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Prospective Multicenter Randomized Phase III Study of Weekly versus Standard Docetaxel plus Doxorubicin (D4) for First-Line Treatment of Metastatic Breast Cancer

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Key Words
Docetaxel · Weekly application · Metastatic breast cancer · Combination chemotherapy

Abstract
Purpose: Previous phase II studies have indicated a greatly reduced hematotoxicity of docetaxel-based regimens administered on weekly schedules. The present trial was initiated to compare the toxicity and efficacy of weekly docetaxel versus its standard 3-weekly application in combination with doxorubicin. ***Methods:*** Patients previously untreated with chemotherapy for metastatic disease were recruited. Inclusion criteria were age <65 years or a Karnofsky Performance Status of 70–100%. All patients in the D4 study received doxorubicin (50 mg/m^2) on the first day of treatment in addition to docetaxel given either at a 3-weekly dose of 75 mg/m^2 every 3 weeks (q3w) or at a weekly dose of 35 mg/m^2 (days 1, 8, and 15; q4w). Treatment was continued until a maximum of 8 cycles, unacceptable toxicity, or disease progression. All patients received standard corticosteroid prophylaxis. ***Results:*** Since interim analysis showed failure to reach a significant difference for the primary endpoint (hematotoxicity, i.e. leukopenia), the study was closed according to the study protocol (85 of 242 patients). A lower-than-expected rate of leukopenia ≥grade 3 was observed in the standard arm of the D4 study compared to the weekly schedule (per-patient analysis: 61.9% q3w vs. 65.1% q1w; $p > 0.05$). Grade 3 and grade 4 fever, diarrhea, and infections occurred more frequently in the standard arm, whereas neurotoxicity and skin/nail disorders were observed more frequently in the weekly arm. Except for fever, none of these differences reached a level of significance. Dose delays, dose reductions, and the rate of omitted doses were increased in the weekly arm. The overall response rate was 44.2% in the weekly arm compared to 52.4% in the standard arm ($p = 0.52$). Time to progression was 6.2 (q1w) versus 10.3 (q3w) months ($p =$

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0.36), and overall survival was 20.5 (q1w) versus 28.7 (q3w) months (p = 0.98). ***Conclusion:*** The present data support the feasibility of both weekly and 3-weekly application of docetaxel in combination with doxorubicin. Nevertheless, given that leukopenia was similar in both arms and the efficacy parameters were at least numerically inferior with the weekly schedule, standard 3-weekly application seems to be preferable for patients requiring combination chemotherapy.

Introduction

Docetaxel (Taxotere®; Sanofi-Aventis, Frankfurt, Germany) is one of the most effective antitumor agents currently available for the treatment of early breast cancer as well as metastatic breast cancer (MBC). In MBC, when compared with the gold standard doxorubicin, docetaxel has shown a significantly superior response rate (RR; 47.8 vs. 33.3%; p = 0.008) and a trend towards a prolonged time to progression (TTP; 26 weeks vs. 21 weeks) [1]. After failure with anthracycline-containing chemotherapy, single-agent docetaxel has demonstrated superior results when compared with mitomycin/vinblastine [RR, TTP, and overall survival (OS)] or methotrexate/5-fluorouracil (RR and TTP), and it has shown equivalent efficacy when compared with vinorelbine/5-fluorouracil (RR, TTP, and OS) [2–4].

When docetaxel is administered at a standard dose of 100 mg/m^2 [every 3 weeks (q3w)], 70–90% of patients develop grade 3/4 neutropenia [1]. Instead of dose reductions, one strategy to reduce toxicity without growth factor support is to apply docetaxel on a weekly schedule. Several studies have indicated that severe hematotoxicity (grade 3/4) could largely be prevented at weekly doses of less than 40 mg/m^2 without impaired efficacy in the first- or second-line setting [5–9]. Moreover, the favorable toxicity profile of weekly scheduled docetaxel was confirmed in 2 randomized phase II/III trials without inferior results regarding TTP or OS [10, 11]. A further rationale for weekly docetaxel might be that standard-dose single-agent docetaxel (100 mg/m^2 q3w) frequently needs to be adjusted to 75 mg/m^2 in pretreated, unfit, or elderly patients [12].

The relatively low rate of severe leukopenia associated with weekly scheduled docetaxel may permit a combination with other cytotoxic agents. Taxanes and anthracyclines are considered among the most active single agents for the treatment of early breast cancer as well as MBC. Consequently, their combined use is a logical step in the search for highly effective chemotherapy combinations. Phase II trials which have investigated such an anthracycline/taxane combination given on a 3-week schedule have shown an improved RR of 46–88% without a higher rate of cardiotoxicity [13–16]. The high RR were attained in patients with unfavorable prognostic factors (multiple metastatic sites, visceral involvement, and prior exposure to adjuvant chemotherapy). However, the dose-limiting factor in these trials was leukopenia. Phase II trials investigating a weekly scheduled anthracycline/taxane combination proved efficient and had a manageable toxicity profile [17, 18]. Considering these prior experiences, the D4 study was designed to evaluate the toxicity and efficacy of a weekly docetaxel/doxorubicin regimen compared to a 3-weekly scheduled standard scheme in younger and medically fit patients with MBC.

Patients and Methods

Patient Selection

The treatment protocol was approved by the local ethics committee and all patients gave their written informed consent before treatment was started.

Patients with MBC, none of whom had received chemotherapy for metastatic disease, were recruited for the trial. Patients were required to have a Karnofsky Performance Status (KPS) ≥70% and an age between 18 and 65 years. Patients who had received prior adjuvant anthracyclines at a cumulative dose ≥200 mg/m^2 or who had a positive history of coronary heart disease with cardiac dysfunction or an impaired left ventricular ejection fraction (EF) were not eligible; cardiac EF had to be normal (≥50%).

Patients were required to have histologically proven MBC, bidimensionally measurable disease, and an anticipated survival of at least 12 weeks. Prior to study entry, hepatic, renal, and hematological functions had to be adequate [leukocyte count ≥3.0 × 10^9/l, platelets ≥100 × 10^9/l, hemoglobin ≥8 g/dl, bilirubin ≤1.25 times the normal range, alanine aminotransferase:aspartate aminotransferase (ALT:AST) ratio ≤3 times the normal range, and alkaline phosphatase ≤2.5 times the normal range].

Patients with bone metastases only and/or steroid (estrogen and/or progesterone) receptor expression without prior endocrine therapy were not eligible for the trial. Additional exclusion criteria were active infections, radiotherapy of more than 25% of marrow-containing bone, clinically overt brain metastases, previous neuropathy ≥grade II, or a history of a second malignancy other than resected basal cell and/or squamous cell carcinoma of the skin.

Patients were not eligible for study enrolment if they were pregnant or lactating, or if they refused effective contraception.

Treatment Regimen

Docetaxel was dissolved in 100 ml of 0.9% saline and given by intravenous (i.v.) infusion over 30 min (35 mg/m^2 weekly) or 60 min (75 mg/m^2 q3w), respectively. Doxorubicin (50 mg/m^2) was dissolved in 250 ml of 0.9% saline and infused for 60 min.

Patients in the D4 study received doxorubicin (50 mg/m^2) on the first day of treatment in addition to docetaxel given either at a 3-weekly dose of 75 mg/m^2 q3w or at a weekly dose of 35 mg/m^2 (days 1, 8, and 15; q4w). Treatment was continued until a maximum of 8 cycles, unacceptable toxicity, or disease progression.

All patients received standard corticosteroid prophylaxis, antiemetics (routinely 5HT3 antagonists), and growth factors (which were allowed at any point) according to the local standards.

Dose Adjustments

In case of myelosuppression on the day of the planned treatment (leukocytes ≤2,000/μl and platelets ≤50,000/μl), further drug administration was postponed for 1 week until bone marrow recovery occurred (leukocytes ≥2,000/μl and platelets ≥50,000/μl). If there was no recovery within the additional rest of 1 week, the patient was excluded from the study. A reduced dose of each drug (–25%) was applied in case of a leukocyte count between 2,000/μl and 3,000/μl and a platelet count between 50,000/μl and 100,000/μl. A full dose of docetaxel and doxorubicin was administered if the blood counts had risen to leukocytes ≥3,000/μl and platelets ≥100,000/μl.

Patients were excluded from the trial in case of nonhematological toxicity ≥grade 3 (excluding alopecia and nausea/vomiting). Dose reductions of 25% (for doxorubicin and docetaxel) were required in case of hematological toxicity grade 3 or 4 complicated by fever, infection, or both. Moreover, a reduced dose (–20%) was required in case of grade 3 diarrhea or mucositis.

Data Collection

Drug administration, KPS, and toxicity or adverse events were recorded after every cycle of treatment. Weekly blood counts were performed. Febrile neutropenia was defined as fever (≥38 °C) with grade 4 neutropenia requiring i.v. antibiotics and/or hospitalization without documented infection. Fluid retention included peripheral edema and/or pleural and pericardial effusions.

Toxicity was graded according to the National Cancer Institute's Common Toxicity Criteria (NCI CTC 2.0) [19]. Imaging studies using ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI) were performed after every 2 cycles of treatment.

Cardiac Surveillance

Patients in the D4 trial underwent echocardiography prior to study entry and then after every second cycle. An EF ≥50% was considered normal. Patients were excluded from the study if the EF decreased to ≤50% or decreased by ≥10% compared to the baseline value.

Response Evaluation

In all patients, tumors were measured by imaging procedures (ultrasound, CT, or MRI) within 14 days prior to study entry and subsequently after every 2 cycles of treatment. A standard evaluation comprised of history, a physical examination, and routine laboratory tests (including a complete blood cell count, chemistry profile, and electrolyte determination) was performed before each treatment.

Patient response was assessed according to standard WHO criteria as follows: Complete response (CR) was defined as the disappearance of all known disease as determined by 2 observations not less than 4 weeks apart, while partial response (PR) was defined as a decrease of at least 50% in the sum of the products of the largest perpendicular diameters of all measurable lesions as determined by 2 observations not less than 4 weeks apart. Stable disease (SD), lasting at least 6 weeks from the start of the study (i.e. the first drug administration), was defined as a <50% decrease and a <25% increase in the sum of the products of the largest perpendicular diameters of all measurable lesions. Progressive disease (PD) was a >25% increase in the size of at least 1 bidimensionally or unidimensionally measurable lesion or the appearance of a new lesion. The occurrence of pleural effusion was considered a sign of progression if verified by positive cytology.

Study Endpoints and Statistics

The primary study endpoint was hematotoxicity (leukopenia). Assuming grade 3 and grade 4 hematotoxicity rates of 70–95% for the standard regimen and 10–20% for the weekly regimen, the calculated sample size for the primary endpoint was 40 patients (20 for each treatment arm), with a statistical power of 80% using a 5% level of significance (Fishers's exact test).

An interim analysis was planned in 80 recruited patients (40 for each treatment arm) for the primary endpoint using α_1 = 0.0052 and α_2 = 0.048 as the levels of significance (O'Brien and Fleming sequential design).

For the secondary endpoint (TTP) the calculated sample size was 242 patients, with the assumption of the noninferiority of the weekly schedule (TTP q3w = 10.3 months and TTP q1w = 9.3 months) (O'Brien and Fleming sequential design). Sample sizes were calculated using NCSS/PASS 2000 software. Further secondary endpoints were OS and RR. TTP was determined by the interval between the initiation of therapy and the first date that disease progression was objectively documented. OS was measured from the date of the start of treatment to the date of death from any cause. All patients were included in the (intent-to-treat) analysis of TTP and survival.

The probabilities of survival and TTP were estimated by Kaplan-Meier analysis, and confidence intervals for the RR were calculated using methods for exact binominal confidence intervals [20, 21].

Results

Patient Characteristics

Patients were recruited between July 2001 and August 2008. Since the scheduled interim analysis showed failure to reach statistical significance for the primary endpoint in the final analysis, the D4 study was closed before achieving its target recruitment (85 of 242 patients). The median observation time was 18.7 months (range 0.3–52.3). The patients' characteristics are presented in table 1.

Toxicity

A summary of the hematological and nonhematological toxicities is given in table 2. A comparably low rate of leukopenia, i.e. ≥grade 3, which was rather similar to the one observed in the weekly arm, was observed in the

standard q3w arm of the D4 study (per-patient analysis: 61.9% q3w vs. 65.1% q1w; $p > 0.05$) even though the rate of grade 4 leukopenia was nearly twice the number in the standard arm (38.1% q3w vs. 20.9 q1w).

Fever was more frequently observed in the 3-week regimen (21.4% q3w vs. 4.7% q1w; $p = 0.03$). Moreover, grade 3 and grade 4 diarrhea and infections occurred more frequently in the standard arm, whereas neurotoxicity (7.0% q1w vs. 0% q3w; $p \geq 0.05$) and skin/nail disorders (11.6% q1w vs. 0% q3w; $p = 0.06$) were observed more frequently in the weekly arm. Except for fever, none of these differences reached the 0.05 level of significance. Other nonhematological toxicities (≥grade 3) were comparable between the 2 schedules.

The median number of applied cycles was 6 (range 1–8) for the standard arm and 5 (range 1–8) for the weekly arm. The median duration of treatment was 105.5 days (range 1–170) for the standard arm and 151 days (range 1–245) for the weekly schedule. Dose reductions and delayed and omitted doses within a cycle were required significantly more often in patients randomized to weekly docetaxel ($p < 0.001$, each). There was a significant difference regarding the percentage of the intended drug delivered within a cycle between the 2 regimens (99.2% standard dose vs. 78.3% weekly dose).

Efficacy

The overall RR was 48.2% (95% CI 37.3–59.3), with 3 CR, 38 PR, 22 SD, and 15 PD (intent-to-treat analysis) (table 3). Seven patients were not evaluable. The overall RR was comparable between the groups of standard or weekly scheduled docetaxel (44.2% q1w vs. 52.4% q3w; $p = 0.52$). Moreover, there was a numerical but not significant difference with regard to TTP (6.2 months q1w vs. 10.3 months q3w; $p = 0.36$) and OS (20.5 months q1w vs. 28.7 months q3w; $p = 0.98$) (table 4; fig. 1). A summary of the response and survival data is given in tables 3 and 4 and in figure 1.

Table 1. Patient characteristics

Characteristics	D4 (n = 85)	
	q1w	q3w
Patients	43	42
Age, years		
Median	54	56
Range	29–70	39–70
KPS, %		
Median	90	90
Range	70–100	70–100
Estrogen and progesterone receptor status		
Positive	32	31
Negative	10	8
Unknown	1	3
Menopausal status		
Premenopausal	11	7
Postmenopausal	32	35
HER-2 status		
Positive (IHC 3+ or 2+ and FISH+)	10	11
Negative (IHC 0 or 1+ or 2+ and FISH–)	22	26
Unknown	11	5
Measurable disease sites		
Lung	20	14
Liver	21	23
Lymph nodes	22	15
Skin	4	2
Skeleton	21	15
Disease sites per patient, n		
1	9	13
2	11	18
≥3	23	11
Prior treatment		
Adjuvant chemotherapy	20	20
(including anthracyclines)	11	7
Adjuvant hormonal therapy	23	22

Discussion

Numerous phase II studies have shown a considerably reduced hematotoxicity, but stable efficacy, of weekly scheduled docetaxel in the first- or second-line setting of MBC [5–9]. These data have been confirmed in 2 randomized phase II/III trials by Rivera et al. [10] and Tabernero et al. [11]. This rather low rate of severe leukopenia associated with weekly scheduled docetaxel may permit its combination with anthracyclines. Both agents are considered among the most active single agents for the treatment of MBC. Consequently, their combined use is a logical step in the search for highly effective chemotherapy combinations.

Previous phase II trials investigated a 3-week scheduled anthracycline/taxane regimen with impressive high RR of 46–88% [13–16]. However, the dose-limiting factor in these trials was leukopenia, leading to the initiation of phase II trials investigating a weekly anthracycline/taxane combination. Such studies have demonstrated efficacy with a manageable toxicity profile [17, 18]. Gamucci et al. [17] reported a considerably low rate of ≥grade 3 neutropenia of 16% of patients who received first-line weekly epirubicin (25 mg/m^2) and docetaxel (25 mg/m^2) for MBC. The regimen was quite effective, with an RR of

Table 2. Toxicity profile (per-patient analysis): hematological and nonhematological toxicity by NCI CTC grade

	A (q3w), %					B (q1w), %					p value (after dichotomization ≤2/≥3)
	0	1	2	3	4	0	1	2	3	4	
Hematological toxicity											
Anemia	14.3	57.1	28.6	0	0	11.6	44.2	34.9	9.3	0	>0.05
Leukopenia	11.9	4.8	21.4	23.8	38.1	11.6	9.3	13.9	44.2	20.9	>0.05
Thrombocytopenia	71.4	21.4	4.8	2.4	0	58.1	27.9	6.9	6.9	0	>0.05
Nonhematological toxicity											
Alopecia	14.3	7.1	78.6	0	0	18.6	9.3	72.1	0	0	>0.05
AP	61.9	35.7	2.4	0	0	62.8	32.6	4.7	0	0	>0.05
Arrhythmias	85.7	9.5	4.8	0	0	90.7	4.7	2.3	2.3	0	>0.05
Bilirubin	97.6	0	2.4	0	0	81.4	16.3	0	2.3	0	>0.05
Constipation	57.1	35.7	7.1	0	0	79.1	9.3	9.3	2.3	0	>0.05
Creatinine	95.2	2.4	0	2.4	0	88.4	11.6	0	0	0	>0.05
Diarrhea	50.0	30.9	14.3	2.4	2.4	65.1	23.3	11.6	0	0	>0.05
Fever	61.9	4.8	11.9	21.4	0	72.1	11.6	11.6	4.7	0	0.03
Fluid retention	76.2	16.7	4.8	2.4	0	69.8	18.6	11.6	0	0	>0.05
Gastrointestinal symptoms	90.5	4.8	2.4	2.4	0	95.4	2.3	2.3	0	0	>0.05
GGT	42.9	26.2	14.3	14.3	2.4	46.5	20.9	6.9	20.9	4.7	>0.05
Infections	50.0	14.3	19.1	11.9	4.8	69.8	6.9	18.6	4.7	0	>0.05
Mucositis	50.0	26.2	16.7	7.1	0	34.9	27.9	27.9	9.3	0	>0.05
Musculoskeletal disorders	97.6	0	2.4	0	0	95.4	4.7	0	0	0	>0.05
Nausea and vomiting	30.9	40.5	19.1	7.1	2.4	53.5	20.9	13.9	11.6	0	>0.05
Neurotoxicity	61.9	28.6	9.5	0	0	55.8	23.3	13.9	4.7	2.3	>0.05
Edema	100.0	0	0	0	0	93.0	0	6.9	0	0	>0.05
Pain	35.7	35.7	21.4	2.4	4.8	62.8	16.3	18.6	2.3	0	>0.05
Skin and nail disorders	85.7	9.5	4.8	0	0	60.5	18.6	9.3	9.3	2.3	>0.05

Table 3. Efficacy: RR (intent-to-treat analysis)

D4	CR	PR	SD	PD	Not evaluable	RR, %	95% CI, %	p
All patients (n = 85)	3	38	22	15	7	48.2	37.3–59.3	
q1w group (n = 43)	1	18	9	10	5	44.2	29.1–60.1	0.52[a]
q3w group (n = 42)	2	20	13	5	2	52.4	36.4–68.0	

[a] RR q1w versus q3w.

60% and a median OS of 25 months. Moreover, Perez-Manga et al. [18] reported on a phase II study which investigated a combination of doxorubicin (50 mg/m^2 q4w) and weekly scheduled docetaxel (36 mg/m^2 days 1, 8, and 15; q4w) for locally advanced or metastatic breast cancer (first line). A consistently low rate of severe neutropenia (≥grade 3) was reported (<10% febrile neutropenia) and RR were considerably high among locally advanced and metastasized patients, i.e. 93 and 64%, respectively.

Lacking randomized data, the D4 study was designed to evaluate the toxicity and efficacy of a weekly docetaxel/doxorubicin regimen compared to the 3-weekly standard scheme in younger and medically fit MBC patients.

In brief, in the primary safety endpoint of the D4 study a significant difference was not reached. The assumption of a markedly reduced hematotoxicity within the weekly schedule was not verified. Surprisingly, the rate of leukopenia (≥grade 3) was rather low in the standard arm, whereas it was not reduced at all in the weekly arm (61.9% q3w vs. 65.1% q1w; $p > 0.05$). Since the primary endpoint was not reached, the D4 study was closed after an interim analysis according to the study protocol (85 of 242

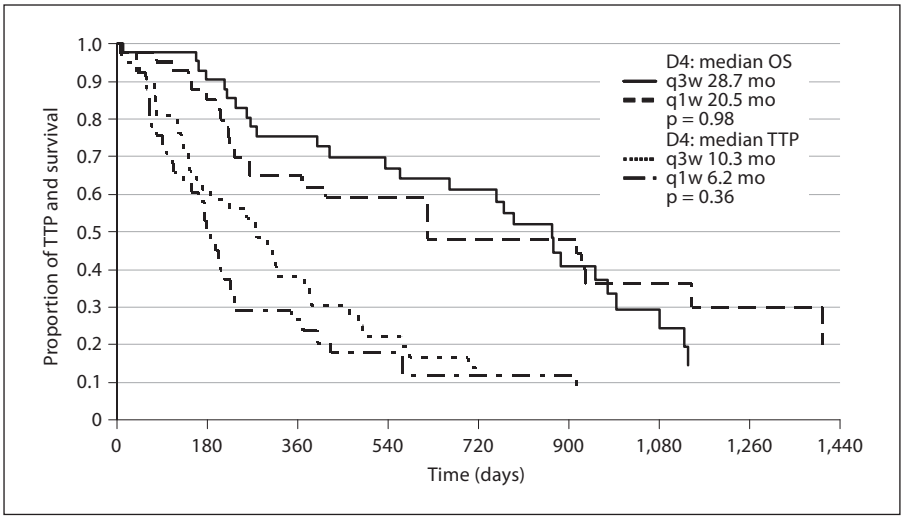

Fig. 1. TTP and OS in the D4 study. mo = Months.

patients). The presumption of a greatly reduced hematotoxicity in the weekly arm was based on the studies of Perez-Manga et al. [17] and Gamucci et al. [18]. Both investigated a weekly scheduled anthracycline/taxane combination which has shown a reduced rate of leukopenia. Thus, we cannot provide a valuable explanation for the relatively high numbers of grade 3 and 4 leukopenia in the weekly docetaxel arm observed in our study.

With regard to nonhematological toxicities, i.e. skin and nail disorders, the known sequelae of weekly administered docetaxel were increased in patients who were randomized to the weekly schedule (11.6% q1w vs. 0% q3w; p = 0.06). Moreover, even more surprisingly, the rate of reduced, delayed, or omitted doses within a cycle was significantly higher among patients receiving weekly docetaxel as follows: 38.3 versus 23.3%, 31.1 versus 10.6%, and 21.9 versus 0%, respectively (q1w vs. q3w; $p < 0.001$, each). Therefore, the percentage of the intended drug delivered within a cycle was greatly reduced in the weekly arm (77.3% q1w vs. 90.3% q3w) (table 5).

It is suspected that this lesser dose contributed to a measurable loss of efficacy even though none of the differences in RR, TTP, and OS reached the level of significance. The RR was 44.2% in the weekly arm compared to 52.4% under the standard regimen (p = 0.52). Moreover, the median TTP and OS were numerically inferior in patients who received the weekly schedule. TTP was 6.2 (q1w) versus 10.3 (q3w) months (p = 0.36), and OS was 20.5 (q1w) versus 28.7 (q3w) months (p = 0.98).

A final statement regarding efficacy is restricted by the limitation that the calculated sample size for the secondary endpoints (TTP and OS) was not reached in the D4 study. Moreover, imbalances regarding the cumulative anthracycline dose between both study arms may contribute to a bias regarding the efficacy parameters (50 mg/m^2 doxorubicin applied q3w in the 'standard arm' vs. q4w in the 'weekly arm'). Nevertheless, the study was ter-

Table 4. Efficacy: TTP and OS

D4	q3w		q1w		p value (log-rank test)
	median	range	median	range	
TTP, months	10.3	1.3–23.8	6.2	0.2–30.5	0.36
OS, months	28.7	0.4–37.9	20.5	0.3–46.8	0.98

Table 5. Toxicity profile: dose modifications

	All (n = 432)	q3w (n = 236)	q1w (n = 196)	p value
Cycles				
Dose reductions[a]	130 (30.09)	55 (23.31)	75 (38.27)	<0.001
Delayed doses[a]	86 (19.91)	25 (10.59)	61 (31.12)	<0.001
Omitted doses[a]	43 (9.95)	0	43 (21.94)	<0.001
Percentage of intended drug delivery	84.29	90.25	77.30	<0.001

[a] Reductions within a cycle; data given as n (%).

minated after the interim analysis due to failure to reach statistical significance in the primary endpoint (leukopenia). The striking trend towards an improved TTP and OS within the standard arm of the D4 study (q3w vs. q1w: TTP 10.3 vs. 6.2 months and OS 28.7 vs. 20.5 months) may be – at least partially – explained by the above mentioned limitations.

In conclusion, the data of the D4 study have surprisingly but unmistakably shown that leukopenia could not be prevented by a weekly schedule of a docetaxel/anthracycline combination despite phase II data indicating a greatly reduced hematotoxicity in favor of the weekly administration of docetaxel. In view of the at least numerically reduced efficacy in the weekly arm as well as the substantially increased nonhematological side effects, this approach seems not to merit further investigation.

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