Bendamustine prolongs progression-free survival in metastatic breast cancer (MBC): a phase III prospective, randomized, multicenter trial of bendamustine hydrochloride, methotrexate and 5-fluorouracil (BMF) versus cyclophosphamide, methotrexate and 5-fluorouracil (CMF) as first-line treatment of MBC

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Two i.v. regimens, bendamustine, methotrexate and 5-fluorouracil (BMF) and cyclophosphamide, methotrexate and 5-fluorouracil (CMF) were compared as first-line therapy in a randomized, open, multicenter phase III trial including 364 patients with metastatic breast cancer (MBC). Bendamustine is an anti-neoplastic agent with alkylating, but also additional, so far unclear, mechanisms of action. We wanted to show the superiority of BMF over CMF in terms of time to progression (TTP) (primary endpoint), overall response, response duration, toxicity and quality of life (QoL). TTP was significantly longer in the BMF group (8.2 versus 6.7 months for CMF) ($p=0.0071$). The effect of BMF on TTP was more pronounced in the stratum 'prior adjuvant therapy, no visceral metastases' ($p=0.034$). Overall response rates and QoL did not significantly differ between the regimens. BMF caused more mucositis and leukopenias. Thus, bendamustine, when replacing cyclophosphamide in the CMF combination, can be expected to produce longer progression-free survival in first-line treatment of MBC. *Anti-Cancer Drugs* **16:871–877**

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Introduction

Benefit from treatment of metastatic breast cancer (MBC) patients has remained modest so far. Although chemotherapy is frequently chosen as the first option, no optimal first-line therapy for MBC has been recommended [1,2].

The combination regimen of cyclophosphamide, methotrexate and 5-fluorouracil (CMF), both in the classical and i.v. variants, causes initial responses in breast cancer. This resulted in its wide use as a regimen for adjuvant and MBC [3,4]. In comparison to other single-agent and polychemotherapies, with and without anthracyclines, CMF yielded at least similar treatment success with moderate toxicity [5].

Bendamustine is an anti-neoplastic drug with a distinct mechanism of action. Its fundamental alkylating effect (due to the 2-chloroethylamine group) is modified by further functional groups, i.e. a benzimidazole ring and a butyric acid side-chain. The patterns of activity of bendamustine compared with other alkylating agents such as chlorambucil and phosphoramide mustard, as well as topoisomerase I inhibitors and anti-metabolites, differ substantially, as identified by the COMPARE algorithm with 60 human tumor cell lines and by microarray characterization of 'signature genes' [6]. The activity profile may explain the minimal cross-resistance between bendamustine and other DNA-damaging anti-neoplastic drugs *in vitro*.

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Bendamustine came to attention in previous pilot and phase II trials in MBC because of a favorable toxicity profile (i.e. no or minor alopecia, low cardiac toxicity) and a low propensity for induction of anti-alkylator cross-resistance, while retaining good anti-cancer effects both in second-line and salvage therapy of patients pre-treated with alkylating regimens and/or anthracyclines. When administered as a single drug (i.v. infusion over 30–60 min at a dosage of 150 mg/m^2 on days 1 and 2 of a 4-week treatment cycle), bendamustine caused objective remissions in up to 27% of heavily pre-treated patients with MBC [7,8]. In second-line therapy of CMF-pre-treated patients, bendamustine combined with doxorubicin and vincristine (BAV regimen) produced remission rates of 48–52%, which compare well with CMF-induced responses [9].

The direct comparison between standard CMF and BMF as experimental regimen was then a logical consequence to ascertain the potential of bendamustine in first-line treatment of MBC, as the need to test new drugs in women with MBC who have not received prior chemotherapy is well understood [10]. Pilot studies of CMF versus BMF in MBC brought about comparable response rates, but the authors were encouraged by the longer duration of remissions on BMF [11,12].

The present study is a prospective, multicenter, randomized, phase III trial in MBC with a sample size calculated to prove longer time to progression (TTP) in the BMF arm as compared to the CMF arm. Although the classical (oral) CMF regimen may be associated with higher efficacy because of higher dose intensity, the i.v. regimen (which is commonly used in Germany) has been chosen to allow for better comparability with the BMF regimen.

Patients and methods

Patients

Patients had to be diagnosed with histologically confirmed breast cancer with primary and/or secondary distant metastases, measurable disease in two dimensions (≥ 1 cm) and no prior chemotherapy for metastatic disease. Age (18–75 years), WHO performance status < 2, absence of severe organ and hematological dysfunction [serum creatinine $\leq 1.5 \times$ upper limit of normal (ULN), GPT, bilirubin $\leq 1.5 \times$ ULN, in the presence of liver metastases $\leq 5 \times$ ULN, white blood cells $\geq 4000/mm^3$, platelets $\geq 100\,000/mm^3$], and life expectancy of at least 3 months were further inclusion criteria (Table 1).

In the study period, November 1996 to September 2001, 364 patients were enrolled and randomized (BMF = 175 and CMF = 189). Fifty-five study centers were included [Germany ($n = 42$), Bulgaria ($n = 7$), UK ($n = 4$) and Belgium ($n = 2$)].

All patients provided written informed consent that was approved by the local ethical authorities. The study was conducted according to the Helsinki Declaration.

Treatment cycle

One treatment cycle normally consisted of 28 days, with drugs being given on days 1 and 8 (Table 2). Treatment was repeated on day 29, provided WBC had reached values of $\geq 3000/mm^3$ and platelets $\geq 100\,000/mm^3$. The non-hematologic toxicities (other than alopecia) had to be National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade 1 or returned to baseline. A maximum of 8 cycles was planned per treatment arm (Table 2).

Efficacy evaluation

Efficacy evaluation employed TTP as the primary efficacy parameter, defined as time between day of randomization and date of progression. If progression had not occurred at individual completion of the study (maximum 8 cycles of treatment), the data were censored at the date of last follow up. Secondary efficacy parameters were response rate, response duration, toxicity and quality of life (QoL).

Table 1 Distribution of demographic data by treatment (ITT population)

Characteristic	BMF (n=162)	CMF (n=162)	Total (n=345)
Median age (years)	61.0	57.0	60.0
Weight (kg)	70.0	70.0	70.0
Height (cm)	162.0	163.0	163.0
Karnofsky performance scale (0–100)	90.0	90.0	90.0
WHO status (0–4) [n (%)]			
0	93 (57.4)	124 (67.8)	217 (62.9)
1	58 (35.8)	50 (27.3)	108 (31.3)
2	8 (4.9)	6 (3.3)	14 (4.1)
not done	3 (1.9)	3 (1.6)	6 (1.7)
Adjuvant treatment [n (%)]	86 (24.9)	102 (29.6)	188 (54.4)
Visceral metastases [n (%)]	105 (30.4)	115 (33.3)	220 (63.8)
Distribution to pre-specified strata [n (%)]			
AT–VM	59 (36.4)	71 (38.8)	130 (37.7)
NAT–VM	46 (28.4)	44 (24.0)	90 (26.1)
AT–NVM	27 (16.7)	31 (16.9)	58 (16.8)
NAT–NVM	30 (18.5)	30 (18.5)	67 (19.4)

AT = adjuvant therapy, NAT = no adjuvant therapy, VM = visceral metastases, NVM = no visceral metastases.

Table 2 Schedule of the BMF and CMF regimens

Group	Drug	Dose	Day	Application
BMF	Bendamustine	120 mg/m^2	1 + 8	i.v. within 30–60 min
	Methotrexate	40 mg/m^2	1 + 8	i.v. within 10 min
	5-Fluorouracil	600 mg/m^2	1 + 8	i.v. over 2 h
	Supportive therapy			
	Dexamethasone	8 mg	1 + 8	i.v. before start of therapy
		2 × 4 mg	2 + 3 and 9 + 10	orally
CMF	Cyclophosphamide	500 mg/m^2	1 + 8	i.v. within 30–60 min
	Methotrexate	40 mg/m^2	1 + 8	i.v. within 10 min
	5-Fluorouracil	600 mg/m^2	1 + 8	i.v. over 2 h
	Supportive therapy			
	Dexamethasone	8 mg	1 + 8	i.v. before start of therapy
		2 × 4 mg	2 + 3 and 9 + 10	orally

For the evaluation of response rates, the best response during therapy, confirmed at least 4 weeks after occurrence, was used. If no data on response had been obtained, the outcome was defined as progressive disease (PD).

Safety evaluation

Safety evaluation was based on the comparison of the toxicities in both therapy groups. Hematological and non-hematological toxicities were evaluated using the NCI-CTC.

Efficacy and safety measurements

Efficacy and safety measurements included physical examination (documentation on body weight, height, body surface area and WHO performance status), ECG, hematology (hemoglobin, leukocytes, including differential count and platelets), serum parameters (aspartate aminotransferase, alanine aminotransferase, partial thromboplastin time, total bilirubin, alkaline phosphatase, total protein, urea, serum creatinine and lactate dehydrogenase), electrolytes (Na^+, K^+ and Ca^{2+}), urine analysis, tumor assessment [evaluation of indicator lesions by X-ray, ultrasound, bone scan, computed tomography (CT) scan and magnetic resonance imaging). Visceral metastases had to be documented by CT scan. Post-study follow-up for patients with complete remission (CR), partial remission (PR) or no change (NC) at study end included tumor assessment (WHO criteria for solid tumors) and physical examination (body weight and performance status) every 3 months.

Statistical methods

To ascertain comparability, a one-sided log-rank test for equality of the intent-to-treat (ITT) and per-protocol (PP) population was used. Randomization was conducted according to centers, considering stratification criteria: prior adjuvant chemotherapy and/or endocrine treatment versus no prior adjuvant therapy, prior anthracyclines versus no prior anthracycline and visceral versus non-visceral metastases.

TTP distribution in the two groups was estimated by the Kaplan–Meier product-limit procedure. The null hypothesis ('TTP is identical in both groups') was tested including the influencing factors 'adjuvant pre-treatment' and 'metastasis' using the Cox regression model [13].

Initially 296 patients had been planned (148 patients per arm). Nineteen patients who had neither received any study medication nor a complete cycle were excluded from ITT efficacy analyses as required by protocol. As the PP analysis including all patients ($n = 259$) who completed at least one treatment cycle, having measurable disease and showing no major protocol violations, showed comparable results, only results obtained in the ITT are reported here. All patients who received at least one application of the study drug were evaluable for safety analysis (safety population: BMF = 169 and CMF = 185).

A planned interim analysis was conducted in February 2000 after 167 patients had been included. An adaptive design was used to allow premature termination of the study after the interim analysis if the p value of the difference in TTP was lower than 0.0207 (premature success) or greater than 0.6 (stopping for futility) and to enable re-calculation of the sample size needed for the second part of the study in case of continuing [14]. As the one-sided p value of the interim analysis was 0.084 the study was continued, recruiting an additional 180 patients.

Results

At baseline, the two groups were well balanced with regard to weight, height, prospectively defined strata and tumor-specific medical history at baseline. Small imbalances concerning age (median age was 61 years in the BMF group and 57 years in the CMF group) and WHO performance status (grade 0: CMF 67.8% versus BMF 57.4%; grade 1: CMF 27.3% versus BMF 35.8%, NS) showed a slightly poorer condition of the BMF patients (Table 1). The maximum observation period was 39 months in the BMF group and 41 months in the CMF group.

Analysis of efficacy according to the primary endpoint (between-group comparison of TTP) revealed a median

TTP for the bendamustine group of 8.2 months [95% confidence interval (CI) 5.6–10.6] compared with 6.7 months (95% CI 5.5–8.0) for patients treated with cyclophosphamide. As the product probability of interim and final analysis ($p = 0.0071$) was lower than the pre-planned margin of significance $c_\alpha = 0.0087$, the difference was significant at an overall level of $\alpha = 0.05$ (one-sided) adjusting for the multiple test situation.

Kaplan–Meier estimates of TTP are depicted in Figure 1. There was no country or center effect on TTP (log-rank test: $p = 0.52$) or effect of center size on TTP (log-rank test: $p = 0.92$) (data not shown).

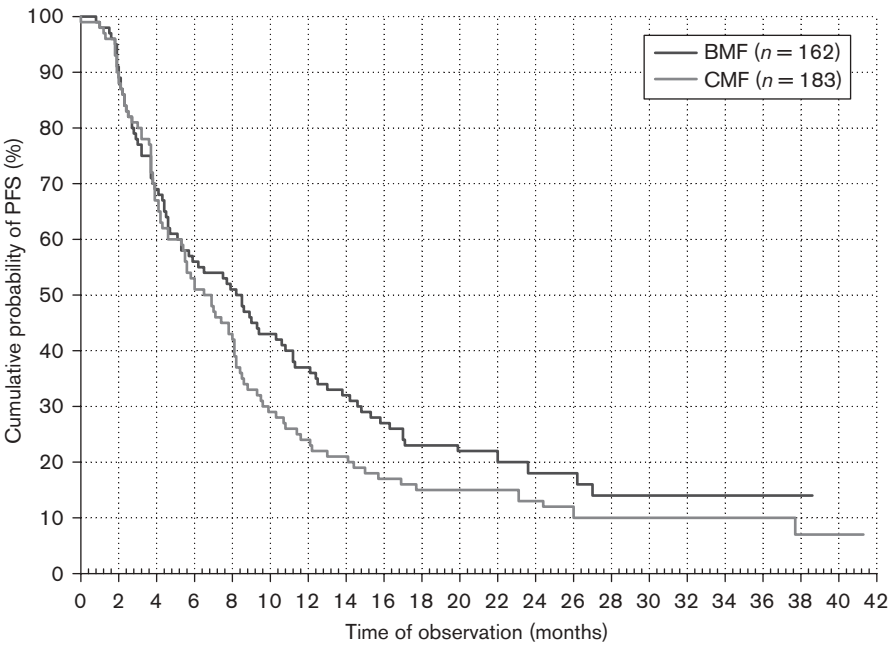
TTP differed significantly between the prospective strata (influencing factors 'adjuvant pre-treatment' and 'site of metastasis', log-rank test: $p = 0.0036$). According to this analysis, patients in both treatment arms belonging to the stratum 'no adjuvant therapy and non visceral metastases' had a significantly longer TTP.

A comparison of treatment effects of BMF versus CMF within the strata brought about a significant TTP difference in favor of BMF for the stratum 'prior adjuvant therapy in patients with non visceral metastases' (log-rank test: $p = 0.034$). Thus, in particular those patients who had received prior adjuvant therapy and who were free from visceral metastases drew more benefit from BMF treatment than from CMF treatment. In this stratum, 15 of 27 patients (55.6%) on BMF, as compared with 27 of 31 (87.1%) on CMF, relapsed during observation (31 months on BMF and 41 months on CMF). This also meant that patients under BMF had a significantly better 2-year rate of progression-free survival (PFS; BMF 25% versus CMF 7.5%) corresponding to a median TTP of 14.6 months for patients on BMF and 4.9 months for patients on CMF.

Analyses of secondary efficacy endpoints did not show any differences. The response rates at the individual end of study were almost the same in both treatment arms (BMF: CR 9.3%, PR 35.2% and NC 48.1%; CMF: CR 7.1%, PR 32.8% and NC 55.7%). Considering only patients with confirmed response, the response rates for both treatment arms were again very similar, but lower than expected (BMF: CR 2.5%, PR 19.8%; CMF: CR 4.4%, PR 18%). Median duration of response was not reached in the four BMF patients with confirmed CR and was 6.8 months for the eight CMF patients. The TTP of those patients who achieved a PR (BMF 19.8% versus CMF 18%) tended to be longer in the BMF arm (14.8 versus 10.3 months) (log-rank test: $p = 0.0764$) (Fig. 2).

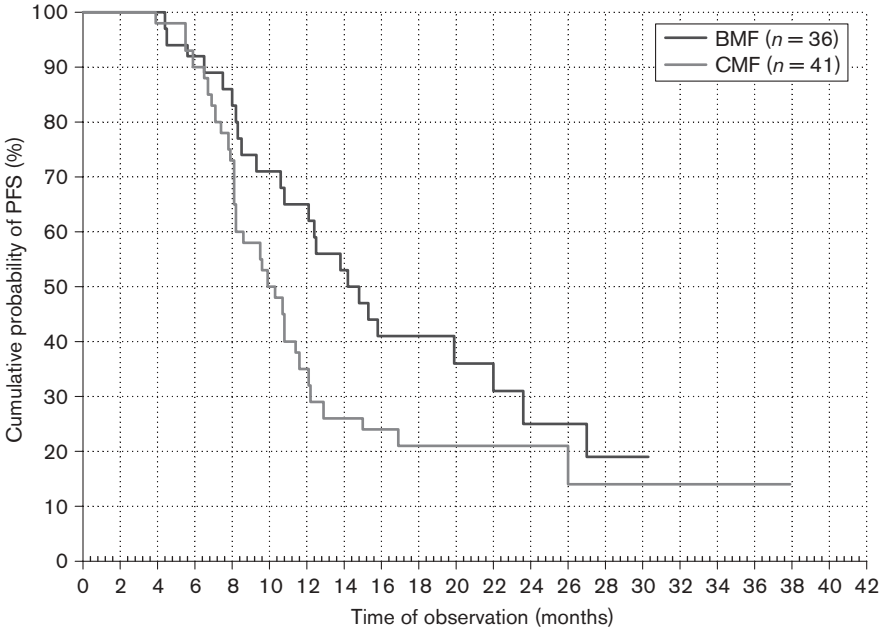
At baseline, QoL scoring (EORTC QLQ-C30) had shown a trend in favor of the CMF group. QoL improvements during and after therapy were in most domains similar in both groups.

Fig. 1



TTP of all patients at the final analysis in months from day of randomization to date of progression (ITT population $n = 345$). The median TTP was 8.2 months for BMF and 6.7 months for CMF (log-rank: $p = 0.0071$).

Fig. 2



TTF of patients with at least partial remission during therapy (ITT population $n=77$). The median TTF was 14.8 months for BMF and 10.3 months for CMF (log-rank: $p=0.0764$).

Safety

All patients who received at least one dose of study chemotherapy were assessed for safety ($n=354$). Patients in the BMF arm received on average 1 cycle of study treatment less than in the CMF arm (4.1 ± 2.3 versus 5.1 ± 2.4 cycles). The vast majority of patients in both treatment groups experienced at least one adverse event and these were usually well-known toxicities of alkylating agents, specifically alopecia, gastrointestinal (diarrhea and nausea/vomiting), hematological toxicity and stomatitis. Leukopenia, stomatitis, thrombocytopenia, hemoglobin reduction and fever occurred significantly more often in the BMF, whereas alopecia, amenorrhea, constipation and increase of transaminases were more frequent in the CMF group. Diarrhea incidence did not differ between the groups (Table 3). CTC grades 3 and 4 toxicities were more common in BMF patients (74.1%) as compared to CMF patients (49.7%) (see Table 3). The BMF-related toxicities, i.e. leukopenia and stomatitis, were usually well controlled and reversible in spite of their severity. Cardiac toxicity, assessed as arrhythmia, cardiac function or ischemia, was observed in a total of 37 patients and was equally distributed in both treatment arms.

However, the duration of the nadir is also of importance. A clinically relevant nadir of 5 days or more in the group with grade 4 leukopenia was observed in only one out of 43 BMF patients, but in five out of 17 patients in the CMF arm.

Discussion

This randomized phase III multicenter trial of BMF versus CMF for first-line treatment of MBC has demonstrated an advantage for patients in the BMF arm with respect to significantly improved TTP. Benefit of the bendamustine-based regimen was also apparent in the response duration, although overall response rates did not significantly differ between the treatment groups. These figures are in concordance with literature data [5,12].

TTP has been defined as a valid surrogate endpoint for clinical studies in MBC and a significant difference in TTP between two treatment groups may imply a survival advantage for single patients. Notwithstanding, chemotherapy of MBC is considered a palliative intervention at this stage, and survival improvement for single patients should not be bought at the cost of higher toxicity and overall QoL impairment for the majority of patients. Although toxicity associated with BMF was relatively more pronounced (particularly leukopenias and stomatitis), it was manageable and reversible. Even though drug-related toxicities of CTC grades 3 and 4 are most relevant in oncology, the significantly higher rate of grade 4 toxicities under BMF must be noted. However, leukopenia with a clinically relevant nadir of 5 days or more in the group with grade 4 leukopenia was observed more often in the CMF group. It is important to notice that cardiac toxicity was low and equally distributed in both treatment arms.

Table 3 Non-hematologic adverse events [*n* (%)] CTC grades 3 and 4

Symptom	BMF (*n*=169)	CMF (*n*=185)	Total (*n*=354)
Alopecia	0 (0.0)	2 (1.1)	2 (0.6)
Appetite	12 (7.1)	15 (8.1)	27 (7.6)
Arrhythmia	2 (1.2)	3 (1.6)	5 (1.4)
Asthenia	9 (5.3)	0 (0.0)	9 (2.5)
Body temperature	7 (4.1)	1 (0.5)	8 (2.3)
Cardiac function	2 (1.2)	2 (1.1)	4 (1.1)
Cardiovascular—other	0 (0.0)	1 (0.5)	1 (0.3)
Consciousness	0 (0.0)	3 (1.6)	3 (0.8)
Constipation	2 (1.2)	3 (1.6)	5 (1.4)
Constitutional symptoms—other	5 (3.0)	2 (1.1)	7 (2.0)
Dermatology—other	1 (0.6)	4 (2.2)	5 (1.4)
Diarrhea	3 (1.8)	3 (1.6)	6 (1.7)
Dyspnea	13 (7.7)	18 (9.7)	31 (8.8)
Edema	3 (1.8)	1 (0.5)	4 (1.1)
Emotionality	0 (0.0)	3 (1.6)	3 (0.8)
Gastrointestinal—other	1 (0.6)	1 (0.5)	2 (0.6)
Hemorrhage (clinical)	4 (2.4)	0 (0.0)	4 (1.1)
Hypertension	6 (3.6)	3 (1.6)	9 (2.5)
Hypotension	0 (0.0)	1 (0.5)	1 (0.3)
Immunology/lymphatics	0 (0.0)	2 (1.1)	2 (0.6)
Infection	15 (8.9)	6 (3.2)	21 (5.9)
Ischemia	3 (1.8)	2 (1.1)	5 (1.4)
Musculoskeletal	2 (1.2)	1 (0.5)	3 (0.8)
Myalgia/arthralgia	6 (3.6)	3 (1.6)	9 (2.5)
Nausea	8 (4.7)	6 (3.2)	14 (4.0)
Neurology—other	0 (0.0)	2 (1.1)	2 (0.6)
Perspiration	1 (0.6)	0 (0.0)	1 (0.3)
Phlebitis/thrombosis/embolism	3 (1.8)	4 (2.2)	7 (2.0)
Pneumonia (not infectious)	8 (4.7)	3 (1.6)	11 (3.1)
Pulmonary—other	1 (0.6)	1 (0.3)	2 (0.6)
Stomatitis	32 (18.9)	7 (3.8)	39 (11.0)
Vomiting	11 (6.5)	5 (2.7)	16 (4.5)
Weight loss	0 (0.0)	1 (0.5)	1 (0.3)

The individualization of treatment strategies has become a scientific focus in breast cancer research. In this context, the most interesting result reported here is the TTP difference in favor of BMF for the prospective stratum 'prior adjuvant therapy in patients with non visceral metastases'. One conclusion from this result is the confirmation of bendamustine's unique mechanism of action and, consequently, the lack of cross-resistance between bendamustine and other alkylators: as most of the adjuvant chemotherapies contain cyclophosphamide or another alkylating drug, a longer treatment response to BMF among patients who relapsed after adjuvant CMF could be expected.

Effects of BMF and CMF on TTP were not distinguishable, however, for patients with 'no prior adjuvant therapy and no visceral metastases', which had the best clinical outcome and a TTP significantly better than the other patients, regardless of the treatment arm (log-rank test: $p = 0.0036$). Here, the hypothesis of Demicheli *et al.* can be taken into account that the recurrence risk for primary breast cancer has a multi-peak pattern and that early recurrences may draw most benefit from CMF adjuvant therapy, while late relapsing patients (corresponding to the stratum 'no prior adjuvant therapy and no visceral metastases') would, when given adjuvant chemotherapy, already have 'gambled away' their chance of high responsiveness to primary CMF, when urgently needed at the time of relapse [15]. It seems likely that in this trial the better clinical outcome of chemonaive patients (and free from visceral metastases) is the hint about a realistic subgroup among MBC patients which still awaits more precise characterization by prognostic biomarkers.

As a conclusion, BMF can be considered as an alternative to CMF for the treatment of (HER2-negative) MBC in general, in view of longer periods of PFS. This is achieved by a moderate, but acceptable, increase in toxicity as compared with CMF. With due caution, because evaluated strata are small, we speculate that due to its unique anti-cancer effect bendamustine presents an option in late-recurrence, non-pre-treated MBC patients and can add to the armamentarium of active drugs.

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Appendix: participating investigators

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