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An exploratory comparative analysis of tyrosine kinase inhibitors or docetaxel in second-line treatment of *EGFR* wild-type non-small-cell lung cancer: a retrospective real-world practice review at a single tertiary care centre

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ABSTRACT

Background Treatment for advanced non-small-cell lung cancer (NSCLC), especially in patients with wild-type *EGFR*, remains limited. Recently, erlotinib, a tyrosine kinase inhibitor (TKI) targeting *EGFR* mutation, was approved as second-line treatment in *EGFR* wild-type NSCLC. Despite evidence of better overall survival (OS) with chemotherapy than with TKI in second-line treatment, data on the use of TKI in the real-life clinical setting remain limited. The present practice review of TKI use for second- and third-line treatment in *EGFR* wild-type NSCLC also compares clinical outcomes for TKI and single-agent docetaxel as second-line treatment.

Methods Our retrospective cohort study included patients with *EGFR* wild-type NSCLC treated at the Jewish General Hospital (Montreal, QC) between 2003 and 2013. Patients received a TKI (erlotinib or gefitinib) in the second and third line or docetaxel in the second line. For each group, we determined OS, disease control rate, progression-free survival (PFS), and event-free survival (EFS).

Results The TKI group included 145 patients, with 92 receiving second-line treatment. In the control group, 53 patients received docetaxel as second-line therapy. In the TKI group, OS was 6.0 months; PFS, 2.7 months; and EFS, 3.0 months. Comparing second-line treatments, OS was 5.3 and 5.0 months respectively ($p = 0.88$), PFS was 2.5 and 1.8 months respectively ($p = 0.041$), and EFS was 3.0 and 1.7 months respectively ($p = 0.009$).

Conclusions In our study cohort, second-line therapy for *EGFR* wild-type NSCLC with TKI (compared with docetaxel) was associated with statistically better PFS and EFS and noninferior OS. Those findings raise the question of whether EFS should also be considered when choosing second-line treatment in this patient population.

Key Words Non-small-cell lung cancer, advanced disease, second-line treatment, tyrosine kinase inhibitors, docetaxel

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BACKGROUND

Lung cancer remains the leading cause of cancer-related mortality worldwide, and non-small-cell lung cancer (NSCLC) constitutes about 85% of all lung cancers[1]. In Canada alone, an estimated 25,000 new cases of lung cancer were diagnosed in 2013. The 5-year mortality rate for this disease remains 14% in men and 20% in women, reflecting only modest advances in anticancer therapy in the past few decades.

Historically, platinum-based chemotherapy was the standard of care in the first-line treatment of NSCLC, regardless of histology and molecular subtype[2]. Recently, the recognition of distinct populations has changed that treatment paradigm: pemetrexed and bevacizumab are used in nonsquamous adenocarcinoma[3,4], crizotinib has been approved in patients with *EML4–ALK* fusion gene[5], and tyrosine kinase inhibitors (TKIs) target disease with mutations in the *EGFR* gene[6,7].

Despite the advent of more targeted therapies, prognosis in advanced NSCLC remains poor, with only 30%–50% of patients being able to tolerate second-line therapy[8]. Important uncertainties persist with respect to the treatment of these patients, most of whom do not carry distinct mutations. Three agents are currently approved for second-line treatment of NSCLC after progression on

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first-line therapy: pemetrexed, docetaxel, and erlotinib (the latter targeting the *EGFR* mutation).

The gene encoding the epidermal growth factor receptor (EGFR) tyrosine kinase is somatically mutated in a substantial fraction of lung cancers, making it an ideal target anticancer therapy[9]. Most activating mutations occur in the tyrosine kinase domain. The most frequent of these are exon 19 deletions that eliminate four amino acids from the tyrosine kinase domain, and exon 21 missense mutations that substitute arginine for leucine at L834R. Those mutations account for about 90% of all *EGFR* mutations and are the target of first-generation TKIs such as erlotinib and gefitinib[10].

However, even in the absence of exon 19 deletion and L834R substitution mutations, erlotinib has been shown to have benefit (compared with best supportive care) in the second-line treatment of NSCLC patients deemed ineligible for further cytotoxic chemotherapy[11]. That finding led in 2004 to the approval of erlotinib, a reversible TKI targeting the *EGFR* mutation, for second-line treatment of *EGFR* wild-type NSCLC. Several phase III trials looking at erlotinib in the second-line treatment of NSCLC supported that decision, although, until recently, none were powered to study *EGFR* wild-type patients specifically (Table I).

In July 2013, Garassino *et al.*[14] compared docetaxel with erlotinib in second-line treatment specifically targeting *EGFR* wild-type NSCLC. Those authors demonstrated better overall survival (OS) with docetaxel than with erlotinib [8.2 months vs. 5.4 months respectively; adjusted hazard ratio: 0.73; 95% confidence interval (CI): 0.53 to 1.00; $p = 0.05$], and better median progression-free survival (PFS: 2.9 months vs. 2.4 months respectively; adjusted hazard ratio: 0.71; 95% CI: 0.53 to 0.95; $p = 0.02$). Another phase III trial by Kawagushi *et al.*[15] showed that PFS was better with docetaxel than with erlotinib (2.9 months vs. 1.3 months, $p = 0.01$) in the subset of *EGFR* wild-type tumours, although the difference did not translate into better OS (10.1 months vs. 9.0 months, $p = 0.91$). Results from both trials suggested better outcomes with single-agent chemotherapy in second-line treatment, although the effect on OS was less clear.

However, real-life data on the use of TKI in the treatment of patients with *EGFR* wild-type NSCLC who have progressed on first-line chemotherapy remain limited. Here, we present a practice review on the use of TKI in second- and third-line *EGFR* wild-type NSCLC at a single tertiary care centre, and we compare clinical outcomes for TKI compared with single-agent docetaxel in the second-line treatment of NSCLC.

METHODS

Population

This retrospective cohort study used electronic database and medical chart review to collect data. All sequential patients who were diagnosed with locally advanced or metastatic *EGFR* wild-type NSCLC between 2003 and 2013 at the Peter Brojde Lung Cancer Centre, Jewish General Hospital (Montreal, QC), and who received TKI as second- or third-line therapy were included. As a comparison sample, a cohort of all TKI-naïve patients who were diagnosed with locally advanced or metastatic *EGFR* wild-type NSCLC between 2003 and 2013 and who were treated with single-agent docetaxel in the second line were also included. The study protocol was approved by the institutional review board at the Jewish General Hospital.

Clinical Outcome Measures

These data were collected for eligible patients:

- Demographic characteristics: age, sex, smoking history (current or ever-smoker, never-smoker)
- Disease characteristics: NSCLC stage (TNM staging), Eastern Cooperative Oncology Group (ECOG) performance status, *EGFR* mutation status, histopathology (for example, squamous, nonsquamous, adenocarcinoma), date of diagnosis
- Treatment history: start and end dates of treatment or indication that treatment was ongoing, treatment discontinuation, reason for treatment discontinuation (if applicable), drug dose and schedule, response to treatment, determination of progression (radiologic or clinical), date of documented response

TABLE I Results of selected randomized phase III trials examining the use of erlotinib after first-line treatment of non-small-cell lung cancer

Reference	Pts (*n*)	Study arms	EGFR-positive (%)	Best response rate (%)	OS (months)	PFS (weeks)
Shepard *et al.,* 2005[11]	731	Erlotinib (E150)	24	8.2	6.7	2.2
		Best supportive care	28	—	4.7	1.8
Capuzzo *et al.,* 2010[12]	889	Maintenance erlotinib (E150)	5	11.9	12.0	12.3
		Best supportive care	6	5.4	11.0	11.1
Ciuleanu *et al.,* 2012[13]	424	Erlotinib (E150)	4	7.9	5.3	6.3
		Docetaxel or pemetrexed	2	6.3	5.5	8.6
Garassino *et al.,* 2013[14]	219	Erlotinib (E150)	0	15.5	5.4	2.4
		Docetaxel	0	3.0	8.2	2.9 Months
Kawaguchi *et al.,* 2014[15]	150	Erlotinib (E150)	31	17.0	14.8	2.0
	151	Docetaxel	61	17.9	12.2	3.2 Months

Pts = patients; OS = overall survival; PFS = progression-free survival; E150 = oral erlotinib 150 mg daily.

Outcomes

Primary Outcomes

The primary objective of the study was to review the real-life practice of TKI use in the second and third line for patients with *EGFR* wild-type advanced or metastatic NSCLC. Treatment patterns were characterized by time to start of TKI from the date of diagnosis of advanced NSCLC, duration of treatment, adverse events, treatment discontinuations, and subsequent line or lines of therapy.

Secondary Outcomes

Secondary outcomes included the disease control rate (DCR), PFS, event-free survival (EFS), and OS (Table II). Assessment of the DCR was made using the Response Evaluation Criteria in Solid Tumors (version 1.1) at time of first radiography after treatment start. Response was categorized as disease control or progressive disease. Progressive disease was defined as at least a 20% increase in the sum of diameters of the target lesions or as the appearance of 1 or more new lesions and was measured by the first available computed tomography images after the start of treatment.

Progression-free survival was defined as time elapsed from the time of TKI or docetaxel treatment initiation to the time of radiologic progression. Event-free survival was defined as the length of time after treatment initiation that the patient remained free of the complications or events that the treatment was intended to prevent or delay. Events included clinical or radiologic progression (or both) leading to discontinuation of treatment, death from any cause, and discontinuation of the TKI because of adverse events. For patients who stopped treatment at the time of radiologic progression, EFS was equal to PFS. Although EFS has not been validated as a clinical measure in randomized trials, we feel that the defined measure better reflects real-world practice, in which, despite radiologic progression, treatment might be continued because of ongoing clinical benefit. Overall survival was defined as the period from the time of treatment initiation to the time of death. Associations between key characteristics and outcomes, including treatment with TKI and the rate of response on TKI therapy, were explored.

We also investigated differences in survival, by demographic and clinical characteristics, for patients with locally advanced or metastatic *EGFR* wild-type NSCLC in the study sample who received second-line TKI treatment and for the representative sample of TKI-naïve NSCLC patients who received second-line docetaxel.

Statistical Analysis

Demographic and clinical data were summarized as means, standard deviations, and medians for continuous variables, and as numbers and percentages for categorical variables. All summarized data are presented separately for the TKI-treated group and the TKI-naïve group.

Clinical outcomes data are presented as the proportion of patients experiencing the outcomes of interest (disease control, progression, survival). Estimates of PFS, EFS, and OS (median, 95% CI) were generated. Kaplan–Meier methods for censored data were used to descriptively evaluate PFS, EFS, and OS.

An exploratory analysis investigated differences in OS between the TKI-treated patients and the TKI-naïve group. For that comparative analysis, log-rank or Breslow statistics were used to make nonparametric comparisons of the Kaplan–Meier analysis (unadjusted analyses).

An exploratory analysis separately presents demographic and clinical data for the second-line TKI-treated *EGFR*-negative group and the TKI-naïve *EGFR*-negative group who received docetaxel in the second line. Differences in key characteristics between the groups were investigated.

The statistical analyses were conducted using IBM SPSS Statistics (version 20: IBM, Armonk, NY, U.S.A.), and statistical significance was accepted at p values of 0.05 or less.

RESULTS

Table III presents the clinico-demographic characteristics of the 145 TKI-treated patients included in the study. Most of the patients were ex-smokers or current smokers (73.8%) who had a good performance status at diagnosis (80.0% ECOG 0–1). Of those patients, 79.3% presented initially with advanced-stage disease (stage IIIB or IV). By the time

TABLE II Definitions of study parameters

Parameter	Definition
Overall survival	The interval from time of treatment initiation to time of death
Disease control rate	Determined using RECIST 1.1 at the time of first radiography evaluation after treatment onset (Disease control was defined as complete response, partial response, or stable disease.)
Progressive disease	At least a 20% increase in the sum of the diameters of target lesions or the appearance of 1 or more new lesions (measured on the first available computed tomography evaluation after start of treatment)
Progression-free survival	The interval from initiation of second- or third-line treatment to radiologic progression
Event-free survival	The duration of second- or third-line treatment (If treatment was discontinued at time of radiologic progression, event-free survival was then equal to progression-free survival.)
Event	Clinical or radiologic progression leading to discontinuation of treatment, death (from any cause), or discontinuation of tyrosine kinase inhibitor because of adverse events

RECIST = Response Evaluation Criteria in Solid Tumors.

of TKI or docetaxel initiation, all patients had advanced or metastatic disease. Adenocarcinoma and bronchoalveolar carcinoma were the primary histologies observed.

A TKI was given to 92 patients in second-line treatment and to 53 patients in third-line treatment (Figure 1). Of the 92 patients who were treated with a TKI in the second line, 26 went on to third-line chemotherapy, and of the 53 who received a TKI in the third line, 20 received fourth-line chemotherapy.

Median time from diagnosis of advanced disease to TKI initiation was 7.4 months (95% CI: 6.84 to 8.02 months). Median time of EFS (measured by the duration of TKI treatment) was 3.0 months (95% CI: 2.6 to 3.47 months). First computed tomography imaging was performed at

TABLE III Baseline patient characteristics

Characteristic	Treatment group				
	Tyrosine kinase inhibitor (TKI)		Docetaxel	*p* Value[a]	TKI
	Second and third line	Second line	Second line		Third line
Patients (*n*)	145	92	49		53
Age (years)					
Mean	63.6	63.8	57.9	0.004	63.5
Range	27–84	27–84	41–80		39–79
Sex [*n* (%)]					
Men	77 (53.1)	47 (51.1)	22 (44.9)	0.391	30 (56.7)
Women	68 (46.9)	45 (48.9)	27 (55.1)		23 (43.4)
Smoking [*n* (%)]					
Nonsmoker	38 (26.2)	27 (29.3)	3 (6.1)	0.001	11 (20.8)
Ex- or current smoker	107 (73.8)	65 (70.7)	46 (93.9)		42 (79.2)
Histology [*n* (%)]					
Adenocarcinoma/BAC	130 (89.7)	85 (92.4)	32 (65.3)	<0.001	45 (84.9)
Other	15 (10.3)	7 (7.6)	17 (34.7)		8 (15.1)
ECOG PS [*n* (%)]					
0–1	116 (80.0)	69 (75.0)	46 (93.9)	0.006	49 (92.5)
>1	29 (20.0)	23 (25.0)	3 (6.1)		3 (5.7)
Stage at initial diagnosis [*n* (%)]					
I–II	12 (8.3)	5 (5.4)	3 (6.1)	0.307	7 (13.2)
IIIA	18 (12.4)	6 (6.5)	15 (30.6)		12 (22.6)
IIIB–IV	115 (79.3)	81 (88.0)	31 (63.3)		34 (64.2)

[a] Second-line docetaxel compared with second-line TKI.
BAC = bronchoalveolar carcinoma; ECOG PS = Eastern Cooperative Oncology Group performance status.

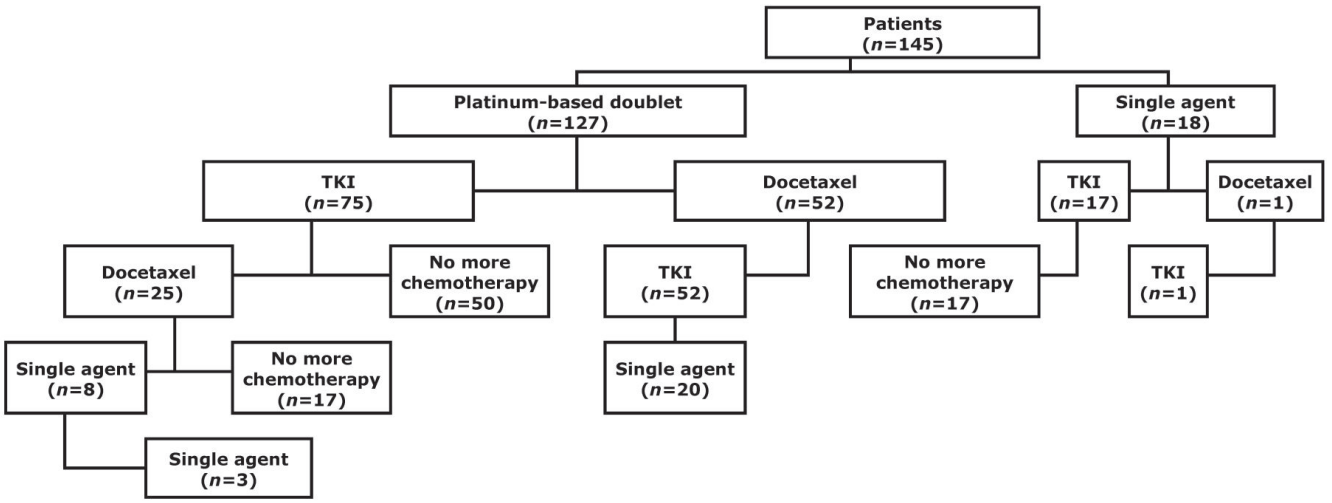

FIGURE 1 Treatment trajectory in patients who received second- and third-line tyrosine kinase inhibitor (TKI).

the average of 3.5 months after initiation of treatment. The DCR in the TKI group was 32.4% (32.6% in second-line treatment and 32.1% in third-line treatment, Table IV). Treatment with TKI continued beyond progression in 28 patients: 16 in the second line (17.4%), and 12 in the third line (22.6%). Median OS was 6.0 months (95% CI: 4.5 to 7.5 months; Figure 2).

Overall, TKIs were well tolerated (Table V). Most patients discontinued treatment because of disease progression (84.0%), with a small proportion discontinuing treatment because of grade 3 or greater side effects (8.3%). At the time of study closure, 9 patients were still receiving TKI treatment, of whom 7 were receiving TKI in the second line, and 2 in the third line.

TABLE IV Disease control rate with second- and third-line treatment using tyrosine kinase inhibitor (TKI) and docetaxel

Treatment	Pts (*n*)	Disease progression [*n* (%)]	
		No	Yes
Second-line docetaxel	49	13 (26.5)	36 (73.5)
Second-line TKI	92	30 (32.6)	62 (67.4)[a]
Third-line TKI	53	17 (32.1)	36 (67.9)[a]
TOTAL	194	60	134

[a] Defined as clinical or radiologic evidence of progression, death from any cause, or discontinuation of TKI because of adverse events.

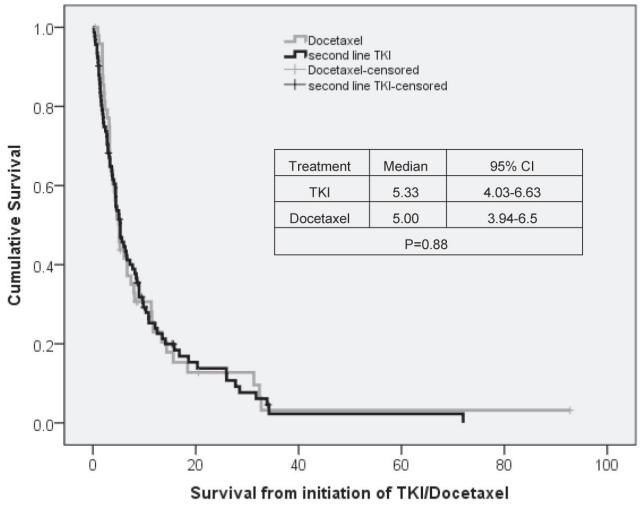

FIGURE 2 Overall survival of patients who received tyrosine kinase inhibitor (TKI) or docetaxel in second-line treatment. Overall survival was defined as time elapsed from treatment initiation to death or study end. CI = confidence interval.

TABLE V Tolerability of tyrosine kinase inhibitors (TKIS) in 145 patients

Reason for TKI discontinuation	Patients [*n* (%)]
Still on TKI at study closure	9 (6.2)
Disease progression	122 (84.1)
Grade 3 or greater	
Rash	5 (3.4)
Diarrhea	3 (2.1)
Weakness	2 (1.4)

Comparison of Second Line TKI and Docetaxel

The number of non-smokers was statistically significantly greater in the TKI group than in the docetaxel group (29.3% vs. 6.1%, $p = 0.001$). A good ECOG performance status was also significantly more prevalent in the TKI group than in the docetaxel group (Table III).

Mean time to initiation of second-line treatment from progression of disease after first-line treatment was similar in both groups: 3.6 ± 5.8 months in the TKI group and 4.6 ± 5.0 months in the docetaxel group. The DCR was better in the second-line TKI group than in the docetaxel group (32.6% vs. 26.5%, Table IV), but the difference did not reach statistical significance. Progression-free survival was significantly better ($p = 0.041$) in the second-line TKI group (2.5 months; 95% CI: 1.9 to 3.1 months) than in the docetaxel group (1.8 months; 95% CI: 1.7 to 2.0 months). Event-free survival was significantly better ($p = 0.009$) in the second-line TKI group (3.0 months; 95% CI: 2.38 to 3.62 months) than in the docetaxel group (1.7 months; 95% CI: 1.57 to 1.89 months). Overall survival was similar in both groups: 5.3 months in the TKI group (95% CI: 4.0 to 6.6 months) and 5.0 months in the docetaxel group (95% CI: 3.9 to 6.5 months). The difference did not reach statistical significance (log rank $p = 0.88$, Figure 2).

DISCUSSION

Before publication of the TAILOR study in July 2013, erlotinib had been used quite extensively in the clinical setting for second-line treatment of NSCLC. However, there is a paucity of data concerning outcomes in patients with *EGFR* wild-type NSCLC receiving a targeted agent, and even fewer data comparing outcomes with the use of TKI or with single-agent chemotherapy.

Overall, patient demographics in the present study are comparable to those in previously published phase III studies studying TKI for the second-line treatment of advanced NSCLC. Median age in the second- and third-line TKI groups (63.6 years) is similar to that in previous pivotal trials[11,14,16] of second-line treatment in advanced NSCLC (61.4, 66, and 59 years respectively). The predominance of a good ECOG performance status and of adenocarcinoma on histology examination is also reflective of other pivotal trials.

Our results seem to show that treatment with TKI in the second-line setting was not inferior to docetaxel therapy. In the second-line TKI group, PFS and EFS were statistically significantly better. Trends toward better DCR and OS were observed with TKI (compared with docetaxel), although the differences were not statistically significant.

The OS in our second-line TKI cohort (5.3 months; 95% CI: 4.0 to 6.6 months) was similar to that reported in the TAILOR study (5.4 months; 95% CI: 4·5 to 6·8 months) and inferior to that reported in the DELTA study (9.0 months). However, in contrast to both the TAILOR and the DELTA studies, OS in the docetaxel group was not superior to that in the TKI group[11,12] (Table I). The better PFS seen with TKI than

with docetaxel differs from the results of both the TAILOR and DELTA trials; the EFS, which was also significantly better in the TKI group than in the docetaxel group, has not previously been measured in randomized trials.

The superior PFS and EFS in our second-line TKI cohort might reflect selection bias at our institution. For instance, the number of non-smokers was statistically significantly higher in the TKI group than in the docetaxel group (Table III). Alternatively, follow-up imaging was not performed at a strict time interval (mean: 3.5 months), and a longer interval between treatment initiation and follow-up imaging could therefore have artificially prolonged PFS. The significance of such results in a retrospective study remains unclear, although it raises the interesting question of whether continuing TKI beyond PFS could improve patient outcomes. Finally, differences in best response after first-line therapy and the variability of such clinical measures, even between large randomized trials (for example, OS of 5.4 months in TAILOR and 9.0 months in DELTA), might account for the trend seen in our study favouring TKI over docetaxel.

In the third-line setting, TKIs do not seem to show a significant decrement in efficacy: our DCR of 32.1% suggests that, even in extensively pre-treated advanced NSCLC, TKIs are an interesting therapeutic option.

The side-effect profile of erlotinib has made it a quite attractive and tolerable option for patients who often have a high symptom burden and poor ECOG performance status by the time they are eligible for second-line treatment. That situation is reflected in the present study: only 10 patients (7.8%) discontinued treatment because of severe side effects. Most patients stopped because of clinical disease progression.

In an effort to identify patients with *EGFR* wild-type NSCLC who would most benefit from TKI treatment, Taguchi and colleagues[17] developed a test that uses mass spectrometry analysis of serum to categorize candidates as likely to have good or poor survival on such treatment. Several retrospective studies have demonstrated that patients with a proteomic test classification of "good" experience a significantly better outcome than do those with a classification of "poor" when treated with EGFR TKIs[18–20]. A phase III randomized trial by Gregorc *et al.* subsequently confirmed that patients with a proteomic test classification of "poor" experienced worse survival on erlotinib than on chemotherapy (hazard ratio: 1.72; 95% CI: 1.08 to 2.74; $p = 0.022$), while those with a classification of "good" experienced no significant difference in OS with either treatment (adjusted hazard ratio: 1.06; 95% CI: 0.77 to 1.46; $p = 0{\cdot}714$)[21]. Although mass spectrometry is promising, its integration into a resource-limited health care setting is less than certain, and the second-line treatment decision in *EGFR* wild-type NSCLC remains largely clinical.

Findings in our study are limited by the relatively small size of the cohort and the retrospective nature of the analysis. Given the study's nature (real-life practice review), follow-up in the form of first imaging after the start of second-line treatment was performed at the clinician's discretion. Hence, some patients underwent imaging within weeks of treatment initiation, and others underwent imaging only months later when they demonstrated significant clinical progression. The median interval between pre- and post-treatment-initiation imaging was 3.5 months, and in 26 cases, patients did not undergo any imaging because they demonstrated early death or clinical progression and were on treatment for only a short time. We therefore chose to use EFS to better describe the patients in whom treatment continued beyond PFS. The EFS parameter has not been integrated into other larger randomized trials, and hence the significance of our EFS findings, while intriguing, remains unclear. Nevertheless, the variability in the timing of imaging and the continuation of treatment both reflect real-life practice. Our data suggest that TKIs are efficacious and well tolerated in the second- and third-line treatment of advanced NSCLC.

CONCLUSIONS

Our study seems to show that second-line TKI could be noninferior to docetaxel, suggesting a continuing role for targeted therapy in advanced NSCLC. In the end, choice of second- and third-line therapy should be individualized based on numerous considerations, including symptom improvement, toxicity, patient comorbidities, convenience, and ease of administration.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin* 2012;62:10–29.
2. Kelly K, Crowley J, Bunn PA Jr, *et al.* Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non-small-cell lung cancer: a Southwest Oncology Group trial. *J Clin Oncol* 2001;19:3210–18.
3. Scagliotti GV, Parikh P, von Pawel J, *et al.* Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol* 2008;26:3543–51.
4. Sandler A, Gray R, Perry MC, *et al.* Paclitaxel–carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006;355:2542–50. [Erratum in: *N Engl J Med* 2007;356:318]
5. Shaw AT, Kim DW, Nakagawa K, *et al.* Crizotinib versus chemotherapy in advanced *ALK*-positive lung cancer. *N Engl J Med* 2013;368:2385–94.
6. 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;12:735–42.
7. Mitsudomi T, Morita S, Yatabe Y, *et al.* on behalf of the West Japan Oncology Group. 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;11:121–8.
8. Tassinari D, Scarpi E, Sartori S, *et al.* Second-line treatments in non–small cell lung cancer. A systematic review of literature and metaanalysis of randomized clinical trials. *Chest* 2009;135:1596–609.
9. Red Brewer M, Yun CH, Lai D, Lemmon MA, Eck MJ, Pao W. Mechanism for activation of mutated epidermal growth factor receptors in lung cancer. *Proc Natl Acad Sci U S A* 2013;110:E3595–604. [Erratum in: *Proc Natl Acad Sci U S A* 2013;110:20344]
10. Pao W, Chmielecki J. Rational, biologically based treatment of *EGFR*-mutant non-small-cell lung cancer. *Nat Rev Cancer* 2010;10:760–74.
11. Shepherd AF, Rodrigues Pereira J, Ciuleanu T, *et al.* on behalf of the National Cancer Institute of Canada Clinical Trials Group. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005;353:123–32.
12. Cappuzzo F, Ciuleanu T, Stelmakh L, *et al.* on behalf of the SATURN investigators. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. *Lancet Oncol* 2010;11:521–9.
13. Ciuleanu T, Stelmakh L, Cicenas S, *et al.* Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (TITAN): a randomised multicentre, open-label, phase 3 study. *Lancet Oncol* 2012;13:300–8.
14. Garassino MC, Martelli O, Broggini M, *et al.* Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type *EGFR* tumours (TAILOR): a randomised controlled trial. *Lancet Oncol* 2013;14:981–8.
15. Kawaguchi T, Ando M, Asami K, *et al.* Randomized phase III trial of erlotinib versus docetaxel as second- or third-line therapy in patients with advanced non-small-cell lung cancer: Docetaxel and Erlotinib Lung Cancer Trial (DELTA). *J Clin Oncol* 2014;32:1902–8.
16. Groen HJ, Socinski MA, Grossi F, *et al.* A randomized, double-blind, phase II study of erlotinib with or without sunitinib for the second-line treatment of metastatic non-small-cell lung cancer (NSCLC). *Ann Oncol* 2013;24:2382–9.
17. Taguchi F, Solomon B, Gregorc V, *et al.* Mass spectrometry to classify non-small-cell lung cancer patients for clinical outcome after treatment with epidermal growth factor receptor tyrosine kinase inhibitors: a multicohort cross-institutional study. *J Natl Cancer Inst* 2007;99:838–46.
18. Stinchcombe TE, Roder J, Peterman AH, *et al.* A retrospective analysis of VeriStrat status on outcome of a randomized phase II trial of first-line therapy with gemcitabine, erlotinib, or the combination in elderly patients (age 70 years or older) with stage IIIB/IV non-small-cell lung cancer. *J Thorac Oncol* 2013;8:443–51.
19. Carbone DP, Ding K, Roder H, *et al.* Prognostic and predictive role of the VeriStrat plasma test in patients with advanced non-small-cell lung cancer treated with erlotinib or placebo in the NCIC Clinical Trials Group BR.21 trial. *J Thorac Oncol* 2012;7:1653–60.
20. Lazzari C, Spreafico A, Bachi A, *et al.* Changes in plasma mass-spectral profile in course of treatment of non–small cell lung cancer patients with epidermal growth factor receptor tyrosine kinase inhibitors. *J Thorac Oncol* 2012;7:40–8.
21. Gregorc V, Novello S, Lazzari C, *et al.* Predictive value of a proteomic signature in patients with non-small-cell lung cancer treated with second-line erlotinib or chemotherapy (PROSE): a biomarker-stratified, randomised phase 3 trial. *Lancet Oncol* 2014;15:713–21.