Re: Topoisomerase II Alpha and Responsiveness of Breast Cancer to Adjuvant Chemotherapy

In a correspondence referring to an article by O’Malley et al. (1), Oakman et al. (2) argued that, with current evidence, they do not believe that HER2 and TOP2A status predict the potential benefit of anthracycline-based treatments to breast cancer patients. We have graphed the O’Malley data (Figure 1), which clearly showed a predictive value of TOP2A abnormal status for 5-year overall survival following anthracycline-based treatment. Abnormal TOP2A status was associated with poor prognosis irrespective of treatment, and importantly, patients with abnormal TOP2A status had an increased chance of survival when treated with anthracycline (cyclophosphamide, epirubicin, and 5-fluorouracil [CEF]) as opposed to cyclophosphamide, methotrexate, 5-fluorouracil (CMF). Thus, the effect of poor prognosis was counteracted by the positive predictive value. The data from O’Malley et al. (1) confirmed the Danish results that were first presented in 2005 (3) and later updated (4) based on a validation performed in connection with Food and Drug Administration approval of the TOP2A marker.

Oakman et al. (2) further argued against combining TOP2A amplification and TOP2A deletion as a single category, abnormal TOP2A status, because they believe that the biological rationale underlying an association between TOP2A deletions and increased anthracycline sensitivity is lacking. However, the initial theory that TOP2A amplifications were related to increased anthracycline sensitivity and that TOP2A deletions were related to decreased sensitivity was based on a very limited number of cell line experiments, and subsequent studies of almost 3000 patient samples (5) have failed to confirm that initial theory. Topoisomerase IIα is a key enzyme and lack of topoisomerase function is lethal to cells. Deletion of TOP2A only involves one of the two alleles, and the remaining allele may still be active, for example, constitutively activated by a mutation. Therefore, it cannot be assumed a priori that deletion of one allele will lead to a decrease or lack of function.

Oakman et al. (2) suggested that TOP2A protein quantity and subcellular localization may be a more useful marker than gene enumeration. However, it is essential for cells to alter protein levels to respond to conditional changes, and an irreversible protein change seems to be most easily achieved by an underlying genetic change. Consequently, changes in protein expression levels are seldom passed on to offspring cells during cell division, whereas genetic changes almost inevitably are passed on. TOP2A protein expression varies during the cell cycle, and it is highly unlikely that a variable feature like TOP2A protein expression will correlate with a constant feature like TOP2A gene aberration.

Finally, Oakman et al. (2) argued that triple-negative breast cancer patients seem to have increased response to anthracyclines. However, the TOP2A status of these patients has not been investigated, and although it was initially assumed that TOP2A aberrations were restricted to HER2-positive patients, this assumption proved to be incorrect upon further study (5).

Thus, in contrast to Oakman et al., we believe that TOP2A aberration is a clinical valuable predictive marker for the effective use of anthracyclines that has been proven by retrospective analyses in two independent clinical trials (1,4) that have used different assays. Although other studies have not been able to prove the connection, those failures can in most cases be explained by an inadequate design of the studies (6–7).

**Figure 1.** Illustration of the data from O’Malley et al. table 3 (1): Patients whose tumors have abnormal topoisomerase II alpha (TOP2A) genetic status have a 5-year overall survival of 43% (95% confidence interval [CI] = 27% to 58%) when treated with cyclophosphamide, methotrexate, 5-fluorouracil (CMF; nonanthracycline arm) and 67% (95% CI = 51% to 79%) when treated with cyclophosphamide, epirubicin, 5-fluorouracil (CEF; anthracycline arm). By contrast, patients with normal TOP2A genetic status have a 5-year overall survival of 76% (95% CI = 68% to 81%) in both treatment arms. The biomarker effect of TOP2A assessment is composed of a prognostic component and a predictive component. The prognostic value of TOP2A can be seen in both treatment arms because patients with TOP2A normal status have better survival than patients with TOP2A abnormal status, both when treated with CEF (dark grey; 76% vs 67%) and with CMF (light grey; 76% vs 43%). The predictive value of TOP2A status is, however, difficult to prove in cohorts in which all patients have been treated with anthracyclines because the predictive value is counteracted by the prognostic component in this treatment. Likewise, the prognostic value cannot be proven in cohorts treated with anthracyclines due to the interfering predictive component. The problem of separating the prognostic and the predictive components is also illustrated by the fact that some TOP2A assessment studies that are based solely on samples from anthracycline-treated patients (6,7) fail to show the predictive effect because it is counteracted by the prognostic effect.

KIRSTEN VANG NIELSEN
NILS BRUNNER

**References**


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Affiliations of authors: Dako A/S, Glostrup, Denmark (KVN); Department of Veterinary Disease Biology, Faculty of Life Sciences, Danish Center for Translational Breast Cancer Research and Sino-Danish Breast Cancer Research Center, University of Copenhagen, Frederiksberg, Denmark (NB).

Correspondence to: Kirsten Vang Nielsen, PhD, Produktionsvej 42, DK-2600 Glostrup, Denmark (e-mail: kirsten.vang@dako.com).

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