ORIGINAL ARTICLE

The Value of Early Depth of Response in Predicting Long-Term Outcome in *EGFR*-Mutant Lung Cancer

Chee Khoon Lee, PhD,[a,b] Sally Lord, MSc,[a,c] Ian Marschner, PhD,[a,d] Yi Long Wu, MD,[e] Lecia Sequist, MD,[f] Rafael Rosell, MD,[g] Masahiro Fukuoka, MD,[h] Tetsuya Mitsudomi, MD,[i] Rebecca Asher, MSc,[a] Lucy Davies, MSc,[a] Val Gebski, MStat,[a] Richard Gralla, MD,[j] Tony Mok, MD,[k] James Chih-Hsin Yang, PhD[l,*]

[a]*NHMRC Clinical Trials Centre, The University of Sydney, Sydney, Australia*
[b]*Clinical Research Unit, St. George Hospital, Sydney, Australia*
[c]*School of Medicine, The University of Norte Dame, Sydney, Australia*
[d]*Department of Statistics, Macquarie University, Sydney, Australia*
[e]*Guangdong Lung Cancer Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangdong, China*
[f]*Massachusetts General Hospital and Harvard Medical School, Boston, United States*
[g]*Catalan Institute of Oncology, Germans Trias i Pujol Health Sciences Institute and Hospital, Barcelona, Spain*
[h]*Department of Medical Oncology, Izumi Municipal Hospital, Osaka, Japan*
[i]*Department of Surgery, Division of Thoracic Surgery, Kindai University Faculty of Medicine, Osaka-Sayama, Japan*
[j]*Albert Einstein College of Medicine, Jacobi Medical Center, Bronx, New York*
[k]*Hong Kong Cancer Institute, Department of Clinical Oncology, Chinese University of Hong Kong, Shatin, China*
[l]*Graduate Institute of Oncology, National Taiwan University and Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan*

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ABSTRACT

Introduction: Traditionally, marked tumor shrinkage has been assumed to portend better outcome. We investigated whether depth of tumor response was associated with improved survival outcomes in advanced *EGFR*-mutant NCLC.

Methods: Individual patient data from randomized trials (EURTAC, IPASS, ENSURE, LUX-Lung 3, and LUX-Lung 6) were used. The association of depth of response with progression-free survival (PFS) and overall survival was examined using landmark analyses. Depth of response based on radiologic assessments at 6 weeks and 12 weeks was calculated as the relative changes in the sum of the longest diameters of the target lesions from baseline.

Results: Of 1081 evaluable patients at 6 weeks with no disease progression, 71.2% achieved Response Evaluation Criteria in Solid Tumors response. Using a landmark analysis, EGFR-TKI was more effective than chemotherapy (PFS hazard ratio = 0.36, $p < .0001$); and was associated with greater mean tumor shrinkage than chemotherapy (35.1% versus 18.5%, $p < .0001$). However, there was no significant difference in the relative PFS benefit between treatment groups across the entire spectrum of tumor shrinkage ($p = .18$ for test of interaction between treatment and continuously measured depth of response). Depth of response at 6 weeks was not associated with PFS when adjusted for treatment effect (hazard ratio = 0.96, $p = .78$). Similar results were obtained for 12-week landmark analysis and for OS outcome.

Conclusions: The PFS advantage of EGFR-TKI over chemotherapy in advanced *EGFR* mutant NCLC is not explained by depth of response at 6 or 12 weeks. It should not be used as a surrogate of benefit in future trials or routine clinical decision making.

Keywords: Depth of response; *EGFR* mutation; Tyrosine kinase inhibitor; Chemotherapy

***Corresponding author.**

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Address for correspondence: James Chih-Hsin Yang, MD, PhD, Graduate Institute of Oncology and Department of Oncology, National Taiwan University, 7, Chung-Shan South Road, Taipei, Taiwan, Taiwan 100. E-mail: chihyang@ntu.edu.tw

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Introduction

Advanced non–small cell lung cancers (NCLC) with epidermal growth factor receptor (*EGFR*) mutations are unique subgroups of NCLC that are classically associated with rapid and sustained responses to *EGFR* tyrosine kinase inhibitor (TKI) therapy. It is also a disease associated with a relatively good prognosis with median overall survival (OS) of approximately 3 years as observed in clinical trials.[1,2] Although most patients with *EGFR*-mutant lung cancers have some degree of clinical benefit from EGFR-TKI treatment, the extent of tumor shrinkage varies widely in practice. The relationships between initial tumor shrinkage and progression-free survival (PFS) and OS may have implications for clinical decision-making, research trial design, and drug development, but have not yet been well described in this patient population.

Traditionally, physicians and patients have assumed that marked tumor shrinkage portends better outcome. In routine practice, radiologic response assessment during the entire treatment course, when combined with other indicators of the patient's condition, are often used to guide clinical decision-making.[3] Although the timing of tumor assessments would differ across different clinical scenarios and vary in different routine practices, achieving rapid and significant tumor shrinkage in the first 1 to 2 months after commencement of systemic therapy would generally assume to be associated with better outcomes. Significant and rapid tumor shrinkage might theoretically lead to improvement of symptoms, delayed cancer progression, and possibly prolonged OS, particularly in patients with aggressive disease with high tumor burden. However, a complete response (CR), (i.e., total disappearance of all visible tumor) is rare and has occurred in less than 5% of patients with *EGFR*-mutant NCLC in first-line randomized controlled trials of EGFR-TKI.[4–11] Approximately 60% to 80% of *EGFR*-mutant patients achieve a partial response (PR) to EGFR TKIs by the Response Evaluation Criteria in Solid Tumors (RECIST), defined as a 30% or greater decrease in the sum of additive diameters of tumor lesions compared to baseline. Another 15% to 30% have stable disease (SD) to EGFR TKIs, where the change in tumor size fails to meet criteria for either response or cancer progression (defined as 20% growth). It remains unclear whether patients with an initial PR derive similar PFS benefit from EGFR-TKI as those with SD.

In clinical research, tumor shrinkage has been used to determine the antitumor activity of new anticancer agents. In screening for drug activity in early-phase clinical trials, agents that predominantly result in SD are often discounted in favor of other compounds that induce large responses. In addition, regulatory bodies are more likely to approve agents with higher response rates.[12] Therefore, it is critical to determine whether SD as a criterion for drug activity, compared with CR or PR, will translate to differential PFS or OS outcomes in *EGFR*-mutant patients.

In this study, we investigated whether the depth of response (DR), defined as the reduction in RECIST tumor measurement compared to baseline, may be a clinically meaningful early signal of treatment benefit and if it could be used as a surrogate for PFS and OS. We investigated this question by analyzing data from five large randomized controlled trials in advanced *EGFR*-mutant NCLC.

Methods

Trials

Individual patient data of those with either *EGFR* mutation exon 19 deletion or exon 21 L858R mutations from five phase III randomized trials — EURTAC, IPASS, ENSURE, LUX-Lung 3, and LUX-Lung 6 — that compared an EGFR-TKI against platinum doublet chemotherapy as front-line treatment for advanced metastatic NCLC were used for this analysis (Supplementary Table 1).[4–8] PFS was the primary endpoint in all studies, and RECIST was used to evaluate response. In all trials, PFS has been defined as time from randomization to disease progression or death from any cause, whichever occurred first in all the trials. The frequency of tumor response evaluation and the criteria used are outlined in Supplementary Table 1.

DR Assessments

Changes in tumor size were expressed as a relative change of the sum of the longest diameters of the target lesions based on trial investigator measurements. Nontarget lesions and newly occurring lesions were not considered in the measurement of change in tumor size.

Statistical Analysis

DR was examined as a surrogate endpoint for survival outcomes of PFS and OS. For DR to be a valid individual-level surrogate, a strong association must exist between DR and outcomes of PFS and OS across patient cohorts independent of the treatment received.[13] We used a landmark analysis at 6 weeks to assess the influence of DR on PFS/OS.[14] Patients who died or had disease progression measured by RECIST before or at 6 weeks were excluded. Those who died or had disease progression were excluded because they were no longer assessable for the PFS outcome at landmark. Patients with no tumor assessment at 6 weeks were excluded due to lack of data. Multivariable analyses, stratified by trial

enrollment, were also performed to adjust for treatment effect and baseline prognostic factors. Because of the exploratory nature of these analyses, no multiplicity adjustments were performed.

A subpopulation treatment effect pattern plot (STEPP) analysis explored treatment-effect heterogeneity across all levels of tumor shrinkage on a continuous scale.[15] Sliding-window STEPP analysis was used with absolute and relative treatment-effect measures with the following parameters: r1 = 200 and r2 = 150, where r1 represents the largest number of patients in common among consecutive subpopulations, and r2 is the number of patients in each subpopulation (r2 > r1).

In sensitivity analysis, we repeated the above analyses to examine the association of DR at 12 weeks with outcomes of PFS and OS.

Results

Of 2316 patients enrolled in the five included trials, 1312 were eligible for the present analysis (Fig. 1, Supplementary Table 1). Among surviving patients with no disease progression, investigator measurements of target lesions at the first evaluation (week 6) were available for 1081 (82.4%) of 1312 patients, and 935 (71.3%) at the second evaluation (week 12). Median follow-up was 35.3 months (range, 0–58.3 months). When assessing for the RECIST best overall response from the entire tumor assessments for each individual, 71.2% had already achieved this best response at week 6. At week 12, 80.6% had the best overall RECIST response. No patient had a CR at week 6 or week 12; all remaining patients had unconfirmed PR or SD.

DR as Individual-Level Surrogate

At 6 weeks, EGFR-TKI, compared with chemotherapy, was associated with greater DR (mean tumor shrinkage: 35.1% vs. 18.5%, $p < .0001$). There was no difference in DR between exon 19 deletions and exon 21 L858R (18.7% vs. 18.3%, $p = .86$) in the chemotherapy arm, but a significant difference in the EGFR-TKI arm (39.3% vs. 29.9%, $p < .0001$) (Supplementary Fig. 1*A*). Findings at 12 weeks were similar (Supplementary Fig. 1*B*).

In a univariable Cox regression analysis, DR had a significant association with PFS (hazard ratio [HR] = 0.58, 95% confidence interval [CI]: 0.44 to 0.78, $p < .0001$) (Table 1). Treatment with EGFR-TKI compared with chemotherapy was also associated with significant PFS improvement (HR = 0.36, 95% CI: 0.31 to 0.42, $p < .0001$) (Table 1). However, after adjusting DR for treatment effect (bivariable model, Table 1) DR was no longer a significant predictor of PFS ($p = .78$), whereas the treatment variable remained statistically significant ($p < .0001$) (Table 1). Multivariable adjustment for other baseline prognostic factors did not change the result significantly.

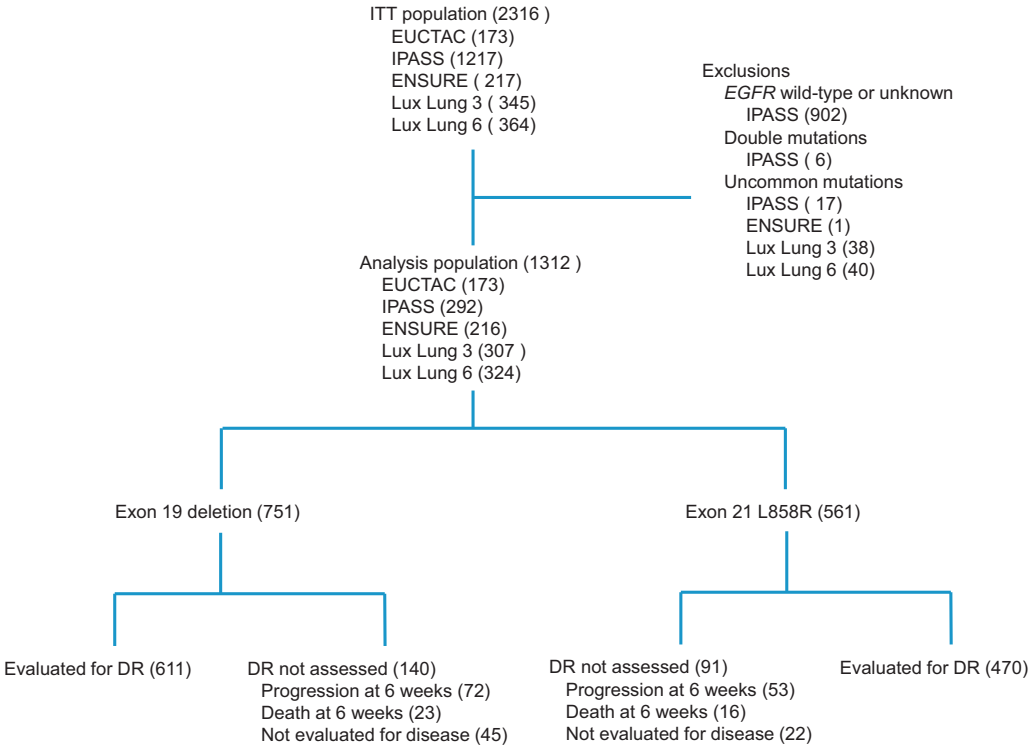

Figure 1. Consort diagram. DR, depth of response.

Table 1. Cox Regression Analysis at 6-Week Landmark

	Univariable Analysis (n = 1081)				Bivariable Analysis (n = 1081)					Multivariable Analysis[a] (n = 1081)				
Parameters	HR	95% CI		*p*	Parameters	HR	95% CI		*p*	Parameters	HR	95% CI		*p*
Progression-free survival														
DR at week 6	0.58	0.44	0.78	<.0001	DR at week 6	0.96	0.70	1.30	0.78	DR at week 6	0.97	0.70	1.33	0.85
EGFR-TKI vs chemotherapy	0.36	0.31	0.42	<.0001	EGFR-TKI vs chemotherapy	0.36	0.31	0.42	<.0001	EGFR-TKI vs chemotherapy	0.36	0.30	0.42	<.0001
										Ever vs non-smoker	1.35	1.14	1.60	.001
										ECOG PS 1 vs 0	1.13	0.96	1.33	.01
										ECOG PS 2 vs 0	1.83	1.24	2.72	
										Pleural metastasis vs none or unknown	1.37	1.15	1.65	.001
										Brain metastasis vs none or unknown	1.35	1.02	1.77	.03
Overall survival														
DR at week 6	0.80	0.59	1.08	.15	DR at week 6	0.83	0.60	1.15	.26	DR at week 6	0.78	0.56	1.09	.15
EGFR-TKI vs chemotherapy	0.89	0.77	1.02	.10	EGFR-TKI vs chemotherapy	0.95	0.81	1.11	.54	EGFR-TKI vs chemotherapy	0.96	0.82	1.13	.65
										Female vs male	0.78	0.66	0.91	.002
										ECOG PS 1 vs 0	1.29	1.08	1.53	<.0001
										ECOG PS 2 vs 0	2.56	1.73	3.77	
										Pleural metastasis vs none or unknown	1.26	1.04	1.52	.02
										Bone metastasis vs none or unknown	1.40	1.17	1.67	<.0001
										Brain metastasis vs none or unknown	1.36	1.05	1.77	.02
										Liver metastasis vs none or unknown	1.45	1.12	1.87	.005

[a]Baseline variables considered in the multivariable model were DR, treatment arm, smoking status, ECOG PS, sex, *EGFR* mutation type, presence of pleural, bone, liver, and brain metastases. Backward selection of these variables was performed and only variables with $p < .05$ were retained in the Cox regression model stratified by trials. DR and treatment arm were only two variables reintroduced to the final model even if they were nonsignificant.

DR, depth of response as a continuous variable; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; CI, confidence interval.

In the STEPP analysis, the treatment effect on PFS remained relatively constant, with no significant heterogeneity across the entire spectrum of tumor shrinkage based on landmark analysis at 6 weeks (treatment-DR interaction $p = .18$) (Fig. 2*A*). EGFR-TKI was also consistently associated with a higher 12-month PFS across the entire spectrum of tumor shrinkage, when compared with chemotherapy (Fig. 2*B*). When the subgroups of exon 19 deletion (Figs. 2*C* and 2*D*) and exon 21 L858R (Figs. 2*E* and 2*F*) were examined separately, the findings were similar. There were no significant interactions between DR and types of *EGFR* mutation in the chemotherapy groups ($p = .17$) and EGFR-TKI groups ($p = .63$). However, the treatment effect on PFS was greater for exon 19 deletion (HR = 0.24, 95% CI: 0.19 to 0.29; $p < .0001$) than exon 21 L858R (HR = 0.54, 95% CI: 0.44 to 0.67; $p < .0001$) (treatment-mutation interaction $p < .0001$). When the landmark analysis was repeated at 12 weeks, similar PFS results were obtained (Supplementary Table 2, Supplementary Figs. 2*A*–2*F*).

DR was not a significant predictor of OS in univariate Cox regression analysis (Table 1). The bivariable model including DR and treatment as well as the multivariable model did not change the result significantly. There was no significant heterogeneity in treatment effect across the entire spectrum of tumor shrinkage based on landmark analysis at 6 weeks (treatment-DR interaction $p = .58$) (Supplementary Figs. 3*A* and 3*B*). There were no significant interaction between DR and type of *EGFR* mutation (exon 19 deletion: Supplementary Figs. 3*C* and 3*D*; exon 21 L858R: Supplementary Figs. 3*E* and 3*F*) in the chemotherapy groups ($p = .13$) or EGFR-TKI arm ($p = .97$). When the landmark analysis was repeated at 12 weeks, similar OS results were obtained (Supplementary Table 2, Supplementary Figs. 4*A*–4*F*).

Discussion

We examined individual patient-level data from five randomized trials of front-line EGFR-TKI versus chemotherapy to assess whether the DR could be used as a surrogate for PFS or OS. Among stable and responding *EGFR* mutant patients, DR at week 6 or week 12 was a poor surrogate for PFS or OS, suggesting that drug development, regulatory approval, and individual clinical treatment decisions should not be made based on DR alone.

We did observe a significant relationship between DR and PFS in univariate Cox regression analysis, but DR was no longer a significant variable after adjustment for treatment effect (EGFR-TKI versus chemotherapy), suggesting that the initial observation was being driven by treatment assignment and not DR. We performed a STEPP analysis that further supports this finding by showing that patients treated with EGFR-TKI, compared with chemotherapy, have consistently greater relative PFS benefit, regardless of their DR at week 6 or 12. Furthermore, the 12-month absolute PFS rate also did not differ according to DR in the EGFR-TKI and chemotherapy groups, respectively.

To date, studies have correlated different aspects of radiological response with long-term survival benefit. In a meta-analysis using data from 14 randomized trials submitted to the U.S. Federal Drug Authority for approval of chemotherapy, EGFR-TKI and other biological agents for advanced NCLC, the objective tumor response (CR and PR) had a strong trial-level association with subsequent PFS.[16] The individual-level analysis also showed that CR and PR groups had better PFS and OS than nonresponders. However, two NCLC studies using individual-patient data from randomized trials also showed that the disease control rate (CR, PR, or SD at 8 weeks) and the PFS at 12 weeks were considered to be more powerful predictors of subsequent OS than the traditional objective tumor response.[17,18] For *EGFR*-mutant lung cancers, data remain conflicting, particularly the association between minimal tumor shrinkage, or nonprogression, and long-term survival outcomes.[19–21]

Several studies have reported a strong association between RECIST tumor response and PFS in advanced lung cancer using trial- and individual-level data. In these studies, patients have been categorized into CR and PR vs SD or progressive disease.[16,19,22] However, in two studies examining the degree of tumor shrinkage quantitatively, DR was not associated with improved survival outcomes, consistent with our finding.[19,20] Furthermore, the methodological approach used in some of these studies was also criticized for not accounting for guarantee-time bias.[23,24] In another study using similar methods to ours in metastatic colorectal cancer patients treated with an anti-*EGFR* monoclonal antibody and chemotherapy, DR correlated with survival outcomes.[25] Different results could potentially be explained by the differences between the cancer types (NCLC vs. colorectal cancer), differences in the treatments being investigated, and differences in trial designs, along with the fact that NCLC studies were enriched with only *EGFR*-mutant patients whereas the colorectal cancer studies contained both *KRAS* wild-type and mutant patients.

The findings of this analysis provide some support for the clinical benefit of SD and contradict the popular belief that only deep response will result in a significant delay in cancer progression. However, our analysis did not distinguish between those with SD that involved minor absolute tumor shrinkage versus minor absolute tumor growth. Regardless, RECIST response evaluation

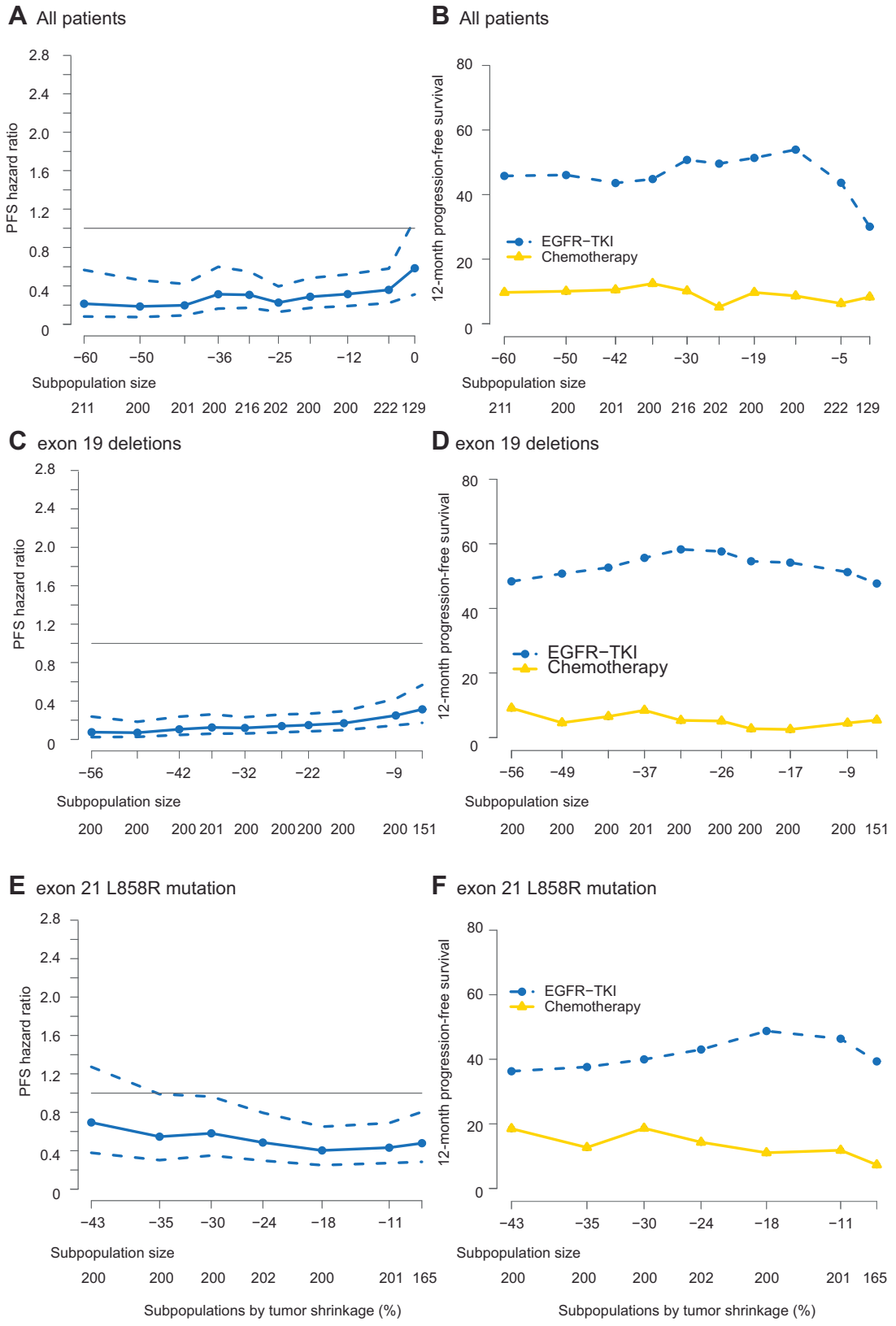

Figure 2. Sliding-window subpopulation treatment effect pattern measured as hazard ratio (HR) for progression-free survival (PFS) in the (*A*) overall population, (*C*) exon 19 deletion, and (*E*) exon 21 L858R mutations subgroups, and also measured as PFS rate at 12 months from landmark across the entire spectrum of tumor shrinkage at 6 weeks in the (*B*) overall population, (*D*) exon 19 deletion, and (*F*) exon 21 L858R mutations subgroups. HR is for the comparison of EGFR-TKI versus chemotherapy; HR < 1 suggests EGFR-TKI superior over chemotherapy, with 95% confidence intervals in dashed lines.

remains a crude assessment that provides limited information about the underlying biology of this disease. Most patients treated with EGFR-TKI will eventually develop drug resistance, predominantly through an additional *EGFR* mutation, *EGFR* T790M, and also via other genotypic changes.[26] Resistance to platinum-based chemotherapy is usually multifactorial, but reduced intracellular cisplatin accumulation and reduced uptake of cisplatin are commonly observed in platinum-resistant cell lines.[27–30] Our study has shown that whether the treatment agent is EGFR-TKI or chemotherapy the time to development of acquired resistance is independent of DR at weeks 6 and 12 in advanced *EGFR*-mutant lung cancer. On the other hand, several small studies have shown that early complete clearance of plasma *EGFR*-mutant cells in EGFR-TKI-treated patients predicts superior survival outcomes.[31,32] The role of plasma *EGFR* mutation testing should be further examined in larger studies to determine whether it would be a valid surrogate for PFS or OS.

A major strength of this paper is our use of five well-conducted randomized controlled trials with more than 1000 patients. Individual-patient data from these studies provide the opportunity to assess individual-level surrogacy. Pooling data from these trials to improve the power of this analysis is possible because these studies have well-established protocols with a similar tumor evaluation process at the same early time points. We used the STEPP analysis as a novel statistical approach to allow us to examine tumor shrinkage across the entire spectrum without restriction to an arbitrary cutpoint. Our study also has several limitations. First, DR was assessed from the sum of RECIST-measurable lesions on conventional computed tomographic scan. We did not consider non-measurable disease and hence underestimate the true overall disease burden. Second, the trials were conducted during different periods and had small differences in terms of frequency and timing of tumor assessment; these differences could impact on how time to disease progression had been defined.[33] As different versions of RECIST were used for the different trials, assessment of volume of disease will also be different, particularly with more stringent criteria for lymph node assessments. However, a study of different advanced cancers has shown that RECIST 1.1 showed a highly concordant response assessment with RECIST 1.0.[34] Third, due to the lack of correlation between DR with PFS/OS at an individual level, it is not meaningful to test further at trial-level. Fourth, we were not able to provide any information on patients with CR as there were none at weeks 6 and 12. We have also not examined the impact of patients with PD as they were assumed to have the worst outcome and were excluded from analysis. Fifth, all tumor assessments were based on local rather than central assessments, and tumor responses were unconfirmed. Furthermore, patients not evaluated for DR were excluded, which may have introduced bias, for example, if patients who had discontinued or did not undergo an imaging assessment at weeks 6 and 12 were missed other than randomly. However, the main reason for exclusion was death or early progression, suggesting that if patient groups had been classified according to early treatment failure (absence of DR, presence of early progression or death) then the OS and PFS differences would have been more pronounced. The landmark approach further minimized guarantee time bias.[35] Despite these approaches, the results of this study should still be considered as hypothesis-generating.

Our study has several important implications. In routine practice, DR should not be used as the main variable to guide clinical treatment decisions. Radiologic response assessment should be supplemented with other indicators of the patient's condition, such as patients' symptoms, to guide clinical decision-making. Recently, a randomized trial that evaluated changes in advanced cancer patients' self-reported symptoms through systematic symptom monitoring has been shown to have superior OS outcome over those who underwent usual care.[36] Regulatory agencies must reconsider the decision to approve drugs based only on high objective tumor response as potentially efficacious agents could be overlooked.

In summary, there is a poor association between DR at week 6 or 12 with long-term survival outcomes in advanced *EGFR*-mutant lung cancer treated with first-line EGFR-TKI or chemotherapy. DR should not be used as a surrogate of benefit in future trials or in routine clinical decision making.

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Supplementary Data

Note: To access the supplementary material accompanying this article, please visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2018.03.010.

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