Caveolin Gene Expression Predicts Clinical Outcomes for Early-Stage HER2-Negative Breast Cancer Treated with Paclitaxel-Based Chemotherapy in the GeparSepto Trial

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ABSTRACT

Background: Caveolin-1 and -2 (*CAV1/2*) dysregulation are implicated in driving cancer progression and may predict response to nab-paclitaxel. We explored the prognostic and predictive potential of *CAV1/2* expression for patients with early-stage HER2-negative breast cancer receiving neoadjuvant paclitaxel-based chemotherapy regimens, followed by epirubicin and cyclophosphamide.

Patients and Methods: We correlated tumor *CAV1/2* RNA expression with pathologic complete response (pCR), disease-free survival (DFS), and overall survival (OS) in the GeparSepto trial, which randomized patients to neoadjuvant paclitaxel- versus nab-paclitaxel–based chemotherapy.

Results: RNA sequencing data were available for 279 patients, of which 74 (26.5%) were hormone receptor (HR)–negative, thus triple-negative breast cancer (TNBC). Patients treated with nab-paclitaxel with high *CAV1/2* had higher probability of obtaining a pCR [*CAV1* OR, 4.92; 95% confidence interval (CI), 1.70–14.22; $P = 0.003$; *CAV2* OR, 5.39; 95% CI, 1.76–16.47; $P = 0.003$] as compared with patients with high *CAV1/2* treated with solvent-based paclitaxel (*CAV1* OR, 0.33; 95% CI, 0.11–0.95; $P = 0.040$; *CAV2* OR, 0.37; 95% CI, 0.12–1.13; $P = 0.082$). High *CAV1* expression was significantly associated with worse DFS and OS in paclitaxel-treated patients (DFS HR, 2.29; 95% CI, 1.08–4.87; $P = 0.030$; OS HR, 4.97; 95% CI, 1.73–14.31; $P = 0.003$). High *CAV2* was associated with worse DFS and OS in all patients (DFS HR, 2.12; 95% CI, 1.23–3.63; $P = 0.006$; OS HR, 2.51; 95% CI, 1.22–5.17; $P = 0.013$), in paclitaxel-treated patients (DFS HR, 2.47; 95% CI, 1.12–5.43; $P = 0.025$; OS HR, 4.24; 95% CI, 1.48–12.09; $P = 0.007$) and in patients with TNBC (DFS HR, 4.68; 95% CI, 1.48–14.85; $P = 0.009$; OS HR, 10.43; 95% CI, 1.22–89.28; $P = 0.032$).

Conclusions: Our findings indicate high *CAV1/2* expression is associated with worse DFS and OS in paclitaxel-treated patients. Conversely, in nab-paclitaxel–treated patients, high *CAV1/2* expression is associated with increased pCR and no significant detriment to DFS or OS compared with low *CAV1/2* expression.

Introduction

Breast cancer is the most common type of cancer and a leading cause of cancer-related mortality in women (1). Classification and treatment of patients with breast cancer is usually based on the expression status of hormone estrogen receptor (ER), progesterone receptor (PR), and HER2 (2). Over the last couple of decades, the survival of patients with breast cancer has been greatly improved with multidisciplinary management. However, many patients die of breast cancer, and patients whose tumors have negative expression of ER, PR, and HER2 [triple-negative breast cancer (TNBC)] have a worse prognosis (1, 3, 4). Therefore, it is important to identify and validate biomarkers to prognosticate and predict efficacy of therapy for patients with HER2-negative breast cancer, both independent of and dependent on hormone receptor (HR) status.

Caveolae are 50 to 100 nm flask-shaped membrane invaginations, which play a pivotal role in endocytosis and transcytosis of nutrients and substances, including albumin (5, 6). Caveolae also play important roles in signal transduction, including EGFR, PDGRF, and IGFR signaling pathways (7–9). Caveolin-1 and -2 proteins, encoded by caveolin-1 (*CAV1*) and caveolin-2 (*CAV2*) genes, respectively, are responsible for the formation of caveolae (9, 10). In particular, CAV1 is the principal structural component of caveolae, whereas CAV2 is not required for caveolae formation (5, 11). Overexpression of caveolin family members has been implicated in driving breast cancer progression and also in predicting response to chemotherapy (12, 13).

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Translational Relevance

Classification and treatment of patients with breast cancer is usually based on the expression status of hormone estrogen receptor (ER), progesterone receptor (PR), and HER2. Patients with breast cancer with tumors classified as ER, PR, and HER2-negative (triple-negative breast cancer), have a worse prognosis. Therefore, it is important to identify and validate biomarkers to prognosticate and predict efficacy of therapy for patients with HER2-negative breast cancer. We explored the prognostic and predictive potential of *Caveolin-1 and -2* RNA expression for patients with early-stage HER2-negative breast cancer randomized to receive neoadjuvant paclitaxel or nab-paclitaxel–based chemotherapy in the GeparSepto trial. Our findings may support therapeutic decision making in HER2-negative breast cancer.

An association of Cav-1 protein expression response to nanoparticle albumin-bound paclitaxel (nab-paclitaxel) response was evidenced by findings in a phase II trial of patients with metastatic non–small cell lung cancer treated with nab-paclitaxel and carboplatin wherein improved response rates and survival were achieved if higher Cav-1 expression was found in the tumor microenvironment (14). In a previous report based on *in vitro* studies, we proposed the mechanism of action underlying the association of Cav-1 expression, and enhanced nab-paclitaxel efficacy was increased uptake via caveolae-mediated endocytosis (15) and a significant disease-free survival (DFS) benefit.

On the basis of our own studies and a report that *CAV1* expression has been shown to be elevated in TNBC (16), we investigated associations between tumor *CAV1* and *CAV2* expression and response to therapy in patients with HER2-negative early breast cancer in the GeparSepto trial wherein patients received either solvent-based paclitaxel (paclitaxel) or nab-paclitaxel, followed by epirubicin and cyclophosphamide chemotherapy for four cycles (every 3 weeks; refs. 17, 18). In the trial, weekly neoadjuvant nab-paclitaxel treatment elicited a greater pathologic complete response (pCR) rate compared with solvent-based paclitaxel (38% with nab-paclitaxel and 29% with paclitaxel; $P = 0.00065$) in patients with early breast cancer, and also demonstrated a significant DFS benefit, but without an impact on overall survival (OS; ref. 19–21).

Here, we present the results of a systematic correlation analysis of tumor *CAV1/2* RNA expression from available RNA sequencing (RNA-seq) data derived from HER2-negative tumors with pCR, DFS, and OS in the GeparSepto trial.

Methods

CAV1 and CAV2 RNA expression data

The GeparSepto trial (NCT01583426) enrolled 1,206 patients with early-stage breast cancer (19–21) after written informed consent for study participation and biomaterial collection. The study was approved by the ethics committees/institutional review boards and the competent authority. The study was approved by the Institutional Review Board at each study center, and was conducted according to the principles of Good Clinical Practice and the Declaration of Helsinki, with monitoring by an academic steering committee.

Pretherapy tissue was analyzed for RNA expression for all HER2-negative tumors with biomaterial available, tumor content of ≥ 20%, and satisfactory RNA quality. Of the 810 patients with HER2-negative tumors, RNA-seq data were available for 279 patients (predefined analyzed population). The remaining 531 patients with HER2-negative breast cancer were defined as the unanalyzed population. For RNA-seq data, *CAV1* and *CAV2* values were log-transformed and then z-transformed (Supplementary Figs. S1A-S1D). *CAV1* and *CAV2* expression values in all patients and in subgroups are shown in Supplementary Table S1. Data derived from The Cancer Genome Atlas (TCGA) on breast invasive carcinoma were analyzed for *CAV1* and *CAV2* RNA and protein (for CAV1) expression using cBioportal (www.cbioportal.org, Firehose Legacy dataset).

Statistical analysis

Statistical analysis was performed using R version 3.3.2 (https://www.R-project.org/). To analyze the effect of *CAV1/2* expression on pCR, logistic regression models were used; the effect on DFS and OS was analyzed by Cox regression models. Covariables for regression models were age (continuous), T-stage (continuous: T1 = 1, T2 = 2, T3 = 3, T4 = 4), N-stage (continuous: N0 = 0, N1 = 1, N2 = 2, N3 = 3), tumor grade (G3 vs. G1–2), Ki67 (continuous), and histology (nonductal vs. ductal). We created "univariate" and "bivariate" (biomarker and the treatment subgroup) regression models without covariables and "multivariate" models each containing all covariables. For *CAV1* and *CAV2*, outcomes were analyzed by continuous expression, which refers to a one-unit increase after transformation, or by dichotomization (<mean vs. ≥mean). For Kaplan–Meier (KM) analysis, dichotomized variables were used to generate curves for DFS and OS. All *P* values are two-sided; the level for significance is 0.05. No adjustments for multiple testing were applied; results are interpreted as exploratory analyses.

Data availability statement

All relevant data are within this article and its supporting information files. The data underlying the results presented in the study are available from GBG. Some restrictions apply due to confidentiality of patient data. Because these data are derived from a prospective clinical trial with ongoing follow-up collection, there are legal and ethical restrictions to share sensitive patient-related data publicly. Interested groups may use the "Cooperation Proposal Form" (https://www.gbg.de/en/research/trafo.php).

Data can be requested in context of a translational research project by sending the form to trafo@gbg.de. Translational research proposals are approved by the GBG scientific boards.

Results

RNA-seq data were available for 279 (34%) of 810 HER2-negative patients in the trial. Of those, 74 (26.5%) of the patients were HR-negative, while 205 (73.5%) were HR-positive. For HR-negative patients, 34 received paclitaxel, while 40 received nab-paclitaxel. For HR-positive patients, 103 received paclitaxel, while 102 received nab-paclitaxel. The tumor and patient characteristics of the analyzed cohort were similar to the unanalyzed cohort (Supplementary Tables S2 and S3) except for a lower percentage of patients with HR-negative breast cancer in the analyzed subset compared with the unanalyzed subset (26.5% vs. 38%) and a higher percentage of patients with HR-positive breast cancer in the analyzed compared with the unanalyzed population (73.5% vs. 62.0%). Otherwise, the analyzed cohort is largely representative of the whole HER2-negative cohort of the trial.

Table 1. Multivariate regression models with interaction test between CAV1/2 (dichotomized at mean) and HR status.

	CAV1			CAV2		
Endpoint	HR-negative OR/HR (95% CI)	HR-positive OR/HR (95% CI)	*P*	HR-negative OR/HR (95% CI)	HR-positive OR/HR (95% CI)	*P*
ypT0N0	0.85 (0.31–2.33)	0.69 (0.28–1.70)	0.770	1.33 (0.48–3.68)	0.67 (0.26–1.70)	0.327
DFS	2.65 (0.95–7.41)	1.14 (0.61–2.14)	0.169	4.40 (1.44–13.46)	1.60 (0.84–3.05)	0.125
OS	3.10 (0.61–15.61)	1.80 (0.82–3.94)	0.551	9.38 (1.13–77.75)	2.05 (0.92–4.58)	0.186

Note: *P* values refer to the interaction.

CAV2 expression is upregulated in patients with TNBC

CAV1 and *CAV2* RNA expression were directly correlated with each other (Pearson correlation coefficient 0.452, Supplementary Fig. S2A). Consistent with these findings, analysis of the invasive breast carcinoma TCGA database containing 1,101 samples also showed a positive correlation of *CAV1* with *CAV2* RNA expression (Pearson coefficient 0.84, Supplementary Fig. S2B). In the GeparSepto trial, there was no difference in *CAV1* expression between HR-negative and HR-positive patients (median, 0.04 vs. −0.01; Wilcoxon *P* value = 0.633). However, HR-negative (thus TNBC) patients had significantly higher *CAV2* expression than HR-positive patients (median, 0.16 vs. −0.19; Wilcoxon *P* value = 0.003; Supplementary Fig. S2C).

pCR

The pCR (ypT0/N0) rates for the various subgroups are shown in Supplementary Table S4. In the multivariate regression models with interaction tests, *CAV1* and *CAV2* expression were not significantly associated with pCR, independent of HR status (**Table 1**; Supplementary Table S5A). As a continuous or dichotomized (mean) variable, CAV1/2 was not significantly associated with pCR in univariate or multivariate prognostic regression models in any subgroups (all G7, HR-negative, HR-positive, paclitaxel, or nab-paclitaxel), although there was a trend for CAV1/2 (mean) to be associated with pCR in the multivariate prognostic regression model for the paclitaxel-treated subgroup (Supplementary Table S5A). Next, we tested the interaction between *CAV1* and *CAV2* expression and treatment group with regard to pCR. In patients with low *CAV1* and *CAV2* expression, there was no significant association with pCR between paclitaxel and nab-paclitaxel subgroups (**Table 2**). However, high *CAV1* expression was associated with a higher chance of having a pCR with nab-paclitaxel compared with paclitaxel (OR, 4.92; 95% CI, 1.70–14.22; $P = 0.003$; $P_{interaction} = 0.02$). Similar findings were seen with high *CAV2* (OR, 5.39; 95% CI, 1.76–16.47; $P = 0.003$; $P_{interaction} = 0.02$). In patients treated with paclitaxel, high *CAV1* expression was associated with a lower chance of having a pCR compared with patients with low *CAV1* (OR, 0.33; 95% CI, 0.11–0.95; $P = 0.040$). A similar trend was observed with *CAV2* (OR, 0.37; 95% CI, 0.12–1.13; $P = 0.082$). Full results can be found in Supplementary Tables S5A, S5B.

DFS

KM survival curve analysis showed no significant difference in DFS according to high or low *CAV1* expression in the overall cohort (**Fig. 1A**). Similar results were obtained from Cox regression models (Supplementary Table S5C). No differences between HR-positive and HR-negative subgroups were found (**Table 1**). CAV2 significantly predicted DFS in the overall cohort in KM analysis (**Fig. 2A**, $P = 0.012$) and regression analysis (Supplementary Table S5C, univariate: $P = 0.013$, multivariate: $P = 0.006$). Although in multivariate regression models with interaction tests, *CAV2* expression did not predict for DFS in patients with HR-negative or HR-positive breast cancer (**Table 1**), more detailed analyses in subgroups revealed that high CAV2 (above mean) prognosticates worse DFS in HR-negative breast cancer (multivariate HR, 4.68; 95% CI, 1.48–14.85; $P = 0.009$; Supplementary Table S5C).

High *CAV1* expression (above mean) was significantly associated with worse DFS in patients treated with paclitaxel in the univariate (HR, 2.42; 95% CI, 1.18–5.00; $P = 0.017$) and multivariate (HR, 2.29; 95% CI, 1.08–4.87; $P = 0.031$) regression models (Supplementary Table S5C) with similar results in KM analyses (**Fig.1B**; $P = 0.013$). No significance was observed in the nab-paclitaxel arm (**Fig. 1C**). The two arms behaved differently in an interaction model with borderline significance ($P = 0.077$; **Table 2**). Interestingly, high *CAV1* expression was significantly associated with worse DFS in the HR-negative patients (**Fig. 1D**), but not HR-positive patients (**Fig. 1E**) by KM analyses.

In contrast to CAV1, high *CAV2* (above mean) was associated with worse DFS in all patients in the univariate (HR, 1.93; 95% CI, 1.15–3.25; $P = 0.013$), multivariate (HR, 2.12; 95% CI, 1.23–3.63; $P = 0.006$) models (Supplementary Table S5C), and in KM analysis (**Fig. 2A**; $P = 0.012$). No significant interaction between low vs. high

Table 2. Multivariate regression models with interaction test between treatment arm (nab-paclitaxel vs. paclitaxel) and CAV1/CAV2 (dichotomized at mean).

	CAV1			CAV2		
Endpoint	Low OR/HR (95% CI)	High OR/HR (95% CI)	*P*	Low OR/HR (95% CI)	High OR/HR (95% CI)	*P*
ypT0N0	0.94 (0.38–2.34)	4.92 (1.70–14.22)	**0.023**	0.95 (0.39–2.29)	5.39 (1.76–16.47)	**0.019**
DFS	1.37 (0.62–3.04)	0.53 (0.27–1.05)	0.077	0.96 (0.40–2.27)	0.70 (0.36–1.34)	0.575
OS	2.47 (0.78–7.80)	0.29 (0.11–0.77)	**0.005**	1.21 (0.36–4.06)	0.47 (0.20–1.10)	0.215

Note: *P* values refer to the interaction. Values less than our threshold for significant ($P < 0.05$) are bolded.

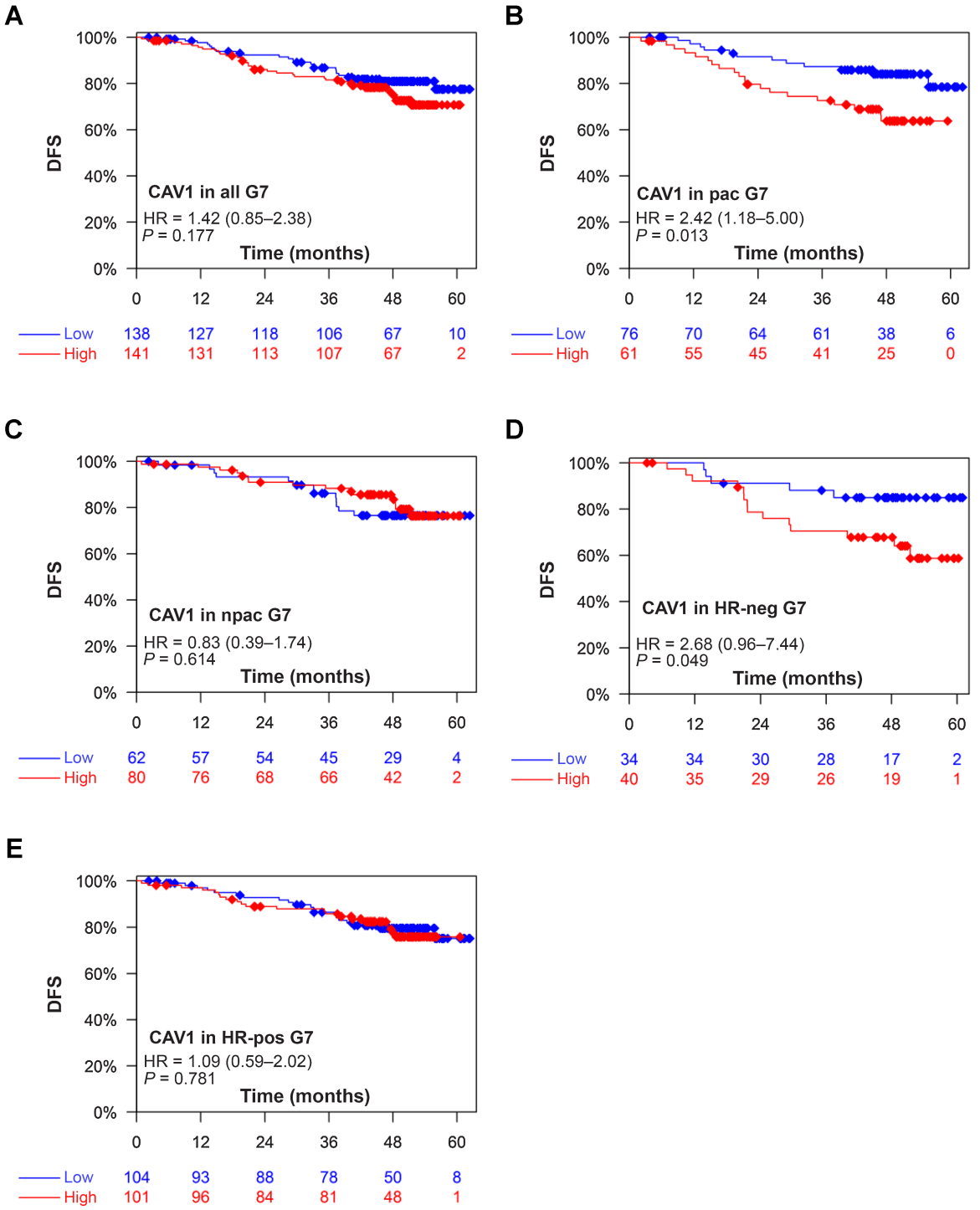

Figure 1.

KM survival curve analysis of DFS with CAV1 expression. **A,** All analyzed group. **B,** Paclitaxel-treated group. **C,** Nab-paclitaxel–treated group. **D,** HR-negative group. **E,** HR-positive group. *CAV1* expression dichotomized by the mean. *P* values are from long-rank test.

CAV2 expression and nab-paclitaxel versus paclitaxel treatments with respect to DFS was noted when adjusting by covariables (**Table 2**). However, on KM analyses, high *CAV2* expression was associated with worse DFS in patients treated with paclitaxel (**Fig. 2B**), but not nab-paclitaxel (**Fig. 2C**). Similar to *CAV1*, high *CAV2* was significantly associated with worse DFS in HR-negative patients (**Fig. 2D**), but not HR-positive patients (**Fig. 2E**). Additional results can be found in Supplementary Tables S5C, S5D.

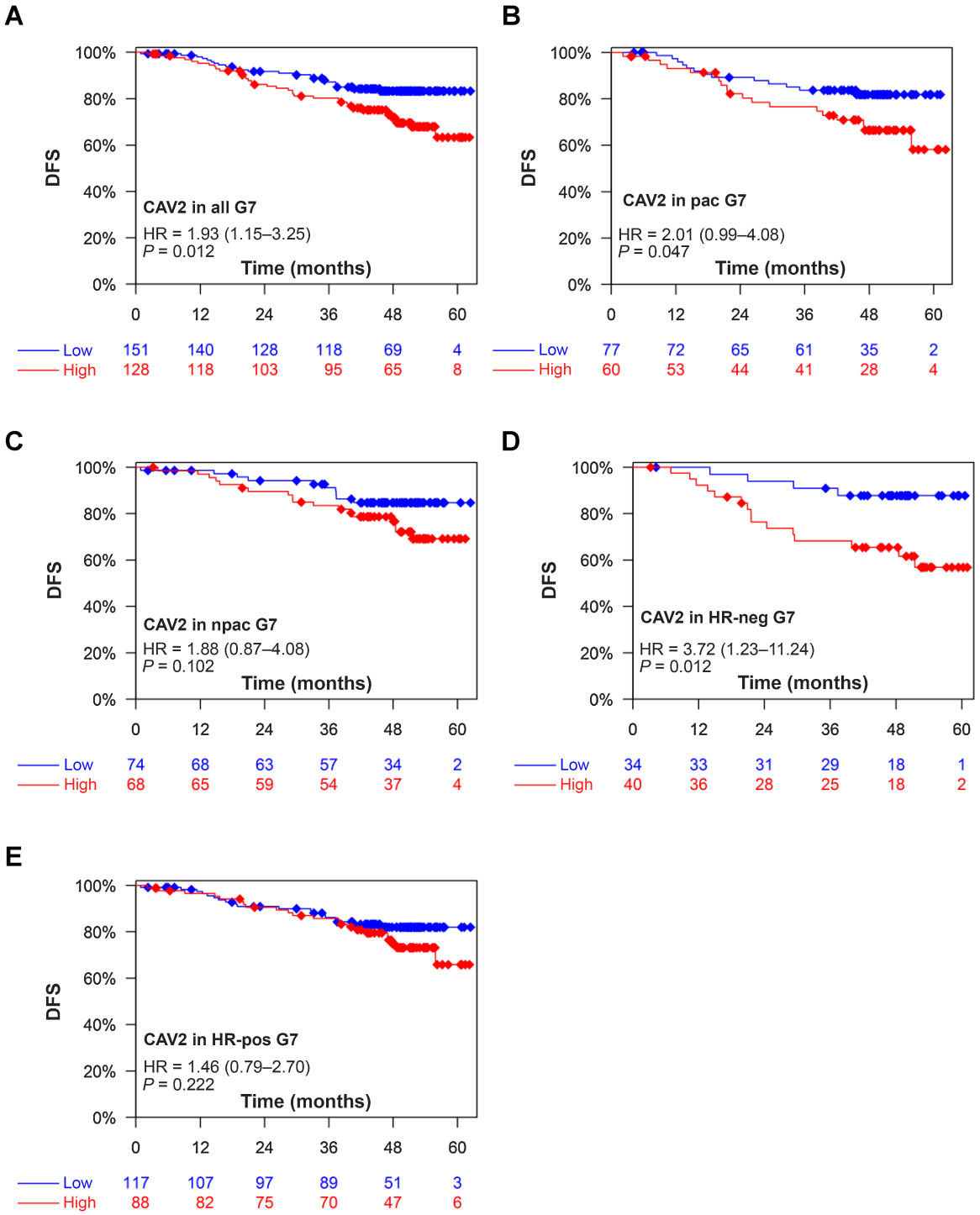

Figure 2.

KM survival curve analysis of DFS with CAV2 expression. **A,** All analyzed group. **B,** Paclitaxel-treated group. **C,** Nab-paclitaxel–treated group. **D,** HR-negative group. **E,** HR-positive group. *CAV2* expression dichotomized by the mean. *P* values are from long-rank test.

OS

In the multivariate regression models for OS with tests for interaction between *CAV1/2* expression and HR status, *CAV2* had a significant effect on OS in the HR-negative subgroup (HR 9.38; 95% CI, 1.13–77.75; $P = 0.038$; **Table 1**), but no other subgroups, including *CAV1*. High *CAV1* (above mean) was associated with worse OS in the paclitaxel-treated patients, similar to DFS, in the univariate (HR, 4.28; 95% CI, 1.57–11.69; $P = 0.005$) and multivariate regression

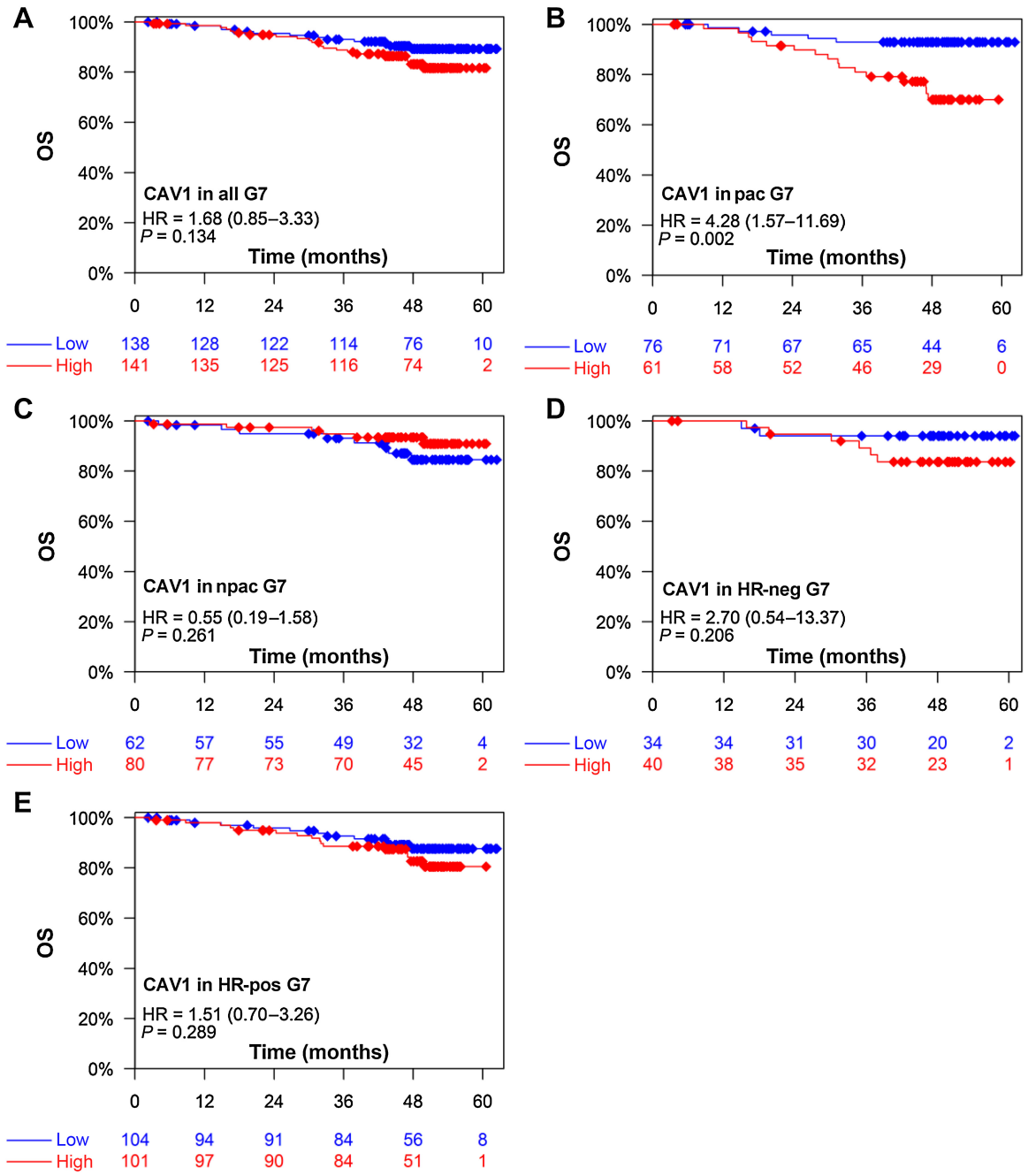

Figure 3.
KM survival curve analysis of OS with CAV1 expression. **A,** All analyzed group. **B,** Paclitaxel-treated group. **C,** Nab-paclitaxel–treated group. **D,** HR-negative group. **E,** HR-positive group. *CAV1* expression dichotomized by the mean. *P* values are from long-rank test.

models (HR, 4.97; 95% CI, 1.73–14.31; $P = 0.003$; Supplementary Table S5C). No significant differences in all patients or in the other subgroups were noted (HR-negative, HR-positive, nab-paclitaxel). Likewise, high *CAV2* (above mean) was associated with worse OS not only in paclitaxel-treated patients (multivariate HR, 4.24; 95% CI, 1.48–12.09; $P = 0.007$), but also in all patients (multivariate HR, 2.51; 95% CI, 1.22–5.17; $P = 0.013$), and in the HR-negative subgroup (multivariate HR, 10.43; 95% CI, 1.22–89.28; $P = 0.032$). Full results can be found in Supplementary Tables S5C, S5E.

We also tested the interaction between *CAV1/2* expression and the treatment arm with regard to OS (**Table 2**). In patients with low *CAV1* expression, OS was not significantly different between paclitaxel and nab-paclitaxel subgroups. However, patients with high *CAV1*

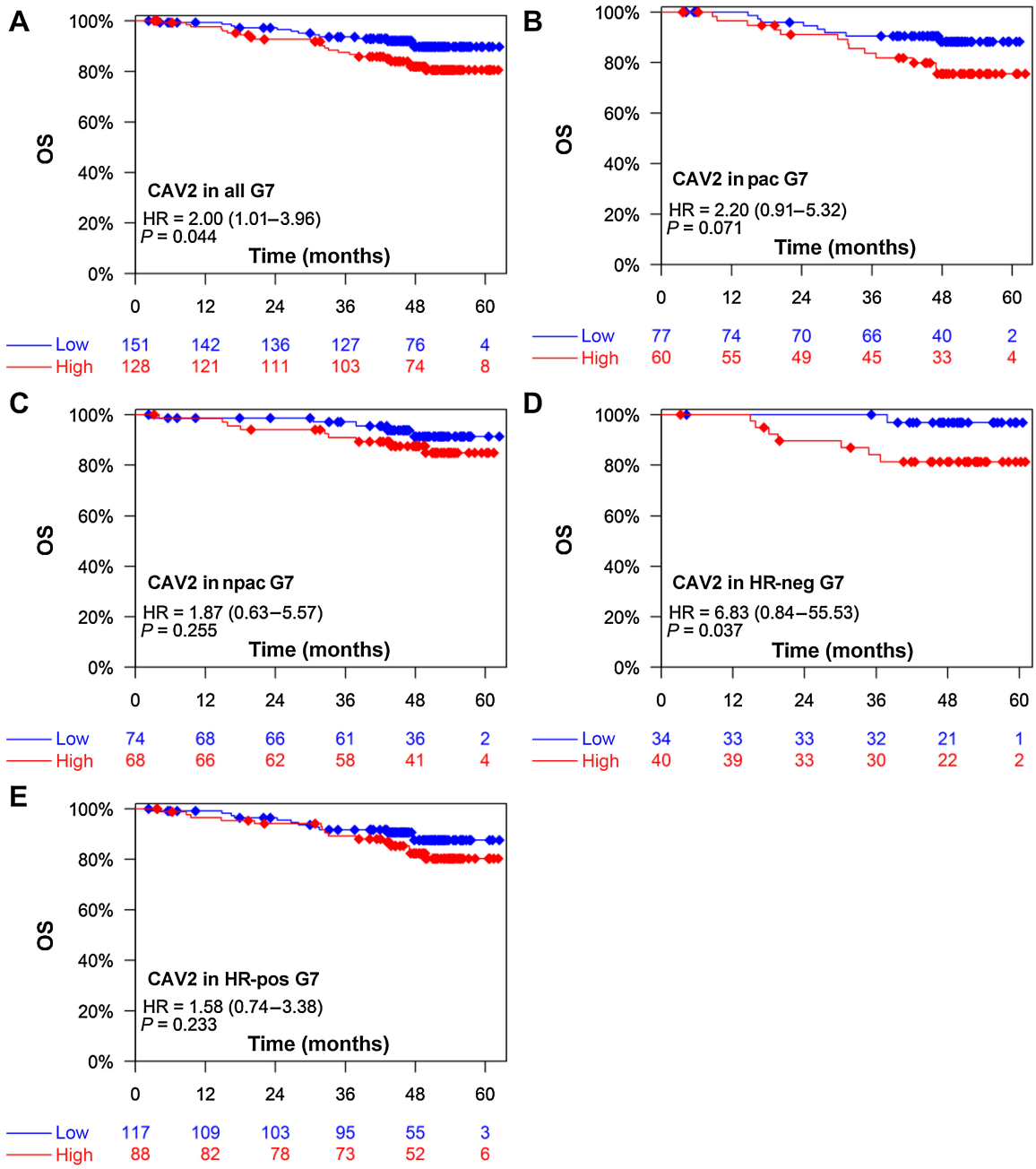

Figure 4.

KM survival curve analysis of OS with CAV2 expression. **A,** All analyzed group. **B,** Paclitaxel-treated group. **C,** Nab-paclitaxel–treated group. **D,** HR-negative group. **E,** HR-positive group. *CAV2* expression dichotomized by the mean. *P* values are from long-rank test.

expression had a better OS (HR, 0.29; 95% CI, 0.11–0.77; $P = 0.013$; $P_{interaction} = 0.005$) when treated with nab-paclitaxel as compared with paclitaxel; whereas patients with high *CAV1* expression treated with paclitaxel had a worse OS compared with patients with low *CAV1* (HR, 5.12; 95% CI, 1.81–14.45; $P = 0.002$; Supplementary Table S5E). In patients with low or high *CAV2* expression, OS was not significantly different according to treatment.

KM survival curve analysis demonstrated no significant differences in OS for all patients (**Fig. 3A**), but high *CAV1* expression was associated with worse OS in the paclitaxel-treated patients (**Fig. 3B**, $P = 0.002$). No differences were observed on the basis of *CAV1* expression in the nab-paclitaxel–treated (**Fig. 3C**), HR-negative (**Fig. 3D**), or the HR-positive (**Fig. 3E**) subgroups. Intriguingly, high *CAV2* expression was significantly associated with worse OS for all patients (**Fig. 4A**; $P = 0.044$) and a trend toward worse OS in paclitaxel-treated patients (**Fig. 4B**). There was no clear difference in OS based on *CAV2* expression for patients treated with nab-paclitaxel (**Fig. 4C**). The worse survival for high *CAV2* expression in all

patients was probably driven by the HR-negative subgroup (**Fig. 4D**; $P = 0.037$), not the HR-positive (**Fig. 4E**) subgroup.

Discussion

In this study, we have investigated the role of *CAV1* and *CAV2* as a prognostic/predictive biomarker in the GeparSepto trial, a randomized phase III trial testing a nab-paclitaxel–based versus paclitaxel-based chemotherapy for patients with early-stage breast cancer (19–21). While our findings are restricted to the HER2-negative patients on this trial, we find that high *CAV1/2* is associated with the lowest chances of obtaining a pCR with paclitaxel. In addition, higher *CAV1* expression is significantly associated with worse DFS and OS in patients treated with paclitaxel, but not with nab-paclitaxel. *CAV2*, commonly co-expressed with *CAV1*, showed similar findings in the paclitaxel-treated arm. In addition, *CAV2* levels are elevated in HR-negative breast cancer compared with HR-positive breast cancer, and higher *CAV2* expression is associated with worse DFS and OS in all patients, particularly in the HR-negative cohort.

CAV1 is a 21–22-kD transmembrane protein enriched in caveolae, and its upregulation has been observed in human melanoma, lung adenocarcinoma, prostate cancer, and renal cell carcinoma (22–26). High CAV1 expression is associated with increased metastasis and poor prognosis in prostate, colon, esophageal squamous cell, liver, and lung cancer (23, 24, 27–31). Importantly, CAV1 protein expression has been shown to be upregulated in the cancer cells of basal-like breast cancer, particularly TNBC (16, 32). However, no differences in *CAV1* RNA expression were observed in our study between HR-negative and HR-positive, HER2-negative breast cancer. The frequent overexpression of CAV1 in aggressive breast cancer subtypes may be due to *CAV1* gene promoter hypomethylation (33). CAV1 may promote the tumorigenesis of breast cancer via involvement in various processes including interacting with Rho-GTPases to stimulate α5-integrin expression and the Src-dependent activation of p130Cas/Rac1, FAK/Pyk2, and Ras/Erk1/2 signaling cascades (12, 13, 34).

Emerging evidence suggests a role for CAV1 in anticancer drug resistance, such as taxane-based chemotherapies. Higher CAV1 protein expression has been linked to paclitaxel resistance in many preclinical studies (35–40). Silencing *CAV1* by siRNA sensitized A549 and CD133+ pancreatic cancer cells to taxane chemotherapy (41, 42). CAV1 was also found to be associated with acquired resistance in paclitaxel-resistant hepatocarcinoma Hep3B cells and downregulation of *CAV1* by siRNA sensitized the cells to paclitaxel (38). Interestingly, it was recently found that pharmacologic downregulation of CAV1 sensitized breast cancer cells to paclitaxel, which was abolished by CAV1 overexpression (43). This evidence suggests an important role for CAV1 upregulation in paclitaxel resistance. We observed that high *CAV1* expression was significantly associated with worse DFS and OS in paclitaxel-treated patients. In addition, we found that *CAV1* and *CAV2* expression were directly correlated with each other in both our dataset and TCGA database. This may explain our finding that high *CAV2* expression was also significantly associated with worse DFS and OS in paclitaxel-treated patients. However, the exact molecular mechanisms by which CAV1 and CAV2 lead to paclitaxel resistance in breast cancer warrant further in-depth preclinical exploration.

Both CAV1 and CAV2 are the principal structural components of caveolae, which are important for albumin uptake in cells (9). Albumin is the primary plasma protein, and the plasma interstitial albumin concentration gradient is critical in regulating tissue fluid balance (44). Endothelial cell surface gp60 glycoprotein (also called albondin) is localized and enriched in caveolae and promotes albumin binding and activation of transcellular albumin transport via caveolae-mediated transcytosis across the endothelial cell monolayer (45). Interaction of gp60 with CAV1 is thought to be a key step in caveolae formation induced by gp60 and migration of the vesicles to the basolateral membrane, followed by the activation of Gi-coupled Src kinase signaling pathway (46). Amounting data have demonstrated that albumin is an effective vehicle for drug delivery (47). We previously reported that CAV1 plays a critical role in the uptake and response of nab-paclitaxel in cancer cells. CAV1 protein levels are positively correlated with nab-paclitaxel sensitivity, while CAV1 downregulation reduced the uptake of albumin and nab-paclitaxel leading to nab-paclitaxel resistance, which was reversed by CAV1 overexpression (15). To develop albumin-based chemotherapies selective for tumors with high CAV1 expression or high levels of caveolar-endocytosis, we recently developed a novel protein–drug conjugate consisting of human serum albumin conjugated to 7-ethyl-10-hydroxy-camptothecin (targeting DNA topoisomerase I), called SSH20. Our results demonstrated that SSH20 is potent, effective, safe, and has improved efficacy in high CAV1-expressing tumors *in vitro* and *in vivo* (48). With the rapid progress and increased application of RNA-seq and proteomics of cancer in clinic practices, detection of *CAV1/2* RNA and protein expression may be important for the stratification of patients for the treatment with or without albumin conjugates.

In the current study, we found that although high *CAV1/2* expression is associated with worse DFS and OS in paclitaxel-treated patients, there was no difference in DFS and OS based on *CAV1/2* expression in the nab-paclitaxel–treated group. Moreover, high *CAV1/2* was associated with a higher chance of obtaining a pCR in the nab-paclitaxel compared with the paclitaxel subgroup. Taken together, it is possible that higher *CAV1/2* expression might lead to enhanced nab-paclitaxel uptake, leading to an offset of the negative implications of higher *CAV1/2* expression observed in paclitaxel-treated tumors. Importantly, the GeparSepto phase III trial showed that patients treated with nab-paclitaxel had a 1.5 times higher chance of having a pCR compared with paclitaxel ($P < 0.001$; refs. 19–21). The largest improvement was noted in patients with HER2-negative, HR-negative disease, which had a 2.6-times increased chance of having a pCR ($P < 0.001$; ref. 19). Our analysis revealed that high *CAV2* was significantly associated with worse DFS and OS in all patients. High *CAV1* was significantly associated with worse DFS only in patients with TNBC. In addition, *CAV2* expression was significantly upregulated in HR-negative compared with HR-positive disease.

We found that patients with high *CAV1* appeared to significantly benefit from nab-paclitaxel compared with paclitaxel with regards to pCR, DFS (trend), and OS. These significant differences were not apparent in the HR-negative subgroup. In addition, we found that patients with tumors expressing high *CAV2* significantly benefited from treatment with nab-paclitaxel compared with paclitaxel in terms of pCR, but not DFS and OS. This was especially true for patients with HR-negative tumors. These data suggest distinct roles for *CAV1* and *CAV2* as prognostic and predictive biomarkers for nab-paclitaxel. While the functions of CAV1 have been extensively studied, data on CAV2 are limited. Our data have shed new light on the potential importance of CAV2 in breast cancer, especially HER2-negative, HR-negative breast cancer that lacks targeted therapy options with very poor prognosis (49).

Some strengths of our study include that the analysis was conducted in patients enrolled in a prospective, randomized controlled clinical trial, the statistical analysis was rigorous and included a multivariate

analysis, and the molecular analysis was hypothesis-based by virtue of being a natural progression from prior preclinical and clinical studies. In addition, sample collection was prospectively planned and part of the trial. However, there are several limitations in the current study. First, the RNA-seq analysis was restricted to HER2-negative patients and limited to 279 patients of the 810 HER2-negative patients due to cost, tissue availability, and tissue quality. We did note an imbalance of HR-positive patients in our group of analyzed patients (Supplementary Table S2), which could have affected the results of the whole analyzed population. Otherwise, the cohort of analyzed patients was largely representative for the overall HER2-negative study population. Nevertheless, the small sample size of 74 patients in the TNBC group does potentially limit the strength of the conclusions that can be drawn from this group (including the pCR findings). In addition, we have not yet analyzed the association of breast cancer CAV1/2 stromal expression with clinical outcomes, as a number of studies have linked stromal CAV1 with response to nab-paclitaxel regimens, albeit with differing results (14, 50). Thus, the predictive role of stromal CAV1 in nab-paclitaxel response may be cancer type–dependent and needs more evaluation. Second, this study analyzed the association of *CAV1/2* RNA expression but not CAV1/2 protein expression with outcomes. We found that there was a positive correlation of RNA with protein expression of CAV1 in the TCGA breast carcinoma dataset (Supplementary Fig. S3). Therefore, it will be critical to validate this correlation and further analyze the protein expression of CAV1 and CAV2 in the tumor and stromal cells of breast tumor tissues. Finally, our findings need to be validated through PCR and/or additional clinical trials containing complete RNA-seq data with both HER2-negative and HER2-positive cancers.

In summary, we have demonstrated that *CAV1* and *CAV2* RNA expression levels can have prognostic/predictive value in early-stage HER2-negative breast cancer with regard to short (pCR) and long term (DFS, OS) outcomes for patients treated with either paclitaxel or nab-paclitaxel–based chemotherapy. This study highlights *CAV1/2* as potential biomarkers of response and prognosis for patients with HER2-negative breast cancer treated with paclitaxel or nab-paclitaxel and may support therapeutic decision-making based on *CAV1/2* expression status. Further validation is warranted in prospective studies.

Authors' Disclosures

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Note

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