Monitoring for response and recurrence in neoadjuvant-treated hormone receptor-positive HER2-negative breast cancer by personalized circulating tumor DNA testing

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Background

- The detection of circulating tumor DNA (ctDNA) may serve as an early predictor of response and recurrence.[1]
- A tumor-informed ctDNA test was used to monitor clinical outcomes in patients with high-risk hormone receptor-positive HER2-negative (HR+HER2-) tumors who received neoadjuvant chemotherapy (NAC) on the I-SPY 2 trial (NCT01042379).

Methods

- Blood samples were collected at pretreatment (T0), during paclitaxel-based treatment (T1 and T2; at 3 and 12 weeks after initiation of treatment with or without an investigational drug), after NAC prior to surgery (T3), 4 weeks after surgery (T4), and annually until a clinical diagnosis of recurrence (T5 onwards) (**Figure 1A**).
- Cell-free DNA was isolated from plasma (N=329 samples) and ctDNA was detected using a personalized, tumor-informed multiplex polymerase chain reaction next generation sequencing-based test (Signatera™) (**Figure 1B**).
- The response endpoints were pathologic complete response and residual cancer burden; the survival endpoint was event-free survival.

Conclusions

- The persistence of ctDNA during neoadjuvant therapy is associated with the extent of residual disease in a cohort of patients with HR+HER2- breast cancer in the I-SPY 2 trial.
- Identifying patients who are not having an optimal response to therapy may be possible by monitoring ctDNA.
- I-SPY 2.2 will test whether ctDNA has utility in redirecting therapy to improve surgical outcomes and subsequent prognosis.

Patient Advocate's Perspective

Using blood-based liquid biopsy to evaluate the presence of circulating tumor DNA (ctDNA) offers a promising approach to revolutionizing early breast cancer management and treatment. ctDNA shed from tumors into the blood can be measured at the start of, during, and after treatment. This study finds that the persistence of ctDNA from HR+/HER2- patients, over the course of treatment and beyond, is associated with poorer (response) outcomes than the absence or reduction of ctDNA. Knowledge gained from this study could identify breast cancers that could recur and require additional or revised treatment. The goal is to identify treatment resistance early enough to avoid metastasis. – Amy L. Delson, UCSF Breast Science Advocacy Core

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1. Magbanua MJM, et al. Annals of Oncology. 2021;32(2):229-239.

Figure 1. Study schema and ctDNA analysis platform

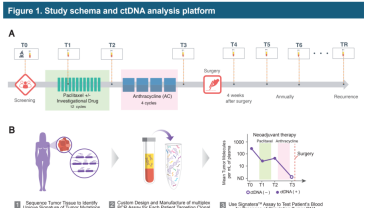

Table 1. Patient demographics and tumor characteristics (All patients, N=66)

Patient characteristics	Age (years)	
Age (mean)	47.5	
Tumor characteristics	**n**	**%**
Clinical T stage (n=58)		
T1/T2	37	63.8
T3/T4	21	36.2
Clinical N stage (n=58)		
Node-negative	16	27.6
Node-positive	42	72.4
Grade (n=66)		
I/II	24	42.9
III	32	57.1
MammaPrint score		
High 1	44	66.7
High 2	22	33.3
Treatment arm		
Paclitaxel	16	24.2
Paclitaxel + Durvalumab + Olaparib	12	18.2
SD-101 + Pembrolizumab	13	19.7
Paclitaxel + Pembrolizumab 8-Cycle + AC	10	15.2
9GN-LIV1A	6	9.1
Hinotecan + Talazoparib	3	4.5
Paclitaxel + Cemiplimab	2	3
Paclitaxel + Ganetespib	2	3
Paclitaxel + Pembrolizumab	1	1.5
Paclitaxel + Cemiplimab + REGN3767	1	1.5
Pathologic complete response		
pCR	10	15.2
no pCR	56	84.8
Residual cancer burden		
RBC 0	10	15.2
RBC I	7	10.6
RBC II	31	47
RBC III	18	27.3

The persistence of ctDNA during neoadjuvant therapy is associated with the extent of residual disease in patients with HR+HER2- breast cancer (I-SPY 2 trial)

Figure 2. Overview plot showing patient ctDNA status over time and recurrences

Figure 2. A. This analysis included 66 patients with HR+HER2- breast cancer who had blood samples collected before, during, and after NAC and had at least one blood sample after surgery with sufficient plasma for analysis. Of the 66 patients, 61 had event-free survival (EFS) data with a median of 1.6 years of follow-up (range: 0.6-5.6 years). Five patients tested ctDNA-positive at least at one time point after surgery. Of these, 2 experienced a recurrence (one local relapse and one distant metastasis) and both tested positive at the time of recurrence. For the patient who developed a distant recurrence (Patient # 58), it was the only blood sample available at a follow-up time point; for the patient who developed a local recurrence (Patient # 27), data from two earlier follow-up time points had tested negative. To date, no recurrences have been observed in those whose test(s) after surgery were negative for ctDNA, demonstrating a negative predictive value (NPV) of 100%. Alternate patient IDs have been indicated in the figure.

Figure 3. ctDNA positivity rates and association between ctDNA status and tumor stage, grade, MammaPrint, pCR and RCB

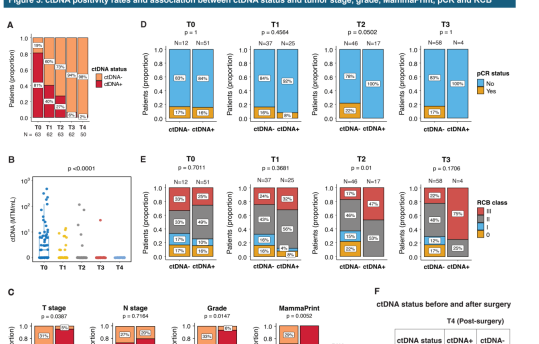

Figure 3. A. The percent ctDNA positivity rates at pretreatment, after NAC prior to surgery, and 4 weeks after surgery were 81.0% (51/63), 6.5% (4/62), and 2% (1/50), respectively. **B.** Significantly lower ctDNA levels were observed after neoadjuvant treatment and surgery. **C.** Significantly higher ctDNA positivity rates at pretreatment (T0) were observed in patients with larger tumors (95% in T3/T4 vs. 69% in T1/T2, Fisher's exact p=0.0387), higher grade tumors (94% in Grade III vs. 67% in Grade I/II, p=0.0147) and by MammaPrint score (100% in High 2 vs. 71% in High 1, p=0.0052). **D.** No significant correlation was observed between ctDNA-positivity and pCR at any time point. **E.** ctDNA-positivity after paclitaxel-based treatment (T2) was significantly associated with RCB II/III status (Fisher's exact p=0.01). All patients in this cohort with persistent ctDNA subsequently had RCB II or III at surgery. **F.** Of the total 66 patients, 47 had paired samples collected after NAC prior to surgery (T3) and at 4 weeks after surgery (T4). Of the 47, 91.5% (43/47) were ctDNA-negative at both time points and 8.5% (4/47) were discordant; 1 was ctDNA-negative after NAC prior to surgery but later tested ctDNA-positive, while 3 were ctDNA-positive and later tested ctDNA-negative. NAC: neoadjuvant chemotherapy; MTM/mL: mean tumor molecules per mL of plasma; pCR: pathologic complete response; RCB: residual cancer burden.