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

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Abstract

Purpose: Single-agent oral chemotherapy is widely used in patients with bone metastases without visceral involvement, especially in hormone receptor–positive metastatic breast cancer (mBC). However, this option has been poorly evaluated in clinical trials. **Methods:** Eligible patients had mBC with predominantly bone but not visceral metastases, were receiving bisphosphonate therapy, and had previously received endocrine therapy (any setting) but not chemotherapy for mBC. Patients received oral vinorelbine 60 mg/m^2 on days 1, 8, 15, and 22 every 4 weeks (escalating to 80 mg/m^2 from cycle 2 in the absence of grade 3/4 toxicity) until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS). Secondary endpoints included clinical benefit rate (complete/partial response or ≥24 weeks' stable disease), overall survival, and safety. **Results:** Seventy patients were treated for a median of 6 cycles (range 1-18). Most (73%) continued treatment until disease progression. After 43 months' median follow-up, median PFS was 8.2 months (95% confidence interval [CI], 5.5-9.8). The clinical benefit rate was 56% (95% CI, 43%-68%). Median overall survival was 35.2 months (95% CI, 26.8-47.1). The most common grade 3/4 adverse event was neutropenia (38% of patients); febrile neutropenia was absent. The most common grade 1/2 adverse events were bone pain, fatigue, and gastrointestinal toxicities. Alopecia was infrequent. **Conclusions:** In patients with hormone receptor–positive mBC, bone disease, and prior endocrine therapy, first-line oral vinorelbine chemotherapy demonstrated long PFS and good tolerability. In this setting, it could be considered as an active oral alternative to intravenous chemotherapy.

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Introduction

In patients with breast cancer, bone is the most common site of metastasis[1] and the first site of relapse in half of those developing metastatic breast cancer (mBC).[2] Bone metastases are more often associated with hormone receptor–positive than hormone receptor–negative mBC,[3,4] and are more common in luminal breast cancer than HER2-positive, basal, or other subtypes.[5,6] Generally the prognosis is better for patients with metastases limited to the

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bone than for those with visceral metastases.[4,7] However, bone metastases cause substantial morbidity, immobility, and skeletal complications, and have a major impact on patients' quality of life.[8]

In patients with hormone receptor–positive mBC, endocrine therapy is the preferred initial treatment unless there is proven endocrine resistance or rapidly progressing disease.[9] Often several lines of endocrine therapy can be given, but ultimately these options will be exhausted and an alternative strategy will be required. Typically this involves chemotherapy. However, there is limited information on the effects of chemotherapy in the specific population of patients with hormone-pretreated mBC and bone metastases without visceral involvement, partly because these patients are often excluded from clinical trials.

Oral chemotherapy (eg, vinorelbine or capecitabine) may be considered an attractive treatment option in patients with slowly progressing disease because it interferes less with patients' daily activities, avoids hospitalization for treatment administration, and may be associated with less-troublesome side effects than with intravenous taxane therapy. Oral vinorelbine has demonstrated single-agent activity in mBC[10] and is of interest in this setting.

Patients and Methods

Study Objectives

NORBREAST-228 was an open-label single-arm international phase II study. The primary objective was to evaluate progression-free survival (PFS) with single-agent oral vinorelbine as first-line chemotherapy for patients with hormone receptor–positive endocrine-pretreated breast cancer with predominant bone metastases and no visceral involvement. PFS was defined as the interval between enrollment into the study until disease progression, death from any cause, or loss to follow-up, whichever occurred earliest.

Secondary objectives were to assess the safety profile of treatment and to evaluate additional efficacy parameters (clinical benefit rate, duration of disease control, time to treatment failure, and overall survival [OS]). Clinical benefit was defined as confirmed complete or partial response, or disease stabilization for ≥24 weeks. Duration of disease control was calculated from the date of enrollment into the study until documented progression, death, start of new anticancer therapy, or loss to follow-up. Time to treatment failure was defined as the interval between study entry and first recorded disease progression, death, withdrawal (because of an adverse event, patient refusal, or loss to follow-up), or start of new anticancer therapy. OS was defined as the interval between enrollment and death from any cause (or loss to follow-up).

The study protocol and all study-related documents were approved by an ethics committee before screening any patients.

Eligibility

Eligible patients were women with histologically confirmed hormone receptor–positive breast carcinoma and documented bone involvement with or without other nonvisceral metastatic disease sites. Hormone receptor positivity was defined as ≥10% of cells stained positive for estrogen and/or progesterone receptor by immunohistochemistry in the primary tumor or metastatic sample. Patients were to have received at least one previous endocrine therapy for breast cancer (in the primary or advanced setting) and be receiving ongoing bisphosphonate therapy started ≥1 month before study entry. Prior (neo)adjuvant chemotherapy was permitted if relapse had occurred ≥6 months after completing chemotherapy. Patients had to be aged ≥18 years, with Karnofsky performance status ≥70% and adequate bone marrow, hepatic, and renal function. All patients provided written informed consent before undergoing any study-specific procedure.

Patients were ineligible if they had any of the following: HER2-positive disease; visceral metastatic involvement (liver, lung, pleura, heart, peritoneum, central nervous system [CNS], spleen, or suprarenal glands metastases); symptoms suggesting CNS involvement or leptomeningeal disease; dysphagia or inability to swallow tablets; or grade ≥2 peripheral neuropathy (National Cancer Institute Common Toxicity Criteria [NCI CTC]). Prior chemotherapy for mBC, prior vinorelbine for early breast cancer, and prior radiotherapy within the preceding 4 weeks were not permitted.

Treatment

Patients received oral vinorelbine on days 1, 8, 15, and 22 every 4 weeks until disease progression, unacceptable toxicity, or patient refusal. In cycle 1, the vinorelbine dose was 60 mg/m^2. If grade 3/4 neutropenia was absent in cycle 1, the dose was escalated to 80 mg/m^2 from cycle 2. Blood count was performed within 24 hours before each dose of vinorelbine. If a patient had grade 2 neutropenia or thrombocytopenia, vinorelbine administration was omitted and blood counts reassessed before the next scheduled administration. No dose reduction was required in subsequent cycles. If a patient had grade 3/4 neutropenia or thrombocytopenia, vinorelbine administration was omitted and blood counts reassessed before the next scheduled administration. All subsequent doses were administered at 60 mg/m^2. If the day 1 vinorelbine dose was delayed for 3 weeks, vinorelbine was discontinued permanently.

Prophylactic antiemetic medication with an oral 5-hydroxytryptamine$_3$ receptor antagonist was recommended immediately before each dose of oral vinorelbine from cycle 1. Corticosteroids were permitted as antiemetic therapy. The prophylactic use of colony-stimulating factor was allowed during study treatment. Granulocyte-stimulating growth factors were permitted in patients who experienced febrile neutropenia, grade 4 asymptomatic neutropenia, or neutropenic infection, according to guidelines at each participating institution.

Concomitant endocrine therapy for mBC was not permitted during study therapy. Treatment with radiotherapy or other antineoplastic agents during study therapy was not allowed; patients requiring radiotherapy were considered to have disease progression and study treatment was discontinued.

Study Assessments

All lesions (measurable and nonmeasurable) were assessed every 3 cycles according to Response Evaluation Criteria in Solid Tumors (RECIST; version 1.0). The same assessment method and technique was used at baseline and throughout the study. Spiral computed tomography (CT) and magnetic resonance imaging were preferred, but if unavailable, sequential CT could be used instead. Intravenous contrast was used for all assessments unless contraindicated.

Bone scintigraphy was performed every 6 cycles; in addition, bone scintigraphy was performed at any time during study

treatment in the event of suspected progression due to skeletal events (increased pain intensity/analgesic consumption, increased alkaline phosphatase or calcium concentration, or pathologic bone fracture). Information on pain intensity, analgesic consumption, alkaline phosphatase concentration, and calcemia was collected at every cycle.

Adverse events were graded according to NCI CTC version 2.

Statistical Analysis

Sample size estimation was based on an assumed median PFS of 4 months for the null hypothesis and 6 months for the alternative hypothesis, a 15-month accrual period, and 12 months' follow-up after the last patient was enrolled. Based on these assumptions, an alpha of 5%, and 90% power, it was estimated that 60 evaluable patients were required. Assuming 10% loss to follow-up, the target sample size was 66 patients.

PFS, time to treatment failure, and OS were estimated using the Kaplan-Meier method with associated 95% confidence intervals (CIs) in the intent-to-treat population. Safety analyses were performed on all treated patients. Analyses of the maximum grade of each adverse event were done per cycle and per patient.

The study was conducted in accordance with the current revision of the Declaration of Helsinki, the International Conference on Harmonisation Guideline for Good Clinical Practice, and local regulations, and was registered with EudraCT, number 2009-014497-18.

Results

Patient Population

Between April 2010 and April 2012, 70 patients were enrolled from 18 centers in France, Austria, Mexico, Poland, Russia, Italy, and Spain. All patients received at least 1 dose of study therapy and were therefore included in the efficacy and safety analysis populations.

The median age was 61 (range, 37-78) years and 34% of patients were aged ≥65 years (Table 1). Most patients (74%) had a baseline Karnofsky performance status ≥90%. Almost half of the patients had moderate (46%) or severe (3%) bone pain at baseline. In accordance with the protocol, all patients were receiving bisphosphonates, most commonly zoledronic acid (74%).

Table 1 Baseline Characteristics (n = 70)

Characteristic	No. of Patients (%)
Age, y	
Median (range)	61 (37-78)
<65	46 (66)
≥65	24 (34)
Karnofsky performance status at baseline	
70%	4 (6)
80%	14 (20)
90%	28 (40)
100%	24 (34)
Metastatic disease at initial diagnosis	8 (11)
Metastatic sites	
Bone	70 (100)
Lymph node	10 (14)
Soft tissue	2 (3)
No. of metastatic organ sites	
1	58 (83)
2	10 (14)
3	2 (3)
Prior (neo)adjuvant chemotherapy	44 (63)
Anthracycline[a]	41 (59)
Taxane[a]	17 (24)
Prior palliative radiotherapy	29 (41)
Prior endocrine therapy	
Adjuvant setting[a]	57 (81)
Advanced setting[a]	37 (53)
1 line	21 (30)
2 lines	12 (17)
3 lines	3 (4)
4 lines	1 (1)
Most common prior endocrine therapies (any setting/line)	
Tamoxifen	47 (67)
Anastrozole	30 (43)
Letrozole	24 (34)
Fulvestrant	15 (21)
Exemestane	12 (17)
Median no. of prior endocrine therapies (range)	2 (1-4)
Median interval between last endocrine therapy and start of study therapy, mo	0.9

[a]More than 1 answer possible.

Treatment Exposure

The date of data cutoff for the final analysis was March 16, 2015. By this time, all patients had discontinued study therapy. The median duration of treatment was 5.8 months (range 0.9-18.4 months) and the median number of cycles delivered was 6 (range 1-18). Overall, 48 patients (69%) received ≥6 cycles, 25 (36%) received ≥9 cycles, and 12 (17%) received ≥12 cycles. The most common reason for treatment discontinuation was disease progression (45 patients [64%] by RECIST; 6 patients [9%] with clinical progression). Only 5 patients (7%) discontinued vinorelbine because of drug-related toxicity (2 cases of nausea and vomiting, 1 case each of persistent grade 3 neutropenia, recurrent leukopenia, and asthenia) and 2 patients (3%) because of non–drug-related toxicity. Eight patients (11%) requested to discontinue treatment, 3 patients (4%) discontinued vinorelbine because they had achieved maximal benefit (after 6 cycles in 2 patients; after 8 cycles in 1 patient), and discontinuation in the remaining patient (1%) was at the investigator's request because of recurrent neutropenia and increased gamma-glutamyl transpeptidase level.

The median number of oral vinorelbine administrations was 24 (range 1-72). At least 1 cycle was delayed at day 1 in 39 patients (56%); 43 patients (61%) missed at least 1 dose on day 8, 15, or 22. The mean delivered dose per patient was 59.9 mg/m^2/wk and the mean relative dose intensity was 79%. In most patients (79%), the dose was escalated to 80 mg/m^2 at cycle 2. Approximately half of all doses (1102 of 2027; 54%) were administered at 80 mg/m^2.

Efficacy

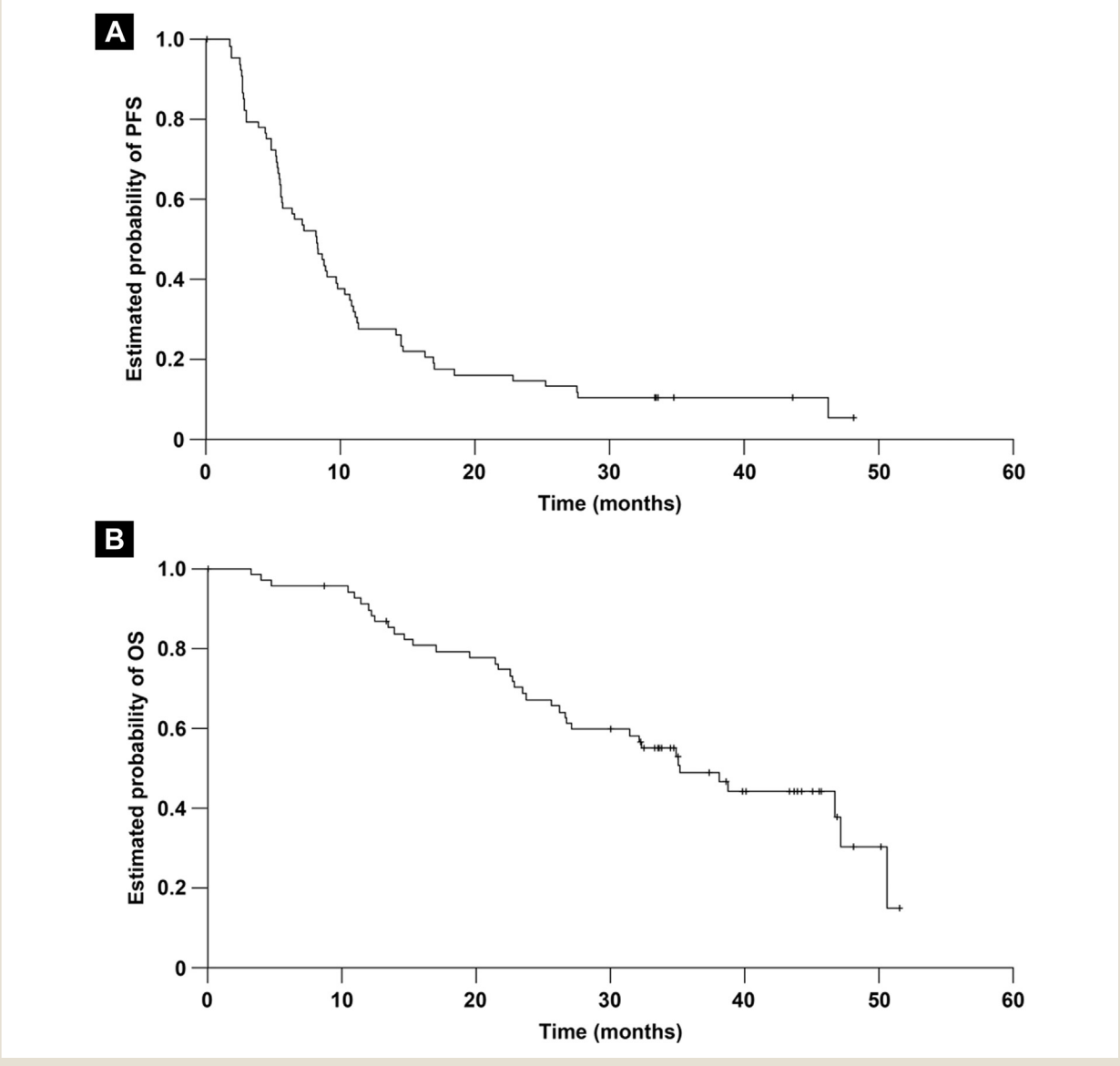
The median duration of follow-up at the time of the final analysis was 43.3 months. At this time, 63 patients (90%) had experienced a PFS event; the remaining 7 patients were alive without evidence of disease progression. Median PFS was 8.2 months (95% CI, 5.5-9.8 months) (Figure 1A).

Response was evaluable in 67 patients. Overall, 2 (3%) of 70 patients achieved a confirmed partial response and 1 (1%) an unconfirmed complete response. A further 36 patients (51%) achieved stable disease sustained for ≥24 weeks, giving an overall clinical benefit rate of 56% (95% CI, 43%-68%). Fifteen additional patients (21%) had stable disease lasting for <24 weeks. The median duration of clinical benefit was 10.9 months (95% CI, 8.6-14.7 months). The median time to treatment failure was 5.6 months (range, 0.1-17.8 months).

At the time of data cutoff, 38 patients (54%) had died (35 from disease progression; 3 from other causes), and 3 (4%) had been lost to follow-up. The remaining 29 patients were still alive. Median OS was 35.2 months (95% CI, 26.8-47.1 months) (Figure 1B).

During treatment, the worst bone pain intensity recorded was severe in 13%, moderate in 47%, mild in 16%, and none in 20% (missing in 4%). Corresponding percentages by cycle were 3%, 31%, 12%, 48%, and 6%. Strong opioids were given concomitantly with study therapy in 13 patients (19%). In approximately one-third of patients (31%), no analgesics were administered during study therapy.

Figure 1 Efficacy of Single-Agent Vinorelbine: (A) Progression-Free Survival; (B) Overall Survival



Abbreviations: OS = overall survival; PFS = progression-free survival.

Table 2 Summary of Grade 3/4 Nonhematologic Adverse Events

Adverse Event, n (%)	Per Patient (n = 70)[a]		Per Cycle (n = 517)[a]	
	Grade 3	Grade 4	Grade 3	Grade 4
Nausea	2 (2.9)	0	2 (0.4)	0
Diarrhea	2 (2.9)	0	2 (0.4)	0
Constipation	1 (1.4)	0	1 (0.2)	0
Fatigue	1 (1.4)	0	1 (0.2)	0
Influenzalike illness	1 (1.4)	0	1 (0.2)	0
Acute cholecystitis	1 (1.4)	0	1 (0.2)	0
Hepatotoxicity	1 (1.4)	0	1 (0.2)	0
Lung infection	1 (1.4)	0	1 (0.2)	0
Tooth infection	1 (1.4)	0	1 (0.2)	0
Neutropenic infection	1 (1.4)	1 (1.4)	1 (0.2)	1 (0.2)
Arthralgia	1 (1.4)	0	1 (0.2)	0
Bone pain	8 (11.4)	0	15 (2.9)	0
Musculoskeletal pain	1 (1.4)	0	1 (0.2)	0
Cerebrovascular accident	0	1 (1.4)	0	1 (0.2)
Ischemic stroke	0	1 (1.4)	0	1 (0.2)
Monoparesis	1 (1.4)	0	1 (0.2)	0
Spinal cord compression	1 (1.4)	0	1 (0.2)	0
Cataract operation	1 (1.4)	0	1 (0.2)	0
Alanine aminotransferase increase[a]	2 (2.9)	0	2 (0.4)	0
Aspartate aminotransferase increase[a]	4 (5.9)	0	7 (1.4)	0
Gamma glutamyltransferase increase[a]	1 (1.5)	0	1 (0.2)	0
Hypokalemia[a]	1 (1.5)	0	1 (0.2)	0
Hypernatremia[a]	1 (1.5)	0	1 (0.2)	0
Hypoglycemia[a]	0	1 (1.5)	0	1 (0.2)
Hyperglycemia[a]	1 (1.5)	0	1 (0.2)	0

[a]Evaluable population for biochemistry: 68 patients, 514 cycles.

Subsequent Chemotherapy

Further chemotherapy after study treatment was reported in 39 patients (56%), most commonly taxanes (22 patients; 31%), anthracyclines (19 patients; 27%), and capecitabine (15 patients; 21%). Fifty-one patients (73%) received further endocrine therapy and 8 (11%) received everolimus.

Safety

Thirty-nine patients (56%) experienced grade 3/4 adverse events. There were no treatment-related deaths. The most common grade 3/4 adverse events were hematologic events, predominantly neutropenia (38% of patients: grade 3, 22%; grade 4, 16%) and leukopenia (29%; grade 3, 25%; grade 4, 4%). Neutropenia was reported at grade 3 intensity in 43 (8%) of 516 cycles evaluable for hematology and grade 4 in 15 cycles (3%). Grade 3 leukopenia was reported in 38 (7%) of 516 cycles and grade 4 in 3 cycles (1%). Grade 3/4 anemia occurred in 4% of patients (grade 3, 1%; grade 4, 3%). There were no cases of febrile neutropenia or grade $\geq$2 thrombocytopenia. Growth factors were administered in 18 patients (26%) during 40 (8%) of 517 cycles.

Except for bone pain, nonhematologic grade 3/4 adverse events were infrequent (Table 2). The most common grade 1/2 adverse events were bone pain (63%), fatigue (56%), diarrhea (51%), nausea (47%), vomiting (46%), constipation (39%), weight decreased (24%), abdominal pain (23%), and pyrexia (21%). Alopecia was reported at grade 1 in 11% of patients and grade 2 in 6%.

Discussion

In this particular population of patients with mBC (endocrine therapy–pretreated hormone receptor–positive disease with bone but not visceral involvement), first-line chemotherapy with oral vinorelbine demonstrated high single-agent activity. Hematologic toxicity was manageable and alopecia was rare. Grade 1/2 nausea and vomiting were frequent and led to treatment discontinuation in 2 patients, but grade 3 episodes were rare and there were no grade 4 episodes. Of note, treatment could be continued until disease progression in most patients, suggesting that toxicities were not cumulative. The NORBREAST-228 trial was designed as a single-arm study, which prevents any comparison with other chemotherapy agents, targeted therapy, or novel agents in this setting. It would perhaps be interesting to compare oral vinorelbine with other oral chemotherapies, most notably capecitabine, in this treatment setting. To the best of our knowledge, there are no published prospective studies of capecitabine in this patient population. Vinorelbine and capecitabine were evaluated in a prospective randomized phase II trial (n = 47), which showed similar antitumor activity of the 2 agents but differing toxicity profiles: there was more hematologic toxicity, neurotoxicity, and nausea/vomiting with

vinorelbine and more diarrhea and hand-foot syndrome with capecitabine.[11]

In our study, the definition of hormone receptor–positive disease was ≥10% staining by immunohistochemistry, which was appropriate at the time the study was designed, but the more recent American Society of Clinical Oncology guidelines recommend a cutoff of 1% tumor cell staining to define estrogen receptor positivity.[12] This represents a challenge when trying to compare our data with more recent trials in the hormone receptor–positive setting.

Regardless of these limitations, the observed median PFS of 8.2 months, 56% clinical benefit rate, and median OS of 35.2 months in our study suggest good clinical activity. Comparison with other data in the literature is difficult because even in the few trials conducted in patients with nonvisceral disease, there are substantial differences in eligibility criteria. A randomized phase II trial evaluating the addition of vandetanib to fulvestrant in patients with progression on previous endocrine therapy demonstrated median PFS of 5 to 6 months, but patients with visceral metastases or prior chemotherapy for mBC were eligible and thus the trial population represented a somewhat different patient population from that enrolled in our study.[13]

More recently, alternatives to chemotherapy after progression on endocrine therapy have entered clinical practice: the mammalian target of rapamycin (mTOR) inhibitor everolimus and the cyclin dependent kinase (CDK)4/6 inhibitor palbociclib. Adding everolimus to exemestane significantly improved PFS and appeared to delay progression of bone metastases in patients with endocrine-resistant mBC in the BOLERO-2 trial.[14-16] In the subgroup of 318 patients without visceral metastases, median PFS was 4.2 months with placebo plus exemestane versus 9.9 months with everolimus plus exemestane.[17] Among 151 patients with bone-only metastases, median PFS was 5.3 versus 12.9 months, respectively. However, direct comparison with our results is inappropriate because of differences in eligibility and study design (including continued administration of endocrine therapy in BOLERO-2 but not in our study). Differences in tolerability also should be taken into account: in BOLERO-2, 19% of patients discontinued everolimus-containing therapy because of adverse events, suggesting substantial toxicity in a setting of relatively indolent disease.

Two randomized phase III trials have shown that adding palbociclib to endocrine therapy significantly improves PFS: PALOMA-3 combined palbociclib with fulvestrant in women with hormone receptor–positive mBC that had progressed on previous endocrine therapy[18,19] and PALOMA-2 combined palbociclib with letrozole in postmenopausal women with estrogen receptor–positive mBC.[20] In the subset of 210 patients with nonvisceral metastases treated in PALOMA-3, median PFS was 11.2 months in patients receiving palbociclib plus fulvestrant versus 5.6 months with placebo plus fulvestrant.[19] Again, the patient population differed slightly from that included in our study, as 1 line of prior chemotherapy for advanced disease was permitted but prior fulvestrant was not. In addition, as with the everolimus results mentioned previously, these data were derived from subgroup analyses, albeit visceral metastasis was a stratification factor in PALOMA-3.

Although mTOR inhibition and CDK4/6 inhibition both represent important new treatment strategies in combination with endocrine therapy, many patients will ultimately require an effective and tolerable chemotherapy. Our study, performed in the setting of predominantly bone-only, nonvisceral endocrine-pretreated mBC, showed that oral vinorelbine is an active and well-tolerated treatment option in this population of patients. This prospective evaluation provides interesting insight into the role of oral chemotherapy in this important patient population.

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Disclosure

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