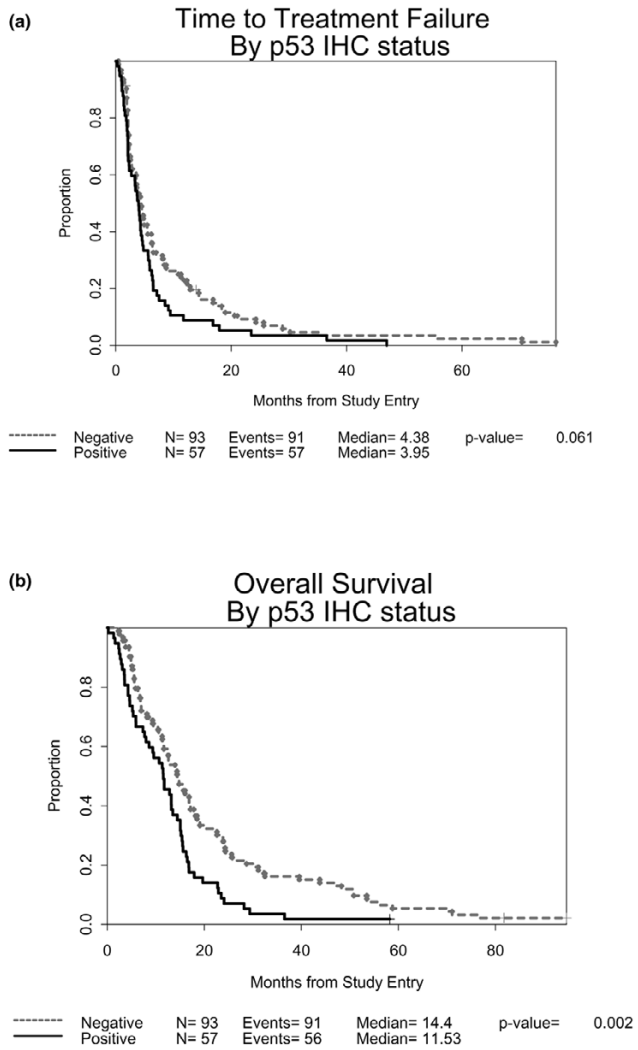
Figure 1



Time to treatment failure and overall survival according to p53 status, as assessed by immunochemistry. **(a)** Time to treatment failure and **(b)** overall survival. Patients were classified as p53 positive (solid line) or p53 negative (dashed line) as determined by immunochemistry with D07 antibody. A positive case is defined as ≥10% positive, localization of nuclear or nuclear and cytoplasmic, and intensity of stain weak, moderate, or intense. IHC, immunohistochemistry.

women and Caucasian women with p53 mutations as assessed by IHC (41% and 38%, respectively; $P = 0.78$) or by sequencing (32% and 26%, $P = 0.48$).

Discussion

We evaluated the relationship among tumor biomarkers, treatment response, and outcomes in a subset of patients with available tumor blocks who were enrolled in a large, prospective, randomized trial of single-agent paclitaxel given as first-line or second-line therapy for metastatic breast cancer. Neither HER2 status nor p53 status significantly affected the treatment response or TTF when HER2 over-expression was scored as 3+ on the HercepTest or FISH positive. Although p53 status and ER status were not predictive of a benefit from therapy, measured by response or TTF, they were both important variables in determining OS in this cohort. Thus, it appears that p53 and ER status behaved as prognostic factors in this study, but they did not add predictive value within the context of response to paclitaxel. Although not surprising, this observation underlines the importance of separating response to therapy from the underlying biology, a distinction first made by McShane and coworkers [40]. In addition, our study provides support for the use of classification systems that include ER, PR, and HER2 status, because the outcomes according to these biomarkers in our cohort are consistent with published data [30,34]. Furthermore, racial differences in the pattern of tumor subtypes are also seen, a finding that translates into differences in survival, even in the metastatic setting.

Other studies have examined response to taxanes based on HER2 status. Seidman and coworkers [16] reported a higher rate of response to paclitaxel in patients with HER2-positive tumors; however, this association was seen only when HER2 status was assessed with the use of the 4D5 antibody, and not when a rabbit polyclonal antibody (pAb-1) was used to determine HER2 status. The authors reported a low level of agreement between the results of the 4D5 assay and an assay with pAb-1. The monoclonal antibody CB11 and the polyclonal antibody used in the HercepTest are known to target different epitopes of HER2 and appear to vary in the specificity of their results. Therefore, in the present study we evaluated the correlation among three methods of measuring HER2 status that have been approved by the US Food and Drug Administration. We found that the results of the CB11 assay, the HercepTest, and FISH were reasonably concordant, with the highest level of agreement between the CB11 assay and FISH.

No association was seen between the rate of response to paclitaxel and HER2 status as assessed by any method. In contrast to our findings, Konecny and coworkers [21] reported a statistically significant increase in response rate to epirubicin and paclitaxel, but not to epirubicin and cyclophosphamide, in women with HER2-positive tumors, as assessed by FISH. One possible explanation for these conflicting results is that the patient populations were not entirely comparable, because all patients in the study reported by Konecny and coworkers received treatment as first-line therapy, whereas in CALGB 9342 paclitaxel was given as either first-line or second-line therapy for metastatic disease. In addition, the treatment regimens were not entirely comparable. There may be an advantage to combining an anthracycline with a taxane in women with HER2-positive tumors; if so, epirubicin plus paclitaxel may be a particularly effective regimen against HER2-positive breast cancer, whereas HER2 status may not influence the likelihood of a response to paclitaxel given alone. Furthermore, FISH techniques differed between these studies and might have influenced the findings. Finally, our sample was relatively