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Single-agent metronomic versus weekly oral vinorelbine as first-line chemotherapy in patients with HR-positive/HER2-negative advanced breast cancer: The randomized Tempo Breast study

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ABSTRACT

Introduction: Single-agent oral vinorelbine is a standard of care for hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer (ABC) that has progressed on endocrine therapy. Metronomic administration may offer a better balance of efficacy and safety than standard regimens, but data from previous trials are scarce.

Methods: In this open-label, multicenter, phase II trial, patients were randomized to oral vinorelbine administered on a metronomic (50 mg three times weekly) or weekly (60 mg/m^2 in cycle 1, increasing to 80 mg/m^2 if well tolerated) schedule. Treatment was continued until disease progression or intolerance. The primary endpoint was disease control rate (DCR, the proportion of patients with a best overall confirmed response of CR, PR, or stable disease lasting 6 months or more).

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Results: One-hundred sixty-three patients were randomized and treated. The DCR was 63.4% (95% confidence interval [CI]: 52.0–73.8) with metronomic vinorelbine and 72.8% (95% CI: 61.8–82.1) with weekly vinorelbine. Weekly vinorelbine was also associated with longer progression-free survival (5.6 vs 4.0 months) and overall survival (26.7 vs 22.3 months) than metronomic vinorelbine, but was associated with more adverse events.
Conclusions: In this randomized phase II trial, single-agent metronomic oral vinorelbine was effective and well tolerated as first-line chemotherapy for patients with HR-positive/HER2-negative ABC. Formal comparisons are not done in this phase II study and one can simply observe that confidence intervals of all endpoints overlap. When deciding for a chemotherapy after failure of endocrine therapy and CDK 4/6 inhibitors, oral vinorelbine might be an option to be given with either schedule.
Clinical trial registration number: EudraCT 2014-003860-19.

1. Introduction

Several treatment options are available for advanced breast cancer (ABC). According to the latest published guidelines and literature, the chemotherapy is an option after failure of endocrine therapy plus CDK4/6 inhibitors (1 or 2 lines of treatment), in most of cases. Single-agent chemotherapy is an option for patients with hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative ABC that is refractory to endocrine therapies with or without targeted agents, or for patients who require rapid reduction of their tumor and/or are in a visceral crisis state [1].

Oral vinorelbine is one of the option for the treatment of ABC based on clinical trial evidence of its effectiveness in the metastatic setting when administered once weekly at a dose of 60–80 mg/m^2, although it is associated with toxicities, such as neutropenia, peripheral neuropathy, and nausea/vomiting [2–5]. An alternative regimen that minimizes toxicities is the metronomic regimen, which entails the use of more frequent fractionated doses far below the maximum tolerated dose (MTD) and continuous drug administration until disease progression or unacceptable toxicity [6–9]. This allows for effective drug concentrations at the tumor site, while simultaneously reducing the incidence of severe toxicities typically associated with MTD-based schedules [10].

Metronomic vinorelbine 50 mg three times weekly demonstrated minimal toxicity and promising efficacy in phase I trials in advanced/metastatic cancers [11–13]. To date, no randomized controlled trials of metronomic vinorelbine have been conducted in patients with ABC. The Tempo Breast study is the first randomized trial of single-agent metronomic vinorelbine in patients with HR-positive/HER2-negative ABC, assessing the efficacy and safety of this treatment as first-line chemotherapy in patients who had previously received endocrine therapy.

2. Methods

2.1. Study design

Tempo Breast was an open-label, multicenter, randomized, parallel-group phase II trial conducted at 43 sites in Europe between December 2015 and December 2017 (EudraCT number 2014-003860-19). The study design is shown in Fig. S1. Patients were stratified at randomization according to center, prior taxane use, prior everolimus use, and the presence of visceral metastases. The patients were enrolled in the era pre-CDK 4/6 inhibitors.

2.2. Patients

Patients aged ≥18 years were eligible for inclusion if they had locally recurrent or metastatic histologically confirmed, HR-positive/HER2-negative adenocarcinoma of the breast that was not amenable to curative surgery or radiotherapy. Other inclusion criteria and reasons for patient ineligibility are listed in the Supplementary Methods.

2.3. Treatments

Study treatment was given on a 3-week cycle (Fig. S1). Patients were randomized 1:1 to metronomic oral vinorelbine 50 mg three times weekly (Arm A) or oral vinorelbine 60 mg/m^2 once weekly in cycle 1, increased to 80 mg/m^2/week in subsequent cycles in the absence of grade 3 or 4 neutropenia (Arm B). Study treatment was continued until disease progression, unacceptable toxicity, or withdrawal of consent. Supportive care and treatment were provided in accordance with local guidelines and investigator's opinion.

2.4. Outcomes

Disease status was evaluated every two cycles (approximately every 6 weeks). The primary endpoint was disease control rate (DCR; Table S1), and was determined using Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1).

The main secondary efficacy endpoints were objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and safety. Additional secondary endpoints included DCR, ORR, and PFS without grade 3–4 toxicity or grade 3–4 neutropenia, duration of disease control, duration of stable disease, and time to treatment failure (TTF; Table S1). Adverse events (AEs) were recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

Post hoc subgroup analyses and univariate/multivariate analyses to identify PFS prognostic factors were also conducted (see Supplementary Methods).

2.5. Ethics

The study was conducted in accordance with the Institut de Recherche Pierre Fabre Clinical Standard Operating Procedures, the ethical principles that have their origin in the Declaration of Helsinki, and subsequent amendments consistent with the International Council for Harmonisation Guidelines on Good Clinical Practice (CPMP/ICH/135/95) and related national regulations. All study documentation was reviewed and approved by the appropriate independent ethics committee(s) in each participating country prior to implementation; all patients provided written informed consent.

2.6. Statistical analysis

Simon's two-stage design was applied [14]. Based on a null hypothesis (H0) for a DCR of 50%, an alternative hypothesis (H1) of 70%, two rounds of testing, a type I error α of <2.5%, and a type II error β of <10%, 73 evaluable patients per treatment arm would be needed. Assuming an attrition rate of 10%, 80 patients per treatment arm were planned to be enrolled. An interim analysis was performed after enrolment of 21 evaluable patients into Arm A to determine whether the study should be stopped or more patients needed to be evaluated. If ≤ 11 patients had complete response (CR), partial response (PR) and/or stable disease, H0 was not rejected, and no further patients were enrolled.

If > 11 patients had CR, PR and/or stable disease, 52 more patients were recruited into that arm. Following the interim analysis, H0 was rejected, and the trial proceeded to full enrollment. A cut-off date of November 7, 2019 was applied for the final analysis.

Efficacy was analyzed for the intent-to-treat (ITT) population (all patients who underwent randomization and received ≥1 dose of study drug), and safety for the safety population (all patients who received ≥1 dose of study drug and had ≥1 post-baseline safety data assessment).

The sample sizes by treatment group were justified based on the two intra-group Simon tests of the DCR, and the same rate of 70% was assumed in the two groups under the alternative hypotheses. Accordingly, there was no rational to conduct comparative statistical tests on efficacy in this trial. Descriptive statistics were used as appropriate (95% confidence intervals [CIs] were calculated using the Clopper-Pearson approach). Estimates of survival for duration of disease control or stable disease, as well as for PFS, OS, and TTF were obtained using the Kaplan-Meier method, with 95% CIs calculated using the Brookmeyer and Crowley method. All statistical analyses were performed using SAS v.9.4.

3. Results

3.1. Patient disposition and characteristics

Among the 54 subjects with screen failure, one died and three withdrew their consent before review of inclusion and exclusion criteria. And fifty were not randomized because they did not meet one inclusion criteria, or they met one exclusion criteria (appendix table). Patient disposition is shown in Fig. 1. Of 164 patients enrolled and randomized to treatment, one patient did not receive treatment due to a protocol violation; thus 163 patients formed the ITT population (82 in Arm A and 81 in Arm B). One patient (Arm B) was excluded from the safety population (162 patients) because follow-up safety data were absent.

At the cut-off date, all except two patients (both in Arm B) had discontinued treatment. Common reasons for discontinuation included progressive disease (PD; $n = 68$ [81.9%] in Arm A, and $n = 57$ [70.4%] in Arm B) and AEs ($n = 7$ [8.5%] in Arm A and $n = 10$ [12.3%] in Arm B). Eighty-eight patients died during follow-up ($n = 48$ in Arm A and $n = 40$ in Arm B), mostly from PD.

Patient demographics and clinical characteristics are shown in Table 1 and Table S2. The treatment groups were well balanced at baseline, except that mean ± standard deviation (SD) time since diagnosis was shorter in Arm A than in Arm B (92.6 ± 76.1 vs 105.9 ± 83.5 months). Overall, 51 patients (31.9%) received only 1 previous line of endocrine therapy and 51 patients (31.3%) received 2 previous lines of endocrine therapy, and 60 patients (36.8%) received 3 or more than 4 lines of endocrine therapy. This reflects a non-contemporary cohort; all the patients were enrolled before the availability of the CDK4/6 inhibitors. The prior anti-cancer therapies are described in Table 1. The anti-endocrine therapies are reported in the supplementary appendix Table S6.

3.2. Exposure to randomized treatment

Patients in Arm B received a higher mean number of cycles but were more likely to have dose modifications due to AEs (Table 2). The mean cumulative dose intensity is slightly higher in the arm A. The mean cumulative dose seems quite similar between the 2 arms: 1755.6 (SD ± 1750.1) in the arm A, and 1827.5 (SD ± 1958.4).

Of the 77 patients in Arm B who received ≥2 cycles, 62 (80.5%) underwent dose escalation to 80 mg/m^2 at cycle 2. Reasons for non-escalation and for <2 cycles are summarized in the Supplemental Results.

3.3. Efficacy

3.3.1. Response rates

The DCR was 63.4% (95% CI: 52.0–73.8) in Arm A and 72.8% (95% CI: 61.8–82.1) in Arm B (Table 3).

The median duration of disease control was 6.9 (95% CI: 4.2–8.6) months in Arm A, and 7.9 (95% CI: 5.7–10.0) months in Arm B. A numerically higher percentage of patients in Arm An achieved disease control without grade 3–4 toxicity (29.3%; 95% CI: 19.7–40.4) compared with Arm B (22.2%; 95% CI: 13.7–32.8). A similar pattern was observed for disease control without grade 3–4 neutropenia (42.7% [95% CI: 31.8–54.1] in Arm A, and 30.9% [95% CI: 21.1–42.1] in Arm B).

The ORR was 17.1% (95% CI: 9.7–27.0) in Arm A and 21.0% (95%

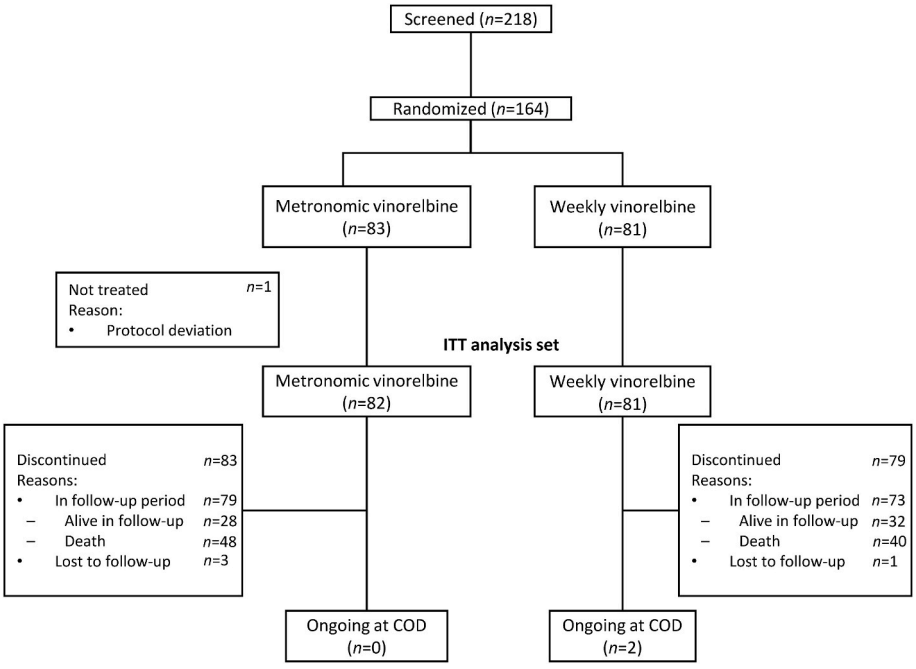

Fig. 1. Patient disposition. COD: cut-off date = November 7, 2019; ITT: intent-to-treat.

Table 1
Patient demographics, baseline clinical characteristics, and prior therapies.

Characteristic	Metronomic vinorelbine (n = 82)	Weekly vinorelbine (n = 81)
Mean ± SD age, years	64.2 ± 10.2	65.5 ± 11.8
Mean ± SD BMI, kg/m^2	27.3 ± 5.3	27.3 ± 5.2
Median KPS, %	90.0	90.0
Mean ± SD time since diagnosis, months	92.6 ± 76.1	105.9 ± 83.5
Disease extent, n (%)		
Locoregional	2 (2.4)	4 (4.9)
Metastatic	80 (97.6)	77 (95.1)
No. of organs involved, n (%)		
1	11 (13.4)	12 (14.8)
2	33 (40.2)	31 (38.3)
≥3	38 (46.3)	38 (46.9)
Organs involved, n (%)		
Lung[a]	36 (43.9)	40 (49.4)
Liver	45 (54.9)	37 (45.7)
Bone[b]	53 (64.6)	49 (60.5)
No. of concomitant diseases per patient, n (%)		
0	13 (15.9)	15 (18.5)
1	20 (24.4)	14 (17.3)
2	15 (18.3)	15 (18.5)
≥3	34 (41.5)	37 (45.7)
Prior therapies, n (%)		
Neoadjuvant therapies		
Anthracyclines	11 (13.4)	13 (16.0)
Taxanes	12 (14.6)	13 (16.0)
Other	12 (14.6)	11 (13.6)
Adjuvant therapies		
Anthracyclines	31 (37.8)	33 (40.7)
Taxanes	21 (25.6)	21 (25.9)
Other	60 (73.2)	66 (81.5)
No. of prior lines of hormonal therapy		
1	23 (28.0)	29 (35.8)
2	31 (37.8)	20 (24.7)
3	13 (15.9)	17 (21.0)
≥4	15 (18.3)	15 (18.5)

BMI: body mass index; KPS: Karnofsky performance status; SD: standard deviation.
[a] The lung designation included the lungs, pleura or malignant pleural effusion.
[b] The majority of patients had bone lesions combined with at least one other lesion (visceral and/or non-visceral).

Table 2
Exposure to randomized medication.

Parameter	Metronomic vinorelbine (n = 82)	Weekly vinorelbine (n = 81)
Total no. of cycles	614	759
Mean ± SD no. of cycles	7.5 ± 7.6	9.5 ± 9.2
Mean ± SD cumulative dose, mg/m^2	1755.6 ± 1750.1	1827.5 ± 1958.4
Mean ± SD relative dose intensity per patient, %	85.0 ± 17.7	75.9 ± 19.0
Mean ± SD dose intensity per patient, mg/m^2/week	75.7 ± 16.9	57.2 ± 14.7
Mean ± SD relative dose intensity per cycle, %	86.8 ± 20.7	80.0 ± 21.3
Mean ± SD dose intensity per cycle, mg/m^2/week	76.4 ± 18.0	62.2 ± 16.8
Patients with ≥1 dose modification, n (%)	58 (70.7)	70 (87.5)
Reasons for dose modification, n (%)		
Adverse event	41 (50.0)	64 (80.0)
Other	35 (42.7)	39 (48.8)

SD: standard deviation

CI: 12.7–31.5) in Arm B. Objective response without grade 3–4 toxicity was observed in eight patients (9.8%; 95% CI: 4.3–18.3) in Arm A and six patients (7.4%; 95% CI: 2.8–15.4) in Arm B. Ten patients (12.2%; 95% CI: 6.0–21.3) and six patients (7.4%; 95% CI: 2.8–15.4), respectively, had an objective response without grade 3–4 neutropenia.

Table 3
Best overall response and time to treatment failure.

	Metronomic vinorelbine (n = 82)	Weekly vinorelbine (n = 81)
CR, n (%)	0	0
PR, n (%)	14 (17.1)	17 (21.0)
Stable disease, n (%)	38 (46.3)	42 (51.9)
DCR, % (95% CI)	63.4 (52.0–73.8)	72.8 (61.8–82.1)
ORR, % (95% CI)	17.1 (9.7–27.0)	21.0 (12.7–31.5)
TTF, months, median (95% CI)	3.0 (2.4–4.2)	4.8 (2.9–5.7)

CI: confidence interval; CR: complete response; DCR: disease control rate; ORR: objective response rate; PR: partial response; TTF: time to treatment failure.

Among those with a best response of stable disease, the median duration of stable disease was 4.2 (95% CI: 4.0–6.7) months in Arm A and 5.7 (95% CI: 5.0–7.8) months in Arm B.

3.3.2. *Survival estimates*

Median PFS and OS were 4.0 (95% CI: 2.8–5.4) and 22.3 (95% CI: 19.0–27.3) months, respectively, in Arm A, and 5.6 (95% CI: 4.4–7.8) and 26.7 (95% CI: 22.2–37.8) months, respectively, in Arm B (Fig. 2).

Estimated PFS rates at 12 and 24 months, and OS rates at 12, 24 and 36 months are reported in Table S3.

With regard to composite endpoints, median PFS without grade 3–4 toxicity was 1.7 (95% CI: 1.4–2.8) months in Arm A and 1.4 (95% CI: 1.3–2.1) months in Arm B (Fig. S2); corresponding values for PFS without grade 3–4 neutropenia were 2.7 (95% CI: 1.4–3.9) months and 2.1 (95% CI: 1.4–2.6) months (Fig. S3).

3.4. *Safety*

Treatment-related AEs of any grade, and of grade ≥3 severity, were less frequent in Arm A than in Arm B (Table 4). Treatment-related grade 3–4 neutropenia was more common in Arm B than Arm A, and grade 3–4 anemia occurred in two patients (2.5%) in Arm B and none in Arm A (Table 4). Treatment-related serious AEs (SAEs) were reported in 4.9% of patients in Arm A versus 8.8% in Arm B (Table 5). Treatment-related AEs necessitating dose reduction or requiring permanent discontinuation were also less common in Arm A than Arm B (Table 5). Two treatment-related deaths occurred in each arm (sepsis and enterocolitis in Arm A, and neutropenic sepsis and cardiac failure in Arm B). Four patients had related SAE in the metronomic arm (neutropenia, enterocolitis, neutropenic sepsis) and 7 patients had a related SAE in the weekly arm (including febrile neutropenia, cardiovascular block, neutropenic sepsis, neutropenic colitis and nausea/vomiting, general physical deterioration). The serious adverse events related to the treatments were summarized in Table S7 in the appendix.

3.5. *Post hoc analyses*

Results of post hoc subgroup analyses based on age and prior hormonal therapy are reported in Table S4.

Table S5 provides results of the univariate and multivariate regression analyses. The univariate analyses identified six potential predictors for PFS; three variables were retained in the final multivariable Cox model: treatment group, liver metastases and body mass index (BMI).

The hazard of progression or death in Arm A (n = 82) tended to be higher than that in Arm B (n = 81) (hazard ratio [HR]: 1.38, 95% CI: 1.00–1.90) as did the hazard of progression or death in the group of patients with liver metastases (n = 82) compared with the group of patients without liver metastases (n = 81) (HR: 1.36, 95% CI: 0.99–1.88). On the other hand, the hazard of progression or death tended to be less in patients with a higher BMI (HR: 0.96, 95% CI: 0.93–0.99).

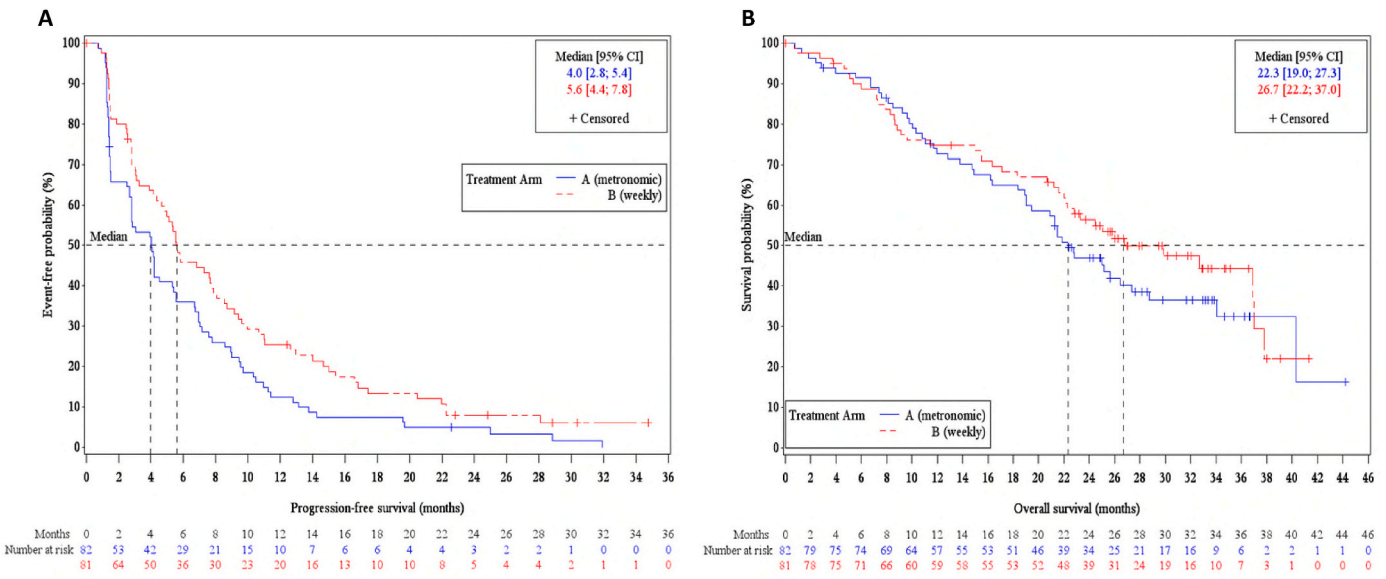

Fig. 2. Kaplan-Meier estimates of progression-free survival (A) and overall survival (B) [ITT analysis]. Arm A refers to metronomic vinorelbine and Arm B refers to weekly vinorelbine. CI: confidence interval; ITT: intent-to-treat.

Table 4
Treatment-related adverse events occurring in ≥5% of patients in any treatment arm, overall and by severity.

Treatment-related AE, n (%)	Metronomic vinorelbine (n = 82)				Weekly vinorelbine (n = 80)			
	Any grade	Grade 3	Grade 4	Grade 5	Any grade	Grade 3	Grade 4	Grade 5
Blood and lymphatic system disorders	27 (32.9)	9 (11.0)	11 (13.4)	0	57 (71.3)	24 (30.0)	18 (22.5)	0
Neutropenia	27 (32.9)	9 (11.0)	11 (13.4)	0	57 (71.3)	23 (28.8)	18 (22.5)	0
Anemia	2 (2.4)	0	0	0	4 (5.0)	2 (2.5)	0	0
Febrile neutropenia	0	0	0	0	2 (2.5)	0	2 (2.5)	0
Gastrointestinal disorders	38 (46.3)	3 (3.7)	0	1 (1.2)	58 (72.5)	6 (7.5)	0	0
Nausea	24 (29.3)	2 (2.4)	0	0	43 (53.8)	2 (2.5)	0	0
Vomiting	7 (8.5)	0	0	0	29 (36.3)	1 (1.3)	0	0
Diarrhea	19 (23.2)	0	0	0	25 (31.3)	1 (1.3)	0	0
Upper abdominal pain	4 (4.9)	0	0	0	6 (7.5)	0	0	0
Constipation	5 (6.1)	1 (1.2)	0	0	5 (6.3)	0	0	0
Dyspepsia	5 (6.1)	0	0	0	2 (2.5)	0	0	0
General disorders and administration site conditions	22 (26.8)	2 (2.4)	0	0	36 (45.0)	2 (2.5)	0	0
Asthenia	13 (15.9)	1 (1.2)	0	0	23 (28.8)	1 (1.3)	0	0
Fatigue	8 (9.8)	1 (1.2)	0	0	9 (11.3)	1 (1.3)	0	0
Infections and infestations	3 (3.7)	0	0	1 (1.2)	5 (6.3)	0	0	1 (1.3)
Neutropenic sepsis	0	0	0	0	1 (1.3)	0	0	1 (1.3)
Sepsis	1 (1.2)	0	0	1 (1.2)	0	0	0	0
Metabolism and nutrition disorders	4 (4.9)	1 (1.2)	0	0	11 (13.8)	0	0	0
Musculoskeletal and connective tissue disorders	2 (2.4)	0	0	0	5 (6.3)	0	0	0
Nervous system disorders	4 (4.9)	0	0	0	10 (12.5)	0	0	0
Paresthesia	0	0	0	0	2 (2.5)	0	0	0
Skin and subcutaneous tissue disorders	3 (3.7)	0	0	0	10 (12.5)	1 (1.3)	0	0
Alopecia	3 (3.7)	0	0	0	8 (10.0)	1 (1.3)	0	0

AE: adverse event

4. Discussion

Metronomic vinorelbine at 50 mg three times weekly was associated with an acceptable DCR of 63.4%, a median duration of disease control of 6.9 months, and median PFS and OS of 4.0 and 22.3 months, respectively. Efficacy outcomes for weekly vinorelbine were 72.8%, 7.9 months, and 5.6 and 26.7 months, respectively. The ORR were respectively: 17.1% in the arm A and 21% in the arm B. Both dosing appeared effective in this population. There was a difference in overall response rates between the 2 arms with a numerically higher ORR in the arm B, although the mean dose intensity per week favored the arm A.

Our study was non-comparative and not powered (i.e., it was statistically underpowered to detect between-group differences), both dosing regimens appeared effective in this patient population, confirming results of previous clinical trials of first-line oral vinorelbine given weekly for patients with ABC [3,4]. A trend of improved tolerability was observed with metronomic vinorelbine, although most AEs in both arms were mild or moderate (grade 1 or 2) in severity. The most frequently reported AEs in both arms involved the same system organ classes and were reported at lower incidences with the metronomic than weekly regimen. Fewer patients receiving the metronomic regimen had treatment-related AEs requiring dose reduction (18.3% vs 37.5%) or permanent discontinuation (4.9% vs 10.0%) compared with the weekly regimen. As a result, patients randomized to metronomic vinorelbine received a higher proportion of the planned therapy than those randomized to the weekly schedule (85.0% vs 75.9%, respectively). The decreased incidence of AEs in the metronomic arm is likely related to the typically lower drug exposure over a shorter time frame (48 h)

Table 5
Overview of serious adverse events and adverse events leading to dose reduction or discontinuation.

Outcome of interest, n (%)	Metronomic vinorelbine (n = 82)		Weekly vinorelbine (n = 80)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
≥1 SAE, regardless of causality	22 (26.8)	20 (24.4)	13 (16.3)	12 (15.0)
≥1 treatment-related SAE	4 (4.9)	4 (4.9)	7 (8.8)	6 (7.5)
≥1 treatment-related AE leading to permanent discontinuation	4 (4.9)	4 (4.9)	8 (10.0)	6 (7.5)
≥1 AE requiring dose reduction, regardless of causality	15 (18.3)	14 (17.1)	31 (38.8)	25 (31.3)
≥1 treatment-related AE requiring dose reduction	15 (18.3)	14 (17.1)	30 (37.5)	25 (31.3)

AE: adverse event; SAE: serious adverse event

compared with weekly administration, even though exposure in the metronomic arm is repeated [10,15]. Composite efficacy/safety endpoints were used to further evaluate this relationship, and although absolute values were small (e.g., median PFS without grade 3–4 toxicity was <60 days in both treatment groups), these results were slightly better with metronomic than weekly vinorelbine. Nevertheless, this improved efficacy/safety balance with metronomic vinorelbine versus weekly vinorelbine did not translate into improved survival, because PD was a far more common reason for treatment discontinuation than poor tolerability.

This randomized phase II study is one the first trial of single-agent metronomic oral vinorelbine as first-line chemotherapy for the treatment of HR-positive/HER2-negative ABC.

These results are consistent with the findings of the XeNa study, a phase II trial that compared metronomic vinorelbine (50 mg three times weekly) plus capecitabine with standard weekly oral vinorelbine (60 mg/m^2 in cycle 1, then increased to 80 mg/m^2) plus capecitabine as first- or second-line chemotherapy in patients with HER2 non-amplified metastatic breast cancer (MBC) [16]. In this study the standard regimen was the same using weekly vinorelbine plus capecitabine. Both regimens demonstrated efficacy (e.g., ORR: 29% vs 24%, median PFS: 6.3 vs 7.1 months, median OS: 22.3 vs 23.3 months), and both treatments were well tolerated [16]. In the XeNa study, the study population included patients with triple negative ABC (around 20%). The authors reported that the patients with triple negative ABC survived longer in the standard arm ($p < 0.01$). Importantly, the XeNa and Tempo Breast study findings are not directly comparable due to differences in the use of standard vinorelbine and the metronomic vinorelbine being part of combination therapy in XeNa, as well as the inclusion of previously treated patients, and vinorelbine dose adjustment in patients aged ≥65 years [16].

The effects of metronomic vinorelbine, used as a single agent or in combination with other cytotoxic drugs, endocrine therapies, or targeted therapies, have been investigated in a variety of settings in patients with breast cancer [16–22], as well as in other solid tumors [9,23]. Despite its increasing popularity as a treatment option [24], the use of oral vinorelbine in a metronomic schedule is still relatively novel compared with the use of this schedule with other chemotherapy agents. Results of ongoing trials will help clarify the place of metronomic vinorelbine therapy in ABC, including the randomized NAME trial (EudraCT 2016-002165-63) in women with HER2-negative ABC [25] and the METEORA-II trial (NCT02954055) in HR-positive/HER2-negative metastatic or locally relapsed breast cancer. Final data for METEORA-II showed an improved median TTF (primary endpoint) for metronomic vinorelbine, cyclophosphamide, and capecitabine (8.3 months) versus weekly paclitaxel (5.7 months) [26].

While the size of our trial and its international, multicenter design are important strengths, it does have some limitations. As previously mentioned, one of the limitations was that our study was not powered to detect a difference between the 2 arms. Furthermore, the patients were enrolled in a pre- CDK 4/6 inhibitors era. This aspect should be considered when interpreting the results as the CDK 4/6 inhibitors were approved starting from 2014 and led to a wide change in the practice with adoption of these new agents in the 1st line metastatic setting of BC (PALOMA 3; MONALEESA 3).

Due to differences in administration schedules, it was not possible to blind patients or investigators to treatment; therefore, investigator bias cannot be excluded. Treatment adherence and therapeutic drug monitoring (this was not logistically possible at some study centers) were not assessed; therefore, an effect of suboptimal adherence or drug concentrations on our findings cannot be determined. Further, the study was not sufficiently powered to detect differences between randomized groups. Finally, our results cannot be generalized to other breast cancer populations.

5. Conclusions

Although the Tempo Breast trial was not powered to detect a difference, single-agent metronomic oral vinorelbine was effective and well tolerated as first-line chemotherapy for patients with HR-positive/HER2-negative ABC who had progressed under endocrine therapy. Formal comparisons are not done in this phase II study and one can simply observe that confidence intervals of all endpoints overlap. When deciding for a chemotherapy after failure of endocrine therapy and CDK 4/6 inhibitors, oral vinorelbine might be an option to be given with either schedule.

Role of the funding source

This work and medical writing assistance was supported by Pierre Fabre Médicament. The study has been funded by Pierre Fabre Médicament. Statistical analysis was managed by Cmed (Paris, France) and funded by Pierre Fabre Médicament. In some territories, trial monitoring was undertaken by the contract research organization Clinipace Accovion and the Spanish Breast Cancer Research Group (GEICAM), funded by Pierre Fabre Médicament. In all other territories, trial monitoring was undertaken by Pierre Fabre Médicament.

Institutional review board statement

The study was conducted in accordance with the Institut de Recherche Pierre Fabre Clinical Standard Operating Procedures, the ethical principles that have their origin in the Declaration of Helsinki, and subsequent amendments consistent with the International Council for Harmonisation (ICH) Guidelines on Good Clinical Practice (CPMP/ICH/135/95) and related national regulations. All study documentation was reviewed and approved by the appropriate independent ethics committee(s) in each participating country prior to implementation.

Informed consent statement

All patients provided written informed consent before any study-specific procedures were undertaken.

Data sharing statement

The main data generated and analyzed during the study (including the post hoc analyses) are included in the manuscript and online supplementary materials. Requests for additional data may be sent to the corresponding author and will be reviewed on a case-by-case basis. To maintain confidentiality, no participant data can be shared.

Prior presentation

Part of this work was presented as a poster at the European Society for Medical Oncology (ESMO) Congress, 16–21 September 2021, Virtual Meeting (abstract 203P).

CRediT authorship contribution statement

Gilles Freyer: Conceptualization, Investigation, Supervision, Writing – original draft, Writing – review & editing. **Noelia Martinez-Jañez:** Investigation, Writing – review & editing. **Bożena Kukielka-Budny:** Investigation, Writing – review & editing. **Malgorzata Ulanska:** Investigation, Writing – review & editing. **Hugues Bourgeois:** Investigation, Writing – review & editing. **Montserrat Muñoz:** Investigation, Writing – review & editing. **Serafin Morales:** Investigation, Writing – review & editing. **Juan Bayo Calero:** Investigation, Writing – review & editing. **Laura Cortesi:** Investigation, Writing – review & editing. **Tamás Pintér:** Investigation, Writing – review & editing. **Markéta Palácová:** Investigation, Writing – review & editing. **Nelli Cherciu:** Investigation, Writing – review & editing. **Edgar Petru:** Investigation, Writing – review & editing. **Johannes Ettl:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Cécilia de Almeida:** Project administration, Writing – review & editing. **Gustavo Villanova:** Conceptualization, Supervision, Writing – review & editing. **Romain Raymond:** Formal analysis, Validation, Writing – original draft, Writing – review & editing. **Christine Ta Thanh Minh:** Writing – original draft, Writing – review & editing. **Ana Rodrigues:** Investigation. **Marina E. Cazzaniga:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing.

Declarations of competing interest

GF: scientific coordinator and principal investigator of the study; participated in advisory boards, acted as a speaker, and conducted training sessions on behalf of Pierre Fabre. NM-J: received consultancy fees from AstraZeneca, Daiichi Sankyo, Pfizer, Novartis, Lilly, Pierre Fabre, Roche, and GSK; and travel support from Roche, AstraZeneca, Pfizer, and Novartis. MM: received personal fees from Roche, Novartis, and Eisai; and other financial support from Roche and Lilly. LC: received honoraria from AstraZeneca, MSD, and Pfizer; Novartis, and Gilead. MP: received consultancy fees from AstraZeneca, Novartis, Pfizer, Eli Lilly, and Amgen. EP: received consultancy fees from AstraZeneca, Daiichi Sankyo, Pfizer, Novartis, Lilly, Pierre Fabre, Roche, and GSK; research funding from Daiichi Sankyo, Pfizer, Lilly, Novartis, Seattle Genetics, AstraZeneca, and Roche; and travel support from AstraZeneca, GSK, Pfizer, Lilly, and GSK. JE: received consultancy fees from AstraZeneca, Daiichi Sankyo, Pfizer, Novartis, Lilly, Pierre Fabre, Roche, and Tesaro; research funding from Daiichi Sankyo, Pfizer, Lilly, Novartis, Seattle Genetics, AstraZeneca, Roche, and Odonate; and travel support from AstraZeneca, Daiichi Sankyo, Celgene, Pfizer, Novartis, Lilly, and Tesaro. AR: received honoraria for participating in advisory boards for Boehringer Ingelheim, Bristol Myers Squibb, and MSD; and in internal training events at Pfizer and AstraZeneca. MEC: participated in an advisory board for Eli Lilly and Pierre Fabre. CdA, GV, RR and CTTM: employees of Pierre Fabre. BK-B, MU, HB, SM, JBC, TP, and NC: no conflicts to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2024.103681.

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