Article published online: 2021-06-08

Original Article

T790M Mutation and Clinical Outcomes with Osimertinib in Patients with Epidermal Growth Factor Receptor-mutant Nonsmall Cell Lung Cancer

Ravi Jaiswal, Rakesh Pinninti, MVT Krishna Mohan, A Santa, Pavan Kumar Boyella, Lavanya Nambaru[1], Sudha S Murthy[1], K Veeriah Chowdary[2], Senthil Rajappa

Departments of Medical Oncology, [1]Laboratory Medicine and [2]Radiodiagnosis, Basavatarakam Indo-American Cancer Hospital and Research Institute, Hyderabad, Telangana, India

Abstract

Introduction: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors TKIs) are highly effective in EGFR-mutant advanced lung cancer. The most common resistance mechanism to EGFR-TKI is the development of T790M mutation in Exon 20. Osimertinib, a highly selective EGFR-TKI, has been approved for use in patients who progress on the first-line TKI and harbor the T790M mutation. **Objective:** The primary objective is to prospectively study the incidence of T790M mutation in patients who progress on the first-line EGFR-TKI. Secondary objectives include clinical characteristics that predict for T790M mutation and outcomes with osimertinib. **Materials and Methods:** This single-center, prospective observational study included 90 patients who progressed on first-line EGFR TKI. All patients had DNA extracted from tissue re-biopsy or plasma circulating tumor DNA (re-biopsy was not feasible or inadequate). T790M mutation was detected using amplification refractory mutation system-polymerase chain reaction, and patients harboring T790M mutation were started on osimertinib (80 mg once daily) until progression or unacceptable side effects. **Results:** At progression, T790M mutation was detected in 47/90 patients (52.2%). On binary logistic regression model analysis, variables that were independently predictive of the development of T790M were younger age (odds ratio [OR] 4.3, 95% confidence interval [CI] 1.14–16.6, P = 0.031); nonerlotinib TKI use (OR 8.3, 95% CI 1.24–55.8, P = 0.029); and pure adenocarcinoma histology (OR 6.2, 95% CI 1.60–24.7, P = 0.008). Forty-six patients were started on osimertinib. The overall response rate and median progression-free survival were 65.21% and 12.45 months (standard deviation [SD] 1.03, 95% CI 10.41–14.48), respectively. Osimertinib was well tolerated with most toxicities being Grade 1 and 2 diarrhea and skin rash. **Conclusions:** In our prospective cohort, half of all patients had a T790M mutation at progression on the first-line EGFR TKI. Tissue biopsy is feasible in the majority of patients. Clinical outcomes with osimertinib were consistent with those reported.

Keywords: *Epidermal growth factor receptor, liquid biopsy, lung cancer, osimertinib, re-biopsy, T790M*

Introduction

The discovery of targetable oncogenic driver mutations has successfully changed the outlook for subsets of advanced nonsmall lung cancer (NSCLC) patients.[1,2] The landscape of therapies for epidermal growth factor receptor (EGFR) driver-mutant advanced NSCLC is fast evolving.[3,4] Multiple EGFR tyrosine kinase inhibitors (EGFR-TKIs) have been proved to be superior to chemotherapy in multiple large Phase III trials and have been approved for clinical use. The average response rate to these TKIs range around 65%–75%, with a median progression-free survival (PFS) and overall survival of around 10–13 months and 22–30 months, respectively.[5-8]

Despite a convincing initial tumor response to EGFR-TKIs, the emergence of resistance to these drugs is almost inevitable in most patients. Although multiple resistance mechanisms have been reported, majority (almost 60%) of patients acquire a secondary mutation of threonine-to-methionine substitution at amino acid position 790 (T790M) in exon 20, leading to clinical resistance to EGFR-TKI.[9-13] T790M results in steric hindrance and increased adenosine triphosphate affinity which decreases EGFR-TKI–mediated inhibition of downstream signaling leading to disease progression. Several studies have found a correlation between clinical variables and the frequency of T790M mutation, but the results are conflicting.[14,15]

How to cite this article: Jaiswal R, Pinninti R, Mohan MV, Santa A, Boyella PK, Nambaru L, *et al.* T790M mutation and clinical outcomes with osimertinib in patients with epidermal growth factor receptor-mutant nonsmall cell lung cancer. Indian J Med Paediatr Oncol 2019;40:73-8.

Address for correspondence:
Dr. Rakesh Pinninti, Basavatarakam Indo-American Cancer Hospital and Research Institute, Hyderabad - 500 034, Telangana, India.
E-mail: pinninti.rakesh@gmail.com

Access this article online

Website: www.ijmpo.org

DOI: 10.4103/ijmpo.ijmpo_215_18

Quick Response Code:

Osimertinib is a highly selective third-generation EGFR-TKI that potently inhibits mutant EGFR and T790M.[16] Recent studies have established the efficacy and safety of osimertinib in T790M-positive advanced NSCLC after progression with prior EGFR-TKI therapy, leading to its approval for this clinical indication.[17,18] Through this study, we aim to investigate the incidence of T790M mutations in our population and explore the associations between clinical characteristics and frequency of T790M mutation and efficacy of osimertinib in NSCLC patients progressing on a first-line EGFR-TKI.

Materials and Methods

Study design

This study is a prospective series of patients with EGFR mutation who progressed on the first-line TKI.

Inclusion and exclusion criteria

The study included a consecutive series of patients who would satisfy the following criteria: the presence of EGFR mutation at diagnosis, treatment with 1st- or 2nd-generation EGFR-TKIs, documented radiologic progression needing a change of therapy. Oligoprogressions were excluded. The study period was between November 2016 and May 2018.

Objectives

The primary objective of the study was to prospectively evaluate the incidence of T790M mutation in patients who progress on the first-line EGFR-TKIs. The secondary objectives were to identify clinical characteristics that were predictive for T790M mutations, objective response rate (ORR), and progression-free survival (defined as the time from the first dose until progression or death) with osimertinib therapy in T790M-positive patients.

Postprogression molecular assessment

Postprogression tumor rebiopsy was performed from a progressing site after obtaining written informed consent. Mutation analyses of EGFR gene including T790M was performed using amplification refractory mutation system-polymerase chain reaction (ARMS PCR) method. In patients in who declined a re-biopsy or in those where biopsy was not possible because of inaccessible lesion, blood sample (10 ml ethylenediaminetetraacetic acid) was screened for T790M on circulating tumor DNA (CTDNA) using Droplet Digital PCR.

Therapeutic interventions

Patients who had T790M mutation were treated with osimertinib 80 mg once daily until progression. Those who did not harbor the mutation were treated as per histology at rebiopsy. Patients with adenocarcinoma were treated with platinum doublet chemotherapy (intravenous pemetrexed at 500 mg/m^2 plus either cisplatin at 75 mg/m^2 or carboplatin area under the curve of five). Those with a small cell histology were treated with platinum and etoposide and radiation as per guidelines. Local radiotherapy was utilized for palliation of painful bone metastases or symptomatic brain metastasis.

Study oversight and statistical analysis

This study was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonisation. The protocol was approved by the Local Human Investigations Committee. Written informed consent was obtained from all patients. Comparisons of the characteristics of the two groups were carried out using the Chi-square test and independent *t*-test or the Fisher's exact test utilized where appropriate. Initially, a bivariate analysis was carried out for probable predictive factors for T790M evolution. Subsequently, factors identified were analyzed independently using the stepwise method in the binary logistic regression analysis. Survival estimates were done using Kaplan–Meier method and comparison between subgroups done using the log-rank test. Two-sided values of $P < 0.05$ were considered statistically significant. Statistical analysis was performed using IBM SPSS version 22.0 software (New York, USA).

Results

Patient characteristics

A total of 90 consecutive patients, comprising 46 men (51.1%) and 44 women (48.9%), who progressed on the first-line TKI were identified based on the inclusion criteria described. The characteristics of these 90 patients are outlined in Table 1. The mean age of the entire cohort was 59.1 years (range 38–87 years). Most patients had good performance score (ECOG PS 1 or 2, 78/90%–86.7%), and the majority were nonsmokers (83/90%–92.2%). Baseline driver mutations consisted of exon 19 deletions in 71.1% (64/90), L858R mutation in 23.3% (21/90) and uncommon mutations in 5.5% (5/90). Gefitinib was used in the first line in 72.2% (65/90), erlotinib in 13.3% (12/90), and afatinib in 14.4% (13/90) patients.

Clinical and molecular characteristics post first-line therapy progression

At progression, 47 of 90 patients (52.2%) had T790M mutation. T790M mutation was identified on repeat tissue biopsy in 82.9% (39/47) and with CTDNA in 17% (8/47). On bivariate analysis, identification of T790M at progression correlated with younger age (80 vs. 44.3% $P = 0.005$), smoking status (56.6 vs. 0%, nonsmokers and smokers, respectively, $P = 0.004$), nonerlotinib TKI use (57.7% vs. 16.7% nonerlotinib and erlotinib, respectively, $P = 0.008$), and pure adenocarcinoma histology at diagnosis (59.7 vs. 22.2%, $P = 0.004$) [Table 1]. On binary logistic regression model analysis, variables that were independently predictive of the development of T790M

Table 1: Comparisons of the clinical characteristics of the two groups relative to entire cohort

Variable	T790M positive (%)[#]	T790M negative (%)	Total cohort (%)	*P**
Number of patients	47 (52.2)	43 (47.7)	90 (100)	NA
Mean age (years)	56.04 (SD: 9.5)	62.5 (SD: 10.03)	59.13 (SD: 10.28)	
<50	16 (34)	4 (9.3)	20 (22.2)	0.005
50 or more	31 (66)	39 (90.7)	70 (78.2)	
Gender				
Male	22 (46.8)	24 (55.8)	46 (51.1)	0.393
Female	25 (53.2)	19 (44.2)	44 (48.9)	
Smoking history				
Nonsmoker	47 (100)	36 (83.7)	83 (92.2)	0.004
Smoker	0 (0)	7 (16.3)	7 (7.8)	
Performance score				
ECOG 1 and 2	41 (87.2)	37 (86)	78 (86.7)	0.869
ECOG 3 and 4	6 (12.8)	6 (14.0)	12 (13.3)	
Histology				
Adenocarcinoma	43 (91.5)	29 (67.4)	72 (80)	0.004
Others	4 (8.5)	14 (32.6)	18 (20)	
EGFR mutation at baseline				
Exon 19	36 (76.6)	28 (65.1)	64 (71.1)	0.309
Exon 21	9 (19.1)	12 (27.9)	21 (23.3)	
Others	2 (4.3)	3 (7)	5 (5.5)	
First-line oral TKI used				
Erlotinib	2 (4.3)	10 (23.3)	12 (13.3)	0.029
Gefitinib	38 (80.9)	27 (62.8)	65 (72.2)	
Afatinib	7 (14.9)	6 (14)	13 (14.4)	
Time to progression on first-line therapy (months)				
<6	4 (8.5)	10 (23.3)	14 (15.6)	0.054
<12	17 (36.2)	24 (55.8)	41 (45.6)	0.062
Between 12-24	26 (55.3)	15 (34.9)	41 (45.6)	0.052
Oral TKI used in first line				
Afatinib versus no afatinib use	7 (14.9) versus 40 (85.1)	6 (14) versus 37 (86.0)	13 (14.4) versus 77 (85.6)	0.89
Erlotinib versus no erlotinib use	2 (4.3) versus 45 (95.7)	10 (23.3) versus 33 (76.7)	12 (13.3) versus 78 (86.7)	0.008

**P* value calculated with the Chi-square test and independent *t*-test or the Fisher's exact test where appropriate, [#]Percentages representative of distribution in individual column. TKI – Tyrosine kinase inhibitor; EGFR – Epidermal growth factor receptor; ECOG – Eastern Cooperative Oncology Group; SD – Standard deviation

were younger age (odds ratio [OR] 4.3, 95% confidence interval [CI] 1.14–16.6, $P = 0.031$), nonerlotinib TKI use (OR 8.3, 95% CI 1.24–55.8, $P = 0.029$), and pure adenocarcinoma histology at diagnosis (OR 6.2, 95% CI 1.60–24.7, $P = 0.008$) [Table 2]. The transformation to small cell carcinoma was identified in two patients (2.2%).

Table 2: Predictive factors for the development of T790M resistance mechanism, selected by binary logistic regression analysis

Variables	Odds ratio	95% CI	*P*
Younger age	4.3	1.14-16.6	0.031
Nonerlotinib TKI use	8.3	1.24-55.8	0.029
Pure adenocarcinoma at diagnosis	6.2	1.60-24.7	0.008

CI – Confidence interval; TKI – Tyrosine kinase inhibitor

Objective response and duration of response to osimertinib in subsequent therapy

Of the 47 patients with T790M mutation, 46 patients received osimertinib as subsequent therapy. At a median follow-up of 15 months, 41.3% (19/46) patients had disease progression including death in 32.5% (13/46) patients [Table 2]. The median PFS on osimertinib was 12.45 months (standard deviation [SD] 1.03, 95% CI 10.41–14.48) [Figure 1]. The overall ORR with osimertinib was 65.21%; with complete responses in 26.08% (12/46) and partial responses in 39.13% (18/46) patients [Table 3]. There was no significant association between PFS and age, gender, performance score, smoking history, type of baseline EGFR mutation, or duration of first-line TKI. The only factor associated significantly with better PFS on osimertinib was the presence of a complete response to first-line TKI therapy (complete response [CR] vs. non-CR, not reached vs. 9.16, SD 3.2, 95% CI 2.81–15.52; $P = 0.049$) [Figure 2]. At a median follow-up of 15 months, 67.3% (33/46) patients were alive in osimertinib cohort. Osimertinib was well tolerated with most toxicities being Grade 1 and 2 diarrhea and skin rash. There was no therapy

Table 3: Treatment outcomes

Variable	First-line TKI use (*n*=90), *n* (%)	Osimertinib as subsequent therapy (*n*=46), *n* (%)	Chemotherapy in 2nd line (*n*=35), *n* (%)
Median PFS (months)	12.35	12.45	5.94
Objective response rate (%)	82.2	65.21	54.3
CR	37/90 (41.1)	12/46 (26.08)	3/35 (8.6)
PR	37/90 (41.1)	18/46 (39.13)	16/35 (45.7)
SD	09/90 (10.0)	9/46 (19.56)	7/35 (20)
PD	07/90 (7.8)	7/46 (15.2)	9/35 (25.7)
Progression events (%)	90/90 (100)	19/46 (41.3)	29/35 (82.8)

TKI – Tyrosine kinase inhibitor; SD – Stable disease; PD – Progressive disease; CR – Complete response; PR – Partial response

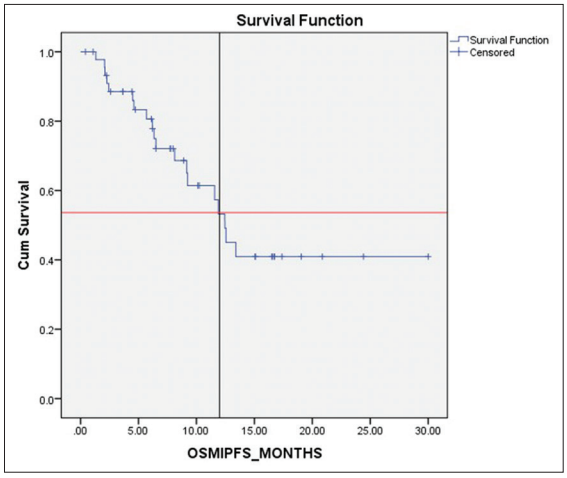

Figure 1: Kaplan–Meier survival curves depicting progression-free survival, median progression-free survival on osimertinib was 12.45 months (standard deviation 1.03, 95% confidence interval 10.41–14.48)

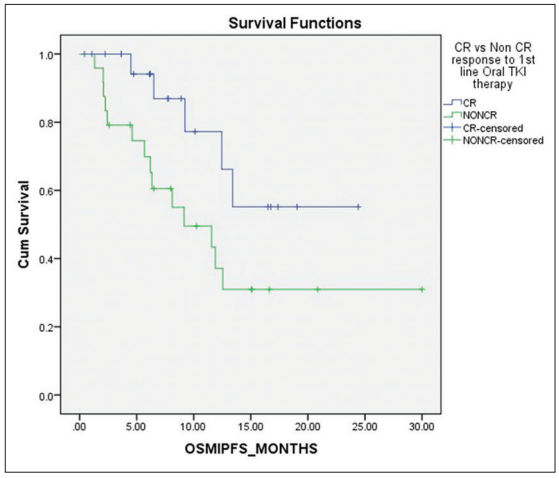

Figure 2: Kaplan–Meier analysis of progression-free survival on osimertinib therapy with respect to response to first- line therapy (complete responses vs. noncomplete responses, not reached vs. 9.16 confidence interval 3.2 95% confidence interval 2.81–15.52; *P* = 0.049)

discontinuation related to adverse effects. There was one patient with interstitial lung disease which recovered with steroid and treatment interruptions and three cardiovascular deaths while on therapy.

Objective response and duration of response to chemotherapy in patients who were T790M negative

Of the 43 patients without T790M mutation at disease progression on the first-line oral TKI therapy, 35 (81.4%) patients had received chemotherapy as subsequent therapy, and 8 (18.6%) patients were considered for supportive care alone. The median PFS with chemotherapy in subsequent therapy was 5.94 months (SD 0.84, 95% CI 4.29–7.60). The overall ORR with subsequent line chemotherapy was 54.3%; with CR in 8.6% (3/35); partial responses in 45.7% (16/35); and stable disease in 20% (7/35) and progressive disease in 25.7% (9/35) patients.

Discussion

In this prospective cohort of 90 patients, who had progressed on the first-line EGFR TKI, T790M mutation was detected in 52.2% of patients. The incidence of T790M mutation was similar in tissue and liquid biopsy at 50.6% and 52.9%, respectively. Younger age, nonerlotinib first-line TKI, and pure adenocarcinoma at diagnosis were predictive of T790M evolution. These factors were previously not reported to be predictive of T790M mutation. Joo *et al*., in their retrospective review, had shown exon 19 deletion to be predictive for T790M evolution which was not the case in our study. Previous studies have indicated a longer duration of EGFR-TKI therapy to be predictive of T790M evolution.[14] In a study by Kawamura *et al*., patients with postsurgery recurrence and total duration of first-line EGFR-TKI treatment more than 1 year significantly predicted for T790M mutation.[15] However, this was not a significant association in our study, but there was a trend toward T790M positivity, when the prior TKI therapy duration was between 12 and 24 months (63.4 vs. 42.9%, *P* = 0.052).

At progression, the biopsy was feasible in 77/90 (85%) patients. In a minority who declined a biopsy or in whom a biopsy was not technically feasible, liquid biopsy was utilized to determine T790M mutation. Although the guidelines recommend liquid biopsy followed by tissue for detection of T790M at progression, we prefer tissue rather than plasma due to logistic convenience and being cost-effective at our institute. Since ARMS-PCR for T790M on tissue is done in house, the results could be obtained within 3–4 working days which is shorter and easier than shipping sample for CTDNA

Table 4: Indian data showing the prevalence of T790M in epidermal growth factor receptor tyrosine kinase inhibitors pretreated driver mutation positive advanced non-small lung cancer

Variable	Zanwar *et al.*[22]	Babu Koyyala *et al.*[21]	Present cohort
Number of patients evaluable for T790M	42	31	90
Tissue rebiopsy rate	114/148 (77)	10/31 (32.2)	77/90 (85)
T790M positivity rate	12/42 (28.6)	17/34 (54.8)	47/90 (52.2)
Tissue	12/42 (28.6)	7/10 (70)	39/77 (50.6)
CTDNA	NR	11/24 (45.8)	9/17 (52.9)
PFS on first-line EGFR TKI (range)	NR	9.3 months (1.5-43)	12.35 months (2.1-38.2)
PFS on osimertinib	NR	NR	12.45 months (SD 1.03)
Clinic response with osimertinib (%)			
Radiological	7/12 (55)[23]	NR	30/46 (65.2)
Clinical benefit	9/12 (75)[23]		39/46 (84.7)

NR – Not reported; SD – Standard deviation; PFS – Progression-free survival; EGFR – Epidermal growth factor receptor; TKI – Tyrosine kinase inhibitor; CTDNA – circulating tumor DNA

analysis to an external laboratory. Moreover, CTDNA can miss up to 30% of T790M mutations mandating the need for a tissue biopsy.[19] The other advantages for tissue sampling include identifying phenotype changes and ability to test for other driver mutations. Two of our 90 patients had small cell transformation.

We believe that the reason for our high success with biopsy was because of close clinical and radiologic monitoring of patients. Although guidelines do not recommend routine radiologic monitoring, we suggest periodic imaging especially because highly effective therapy is available for patients with T790M mutation. There are instances where major progressions which can be minimally symptomatic are missed by just clinical monitoring. This can lead to rapid clinical deterioration and hence the window for biopsy and subsequent therapy being missed. Deterioration in PS can also mean that they are not candidates for chemotherapy.

The ORR (65.21%) and median PFS (12.45 months) with osimertinib were consistent with that of previously reported in the literature.[16-18,20] The incidence of T790M mutation in our study was consistent with that reported in the literature both in Caucasians and Asians.[12-14,21] The Indian data with osimertinib usage are sparse; ours is the only study that had systematically analyzed the clinical outcomes with osimertinib in EGFR-TKI pretreated driver mutation-positive advanced NSCLC [Table 4]. The only factor associated significantly with better PFS on osimertinib in subsequent therapy was the presence of a complete response to the first-line oral TKI therapy. Patients who received osimertinib (T790M positive) had a longer PFS compared to those who received chemotherapy (T790M negative) for subsequent therapy, reiterating the importance of testing for T790M mutation at progression. Osimertinib was well tolerated with hardly any Grade 3 or 4 adverse events and no therapy discontinuations related to toxicities.

The strength of the study is prospective study design, high biopsy rate, and almost everyone with T790M positive received osimertinib. The drawbacks are heterogeneity in preferred agent in the first-line therapy and short follow-up period. The clinical correlates identified in this observational study for T790M evolution was unique and required validation in further studies.

Conclusions

In our prospective cohort, half of all patients had a T790M mutation at progression on the first-line EGFR TKI. Tissue biopsy is feasible in majority of patients. The clinical outcomes with osimertinib were consistent with those reported.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, *et al.* Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004;350:2129-39.
2. Kwak EL, Bang YJ, Camidge DR, Shaw AT, Solomon B, Maki RG, *et al.* Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med 2010;363:1693-703.
3. Yang JC, Sequist LV, Geater SL, Tsai CM, Mok TS, Schuler M, *et al.* Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: A combined post-hoc analysis of LUX-lung 2, LUX-lung 3, and LUX-lung 6. Lancet Oncol 2015;16:830-8.
4. Ramalingam SS, Jänne PA, Mok T, O'Byrne K, Boyer MJ, Von Pawel J, *et al.* Dacomitinib versus erlotinib in patients with advanced-stage, previously treated non-small-cell lung cancer (ARCHER 1009): A randomised, double-blind, phase 3 trial. Lancet Oncol 2014;15:1369-78.
5. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, *et al.* Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): A multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13:239-46.

6. Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, *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. Han JY, Park K, Kim SW, Lee DH, Kim HY, Kim HT, *et al.* First-SIGNAL: First-line single-agent iressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung. J Clin Oncol 2012;30:1122-8.
8. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, *et al.* Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010;362:2380-8.
9. Kobayashi S, Boggon TJ, Dayaram T, Jänne PA, Kocher O, Meyerson M, *et al.* EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. N Engl J Med 2005;352:786-92.
10. Yun CH, Mengwasser KE, Toms AV, Woo MS, Greulich H, Wong KK, *et al.* The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP. Proc Natl Acad Sci U S A 2008;105:2070-5.
11. Pao W, Miller VA, Politi KA, Riely GJ, Somwar R, Zakowski MF, *et al.* Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. PLoS Med 2005;2:e73.
12. Kosaka T, Yatabe Y, Endoh H, Yoshida K, Hida T, Tsuboi M, *et al.* Analysis of epidermal growth factor receptor gene mutation in patients with non-small cell lung cancer and acquired resistance to gefitinib. Clin Cancer Res 2006;12:5764-9.
13. Yu HA, Arcila ME, Rekhtman N, Sima CS, Zakowski MF, Pao W, *et al.* Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. Clin Cancer Res 2013;19:2240-7.
14. Joo JW, Hong MH, Shim HS. Clinical characteristics of T790M-positive lung adenocarcinoma after resistance to epidermal growth factor receptor-tyrosine kinase inhibitors with an emphasis on brain metastasis and survival. Lung Cancer 2018;121:12-7.
15. Kawamura T, Kenmotsu H, Omori S, Nakashima K, Wakuda K, Ono A, *et al.* Clinical factors predicting detection of T790M mutation in rebiopsy for EGFR-mutant non-small-cell lung cancer. Clin Lung Cancer 2018;19:e247-52.
16. Jänne PA, Yang JC, Kim DW, Planchard D, Ohe Y, Ramalingam SS, *et al.* AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. N Engl J Med 2015;372:1689-99.
17. Mok TS, Wu YL, Ahn MJ, Garassino MC, Kim HR, Ramalingam SS, *et al.* Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. N Engl J Med 2017;376:629-40.
18. Akamatsu H, Katakami N, Okamoto I, Kato T, Kim YH, Imamura F, *et al.* Osimertinib in Japanese patients with EGFR T790M mutation-positive advanced non-small-cell lung cancer: AURA3 trial. Cancer Sci 2018;109:1930-8.
19. Passiglia F, Rizzo S, Di Maio M, Galvano A, Badalamenti G, Listì A, *et al.* The diagnostic accuracy of circulating tumor DNA for the detection of EGFR-T790M mutation in NSCLC: A systematic review and meta-analysis. Sci Rep 2018;8:13379.
20. Goss G, Tsai CM, Shepherd FA, Bazhenova L, Lee JS, Chang GC, *et al.* Osimertinib for pretreated EGFR Thr790Met-positive advanced non-small-cell lung cancer (AURA2): A multicentre, open-label, single-arm, phase 2 study. Lancet Oncol 2016;17:1643-52.
21. Babu Koyyala VP, Batra U, Jain P, Sharma M, Goyal P, Medisetty P, *et al.* Frequency of T790M mutations after progression on epidermal growth factor receptor tyrosine kinase inhibitor in metastatic non-small cell lung cancer in Indian patients: Real-time data from tertiary cancer hospital. Lung India 2018;35:390-4.
22. Zanwar S, Noronha V, Joshi A, Patil VM, Chougule A, Kumar R, *et al.* Repeat biopsy in epidermal growth factor receptor mutation-positive nonsmall cell lung cancer: Feasibility, limitations, and clinical utility in Indian patients. Indian J Cancer 2017;54:280-4.
23. Noronha V, Majumdar S, Joshi A, Patil V, Trivedi V, Chougule A, *et al.* Osimertinib in Indian patients with T790M-positive advanced nonsmall cell lung cancer. South Asian J Cancer 2017;6:143.