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Response

Response to Di Cosimo, Torri, and Porcu

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We are grateful to Di Cosimo, Torri, and Porcu for their valuable comment on our article. We showed that the presence of circulating tumor cells (CTCs) as assessed 2 years after chemotherapy was prognostic for poor disease-free survival (DFS) and overall survival (OS). Di Cosimo et al. raise the question of clinical relevance of this finding by recalculating positive and negative predictive values for a 0- to 40-month interval.

Unfortunately, we were unable to reproduce the results of the statistical analysis by Di Cosimo et al. and could not reconcile all data presented in the text with the data shown in their analysis. For example, when calculating the negative predictive value (NPV) for the full data set as analyzed in our study, we obtained an NPV of 92.7% (824 out of 889 patients that were CTC-negative 2 years after the end of chemotherapy had no relapse during follow-up). Despite this, Cosimo et al. raise an important issue that needs consideration.

When taking care of patients with early-stage breast cancer (EBC), one of the most frequently asked questions is: "How will I be followed for signs of disease recurrence?" The current recommendation—to follow largely by clinical examination and annual mammography—is often met with uncertainty and the concern that the chance of early detection of recurrence might be missed. We have addressed this clinically relevant question in our article by assessing follow-up data with regard to CTC status for 1087 patients with EBC and showed that the presence of CTCs 2 years after chemotherapy was associated with poor outcome, with hazard ratios obtained in fully adjusted multivariable Cox proportional hazards models of 2.34 (95% confidence interval = 1.52 to 3.60) and 4.01 (95% confidence interval = 2.09 to 7.67) for disease-free survival and overall survival respectively.

These results were obtained using widely accepted statistical methods for the assessment of the prognostic value of tumor markers. In addition, the lead-time issue as mentioned by Di Cosimo et al. was accounted for by using a landmark approach (1). While acknowledging the limitations of any statistical modeling and recognizing that using alternative statistical approaches as suggested by Di Cosimo et al. might retrieve different results, we argue that our results are clinically meaningful and important for the patients.

As pointed out in the editorial by Sparano and Henry (2), solving the conundrum of an optimal follow-up regimen of patients surviving EBC will most probably need a multifaceted approach that gives us sufficient detail to personalize real-life clinical decisions for breast cancer patients outside of clinical trials. There is an urgent need for biomarkers detecting minimal residual disease and the development of "post-adjuvant therapies" performed at the time of early relapse detection by CTCs or other liquid biopsy markers (3). We fully agree with Di Cosimo et al. that the clinical utility of CTC assessment during follow-up has yet to be proven. Nevertheless, we are happy that our data might stimulate the scientific community to answer our patients' call for a risk-adapted follow-up by conducting clinical trials specifically designed for survivors of EBC.

Note

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