Final analysis of the prospective WSG-AGO EC-Doc versus FEC phase III trial in intermediate-risk (pN1) early breast cancer: efficacy and predictive value of Ki67 expression†


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Background: Taxane-based adjuvant chemotherapy is standard in node-positive (N+) early breast cancer (BC). The magnitude of benefit in intermediate-risk N+ early BC is still unclear. WSG-AGO epirubicine and cyclophosphamide (EC)-Doc is a large trial evaluating modern taxane-based chemotherapy in patients with 1–3 positive lymph nodes (LN) only.

Patients and methods: A total of 2011 BC patients (18–65 years, pN1) were entered into a randomized phase III trial comparing 4 × E90C600 q3w followed by 4 × docetaxel100 q3w (n = 1008) with the current standard: 6 × F500E100C500 q3w (n = 828) or C600M40F600 d1, 8 × q4w (n = 175). Primary end point was event-free survival (EFS); secondary end points were overall survival (OS), toxicity, translational research, and quality of life. Central tumor bank samples were evaluable in a representative collective (n = 772; 40%). Ki-67 was assessed centrally in hormone receptor-positive disease as a surrogate marker for the distinction of luminal A/B-like tumors.

Results: Baseline characteristics were well balanced between study arms in both main study and central tumor bank subset. At 59-month median follow-up, superior efficacy of EC-Doc [versus FEC (a combination of 5-fluorouracil, epirubicin, and cyclophosphamide)] was seen in EFS and OS: 5-year EFS: 89.8% versus 87.3% (P = 0.034); both tests one-tailed. EC-Doc caused more toxicity. In hormone receptor-positive (HR)+ disease, only high-Ki-67 tumors (≥20%) derived significant benefit from taxane-based therapy: hazard ratio = 0.39 (95% CI 0.18–0.82) for EC-Doc versus FEC (test for interaction; P = 0.01).

Conclusion: EC-Doc significantly improved EFS and OS versus FEC in intermediate-risk BC (1–3 LN) only. The added value of Ki-67 has to be interpreted with caution in the context of overtreatment of small tumors.

Clinical Trial number: ClinicalTrials.gov, NCT02115204.

Key words: adjuvant chemotherapy, node-positive breast cancer, luminal A/B-like subtypes, overtreatment

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introduction

WSG-AGO epirubicine and cyclophosphamide (EC)-Doc is one of the first-generation trials comparing taxane versus non-taxane-based regimens (Figure 1). When the trial was planned, early results from CALGB 9344 suggested superiority of sequential taxanes ($4 \times$ doxorubicine (A) and cyclophosphamide (C) (AC) → $4 \times$ paclitaxel) over four courses of AC in node-positive (N+) breast cancer (BC) [1]. In contrast to the original CALGB regimen, WSG EC-Doc trialists decided to replace doxorubicin by epirubicin and to use less neurotoxic docetaxel instead of paclitaxel [2]. The control represents the national standard at that time, which preferred 5-fluorouracil (F), epirubicin (E), and cyclophosphamide (C) (FE100C) but still allowed CMF (a combination of cyclophosphamide, methotrexate, and 5-fluorouracil). Only N1 patients were eligible, since the question was whether better survival would outweigh additional toxicity and longer chemotherapy duration in this intermediate-recurrence-risk population. According to the St Gallen Consensus at that time, adjuvant chemotherapy was routinely advised in all N+ tumors, independently from extent of nodal involvement. Beyond tumor burden, later Consensus considered tumor biology to be another important discriminator for adjuvant decision making. Particularly proliferation markers (Ki-67) were recommended for identification of luminal A-like tumors with excellent prognosis potentially over-treated with chemotherapy [3].

In addition to the outcome data, therefore, we investigated retrospectively potential immunohistological predictors of taxane outcome on a representative tumor bank subset [3–5].

methods

eligibility criteria

Eligible patients were 18–65 years old and had histologically proved BC, pT1-3 with 1–3 positive lymph nodes (LN). M0 status had to be proved by chest X-ray, liver ultrasound, and bone scan. Surgical requirements included free margins and >10 removed LN. Patients were eligible with a performance status eastern cooperative oncology group <2; patients with major organ dysfunction, preexisting peripheral polyneuropathy, pregnancy, or inflammatory/sequential BCs were excluded. Enrollment within 42 days of surgery was mandatory. Written informed consent was obtained before randomization. The protocol and central tumor bank sub-study was approved by local ethics committee/institutional review boards and conducted according to the Declaration of Helsinki and European GCP criteria.

Randomization was carried out according to a stratified permuted-block design, with center as the sole stratification factor.

treatment

In the control arm, it was at the discretion of the investigating center to give six cycles CMF (cyclophosphamide 600 mg/m² i.v./methotrexate 40 mg/m² i.v./ 5-fluorouracil 600 mg/m² i.v. Day 1/8 q28) or six cycles FEC (5-fluorouracil 500 mg/m² i.v./epirubicin 100 mg/m² i.v./cyclophosphamide 500 mg/m² i.v. q21) as standard; the initial choice was binding. Within the experimental arm, patients received $4 \times$ epirubicin 90 mg/m² i.v./cyclophosphamide 600 mg/m² i.v. q21, followed by $4 \times$ docetaxel 100 mg/m² i.v. q21. Prophylactic granulocyte-colony stimulating factor was recommended at onset of taxanes. Endocrine therapy and radiotherapy were given according to the national guidelines [6]. When the HERA trial started in 2001, EC-Doc trial was accepted as a feeder trial.

follow-up

Follow-up examinations were carried out at 3-month intervals for 2 years and at 6-month intervals thereafter.

central tumor bank sub-study

Paraffin-embedded tumor blocks were collected for 786 of 1950 patients (40%), with available 5-year follow-up or experienced relapse or death at time of analysis. Tissue microarrays (TMAs; diameter 2 mm) were constructed after histopathological review (A.H.) from one morphologically representative region. Central grading was carried out on H&E slides. Central immunohistochemistry was evaluated on TMAs (estrogen-receptor/progesterone-receptor, Ki-67) by two experienced breast pathologists (H.H.K. and A.H). Slides from TMAs were stained for ER (rabbit (SP1), Ventana), PR (mouse antibody 16, Novocastra), and Ki-67 (MIB-1 mouse, DAKO), according to standard procedures. Tumors were classified as ER- or PR-positive if moderate or strong immunostaining was present in >1% of tumor nuclei.

Figure 1. Design of the study. *AH: anti-hormonal.
statistics

Primary end point was event-free survival (EFS): time interval from randomization to first event (relapse, death during therapy, and second malignancy) or observation time if event-free (censored). For groups, EFS refers to fraction surviving event-free as a function of time interval (Kaplan–Meier estimate).

The trial was designed to test the hypothesis of superior EFS, characterized by the hazard ratio (HR) of EC-Doc to control, according to a one-sided log-rank test at 5% type I error; Statistical analysis was planned 5 years after last patient in by intention to treat (ITT). With 2000 patients, power of 80% was computed for this test assuming 5-year EFS for 6 × FEC/CMF of 71.1%, and HR for EC-Doc corresponding to 5-year EFS improvement of 5%. A one-tailed superiority test was appropriate, because inferiority of EC-Doc is not clinically relevant, due to its known, more severe toxicity. Nonetheless, all P-values reported here are two-sided unless otherwise stated; Cox model HRs are reported with two-sided 95% confidence intervals. While the statistical plan included a combined analysis of the FEC/CMF (control) arm, separate analyses were carried out for FEC-treated patients.

Associations among discrete variables were assessed by Fisher’s exact test.

findings

patient characteristics

From April 2000 to August 2005, 2012 patients were enrolled in 165 centers, and 1950 (97%) were eligible for ITT analysis. Main reasons for ineligibility were missing informed consent and severe violation of inclusion criteria. For the control arm, 152 centers opted for FEC, 13 for CMF; 177 (9%) patients were assigned to CMF. For ITT analysis, 978 EC-Doc and 972 control (FEC/CMF: 795/177) patients were included. There are no significant differences in baseline characteristics between the study arms (see Table 1 below). Median age was 52. Two-thirds

Table 1. Summary of patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>CMF (n = 177)</th>
<th>FEC (n = 795)</th>
<th>EC-Doc (n = 978)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>53.9</td>
<td>51.5</td>
<td>51.9</td>
<td>0.233</td>
</tr>
<tr>
<td>Premenopausal (%)</td>
<td>38.4</td>
<td>46.3</td>
<td>44.5</td>
<td>0.274</td>
</tr>
<tr>
<td>Postmenopausal (%)</td>
<td>61.6</td>
<td>48.5</td>
<td>55.5</td>
<td></td>
</tr>
<tr>
<td>&lt;35 (%/n)</td>
<td>2.3/4</td>
<td>4.7/37</td>
<td>3.8/37</td>
<td>0.327</td>
</tr>
<tr>
<td>Median tumor size (cm)</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
<td>0.557</td>
</tr>
<tr>
<td>Breast-conserving therapy (%)</td>
<td>66.6</td>
<td>68.3</td>
<td>66.5</td>
<td>0.626</td>
</tr>
<tr>
<td>G1/2 (%)</td>
<td>68.5/115</td>
<td>63.3/489</td>
<td>64.9/607</td>
<td>0.187</td>
</tr>
<tr>
<td>G3 (%)</td>
<td>31.5/53</td>
<td>36.7/284</td>
<td>35.1/329</td>
<td></td>
</tr>
<tr>
<td>ER and/or PR positive (%)</td>
<td>81.4/144</td>
<td>77.6/617</td>
<td>77.4/757</td>
<td>0.514</td>
</tr>
<tr>
<td>ER and PR negative (%)</td>
<td>16.9/30</td>
<td>20.8/165</td>
<td>19.5/191</td>
<td></td>
</tr>
<tr>
<td>HER2+++ (%)</td>
<td>14.7/26</td>
<td>16.6/132</td>
<td>15.1/148</td>
<td>0.677</td>
</tr>
<tr>
<td>Ki67 (%)</td>
<td>60.9/28</td>
<td>58.0/102</td>
<td>64.5/147</td>
<td>0.408</td>
</tr>
<tr>
<td>HR+/Ki67 &lt;20%</td>
<td>39.1/18</td>
<td>42.0/74</td>
<td>35.5/81</td>
<td></td>
</tr>
</tbody>
</table>

Apart from local pathology.

bBy central pathology.

Table 2. Summary of patients with first events

<table>
<thead>
<tr>
<th></th>
<th>EC-Doc (n = 978)</th>
<th>Control (n = 972)</th>
<th>CMF (n = 177)</th>
<th>FEC (n = 795)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>101 (10.3%)</td>
<td>131 (13.5%)</td>
<td>34 (19.2%)</td>
<td>97 (12.2%)</td>
</tr>
<tr>
<td>Relapse of breast cancer</td>
<td>78 (7.9%)</td>
<td>117 (11.9%)</td>
<td>31 (17.5%)</td>
<td>86 (10.7%)</td>
</tr>
<tr>
<td>Local only, regional only, or both</td>
<td>11 (1.1%)</td>
<td>25 (2.6%)</td>
<td>7 (4.0%)</td>
<td>18 (2.3%)</td>
</tr>
<tr>
<td>Distant (with or without local or regional)</td>
<td>67 (6.7%)</td>
<td>92 (9.4%)</td>
<td>24 (13.6%)</td>
<td>68 (8.4%)</td>
</tr>
<tr>
<td>Second primary cancer</td>
<td>23 (2.4%)</td>
<td>14 (1.4%)</td>
<td>3 (1.7%)</td>
<td>11 (1.4%)</td>
</tr>
<tr>
<td>Contralateral breast cancer</td>
<td>12 (1.2%)</td>
<td>8 (0.8%)</td>
<td>1 (0.6%)</td>
<td>7 (0.9%)</td>
</tr>
<tr>
<td>Other cancers</td>
<td>11 (1.1%)</td>
<td>6 (0.6%)</td>
<td>2 (1.1%)</td>
<td>4 (0.5%)</td>
</tr>
<tr>
<td>Death without any evidence of cancer</td>
<td>4 (0.4%)</td>
<td>4 (0.4%)</td>
<td>0 –</td>
<td>4 (0.5%)</td>
</tr>
</tbody>
</table>

*Leukemia 2 EC-Doc, 0 CMF, and 0 FEC.
had breast-conserving therapy; 79.5% had hormone receptor-positive (HR+) disease.

Baseline characteristics of the central pathology subpopulation were comparable to those of the entire trial population: 73.6% HR+, median Ki-67 20%.

efficacy
At median follow-up of 59 months, 232 events occurred (EC-Doc 101 and FEC/CMF 131; see Table 2).

Concerning the primary end point (EFS), superiority of EC-Doc versus control by ITT was demonstrated ($P = 0.013$) according to the planned one-sided log-rank test (two-tailed $P = 0.026$; Figure 2A); estimated 5-year EFS rates for EC-Doc and control were 89.8% versus 86.6%. Comparing EC-Doc with FEC alone also suggested superiority of EC-Doc (one-tailed $P = 0.038$, two-tailed $P = 0.076$; log-rank; Figure 2B); 5-year EFS rates were 89.8% versus 87.3%. Corresponding univariate Cox HRs were HR = 0.74 (95% CI 0.57–0.97) for EC-Doc versus control and HR = 0.77 (95% CI 0.58–1.03) for EC-Doc versus FEC. After adjusting for LN (2/3 versus 1), tumor size ($\geq 2$ versus $< 2$ cm), age ($\geq 50$ versus $< 50$), and HR status, EC-Doc was associated with significantly better relapse-free survival (HR = 0.71; 95% CI 0.53–0.96, $P = 0.04$) than FEC (Figure 2C).

The OS advantage of EC-Doc versus control (supplementary Figure S1A, available at Annals of Oncology online) corresponds to a HR of 0.70 (95% CI 0.49–0.99; two-tailed $P = 0.046$). Of the 122 deaths, 50 occurred in the EC-Doc and 72 in the control arm. Estimated 5-year OS rates were 94.5% (EC-Doc) versus 92.2% (control). Comparison of OS for EC-Doc versus FEC is shown in supplementary Figure S1B, available at Annals of Oncology online with a HR of 0.70 (95% CI 0.47–1.03; two-tailed $P = .068$, one-tailed $P = .034$) suggesting superiority of EC-Doc; 5-year OS was 94.5% versus 92.8%.

Five-year BC-specific survival rates were 95.4% versus 92.8% for EC-Doc versus FEC, 95.4% versus 93.4% for EC-Doc versus FEC/CMF (two-tailed $P = 0.02$) and 95.4% versus 93.4% for EC-Doc versus FEC (two-tailed $P = 0.036$), respectively.

protocol adherence
In the EC-Doc arm, 794 patients (81.2%) completed all eight cycles, and in the control arm, 870 patients completed all six cycles: FEC 721 (90.7%); CMF 149 (84.2%). Figure 3 shows detailed discontinuation information. Dose reductions >25% were reported for 182 cycles involving $n = 104$ patients (10.6%) from EC-Doc versus 43 cycles involving $n = 29$ patients (3%) from FEC/CMF. Nine (EC-Doc) and 12 patients (control) received trastuzumab in the HERA trial.

toxicity
Supplementary Table S2, available at Annals of Oncology online summarizes grade 3/4 (NCI-CTC v2.0) toxicity by cycle and patient. In terms of acute toxicity, EC-Doc causes significantly more anemia and thrombocytopenia. Febrile neutropenia incidence reported as adverse event was 3.7% for EC-Doc versus 2.1% for FEC. EC-Doc caused significantly more mucositis, arthralgia, pain, and neuropathy, with a marked increase when changing from EC to docetaxel. Neurotoxicity was documented during chemotherapy, persisting polyneuropathy during follow-up. The protocol suggested a 25% dose reduction in case of °2 and discontinuation in °3 neuropathy. By end of therapy, neurotoxicity of any grade (°3/4) was reported in 19.1% (4.0%) of patients receiving EC-Doc versus 6.5% (1.0%) of control.

Long-term neurotoxicity (any grade) in the EC-Doc arm was documented in 14.2% of patients after 6 months, 11.0% after
1 year, and 7.4% after 2 and 3 years. Persisting peripheral neuropathy (any grade) after 2 years of follow-up was reported in 3.2% for EC-Doc (FEC 0.6%).

Chemotherapy-induced amenorrhea was recorded in a representative subgroup of premenopausal women from both arms (EC-Doc: 106 and control: 103). Amenorrhea rates were non-significantly higher in the EC-Doc arm (74% versus 62%, \( P = 0.06 \)). Due to the small sample size, this subgroup does not qualify for survival analysis.

**quality of life**

Of 1950 patients, 1343 (69%) completed EORTC QLQ 30 and were evaluable for QoL assessment. Baseline QoL values were similar with a mean score of 62/100 on a Global Health Status scale. At the end of treatment, mean scores had decreased to 45.4 for EC-Doc and to 53.5 for control (\( P < 0.0001 \), T-test). Mean Global Health scores after 1 year exceeded baseline for both EC-Doc (67.4, \( P < 0.001 \)) and control (70.1, \( P < 0.001 \)); the advantage of control compared with EC-Doc persisted (\( P = 0.02 \)).

**central tumor bank sub-study**

Ki-67 was a prognostic marker for EFS in HR+ disease (Ki-67, HR = 2.39, 95% CI 1.4–4.09). Ki-6720 classified 62% (\( n = 277/450 \)) tumors as low-proliferating luminal A-like, and 38% as luminal B-like.

Chemotherapy benefit was associated with tumor biology as follows: in univariate analysis, the superiority of EC-Doc compared with FEC was similar in HR+ (HR = 0.62, 95% CI 0.37–1.05, \( P = 0.07 \)) and HR− diseases (HR = 0.64, 95% CI 0.34–1.20, \( P = 0.17 \)). However, in the ‘luminal B-like’ subgroup, 5-year EFS strongly favors EC-Doc versus FEC (89% versus 74%; HR = 0.38; 95% CI 0.18–0.82); in the ‘luminal A-like’ subgroup, the corresponding 5-year EFS were 92% versus 93.5% (HR = 1.30; 95% CI 0.5–3.56).

These associations persisted in multivariate analysis of EFS. Considering HR+ disease and entering age, tumor size, LN, luminal B-like, therapy, as well as all factor–times–therapy interactions resulted in a Cox model containing only luminal B-like (HR = 4.56, 95% CI 2.41–8.64, \( P < 0.001 \)) and its interaction with therapy (HR = 0.379, 95% CI 0.181–0.794, \( P = 0.01 \)). The

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**Figure 3.** Consort diagram: EC-Doc: epirubicin/cyclophosphamide 4× followed by docetaxal 4×; FEC: 5-fluorouracil/cyclophosphamide/epirubicin 6×; CMF: 5-fluorouracil/cyclophosphamide/methotrexat 6×.
interaction implies strong benefit for a luminal B-patient receiving EC-Doc instead of FEC. She would still have a higher risk than a luminal A-patient, but her HR compared with luminal A-like would decrease from 4.56 to 1.73.

**interpretation**

The WSG-AGO EC-Doc data have confirmed superiority of EC-Doc in terms of EFS and OS to FE100C/CMF in patients with 1–3 involved LNs. The effects were independent of age, hormone, and HER2 receptor status and grading. Due to the trial design there are several limitations, the data only refer to patients younger than 65 and testing is one-sided since inferiority of EC-Doc is not clinically relevant, due to its higher toxicity, longer duration and higher costs. Furthermore, CMF is considered as a weak comparator according to the EBCTG meta-analysis [7]. Therefore, two important issues raise: whether CMF/FE100C is an adequate control and how EC-Doc compares to other taxane-based standards. Only 9% of patients received CMF and since the evaluation of the FEC subset (91%) confirmed superiority of EC-Doc, the control arm discussion will focus on FE100C. FE100C was chosen because it is a widely used standard in Germany, shorter and less toxic than Canadian FE120C, but still allowing a reasonable dose–intensity for epirubicin.

Two other large randomized trials ADEBAR [8] (6 × FE120C versus 4 × EC–4 × Doc) and TACT [9] (8 × FE60C versus 4 × FE60C–4 × Doc) using FEC with higher/lower cumulative doses of anthracyclines neither detected significant survival benefit from addition of taxanes. Early results from MA-21 confirm equi-effectivity of Canadian FE120C with E120Cq2w → paclitaxel × 4 q3w [10]. French FE100C, used here, was compared, in PACS-001, with 3 × FE100C–3 × Doc in N+ BC. The results of the PACS-001 trial confirm the superior outcome of the EC-Doc trial in the taxane-containing arm [11]. In summary, therefore, FE100C seems to be a reliable comparator though potentially inferior to FE120C.

Another concern is the relative efficacy of our experimental arm, compared with current anthracyline/taxane standards. Sparano et al. [12] demonstrated superior disease-free survival in patients receiving AC-Doc q3w (HR 1.23) and those receiving AC → paclitaxel weekly (HR 1.27) compared with AC → paclitaxel 175 q3w. CALGB-9741 demonstrated superiority of q2w versus q3w scheduling of AC → paclitaxel in N+ BC [13]. This dose-dense regimen is equivalent to 6 × docetaxel (T), doxorubicine (A) and cyclophosphamide (C) (TAC) in another trial [14] and 6 × TAG is as good as EC-Doc in BCIRG 005. In summary, EC-Doc is therefore one of the adequate taxane-based standard.

Nevertheless, in our trial, absolute survival differences are small and toxicity profile is a reasonable second discriminator for choosing an adjuvant regimen. Our data demonstrate that even after 1 year, QoL parameters are negatively influenced by EC-Doc, and a higher rate of chemotherapy-induced amenorrhea—probably due to longer therapy duration—must be taken into account. In terms of long-term neurotoxicity, BCIRG-005 trial [15] (AC-Doc versus 6 × TAC) reports more grade 3–4 neurotoxicity (1.5% versus 0.3%) for AC-Doc. In our own trial, we observed grade 3–4 neurotoxicity in 3.8% of patients for EC-Doc, which is comparable to other studies. Weekly paclitaxel generates more grade 2–4 neuropathy (27% versus 20%) than 3-weekly paclitaxel [12]. Concerning cardiotoxicity, correlation of grade 3–4 toxicity with cumulative anthracycline doses is well documented. Ten-year data from BCIRG 001 [16] comparing TAC versus 5-fluorouracil (F), doxorubicine (A) and cyclophosphamide (C) (FAC) report grade 3–4 cardiotoxicity in 3% versus 2%, respectively. In the same trial, six and three cases of leukemia/myelodysplastic syndrome (MDS) were reported for TAC and FAC, respectively. Retrospective analysis of NCCN data does not document a relevant increase of leukemia/MDS rates by the addition of taxanes [17].

In summary, our 5-year OS of 94.5% (EC-Doc) and 92.8% (FEC) can be considered excellent and reported toxicity compared reasonably with other taxane-containing regimens. Nevertheless, our present biological understanding implies over-treatment with taxanes or chemotherapy in general, especially in HR+ disease, where genomic signatures identify low-risk subgroups in up to 62% of cases [18].

Since these genomic tests are not yet routinely available, the International St Gallen Consensus has suggested to use Ki-67 in HR+ tumors as an interim surrogate marker for distinguishing luminal A- versus B-like subtypes [3]. A recently published meta-analysis demonstrated, using multivariate analysis, that Ki-67 is an excellent prognosticator, but not a predictor of chemotherapy benefit [19]. Several retrospective analyses found luminal B-like subtype to be a significant predictor for docetaxel benefit [4, 5, 20]. In contrast, Martin et al. [21] did not find any difference for FEC → weekly paclitaxel over FEC alone in the high-Ki-67 group. In the present study, luminal B-like subtype defined by a 20% Ki-67 cutoff as in PACS-01 [5] was predictive for EC-Doc benefit; 61% of HR+ tumors were luminal A-like and had excellent 5-year EFS of 93.5%, irrespective of chemotherapy regimen. In contrast, patients with luminal B-like tumors derived substantial benefit from EC-Doc (61% risk reduction).

In conclusion, our retrospective analysis of a representative patient subset using central Ki-67 for luminal sub-typing suggests that taxanes may be omitted in a substantial number of patients with hormone-sensitive, luminal A-like disease with limited nodal involvement. Clinical utility of this statement will increase with further standardization of Ki-67 and should be re-evaluated when PAM 50 becomes routinely available.

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**references**