Personalized circulating tumor DNA (ctDNA) testing, intervention, and temporal dynamics in ER+/HER2- early-stage breast cancer (LEADER)

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Arielle J. Medford[1,2], Carly Bess Scalise[3], Simrita Dhulekar[1], Zachary Smolar[1], Andrzej Niemierko[1], Ekaterina Kalashnikova[3], Angel Rodriguez[3], Laura M. Spring[1], Janice Kim[1], Amy Comander[1], Aron Rosenstock[1], Jeffrey Peppercorn[1], Jennifer Shin[1], Lowell Schnipper,[4] Heather Benjamin[1], Steven J. Isakoff[1], Leif Ellisen[1], Dejan Juric[1], Beverly Moy[1], Minetta C. Liu[3], Alexey Aleshin[3], Aditya Bardia[5]

[1]Mass General Brigham Cancer Institute and Harvard Medical School, Boston, MA, USA; [2]Broad Institute of MIT and Harvard, Boston, MA, USA; [3]Natera, Inc., Austin, TX, USA; [4]Beth Israel Deaconess Medical Center, Boston, MA; [5]UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA.

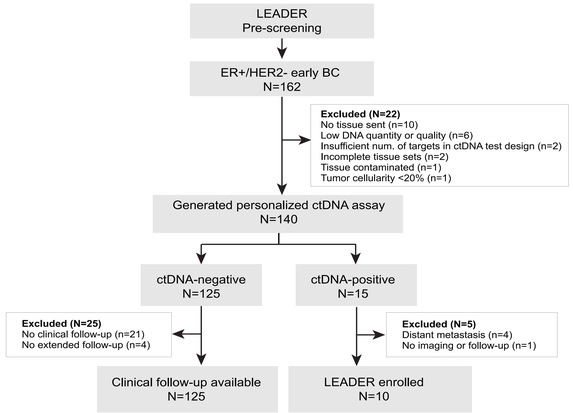
Background

- Detectable circulating tumor (ct)DNA after definitive therapy for breast cancer, termed molecular residual disease, is associated with a very high risk of cancer recurrence.[1,2]
- The phase II LEADER study (NCT03285412) evaluated the efficacy of adding the CDK4/6 inhibitor ribociclib to adjuvant endocrine therapy for patients with ER+/HER2- early-stage breast cancer (eBC) and detectable ctDNA after definitive surgery.[3]

Methods

- All patients completed surgical resection prior to ctDNA testing, as well as adjuvant chemotherapy and radiation (if indicated), and were receiving adjuvant endocrine therapy when they underwent ctDNA testing.
- ctDNA testing was performed via a personalized, tumor-informed mPCR-NGS assay (Signatera™, Natera, Inc.).
- Patients with detectable ctDNA during surveillance were then enrolled in LEADER and treated with 400 mg daily ribociclib with an aromatase inhibitor for 1 year. Premenopausal patients also received ovarian suppression.
- Imaging studies at the time of ctDNA detection were not required and were left to the discretion of the treating physician. On-treatment plasma samples were collected serially during follow-up visits at 3, 6, and 12 months after starting ribociclib treatment.
- The primary endpoint was the proportion of patients with molecular response at completion of 12 cycles of adjuvant ribociclib.

Figure 1. CONSORT diagram



Our findings highlight the clinical utility of ctDNA monitoring in ER+/HER2− early breast cancer, aiding in patient selection for trial enrollment and as an early predictor of relapse

Figure 2. A) Cumulative ctDNA-positivity rate, B) Clinical outcomes in ctDNA-negative patients, C-D) Clinical outcomes in ctDNA-positive patients

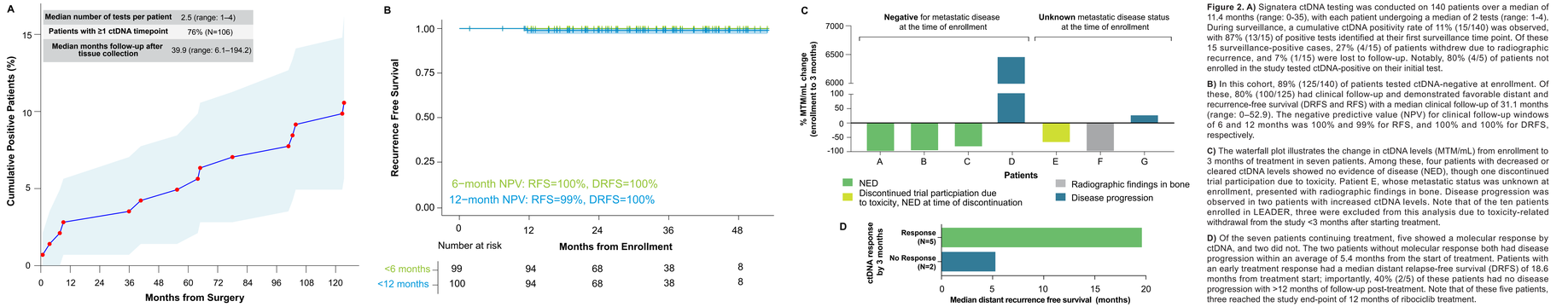


Figure 2. A) Signatera ctDNA testing was conducted on 140 patients over a median of 11.4 months (range: 0-35), with each patient undergoing a median of 2 tests (range: 1-4). During surveillance, a cumulative ctDNA positivity rate of 11% (15/140) was observed, with 87% (13/15) of positive tests identified at their first surveillance time point. Of these 15 surveillance-positive cases, 27% (4/15) of patients withdrew due to radiographic recurrence, and 7% (1/15) were lost to follow-up. Notably, 80% (4/5) of patients not enrolled in the study tested ctDNA-positive on their initial test.

B) In this cohort, 89% (125/140) of patients tested ctDNA-negative at enrollment. Of these, 80% (100/125) had clinical follow-up and demonstrated favorable distant and recurrence-free survival (DRFS and RFS) with a median clinical follow-up of 31.1 months (range: 0–52.9). The negative predictive value (NPV) for clinical follow-up windows of 6 and 12 months was 100% and 99% for RFS, and 100% and 100% for DRFS, respectively.

C) The waterfall plot illustrates the change in ctDNA levels (MTM/mL) from enrollment to 3 months of treatment in seven patients. Among these, four patients with decreased or cleared ctDNA levels showed no evidence of disease (NED), though one discontinued trial participation due to toxicity. Patient E, whose metastatic status was unknown at enrollment, presented with radiographic findings in bone. Disease progression was observed in two patients with increased ctDNA levels. Note that of the ten patients enrolled in LEADER, three were excluded from this analysis due to toxicity-related withdrawal from the study <3 months after starting treatment.

D) Of the seven patients continuing treatment, five showed a molecular response by ctDNA, and two did not. The two patients without molecular response both had disease progression within an average of 5.4 months from the start of treatment. Patients with an early treatment response had a median distant relapse-free survival (DRFS) of 18.6 months from treatment start; importantly, 40% (2/5) of these patients had no disease progression with >12 months of follow-up post-treatment. Note that of these five patients, three reached the study end-point of 12 months of ribociclib treatment.

Figure 3. A-C) ctDNA detection and outcomes after ribociclib, D) Correlation with ctDNA velocity with relapse status

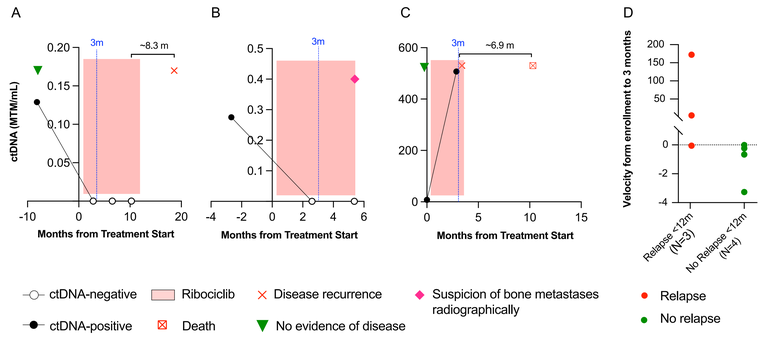


Figure 3. A) This patient without metastatic disease achieved ctDNA clearance within the first three months of treatment and maintained a sustained molecular response to ribociclib. However, approximately seven months after treatment discontinuation, the patient experienced progression to the CNS and bone. This case underscores the importance of post-treatment ctDNA testing for monitoring risk of progression.

B) This patient, initially presenting with unknown baseline metastatic disease, achieved ctDNA clearance within the first three months of treatment, followed by a subsequent ctDNA-negative test. However, a new bone lesion observed 5.4 months into treatment led to the suspicion of bone metastases and treatment discontinuation. There was no baseline imaging, and given the sustained ctDNA response, it is unclear if these findings were treatment-related bone flare or new metastatic disease.

C) This patient without metastatic disease experienced a rapid increase in ctDNA levels (MTM/mL) during the initial three months of treatment, followed by distant progression and subsequent death.

D) Scatter plot of ctDNA velocity (change in MTM/mL over time) for patients who tested ctDNA-positive at enrollment to 3-months on-treatment time point. Patients are grouped by best response within the first year: Relapse (N=3) for those with disease relapse, and No Relapse (N=4) for those without. Of six patients with negative baseline imaging, one relapsed within 4 months of starting ribociclib, and two relapsed after 12 months of treatment. Note that three enrolled patients were excluded from this analysis due to toxicity-related withdrawal at <3 months of treatment.

Conclusions

- ctDNA positivity during surveillance accurately identified patients at high risk of recurrence.
- Persistent ctDNA negativity was associated with better RFS and DRFS.
- Patients exhibiting favorable ctDNA dynamics during the initial three cycles of therapy experienced fewer and delayed relapse events compared to those with unfavorable dynamics.
- These findings support the utility of ctDNA-based molecular surveillance to evaluate therapeutic interception and monitoring treatment response in ER+/HER2- eBC.

References

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Disclosures

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