Table 7

Race according to biomarkers

Biomarker	Race		*P* value[a]
	Caucasian	African-American	
ER positive	58/109 (53%)	13/32 (41%)	0.21
HER2 positive	27/121 (22%)	3/34 (9%)	0.08
Triple negative	26/121 (21%)	16/34 (47%)	0.003

[a]*P* values were obtained using a test of proportions. ER, estrogen receptor.

result of hormone receptor status need to be considered in analyses of trials in the metastatic setting, even among patient populations that have previously received hormonal therapy.

We further evaluated the relationship among p53 status, race, and outcomes in this cohort. We found that the presence of p53 over-expression, as detected by IHC, was not predictive of the response to paclitaxel but was associated with significantly diminished OS. There are two possible explanations for these findings. First, mutations in p53 may lead to genomic instability *in vitro*, with resistant clones arising more rapidly in these tumors, even though the initial response to therapy is the same as that in tumors without p53 mutations. It is also possible that other tumor features that predict a worse prognosis are associated with p53 mutations and influence survival without affecting response to therapy.

In this study p53 over-expression, as determined by IHC, was associated with decreased survival, but p53 mutations identified by sequence analysis were not. Explanations include the possibility that certain p53 mutations have little effect on the tumor phenotype, whereas the presence of p53 stabilization is a surrogate for a mutation with a functional effect. The study was not sufficiently powered to allow for a rigorous examination of the interaction between mutation type and clinical outcome. Furthermore, previously described p53 mutations were not detected in approximately one-quarter of cases in which the IHC assay for p53 was positive. We used stringent criteria for the classification of mutations; only those included in the p53 mutation database maintained at Hôpital Necker-Enfants Malades were considered true mutations. Furthermore, it is possible that some of the mutations identified by sequencing but not included in the database represent true functional mutations.

Large, population-based studies have documented racial disparities in breast cancer outcomes [43]. As demonstrated by Polite and coworkers [44], self-reported African-American women from CALGB 9342 had decreased survival as compared with their Caucasian counterparts, even with adjustment for other factors. In this biomarker substudy, we observed the association between African-American race and worse outcome. A potential explanation for these findings is the observation that these patients were twice as likely to have tumors that were negative for ER, PR and HER2, and triple-negative status was itself associated with significantly poorer OS. Because we did not collect data on post-study treatment, we cannot rule out differences in care received after the study as a cause of the observed disparity. However, our results extend the observations of Olopade [36] and Carey [35] and their groups, who reported that basal-like tumors are more common in women of African ancestry. Because the basal-like phenotype has been associated with a poor prognosis, our findings suggest that differences in the biologic features of tumors may explain the decreased survival of African-American women in our study. To our knowledge, this is the first study to demonstrate that the association between a poor prognosis and the triple-negative phenotype persists in women with metastatic breast cancer.

The study had several limitations. First, we were able to obtain adequate tumor blocks from only approximately one-third of patients enrolled in CALGB 9342. As a result, the power to detect all but substantial differences in outcomes based on biomarkers was limited. Second, we cannot rule out the possibility that the dose-response curve for paclitaxel differs according to HER2 status; unfortunately, our sample was not large enough to carry out such an analysis. Third, 90% of the biomarker assays were performed on blocks from primary tumors (and 10% on blocks from synchronous lymph-node metastases), on the assumption that HER2 status is stable over time regardless of disease progression or interim therapies. A recent abstract has questioned this assumption [45], reporting discordance in HER2 expression between primary and metastatic sites in eight (14%) of 58 patients. Finally, patterns of gene expression may ultimately be more useful than single gene markers in predicting the response to therapy [46-48].

Conclusion

Molecular subtyping has become commonplace in breast cancer, but the implications of molecular markers in patients with metastatic disease remains unclear. This study suggests that tumor response is not dictated by p53, HER2 or ER status, but that these tumor features impact on tumor regrowth and death in patients with metastatic breast cancer. In addition, the