Original Article

Significance of Serum Carcinoembryonic Antigen and CA 15-3 in Monitoring Advanced Breast Cancer Patients Treated with Systemic Therapy: A Large-Scale Retrospective Study

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***Objective*:** The significance of serum carcinoembryonic antigen (CEA) and CA 15-3 in monitoring advanced breast cancer is still controversial. To clarify this issue, the Tumor Marker Study Group of the Japanese Breast Cancer Society conducted a large-scaled retrospective study.

***Methods*:** The findings from four clinical trials and seven institutes of 528 patients with advanced breast cancer were collected. Three-hundred forty-eight patients, in whom both serum CEA and CA 15-3 were measured during therapy, were selected for analysis.

***Results*:** The pretreatment positivity rate of CA 15-3 was significantly higher than that of CEA ($p < 0.0001$). Time-to-progression (TTP) in CEA- and CA 15-3-positive patients was significantly shorter than TTP in negative patients. The changes in either marker level correlated well with response to therapy in marker-positive patients but not in negative patients. TTP in the marker-positive patients with a greater than 20%-reduction in either marker level during therapy was significantly longer than that in positive patients without such a reduction ($p < 0.01$ for CEA and CA 15-3).

***Conclusion*:** CA 15-3 is more useful for monitoring advanced breast cancer than CEA and a greater than 20%-reduction in marker levels suggests longer TTP in pretreatment marker-positive patients.

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Key words: Breast cancer, CEA, CA 15-3, Systemic therapy, Time-to-progression

Breast cancer-oriented tumor markers have been used for several purposes as follows: 1) detecting early breast cancer, 2) determining the stage of disease, 3) predicting relapse, 4) detecting non-symptomatic relapse, 5) assessing response to therapy, and 6) monitoring clinical courses. However, according to the Clinical Guidelines of the American Society of Clinical Oncology[1] and others[2,3], most of the above uses are unacceptable for routine use in clinics because of a lack of scientific evidence showing clinical benefit. In contrast, various new breast cancer-oriented tumor markers have been developed and utilized in clinics in Japan[4-7]. Therefore, to investigate the significance of measuring tumor markers in patients with breast cancer, the Tumor Marker Study Group was organized by the Japanese Breast Cancer Society in June 2001. This study group conducted the present large-scale retrospective study in addition to an ongoing prospective study. Since carcinoembryonic antigen (CEA) and CA 15-3 were to be measured in the majority of patients recruited for this retrospective study, these two tumor markers were selected for analysis.

Serum CEA and CA 15-3 are circulating tumor markers that have long been used for monitoring breast cancer patients[8]. However, recent studies have suggested that the routine use of CEA is inferior to CA 15-3, and may be clinically useless because of the low sensitivity of CEA in breast cancer[9-12]. Thus the significance of serum CEA for monitoring breast cancer patients is still contro-

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Abbreviations:
CEA, Carcinoembryonic antigen; TTP, Time-to-progression; CR, Complete response; PR, Partial response; NC, No change; PD, Progressive disease

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versial.

It is time-consuming and expensive to assess responses to therapy in patients with metastatic breast cancer to multiple organs, in particular to bone. It has been suggested that the evaluation of tumor markers for assessing response to therapy for advanced breast cancer would be a much-needed clinical tool[1]. However, there is little scientific evidence to confirm that tumor marker assays can be used to assess response to therapy in patients with advanced breast cancer[13-17].

It has been suggested that the serum levels of tumor markers parallel the tumor burden[10]. If so, changes in tumor marker levels correlate well with response to therapy. However, according to the New Guidelines to Evaluate the Response to Treatment in Solid Tumors[18], tumor markers alone cannot be used to assess responses to therapy. However, two disease-specific and -sensitive tumor markers, prostate-specific antigen and CA125 are being validated by clinical trials. This prompted us to analyze the relation between the changes in serum tumor marker levels and the response to therapy in the present study. In addition, because time-to-progression (TTP) has been recognized as an important parameter of clinical benefit in patients with advanced breast cancer, the relation between tumor marker levels and TTP was also analyzed.

Patients and Methods

Patients

Data concerning 528 patients with advanced breast cancer were collected from four recent clinical trials (phase II trials for leuprorelin conducted by Takeda Chemical Industries, Ltd., for anastrozole by AstraZeneca and for paclitaxel by Bristol Pharmaceuticals; and a phase III trial for fadrozole by Novartis Pharma and Chugai Pharmaceuticals) and seven institutes (Kumamoto City Hospital, Kawasaki Medical School, Osaka City University Medical School, Hyogo Prefecture Hospital for Adult Diseases, Osaka University School of Medicine, Yodogawa Christian Hospital and Saiseikai Nakatsu Hospital). To investigate the relation between tumor maker levels and response to therapy, a total of 348 patients (66.0%), in whom both serum CEA and CA 15-3 were measured before and after systemic therapies for breast cancer, were selected as the study subjects. Since this study included patients entered into phase II trials, in which overall survival was not a secondary endpoint, only TTP was analyzed.

Measurement of CEA and CA 15-3

Serum CEA levels were measured by the CEA-RIA MAb kit (Abbott Laboratories, Inc., Chicago, IL) or the CEA-CLIA kit (Sysmex, Co., Ltd., Kobe) using a cut-off value of 5 ng/ml. Serum CA 15-3 levels were measured by the Centocor CA 15.3 RIA kit (Fujirebio Diagnostics Inc., Malvern, PA) using a cut-off value of 30 units/ml. Blood samples were transferred to commercial laboratories authorized by the Ministry of Health, Labor and Welfare in Japan and assayed. Quality control for the measurement of these markers was strictly performed in each laboratory. The coefficients of intra- and interassay variations for both markers in each laboratory were less than 10%. Samples above the standard curve were retested with appropriate dilutions. Tumor marker-positive patients were defined as patients with pretreatment CEA levels of greater than 5 ng/ml or CA 15-3 levels of greater than 30 units/ml.

Response to Therapy and Blood Sampling

According to the UICC criteria[19], four categories of complete response (CR), partial response (PR), no change (NC) and progressive disease (PD) were applied. Tumor markers were measured using blood samples obtained within two weeks before the start of systemic therapies and within two weeks before or after the day when best responses were assessed. To investigate changes in tumor marker levels, the percentage of marker levels when best response was assessed was calculated as follows: (marker level at time of best response/marker level before therapy) × 100.

When evaluating changes in the percentages of tumor marker levels before and after therapy, an increase or decrease of greater than 20% was considered significant because the coefficient of assay variations for CEA and CA 15-3 were less than 10%, respectively[16].

Statistical Analysis

Tumor marker levels, age and disease-free interval are expressed as means ± SD or the median and ranges. Differences among groups in the marker levels and the percentages of the marker levels during therapy were assessed using ANOVA. Differences among groups in terms of tumor marker positivity rates were assessed using cross-tabu-

Table 1. Pretreatment Positive Rates for Serum CEA and CA 15-3 in Patients with Advanced Breast Cancer

	No. of patients	CEA	CA 15-3	*p* value*	CEA and/or CA 15-3**
Overall	348	30.5%	44.0%	< 0.0001	55.2%
Main target lesion					
Soft tissue	116	18.1%	26.7%	0.0033	35.3%
Bone	96	30.2%	50.0%	0.0145	59.4%
Lung	71	31.0%	36.6%	0.0357	50.7%
Liver	42	59.5%	71.4%	0.5509	90.5%
Pleura	20	40.0%	80.0%	0.4936	85.0%
Others	3	33.3%	66.7%	0.0833	100%

*Comparison between CEA and CA 15-3
**Positive rates for CEA and/or CA 15-3

lation tables and chi-square analysis. To determine whether tumor marker levels before and during therapy are predictive of TTP, several demographic and clinical variables were analyzed using a Cox proportional hazards multivariate model. The variables were age, disease-free interval, number of prior treatments, main target lesion (liver metastasis or not), therapy (endocrine therapy alone or other), pretreatment tumor marker levels (positive or negative for each marker), tumor marker levels during therapy (greater than 20%-reduction or not) and response to therapy (objective response or not). TTP curves were generated using the Kaplan-Meier product limit method and analyzed by the Mantel-Cox logrank test. Two-sided *p* values less than 0.05 were regarded as statistically significant. All calculations were made using StatView computer software (ATMS Co., Tokyo).

Results

Patient Characteristics

Of 348 patients, 331 (95.1%) had recurrent breast cancer, nine had stage Ⅳ disease and eight had locally advanced disease. The median age of the subjects was 55 years (range: 24-84). The median disease-free interval of the patients with recurrence was 36 months (range: 2-364). Two hundred-nineteen patients (62.9%) received first-line therapies, 89 received second-line, 23 received third-line, 14 received fourth-line and three received fifth-line therapies. Two-hundred-forty-five patients (70.4%) received endocrine therapy alone, 68 (19.5%) received chemotherapy alone, and 35 (10.0%) received chemo-endocrine therapy. CR was obtained in 34 patients (9.8%), PR in 111 (31.9%), NC in 128 (36.8%) and PD in 75 (21.6%). The main target lesions for therapy were soft tissue disease in 116 patients (33.3%), bone metastasis in 96 (27.6%), lung metastasis in 71 (20.4%), liver metastasis in 42 (12.1%), pleural metastasis in 20 (5.7%) and other lesions in three patients (0.9%).

Pretreatment Positivity Rates and Serum Levels of CEA and CA 15-3

As shown in Table 1, pretreatment tumor marker positivity rates were 30.5% for CEA, 44.0% for CA 15-3 and 55.2% for CEA and/or CA 15-3. The CA 15-3 positivity rate was significantly higher than the CEA positivity rate in all patients ($p < 0.0001$). With regard to the main target lesions for therapy, the CA 15-3 positivity rate was significantly higher than the CEA positivity rate in patients with soft tissue disease, lung or bone metastases (26.7% vs. 18.1%; 36.6% vs. 31.0%; and 50.0% vs. 30.2%, respectively).

The pretreatment serum CEA level in patients with pleural metastases (87.4 ± 234.3 ng/ml) was significantly higher than that in patients with any other target lesion ($p < 0.05$ in each comparison). The pretreatment serum CA 15-3 level in patients with liver metastases (160.2 ± 301.0 units/ml) was significantly higher than that of patients with soft tissue diseases or lung metastases ($p < 0.05$ in each comparison).

Correlation between Response to Therapy and Changes in the Serum CEA and CA 15-3 Levels

The percentage of CEA levels when best response was assessed were 74.9 ± 86.9% (4.1-266.7) for CR, 81.1 ± 92.9% (1.0-380.2) for PR, 152.3 ±

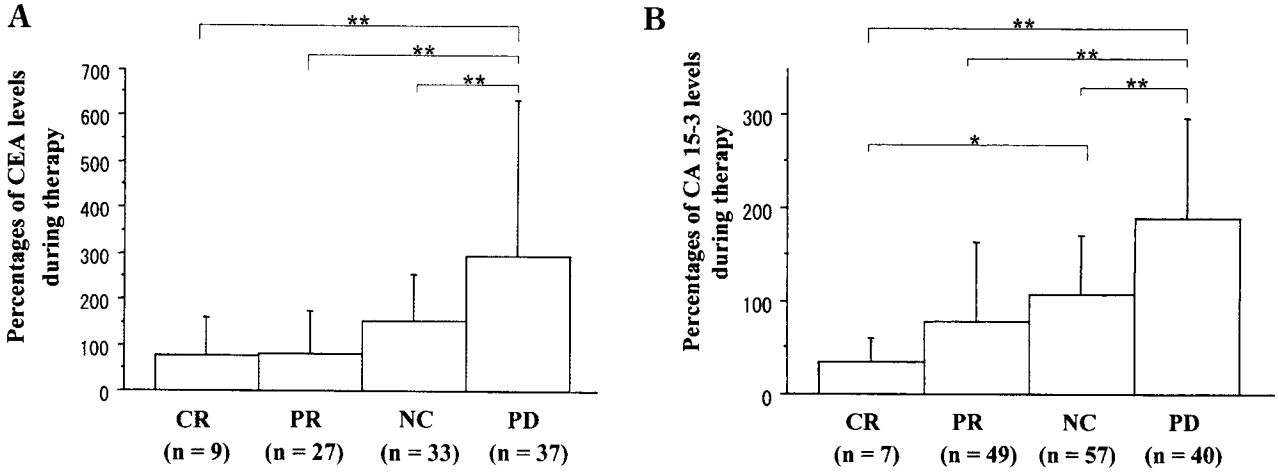

Fig 1. Percentages of serum tumor marker levels (A, CEA levels; B, CA 15-3 levels) during therapy compared with their pretreatment levels in advanced breast cancer patients divided by response to therapy. Percentages were calculated as described in Patients and Methods. Values are the mean + SD. *, $p < 0.05$; **, $p < 0.01$.

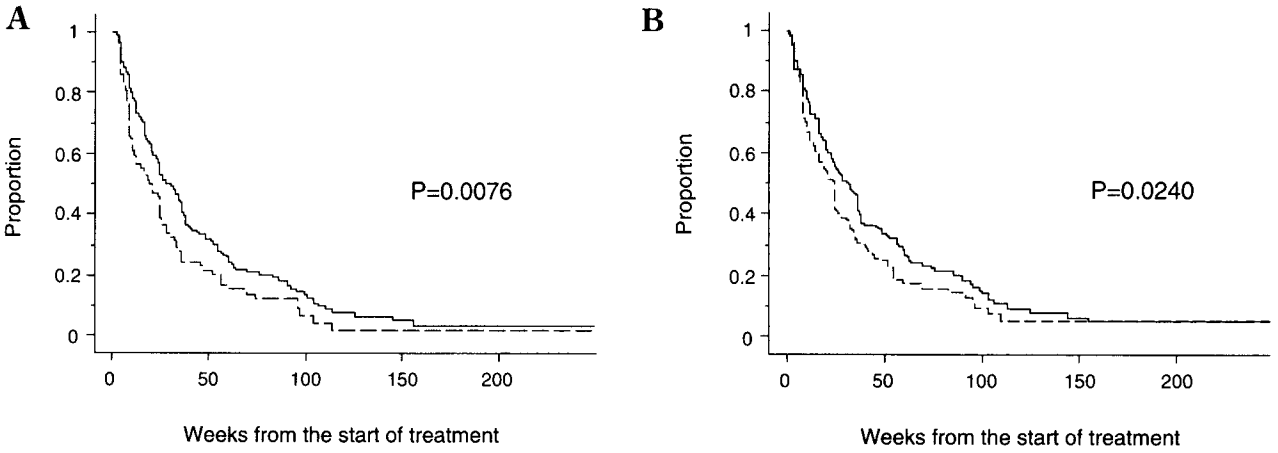

Fig 2. TTP of patients with advanced breast cancer by pretreatment tumor marker levels (A, CEA levels; B, CA 15-3 levels). Tumor marker-positive patients were defined as patients with pretreatment CEA levels of greater than 5 ng/ml or with pretreatment CA 15-3 levels of greater than 30 units/ml. —, marker-negative patients (n = 241 for CEA; n = 194 for CA 15-3); ----, marker-positive patients (n = 107 for CEA; n = 154 for CA 15-3).

101.3% (29.0-405.9) for NC and 294.3 ± 338.6% (54.3-1928.2) for PD in CEA-positive patients. The change in patients with PD was significantly higher than in those with CR, PR or NC ($p < 0.01$ in each comparison). The changes in CEA levels correlated well with response to therapy in these patients (Fig 1A). However, in CEA-negative patients, changes in CEA levels did not correlate with response to therapy (data not shown).

The percentage of CA 15-3 levels when best responses were assessed were 35.5 ± 23.8% (1.0-66.7) for CR, 77.8 ± 85.4% (7.6-554.0) for PR, 107.3 ± 64.3% (22.9-421.0) for NC and 189.8 ± 107.3% (55.0-634.1) for PD in CA 15-3-positive patients. Those patients with PD had significantly higher CA 15-3 levels than those with CR, PR or NC ($p < 0.01$ in each comparison). In addition, patients with CR had significantly lower CA 15-3 levels than those with NC ($p = 0.0330$). The changes in the CA 15-3 levels correlated well with the response to therapy in these patients (Fig 1B), but not in CA 15-3-negative patients (data not shown).

Tumor Marker Levels and TTP

As shown in Fig 2A, TTP in CEA-positive patients was significantly shorter than in CEA-negative patients (median TTP of 19 weeks and 28 weeks, respectively; $p = 0.0076$). Similarly, TTP in CA 15-3-positive patients was significantly shorter than in CA 15-3-negative patients (median TTP of 22 weeks and 29.5 weeks, respectively; $p = 0.0240$; Fig 2B).

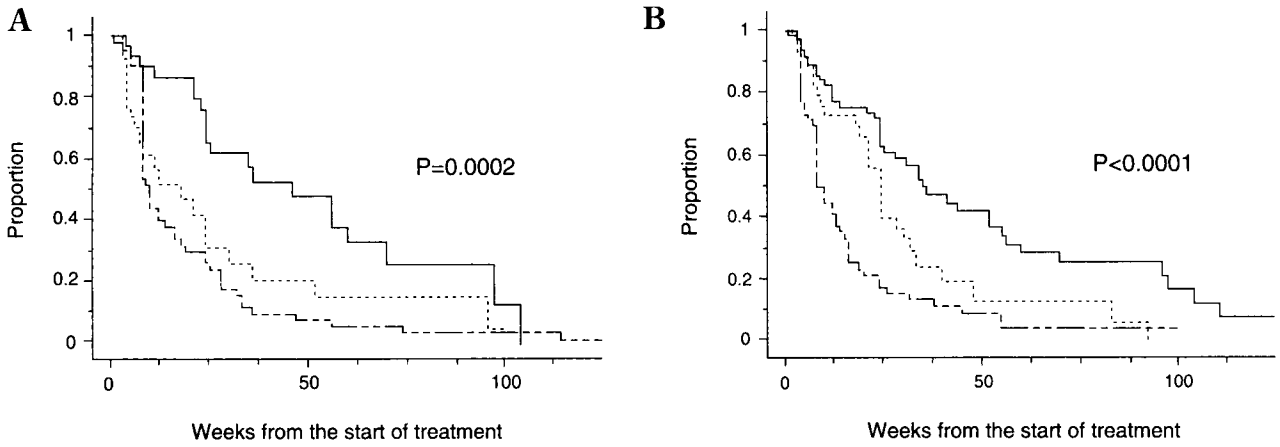

Fig 3. TTP of tumor marker-positive patients with advanced breast cancer by tumor marker levels during therapy (A, CEA levels; B, CA 15-3 levels). D (—), N (·····) and U (- - -) groups include patients with a greater than 20%-reduction, within a 20%-change and with a greater than 20% increase in each tumor marker level when best responses were assessed, respectively.

Table 2. Relative Risk of Progression by the Final Cox Proportional Hazards Multivariate Model (n = 326)

Factors	Relative risk of progression	95% confidence interval	*p* value
Pretreatment CA 15-3-negative	0.652	0.501-0.848	0.0014
Greater than 20%-reduction of CEA levels	0.631	0.453-0.877	0.0062
Greater than 20%-reduction of CA 15-3 levels	0.695	0.497-0.971	0.0330
Objective response	0.484	0.361-0.647	< 0.0001
Number of prior treatments	1.263	1.107-1.438	0.0005
Disease-free interval (months)	0.995	0.992-0.998	0.0005

To investigate the relation between the changes in the marker levels and TTP, tumor marker-positive patients were divided into 3 groups, D, N, and U. In groups D, N, and U, the percentages of the marker levels when best responses were assessed were less than 80% (greater than 20%-reduction compared with before therapy), between 80-120% (a ±20%-change), and greater than 120% (a greater than 20%-increase), respectively.

As shown in Fig 3A, TTP for group D was significantly longer than that for groups N and U in CEA-positive patients (median TTP; 42 weeks for group D, 15 weeks for group N and 9.5 weeks for group U; $p = 0.0002$). Similarly, in CA 15-3-positive patients, the TTP for group D was significantly longer than that for groups N and U (median TTP; 36 weeks for group D, 17 weeks for group N and 7 weeks for group U; $p < 0.0001$; Fig 3B).

To clarify the predictive value of the tumor marker levels before and during therapy for TTP, a Cox proportional hazards multivariate model was applied. Pretreatment CA 15-3-negativity and a greater than 20%-reduction in CEA or CA 15-3 levels during therapy in addition to objective responses, longer disease-free interval and a smaller number of prior treatments were significantly predictive of longer TTP in the final model (Table 2).

Discussion

With regard to the positivity rates of tumor markers before starting therapies, CA 15-3 was significantly more sensitive than CEA in this study, as suggested in previous studies[9-12]. In particular, the CA 15-3 positivity rate was 50.0% and the CEA positivity rate was 30.2% in patients with bone metastases (Table 1). Since bone metastasis is a difficult target organ in which to assess the response to therapy, CA 15-3 seems to be more useful for monitoring patients with bone metastasis than CEA. However, 39 (11.2%) of 348 patients with various metastatic sites were positive for CEA but not for CA 15-3. In these patients, CEA may be more useful for assessing the response to therapy than CA15-3. These findings suggest that a combination assay of CA 15-3 and CEA may be

superior to either CA 15-3 or CEA alone for assessing the response to therapy in patients with advanced breast cancer.

Changes in both CA 15-3 and CEA levels correlated well with response to therapy in patients with pretreatment marker levels elevated above the cut-off value but not in patients with pretreatment marker levels below the cut-off value. The CA 15-3 levels appeared to parallel responses to therapy better than CEA (Fig 1). These findings suggest that when tumor marker levels are used to assist assessment of the response to therapy in patients with advanced breast cancer, each tumor marker level should be higher than the cut-off value prior to starting therapy, and the changes in CA 15-3 levels may correlate with the responses to therapy better than changes in CEA levels.

When considering how to assess the responses to therapy using the changes in the tumor marker levels before and after therapy, some questions remain to be answered: 1) which tumor marker is most suitable for this purpose? 2) what percentage of change in tumor marker levels correlates well with response to therapy? 3) when is the best time to measure tumor markers after starting therapy? Unfortunately, these questions cannot be answered by this retrospective study because of the marked heterogeneity in the patient population concerning the therapeutic methods and the main target lesions and in the timing of blood sampling. Therefore, the Tumor Marker Study Group of the Japanese Breast Cancer Society has started a prospective study to answer these questions.

It should be noted that the pretreatment levels of both CA 15-3 and CEA were predictive of TTP (Fig 2). It is possible that tumor marker-positive patients have more extensive disease, that their response to therapy is less favorable and that their TTP is shorter than that of negative patients. However, the Cox proportional hazards multivariate model showed that pretreatment CA 15-3 negativity was an independent favorable factor for longer TTP (Table 2) but this was not the case for pretreatment CEA negativity. It has been suggested that serum levels of circulating tumor markers, such as CEA and CA 15-3, appear to be a function of tumor burden[10]. If so, pretreatment CA 15-3 positivity simply reflects a larger tumor burden and should not be an independent predictor of shorter TTP. Interestingly, a recent study suggested that a circulating tumor marker, an extracellular domain of HER2, is an independent prognostic factor in patients with metastatic breast cancer[20]. In addition, it was reported that pretreatment positivity for CA 15-3 is an independent predictor for shorter overall survival in breast cancer patients at first relapse[21]. These findings suggest that circulating CA 15-3 might induce relative resistance to certain therapies in advanced breast cancer.

The findings of the present study have revealed for the first time that a greater than 20%-reduction of either the CA 15-3 or CEA level is also an independent predictor for longer TTP. In addition, an objective response to therapy, longer disease-free interval and a smaller number of prior treatments were independent favorable predictors for longer TTP as expected. These findings suggest that if a certain treatment provides a greater than 20%-reduction in the serum CA 15-3 or CEA level during therapy, it may be expected that the patients will have longer TTP regardless of objective response. These findings also support the hypothesis that changes in tumor marker levels during therapy are helpful to assess favorable responses to therapy in patients with advanced breast cancer.

To our knowledge, this is the largest retrospective study analyzing the relation between changes in tumor marker levels and responses to therapy in patients with advanced breast cancer. The present study provides some relatively definitive conclusions as follows: 1) the positivity rate of CA 15-3 was higher than that of CEA in patients with advanced breast cancer, 2) changes in the CEA and CA 15-3 levels correlated well with the response to therapy only in tumor marker-positive patients, 3) a high pretreatment level of CA 15-3 was an independent risk factor for shorter TTP, and 4) a greater than 20%-reduction in the serum CEA or CA 15-3 levels during therapy was an independent favorable factor for longer TTP. However, these findings should be carefully evaluated because the study was retrospective. Prospective studies are needed to make more definitive conclusions on the utility of tumor markers in breast cancer patients.

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