOG0401). *J Thorac Oncol* 2010;5:105–109.

24. Kaira K, Sunaga N, Tomizawa Y et al. A phase II study of amrubicin, a synthetic 9-aminoanthracy-

cline, in patients with previously treated lung cancer. *Lung Cancer* 2010;69:99–104.

25. Igawa S, Takahashi T, Nakamura Y et al. Efficacy of amrubicin for non-small cell lung cancer after failure of two or more prior chemotherapy regimens. *Anticancer Res* 2008;28:3855–3858.

26. Song Z, Yu Y, Chen Z et al. Third-line therapy for advanced non-small-cell lung cancer patients: Feasible drugs for feasible patients. *Med Oncol* 2011;28(suppl 1):S605–S612.

27. Hotta K, Fujiwara Y, Kiura K et al. Relationship between response and survival in more than 50,000 patients with advanced non-small cell

lung cancer treated with systemic chemotherapy in 143 phase III trials. *J Thorac Oncol* 2007;2:402–407.

28. Maruyama R, Nishiwaki Y, Tamura T et al. Phase III study, V-15–32, of gefitinib versus docetaxel in previously treated Japanese patients with non-small-cell lung cancer. *J Clin Oncol* 2008;26:4244–4252.

29. Ohe Y, Ichinose Y, Nakagawa K et al. Efficacy and safety of two doses of pemetrexed supplemented with folic acid and vitamin B12 in previously treated patients with non-small cell lung cancer. *Clin Cancer Res* 2008;14:4206–4212.

Impact of EGFR Inhibitor in Non-Small Cell Lung Cancer on Progression-Free and Overall Survival: A Meta-Analysis

Chee Khoon Lee, Chris Brown, Richard J. Gralla, Vera Hirsh, Sumitra Thongprasert, Chun-Ming Tsai, Eng Huat Tan, James Chung-Man Ho, Da Tong Chu, Adel Zaatar, Jemela Anne Osorio Sanchez, Vu Van Vu, Joseph Siu Kie Au, Akira Inoue, Siow Ming Lee, Val Gebski, James Chih-Hsin Yang

Manuscript received August 17, 2012; revised January 5, 2013; accepted February 15, 2013.

Correspondence to: James Chih-Hsin Yang, MD, PhD, Graduate Institute of Oncology and Cancer Research Center, National Taiwan University College of Medicine, Taipei 10051, Taiwan (e-mail: chihyang@ntu.edu.tw).

Background The epidermal growth factor receptor (EGFR) signaling pathway is crucial for regulating tumorigenesis and cell survival and may be important in the development and progression of non-small cell lung cancer (NSCLC). We examined the impact of EGFR-tyrosine kinase inhibitors (TKIs) on progression-free survival (PFS) and overall survival (OS) in advanced NSCLC patients with and without EGFR mutations.

Methods Randomized trials that compared EGFR-TKIs monotherapy or combination EGFR-TKIs-chemotherapy with chemotherapy or placebo were included. We used published hazard ratios (HRs), if available, or derived treatment estimates from other survival data. Pooled estimates of treatment efficacy of EGFR-TKIs for the EGFR mutation-positive (EGFRmut⁺) and EGFR mutation-negative (EGFRmut⁻) subgroups were calculated with the fixed-effects inverse variance weighted method. All statistical tests were two-sided.

Results We included 23 eligible trials (13 front-line, 7 second-line, 3 maintenance; n = 14570). EGFR mutation status was known in 31% of patients. EGFR-TKIs treatment prolonged PFS in EGFRmut⁺ patients, and EGFR mutation was predictive of PFS in all settings: The front-line hazard ratio for EGFRmut⁺ was 0.43 (95% confidence interval [CI] = 0.38 to 0.49; *P* < .001), and the front-line hazard ratio for EGFRmut⁻ was 1.06 (95% CI = 0.94 to 1.19; *P* = .35; *P*_{interaction} < .001). The second-line hazard ratio for EGFRmut⁺ was 0.34 (95% CI = 0.20 to 0.60; *P* < .001), and the second-line hazard ratio for EGFRmut⁻ was 1.23 (95% CI = 1.05 to 1.46; *P* = .01; *P*_{interaction} < .001). The maintenance hazard ratio for EGFRmut⁺ was 0.15 (95% CI = 0.08 to 0.27; *P* < .001), and the maintenance hazard ratio for EGFRmut⁻ was 0.81 (95% CI = 0.68 to 0.97; *P* = .02; *P*_{interaction} < .001). EGFR-TKIs treatment had no impact on OS for EGFRmut⁺ and EGFRmut⁻ patients.

Conclusions EGFR-TKIs therapy statistically significantly delays disease progression in EGFRmut⁺ patients but has no demonstrable impact on OS. EGFR mutation is a predictive biomarker of PFS benefit with EGFR-TKIs treatment in all settings. These findings support EGFR mutation assessment before initiation of treatment. EGFR-TKIs should be considered as front-line therapy in EGFRmut⁺ advanced NSCLC patients.

J Natl Cancer Inst;2013;105:595-605

The greatest changes in the treatment of advanced non-small cell lung cancer (NSCLC) have been novel molecular-targeted agents and the concomitant ability to personalize treatment. Controversy continues in many areas related to the incorporation of these changes into clinical medicine. How should such therapy be selected for individual patients? Is molecular testing required or is the use of demographic factors (such as histologic NSCLC type, sex, smoking history) sufficient for personalizing therapy? Questions remain concerning whether therapy with chemotherapy or with agents affecting the epidermal growth factor receptor (EGFR) influence progression-free survival (PFS) and/or overall survival (OS) in patients who do or do not harbor known mutations associated with EGFR. Is PFS a good surrogate for OS, or is PFS a useful endpoint on its own? Data directed at answering these controversies can guide oncologists

in interpreting trials and in making more appropriate diagnostic and therapeutic choices for hundreds of thousands of patients each year.

The objective of this meta-analysis is to estimate better the treatment effect of EGFR-tyrosine kinase inhibitors (TKIs) on PFS and OS while examining for heterogeneity of treatment effects between groups of patients with and without EGFR mutations. The EGFR signaling pathway is crucial for regulating tumorigenesis and cell survival and may be overexpressed in the development and progression of NSCLC (1-3). Patients with activating somatic mutations in the region of the EGFR gene that encodes the tyrosine kinase domain are highly responsive to EGFR-TKIs (4-6). Previously published meta-analyses have been limited by studying the minority of patients with NSCLC—that is, the influence of EGFR-TKIs only in the population of patients harboring EGFR

mutations and predominantly in the front-line treatment setting (7–9). These meta-analyses have not demonstrated an OS advantage for patients with EGFR mutation treated with EGFR-TKIs. This analysis uses all trial data available to date and examines the effect of EGFR-TKIs treatment in major clinical settings—front-line, maintenance, and second-line or subsequent therapies. Additionally, the impact of EGFR-TKIs-chemotherapy combinations compared with EGFR-TKIs monotherapy is also explored. It is now recognized that as with EGFR mutations, other genetic alterations [such as EML-ALK abnormalities (10) and ROS-1 mutations (11)] are also more common in nonsmokers with adenocarcinoma, but these latter groups do not benefit from EGFR-TKIs-directed therapy. Such findings highlight the need for more specific molecular testing of patients and the need to include the most recent data from meta-analyses to understand better the treatment effects.

Individual trials and meta-analyses have clearly indicated that PFS and response rates are improved in patients with EGFR mutation who are treated with EGFR-TKIs, when compared with chemotherapy (7–9). The impact on OS is less clear, especially in patients treated beyond first-line therapy. Two separate trials have indicated that erlotinib is effective as second-line (12) and maintenance (13) therapy, with no statistically significant difference in treatment effect between those with EGFR mutation and wild-type tumors. However, a recent trial reported that chemotherapy was superior over erlotinib as second-line treatment for patients without EGFR mutations in exon 19 or 21 (14). Clearly, newer and larger meta-analyses are required to resolve these differences. Definitive analyses can provide stronger rationales for the choice of a specific therapy and can result in better utilization of health-care resources with these costly agents. For these reasons, we conducted this meta-analysis, which included the largest number of studies and patients to date with known EGFR mutation status and tested both PFS and OS as outcomes.

Methods

Study Eligibility and Identification

All randomized trials of EGFR-TKIs monotherapy vs any chemotherapy, EGFR-TKIs and chemotherapy vs the same chemotherapy alone, and EGFR-TKIs monotherapy vs placebo or best supportive care were eligible for inclusion.

Trials were identified from previous meta-analyses (7–9), and a search of Medline, Embase, CancerLit, and the Cochrane Central Register of Controlled Trials (CENTRAL) using the following terms: lung neoplasms, non-small cell lung cancer, gefitinib, erlotinib, EGFR, meta-analysis, systemic review, randomized, and clinical trials. Database searches were restricted to articles published in the English language between January 1, 2004, and June 6, 2012. Trials that enrolled patients with prior EGFR-TKIs treatment were excluded. Abstracts from conference proceedings of the American Society of Clinical Oncology, the European Society for Medical Oncology, and the World Lung Cancer Conference were searched to identify unpublished studies. Individual study sponsors (Hoffmann-La Roche and AstraZeneca) were contacted for relevant presentation slides and posters from these conferences when they were inaccessible from the websites. Individual investigators were also contacted if essential information relevant to this meta-analysis was unavailable from these sources.

Data Extraction

Information recorded from each trial included study name, year of publication or conference presentation, study design, line of treatment, and clinicopathological and demographic data. Mutational analysis data were also extracted, and the different methods of EGFR mutation assessment were recorded. We classified patients as EGFR mutation-positive (EGFRmut⁺) based on the presence of a mutation as detected using molecular assessment tools such as Sanger sequencing, polymerase chain reaction clamp, and amplification refractory mutation system. Patients were classified as EGFR mutation-negative (EGFRmut⁻) if no mutation was detected. We did not classify patients' EGFR mutation status based on immunohistochemistry and fluorescent in situ hybridization for EGFR gene copy numbers. Most trials analyzed exons 19 and 21 for EGFR mutations, and some trials also included exons 18 and 20.

Data were extracted independently by three authors (J. C.-H. Yang, C. K. Lee, and C. Brown), and discrepancies were resolved by consensus including a fourth author (V. GebSKI).

Statistical Analyses

We extracted the hazard ratios (HRs) and the associated 95% confidence intervals (CIs) for PFS and OS outcomes to assess treatment efficacy within the EGFRmut⁺ and EGFRmut⁻ subgroups. Where available, we included the most updated OS data. If hazard ratios and confidence intervals were not reported, these were estimated where possible using the methods of Parmar (15).

Pooled estimates of the treatment efficacy of EGFR-TKIs for the EGFRmut⁺ and EGFRmut⁻ subgroups were calculated by using the fixed-effects inverse variance weighted method. We performed indirect comparisons to quantify the benefits of adding chemotherapy to EGFR-TKIs over EGFR-TKIs alone in both subgroups.

A sensitivity analysis was also conducted to examine the impact of the overall results from this study by limiting the analyses on front-line trials that were known to have determined EGFR mutation based on exons 19 and 21 only.

We used the χ^2 Cochran Q test to detect for heterogeneity across the different studies and between subgroups defined by EGFR mutation status, study setting, and study design. The nominal level of significance was set at 5%. All 95% confidence intervals were two-sided.

Cochrane Review Manager (version 5, Cochrane Collaboration, Copenhagen, Denmark, <http://ims.cochrane.org/home>) was used for all analyses.

Results

The search strategy identified 40 studies, of which 23 (12–14,16–44) were eligible for inclusion in this meta-analysis (Figure 1). Trial data were obtained from published manuscripts and conference abstracts for 19 trials, and additional data on treatment efficacy by EGFRmut⁺ and EGFRmut⁻ subgroups were obtained directly from study investigators for four studies [ISEL (41), V-15-32 (31), TOPICAL (43), and IFCT-GFPC 0502 (32, 44)]. Treatment estimates for the TALENT study (37) were calculated on the basis of data extracted from presented survival curves. The hazard ratios for OS for ISEL (41), IFCT-GFPC 0502 (32,44), and V-15-32 (31) were estimated on the basis of the observed number of deaths. In all other studies, hazard ratios and associated variances were obtained directly from trial reports.

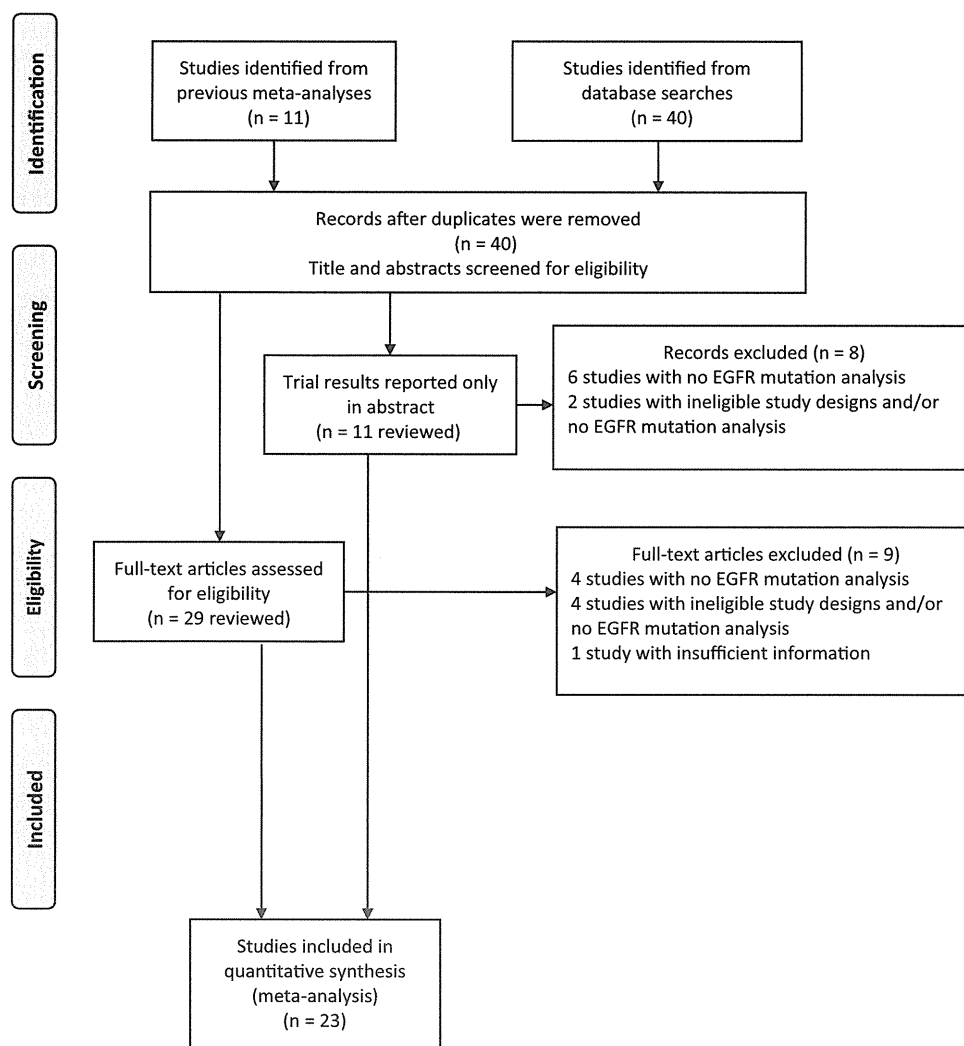


Figure 1. Flow diagram showing inclusion and exclusion of studies. EGFR = epidermal growth factor receptor.

A total of 14570 patients participated in these 23 trials. EGFR mutation status, as determined by mutation analysis only, was known for at least 31% ($n = 4473$) of trial patients. [In the TALENT study (37), the treatment comparisons for the subgroups were reported, but the number of patients in each subgroup was unknown.] Clinicopathological and demographic characteristics of patients enrolled in these studies are summarized in Table 1.

Trials investigated EGFR-TKIs for front-line therapy in treatment-naïve patients ($n = 13$ trials), second-line or subsequent treatment after failure of chemotherapy ($n = 7$ trials), and maintenance treatment in patients with nonprogressive disease after front-line chemotherapy ($n = 3$ trials). Among the 13 front-line studies, eight compared EGFR-TKIs as monotherapy vs chemotherapy (16–21,23,27,33–35,38), four compared EGFR-TKIs with chemotherapy vs chemotherapy alone (22,24–26,37,45), and one was a placebo-controlled trial (36,43). Among the seven second-line and subsequent treatment trials, five compared EGFR-TKIs as monotherapy vs chemotherapy (12,14,28,29,31,42), and two were placebo-controlled studies (39–41). All three maintenance studies had a placebo arm (13,30,32,44).

Benefit of EGFR-TKIs on PFS in Different Settings

Data on PFS were available from 21 trials except ISEL (41) and BR21 (39). The treatment effect of EGFR-TKIs in different settings is shown in Figure 2. The test of interaction between treatment and EGFR mutation status was statistically significant (front-line setting: $P < .001$; second-line or subsequent treatment: $P < .001$).

In EGFRmut⁺ patients, EGFR-TKIs treatment was associated with a lower risk of disease progression in the front-line setting (HR = 0.43; 95% CI = 0.38 to 0.49; $P < .001$) and second-line or subsequent treatment (HR = 0.34; 95% CI = 0.20 to 0.60; $P < .001$).

In EGFRmut⁻ patients, EGFR-TKIs did not show a treatment advantage in the front-line setting or beyond. There was no statistically significant difference between EGFR-TKIs and chemotherapy in reducing the risk of disease progression in front-line therapy (HR = 1.06; 95% CI = 0.94 to 1.19; $P = .35$). EGFR-TKIs treatment was statistically significantly inferior to chemotherapy in second-line or subsequent therapy (HR = 1.23; 95% CI = 1.05 to 1.46; $P = .01$).

Maintenance therapy with EGFR-TKIs compared with placebo was effective in reducing the risk of disease progression in EGFRmut⁺

Table 1. Demographic characteristics of patients*

Study name (year) (reference)	Treatment comparison	EGFR mutation assessment method	No. of EGFR ⁺ patients (%)	No. of EGFR ⁻ patients (%)	No. of EGFR unknown patients (%)	Age, y, median	Asian, %	Males, %	Present/ former smokers, %	Adeno- carcinoma, %
Front-line treatment										
INTACT 1 (2004) (24,43)	Gefitinib + CisG vs CisG	Direct sequencing	32 (2)	280 (13)	1818 (85)	60	6	74	NK	46
INTACT 2 (2004) (25,43)	Gefitinib + CP vs CP					62	NK	60	NK	55
TRIBUTE (2005) (22)	Erlotinib + CP vs CP	Direct sequencing	29 (3)	198 (18)	851 (79)	63	3	61	89	61
TALENT (2007) (26,37)	Erlotinib + CisG vs CisG	NK	NK	NK	NK	61	4	77	NK	38
IPASS (2009) (19,20)	Gefitinib vs CP	ARMS	261 (21)	176 (15)	780 (64)	57	100	21	6	96
NEJ002 (2010) (17,38)	Gefitinib vs CP	PCR clamp	228 (100)	0	0	63‡	100	36	38	94
TOWG† (2010) (27)	Erlotinib vs CV	Direct sequencing	10 (4)	75 (26)	199 (70)	76	NK	68	83	50
TOPICAL (2010) (36,43)	Erlotinib vs placebo	SequenomOncoCarta Panel	28 (4)	362 (54)	280 (42)	77	2	61	95	38
WJTOG3405* (2010) (21,33)	Gefitinib vs CisD	Direct sequencing, PCR clamp	172 (100)	0	0	64	100	31	31	97
OPTIMAL* (2011) (16,35)	Erlotinib vs CG	Direct sequencing	154 (100)	0	0	58	100	41	29	87
First-SIGNAL (2012) (23)	Gefitinib vs CisG	Direct sequencing	43 (14)	54 (17)	212 (69)	57	100	11	NK	NK
EURTAC* (2012) (18)	Erlotinib vs platinum-G or platinum-D	Direct sequencing	173 (100)	0	0	65	0	27	31	92
LUX Lung 3† (2012) (34)	Afatinib vs CisPem	TheraScreen EGFR29	345 (100)	0	0	61	72	35	32	100
Maintenance therapy										
IFCT-GFPC 0502* (2010) (32)	Erlotinib or G vs placebo	NK	8 (3)	106 (34)	196 (63)	58	0	73	90	65
SATURN (2010) (13)	Erlotinib vs placebo	Direct sequencing	49 (6)	388 (44)	452 (50)	60	15	74	83	45
INFORM (2011) (30)	Gefitinib vs placebo	NK	30 (10)	49 (17)	217 (73)	55	100	59	46	71
Second-line/subsequent treatment										
ISEL (2005) (41)	Gefitinib vs placebo	Direct sequencing, ARMS	26 (2)	189 (11)	1477 (87)	62	20	67	78	45
BR21 (2005) (39,40)	Erlotinib vs placebo	Direct sequencing, ARMS	34 (5)	170 (23)	527 (72)	61	13	65	75	50
INTEREST (2008) (28,29)	Gefitinib vs D	Direct sequencing	44 (3)	253 (17)	1169 (80)	61	22	65	80	54
V-15-32 (2008) (31)	Gefitinib vs D	Direct sequencing	31 (6)	26 (6)	432 (88)	NK	100	62	68	78
TITAN (2012) (12)	Erlotinib vs pemetrexed or D	Direct sequencing	11 (3)	149 (35)	264 (62)	59	13	76	83	50
TAILOR† (2012) (14)	Erlotinib vs D	Direct sequencing	0	219 (100)	0	67	0	68	77	69
KCSG-LU08-01 (2012) (42)	Gefitinib vs Pem	Direct sequencing	33 (24)	38 (28)	64 (48)	61	100	15	0	100

* ARMS = amplification refractory mutation system; CG = carboplatin-gemcitabine; CisD = cisplatin-docetaxel; CisG = cisplatin-gemcitabine; CisPem = cisplatin-pemetrexed; CP = carboplatin-paclitaxel; CV = carboplatin-venorelbine; D = docetaxel; EGFR⁺ = presence of epidermal growth factor receptor mutation; EGFR⁻ = absence of epidermal growth factor receptor mutation; G = gemcitabine; NK = not known; PCR = polymerase chain reaction; PEM = pemetrexed.

* EGFR mutation based on exon 19 and exon 21 only.

† Trials reported in abstract format.

‡ Median age not available; mean age calculated instead.

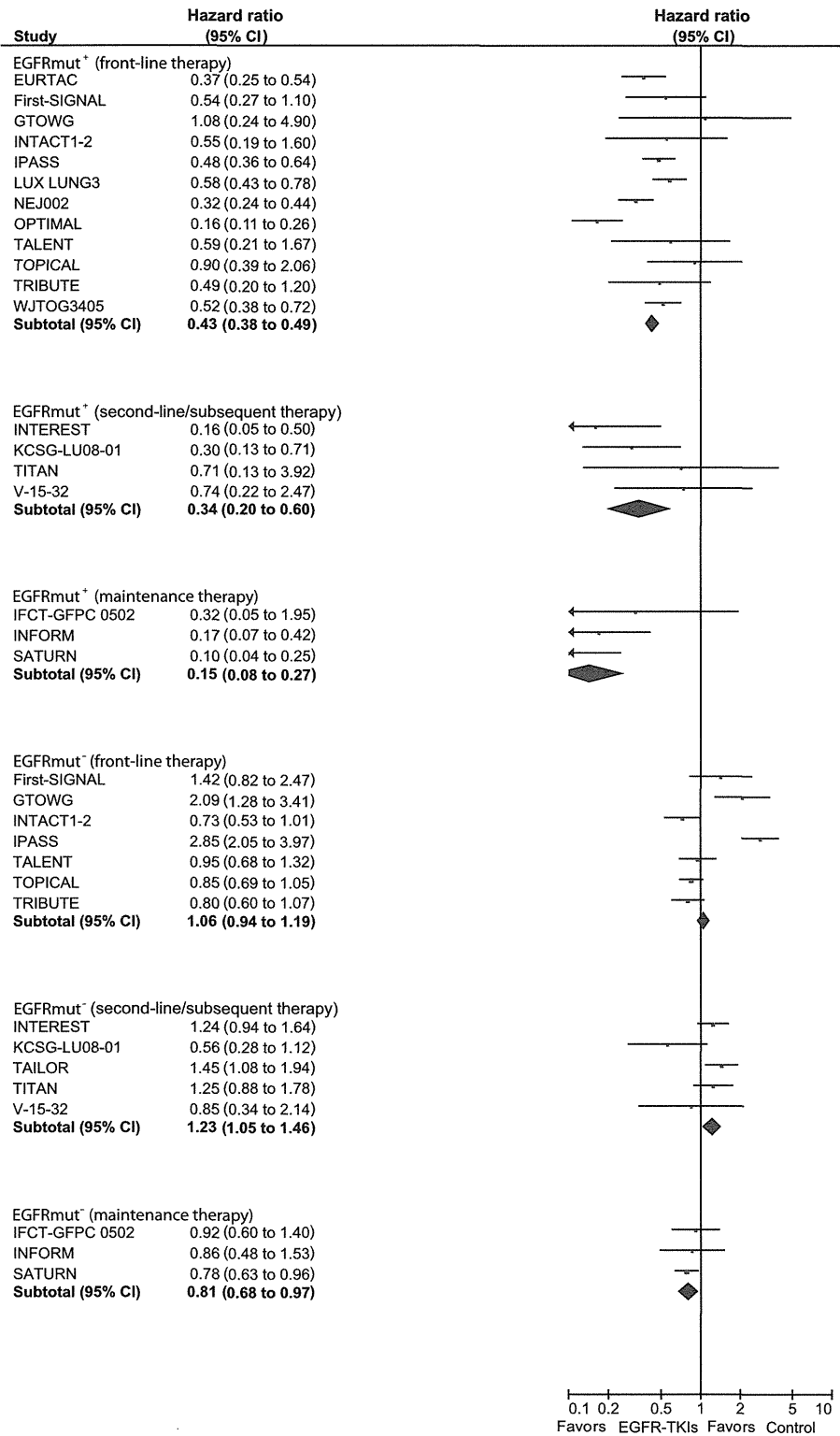


Figure 2. Forest plot of hazard ratios comparing progression-free survival in subgroups of epidermal growth factor receptor (EGFR) mutation-positive (EGFRmut⁺) and EGFR mutation-negative (EGFRmut⁻) patients who received EGFR-tyrosine kinase inhibitors (TKIs) vs control. Hazard ratios for each trial are represented by the **squares**, and the **horizontal line** crossing the square represents the 95% confidence interval (CI). The **diamonds** represent the estimated overall effect based on the meta-analysis fixed effect of the trials. All statistical tests were two-sided.

and EGFRmut⁻ subgroups (EGFRmut⁺: HR = 0.15, 95% CI = 0.08 to 0.27, $P < .001$; EGFRmut⁻: HR = 0.81, 95% CI = 0.68 to 0.97, $P = .02$). The test of interaction between treatment and EGFR mutation status was statistically significant ($P < .001$).

Effect of EGFR-TKIs Combined With Chemotherapy on PFS

Data were available for four trials [INTACT 1 and 2 (45), TRIBUTE (22) and TALENT (37)] that combined EGFR-TKIs with chemotherapy. Combination EGFR-TKIs and chemotherapy compared with chemotherapy alone was effective in reducing the risk of disease progression in both subgroups (EGFRmut⁺: HR = 0.54, 95% CI = 0.30 to 0.95, $P = .04$; EGFRmut⁻: HR = 0.82, 95% CI = 0.68 to 0.98, $P = .03$; treatment-by-EGFR mutation status interaction: $P = .17$) (Figure 3). When EGFR-TKIs monotherapy was compared with chemotherapy, EGFR-TKIs treatment was associated with a reduced risk of disease progression in the EGFRmut⁺ subgroup (HR = 0.42; 95% CI = 0.37 to 0.48; $P < .001$) but an increased risk in the EGFRmut⁻ subgroup (HR = 1.56; 95% CI = 1.36 to 1.80; $P < .001$).

Within the EGFRmut⁺ subgroup, an indirect comparison of data available from these trials indicates EGFR-TKIs treatment in combination with chemotherapy was not more effective than EGFR-TKIs alone in reducing the risk of disease progression (HR = 1.42; 95% CI = 0.80 to 2.53; $P = .23$). By contrast, within the EGFRmut⁻ subgroup, EGFR-TKIs treatment in combination with chemotherapy was more effective in reducing the risk of disease progression than EGFR-TKIs alone (HR = 0.51; 95% CI = 0.43 to 0.62; $P < .001$).

Effect of EGFR-TKIs on OS in Different Settings

Data on OS were available from 19 trials except Lux Lung 3 (34), TAILOR (14), KCSG-LU08-01 (42), and INFORM (30). Subgroup analyses by treatment setting are summarized in Figure 4. The test interaction for treatment and EGFR

mutation status was not statistically significant (front-line setting: $P = .91$; second-line or subsequent therapy: $P = .37$). For EGFRmut⁺ patients, there was no treatment advantage of EGFR-TKIs in the front-line setting (HR = 1.01; 95% CI = 0.87 to 1.18; $P = .86$) or for second-line or subsequent therapy (HR = 0.74; 95% CI = 0.45 to 1.19; $P = .21$) in the risk of death. Similar results were observed in EGFRmut⁻ patients.

Only two studies [SATURN (13) and IFCT-GFPC 0502 (32,44)] reported OS in the maintenance setting. There was no clear benefit of treatment with EGFR-TKIs over placebo in either EGFRmut⁺ patients (HR = 0.78; 95% CI = 0.33 to 1.84; $P = .57$) or EGFRmut⁻ patients (HR = 0.84; 95% CI = 0.69 to 1.04; $P = .10$). The test for interaction between treatment and EGFR mutation status was not statistically significant ($P = .87$).

Publication Bias

In this meta-analysis, the overall treatment effect was not statistically significant for the OS outcome. Any potential publication bias through the exclusion of non-statistically significant studies would therefore not have influenced these results.

Sensitivity Analysis

EGFR mutation, based on exons 19 and 21 only, was known to have been examined in three trials in a front-line setting (Table 1). One trial (34) provided the treatment estimate for PFS limited to patients with exons 19 and 21 only. In the front-line setting, similar qualitative results were obtained when the analyses were limited to only these four trials on PFS and OS outcomes for the EGFRmut⁺ subgroup (Supplementary Figures 1 and 2, available online).

Discussion

This study extends the analysis beyond prior publications of the most clinically important molecular factor relevant to the treatment

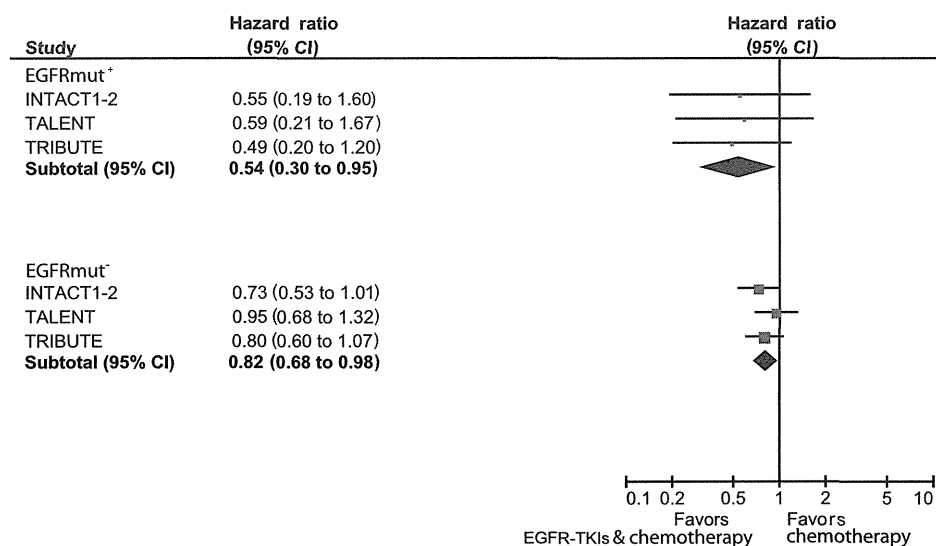


Figure 3. Forest plot of hazard ratios comparing progression-free survival in subgroups of epidermal growth factor receptor (EGFR) mutation-positive (EGFRmut⁺) and EGFR mutation-negative (EGFRmut⁻) patients who received EGFR-tyrosine kinase inhibitors (TKIs) and chemotherapy vs chemotherapy. Hazard ratios for each trial are represented by the squares, and the horizontal line crossing the square represents the 95% confidence interval (CI). The diamonds represent the estimated overall effect based on the meta-analysis fixed effect of the trials. All statistical tests were two-sided.

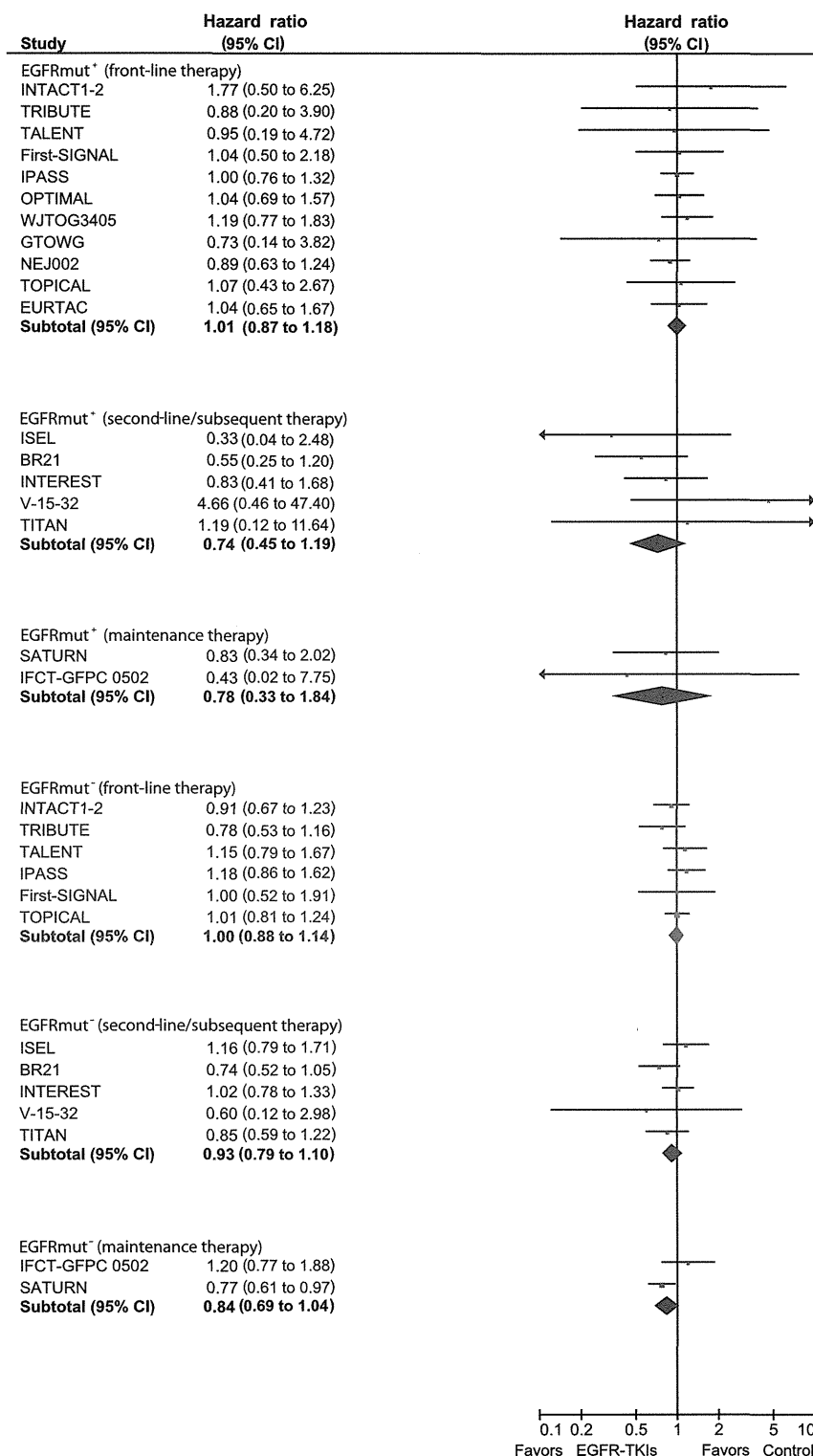


Figure 4. Forest plot of hazard ratios comparing overall survival in subgroups of epidermal growth factor receptor (EGFR) mutation–positive (EGFRmut⁺) and EGFR mutation–negative (EGFRmut⁻) patients who received EGFR–tyrosine kinase inhibitors (TKIs) vs control. Hazard ratios for each trial are represented by the **squares**, and the **horizontal line** crossing the square represents the 95% confidence interval (CI). The **diamonds** represent the estimated overall effect based on the meta-analysis fixed effect of the trials. All statistical tests were two-sided.

of NSCLC. Increased confidence in the findings is evident through the incorporation of results from 23 trials in nearly 15 000 patients with more than 4000 having molecular analysis. Additionally, this study approached issues not addressed in prior meta-analyses. As such, results from this study have implications for treatment and for study interpretation and design.

This meta-analysis summarizes the best available evidence to guide the use of EGFR-TKIs in patients with advanced NSCLC. EGFR-TKIs treatment is associated with 57% and 66% reduction in the risk of disease progression in EGFRmut⁺ patients in front-line and second-line settings, respectively, but with no benefit in EGFRmut⁻ patients (Figure 2). This study also demonstrates that EGFR mutation is an important predictive biomarker of TKIs treatment benefit in terms of PFS for all settings: front-line, maintenance, and second-line or subsequent therapy. This study demonstrates for the first time that the magnitude of effect on PFS for EGFRmut⁺ patients is similar in patients receiving EGFR-TKIs in either the first- or second-line setting (HR = 0.43 and 0.34, respectively).

Even with mutational analyses in more than 4000 patients and with a large PFS benefit, this meta-analysis does not demonstrate OS advantage with EGFR-TKIs. Regardless of EGFR mutation status, the overall treatment effects on OS were similar. The frequently suggested reason for this lack of OS effect is the confounding effect of postprogression therapy between the randomization arms. None of the front-line trials prohibited patients from crossing over to the other treatment arm, and crossover was increasingly frequent over the decade during which these trials were conducted. For example, the NEJ002 trial randomly assigned patients to receive either gefitinib or chemotherapy. Not only did most patients receive subsequent treatment, but 94.6% of patients in the chemotherapy arm were reported to have received second-line gefitinib on disease progression (17). A recent systematic review of chemotherapy trials also indicated that PFS advantage is unlikely to be associated with an OS advantage with increasing impact of salvage therapy and that the prolongation of survival postprogression might limit the role of OS for assessing true efficacy derived from front-line therapy (46). Moreover, analysis of a recent trial indicated that compared with EGFRmut⁻ patients, twice as many EGFRmut⁺ patients responded to chemotherapy (28). Crossover effects, lack of blinding in experimental arms, and other factors that have been previously discussed can make PFS a difficult surrogate for OS (47–49). Ongoing work is still required to demonstrate the impact of other clinically meaningful benefits of EGFR-TKIs beyond survival and PFS for these patients.

Controversy continues regarding the role of the addition of EGFR-TKIs in patients receiving chemotherapy. For this reason, we analyzed this issue in four large, published, prospective, randomized trials in front-line treatment [INTACT 1 and 2 (45), TALENT (37), and TRIBUTE (22)]. Pooled results from these four front-line trials showed that combining EGFR-TKIs with chemotherapy over chemotherapy alone statistically significantly delayed disease progression in both the EGFRmut⁺ and EGFRmut⁻ subgroups. Preclinical studies (50,51) have demonstrated a synergistic effect of combining EGFR-TKIs with chemotherapy. However, indirect comparison of trial arms suggests that combined EGFR-TKIs treatment and chemotherapy is not more effective than EGFR-TKIs alone in reducing the risk of disease progression

in EGFRmut⁺ patients (HR = 1.42; 95% CI = 0.80 to 2.53; $P = .23$). A lack of additional benefit was confirmed in a prospective phase II trial (52) in which erlotinib monotherapy was compared with erlotinib chemotherapy combination in the EGFRmut⁺ subgroup (median PFS 14.1 vs 17.2 months).

This meta-analysis provides information to define better the relative effectiveness of EGFR-TKIs for EGFRmut⁻ patients. In front-line therapy, there was a non-statistically significant difference between EGFR-TKIs and control in reducing the risk of disease progression (pooled HR = 1.06; $P = .35$). This finding is consistent with previous *in vitro* studies that demonstrated a lack of sensitivity of wild-type EGFRmut⁻ receptor lung tumor to EGFR-TKIs treatment (4–6). Although a small benefit of EGFR-TKIs over placebo in the EGFRmut⁻ subgroup has been demonstrated in three maintenance studies [SATURN (13), INFORM (30), and IFCT-GFPC 0502 (32,44)] (pooled HR = 0.81; 95% CI = 0.68 to 0.97; $P = .02$), it must be realized that this benefit is markedly and both clinically and statistically significantly greater in EGFRmut⁺ subgroups (pooled HR = 0.15; 95% CI = 0.08 to 0.27; $P < .001$), and the test of interaction between EGFR mutation status and treatment is highly statistically significant ($P < .001$).

This meta-analysis also examined the role of EGFR mutation in selecting patients for second-line or subsequent treatment. A 2012 editorial has illustrated the debate in this area (53). Although trials have differed in their results, one study (TAILOR) reported that chemotherapy was statistically significantly superior over erlotinib in terms of tumor response and PFS (OS results are not yet available) in patients without EGFR mutations in exon 19 or 21 undergoing second-line treatment, but the data remain premature and only available as a conference presentation (14). In the current meta-analysis, pooled results from trials of second-line and subsequent therapies demonstrated that treatment with EGFR-TKIs treatment, compared with chemotherapy, was associated with a 66% reduction in the risk of disease progression in the EGFRmut⁺ subgroup (Figure 2). In contrast, EGFR-TKIs treatment, compared with chemotherapy, was 23% inferior (Figure 2) in delaying disease progression (but not OS) in EGFRmut⁻ patients with good performance status who were suitable to receive chemotherapy. The test of interaction between EGFR mutation status and second-line or subsequent treatment was statistically significant ($P < .001$), suggesting that EGFR mutation is still an important treatment effect modifier and should be used to guide treatment decisions in this setting. Interestingly, updated results from the TOPICAL trial demonstrated that rash during the first cycle predicted PFS benefits with erlotinib in the EGFRmut⁻ subgroup (43).

This meta-analysis has several strengths. We performed a comprehensive review, reported the most up-to-date published data, and contacted individual investigators to obtain relevant unpublished data. By examining both the EGFRmut⁺ and EGFRmut⁻ subgroups, the value of EGFR mutation status as a treatment effect modifier can be adequately assessed. This meta-analysis also overcomes the problem of inadequate power of individual studies to compare subgroups. For example, only six studies (16,18,19,21,34,38) included in this review had EGFRmut⁺ results for more than 50 patients. Reliable interpretation of independent treatment effects in most of the individual studies in this review is not possible because of small sample sizes. Altogether, more than 4000 patients with mutational

analysis were included in this study. A major strength of this current meta-analysis is that the pooled results allow examination of second-line and maintenance treatment as well as elucidation of the effect of adding EGFR-TKIs to chemotherapy.

There are also limitations that should be noted from this analysis. Firstly, we assumed that all EGFR-TKIs, including gefitinib, erlotinib, and afatinib, have equivalent therapeutic efficacy for both the EGFRmut⁺ and EGFRmut⁻ subgroups. Secondly, EGFR mutation status was only assessed in 31% of patients enrolled in eligible trials, with treatment efficacy estimated from small numbers of EGFRmut⁺ patients identified in many of these trials (Table 1). The potential influence on the results of restricting our analyses to this subset of patients is unknown. We further obtained efficacy data in the subgroups with known EGFR mutation status through personal communication with investigators of four trials (31,32,41,43). Although these subgroup data have not been published, the primary trial outcomes of these studies have been peer reviewed. Although nearly 15 000 patients were included in the analysis, the fact that only a minority had reported mutational analysis limits the ability to address several issues. Sequencing was the most commonly used method to detect EGFR mutation, and it has poor sensitivity in detecting EGFR mutant alleles in DNA samples extracted from tumors (54). These DNA samples may contain both malignant and nonmalignant (from adjacent normal or tumor stroma) cells and hence may impact the outcome of this meta-analysis through misclassification of patients' EGFR mutation status. Moreover, mutation of EGFR exons 19 and 21 are sensitizing mutations predictive of PFS benefit with EGFR-TKIs, whereas de novo mutations in exon 20 might reduce the effectiveness of EGFR-TKIs (55–57). In this meta-analysis, patients classified as EGFRmut⁺ in some trials included those with mutations in exon 20. However, when we restricted our analysis to studies that classified patients as EGFRmut⁺ based on presence of EGFR exon 19 and exon 21 mutations, we observed similar quantitative results. In front-line therapy, information on crossover and postprogression therapies was often not available, so adjustments could not be made to account for the lack of OS benefit in EGFRmut⁺ patients treated with EGFR-TKIs.

Many reports have confirmed that EGFR mutations are more commonly found in patients with adenocarcinoma and in patients with low- and never-smoking histories. These factors have led to the debate as to whether knowledge of such demographic factors, rather than use of molecular studies, would be sufficient for treatment. The current meta-analysis, which examines multiple treatment settings, demonstrates that EGFR mutation status should guide personalization of treatment. Additionally, recent findings have reported that these same demographic features are more common in other genetic differences [such as those associated with EML-ALK translocations (10) and ROS 1 mutations (11)] that are not beneficially affected by EGFR-TKIs and for which specific therapy is available. Determining mutational status can avoid side effects of either EGFR-TKIs or chemotherapy and can lead to rational decision making. In that only the minority of all patients with NSCLC will have EGFR or other treatment-altering mutations, and because nearly all lung cancer therapy is costly, molecular analysis is increasingly important from clinical, scientific, and economic perspectives.

In conclusion, based on this meta-analysis, treatment with EGFR-TKIs statistically significantly delays disease progression in

EGFRmut⁺ patients but has no demonstrable impact on OS. EGFR mutation is a predictive biomarker of benefit with EGFR-TKIs treatment in delaying disease progression in front-line, second-line, and subsequent therapy and in maintenance settings. These findings support assessment of EGFR mutation status before initiation of EGFR-TKIs treatment and indicate that EGFR-TKIs should be considered as front-line therapy in EGFRmut⁺ patients with advanced NSCLC.

References

1. Sato M, Shames DS, Gazdar AF, Minna JD. A translational view of the molecular pathogenesis of lung cancer. *J Thorac Oncol.* 2007;2(4):327–343.
2. Sun S, Schiller JH, Gazdar AF. Lung cancer in never smokers—a different disease. *Nat Rev Cancer.* 2007;7(10):778–790.
3. Tang X, Shigematsu H, Bekele BN, et al. EGFR tyrosine kinase domain mutations are detected in histologically normal respiratory epithelium in lung cancer patients. *Cancer Res.* 2005;65(17):7568–7572.
4. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med.* 2004;350(21):2129–2139.
5. Paez JG, Jänne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science.* 2004;304(5676):1497–1500.
6. Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancers from “never smokers” and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc Natl Acad Sci U S A.* 2004;101(36):13306–13311.
7. Bria E, Milella M, Cuppone F, et al. Outcome of advanced NSCLC patients harboring sensitizing EGFR mutations randomized to EGFR tyrosine kinase inhibitors or chemotherapy as first-line treatment: a meta-analysis. *Ann Oncol.* 2011;22(10):2277–2285.
8. Petrelli F, Borgonovo K, Cabiddu M, Barni S. Efficacy of EGFR tyrosine kinase inhibitors in patients with EGFR-mutated non-small-cell lung cancer: a meta-analysis of 13 randomized trials. *Clin Lung Cancer.* 2012;13(2):107–114.
9. Gao G, Ren S, Li A, et al. Epidermal growth factor receptor-tyrosine kinase inhibitor therapy is effective as first-line treatment of advanced non-small-cell lung cancer with mutated EGFR: a meta-analysis from six phase III randomized controlled trials. *Int J Cancer.* 2012;131(5):E822–829.
10. Kwak EL, Bang Y-J, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med.* 2010;363(18):1693–1703.
11. Shaw AT, Camidge DR, Engelman JA, et al. Clinical activity of crizotinib in advanced non-small cell lung cancer (NSCLC) harboring ROS1 gene rearrangement. *J Clin Oncol.* 2012;30(15 suppl):7508.
12. Ciuleanu T, Stelmakh L, Cicenans S, et al. Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (TITAN): a randomised multicentre, open-label, phase 3 study. *Lancet Oncol.* 2012;13(3):300–308.
13. Cappuzzo F, Ciuleanu T, Stelmakh L, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. *Lancet Oncol.* 2010;11(6):521–529.
14. Garassino MC, Martelli O, Bettini A, et al. TAILOR: phase III trial comparing erlotinib with docetaxel in the second-line treatment of NSCLC patients with wild-type (wt) EGFR. *J Clin Oncol.* 2012;30(15 suppl):LBA7501.
15. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med.* 1998;17(24):2815–2834.
16. Zhou C, Wu Y-L, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol.* 2011;12(8):735–742.
17. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med.* 2010;362(25):2380–2388.

18. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol.* 2012;13(3):239–246.
19. Mok TS, Wu Y-L, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med.* 2009;361(10):947–957.
20. Fukuoka M, Wu Y-L, Thongprasert S, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). *J Clin Oncol.* 2011;29(21):2866–2874.
21. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol.* 2010;11(2):121–128.
22. Herbst RS, Prager D, Hermann R, et al. TRIBUTE: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. *J Clin Oncol.* 2005;23(25):5892–5899.
23. Han J-Y, Park K, Kim S-W, et al. First-SIGNAL: First-line single-agent irressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung. *J Clin Oncol.* 2012;30(10):1122–1128.
24. Giaccone G, Herbst RS, Manegold C, et al. Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial—INTACT 1. *J Clin Oncol.* 2004;22(5):777–784.
25. Herbst RS, Giaccone G, Schiller JH, et al. Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial—INTACT 2. *J Clin Oncol.* 2004;22(5):785–794.
26. Gatzemeier U, Pluzanska A, Szczesna A, et al. Phase III study of erlotinib in combination with cisplatin and gemcitabine in advanced non-small-cell lung cancer: the Tarceva Lung Cancer Investigation Trial. *J Clin Oncol.* 2007;25(12):1545–1552.
27. Reck M, Von Pawel J, Fischer JR, et al. Erlotinib versus carboplatin/vinorelbine in elderly patients (age 70 or older) with advanced non-small cell lung carcinoma (NSCLC): a randomized phase II study of the German Thoracic Oncology Working Group. *J Clin Oncol.* 2010;28(15 suppl):7565.
28. Douillard J-Y, Shepherd FA, Hirsh V, et al. Molecular predictors of outcome with gefitinib and docetaxel in previously treated non-small-cell lung cancer: data from the randomized phase III INTEREST trial. *J Clin Oncol.* 2010;28(5):744–752.
29. Kim ES, Hirsh V, Mok T, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. *Lancet.* 2008;372(9652):1809–1818.
30. Zhang L, Ma S, Song X, et al. Gefitinib versus placebo as maintenance therapy in patients with locally advanced or metastatic non-small-cell lung cancer (INFORM; C-TONG 0804): a multicentre, double-blind randomised phase 3 trial. *Lancet Oncol.* 2011;13(5):466–475.
31. Maruyama R, Nishiwaki Y, Tamura T, et al. Phase III study, V-15-32, of gefitinib versus docetaxel in previously treated Japanese patients with non-small-cell lung cancer. *J Clin Oncol.* 2008;26(26):4244–4252.
32. Perol M, Chouaid C, Milleron BJ, et al. Maintenance with either gemcitabine or erlotinib versus observation with predefined second-line treatment after cisplatin-gemcitabine induction chemotherapy in advanced NSCLC: IFCT-GFPC 0502 phase III study. *J Clin Oncol.* 2010;28(15 suppl):7507.
33. Mitsudomi T, Morita S, Yatabe Y, et al. Updated overall survival results of WJTOG 3405, a randomized phase III trial comparing gefitinib (G) with cisplatin plus docetaxel (CD) as the first-line treatment for patients with non-small cell lung cancer harboring mutations of the epidermal growth factor receptor (EGFR). *J Clin Oncol.* 2012;30(15 suppl):7521.
34. Yang JC-H, Schuler MH, Yamamoto N, et al. LUX-Lung 3: a randomized, open-label, phase III study of afatinib versus pemetrexed and cisplatin as first-line treatment for patients with advanced adenocarcinoma of the lung harboring EGFR-activating mutations. *J Clin Oncol.* 2012;30(15 suppl):LBA7500.
35. Zhou C, Wu YL, Liu X, et al. Overall survival (OS) results from OPTIMAL (CTONG0802), a phase III trial of erlotinib (E) versus carboplatin plus gemcitabine (GC) as first-line treatment for Chinese patients with EGFR mutation-positive advanced non-small cell lung cancer (NSCLC). *J Clin Oncol.* 2012;30(15 suppl):7520.
36. Lee S, Rudd R, Khan I, et al. TOPICAL: Randomized phase III trial of erlotinib compared with placebo in chemotherapy-naïve patients with advanced non-small cell lung cancer (NSCLC) and unsuitable for first-line chemotherapy. *J Clin Oncol.* 2010;28(15 suppl):7504.
37. Gatzemeier U, Heller A, Foerzler D, et al. Exploratory analyses EGFR, KRAS mutations and other molecular markers in tumors of NSCLC patients (pts) treated with chemotherapy +/- erlotinib (TALENT). *J Clin Oncol.* 2005;23(16 suppl):7028.
38. Inoue A, Kobayashi K, Maemondo M, et al. Final overall survival results of NEJ002, a phase III trial comparing gefitinib to carboplatin (CBDCA) plus paclitaxel (TXL) as the first-line treatment for advanced non-small cell lung cancer (NSCLC) with EGFR mutations. *J Clin Oncol.* 2011;29(15 suppl):7519.
39. Zhu C-Q, da Cunha Santos G, Ding K, et al. Role of KRAS and EGFR as biomarkers of response to erlotinib in National Cancer Institute of Canada Clinical Trials Group Study BR.21. *J Clin Oncol.* 2008;26(26):4268–4675.
40. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med.* 2005;353(2):123–132.
41. Thatcher N, Chang A, Parikh P, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet.* 2005;366(9496):1527–1537.
42. Sun JM, Lee KH, Kim SW, et al. Gefitinib versus pemetrexed as second-line treatment in patients with non-small cell lung cancer previously treated with platinum-based chemotherapy (KCSG-LU08-01) [published online ahead of print June 6, 2012]. *Cancer.* 2012. doi:10.1002/cncr.27630.
43. Lee SM, Khan I, Upadhyay S, et al. First-line erlotinib in patients with advanced non-small-cell lung cancer unsuitable for chemotherapy (TOPICAL): a double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2012;13(11):1161–1170.
44. Pérol M, Chouaid C, Pérol D, et al. 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.* 2012;30(28):3516–3524.
45. Bell DW, Lynch TJ, Haselet SM, et al. Epidermal growth factor receptor mutations and gene amplification in non-small-cell lung cancer: molecular analysis of the IDEAL/INTACT gefitinib trials. *J Clin Oncol.* 2005;23(31):8081–8092.
46. Hotta K, Kiura K, Fujiwara Y, et al. Role of survival post-progression in phase III trials of systemic chemotherapy in advanced non-small-cell lung cancer: a systematic review. *PLoS One.* 2011;6(11):e26646.
47. Fleming TR. Standard versus adaptive monitoring procedures: a commentary. *Stat Med.* 2006;25(19):3305–3312.
48. Fleming TR, Rothmann MD, Lu HL. Issues in using progression-free survival when evaluating oncology products. *J Clin Oncol.* 2009;27(17):2874–2880.
49. Dodd LE, Korn EL, Freidlin B, et al. Blinded independent central review of progression-free survival in phase III clinical trials: important design element or unnecessary expense? *J Clin Oncol.* 2008;26(22):3791–3796.
50. Ciardiello F, Caputo R, Bianco R, et al. Antitumor effect and potentiation of cytotoxic drugs activity in human cancer cells by ZD-1839 (Iressa), an epidermal growth factor receptor-selective tyrosine kinase inhibitor. *Clin Cancer Res.* 2000;6(5):2053–2063.
51. Sirotmak FM, Zakowski MF, Miller VA, Scher HI, Kris MG. Efficacy of cytotoxic agents against human tumor xenografts is markedly enhanced by coadministration of ZD1839 (Iressa), an inhibitor of EGFR tyrosine kinase. *Clin Cancer Res.* 2000;6(12):4885–4892.
52. Jänne PA, Wang X, Socinski MA, et al. Randomized phase II trial of erlotinib alone or with carboplatin and paclitaxel in patients who were never or light former smokers with advanced lung adenocarcinoma: CALGB 30406 trial. *J Clin Oncol.* 2012;30(17):2063–2069.
53. Luis P-A. Beyond first-line NSCLC therapy: chemotherapy or erlotinib? *Lancet Oncol.* 2012;13(3):225–227.

54. Tsiatis AC, Norris-Kirby A, Rich RG, et al. Comparison of Sanger sequencing, pyrosequencing, and melting curve analysis for the detection of KRAS mutations: diagnostic and clinical implications. *J Mol Diagn.* 2010;12(4):425–432.
55. Maheswaran S, Sequist LV, Nagrath S, et al. Detection of mutations in EGFR in circulating lung-cancer cells. *N Engl J Med.* 2008;359(4):366–377.
56. Rosell R, Molina MA, Costa C, et al. Pretreatment EGFR T790M mutation and BRCA1 mRNA expression in erlotinib-treated advanced non-small-cell lung cancer patients with EGFR mutations. *Clin Cancer Res.* 2011;17(5):1160–1168.
57. Su K-Y, Chen H-Y, Li K-C, et al. Pretreatment epidermal growth factor receptor (EGFR) T790M mutation predicts shorter egfr tyrosine kinase inhibitor response duration in patients with non-small-cell lung cancer. *J Clin Oncol.* 2012;30(4):433–440.

Funding

This work was partially supported by an educational grant from Boehringer Ingelheim.

Notes

We thank the investigators of ISEL, V-15-32, and IFCT-GFPC 0502, and AstraZeneca for providing us with unpublished data for this meta-analysis. We also thank the members of the Australasian Lung Cancer Trials Group and Dr Sally

Lord (NHMRC Clinical Trials Centre) for the helpful comments. We acknowledge the editorial support provided by Ms Rhana Pike and Ms Stefanie Chuah.

Affiliations of authors: National Health and Medical Research Council Clinical Trials Centre, University of Sydney, Sydney, Australia (CKL, CB, VG); Albert Einstein College of Medicine, Jacobi Medical Center, South Bronx, New York (RJG); McGill University Health Center, Royal Victoria Hospital, Montreal, Canada (VH); Maharaj Nakorn Chiang Mai Hospital, Chiang Mai University, Chiang Mai, Thailand (ST); Department of Chest Medicine, Taipei Veterans General Hospital, Taipei, Taiwan (C-MT); Department of Medical Oncology, National Cancer Center, Singapore (EHT); Department of Medicine, University of Hong Kong, Hong Kong, China (JC-MH); Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China (DTC); Gleneagles Hospital, Penang, Malaysia (AZ); St Paul of Chartes, Medical Specialty Center, Perpetual Succor Hospital, Cebu City, Philippines (JAOS); Ho Chi Minh City's Oncology Hospital, Ho Chi Minh City, Vietnam (VWV); Department of Clinical Oncology, Queen Elizabeth Hospital, Hong Kong, China (JSKA); Department of Respiratory Medicine, Tohoku University Hospital 1-1, Sendai, Japan (AI); Department of Oncology, University College London (UCL) Cancer Institute and UCL Hospitals, London, United Kingdom (SML); Graduate Institute of Oncology and Cancer Research Center, National Taiwan University College of Medicine, Taipei, Taiwan (JC-HY).



Randomized phase II trial of uracil/tegafur and cisplatin versus vinorelbine and cisplatin with concurrent thoracic radiotherapy for locally advanced unresectable stage III non-small-cell lung cancer: NJLCG 0601

Shunichi Sugawara^{a,*}, Makoto Maemondo^b, Motoko Tachihara^c, Akira Inoue^d, Osamu Ishimoto^a, Tomohiro Sakakibara^d, Kazuhiro Usui^e, Hiroshi Watanabe^a, Nobumichi Matsubara^b, Kana Watanabe^b, Kenya Kanazawa^c, Takashi Ishida^c, Yasuo Saijo^f, Toshihiro Nukiwa^d, North Japan Lung Cancer Study Group^g

^a Department of Pulmonary Medicine, Sendai Kousei Hospital, 4-15 Hirosemachi, Aoba-ku, Sendai 980-0873, Japan

^b Department of Respiratory Medicine, Miyagi Cancer Center, 47-1 Nodayama, Medeshima-Shiode, Natori 981-1293, Japan

^c Department of Pulmonary Medicine, Fukushima Medical University, Hikarigaoka-1, Fukushima 960-1295, Japan

^d Department of Respiratory Medicine, Tohoku University, 1-1 Seiryomachi, Aoba-ku, Sendai 980-8574, Japan

^e Division of Respiratory, NTT Medical Center Tokyo, 5-9-22 Higashi Gotanda, Shinagawa-ku, Tokyo 141-0022, Japan

^f Department of Medical Oncology, Hirosaki University Graduate School of Medicine, 5 Zaifu-cho, Hirosaki 036-8562, Japan

^g Sendai, Japan

ARTICLE INFO

Article history:

Received 28 November 2012

Received in revised form 14 March 2013

Accepted 8 April 2013

Keywords:

UFT

Vinorelbine

Cisplatin

Chemoradiotherapy

Locally advanced

Non-small-cell lung cancer

Randomized phase II trial

ABSTRACT

Introduction: The optimal chemotherapy with thoracic radiotherapy (TRT) for locally advanced non-small-cell lung cancer (NSCLC) remains to be established. This randomized phase II study of concurrent chemoradiotherapy was conducted to compare uracil/tegafur (UFT) and cisplatin with vinorelbine and cisplatin for stage III NSCLC.

Patients and methods: Patients with unresectable stage III NSCLC were randomized to receive UP (400 mg/m² UFT on days 1–14 and 29–42 and 80 mg/m² cisplatin on days 8 and 36) or NP (20 mg/m² vinorelbine on days 1, 8, 29, and 36 and 80 mg/m² cisplatin on days 1 and 29). TRT began on day 1 (total 60 Gy in 30 fractions).

Results: Of 70 enrolled patients, 66 were evaluable for efficacy and safety. The overall response rates were 80% (95% CI: 67–93%) and 71% (95% CI: 55–87%) for the UP arm and the NP arm. With a median follow-up of 20.2 months, the progression-free survival and median survival time were 8.8 and 26.9 months in the UP arm, and 6.8 and 21.7 months in the NP arm. The 2-/3-year survival rates were 51.0/34.3% and 46.9/33.4% for the UP arm and the NP arm, respectively. Grade 3/4 neutropenia occurred in 20% and 58% of patients in the UP and NP arms, respectively.

Conclusion: Combined with concurrent TRT, the UP arm achieved better efficacy and safety compared with the NP arm, suggesting it to be a promising candidate as a standard regimen for locally advanced NSCLC. Further evaluation of the UP arm is warranted.

© 2013 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Lung cancer remains the leading cause of death related to cancer worldwide [1]. Non-small-cell lung cancer (NSCLC) accounts for 80% of lung cancer cases, and approximately 30% of NSCLC patients present with locally advanced disease [2].

In the 1980s, US cooperative groups showed that cisplatin-based, second-generation chemotherapy followed by thoracic

radiotherapy (TRT) for stage III NSCLC improved median survival time (MST) and 5-year survival compared with TRT alone [3,4]. In the 1990s, two randomized studies that compared concurrent versus sequential cisplatin-based, second-generation chemoradiotherapy demonstrated that the concurrent approach provided superior survival outcome, although it was also associated with greater toxicity [5,6]. However, even in a meta-analysis, the superiority of concurrent chemoradiotherapy to sequential one was reported [7]. Thus, concurrent chemoradiotherapy is regarded as the standard treatment for locally advanced NSCLC.

During the last decade, platinum-based third-generation chemotherapies, such as paclitaxel, vinorelbine, gemcitabine,

* Corresponding author. Tel.: +81 22 222 6181; fax: +81 22 713 8013.

E-mail address: swara357@cat-v.ne.jp (S. Sugawara).

and docetaxel, have been proven to improve the survival of patients with metastatic NSCLC compared with second-generation chemotherapies [8–10]. In addition, several phase I and II studies of third-generation chemotherapy with concurrent TRT for locally advanced NSCLC provided promising survival outcomes [11–17]. However, it seems to be difficult to deliver full doses of the above-described regimens because of dose-limiting toxicities.

Concurrent chemoradiotherapy with vinorelbine and cisplatin (NP) is one of the commonly used regimens for locally advanced NSCLC in Japan, yielding a reasonable response rate, median survival time (MST), and 3-year survival rate in a phase I trial and retrospective analysis [17,18]. Subsequently, in a recent phase III study comparing second- and third-generation regimens with concurrent TRT for unresectable stage III NSCLC, weekly paclitaxel, carboplatin, and TRT followed by 2 courses of triweekly consolidation provided good results in terms of both efficacy and toxicity [19]. And also weekly docetaxel, cisplatin and TRT provided better efficacy and hematological toxicities [20]. It has therefore been suggested that these regimens should be regarded as standard treatments for locally advanced NSCLC.

Although UFT, an oral preparation of uracil and tegafur, is seldom used for metastatic NSCLC, two phase II studies of UFT plus cisplatin (UP) in advanced NSCLC have exhibited efficacy almost equivalent to other potent regimens [21,22]. Moreover, a full dose regimen of UP chemotherapy with concurrent TRT for locally advanced NSCLC in a multi-institutional phase II trial has shown a promising outcome with low hematological toxicity [23].

The optimal combination chemotherapy with TRT for locally advanced NSCLC remains to be established. Thus, to select a proper candidate for a phase III study of chemoradiotherapy, we conducted a randomized phase II study comparing the UP arm with the NP arm.

2. Patients and methods

2.1. Patient eligibility

The study population consisted of patients between 20 and 75 years of age inclusive, with cytologically or histologically confirmed NSCLC with unresectable stage IIIA or IIIB disease. Mediastinoscopies were not performed and lymph node metastases were clinically diagnosed based on the results of computed tomography (CT) scan and/or positron emission tomography (PET) scan. Unresectable stage IIIA disease was defined by the presence of multiple/bulky N2 mediastinal lymph nodes on CT such that, in the judgment of the treating investigator, the patients were unsuitable as candidates for surgical resection. Patients were required to have lesions measurable with the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0.

Other eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, no prior systemic chemotherapy, TRT or thoracic surgery. Laboratory requirements included a white blood cell count of 4000 mm^{-3} or more, a neutrophil count of 2000 mm^{-3} or more, a platelet count of $100,000\text{ mm}^{-3}$ or more, a hemoglobin level of 10 g/dL or more, a total bilirubin level of 1.5 mg/dL or less, an AST/ALT value of twice the upper normal limit or less, a creatinine level of 1.5 mg/dL or less, a creatinine clearance of 60 mL/min or more, and partial pressure of arterial oxygen of 60 torr or more.

Patients were ineligible if they had concomitant malignancies, active infectious diseases, serious complications such as ileus, uncontrolled diabetes mellitus, heart failure, renal failure, or hepatic failure, malignant pleural or pericardial effusion, interstitial pneumonitis or pulmonary fibrosis apparent on chest X-ray, and other medical problems regarded as making them ineligible for this study by physicians. Lactating, pregnant or possibly pregnant

women, or those willing to become pregnant were also excluded. The study protocol was approved by the institutional review board of each hospital concerned and written informed consent was obtained from each patient.

Prestudy radiographic assessment to document tumor staging for eligibility included CT of the thorax including the upper abdomen, brain CT or magnetic resonance imaging and radioisotopic bone scan. PET scan was allowed to be substituted for radioisotopic bone scan.

2.2. Treatment schedules

Patients were randomly assigned to one of two treatment arms (UP arm and VP arm) as shown in Fig. 1 (CONSORT diagram), stratified by gender (male *v* female), age (59 or younger *v* 60–64 *v* 65–69 *v* 70–75), histology (adenocarcinoma *v* squamous cell carcinoma *v* large cell carcinoma *v* other), and clinical stage (IIIA *v* IIIB).

In the UP arm, oral UFT ($400\text{ mg/m}^2/\text{day}$) twice daily before meals from days 1 to 14 and from days 29 to 42 and cisplatin (80 mg/m^2) via intravenous infusion on days 8 and 36 were administered. According to body surface area (BSA), the actual dose of UFT was modified as follows: BSA less than 1.25 m^2 , 500 mg/day (300 mg in the morning and 200 mg in the evening); BSA 1.25 m^2 or more, 600 mg/day (300 mg b.i.d.). Concurrent TRT was given in daily fractions of 2 Gy from day 1 up to a total of 60 Gy in 30 fractions over a 6-week period. In the NP arm, vinorelbine (20 mg/m^2) on days 1, 8, 29, and 36 and cisplatin (80 mg/m^2) on days 1 and 29 were administered intravenously. The schedule of TRT was the same as that of the UP arm.

Two cycles of additional treatment with the same dosage were optionally permitted in both arms as consolidation chemotherapy. There was no evidence that consolidation chemotherapy prolonged overall survival for locally advanced NSCLC. Therefore, consolidation chemotherapy was considered at the investigator's discretion.

2.3. Radiotherapy

Radiotherapy began on day 1 of chemotherapy in both arms with a linear accelerator photon beam of 4 MV or more.

In this study, both 2D and 3D treatment planning systems were allowed. Radiation doses were specified at the center of the target volume. 3D dose constraints for both planning target volume and normal-risk organs were not determined in the protocol. The doses were calculated assuming tissue homogeneity with correction for lung tissues in 3D treatment planning. As it turned out, 3D treatment planning was performed for all 66 patients who received radiotherapy.

The initial 40 Gy was delivered to the large field target volume, which included the primary tumor, ipsilateral hilum, and mediastinum. No prophylactic irradiation of the supraclavicular fossa area was given. The other 20 Gy was delivered to a pair of oblique fields to avoid excess irradiation of the spinal cord.

2.4. Treatment modifications

The administration of cisplatin was withheld on either arm if there was a decrease in the leukocyte count to below 3000 mm^{-3} , or the neutrophil count to under 1500 mm^{-3} , or the platelet count to less than $100,000\text{ mm}^{-3}$, or if grade 2 or more nonhematological toxicities were observed, except for alopecia, anorexia, and malaise, until resolution of toxicity to grade 0 or 1. In the UP arm, UFT was stopped and then reduced in subsequent cycles from 600 mg or 500 mg to 400 mg or 300 mg , respectively if any grade 4 hematological toxicities, or grade 3 or worse nonhematological toxicities, except for alopecia, anorexia, or malaise, were observed. Whenever grade 2 diarrhea or stomatitis occurred, UFT was reduced. In the NP

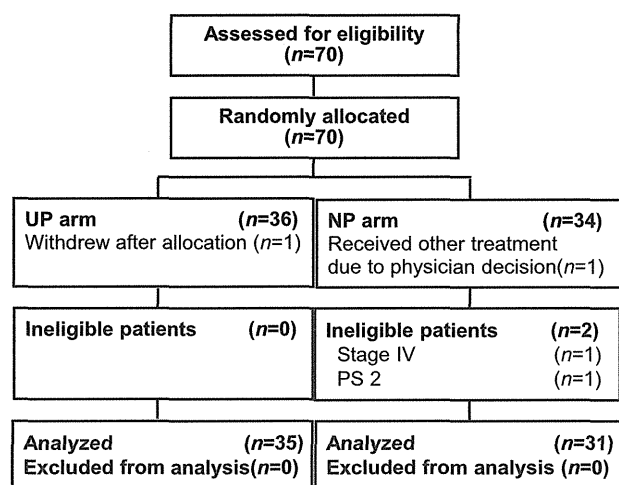


Fig. 1. CONSORT diagram. UP, uracil/tegafur and cisplatin; NP, vinorelbine and cisplatin.

arm, the administration of vinorelbine on days 8, 29, or 36 was omitted and a delay of up to 7 days was permitted if any grade 2 or worse hematological or nonhematological toxicities were observed. TRT was withheld on either arm in cases of any grade 4 hematological toxicities, grade 3 or worse esophagitis or dermatitis, grade 1 or worse fever, or any sign of pneumonitis. Any patient unable to receive a subsequent cycle within 7 days was removed from the protocol treatment, but was included in the study analysis.

2.5. Evaluation of efficacy and safety

All eligible patients who received any protocol treatment were regarded as evaluable for efficacy and safety. Complete blood cell counts and biochemistry tests were performed once a week during the treatment period. Thoracic CT was performed every 4 weeks during and after the treatment period until progressive disease was recognized.

The response was evaluated according to RECIST version 1.0 in the extramural review. Progression-free survival (PFS) was defined as the period from the date of randomization to the date when disease progression was first observed or death occurred. Overall survival (OS) was defined as the period between randomization and death from any cause. Toxicities were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

2.6. Statistical analysis

The primary endpoint was overall response rate (ORR), and secondary endpoints included PFS, OS, and the level of toxicity. Assuming that an ORR of 80% in eligible patients would indicate potential usefulness, while an ORR of 60% would be the lower limit of interest, with $\alpha = 0.05$ and $\beta = 0.20$, the estimated required accrual was 33 patients in each arm. Allowing for dropouts, the accrual goal was determined to be 35 patients in each arm.

Fisher's exact test was used to estimate the correlation among different variables between arms. Survival estimation was performed according to the Kaplan–Meier method.

3. Results

3.1. Patient characteristics

Between February 2006 and May 2009, 70 patients were enrolled from 5 institutions and were allocated to the UP arm

Table 1
Characteristics of patients in each treatment arm.

Characteristic	UP arm (n=35)		NP arm (n=31)		P
	No.	%	No.	%	
Gender					0.6841
Male	28	80.0	26	83.9	
Female	7	20.0	5	16.1	
Age (years)					0.8326
Median	62		61		
59≥	12	34.3	14	45.2	
60–64	10	28.6	8	25.8	
65–69	7	20.0	5	16.1	
70–75	6	17.1	4	12.9	
PS (ECOG)					0.8281
0	16	45.7	15	48.4	
1	19	54.3	16	51.6	
Histology					0.4765
Adenocarcinoma	17	48.6	19	61.3	
Squamous cell carcinoma	15	42.9	11	35.5	
Large cell carcinoma	2	5.7	0	0	
Other	1	2.9	1	3.2	
Stage					0.8888
IIIA	13	37.1	11	35.5	
IIIB	22	62.9	20	64.5	

($n = 36$) and NP arm ($n = 34$). Of the 70 patients enrolled, 4 patients were excluded from final analysis, including one patient due to withdrawal of the informed consent before the allocated treatment, 2 patients due to ineligibility (stage IV and PS 2), and 1 patient who received a different regimen based on the physician's judgment instead of the protocol treatment. Eventually 66 patients (UP arm, $n = 35$ and NP arm, $n = 31$) were evaluable for efficacy and safety (CONSORT diagram, Fig. 1). No remarkable differences in demographic characteristics were found between the two treatment arms (Table 1).

3.2. Treatment administered

As shown in Table 2, the median number of treatment cycles was 3 (range 1–4) in both arms. 94.3% of patients in the UP arm and 93.5% of patients in the NP arm underwent the projected two cycles of chemotherapy and concurrent TRT. As consolidation chemotherapy, 60% of patients in the UP arm and 58.1% of patients in the NP arm received the additional treatment with the same regimen as allowed by the protocol. Main reason for quitting chemotherapy after two cycles of the protocol treatment was investigator's discretion. Most of patients who received consolidation chemotherapy completed 4 cycle of treatment altogether as long as the progression was not observed.

In all except 1 patient in each arm, 60 Gy concurrent TRT was completed.

Table 2
Treatment delivery.

	UP arm (n=35)		NP arm (n=31)	
	No.	%	No.	%
Cycle number				
1	2	5.7	2	6.5
2	12	34.3	11	35.5
3	5	14.3	7	22.6
4	16	45.7	11	35.5
Median		3.0		3.0
TRT (Gy)				
60	34	97.1	30	96.8
50–59	0	0	1	3.2
40–49	1	2.9	0	0
Median		60.0		60.0

Table 3
Objective response rates.

	UP arm (n = 35)		NP arm (n = 31)	
	No.	%	No.	%
Complete response	2	5.7	1	3.2
Partial response	26	74.3	21	67.7
Stable disease	7	20.0	7	22.6
Progressive disease	0	0.0	2	6.5
Response rate (CR + PR ^a)	28	80.0	22	71.0

^a $P=0.5659$.

3.3. Efficacy

In the UP arm, the ORR was 80% (95% CI, 67–93%), including 2 patients (6%) with a complete response (CR), 26 (74%) with a partial response (PR), and no patient with progressive disease (PD). In the NP arm, the ORR was 71% (95% CI, 55–87%), including 1 patient (3%) with CR, 21 (68%) with PR, and 2 (6%) with PD (Table 3). Although the response rate in the UP arm was superior to that in the NP arm, this difference between two arms was not statistically significant ($P=.566$).

The PFS and OS data are shown in Fig. 2. With a median follow-up of 20.2 months, 40 patients had died. The median PFS were 8.8 months (95%CI, 6.7–11.1 months) in the UP arm, and 6.8 months (95%CI, 5.2–9.6 months) in the NP arm, respectively. The MST in the UP arm was 26.9 months (95% CI, 16.3–52.9 months) compared with 21.7 months (95% CI, 14.5–45.3 months) in the NP arm. The 2-/3-year survival rates were marginally higher in the UP arm (51.0/34.3%) than that in the NP arm (46.9/33.4%).

The sites of first failure among 31 recurrent cases in the UP arm, 12 (38.7%) were local and 19 (61.3%) were distant including 11 patients with brain metastasis, whereas among 26 recurrent cases in the NP arm, 14 (53.8%) were local, 12 (46.2%) were distant, including 6 with brain metastasis (data not shown).

3.4. Safety

Grade 3 or worse toxicities in each arm are shown in Table 4. Grades 3 and 4 neutropenia and febrile neutropenia were significantly more frequent in the NP arm than in the UP arm ($P=.002$ and $.044$, respectively). Although anorexia, nausea/vomiting, and diarrhea over grade 3 tended to be more frequent in UP arm, there were no statistically significant differences between the two arms in these categories. No one had grade 3 or worse esophagitis in either arm. Two patients in the NP arm died of radiation pneumonitis approximately five months after the completion of 60 Gy of TRT.

4. Discussion

We set out to compare oral fluoropyrimidine with third-generation anticancer agent in platinum-based chemoradiotherapy for locally advanced stage III NSCLC. The combined modality strategy with chemotherapy and concurrent TRT is considered as a standard treatment for locally advanced unresectable NSCLC. However, the optimal chemotherapy regimen remains to be determined. Two randomized phase III studies comparing third-generation regimen with second-generation regimen combined with concurrent TRT showed superior survival outcomes in third-generation regimen [19,20]. Moreover, based on recent randomized phase II and III studies, weekly carboplatin and paclitaxel with TRT has become a commonly used regimen, and is regarded as the reference arm for future phase III studies [16,19].

In this trial, we adopted the response rate as a primary endpoint because it is not influenced by post trial treatment. On the other hand, most of recent chemoradiotherapy phase II trials choose 2-year survival rate or PFS as primary endpoint. Thus, we also carefully followed-up for PFS and OS. Both the UP arm and NP arm showed a reasonably good response rate and survival outcomes in the present study. These data were comparable to those of third-generation regimens in other previous phase II and III trials. As to the primary endpoint, the ORR of the UP arm was better, but not with statistical significance, than that of the NP arm. In addition, the median PFS, the median OS, and the 2-year survival rate in the UP arm were better than those in the NP arm. There was a non-significant trend toward more favorable survival data in the UP arm than the NP arm although the small sample size in this study prevented reaching a definite conclusion.

It cannot be denied that epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib could contribute to long-term survival. EGFR mutation screening was not routinely performed in this study, because this examination was not available at the start of this study. Among 36 patients (UP arm, $n=20$ and NP arm, $n=16$) who subsequently underwent EGFR mutation screening, 5 patients in the UP arm and 3 patients in the NP arm harbored mutated EGFR (data not shown). Only 2 of them, both in the UP arm achieved PR and long-term survival. Hence, it is difficult to evaluate whether the use of EGFR-TKIs would have resulted in better survival outcomes.

It is noteworthy in the present study that hematological toxicities were very mild in the UP arm. In particular, the incidence of grade 3 or worse neutropenia in the UP arm was remarkably lower than not only in the NP arm of this study but also in the other regimens referred to above. Moreover, no febrile neutropenia was observed in the UP arm. Although grade 3 gastrointestinal toxicities which are common in fluoropyrimidines were more frequent in the UP arm than in the NP arm, they were all reversible and manageable thus this does not seem to be a critical impact. Therefore, UP

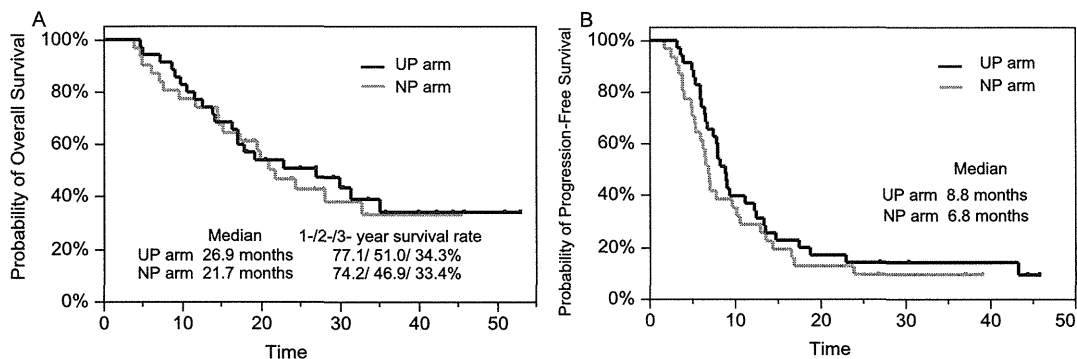


Fig. 2. (A) Overall survival and (B) progression free survival in each arm.

Table 4
Grade 3 or worse toxicity.

	UP arm (n = 35)				NP arm (n = 31)				P
	Grade		≥Grade 3		Grade		≥Grade 3		
	3	4	No.	(%)	3	4	No.	(%)	
Hematologic									
Leucopenia	7	1	8	22.9	14	5	19	61.3	0.0024
Neutropenia	3	4	7	20.0	8	10	18	58.1	0.0022
Anemia	2	0	2	5.7	2	0	2	6.5	1.000
Thrombocytopenia	1	0	1	2.9	1	0	1	3.2	1.000
Febrile neutropenia	0	0	0	0	4	0	4	12.9	0.0437
Non-hematologic									
Anorexia	5	0	5	14.3	3	0	3	9.7	0.7132
Nausea/vomiting	4	0	4	11.4	2	0	2	6.5	0.6762
Diarrhea	2	0	2	5.7	0	0	0	0	0.4942
Infection	0	0	0	0	2	0	2	6.5	0.2168
Pneumonitis	2	0	2	5.7	0	2 ^a	2	6.5	1.000

^a Both patients died of radiation pneumonitis.

might rise to a less toxic new standard regimen in comparison with the third-generation regimen for locally advanced NSCLC.

S-1 is a novel oral fluoropyrimidine agent designed for enhancing anticancer activity and reducing gastrointestinal toxicity. Indeed, it showed potent activity not only as a single agent but also in combination with CDDP for metastatic NSCLC [24,25]. In addition S-1 plus CDDP with concurrent TRT in a phase II study yielded high response rates, good survival data, and only mild toxicities [26,27]. Therefore oral fluoropyrimidines such as UFT and S-1 hereafter may play an important role in terms of concurrent chemoradiotherapy for locally advanced NSCLC.

As a limitation of this study, the radiation technique was old-fashioned. At the start of this multi-institutional study, 3D treatment planning system using CT was not available at all institutions. Therefore, both 2D and 3D treatment planning systems were allowed in the protocol. Because 3D dose constraints for both planning target volume and normal-risk organs were not determined by modern radiation technologies, the quality of radiotherapy in this study might have been rather lowered.

In conclusion, combined with concurrent TRT, UP achieved more favorable efficacy and safety than NP, suggesting it to be a promising candidate as a standard regimen with concurrent TRT for locally advanced NSCLC. Further evaluation of this regimen is warranted in a phase III setting in comparison with platinum-based third-generation chemotherapy with concurrent TRT.

Conflict of interest statement

None declared.

Acknowledgements

We thank to all the patients and their families as well as all the investigators for their support in this study. We are indebted to Prof J. Barron.

References

- [1] Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin* 2009;59:225–49.
- [2] van Meerbeek JP. Staging of non-small cell lung cancer: consensus, controversies and challenges. *Lung Cancer* 2001;34(Suppl. 2):S95–107.
- [3] Dillman RO, Seagren SL, Propert KJ, Guerra J, Eaton WL, Perry MC, et al. A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer. *N Engl J Med* 1990;323:940–5.
- [4] Sause W, Kolesar P, Taylor SIV, Johnson D, Livingston R, Komaki R, et al. Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer. *Chest* 2000;117:358–64.

- [5] Furuse K, Fukuoka M, Kawahara M, Nishikawa H, Takada Y, Kudoh S, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 1999;17:2692–9.
- [6] Curran WJ, Scott CB, Langer CJ, Komaki R, Lee JS, Hauser S, et al. Long-term benefit is observed in a phase III comparison of sequential vs concurrent chemoradiation for patients with unresected stage III NSCLC: RTOG 9410. *Proc Am Soc Clin Oncol* 2003;22:621.
- [7] O'Rourke N, Roqué I, Figuls M, Farré Bernadó N, Macbeth F. Concurrent chemoradiotherapy in non-small cell lung cancer. *Cochrane Database Syst Rev* 2010;6(Jun). CD002140.
- [8] Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002;346:92–8.
- [9] Bunn Jr PA, Kelly K. New chemotherapeutic agents prolong survival and improve quality of life in non-small cell lung cancer: a review of the literature and future directions. *Clin Cancer Res* 1998;4:1087–100.
- [10] Hoffman PC, Mauer AM, Vokes EE. Lung cancer. *Lancet* 2000;355:479–85.
- [11] Masters GA, Haraf DJ, Hoffman PC, Drinkard LC, Krauss SA, Ferguson MK, et al. Phase I study of vinorelbine, cisplatin, and concomitant thoracic radiation in the treatment of advanced chest malignancies. *J Clin Oncol* 1998;16:2157–63.
- [12] Yamada M, Kudoh S, Fukuda H, Nakagawa K, Yamamoto N, Nishimura Y, et al. Dose-escalation study of weekly irinotecan and daily carboplatin with concurrent thoracic radiotherapy for unresectable stage III non-small cell lung cancer. *Br J Cancer* 2002;87:258–63.
- [13] Kiura K, Ueoka H, Segawa Y, Tabata M, Kamei H, Takigawa N, et al. Phase I/II study of docetaxel and cisplatin with concurrent thoracic radiation therapy for locally advanced non-small-cell lung cancer. *Br J Cancer* 2003;89:795–802.
- [14] Vokes EE, Herndon 2nd JE, Crawford J, Leopold KA, Perry MC, Miller AA, et al. Randomized phase II study of cisplatin with gemcitabine or paclitaxel or vinorelbine as induction chemotherapy followed by concomitant chemoradiotherapy for stage IIIB non-small-cell lung cancer: Cancer and Leukemia Group B Study 9431. *J Clin Oncol* 2002;20:4191–8.
- [15] Gandara DR, Chansky K, Albain KS, Leigh BR, Gaspar LE, Lara Jr PN, et al. Consolidation docetaxel after concurrent chemoradiotherapy in stage IIIB non-small-cell lung cancer: Phase II Southwest Oncology Group Study S9504. *J Clin Oncol* 2003;21:2004–10.
- [16] Belani CP, Choy H, Bonomi P, Scott C, Travis P, Haluschak J, et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multimodality protocol. *J Clin Oncol* 2005;23:5883–91.
- [17] Sekine I, Noda K, Oshita F, Yamada K, Tanaka M, Yamashita K, et al. Phase I study of cisplatin and vinorelbine for unresectable stage III non-small-cell lung cancer. *Cancer Sci* 2004;95:691–5.
- [18] Naito Y, Kubota K, Nihei K, Fujii T, Yoh K, Niho S, et al. Concurrent chemoradiotherapy with cisplatin and vinorelbine for stage III non-small-cell lung cancer. *J Thorac Oncol* 2008;3:617–22.
- [19] Yamamoto N, Nakagawa K, Nishimura Y, Tsujino K, Satouchi M, Kudo S, et al. Phase III study comparing second- and third-generation regimens with concurrent thoracic radiotherapy in patients with unresectable stage III non-small-cell lung cancer: West Japan Thoracic Oncology Group WJTOG0105. *J Clin Oncol* 2010;28:3739–45.
- [20] Segawa Y, Kiura K, Takigawa N, Kamei H, Harita S, Hiraki S, et al. Phase III trial comparing docetaxel and cisplatin combination chemotherapy with mitomycin, vindesine, and cisplatin combination chemotherapy with concurrent thoracic radiotherapy in locally advanced non-small-cell lung cancer: OLCSCG 0007. *J Clin Oncol* 2010;28:3299–306.
- [21] Ichinose Y, Yoshimori K, Yoneda S, Kuba M, Kudoh S, Niitani H. UFT plus cisplatin combination chemotherapy in the treatment of patients with advanced nonsmall cell lung cancer: a multiinstitutional phase II trial. *Cancer* 2000;88:318–23.

- [22] Saito J, Nakai Y, Saijo Y, Nukiwa T, Koinumaru S, Matsuura Y, et al. A phase II trial of oral UFT plus cisplatin (CDDP) in patients with non-small cell lung cancer (NSCLC). *Lung Cancer* 2001;31:285–93.
- [23] Ichinose Y, Nakai Y, Kudoh S, Semba H, Yoshida S, Nukiwa T, et al. Uracil/tegafur plus cisplatin with concurrent radiotherapy for locally advanced non-small-cell lung cancer: a multiinstitutional phase II trial. *Clin Cancer Res* 2004;10:4369–73.
- [24] Kawahara M, Furuse K, Segawa Y, Yoshimori K, Matsui K, Kudoh S, et al. Phase II study of S-1, a novel oral fluorouracil, in advanced non-small-cell lung cancer. *Br J Cancer* 2001;85:939–43.
- [25] Ichinose Y, Yoshimori K, Sakai H, Nakai Y, Sugiura T, Kawahara M, et al. S-1 plus cisplatin combination chemotherapy in patients with advanced non-small cell lung cancer: a multiinstitutional phase II trial. *Clin Cancer Res* 2004;10:7860–4.
- [26] Ohyanagi F, Yamamoto N, Horiike A, Harada H, Kozuka T, Murakami H, et al. Phase II trial of S-1 and cisplatin with concurrent radiotherapy for locally advanced non-small-cell lung cancer. *Br J Cancer* 2009;101:225–31.
- [27] Ichinose Y, Seto T, Sasaki T, Yamanaka T, Okamoto I, Takeda K, et al. S-1 plus cisplatin with concurrent radiotherapy for locally advanced non-small cell lung cancer. *J Thorac Oncol* 2011;6:2069–75.