Final Results of the Randomized Phase II NorCap-CA223 Trial Comparing First-Line All-Oral Versus Taxane-Based Chemotherapy for HER2-Negative Metastatic Breast Cancer

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Abstract

This randomized phase II trial compared first-line all-oral vinorelbine/capecitabine, gemcitabine/paclitaxel, and gemcitabine/docetaxel for HER2-negative metastatic breast cancer. Disease control rates (primary end point) were 73%, 78%, and 80%, respectively; median progression-free survival was 7.6, 9.0, and 11.4 months; median overall survival was 30 to 31 months with all regimens. All-oral vinorelbine/capecitabine is an active first-line regimen, and avoids alopecia and frequent intravenous administrations.

Background: The purpose of this study was to evaluate the efficacy of 3 first-line chemotherapy combination regimens for HER2-negative metastatic breast cancer (mBC). **Patients and Methods:** In this open-label, 3-arm, randomized phase II trial, patients were randomized to all-oral NORCAP (vinorelbine/capecitabine), GEMPAC (gemcitabine/paclitaxel), or GEMDOC (gemcitabine/docetaxel) as first-line chemotherapy for HER2-negative mBC. Stratification factors were center, previous (neo)adjuvant anthracycline, and age. The primary end point was disease control rate (DCR; complete or partial response, or stable disease for ≥3 months). **Results:** The DCR was 73% (95% confidence interval [CI], 59-85) with NORCAP (36 of 49 patients), 78% (95% CI, 64-88) with GEMPAC (39 of 50 patients), and 80% (95% CI, 66-90) with GEMDOC (40 of 50 patients). Objective response rates were 33% (16 of 49 patients), 24% (12 of 50 patients), and 50% (25 of 50 patients), respectively; median progression-free survival was 7.6, 9.0, and 11.4 months, respectively. Median overall survival was 30 to 31 months with all regimens. The most common Grade ≥3 adverse event with each regimen was neutropenia (24 patients [50%], 23 patients [46%], and 43 patients [86%], respectively). The most common nonhematological Grade ≥3 adverse event was fatigue. Grade 2 alopecia occurred in 36 patients (72%) who received GEMPAC and 38 patients (76%) who received GEMDOC, but only 4 patients (8%) who received NORCAP. There was no evidence of a detrimental effect of NORCAP on quality of life. **Conclusion:** All-oral NORCAP is an active first-line chemotherapy regimen and might be offered as an alternative to first-line taxane-based therapy for HER2-negative mBC, particularly if patients wish to avoid alopecia or frequent intravenous administrations.

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Introduction

In HER2-negative metastatic breast cancer (mBC), chemotherapy remains a key component of treatment; however, there is no single standard of care regimen and a number of treatment options are available. The selection of a particular chemotherapy regimen is influenced by multiple factors, including patient and disease characteristics, previous treatment, comorbidities, and patient preference. Sequential single-agent chemotherapy is preferred in many patients because treatment is generally more tolerable with less impairment of quality of life.[1-3] However, in patients with rapid clinical progression, life-threatening visceral metastases, or requiring rapid disease or symptom control, combination chemotherapy is usually more appropriate.[1] Taxane-based combination regimens are among the most active treatments for mBC. Approved options for anthracycline-pretreated mBC include docetaxel in combination with capecitabine or paclitaxel in combination with gemcitabine. Both regimens showed significantly superior time to disease progression, response rate, and overall survival (OS) compared with single-agent taxane, but with greater toxicity.[4,5] Randomized phase III trials that compared taxane-based chemotherapy doublets for mBC support the high activity of such regimens but showed substantial toxicity.[6-9] In 2 phase III trials comparing gemcitabine/docetaxel versus capecitabine/docetaxel, up to 28% of patients discontinued treatment because of toxicity.[6,7,10]

For many patients, an active all-oral combination chemotherapy regimen that avoids the need for intravenous treatment administration visits at the clinic might be preferable. Moreover, avoidance of alopecia, which is commonly associated with taxane-based regimens, is attractive to many patients, especially if they have already received taxane therapy in the adjuvant setting. An all-oral combination regimen of vinorelbine and capecitabine might provide a convenient and effective alternative to intravenous taxane-based regimens. Both agents have shown activity in mBC, alone and in combination regimens.[4,10-13] In addition, vinorelbine and capecitabine show nonoverlapping safety profiles and preclinical synergy.[14] Vinorelbine upregulates thymidine phosphorylase, a critical enzyme in the activation of capecitabine at the tumor site,[15] providing a biological rationale for combining these 2 agents.

In 3 phase I studies that evaluated oral vinorelbine in combination with capecitabine, a 3-weekly schedule with capecitabine given at a dose of 1000 mg/m^2 twice daily and oral vinorelbine given at 60 to 80 mg/m^2 on days 1 and 8 was found to be feasible, with promising activity.[16-18] A subsequent phase II study evaluated capecitabine 1000 mg/m^2 twice daily on days 1 through 14 in combination with vinorelbine 60 mg/m^2 on days 1 and 8 of each 21-day cycle (escalating to 80 mg/m^2 if the first cycle was well tolerated) as first-line therapy for HER2-negative mBC.[19] The regimen showed a 51% objective response rate, median progression-free survival (PFS) of 8.4 months, and median OS of 29.2 months. Phase II studies of slightly different regimens in mixed first- and second-line settings supported these findings.[20-23]

The aim of the present international, open-label, randomized phase II trial was to evaluate the efficacy of an all-oral combination and 2 all-intravenous combinations as first-line therapy for HER2-negative mBC.

Patients and Methods

Patients

Eligible patients were female, aged ≥18 years, with Karnofsky performance status ≥70%, histologically confirmed HER2-negative mBC, and no previous chemotherapy for metastatic disease. Previous adjuvant or neoadjuvant chemotherapy was permitted if it had been completed at least 6 months before the diagnosis of metastatic disease. Previous endocrine therapy for early or advanced disease was allowed. Radiotherapy completed ≥4 weeks before study entry was permitted, although previous radiotherapy to target lesions was not allowed. All patients had to have adequate bone marrow, hepatic, and renal function, and provide written informed consent. Patients were not eligible if they had previously received treatment with a vinca alkaloid, capecitabine, gemcitabine, paclitaxel, or docetaxel, or if they had symptoms suggesting central nervous system involvement or leptomeningeal metastases, or if they were pregnant or lactating. Patients were also excluded if they had: malabsorption syndrome or disease significantly affecting gastrointestinal function; undergone major resection of the stomach or proximal small bowel that could affect absorption of capecitabine or oral vinorelbine; previously experienced a severe unexpected reaction to fluoropyrimidine therapy (with or without documented dihydropyrimidine dehydrogenase deficiency), or known hypersensitivity to 5-fluorouracil; or had ongoing peripheral neuropathy of Grade ≥2.

Study Design

The primary objective of this open-label, 3-arm, multinational, randomized phase II trial was to determine the disease control rate (DCR) of 3 regimens: NORCAP (oral vinorelbine with oral capecitabine), GEMPAC (gemcitabine with paclitaxel), and GEMDOC (gemcitabine with docetaxel) as first-line treatment for HER2-negative mBC. The DCR was defined as the total number of patients achieving complete response, partial response, or stable disease (sustained for at least 3 months).

Secondary objectives were to assess the safety, efficacy, and quality of life associated with the 3 regimens. Prespecified efficacy end points were: DCR in the evaluable population; objective response rate; duration of disease control, stable disease, and response; PFS; time to treatment failure; and OS. During the study, patients were asked to complete the Functional Assessment of Cancer Therapy (FACT) for Breast Cancer (FACT-B) questionnaire to measure health-related quality of life. The FACT-B questionnaire includes the FACT-General core subscale, which evaluates physical, social/family, emotional, and functional well-being, as well as the breast cancer subscale, which evaluates additional items related to quality of life.

The trial was conducted according to the Declaration of Helsinki, the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice (ICH topic E6, step 5), and local rules. The protocol and all study materials were approved by an independent ethics committee.

Statistical Design

A DCR of 50% was chosen as the minimum acceptable DCR for an active regimen in this population of patients. On the basis of the Fleming method for sample size calculations, 45 evaluable patients

in each treatment arm (135 evaluable patients overall) would provide 80% power to reject a DCR of 50% at an α level of 0.05. Assuming that 10% of patients would not be evaluable, the target sample size for accrual was 150 patients (50 patients per arm).

Patients were stratified according to center, previous (neo)adjuvant anthracycline therapy (yes vs. no), and age (<65 vs. ≥65 years), and randomized 1:1:1 to 1 of the 3 treatment arms.

Efficacy analyses were performed using the intent to treat (ITT) population. Sensitivity analyses were based on the evaluable population, defined as all patients without a major eligibility criterion violation who continued in the study until the first tumor assessment (cycle 2) and had at least 1 tumor assessment after baseline. Safety analyses were based on all patients who received treatment and completed at least 1 assessment after randomization.

Treatment

Patients were randomized to receive 1 of 3 chemotherapy doublets repeated in every 21-day cycle. In the NORCAP arm, patients received oral vinorelbine 60 mg/m^2 on days 1 and 8 of cycle 1, increased to 80 mg/m^2 on days 1 and 8 from cycle 2 onward in the absence of Grade 3 or 4 toxicity in cycle 1, in combination with capecitabine 1000 mg/m^2 twice daily on days 1 to 14 of each cycle. Antiemetic treatment with oral 5-hydroxytryptamine$_3$ antagonists was recommended before each vinorelbine intake. The dose modification scheme in the event of hematological toxicity is shown in Supplemental Table 1 in the online version. In the GEMPAC arm, patients received intravenous gemcitabine 1250 mg/m^2 on days 1 and 8 in combination with intravenous paclitaxel 175 mg/m^2 on day 1. In the GEMDOC arm, intravenous gemcitabine was given at a dose of 1000 mg/m^2 in combination with intravenous docetaxel 75 mg/m^2 on day 1. Corticosteroid premedication was mandatory before each taxane administration in arms B and C. Concomitant endocrine therapy was not permitted. Prophylactic colony-stimulating factor was also prohibited; use of granulocyte colony-stimulating factor (G-CSF) was permitted according to institution guidelines in patients who developed febrile neutropenia, Grade 4 asymptomatic neutropenia, or neutropenic infection, but was to be documented in the study case report form. Chemotherapy was continued until disease progression, unacceptable toxicity, or patient refusal. If 1 component of the combination regimen was discontinued because of toxicity before disease progression, the patient was considered to be 'off treatment.' The other drug could be continued at the recommended single-agent dose at the discretion of the investigator.

Study Assessments

Efficacy was assessed every 2 cycles using Response Evaluation Criteria in Solid Tumors (version 1.0) until disease progression. Adverse events were recorded at each visit and graded according to National Cancer Institute Common Toxicity Criteria (version 2.0). Blood counts were performed on days 1 and 8 of each cycle. FACT-B questionnaires were to be completed by patients before randomization, before cycles 2, 4, 6, and every subsequent 2 cycles, and at the end of study treatment. Questionnaires from all patients who completed at least 2 quality of life questionnaires (including the prerandomization questionnaire) were included in the analyses of quality of life. Patients were followed every 3 months for survival status and anticancer therapy until death.

Results

Patient Population

Between March 2007 and December 2009, 152 patients were enrolled from 23 centers in 13 countries. Three patients were randomized but did not receive treatment (2 patients randomized to NORCAP, 1 randomized to GEMDOC) because of ineligibility in 2 patients and withdrawal of consent in 1 patient. Therefore the ITT efficacy analyses and safety analyses were based on 149 patients (148 patients for hematological toxicities). As shown in Table 1, patient characteristics were generally well balanced between the treatment arms. The patient population typified a group of patients suitable for combination chemotherapy: approximately 80% had visceral disease and approximately half had at least 3 metastatic organ sites at study entry, although there were slight imbalances between treatment arms for this parameter.

Treatment Exposure

Figure 1 shows treatment exposure according to treatment arm over time. The median number of cycles administered was 6 (range, 1-37) in

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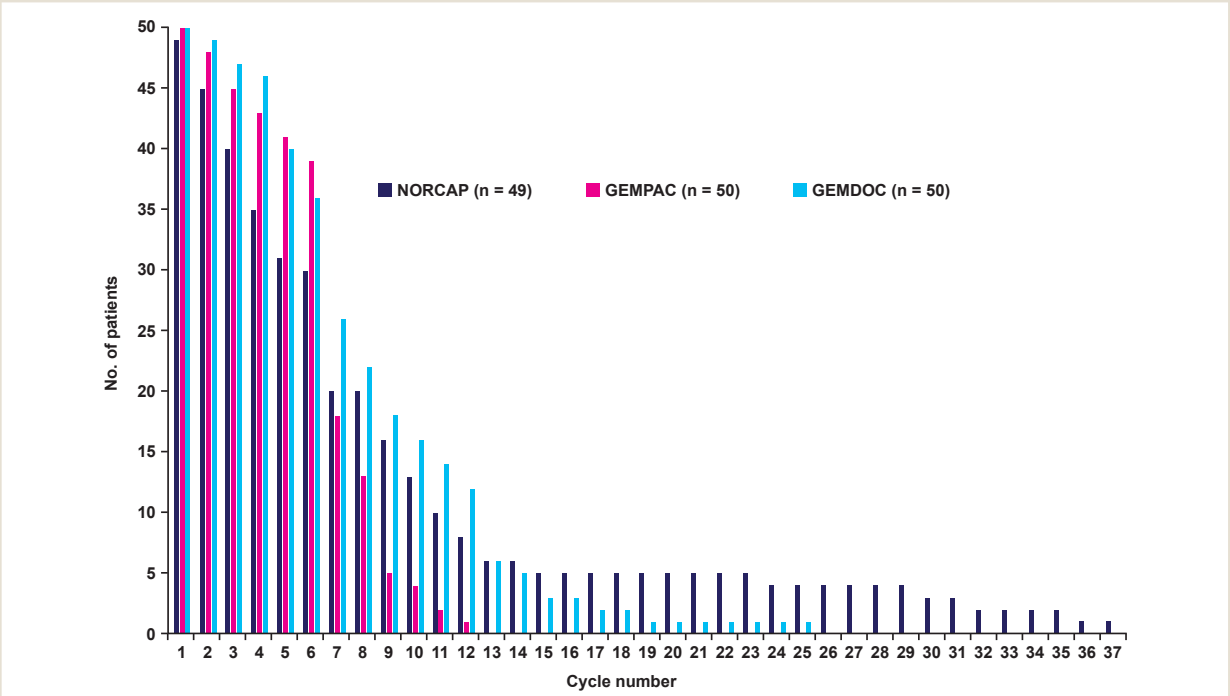
Table 1 Patient Characteristics

Characteristic	NORCAP (n = 49)	GEMPAC (n = 50)	GEMDOC (n = 50)
Age, Years			
Median (range)	58 (33-76)	56 (29-78)	57 (33-77)
≥65 years	9 (18)	10 (20)	12 (24)
Karnofsky Performance Status			
70	5 (10)	2 (4)	0
80	7 (14)	12 (24)	11 (22)
90	16 (33)	14 (28)	19 (38)
100	18 (37)	19 (38)	18 (36)
≥70 But value missing	3 (6)	3 (6)	2 (4)
Hormone Receptor Status			
ER-positive	37 (76)	34 (68)	36 (72)
PgR-positive	33 (67)	33 (66)	34 (68)
ER- and/or PgR-positive	40 (82)	42 (84)	37 (74)
Previous Endocrine Therapy	29 (59)	32 (64)	33 (66)
Advanced disease	11 (22)	15 (30)	20 (40)
Previous Chemotherapy	24 (49)	23 (46)	29 (58)
Anthracycline	19 (39)	21 (42)	21 (42)
Measurable Disease at Baseline	46 (94)	45 (90)	49 (98)
Metastatic Organ Sites			
≥3	26 (53)	22 (44)	29 (58)
Visceral	39 (80)	41 (82)	37 (74)
Liver	24 (49)	26 (52)	24 (48)
Lung	23 (47)	25 (50)	20 (40)

Data are presented as n (%) except where otherwise noted.
Abbreviations: ER = estrogen receptor; GEMDOC = gemcitabine/docetaxel; GEMPAC = gemcitabine/paclitaxel; NORCAP = oral vinorelbine with oral capecitabine; PgR = progesterone receptor.

Figure 1 Treatment Exposure According to Treatment Arm



Abbreviations: GEMDOC = gemcitabine/docetaxel; GEMPAC = gemcitabine/paclitaxel; NORCAP = oral vinorelbine with oral capecitabine.

the NORCAP arm, 6 (range, 1-12) in the GEMPAC arm, and 7 (range, 1-25) in the GEMDOC arm, corresponding to 19, 19, and 21 weeks, respectively. At cycle 6, more patients in the taxane-containing arms than the NORCAP arm remained on treatment; however, a notable number of patients in the NORCAP arm continued treatment beyond cycle 6, with 5 patients still receiving treatment at cycle 23. In almost all patients, both components of the combination regimen were discontinued at the same time (ie, patients received doublet chemotherapy throughout study treatment).

There were notable differences in relative dose intensity between the treatment arms. In the NORCAP arm, the median relative dose intensity was 81% for oral vinorelbine and 79% for capecitabine. The oral vinorelbine dose was escalated to 80 mg/m^2 at cycle 2 in 35 patients (78%) (and at a later cycle in a further 3 patients [6%]). Median relative dose intensity of gemcitabine was 84% in the GEMPAC arm and 58% in the GEMDOC arm. Median taxane relative dose intensity was 95% for paclitaxel in the GEMPAC arm and 91% for docetaxel in the GEMDOC arm.

The proportions of patients who required a chemotherapy dose delay were similar in the 3 treatment arms (NORCAP arm: vinorelbine 34 patients [69%], capecitabine 32 patients [65%]; GEMPAC arm: gemcitabine 31 patients [62%], paclitaxel 28 patients [56%]; GEMDOC arm: gemcitabine 34 patients [68%], docetaxel 31 patients [62%]). In the NORCAP arm, 24 patients (49%) omitted at least 1 vinorelbine dose and 33 patients (67%) omitted at least 1 capecitabine dose. Gemcitabine and taxane doses were omitted in 30 and 0 patients (60% and 0%), respectively, in the GEMPAC arm, and 48 patients and 1 patient (96% and 2%), respectively, in the GEMDOC arm. Gemcitabine doses were most commonly omitted because of hematological toxicity.

Efficacy

The DCR was 73% (95% confidence interval [CI], 59-85) in the NORCAP arm (36 of 49 patients), 78% (95% CI, 64-88) in the GEMPAC arm (39 of 50 patients), and 80% (95% CI, 66-90) in the GEMDOC arm (40 of 50 patients) (Table 2). Because the 95% CIs exceeded 50% in all 3 arms and a DCR of less than 50% could be excluded, the primary objective was met. The sensitivity analysis in the evaluable population of 137 patients showed similar results, with DCRs of 80% (36 of 45 patients), 89% (39 of 44 patients), and 83% (40 of 48 patients) for NORCAP, GEMPAC, and GEMDOC, respectively. Objective response rates in the ITT population were 33% (16 of 49 patients) in the NORCAP arm, 24% (12 of 50 patients) in the GEMPAC arm, and 50% (25 of 50 patients) in the GEMDOC arm (Table 2).

At the time of database closure, all but 9 patients had experienced a PFS event and 103 patients (69%) had died. Median PFS was 7.6 months with NORCAP, 9.0 months with GEMPAC, and 11.4 months with GEMDOC (Table 2; Figure 2); 95% CIs were overlapping and numerical differences between treatment arms varied over time. Median OS was 30 to 31 months in all 3 treatment arms (Table 2; Figure 3).

Safety

As shown in Table 3, the most common Grade ≥3 adverse event in all 3 treatment arms was neutropenia, occurring in 24 patients (50%) in the NORCAP arm, 23 patients (46%) in the GEMPAC

Table 2 Summary of Efficacy

Outcome	NORCAP (n = 49)	GEMPAC (n = 50)	GEMDOC (n = 50)
Best Objective Response, n (%)			
Complete response	1 (2)	0	1 (2)
Partial response	15 (31)	12 (24)	24 (48)
Stable disease	23 (47)	29 (58)	17 (34)
<3 Months	3 (6)	2 (4)	2 (4)
≥3 Months	20 (41)	27 (54)	15 (30)
Progressive disease	6 (12)	3 (6)	6 (12)
Not evaluable	4 (8)	6 (12)	2 (4)
Disease Control Rate, n (%) [95% CI]	36 (73) [59-85]	39 (78) [64-88]	40 (80) [66-90]
Objective Response Rate, n (%) [95% CI]	16 (33) [20-48]	12 (24) [13-38]	25 (50) [36-64]
Median Duration of Disease Control, Months (95% CI)	8.1 (6.1-25.8)	8.0 (6.0-9.0)	13.1 (9.9-25.4)
Median Duration of Response, Months (95% CI)	6.2 (4.4-NR)	7.8 (4.0-10.0)	10.4 (6.6-NR)
Progression-Free Survival			
Events, n (%)	47 (96)	47 (94)	46 (92)
Median, months (95% CI)	7.6 (6.0-11.0)	9.0 (7.0-11.2)	11.4 (7.6-13.8)
Time to Treatment Failure			
Events, n (%)	49 (100)	50 (100)	50 (100)
Median, months (95% CI)	4.6 (3.2-6.0)	4.8 (4.6-5.6)	5.2 (4.4-6.8)
Overall Survival			
Events, n (%)	31 (63)	37 (74)	35 (70)
Median, months (95% CI)	30.2 (24.0-42.2)	29.6 (21.2-42.2)	31.0 (24.2-40.0)

Abbreviations: GEMDOC = gemcitabine/docetaxel; GEMPAC = gemcitabine/paclitaxel; NORCAP = oral vinorelbine with oral capecitabine; NR = not reached.

arm, and 43 patients (86%) in the GEMDOC arm. Febrile neutropenia was reported in 6 patients (12%) who received NORCAP and 3 patients (6%) who received GEMDOC (no cases in the GEMPAC arm). In addition, there were 2 toxic deaths in the NORCAP arm due to neutropenic infection and 1 in the GEMPAC arm due to septic shock. G-CSF was administered to 9 patients (18%) in the NORCAP arm, 10 patients (20%) in the GEMPAC arm, and 20 patients (40%) in the GEMDOC arm.

The most common nonhematological Grade ≥3 adverse event in all 3 treatment arms was fatigue. In the NORCAP arm, 5 patients (10%) experienced Grade 3 vomiting (no Grade 4) and 4 patients (8%) experienced Grade 3 hand-foot syndrome. Grade ≥3 dyspnea was reported in 5 patients (10%) in the GEMPAC arm. Grade 2 alopecia occurred in approximately three-quarters of patients in the 2 taxane-containing arms (36 patients [72%] in the GEMPAC arm, 38 patients [76%] in the GEMDOC arm) but was uncommon in patients treated with NORCAP (4 patients [8%]).

Quality of Life

Quality of life was evaluable in 103 (68%) of the randomized patients (31 patients [61%] in the NORCAP arm, 33 patients [66%] in the GEMPAC arm, and 39 patients [76%] in the GEMDOC arm). For the week 18 assessment, evaluable questionnaires were available from 17, 25, and 26 patients in the NORCAP, GEMPAC, and GEMDOC treatment arms, respectively. Quality of life results at weeks 6, 12, and 18 indicated modest changes from baseline for the different subscales in all 3 treatment arms. There was no evidence of a detrimental effect of NORCAP on quality of life, although the limited sample size and attrition limit the ability to interpret the results.

Poststudy Chemotherapy

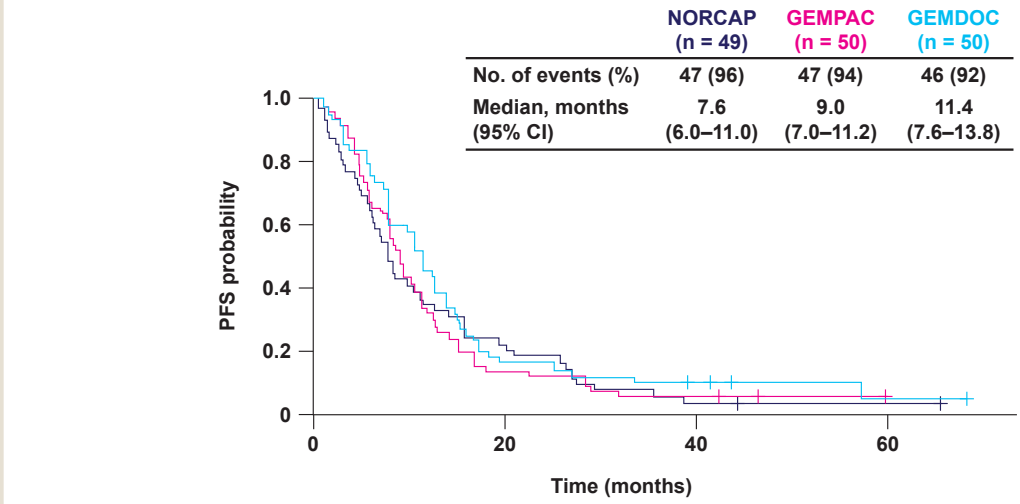
Most patients received further chemotherapy after stopping study therapy: 39 patients (80%) in the NORCAP arm (including a taxane in 29 of these 39 patients), 36 patients (72%) in the GEMPAC arm (including capecitabine in 24 of the 36 patients, an anthracycline in 21, and a taxane in 9), and 32 patients (64%) in the GEMDOC arm (including capecitabine in 29 of the 32 patients, an anthracycline in 14, and a taxane in 5).

Discussion

In this randomized phase II trial, the 73% DCR with an all-oral regimen of vinorelbine and capecitabine shows that this is an active regimen and might be offered as an alternative to first-line taxane-based therapy. The high DCR was supported by the median OS of 30 months with NORCAP—within the range observed with the 2 taxane/gemcitabine combination regimens. Median PFS was numerically longest in the GEMDOC arm and shortest in the NORCAP arm, however, the Kaplan−Meier curves were broadly overlapping, with the largest difference coinciding with the medians and smaller differences at other time points.

The efficacy of the all-oral NORCAP regimen in the present trial was consistent with findings reported by Tubiana-Mathieu et al in their phase II study in which this regimen was evaluated in the first-line setting[19] (median PFS of approximately 8 months in both studies; clinical benefit rate of 63% in the previous study vs. 73% in the present study; median OS of 29 months vs. 30 months, respectively). The efficacy of the taxane-containing regimens in the present trial was within the range reported in recent trials comparing chemotherapy doublets, taking

Figure 2 Progression-Free Survival



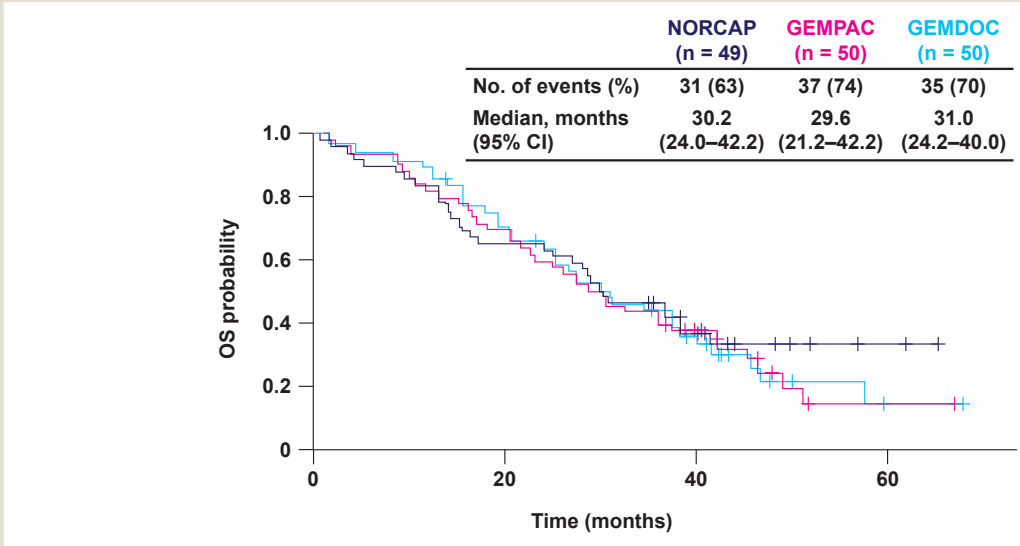
Abbreviations: GEMDOC = gemcitabine/docetaxel; GEMPAC = gemcitabine/paclitaxel; NORCAP = oral vinorelbine with oral capecitabine; PFS = progression-free survival.

into account differences in treatment setting, previous anthracycline exposure, and follow-up.[6,8-10]

The similar median OS in the 3 treatment arms is noteworthy. Although crossover to a specific chemotherapy agent after discontinuation of study treatment was not mandated, 59% of patients in the NORCAP arm subsequently received taxane-containing therapy, and 48% and 58% of patients in the GEMPAC and GEMDOC arms, respectively, received capecitabine. This observation might suggest that delaying taxane therapy until second-line or later settings does not compromise OS, although the limitations of a relatively small randomized phase II trial prevent any definitive conclusions.

The safety profile of NORCAP was characterized by neutropenia, vomiting, hand-foot syndrome, and diarrhea, consistent with the known safety profiles of oral vinorelbine (neutropenia and vomiting) and capecitabine (hand-foot syndrome and diarrhea). As with efficacy, safety findings were very similar to those reported in the phase II study by Tubiana-Mathieu et al (Grade 3/4 neutropenia in 49% of patients in the previous study vs. 50% in the present study; Grade 3/4 vomiting in 9% vs. 10%, respectively; hand-foot

Figure 3 Overall Survival



Abbreviations: GEMDOC = gemcitabine/docetaxel; GEMPAC = gemcitabine/paclitaxel; NORCAP = oral vinorelbine with oral capecitabine; OS = overall survival.

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Table 3 Summary of Grade 3 and 4 Adverse Events (Worst Grade per Patient, Irrespective of Relationship to Treatment and Occurring in >1 Patient)

Adverse Event	NORCAP (n = 49)[a]		GEMPAC (n = 50)		GEMDOC (n = 50)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Neutropenia	25	25	36	10	30	56
Fatigue	12	0	18	2	24	0
Febrile Neutropenia	0	12	0	0	0	6
Dyspnea	4	0	6	4	4	0
Vomiting	10	0	2	0	2	0
Nausea	8	0	4	0	2	0
Anemia	0	2	4	0	8	0
Hand-Foot Syndrome	8	0	0	0	0	0
Diarrhea	6	0	6	0	2	2
Peripheral Sensory Neuropathy	4	0	6	0	2	0
Abdominal Pain	6	0	2	0	0	0
Thrombocytopenia	0	0	0	0	2	4
Ileus	4	2	0	0	0	0
Pleural Effusion	2	0	4	2	2	0
Pulmonary Embolism	0	6	0	0	0	2
Deep Vein Thrombosis	6	0	0	0	4	0
Urinary Tract Infection	2	0	6	0	0	0
Neutropenic Infection	4	0	0	0	6	0
Syncope	2	0	6	0	0	0
Peripheral Edema	0	0	0	0	6	0
Myalgia	2	0	4	0	2	0
Dehydration	2	2	0	2	2	0
Anorexia	2	2	0	0	0	0
Back Pain	4	0	0	0	2	0
Bone Pain	0	0	4	0	2	0
Hip Fracture	4	0	0	0	0	0
Stomatitis	2	0	0	0	2	0
Paresthesia	0	2	2	0	0	0

Data are presented as percentages of patients.
Abbreviations: GEMDOC = gemcitabine/docetaxel; GEMPAC = gemcitabine/paclitaxel; NORCAP = oral vinorelbine with oral capecitabine.
[a]One patient was unevaluable for hematological toxicity.

syndrome in 4% vs. 8%, respectively).[19] As anticipated, the incidence of Grade 2 alopecia was very low with the oral doublet (8%), in contrast to rates of 72% and 76% with the 2 taxane-containing regimens. This might be an important consideration when discussing treatment options with patients. The good tolerability of the NORCAP regimen is also suggested by the relatively high dose intensity delivered. Quality of life analyses were limited by the small numbers of patients available in each arm at each time point, but no detrimental effect on quality of life was observed in the NORCAP arm.

The patient population in the present trial had relatively aggressive disease, including visceral metastases in more than three-quarters of patients, and patients were considered suitable for combination chemotherapy. Although the study design did not enable comparisons with sequential administration of single-agent vinorelbine and capecitabine, a previously published randomized trial that compared these strategies suggested that, despite similar efficacy of the combination and sequential regimens in the overall population of patients, PFS and OS were significantly better with combination therapy than with sequential administration in the subset of patients with liver metastases,[15] representing a population corresponding more closely to those requiring combination chemotherapy.

As noted previously, one of the limitations of the present trial is the relatively small sample size, which prevented statistical power to compare efficacy between the 3 regimens. However, several large randomized phase III trials that compared different chemotherapy doublets or schedules of chemotherapy doublets have failed to detect significant differences in efficacy.[6,7,10,13] The potential benefits of the all-oral combination relate more to tolerability, patient acceptability, and reduced effect on daily activities than anticipated superior efficacy, and noninferiority trials bring other challenges, including the need for even larger sample sizes.[24]

Another potential criticism might be the choice of comparator regimens. In many countries, bevacizumab is approved in combination with either paclitaxel or capecitabine as first-line therapy for HER2-negative mBC, and might offer similar efficacy to chemotherapy doublets and avoidance of alopecia.[25,26] However,

the toxicity profile of bevacizumab is not insignificant and for this reason, this agent is not available as a reimbursed anticancer therapy in many countries. An alternative regimen—weekly single-agent paclitaxel—has shown improved efficacy and tolerability compared with gemcitabine and docetaxel in a randomized phase III trial,[8] although 44% of patients reported Grade 3 alopecia. Regardless of such comparisons, the present trial showed that an all-oral regimen of NORCAP is active, with a high DCR and OS duration similar to that seen with taxane-based intravenous regimens. NORCAP might be offered as an active alternative to chemotherapy doublets in patients who require intensive therapy but with a preference for oral over intravenous therapy, or who wish to avoid alopecia, or whose disease has progressed rapidly with primary taxane-containing therapy. These findings are similar to the conclusions of the randomized phase II trial in anthracycline-pretreated mBC, in which the efficacy of all-oral NORCAP combination therapy was reported to be similar to that of capecitabine and docetaxel combination therapy.[27]

Conclusion

All-oral NORCAP should be considered when discussing first-line treatment options with patients, particularly if avoidance of alopecia or frequent clinic visits for intravenous therapy are important to individual patients.

Clinical Practice Points

- In some situations, chemotherapy doublets are the preferred first-line treatment option for mBC, yet there is no standard first-line chemotherapy doublet regimen. Taxane-based combination regimens are associated with substantial toxicity and the inconvenience of intravenous administration.
- In this 3-arm randomized phase II trial, an all-oral regimen of NORCAP showed a DCR of 73% (95% CI, 59%-85%), similar to the rates observed with intravenous taxane-based regimens and exceeding the threshold defined as clinically active when the trial was designed.
- Median PFS was slightly shorter with the all-oral regimen than the taxane-based regimens, but median OS was remarkably similar at 30 to 31 months with all 3 regimens.
- Grade 2 alopecia occurred in approximately three-quarters of patients who received taxane-based doublets but only 8% of patients who received the all-oral nontaxane regimen.
- On the basis of these results, we consider that an all-oral NORCAP regimen is an active first-line chemotherapy doublet and might be offered as an alternative to first-line taxane-containing doublets for HER2-negative mBC, particularly if patients wish to avoid alopecia or frequent clinic visits for intravenous therapy administration.

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Disclosure

A. Chan has acted in a consultant/advisory role for Amgen and Eisai and has received travel expenses from Pierre Fabre. A. Barnadas has acted in a consultant/advisory role for Pierre Fabre. D. Rauch has acted in a consultant/advisory role for Pierre Fabre. G. Villanova is an employee of Pierre Fabre. The remaining authors have stated that they have no conflicts of interest.

Supplemental Data

Supplemental table accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.clbc.2016.06.014.

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Supplemental Table 1 Management of Hematological Toxicity With Oral Vinorelbine/Capecitabine

Toxicity	Cycle 1, Day 8	Cycle 2 and Onward, Day 1	Cycle 2 and Onward, Day 8
Grade 0/1 (Neutrophil Count ≥1.5 × 10^9/L and Platelet Count ≥75 × 10^9/L)	No vinorelbine or capecitabine dose modification		
Grade 2 (Neutrophil Count ≥1 and <1.5 × 10^9/L and/or Platelet Count ≥50 and <75 × 10^9/L)	Hold vinorelbine. If resolved to Grade 0/1 by day 10, administer on day 10 at 60 mg/m^2 No capecitabine dose modification	Delay vinorelbine and interrupt capecitabine until day 8 Restart vinorelbine at 80 mg/m^2 and capecitabine at 1000 mg/m^2	Hold vinorelbine. If resolved to Grade 0/1 by day 10, administer on day 10 at 60 mg/m^2 No capecitabine dose modification
Grade 3 (Neutrophil Count ≥0.5 and <1 × 10^9/L and/or Platelet Count ≥10 and <50 × 10^9/L)	Omit vinorelbine. If resolved to Grade ≤2 by day 15, restart cycle 2 at 80 mg/m^2. If Grade 3/4, administer at 60 mg/m^2 for all subsequent cycles (no dose escalation) Interrupt capecitabine until resolved to Grade ≤2, then restart at 1000 mg/m^2	Delay vinorelbine. If resolved to Grade ≤2 by day 8, restart the next cycle at 80 mg/m^2 when resolved to Grade 0/1. If Grade 3/4 at day 8, administer at 60 mg/m^2 when resolved to Grade 0/1 and do not escalate for any subsequent cycle Interrupt capecitabine until day 8, then restart at 1000 mg/m^2	Omit vinorelbine. If resolved to Grade ≤2 by day 15, restart the next cycle at 80 mg/m^2. If Grade 3/4, administer at 60 mg/m^2 for all subsequent cycles (no dose escalation) Interrupt capecitabine until resolved to Grade ≤2, then restart at the same dose as the previous cycle
Grade 4 (Neutrophil Count <0.5 × 10^9/L and/or Platelet Count <10 × 10^9/L)	Omit vinorelbine. Administer at 60 mg/m^2 for all subsequent cycles (no dose escalation) Interrupt capecitabine for the rest of the cycle. Restart at 750 mg/m^2 at cycle 2	Delay vinorelbine. Administer at 60 mg/m^2 for all subsequent cycles (no dose escalation) Interrupt capecitabine for 1 week. Restart at 75% of the previous dose	Omit vinorelbine. Administer at 60 mg/m^2 for all subsequent cycles (no dose escalation) Interrupt capecitabine for the rest of the cycle. Restart at 75% of the dose given in the previous cycle