Personalized circulating tumor DNA testing for detection of progression and treatment response monitoring in patients with metastatic invasive lobular carcinoma

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Background

- Metastatic invasive lobular carcinoma (mILC) presents unique clinical challenges and can be difficult to monitor radiographically.
- More accurate biomarkers are needed for real-time assessment of response to treatment.
- This real-world study demonstrates the feasibility of longitudinal ctDNA testing for treatment response monitoring in patients with mILC.

Methods

- Longitudinal plasma samples (n=333) were collected from 66 patients with mILC treated between 5/20/21 and 10/4/23.
- A personalized, tumor-informed assay (Signatera™, Natera, Inc.) was used for the detection and quantification of ctDNA in plasma samples.

Figure 1. Signatera workflow

Table 1. Patient characteristics (N=66)

Parameter	Value (range) or # Patients (%)
Median age at baseline* in years	62.6 (32.2-79.7)
Tumor type	
HR+HER2-	56 (84.9)
HR+HER2+	6 (9.1)
HR-HER2+	1 (1.5)
Triple negative breast cancer (TNBC)	2 (3.0)
Not available	1 (1.5)
Treatment	
Endocrine therapy	55 (83)
CDK4-6 targeted therapy	41 (62)
Chemotherapy	37 (56)
Radiotherapy	33 (50)
HER2 targeted therapy	12 (18)
Other	10 (15)
Site of metastasis	
Bone and/or GI	44 (66.7)
Lung, liver, and/or skin (no bone)	20 (30.3)
CNS only	1 (1.5)
Not available	1 (1.5)
ctDNA status	
Serially positive	39 (59.1)
Serially negative	14 (21.2)
Mixed	13 (19.8)
CA 15-3 levels (N=23)**	
≥30 U/mL at any time point	19 (82.6)
<30 U/mL at all time points	4 (17.4)
CA 27-29 levels (N=21)***	
≥38 U/mL at any time point	20 (95.2)
<38 U/mL at all time points	1 (4.8)

*Baseline: diagnosis of metastatic disease. **Of the 23 patients with CA 15-3 results, 17 (74%) were ctDNA-positive at least at one time point. ***Of the 21 patients with CA 27-29 results, 16 (76.2%) were ctDNA-positive at least at one time point. Abbreviations: GI, gastrointestinal; CNS, central nervous system.

Figure 2. Genomic alterations detected by whole exome sequencing

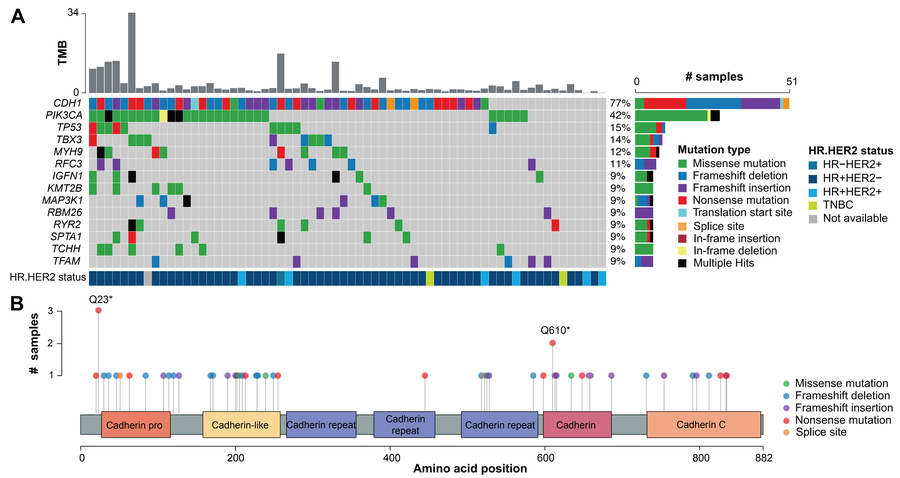

Figure 2. A. Oncoplot summarizing genomic features for all (N=66) patients in this cohort. The most frequent variants observed were: *PIK3CA* H1047R (12/66, 18.2%), *PIK3CA* N345K (4/66, 6.1%), *ESR1* D538G (3/66, 4.5%), and *CDH1* Q23* (3/66, 4.5%). **B.** Lolliplot showing *CDH1* mutations detected by whole exome sequencing in our cohort.

Figure 3. ctDNA detection rate and association of on-treatment ctDNA dynamics with clinical benefit

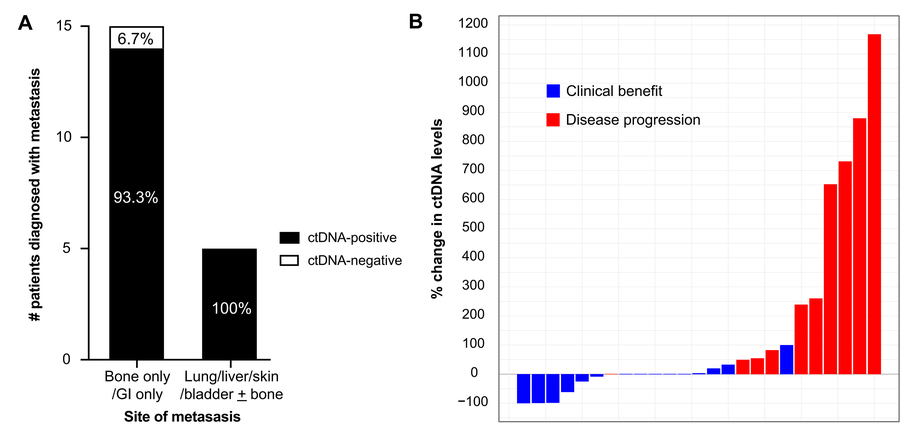

Figure 3. A. Bar plot showing ctDNA status of patients with mILC categorized by location of metastases. ctDNA status was considered evaluable if ctDNA testing occurred within 3 months of diagnosis. An additional 29 patients had bone only and/or GI metastases but did not have evaluable ctDNA at the time of diagnosis. An additional 15 patients had lung/liver/axillary/skin ± bone metastases but did not have evaluable ctDNA at the time of diagnosis. **C**. Waterfall plot showing the association of on-treatment ctDNA dynamics with clinical benefit. All (N=6, 100%) treatment events that resulted in a decrease in ctDNA levels led to clinical benefits, whereas only 31% (4/13) of treatment events that resulted in an increase in ctDNA levels led to clinical benefits. Among the 6 treatment events with no associated change in ctDNA levels, 83% (5/6) resulted in clinical benefit.

Figure 4. Prognostic value of ctDNA testing in patients with mILC receiving treatment

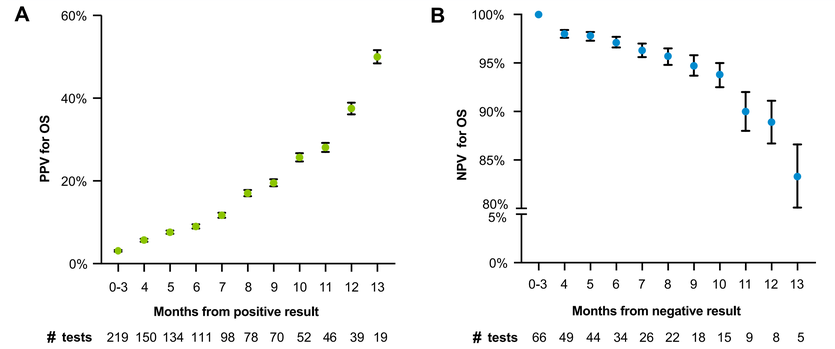

Figure 4. PPV and NPV for subsequently predicting a survival event over different timeframes after a positive (A) or negative (B) ctDNA test. Error bars indicate 95% confidence intervals. Notably, NPV remained high (>95%) at 7 months after each negative ctDNA test. Abbreviations: OS, overall survival; PPV, positive predictive value; NPV, negative predictive value.

Figure 5. Patient-specific changes in ctDNA levels in response to treatment

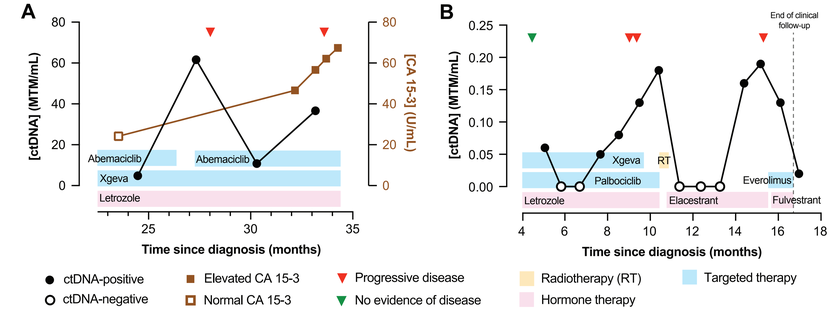

Figure 5. Patient-specific plots depicting treatment regimens, disease status by imaging, and changes in ctDNA levels in response to treatment. **A.** In a patient with ER+HER2- mILC, ctDNA increased after a month of interruption in abemaciclib therapy and restaging revealed progression of the disease. Resumption of abemaciclib therapy for 6 months resulted in an initial and transient molecular response. **B.** A patient with HR+HER- mILC, initially had response to a combination of targeted and hormone therapies. However, molecular recurrence was later observed, which triggered imaging and a biopsy-confirmed recurrence. Radiotherapy and switching to a different hormone therapy led to transient ctDNA clearance. However, subsequent on-therapy ctDNA detection triggered PET-CT which confirmed disease progression. The patient was then switched to a third-line therapy. Abbreviations: MTM, mean tumor molecules.

Conclusions

- ctDNA detection and dynamics correlated with clinical status determined by conventional monitoring tools in mILC patients.
- Personalized, longitudinal ctDNA testing may have utility in detecting progression and monitoring treatment response in patients with mILC.

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