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Personalized Whole-Genome-Based ctDNA Dynamics During Neoadjuvant Therapy Across Breast Cancer Subtypes: Early Insights From MONITOR-Breast

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Background

- In patients with breast cancer who receive neoadjuvant treatment, therapy adjustments are primarily guided by predefined imaging and clinical assessments. Circulating tumor DNA (ctDNA)–based molecular residual disease (MRD) testing offers a real-time approach to evaluate treatment response.
- Prior studies have generally examined binary MRD status at sparse timepoints, resulting in limited resolution and a lack of quantitative data on treatment response.
- The MONITOR-Breast study employs a tumor-informed, whole-genome sequencing (WGS)–based assay with frequent ctDNA sampling across the neoadjuvant period (**Figure 1a, 1b**). Here, we report initial results from an exploratory analysis of this multi-center, prospective study and provide a quantitative, high-resolution dataset on ctDNA dynamics.

Methods

- Patients with stage I-III breast cancer of any subtype who were planning to receive neoadjuvant chemotherapy were prospectively enrolled in MONITOR-Breast.
- WGS of core needle biopsy tissue from primary tumor was used to design individualized capture panels with up to 1,000 tracking variants (**Figure 1a**). Blood was collected for ctDNA assessment as depicted in **Figure 1b**.

Figure 1a. Precise MRD®, Myriad Genetics

Precise MRD is a tumor-informed assay that uses WGS to identify up to 1,000 variants to build bespoke panels that detect ctDNA in plasma at ultrasensitive levels (LOD95 < 5 PPM).

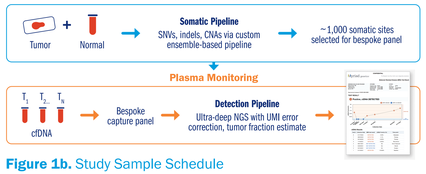


Figure 1b. Study Sample Schedule

Blood was collected at diagnosis, each neoadjuvant treatment cycle, end of treatment, surgery, and post-surgery.

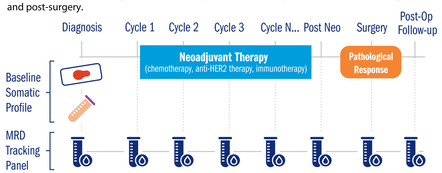


Figure 1c. Study Inclusion

Table 1. Patient, Tumor, and Treatment Characteristics

Characteristic	N=82, n (%)
Median age at enrollment [range], years	55 [31,80]
Subtype	
HR+ HER2-	20 (24)
HR+ HER2+	20 (24)
HR- HER2+	8 (10)
TNBC	34 (42)
Clinical stage	
I	21 (26)
II	45 (55)
III	16 (20)
Histology	
Invasive ductal carcinoma	75 (92)
Invasive lobular carcinoma	6 (7)
Mucinous carcinoma	1 (1)
Tumor type	
Single primary	79 (96)
Multiple primaries	3 (4)
Neoadjuvant treatment	
Chemotherapy	82 (100)
HER2 targeted therapy	28 (34)
Immunotherapy	37 (45)
Pathologic response (n=62)	
Pathologic complete response (pCR)	36 (54)
Residual disease (RD)	31 (46)

Results

- After applying inclusion criteria (**Figure 1c**), 82 patients had baseline ctDNA results available for analysis. Patient and tumor characteristics are described in **Table 1**.
- 807 plasma samples were analyzed, ranging from 2 to 16 timepoints per patient (median=10). Follow-up time ranged from 6 to 30 months (median=15). 67 patients had confirmed pathologic response data available.
- Baseline ctDNA, prior to any neoadjuvant treatment initiation, was detected in 76 of 82 (93%) patients, with tumor fraction ranging from 4.3 parts per million (PPM) to 610,011 PPM (median 971) (**Figure 2**).
- Many patients showed robust ctDNA clearance during neoadjuvant chemotherapy (NAC) (**Figure 3a**). ctDNA levels declined rapidly across cycles: by 50 days after therapy initiation, 58% were ctDNA-, and by day 100, 70% were ctDNA- (**Figure 3b**). HER2+ and TNBC tumors demonstrated faster clearance compared to HR+ tumors (**Table 2**).

Figure 2. Baseline ctDNA Levels

Baseline ctDNA levels for all 82 patients and subdivided as labeled. 59 (78%) patients were ctDNA+ > 100 PPM, 17 (21%) were ctDNA+ < 100 PPM, and 6 (7%) were ctDNA-.

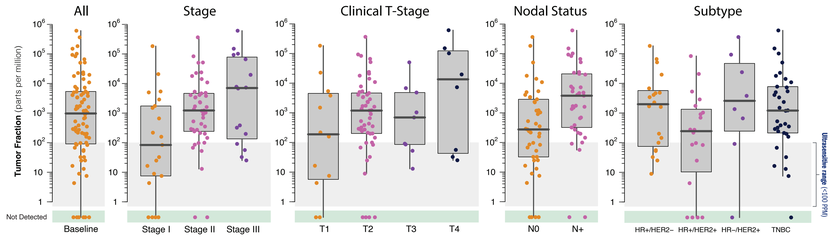


Figure 3a. Rapid ctDNA Clearance Observed for Majority of Patients

Swimmer plots show ctDNA levels (circles), treatments (lines), and pathological response (open squares), if known, for 60 of 82 (73%) patients in which ctDNA levels became persistently negative.

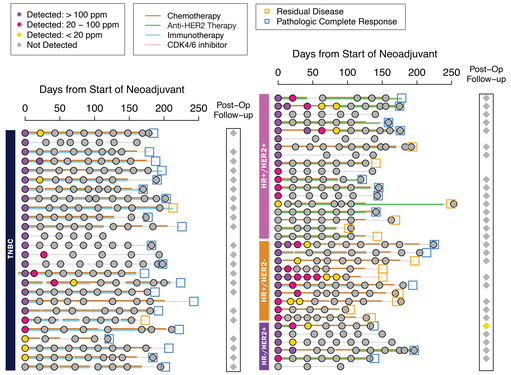


Figure 3b. ctDNA Clearance Dynamics

Spider plot shows the magnitude and timing for ctDNA clearance for the 60 patients shown in 3A.

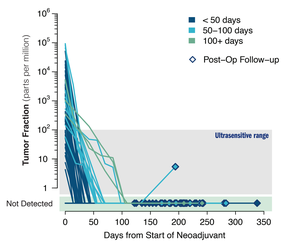


Table 2. ctDNA Clearance Dynamics by Subtype

Subtype	N	<50 days N (%)	<100 days N (%)	Before surgery N (%)
TNBC	34	24 (71%)	25 (74%)	26 (76%)
HR+ / HER2+	20	13 (65%)	16 (80%)	18 (90%)
HR- / HER2+	8	4 (50%)	6 (75%)	6 (75%)
HR+ / HER2-	20	5 (25%)	10 (50%)	10 (50%)
All	82	46 (58%)	57 (70%)	60 (73%)

- ctDNA levels were consistently positive in 12 (15%) patients; all 8 patients with pathological response data (100%) had residual disease, and patients were more likely to remain ctDNA+ following surgery ($p < 0.001$, **Figure 4**). A small set of patients had initially ctDNA- results followed by detection at the <20 PPM level (**Figure 5**).
- ctDNA- results at the end of therapy were significantly associated with pCR (p=0.0003, **Figure 6**).

Figure 4. Persistently ctDNA+ Patients at Higher Risk

Swimmer plots show ctDNA levels (circles), treatments (lines), and pathological response (open squares), if known, for 12 (15%) patients persistently ctDNA+. 8 patients had residual disease after NAC and 5 remained ctDNA+ after surgery.

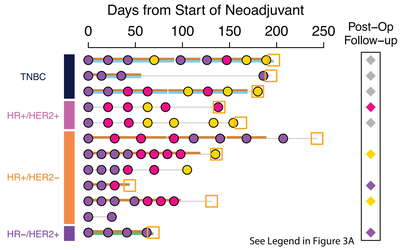


Figure 5. Intermittent ctDNA+ Associated with Residual Disease

Swimmer plots show ctDNA levels (circles), treatments (lines), and pathological response (open squares), if known, for 10 (12%) patients who became ctDNA+ after clearance. These patients were 12x more likely to have residual disease at surgery, compared to patients who persistently cleared ctDNA ($p = 0.01$, Fisher's exact test).

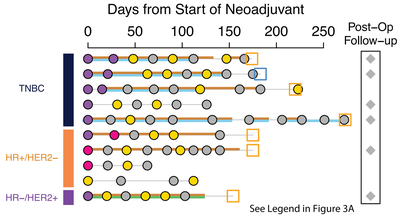
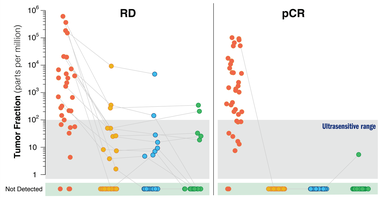
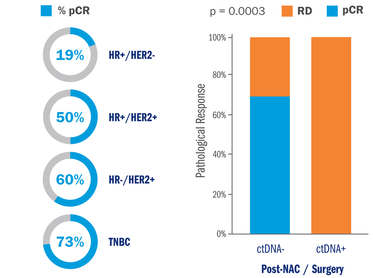


Figure 6. ctDNA Association with Pathological Response

(top) ctDNA levels at select timepoints. Lines connect patient timepoints for those ctDNA+ at lastest NAC, following NAC, and/or following surgery. All patients with pathologic complete response (pCR) cleared ctDNA prior to surgery. In contrast, those with residual disease (RD) were more likely to have detectable ctDNA prior to surgery, often at the ultrasensitive level. (bottom) ctDNA clearance was significantly associated with pCR (p=0.0003, Fisher's exact test).





Conclusions

- Ultrasensitive, personalized ctDNA monitoring enables high-resolution tracking of treatment response.
- ctDNA clearance following neoadjuvant therapy was significantly associated with pCR. Additional analyses are required to determine the association between ctDNA clearance dynamics and association with pCR.
- These findings establish the feasibility and clinical relevance of integrating ultrasensitive ctDNA assays into real-time neoadjuvant treatment management.

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