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ORIGINAL ARTICLE

Metronomic treatment of vinorelbine with oral capecitabine is tolerable in the randomized Phase 2 study XeNa including patients with HER2 non-amplified metastatic breast cancer

Anne Sofie Brems-Eskildsen[a], Søren Linnet[b], Hella Danø[c], Adam Luczak[d], Peter Michael Vestlev[e], Erik Hugger Jakobsen[f], Jeppe Neimann[a], Charlotte Buch Jensen[a], Trine Dongsgaard[b] and Sven Tyge Langkjer[a]

[a]Department of Oncology, University Hospital of Aarhus, Aarhus, Denmark; [b]Department of Oncology, Region Hospital of West Jutland, Herning, Denmark; [c]Department of Oncology, Region Hospital in Hilleroed, Hillerod, Denmark; [d]Department of Oncology, University Hospital of Aalborg, Aalborg, Denmark; [e]Department of Oncology, Roskilde Hospital, Roskilde, Denmark; [f]Department of Oncology, Region Hospital in Esbjerg, Esbjerg, Denmark

ABSTRACT

Background: Metronomic treatment is hypothesized to be less toxic and more effective as compared to standard maximal tolerable dosing treatment in metastatic cancer disease.

Material and methods: We tested the metronomic treatment principle with vinorelbine in a randomized phase 2 setting combined with standard capecitabine treatment in the XeNa trial with Clinical Trials.gov identifier number: NCT0141771. 120 patients with disseminated HER2 non-amplified breast cancer were included. Randomization was between Arm A: vinorelbine 60 mg/m^2 day 1 + day 8 in the first cycle followed by 80 mg/m^2 day 1 + day 8 in the following cycles or Arm B: vinorelbine 50 mg three times a week. Capecitabine 1000 mg/m^2 twice a day for days 1–14 was administered in both arms.

Results: The treatment was generally well-tolerated. The response rate (RR) was 24% (arm A) *versus* 29% (arm B) ($p = .67$). The clinical benefit rate (CBR) 46.8% (arm A) *versus* 51.7% (arm B) ($p = .72$). We found a median progression-free survival (PFS) of 7.1 months (95% confidence interval [CI] 3.9–10.3) in arm A and 6.3 months (95% CI 4.1–8.5) in arm B ($p = .25$) whereas median overall survival (OS) was 23.3 months (95% CI 20.2–26.4) in arm A and 22.3 months (95% CI 14.3–30.3) in arm B ($p = .76$).

Conclusions: We confirmed that the combination of vinorelbine and capecitabine was well tolerated. Metronomic treatment can be used with acceptable adverse events (AEs), but we did not find significant difference in the effect compared to the standard treatment.

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KEYWORDS
Breast cancer; metronomic treatment; randomized trial

Introduction

Breast cancer is a chemosensitive disease and a combined strategy of surgery, chemotherapy, radiotherapy, antioestrogen, and antibody treatment is now used rather successfully both in early and advanced disease. Improvements in adjuvant treatment of breast cancer have changed the recurrence rate of the disease but patients still develop life-threatening distant metastases and recurrent disease, and a number of patients are diagnosed with a primary disseminated disease [1,2].

Once the disease becomes disseminated, the purpose of the treatment is to stabilize the disease, minimize the symptoms, and increase survival time [3,4]. Taxanes and anthracyclines are, when looking at the response rates (RRs), the most effective drugs but are also rather toxic, with a high rate of adverse events (AEs) including cardiac morbidity and febrile neutropenia. New ways to use the well-known drugs are needed as a more chronic and stable phase of the disease can sometimes be achieved.

Metronomic treatment could be one of these new ways. The treatment is defined as frequent administration of minimal effective dose (e.g. one third of maximum tolerable dose) without prolonged breaks [5]. Metronomic treatment can in theory reduce the risk of development of resistant clones and influence angiogenesis in the tumor due to the continuously lower chemotherapeutic pressure. Preclinical data also suggest that the immune cells are affected, leading to a higher cytotoxic immune effect and better antigen presentation [5–12].

Capecitabine [13–15] and vinorelbine [16–21] have been chosen for this study as both drugs are well known in the treatment of breast cancer, both drugs have an oral formulation; both drugs have an acceptable and not overlapping toxicity profile. The combination is considered 'an ideal combination' [22,23]. Administrating these drugs orally makes absorption, first-pass metabolism and distribution of the chemotherapy important to consider in order to determine the effective doses in the patient. The difference between intravenous and oral doses is well studied [17,24,25] as well as the optimal maximal tolerable dose for the combined

CONTACT Anne Sofie Brems-Eskildsen sofie@brems-eskildsen.dk Department of Oncology, University Hospital of Aarhus, Aarhus, Denmark

treatment [26–28]. Vinorelbine belongs to the group of vinca alkaloids, which block cell division in G2/M phase of the cell cycle by inhibiting the assembly of microtubule in the cell division [21]. Capecitabine is a Fluorouracil prodrug that needs to be activated in the body by the enzyme thymidine phosphorylase and thereafter act as an antimetabolite in the DNA synthesis [14].

Metronomic treatment has been studied in metastatic breast cancer patients in the VICTOR-2 study with capecitabine and vinorelbine. The optimal schedule is recommended to be vinorelbine 40 mg thrice a week in combination with a fixed dose of capecitabine of 500 mg twice daily. Navalbine Oral® has a half-life of 40 h and administration three times a week is suggested as an optimal schedule. The study was carried out with limited toxicity [29–31]. Several other studies have been carried out with different drugs, in combination or as single agents, primarily in Phase 1 and 2 trials [12,32].

To our knowledge this is the first randomized Phase 2 study with the combination of vinorelbine and capecitabine, comparing metronomic *versus* conventional maximal tolerable dosing. The primary endpoint was to decide the objective response rate (ORR) in both treatment arms. Secondary endpoints were to define the toxicity and safety profile of the combined treatment, define time to response, time to progression, and overall survival (OS).

Patients and methods

We have included 120 women, from 2012 to 2015, treated at six Oncology Outpatient Clinics in Denmark. All women had HER2 non-amplified metastatic breast cancer. The treatment was given as first or second-line chemotherapy treatment for metastatic disease. The patients had previously received adjuvant treatment with anthracyclines, and they must have progressed on or been considered unfit for taxanes.

The included patients had measurable disease according to RESIST, a performance status of at least 2, expected lifetime of at least 16 weeks and an age over 18 years. There had to be a signed informed consent, and the patients needed to be able to swallow the capsule. The exclusion criteria were prior treatment with capecitabine or vinorelbine, pregnancy, other current or prior malignant disease, inadequate liver, renal, or bone marrow function.

The study was designed as an open-labeled randomized Phase 2 study. The patients were randomized (1:1) between arm A and arm B. All patients in both arms were treated with oral capecitabine 1000 mg/m^2 twice daily for day 1–14, and the randomization was between oral vinorelbine 60 mg/m^2 given day 1 and day 8 increased to 80 mg/m^2 in the second cycle if well tolerated or oral vinorelbine three times a week without treatment breaks. Patients aged 65 and older received treatment according to dose level −1. The study design is shown in Figure 1.

AEs were reported by the patients and collected at each visit, and reports were made in case of hospitalization. In case of unacceptable side effects (CTC grade 3 or 4) treatment dose was reduced as seen in Tables 1 and 2. Treatment was continued as long, as it was well tolerated and effective. Evaluation of the effect was done after every three cycles with CT of thorax and upper abdomen and MR scan of columnar.

The statistical analysis was performed using SPSS version 20 (SPSS Inc., Chicago, IL). All randomized patients are included in the intention-to-treat population. The NCI-CTC classification version 3.0 (Bethesda, MD) was used to classify AEs. The primary endpoint was to assess the ORR according to RESIST 1.0 criterion's [33] and to compare the RR for the two treatment arms. We calculated a clinical benefit rate (CBR) defining a clinical meaningful response as objective response (CR and PR) or stable disease (SD) for at least 6 months. We compared the CBR between the two treatment arms.

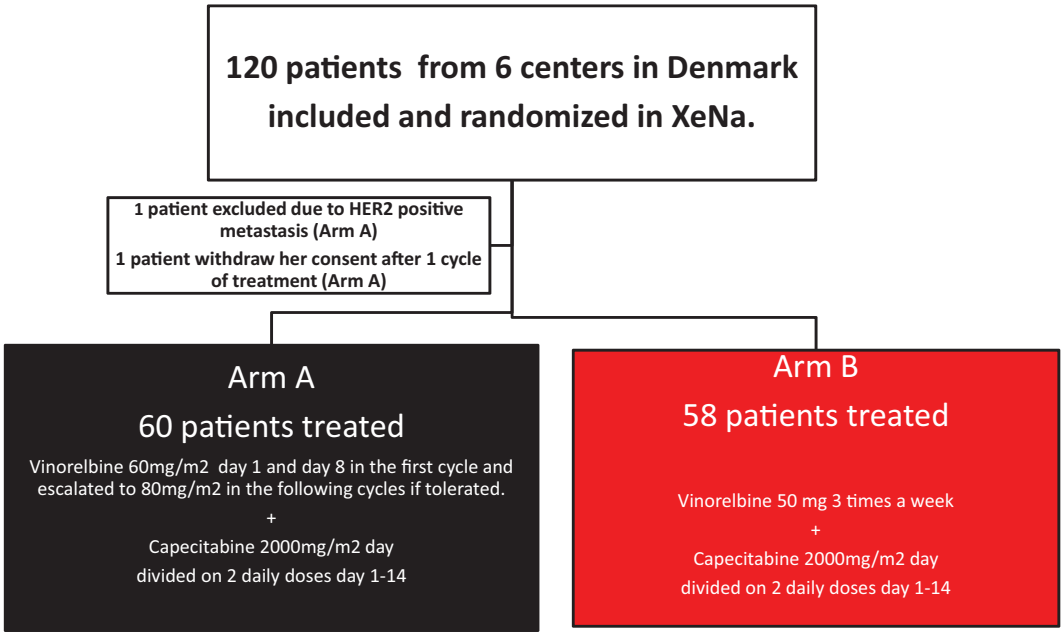


Figure 1. Trial flowchart for the XeNa trial. Patients over 65 start at dose level −1 and are not increased. If one drug is reduced both drugs are given in the new dose. Blood samples were taken day 1 and day 8 in the first cycle, and only day 1 in the following cycle if satisfactory.

Table 1. Standard dose packages ARM A.

First cycle: Vinorelbine 60 mg/m^2+ Capecitabine 2000 mg/m^2 p.o.					Second cycle if well tolerated: Vinorelbine 80 mg/m^2 + Capecitabine 2000 mg/m^2 p.o.			
Surface m^2		Dose level 0	−1 (75 %)	−2 (50%)	Surface m^2	Dose level 0	−1 (75 %)	−2 (50%)
≤1.54 m^2	Vinorelbine	90 mg	70 mg	45 mg	≤1.54 m^2	120 mg	90 mg	60 mg
	Capecitabine	3000 mg	2300 mg	1500 mg		3000 mg	2300 mg	1500 mg
1.55–1.71 m^2	Vinorelbine	100 mg	80 mg	50 mg	1.55–1.71 m^2	130 mg	100 mg	60 mg
	Capecitabine	3300 mg	2500 mg	1650 mg		3300 mg	2500 mg	1650 mg
1.72–1.90 m^2	Vinorelbine	110 mg	80 mg	50 mg	1.72–1.90 m^2	140 mg	110 mg	70 mg
	Capecitabine	3650 mg	2800 mg	1800 mg		3650 mg	2800 mg	1800 mg
>1.90 m^2	Vinorelbine	120 mg	90 mg	60 mg	>1.90 m^2	160 mg	120 mg	80 mg
	Capecitabine	4000 mg	3000 mg	2000 mg		4000 mg	3000 mg	2000 mg

Patients over 65 years start at doses −1 and are not increased. Others are increased in 2 cycles if the treatment is well tolerated.
If one drug is reduced due to frailty or adverse events both drugs are given in the new doses.

Table 2. Standard dose packages ARM B.

Vinorelbine 50 mg+ Capecitabine 2000 mg/m^2 p.o.			
	Dose level		
Surface m^2	0	−1 (75 %)	−2 (50%) Vinorelbine −3 (50%) Capecitabine
Vinorelbine tablets are given Monday, Wednesday, and Friday for all 3 weeks in the cycles.			
All patients	50 mg	40 mg	30 mg
Capecitabine is prescribed according to surface of the patient			
The total dose is split into two and given twice a day for days 1–14 as tablets.			
≤1.54 m^2	3000 mg	2300 mg	1500 mg
1.55–1.71 m^2	3300 mg	2500 mg	1650 mg
1.72–1.90 m^2	3650 mg	2800 mg	1800 mg
>1.90 m^2	4000 mg	3000 mg	2000 mg

Patients over 65 years start at doses −1 and are not increased. If one drug is reduced due to frailty or adverse events both drugs are given in the new doses.

Secondary endpoints were to define the toxicity and safety profile of the combined treatment, progression-free survival (PFS), and OS and compare them between the two treatment arms.

Subgroup analysis of patients under *versus* over 65 years, patients with ER-negative *versus* ER-positive tumors, patients needed treatment in reduced dose *versus* full-dose treatment and patients in performance status 0–1 *versus* 2 are analyzed, as they represent clinically relevant subgroups in the outpatient population.

In the power calculation an assumption for ORR, a minimal desirable ORR, was 30% in the current population, and a desirable increase in ORRas an indication of further studies warranted, was 50%. We needed 50 patients in each arm and included 60 to ensure 50 evaluable patients in each arm. The null-hypothesis is equal ORR in the two treatment arms.

The study has the ClinicalTrials.gov Identifier NCT01941771 and was approved by the Danish Ethic authority (VEK) number: 1-10-72-84-12 and the Danish Medical authority (EUDRACT no. 2011-003564-72).

Results

The patient characteristics are shown in Table 3. The number of cycles ranged between 1 and 48 in both arms and 21% of the patients received more than 15 cycles equal to more than 1-year of treatment as seen in Table 4. Rather surprisingly only 54 (45%) patients managed to complete the full dose treatment. Significantly more patients in arm B started out at dose level −1 mostly due to the number of patients over 65 years old (<0.01). The number of subsequent dose reductions, on the other hand, was significantly higher in arm A than in arm B especially due to leukopenia during treatment (<0.01).

The RRs are as seen in Table 4. Our ORR was 24% (95% CI 13.4–34.6) in arm A and 29% (95% CI 17.3–40.7) in arm B and are not significantly different in the two treatment arms ($p = .18$). The CBR was calculated for the patients who have benefited with ORR or SD for more than 6 months and was 46.8% (95% CI 34.6–59.4) in arm A and 51.7% (95% CI 39.1–64.9) in arm B ($p = .72$).

When we looked at the PFS, treatment time, and OS the two arms were comparable as seen in Table 4. The OS in arm A was 23.3 months (95% CI 20.2–26.4) and 22.3 months (95% CI 14.3–30.3) in arm B. PFS was 7.1 months (95% CI 3.9–10.3) in arm A and 6.3 months (95% CI 4.1–8.5) in arm B. The median follow-up time was 33.5 months. OS and PFS are shown in Figure 2.

The frequency of reported AE in both treatment arms was rather low and both treatments were well tolerated and safe (Table 5). Considering all the AEs, the total amount of reported AE was lower for all grades of AE in the metronomic arm, but there was no significant difference between the side-effects in the different arms, when we compare the proportion of patients experiencing a particular side-effect in the two treatment arms as seen in Table 5. Looking at the hematological side effects in absolute numbers, leukopenia and neutropenia occurred more frequently in arm A and anemia in arm B, but yet no statistical differences were observed between arms. Only few patients experienced

Table 3. Patient characteristics.

		Arm A ($n = 62$)	% of Arm A	Arm B ($n = 58$)	% of Arm B	All ($N = 120$)	% All
Age	<65	45	73	31	53	76	63
	≥65	17	27	27	47	44	37
	Median	60.8		60.9		61	
PS	0	28	45	17	29	45	38
	1	30	48	37	64	67	56
	2	4	7	4	7	8	7
Menopause status	Pre	7	11	9	16	16	13
	Post	54	87	49	85	103	86
ER status	Positive	51	82	45	78	96	80
	Negative	10	16	12	21	22	18
Her2 status	Negative	61	98	58	100	119	99
	Positive	1	2	0	0	1	1
Primary disseminated disease	Yes	16	26	12	21	28	23
	No	43	69	45	77	88	73
Histology type	IDC	51	82	47	81	98	82
	ILC	6	10	7	12	13	11
	Other	2	3	3	5	5	4
Number of organs	1	10	16	8	14	18	15
with metastatic disease	2	19	30	19	33	38	32
	3	20	32	17	29	37	31
	4 and more	11	18	14	24	25	21
Organs involved	Bone	49	79	43	74	92	77
	Liver	24	39	29	50	53	44
	Lung	26	42	19	33	45	38
	Skin	10	16	3	5	13	11
	Lymph nodes	27	44	25	43	52	43
	Pleura	12	19	24	41	36	30
	Other	7	11	13	22	20	17
Visceral involvement	Yes	48	77	50	86	98	82
(pleura, lung, and liver)	No	11	18	8	14	19	16
Bone only	Yes	7	11	4	7	11	9
	No	52	84	54	93	106	88
Previous treatment							
Primary operation for early breast cancer	No	11	18	7	12	18	15
	Yes	49	79	50	86	99	83
Adjuvant radiation therapy	Yes	35	57	49	85	84	70
	No	25	40	7	12	32	27
Adjuvant chemotherapy	Yes	36	58	41	71	77	64
(EC tax, CEF, CEM, READ, and other)	No	25	40	17	29	42	35
Adjuvant endocrine treatment	Yes	33	53	40	69	73	61
	No	28	45	17	29	45	38
Endocrine treatment for	Yes	31	50	25	43	56	47
metastatic disease	No	29	47	32	55	61	51
Line of chemotherapy for XENA	1	22	36	15	26	37	31
regime for metastatic disease	2	37	60	40	69	77	64
Type of first- line treatment	Taxotere/taxol	19	31	28	48	47	39
	Epirubicin	17	27	11	19	28	23
	Other	1	2	1	2	2	2

febrile neutropenia in both arms. Among the non-hematological side-effects, the reported classical side effects, such as nausea, vomiting, diarrhea, alopecia, and neutropenia and hand foot skin syndrome and stomatitis were equal in the treatment arms. The study was considered safe throughout the entire study. The serious AEs were equally represented and acceptable in both treatment arms.

The patients in both treatment arms receiving reduced doses achieved the same efficacy, and surprisingly there was significantly better OS ($p < .01$) and PFS ($p = .04$) among the patients receiving dose reduced treatment in both arm A and arm B, but the group receiving full-dose treatment was relatively small. The better OS and PFS could also be biased by the age group as patients over 65 years were dose reduced per protocol, but there were no significantly different OS between patients below or over 65 years ($p = .45$) in arm A and arm B. Patients having triple-negative disease survived longer in the non-metronomic arm A ($p < .01$). Patients with performance status 0 did not have a longer PFS in arm A or B ($p = .91$)).

Discussion

The goal for treatment of patients with metastatic breast cancer is to relieve symptoms and prolong survival with the best possible quality of life. Palliation, therefore, needs to be balanced against survival and toxicity. Keeping the disease on a stable level and obtaining a more chronic phase of the disease must be the second-best option, when cure is impossible.

The frequencies of reported AE in both treatment arms were rather low and both treatments were well tolerated. In particular, the rate of febrile neutropenia was low in both arms. Looking at the hematological side effects in absolute

numbers, leukopenia and neutropenia occurred more frequently in arm A and anemia in arm B, but yet no statistical differences were observed between arms as seen in Table 5. This observation could be due to the more continuous pressure on the bone marrow in the metronomic treatment arm.

When we compared our results in the non-metronomic arm to previous studies using the same dosing of the drugs in combination [2,34,35] our results are in the middle. The OR, in the previous rather small studies, ranges from 20 to 56%, PFS from 3.4 to 10.5 months, and OS from 11.3 to 29 months. Overall, the combined regimen was also described as well tolerated in previous studies.

The effect of capecitabine alone in a previous study had an ORR of 26% [13]. Vinorelbine as monotherapy was studied in rather small studies and the RRs were found in the range from 12 to 60% [16–20,36,37]. The large range reflects the rather small sample sizes, and a direct comparison is therefore difficult.

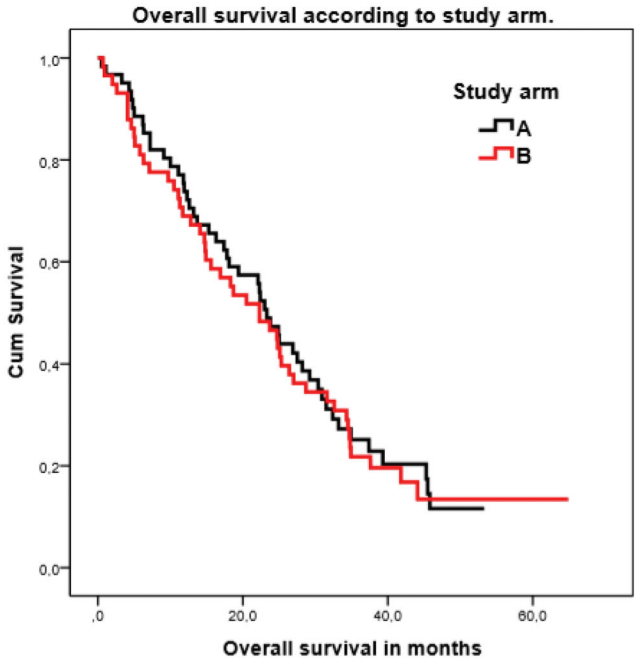
Patients in the older age-group (over 65 years) tolerated the treatment well in our study, and the treatment seems suitable for all age groups. Surprisingly, we found a significant better PFS ($p = .04$) and OS ($p < .01$) in the dose reduced group, but it may be due to a low number in the patients receiving full treatment. Patients with triple-negative disease had shorter OS ($p < .01$) in the metronomic treatment arm, but PFS was not significantly different ($p = .38$).

Since the study was designed, capecitabine has successfully been used in a metronomic schedule [29,31]. We have only one variable in this study, but it could be interesting to examine how well a pure metronomic arm will perform in a randomized way. Currently, the randomized study NAME

Table 4. Treatment response.

		Arm A $n = 62$	Arm B $n = 58$	Total $N = 120$	p Value Log-rank test
Best response	CR	2	1	3	
	PR	13	16	29	
	SD	25	18	43	
	PD	12	15	27	
	NE	10	8	18	
Objective response rate (ORR)	CR + PR	15 (24%)	17 (29%)	32 (27%)	.18
	95% CI	13.4–34.6%	17.3–40.7%	19.0–34.9%	
Stable disease (SD) for ≥ 6 months		14 (23%)	13 (22%)	27 (23%)	
Clinical benefit rate (CBR) (ORR + SD ≥ 6 months)		29 (47%)	30 (52%)	59 (49%)	.72
	95% CI	34.6–59.4%	39.1–64.9%	40.0–57.9%	
PFS median	Months	7.1	6.3	6.8	.25
	95% CI	3.9–10.3	4.1–8.5	5.1–8.5	
OS median	Months	23.3	22.3	23.0	.76
	95% CI	20.2–26.4	14.3–30.3	18.5–27.5	
Number of cycles	<3	11	13	24	
	3–5	19	15	34	
	6–8	12	6	18	
	9–14	7	11	18	
	15–30	8	10	18	
	31–50	5	3	8	
Start dose reduction	0	45	27	72	<.01
	−1	16	31	47	
Reduction during treatment	0	18	36	54	
	−1	29	9	38	<.01
	−2	14	13	27	
Reason for reduction at start	Age ≥ 65	11	24	35	
	Frailty before start	2	4	6	
	Full dose despite age ≥ 65	5	3	8	
	Diarrhea	1	0	1	
	Leucopenia	2	0	2	
	Neutropenia	0	1	1	
	Weight loss	1	0	1	
Reason for reduction during treatment	Nausea	1	2	3	
	Hand foot	8	5	13	
	Leucopoenia	8	1	9	
	Neutropenia	11	5	16	
	Neuropathia	2	0	2	
	Diarrhea	1	0	1	
	Fatigue	0	1	1	
	Febrile neutropenia	1	0	1	
	Increased liver enzymes	3	2	5	
	AE not specified	7	5	12	
Reason for end of study	Progression	39	42	81	
	Toxicities	10	7	17	
	Patients wish	6	4	10	
	Doctors wish	1	3	4	
	Other	4	2	6	
	Still treated	2	0	2	

Treatment response, number of cycles as well as dose reductions in the study, and reasons for end of study.



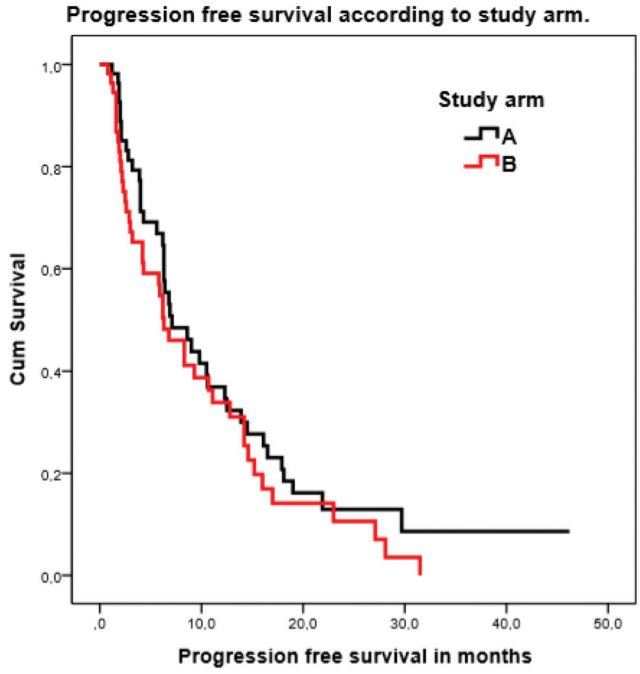


Figure 2. Overall survival and progression-free survival in the two study arms.

Table 5. Worse adverse event in number of patients.

	Arm A $n=62$							Arm B $n=58$							Fischer exact test
Grade	0	1	2	3	4	5	All	0	1	2	3	4	5	All	*p* Value
Hematological AE															
Anemia	58	4					4	50	3	5				8	.23
Leukopenia	50	9	1	1	1		12	50	2	4	1	1		8	.47
Neutropenia	36	7	9	6	4		26	41	3	11	2	1		17	.18
Thrombocytopenia	59	2			1		3	57	1					1	.62
Classical chemotherapy AE															
Alopecia	57	4	1				5	57		1				1	.21
Anorexia	62						0	55	2		1			3	.11
Arrhythmia	60	1		1			2	57			1			1	1.00
Bleeding	59	2		1			3	55	1	1	1			3	1.00
Constipation	44	11	7				18	41	13	4				17	1.00
Decreasing PS	53	1	1	7			9	53		3	1	1		5	.40
Diarrhea	28	19	14	1			34	28	23	4	3			30	.85
Dyspepsia	56	4	2				6	55	1	2				3	.49
Dysphagia	60	2					2	58						0	.50
Fatigue	36	14	6	5	1		26	31	6	11	9	1		27	.71
Hand-foot skin	29	16	14	3			33	29	16	10	3			29	.86
Mucositis	35	14	11	2			27	33	18	6	1			25	1.00
Nail changes	55	6	1				7	53	4	1				5	.76
Nausea	33	15	12	2			29	37	11	8	2			21	.27
Vomiting	51	3	8				11	50	4	1	3			8	.62
Ascites	62						0	56			2			2	.23
Chills	56	6					6	53	3	2				5	1.00
Coughing	55	1	6				7	56	1		1			2	.17
Cystitis	57		4	1			5	53	1	3	1			5	1.00
Dyspnea	43	8	7	4			19	44	6	5	3			14	.54
Edema	55	7					7	53	4	1				5	.76
Febrile neutropenia	60			1	1		2	56			2			2	1.00
Fever	51	5	4	2			11	43	6	5	4			15	.38
Hypertension	62						0	57	1					1	.48
Hypotension	61		1				1	57			1			1	1.00
Infection	54		4	3	1		8	48	1	5	4			10	.61
Lung edema	61					1	1	58						0	1.00
Multiorgan failure	62						0	57					1	1	.48
Pleural effusion	58		2	2			4	52		3	3			6	.52
Pneumonia	60		2				2	56		2				2	1.00
Thrombosis/embolism	55		1	2	4		7	53		3	1	1		5	.76
Abdominal pain	52	6	3	1			10	48	6	4				10	1.00

(*continued*)

Table 5. Continued.

	Arm A $n = 62$							Arm B $n = 58$							Fischer exact test
Grade	0	1	2	3	4	5	All	0	1	2	3	4	5	All	p Value
Back pain	54	4	3	1			8	53	1	1	3			5	.56
Chest pain	58	3	1				4	54	1	3				4	1.00
Headache	60	1	1				2	55	1	2				3	.67
Muscle- and joint- affection	50	9	3				12	46	6	4	2			12	1.00
Neuropathy	40	11	7	4			22	39	12	3	4			19	.85
Pain	50	6	6				12	51	3	3	1			7	.32
Other	44	9	4	5			18	44	7	7				14	.68
Dehydration	61			1			1	58						0	1.00
Depression	60	2					2	56	1	1				2	1.00
Dizziness	56	5		1			6	55	1	2				3	.49
Fracture	60		1	1			2	57		1				1	1.00
Hot flushes	61		1				1	57	1					1	1.00
Insomnia	61	1					1	54	3	1				4	.20
Other	61	1					1	57	1					1	1.00
Vision impairment	59		2	1			3	57		1				1	.62
Weight loss	61			1			1	57		1				1	1.00
Laboratory AE															
Elevated bilirubin	62						0	56	2					2	.23
Elevated creatinine	60	1	1				2	53	3	2				5	.26
Elevated LDH	59	3					3	54	4					4	.71
Hypercalcemia	59	3					3	56	2					2	1.00
Hyperkalemia	62						0	56	2					2	.23
Hypocalcaemia	59	2	1				3	57		1				1	.62
Hypokalemia	57	2		3			5	53	4	1				5	1.00
Transaminasemia	43	8	5				13	47	9	1	1			11	.65
Total		229	153	58	13	1	454		194	133	61	5	1	394	–

We have used the total of patients experiencing a particular event in each arm, when calculating the p value.

with metronomic daily vinorelbine as monotherapy is now recruiting (EUDRACT no 2016-002165-63).

Conclusion

To our knowledge, this was the first randomized Phase 2 study investigating the effect of metronomic treatment compared to standard treatment. When we compared our results to other investigators, our RRs were comparable in the non-metronomic arm.

The study has shown metronomic treatment is possible with low frequencies of AEs, and it is possible to receive good RRs and high CBRs.

However, metronomic treatment in this form is not more effective measured by RR, CBR, PFS, and OS as compared to standard dosing of chemotherapy. There was a significant shorter survival among the patients with a triple-negative tumor receiving metronomic treatment. Metronomic treatment might have a place in cancer treatment in the less aggressive breast cancer subtypes to keep the disease at chronic state, but in this study, we did not find a better effect of the metronomic treatment.

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Disclosure statement

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