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Updated survival outcomes of NEJ005/TCOG0902: a randomised phase II study of concurrent versus sequential alternating gefitinib and chemotherapy in previously untreated non-small cell lung cancer with sensitive *EGFR* mutations

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ABSTRACT

Background The North-East Japan Study Group (NEJ) 005/Tokyo Cooperative Oncology Group (TCOG) 0902 study has reported that first-line concurrent and sequential alternating combination therapies of an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (gefitinib) plus platinum-based doublet chemotherapy (carboplatin/pemetrexed) offer promising efficacy with predictable toxicities for patients with *EGFR*-mutant non-small cell lung cancer. However, overall survival (OS) data were insufficient in the primary report because of the lack of death events.

Patients and methods Progression-free survival (PFS) and OS were re-evaluated at the final data cut-off point (March 2017) for the entire population (n=80).

Results At the median follow-up time of 35.6 months, 88.8% of patients had progressive disease and 77.5% of patients had died. Median PFS was 17.5 months for the concurrent regimen and 15.3 months for the sequential alternating regimen (P=0.13). Median OS was 41.9 and 30.7 months, respectively (P=0.036). Updated response rates were similar in both groups (90.2% and 82.1%, respectively; P=0.34). Patients with Del19 tumours displayed relatively better OS (median: 45.3 vs 33.3 months, respectively) than those with L858R (31.4 vs 28.9 months, respectively). No severe adverse events, including interstitial lung disease, occurred in the period since the primary report.

Conclusions This updated analysis confirms that PFS is improved with first-line combination therapy compared with gefitinib monotherapy and that the concurrent regimen, in particular, offers an OS benefit of 42 months in the *EGFR*-mutated setting. Our ongoing NEJ009 study will clarify whether this combination strategy can be incorporated into routine clinical practice.

Trial registration number UMIN C000002789, Post-results.

Key questions

What is already known about this subject?

► First-line epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are currently the mainstay for systemic therapy of advanced *EGFR*-mutant non-small cell lung cancer (NSCLC). However, there is an unmet need for more effective treatment strategies in *EGFR*-mutant NSCLC, such as the combination of EGFR-TKIs with other agents.

What does this study add?

► This study examined the efficacy and safety of the combination of an EGFR-TKI (gefitinib) and platinum-based doublet chemotherapy (carboplatin/pemetrexed) in patients with untreated *EGFR*-mutant NSCLC.

How might this impact on clinical practice?

► First-line combination therapies of gefitinib and carboplatin/pemetrexed offer promising efficacy with predictable toxicities in an *EGFR*-mutated setting. Ongoing phase III studies will provide critical data to clarify whether this combination strategy can be incorporated into routine clinical practice.

INTRODUCTION

Molecularly targeted therapies elicit dramatic responses in cancers with driver mutations. Numerous studies have demonstrated the superiority of first-line epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) over standard chemotherapy in regard to progression-free survival (PFS), response and quality of life for non-small cell

lung cancer (NSCLC) with sensitive *EGFR* mutations.[1–8] Thus, first-line EGFR-TKI is currently the mainstay for systemic therapy of advanced *EGFR*-mutant NSCLC.

However, median PFS with gefitinib monotherapy is 9–10 months in these patients and more effective treatment strategies, such as the combination of EGFR-TKIs with other agents, are warranted. Even in this new treatment era, the essential component of lung cancer treatment still tends to be anchored in cytotoxic chemotherapy. Recently, first-line combination of EGFR-TKIs with cytotoxic chemotherapies has been evaluated for patients with *EGFR*-mutant NSCLC.[9–14] Among them, the North-East Japan Study Group (NEJ) 005/Tokyo Cooperative Oncology Group (TCOG) 0902 study has demonstrated in a primary report that first-line concurrent and sequential alternating combination therapies of gefitinib plus chemotherapy (carboplatin/pemetrexed) offer promising efficacy with predictable toxicities.[9]

Although not powered to assess overall survival (OS), the results from this study were striking in that the concurrent regimen, in particular, offered an OS benefit of 42 months. However, OS data were insufficient because of the lack of death events in the primary report. In the current report, we have updated the data for PFS, OS and safety for a longer follow-up period in the NEJ005/TCOG0902 study cohort.

PATIENTS AND METHODS
Study design and treatment
This study was conducted according the Declaration of Helsinki. Each patient provided written informed consent prior to enrolment. The details regarding patient eligibility and treatment have previously been described.[9] Briefly, eligibility stipulated the presence of advanced NSCLC harbouring sensitive *EGFR* mutations, absence of the resistant *EGFR* mutation T790M, no history of chemotherapy and an age of 75 years or younger. Patients were stratified according to sex and clinical stage of NSCLC (IIIB, IV or postoperative relapse).

Eighty patients were randomly assigned to receive either a concurrent or sequential alternating regimen (online supplementary figure 1). Patients in the concurrent regimen group received concurrent gefitinib (250 mg daily) and carboplatin ($6 \times$ area under the curve, day 1)/pemetrexed ($500 \, mg/m^2$, day 1) in a 3-week cycle up to six cycles, followed by concurrent gefitinib and pemetrexed maintenance until disease progression, unacceptable toxicity or death. Patients in the sequential alternating regimen group initially received 8 weeks of gefitinib and then two cycles of carboplatin/pemetrexed; this sequential treatment was repeated up to three times (carboplatin/pemetrexed was repeated up to six cycles), followed by alternating gefitinib and pemetrexed maintenance. When patients received four cycles or more of carboplatin/pemetrexed with gefitinib, the induction therapy was considered complete. Continuation of gefitinib alone was permitted when carboplatin/pemetrexed or pemetrexed was terminated.

Patients were enrolled from January 2010 to April 2012. The protocol was amended to follow enrolled patients for a longer period and the final analysis was conducted after a 5-year follow-up period (31 March 2017).

Treatment assessment
Tumour responses were assessed with CT or MRI (when clinically indicated), before and during treatment, and were repeated at least every 2 months until disease progression. Responses were classified as complete response, partial response, stable disease, progressive disease (PD) or non-evaluable, on the basis of Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Progression was defined as PD according to RECIST 1.1, clinical progression as judged by the investigator or death from any cause. Progression and clinical response data were all confirmed in an independent central review by members who were not aware of the treatment assignments. The National Cancer Institute Common Terminology Criteria for Adverse Events 3.0 was used to grade adverse events.

Study outcomes
The primary objective was to select the arm with superior PFS. Secondary endpoints included OS, objective tumour responses and toxicity profiles. This study was not designed to have adequate power to detect a statistically significant difference in efficacy and safety between the two regimens; thus, reported P values are to be interpreted as exploratory.

Statistical analysis
PFS was evaluated from the date of randomisation to the date on which progression was first confirmed by the central review assessment. OS was evaluated from the date of randomisation to the date of death from any cause. For patients without any events, data were censored on the last date with non-event status. The probability of PFS or OS was estimated using the Kaplan-Meier method and survival curves compared using the log-rank test. HRs and 95% CIs were calculated using a Cox proportional-hazards analysis with sex and clinical stage as covariates. The response rate and rate of toxic effects were compared between the two groups with Fisher's exact test. Statistical analysis was carried out using SAS V.9.1.3 (SAS, Cary, North Carolina, USA).

RESULTS
Patient characteristics
From January 2010 to April 2012, 80 patients were randomly assigned for treatment: 41 to the concurrent regimen and 39 to the sequential alternating regimen. The demographics and disease characteristics of the patients were well-balanced between the treatment groups, except for major *EGFR* mutation subtypes (table 1). All patients had adenocarcinoma and the majority had stage IV disease. All the patients received at least one dose of the study treatment. In this updated analysis, at the median follow-up time of 35.6 months, 88.8% of patients (36

Table 1 Baseline characteristics of patients

Characteristics	Concurrent regimen n=41 No. of patients (%)	Sequential alternating regimen n=39 No. of patients (%)
Gender		
Male	15 (36.6%)	13 (33.3%)
Female	26 (63.4%)	26 (66.7%)
Age		
Median	62	61
Range	41–75	39–75
Smoking status		
Never smoked	22 (53.7%)	22 (56.4%)
Previous or current smoker	19 (46.3%)	17 (43.6%)
ECOG performance status score		
0	21 (51.2%)	17 (43.6%)
1	19 (43.9%)	22 (56.4%)
2	1 (2.4%)	0 (0%)
Histologic diagnosis		
Adenocarcinoma	41 (100.0%)	39 (100.0%)
Clinical stage		
IIIB	2 (4.9%)	1 (2.6%)
IV	37 (90.2%)	36 (92.3%)
Postoperative relapse	2 (4.9%)	2 (5.1%)
Type of *EGFR* mutation		
Exon 19 deletion	24 (58.5%)	17 (43.6%)
L858R	17 (41.5%)	20 (51.3%)
Others	0 (0%)	2 (5.1%)

ECOG, eastern cooperative oncology group; EGFR, epidermal growth factor receptor.

patients in the concurrent regimen group and 35 patients in the sequential alternating regimen group) had PD and 77.5% of patients (30 patients in the concurrent regimen group and 32 patients in the sequential alternating regimen group) had died.

Treatment delivery

In the concurrent regimen group, six patients discontinued induction treatment and did not proceed to maintenance treatment due to toxicities. The remaining 35 patients (85.4%) received maintenance treatment after completion of induction (gefitinib plus pemetrexed, n=30; gefitinib alone, n=5). In this updated analysis, the median number of cycles of pemetrexed maintenance was 13 (range, 1–75). The median duration of gefitinib treatment (excluding interruption) was 14.6 months (range, 2.9–86.4 months) until RECIST progression or censor and 17.3 months for the entire treatment period (with the same range, since there were patients still on the protocol treatment).

In the sequential alternating regimen group, 15 patients discontinued induction treatment and did not proceed to maintenance therapy (progression, n=6; toxicities, n=8; withdrawn, n=1). The remaining 24 patients (61.5%) received maintenance treatment after induction (gefitinib plus pemetrexed, n=17; gefitinib alone, n=7). In this updated analysis, the median number of cycles of pemetrexed maintenance was 7 (range, 1–46). The median duration of gefitinib treatment (excluding interruption) was 9.3 months (range, 0.3–62.2 months) until RECIST progression or censor and 11.4 months for the entire treatment period (with the same range).

In both groups, after discontinuation of induction treatment (before completion of four cycles of carboplatin/pemetrexed and gefitinib), the majority of patients received gefitinib monotherapy.

Efficacy

Data for patients without progression (three patients in the concurrent therapy group and two patients in the sequential alternating regimen group) or for those who started off-study second-line treatment before confirmation of progression (two patients in each group) were censored at the time of data cut-off (31 March 2017). The updated median PFS was 17.5 months (95% CI, 9.7 to 21.9 months) for the concurrent regimen and 15.3 months (95% CI, 11.2 to 17.4 months) for the sequential alternating regimen (HR 0.68 (95% CI, 0.42 to 1.12); P=0.13; figure 1). However, it is of note that the updated OS was significantly different between the groups. Median OS was 41.9 months (95% CI, 31.8 to 58.0) in the concurrent regimen group and 30.7 months (95% CI, 22.7 to 38.3 months) in the sequential alternating regimen group (HR 0.58 (95% CI, 0.34 to 0.97); P=0.036; figure 2). Interestingly, 2-year survival was 31.5% in the concurrent regimen group. Updated response rates were similar in both groups (90.2% and 82.1%, respectively; P=0.34), whereas the disease control rates were 100% and 92.3% (P=0.11; table 2).

In an exploratory analysis of patients who had the common mutations Del19 or L858R, patients showed no significant differences in PFS based on the type of mutation (figure 3A). In contrast, patients with Del19 displayed relatively better OS (median: 45.3 and 33.3 months for the concurrent and sequential alternating regimens, respectively) than those with L858R (31.4 and 28.9 months, respectively; figure 3B).

Radiographic assessment of RECIST progression

Online supplementary table 1 summarises the imaging findings at the time of RECIST progression. Approximately one quarter of patients in each group had progression of primary lesions and 11%–19% of patients progressed with new pulmonary lesions. In each group, 29%–36% of patients also had CNS (central nervous
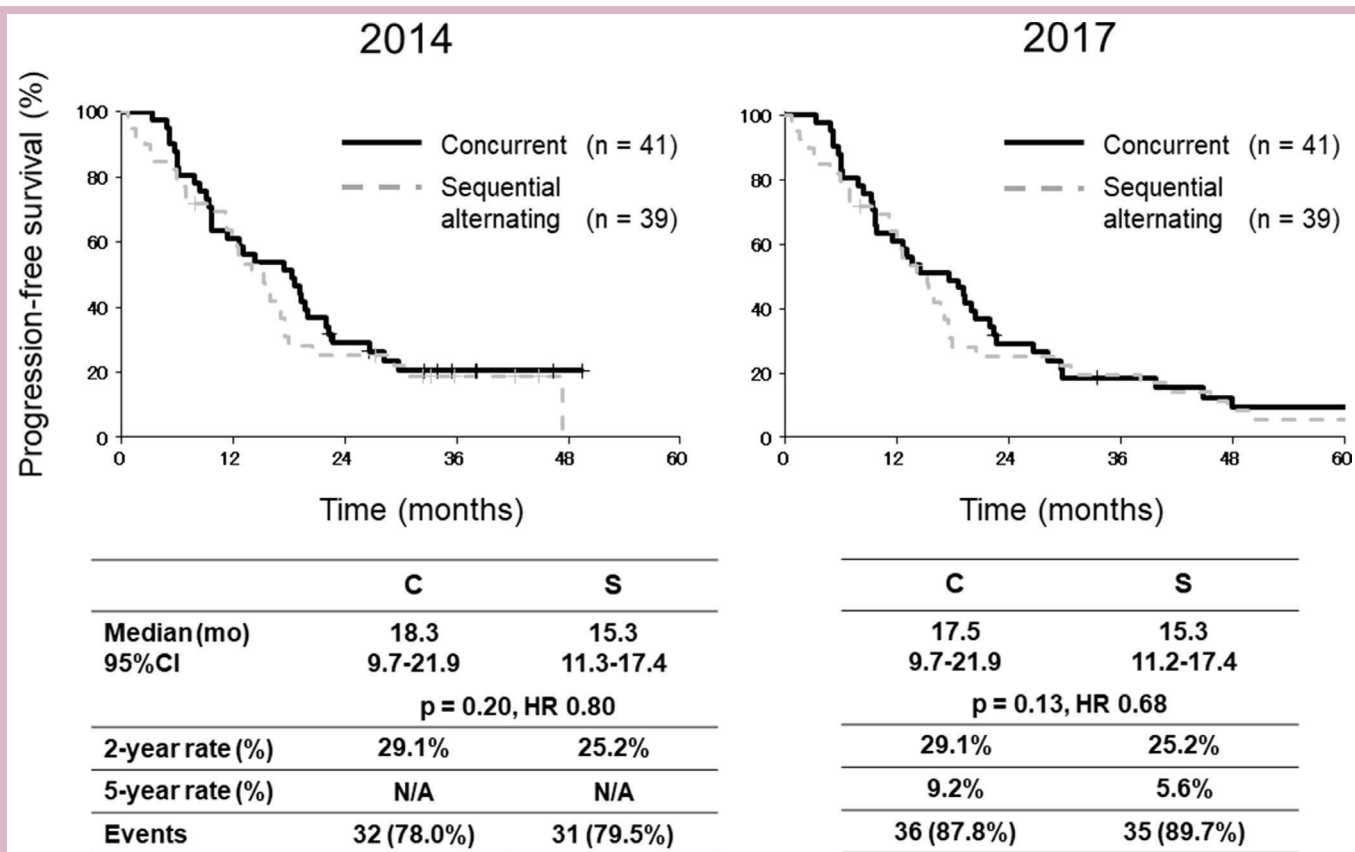
Figure 1 Updated Kaplan-Meier curve of progression-free survival for all randomly assigned patients.

system; brain and meningitis carcinomatosa) progression. The other sites in which more than three patients showed disease progression included the pleura, pleural effusion, bone, lymph nodes and liver.

Treatment post-RECIST progression

Next, we examined postprogression therapy (online supplementary table 2). In the concurrent regimen group, 7 patients (19.4%) received gefitinib+pemetrexed, 10 patients (27.8%) received gefitinib and 1 patient (2.8%) received pemetrexed, whereas in the sequential alternating regimen group, 5 patients (14.3%) received gefitinib+pemetrexed, 16 patients (45.7%) received gefitinib and 2 (5.7%) patients received pemetrexed. Taken together, more than half of patients received protocol treatment beyond RECIST progression (50.0% and 65.7% in the concurrent and sequential alternating regimen group, respectively). The remaining patients in each group switched to alternative therapy, with the majority receiving docetaxel or erlotinib.

Of the patients who received protocol treatment beyond RECIST progression, 41.7% (15/36) had subsequent treatment in the concurrent regimen group, while 51.4% (18/35) received treatment in the sequential alternating regimen group. Of patients who switched to other therapy, 30.6% (11/36) and 17.1% (6/35) were given subsequent treatment in the concurrent and sequential alternating regimen groups, respectively. Eventually,

one patient in the concurrent regimen group and two patients in the sequential alternating regimen group received osimertinib after the T790M resistance mutation emerged in their tumours.

Safety

The primary safety data have previously been described.[9] Briefly, we recorded no fatal events; a total of four cases of interstitial lung disease (5% of all patients) occurred (grade 1 and grade 2 events in the concurrent and grade 2 and grade 4 events in the sequential alternating regimen group), but they were reversible and not fatal. No severe adverse events, including interstitial lung disease, have occurred in the follow-up period since the primary report.

DISCUSSION

Our updated analysis demonstrates that the first-line combination therapy of an EGFR-TKI (gefitinib) plus a platinum-based doublet chemotherapy (carboplatin/pemetrexed) offers promising efficacy for patients with *EGFR*-mutant NSCLC. Median PFS from this study was promising, being 17.5 months for the concurrent regimen and 15.3 months for the sequential alternating regimen. In regard to the secondary end point of OS, it is noteworthy that median survival times were similar to those of the primary report (41.9 and 30.7 months in the concurrent and sequential alternating regimen groups,
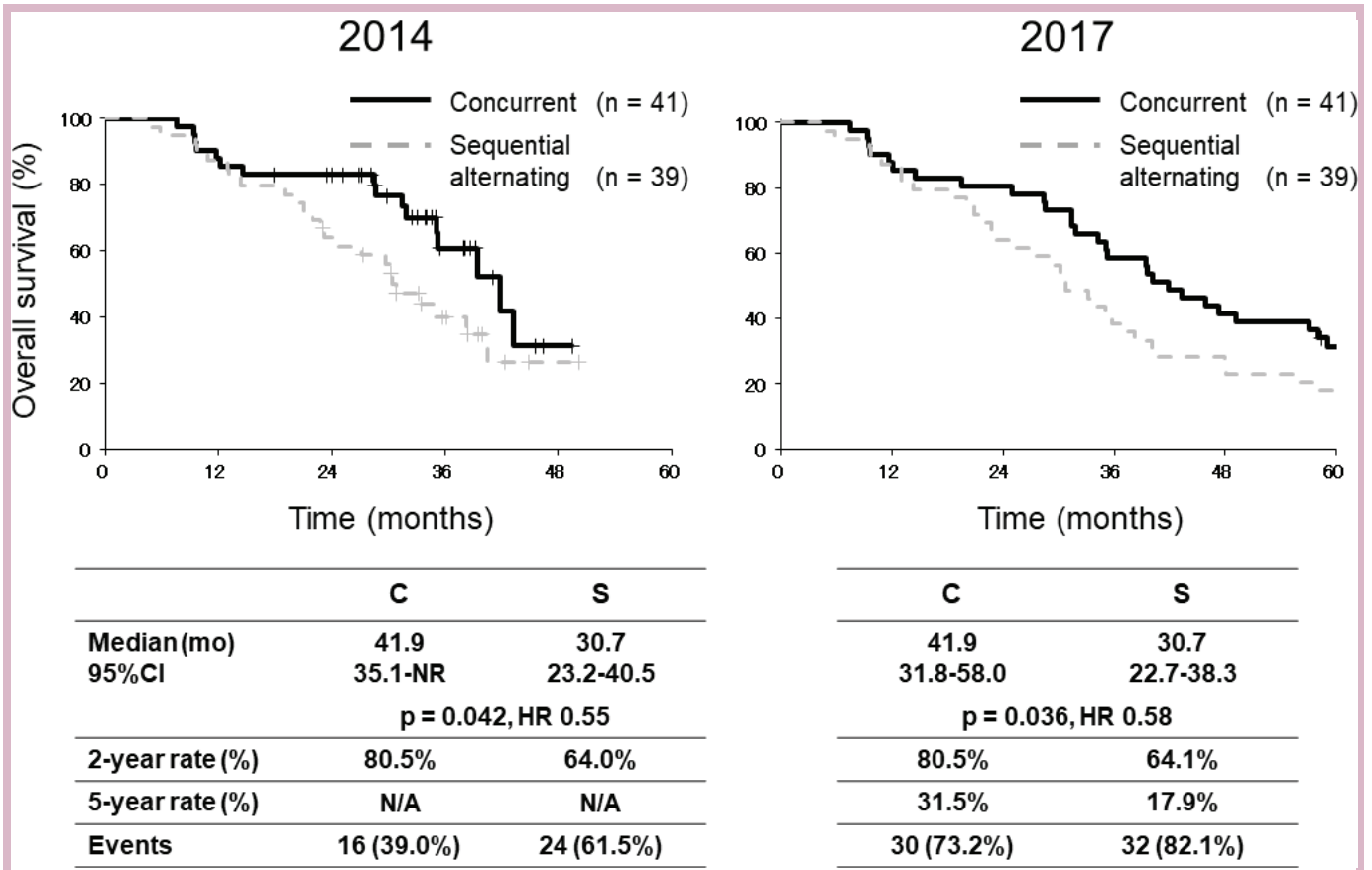
Figure 2 Updated Kaplan-Meier curve of overall survival for all randomly assigned patients.

respectively; 2-year survival was 31.5% in the concurrent regimen group). In addition, the combination of gefitinib and carboplatin/pemetrexed did not appear to have additive toxicity in a longer follow-up period.

In this study, despite the identical PFS between the groups, better OS was observed in the concurrent regimen group. Some mechanisms for de novo EGFR-TKI resistance have been reported[15] and several patients elicited initial progression with gefitinib monotherapy in the sequential alternating regimen group. The concurrent

strategy with cytotoxic agents might circumvent such resistance. In addition, the period of exposure to gefitinib was longer in the concurrent regimen group, partly due to the treatment schedule design. The increased exposure to gefitinib, accompanied by increased pemetrexed maintenance, might lead to long-term clinical benefit with the concurrent regimen.

We also identified a difference in OS in relation to common *EGFR* mutation types. Patients with Del19 tumours had a longer OS than those with L858R tumours,

Table 2 Best overall response according to RECIST criteria

	Concurrent regimen (n=41)	Sequential alternating regimen (n=39)	P value
Objective response*	37 (90.2%) (76.9%–97.3%)	32 (82.1%) (66.5%–92.5%)	0.34
Disease control	41 (100%) (91.4%–100.0%)	36 (92.3%) (79.1%–98.4%)	0.11
Complete response	2 (4.9%)	3 (7.7%)	
Partial response	35 (85.4%)	29 (74.4%)	
Stable disease	4 (9.8%)	4 (10.3%)	
Progressive disease	0 (0.0%)	3 (7.7%)	

P value by Fisher's exact test.
Likewise, the percentage of patients with an objective response or a stable disease was considered to be the rate of disease control.
 *The percentage of patients in whom there was either a complete or a partial response was considered to be the rate of objective response.
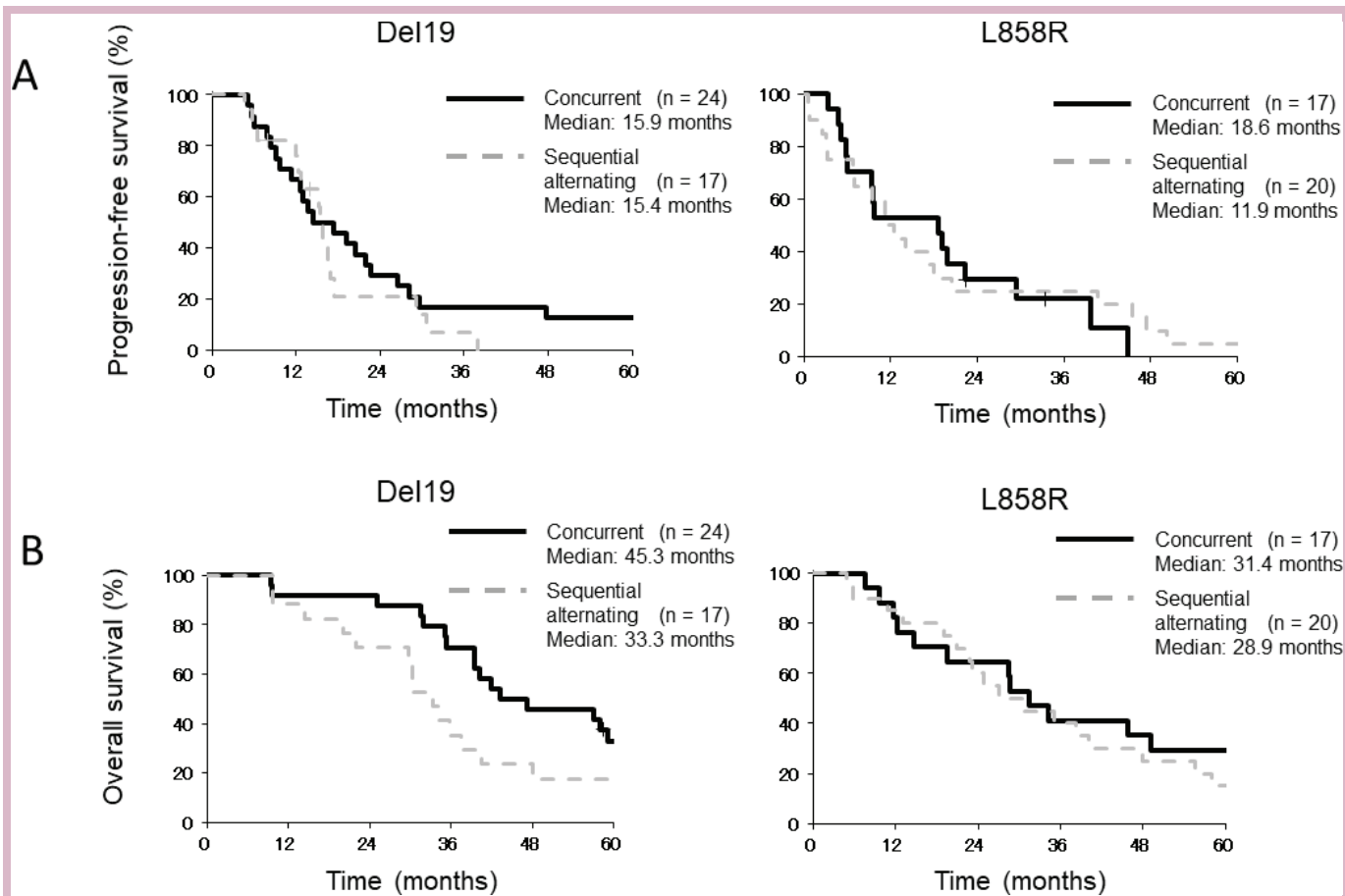RECIST, Response Evaluation Criteria in Solid Tumors.

Figure 3 Updated Kaplan-Meier curves of progression-free survival (A) and overall survival (B) according to the type of common mutation.

in both treatment groups. In the Del19 tumour group, OS was longer for patients in the concurrent regimen group than in the sequential alternating regimen group. Since no reports have previously shown PFS or OS differences between Del19 or L858R populations with gefitinib monotherapy, including our NEJ002 study (data not shown), mutation subtype was not a stratification factor in the current study. These observations warrant further exploration of the biological mechanisms underlying the survival differences associated with these two common *EGFR* genotypes.

The T790M mutation of *EGFR* is the most common cause of acquired resistance to EGFR-TKIs, being found in up to 50% of patients treated with first-generation and second-generation EGFR-TKIs.[16–20] The frequency in the emergence of the T790M mutation or other resistance mechanisms might be altered by adding cytotoxic agents to EGFR-TKIs. We have not examined the resistance mechanisms at the time of RECIST progression. However, to examine acquired resistance with sequential gefitinib and cisplatin/pemetrexed combinations, such exploratory research is currently being conducted in parallel with a phase III trial (JCOG1404/WJOG8214L; UMIN000020242).

Current research is focused on combining novel and targeted therapies to achieve additional benefit in the *EGFR*-mutated NSCLC population. Ongoing clinical trials for these patients include those assessing EGFR-TKIs combined with cytotoxic agents (like the present study),[9–14] antiangiogenic agents[21] and immune check point inhibitors.[22] The Japanese JO25567 study has shown promising efficacy of erlotinib and bevacizumab,[21] and our ongoing NEJ026 trial will provide a phase III evaluation of the erlotinib and bevacizumab combination.

Recently, third-generation osimertinib monotherapy has demonstrated superior PFS compared with gefitinib or erlotinib monotherapy, for patients with *EGFR*-mutated NSCLC in the FLAURA study (median PFS 18.9 vs 10.2 months).[23] Thus, the algorithm for future first-line treatment strategies will dramatically change in this population. After comparing the efficacy and safety profile of the new strategies, including the combination of EGFR-TKIs and cytotoxic agents, and most importantly, carefully examining patients status, there may be several options for optimal first-line treatment in the future.

As we mentioned in the primary report, one limitation of this study is related to the nature of phase II evaluation; specifically, this study was not designed to formally

identify differences in efficacy and safety between the two regimens. Therefore, the findings obtained in this study should not be considered definitive. Second, we have not evaluated the clinical outcome of subsequent treatment in this study cohort, which might affect OS results. However, a substantial proportion of patients had subsequent treatment in both groups and the proportion of patients who received such treatment was similar.

In conclusion, our updated analysis confirms that first-line gefitinib plus carboplatin/pemetrexed combination improves PFS compared with the reported PFS with gefitinib monotherapy and that the concurrent regimen, in particular, offers an OS benefit of 42 months in the *EGFR*-mutated setting. We are now conducting the phase III NEJ009 (UMIN000006340) study to compare the concurrent strategy with standard gefitinib monotherapy in the *EGFR*-mutated setting. Together with other ongoing phase III trials, NEJ009 will clarify whether this combination strategy can be incorporated into routine clinical practice.

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