Editorial

Molecular minimal residual disease in resected non-small cell lung cancer (NSCLC): results of specifically designed interventional clinical trials eagerly awaited

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Since the initial discovery of cell free DNA in blood (1), the evolution of molecular techniques has allowed the detection of gene alterations in plasma as well as in other biological fluids (2). Detection of molecular alterations in circulating tumor DNA (ctDNA) has now many potential clinical applications (3), in particular in non-small cell lung cancer (NSCLC) (4,5).

Today, ctDNA analysis is a commonly used approach to select NSCLC patients by identifying genomic alterations for first-line targeted treatments [such as epidermal growth factor receptor (EGFR)] and also for later lines identifying resistance mutations (6,7). The use of ctDNA testing in this setting has been approved by the Food and Drug Administration and by the European Medicine Agency. A recent study demonstrated that this approach increased the overall survival (OS) of patients (8).

Beside this well validated use, there are many other potential applications of ctDNA testing, such as cancer screening, treatment monitoring, detection of minimal residual disease (MRD) and molecular relapse monitoring (9).

The performance of ctDNA detection for the assessment of MRD (molecular MRD) in resected early-stage NSCLC patients has been evaluated in several studies. Michela Verzè and her colleagues performed a systematic review of these studies (10). They selected and included 13 studies in their analysis. All were retrospective series. The number of patients tested was limited (from 5 to 330 patients), with most of them (10 out 13) based on the analysis of less than 80 patients. The methodology used was also quite heterogeneous: the stage of tumors was not always the same, pre-operative ctDNA status and tumor genotyping were not available in all studies, blood samples were collected at different time points following surgery, and different blood processing and technical approaches were used to detect gene mutation. At the end, the detection rate of post-resection molecular MRD ranged between 6.4% and 46.2%. Despite this heterogeneity, all 8 studies that evaluated the prognostic value of MRD demonstrated that ctDNA-positive patients after surgery had a shorter relapse-free survival (RFS) and OS than ctDNA-negative patients. Similar conclusions were drawn in recent studies based on the analysis of 88 (11) and 261 (12) stage I–III NSCLC patients. In both studies, molecular MRD was clearly prognostic, the detection of ctDNA indicating the persistence of clinically occult disease (locally or as micro-metastases).

Clinical trials designed to further validate these findings

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are presented in the review (10). We might also have in the near future results from clinical trials evaluating different treatments in the adjuvant setting, such as the ADAURA trial for EGFR-mutated NSCLC patients (13), and the Impower010 trial evaluating adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA NSCLC (14).

But more importantly, the clinical utility of molecular MRD detection in clinical practice remains to be evaluated in prospective interventional clinical trials. One potential application would be to prevent overtreatment in a potentially cured population and avoid unnecessary adjuvant treatments. This would reduce adverse events and also decrease the "financial toxicity" of expensive treatments.

A typical illustration of the clinical use of molecular MRD testing in this setting was recently demonstrated in colorectal cancer (15). Stage II colon cancer patients were randomized following R0 resection. In the experimental arm, patients with a ctDNA-positive result at 4 or 7 weeks after surgery were treated by oxaliplatin-based or fluoropyrimidine chemotherapy, while ctDNA-negative patients were not treated. ctDNA-guided management was non-inferior to standard management for 2-year RFS (93.5% *vs.* 92.4%). But only approximately half of patients in the ctDNA-guided arm received adjuvant chemotherapy compared to standard management (15.3% *vs.* 27.9%, odds ratio 2.14; P=0.002). This demonstrated that a ctDNA-guided approach can reduce adjuvant chemotherapy use without compromising RFS. Similar studies are ongoing in NSCLC: in the NCT04585477 trial, ctDNA-positive patients after surgery receive durvalumab, whereas ctDNA-negative patients receive standard of care and no treatment. The NCT05536505 trial explores the efficacy of postoperative adjuvant EGFR-TKIs therapy based on molecular MRD status in patients with stage IB–IIIB EGFR-mutant NSCLC: MRD positive patients receive icotinib, and MRD negative patients are followed-up (as long as ctDNA is undetectable). In the MeRmaiD-2 trial (NCT04642469) patients with stage II–III NSCLC are enrolled after complete resection plus optional neoadjuvant and/or adjuvant therapy. ctDNA-positive patients are randomized to receive durvalumab or placebo.

Another application of interest would be to identify patients at highest risk of relapse (based on the detection of ctDNA) thus allowing treatment escalation. The benefit of a treatment intensification in post-surgery is being evaluated. For instance, the NCT05460195 trial is evaluating the combination of sintilimab and anlotinib in MRD positive patients, whereas MRD negative patients will receive sintilimab as monotherapy.

In both setting, the performance (both sensitivity and specificity) of the MRD testing is a key issue, requiring standardization of pre-analytical and analytical processes. The nature of blood collection and its processing is not a matter of debate anymore. It is now well established that plasma must be used, and that blood must be processed within 3–4 hours if collected in EDTA tubes, or within 7–10 days if collected in tubes which stabilizes nucleated blood cells (6,16,17). Other aspects must be clearly defined. When should the blood sample be collected after surgery? The half-life of ctDNA is rather short: 35 minutes, as measured in patients who underwent curative-intent lung resection (18). But to make sure that all circulating DNA molecules released by the tumor have disappeared following surgery, it would seem reasonable to perform the blood draw within 2 to 4 weeks post-surgery (18). And this would allow enough time to perform the test before treatment initiation. Finally, which molecular assay is the most appropriate? There are 2 main strategies to detect gene mutations:

Direct next-generation sequencing (NGS) of plasma to detect the presence of ctDNA (targeted sequencing, whole genome sequencing). No tumor biopsy is required, which is convenient, but requires the use of procedures (including bioinformatics) to correct for instance for clonal hematopoiesis of indeterminate potential. Otherwise false positive results will be produced, reducing the specificity of this approach.

In the tumor informed procedure, sequencing of tumor tissue is first performed, to identify molecular alterations. A personalized ctDNA assay (NGS or digital PCR) is developed to detect the mutations identified in the resected tumor in ctDNA. This strategy might overcome specificity issues. Several commercially available solutions are available and can be used in this setting.

Both strategies are based on the detection of gene mutations, but DNA methylation could also be a powerful approach in the future. The molecular MRD assay would not rely on the detection of specific DNA mutations, and a single "universal" assay could be used for all patients, as recently described for early detection (19). In all cases, the limit of detection of the assay must be perfectly established and controlled.

To conclude, MRD through ctDNA testing might be a promising approach to guide adjuvant therapy in resected NSCLC patients. But more work is required, in particular

to standardize the methods used in future specifically designed prospective interventional clinical trials.

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References

1. Mandel P, Metais P. Nuclear Acids In Human Blood Plasma. C R Seances Soc Biol Fil 1948;142:241-3.
2. Tivey A, Church M, Rothwell D, et al. Circulating tumour DNA - looking beyond the blood. Nat Rev Clin Oncol 2022;19:600-12.
3. Yang M, Forbes ME, Bitting RL, et al. Incorporating blood-based liquid biopsy information into cancer staging: time for a TNMB system? Ann Oncol 2018;29:311-23.
4. Malapelle U, Pisapia P, Pepe F, et al. The evolving role of liquid biopsy in lung cancer. Lung Cancer 2022;172:53-64.
5. Rolfo C, Mack P, Scagliotti GV, et al. Liquid Biopsy for Advanced NSCLC: A Consensus Statement From the International Association for the Study of Lung Cancer. J Thorac Oncol 2021;16:1647-62.
6. Heitzer E, van den Broek D, Denis MG, et al. Recommendations for a practical implementation of circulating tumor DNA mutation testing in metastatic non-small-cell lung cancer. ESMO Open 2022;7:100399.
7. Bennouna J, Girard N, Audigier-Valette C, et al. Phase II Study Evaluating the Mechanisms of Resistance on Tumor Tissue and Liquid Biopsy in Patients With EGFR-mutated Non-pretreated Advanced Lung Cancer Receiving Osimertinib Until and Beyond Radiologic Progression: The MELROSE Trial. Clin Lung Cancer 2020;21:e10-4.
8. Jee J, Lebow ES, Yeh R, et al. Overall survival with circulating tumor DNA-guided therapy in advanced non-small-cell lung cancer. Nat Med 2022;28:2353-63.
9. Pascual J, Attard G, Bidard FC, et al. ESMO recommendations on the use of circulating tumour DNA assays for patients with cancer: a report from the ESMO Precision Medicine Working Group. Ann Oncol 2022;33:750-68.
10. Verzè M, Pluchino M, Leonetti A, et al. Role of ctDNA for the detection of minimal residual disease in resected non-small cell lung cancer: a systematic review. Transl Lung Cancer Res 2022;11:2588-600.
11. Gale D, Heider K, Ruiz-Valdepenas A, et al. Residual ctDNA after treatment predicts early relapse in patients with early-stage non-small cell lung cancer. Ann Oncol 2022;33:500-10.
12. 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.
13. Wu YL, Tsuboi M, He J, et al. Osimertinib in Resected EGFR-Mutated Non-Small-Cell Lung Cancer. N Engl J Med 2020;383:1711-23.
14. Felip E, Altorki N, Zhou C, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-

IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. Lancet 2021;398:1344-57.
15. Tie J, Cohen JD, Lahouel K, et al. Circulating Tumor DNA Analysis Guiding Adjuvant Therapy in Stage II Colon Cancer. N Engl J Med 2022;386:2261-72.
16. Normanno N, Denis MG, Thress KS, et al. Guide to detecting epidermal growth factor receptor (EGFR) mutations in ctDNA of patients with advanced non-small-cell lung cancer. Oncotarget 2017;8:12501-16.
17. Denis MG, Knol AC, Théoleyre S, et al. Efficient Detection of BRAF Mutation in Plasma of Patients after Long-term Storage of Blood in Cell-Free DNA Blood Collection Tubes. Clin Chem 2015;61:886-8.
18. Chen K, Zhao H, Shi Y, et al. Perioperative Dynamic Changes in Circulating Tumor DNA in Patients with Lung Cancer (DYNAMIC). Clin Cancer Res 2019;25:7058-67.
19. Jamshidi A, Liu MC, Klein EA, et al. Evaluation of cell-free DNA approaches for multi-cancer early detection. Cancer Cell 2022;40:1537-1549.e12.

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