ORIGINAL ARTICLE

Monitoring of Circulating Tumor DNA and Indication of De-Escalation Adjuvant Targeted Therapy for *EGFR*-Mutated NSCLC After Complete Resection

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ABSTRACT

Introduction: EGFR tyrosine kinase inhibitor (TKI) is the standard adjuvant treatment for patients with stages IB to IIIA *EGFR*-mutated NSCLC. Nevertheless, adapting this approach to include a molecular residual disease (MRD)-guided de-escalation strategy warrants further investigation.

Methods: From January 2019 to December 2022, 71 patients with stages I to III NSCLC and *EGFR* (exon 19 deletion or L858R) mutations were enrolled in this observational study. A total of 375 blood samples were analyzed using the MRD_Navigator assay. Among them, 27 patients suspended EGFR TKI treatment based on undetectable MRD and were thus included in the adaptive, de-escalation group.

Results: Overall, the sensitivity of longitudinal MRD was 86.2%. Only four patients (11.8%) recurred with longitudinal undetectable MRD, indicating a negative predictive value of 88.2%. Of the patients who had detectable MRD after surgery, nine subsequently received EGFR TKI treatment, with only one (11.1%) achieving persistent circulating tumor DNA clearance post–EGFR TKI. Furthermore, 22 patients with stages IB to III disease who had previously suspended their TKI treatment based on undetectable MRD were included in the adaptive group, with an average duration of TKI 3.9 (range: 0–35.0) months. The 2-year disease-free survival rate of these 22 patients was 80.2%, and the median was not reached. Five patients (n = 5 of 22, 22.7%) had disease recurrence during the period of drug cessation but were stable under EGFR TKI treatment until the latest follow-up. Two patients remained in complete remission.

Conclusions: Our initial findings underscore the potential of an adaptive, de-escalation approach to adjuvant EGFR TKIs based on circulating tumor DNA-MRD monitoring.

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Introduction

Long-term targeted therapy has become the standard treatment for patients with *EGFR*-mutated NSCLC after complete resection.[1–5] The milestone ADAURA study revealed the overwhelming efficacy of osimertinib in this context; the 4-year disease-free survival (DFS) rate reached 73% in the osimertinib group versus 38% in the placebo group[6] and the 5-year overall survival (OS) rate was 88% versus 78%.[7] In the updated analysis of the ADAURA study, molecular residual disease (MRD) detection revealed that 25% of patients (n = 28) in the osimertinib group experienced MRD or DFS events, most of which (n = 19 of 28, 68%) occurred post-adjuvant osimertinib. In addition, the 5-year OS rate difference between the groups was only 10%. This raises the question of whether long-term, fixed 3-year tyrosine kinase inhibitor (TKI) use is indeed the optimal strategy.

In recent years, MRD detection through ultra-deep sequencing of circulating tumor DNA (ctDNA) has revealed consistent clinical effectiveness. In our previous study,[8] we confirmed the value of ctDNA-MRD detection for monitoring in a cohort of 261 patients with NSCLC who underwent complete resection. Moreover, subgroup analysis revealed that patients with detectable MRD could benefit from adjuvant therapy, whereas patients with undetectable MRD cannot benefit. Similar results have also been observed in other studies.[9–12] To further explore MRD-guided adaptive therapy for lung cancer, we conducted a pilot study involving 60 patients with oligo-persistent NSCLC who had received EGFR TKI therapy and achieved complete remission after local consolidative therapy.[13] On the basis of undetectable MRD and normal carcinoma embryonic antigen levels, we ceased the TKI treatment. The median progression-free survival was 18.4 months and the median treatment break duration was 9.1 months. These data imply that MRD-guided adaptive strategy for noncontinuous TKI therapy has potential.

The eco-evolutionary dynamic theory of Gatenby et al.[14–16] describes the theoretical basis of the adaptive therapy strategy, which involves the use of repeated on–off treatment cycles. On the basis of Darwinian principles, adaptive therapy theoretically enables the tumor cells with a treatment-sensitive phenotype to have a competitive advantage over those with a resistant phenotype. In vivo studies have suggested that there is heterogeneity in the clonal fitness of EGFR TKI–sensitive phenotype tumor cells and EGFR TKI–resistant tumor cells.[17–20]

On the basis of these findings, we enrolled patients with stages I to III *EGFR*-mutated NSCLC after complete resection in this prospective study. We aimed to assess the efficiency of high-coverage ctDNA-MRD monitoring and explore the feasibility of adaptive, de-escalation EGFR TKI therapy guided by ctDNA-MRD.

Materials and Methods

Study Design and Samples

From January 2019 to December 2022, patients with pathologic stages I to III (American Joint Committee on Cancer eighth edition) and *EGFR* (exon 19 deletion [del] or L858R)-mutated NSCLC who underwent complete resection at Guangdong Provincial People's Hospital were screened. Patients with less than two ctDNA-MRD tests after surgery were excluded (Fig. 1*A*). Patient demographic characteristics, including age, sex, smoking history, performance status, histologic subtypes, and history of EGFR TKI treatment, were collected. The landmark time point was defined as the point of blood sample collection within 3 months after surgery, and the longitudinal time points were defined as every 3 to 6 months since landmark detection. All patients provided written informed consent, and the study was reviewed and approved by the Institutional Review Board of Guangdong Provincial People's Hospital (approval number 2018319H [R1]).

ctDNA-MRD Assay

The MRD assay (MRD_Navigator, Beijing GenePlus Technology Co., Ltd.) used in this trial has been reported previously.[8] For tumor tissue samples, a 1021 cancer-related–gene panel covering approximately 1.5 Mbp of the human genome was used for analysis. Peripheral blood samples were analyzed using a 338-gene panel that covers 550 Kbp of the human genome, specifically for lung cancer, colorectal cancer, and hepatocellular carcinoma. The annotated variants that met the following criteria were filtered out: (1) variants present in matched germline DNA, (2) variants occurring at a population frequency of more than 1% in ExAc (version 0.3.1) or the 1000 Genomes Project, (3) variants with positional depth less than 300×, and (4) background errors were further filtered by an in-house list of recurrent artifacts based on a background-estimated variant allele frequency distribution model, which was constructed by sequencing a set of plasma samples from approximately 500 healthy individuals.

Depending on whether the plasma variants were identified in the matched tumor tissue, the resulting plasma variants were classified as tissue or nontissue

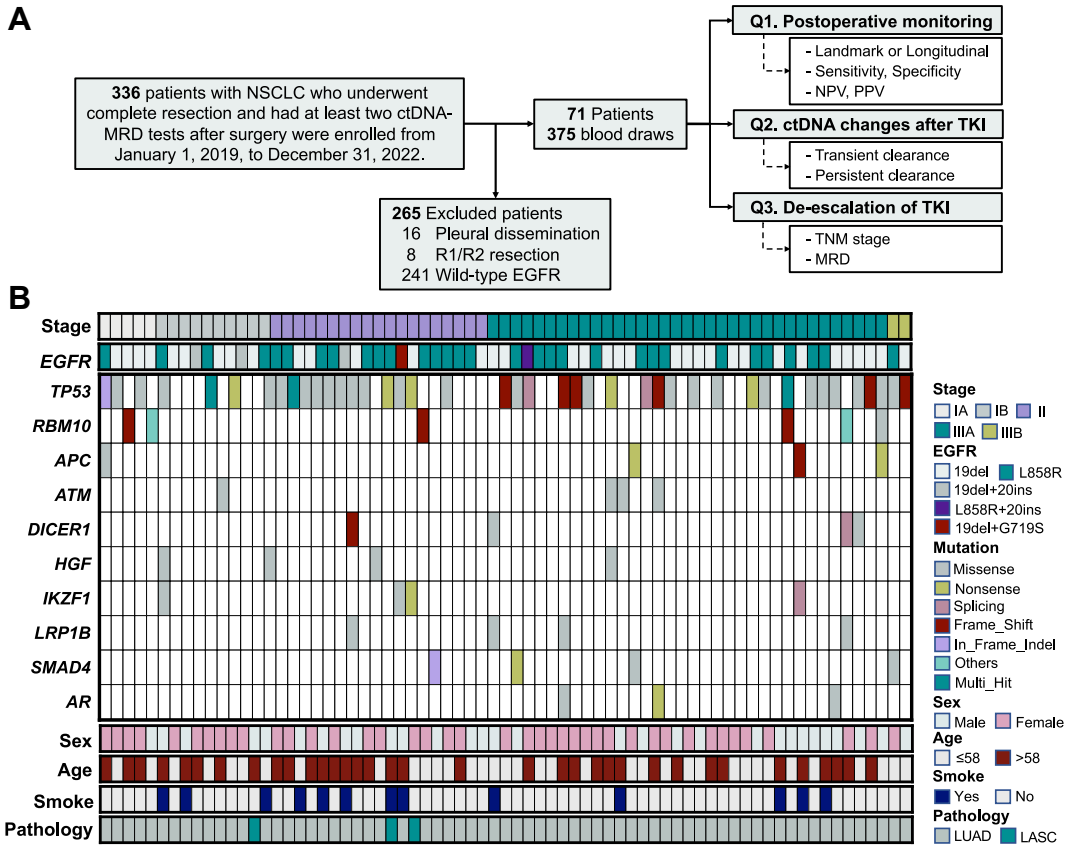

Figure 1. Study flow chart and baseline characteristics. (*A*) Study flow chart. Patients with stages I to III (AJCC eighth version), *EGFR* (exon 19 del or L858R)-mutated NSCLC were enrolled. (*B*) Heat map plot of baseline characteristics of each patient. AJCC, American Joint Committee on Cancer; ctDNA, circulating tumor DNA; del, deletion; ins, insertion; LUAD, lung adenocarcinoma; LASC, lung adenosquamous cell carcinoma; MRD, molecular residual disease; NPV, negative predictive value; PPV, positive predictive value; TKI, tyrosine kinase inhibitor.

derived. The tissue-derived variants exhibited considerable differences in background errors and were considered reliable. When the following conditions were met, tissue-derived variants were considered to be true somatic mutations: for tissue-specific driver mutations, more than or equal to two high-quality support reads; and for other tissue-specific nonrecurrent mutations, more than or equal to four high-quality support reads. For nontissue-derived variants, the reliable somatic mutations were identified if they met the following stringent conditions: (1) for hotspot mutations, more than or equal to four high-quality support reads; (2) for nonhotspots, more than or equal to 8 high-quality support reads; and (3) clonal hematopoiesis was filtered by both backlist and deep sequencing results of paired white blood cell genomic DNA. A plasma sample positive for ctDNA was defined as having at least one detected variant.

De-Escalation of EGFR TKI

The adaptive, de-escalation EGFR TKI group included patients with stages IB to III disease who received adaptive EGFR TKI treatment guided by dynamic MRD monitoring after surgery. Patients eligible for cessation of EGFR TKI therapy met the following criteria: no radiologically suspicious lesions and undetectable MRD. Two categories of patients were included: those who were exempted from TKI treatment postoperatively and those who ceased TKI treatment after a period of use on undetectable MRD. This de-escalation strategy was fully disclosed to patients, with particular emphasis on the potential risk of disease recurrence during the treatment suspension period.

After the discontinuation of TKI treatment, patients underwent regular imaging and MRD monitoring. Reinitiating EGFR TKI therapy was required on detecting an MRD signal or suspicious lesions on images. Nevertheless, given the observational nature of the study, the timing of EGFR TKI initiation could not be standardized across all patients. When initial detectable MRD signals occur with no suspicious lesions on images, patients are advised to undergo follow-up MRD and imaging assessments. If two consecutive MRD tests yield positive results, then initiation of EGFR TKI therapy is warranted.

Statistical Analysis

The data cutoff date for survival analyses was March 31, 2024. DFS was defined as the date from complete surgical resection to the date of recurrence or death from any cause, whichever occurred first. The Kaplan–Meier method was used to describe the survival outcomes. A log-rank test was used to determine hazard ratios. Median follow-up was estimated using the reverse Kaplan–Meier method. Mann–Whitney *U* test or chi-square test was used to compare the differences between groups. For calculating positive predictive value (PPV) and negative predictive value (NPV) of landmark MRD, at least three months of follow-up is required after the landmark assessment. Similarly, longitudinal MRD NPV necessitates three months of follow-up after the last negative result, whereas PPV requires three months of follow-up after the first positive result. Sensitivity for MRD is the proportion of patients who recur and have a detectable MRD result before recurrence. Specificity for MRD is the proportion of patients who do not recur and have longitudinally undetectable MRD. Lead time was calculated for recurrent patients with detectable ctDNA and is defined as the duration from the first ctDNA-positive result to the occurrence of recurrence. All *p* values were based on two-sided testing with statistically significant differences at *p* less than or equal to 0.05. Statistical analyses were performed using R software (version 4.3.0) and GraphPad PRISM 8.0. (GraphPad Software).

Results

Demographics and Sample Description

A total of 71 patients were enrolled in this study (Fig. 1*A*). The median age of the patients was 58 (27–82) years, and 95.8% had lung adenocarcinoma. Furthermore, 5, 10, 19, 35, and 2 patients had stage IA, IB, II, IIIA, and IIIB disease, respectively. *EGFR* exon 19 del were observed in 39 patients (54.9%), and the L858R mutation was present in 32 patients (45.1%). In addition, three patients had *EGFR* 19 del and *EGFR* exon 20 insertions, one had *EGFR* L858R and *EGFR* exon 20 insertions, and one had *EGFR* 19 del and *EGFR* G719S (Fig. 1*B*).

A total of 31 recurrent cases (43.7%) were recorded in the median follow-up period of 41.0 months. The median DFS was 37.8 months (Supplementary Fig. 1*A*). The 2-year DFS rate for patients with stages I, II, and III disease was 86.2%, 62.0%, and 65.3%, respectively (Supplementary Fig. 1*B*).

ctDNA-MRD Detection and Disease Recurrence

At the landmark time point, owing to nine patients starting MRD monitoring more than 3 months after surgery, 62 patients were included in the landmark analysis, of whom 12 (19.4%) had detectable MRD, with a sensitivity of 38.5% (95% confidence interval [CI]: 19.8%–57.2%; Fig. 2*A*). By integrating the longitudinal time points, the sensitivity increased to 86.2% (95% CI: 73.7%–98.8%). The PPV and NPV of longitudinal MRD were 71.4% (95% CI: 56.5%–86.4%) and 88.2% (95% CI: 77.4%–99.1%), respectively (Fig. 2*B*). Only four patients (11.8%) had recurrence with longitudinal undetectable MRD, and two of them presented brain-only metastases. The median ctDNA lead time was 12.9 (95% CI: 9.7–16.2) months (Table 1). Considering that *TP53* is the most common co-mutation in *EGFR*-mutated NSCLC, we conducted a further analysis and found that both landmark and longitudinal MRD monitoring had comparable efficacy in detecting recurrence, regardless of

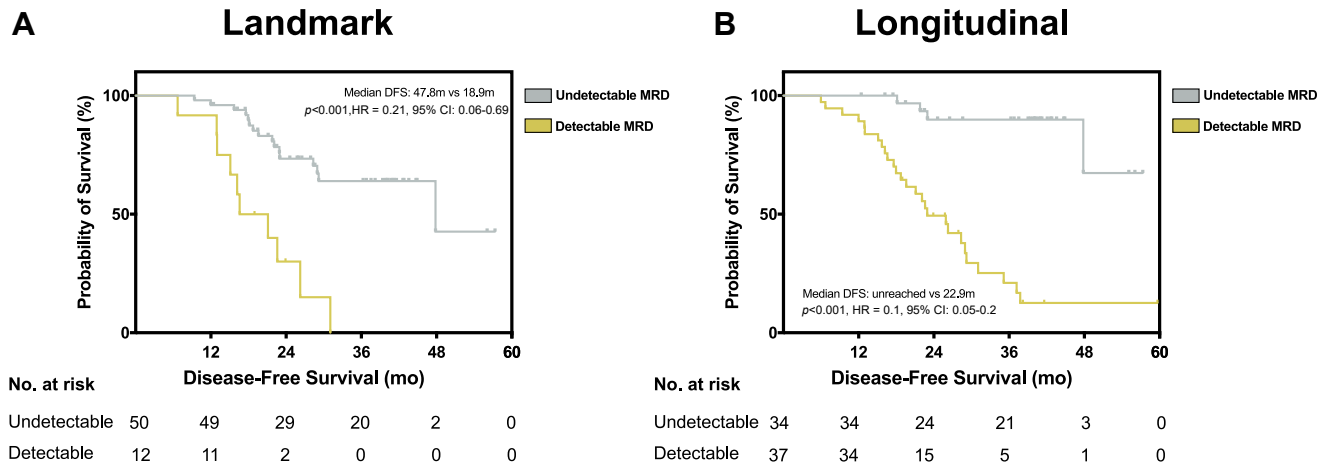

Figure 2. ctDNA-MRD monitoring after surgery. (*A*) Kaplan-Meier analysis of DFS stratified by landmark MRD status: detectable (n = 12) versus undetectable (n = 50). (*B*) Kaplan-Meier analysis of DFS stratified by longitudinal MRD status: detectable (n = 37) versus undetectable (n = 34). CI, confidence interval; ctDNA, circulating tumor DNA; DFS, disease-free survival; HR, hazard ratio; MRD, molecular residual disease.

Table 1. Performance Parameters of ctDNA-MRD Detection in Different Groups

Factors	Overall (N = 71, %)	Stage (%)			*p* Value
		I	II	III	
Landmark					
Detectable rate	19.4	15.4	16.7	22.6	0.839
Sensitivity	38.5	33.3	25.0	46.7	0.723
Specificity	94.4	90.0	90.0	100.0	0.302
PPV	83.3	50.0	66.7	100.0	0.152
NPV	68.0	81.8	60.0	66.7	0.538
Longitudinal					
Detectable rate	50.7	33.3	44.4	61.1	0.174
Sensitivity	86.2	50.0	85.7	94.4	0.075
Specificity	75.6	75.0	81.8	72.2	0.901
PPV	71.4	40.0	75.0	77.3	0.267
NPV	88.2	80.0	90.0	92.9	0.803
Median lead time (mo)	12.9	13.0	5.1	15.6	0.060

ctDNA, circulating tumor DNA; MRD, molecular residual disease; NPV, negative predictive value; PPV, positive predictive value.

the presence or absence of concurrent *TP53* mutations (Supplementary Fig. 2*A*–*C*). Thus, these data confirmed the high efficacy of ctDNA-MRD monitoring for patients with *EGFR*-mutated NSCLC after surgery.

ctDNA Clearance After EGFR TKI Treatment

Among those 49 patients who received adjuvant EGFR TKI treatment, nine had landmark detectable MRD. The median DFS was 21.1 months (95% CI: 15.1 to Inf months). Notably, only one patient (n = one of nine, 11.1%) achieved persistent ctDNA clearance after targeted therapy and remained recurrence free at the latest follow-up (Fig. 3*A*). Of the remaining patients, 33.3% continued to have detectable MRD and 44.4% had transient ctDNA clearance; one other patient (11.1%) developed disease recurrence shortly thereafter (Fig. 3*B*–*D*).

Feasibility of De-Escalation of EGFR TKI Treatment

We investigated the feasibility and safety of the adaptive EGFR TKI strategy. In this cohort, 22 patients with stages IB to III disease had previously suspended their TKI treatment based on undetectable MRD. Among these patients, 17 (77.3%) did not initiate EGFR TKI therapy postsurgery (Fig. 4, scenario 1) and five underwent TKI therapy for a period postsurgery and subsequently discontinued it according to undetectable MRD (scenario 2). The detailed baseline characteristics are described in Table 2. The average duration of TKI therapy for these 22 patients was only 3.9 (0–35.0) months. The 2-year DFS rate was 80.2%, and the median DFS was not reached. As a reference, 41 concurrent patients in this cohort, which consisted of 12 patients with stage II disease and 29 with stage III disease, received conventional EGFR TKI treatment. The mean duration of TKI was 20.6 (range: 0–41.6) months (Supplementary Fig. 3*A*). The 2-year DFS rate was 57.1%, and the median DFS was 29.0 months (95% CI: 22.6 to Inf months). On initial analysis, no significant survival disadvantage was observed in the de-escalation group (Supplementary Fig. 3*B* and *C*).

In scenario 1, most patients (n = nine of 17) maintained undetectable MRD and exhibited no radiologic evidence of recurrence, and thus continued TKI suspension. Six other patients developed detectable MRD and two experienced disease recurrence despite having undetectable MRD. Among the six patients with detectable MRD, three experienced simultaneous recurrence, one initiated TKI therapy, and the remaining two continued their TKI suspension as their subsequent MRD test results were negative (Fig. 4). In scenario 2, the median of previous TKI therapy was 7.3 (4.0–35.0) months. Three patients (n = three of five, 60%) developed detectable MRD in the subsequent period. Of these, two patients initiated TKI therapy, and both remained disease free (Fig. 4). Nevertheless, all patients with disease recurrence in the adaptive cohort were stable in response to EGFR TKI treatment until the latest follow-up, and two patients remained in complete remission.

The aforementioned data indicate that conducting prospective interventional de-escalation TKI clinical trials in the future will require rigorous MRD monitoring and crucial patient communication for informed consent.

Discussion

Our study supports postoperative monitoring of ctDNA-MRD in patients with *EGFR*-mutated NSCLC. The NPV of longitudinal MRD reached 88.2%. The overall sensitivity was 86.2%, with a median lead time of 12.9

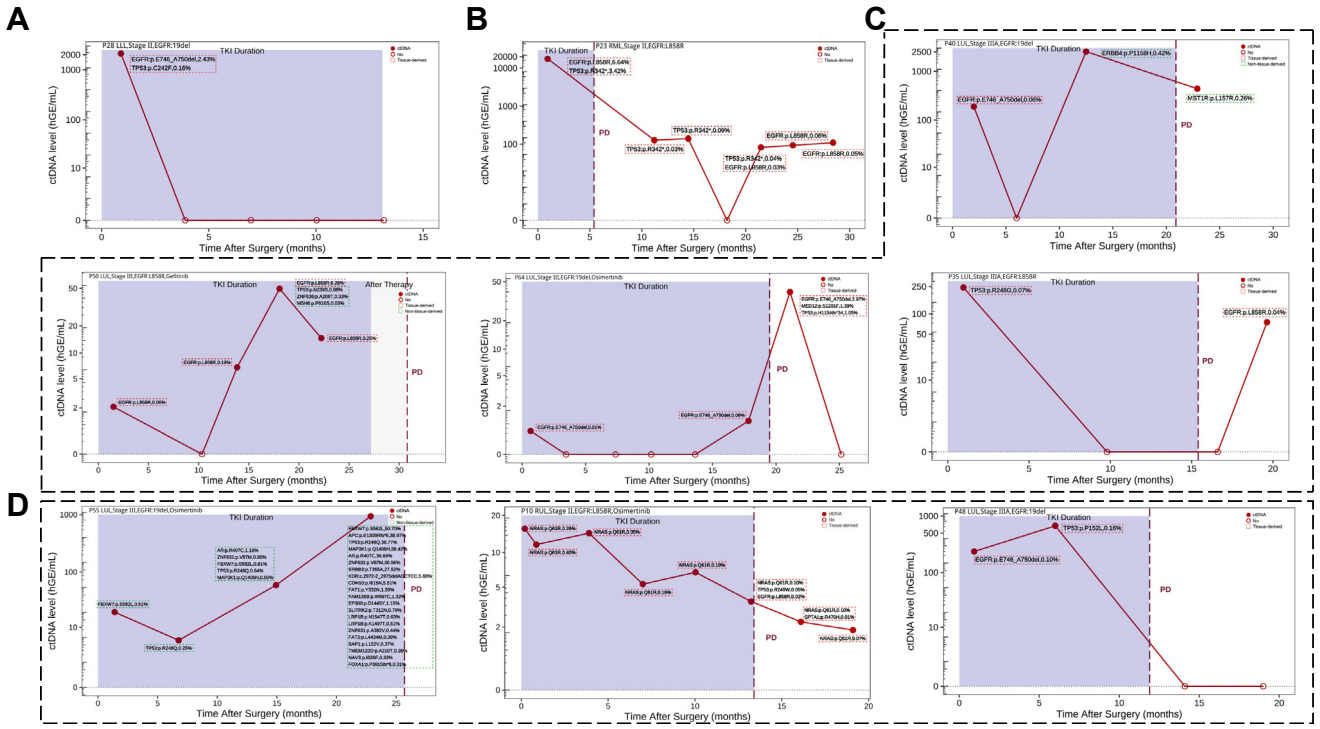

Figure 3. Schematic representation of dynamic ctDNA changes in nine patients with landmark detectable MRD receiving EGFR TKI. (*A*) Patient reached persistent ctDNA clearance. (*B*) Patients experienced rapid recurrence after landmark detectable MRD. (*C*) Four patients exhibited transient ctDNA clearance, but ultimately experienced disease recurrence. (*D*) Three patients did not achieve ctDNA clearance throughout their treatment course and consequently experienced recurrence of their disease. ctDNA, circulating tumor DNA; del, deletion; hGE, haploid genome equivalent; LUL, left upper lobe; MRD, molecular residual disease; PD, progression disease; TKI, tyrosine kinase inhibitor.

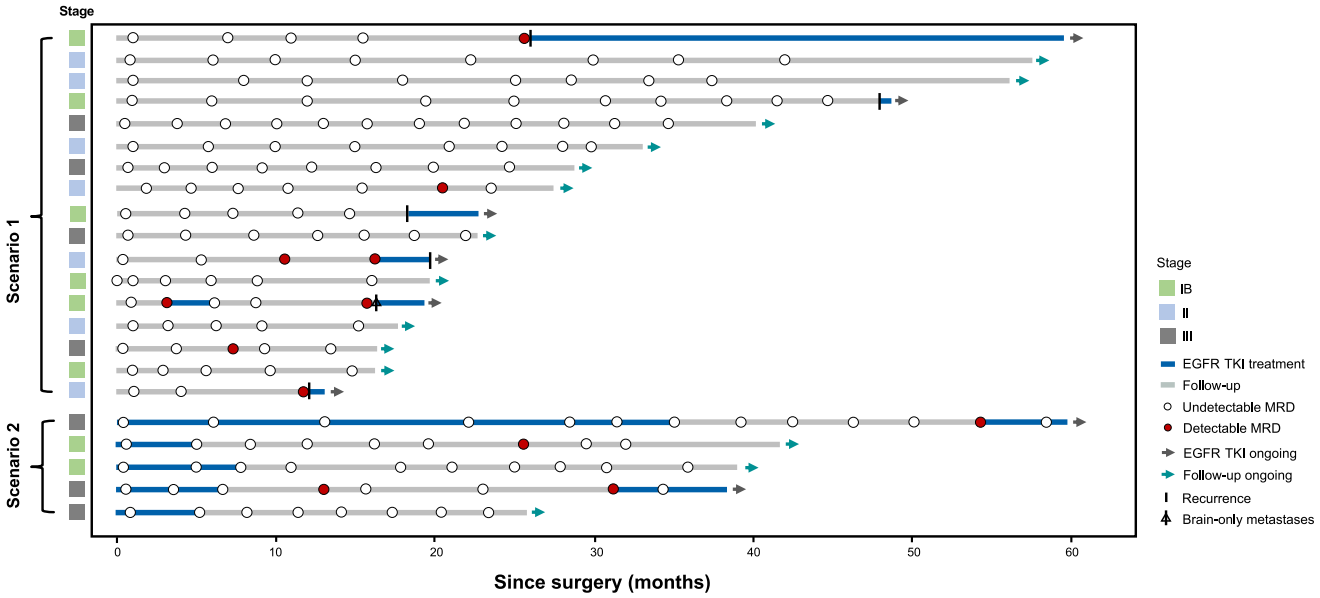

Figure 4. Summary of serial ctDNA samples of 22 patients who received adaptive, de-escalation EGFR TKI strategy. Patients are stratified and ordered based on the duration since the initiation of adjuvant EGFR TKI therapy or surgery and according to distinct clinical scenarios. Scenario 1: patients had never received EGFR TKI until the latest follow-up or discontinued their medication according to the longitudinal undetectable MRD. Scenario 2: patients ceased TKI treatment after a period of use on undetectable MRD. Red dots indicate detectable ctDNA. Gray dots indicate undetectable ctDNA. Blue bars indicate TKI treatment period. Gray bars indicate no treatment period. ctDNA, circulating tumor DNA; MRD, molecular residual disease; TKI, tyrosine kinase inhibitor.

Table 2. Clinicopathologic Factors of 22 Patients Who Received Adaptive, De-Escalation EGFR TKI Treatment

Factors	Patients (N = 22)
Age, median (range), y	58 (27-72)
Sex	
Male	11
Female	11
Smoking	
Yes	3
No	19
Pathologic type	
LUAD	21
LASC	1
TNM stage	
IB	7
II	7
IIIA	8
IIIB	0
EGFR mutations	
19del	10
L858R	7
19del/L858R+20ins/G719S	5

del, deletion; ins, insertion; LASC, lung adenosquamous cell carcinoma; LUAD, lung adenocarcinoma; TKI, tyrosine kinase inhibitor.

months. More importantly, this study could help inform the feasibility of adaptive, de-escalation of EGFR TKI treatment. Nevertheless, this was not a randomized study and could only provide an initial signal for the adaptive EGFR TKI strategy. A well-designed, prospective study with a large sample is warranted to confirm this conclusion.

Findings from the TRACERx series of studies indicate that, compared with squamous cell carcinoma, adenocarcinoma exhibits a low-ctDNA shedding phenotype.[21,22] A retrospective study found that, based on tissue-to-plasma genotype comparison, patients with EGFR mutations exhibited lower ctDNA variant allele frequency levels ($p = 0.077$).[23] Therefore, effective MRD monitoring in early- to mid-stage postoperative *EGFR*-mutated patients presents a greater challenge. In this cohort, four patients experienced recurrence despite having longitudinally undetectable MRD (one stage IB, two stage II, and one stage IIIA), resulting in a longitudinal MRD NPV of 88.2% and a sensitivity of 86.2% (Table 1). Two of these patients (50.0%) had brain-only metastases, consistent with previous findings.[8,13] Notably, both patients received postoperative EGFR TKI, highlighting that the challenge of detecting brain-only metastases through blood MRD testing remains, regardless of adaptive targeted therapy.

Two noteworthy observations were made in this study. The first was the correlation between ctDNA clearance and EGFR TKI treatment. The notably low rate of persistent ctDNA clearance (one of nine, 11.1%) with EGFR TKI treatment was unexpected. Drawing from the data of the TRACERx study,[21] of 12 preadjuvant MRD-positive patients, only one had persistent clearance and did not relapse until death. Four patients had transient ctDNA clearance, and eventually, all patients relapsed. The remaining four patients never had ctDNA clearance, and all patients relapsed. Thus, the escalation of adjuvant therapy targeting landmark detectable MRD requires further research and resolution.

The second noteworthy result was the ctDNA clearance in patients who received adaptive TKI. Four patients (18.2%) experienced ctDNA clearance without any treatment in this context. This observation may be attributed to the sensitivity of MRD detection. Nevertheless, considering that no recurrence occurred in these patients, we re-evaluated the underlying biological significance of ctDNA clearance.

Although the findings are promising, the relatively small sample size and observational design introduce inherent limitations. Future randomized controlled trial with larger cohorts are necessary to confirm the efficacy of MRD monitoring in guiding treatment decisions for patients with *EGFR*-mutated NSCLC in the adjuvant setting.

Overall, the advantages of ctDNA-MRD monitoring were well reflected in the postoperative context in patients with *EGFR*-mutated NSCLC. These preliminary findings lend some initial support to the adaptive de-escalation strategy for adjuvant EGFR TKIs based on ctDNA-MRD monitoring. CTONG 2105 (NCT05536505) and CTONG 2201 (NCT05457049), two prospective clinical trials on the de-escalation strategy of adjuvant therapy, are currently underway.

CRediT Authorship Contribution Statement

Song Dong: Conceptualization, Resources, Data curation, Supervision, Investigation, Project administration, Writing–review and editing.

Bingfa Yan: Data curation, Formal analysis, Validation, Investigation, Visualization, Writing–original draft, Writing–review and editing.

Si-Yang Liu: Validation, Investigation, Writing–review and editing.

Xuan Gao: Data curation, Formal analysis, Validation, Investigation, Visualization, Writing–original draft, Writing–review and editing.

Hui-Zhao Hong: Data curation, Formal analysis, Investigation, Visualization.

Hong-Ji Li: Data curation, Formal analysis, Investigation, Visualization.

Wei Gao: Resources, Data curation, Visualization, Methodology.

Hong-Hong Yan: Resources, Data curation, Formal analysis, Supervision, Validation, Investigation, Visualization, Methodology.

Si-Yang Maggie Liu: Resources, Writing–review and editing.

Hai-Yan Tu: Resources, Writing–review and editing.

Yi Pan: Resources, Writing–review and editing.

Qing Zhou: Resources, Supervision, Methodology, Writing–review and editing.

Xue-Ning Yang: Resources, Supervision, Writing–review and editing.

Xue-Feng Xia: Resources, Methodology.

Xin Yi: Resources, Methodology.

Wen-Zhao Zhong: Resources, Supervision, Funding acquisition, Methodology, Writing–review and editing.

Yi-Long Wu: Conceptualization, Investigation, Visualization, Funding acquisition, Writing–original draft, Writing–review and editing.

Jia-Tao Zhang: Conceptualization, Resources, Formal analysis, Visualization, Methodology, Funding acquisition, Writing–original draft, Writing–review and editing.

Disclosure

Dr. Zhou declares receiving speaker fees from AstraZeneca and Roche. Dr. Zhong declares receiving speaker fees from AstraZeneca and Roche. Dr. Wu declares receiving speaker fees from AstraZeneca, Eli Lilly, Pfizer, Roche, and Sanofi. The remaining authors declare no conflict of interest.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2024.100758.

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