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Evaluation of time to failure of strategy as an alternative surrogate endpoint in patients with lung cancer with EGFR mutations

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ABSTRACT

Background Epidermal growth factor receptor (EGFR) is one of the most common oncogenes in non-small cell lung cancer (NSCLC). EGFR-tyrosine kinase inhibitor (TKI) and platinum-doublet chemotherapy (PT) are effective regimens in patients with NSCLC harbouring EGFR mutations. Among these patients, progression-free survival (PFS) has been used as a surrogate endpoint; however, it may not correlate with overall survival (OS) due to crossover. Time to failure of strategy (TFS) has been proposed as an alternative endpoint in advanced colorectal cancer clinical trials where multiple effective therapies are provided either in combination or sequentially. Nevertheless, it remains unclear whether TFS is useful in lung cancer trials.

Patients and methods We retrospectively reviewed patients with NSCLC harbouring EGFR mutations who chose a treatment strategy consisting of EGFR-TKI and PT as the initial two regimens at the National Cancer Center Hospital. We evaluated the relationship between PFS and OS and between TFS and OS.

Results Between May 2005 and April 2015, a total of 374 patients were diagnosed with NSCLC harbouring EGFR mutations. Among them, 158 patients were eligible for analysis. The median PFS, TFS and OS of the patients were 11.2 months (95% CI 9.9 to 12.6), 21.3 months (95% CI 18.6 to 26.2) and 36.6 months (95% CI 32.0 to 41.8), respectively. OS and TFS, but not PFS, were better in patients who received PT then EGFR-TKI compared with those who received the opposite schedule. The non-parametric Spearman's rank correlation coefficients (r) between PFS and OS and between TFS and OS were 0.54 and 0.85, respectively.

Conclusions This is the first report describing TFS data among patients with NSCLC with EGFR mutations who received EGFR-TKI and PT as the initial two regimens. TFS was acceptable as a surrogate endpoint for OS. Further validation in clinical trials is needed.

Key questions

What is already known about this subject?

- In clinical trials of advanced non-small cell lung cancers (NSCLC) harbouring an epidermal growth factor receptor mutation, progression-free survival (PFS) is commonly used as surrogate endpoint for overall survival (OS).
- A previous study showed that there was no association between OS and PFS in advanced NSCLC.

What does this study add?

- This is the first report describing time to failure of strategy (TFS) data among patients with NSCLC.
- We evaluated the correlation between PFS and OS, and between TFS and OS.
- TFS is a possible surrogate endpoint for OS.

How might this impact on clinical practice?

- Given the increasing number of effective agents, TFS could be a better surrogate endpoint for OS, especially when there are two or more effective treatments.

INTRODUCTION

Lung cancer is the most common cause of cancer-related death in both males and females.[1] Despite the development of diagnostic technologies, most patients have advanced disease when they are diagnosed.[2] The general standard treatment for patients with advanced non-small cell lung cancer (NSCLC) with or without oncogenic genomic alteration is chemotherapy, which is performed to prolong their survival or reduce their symptoms. Precision medicine, especially targeted therapy, which is determined based on genetic characteristics, currently plays an important role in NSCLC treatment. Epidermal growth factor receptor (EGFR) is one of the most common oncogenes, and EGFR-tyrosine kinase inhibitors (TKI) confer significantly prolonged progression-free survival (PFS) in patients with NSCLC with EGFR mutations compared with patients who receive platinum-doublet chemotherapy (PT).[3–5] Thus, EGFR-TKIs are widely accepted as the standard first-line regimen for such patients.

Overall survival (OS) is the gold standard for evaluating the efficacy of cancer treatment. However, OS assessments require long-term follow-up and a large number of participants in clinical trials. Surrogate endpoints have therefore been used to shorten the assessment time of new agents and reduce costs. PFS is one of the most commonly used surrogate endpoints in lung cancer trials. The recommendation of an EGFR-TKI as a first-line cancer treatment is based on the aforementioned results showing a better PFS in comparison with PT, but no statistical difference in OS has been demonstrated. This discordance was also seen in several clinical trials of other targeted therapies for NSCLC. A previous meta-analysis showed that there was no association between OS and PFS in advanced NSCLC.[6] Since the number of effective agents for lung cancer treatment is increasing, other surrogate endpoints that result in better OS are needed.

Time to failure of strategy (TFS) is an alternative endpoint that has been proposed for advanced colorectal cancer trials.[7] TFS is defined as the interval between the initiation of treatment and the time at which one of the following events first occurs: the addition of any agent not in the primary strategy, progression on full therapy, progression and no subsequent therapy, or death (online supplementary figure S1). PFS is also an accepted endpoint in advanced colorectal cancer trials. Nevertheless, it is unlikely to reflect fully the benefits of treatment when drug holidays or planned discontinuations of treatment followed by reinitiation of the prior treatment are used. In contrast, TFS includes the duration of the reinitiated treatment. Additionally, when two effective regimens are administered sequentially, TFS can be used to evaluate the order of their administration. In advanced colorectal cancer, TFS showed a good correlation with OS.[8] However, no studies have evaluated TFS in the treatment of NSCLC.

In this study, we evaluated the TFS for two NSCLC treatments. Since EGFR-TKIs and PT are both effective for patients with NSCLC harbouring EGFR sensitising mutations, it is important not to miss the opportunity to expose these 'key drugs'. The strategy, which included the administration of EGFR-TKI and PT as the initial two regimens (TKI-PT strategy), is considered standard treatment. Therefore, we conducted individual-level analyses of the relationships between PFS and OS and between TFS and OS in patients who chose the TKI-PT strategy.

PATIENTS AND METHODS

Patients who were diagnosed with advanced or recurrent NSCLC harbouring EGFR mutations at the National Cancer Center Hospital between May 2005 and April 2015 were evaluated. Patients who met the following inclusion criteria at diagnosis were considered to be eligible for the TKI-PT strategy. The inclusion criteria were an age of ≤75 years, an Eastern Cooperative Oncology Group performance status of 0–2, adequate organ function and the absence of definite reasons to choose another strategy (eg, the patient's preference, participation in clinical trials or the physician's choice). Patients who received adjuvant chemotherapy or chemoradiotherapy with platinum agents were excluded. We divided the patients into two groups: group 1, which included patients who received EGFR-TKI as the first-line treatment and PT as the second-line treatment, and group 2, which included patients who received these treatments in the opposite order. Confidentiality of patients' data was maintained.

We evaluated the treatment strategy consisting of EGFR-TKI and PT as the initial two regimens. Thus, TFS was defined as the interval between the beginning of the first-line treatment and the first of the following events: the addition of new therapeutic agents that were not included in the strategy, progression after receiving both EGFR-TKI and PT treatments, progression during the treatment strategy and being unable to receive subsequent further treatment, and death.

When the treatment was changed because of adverse events, we considered all agents as a single treatment regimen as long as the administered agents were in the same class. These substitutions included cisplatin to carboplatin because of renal toxicity or emetogenicity, paclitaxel to pemetrexed because of peripheral neuropathy, gefitinib to erlotinib because of liver toxicity and erlotinib to gefitinib because of a severe skin rash.

Kaplan-Meier methods were used to calculate PFS, TFS and OS. We used Spearman's rank correlations and linear regression models to evaluate the correlations between PFS and OS, and between TFS and OS. All statistical analyses were performed with JMP Pro software, V.13.0 (SAS Institute, Cary, NC, USA).

RESULTS

During the study period, 374 patients were diagnosed with NSCLC harbouring EGFR mutations. Among them, 216 did not choose the TKI-PT strategy. The most common reasons were enrolment in a clinical trial (n=43), being older than 75 years (n=42) and receiving platinum-containing adjuvant chemotherapy (n=35). Thirteen patients who were <75 years of age and had a performance status of 2 did not choose the strategy based on a physician's comprehensive evaluation. A complete list of the reasons is shown in figure 1. Finally, 158 patients fulfilled the criteria and chose the TKI-PT strategy. Among them, 132 were in group 1 and 26 were in group 2. Sixteen patients in group 1 (12%) could not receive the second-line treatment. The reasons were decreased performance status (n=15) and death due to complications (n=1). The median follow-up time was 31.6 months (range, 1.5–135.8 months). At the cut-off point, 101 patients were dead . The characteristics of the patients are shown in table 1. Among the 158 patients, 127 (81%) received gefitinib. Eleven patients (7%) had to change to another EGFR-TKI because of adverse events. For the PT regimens, 92 (58%) patients received cisplatin and pemetrexed. The second

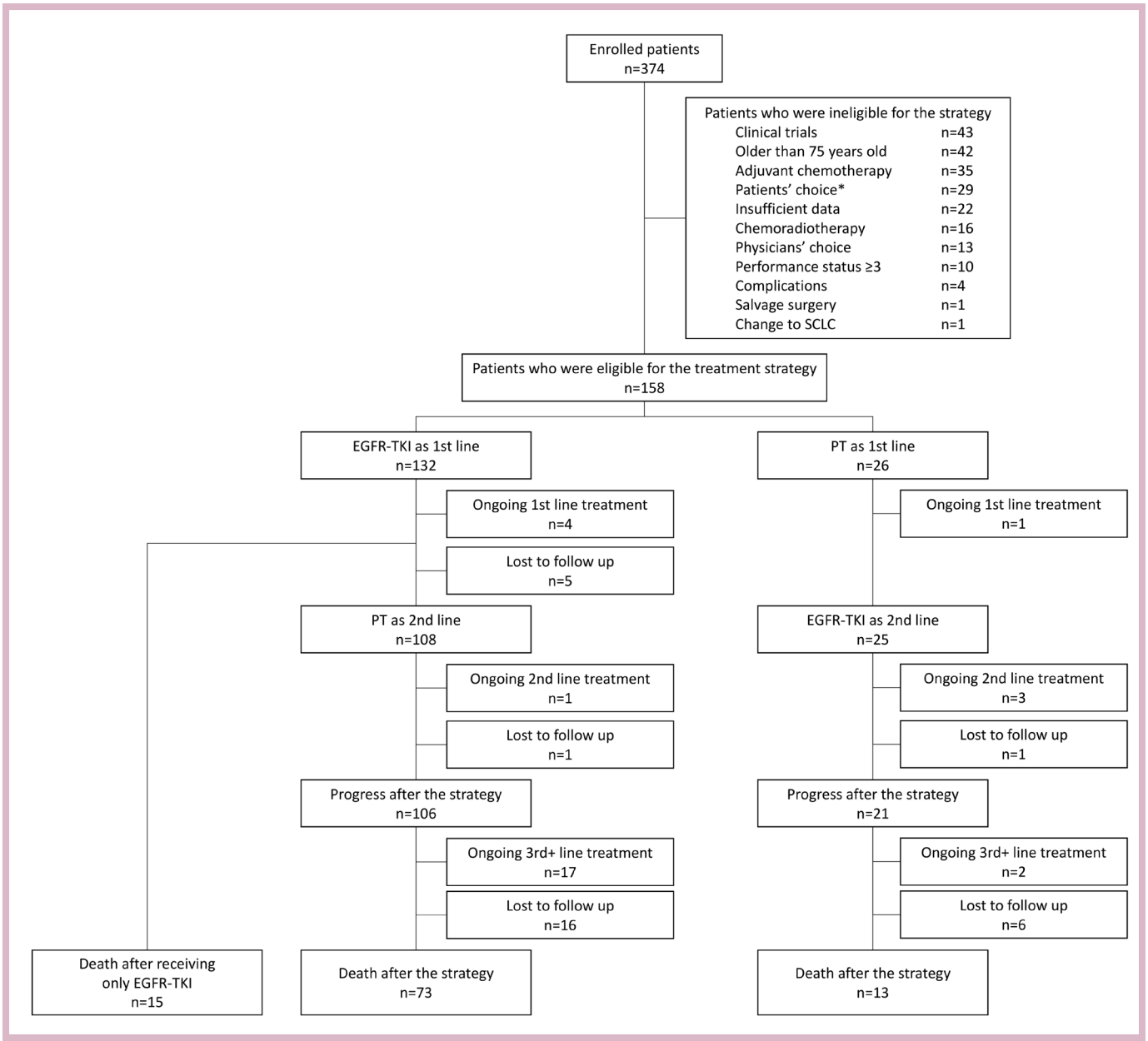

Figure 1 Flow chart of the patient selection process. *Patients who refused to receive platinum-doublet chemotherapy (PT) before first-line treatment were excluded. EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; SCLC, small cell lung cancer.

most frequent regimen was carboplatin and paclitaxel with or without bevacizumab.

Figure 2 shows the three plots where patients are listed in descending order of PFS, TFS and OS. Patients with arrows on the right edge indicate censored cases.

Figure 3 shows the Kaplan-Meier curves. The median PFS, TFS and OS of the patients were 11.2 months (95% CI 9.9 to 12.6), 21.3 months (95% CI 18.6 to 26.2) and 36.6 months (95% CI 32.0 to 41.8), respectively (figure 3A). The median PFS was 11.5 months (95% CI 10.0 to 12.7) in group 1 and 9.8 months (95% CI 6.4 to 13.1) in group 2 (p=0.53) (figure 3B). The median TFS was 20.1 months (95% CI 17.5 to 22.1) in group 1 and 29.7 months (95% CI 21.3 to 35.0) in group 2 (p=0.02) (figure 3C). The median OS was 34.3 months (95% CI 28.8 to 39.3) in group 1 and 54.7 months (95% CI 45.9 to 110.9) in group 2 (p=0.01) (figure 3D). OS and TFS were significantly different between the two groups.

Figure 4 shows the relationships between PFS and OS, and between TFS and OS. In the overall population, TFS showed a significant correlation with OS (r=0.85, p<0.0001), whereas PFS showed only a weak correlation (r=0.54, p<0.0001). These findings were also seen in both groups.

Discussion

This is the first study describing TFS data in NSCLC treatment. The data show that TFS had a better correlation

Table 1 Patient characteristics

	Total (n=158)	Group 1 EGFR-TKI→PT (n=132)	Group 2 PT→EGFR-TKI (n=26)
Age, median (range)	62 (26–81)	62 (26–81)	62 (45–73)
Sex, n (%)			
Male	61 (39)	46 (35)	15 (58)
Female	97 (61)	86 (65)	11 (42)
Performance status			
0/1/≥2	65/81/12	50/70/12	15/11/0
Baseline brain metastasis, n (%)			
Positive	39 (25)	34 (26)	5 (19)
Negative	119 (75)	98 (74)	21 (81)
EGFR mutation, n (%)			
Exon 19del	83 (53)	75 (57)	8 (31)
Exon 21L858R	68 (43)	54 (41)	14 (54)
Other	7 (4)	3 (2)	4 (15)
Type of EGFR-TKI, n (%)			
Gefitinib	127 (81)	108 (82)	19 (73)
Erlotinib	20 (13)	17 (13)	3 (12)
Erlotinib+bevacizumab	5 (3)	5 (4)	0
Afatinib	5 (3)	2 (2)	3 (12)
Not administered	1 (1)	0	1 (4)
Regimen of PT, n (%)			
CDDP+PEM	92 (58)	78 (59)	14 (54)
CBDCA+PTX±BEV	29 (18)	18 (14)	11 (42)
CBDCA+PEM±BEV	11 (7)	11 (8)	0
Others	2 (1)	1 (1)	1 (4)
Not administered	24 (15)	24 (18)	0
Best response to EGFR-TKI, n (%)			
CR/PR	93 (59)	79 (60)	14 (54)
SD	55 (35)	47 (36)	8 (30)
PD	6 (4)	4 (3)	2 (8)
NE	4 (3)	2 (2)	2 (8)
Best response to PT*, n (%)			
CR/PR	40 (25)	27 (20)	13 (50)
SD	70 (44)	58 (44)	12 (46)
PD	21 (13)	21 (16)	0
NE	27 (17)	26 (20)	1 (4)
EGFR T790M status, n (%)			
Positive	24 (15)	19 (14)	5 (19)
Negative	25 (16)	23 (17)	2 (8)
Not examined	109 (69)	90 (68)	19 (73)

Continued

Table 1 Continued

	Total (n=158)	Group 1 EGFR-TKI→PT (n=132)	Group 2 PT→EGFR-TKI (n=26)
Subsequent therapies, n (%)			
0	45 (28)	42 (32)	3 (12)
1	51 (32)	41 (31)	10 (38)
≥2	51 (32)	43 (33)	8 (31)
On treatment	11 (7)	6 (5)	5 (19)

The response to treatment was determined based on Response Evaluation Criteria in Solid Tumors, version 1.1.
BEV, bevacizumab; CBDCA, carboplatin; CDDP, cisplatin; CR, complete response; EGFR, epidermal growth factor receptor; NE, not able to be evaluated; PD, progressive disease; PEM, pemetrexed; PR, partial response; PT, platinum-doublet chemotherapy; PTX, paclitaxel; SD, stable disease; TKI, tyrosine kinase inhibitor.

with OS than PFS among patients with NSCLC with EGFR mutations who received an EGFR-TKI and PT as the initial two regimens.

PFS is a valid surrogate endpoint in several cancers, including advanced colorectal cancer,[9 10] pancreatic cancer[11] and late-stage small cell lung cancer.[12] In contrast, its surrogacy in patients with NSCLC is controversial.[13] PFS does reflect the efficacy of anticancer treatments to a certain extent. Treatments with a longer PFS have a stronger anticancer relevance than those with a shorter PFS. In addition, because advanced NSCLC is a life-threatening condition, early access to innovative treatment is beneficial. Therefore, accelerated approval has been granted based on PFS, which can be measured earlier than OS. However, considering the evaluation of the whole treatment strategy with various types of effective treatments that can be administered sequentially, such as EGFR-TKIs and cytotoxic chemotherapies, the PFS does not correlate with the OS. Thus, it is not an ideal surrogate endpoint to change actual treatment. PFS has also been employed in several clinical trials evaluating the efficacy of adding new agents to conventional ones. However, if the new agents are effective as single agents, the efficacy of the addition of these agents should be compared with sequential administration. For these trials, PFS is not an appropriate surrogate endpoint.

TFS is an alternative endpoint, which has been used to compensate for PFS weaknesses in colorectal cancer trials. FOLFOX and FOLFIRI showed similar efficacies with different toxicity profiles for patients with

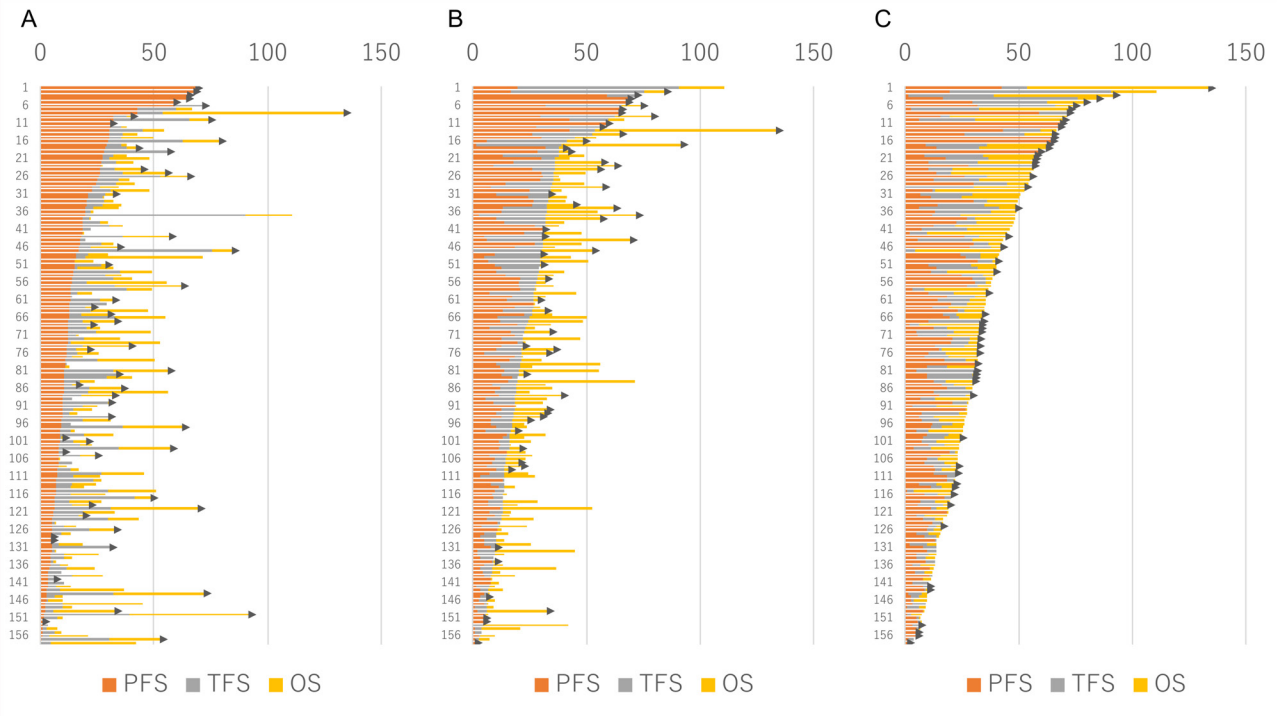

Figure 2 Swimmer's plot. (A–C) In descending order: progression-free survival (PFS), time to failure of strategy (TFS) and overall survival (OS). The order of the bars indicates that OS looks better in (B) than (A).

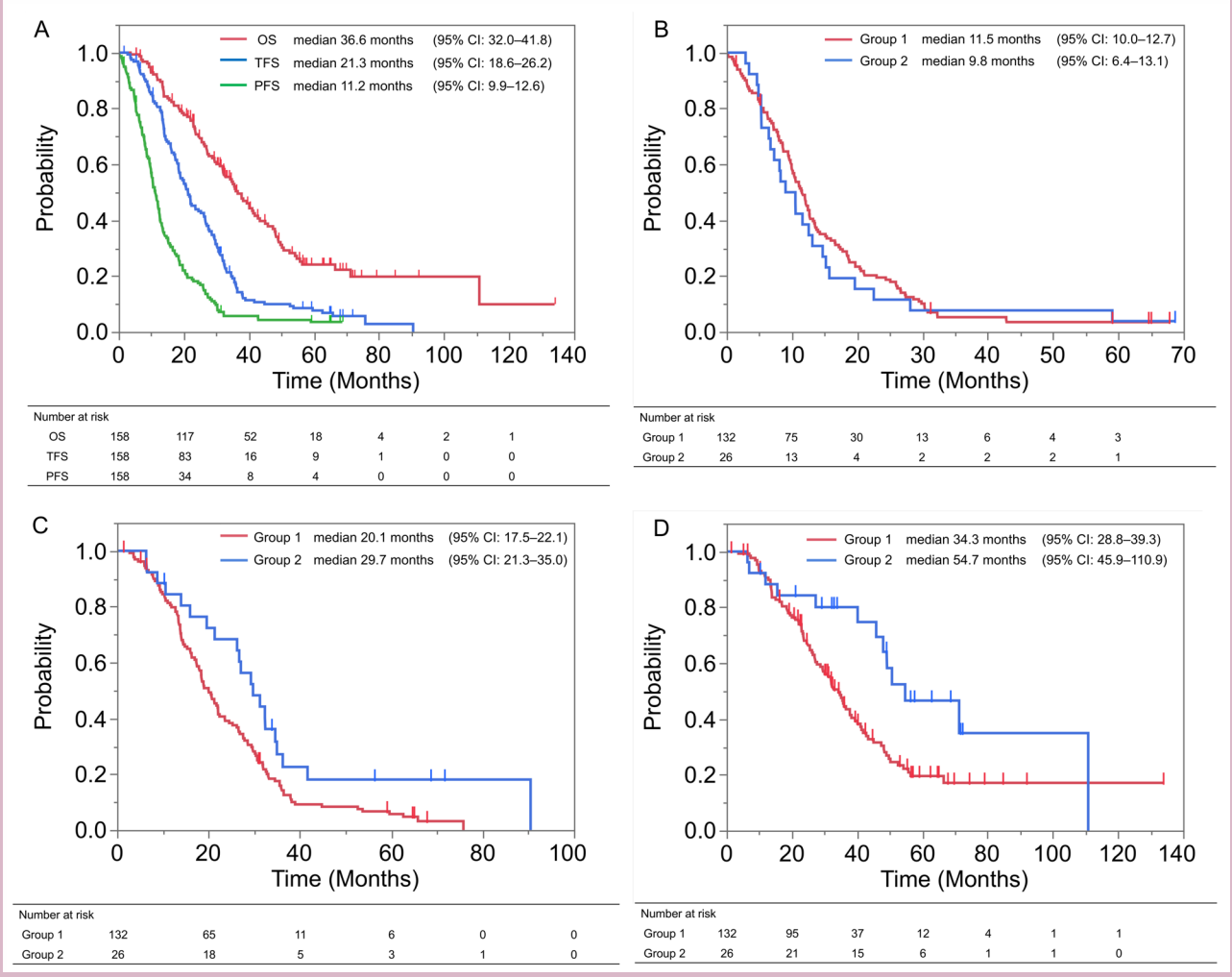

Figure 3 Kaplan-Meier curves. (A) The progression-free survival (PFS), time to failure of strategy (TFS) and overall survival (OS) of all patients. (B) The PFS of patients in group 1 and group 2. (C) The TFS of patients in group 1 and group 2. (D) The OS of patients in group 1 and group 2.

advanced colorectal cancer, so they could be administered sequentially.[14 15] In addition, because of the cumulative toxicity of oxaliplatin, 'stop-and-go' administration of FOLFOX has been used.[16] TFS is thought to be able to measure properly the treatment effects of such strategies. Advanced NSCLC treatment uses similar protocols. Several types of agents are available, including TKIs, monoclonal antibodies, immune checkpoint inhibitors and conventional cytotoxic agents. Since they have biologically different anticancer mechanisms, most patients receive more than two regimens. The difference in PFS does not necessarily result in a difference in OS because of subsequent therapies, and if there is any interaction in each regimen, TFS is a better surrogate endpoint. Nevertheless, in NSCLC trials, TFS data have not been collected. To the best of our knowledge, this is the first study describing TFS for the treatment of patients with NSCLC.

The second PFS involves a similar concept. It is defined as the time from randomisation to progression or death after second-line treatment.[14] This is almost the same as the TFS when a sequence of several treatments is being evaluated. However, when trials are designed to evaluate combination treatments with agents that are effective as single agents (eg, gefitinib with or without pemetrexed), a second PFS is only applied to the sequential treatment arm; therefore, TFS is more suitable than a second PFS value (online supplementary figure S2).

There are several limitations to this study. First, the superiority of TFS over PFS can be explained by a longer follow-up time. However, the TFS was approximately 10 months shorter than the OS value. Since there is an increasing number of new agents, this difference is important in the use of early assessments for innovative treatments. Second, the following must be determined to show surrogacy: (1) if there is a correlation between the surrogate endpoint and true endpoint on an individual level, and (2) if there is a correlation between the treatment effects on the two endpoints at a trial level.[17] Since we only showed a patient-level correlation, further information about TFS for lung cancer trials is needed.

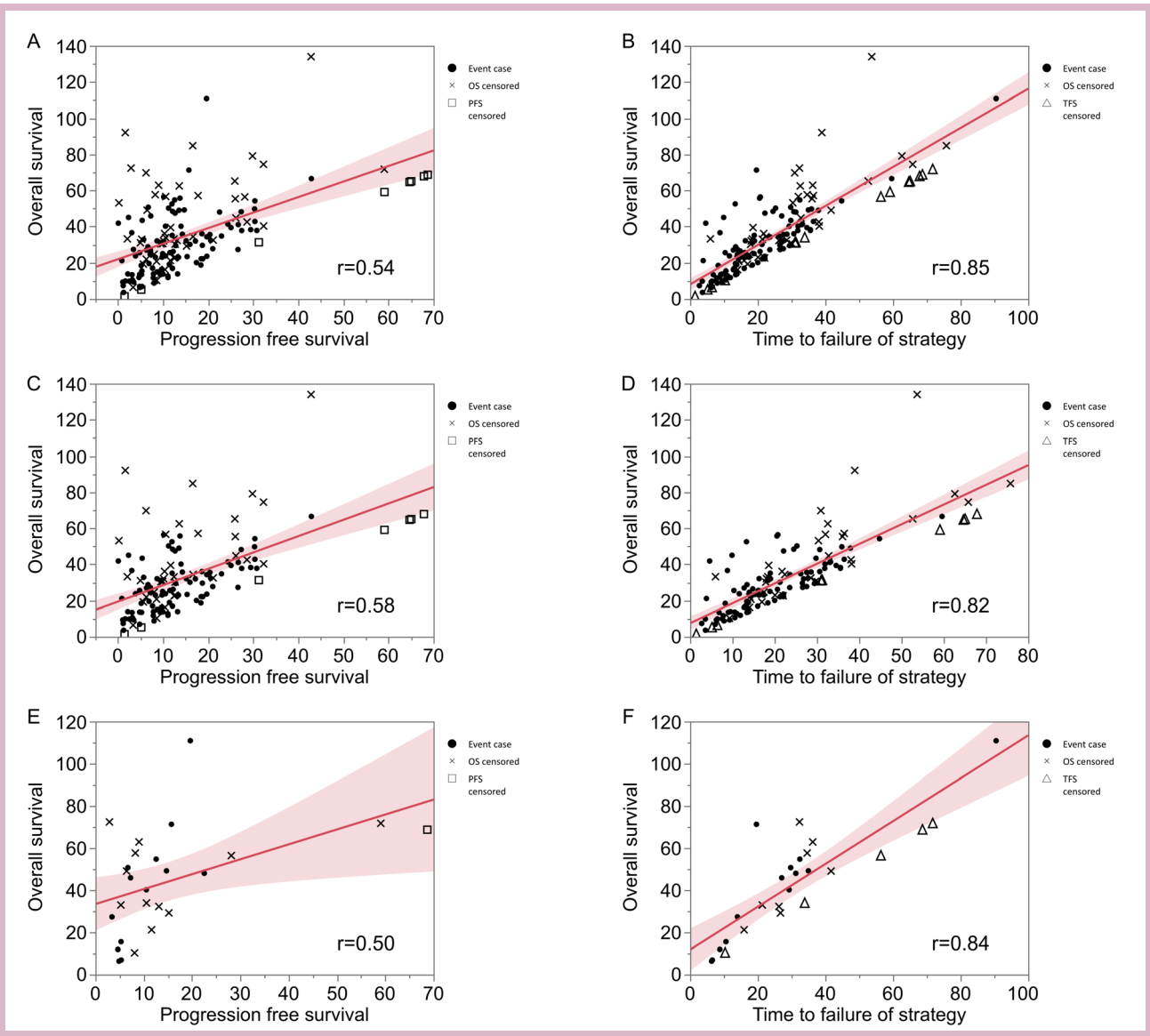

Figure 4 Correlation analysis with patient-level data. (A, C, E) The relationships between progression-free survival (PFS) and overall survival (OS) in all patients, in group 1 and in group 2. (B, D, F) The relationships between time to failure of strategy (TFS) and OS in all patients, in group 1 and in group 2. *The r values represent Spearman's rank correlation coefficients.

In summary, TFS had a better correlation with OS than PFS among patients with NSCLC with EGFR mutations who received EGFR-TKI and PT as the initial two regimens. TFS is therefore an acceptable surrogate endpoint for OS, but further validation in clinical trials and assessments of extrapolations are needed.

Contributors YS designed the study and wrote the initial draft of the manuscript. YG contributed to analysis and interpretation of data, and assisted in the preparation of the manuscript. All other authors have contributed to data collection and interpretation, and critically reviewed the manuscript. All authors approved the final version of the manuscript.

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Competing interests YG has had consulting/advisory roles for Eli Lilly, Chugai, Taiho Pharmaceutical, Boehringer Ingelheim, Pfizer and Novartis; served on speakers' bureaus for AstraZeneca, Eli Lilly, Chugai, Taiho Pharmaceutical, Boehringer Ingelheim, Ono Pharmaceutical, Bristol-Myers Squibb, Pfizer, MSD, Shionogi Pharma and Novartis; and received research funding from AbbVie, Eli Lilly, Taiho Pharmaceutical, Bristol-Myers Squibb and Ono Pharmaceutical. YM has served on speakers' bureau for Cook Medical, Olympus and AstraZeneca; and received research funding from Hitachi, Hitachi High-Technologies and Boston Scientific. SK has received research funding from AstraZeneca, Ono Pharmaceutical and AbbVie; and received honoraria from AstraZeneca, Ono Pharmaceutical, Bristol-Myers Squibb and Chugai. HH has received research funding from MSD, Bristol-Myers Squibb, Ono Pharmaceutical, Merck Serono, Novartis, Astellas, Chugai, Taiho Pharmaceutical and Genomic Health; and received honoraria from Eli Lilly. YF has received research funding from AbbVie, AstraZeneca, Chugai, Daiichi Sankyo, Eisai, Eli Lilly, Incyte, Merck Serono, MSD, Novartis and Bristol-Myers Squibb; and served on speakers' bureaus from AstraZeneca, MSD, Taiho Pharmaceutical, Bristol-Myers Squibb and Ono Pharmaceutical. NY has had consulting/advisory roles for Eisai, Takeda, Otsuka and Boehringer Ingelheim; and received research funding from Eli Lilly, Quintiles, Astellas, Chugai, Eisai, Taiho Pharmaceutical, Bristol-Myers Squibb, Pfizer, Novartis, Daiichi Sankyo, Bayer, Boehringer Ingelheim, Kyowa Hakko Kirin, Takeda and Ono Pharmaceutical; and served on speakers' bureaus from Bristol-Myers Squibb, Pfizer, AstraZeneca, Eli Lilly, Ono Pharmaceutical and Chugai. YO has

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