

## Interaction between p53 Staining and High-Dose Chemotherapy in Breast Cancer

**To the Editor:** Kroger et al. (1) recently reported an interesting observation, suggesting an interaction between p53 immunohistochemical staining and high-dose chemotherapy in breast cancer. If their finding that patients staining positive for p53 seems to benefit from high-dose therapy, whereas patients with tumors not staining for p53 do not, is confirmed by others, it may influence clinical practice and extend our biological understanding of the role of p53 executing cell death in response to therapy. Yet we like to air some cautions when interpreting their data.

First, immunohistochemical staining is not a very good surrogate marker for p53 inactivation caused by mutation; ~30% of p53 mutations do not stain and some tumors with wild-type p53 may stain positive due to accumulation of p53 caused by binding to other cellular proteins (2, 3). The mutations not staining relate to nonsense mutations and gene deletions in particular. In our own study on the predictive role of p53 status to doxorubicin monotherapy (3, 4), we recorded a predictive value of p53 mutations detected through gene sequencing, whereas p53 immunostaining did not predict outcome, as most of the mutated tumors resistant to therapy did not express p53 by immunostaining. Although the Vienna group found p53 mutations as well as immunostaining to predict resistance to anthracyclines in breast cancer (5), interestingly they found gene mutations but not immunostaining predictive for response in rectal cancer (6). Reviewing the literature, there are several studies revealing p53 immunostaining not to predict drug sensitivity in breast cancer (see refs. 7, 8 for references), contrasting the general positive finding in studies analyzing p53 mutation status by gene sequencing (3, 5, 9). We believe immunostaining to be a suboptimal technique identifying p53 mutations in breast cancer and strongly recommend other investigators trying to confirm the results of Kroger et al. to use gene sequencing.

Finally, we do not agree with the authors in their interpretation of our studies claiming that loss of p53 function do not influence sensitivity to chemotherapy. Rather, we

believe the finding of tumors harboring wild-type p53 not responding to therapy could be due to mutations in other genes involved in the "p53 pathway." This view was recently substantiated by the finding of a patient expressing chemoresistance harboring a nonsense mutation in the *CHEK2* gene (10). The finding of tumors responding to therapy despite harboring p53 mutations could be due to redundant pathways acting in concert (11).

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