

Title: Adjuvant chemotherapy with or without darbepoetin alpha in node-positive breast cancer: survival and quality of life analysis from the prospective randomized WSG ARA Plus trial

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Background: Darbepoetin alpha (ARA) is currently used to reduce chemotherapy-associated anemia (CAA) rates in various solid tumors. A possible negative impact of ARA on patient survival has been suggested in some clinical trials. The objective of the prospective randomized phase III ARA Plus trial is to compare the survival effect of darbepoetin alpha use (ARA+/ARA-) in combination with modern standard adjuvant chemotherapy targeting guideline-recommended Hb-levels in high-risk breast cancer (BC).

Methods: ARA Plus compared 6 cycles T₇₅A₅₀C₅₀₀ q3w or 6 cycles F₅₀₀E₁₀₀C₅₀₀ q3w (at discretion of each center) in patients with node positive BC (aged 18-65 years). Patients were randomized to darbepoetin (ARA+) 500 µg q3w until completion of radiotherapy or to standard supportive care (ARA-). ARA was started at Hb-levels ≤13 g/dL (amendment 01/2008: Hb ≤12 g/dL) and stopped at >14 g/dL (>12 g/dL). Primary endpoint is event-free survival (EFS: relapses, death without disease evidence, second malignancy). Overall survival (OS), toxicity, Hb-levels and quality of life are secondary endpoints. Survival analysis was planned after 7 years of study duration. EFS was tested using χ^2 -test ($\alpha=0.05$) with a statistical power of $\beta=80\%$ and log-rank test. Quality of life was measured using FACT questionnaires at beginning of therapy, mid, end of therapy, and at 1 year afterwards.

Results: 1234 pts (616 ARA+/618 ARA-) from 70 centres in Germany were randomized between 01/04 and 06/08. 1198 intent to treat patients (ITT) were analysed (1096 TAC; 102 CEF). Baseline characteristics were well balanced in ARA+ and ARA- arms: median age 53/53 years; tumor size 2.4/2.4cm; number of + LN 3/3; HR+ 80%/ 83.5%, G3 40.7%/36.7%. Toxicity data have been reported earlier (SABCS 2008).

At median follow up of 40 months, 168 events (81 ARA+, 83 ARA-) and 134 relapses (65 ARA+, 69 ARA-) were reported. There was no significant difference in 3-year EFS between ARA+ and ARA- arms (89.2% vs. 87.6%, $p=0.97$, χ^2 -test). 37 deaths were reported in the ARA- and 36 in the ARA+ arm. 3-year OS was 95.4% and 95.1% for ARA+ and ARA-, respectively ($p=0.85$). Only nodal involvement (≥ 4 vs. 1-3), negative HR, tumor size >2 cm and G3 were significant survival predictors by multivariate analysis. Unplanned retrospective analysis revealed better EFS for ARA+ vs. ARA- in HR- ($p=0.05$), and no difference in HR+ group ($p=0.6$). In ARA+ patients, Hb-levels were stable over the whole treatment period with rare overstimulation. In ARA- patients, Hb-levels decreased during therapy (median of all cycles ARA+/ARA-: 12.5/11.6 g/dL). There was no correlation between mean Hb-levels and survival in either study arm.

There were no significant differences in mean FACT scores changes (general, anemia, cognitive) from begin to end of therapy in either study arm. More detailed analyses are ongoing.

Conclusions: To date, the WSG ARA plus trial is the only prospectively randomized trial in early high-risk BC exclusively focusing on the impact of adjuvant ARA on patient outcome. Supportive administration of ARA appears to be safe and to have no significant survival effect when used in combination with TAC or CEF according to current guidelines.