Comparison of first-generation EGFR-TKIs (gefitinib, erlotinib, and icotinib) as adjuvant therapy in resected NSCLC patients with sensitive EGFR mutations

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Background: Several randomized controlled trials have suggested that adjuvant epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) were associated with prolonged disease-free survival (DFS) in EGFR-mutated NSCLC patients after radical resection, comparing with chemotherapy or placebo. We aimed to compare the effectiveness of different first-generation EGFR-TKIs as adjuvant treatment in real-world setting.

Methods: Early-stage EGFR mutated NSCLC patients who underwent radical resection and treated with first-generation EGFR-TKIs (gefitinib, erlotinib, icotinib) as adjuvant therapy between Feb 2010 and Jan 2019 were retrieved from a prospectively-maintained database in our center. The primary endpoint was DFS in stage II/III (TNM 8th) patients with exploratory endpoint regarding DFS in stage I patients. Sensitivity analyses were based on propensity score matched (PSM) cohorts. Treatment failure patterns among different TKIs were also compared.

Results: Of 588 eligible patients, 198 patients (33.7%) received gefitinib, 106 patients (17.9%) received erlotinib, and 284 patients (48.2%) received icotinib. The median DFS of stage II/III patients in the gefitinib, erlotinib and icotinib group were 36.1 months (95% CI, 23.9–49.4), 42.8 months (95% CI, 29.6–97.8), and 32.5 months (95% CI, 23.9–49.4), respectively, with no significant difference (log-rank test P=0.22). There was also no significant difference in DFS among stage I patients receiving different TKIs (P=0.12). PSM adjustments and multivariate analyses adjusting for other confounders revealed similar results. In addition, there were no significant differences in treatment failure pattens in different EGFR-TKI arms, especially in terms of brain metastases (6.1% in gefitinb, 7.5% in erlotinib, 3.9% in icotinib) and bone metastases (8.6% in gefitinb, 9.4% in erlotinib, 7.0% in icotinib).

Conclusions: This first and largest real-world study showed that gefitinib, erlotinib, and icotinib demonstrated comparable clinical effectiveness as adjuvant therapy for patients with early-stage EGFR mutated NSCLC.

Introduction

In recently years, a significantly higher proportion of early stage non-small cell lung cancer (NSCLC) had been detected due to the usage of low-dose helical computed tomography (CT) in tumor screening (1). Nevertheless, even stage I NSCLC patients who undertook curative-intent resection was reported a 10.4% of 5-year lung cancer—specific mortality (2). Platinum-doublet chemotherapy are standard adjuvant treatment for early-stage resected NSCLC, however, its efficacy was modest with a 5-year absolute benefit of only in 5% (3). Better treatment strategies to improve the survival of those patients have been urgently expected by clinicians.

Several pivotal trials have revealed that epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) were more effective than cytotoxic chemotherapy in the first-line treatment of advanced NSCLC with mutated EGFR (4-8). Subsequently, first generation EGFR-TKIs, such as erlotinib and gefitinib, have been demonstrated to improve the DFS of EGFR-mutant patients with resected early-stage lung cancers (9-11). Recently, a randomized phase III trial (ADJUVANT/CTONG1104) comparing gefitinib *vs.* chemotherapy in EGFR-mutant patients with completely resected NSCLC confirmed that adjuvant gefitinib achieved superior DFS than chemotherapy did (12). Thus, adjuvant EGFR-TKIs are now considered as a treatment option for resected NSCLC with sensitive EGFR mutations.

The first-generation EGFR-TKIs included icotinib, erlotinib and gefitinib. Previous trial has suggested no difference in progressive-free survival (PFS) among different first-generation EGFR-TKIs in advanced NSCLC patients harboring EGFR mutations (13). However, in EGFR-mutant NSCLC patients after radical resection, it is still unclear whether different first-generation EGFR-TKIs can affect DFS as adjuvant treatment. Therefore, we performed a retrospective study to compare the clinical efficacy among three first-generation EGFR-TKIs as adjuvant treatment for EGFR-mutant NSCLC patients who underwent curative-intent resection.

We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/tlcr-21-649).

Methods

Study design

This is a retrospective study of a prospectively maintained cohort. The aims of this study were to compare the efficacy among three first-generation EGFR-TKIs as adjuvant treatment and the recurrence pattern in patients with completely resected EGFR-mutant NSCLC. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Ethical Committee for Clinical Investigation of First Affiliated Hospital of Guangzhou Medical University (ethical No. 2015). Every patient informed consent was collected before surgery.

Patients and treatments

Inclusion criteria for the patients in this study were as following: (I) consecutive patients with resected EGFR-positive NSCLC who received postoperative EGFR inhibitor at our hospital between February 2010 and January 2019 (II) treated with first-generation EGFR-TKIs. Patients were excluded if they underwent incompletely surgical resection [Chinese guidelines on the diagnosis and treatment of primary lung cancer (2019)], received radiotherapy or chemotherapy after surgery, or failed to have EGFR-TKI within two months after surgery. The dose of icotinib was 150 mg tid, erlotinib was 150 mg qd, and gefitinib was 250 mg qd.

Endpoints

The primary endpoint was disease-free survival (DFS) in stage II/III (TNM 8th) patients with exploratory endpoint regarding DFS in stage I patients, which defined as time from having the resection surgery to documented disease relapse or death. Subgroup analyses were performed based on stage and EGFR mutation type.

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Follow-up

We undertook radiological assessments with CT every 3 months for the first 2 years after surgery, every 6 months over the next 3 years. The use of PET or MRI imaging or other clinical technical equipment for further evaluation of the disease was under the physician's discretion. Patients lost to follow-up were censored on the date of last imaging. Data collection was terminated on November 12, 2019.

Identification of EGFR mutation

Genetic analysis to determine EGFR mutation was performed by central laboratory testing using amplification-refractory mutation system PCR. Additionally, next generation sequencing (NGS) was also applied to identify the EGFR mutation status.

Statistical analysis

P values were calculated based on Fisher's exact test for categorical variables and analysis of variance (ANOVA) for continuous variables in the baseline characteristics of patients. DFS curves were drawn using the Kaplan-Meier method, and statistical differences were calculated by a two-sided log-rank test. Values of P<0.05 were considered as statistically significant. Hazard ratio (HR) and 95% CIs were estimated using a Cox proportional-hazards regression model. For the subgroup analysis, the same method was used to calculated DFS after categorizing the patients by age, sex, smoking status, stage, EGFR mutation status, lymph node status, and pathology. Multivariate Cox proportional hazards regression model was used to evaluate independent predictive factors associated with DFS. Propensity score matching (PSM) was used to adjust for known baseline characteristics. All statistical analyses were conducted using SPSS version 17.0 or SAS version 9.4 and plotting was made by R software version 3.6.0.

Results

Patient characteristics

A total of 588 EGFR-positive patients who underwent radical surgery of NSCLC were enrolled. Of those patients, 284 patients (48.2%) received icotinib, 106 patients (17.9%) received erlotinib and 198 patients (33.7%) received gefitinib as adjuvant therapy. The median duration of treatment for icotinib, erlotinib and gefitinib were 17.7 months (range,

0.6–28.1 months), 20.1 months (range, 1.1–26.0 months) and 18.6 months (range, 0.5–28.8 months), respectively. The median age was 60 years (range, 26–80 years) and 360 patients (60.9%) were female; 565 patients (95.6%) had adenocarcinoma and about three-quarters were non-smokers. Regarding mutation type, 192 patients had a deletion in exon 19, 237 had a missense mutation in exon 21 (L858R), and 18 had other type of EGFR mutations. Most of the demographic characteristics were balanced between three treatment groups, while the icotinib-treated group had higher proportion of stage I disease patients (*Table 1*).

DFS in stage II/III patients treated with each TKIs

The median DFS was 50.8 months (95% CI: 41.5–60.0) for all patients. Median DFS was 42.5 months (95% CI: 29.9–55.1) in gefitinib arm, 53.9 months (95% CI: 33.1–74.6) in the erlotinib arm and 55.2 months (95% CI: 41.2–69.2) in the icotinib arm, DFS was not statistically significantly different among the three arms in stage I-III patients (log-rank test P=0.11).

The median DFS of stage II/III patients in the gefitinib, erlotinib and icotinib group were 36.1 months (95% CI: 23.9–49.4), 42.8 months (95% CI: 29.6–97.8), and 32.5 months (95% CI: 23.9–49.4), respectively. There was no significant difference in DFS among three groups (log-rank test P=0.22; *Figure 1*). Using Cox proportional hazards regression to adjust for possible confounders, our results showed that the HR of DFS for erlotinib versus icotinib was 0.85 (95% CI: 0.45–1.58, P=0.60), and the HR of DFS for gefitinib versus icotinib was 1.25 (95% CI: 0.74–2.12, P=0.41) (*Table 2*). PSM adjustments revealed similar results (Supplementary material).

Subgroup analysis and exploration analysis

We also analyzed the DFS in three groups of patients with respect to various disease stage. In stage II subgroup, median DFS in patients treated with icotinib, erlotinib and gefitinib were 32.9, 64.8 and 30.1 months, respectively. In stage III population, median DFS in patients received with icotinib, erlotinib and gefitinib were 32.9, 40.3 and 36.7 months, respectively. The differences in DFS among three treatment groups were not significant regardless of disease stage (stage II, P=0.16; stage III, P=0.96) and EGFR mutation types (Exon 19 deletion, P=0.83; Exon 21 Leu858Arg, P=0.23) (*Table 3, Figure 2*).

In stage I subgroup, median DFS in patients treated with

Table 1 Baseline characteristics of the study participants

Clinicopathologic parameters	Icotinib (n=284)	Erlotinib (n=106)	Gefitinib (n=198)	P value
Age (year)				0.43
<60	113 (39.8%)	47 (44.3%)	90 (45.5%)	
≥60	171 (60.2%)	59 (55.7%)	108 (54.5%)	
Sex				0.41
Female	170 (59.9%)	71 (67.0%)	119 (61.2%)	
Male	114 (40.1%)	35 (33.0%)	79 (38.8%)	
Smoke status				0.31
Never	215 (75.7%)	72 (67.9%)	138 (69.7%)	
Former	15 (5.3%)	4 (3.8%)	10 (5.1%)	
Current	37 (13.0%)	16 (15.1%)	30 (15.2%)	
Unknown	17 (6%)	14 (13.2%)	20 (10.1%)	
Stage				<0.05
I	169 (59.5%)	43 (40.6%)	101 (51.0%)	
II	42 (14.8%)	21 (19.8%)	26 (13.1%)	
III	73 (25.7%)	42 (39.6%)	71 (35.9%)	
N stage				<0.05
0	185 (65.1%)	47 (44.3%)	110 (55.6%)	
1	32 (11.3%)	21 (19.8%)	22 (11.1%)	
2	67 (23.6%)	35 (33.0%)	65 (32.8%)	
3	0 (0%)	3 (2.8%)	1 (0.05%)	
Resection type				0.99
Sublobectomy	41 (14.4%)	14 (13.2%)	27 (13.6%)	
Lobectomy	24 (84.9%)	91 (85.8%)	170 (85.9%)	
Pneumonectomy	2 (0.7%)	1 (0.9%)	1 (0.5%)	
EGFR mutation status				<0.05
Exon 19 deletions	75 (26.4%)	39 (36.8%)	78 (39.4%)	
Exon 21 Leu858Arg	109 (38.4%)	57 (53.8%)	71 (35.9%)	
Others	8 (2.8%)	2 (1.9%)	8 (4.0%)	
Unknown	92 (32.4%)	8 (7.5%)	41 (20.7%)	
Pathology				0.97
Adenocarcinoma	272 (96.5%)	104 (98.1%)	189 (95.5%)	
Adenosquamous	5 (1.8%)	2 (1.9%)	5 (2.5%)	
Squamous carcinoma	2 (0.7%)	0 (0%)	3 (1.5%)	
Large cell carcinoma	1 (0.4%)	0 (0%)	0 (0%)	
Others	2 (0.7%)	0 (0%)	1 (0.5%)	
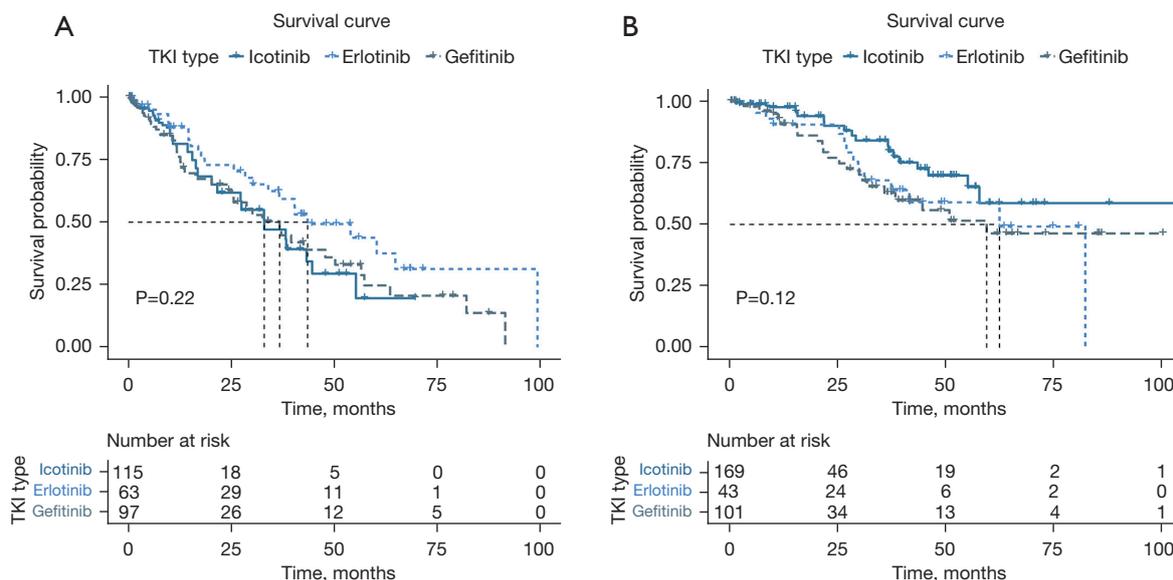
Figure 1 Kaplan-Meier curves for disease-free survival of (A) stage II/III and (B) stage I patients treating different TKIs. TKIs, tyrosine kinase inhibitors; HR, hazard ratio.

icotinib, erlotinib and gefitinib were not reached (NR), 62.4 and 59.4 months, respectively. Nevertheless, multivariant analysis revealed that erlotinib and gefitinib tend to have an inferior DFS than icotinib in stage I NSCLC patients (*Table 3, Figure 1*).

Failure pattern analysis

The most common sites of metastasis in overall population were lung (9.8%), followed by bone (8.0%), the central nervous system (CNS) (5.2%), lymph node (3.4%), the intra-abdominal region (1.7%), pleural effusion (0.8%) and liver (0.8%) (*Table 4*). A decreased incidence of lung metastasis was noted in the icotinib group [19 (6.7%), 15 (14.2%), 24 (12.1%), respectively, P=0.038]. Additionally, spatial-temporal treatment failure patterns did not differ among three treatment arms, in terms of brain metastases (6.1% in gefitinb, 7.5% in erlotinib, 3.9% in icotinib) and bone metastases (8.6% in gefitinb, 9.4% in erlotinib, 7.0% in icotinib), etc. (*Table 4*).

Discussion

EGFR-mutant NSCLC patients have achieved enormous benefits form TKI therapy regardless of disease stage. However, it is still urgent to further explore whether different TKIs result in diverse treatment outcomes. Our

recent network analysis demonstrated that the efficacy of three first-generation EGFR-TKIs were showed to be similar for advanced NSCLC patients with EGFR mutation (14). Similarly, in this study regarding early stage, it was showed that DFS among three first-generation EGFR-TKIs did not differ in the adjuvant therapy of completely resected NSCLC patients with EGFR-positive. To the best of our knowledge, it is the first real-world study to compared the impact of three first-generation EGFR-TKIs on radical resected early-stage NSCLC patients harboring EGFR mutations.

Previously, a meta-analysis including 5 randomized controlled trials demonstrated that adjuvant EGFR-TKIs had a better DFS compared to placebo and chemotherapy in EGFR-mutant NSCLC patients (13). In addition, two retrospective studies reported that adjuvant erlotinib or gefitinib presented a low rate of recurrence in resected stage I-III NSCLC with EGFR mutation (10,15). In these evidences, TKIs were proved to be a promising option as an adjuvant therapy for selected patients with resected NSCLC. These evidences encouraged TKIs become a good option as an adjuvant therapy for selected patients. Up to now, there are three generations of EGFR inhibitors approved by the FDA to target this kinase, including first-generation (icotinib, erlotinib, gefitinib), second-generation (afatinib, dacomitinib) and third-generation (osimertinib). Our study revealed that no significant differences of DFS

Table 2 Univariate and multivariate analysis of DFS in stage II/III patients

Features	Univariate analysis	P value	Multivariate analysis	P value
Age (year)				
<60	Reference		Reference	
≥60	1.12 (0.75–1.69)	0.58	1.13 (0.72–1.78)	0.59
Sex				
Female	Reference		Reference	
Male	2.10 (1.38–3.18)	0.0001	2.15 (1.24–3.73)	0.007
Smoke status				
Never	Reference		Reference	
Former	1.94 (0.96–3.95)	0.065	0.83 (0.33–2.08)	0.69
Current	2.26 (1.35–3.79)	0.002	1.33 (0.69–2.56)	0.40
Unknown	0.72 (0.34–1.53)	0.40	0.86 (0.39–1.91)	0.71
Resection type				
Sublobectomy	Reference		Reference	
Lobectomy	1.02 (0.41–2.53)	0.96	1.11 (0.43–2.92)	0.83
Pneumonectomy	2.25 (0.60–8.41)	0.23	3.76 (0.78–18.17)	0.10
EGFR mutation status				
Exon 19 deletions	Reference		Reference	
Exon 21 Leu858Arg	1.29 (0.81–2.05)	0.28	0.99 (0.59–1.66)	0.97
Others	2.34 (0.98–5.59)	0.056	2.40 (0.94–6.17)	0.07
Unknown	1.49 (0.80–2.78)	0.21	0.91 (0.47–1.75)	0.78
TKI				
Icotinib	Reference		Reference	
Erlotinib	0.68 (0.39–1.18)	0.17	0.85 (0.45–1.58)	0.60
Gefitinib	1.04 (0.64–1.69)	0.87	1.25 (0.74–2.12)	0.41

among three first-generation EGFR-TKIs as adjuvant treatment. However, safety and tolerability in our study were scarce.

To date, seven trials investigating EGFR-TKIs in the adjuvant setting have been completed and significant improved DFS with first-generation of EGFR-TKIs was observed in the EVAN (erlotinib versus chemotherapy), ADJUVANT (gefitinib versus chemotherapy) and EVIDENCE (icotinib versus chemotherapy) (12,16,17). In addition, ADAURA trail conducted by Wu *et al.* showed Osimertinib yield a remarkable improvement DFS in early-stage, EGFR-mutant patients as adjuvant therapy compared with placebo (18). However, adjuvant chemotherapy (ACT) was involved in EGFT-TKI arm in ADAURA rather than in EVAN, ADJUVANT and EDVIDENCE trials. It remains unclear whether ACT could also contribute to the striking DFS benefit. Besides, unlike 3 years of duration in the ADAURA trial, duration of first-generation EGFR-TKIs was a maximum of 2 years. Further studies to elucidate whether longer treatment exposure of first-generation EGFR-TKIs would have positive impact on OS are warranted.

The subgroup results based on the disease stage and EGFR mutation status were similar to the overall outcome. However, multivariant analysis presented that gefitinib tend to have an inferior DFS than icotinib in stage I NSCLC

Table 3 Exploration analysis and subgroup analysis

| Variables	Median DFS (months)	P value	Univariate analysis	P value	Multivariate analysis	P value
Stage I		0.12				
Icotinib	NR		Reference		Reference	
Erlotinib	62.4 (46.1–78.6)		1.81 (0.90–3.61)	0.10	2.00 (0.97–4.13)	0.06
Gefitinib	59.4 (NC)		1.76 (0.95–3.23)	0.07	1.79 (0.96–3.34)	0.07
Stage II		0.16				
Icotinib	32.9 (6.3–59.5)		Reference		Reference	
Erlotinib	64.8 (38.7–90.8)		0.40 (0.14–1.56)	0.09	0.39 (0.10–1.56)	0.18
Gefitinib	30.0 (23.6–36.5)		1.10 (0.45–2.69)	0.83	0.55 (0.19–1.58)	0.27
Stage III		0.96				
Icotinib	32.9 (19.2–46.5)		Reference		Reference	
Erlotinib	40.3 (25.7–54.7)		0.90 (0.47–1.72)	0.75	1.15 (0.56–2.38)	0.71
Gefitinib	36.7 (17.6–46.0)		0.97 (0.55–1.74)	0.93	1.81 (0.94–3.47)	0.08
Exon19 deletions		0.83				
Icotinib	44.6 (12.1–77.1)		Reference		Reference	
Erlotinib	43.5 (NC)		0.76 (0.31–1.88)	0.55	1.01 (0.36–2.88)	0.98
Gefitinib	39.5 (36.6–50.3)		0.92 (0.41–2.05)	0.83	0.75 (0.29–1.94)	0.55
Exon21 Leu858Arg		0.23				
Icotinib	40.4 (NC–82.2)		Reference		Reference	
Erlotinib	50.8 (22.0–79.5)		0.53 (0.23–1.22)	0.53	0.81(0.30–2.16)	0.67
Gefitinib	56.5 (37.7–75.2)		0.96 (0.44–2.09)	0.91	1.53(0.62-3.78)	0.35

NR, not reached; NC, not calculable.

patients. The previous study reported 80% 5-year survival for those patients with (p)stage IA disease and 72% for those with (p)stage IB NSCLC (19). It means that even patients with completely resected stage I NSCLC have a risk of recurrence. A meta-analysis in 2008 demonstrated adjuvant chemotherapy had a similar detrimental effect in patients with stage IA stage NSCLC (20). Moreover, the benefit of cytotoxic chemotherapy to stage IB disease remains controversial. Considering that adjuvant chemotherapy displayed limited improvements in survival of stage I NSCLC patients, adjuvant EGFR-TKIs might be an option for those patients harboring EGFR mutation.

Retrospective study conducted by Park *et al.* revealed that the most common recurrence sites for resected N1-stage II lung adenocarcinoma patients who received adjuvant platinum-based chemotherapy were lungs (48.9%), followed by bone (22.5%) and the brain (20.9%) (21). Nevertheless,

prospective study focusing on EGFR mutant patients, stage II–IIIA (N1-N2) NSCLC showed CNS metastases were the most common recurrence events in TKI group (27.4%), while extracranial metastases accounted for the highest proportion of recurrence events in chemotherapy group (24.1%) (22). Our study, including 588 patients with EGFR mutation-positive, stage I–III NSCLC, found that the most common site of metastasis was lung (9.8%), followed by bone (8.0%), CNS (5.2%). There was no difference among three treatment groups in current study, but a decreased incidence of lung metastasis was noted in the icotinib group.

Limitations of our study include the fact that this is a retrospective analysis, prospective analysis is needed to further illustrate these issues. Another limitation is that, overall survival (OS) data were unmatured. However, whether different first-generation EGFR-TKIs had different effects on OS remained unclear. Besides, as
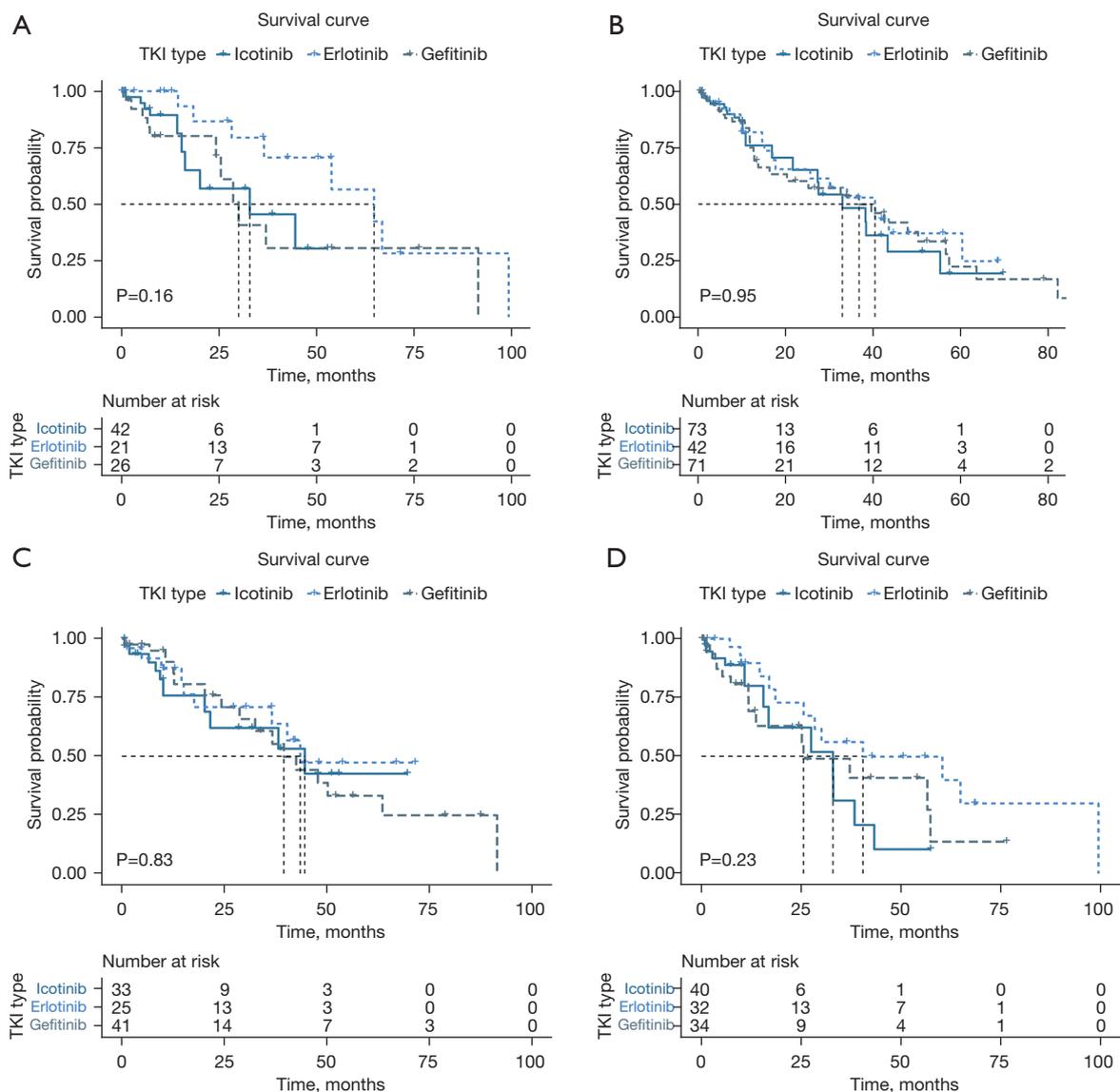
Figure 2 Kaplan-Meier curves of disease-free survival in (A) stage II, (B) stage III patients, (C) EGFR 19 del, and (D) EGFR 21 L858R subpopulations receiving different TKIs. TKIs, tyrosine kinase inhibitors; HR, hazard ratio.

Table 4 Failure patterns of different EGFR-TKIs

Initial recurrence sites	Icotinib (n=285)	Erlotinib (n=106)	Gefitinib (n=199)	P value
Bone	20 (7%)	10 (9.4%)	17 (8.6%)	0.69
Brain	11 (3.9%)	8 (7.5%)	12 (6.1%)	0.29
Lung	19 (6.7%)	15 (14.2%)	24 (12.1%)	0.04
Regional lymph nodes	5 (1.8%)	6 (5.7%)	9 (4.5%)	0.09
Pleura	3 (1.1%)	1 (0.9%)	1 (0.5%)	0.52
Liver	1 (0.4%)	2 (1.9%)	2 (1.0%)	0.38
Adrenal	4 (1.4%)	1 (0.9%)	5 (2.5%)	0.52

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mentioned above, toxicity evaluation was absent in our study. Thus, we conducted multivariate analyses adjusting for confounders including treatment duration, and which showed similar results. Finally, treatment selection bias was inevitable in this study; however, since all patients received first-generation TKIs, the impact might be limited.

Conclusions

In summary, our study demonstrated that no DFS difference was observed among three first-generation EGFR-TKIs in patients with EGFR mutation-positive, radial resected, early-stage NSCLC. However, the data about safety and OS required further analysis.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://dx.doi.org/10.21037/tlcr-21-649

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Total Sample Size = 588 (Icotinib: erlotinib: gefitinib = 284:106:198)
Median follow up time (months): Icotinib: erlotinib: gefitinib = 22.6:39.4:25.3

Scenario 1

Matching ratio = 1:1:1; Matched pairs = 95; all p-values > 0.05
Median follow up time after matching (months): Icotinib: erlotinib: gefitinib = 32.1: 41.0 : 25.3

Variables	P-value before matching	After matching			
		Icotinib (N=95)	Erlotinib (N=95)	Gefitinib (N=95)	p-value
Age group	0.424				0.750
<60		45 (47.4)	41 (43.2)	46 (48.4)	
>=60		50 (52.6)	54 (56.8)	49 (51.6)	
Sex	0.408				0.719
Female		57 (60.0)	62 (65.3)	57 (60.0)	
Male		38 (40.0)	33 (34.7)	38 (40.0)	
Smoke status	0.301				0.846
Never		60 (63.2)	67 (70.5)	64 (67.4)	
Former		4 (4.2)	4 (4.2)	2 (2.1)	
Current		21 (22.1)	14 (14.7)	19 (20.0)	
Unknown		10 (10.5)	10 (10.5)	10 (10.5)	
EGFR mutation status	<0.001				0.930
Exon 19 deletions		32 (33.7)	35 (36.8)	39 (41.1)	
Exon 21 Leu85Arg		54 (56.8)	50 (52.6)	46 (48.4)	
Others		1 (1.1)	2 (2.1)	1 (1.1)	
Unkonwn		8 (8.4)	8 (8.4)	9 (9.5)	
Stage	0.007				0.774
I		44 (46.3)	43 (45.3)	41 (43.2)	
II		18 (19.0)	16 (16.8)	13 (13.7)	
III		33 (34.7)	36 (37.9)	41 (43.2)	
N Stage	0.001				0.814
0		52 (54.7)	47 (49.5)	44 (46.3)	
1		12 (12.6)	15 (15.8)	14 (14.7)	
2		31 (32.6)	33 (34.7)	37 (39.0)	
Resection type	0.993				0.761
Sublobectomy		14 (14.7)	12 (12.6)	10 (10.5)	
Lobectomy		80 (84.2)	82 (86.3)	85 (89.5)	
Pneumonectomy		1 (1.1)	1 (1.1)	0	
Pathology	0.950				>0.999
Adenocarcinoma		94 (98.9)	93 (97.9)	94 (98.9)	
Adenosquamous		1 (1.1)	2 (2.1)	1 (1.1)	

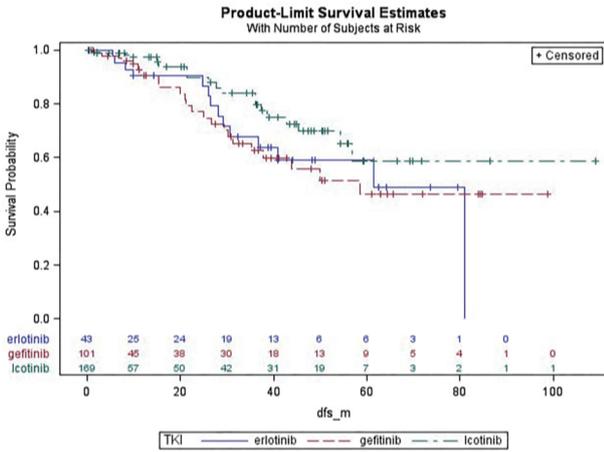P-values were calculated based on Fisher's exact test.

A: Before matching
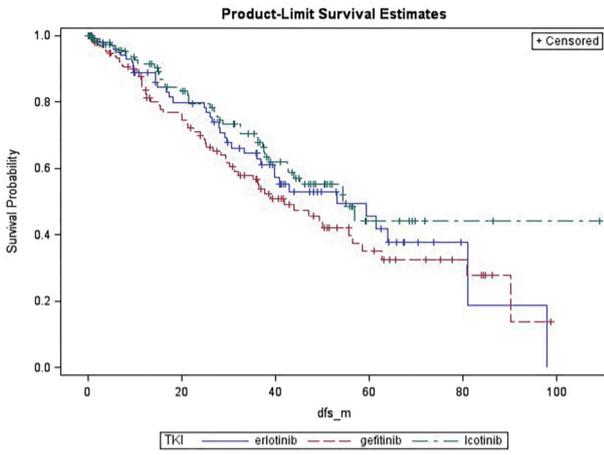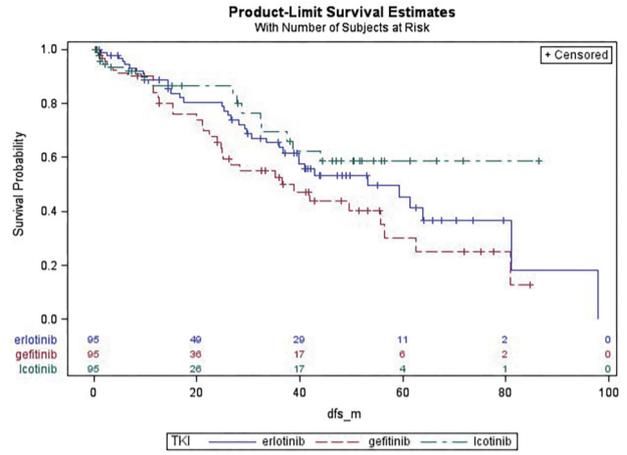
Product-Limit Survival Estimates

	Icotinib (N=284)	Erlotinib (N=106)	Gefitinib (N=198)	Log-rank P value
Event, n (%)	49 (17.3)	39 (36.8)	63 (31.8)	
Median DFS (95% CI), months	54.4 (42.6, NA)	53.1 (36.8, 81.1)	41.9 (30.2, 56.4)	0.112

B: After matching

Product-Limit Survival Estimates — With Number of Subjects at Risk

	Icotinib (N=95)	Erlotinib (N=95)	Gefitinib (N=95)	Log-rank P value
Event, n (%)	18 (18.9)	36 (37.9)	35 (36.8)	
Median DFS (95% CI), months	NA (37.6, NA)	53.1 (36.8, 81.1)	36.5 (24.7, 56.4)	0.154

Subgroup analysis: Stage = I

A: Before matching

Product-Limit Survival Estimates — With Number of Subjects at Risk

	Icotinib (N=169)	Erlotinib (N=43)	Gefitinib (N=101)	Log-rank P value
Event, n (%)	19 (11.2)	14 (32.6)	23 (22.8)	
Median DFS (95% CI), months	NA (54.2, NA)	61.5 (30.6, 81.1)	58.5 (31.2, NA)	0.122

B: After matching

Product-Limit Survival Estimates — With Number of Subjects at Risk
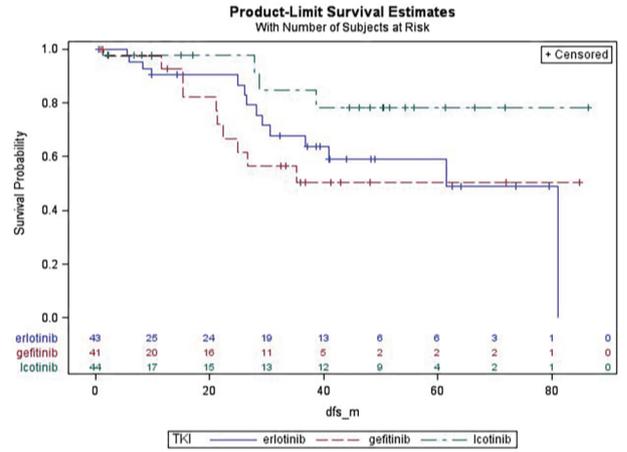
	Icotinib (N=44)	Erlotinib (N=43)	Gefitinib (N=41)	Log-rank P value
Event, n (%)	4 (9.1)	14 (32.6)	10 (24.4)	
Median DFS (95% CI), months	NA (38.6, NA)	61.5 (30.6, 81.1)	NA (21.3, NA)	0.134

Subgroup analysis: Stage = II or III
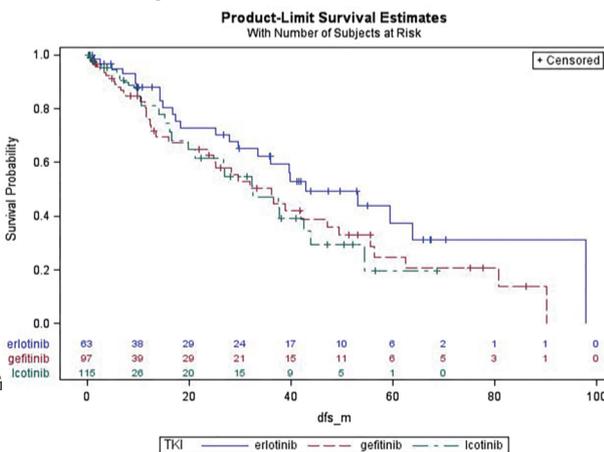
A: Before matching

Product-Limit Survival Estimates — With Number of Subjects at Risk

	Icotinib (N=115)	Erlotinib (N=63)	Gefitinib (N=97)	Log-rank P value
Event, n (%)	30 (26.1)	25 (39.7)	40 (41.2)	
Median DFS (95% CI), months	32.5 (19.9, 43.9)	42.8 (29.6, 97.8)	36.1 (23.9, 49.4)	0.223

B: After matching

Product-Limit Survival Estimates — With Number of Subjects at Risk
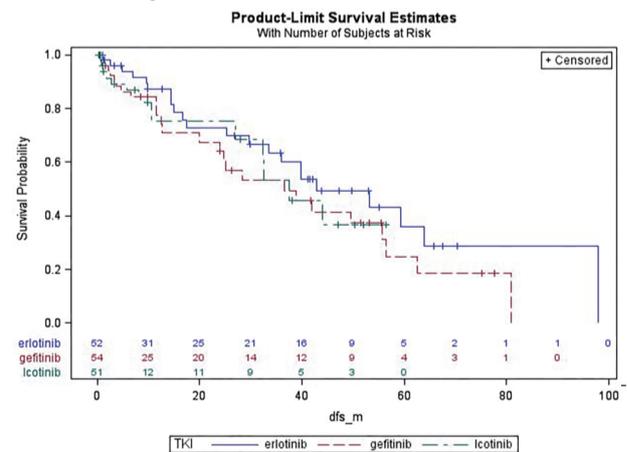
	Icotinib (N=51)	Erlotinib (N=52)	Gefitinib (N=54)	Log-rank P value
Event, n (%)	14 (27.5)	22 (42.3)	25 (46.3)	
Median DFS (95% CI), months	37.6 (27.0, NA)	42.8 (29.6, 63.8)	36.5 (19.9, 55.7)	0.431

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Scenario 2: treatment duration was included into logistic model as a covariate to calculate propensity score

Matching ratio = 1:1:1; Matched pairs = 92; all p-values > 0.05
Median follow up time after matching (months): Icotinib: erlotinib: gefitinib = 20.7: 38.7: 24.0

Variables	P-value before matching	After matching			p-value
		Icotinib (N=92)	Erlotinib (N=92)	Gefitinib (N=92)	
Age group	0.424				0.886
<60		40 (43.5)	40 (43.5)	37 (40.2)	
>=60		52 (56.5)	52 (56.5)	55 (59.8)	
Sex	0.408				>0.999
Female		59 (64.1)	58 (63.0)	58 (63.0)	
Male		33 (35.9)	34 (37.0)	34 (37.0)	
Smoke status	0.301				0.954
Never		70 (76.1)	64 (69.6)	65 (70.7)	
Former		3 (3.3)	4 (4.4)	4 (4.4)	
Current		10 (10.9)	15 (16.3)	13 (14.1)	
Unknown		9 (9.8)	9 (9.8)	10 (10.9)	
EGFR mutation status	<0.001				0.558
Exon 19 deletions		26 (28.3)	34 (37.0)	32 (34.8)	
Exon 21 Leu85Arg		55 (59.8)	48 (52.2)	51 (55.4)	
Others		0	2 (2.2)	0	
Unkonwn		11 (12.0)	8 (8.7)	9 (9.8)	
Stage	0.007				0.628
I		46 (50.0)	41 (44.6)	43 (46.7)	
II		14 (15.2)	14 (15.2)	9 (9.8)	
III		32 (34.8)	37 (40.2)	40 (43.5)	
N Stage	0.001				0.857
0		50 (54.4)	45 (48.9)	43 (46.7)	
1		13 (14.1)	12 (13.0)	11 (12.0)	
2		29 (31.5)	34 (37.0)	37 (40.2)	
3		0	1 (1.1)	1 (1.1)	
Resection type	0.993				0.719
Sublobectomy		9 (9.8)	12 (13.0)	13 (14.1)	
Llobectomy		82 (89.1)	80 (87.0)	79 (85.9)	
Pneumonectomy		1 (1.1)	0	0	
Pathology	0.950				>0.999
Adenocarcinoma		90 (97.8)	90 (97.8)	90 (97.8)	
Adenosquamous		2 (2.2)	2 (2.2)	2 (2.2)	
Treatment Duration, months	<0.001				0.332
Mean (SD)		16.2 (10.1)	15.1 (8.6)	14.3 (7.1)	

P-values were calculated based on Fisher's exact test for categorical variables and analysis of variance (ANOVA) for continuous variables.
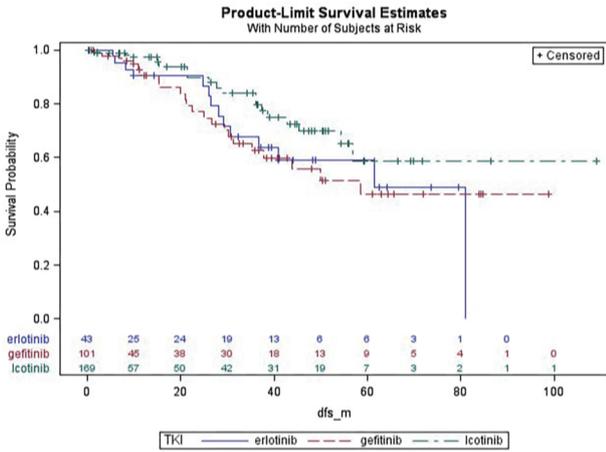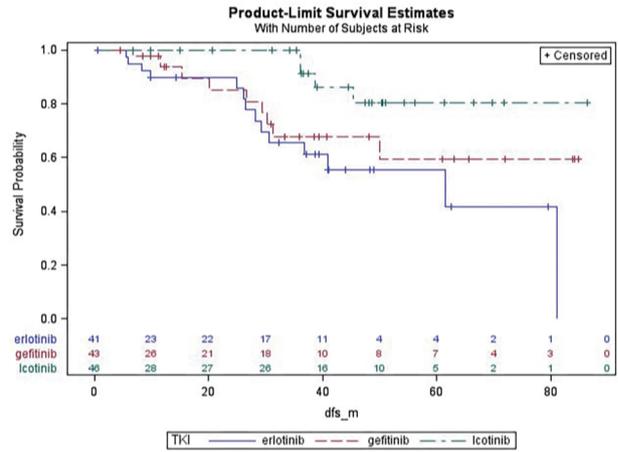
A: Before matching
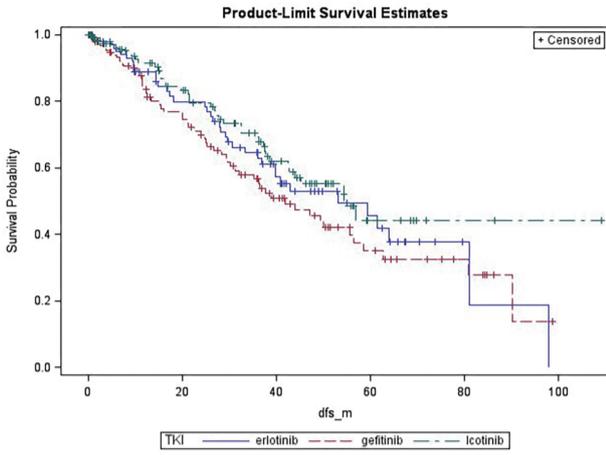
B: After matching
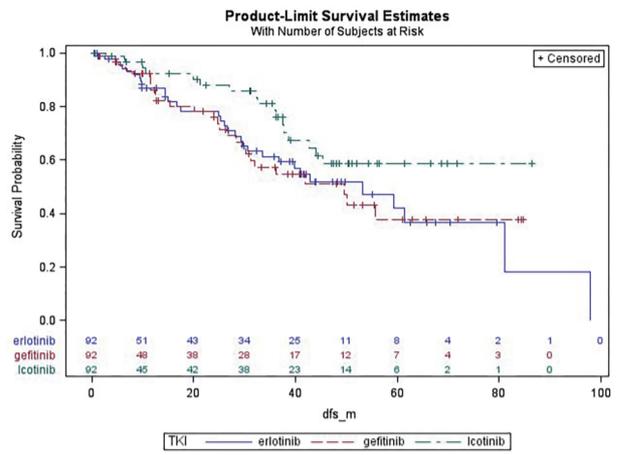
	Icotinib (N=284)	Erlotinib (N=106)	Gefitinib (N=198)	Log-rank P-value	Icotinib (N=92)	Erlotinib (N=92)	Gefitinib (N=92)	Log-rank P-value
Event, n (%)	49 (17.3)	39 (36.8)	63 (31.8)		18 (19.6)	34 (37.0)	28 (30.4)	
Median DFS (95% CI), months	54.4 (42.6, NA)	53.1 (36.8, 81.1)	41.9 (30.2, 56.4)	0.112	NA (42.6, NA)	53.1 (30.6, 81.1)	49.4 (29.4, NA)	0.077

Subgroup analysis: Stage = I

A: Before matching

B: After matching

	Icotinib (N=169)	Erlotinib (N=43)	Gefitinib (N=101)	Log-rank P-value	Icotinib (N=46)	Erlotinib (N=41)	Gefitinib (N=43)	Log-rank P-value
Event, n (%)	19 (11.2)	14 (32.6)	23 (22.8)		4 (8.7)	14 (34.1)	9 (20.9)	
Median DFS (95% CI), months	NA (54.2, NA)	61.5 (30.6, 81.1)	58.5 (31.2, NA)	0.122	NA (NA, NA)	61.5 (29.2, 81.1)	NA (31.2, NA)	0.011

Subgroup analysis: Stage = II or III

A: Before matching

B: After matching

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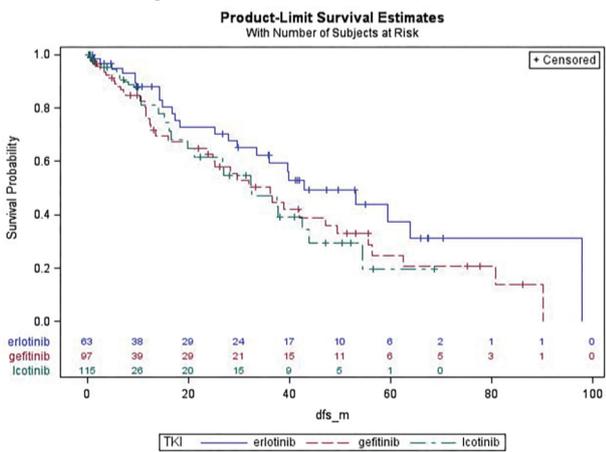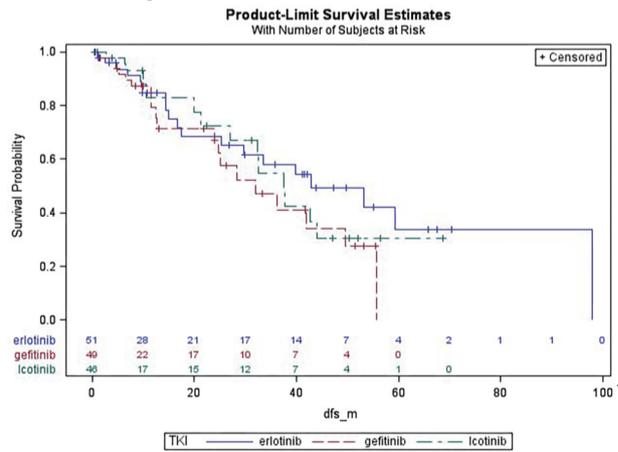
	Icotinib (N=115)	Erlotinib (N=63)	Gefitinib (N=97)	Log-rank P-value	Icotinib (N=46)	Erlotinib (N=51)	Gefitinib (N=49)	Log-rank P-value
Event, n (%)	30 (26.1)	25 (39.7)	40 (41.2)		14 (30.4)	20 (39.2)	19 (38.8)	
Median DFS (95% CI), months	32.5 (19.9, 43.9)	42.8 (29.6, 97.8)	36.1 (23.9, 49.4)	0.223	37.6 (21.2, NA)	42.8 (25.2, 97.8)	32.0 (23.9, 49.4)	0.442