The Pathologic Response Evaluation and Detection in Circulating Tumor-DNA Study: Ultrasensitive Circulating Tumor-DNA Assessment of Breast Cancer Minimal Residual Disease

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ABSTRACT

PURPOSE Patients with stage II/III human epidermal growth factor receptor 2 (HER2)–positive or triple-negative breast cancer (TNBC) frequently receive neoadjuvant therapy (NAT). Although pathologic complete response (pCR) correlates with improved outcomes, many non-pCR patients have long-term survival. Circulating tumor-DNA (ctDNA) minimal residual disease (MRD) assessment may provide additional or superior risk stratification.

METHODS Pathologic Response Evaluation and Detection in Circulating Tumor-DNA is a prospective, multicenter study evaluating ctDNA as a biomarker of treatment response using a tumor-informed, ultrasensitive (<100 parts per million) assay. The primary objective was to determine whether the negative predictive value (NPV) of post-NAT ctDNA for pCR was ≥90%. A prespecified secondary objective for the TNBC cohort was to assess associations between ctDNA and 5-year invasive disease-free survival (IDFS). ctDNA was evaluated at baseline, after NAT before surgery, and after surgery.

RESULTS Of 227 enrolled patients, 220 were evaluable for pCR (48% HER2-positive; 52% TNBC) and 91 patients (41%) had pCR. The primary objective was not met. Although all patients with pCR were ctDNA-negative after NAT, 40% of non-pCR patients were also ctDNA-negative (NPV, 60% [95% CI, 0.50 to 0.69]). However, the prespecified secondary objective was met. Detectable ctDNA after NAT was prognostic for recurrence (hazard ratio [HR], 8.9 [95% CI, 2.4 to 33]; $P = .001$), independent of pCR. Additionally, detectable ctDNA after surgery identified patients at extremely high recurrence risk (HR, 128 [95% CI, 15 to 1,083]; $P < .001$), while ctDNA-negative patients after surgery had 94% 5-year IDFS.

CONCLUSION In HER2-positive breast cancer and TNBC, ctDNA after NAT does not discriminate pCR from non-pCR. However, ctDNA provides markedly superior prognostic stratification, identifying patients with exceptional outcomes and those at extreme risk. These findings support ctDNA-guided therapeutic de-escalation and escalation strategies.

ACCOMPANYING CONTENT

Data Sharing Statement

Data Supplement

Protocol

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INTRODUCTION

Patients with stage II or III human epidermal growth factor receptor 2 (HER2)–positive or triple-negative breast cancer (TNBC) are often treated with neoadjuvant therapy (NAT) before surgery. Pathologic complete response (pCR) after NAT is associated with improved survival in these subtypes,[1-3] although some patients remain at risk for

CONTEXT

Key Objective

Can an ultrasensitive (<100 part per million detection), tumor-informed circulating tumor-DNA (ctDNA) assay serve as a diagnostic tool to detect minimal residual disease in early-stage triple-negative breast cancer (TNBC) with high accuracy?

Knowledge Generated

Ultrasensitive ctDNA detection after neoadjuvant therapy and after surgery demonstrates that ctDNA status can serve as a diagnostic marker of residual disease for patients with TNBC. After surgery and adjuvant therapies, ultrasensitive assessment of ctDNA demonstrates that all ctDNA-positive patients will recur, and that 94% of ctDNA-negative patients remain disease-free at 5 years (hazard ratio, 128 [95% CI, 15 to 1,083]; $P < .001$).

Relevance *(K.D. Miller)*

Ultrasensitive ctDNA testing distinguishes patients with very different risks of recurrence. However, routine use cannot be recommended and may lead to harm if effective therapies are withheld in those who are ctDNA-negative and ineffective, but toxic therapies are offered to those who are ctDNA-positive.*

*Relevance section written by *JCO* Senior Deputy Editor Kathy D. Miller, MD.

recurrence. Conversely, many patients without pCR have favorable outcomes, underscoring that risk stratification beyond pCR is needed.[4] Indeed, pCR and outcomes vary widely across clinical trials depending on breast cancer subtype, systemic therapies used, and the definition of pCR.[5] Regardless, most patients who receive NAT but have residual cancer at surgery (non-pCR) receive adjuvant therapy to eradicate microscopic, minimal residual disease (MRD).[6,7] Unfortunately, this paradigm exposes non-pCR patients without MRD to unnecessary toxicity since there are currently no reliable diagnostic tests to measure MRD accurately.

Liquid biopsies assessing circulating tumor-DNA (ctDNA) are used routinely to predict response to targeted therapies for many cancers.[8] Recent studies have evaluated the potential of ctDNA to guide therapies for early-stage breast cancer.[9-11] Here, we report results from the Pathologic Response Evaluation and Detection in Circulating Tumor-DNA (PREDICT-DNA) study, launched in 2016 by the Translational Breast Cancer Research Consortium (TBCRC) and the Johns Hopkins Clinical Research Network (JHCRN). PREDICT-DNA is a large prospective, multicenter study to independently validate ctDNA as a biomarker for treatment response and recurrence in early-stage, HER2-positive (any hormone receptor status) breast cancer or TNBC. The primary objective of PREDICT-DNA was to determine the negative predictive value (NPV) of undetectable ctDNA for predicting pCR after NAT. A prespecified secondary objective was to estimate the prognostic value of ctDNA for 5-year invasive disease-free survival (IDFS) in TNBC patients after completion of locoregional and systemic therapies.

METHODS

Patients

The PREDICT-DNA trial enrolled patients from 2016 to 2018 across 24 TBCRC and JHCRN sites in the United States. Patients were eligible for enrollment if they were age at least 18 years, and had a diagnosis of untreated, stage II or III (T1c, nodal stage N1-2, or tumor stage T2-4, nodal stage N0-2, per anatomic staging criteria of the American Joint Committee on Cancer, 7th edition[12]), HER2-positive (any hormone receptor status) breast cancer or TNBC for whom NAT was planned and would be projected to have at least a 30% rate for pCR. Full eligibility criteria are included in the trial protocol available with the full text of this article.

Study Design

This prospective multi-institutional study collected blood, tumor tissue, and clinical data for clinical validation. Blood samples were collected at baseline before NAT was initiated (T0) and at completion of NAT before surgery (T1). Blood samples were additionally collected at 6 months and then yearly for up to 5 years for analysis of secondary aims (T2 and beyond). Tumor NGS and personalized informed ctDNA assays were performed as previously described.[13] Complete methods are provided in the Data Supplement (online only). Clinical data were blinded to research team members performing the ctDNA analyses.

Assessments

Clinical data were collected, including biopsy and surgery pathology reports and notes from the original diagnosis,

information regarding NAT regimens, and twice yearly clinical reports regarding recurrence and survival for up to 5 years. pCR was defined as no residual invasive or in situ disease in the breast and ipsilateral lymph nodes after NAT.

Statistical Analysis

For the primary objective, the sample size was calculated by simulation to provide a ≥90% probability of yielding at least 37 ctDNA-negative patients at T1, which would afford >80% power when the true NPV = 0.90 using a one-sided binomial test with H0 = 0.80 and alpha = .05. Additional assumptions for the primary objective were that 85% of patients would be evaluable for ctDNA, that 24% of patients would have pCR, and 80% of those, or approximately 20% of the total, would be disease-free and ctDNA-negative, and allowance was made for attrition.

A prespecified secondary objective was to validate the association of presence or absence of ctDNA and IDFS in TNBC patients. HER2-positive patients were not included for this prespecified secondary objective due to the expected low recurrence rate, although data were still analyzed. For the prespecified secondary objective, rates are calculated as simple proportions and presented with exact binomial confidence intervals. Survival curves are estimated by using the Kaplan-Meier method and compared using the log-rank test. Multivariate analyses are performed using Cox regression. Summary statistics, including hazard ratios, survival rates at 3-year and 5-year time points, and median survival time, are presented with confidence intervals, and *P* values when relevant. Landmark analyses are used to evaluate T1 blood samples for patients who completed surgery, as well as to evaluate early detection of relapse in postsurgical blood samples collected at T2 and beyond.

RESULTS

Patient Characteristics

Between 2016 and 2018, 227 participants were enrolled across 24 sites in the United States. The number of patients eligible at each point for ctDNA analysis is shown in Figure 1. Two hundred twenty patients were evaluable for pCR, and 183 patients were included in the ctDNA study cohort, as shown in Table 1, and were representative of the overall population. Of these 183 patients, 97 (53%) had TNBC and 86 (47%) had HER2-positive disease. The mean (±standard deviation) age at diagnosis was 49.1 ± 12.5 years (median, 50.5) for HER2-positive disease and 48.4 ± 12.3 years (median, 47.0) for TNBC subgroups. The majority of patients (75%) were diagnosed with clinical stage II disease (HER2-positive, 71%; TNBC, 79%).

Patients were treated with cytotoxic chemotherapy regimens appropriate for their subtype, primarily dose-dense doxorubicin followed by paclitaxel (ddAC-T) for TNBC (58%), and docetaxel/carboplatin/trastuzumab/pertuzumab or ddAC-T plus trastuzumab and pertuzumab for HER2-positive disease (65% and 17%, respectively; Data Supplement, Table S1). Of note, the KEYNOTE 522 regimen was not approved in patients with TNBC during the study period, although four patients with triple-negative disease may have received neoadjuvant immunotherapy on randomized, placebo-controlled trials. pCR was observed in 91 of 220 evaluable patients (41%), including 50% (52 of 105 patients) of those with HER2-positive disease and 41% (47 of 115 patients) of those with TNBC. Adjuvant capecitabine was approved in 2017 for TNBC patients with non-pCR and was allowed after a study amendment. Additional adjuvant therapies were also permitted, either through clinical trials or off-label use (Data Supplement, Table S2).

As shown in Figure 2, 165/177 (93%) evaluable patients had detectable ctDNA at T0, with a higher rate of ctDNA detection in patients with TNBC (90/91; [99%]) compared with HER2-positive disease (74/86; [86%]; Fisher exact test $P = .001$). Of note, of the 97 evaluable patients with TNBC with at least one ctDNA sample, 91 had a baseline ctDNA (T0) assessment. Among patients with HER2-positive disease, those with hormone receptor–positive tumors were less likely to have detectable ctDNA (49/59; [83%]) compared with those with hormone receptor–negative disease (25/27; [93%]; Fisher exact test $P = .32$).

Clearance of ctDNA After NAT Does Not Predict for pCR Versus Non-pCR

The primary objective of PREDICT-DNA was to determine whether undetectable ctDNA at the post-NAT time point (T1) would predict pCR with an acceptably low false-negative rate. The rationale was that if NPV was ≥90%, future studies could address whether patients with detectable ctDNA at baseline who cleared their ctDNA to undetectable levels after NAT could safely forego surgery. Among 100 of 129 evaluable patients with undetectable ctDNA at T1, 40 had non-pCR at surgery, resulting in an NPV of 60% (95% CI, 0.50 to 0.69), which did not meet the primary objective of the study (Data Supplement, Table S3).

ctDNA Status at T1 Is Prognostic of Disease Recurrence

To determine whether T1 ctDNA status provides prognostic information independent of established clinicopathologic risk factors, we initially performed an unplanned multivariable Cox proportional hazards analysis for IDFS in the combined HER2-positive breast cancer and TNBC cohorts. The Data Supplement (Fig S1) shows the fraction of patients lost to follow-up over 6 years after surgery. Median follow-up time was 4.67 years for the entire cohort and 4.66 years for evaluable patients with ctDNA. Median follow-up was 4.53 years for triple-negative patients and 4.83 years for HER2-positive patients. Models were adjusted for key baseline variables, including nodal status (positive *v* negative), pCR versus non-pCR, tumor grade (1, 2, 3), and patient age. In these adjusted analyses, T1 ctDNA

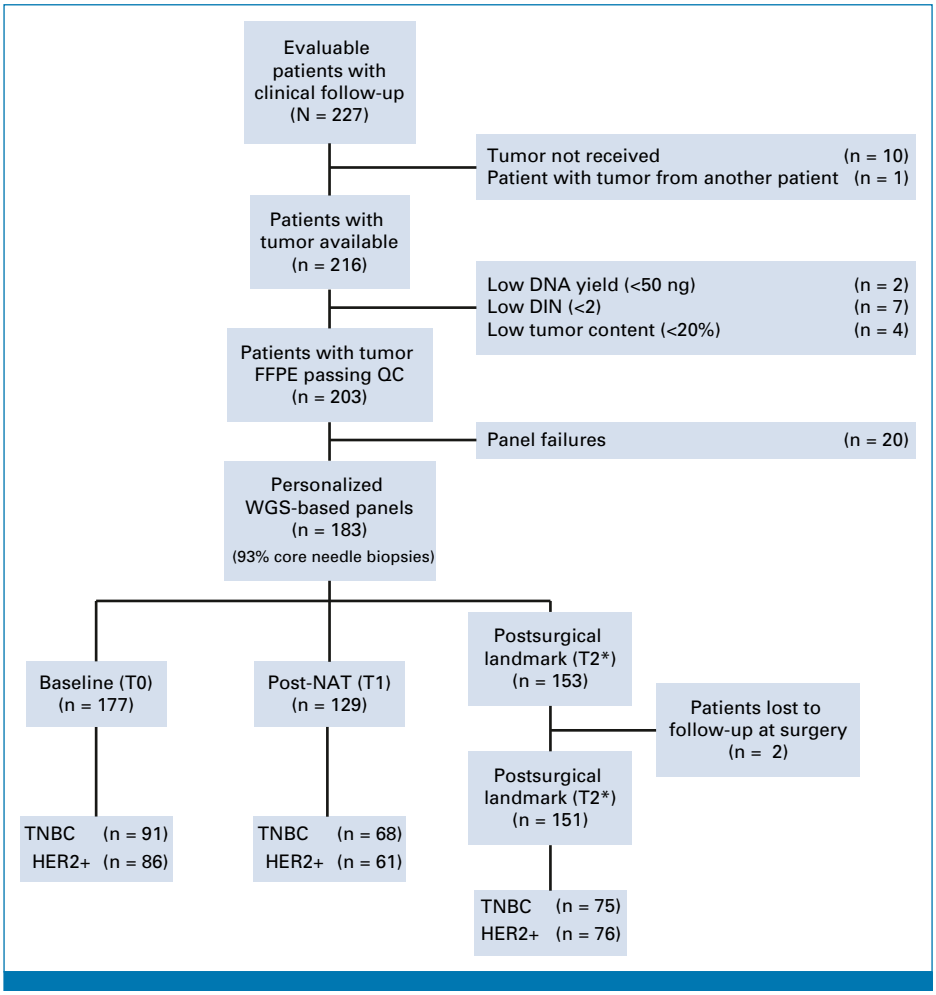

FIG 1. CONSORT diagram for the PREDICT-DNA trial. DIN, DNA integrity number; FFPE, formalin-fixed paraffin-embedded; HER2+, human epidermal growth factor receptor 2-positive; TNBC, triple-negative breast cancer; WGS, whole genome sequencing; QC, quality control.

status remained the most significant independent prognostic signal of IDFS across all patients. Specifically, compared with patients who tested ctDNA-negative at T1, patients who were ctDNA-positive at T1 exhibited a significantly increased risk of recurrence (hazard ratio [HR], 8.9 [95% CI, 1.92 to 41.1]; $P = .005$). Non-pCR (HR, 1.5 [95% CI, 0.28 to 8.5]; $P = .62$) and positive nodal status (HR, 1.5 [95% CI, 0.49 to 4.7]; $P = .47$) were not significant independent predictors in this model (Data Supplement, Fig S2A).

T1 ctDNA Status in Patients With TNBC

As a prespecified secondary objective, we assessed the prognostic value of ctDNA and IDFS for patients with TNBC. Patients with non-pCR (59%) had a lower 3- and 5-year IDFS rate compared with those who had pCR (76% *v* 95%, and 76% *v* 90%, respectively), although the association was not statistically significant (HR, 3.4 [95% CI, 0.75 to 16]; $P = .11$; Fig 3A). Of note, three of the 40 non-pCR patients had in situ only disease after NAT, although a fourth patient had in situ disease with nodal involvement (Table 2). By contrast, patients with detectable ctDNA at T1 had a much lower 3- and 5-year IDFS rates compared with those with undetectable ctDNA (57% *v* 95%, and 57% *v* 92%, respectively), which was highly significant (HR, 8.9 [95% CI, 2.4 to 33]; $P = .001$; Fig 3B). Notably, all patients with detectable ctDNA at T1 were also non-pCR.

Undetectable ctDNA at T1 was associated with favorable outcomes irrespective of pCR status (Fig 3C). Fifty percent of patients with TNBC who had non-pCR did not have detectable ctDNA at T1 (Table 2). Patients who were non-pCR, but ctDNA-negative, had an estimated 3-year IDFS rate of 94% (HR, 12 [95% CI, 1.6 to 90]; $P = .017$), similar to the 96% 3-year IDFS rate observed among patients who had pCR (HR, 7.1 [95% CI, 1.5 to 33]; $P = .012$). Furthermore, in a bivariate Cox regression model of patients with TNBC adjusting for both T1 ctDNA and pCR, only T1 ctDNA status remained as an independent, statistically significant predictor for recurrence (HR for ctDNA positivity, 12 [95% CI, 1.52 to 95]; $P = .019$), unlike pCR status (HR for

TABLE 1. Demographic and Clinical Characteristics of Evaluable Patients

Patient Characteristic	HER2, n = 86 (47%)	TNBC, n = 97 (53%)	Overall, N = 183 (100%)
Age at diagnosis, years			
Mean (SD)	49.1 (12.5)	48.4 (12.3)	48.7 (12.3)
Median	50.5	47.0	48.0
Min, max	25.0, 76.0	24.0, 78.0	24.0, 78.0
Stage, No. (%)			
I	1 (1)	0 (0)	1 (1)
II	61 (71)	77 (79)	138 (75)
III	24 (28)	20 (21)	44 (24)
Estrogen receptor, No. (%)			
Neg	27 (31)	96 (99)	123 (67)
Pos	59 (69)	1 (1.0)	60 (33)
Menopausal status, No. (%)			
Postmenopausal	37 (43)	41 (42)	78 (43)
Premenopausal	49 (57)	56 (58)	105 (57)
Surgery, No. (%)			
Lumpectomy	37 (43)	40 (41)	77 (42)
Mastectomy	46 (53)	56 (58)	102 (56)
No surgery/unknown	3 (4)	1 (1)	4 (2)

Abbreviations: HER2, human epidermal growth factor receptor 2; SD, standard deviation; TNBC, triple-negative breast cancer.

non-pCR, 1.7 [95% CI, 0.15 to 18]; $P = .68$; Data Supplement, Fig S2B). In a preliminary, unplanned analysis, we evaluated the ctDNA detected in the ultrasensitive (<100 parts per million [PPM]) versus nonultrasensitive (≥100 PPM) range. Ultrasensitive ctDNA detection, which accounted for 45% of the T1 ctDNA detections, had a recurrence risk comparable with detections in the nonultrasensitive range, with a 3-year IDFS rate of patients with ultrasensitive detections at 74% and those categorized as nonultrasensitive detections at 45% (HR, 2.9 [95% CI, 0.59 to 14]; $P = .19$; Fig 2D).

Of the non-pCR patients with TNBC (excluding patient 4-002 who was randomly assigned on a trial), all underwent definitive surgery after NAT, and 23/39 (59%) received adjuvant therapy (Table 2). The majority of these patients (14/23; 61%) received capecitabine, although some received platinum, and among evaluable patients, one received pembrolizumab. To assess whether adjuvant therapy affected the prognostic significance of the T1 time point for patients with triple-negative disease, we performed an exploratory analysis of non-pCR patients stratified by T1 ctDNA status. Among ctDNA-negative patients, 7/18 (39%) nonrecurrent patients and the single recurrent patient (1/1, 100%) received adjuvant systemic therapy ($P = .42$, Fisher exact test). Among ctDNA-positive patients, 7/11 (64%) nonrecurrent patients and 8/9 (89%) recurrent patients received adjuvant systemic therapy ($P = .32$, Fisher exact test). This analysis does not provide clear evidence that adjuvant therapy affects the prognostic value of the T1 ctDNA assessment.

T1 ctDNA Status in Patients With HER2-Positive Breast Cancer

We performed a post hoc exploratory analysis evaluating the association of recurrence risk with pCR and ctDNA at T1 in patients with HER2-positive breast cancer. In this cohort, pCR status after NAT was found not to be significantly associated with recurrence risk (Data Supplement, Fig S3A). The 3-year IDFS rate for patients with non-pCR was 84%, compared with 93% for those with pCR (HR, 1.1 [95% CI, 0.27 to 4.3]; $P = .92$). However, patients with T1 ctDNA-positive results had a lower 3-year IDFS rate (62%) compared with those without detectable ctDNA (93%; HR, 4.4 [95% CI, 1 to 18]; $P = .045$; Data Supplement, Fig S3B). In an unplanned multivariate analysis evaluating the prognostic significance of both pCR status and T1 ctDNA detection, ctDNA status showed the stronger association with outcome, although neither factor achieved statistical significance (Data Supplement, Fig S2C). Similar to patients with TNBC, T1 ctDNA negativity was associated with favorable outcomes regardless of pCR status. The 3-year IDFS of patients with T1 ctDNA-negative status was similar in patients with non-pCR or pCR (94% and 93%, respectively; Data Supplement, Fig S3C). Because of the small number of recurrences, analysis between ctDNA-positive results in the ultrasensitive versus nonultrasensitive range was not performed.

Postsurgical ctDNA Is Prognostic for Disease Recurrence

We conducted a postsurgical landmark window analysis of IDFS and ctDNA status of any plasma sample collected up to

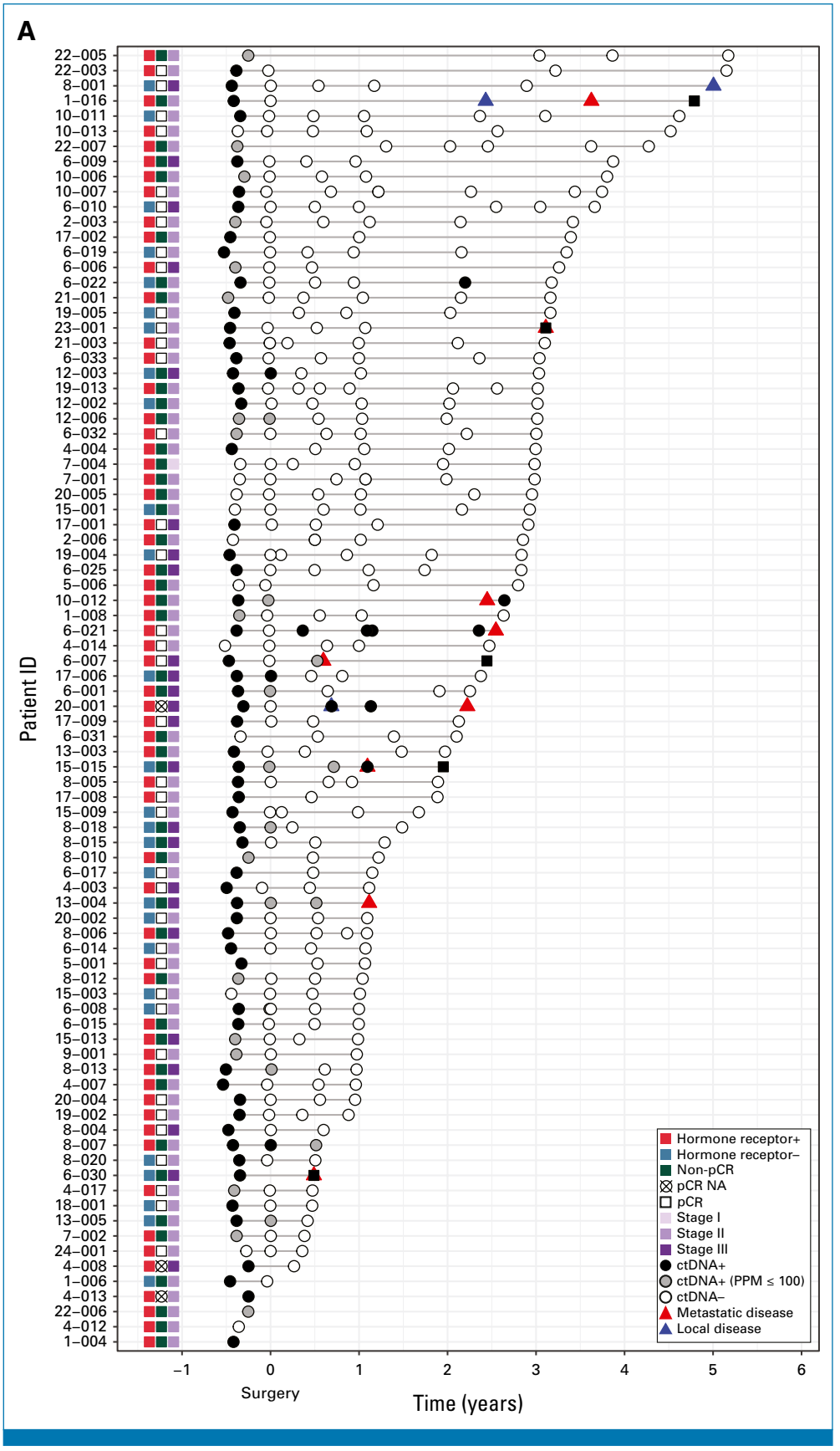

FIG 2. Study cohort with ctDNA. Swimmer plots of patients with (A) HER2-positive breast cancer and (B) triple-negative breast cancer. The first circle represents the T0 ctDNA baseline samples, the second circle represents T1 ctDNA after NAT before surgery, and subsequent (continued on following page)

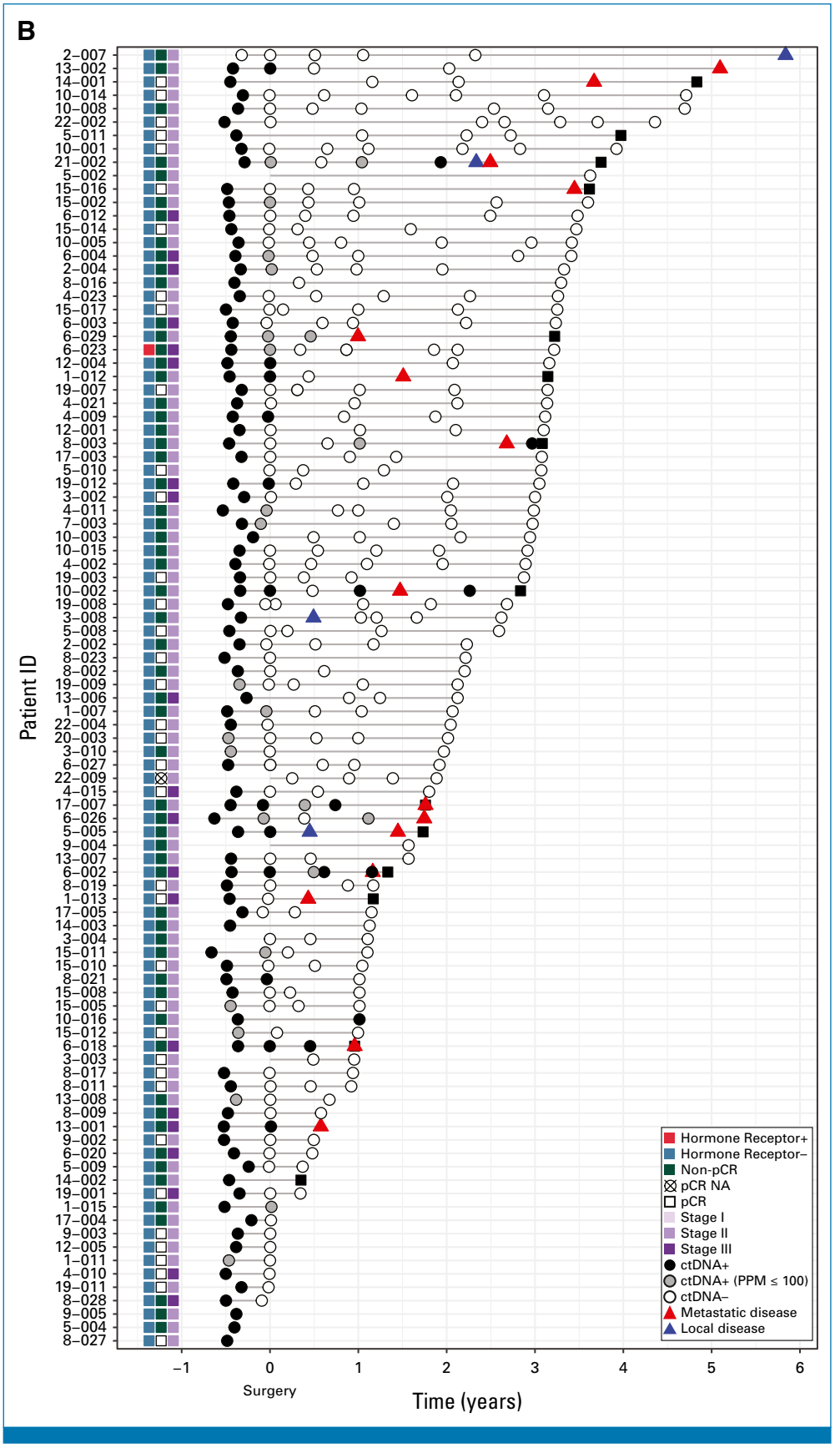

FIG 2. (Continued). circles are additional ctDNA time points after surgery. ctDNA, circulating tumor-DNA; HER2, human epidermal growth factor receptor 2; NAT, neoadjuvant therapy; pCR, pathologic complete response; PPM, parts per million.

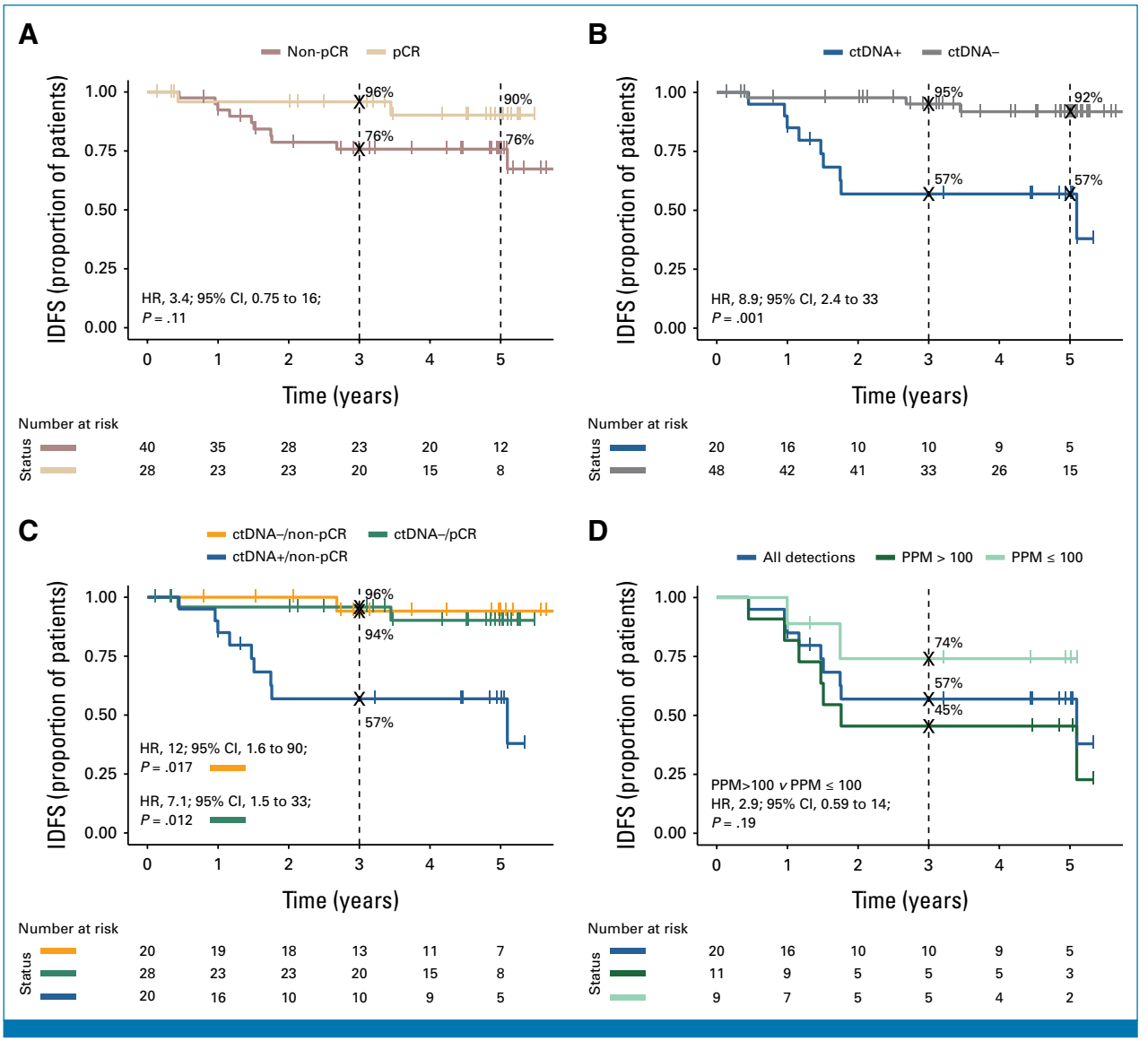

FIG 3. T1 ctDNA status is prognostic of IDFS in patients with triple-negative breast cancer. KM estimates of IDFS according to (A) pCR or non-pCR, (B) T1 ctDNA status, (C) T1 ctDNA and pCR status, and (D) T1 ctDNA level (ultrasensitive [<100 PPM] or nonultrasensitive [≥100 PPM]). Global *P* value was calculated using a log-rank test. Tick marks indicate censored data. ctDNA, circulating tumor-DNA; HR, hazard ratio; IDFS, invasive disease-free survival; KM, Kaplan-Meier; pCR, pathologic complete response; PPM, parts per million.

12 months after surgery, hereafter designated T2*. Post-surgical ctDNA status was evaluated for 153 patients who provided at least one plasma sample within the first year after surgery. When multiple samples were collected in this period, the last ctDNA test was used. Two patients, one HER2-positive breast cancer and the other with TNBC, had no clinical follow-up after their T2* blood draw. Of the remaining 151 patients, a total of 136 (90%) were ctDNA-negative at T2*, of which 135/136 (99%) patients did not relapse by 3 years, and 132/136 (97%) did not relapse by 5 years.

Conversely, A total of 15/151 (10%) of these patients were ctDNA-positive at T2*. Thirteen of these 15 patients (87%) had at least 3 years of follow-up, and all had recurrence during this period. Nine of these 13 patients (69%) had ctDNA detected in the ultrasensitive range (<100 PPM). ctDNA positivity at T2* predated the clinical recurrence, with a median lead time of 7.9 months (range, 5.5-20.3 months) for eight patients with TNBC, and 5.9 months (range, 0.8-26.6 months) for five HER2-positive patients.

Postsurgical T2* ctDNA and Recurrence in Patients With TNBC

Patients with TNBC who were ctDNA-negative at T2* exhibited the lowest risk of recurrence, with 98% and 94% remaining recurrence-free at 3 and 5 years, respectively (median IDFS not reached; Fig 4A). Patients who were T2* ctDNA-positive had the highest risk of recurrence (HR, 128

TABLE 2. Clinical-Pathologic Features of T1 ctDNA-Negative and ctDNA-Positive Patients With Non–Pathologic Complete Response and Triple-Negative Breast Cancer

Patient	T1 ctDNA	Residual Disease	Adjuvant Therapy	T2* ctDNA	Recurrence
2-002	Negative	ypTis, ypNmi	None	Negative	No
2-007	Negative	ypT1a, ypN0	None	Negative	No
3-004	Negative	ypT1, ypN0	Carboplatin	Negative	No
3-010	Negative	ypT1c, ypN0	None	Not available	No
4-002	Negative	ypT1a, ypN0	PARP inhibitor *v* placebo (trial)	Negative	No
5-009	Negative	ypT1mi, ypN0	None	Negative	No
6-003	Negative	ypT1c, ypN0	Carboplatin	Negative	No
6-012	Negative	ypT2, ypN0	Capecitabine	Negative	No
6-020	Negative	ypT1c, ypN0	Capecitabine	Negative	No
8-002	Negative	ypT1a, ypN0	None	Negative	No
8-003	Negative	ypT1a, ypN0	Cisplatin	Positive	Yes
8-028	Negative	ypT1mic, ypN0	None	Not available	No
10-005	Negative	ypT1c, ypN1a	Cisplatin	Negative	No
10-008	Negative	ypT1b, ypN0	Capecitabine	Negative	No
10-015	Negative	ypT1c, ypN0	None	Negative	No
13-007	Negative	ypTis, ypN0	None	Negative	No
13-008	Negative	ypT1mi, ypN0	None	Negative	No
15-008	Negative	ypTis, ypN0	None	Negative	No
17-003	Negative	ypT1b, ypN0	Capecitabine	Negative	No
17-005	Negative	ypTis, ypN0	None	Negative	No
1-007	Positive	ypTX, ypN1mi	Capecitabine	Negative	No
1-012	Positive	ypT2, ypN1mi	Capecitabine	Negative	Yes
4-009	Positive	ypT2, ypN1mi	Capecitabine	Negative	No
4-011	Positive	ypT1mi, ypN3a	Capecitabine	Negative	No
5-005	Positive	ypT1c, ypN0	Capecitabine	Not available	Yes
6-002	Positive	ypT2, ypN1mi	Capecitabine	Positive	Yes
6-004	Positive	ypT1, ypN0	None	Negative	No
6-018	Positive	ypT2, ypN1a	HP[a]	Positive	Yes
6-023	Positive	ypT1a,ypN0 (i+)	Capecitabine	Negative	No
6-026	Positive	ypT1c(m), ypN1a	Carboplatin	Positive	Yes
6-029	Positive	ypT1b, ypN1mi	Carboplatin	Positive	Yes
7-003	Positive	ypT2, ypN1a	AC	Negative	No
8-021	Positive	ypT1, ypN1	Capecitabine	Negative	No
10-002	Positive	ypT3, ypN2	AC, HP, AI[b]	Positive	Yes
12-004	Positive	ypT2, ypN0	Capecitabine, pembrolizumab	Not available	No
13-002	Positive	ypT2, ypN0	None	Negative	Yes
15-002	Positive	ypT1b, ypN0	None	Negative	No
15-011	Positive	ypT1a, ypN0	None	Negative	No
17-007	Positive	ypT2, ypN1a	Capecitabine	Positive	Yes
19-012	Positive	ypT2, ypN0	None	Negative	No

Abbreviations: AC, doxorubicin, cyclophosphamide; AI, aromatase inhibitor; ctDNA, circulating tumor-DNA; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HP, trastuzumab, pertuzumab; PR, progesterone receptor.
[a]Tumor converted from triple-negative at biopsy to ER−/PR−, HER2+ at surgery.
[b]Tumor converted from triple-negative at biopsy to ER−/PR+, HER2+ at surgery.

[95% CI, 15 to 1,083]; $P < .001$) and shorter median IDFS (approximately 21 months). Prognosis could be further stratified by considering both T1 ctDNA status and T2* ctDNA status (Fig 4B). For this analysis, of the 20 patients with TNBC who were ctDNA-positive at the T1 time point, 18 had evaluable ctDNA samples at both T1 and T2*. Twelve patients were ctDNA-positive at T1, but ctDNA-negative at T2*, and this group showed a trend toward increased risk of

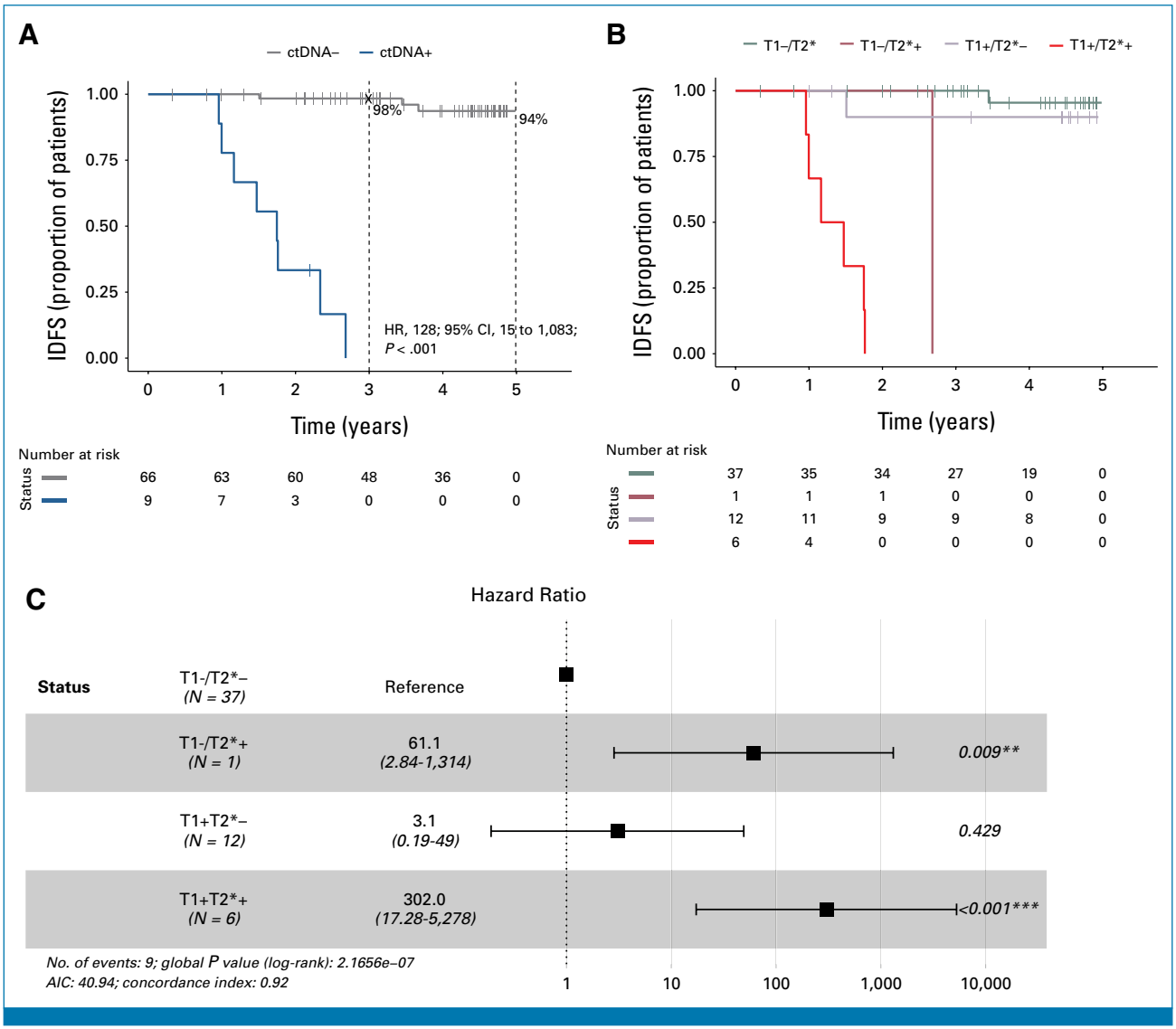

FIG 4. T2* postsurgical ctDNA status is prognostic of outcomes. KM estimates of IDFS in patients with TNBC according to (A) T2* postsurgical ctDNA status and (B) T1 and T2* combined status. (C) Forest plot of hazard ratios for IDFS using T1 and T2* ctDNA status in patients with TNBC. Global *P* value was calculated using a log-rank test. Tick marks indicate censored data. ctDNA, circulating tumor-DNA; IDFS, invasive disease-free survival; KM, Kaplan-Meier; TNBC, triple-negative breast cancer.

recurrence compared with persistently ctDNA-negative patients (HR, 3.1 [95% CI, 0.19 to 49]; $P = .42$), with two of the 12 patients having recurrence, although this was not statistically significant (Figs 4B and 4C, Table 2). The two patients who recurred included one with metaplastic breast cancer and brain metastases diagnosed 60 months after surgery, and another patient who recurred with lung metastases 18 months after surgery. Conversely, a single patient, who converted from ctDNA-negative at T1 to ctDNA-positive at T2*, also recurred (HR, 61.1 [95% CI, 2.84 to 1,314]; $P = .009$; Figs 4B and 4C, Table 2). Patients with ctDNA-positive results at both T1 and T2* had the highest risk of recurrence (six recurrences among 6 patients) and a median IDFS of 15.8 months (HR, 302 [95% CI, 17.28 to 5,278]; $P < .001$).

Postsurgical T2* ctDNA and Recurrence in Patients With HER2-Positive Breast Cancer

Similar to patients with TNBC, patients with HER2-positive breast cancer who were ctDNA-negative at T2* exhibited the lowest risk of recurrence. All ctDNA-negative patients remained recurrence-free at 3 years (median IDFS not reached). Conversely, patients who were ctDNA-positive at T2* had a significantly higher risk of recurrence (HR, 263 [95% CI, 27.2 to 3,538]; $P < .001$) and shorter median IDFS (approximately 13.3 months; Data Supplement, Fig S4A). Akin to the TNBC cohort, prognosis could be further stratified by considering T1 ctDNA status in addition to the ctDNA status at T2*. Patients with ctDNA-positive results at T1 who remained ctDNA-positive at T2* had shorter median IDFS

than patients who were ctDNA-negative at T1 (18.9 months *v* 13.4 months; Data Supplement, Fig S4B). For this HER2-positive subgroup, a small number of recurrence events resulted in sparse data, rendering the point estimate of the hazard ratio imprecise.

DISCUSSION

To our knowledge, PREDICT-DNA is the first multicenter prospective study designed to analyze the association between ctDNA and pCR in patients with stage II and III breast cancer undergoing NAT using an ultrasensitive ctDNA assay. Our primary objective was not met, showing that clearance of ctDNA at T1 has an NPV of 60%. However, the analysis of our prespecified secondary objective demonstrates that clearance of ctDNA at T1 is an independent, and possibly superior, prognostic indicator of IDFS at 3 and 5 years compared with pCR, with a HR of 8.9 (95% CI, 2.4 to 33; $P = .001$) for patients with TNBC. Moreover, postsurgical ctDNA status (T2*) for patients with TNBC also had strong prognostic significance, with ctDNA-positive patients having a much worse prognosis than ctDNA-negative patients (HR, 128 [95% CI, 15 to 1,083]; $P < .001$), regardless of pCR status.

Since the design of this trial, the standard neoadjuvant regimen for stage II/III TNBC in the United States has shifted to four chemotherapy agents (paclitaxel, carboplatin, doxorubicin, and cyclophosphamide) plus pembrolizumab.[14] Although this improves pCR rates, IDFS, and overall survival, it markedly increases grade 3/4 toxicities[14,15] and continues pembrolizumab adjuvantly, which is challenging for patients already experiencing immune-related side effects neoadjuvantly.[15] Many patients with non-pCR also receive adjuvant pembrolizumab and capecitabine per KEYNOTE 522 and CREATE-X.[6,14,16] In our study, four patients may have received neoadjuvant immunotherapy and two patients (one overlapping patient) may have received adjuvant pembrolizumab on clinical trials, but whether drug or placebo was administered is unknown. Additionally, three patients were known to have received adjuvant pembrolizumab with two (8-017 and 8-019) having pCR (Fig 2, Data Supplement, Table S2). Regardless, the majority did not receive this quintuplet regimen. This may amplify the impact of our findings: 50% of patients with non-pCR, TNBC were T1 ctDNA-negative, yet had similar outcomes as patients with pCR, and none of these patients received adjuvant pembrolizumab (Table 2). Thus, ultrasensitive ctDNA detection may function more as a diagnostic tool defining MRD status independent of therapy, akin to imaging, rather than solely a predictive/prognostic biomarker. Supporting this, patients converting from T1 ctDNA-positive to T2* ctDNA-negative had excellent outcomes, suggesting ctDNA/MRD clearance from surgery and/or adjuvant therapy. Notably, these patients represent the T1 ctDNA-positive, nonrecurrent cohort (IDFS at 3 and 5 years: 57% for both; Fig 3B, Table 2). Although this might appear to represent false positives, T2* ctDNA assessment reveal a striking dichotomy in outcomes between ctDNA-positive versus ctDNA-negative patients (Fig 4A), demonstrating that postsurgical assessment further refines risk stratification. Overall, these data highlight the strong prognostic value of T1 ctDNA and demonstrate the added utility of T2*, plausibly reflecting the impact of surgery and/or adjuvant therapy in those who convert to ctDNA-negative.

A key aspect of this study was the use of a next-generation ultrasensitive ctDNA detection assay, defined as ctDNA detection with a sensitivity of <100 cancer DNA molecules per one million wild-type DNA molecules, or <100 PPM, as previously described.[13] This tumor-informed assay is capable of ctDNA detection down to 1 PPM and affords high specificity with high sensitivity by virtue of assaying 200 to 1,800 individual somatic mutations for each patient's tumor. These personalized tumor-specific mutations are then queried for, using the patient's cell-free DNA sample. The use of an ultrasensitive assay identified ctDNA positivity at the baseline T0 time point in 93% of patients. Additionally, approximately half of our patients with TNBC and detectable T1 ctDNA were identified in the ultrasensitive range, yet these patients remained at risk for recurrence. The ultrasensitive detection of ctDNA likely contributes to the validity of T1 ctDNA as an independent prognostic marker for our study, and is consistent with the presence of ctDNA being a prognostic indicator, as in other studies.[17]

The results of this study also support correlative studies of several early-stage breast cancer trials, which analyzed ctDNA dynamics during NAT in patients with various breast cancer subtypes.[9-11] However, important differences between all these studies should be noted, including the timing of blood draws, different definitions of pCR, use of ctDNA assays with ultrasensitive versus sensitive detection for MRD, and other parameters unique for each study.[18] Thus, direct comparisons between studies cannot be made, although the totality of evidence suggests ctDNA detection for MRD is reproducible and feasible to guide future clinical decisions for early-stage breast cancers. Our study has several important and distinct factors among these studies: (1) To our knowledge, it is the first multi-institutional prospective study with prespecified objectives to evaluate the prognostic relationship of ctDNA with outcome using an ultrasensitive ctDNA test, (2) the T1 ctDNA time point is an independent biomarker of prognosis for stage II/III TNBC patients undergoing NAT and possibly superior to pCR, and (3) to our knowledge, it is the first study to use a postsurgical landmark analysis to definitively demonstrate that for patients with TNBC, ctDNA positivity uniformly is associated with disease recurrence, whereas ctDNA-negative patients, even those who were ctDNA-positive before surgery, have excellent outcomes. We believe these striking results have clinically validated ctDNA MRD assessment for early-stage TNBCs, and provide more precision and accuracy than past studies because of the use of ultrasensitive ctDNA detection.

Our study has several limitations, including the lack of multiple time point collections during the course of NAT, and a limited number of blood samples collected beyond 1 year postsurgery. Although statistically significant, the number of patients for some of our analyses was relatively small. However, for the T1 time point analysis for patients with TNBC, preliminary results from a similar study (SCANDARE) using the same ultrasensitive assay showed nearly identical results, confirming the reproducibility and validity of our findings.[19] We did not determine residual cancer burden (RCB)[20] scoring on all our patients, precluding comparisons of ctDNA with RCB scores. Finally, the inclusion of in situ disease as non-pCR may have improved this group's IDFS, lessening the impact of pCR as a prognostic indicator in our study.

In summary, to our knowledge, the PREDICT-DNA trial is the first multicenter prospective ctDNA trial in stage II or III patients with HER2-positive breast cancer or TNBC to show that clearance of ctDNA after NAT is an independent, and potentially superior, prognostic indicator of risk recurrence for patients with triple-negative disease. PREDICT-DNA also found that ctDNA MRD assessment up to 1 year after surgery can further refine the risk of recurrence with high accuracy. However, we strongly emphasize that these data clinically validate the assay, but further studies addressing clinical utility are needed before we can consider ctDNA MRD assessment as practice-changing. Importantly, ctDNA-positive patients face a substantially higher risk of recurrence, and may be appropriate candidates for enrollment in trials targeting molecular recurrence (eg, ASPRIA, ClinicalTrials.gov identifier: NCT04434040). These data also suggest that ctDNA-guided risk assessment could lead to more efficient trial designs by its use as an integral biomarker to safely exclude patients from unneeded additional therapies, that is, de-escalation trials. Conversely, escalation trials could be more robustly powered by enrolling only patients with the highest risk for recurrence, for example, ctDNA-positive patients, thus enabling smaller and more efficient trial design for early-stage disease.

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The Pathologic Response Evaluation and Detection in Circulating Tumor-DNA Study: Ultrasensitive Circulating Tumor-DNA Assessment of Breast Cancer Minimal Residual Disease

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