patients treated with preoperative prophylaxis. Because the prophylaxis regimen included a corticosteroid, we monitored our outcomes for wound complications. Although the complication rate was two-fold greater in patients receiving prophylaxis and dye compared with those receiving neither, this was not statistically significant. Several mechanisms of action behind adverse reactions to isosulfan blue dye have been postulated, but none have been confirmed. We are currently investigating the molecular basis of these adverse reactions.

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HER2/neu Expression and Hormonal Therapy in Early Breast Cancer: Can Muddy Waters Become Clear?

To the Editor: We have read with great interest the paper by Love et al [1] about the relationship between *HER2/neu* expression and response to adjuvant endocrine therapy in premenopausal women with breast cancer. Whereas *HER2/neu* and estrogen receptor (ER) are believed to be important cell survival and cell death factors in human breast cancer, if and how they interact to confer resistance to hormone therapy is still in debate. Several observations are consistent with a major role for c-erbB2 in the development of endocrine resistance, considering also the *HER2/neu* acquired expression during hormonal therapy, either by clone selection or by phenotype modification caused by tamoxifen [2,3]. However, the results reported by Love et al [1] suggest a discrepancy between the clinical and preclinical scenario. Although *HER2/neu* is confirmed to be an independent prognostic indicator of poor overall survival, surprisingly it seems to predict a better response to tamoxifen and ovarian ablation in ER-positive premenopausal early breast cancer patients. We are grateful to the authors for their pioneering observation, even though we think that some comments are needed.

The authors made a secondary analysis from previous data obtained prospectively in a randomized trial designed to investigate the impact of adjuvant endocrine manipulations compared with observation and delayed endocrine interventions at recurrence in premenopausal women with breast cancer, regardless of hormone receptor and *HER2/neu* status [4]. Of 709 original patients, only 282 are considered, and differently collected and outcome variables are compared in these subgroups [1]. Even though Love's study lacks power [5], the *P* values, regarding *HER2/neu* overexpression and response to adjuvant oophorectomy and tamoxifen, are statistically significant at univariate analysis, suggesting a quantitative interaction at multivariate analysis. However, in the statistical methods section, the authors do not mention any likelihood of false-positive results caused by repeated analyses. The reader is not informed about the use of any corrective methods; thus, significant *P* values could run the risk of only being borderline, if one takes into consideration the items of multiple significant testing and the small number of patients studied. Love et al previously stated [4] that women with recurrent breast cancer were treated with oophorectomy plus tamoxifen or oophorectomy or tamoxifen alone in a rate of 23%, 1%, and 52% respectively, whereas 19% of these patients did not receive any hormonal treatment. However, exploring interactions between *HER2/neu* and treatment status [1], the authors do not report the hormone-receptor and *HER2/neu* status of women whose disease recurred. Whether patients with disease recurrence are considered or not in the control group, it is noteworthy that at univariate analysis differences in disease-free survival for *HER2/neu*-negative patients are robustly significant with respect to endocrine treatment, whereas these results become statistically weak when their overall survival is examined. It might be interesting if authors could speculate on these findings; that is, report on *HER2/neu* expression in patients dying as a result of causes other than breast cancer. In addition, although the results of Love's study are consistent in showing greater benefit to the *HER2/neu*-positive subgroup given adjuvant treatment, the available data are not sufficiently long-term to draw any definitive conclusion.

Finally, Love et al do not point to the role of the luteal phase of the menstrual cycle with respect to the efficacy of

surgical oophorectomy plus tamoxifen in premenopausal women with early breast cancer [6]. It would be interesting to test whether timing of initiation of endocrine manipulations during a given menstrual cycle phase might exert a positive or negative effect in clinical outcomes for breast cancer patients who overexpress *HER2/neu*. The multivariate analysis in the 177 ER-negative *HER2/neu* patient groups failed to demonstrate any treatment effect or interaction with *HER2/neu* status. These findings could be discussed in the light of the current evidence that ER-negative tumors frequently show low c-erbB2 levels (defined as the mean value minus one standard deviation) and that hypoexpression appears to be worse than overexpression for disease-free survival in breast cancer patients [7].

Data about the role of *HER2/neu* in selecting endocrine therapy are virtually nonexistent and, before considering this marker as being pivotal in drawing treatment strategy, additional trials are needed. Nevertheless, the results reported by Love et al are exciting and suggest new approaches for treatment of premenopausal early breast cancer patients with ER-positive and *HER2/neu*-overexpressing tumors.

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Acute Lymphoblastic Leukemia–Relapse Study of the Berlin-Frankfurt-Münster Group (ALL-REZ BFM) Experience: Early Treatment Intensity Makes the Difference

To the Editor: In his editorial [1], Dr Schiffer explores reasons for differences in outcome between treatment regimens for acute lymphoblastic leukemia (ALL). The event-free survival (EFS) may be up to 26% higher in children and adolescents [2], as compared with adults. In addition to the reasons that are inherent to the individual disease, he notes that treatment realization may be stricter and more compliant in the pediatric setting, but that corroborating data would be sparse. From our multicenter studies of children and adolescents with first relapse of B precursor acute lymphoblastic leukemia in Germany (Acute Lymphoblastic Leukemia-Relapse [ALL-REZ] Berlin-Frankfurt-Münster [BFM] group studies 90 and 95/96; national patient coverage, $> 90\%$), we supply evidence for the importance of timely scheduled early intensive treatment assessed by the time difference (referred to as TD1) between start of the first and the second induction chemotherapy course.

In study ALL-REZ BFM 90, this time difference was scheduled to be 21 days, but protocol guidelines advised for course start as soon as possible with regard to clinical condition and hematologic reconstitution. In about one third of the patients, TD1 was 21 to 24 days, one third continued notably earlier, and one third experienced a delay. In subgroups of up to 20, 21 to 24, and more than 24 days of TD1, EFS estimates at 5 years were 0.49 ± 0.06, 0.40 ± 0.05, and 0.33 ± 0.06 ($n = 82$, 109, and 92, respectively; log-rank test $P = .02$; median observation time 10.5 years since study entry at re-evaluation in April 2003 [3]).

For the consecutive study ALL-REZ BFM 95/96, comparable results of an earlier analysis [4] led to a study design with TD1 schedule of only 14 days. To allow for the compressed time schedule, two induction chemotherapy courses from earlier studies (ALL-REZ BFM 85 and 87) were used. The first course contained no mercaptopurine and cytarabine, and the second contained no thioguanine, methotrexate, daunorubicin, or ifosfamide, but contained cytarabine as compared with study ALL-REZ BFM 90 (details in [5]). Subsequent chemotherapy courses and study inclusion criteria remained nearly unchanged. It was prospectively studied how TD1 variability and randomly given granulocyte colony-stimulating factor were related to outcome. As a result, median TD1 was 15 days (interquartile range, 14 to 18 days; 318 patients; data on TD1 were not yet available in 44 patients; median observation time, 4.6 years). Four patients with extreme delay of the second