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Original article

Randomized phase II study evaluating weekly oral vinorelbine versus weekly paclitaxel in estrogen receptor-positive, HER2-negative patients with advanced breast cancer (NorBreast-231 trial)

Matti Aapro [a, *], Manuel Ruiz-Borrego [b], Roberto Hegg [c], Bozena Kukielka-Budny [d], Serafin Morales [e], Saverio Cinieri [f], Ruffo Freitas-Junior [g], Laura Garcia-Estevez [h], Ewa Szombara [i], Giuliano Santos Borges [j], Rodolfo Passalacqua [k], Helene Hervieu [l], Mélanie Groc [m], Gustavo Villanova [l]

[a] Breast Center, Genolier Cancer Center, Genolier, Switzerland
[b] Hospital Virgen del Rocío, Avenida Manuel Siurot s/n, Seville, 41013, Spain
[c] Perola Byington Reference Center, Av Brig Luis Antonio 733, lj 8/9, São Paulo, Brazil
[d] Centrum Onkologii Ziemi Lubelskiej im. św. Jana z Dukli Oddział Onkologii Klinicznej, ul, Dr K. Jaczewskiego 7, 20-090, Lublin, Poland
[e] Hospital Arnau de Vilanova, Lleida, Calle Lleida 147, Alpicat 25110, Lleida, Spain
[f] Senatore Antonio Perrino Hospital, ASL Brindisi Via Statale 7 (Via Appia), 72100 Brindisi, Italy
[g] Breast and Gynecology Unit, Araujo Jorge Hospital, Goias Anticancer Association, Rua 239, 206 Setor Universitario, 74175-120, Goiania, Brazil
[h] Centro Integral Oncologico Clara Campal, C/Oña 10, 28050, Madrid, Spain
[i] Marie Curie Oncology Center, ul. Roentgena 5, 02-781, Warsaw, Poland
[j] Centro de Novos Tratamentos Itajaí - Clínica de Neoplasias Litoral Aderbal Ramos da Silva, 148, Centro, Itajaí/SC/Brasil, CEP, 88301-220, Brazil
[k] Istituti Hospitalieri di Cremona, Viale Concordia 1, 26100, Cremona, Italy
[l] Pierre Fabre Médicament, 45 Place Abel Gance, 92654, Boulogne-Billancourt, France
[m] Pierre Fabre Laboratories, Langalde, 3 avenue Hubert Curien, BP13562, 31035, Toulouse, CEDEX, France

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ABSTRACT

Background: Single-agent paclitaxel and vinorelbine are recommended treatments for advanced breast cancer (ABC) non-responsive to hormone therapy and without visceral crisis. This phase II trial compared first-line oral vinorelbine versus weekly paclitaxel for ABC.

Methods: Eligible female patients had measurable locally recurrent/metastatic estrogen receptor-positive HER2-negative breast cancer and had received prior endocrine therapy (any setting) but no chemotherapy for ABC. Patients were stratified by prior taxane and visceral metastases and randomized to either oral vinorelbine 80 mg/m^2 (first cycle at 60 mg/m^2, escalated to 80 mg/m^2 in the absence of grade 3/4 toxicity) or intravenous paclitaxel 80 mg/m^2 on days 1, 8, and 15 every 3 weeks until disease progression or unacceptable toxicity. The primary endpoint was disease control rate (DCR; confirmed complete or partial response, or stable disease for $\geq$6 weeks).

Results: The 131 randomized patients had received a median of 2 prior endocrine therapies; >70% had prior (neo)adjuvant chemotherapy and 79% visceral metastases. DCR was 75.8% (95% confidence interval: 63.6–85.5%) with vinorelbine and 75.4% (63.1–85.2%) with paclitaxel. The most common grade 3/4 adverse events were neutropenia (52%), fatigue (11%), and vomiting (5%) with vinorelbine, and neutropenia (17%), dyspnea (6%), hypertension (6%), and peripheral sensory neuropathy (5%) with paclitaxel. Grade 2 alopecia occurred in 2% of vinorelbine-treated and 34% of paclitaxel-treated patients. Neither arm showed relevant global health status changes.

Conclusion: Oral vinorelbine and paclitaxel demonstrated similar DCRs (~75%). Safety profiles differed and, together with administration route and convenience, may influence treatment choice (EudraCT number, 2012-003530-16).

* Corresponding author. Genolier Cancer Centre, Clinique de Genolier, Case Postale 100, Route du Muids 3, 1272, Genolier, Switzerland.
E-mail addresses: maapro@genolier.net (M. Aapro), ruizsabater@gmail.com (M. Ruiz-Borrego), robertohegg@gmail.com (R. Hegg), bozena-budny@wp.pl (B. Kukielka-Budny), serafinmorales01@gmail.com (S. Morales), saverio.cinieri@ieo.it (S. Cinieri), ruffojr@terra.com.br (R. Freitas-Junior), lgestevez@mdanderson.es (L. Garcia-Estevez), eszombara@coi.waw.pl (E. Szombara), giuliano_borges@yahoo.com.br (G.S. Borges), r.passalacqua@asst-cremona.it (R. Passalacqua), helene.hervieu@pierre-fabre.com (H. Hervieu), melanie.groc@pierre-fabre.com (M. Groc), gustavo.villanova@pierre-fabre.com (G. Villanova).

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1. Background

For patients with advanced breast cancer (ABC) and no real prospect of cure, an important goal of treatment is to maintain the best possible quality of life (QoL). Treatment convenience and compliance are also important considerations [1,2].

Today, initial treatment for hormone receptor-positive disease usually involves endocrine therapy with or without cyclin-dependent kinase (CDK) 4/6 inhibitors [3]. In patients who do not respond to these agents or whose disease progresses on such treatments, current guidelines typically favor sequential monotherapy over combination chemotherapy [4]. In patients with taxane-naïve disease, taxane monotherapy is often considered the treatment of choice. However, vinorelbine is an effective alternative, particularly if avoidance of alopecia is a priority for the patient [4]. In patients who have received taxane therapy in the (neo) adjuvant setting, preferred first-line single-agent options are capecitabine, vinorelbine, and eribulin. Taxane re-exposure is generally acceptable if disease-free survival exceeds 1 year.

The activity and favorable tolerability profiles of paclitaxel and vinorelbine are well documented in the literature [5–8]. However, to the best of our knowledge, the effects of oral vinorelbine and weekly paclitaxel have never been evaluated in a head-to-head trial. Here we report an international open-label randomized phase II trial (EudraCT number 2012-003530-16) comparing these 2 treatment options in the first-line setting.

2. Patients and methods

2.1. Patient population

Eligible patients were women who had histologically confirmed adenocarcinoma of the breast, with documented locally recurrent or metastatic disease that was measurable according to Response Evaluation Criteria for Solid Tumors (RECIST) version 1.1 and not amenable to curative surgery or radiotherapy. Disease had to be estrogen receptor positive ($\geq$10% positive stained cells by immunohistochemistry [IHC] on the primary or metastatic tumor sample) and HER2 negative (IHC 0/1, or IHC 2 + and negative in situ hybridization assessment of a primary or metastatic tumor sample). There were no requirements for progesterone receptor status. Patients were required to have received at least 1 previous endocrine therapy for breast cancer in any setting. Prior chemotherapy for advanced disease was not permitted, but prior (neo)adjuvant chemotherapy was allowed if completed $\geq$6 months before disease recurrence. Concomitant endocrine therapy for ABC was not permitted.

Additional inclusion criteria included age $\geq$18 years; Karnofsky performance score $\geq$70%; life expectancy $\geq$16 weeks; adequate bone marrow, hepatic, and renal function; and written informed consent before completing any study-related procedure.

Patients with symptoms suggesting central nervous system involvement or leptomeningeal metastases were ineligible, as were patients with malabsorption syndrome, disease significantly affecting gastrointestinal function, major resection of the stomach or proximal small bowel that could affect absorption of oral vinorelbine, dysphagia, or inability to swallow tablets. Patients with ongoing grade $\geq$2 peripheral neuropathy were also excluded.

2.2. Treatment

Eligible patients were stratified using the Pocock minimization procedure based on the following stratification factors: center; prior taxane (yes/no); and presence of visceral metastases (any of the following sites: liver, lung, pleura, heart peritoneum, spleen, suprarenal glands; yes/no). Patients were randomized in a 1:1 ratio to either vinorelbine or paclitaxel.

Patients randomized to Arm A received oral vinorelbine at a dose of 60 mg/m^2 on days 1, 8, and 15 of cycle 1. In the absence of grade 3/4 toxicity, the dose was escalated to 80 mg/m^2 from cycle 2 onward. Patients randomized to Arm B received paclitaxel 80 mg/m^2 as a 1-h intravenous infusion on days 1, 8, and 15. In both arms, treatment cycles were repeated every 3 weeks until documented disease progression, unacceptable toxicity, or patient refusal.

2.3. Study assessments

All lesions were assessed at baseline and every 6 weeks thereafter according to RECIST version 1.1, until disease progression. Adverse events were recorded at every cycle and graded using the National Cancer Institute Common Terminology Criteria version 2.0. Complete blood cell counts were performed every week. Serum chemistry was assessed at baseline and then on day 1 of each cycle. QoL was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire core module (QLQ-C30), completed at baseline (before randomization) and then before each even-numbered cycle (ie cycles 2, 4, 6, 8, etc.) until the end of study therapy.

Patients were followed for safety until 30 days after the last study treatment administration. After disease progression, information on performance, disease, and survival status and further therapy was collected every 3 months until death, withdrawal of consent, or study closure, whichever occurred first. End of study was defined as the date when at least 80% of the randomized patients had documented disease progression.

2.4. Statistical analysis

The primary objective of the trial was to evaluate the disease control rate (DCR) of weekly oral vinorelbine and weekly paclitaxel in patients with estrogen receptor-positive HER2-negative ABC. DCR was defined as the sum of patients with confirmed complete response, confirmed partial response, or stable disease maintained for $\geq$6 weeks ($\pm$7 days), reported with corresponding 95% confidence intervals (CIs).

The one-sample multiple testing procedure for phase II clinical trials described by Fleming was used [9]. The null hypothesis (H0) was for a true DCR $\leq$50%; the alternative hypothesis H1 was for a DCR $\geq$70%. Based on these assumptions and one-sided testing with an alpha level $\leq$0.05 and a beta level $\leq$0.1, it was calculated that 56 evaluable patients were to be enrolled in each arm of this randomized phase II trial. Assuming a 10% dropout rate, it was planned to enroll 124 patients. Secondary endpoints were duration of disease control, overall response rate (ORR), duration of response, duration of stable disease, progression-free survival (PFS), time to treatment failure, overall survival (OS), safety, and QoL. Duration of disease control was calculated from the date of randomization until documented disease progression or death from any cause in patients with a complete or partial response or stable disease. Patients who received any new anti-cancer therapy before disease progression were censored at the start of this new therapy. Time-related endpoints were estimated using the Kaplan–Meier method; medians were reported with 95% CIs. All reported analyses are based on the intention-to-treat (ITT) population unless otherwise specified. Subgroup analyses of response according to stratification factors (except center) were performed.

3. Results

A total of 131 patients were enrolled from 26 centers in 6

countries (France, Italy, Spain, Argentina, Brazil, and Poland) between February 2013 and April 2015. Of these, 66 were randomized to receive oral vinorelbine and 65 to weekly paclitaxel (Fig. 1). All 131 patients received at least 1 dose of study therapy and were therefore included in both the ITT and the safety populations. Baseline characteristics were well balanced between the treatment arms in this population of patients with relatively slowly progressing disease (Table 1).

Data cutoff for this final analysis was December 18, 2017. The median duration of follow-up was 25.7 months (range 0.4–52.6 months) in the oral vinorelbine arm and 22.3 months (range 0.4–55.2 months) in the paclitaxel arm. All but 2 patients had discontinued treatment at the time of data cutoff. The 2 patients still on treatment were both in the oral vinorelbine arm and had received 46 and 55 cycles, respectively. The most common reason for treatment discontinuation was disease progression (81% of the oral vinorelbine arm versus 54% of the paclitaxel arm), followed by adverse events (6% versus 22%, respectively). Overall, 38% of oral vinorelbine-treated and 14% of paclitaxel-treated patients had at least 1 dose reduction. Most oral vinorelbine dose reductions were due to neutropenia. In the oral vinorelbine arm, the dose was escalated to 80 mg/m^2 at cycle 2 in 75% of patients. Treatment was delayed at least once in 64% of oral vinorelbine-treated and 55% of paclitaxel-treated patients. Most delays in both arms lasted for $\leq$7 days. The proportion of patients missing at least 1 dose was identical in the 2 arms (71%); the reason for most dose omissions was hematologic toxicity.

The median duration of treatment was 4.4 months (range 0.7–38.2 months) in the oral vinorelbine arm versus 5.0 months (range 0.7–32.7 months) in the paclitaxel arm. This represents a median of 6 cycles (range 1–55) for oral vinorelbine and 7 cycles (range 1–44) for paclitaxel. Similar proportions of patients received at least 6 cycles (56% for oral vinorelbine versus 60% for paclitaxel) and at least 12 cycles (20% in both arms). More patients in the oral vinorelbine arm than the paclitaxel arm continued to 18 cycles and beyond (12% versus 3%, respectively).

The DCR in the ITT population was 75.8% (2-sided 95% CI: 63.6–85.5%) in the oral vinorelbine arm and 75.4% (2-sided 95% CI: 63.1–85.2%) in the paclitaxel arm. These included confirmed ORRs of 19.7% (95% CI: 10.9–31.3%) with oral vinorelbine and 40.0% (95% CI: 28.0–52.9%) with paclitaxel. In a supportive analysis of the 119 patients evaluable for response (60 in the oral vinorelbine arm, 59 in the paclitaxel arm), the DCRs were 80.0% (2-sided 95% CI: 67.7–89.2%) in the oral vinorelbine arm and 79.7% (2-sided 95% CI: 67.2–89.0%) in the paclitaxel arm. Exploratory subgroup analyses according to the stratification factors 'prior taxane' and 'presence of visceral metastases' suggested a more favorable DCR with vinorelbine in taxane-pretreated patients and patients with no visceral metastases, and a more favorable DCR with paclitaxel in patients who were taxane naïve (Table 2).

In responding patients, the median time to first response was 2.8 months (95% CI: 1.4–4.2 months) in the oral vinorelbine arm and 2.3 months (95% CI: 1.5–2.9 months) in the paclitaxel arm. In patients with disease control, the median duration of disease control was 5.8 months (95% CI: 5.0–8.7 months) in the oral vinorelbine arm (n = 50) versus 8.7 months (95% CI: 7.0–10.0 months) in the weekly paclitaxel arm (n = 49). Median duration of response was 4.8 months (95% CI: 4.2–not evaluable) (n = 13) with oral vinorelbine versus 6.2 months (95% CI: 4.2–8.8 months) (n = 26) with paclitaxel. The median duration of stable disease (including patients with stable disease for <6 weeks) was 5.5 months (95% CI: 4.4–6.8 months) versus 7.0 months (95% CI: 3.4–8.7 months) in vinorelbine- and paclitaxel-treated patients, respectively.

At the time of data cutoff, disease progression or death had been recorded in 124 patients (62 oral vinorelbine-treated patients [94%] and 62 paclitaxel-treated patients [95%]). Median PFS was 5.5 months (95% CI: 4.3–6.8) with vinorelbine versus 6.4 months (95% CI: 5.1–8.3) with paclitaxel (Fig. 2A). One-year PFS rates estimated by Kaplan–Meier methodology were 17.3% versus 22.9% in vinorelbine- and paclitaxel-treated patients, respectively. Time to treatment failure was 4.2 months (95% CI: 3.3–5.1) in the oral vinorelbine arm and 4.6 months (95% CI: 2.7–5.5) in the paclitaxel arm (Fig. 2B).

At the data cutoff, 48 patients (73%) in the oral vinorelbine arm and 48 (74%) in the paclitaxel arm had died. The most common cause of death was disease progression (45 of 48 patients [94%] in the oral vinorelbine arm versus 37 of 48 patients [77%] in the paclitaxel arm). Five patients in the paclitaxel arm died from a non-related adverse event (1 case each of: diarrhea, pulmonary embolism, non-neutropenic infection, gastrorrhagia/circulatory insufficiency, and stroke). Of the remaining patients, the cause of death was contusion capitis in 1 vinorelbine-treated patient and multiple organ failure, heart failure, and pulmonitis with cardiac insufficiency each in 1 paclitaxel-treated patient. Cause of death was unknown in 2 patients in the oral vinorelbine arm and 3 patients in the paclitaxel arm. Median OS was 27.6 months (95% CI: 20.2–34.5 months) in the oral vinorelbine arm and 22.3 months (95% CI: 13.5–27.6 months) in the paclitaxel arm (Fig. 2C); 1-year OS rates by Kaplan–Meier methodology were 78% versus 68%, respectively.

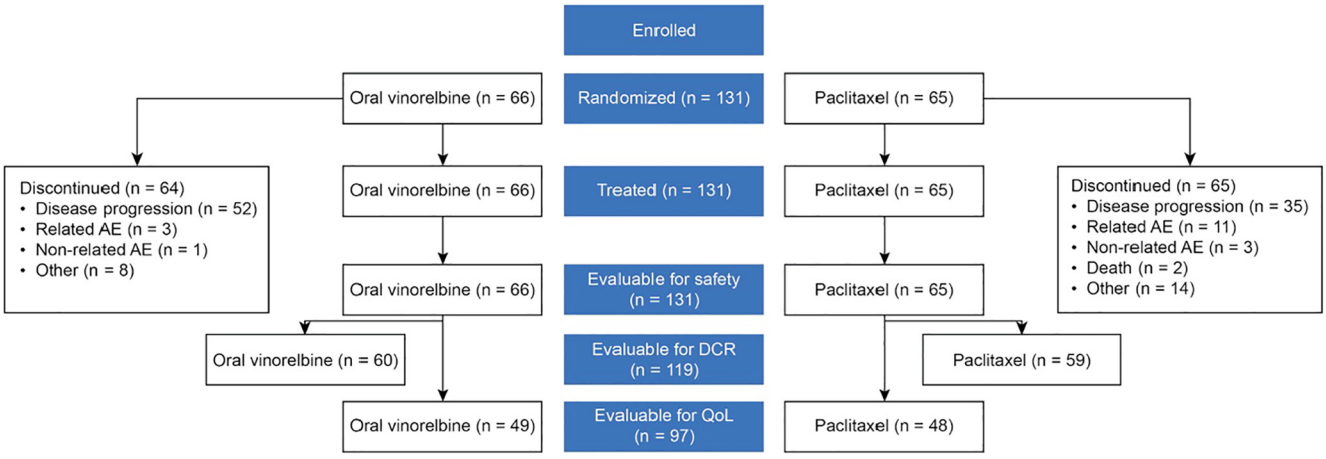

Fig. 1. CONSORT flow diagram. AE, adverse event; DCR, disease control rate; QoL, quality of life.

Table 1
Patient characteristics and prior treatment history.

Characteristic		Oral vinorelbine (n = 66)	Paclitaxel (n = 65)
Age, years	Median (range)	58 (35–79)	61 (40–86)
	<65, n (%)	42 (64)	40 (62)
	≥65, n (%)	24 (36)	25 (39)
Karnofsky performance status	Median	100	90
	70, n (%)	1 (2)	9 (14)
	80, n (%)	9 (14)	16 (25)
	90, n (%)	16 (24)	12 (18)
	100, n (%)	40 (61)	28 (43)
Prior hormone therapy	Median no. of regimens (range)	2 (0–6)	2 (1–6)
	Neoadjuvant, n (%)	2 (3)	3 (5)
	Adjuvant, n (%)	53 (80)	53 (82)
	Advanced, n (%)	36 (55)	34 (52)
Prior everolimus	n (%)	2 (3)	3 (5)
Prior (neo)adjuvant chemotherapy, n (%)	Any	49 (74)[a]	47 (72)
	Anthracycline	44 (67)	40 (62)
	Taxane	27 (41)	27 (42)
	Anthracycline and taxane	27 (41)	24 (37)
Time from last hormone therapy to study therapy, months	Median (range)	1 (0–63)	1 (0–172)
Time from diagnosis of breast cancer to study entry, months	Median (range)	59 (3–269)	55 (13–296)
Visceral involvement, n (%)		52 (79)	51 (78)
	Liver metastases	30 (45)	30 (46)
	Lung metastases	30 (45)	31 (48)
Bone metastases, n (%)		42 (64)	44 (68)
No. of metastatic sites, n (%)	0	1 (2)	2 (3)
	1	16 (24)	10 (15)
	2	21 (32)	22 (34)
	≥3	28 (42)	31 (48)

[a] Includes 1 patient treated with chemotherapy for advanced disease (protocol violation).

Table 2
Objective response and disease control rates according to stratification factors.

Subgroup	Endpoint	Response n (%)	
		Oral vinorelbine	Paclitaxel
Prior taxane		(n = 25)	(n = 24)[a]
	Confirmed response	3 (12)	9 (38)
	Disease control	21 (84)	16 (67)
No prior taxane		(n = 41)[b]	(n = 41)[c]
	Confirmed response	10 (24)	17 (42)
	Disease control	29 (71)	33 (80)
Visceral metastases		(n = 52)[b]	(n = 51)[b]
	Confirmed response	7 (13)	22 (43)[b]
	Disease control	36 (69)	38 (75)
No visceral metastases		(n = 14)	(n = 14)[b]
	Confirmed response	6 (43)	4 (29)
	Disease control	14 (100)	11 (79)

[a] Missing in 1 patient.
[b] Missing in 2 patients.
[c] Missing in 3 patients.

During follow-up, 31 patients (47%) in the oral vinorelbine arm and 27 (42%) in the paclitaxel arm received further chemotherapy.

Safety results are summarized in Table 3 and Fig. 3. Incidences of adverse events overall and by grade were similar in the 2 treatment arms, but there were qualitative differences in the safety profiles. In the oral vinorelbine arm, the most common adverse events (all grades) were neutropenia (85%), anemia (82%), nausea (59%), vomiting (50%), and fatigue (45%), and the most common grade 3/4 adverse events were neutropenia (52%) and fatigue (11%). In the paclitaxel arm, the most common adverse events (all grades) were anemia (86%), neutropenia (63%), fatigue (49%), and alopecia (45%). The most common grade 3/4 adverse event in the paclitaxel arm was neutropenia (17%). Nausea and vomiting were more common with oral vinorelbine, whereas peripheral sensory neuropathy, dyspnea, paresthesia, and alopecia were more common with paclitaxel. There were no treatment-related deaths in either arm. Grade 3/4 serious adverse events were reported in 13 patients (20%) in the vinorelbine arm and 17 patients (26%) in the paclitaxel arm, although only a minority were considered by the investigators to be treatment related (details in Table 3).

QoL questionnaires were completed at baseline and at least 1 subsequent timepoint in 97 patients (49 of 66 [74%] in the vinorelbine arm and 48 of 65 [74%] in the paclitaxel arm). There was similar attrition over time in both treatment arms. Global health status improved over time after an initial decline in the oral vinorelbine arm; it improved until cycle 5 before deteriorating over time in the paclitaxel arm. However, mean change from baseline showed no clinically meaningful differences from baseline (>10-point change) in either arm. Physical function scores showed some fluctuation over time in the oral vinorelbine arm, with clinically relevant deterioration at cycles 3 (mean change −11.5) and 9 (mean change −11.8), which subsequently recovered. Role functioning also showed an early deterioration in the oral vinorelbine arm (mean −10.2 at cycle 1; −13.6 at cycle 3; −11.5 at cycle 9) but recovered in subsequent cycles.

4. Discussion

In the NorBreast-231 trial, oral vinorelbine and weekly paclitaxel showed similar activity when given as first-line chemotherapy in patients with endocrine-pretreated estrogen receptor-positive HER2-negative ABC. The DCR was approximately 75% in both treatment arms. Patients in the paclitaxel arm had an ORR

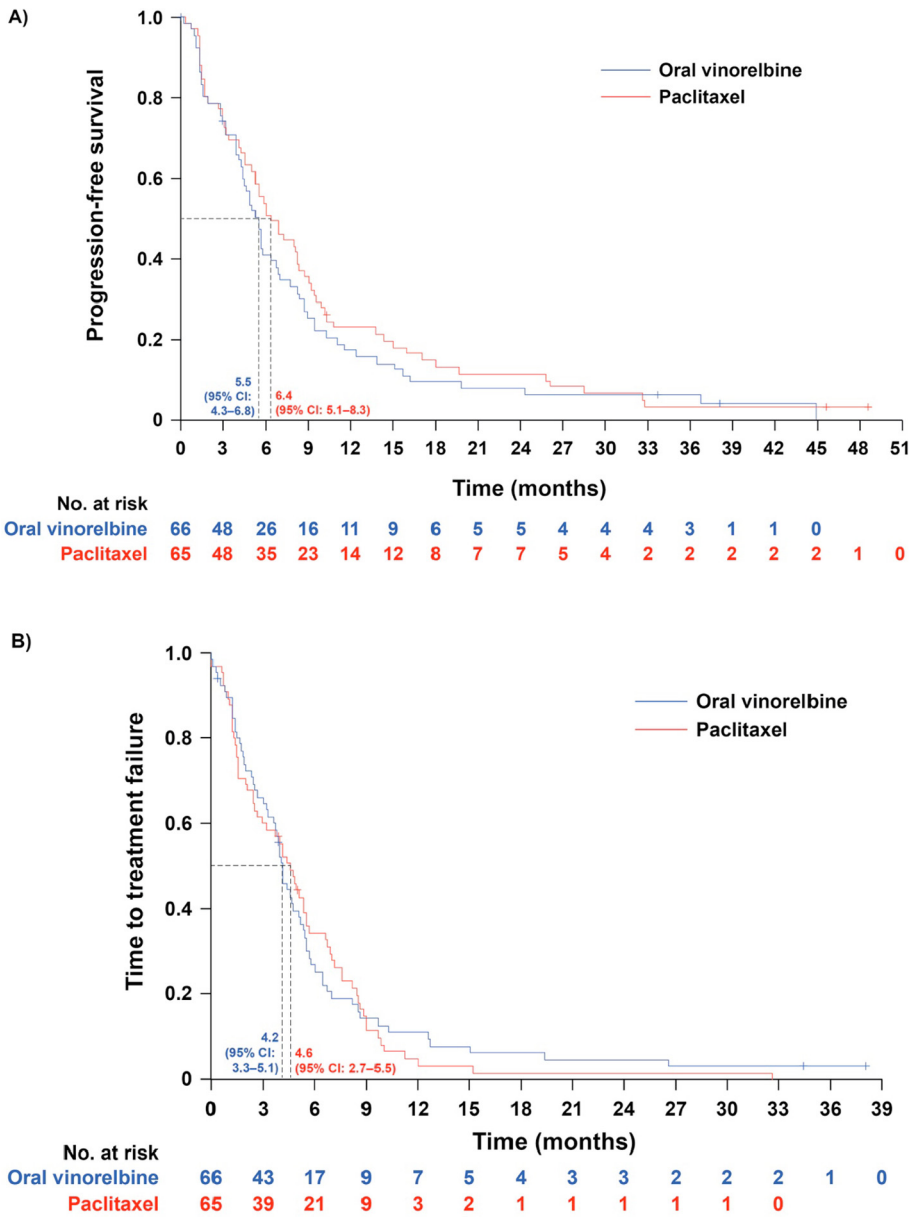

Fig. 2. (A) Progression-free survival (ITT population); (B) Time to treatment failure (ITT population); (C) Overall survival (ITT population). ITT, intention-to-treat.

twice as high as those in the oral vinorelbine arm. This finding is consistent with a published meta-analysis showing superior ORR with a taxane versus vinorelbine [10]. However, the improvement in ORR did not translate into better PFS, time to treatment failure, or OS.

The efficacy of vinorelbine in this study was consistent with published single-arm studies in a similar setting [11], slightly more favorable than in an early study in an unselected first-line population [12], and lower than in a recent study in patients with non-visceral disease [13], as expected given the typical prognosis in this population. Consistent with previous experience with these 2 regimens [1,5], the safety profiles differed between treatment arms. Oral vinorelbine was associated with more nausea/vomiting, neutropenia, and rare cases of febrile neutropenia, whereas weekly paclitaxel was associated with more peripheral neuropathy, paresthesia, and alopecia. Global health status appeared to improve over time in the vinorelbine arm, whereas a modest decrease was observed in the paclitaxel arm. This may reflect the less frequent cumulative toxicities with oral vinorelbine, as well as the more convenient oral administration route. However, interpretation of QoL results is limited by the small numbers of patients with evaluable questionnaires, particularly in later cycles. For example, the incidence of grade 3/4 dyspnea with paclitaxel was not reflected in QoL scores, perhaps because of attrition (patients with symptoms may have stopped treatment and/or QoL questionnaire completion), or because the sample sizes were too small to detect meaningful changes or differences, or because physicians and patients perceive and report side effects differently.

A limitation of the trial is the relatively small sample size and the resulting lack of power to demonstrate non-inferiority.

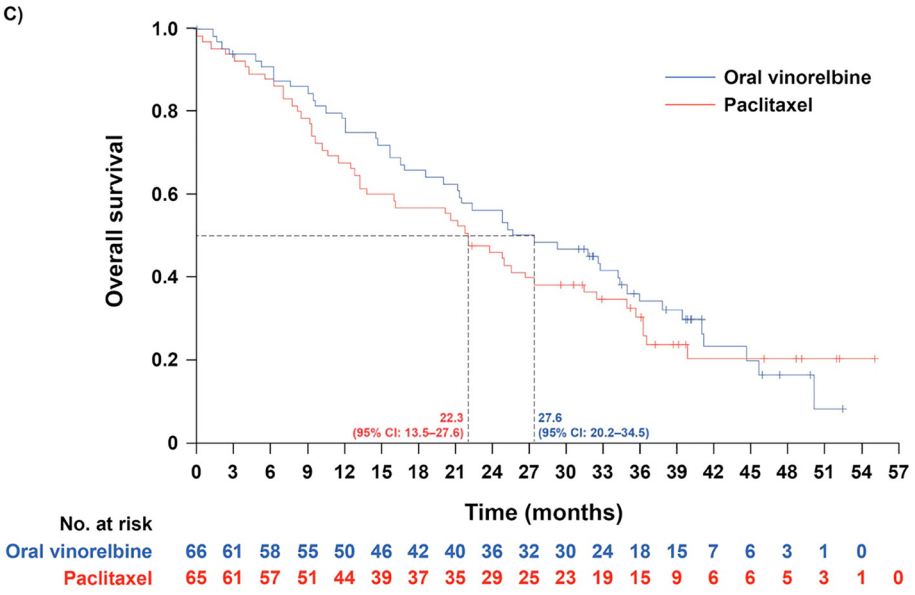

Fig. 2. (*continued*).

However, the results provide some reassurance that selection of oral vinorelbine as the first line of chemotherapy after failure of endocrine therapy is a reasonable option to be discussed with patients. Physician and patient preference may play an important role when considering differences in tolerability and administration route. Provided efficacy and tolerability are not compromised, oral chemotherapy can be attractive to patients because of the associated benefits in convenience, and avoidance of clinic visits and impact on daily activities [14]. The high DCR and favorable safety profile of vinorelbine (particularly the lack of alopecia) in this study are of interest in the context of guideline recommendations for single-agent chemotherapy in preference to combination regimens in most cases [4]. Although combination chemotherapy regimens offer higher response rates, other efficacy endpoints as well as safety are important considerations when selecting the most appropriate treatment.

Solvent-based paclitaxel is widely used in many countries and was considered a reasonable comparator in NorBreast-231. However, some clinicians may prefer nab-paclitaxel if available. Nab-paclitaxel showed a more favorable efficacy and safety profile compared with solvent-based taxane only when administered as a 3-weekly schedule [15,16]. In the randomized phase III CALGB 40502/NCCTG N063H (Alliance) trial, nab-paclitaxel showed a trend towards inferior efficacy compared with weekly solvent-based paclitaxel, and the nab-paclitaxel arm was closed for futility [17].

An important change in the management of hormone receptor-positive breast cancer in recent years has been the introduction of CDK 4/6 inhibitors. Three agents in this class (palbociclib, ribociclib, and abemaciclib) have demonstrated significant improvements in PFS when added to an aromatase inhibitor in patients naïve or pre-exposed to endocrine therapy [18–20], and CDK 4/6 inhibitors are now a treatment option in this setting.

Oral vinorelbine is currently attracting research interest as metronomic therapy [21]. The European Society for Medical Oncology International Consensus Guidelines for Advanced Breast

Table 3
Overview of safety.

No. of patients (%)	Oral vinorelbine (n = 66)	Paclitaxel (n = 65)
Patients with ≥1 AE	65 (98)	65 (100)
1 AE	10 (15)	1 (2)
2 AEs	6 (9)	3 (5)
≥3 AEs	49 (74)	61 (94)
Any grade AE	65 (98)[a]	65 (100)
Grade 1	7 (11)	4 (6)
Grade 2	34 (52)	36 (55)
Grade 3	20 (30)	20 (31)
Grade 4	3 (5)	5 (8)
Patients with at least 1 serious AE[b]	15 (23)	21 (32)

AE, adverse event.
[a] Grade not known for one AE.
[b] Grade 3/4 serious AEs were reported in 13 patients (20%) in the vinorelbine arm, comprising 1 case each of: disease progression; pulmonary embolism; and **granulocytopenia** (each grade 4); disease progression; rectal cancer; pneumonia; erysipelas; **vomiting; abdominal pain** and **constipation** (in the same patient); cough; femur fracture; **neutropenia;** fatigue and vertigo (in the same patient) (each grade 3). Grade 3/4 serious AEs were reported in 17 patients (26%) in the paclitaxel arm, comprising: 2 cases each of grade 3 pneumonia (with grade 3 dyspnea in 1 patient); grade 3 asthenia; and grade 3 femur fracture; and 1 case each of: colon cancer; **neutropenia;** pathological fracture (each grade 4); grade 4 dyspnea and grade 3 lung infiltration (in the same patient); erysipelas; **bronchopneumonia** and rhabdomyolysis (in the same patient); upper abdominal pain; ascites; gastric hemorrhage and cardiovascular insufficiency and pulmonary embolism (all in the same patient); activated partial thromboplastin time prolonged; and lymphedema (each grade 3). Only those shown in **bold** were considered related to treatment (4 patients [6%] in the vinorelbine arm and 3 patients [5%] in the paclitaxel arm).

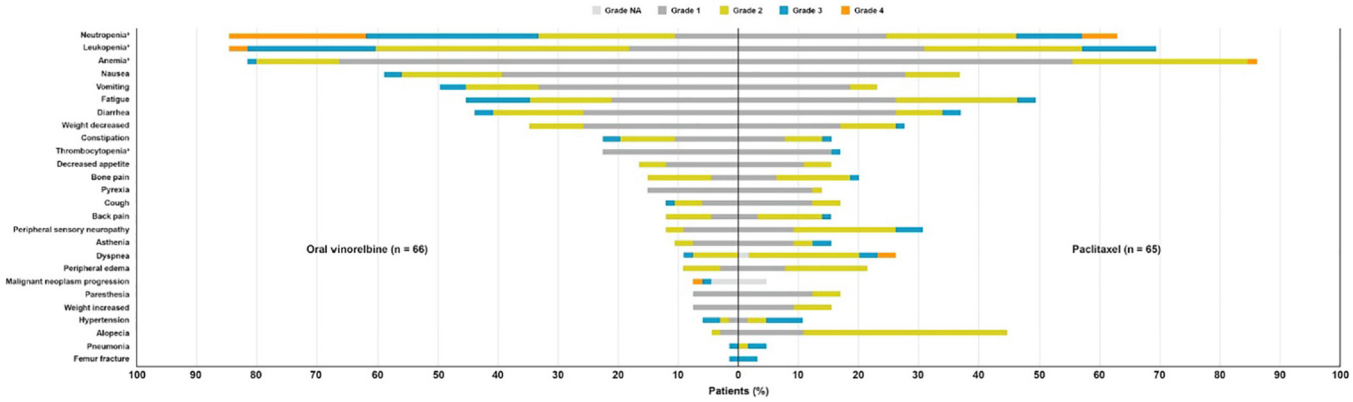

Fig. 3. Most common adverse events by treatment arm (any grade in >15%; grade 3/4 in >2%). [a]Recorded as laboratory events. NA, not available.

Cancer (ABC4) specifically mention that metronomic chemotherapy is a reasonable treatment option for patients not requiring rapid tumor response, although randomized trials are required to accurately compare metronomic chemotherapy regimens with standard dosing regimens [4]. Several ongoing trials are evaluating metronomic schedules of vinorelbine. The randomized phase II TEMPO-BREAST trial (EudraCT number: 2012-003530-16), which has similar inclusion criteria to NorBreast-231, is evaluating a weekly versus a metronomic schedule in patients with ABC. The randomized phase II METEORA-II trial (NCT02954055) is comparing weekly paclitaxel versus metronomic VEX (daily oral cyclophosphamide 50 mg plus low-dose oral capecitabine plus oral vinorelbine 40 mg on days 1, 3, and 5 each week) in patients with estrogen receptor-positive, HER2-negative metastatic or locally relapsed breast cancer. In view of initial results from a single-arm study evaluating the all-oral metronomic VEX regimen [22], one may argue that a direct comparison of VEX and CDK 4/6 inhibitors should be considered if the METEORA-II trial confirms the activity of VEX.

Notwithstanding evolution in the treatment algorithm, results from NorBreast-231 suggest that physicians can offer some flexibility in treatment choice for patients requiring chemotherapy after progression on endocrine therapy. Considerations such as cost, tolerability, and administration schedule may be increasingly important to payers and patients given the present results, which indicate similar DCR and PFS results between the 2 arms.

Ethical standards

The trial was performed in accordance with the principles stated in the Declaration of Helsinki and subsequent amendments and in accordance with the Good Clinical Practice Guideline (CPMP/ICH/135/95). All documents required by national regulations and any other informative documents requested were submitted to an Ethics Committee for review and approval.

Conflicts of interest

M. Aapro is a consultant to Pierre Fabre Médicament and has also received honoraria for presentations at meetings. M. Ruiz Borrego has participated in advisory boards for Pierre Fabre, Roche, Pfizer, Amgen, Celgene, and Lilly, and has been a speaker for Pierre Fabre, Roche, Pfizer, Novartis, and Celgene. R. Passalacqua has received honoraria and payment for expert testimony from Ipsen, Pfizer, Sanofi, Bristol-Myers Squibb, and Janssen, and has received research grants from Amgen, Roche, and Pierre Fabre. H. Hervieu, M. Groc, and G. Villanova are employees of Pierre Fabre Médicament, France. R. Hegg, B. Kukielka-Budny, S. Morales, S. Cinieri, R. Freitas-Junior, L. Garcia-Estevez, E. Szombara, and G. Santos Borges declare no conflict of interest.

Role of the funding source

This trial was sponsored by Pierre Fabre Médicament, France. The sponsor was involved in the design of the trial. Representatives of the sponsor are among the authors and thus were involved in review and finalization of the manuscript. The first author was responsible for the final decision to submit the manuscript for publication.

Data sharing statement

Currently no mechanism is in place to allow sharing of individual deidentified participant data. Requests sent to gustavo.villanova@pierre-fabre.com at Pierre Fabre Médicament, 45 Place Abel Gance, 92654 Boulogne-Billancourt, France, will be considered on a case-by-case basis.

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References

[1] Aapro MS, Conte P, Esteban González E, Trillet-Lenoir V. Oral vinorelbine: role in the management of metastatic breast cancer. Drugs 2007;67:657–67. https://doi.org/10.2165/00003495-200767050-00002.

[2] Barni S, Mouysset JL, Sediva M, Zamagni C, Garau I. Brio: a European prospective observational study to assess the burden of disease and treatment in metastatic breast cancer (Mbc) patients treated with oral vinorelbine

(Nvboral) or intravenous vinorelbine (Ivvino). Value Health 2014;17(7):A647. https://doi.org/10.1016/j.jval.2014.08.2345.
[3] Abraham J, Coleman R, Elias A, Holmes FA, Kalinsky K, Kittaneh M, et al. Breast Cancer Therapy Expert Group (BCTEG). Use of cyclin-dependent kinase (CDK) 4/6 inhibitors for hormone receptor-positive, human epidermal growth factor receptor 2-negative, metastatic breast cancer: a roundtable discussion by the Breast Cancer Therapy Expert Group (BCTEG). Breast Cancer Res Treat 2018;171:11–20. https://doi.org/10.1007/s10549-018-4783-1.
[4] Cardoso F, Senkus E, Costa A, Papadopoulos E, Aapro M, André F, et al. 4th ESO–ESMO international consensus guidelines for advanced breast cancer (ABC 4). Ann Oncol 2018;29:1634–57. https://doi.org/10.1093/annonc/mdy192.
[5] Ghersi D, Willson ML, Chan MM, Simes J, Donoghue E, Wilcken N. Taxane-containing regimens for metastatic breast cancer. Cochrane Database Syst Rev 2015;6:CD003366. https://doi.org/10.1002/14651858.CD003366.pub3.
[6] Seidman AD, Berry D, Cirrincione C, Harris L, Muss H, Marcom PK, et al. Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B Protocol 9840 2008. J Clin Oncol 2008;26:1642–9. https://doi.org/10.1200/JCO.2007.11.6699.
[7] Galano G, Caputo M, Tecce MF, Capasso A. Efficacy and tolerability of vinorelbine in the cancer therapy. Curr Drug Saf 2011;6:185–93. https://doi.org/10.2174/157488611797579302.
[8] Aapro M, Finek J. Oral vinorelbine in metastatic breast cancer: a review of current clinical trial results. Cancer Treat Rev 2012;38:120–6. https://doi.org/10.1016/j.ctrv.2011.05.005.
[9] Fleming TR. One-sample multiple testing procedure for phase II clinical trials. Biometrics 1982;38(1):143–51.
[10] Xu YC, Wang HX, Tang L, Ma Y, Zhang FC. A systematic review of vinorelbine for the treatment of breast cancer. Breast J 2013;19:180–8. https://doi.org/10.1111/tbj.12071.
[11] Mansour M, Mourad C. Phase II study of single agent oral vinorelbine as first-line treatment in patients with HER-2 negative metastatic breast cancer. Cancer Chemother Pharmacol 2013;72:429–35. https://doi.org/10.1007/s00280-013-2216-8.
[12] Freyer G, Delozier T, Lichinister M, Gedouin D, Bougnoux P, His P, et al. Phase II study of oral vinorelbine in first-line advanced breast cancer chemotherapy. J Clin Oncol 2003;21:35–40. https://doi.org/10.1200/jco.2003.09.057.
[13] Steger GG, Dominguez A, Dobrovolskaya N, Giotta F, Tubiana-Mathieu N, Pecherstorfer M, et al. Single-agent oral vinorelbine as first-line chemotherapy for endocrine-pretreated breast cancer with bone metastases and no visceral involvement: NORBREAST-228 phase II study. Clin Breast Cancer 2018;18:e41–7. https://doi.org/10.1016/j.clbc.2017.05.012.
[14] Findlay M, von Minckwitz G, Wardley A. Effective oral chemotherapy for breast cancer: *pill*ars of strength. Ann Oncol 2008;19:212–22. https://doi.org/10.1093/annonc/mdm285.
[15] Aapro M, Tjulandin S, Bhar P, Gradishar W. Weekly nab-paclitaxel is safe and effective in ≥65 years old patients with metastatic breast cancer: a post-hoc analysis. Breast 2011;20(5):468–74. https://doi.org/10.1016/j.breast.2011.07.005.
[16] Gradishar WJ, Tjulandin S, Davidson N, Shaw H, Desai N, Bhar P, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol 2005 1;23:7794–803. https://doi.org/10.1200/JCO.2005.04.937.
[17] Rugo HS, Barry WT, Moreno-Aspitia A, Lyss AP, Cirrincione C, Leung E, et al. Randomized phase III trial of paclitaxel once per week compared with nanoparticle albumin-bound nab-paclitaxel once per week or ixabepilone with bevacizumab as first-line chemotherapy for locally recurrent or metastatic breast cancer: CALGB 40502/NCCTG N063H (Alliance). J Clin Oncol 2015;33:2361–9. https://doi.org/10.1200/JCO.2014.59.5298.
[18] Turner NC, Ro J, André F, Loi S, Verma S, Iwata H, et al. PALOMA3 Study Group. Palbociclib in hormone-receptor-positive advanced breast cancer. N Engl J Med 2015;373:209–19. https://doi.org/10.1056/NEJMoa1505270.
[19] Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im SA, et al. Phase III randomized study of ribociclib and fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: MONALEESA-3. J Clin Oncol 2018;36:2465–72. https://doi.org/10.1200/JCO.2018.78.9909.
[20] Sledge Jr GW, Toi M, Neven P, et al. MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2- advanced breast cancer who had progressed while receiving endocrine therapy. J Clin Oncol 2017;35:2875–84. https://doi.org/10.1200/JCO.2017.73.7585.
[21] Cazzaniga ME, Munzone E, Montagna E, Pappagallo G. Treatment of advanced breast cancer with a metronomic schedule of oral vinorelbine: what is the opinion of Italian oncologists? Expert Rev Anticancer Ther 2018;18:805–14. https://doi.org/10.1080/14737140.2018.1489244.
[22] Montagna E, Palazzo A, Maisonneuve P, Cancello G, Iorfida M, Sciandivasci A, et al. Safety and efficacy study of metronomic vinorelbine, cyclophosphamide plus capecitabine in metastatic breast cancer: a phase II trial. Cancer Lett 2017;400:276–81. https://doi.org/10.1016/j.canlet.2017.01.027.