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Final results from the prospective phase III WSG-ARA trial: impact of adjuvant darbepoetin alfa on event-free survival in early breast cancer

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Background: WSG-ARA plus trial evaluated the effect of adjuvant darbepoetin alfa (DA) on outcome in node positive primary breast cancer (BC).

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**Patients and methods:** One thousand two hundred thirty-four patients were randomized to chemotherapy either with DA (DA+; n = 615) or without DA (DA−; n = 619). DA (500 µg q3w) was started at hemoglobin (Hb) levels <13.0 g/dl (<12 g/dl after DA label amendment) and stopped at Hb levels ≥14.0 g/dl (12 g/dl after label amendment). Primary efficacy end point was event-free survival (EFS); secondary end points were toxicity, quality of life (QoL) and overall survival (OS).

**Results:** Venous thrombosis (DA+: 3.0%, DA−: 1.0%; P = 0.013) was significantly higher for DA+, but not pulmonary embolism (0.3% in both arms). Median Hb levels were stable in DA+ (12.6 g/dl) and decreased in DA− (11.7 g/dl). Hb levels >15 g/dl were reported in 0.8% of cycles. QoL parameters did not significantly differ between arms. At 39 months, DA had no significant impact on EFS (DA+: 89.3%, DA−: 87.5%; P_{log-rank} = 0.55) or OS (DA+: 95.5%, DA−: 95.4%; P_{log-rank} = 0.77).

**Conclusions:** DA treatment did not impact EFS or OS in routine adjuvant BC treatment.

**Key words:** anemia, breast cancer, adjuvant chemotherapy, epoetin, safety

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**introduction**

In the late 1990s, potentially negative impacts of anemia, tumor hypoxia, or transfusion-related immune suppression on cancer therapy efficacy and survival were discussed. Early trials focusing on anemia correction and reduction of transfusion needs with erythropoiesis-stimulating agents (ESAs) suggested survival benefits in patients with advanced solid tumors [1]. Subsequent trials tested impact of ESAs on survival, with heterogeneous results reported in meta-analyses [2, 3]. Two randomized trials in metastatic [4] and neoadjuvant [5] breast cancer settings reported early mortality increases in ESA arms.

Results in head and neck cancer [6] and in breast cancer (BC) [4] intensified safety concerns. ESAs are approved for the treatment of chemotherapy-induced anemia in the USA and the EU, but labeling includes safety concerns. To our knowledge, the WSG-ARA plus trial is the only trial testing adjuvant ESA impact on event-free survival (EFS) as primary end point in early BC.

**patients and methods**

**WSG-ARA plus** was a prospective, multicenter, phase III trial. The trial design (supplementary Figure S1, available at *Annals of Oncology* online) provided for standard adjuvant chemotherapy ± darbepoetin alfa (DA+/DA−). Primary BC patients (M₀ age ≥18 years, pT1-3, ≥10 resected nodes, free margins, ECOG<2) were eligible. Exclusion criteria were creatinine level >1.4 mg/dl, bilirubin level >2.0 mg/dl, congestive heart failure, uncontrolled hypertension, pre-existing polyneuropathy, other severe comorbidities, hematopoietic insufficiency, previous cancer history, pregnancy, breast feeding, or participation in another clinical trial. Written informed consent was obtained before randomization. The protocol was approved by the local ethics committee/institutional review board; the trial was conducted according to Declaration of Helsinki and European GCP criteria.

Patients were randomized centrally within 42 days after surgery (permitted block, stratified by center). Patients received either 6 × French F₅₀₀₋₁₀₀₀ or 6 × T₇₅₋₅₀₀ at 3-week intervals (at discretion of center). Following chemotherapy start, and continuing through radiotherapy, DA+ patients were scheduled to begin weekly DA 300 µg at hemoglobin (Hb) level of ≤13.5 g/dl, stopping if Hb≥14 g/dl; re-start recommended if Hb≥13.5 g/dl (300 µg DA Q3W). After December 2004, these starting and re-starting Hb levels were reduced to 13.0 g/dl, stopping level at 14.0 g/dl, and treatment was started with DA 500 µ g Q3W. In 2008, taking national safety concerns into account, the steering committee recommended lowering the starting/stopping Hb levels for DA to 12 g/dl. Oral iron (FeSO₄ 300–325 mg) was recommended for below-normal serum ferritin. Transfusion was advised for Hb levels ≤8 g/dl. Other adjuvant therapies were administered according to national guidelines.

For the first 2 years, follow-up examinations were carried out every 3 months, thereafter twice yearly.

Data management and monitoring were conducted in compliance with ICH/GCP guidelines and applicable national regulations. Toxicity analysis included adverse events and all laboratory data; adverse events were graded by the National Cancer Institute’s Common Toxicity Criteria (Version 3) and reported before every course. Monitoring included reconciliation of all serious adverse event databases. Two Functional Assessment of Cancer Therapy (FACT) questionnaires (anemia (FACT-An) and cognitive (FACT-Cog)) were obtained before first drug intake, before each cycle, following each therapy visit and at 6-month follow-up. An additional FACT-Cog questionnaire was obtained 1 year after end of therapy.

**statistics**

The primary end point was EFS; ‘event’ refers to relapse, death without evidence of disease, or second malignancy. The trial was designed to detect a 5-year EFS difference of 6.8%, corresponding to a hazard ratio (HR) for DA+ to DA− of 0.77 (or HR for DA− to DA+ of 1.3) in the intention-to-treat (ITT) population, with 80% power allowing a one-sided 5% type-I error. Assuming 5-year EFS for 6 × TAC of 65%, required sample size was 1234 patients (359 events); statistical analysis was planned 5 years after last patient in. Survival curves were estimated by the product-limit method and compared by the log-rank test. Since actual median follow-up was 39 months (study shortened due to patients’ insurance coverage), 3-year EFS and the secondary end point overall survival (OS) are reported with two-sided 95% confidence intervals (95% CIs). Toxicity and quality of life (QoL) were also secondary end points. Effects of treatment within HR-positive and -negative subgroups were assessed by univariate Cox regression analysis (unplanned).

**results**

**patient characteristics**

From January 2004 to June 2008, 1234 patients were enrolled from 70 centers; 615 were randomized to DA+, 619 to DA−; 105 patients received FEC; and 1129 received TAC (supplementary Table S2, available at *Annals of Oncology* online). One thousand...
one hundred seventy patients (DA+: 585, DA−: 585) were eligible for ITT and 1016 (DA+: 526, DA−: 490) for per protocol analysis (Figure 1).

toxicity
Safety data refer to 1199 patients (DA+: 598, DA−: 601) and 6884 chemotherapy cycles (DA+: 3445, DA−: 3449). Nonhematological toxicity, leukopenia, and thrombocytopenia toxicity grades were virtually identical in the arms. DA+ was associated with more thrombosis (18 versus 6 cases, \( P = 0.013 \)). Four pulmonary embolisms/arterial embolic events occurred (two in each arm). Two therapy-related septic deaths in the DA+ arm were attributed to chemotherapy.

Hb levels
Figure 2 shows mean Hb levels during treatment course. Prevalence of anemia was higher in DA−: [grade 2 (Hb: 10–8.0 g/dl): DA+: 10.9%, DA−: 23.8%; \( P = 0.025 \)]; [grade 3 (Hb: 8.0–6.5 g/dl) (DA+: 1.2%, DA−: 2%; n.s.)]. A small proportion of DA+ (0.9%) and DA− (0.5%) patients experienced Hb levels >15 g/dl.

quality of life
The arms did not differ significantly regarding changes in either total FACT-An, or FACT-Cog scores, or any individual parameter.

<table>
<thead>
<tr>
<th>Safety population DA− (n = 601)</th>
<th>Safety population DA+ (n = 598)</th>
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<tbody>
<tr>
<td>ITT population TAC N= 534 FEC N= 51</td>
<td>ITT population TAC N= 532 FEC N= 53</td>
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<tr>
<td>Completed therapy (n = 545)</td>
<td>Completed therapy (n = 549)</td>
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<tr>
<td>Therapy per protocol (n = 490)*</td>
<td>Therapy per protocol (n = 526)</td>
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<th>Reasons for premature end of CHT:</th>
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<tr>
<td>Refused (n = 7)</td>
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<tr>
<td>Disease progression (n = 1)</td>
</tr>
<tr>
<td>Toxicity (n = 26)</td>
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<tr>
<td>Protocol violation (n = 1)</td>
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<tr>
<td>Lost to follow up (n = 1)</td>
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<tr>
<td>Other (n = 4)</td>
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<tr>
<th>Reasons for premature end of follow up:</th>
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<tr>
<td>Lost to follow up (n = 35)</td>
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<tr>
<td>Refusal (n = 3)</td>
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<tr>
<td>Death (n = 38)</td>
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Mean (±SD) FACT-An scores were 166.2 (±24.7) in DA+ (\( n = 376 \)) and 145.5 (±24.8) in DA− (\( n = 387 \)) initially, 136.9 (±32.5) in DA+ (\( n = 366 \)) and 133.9 (±32.2) in DA− (\( n = 330 \)) following therapy. Mean change was −9.0 (±24.6) in DA+ (\( n = 270 \)) and −10.1 (±23.2) in DA− (\( n = 199 \)).

Perceived cognitive impairment (PCI) scores were 64.0 (±11.1) in DA+ (\( n = 372 \)) and 64.4 (±9.6) in DA− (\( n = 366 \)) initially, 60.3 (±12.4) in DA+ (\( n = 356 \)) and 59.4 (±14.4) in DA− (\( n = 321 \)) following therapy. Mean change in PCI was −3.3 (±10.5) in DA+ (\( n = 264 \)) and −4.7 (±10.0) in DA− (\( n = 264 \)). Mean and SD of ‘impact of PCI on QoL’ were virtually identical in the arms both initially (13.9 ± 3.7) and following therapy (12.9 ± 4.2), with a change of about (−1.0 ± 4.0) in both arms. Perceived cognitive abilities were also very similar both initially and following therapy, with zero or small changes in mean values.

survival
At median follow-up of 39 months, 77 events (12.5%) were reported in the DA+ arm and 82 (13.3%) in the DA− arm (\( P_{\text{log-rank}} = 0.55 \)). Estimated 3-year EFS rates from ITT analysis (Figure 3) were 89.3% (86.4%–91.7%) for DA+ versus 87.5% (84.4%–90.0%) for the DA− arm; corresponding hazard ratio was 0.85 (95% CI 0.62–1.16; \( P_{\text{log-rank}} = 0.55 \)). Three-year EFS estimates per protocol were comparable (90.8% versus 87.7%; hazard ratio = 0.74; \( P = 0.21 \)). A trend (\( P = 0.06 \)) favoring DA+ in 3-year EFS was seen in hormone-receptor-negative (HR−), but not HR+ tumors.

*\( N = 39 \) patientes excluded due to use of ESA

Figure 1. CONSORT diagram showing flow of patients’ progress through the study.
Figure 2. Hb values over treatment time.

Figure 3. EFS in the ITT population.
Thirty-three deaths (5.4%) occurred in DA+ and 37 (6.0%) in DA− (log-rank = 0.77). Three-year OS estimates for DA+ versus DA− by ITT were 95.5% (93.3%–97.0%) versus 95.4% (93.2%–96.9%); estimated 3-year hazard ratio was 1.0 (log-rank = 0.77) (supplementary Figure S3, available at Annals of Oncology online). OS estimates per protocol were comparable (3-year OS: 96.1% (93.8%–97.5%) versus 97.9% (96.1%–98.8%), n.s.).

**discussion**

The WSG-ARA plus trial included 1234 patients from 70 sites in Germany. It is the largest ESA trial in BC, and the only adjuvant trial addressing survival after adjuvant ESA as primary end point. The trial was designed to test whether a ΔHb of >2 g/dl would be therapeutically beneficial, with a 5-year EFS difference of 6.8% as primary end point of the study in a superiority design. Under the restrictions of ESA use described above, Hb levels around 12.6 g/dl were maintained in the DA+ arm, whereas Hb levels continuously decreased in the DA− arm. The overall ΔHb under this moderately hematotoxic standard regimen was 1 g/dl. At 39 months, EFS and OS did not differ significantly between study arms. The DA+ group did show increased thromboembolic events (OR 3.1, 95% CI 1.1–8.7), while the rate of pulmonary embolisms was not affected. Similar findings were obtained in several previous studies [3]. Secondary end points such as QoL parameters as measured by FACT-An and FACT-Cog were also not altered, probably due to the low overall ΔHb.

Safety concerns resulted from head and neck cancer trials [6, 7] using ESAs to maintain Hb >14 g/dl reported negative impact on local control and DFS but were not confirmed by other head and neck cancer trials [8]. A phase III trial [9] in cervical cancer patients receiving postoperative radiochemotherapy ± ESA showed improved 5-year DFS. In non-Hodgkin lymphoma treated by CHOP chemotherapy, both beneficial [10] and neutral effects were seen [11].

To address the key issue of ESA safety, exploratory noninferiority analysis was carried out here: for EFS, the hazard ratio for DA+ compared with DA− was 0.85 (formal 95% CI 0.62–1.16). Combining the upper confidence limit (1.16) with 3-year EFS in this trial, these results suggest that DA+ is unlikely to be inferior to DA− by more than 1.8% regarding 3-year EFS or (extrapolating with proportional hazards) about 2.8% regarding 5-year EFS. If the trial had produced 359 events (instead of 159) as originally planned, then the 95% CI would have been narrower, e. g. 0.68–1.05.

In summary, these results—and those of meta-analyses reporting odds ratios in the range of 0.66 [9] to 7.47 [12] for different cancer types—suggest that distinct cancer entities should be considered separately:

In BC, the BEST trial [4] included 939 mainly nonanemic metastatic BC patients randomized to receive 40 000 IU epoetin alfa weekly versus placebo for 12 months. Notably, 12-month OS was poorer in the epoetin alfa arm (70% versus 76%, ITT), with excess deaths predominating during the first 4 months underlying certain criticism regarding result interpretation of the trial [13]. The multicenter neoadjuvant phase III AGO PREPARE [14] trial included mainly nonanemic HER2-negative BC patients with tumors >2 cm, randomized to sequential dose-intense, dose-dense epirubicin/paclitaxel (Q2W) followed by conventional CMF versus conventionally scheduled 4 × EC → 4 × paclitaxel, further randomized to DA±. The mean Hb difference was 1 g/dl, 13.6 (DA+) versus 12.6 (DA−). DA did not impact pathological complete response (pCR), but 3-year DFS tended lower in DA+ (74.3% versus 80.0%, P = 0.06) [14].

In the adjuvant BC setting, the ETC trial [15], the WSG-ARA trial, and exploratory analysis of NSABP B-38 [16]) have not detected survival differences by ESA. The ETC trial of dose-intense/dense sequential epirubicin–paclitaxel–cyclophosphamide versus EC→paclitaxel (Q3W) in high-risk patients (n = 1284) randomized 643 ETC patients to epoetin alfa versus control (n = 319) [15]; 5-year OS rates were 80.7% versus 82.3%, respectively [15].

The NSABP B-38 trial compared TAC to dose-dense, AC-paclitaxel (q2w) ± Gemcitabine in 4894 mostly HER2-, node-positive BC patients; ESA was obligatory for Hb ≤11 g/dl. No significant DFS differences between study arms were reported (5.3-year median follow-up). Similarly to WSG-ARA, grade 2 anemia in the TAC arm was 12%; incidence was 24% for dose-dense AC-paclitaxel and 31% for AC-PG, with 35%, 47%, and 51% of patients receiving ESA’s, respectively, or 2149 ESA-treated patients overall versus n = 2692 without ESA. Exploratory analysis revealed no differences regarding DFS (HR = 1.02) or OS (HR = 1.04) [16].

Variations in impact of ESA use in different BC stages could be related to trial issues: the two trials [4, 14] showing possible detrimental effects of ESA use had common features: excess early mortality, but otherwise similar outcomes (EFS, pCR) between ESA groups. Moreover, trial characteristics (unbalanced baseline risks, high dropout rates) may have contributed to OS differences.

On the other hand, a hypothetical biological mechanism strong enough to cause early deaths cannot be ruled out a priori. However, the existence of an underlying tumor-stimulating mechanism has been questioned based on the available preclinical evidence [17]. The hypothesis of overstimulation also is not entirely consistent with observed similar Hb distributions in all four treatment arms (BEST ~13 g/dl [4], PREPARE 13.6 g/dl [14]; ETC 12.56 g/dl [15]; ARA 12.6 g/dl).

In terms of correction of chemotherapy-induced anemia, there is broad consensus that patients benefit from ESA use [1, 18–20]. Association of ESAs with reduced fatigue symptoms and improved QoL [18, 21–26] as reported by some retrospective trials, were not observed here; however, in the standard regimens used in this trial, symptomatic anemia may be less severe than for example in dose-dense BC protocols.

Currently, ESA use is not recommended in patients whose cancer has high curative probability. In view of the recently published AGO-ETC trial and, particularly, the WSG-ARA plus results presented here, revision of this recommendation for early BC patients may be a valuable topic for discussion. Use of ESA can be considered as an alternative to transfusions in the selected group of patients with symptomatic, mostly intensive, adjuvant chemotherapy-induced anemia [15, 16].

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Disclosure

UN received honoraria from Sanofi-Aventis and AMGEN. REK is an immediate family member of Nadia Harbeck, who had a consultant or advisory role for Sanofi-Aventis. She also received honoraria from Sanofi-Aventis. TR received honoraria from AMGEN. All remaining authors have no declared conflicts of interest.

References


