Sequential Treatment with Epirubicin/Cyclophosphamid, Followed by Docetaxel vs. FEC120 in the Adjuvant Treatment of N+ Breast Cancer Patients: Final Survival Analysis of the German ADEBAR Phase III Study

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Background
Based on meta-analytic evidence, taxane containing adjuvant chemotherapy has been established as standard treatment in node-positive breast cancer. However, in the MA-21 study, adriamycin-cyclophosphamide, followed by paclitaxel (AC-P) was significantly inferior to FEC120. We prospectively compared a sequential epirubicin-docetaxel chemotherapy regimen to FEC120.

Methods
The ADEBAR study was a multicenter phase III trial (n=1502) to evaluate whether breast cancer (BC) pts with > 3 axillary lymph node metastases benefit from a sequential anthracycline-docetaxel regimen (E90C–D: 4 cycles epirubicin [E] 90 mg/m² plus cyclophosphamide [C] 600 mg/m² q21 days followed by 4 cycles docetaxel [D] 100mg/m² q21 days) compared to dose-intensive anthracycline-containing polychemotherapy (FE120C: 6 cycles E 60 mg/m² d 1+8, 5-FU 500mg/m² d 1+8 and C 75 mg/m² d 1-14, q4 weeks).(Fig 1) The Overall observation time (median – 95%CI) was 49.5 (47.4 – 51.3) months .

Results
Treatment was stopped prematurely in 3.7% of the pts in the E90C–D arm and in 8.0% in the FE120C arm due to toxicity (p=0.0009). Antibiotic treatment was given in 10.4% (E90C–D) vs. 19.7% (FE120C), G-CSF support in 39.2% vs 61.4 % and erythropoietin stimulation in 8.7% vs. 20.0%, respectively (p<0.0001). Haematological toxicity (leucopenia, neutropenic fever, thrombocytopenia, anemia) was significantly higher in the FE120C arm.

At the time of the current analysis, 369 events of recurrence of breast cancer, were observed: 166 events in the FE120C group and 193 in the E90C–D group. The unadjusted hazard ratio (HR) was 0.877 (95 percent confidence interval, 0.722 to 1.065; p=0.3819, log-rank test). Overall survival in the two groups was not significantly different: (131 deaths with FE120C vs. 134 with E90C–D (HR 0.996, 0.783-1.267, p=0.9691). Subgroup analyses, stratifying for tumor size, lymph node involvement, hormone receptor and HER2-neu status showed no significant difference between the two treatment arms.

Table 1: Multivariate survival analysis

<table>
<thead>
<tr>
<th>Therapy</th>
<th>HR</th>
<th>95%-CI</th>
<th>HR</th>
<th>95%-CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>E90C–D vs. FEC120C</td>
<td>1.009</td>
<td>0.818 – 1.243</td>
<td>0.925</td>
<td>0.719 – 1.190</td>
</tr>
<tr>
<td>Tumor size (T1 vs. T2-4)</td>
<td>1.279 *</td>
<td>1.119 – 1.463</td>
<td>1.259 *</td>
<td>1.071 – 1.480</td>
</tr>
<tr>
<td>Lymph node involvement (N0 vs. N1-3)</td>
<td>1.470 *</td>
<td>1.267 – 1.705</td>
<td>1.230 *</td>
<td>1.029 – 1.472</td>
</tr>
<tr>
<td>Grading (G1 vs. G2-3)</td>
<td>2.261</td>
<td>0.933 – 5.477</td>
<td>2.493</td>
<td>0.797 – 7.799</td>
</tr>
<tr>
<td>Hormone Receptor Status (neg. vs. pos.)</td>
<td>1.843 *</td>
<td>1.474 – 2.304</td>
<td>2.210 *</td>
<td>1.696 – 2.880</td>
</tr>
<tr>
<td>Her-2-neu (neg. vs. pos.)</td>
<td>0.803</td>
<td>0.640 – 1.007</td>
<td>1.060</td>
<td>0.972 – 1.156</td>
</tr>
</tbody>
</table>

Conclusion
Different toxicity profiles given, hematological toxicity in the FE120C group was more severe than in the E90C–D. In contrast to AC-P in earlier studies, EC-Doc  provides a feasible and effective alternative option to dose-intensified FEC with different safety profile in this high risk breast cancer cohort.

Acknowledgment
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Figure 1: ADEBAR trial design

Figure 2: Disease free survival

Figure 3 a-d: Disease Free Survival Analysis in Subgroups

Table: Multivariate survival analysis