Predictive and prognostic significance of circulating tumor DNA dynamics in response-predictive subtypes (RPS) of breast cancer: Results from the I-SPY2 trial

M. Magbanua[1], D. Wolf[1] , N. Manon [1] , R. Sayaman[1], L. Brown Swigart [1] , G. Hirst [1] , C. Yau[2] , W. Li[3] , C. Isaacs[4] , R. Shatsky [5] , A. Clark [6] , A. Zimmer [7] , A. Delson [8] , J. Perlmutter [9] , M. Liu [10] , P. Pohlmann [11] , N. Hylton [3] , R. Nanda [12] , D. Yee [13] , W. Symmans [14] , L. Esserman [2] , H. Rugo [15] , A. DeMichele [6] , L. van 't Veer [1]

[1] Laboratory Medicine, University of California San Francisco, San Francisco, CA, [2] Department of Surgery, University of California San Francisco, San Francisco, CA, [3]Department of Radiology, University of California San Francisco, San Francisco, CA, [4] Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, San Francisco, DC, [5] Department of Medicine, University of California San Diego, San Diego, CA, [6] Division of Hematology/Oncology, University of Pennsylvania, Philadelphia, PA, [7] Division of Hematology/Oncology, Oregon Health and Science University, Portland,OR, [8] Breast Science Advocacy Core, University of California San Francisco, San Francisco, CA, [9] ISPY2 Advocacy Group, University of California San Francisco, San Francisco, CA, [10] NA, Natera Inc, San Carlos, CA, [11] Department of Breast Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, [12] Department of Hematology and Oncology, University of Chicago, Chicago, IL, [13] Division of Hematology, Oncology, and Transplantation, University of Minnesota, Minneapolis, MN, [14] Department of Pathology, University of Texas MD Anderson Cancer Center, Houston,TX, [15] Division of Hematology/Oncology, University of California San Francisco, San Francisco, CA.

BACKGROUND

- ctDNA dynamics are emerging as a component of promising biomarker for predicting treatment response and survival.
- Here, we examined the prognostic and predictive significance of ctDNA in the context of a novel transcriptomic subtyping schema, called response-predictive subtypes (RPS), that was developed in I-SPY2 to predict neoadjuvant therapy (NAT) response.
- The schema combined immune, DNA repair deficiency (DRD), and luminal expression signatures in pretreatment tumors, with HR and HER2 status.
- The RPS is an evolving schema that is updated, based on new findings from I-SPY2 and other neoadjuvant breast cancer clinical trials, to improve its predictive accuracy.
- We examined the correlation between ctDNA dynamics and residual cancer burden (RCB) after NAT and distant recurrence-free survival (DRFS) across RPS.
- In I-SPY2, we integrate changes in ctDNA with imaging changes by MRI functional tumor volume (FTV) to obtain response prediction driven by direct tumor (FTV) and circulating biomarkers (ctDNA).

METHODS

- This is a retrospective study involving 719 patients with high-risk early-stage breast cancer who were enrolled in the I-SPY2 trial (NCT01042379) between 2010-2022.
- ctDNA was detected in blood collected at baseline (T0) and on-treatment at week 3 (T1) and week 12 (T2, post-paclitaxel before anthracycline), and post-NAT before surgery (T3) using a personalized tumor-informed 16-plex mPCR-NGS assay (Signatera, Natera, Inc.).
- Patients with ctDNA data were grouped by ctDNA dynamics. We assessed the correlation between ctDNA dynamics with RCB using Fisher's Exact tests. Cox regression analysis was performed to compare DRFS between groups.
- The RPS was then divided into 2 groups, "treatment-sensitive" and "treatment-resistant", based on response rates observed in 10 I-SPY2 regimens (Figure 1).

Patients and their breast cancer subtypes

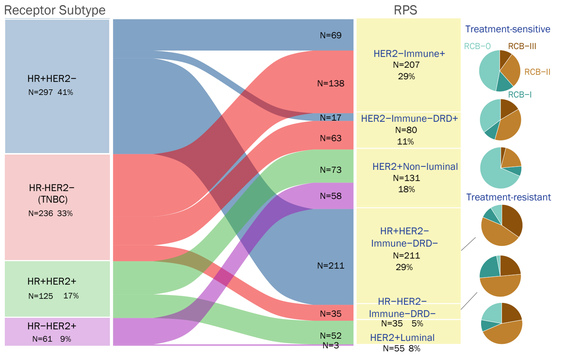


Figure 1. RPS were grouped into treatment-sensitive, i.e., those with high pathological complete response (pCR) rates [HER2-Immune+ (n=207, 29%), HER2-Immune-DRD+ (n=80, 11%), and HER2+Non-luminal (n=131, 18.%)] when treated with the best matched therapeutic option (e.g., immunotherapy for HER2-Immune+) vs. treatment-resistant, i.e., those that have shown low pCR rates to nearly every class of agent/combination tested in I-SPY2 to date [HR+HER2-Immune-DRD- (n=211, 29%), HR-HER2-Immune-DRD- (n=35, 5%), and HER2+Luminal (n=55, 8%)].

Prognostic value of ctDNA dynamics

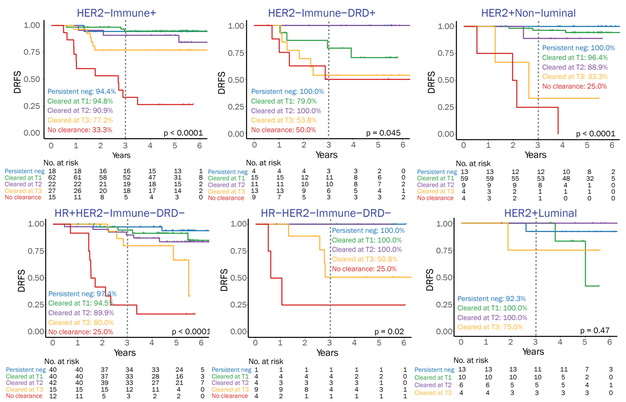


Figure 4. Survival curves across RPS categorized as "treatment-sensitive" (top panel) or "treatment-resistant" (bottom panel) were visualized using the Kaplan-Meier analysis. Patients with complete ctDNA data for 4 time points were stratified by ctDNA dynamics: (1) persistent ctDNA -negative, (2) cleared at T1 or week 3, (3) cleared at T2 or week 12, (4) cleared at T3 or post-neoadjuvant therapy, and (5) no ctDNA clearance at T3. The 3-year distant recurrence-free survival (DRFS) rates are shown for each group.

ctDNA dynamics in HER2-Immune+ subtypes

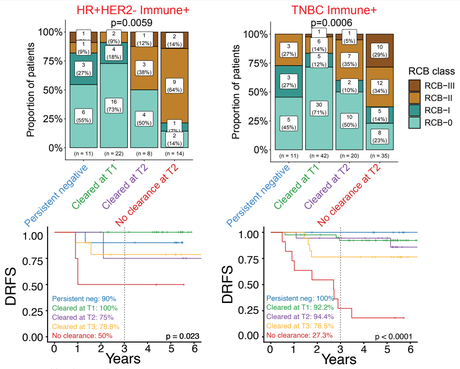


Figure 5. Predictive and prognostic significance of ctDNA dynamics in HER2-Immune+ patients with HR+ or TN breast cancers.

Early ctDNA dynamics

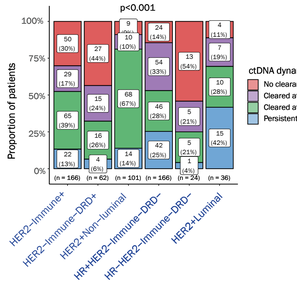


Figure 2. Patients across RPS stratified by early ctDNA dynamics: persistent negative, cleared at T1 (week 1) or T2 (week 12), and no clearance at T2 (week 12). The RPS were categorized as "treatment-sensitive" or "treatment-resistant".

Predictive value of ctDNA dynamics

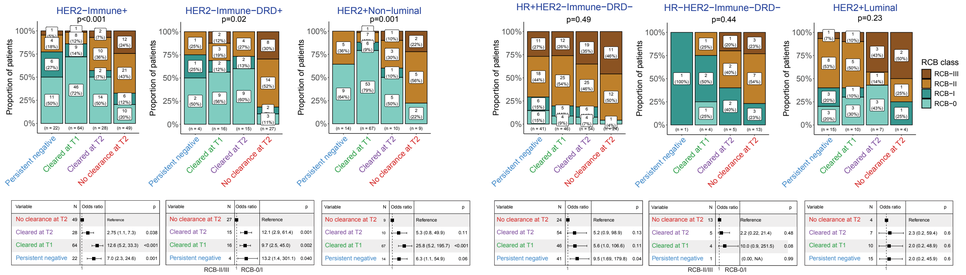


Figure 3. The bar plots show the proportion of residual burden (RCB) classes in each early ctDNA dynamics group. The percentages may not add up to 100% due to rounding. The p-values were calculated using the Chi-squared test. Forest plots from logistic regression analyses show the estimated odds ratio and 95% confidence intervals. The p-values were calculated from likelihood ratio tests.

CONCLUSIONS

- The proportion of patients who cleared ctDNA early varied significantly across RPS, ranging from 21% (HR-HER2-Immune-DRD-) to 67% (HER2+Non-luminal).
- In the treatment-sensitive RPS, we observed a strong association between early ctDNA clearance and treatment response. Early ctDNA clearance significantly improved the odds of achieving an RCB-0/RCB-I.
- Patients who did not clear ctDNA post-NAT had significantly shorter DRFS than other groups across all RPS (all log-rank p<0.05), except in the HER2-positive/Luminal subtype, where none were ctDNA-positive post-NAT.

FUTURE DIRECTIONS

The new iteration of the I-SPY2 trial, called I-SPY2.2, still retains a subtype-driven approach that uses the RPS schema to optimize treatment selection. While the RPS continues to evolve based on results from I-SPY2.2 and other neoadjuvant breast cancer trials, our findings offer insights into how ctDNA assessment can be combined with transcriptomic subtyping of breast cancers. Ongoing studies in I-SPY2.2 examine how ctDNA, along with imaging and pathology information, can complement the updated RPS schema to enhance prediction of treatment response and survival.

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