Editorial Commentary

Liquid biopsy in advanced and metastatic breast cancer: translating prognostic value to clinical implementation

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The landscape of precision oncology is rapidly evolving, with advancements in ultrasensitive assays now allowing for the measurement of diverse types of circulating tumor elements in patients diagnosed with cancer. The prognostic value of the circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA) has been consistently demonstrated across various liquid biopsy platforms in both early and metastatic breast cancer, whether using a tumor-informed ("bespoke") or tumor-agnostic approaches (1). Despite this considerable progress, a critical challenge remains: translating the clinical potential of the liquid biopsy into actionable clinical decisions that improve patient outcomes.

The validation of the liquid biopsy as a discriminative biomarker for risk stratification among patients with similar clinical presentations holds particular promise. This approach could enable greater personalization of treatment decision-making with more nuanced clinical decisions for monitoring for disease recurrence, with the goal of improving clinical outcomes while reducing treatment-associated toxicity. The study by Zhang and colleagues in this issue of *Clinical Cancer Research* makes important contributions to our understanding of how distinct components of the liquid biopsy achieved at diagnosis may be utilized to refine risk stratification and prognostication in advanced or metastatic breast cancer (2).

The present study in context

This observational cohort study provides compelling evidence for the differential distribution and prognostic significance of liquid biopsy markers for patients with advanced and metastatic breast cancer. The authors present data from 38 Stage III and 254 Stage IV patients diagnosed with breast cancer treated at a single institution between 2016–2019, offering a comprehensive analysis of CTCs, CTC clusters, and mutational alterations of ctDNA.

The striking differences in rates of CTC detection between patients with metastatic versus advanced disease (≥1 CTC: 63% *vs.* 26%; ≥5 CTCs: 41% *vs.* 16% for Stage IV *vs.* III, respectively) establishes a clear biological distinction that is prognostic for clinical outcomes. This is consistent with previously published findings of a "dose"-response relationship between number of CTCs and survival in both early-stage and metastatic breast cancer (3,4).

Perhaps most notably, the study identifies three distinct potential prognostic groups of patients based on CTC status, defined as ≥1 versus 0 detected CTCs at baseline: Stage III patients without detectable CTCs had the longest progression-free survival (PFS), CTC-positive Stage III and CTC-negative Stage IV patients demonstrated similar intermediate PFS, while Stage IV patients with ≥1 CTC

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had the shortest PFS. This granular stratification supports the potential for CTC status as a critical prognostic biomarker that complements traditional staging. While a previous pooled analysis of patients with metastatic disease utilized CTC-positive status, defined as 5+ CTCs, to identify prognostic subgroups (Stage $IV_{indolent}$ versus Stage $IV_{aggressive}$), this finding reinforces the prognostic potential for ≥1 detected CTC for patients with both early or metastatic disease, and posits the potential clinical utility of CTC status as a numeric (versus dichotomous) variable.

The exclusive presence of CTC clusters in Stage IV disease (11% of patients) and their association with worse PFS reinforces their biological significance in disease progression. While rare, CTC clusters, defined as a group of 2 to 100 tumor cells with strong cell-cell adhesions accompanied by an ambulatory local "microenvironment" of platelets, immune cells, and cancer-associated fibroblasts, demonstrate up to 50-fold greater metastatic potential than single CTCs (5). The demonstration of a "dose-dependent" relationship between cluster number and clinical outcomes provides additional granularity for risk assessment and suggests potential systemic therapeutic targeting opportunities.

Mutational analysis of ctDNA revealed important stage-specific alterations, with PIK3CA and BRAF identified as leading gene alterations among patients with Stage IV compared with Stage III disease (3.5- and 3.4-fold, respectively). The association between specific mutations (PIK3CA and ESR1) with worse clinical outcomes and dissemination to specific metastatic sites (e.g., PIK3CA to the liver; BRAF and ERBB2 to the lung) offers intriguing possibilities for improved prediction of distant metastatic spread and potential targeted systemic or even locoregional therapeutic approaches.

Clinical utility: the critical gap

Despite these promising findings, the path for liquid biopsy to meaningfully change clinical practice remains unclear. To date, there have been few prospective clinical trials that demonstrate the clinical value of liquid biopsy assessment for patients diagnosed with breast cancer beyond its known value as an established biomarker for prognostic assessment and monitoring of metastatic disease burden. While the SWOG-S0500 trial confirmed the prognostic value of CTC detection in patients with metastatic breast cancer, early switching of cytotoxic therapy based on persistent CTCs after 21-days of first-line systemic therapy was not effective in prolonging overall survival (OS) (6). Of note, patients in this trial who experienced a decrease in CTCs with systemic therapy from ≥5 cells at baseline to <5 after the first cycle of chemotherapy experienced longer median OS compared with patients with persistently high CTCs (≥5 CTCs) a both timepoints. These results are consistent with those from others in the metastatic setting supporting a role for CTC response as a meaningful prognostic biomarker that could be utilized to guide subsequent treatment strategies (7-10).

Importantly, the recently published STIC CTC trial provides the first evidence that utilization of circulating tumor material to guide treatment decisions for patients has the potential to improve patient outcomes for patients with metastatic breast cancer (11). Patients with ≥5 CTCs who were randomized to biomarker-directed choice of systemic therapy and received chemotherapy experienced significantly longer median OS compared with patients who were randomized to *a priori* physician choice and received endocrine therapy alone. Furthermore, patients with <5 CTCs on the biomarker-directed treatment arm who received hormone therapy demonstrated non-inferior OS compared with patients who received clinician-directed chemotherapy. These results exemplify the potential for utilization of circulating tumor material to improve clinical outcomes and/or decrease treatment toxicity via therapeutic acceleration as well as de-escalation based on appreciated burden of disseminated metastatic disease.

The concept of molecular residual disease (MRD), defined as the detection of circulating tumor material following definitive management (systemic therapy, surgery, radiotherapy) in a patient with early stage disease, may offer an additional potential bridge between prognostic value and clinical utility (12). Persistence versus clearance of circulating tumor material (CTCs, ctDNA) by longitudinal measurement throughout and following definitive management has more recently emerged as a potential meaningful prognostic surrogate biomarker for treatment response and clinical outcomes. Serial assessment of MRD may facilitate personalized risk stratification that can be utilized to guide decisions regarding therapeutic acceleration versus deintensification throughout definitive management. While a number of studies have demonstrated response in measured circulating tumor elements during systemic therapy as well as increased sensitivity and discriminatory capacity with combined assessment of ctDNA and CTCs, few have demonstrated that MRD response with treatment is associated with clinical outcomes (13-15). Our group recently demonstrated that clearance of tumor-informed ctDNA—

but not CTCs—following neoadjuvant chemotherapy was significantly associated with pathologic complete response (pCR), while persistence of ctDNA 12 weeks following initiation of neoadjuvant chemotherapy (mid-NAC) was associated with worse outcomes (16). Pre-treatment CTCs have previously been identified as a prognostic biomarker for local failure, while our group and others have reported the association of CTCs as well as disseminated tumor cells (DTCs) as a potential predictive biomarker for benefit of adjuvant radiotherapy in early breast cancer (3,17,18). These findings support the proposed hypothesis that MRD may signal the presence of persistent locoregional disease that is not sufficiently accounted for by assessment of pCR and may be effectively cured with radiotherapy. Taken together, growing evidence suggests that different circulating tumor elements may have unique clinical utilities for distinct disease stages or time points throughout treatment. Prospective clinical trials further evaluating the clinical utility of the detection of and dynamics of circulating tumor material throughout definitive management are required.

The path to clinical implementation

With consideration of the above, two types of interventional trials appear critical for establishing clinical utility of longitudinal measurement of MRD in patients with early breast cancer: (I) therapeutic acceleration (pharmaceutical; radiotherapy) trials among patients with detectable MRD; (II) de-escalation from standard-of-care therapy among those without MRD [e.g., omission of chemotherapy following breast surgery—with persistence of MRD-negative status following radiotherapy (if indicated)]. Importantly, while clearance of circulating tumor material may be an appropriate short-term primary outcome for interception trials following a determined time on therapy, it will be important to demonstrate a statistical benefit (or non-inferiority) of a biomarker-driven pathway for clinical outcomes. The process achieved for validation of pCR as an FDA-approved surrogate biomarker for accelerated drug approval in early breast cancer may be an appropriate model for MRD (19). While the specifics of appropriate study design for both interception and de-escalation clinical trials remains a point of academic debate, the FDA is now providing guidance regarding the potential ethical dilemmas in this space (e.g., clinical equipoise) (20).

There are several interception clinical trials in early breast cancer that are ongoing such as the LEADER (NCT03285412), DARE (NCT04567420), EORTC TREAT ctDNA (2129-BCG), TRAK-ER (NCT04985266), and ASPRIA (NCT04434040) clinical trials. The recently published c-TRAK TN trial was the first published interception clinical trial for patients with high-risk non-metastatic triple negative breast cancer to evaluate the clinical utility of ctDNA surveillance to guide recommendations for adjuvant pembrolizumab (21). By 12 months following start of ctDNA surveillance, ctDNA was detected in 27% of patients (56% in high-risk and 12% in moderate-risk), and the majority (72%) of patients allocated to receive pembrolizumab had appreciable metastatic disease at the time of ctDNA detection, with all achieving disease relapse. This study has important implications for the design of future interception clinical trials in MRD for patients with high-risk disease, including a potential benefit in earlier ctDNA testing to appreciate maximal lead-time prior to clinical disease recurrence, as well as more frequent longitudinal ctDNA monitoring to improve early detection and treatment outcomes. In regards to de-escalation clinical trials, the breast cancer community can learn from the colon cancer experience in which a ctDNA-guided approach in stage II colon cancer demonstrated non-inferiority of omission of adjuvant chemotherapy compared to those with a standard treatment approach (22).

Conclusion

The integration of liquid biopsy into clinical practice, particularly through the ultrasensitive detection of CTCs and tumor-informed ctDNA, marks a significant advancement in precision oncology for breast cancer. While these technologies offer clear prognostic value and insights into disease biology, their translation into actionable clinical strategies that will change management remains the critical (and formidable) next step. The findings by Zhang *et al.* underscore the potential for circulating tumor elements to refine risk stratification, with the potential to inform treatment personalization and improve patient outcomes. To effectively bridge the appreciable gap between prognostic value and clinical implementation, well-designed prospective interception and de-escalation trials are crucial to establish the clinical utility of longitudinal monitoring of MRD to inform treatment decisions and demonstrate a measurable impact on clinical outcomes. With continued research and prospective validation, the liquid biopsy holds the potential to transform treatment paradigms, offering a truly personalized approach to breast cancer care while

minimizing unnecessary toxicity.

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