Clinical implications of plasma EGFR T790M and ctDNA shedding across metastatic sites in plasma- or tissue-confirmed EGFR-mutant non-small cell lung cancer treated with lazertinib: a prospective multicenter cohort study

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Background: Third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors improve outcomes in EGFR T790M-positive non-small cell lung cancer (NSCLC), but the prognostic value of plasma-detected T790M remains uncertain. We evaluated the clinical significance of baseline plasma T790M in patients treated with lazertinib, accounting for metastatic distribution and coexisting genomic alterations.

Methods: In this prospective multicenter cohort, we analyzed 117 patients with EGFR-mutant NSCLC who received lazertinib after T790M confirmation in tissue or plasma. Plasma EGFR mutations were profiled using next-generation sequencing before treatment. Progression-free survival (PFS) and overall survival (OS) were compared by plasma T790M status, metastatic sites, and co-alterations.

Results: Of 117 patients, 92 were plasma T790M-positive and 25 were plasma T790M-negative. Plasma T790M positivity was associated with shorter PFS (10.0 *vs.* 23.0 months, P=0.03) and OS (20.0 months *vs.* not reached, P=0.006). All patients with liver or adrenal metastases were plasma T790M-positive, and involvement of either site predicted poorer outcomes than in patients without these metastases. Bone metastasis also portended a worse prognosis, irrespective of plasma T790M status. Among co-alterations,

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EGFR C797S or MYC alterations correlated with shorter PFS.

Conclusions: Baseline plasma T790M, interpreted alongside metastatic distribution, provided prognostic information in EGFR-mutant NSCLC treated with lazertinib. Liver and adrenal metastases occurred exclusively in plasma T790M-positive patients and were associated with markedly worse outcomes, consistent with a ctDNA-shedding phenotype. Bone metastasis was an adverse prognostic factor independent of plasma T790M, underscoring the combined prognostic impact of molecular and metastatic features.

Keywords: Non-small cell lung cancer (NSCLC); plasma epidermal growth factor receptor T790M (plasma EGFR T790M); metastatic distribution; prognosis; lazertinib

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Introduction

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have markedly improved outcomes in patients with advanced non-small cell lung cancer (NSCLC) harboring sensitizing EGFR mutations (1,2). While third-generation TKIs such as osimertinib are now established as the preferred first-line therapy in the United States and Europe, first-generation TKIs (e.g., gefitinib, afatinib) remain widely used as initial treatment in many Asian, Latin American, and other resource-constrained regions, largely due to local guidelines and cost constraints. In settings where first-generation TKIs continue to serve as frontline therapy, acquired resistance is inevitable, with approximately half of cases attributable to the secondary EGFR T790M mutation. Third-generation EGFR-TKIs, including osimertinib and lazertinib, constitute the current standard of care for T790M-mediated resistance (3,4). Third-generation EGFR-TKIs, including osimertinib and lazertinib, are standard therapies for T790M-mediated resistance (5,6).

Plasma-based liquid biopsy enables noninvasive detection of EGFR mutations and real-time monitoring of tumor evolution (7). Although plasma T790M testing guides treatment selection, its biological and prognostic relevance remains uncertain, with prior studies reporting conflicting results. Several reports associated plasma T790M positivity with aggressive disease and poorer outcomes (8,9), whereas others showed comparable or even favorable outcomes under third-generation EGFR-TKI therapy (10,11). For example, a pilot study of patients with T790M-positive NSCLC treated with osimertinib found worse outcomes in plasma T790M-positive (pT790M+) cases than in those without or with low-level plasma mutations (8). Zheng *et al.* similarly reported inferior overall survival (OS) among patients with T790M-positive circulating tumor DNA (ctDNA) compared with those without detectable plasma T790M (9). Conversely, a recent retrospective analysis of second-line osimertinib associated higher plasma T790M

Highlight box

Key findings

- Baseline plasma epidermal growth factor receptor (EGFR) T790M positivity was associated with significantly shorter progression-free survival and overall survival in patients with EGFR-mutant non-small cell lung cancer (NSCLC) treated with lazertinib.
- Liver or adrenal metastases occurred exclusively in plasma T790M-positive patients and were associated with markedly worse outcomes.
- Bone metastasis was an adverse prognostic factor independent of plasma T790M status.

What is known and what is new?

- Third-generation EGFR tyrosine kinase inhibitors improve outcomes in T790M-positive EGFR-mutant NSCLC; however, the prognostic significance of plasma-detected T790M remains unclear.
- This study demonstrates that baseline plasma T790M, when interpreted in conjunction with metastatic distribution, provides clinically meaningful prognostic information in lazertinib-treated patients. In particular, liver and adrenal metastases reflect a circulating tumor DNA-shedding phenotype closely linked to plasma T790M positivity and poor survival.

What is the implication, and what should change now?

- Plasma T790M should be regarded not only as a resistance marker but also as a surrogate of tumor burden and biological aggressiveness.
- Integrating plasma T790M status with metastatic patterns—especially liver, adrenal, and bone involvement—and co-occurring genomic alterations may improve risk stratification and inform treatment planning in EGFR-mutant NSCLC patients receiving lazertinib.

mutation load with a superior disease control rate (10). In the phase 1 AURA study, pT790M+ predicted a higher objective response rate to osimertinib without a clear survival difference (11). These discrepancies leave the prognostic role of plasma-detected T790M unresolved.

Given the conflicting results, the prognostic relevance of plasma-detected T790M in patients treated with third-generation EGFR-TKIs remains to be elucidated, particularly in those receiving lazertinib. Although its clinical use is increasing, few data link plasma T790M status to outcomes or broader biology, including metastatic distribution and coexisting genomic alterations. We therefore evaluated whether baseline plasma T790M detection predicts prognosis in EGFR-mutant NSCLC treated with lazertinib and examined associations with metastatic distribution and plasma next-generation sequencing (NGS)-identified co-alterations. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2025-aw-1216/rc).

Methods

Study population and design

We conducted a prospective, multicenter cohort study at nine hospitals in South Korea—Asan Medical Center, Seoul and Eunpyung St. Mary's Hospital, Severance Hospital, Kyungpook National University Hospital, Chonnam National University Hwasun Hospital, Pusan National University Pusan and Yangsan Hospital, and Chungnam National University Hospital—from November 30, 2021 to June 30, 2024. Eligible adults (≥20 years) had histologically or cytologically confirmed advanced or metastatic NSCLC per the 8th edition American Joint Committee on Cancer/Union for International Cancer Control staging system. Inclusion required an EGFR T790M mutation confirmed by tissue or plasma testing using real-time polymerase chain reaction (PCR) or droplet digital PCR, according to each institution's available assay. Additional criteria were availability of plasma EGFR results; prior first- or second-generation EGFR-TKI therapy with planned initiation of lazertinib; an Eastern Cooperative Oncology Group performance status of 0–2 without deterioration within 2 weeks before enrollment; and written informed consent before any study-specific procedures. Exclusion criteria were prior exposure to third-generation EGFR-TKIs or concurrent/previous malignancies other than adequately treated non-melanoma skin cancers, cervical intraepithelial neoplasia, breast ductal carcinoma *in situ*, thyroid cancer, or cancers considered cured with at least 3 years of remission. All consecutive eligible patients were prospectively enrolled. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Institutional Review Board of Asan Medical Center (IRB No. 2021-1705) and approved by institutional review boards of all participating centers, which permitted use of patient data in accordance with local regulations. All patients provided written informed consent prior to participating in this study.

Blood sample collection and processing

Peripheral blood samples (10 mL) were obtained before starting lazertinib. All samples were processed within 2 hours of collection using the CD-OPR-2000 device and CD-LBx 1 cartridge to separate plasma from whole blood. The separated plasma was assigned a unique study-specific identification code to ensure anonymization and was subsequently stored in a deep freezer until analysis. Stored samples were periodically transferred to Klinoomics Inc. (Seoul, Republic of Korea) for NGS profiling.

Outcomes

The primary endpoint was progression-free survival (PFS) in EGFR-mutant NSCLC treated with lazertinib. We assessed the prognostic relevance of baseline plasma EGFR T790M status in relation to metastatic sites and plasma NGS-identified genomic co-alterations. The secondary endpoint was OS according to metastatic sites.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) and compared using the Student *t*-test. Categorical variables were compared using the Chi-squared test. Survival was estimated by the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazards regression examined associations between PFS and patient or tumor characteristics. Median times to events were reported with two-sided 95% confidence intervals (CIs). All P values were two-sided; statistical significance was set at $P<0.05$. Analyses were performed in R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics of the study cohort

A total of 117 patients with EGFR-mutant NSCLC who initiated lazertinib after confirmation of the T790M mutation in either tissue or plasma were included. Of these, 92 were pT790M+ and 25 were plasma T790M-negative (pT790M–). The mean age at lazertinib initiation was 63.6±10.1 years, and 32.5% were male. The proportion of never-smokers did not differ significantly between the plasma T790M-negative and -positive groups (84.0% *vs.* 67.4%; P=0.27). Most patients had adenocarcinoma (99.1%); one patient in the T790M-positive group had squamous cell carcinoma. EGFR mutations were confirmed by tissue in 67 patients (57.3%) and by plasma in 50 (42.7%) (*Table 1*).

Most patients received lazertinib as second-line therapy, and prior EGFR-TKI use was similar between groups, with gefitinib (49.6%) and afatinib (40.2%) most commonly administered. Baseline metastatic sites included bone (50.5%), pleura (51.4%), brain (37.6%), liver (13.8%), and adrenal gland (7.3%). The prevalence of brain, bone, and pleural metastases did not differ significantly between plasma T790M-positive and -negative patients. Notably, liver and adrenal metastases occurred only in pT790M+ group.

Clinical outcomes according to plasma EGFR T790M status

Patients with pT790M+ (n=92) had significantly shorter PFS than those without detectable plasma T790M (n=25) [median: 10.0 months (95% CI: 7.0–14.0) *vs.* 23.0 months (95% CI: 12.0–not reached); P=0.03]. Similarly, OS was inferior in the pT790M+ group [median: 20.0 months (95% CI: 14.0–not reached)] compared with the pT790M– group [median: not reached (95% CI: not reached–not reached); P=0.006] (*Figure 1*).

Clinical outcomes stratified by plasma EGFR T790M status and baseline metastasis sites

We further analyzed PFS and OS by plasma EGFR T790M status, stratified by baseline metastatic sites (*Figures 2,3*). All patients with liver metastasis were pT790M+ and had significantly shorter PFS than those without liver involvement. Median PFS was 3.0 months (95% CI: 2.0–17.0) in the pT790M+ group with liver metastasis, 12.0 months (95% CI: 9.0–16.0) in the pT790M+ group without liver metastasis (P=0.003), and 23.0 months (95% CI: 12.0–not reached) in the pT790M– group without liver metastasis (P<0.001; *Figure 2A*). OS followed a similar pattern: patients with both pT790M+ and liver metastasis had shorter OS than those without either factor [median OS =17.0 months (95% CI: 3.0–not reached) *vs.* 19.0 months (95% CI: 14.0–not reached); P=0.02; *Figure 3A*].

Similarly, all patients with adrenal metastasis were pT790M+ and had inferior PFS compared with those without adrenal involvement. Within the pT790M+ subgroup, adrenal metastasis was associated with a markedly shorter median PFS [6.5 months (95% CI: 2.0–not reached)] than in those without adrenal metastasis [11.0 months (95% CI: 7.0–15.0); P=0.001]. By contrast, pT790M– patients without adrenal involvement had a median PFS of 23.0 months (95% CI: 12.0–not reached) (overall P=0.007; *Figure 2B*). OS showed a similar pattern; among pT790M+ patients, those with adrenal metastasis had numerically shorter OS than those without [11.0 months (95% CI: 2.0–not reached) *vs.* 20.0 months (95% CI: 14.0–not reached); P=0.17]. The median OS was not reached in patients negative for plasma T790M and without adrenal metastasis, who had the most favorable outcomes (overall P=0.007; *Figure 3B*). Notably, bone metastasis was associated with shorter PFS regardless of plasma T790M status [median PFS =8.0 months (95% CI: 5.0–11.0) for T790M-positive patients with bone metastasis and 7.0 months (95% CI: 3.0–not reached) for T790M-negative patients with bone metastasis]. Conversely, among patients without bone metastasis, PFS differed markedly by plasma T790M status: 16.0 months (95% CI: 3.0–not reached) in the T790M-positive group *vs.* not reached (95% CI: 23.0–not reached) in the T790M-negative group (P<0.001; *Figure 2C*). For OS, among pT790M+ patients, those with bone metastasis had a significantly shorter median OS than those without bone involvement [11.0 months (95% CI: 8.0–21.0) *vs.* not reached (95% CI: 18.0–not reached); P=0.001] (*Figure 3C*).

For brain metastasis pT790M+ patients had similarly short median PFS regardless of brain involvement [11.0 months (95% CI: 7.0–19.0) and 10.0 months (95% CI: 7.0–15.0), respectively]. Among pT790M– patients, the median PFS was not reached for those with brain metastasis, and patients without brain involvement had the most favorable outcome, with a median PFS of 23.0 months (95% CI: 12.0–not reached). Overall, brain metastasis did not significantly affect PFS (overall P=0.16; *Figure 2D*). For OS, pT790M+ patients had poorer outcomes irrespective of

Table 1 Baseline characteristics at lazertinib initiation by plasma EGFR T790M status by NGS

Characteristics	Total (n=117)	T790M+ (n=92)	T790M– (n=25)	P value
Age (years)	63.6±10.1	63.2±10.3	65.4±9.5	0.32
Sex				0.77
Male	38 (32.5)	31 (33.7)	7 (28.0)	
Female	79 (67.5)	61 (66.3)	18 (72.0)	
Smoking status				0.27
Never smoker	83 (70.9)	62 (67.4)	21 (84.0)	
Former smoker	8 (6.8)	7 (7.6)	1 (4.0)	
Current smoker	26 (22.2)	23 (25.0)	3 (12.0)	
Histologic type				>0.99
Adenocarcinoma	116 (99.1)	91 (98.9)	25 (100.0)	
Squamous cell carcinoma	1 (0.9)	1 (1.1)	0 (0.0)	
EGFR mutation confirmation method				0.002
Tissue	67 (57.3)	45 (48.9)	22 (88.0)	
Plasma	50 (42.7)	47 (51.1)	3 (12.0)	
Lazertinib line of therapy				0.56
2	89 (76.1)	68 (73.9)	21 (84.0)	
3	12 (10.3)	10 (10.9)	2 (8.0)	
≥4	16 (13.7)	14 (15.2)	2 (8.0)	
Previous EGFR-TKI				
Gefitinib	58 (49.6)	42 (45.7)	16 (64.0)	0.16
Erlotinib	12 (10.3)	10 (10.9)	2 (8.0)	0.96
Afatinib	47 (40.2)	40 (43.5)	7 (28.0)	0.24
Dacomitinib	9 (7.7)	7 (7.6)	2 (8.0)	>0.99
Baseline metastatic sites[†]				
Brain	41 (37.6)	33 (38.8)	8 (33.3)	0.80
Bone	55 (50.5)	45 (52.9)	10 (41.7)	0.46
Liver	15 (13.8)	15 (17.6)	0 (0.0)	0.06
Adrenal gland	8 (7.3)	8 (9.4)	0 (0.0)	0.26
Pleura	56 (51.4)	42 (49.4)	14 (58.3)	0.59

Data are presented as mean ± standard deviation or n (%). [†], at lazertinib initiation. EGFR, epidermal growth factor receptor; NGS, next-generation sequencing; TKI, tyrosine kinase inhibitor.

brain involvement: 21.0 months (95% CI: 12.0–not reached) in those with brain metastasis *vs.* 17.0 months (95% CI: 13.0–28.0) in those without. Among pT790M– patients, the median OS was not reached in either subgroup, indicating more favorable long-term outcomes. Overall, OS differed significantly among the four groups (P=0.044; *Figure 3D*).

A comparable trend was observed with pleural metastasis. pT790M+ patients had shorter PFS regardless of pleural involvement [11.5 months (95% CI: 7.0–17.0) *vs.* 9.0 months (95% CI: 6.0–16.0)], whereas T790M-negative

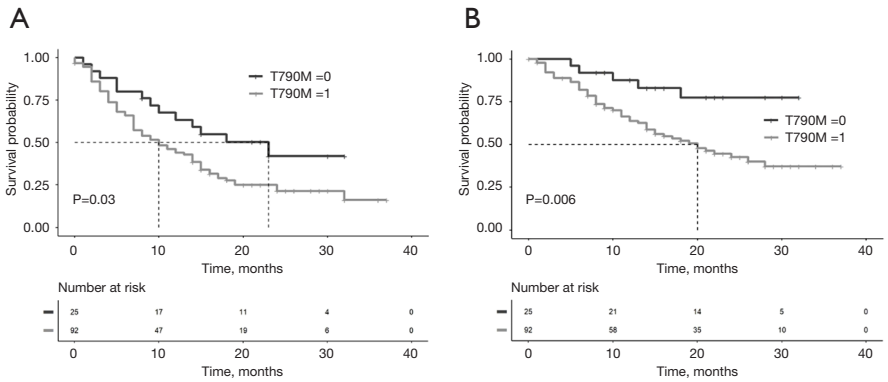

Figure 1 Kaplan-Meier curves for (A) progression-free survival and (B) overall survival by baseline plasma EGFR T790M status in patients treated with lazertinib. EGFR, epidermal growth factor receptor.

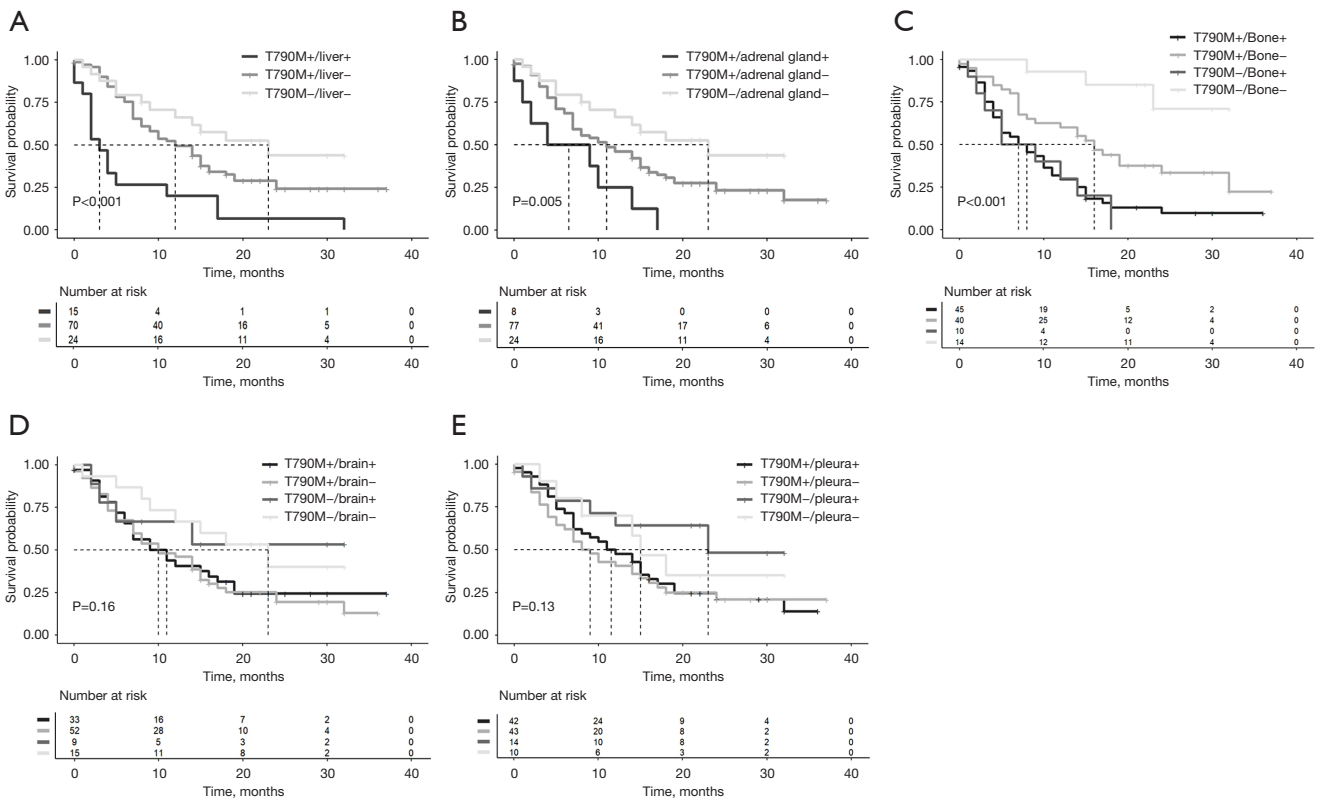

Figure 2 Kaplan-Meier curves for progression-free survival stratified by baseline plasma EGFR T790M status and metastatic sites in patients treated with lazertinib. (A) T790M and liver metastasis. (B) T790M and adrenal gland metastasis. (C) T790M and bone metastasis. (D) T790M and brain metastasis. (E) T790M and pleural metastasis. EGFR, epidermal growth factor receptor.

patients had longer PFS [23.0 months (95% CI: 12.0–not reached) and 15.0 months (95% CI: 8.0–not reached)]. For OS, the pattern was similar, with median OS of 24.0 months (95% CI: 14.0–not reached) and 17.0 months (95% CI: 10.0–not reached) in the T790M-positive subgroups, while the median OS was not reached in T790M-negative patients without pleural metastasis. Pleural involvement itself did not significantly affect PFS or OS (*Figure 3E*).

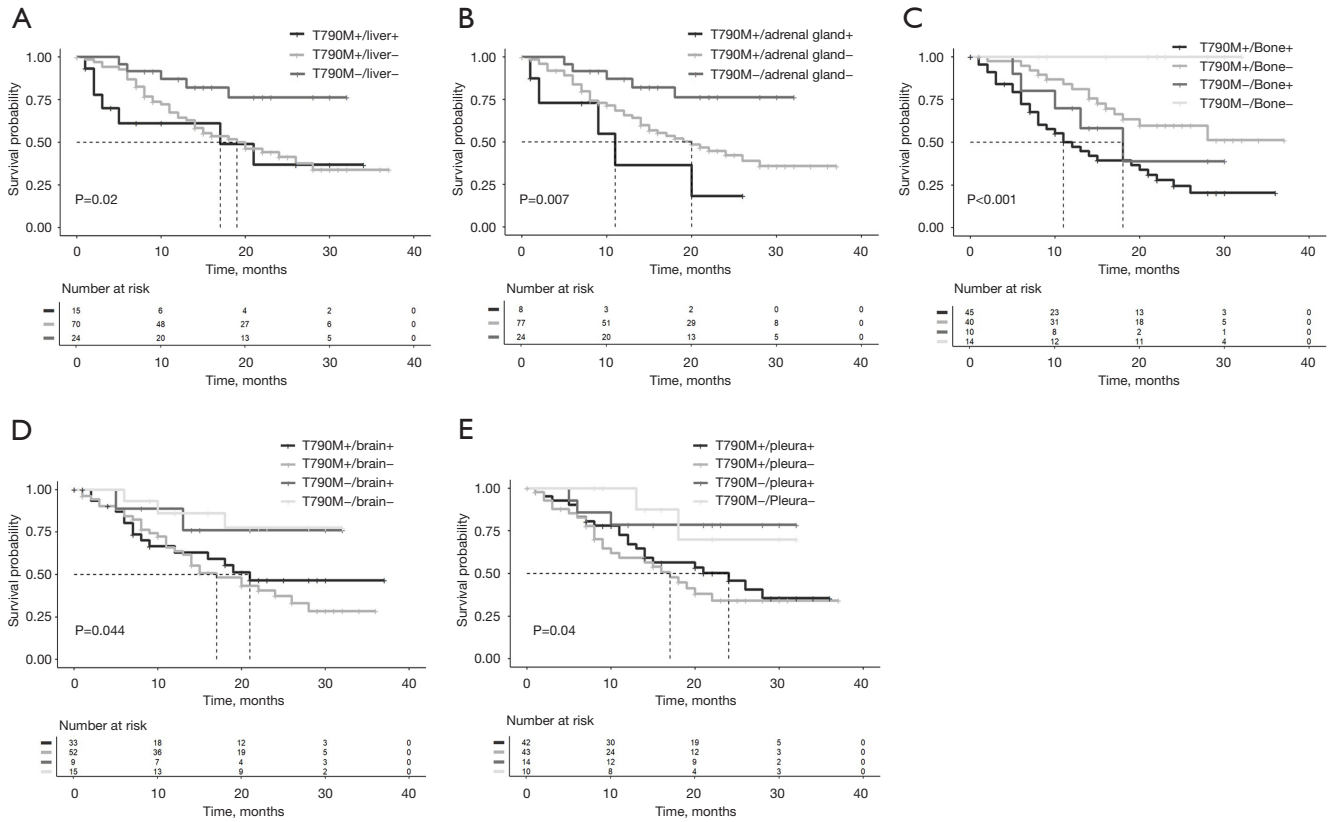

Figure 3 Kaplan-Meier curves for overall survival stratified by baseline plasma EGFR T790M status metastatic sites in patients treated with lazertinib. (A) T790M and liver metastasis. (B) T790M and adrenal gland metastasis. (C) T790M and bone metastasis. (D) T790M and brain metastasis. (E) T790M and pleural metastasis. EGFR, epidermal growth factor receptor.

Clinical outcomes stratified by plasma EGFR T790M status and genomic co-alterations

We next evaluated PFS by plasma EGFR T790M status stratified by genomic co-alterations identified by plasma NGS (*Figure 4*); detailed NGS profiles are summarized in Table S1.

At baseline, a subset of T790M-positive patients harbored EGFR C797S before initiation of lazertinib. Patients harboring both EGFR C797S and plasma T790M had significantly shorter PFS than those who were pT790M+ without EGFR C797S [median PFS =3.0 months (95% CI: 1.0–not reached) *vs.* 10.0 months (95% CI: 7.0–15.0); P=0.005]. In contrast, patients negative for both plasma T790M and EGFR C797S had a median PFS of 18.0 months (95% CI: 10.0–not reached) (overall P=0.005), supporting C797S as a clinically relevant resistance mechanism (*Figure 4C*). MYC alterations were uncommon and associated with numerically worse prognosis. Patients with both plasma T790M and MYC alterations had a median PFS of 5.0 months (95% CI: 3.0–not reached), compared with 10.0 months (95% CI: 7.0–15.0) in those with plasma T790M positivity without MYC alterations and 23.0 months (95% CI: 10.0–not reached) in patients negative for both alterations (overall P=0.06) (*Figure 4D*). By contrast, PI3CA and TP53 alterations were not significantly associated with PFS in this cohort (P=0.11 and P=0.13, respectively), although numerical trends toward poorer outcomes were observed in patients with these alterations (*Figure 4A*,*4B*).

Prognostic factors associated with PFS

In the univariable analysis, pT790M+ was significantly associated with shorter PFS [hazard ratio (HR) =3.368 (95% CI: 1.340–8.465); P=0.01]. Among baseline metastatic sites, bone metastasis was likewise a strong prognostic factor [HR =3.531 (95% CI: 1.927–6.468); P<0.001]. Other clinical

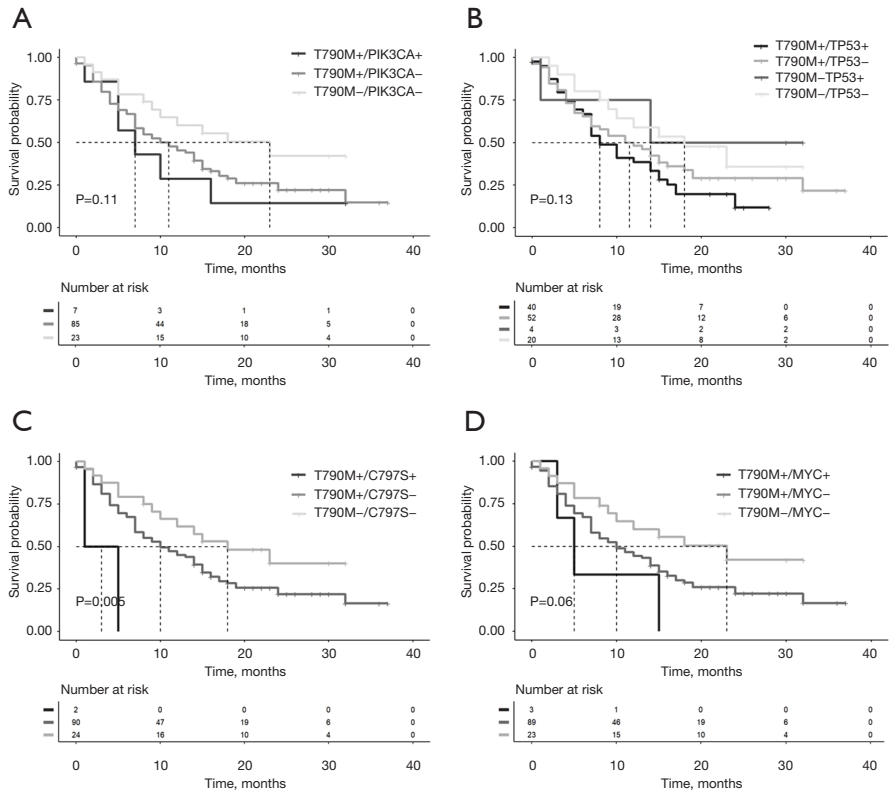

Figure 4 Kaplan-Meier curves for progression-free survival stratified by baseline plasma EGFR T790M status and co-mutations detected by plasma NGS in patients treated with lazertinib. (A) T790M and PIK3CA. (B) T790M and TP53. (C) T790M and C797S. (D) T790M and MYC. EGFR, epidermal growth factor receptor; NGS, next-generation sequencing.

characteristics—including age, sex, smoking history, line of lazertinib treatment, and the presence of liver, brain, pleural, or adrenal metastases—were not significantly associated with PFS. For co-mutations detected by plasma NGS, EGFR C797S [HR =2.892 (95% CI: 1.193–7.014); P=0.02] and MYC alterations [HR =3.264 (95% CI: 1.010–10.550); P=0.048] were associated with worse outcomes, whereas TP53 and PI3CA alterations were not statistically significant.

In a multivariable model adjusting for clinical variables, including treatment line and liver or adrenal metastases, plasma EGFR T790M positivity remained an independent predictor of shorter PFS [HR =2.911 (95% CI: 1.132–7.483); P=0.03]. Bone metastasis was likewise an independent prognostic factor [HR =3.585 (95% CI: 1.942–6.618); P<0.001] (*Table 2*).

Discussion

This study evaluated the prognostic implications of plasma EGFR T790M positivity in Asian patients with EGFR-mutant NSCLC treated with lazertinib, a third-generation EGFR-TKI. We examined how baseline plasma T790M status relates to metastatic disease distribution. In our cohort, pT790M+ was associated with shorter PFS and OS than pT90M–. When stratified by metastatic site, all patients with liver or adrenal metastases were pT790M+, and those with either site had the shortest median PFS *vs.* patients without these metastases, suggesting a link to systemic disease burden and ctDNA-shedding biology. Notably, bone metastasis portended worse outcomes regardless of plasma T790M status.

Several studies have reported that patients with pT790M+ had shorter OS and PFS than those without detectable plasma T790M, particularly after EGFR-TKI resistance (8,9,12). In a pilot study of 40 patients with T790M-positive NSCLC treated with osimertinib, pT790M+ was associated with poorer prognosis compared with patients without or with low-level plasma mutations, indicating that the absence or low abundance of plasma

Table 2 Cox regression analysis for progression-free survival in lazertinib-treated patients with EGFR-mutant non-small cell lung cancer

Characteristics	Unadjusted		Multivariable	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.018 (0.992–1.045)	0.18	–	–
Female	0.919 (0.524–1.612)	0.77	–	–
Ever-smoker	1.263 (0.933–1.710)	0.13	–	–
Line of lazertinib treatment				
2	Reference		Reference	
3	1.642 (0.728–3.700)	0.23	2.282 (0.934–5.574)	0.07
≥4	1.759 (0.892–3.467)	0.10	1.783 (0.874–3.639)	0.11
Plasma EGFR T790M	3.368 (1.340–8.465)	0.01	2.911 (1.132–7.483)	0.03
Baseline metastatic site				
Liver	1.657 (0.745–3.686)	0.22	–	–
Bone	3.531 (1.927–6.468)	<0.001	3.585 (1.942–6.618)	<0.001
Adrenal gland	2.359 (0.934–5.957)	0.07	1.913 (0.713–5.131)	0.02
Brain	0.920 (0.514–1.647)	0.78	–	–
Pleura	0.781 (0.450–1.354)	0.38	–	–
Co-mutations (plasma NGS)				
TP53 alteration	1.631 (0.948–2.806)	0.08	–	–
PI3CA alteration	2.057 (0.817–5.180)	0.13	–	–
EGFR C797S alteration	2.892 (1.193–7.014)	0.02	–	–
MYC alteration	3.264 (1.010–10.550)	0.048	–	–

CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; NGS, next-generation sequencing.

T790M was associated with better treatment response and survival outcomes (8). Likewise, Zheng *et al.* found that among 117 patients with acquired TKI resistance, those with T790M-positive ctDNA had significantly shorter OS than T790M-negative patients (median OS =26.9 months *vs.* not reached; P=0.0489) (9). Notably, in a retrospective study of 32 patients with T790M-mutant NSCLC, Agarwal *et al.* also reported that patients with plasma-detected T790M had shorter PFS and OS than those with tissue-detected T790M (13). Taken together, these findings indicate that detectable plasma T790M reflects a high tumor burden and aggressive disease biology, underscoring its potential role as a poor prognostic biomarker in patients with EGFR-mutant NSCLC.

Discrepancies across studies may reflect the dual role of T790M as both a predictive and prognostic marker (11,14,15). Regarding treatment response, pT790M+ has been associated with higher response or disease control rates with third-generation EGFR-TKIs (11,15). For example, in a retrospective study involving 216 patients enrolled in the escalation and expansion cohorts of the phase 1 AURA study of osimertinib for advanced EGFR-mutant NSCLC, patients with plasma T790M positivity demonstrated a higher objective response rate than those without (63% *vs.* 46%, P=0.01), whereas PFS did not differ significantly between groups (9.7 *vs.* 8.2 months; P=0.19) (11). Likewise, in a study of 108 patients with advanced or recurrent stage IV EGFR-mutant NSCLC, Wang *et al.* reported that patients with pT790M+ had a significantly longer median PFS than those without (13.1 *vs.* 10.8 months; P=0.01) (15). They suggested that T790M presence may indicate a relatively indolent, homogeneous resistance mechanism, whereas its absence may reflect a more aggressive, heterogeneous resistance pattern (15). Similarly, in a cohort

of 460 patients with disease progression after first-line EGFR-TKI therapy, Tung *et al.* reported no significant difference in post-progression OS between patients with pT790M+ and those without (17.4 months *vs.* not reached; P=0.60) (14). Such discrepancies may arise from the dual biological nature of pT790M+, which not only reflects a high tumor burden and ctDNA shedding but also indicates a relatively indolent resistance mechanism that remains targetable by EGFR-TKI therapy. Consequently, the prognostic implications of plasma T790M may vary by clinical setting and remain to be conclusively determined.

In addition to these biological factors, differences in treatment sequence should also be considered when interpreting survival patterns in T790M-positive disease. In our cohort, all patients received first-generation EGFR-TKIs as initial therapy and were subsequently treated with lazertinib upon disease progression. This real-world sequential approach differs from clinical settings where third-generation TKI is used as first-line therapy, and such variation in treatment practice may contribute to the inconsistent prognostic findings reported across studies. Accordingly, the prognostic implications of plasma T790M should be interpreted within the context of the underlying treatment strategy.

We aimed to clarify the prognostic significance of pT790M+ in Asian patients with EGFR-mutant NSCLC treated with lazertinib by integrating metastatic site distribution. Unlike prior studies that focused primarily on treatment response, our analysis emphasized the biological and clinical implications of baseline plasma T790M detection. pT790M+ was associated with shorter PFS and OS; notably, all patients with liver or adrenal metastases were pT790M+. Patients with these visceral metastases had particularly poor outcomes, suggesting that plasma-detectable T790M reflects a shedding phenotype characterized by high tumor burden and aggressive disease biology. Several studies have shown that cell-free DNA shedding is markedly increased in metastatic disease (16-19). In particular, vascular invasion and metastases are key predictors of ctDNA release (20), implying easier access to the circulation through disrupted vasculature. Consequently, metastases in highly vascular organs, such as the liver and adrenal glands, likely contribute to greater cell-free DNA burden and higher detectability of plasma T790M, which may be associated with more aggressive disease and poorer clinical outcomes. Indeed, several studies have reported that liver or adrenal metastases are associated with poor prognosis in patients with NSCLC (21-24). In a retrospective study of 409 patients with stage IV NSCLC, Ashour Badawy *et al.* showed that both liver and adrenal metastases were significantly associated with shorter OS (P<0.001 and P=0.01, respectively) (21). Similarly, in a retrospective cohort of 729 patients with metastatic NSCLC, Tamura *et al.* reported that liver and adrenal metastases independently predicted worse survival, with adjusted HRs of 1.55 (95% CI: 1.22–1.96) and 1.83 (95% CI: 1.47–2.28), respectively (P<0.001 for both) (22). In a large population-based analysis using the Surveillance, Epidemiology, and End Results (SEER) database, Yang *et al.* reported that among patients with NSCLC, liver metastasis conferred the highest disease-specific mortality (78.3%), followed by bone (73.2%), brain (72.7%), and lung (65.4%) metastases. The crude HR for liver metastasis was 1.391 (95% CI: 1.318–1.468), indicating the most adverse prognostic impact among metastatic sites (24). Collectively, these data support that pT790M+ represents an aggressive, high-shedding tumor biology associated with extensive systemic dissemination. Given these findings, this high-risk subgroup warrants a more detailed consideration of potential therapeutic strategies. First, upfront or early incorporation of combination regimens, such as third-generation EGFR-TKIs combined with platinum-pemetrexed chemotherapy, may provide deeper and more durable disease control in patients at high risk of early progression as recent trials have demonstrated that EGFR-TKI-chemotherapy combinations significantly improve PFS and delay the emergence of resistance compared with EGFR-TKI monotherapy. Second, because high-shedding tumors release measurable ctDNA, these patients may be suitable candidates for ctDNA-guided treatment escalation, enabling earlier therapeutic intervention upon detection of molecular progression rather than waiting for radiographic relapse. Third, targeted approaches aimed at common bypass pathways observed in aggressive disease, such as MET amplification or other oncogenic co-drivers, may be clinically relevant for this subgroup.

In our cohort, bone metastasis independently predicted shorter PFS, irrespective of plasma T790M status, and was a strong adverse prognostic factor. Evidence on the prognostic impact of bone metastasis in NSCLC is limited; however, several reports link bone involvement to poorer treatment response and worse outcomes (24-26). In Yang *et al.*, bone metastasis was associated with the second-worst disease-specific survival and remained independently linked to higher mortality after adjustment for age, sex, tumor size, and nodal status [crude HR =1.116 (95%

CI: 1.067–1.167); P<0.001] (24). Similarly, Landi *et al.* analyzed 1,959 patients with advanced NSCLC treated with nivolumab and found that bone metastasis independently predicted worse outcomes, including shorter PFS (3.0 *vs.* 4.0 months) and OS (7.4 *vs.* 15.3 months), and a higher risk of death (HR =1.50–1.78; both P<0.001) (25). A recent meta-analysis of 13 studies (n=3,681; 37.6% with bone metastasis) identified bone metastasis as a significant adverse prognostic factor among patients receiving immune checkpoint inhibitors (26). Specifically, bone metastasis conferred a 45% higher risk of death [HR =1.45 (95% CI: 1.30–1.62); P<0.001] and a 40% higher risk of progression [HR =1.40 (95% CI: 1.25–1.58); P<0.001] (26). The unfavorable prognosis associated with bone metastasis likely reflects the distinctive biology of the bone microenvironment (27). Bone tissue creates a niche enriched with cytokines, growth factors, and extracellular matrix proteins that promote tumor proliferation, angiogenesis, and immune evasion. Interactions between tumor cells and bone stromal components—osteoclasts, osteoblasts, and marrow-derived immune cells—establish a "vicious cycle" that amplifies osteolytic activity and tumor growth (27-29). Specifically, osteoclast activation and release of transforming growth factor-β and interleukin-6 have been implicated in tumor progression and therapeutic resistance (27,30). In addition, the hypoxic, immunosuppressive bone marrow milieu favors tumor cell survival and contributes to resistance to systemic therapies, including EGFR-TKIs and immune checkpoint inhibitors (31-33). This protective microenvironment functions as a non-genetic, tumor-extrinsic mechanism of resistance that can override the molecular characteristics reflected in circulating ctDNA, which may explain why bone metastasis remained an independent adverse prognostic factor irrespective of plasma T790M status in our cohort. Together, these microenvironment-driven mechanisms may underlie the strong adverse prognostic impact of bone metastasis observed in our study, underscoring its distinct role beyond the systemic tumor burden captured by plasma T790M detection.

Concurrent genomic alterations suggested heterogeneity within pT790M+ disease. Baseline EGFR C797S mutations before lazertinib were associated with shorter PFS, indicating preexisting on-target resistance that may limit lazertinib efficacy. Although few studies have examined the prognostic impact of concurrent EGFR C797S, Park *et al.* described a clinical case illustrating this alteration as a prototypical on-target resistance mechanism (34). EGFR C797S is among the most frequent resistance mechanisms to third-generation EGFR-TKIs, occurring in approximately 20–30% of resistant cases (35). Tumors acquiring EGFR C797S typically retain T790M, conferring cross-resistance to multiple EGFR inhibitors, including osimertinib and lazertinib (35). Meanwhile, MYC alterations were uncommon and not statistically significant, but carriers had numerically shorter PFS, consistent with prior reports (36,37). Overall, these findings indicate that the prognostic and predictive significance of plasma T790M is shaped by the genomic context, underscoring the need for integrated molecular profiling to refine therapeutic stratification in EGFR-mutant NSCLC.

Beyond genomic factors, evolving treatment practices further affect the interpretation of plasma T790M. Sequential treatment with first-generation EGFR-TKIs followed by a third-generation agent remains common in several Asian and resource-limited regions where access to upfront third-generation TKIs is constrained; thus, our cohort reflects a real-world practice pattern still relevant in these settings. However, treatment strategies are rapidly evolving. First-line third-generation TKIs have become the global standard of care, and combination regimens, such as osimertinib plus platinum-pemetrexed, are increasingly being adopted (38). With more intensive initial therapy, resistance mechanisms are expected to become more heterogeneous, and T790M alone may not sufficiently characterize post-TKI resistance biology. In this context, broader liquid biopsy markers, including quantitative EGFR mutation burden and comprehensive ctDNA profiling, may better reflect tumor burden, molecular evolution, and emerging resistance. These developments suggest that the clinical role of T790M testing will continue to evolve, transitioning from a single predictive biomarker to part of an integrated molecular strategy for guiding subsequent treatment decision-making.

This study has several limitations. First, the cohort consisted exclusively of Korean patients, which limits generalizability, particularly given known ethnic differences in EGFR mutation patterns, co-mutation profiles, and clinical outcomes. Therefore, validation in larger cohorts with broader ethnic representation will be essential to determine whether our findings are applicable across diverse populations. Second, the small sample size—especially within some metastatic subgroups—reduced statistical power and precision. Third, because only plasma-based NGS was performed without paired tissue sequencing, some genomic alterations may have been underestimated

or misclassified, particularly given the known variability in ctDNA shedding across patients and disease states. Incorporating matched tissue–plasma analyses in future studies will be important to improve the accuracy and completeness of genomic profiling. Fourth, heterogeneity in prior treatments and disease burden could have influenced both plasma T790M detectability and outcomes. Finally, OS data were immature for some patients, warranting validation in larger prospective cohorts with longer follow-up.

Conclusions

When considered with metastatic distribution, plasma EGFR T790M status provided meaningful prognostic information in patients with EGFR-mutant NSCLC treated with lazertinib. Liver and adrenal metastases occurred exclusively in pT790M+ patients and were associated with worse prognosis, suggesting a link to a ctDNA-shedding phenotype. Additionally, bone metastasis was an independent adverse prognostic factor irrespective of plasma T790M status.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Institutional Review Board of Asan Medical Center (IRB No. 2021-1705) and approved by institutional review boards of all participating centers, which permitted use of patient data in accordance with local regulations. All patients provided written informed consent prior to participating in this study.

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