

OPEN

# Baseline, Trend, and Normalization of Carcinoembryonic Antigen as Prognostic Factors in Epidermal Growth Factor Receptor-Mutant Nonsmall Cell Lung Cancer Patients Treated With First-Line Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors

Yu-Mu Chen, MD, Chien-Hao Lai, MD, Huang-Chih Chang, MD, Tung-Ying Chao, MD, Chia-Cheng Tseng, MD, Wen-Feng Fang, MD, Chin-Chou Wang, MD, Yu-Hsiu Chung, MD, Kuo-Tung Huang, MD, Hung-Cheng Chen, MD, Ya-Chun Chang, MD, and Meng-Chih Lin, MD

**Abstract:** Among epidermal growth factor receptor (*EGFR*) mutation status unknown nonsmall cell lung cancer (NSCLC) patients, those with higher carcinoembryonic antigen (CEA) level are more likely to respond to *EGFR*-tyrosine kinase inhibitors (TKIs) because they tend to have mutant epidermal growth factor receptor (*EGFR*). However, patients with higher CEA also have more tumor burden. With the above paradoxical evidence, it is prudent to understand the prognostic significance of baseline CEA in patients with *EGFR*-mutant NSCLC treated with first-line *EGFR*-TKIs. The clinical significance of the trend in CEA after treatment and the impact of CEA normalization during *EGFR*-TKI therapy are also unknown and potentially important.

A total of 241 patients who received first-line *EGFR*-TKIs were included. As to baseline CEA, patients were divided into normal, low, and high baseline CEA by cut point determined by receiver operating characteristic curves. As to CEA responses, patients were divided into 3 groups accordingly to their amount of CEA change after taking TKIs. In group A, 1-month follow-up CEA level decreased more than 35% with nadir CEA normalization; in group B, 1-month follow-up CEA level decreased more than 35% without nadir CEA normalization; and in group C, 1-month follow-up CEA level decreased less than 35% or increased.

Patients with higher baseline CEA levels had shorter progression-free survival (PFS) and overall survival (OS) (CEA > 32 vs 5–32 vs < 5 ng/mL, PFS = 8.8 vs 11.3 vs 14.4 months, respectively,  $P < 0.001$ ; OS = 17.8 vs 22.0 vs 27.9 months, respectively,  $P = 0.01$ ). For trend and CEA normalization in groups A, B, and C, PFS was 14.3, 10.6, and 7.1 months, respectively ( $P < 0.001$ ); OS was 29.7, 20.0, and 16.2 months, respectively ( $P < 0.001$ ).

Editor: Manal Salah-Eldin.

Received: August 25, 2015; revised and accepted: November 12, 2015.

From the Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Chang Gung Memorial Hospital-Kaohsiung Medical Center, Chang Gung University College of Medicine, Kaohsiung (YMC, CHL, HCC, TYC, CCT, WFF, CCW, YHC, KTH, HCC, YCC, MCL); and Department of Respiratory Care, Chang Gung Institute of Technology, Chiayi, Taiwan (WFF).

Correspondence: Meng-Chih Lin, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Chang Gung Memorial Hospital, No. 123, Ta-Pei Road, Niao-Sung District, Kaohsiung City, Taiwan (e-mail: mengchih@adm.cgmh.org.tw).

The authors have no conflicts of interest to disclose.

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

This is an open access article distributed under the Creative Commons Attribution License 4.0, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. ISSN: 0025-7974

DOI: 10.1097/MD.0000000000002239

Baseline, trend, and normalization of CEA levels are potential prognostic markers for patients with *EGFR*-mutant advanced NSCLC treated with first line *EGFR*-TKIs.

(*Medicine* 94(50):e2239)

**Abbreviations:** CEA = carcinoembryonic antigen, CT = computed tomography, DM = diabetes mellitus, ECOG = Eastern Cooperative Oncology Group, *EGFR* = epidermal growth factor receptor, NSCLC = nonsmall cell lung cancer, OS = overall survival, PFS = progression-free survival, PS = performance status, ROC = receiver operating characteristic, TKI = tyrosine kinase inhibitor.

## INTRODUCTION

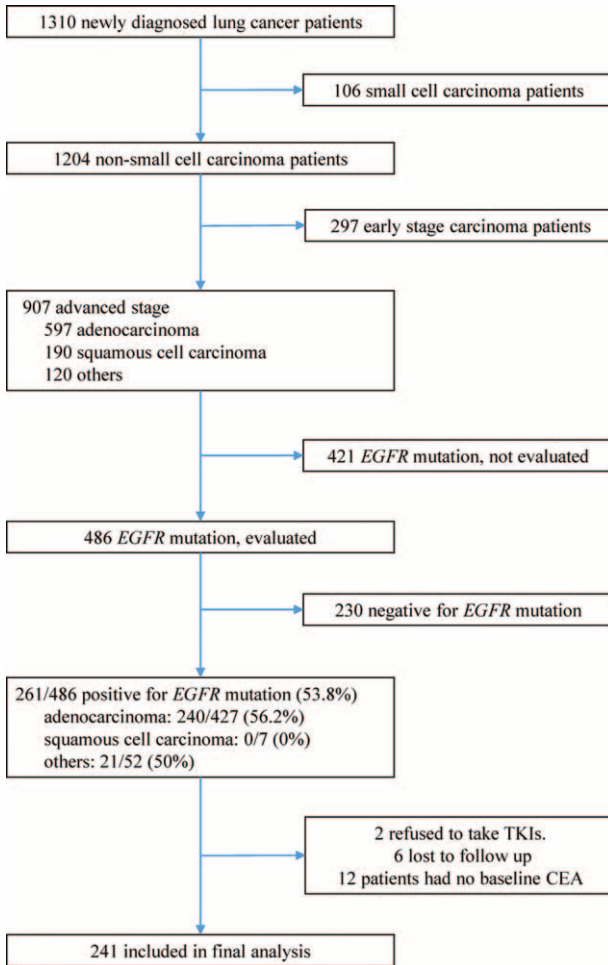
The incidence of lung cancer is increasing in Taiwan, and it is the leading cause of cancer-related death worldwide.<sup>1,2</sup> Asian lineage, never-smoker, and adenocarcinoma histology are well-known predictors of nonsmall cell lung cancer (NSCLC) patients harboring epidermal growth factor receptor (*EGFR*) mutations.<sup>3–8</sup>

In NSCLC patients harboring *EGFR* mutation, *EGFR*-tyrosine kinase inhibitors (TKIs) can improve quality of life, progression-free survival (PFS), and overall survival (OS).<sup>9</sup> Several clinical parameters have been shown to affect the efficacy of *EGFR*-TKIs, including major mutation type, adenocarcinoma histology, tumor burden, Eastern Cooperative Oncology Group (ECOG) performance status (PS), baseline carcinoembryonic antigen (CEA) level, and lymphocyte-to-monocyte ratio.<sup>10–17</sup>

Previous studies in *EGFR* nonselective patients revealed that patients with a higher baseline CEA level are more likely to respond to *EGFR*-TKIs and have longer PFS.<sup>13–15</sup> This phenomena may be attributed to a higher *EGFR* mutation rate in patients with higher CEA levels.<sup>14,18</sup> However, previous studies also revealed that higher CEA level was correlated with higher tumor burden and more advanced stage.<sup>19</sup>

To the best of our knowledge, the prognostic significance of baseline CEA and the trend in CEA in patients with advanced-stage NSCLC with *EGFR* mutations who are treated with first-line *EGFR*-TKIs has not been well studied. In addition, the clinical significance of CEA levels normalization in CEA elevated patients during *EGFR*-TKIs therapies is not well known.

Therefore, we conducted a retrospective analysis to investigate the influence of baseline, trend, and normalization of



**FIGURE 1.** Inclusion, screening, and group assignment of patients. Among 1310 nonsmall cell lung cancer patients diagnosed between January 2011 and October 2013, 241 patients were included into final analysis.

CEA on clinical outcomes including PFS and OS in patients with NSCLC and *EGFR* mutation.

**MATERIAL AND METHODS**

**Patient and Clinical Characteristics**

From January 2011 to October 2013, this retrospective study was conducted at Chang Gung Memorial Hospital, Kaohsiung Medical Center in Taiwan. We included patients aged more than 18 years with pathologically (either histologically or cytologically) confirmed advanced stage, *EGFR*-mutant NSCLC who were receiving first-line *EGFR*-TKI. Patients who had previously received targeted therapy, chemotherapy, or immunological therapy were excluded.

Baseline assessments, including clinical characteristics, serum CEA, chest radiography and computed tomography (CT), brain magnetic resonance imaging, and bone scan were performed within 4 weeks before initiation of *EGFR*-TKIs.

Clinical characteristics were recorded including age, gender, diabetes mellitus (DM) history, smoking history, type of *EGFR* mutation, TNM status, number of distant metastases, and ECOG PS. Serial CEA data were collected if the patients'

**TABLE 1.** Clinical Characteristics of Patients

	Data
Age (mean ± SD), years	64.9 ± 12.4
Baseline CEA (mean ± SD)	205.0 ± 730.3
CEA at month one (mean ± SD)	64.8 ± 171.9
Nadir CEA (mean ± SD)	39.1 ± 85.4
T	
1	23 (9.5)
2	53 (22.0)
3	39 (16.2)
4	126 (52.3)
N	
0	47 (19.5)
1	23 (9.5)
2	76 (31.5)
3	95 (39.4)
No. of distant metastases, n, %	
0	29 (12.0)
1	120 (49.8)
2	54 (22.4)
>2	38 (15.8)
ECOG PS, n, %	
0	45 (18.7)
1	151 (62.7)
2	24 (10.0)
3	16 (6.6)
4	5 (2.1)
PFS (median), months	10.3
OS (median), months	22.0

CEA = carcinoembryonic antigen, ECOG = Eastern Cooperative Oncology Group, OS = overall survival, PFS = progression free survival, PS = performance status.

baseline CEA level was ≥5 ng/mL. Trend of CEA level was obtained by dividing the 1-month CEA by the baseline CEA. CEA normalization was the lowest CEA among who had <5 ng/mL CEA levels during TKI therapy. The study was reviewed and approved by the Institutional Review Board of Chang Gung Memorial Hospital-Kaohsiung Medical Center, and informed consent was waived.

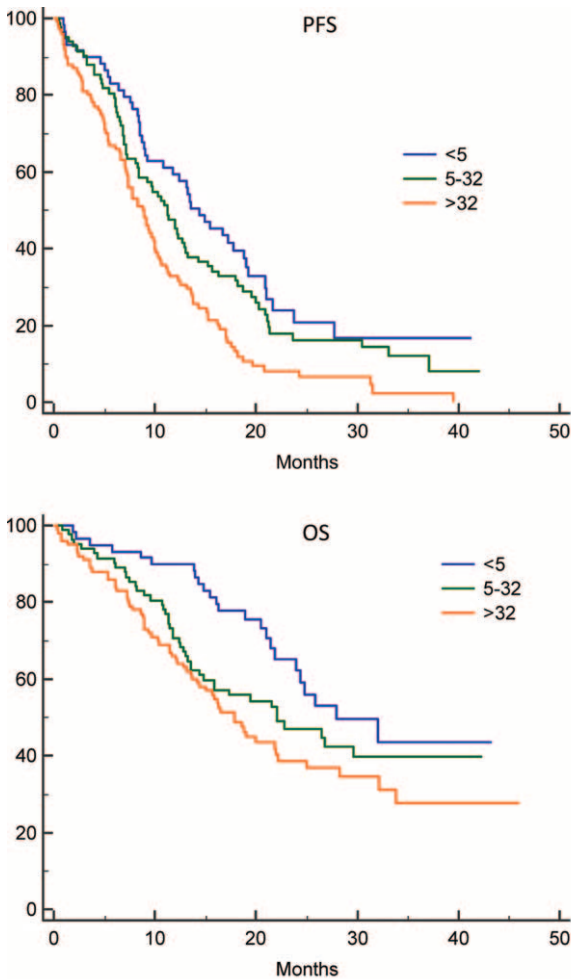
**Testing of *EGFR* Mutation**

We obtained tumor specimens by CT-guided biopsy, bronchoscopy, pleural effusion cytology, or surgical biopsy. We used SCORPIONS and ARMS polymerase chain reaction (*EGFR* RGQ PCR Kit; Qiagen, Venlo, The Netherlands)<sup>20</sup> for *EGFR* mutation analyses. We defined patients as having common mutations if they had pure exon 19 deletions or L858R mutations. Patients were defined as having uncommon mutations if they had mutations other than exon 19 deletions or L858R mutations or compound mutations.

**Response Evaluation of *EGFR*-TKI Treatment**

For tumor response and disease status evaluation, patients underwent chest radiography at least once pre-month and chest CT every 2 to 3 months. Additional chest radiography and CT will be arranged whenever disease progression was suspected by clinician.

Disease status was evaluated using Response Evaluation Criteria in Solid Tumors criteria 1.1 by the clinician.<sup>21</sup> PFS was



Baseline CEA	n	PFS	p	OS	p
<5	59	14.4	0.202	27.9	0.071
5-32	82	11.3		22.0	
>32	100	8.8		17.8	

0.219

**FIGURE 2.** Impact of baseline carcinoembryonic antigen on epidermal growth factor receptor mutant nonsmall cell lung cancer patients treated with first-line tyrosine kinase inhibitors therapy. (Top) PFS between high, low, and normal baseline carcinoembryonic antigen patients; (bottom) OS between high, low, and normal baseline carcinoembryonic antigen patients. OS = overall survival, PFS = progression-free survival.

defined as the time interval between the initiation of EGFR-TKIs administration and disease progression, death before disease progression, or the final visit before the end of follow-up.<sup>16</sup> OS was defined as the time interval between the initiation of EGFR-TKIs administration and death, final visit before the end of follow-up or loss to follow-up.

**Statistical Analyses**

Statistical analyses were performed using MedCalc (version 14.10.2). We used PFS longer or shorter than 12 months as binary variable for receiver operating characteristic (ROC)

**TABLE 2.** Univariable and Multivariable Analyses of Baseline Characteristics and Progression-Free Survival

	Univariable Analysis			Multivariable Analysis				
	n	Median (m)	P	HR	95% CI	P		
Age								
>65	119	11.5	0.10					
≤65	122	10.0						
Gender								
Male	100	10.4	0.10					
Female	141	10.9						
DM								
Yes	46	10.5	0.71					
No	195	10.4						
Smoking history								
Nonsmoker	164	11.0	0.64					
Smoker	77	9.5						
EGFR Mutation								
Common	217	11.3	<0.001	1	1.387–3.420	0.001		
Uncommon	24	4.8						
Baseline CEA, ng/mL								
>32	100	8.8	<0.001	1.715	1.178–2.495	0.005*		
5–32	82	11.3		1.181			0.804–1.734	0.40 <sup>†</sup>
<5	59	14.4		1				
Distant metastases								
>2	38	6.5	<0.001	1.928	1.328–3.420	0.001		
≤2	203	11.6		1				
PS								
ECOG 0–1	196	11.5	<0.001	1	1.210–2.413	0.002		
ECOG 2–4	45	5.1		1.709				

CEA = carcinoembryonic antigen, CI = confidence interval, DM = diabetes mellitus, ECOG = Eastern Cooperative Oncology Group, EGFR = epidermal growth factor receptor, PFS = progression-free survival, PS = performance status.

\* Baseline CEA > 32 versus <5 ng/mL.

<sup>†</sup> Baseline CEA 5–32 versus <5 ng/mL.

curves since median PFS in NSCLC patients harboring EGFR mutation treated with first line EGFR TKIs were 9.2 to 13.7 months in previous studies.<sup>22–26</sup> ROC curves and Youden index were used to determine the optimal cut-off value for baseline and trend of CEA as prognostic factors. Univariable analysis of PFS and OS durations was performed using the Kaplan–Meier method and the log-rank test. Variables with P < 0.05 in univariable analysis were included into multivariable analysis using Cox proportional hazards regression test. The Kruskal–Wallis test was used for assessing the relationship between baseline CEA and TNM status as well as ECOG PS. A 2-sided P value less than 0.05 was considered statistically significant.

**RESULTS**

**Patient Characteristics**

Between January 2011 and October 2013, 1310 lung cancer patients were diagnosed (Fig. 1). Of 486 patients screened for EGFR mutations, 261 (53.7%) patients had EGFR-mutant NSCLC. Six patients were lost to follow-up, 2 patients refused to undergo treatment with TKIs, and 12 patients had no pretreatment serum CEA data. The final analysis data set consisted of 241 patients. The median follow-up time of study patients was 24 months, and the longest follow-up time was 45 months. The mean age of the study population was 64.9 years, median PFS was 10.3 months, and median OS was 22.0 months

**TABLE 3.** Univariable and Multivariable Analyses of Baseline Characteristics and Overall Survival

	Univariable Analysis			Multivariable Analysis		
	n	OS, Median (m)	P	HR	95% CI	P
Age						
>65	119	13.4	0.30			
≤65	122	22.1				
Gender						
Male	100	19.5	0.19			
Female	141	23.0				
DM						
YES	46	21.3	0.96			
NO	195	23.0				
Smoking history						
Nonsmoker	164	22.5	0.22			
Smoker	77	21.3				
EGFR Mutation						
Common	217	21.4	0.20			
Uncommon	24	13.5				
Baseline CEA, ng/mL						
>32	100	17.8	0.01	1.718	1.060–2.782	0.03*
5–32	82	22.0		1.526	0.927–2.512	0.10†
<5	59	27.9		1		
Distant metastasis						
>2	38	10.5	<0.001	2.211	1.445–3.384	<0.001
≤2	203	23.0		1		
PS						
ECOG 0–1	196	24.5	<0.001	1		<0.001
ECOG 2–4	45	8.4		2.884	1.951–4.262	

CEA = carcinoembryonic antigen, CI = confidence interval, DM = diabetes mellitus, ECOG = Eastern Cooperative Oncology Group, EGFR = epidermal growth factor receptor, OS = overall survival, PS = performance status.

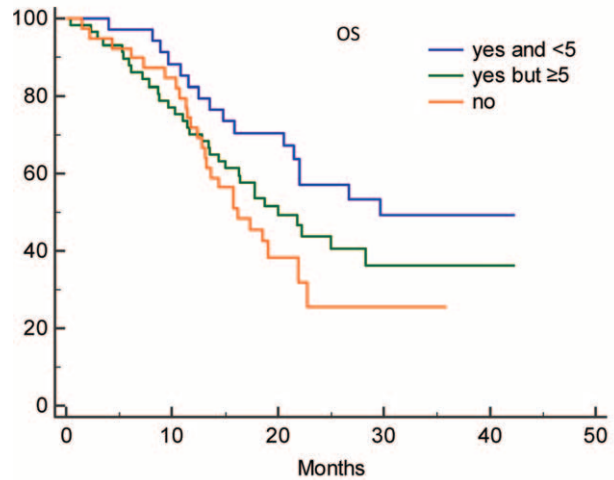
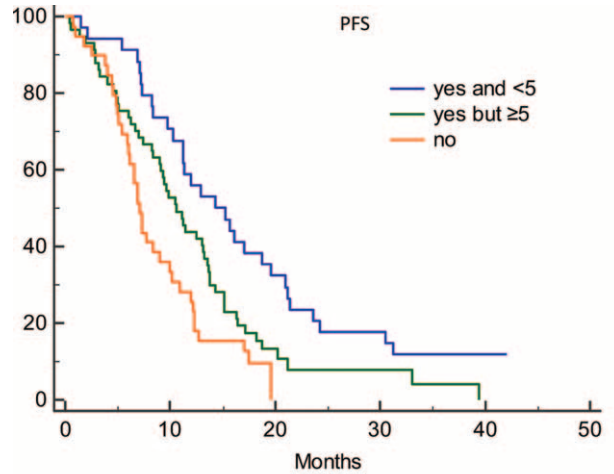
\* Baseline CEA > 32 versus < 5 ng/mL.

† Baseline CEA 5–32 versus < 5 ng/mL.

(Table 1). The baseline CEA was  $\geq 5$  ng/mL in 182 of 241 patients. Among these 182 patients, serial follow-up of CEA data were available for 130 patients. The baseline, follow-up, and nadir CEA levels are shown in Table 1. At the last follow-up, 205 (85.1%) patients showed disease progression and 129 (53.5%) had died. The best cut-off points for baseline and trend of CEA determined by ROC curve analysis were 32 ng/mL and 0.65 (35% decreasing from baseline), respectively. Based on above cut-off value for baseline CEA, patients were classified as high, low, and normal baseline CEA levels. Based on above cut-off value for trend of CEA, patients were classified as having a positive CEA response if their 1 month CEA decreased more than 35% compared with the baseline CEA, otherwise they were classified as no CEA response.

**Survival Analysis of Baseline Clinical Factors**

Patients with shorter PFS duration in the univariable analysis of clinical parameters included uncommon EGFR mutations ( $P < 0.001$ ), higher baseline CEA ( $P < 0.001$ ) (Fig. 2), more distant metastases ( $P < 0.001$ ), and poor ECOG PS ( $P < 0.001$ ) (Table 2). Age older or younger than 65 years, sex, history of DM, and smoking had no influence on PFS duration. Clinical predictive factors for a shorter PFS duration in multivariable analysis were uncommon EGFR mutations (HR 2.178,  $P = 0.001$ ), baseline CEA > 32 ng/mL (HR 1.715,

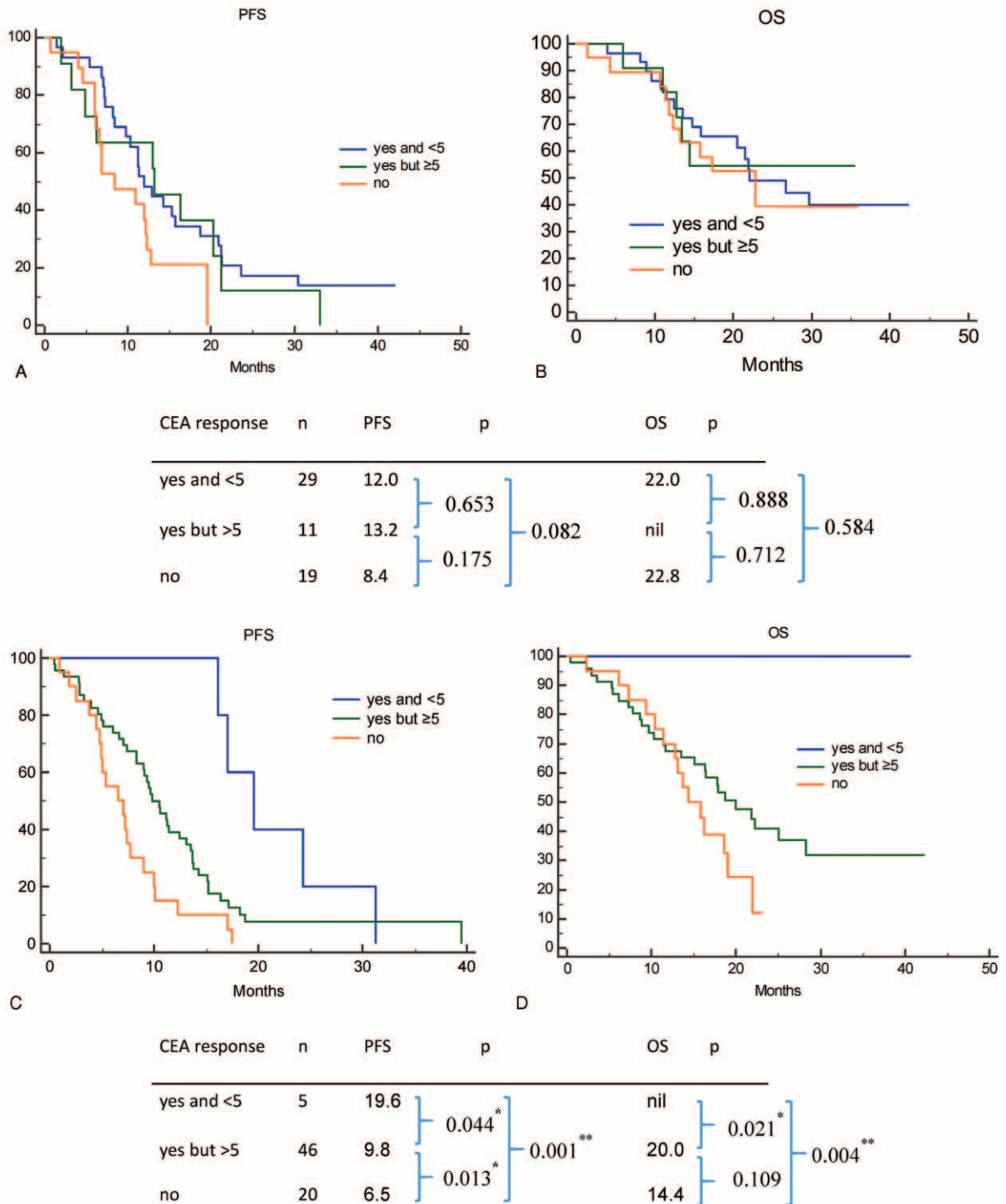


CEA response	n	PFS	p	OS	p
yes and <5	34	14.3	0.017*	29.7	0.017*
yes but >5	57	10.6		20.0	
no	39	7.1		16.2	

**FIGURE 3.** Impact of trend and normalization of CEA on epidermal growth factor receptor mutant nonsmall cell lung cancer patients treated with first-line tyrosine kinase inhibitors therapy. (Top) PFS in 3 subgroup patients: patients with both CEA response and normalization, with CEA response but without normalization, and in patients without CEA response; (bottom) OS in 3 subgroup patients mentioned before. CEA = carcinoembryonic antigen, OS = overall survival, PFS = progression-free survival.

$P = 0.005$ ), more distant metastases (HR 1.928,  $P = 0.001$ ), and poor ECOG PS (HR 1.709,  $P = 0.002$ ) (Table 2).

Patients with shorter OS duration in the univariable analysis of clinical parameters included higher baseline CEA ( $P = 0.01$ ), more distant metastases ( $P < 0.001$ ), and poor ECOG PS ( $P < 0.001$ ) (Table 3). Age older or younger than 65 years, sex, history of DM and smoking, and type of EGFR mutation had no influence on OS duration. Clinical predictive factors for a shorter OS duration in multivariable analysis included baseline CEA > 32 ng/mL (HR 1.718,  $P = 0.03$ ), more



**FIGURE 4.** Impact of trend and normalization of CEA on patients with high or low baseline CEA among epidermal growth factor receptor mutant nonsmall cell lung cancer patients treated with first-line tyrosine kinase inhibitors therapy. Impact of trend and normalization of CEA on PFS (A) and OS (B) in patients with lower baseline CEA (baseline CEA 5–32); impact of trend and normalization of CEA on PFS (C) and OS (D) in patients with higher baseline CEA (baseline CEA > 32). CEA = carcinoembryonic antigen, OS = overall survival, PFS = progression-free survival.

**TABLE 4.** Association Between Pretreatment Carcinoembryonic Antigen Levels and Clinical Parameters

	CEA, ng/mL, Median ± IQR	Average Rank	P Value,	Different ( <i>P</i> < 0.05) From Each Factor
T			0.020	
1	5.0 ± 30.0	88.0		Vs 2 and 4
2	30.4 ± 87.1	123.6		Vs 1
3	8.1 ± 82.9	105.0		Vs 4
4	23.5 ± 102.1	130.9		Vs 1 and 3
N			0.024	
0	8.5 ± 38.0	99.5		Vs 3
1	24.1 ± 38.3	120.1		Not significant
2	15.0 ± 87.5	115.6		Not significant
3	32.9 ± 134.7	136.2		Vs 0
Distant metastasis organ(s)			<0.001	
0	6.7 ± 22.0	86.43		Vs 1, 2, and 3
1	19.4 ± 97.1	122.00		Vs 0 and 3
2	58.0 ± 180.4	144.15		Vs 0
≥3	78.4 ± 114.0	155.57		Vs 0 and 1
ECOG PS			<0.001	
0	7.0 ± 22.0	86.43		Vs PS 1, 2, and 3
1	27.0 ± 103.0	122.00		Vs PS 0 and 3
2	28.2 ± 74.5	142.14		Vs PS 0
3	55.1 ± 195.1	156.08		Vs PS 0 and 1
4	57.0 ± 188.4	153.12		Not significant

ECOG = Eastern Cooperative Oncology Group, PS = performance status.

distant metastases (HR 2.211, *P* < 0.001), and poor ECOG PS (HR 2.884, *P* < 0.001) (Table 3).

### CEA Response and Normalization

Patients were divided into 3 groups accordingly to their CEA response (Fig. 3). In group A, patients had both a CEA response and normalization; in group B, patients had a CEA response and but had no CEA normalization; and in group C, patients were nonresponders. PFS duration was 14.3, 10.6, and 7.1 months in groups A, B, and C, respectively (*P* < 0.001). OS was 29.7, 20.0, and 16.2 months in groups A, B, and C, respectively (*P* < 0.001). We also further evaluated impact of baseline CEA on trend and normalization of CEA (Fig. 4). In patients with lower baseline CEA (baseline CEA: 5–32), trend and normalization of CEA had no significant prognostic effect for PFS (*P* = 0.166) and OS (*P* = 0.847). However, in patients with higher baseline CEA (CEA > 32), trend and normalization of CEA are prognostic factors for PFS (*P* = 0.002) and OS (*P* = 0.010).

### Association Between Baseline CEA and TNM or ECOG PS

Patients with higher CEA had more aggressive tumor behavior (*P* = 0.020) more lymph node involvement (*P* = 0.024) and more distant metastasis (*P* < 0.001) (Table 4). Patients with higher CEA also had a worse ECOG PS. In patients with PS 0, 1, 2, 3, and 4, the median CEA was 7.0, 27.0, 26.1, 55.1, and 57.0, respectively (*P* < 0.001).

### DISCUSSION

CEA is a glycoprotein found in patients with carcinoma such as colon, rectum, stomach, pancreas, liver, and lung and in patients with inflammatory bowel disease.<sup>27</sup> As a well-known

tumor marker in colorectal cancer,<sup>28</sup> role of CEA in lung cancer is still debated.

Our study demonstrated that baseline, trend, and normalization of CEA are potential prognostic factors in patients with NSCLC treated with first line EGFR-TKIs. Previous studies have revealed that higher baseline CEA level was associated with a worse prognosis in patients with early-stage gastric cancer, patients with lung cancer who underwent tumor resection,<sup>29–31</sup> and in patients with advanced colorectal cancer treated with bevacizumab-based therapies.<sup>32</sup> CEA has been reported to be crucial in colon cancer cells metastasis via cell adhesion to E- and L-selectin<sup>33</sup> and correlated with higher tumor burden and more distant metastases.<sup>34</sup> Paradoxically, however, previous studies in *EGFR* nonselective patients revealed that patients with higher CEA were more likely to respond to EGFR-TKIs and have a better prognosis.<sup>13–15</sup> Some believe that this discrepancy is because patients with higher CEA levels are more likely to have a positive *EGFR* mutation.<sup>14,18</sup> After removing *EGFR* mutation status as a confounding factor, our study revealed that higher baseline CEA was associated with worse outcomes in *EGFR*-mutant patients treated with EGFR-TKIs, which was in line with study focus on colorectal cancer treated with bevacizumab-based therapies.<sup>32</sup>

Previous studies revealed that CEA response after operation and response to chemotherapy were prognostic factors in patients with NSCLC.<sup>13,35,36</sup> Previous studies also revealed that normalization of CEA after surgery was a prognostic factor in patients with early-stage gastric, rectal, and lung cancer.<sup>37–39</sup> However, the impact of CEA trend and normalization in patients treated with EGFR-TKIs is not well known. Our study revealed that CEA trend and normalization was a prognostic factor in *EGFR*-mutant patients treated with first line TKIs. However, this effect was only seen in patients with higher baseline CEA.

Our study had several limitations. First, we had no serial data of tumor burden, such as positron emission tomography metabolic tumor volume or total lesion glycolysis. Thus, the correlation between tumor burden and serum CEA level was not available. Second, we had no baseline and serial data of CYFRA 21-1, and neuron specific enolase, since recent studies revealed their prognostic effects in NSCLC patients.<sup>40</sup> Thus, correlation between CEA, CYFRA 21-1, and neuron specific enolase became unavailable. Third, because our study was a retrospective study with a small patient population, a prospective trial is needed to validate these results.

In conclusion, our study revealed baseline, trend, and normalization of CEA are potential prognostic markers in EGFR-mutant NSCLC patients treated with first-line EGFR-TKI therapy.

### ACKNOWLEDGMENTS

The authors thank Tsui-Ping Tang and I-Chun Lin for data collection.

### REFERENCES

- Henley SJ, Richards TB, Underwood JM, et al. Lung cancer incidence trends among men and women – United States, 2005–2009. *MMWR Morb Mortal Wkly Rep*. 2014;63:1–5.
- Wang BY, Huang JY, Cheng CY, et al. Lung cancer and prognosis in Taiwan: a population-based cancer registry. *J Thorac Oncol*. 2013;8:1128–1135.
- 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 Nat Acad Sci U S A*. 2004;101 (36):13306–13311.
- Tokumo M, Toyooka S, Kiura K, et al. The relationship between epidermal growth factor receptor mutations and clinicopathologic features in non-small cell lung cancers. *Clin Cancer Res*. 2005;11:1167–1173.
- Kosaka T, Yatabe Y, Endoh H, et al. Mutations of the epidermal growth factor receptor gene in lung cancer: biological and clinical implications. *Cancer Res*. 2004;64:8919–8923.
- Jida M, Toyooka S, Mitsudomi T, et al. Usefulness of cumulative smoking dose for identifying the EGFR mutation and patients with non-small-cell lung cancer for gefitinib treatment. *Cancer Sci*. 2009;100:1931–1934.
- Gazdar AF. Tyrosine kinase inhibitors and epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer: to test or not to test? *Medicine*. 2011;90:168–170.
- Wu JY, Shih JY, Chen KY, et al. Gefitinib therapy in patients with advanced non-small cell lung cancer with or without testing for epidermal growth factor receptor (EGFR) mutations. *Medicine*. 2011;90:159–167.
- Kato T, Yoshioka H, Okamoto I, et al. Afatinib versus cisplatin plus pemetrexed in Japanese patients with advanced non-small cell lung cancer harboring activating EGFR mutations: subgroup analysis of LUX-Lung 3. *Cancer Sci*. 2015.
- Chiu CH, Yang CT, Shih JY, et al. Epidermal growth factor receptor tyrosine kinase inhibitor treatment response in advanced lung adenocarcinomas with G719X/L861Q/S768I mutations. *J Thorac Oncol*. 2015.
- Shukuya T, Takahashi T, Kaira R, et al. Efficacy of gefitinib for non-adenocarcinoma non-small-cell lung cancer patients harboring epidermal growth factor receptor mutations: a pooled analysis of published reports. *Cancer Sci*. 2011;102:1032–1037.
- Park JH, Kim TM, Keam B, et al. Tumor burden is predictive of survival in patients with non-small-cell lung cancer and with activating epidermal growth factor receptor mutations who receive gefitinib. *Clin Lung Cancer*. 2013;14:383–389.
- Facchinetti F, Aldigeri R, Aloe R, et al. CEA serum level as early predictive marker of outcome during EGFR-TKI therapy in advanced NSCLC patients. *Tumour Biol*. 2015.
- Zhang Y, Jin B, Shao M, et al. Monitoring of carcinoembryonic antigen levels is predictive of EGFR mutations and efficacy of EGFR-TKI in patients with lung adenocarcinoma. *Tumour Biol*. 2014;35:4921–4928.
- Jung M, Kim SH, Lee YJ, et al. Prognostic and predictive value of CEA and CYFRA 21-1 levels in advanced non-small cell lung cancer patients treated with gefitinib or erlotinib. *Exp Ther Med*. 2011;2:685–693.
- Chen YM, Lai CH, Chang HC, et al. Baseline and trend of lymphocyte-to-monocyte ratio as prognostic factors in epidermal growth factor receptor mutant non-small cell lung cancer patients treated with first-line epidermal growth factor receptor tyrosine kinase inhibitors. *PLoS One*. 2015;10:e0136252.
- Lie CH, Chang HC, Chao TY, et al. First- or second-line gefitinib therapy in unknown epidermal growth factor receptor mutants of non-small-cell lung cancer patients treated in Taiwan. *Clin Lung Cancer*. 2011;12:116–124.
- Wang WT, Li Y, Ma J, et al. Serum carcinoembryonic antigen levels before initial treatment are associated with EGFR mutations and EML4-ALK fusion gene in lung adenocarcinoma patients. *Asian Pac J Cancer Prev*. 2014;15:3927–3932.
- Chen X, Wang X, He H, et al. Combination of circulating tumor cells with serum carcinoembryonic antigen enhances clinical prediction of non-small cell lung cancer. *PLoS One*. 2015;10:e0126276.
- Horiike A, Kimura H, Nishio K, et al. Detection of epidermal growth factor receptor mutation in transbronchial needle aspirates of non-small cell lung cancer. *Chest*. 2007;131:1628–1634.
- Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228–247.
- Zhou C, Wu YL, 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;12:735–742.
- 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 (EUR-TAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2012;13:239–246.
- Wu YL, Zhou C, Liang CK, et al. First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: analyses from the phase III, randomized, open-label, ENSURE study. *Ann Oncol*. 2015;26:1883–1889.
- 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;11:121–128.
- Wu YL, Zhou C, Hu CP, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. *Lancet Oncol*. 2014;15:213–222.

27. Vincent RG, Chu TM, Fergen TB, et al. Carcinoembryonic antigen in 228 patients with carcinoma of the lung. *Cancer*. 1975;36:2069–2076.
28. Wang JY, Tang R, Chiang JM. Value of carcinoembryonic antigen in the management of colorectal cancer. *Dis Colon Rectum*. 1994;37:272–277.
29. Tomita M, Ayabe T, Chosa E, et al. Correlation between serum carcinoembryonic antigen level and histologic subtype in resected lung adenocarcinoma. *Asian Pac J Cancer Prev*. 2015;16:3857–3860.
30. Tomita M, Matsuzaki Y, Edagawa M, et al. Prognostic significance of preoperative serum carcinoembryonic antigen level in lung adenocarcinoma but not squamous cell carcinoma. *Ann Thorac Cardiovasc Surg*. 2004;10:76–80.
31. Deng K, Yang L, Hu B, et al. The prognostic significance of pretreatment serum CEA levels in gastric cancer: a meta-analysis including 14651 patients. *PLoS One*. 2015;10:e0124151.
32. Prager GW, Braemswig KH, Martel A, et al. Baseline carcinoembryonic antigen (CEA) serum levels predict bevacizumab-based treatment response in metastatic colorectal cancer. *Cancer Sci*. 2014;105:996–1001.
33. Thomas SN, Zhu F, Schnaar RL, et al. Carcinoembryonic antigen and CD44 variant isoforms cooperate to mediate colon carcinoma cell adhesion to E- and L-selectin in shear flow. *J Biol Chem*. 2008;283:15647–15655.
34. Kashiwabara K, Saeki S, Sasaki J, et al. Combined evaluation of postoperative serum levels of carcinoembryonic antigen less than or equal to 2.5 ng/ml and absence of vascular invasion may predict no recurrence of stage I adenocarcinoma lung cancer. *J Thorac Oncol*. 2008;3:1416–1420.
35. Fukuoka M, Takada M, Kamei T, et al. [Serial measurements of serum carcinoembryonic antigen (CEA) and neuron-specific enolase (NSE) during chemotherapy of patients with inoperable lung cancer]. *Gan To Kagaku Ryoho*. 1987;14 (3 Pt 2):871–880.
36. Lin XF, Wang XD, Sun DQ, et al. High serum CEA and CYFRA21-1 levels after a two-cycle adjuvant chemotherapy for NSCLC: possible poor prognostic factors. *Cancer Biol Med*. 2012;9:270–273.
37. Nam DH, Lee YK, Park JC, et al. Prognostic value of early postoperative tumor marker response in gastric cancer. *Ann Surg Oncol*. 2013;20:3905–3911.
38. Kleiman A, Al-Khamis A, Farsi A, et al. Normalization of CEA levels post-neoadjuvant therapy is a strong predictor of pathologic complete response in rectal cancer. *J Gastrointest Surg*. 2015;19:1106–1112.
39. Sakao Y, Nakazono T, Sakuragi T, et al. Predictive factors for survival in surgically resected clinical IA peripheral adenocarcinoma of the lung. *Ann Thorac Surg*. 2004;77:1157–1161discussion 1161–1152.
40. Cedres S, Nunez I, Longo M, et al. Serum tumor markers CEA, CYFRA21-1, and CA-125 are associated with worse prognosis in advanced non-small-cell lung cancer (NSCLC). *Clin Lung Cancer*. 2011;12:172–179.