Predictive value of HER2, Topoisomerase-II (Topo-II) and Tissue Inhibitor of Metalloproteinases (TIMP-1) for efficacy of taxane-based chemotherapy in intermediate risk breast cancer–results from the EC-Doc trial.

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Abstract

Background: Despite extensive research, there is still no consensus on optimal predictors for use of taxane-based chemotherapy (cht) in early breast cancer. Some studies have revealed HER2 as a significant predictive marker for efficacy of taxanes and anthracyclines. TIMP-1 and Topo-II are reported to be predictive for anthracycline efficacy. In our previous reports, both Ki-67>20% and central G3 status emerged as significant predictors for taxane benefit. We have now compared HER2 and Topo-II (as protein expression and gene amplification) and TIMP-1 immunoreactivity as well as factor combinations (HT (HER2/TIMP 1) and 2T (Topo-II/TIMP-1) regarding their predictive value for benefit from taxane-based cht.

Methods: The EC-Doc trial randomized 1950 patients with 1-3 positive LN to 6x CEF/CMF vs. 4xEC-4xDoc. Significantly better DFS and OS favoring EC-Doc have been previously reported (Nitz et al., SABCS 2008). Protein expression and gene amplification data as well central histology/grade were available for 772 patients. Survival analysis was performed using Cox proportional hazards and Kaplan-Meier statistics. Analysis of HER2 survival impact status was prospectively planned.

Results: The entire and the investigated study populations did not differ regarding baseline characteristics. After median follow up of 64 months, both DFS (5y 90% vs. 80%, p=0.006) and OS (5y 95% vs. 92%, p=0.022) rates significantly favored EC Doc vs. CEF in this cohort as well. HER2 over-expression (3+ and/or FISH>2.0) was reported in 158 tumors (20%), Topo-II aberration (deletion or amplification) was reported in 78 (49.4%) HER2+ and in 83 (13.6%) HER2-negative tumors; 496 tumors were classified as TIMP-1 immunoreactive (65.2%). None of these factors were significantly prognostic for EFS in this collective. Regarding DFS, EC-Doc was strongly superior to FEC in HER2+ tumors (HR=0.29, 95%CI: 0.12-0.7, p=0.006) but not in HER2- tumors (p=0.18). In Topo-II aberrated tumors, the benefit of EC-Doc was remarkably strong (HR=0.28, 95% CI: 0.11-0.69, p=0.006), whereas the benefit was not significant in Topo-II normal tumors (p=0.16), which comprise more than ¾ of the total. In contrast, Topo-II protein overexpression (>10%) was not associated with a stronger benefit in either subgroup. The superiority of EC-Doc to FEC was significant in the larger group of TIMP-1 immunoreactive tumors (HR=0.57, p=0.025) but not in TIMP-1 negative tumors (p=0.14), similar behavior was seen in “HT” and “2T” subgroups (significance with HR about 0.5 in the “+” subgroups).

In a multivariate model for DFS including age, tumor size, Ki-67, central grade, HR, HER2, TOPO_II aberration, TIMP-1 status, therapy and interactions of all these factors with therapy arm, the only significant therapy interaction was that of (high) Ki-67 (HR=0.76, 95% CI: 0.59-0.98, p=0.03); significant main effects in this model were age, central grade, and Ki-67.

Conclusions: These data suggest predictive significance for Topo-II aberration, TIMP immunoreactivity and HER2 over-expression as well as a multivariate predictive significance of high Ki-67 for enhanced benefit of taxane-based cht.

Background

- Breast cancer (BC) patients with 1-3 positive lymph nodes belong to the intermediate risk group, and chemoendocrine therapy (in HR+ disease) is current standard of care in all N+ patients. Identification of pt subgroups with favorable outcome is urgently needed to prevent substantial overtreatment of 50-70%[1]
- Previous studies reported predictive effect of HER-2[2], topoisomerase II status[3] and tissue metallopeptidase inhibitor 1 TIMP-1 status[4] for efficacy of anthracyclines and taxanes.
- Aim of the study was to investigate these markers among other prognostic markers as predictive markers for taxane efficacy within the randomized cohort of intermediate risk patients.

Methods

- Treatment details are given in **Figure 1**.
- Primary tumor samples from all cases with either relapse or completed 5 years of follow up (in September 2009) were retrieved for the central tumor bank.
- Tumor samples from 772 patients (40% of the original study population) were included in the analysis
- Non-ITT pts (n=6) and pts treated by CMF (due to marginal clinical impact; n=87) were excluded
- ER, PR were considered positive if moderate or strong immunostaining was seen in >1% of tumor nuclei. HER2 was considered positive if scored as 3+ according to HercepTest criteria; if 2+ FISH had to show amplification (ratio ≥2.0). Ki-67 was positive if nuclear staining was seen in ≥ 20% tumor cells[5].
- Topo-II was considered as abnormal if deletion (<0.8) or amplification (>2.0) within FISH analysis
- Topo-II protein expression was considered as positive if >10% of nuclei were stained as positive.
- Immunostaining of tissue sections was assessed semiquantitatively using plus and minus symbols as a measure of TIMP-1 immunoreactivity in the epithelial breast cancer cells.
- HER2-negative and TIMP-1 immunoreactive tumors were classified as HT nonresponsive and otherwise HT responsive.
- Tumors with normal TOP2A status and TIMP-1 immunoreactivity were classified as 2T-nonresponsive and otherwise 2T-responsive[4].
- Statistical analysis used the Kaplan-Meier method to estimate cumulative survival time probabilities. The log-rank test (p<0.05) was applied to test for survival differences according to treatment. Univariate Cox analysis for DFS was performed for each individual marker; together with treatment, those markers with significant univariate results were entered into multivariate forward stepwise Cox analysis for EFS.

Results

- Baseline characteristics were similar between the tumor bank (n=772) and the entire study population (n=1950).
- Median age was 52 years, median tumor size 2.1 cm, 46% of patients had 1 positive lymph node
- After median follow up of 64 months, event-free survival was superior in both the whole study population (data submitted for publication) and the tumor bank subgroup (5 year DFS EC-Doc vs. FEC: 90% vs. 80%, p=0.006) (**Figure 2**.)

Figure 1. Design of the study

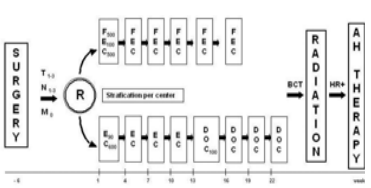
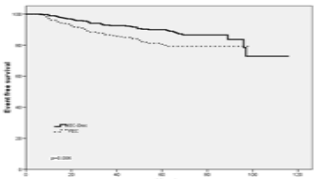
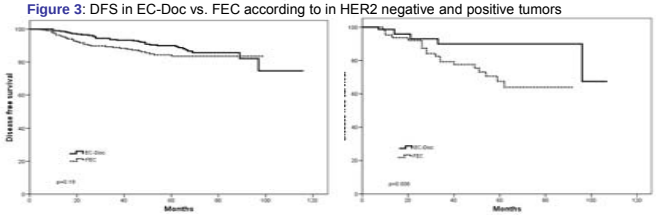


Figure 2. Event-free survival by treatment arm

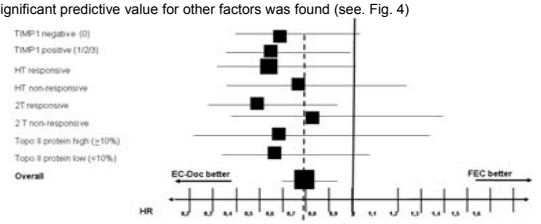


- Central grade was distributed as follows: G 1/2/3 (n/%): 33(4.3%)/285(37.4%)/445/(58.3%)
- HER2 over-expression (3+ and/or FISH>2.0) was reported in 158 tumors (20%). Positive correlations are reported between positive HER2 status and Ki-67 overexpression (r=0.274, p<0.001), poor grade (r=0.223, p<0.001) and Topo-II aberration (s. below).
- Topo-II aberration (deletion or amplification) was reported in 78 (49.4%) HER2+ and in 83 (13.6%) HER2-negative tumors (Spearman correlation r=0.351, p<0.001). There is also a weak positive correlation with poor grade (r=0.132, p<0.001)
- Topo-II overexpression was reported in 202 tumors (31.2%) and was moderately but significantly positively correlated with Ki-67 expression (Spearman correlation r=0.213, p<0.001) and poor grade (r=0.145, p<0.001)
- 496 tumors were classified as TIMP-1 immunoreactive (65.2%). No significant correlations between TIMP-1 immunoreactivity and other markers (grade, Ki-67, HER2, Topo-II status) were observed.
- 362 tumors were classified as HT responsive (47.6%) and 398 as non-responsive (52.4%)
- 335 tumors were 2T responsive (48.3%) and 358 as 2T non-responsive (51.7%).
- Univariate prognostic analysis: Only Ki-67 overexpression, central G3, young age of patients (<50 years old) and negative HR status were prognostic markers regarding DFS.
- EC-Doc was strongly superior to FEC in HER2+ tumors (HR=0.29, 95%CI: 0.12-0.7, p=0.006) but not in HER2- tumors (p=0.18). (Fig 3 a and b).
- In tumors with Topo-II aberration, the benefit of EC-Doc was remarkably strong (HR=0.28, 95% CI: 0.11-0.69, p=0.006), whereas the benefit was not significant in Topo-II normal tumors (p=0.16).

Figure 3: DFS in EC-Doc vs. FEC according to in HER2 negative and positive tumors



- No significant predictive value for other factors was found (see. Fig. 4)



- After including treatment, all factors and their interaction with treatment, central grade, Ki-67 overexpression and younger age of patients and the interaction of EC-Doc with Ki-67 were significant predictors for survival

Table 1. Multivariate analysis on DFS

		P value	HR	95% CI	
Age	≤ 50 vs. > 50 years old	0.05	1.6	1.0	2.57
Ki-67	≥20% vs. <20%	0.01	0.43	1.18	3.76
Central grade	G3 vs. G1/2	0.001	5.63	2.2	14.47
Interaction					
Therapy*Ki-67 (high)		0.03	0.76	0.59	0.98

Conclusions

- HER-2, Topo II aberration and nominally TIMP-1 are shown as significant predictive factors for taxane benefit in the randomized collective with intermediate risk BC.
- However, the predictive effect of HER-2 and Topo-II seem to be related to the proliferative effects of these markers, as shown by multivariate interaction analysis.

References

1. Nitz et al., SABCS 2008.; 2. Hayes et al. NEJM 2008; 3. Slamon et al. NEJM 2011 4.Ejlertsen et al. JCO 2010; 5. Penault-Llorca et al JCO 2009

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