Editorial Commentary

Can circulating tumor DNA guide treatment de-escalation in metastatic lung adenocarcinoma harboring actionable genomic alterations?

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In a recently published article, Dong and colleagues report on the outcomes of a proof of concept trial of circulating tumor DNA (ctDNA) guided treatment de-escalation in patients with metastatic or locally advanced, unresectable adenocarcinoma of the lung (1). The trial included 60 patients whose tumors harbored actionable genomic alterations (AGA) in epidermal growth factor receptor (EGFR), *ALK*, or *ROS1* and were receiving targeted therapies as first or second line of treatment. All patients received local consolidative treatment (LCT, surgery and/or radiotherapy) to all known tumor sites and had to have normal serum carcinoembryonic antigen (CEA) levels and no evidence of ctDNA following LCT. A tumor tissue-informed next-generation sequencing (NGS) liquid biopsy (LB) panel involving 338 genes was used for ctDNA testing (2). Patients were followed-up 6 weeks after treatment interruption and every three months thereafter with chest computed tomography (CT) scans, CEA levels, and LB. In patients with an increase in CEA levels and/or ctDNA positivity, treatment was resumed, but could be interrupted again in case of subsequent CEA/ctDNA clearance on follow-up testing.

By far the most common AGA was *EGFR* in 56 of 60 patients (93%). With a median time of follow-up of 19.2 months (range, 3.8–29.7 months), 14 of 60 patients (23%) were still CEA/ctDNA negative and had no radiographic disease progression (cohort A). In contrast, treatment had to be resumed in 31 patients (52%) following CEA or ctDNA detection in the absence of disease progression (cohort B) whereas 15 patients (25%) had radiographic disease progression without prior CEA/ctDNA positivity (cohort C). Median progression-free survival (PFS) was unreached, 20.2 months [95% confidence interval (CI), 12.9–27.4] and 5.5 months (95% CI, 1.5–7.2) in cohorts A, B, and C, respectively. Median PFS in the overall cohort was 18.4 months (95% CI, 12.6–24.2).

This trial aims to de-escalate treatment in a carefully selected low-risk population and we highly appreciate the authors' efforts. Their approach is in diametric opposition to the trend of treatment intensification in *EGFR*-mutated non-small cell lung cancer (NSCLC). For example, the FLAURA2 trial recently demonstrated improved PFS with the addition of platinum-based chemotherapy to osimertinib (3) as did MARIPOSA for the bispecific MET- and EGFR-binding antibody amivantamab with the third-generation EGFR tyrosine kinase inhibitor (TKI) lazertinib over osimertinib alone (4). Of note, overall survival (OS)

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data are still immature for these trials. Unsurprisingly, both regimens were associated with increased toxicity. Although many patients may benefit from such intensified therapies, not all patients necessarily require them.

Utilizing ctDNA as surrogate for disease burden in solid cancers is often referred to as minimal residual disease (MRD), a term coined in the context of chronic myeloid leukemia (CML). Following international guidelines, CML patients who achieve MRD negativity for 2 to 3 years (depending on the depth of response) and having received treatment for a minimum of 5 years may stop treatment and receive MRD monitoring only (5). This treatment-free remission is maintained in ~50% of patients (5). Of note, CML is a disease with quite distinct features compared to NSCLC and is particularly suitable for ctDNA detection given its liquid nature. In contrast, it has been shown that 20–30% of NSCLC are not detectable using ctDNA at baseline, when tumor burden is highest, regardless of whether tumor-informed or tumor-agnostic assays are used (6-8), although larger tumor volume and higher metastatic burden are associated with increased detection rates (9). In addition, it may be noted that plasma ctDNA appears to have low sensitivity for intracranial disease (10,11), which may render the central nervous system (CNS) a blind spot of ctDNA-guided treatment de-escalation trials.

Besides these limitations, on-treatment ctDNA trajectories have consistently been shown to have prognostic impact in NSCLC (2,6,8,12-15). In FLAURA, median PFS in patients with ctDNA persistence after 3 weeks of first-line osimertinib treatment was 11.3 months (95% CI, 9.5–16.5) compared to 19.8 [95% CI, 15.1–not calculable (NC)] in patients with ctDNA clearance (6). Consequently, several trials are evaluating ctDNA as biomarker to guide (and limit) treatments by either treatment escalation in patients with ctDNA persistence or de-escalation in those with ctDNA clearance, as previously reviewed (16). For example, in the ongoing PACE-LUNG trial, patients with *EGFR*-mutated NSCLC on osimertinib receive additional four cycles of platinum-based chemotherapy in case of ctDNA positivity after 3 weeks of osimertinib monotherapy (17). Preliminary data of L-BRITE, which investigates on a similar approach with the first-generation TKI gefitinib, have been published and appear to be promising (18).

In the current trial, CEA/ctDNA monitoring was able to identify the majority of cases with active or recurring disease (67%, i.e., 75% of the overall trial cohort) prior actual disease progression based on radiographic response evaluation criteria (RECIST). This aligns with data from the FLAURA trial. In FLAURA, 73% of patients with progressive disease (PD) on osimertinib treatment had LB progression prior radiographic PD, whereas 27% had RECIST progression without prior LB progression (13). Median lead time from ctDNA to RECIST progression was 3.4 months (interquartile range, 1.4–5.3 months).

The probably biggest concern with CEA/ctDNA-guided treatment de-escalation is the uncertainty whether patients who show PD without prior CEA/ctDNA positivity can be adequately salvaged following treatment resumption. OS and post-progression treatment data have not yet been reported for the Dong trial and it will be of high interest to see whether there are differences in OS in the two latter cohorts. In addition, data on co-mutations have also not been reported so far. However, it will remain unclear whether a possibly shorter OS in the cohort of progressive patients without CEA/ctDNA positivity is due to inadequate monitoring or rather biological differences between tumors (i.e., tumor aggressiveness). Another potential issue may be the risk of disease flare, a concept of disease progression previously described as rapidly following TKI discontinuation in TKI resistant NSCLC (19). Nevertheless, it appears that most patients in cohort B were able to clear CEA/ctDNA again after drug re-exposure and most patients in fact had more than one (in several cases up to four) treatment-free periods, indicating the feasibility of the trial's approach. Finally, the median PFS in the overall cohort of 18.4 months appears promising given the fact that first-, second-, and third-generation TKI were used.

Adopting a treatment de-escalation strategy in routine care requires confirmation of non-inferiority from an adequately powered randomized trial and the large number of patients required for such a trial is a major challenge in face of this highly selected population. However, this trial would not only have the chance to improve quality of life but also mitigate the financial burden of disease. Considering the continuously increasing economic cost of oncology treatments, this is highly relevant both in low-income and in high-income countries where lung cancer accounts for the largest share in economic cost because of targeted therapies and checkpoint inhibitors (20).

In fact, from a health economic point of view, such a confirmatory trial would probably be self-funding. Estimating roughly 900 patients being required to demonstrate non-inferiority, median PFS of 19 months (corresponding to a mean PFS of roughly 28.6 months, assuming exponential distribution), a ratio between treatment-free time and overall time on trial of 0.5 in the

experimental arm, and 2,500$ for tissue NGS at baseline, 2,000$ for every LB, and 5,000$ per month for drug costs, more than 12 million dollars could be saved by simply conducting this trial compared to treatment outside of the trial. The extent of the savings would largely depend on the selection of participating countries, as the prices for anticancer drugs differ considerably between regions (21). However, this sum could probably cover further trial costs, first and foremost additional treatment costs by LCT (in the metastatic setting), but also for imaging evaluation (RECIST), site and regulatory fees, trial administration, etc. Obviously, such a trial would have the potential to be practice-changing.

Besides, the concept of ctDNA-based treatment de-escalation may also be applied to adjuvant therapy in resected NSCLC where osimertinib and alectinib are approved for *EGFR*-mutated and *ALK*-rearranged tumors, respectively (22,23), or to maintenance osimertinib in *EGFR*-mutated locally advanced, unresectable NSCLC after definitive chemoradiotherapy (24). In fact, a randomized pilot study of ctDNA-guided osimertinib maintenance *vs.* observation alone in resected *EGFR*-mutated disease is currently recruiting patients (ECTOP-1022, NCT06323148).

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Footnote

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References

1. Dong S, Wang Z, Zhang JT, et al. Circulating Tumor DNA-Guided De-Escalation Targeted Therapy for Advanced Non-Small Cell Lung Cancer: A Nonrandomized Controlled Trial. JAMA Oncol 2024;10:932-40.
2. Zhang JT, Liu SY, Gao W, et al. Longitudinal Undetectable Molecular Residual Disease Defines Potentially Cured Population in Localized Non-Small Cell Lung Cancer. Cancer Discov 2022;12:1690-701.
3. Planchard D, Feng PH, Karaseva N, et al. Osimertinib plus platinum-pemetrexed in newly diagnosed epidermal growth factor receptor mutation-positive advanced/metastatic non-small-cell lung cancer: safety run-in results from the FLAURA2 study. ESMO Open 2021;6:100271.
4. Cho BC, Lu S, Felip E, et al. Amivantamab plus Lazertinib in Previously Untreated EGFR-Mutated Advanced NSCLC. N Engl J Med 2024;391:1486-98.
5. Hochhaus A, Baccarani M, Silver RT, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia 2020;34:966-84.
6. Zhou C, Imamura F, Cheng Y, et al. Early clearance of plasma EGFR mutations as a predictor of response to osimertinib and comparator EGFR-TKIs in the FLAURA trial. J Clin Oncol 2019;37:9020.

7. Wang N, Zhang X, Wang F, et al. The Diagnostic Accuracy of Liquid Biopsy in EGFR-Mutated NSCLC: A Systematic Review and Meta-Analysis of 40 Studies. SLAS Technol 2021;26:42-54.
8. Mok T, Wu YL, Lee JS, et al. Detection and Dynamic Changes of EGFR Mutations from Circulating Tumor DNA as a Predictor of Survival Outcomes in NSCLC Patients Treated with First-line Intercalated Erlotinib and Chemotherapy. Clin Cancer Res 2015;21:3196-203.
9. Chabon JJ, Hamilton EG, Kurtz DM, et al. Integrating genomic features for non-invasive early lung cancer detection. Nature 2020;580:245-51.
10. Romero A, Serna-Blasco R, Alfaro C, et al. ctDNA analysis reveals different molecular patterns upon disease progression in patients treated with osimertinib. Transl Lung Cancer Res 2020;9:532-40.
11. Azad TD, Nanjo S, Jin MC, et al. Quantification of cerebrospinal fluid tumor DNA in lung cancer patients with suspected leptomeningeal carcinomatosis. NPJ Precis Oncol 2024;8:121.
12. Jänne PÄ, Kobayashi K, Robichaux J, et al. FLAURA2: Exploratory analysis of baseline and on-treatment plasma EGFRm dynamics in patients with EGFRm advanced NSCLC treated with first-line osimertinib ± platinum-pemetrexed. Cancer Res 2024;84:CT017.
13. Gray JE, Markovets A, Reungwetwattana T, et al. Longitudinal Analyses of Circulating Tumor DNA for the Detection of EGFR Mutation-Positive Advanced NSCLC Progression During Treatment: Data From FLAURA and AURA3. J Thorac Oncol 2024;19:1525-38.
14. Felip E, Cho BC, Gutiérrez V, et al. Amivantamab plus lazertinib versus osimertinib in first-line EGFR-mutant advanced non-small-cell lung cancer with biomarkers of high-risk disease: a secondary analysis from MARIPOSA. Ann Oncol 2024;35:805-16.
15. Hellmann MD, Nabet BY, Rizvi H, et al. Circulating Tumor DNA Analysis to Assess Risk of Progression after Long-term Response to PD-(L)1 Blockade in NSCLC. Clin Cancer Res 2020;26:2849-58.
16. Desai A, Vázquez TA, Arce KM, et al. ctDNA for the Evaluation and Management of EGFR-Mutant Non-Small Cell Lung Cancer. Cancers (Basel) 2024;16:940.
17. Acker F, Aguinarte L, Althoff F, et al. Study Design and Rationale for the PACE-LUNG Trial: A Multicenter, Single-Arm, Phase II Clinical Trial Evaluating the Efficacy of Additional Chemotherapy for Patients with EGFRm NSCLC with the Continued Presence of Plasma ctDNA EGFRm at Week 3 After Start of Osimertinib First-Line Treatment. Clin Lung Cancer 2022;23:e473-7.
18. Baskarane H, Malik PS, Jain D, et al. P1.12A.12 Liquid Biopsy-Based Risk Stratification And Intensification of Treatment in EGFR Mutated Advanced NSCLC (L-BRITE)-Preliminary Analysis. J Thorac Oncol 2024;19:S197-8.
19. Chaft JE, Oxnard GR, Sima CS, et al. Disease flare after tyrosine kinase inhibitor discontinuation in patients with EGFR-mutant lung cancer and acquired resistance to erlotinib or gefitinib: implications for clinical trial design. Clin Cancer Res 2011;17:6298-303.
20. Chen S, Cao Z, Prettner K, et al. Estimates and Projections of the Global Economic Cost of 29 Cancers in 204 Countries and Territories From 2020 to 2050. JAMA Oncol 2023;9:465-72.
21. Leighl NB, Nirmalakumar S, Ezeife DA, et al. An Arm and a Leg: The Rising Cost of Cancer Drugs and Impact on Access. Am Soc Clin Oncol Educ Book 2021;41:1-12.
22. Tsuboi M, Herbst RS, John T, et al. Overall Survival with Osimertinib in Resected EGFR-Mutated NSCLC. N Engl J Med 2023;389:137-47.
23. Wu YL, Dziadziuszko R, Ahn JS, et al. Alectinib in Resected ALK-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2024;390:1265-76.
24. Lu S, Kato T, Dong X, et al. Osimertinib after Chemoradiotherapy in Stage III EGFR-Mutated NSCLC. N Engl J Med 2024;391:585-97.

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