# Phase II study of an oxaliplatin/vinorelbine combination in patients with anthracycline- and taxane-pre-treated metastatic breast cancer

Thierry Petit[a], Abdellatif Benider[b], Alejandro Yovine[c], Philippe Bougnoux[d], Dominique Spaeth[e], Frédérique Maindrault-Goebel[f], Daniel Serin[g], Jean-Dominique Tigaud[h], Jean Christophe Eymard[i], Hélène Simon[j], Brigitte Bertaux[k], Silvano Brienza[k] and Esteban Cvitkovic[c]

**A phase II study was conducted to evaluate the safety and efficacy of an oxaliplatin (OXA)/vinorelbine (VNB) combination in metastatic breast cancer (MBC) patients pre-treated with anthracyclines and taxanes. Patients received OXA at 130 mg/m$^2$ (2-h i.v.), day 1, and VNB days 1 and 8 at 24–26 mg/m$^2$ repeated every 3 weeks. Forty-two patients (median age 54; 64% with liver metastasis, 67% taxane resistant/refractory and 38% anthracycline resistant/refractory) were treated. A median of 4 cycles of treatment was given per patient, with 31% receiving 6 or more. Eleven partial responses and 16 patients with stable disease (five lasting more than 4 months) in 41 eligible patients were seen, for an overall response rate of 26.8% (95% confidence interval 14.2–42.9). Median follow-up was 15.9 months (7.2–30.6), median time to progression was 3.4 months and estimated overall survival was 12.7 months (20 events). Thirty-three patients experienced (National Cancer Institute Common Toxicity Criteria version 2) grade 3–4 neutropenia (one case of febrile neutropenia) and three patients had severe constipation requiring hospitalization. Nine patients developed grade 3 OXA-specific neurotoxicity. There were no treatment-related deaths. We conclude that OXA 130 mg/m$^2$ (day 1) and VNB 24 mg/m$^2$ (day 1 and 8) combination given every 3 weeks is effective with a good safety profile in MBC patients previously treated with anthracyclines and taxanes.** *Anti-Cancer Drugs* **17:337–343 © 2006 Lippincott Williams & Wilkins.**

**Anti-Cancer Drugs** 2006, **17**:337–343

**Keywords: anthracycline, breast cancer, oxaliplatin, pre-treated, taxane, vinorelbine**

[a]Centre Paul Strauss, Strasbourg, France, [b]Centre d'Oncologie, CHU Averroes, Casablanca, Morocco, [c]CAC, Kremlin-Bicêtre, France, [d]CHU Bretonneau, Clinique d'Oncologie et Radiothérapie, Tours, France, [e]Centre Alexis Vautrin, Vandoeuvre Les Nancy, France, [f]Hôpital Saint Antoine, Paris, France, [g]Clinique Sainte Catherine, Avignon, France, [h]Hôpital Edouard Herriot, Lyon, France, [i]Institut Jean Godinot, Reims, France, [j]CHU de Brest–Hôpital Morvan, Brest, France and [k]Debioclinic, Charenton le Pont, France.

Correspondence to A. Yovine, CAC, 18–20 rue Pasteur, 94278 Le Kremlin-Bicêtre, France.
Tel: +33 1 45 15 40 40; fax: +33 1 45 15 40 41;
e-mail: a.yovine@caconcology.com

**Received** 26 August 2005 **Accepted** 30 November 2005

## Introduction

Breast cancer is the most common cancer diagnosed in women and is second to lung cancer in terms of female mortality [1]. Despite improvements in control of localized disease, recurrent metastatic breast cancer (MBC) remains common and survival from first relapse is approximately 2 years, depending on multiple prognostic factors [2]. Systemic chemotherapy is widely used in MBC; the most commonly used agents being anthracyclines and taxanes, with growing evidence that patients may benefit from the combined application of both compounds [3]. Their combination, both in adjuvant and first-line metastatic settings, is rapidly increasing, creating a need for new treatment strategies for patients with progressive disease after these therapies or at risk of developing cumulative toxicities.

The success of further chemotherapies after failure of anthracyclines and taxanes has been generally modest. Active single agents yield response rates of 15–30% in this setting [4–7] and their sequential use is preferred for the management of patients with limited asymptomatic disease. For patients with more extensive or symptomatic disease, many oncologists prefer combination therapies because, even if the advantage in terms of survival has not been demonstrated to date, they seem to offer better results in terms of response rate and progression-free survival that could be translated to better control of symptoms. The most promising combinations are those including 5-fluorouracil (5-FU) or capecitabine with platinum compounds, vinorelbine (VNB) or gemcitabine [8–11]. However, the best choice of treatment in this difficult clinical setting is still a matter of controversy and requires further investigation.

VNB, a vinca alkaloid derivative, interferes with tubulin assembly during mitosis and is active as a single agent in MBC, with response rates of 15–44% depending on

0959-4973 

previous treatment [4,12,13]. VNB has been extensively evaluated in combination regimens and remarkable results have been achieved in combination with taxanes [14], 5-FU [15,16] and cisplatin [11]. The main dose-limiting toxicities are severe neutropenia, peripheral sensory neuropathy and neuro-constipation.

Oxaliplatin (OXA) is a diaminocyclohexane platinum compound that binds DNA, blocking replication and transcription, resulting in apoptosis [17]. Cells with mismatch repair deficiency, resistant to a variety of anti-cancer drugs including doxorubicin and several platinum compounds, are sensitive to OXA [18,19]. Human breast cancer has shown decreased mismatch repair with epigenetic mechanisms after doxorubicin-based treatment [20]. OXA has shown preclinical activity in paclitaxel- and anthracycline-resistant cell lines and additive or synergistic cytotoxicity with most agents tested to date [18]. It has shown activity in MBC patients previously treated with anthracyclines and/or taxanes both as a single agent [21] and in combination with 5-FU [8]. It has a favorable safety profile, limited to mild hematotoxicity and characteristic cumulative neurosensory toxicity that is largely reversible after treatment discontinuation [22].

The rationale for combining OXA and VNB in this phase II trial was that both are active in MBC, and each agent has a different mechanism of action, which may aid in circumventing resistance. Furthermore, preclinical synergy has been reported between VNB and platinum compounds [18,23]. Another phase II trial was started simultaneously to investigate the addition of continuous infusion 5-FU to the OXA/NVB combination in the same indication [24].

OXA 130 mg/m$^2$ every 3 weeks and VNB 26 mg/m$^2$ on days 1 and 8 of a 21-day cycle has been shown to be feasible and safe in non-small cell lung cancer [25]. Given the prevalence of hepatic metastases in MBC, a factor that alters the pharmacodynamics of VNB, a slightly lower starting dose of VNB (24 mg/m$^2$/day) was used in this study to provide a wider safety profile for pre-treated and fragile patients [26].

## Patients and methods

Women over 18 years old with a WHO performance status (PS) of 2 or better and confirmed MBC were eligible. To be eligible, patients had to have received at least one taxane-based regimen and an anthracycline regimen administered either as adjuvant therapy or for metastatic disease, and no more than three lines of chemotherapy (including adjuvant treatment); have documented disease progression within 12 months of the most recent taxane-containing regimen; and at least one unidimensionally measurable lesion measured by appropriate imaging within 4 weeks of inclusion. Patients were excluded if they had received previous chemotherapy within 4 weeks of enrollment (6 weeks for nitrosoureas and mitomycin C) or prior radiation treatment of any target lesions; had brain metastases; had only bone metastases, carcinomatous lymphangitis, ascites or pleural effusion as proof of metastatic disease; had grade 2 or higher [National Cancer Institute Common Toxicity Criteria (NCI-CTC)] peripheral neuropathy; or had received prior treatment with either of the trial drugs or any other platinum compound. Signed informed consent was obtained from all patients according to French and Moroccan legal requirements.

This was a multicenter, phase II, single-arm trial of the combination of VNB given as an i.v. bolus of 24 mg/m$^2$ on days 1 and 8, and OXA given on day 1 over 2 h every 3 weeks. In patients with less than grade 2 toxicity during cycle 1, VNB was to be increased to 26 mg/m$^2$ on days 1 and 8 for subsequent cycles. Treatment was continued until disease progression, unacceptable toxicity or patient refusal. If grade 4 thrombocytopenia and/or grade 4 neutropenia occurred, day 8 VNB was omitted. If these toxicities lasted more than 1 week or were accompanied by fever or infection, the OXA dose was reduced to 100 mg/m$^2$ and VNB was reduced by successive steps of 2 mg/m$^2$ to a minimum of 20 mg/m$^2$ before treatment was discontinued. Doses were delayed to allow the patient to recover to at least 1500 neutrophils/mm$^3$ or 100 000 platelets/mm$^3$, with a maximum delay of 2 weeks before the patient was taken off study. No granulocyte colony-stimulating factor was to be used. If acute pharyngolaryngeal dysesthesia occurred, the OXA infusion was made over 6 h. In the event of paresthesia accompanied by pain lasting for more than 1 week, OXA was reduced to 100 mg/m$^2$ and VNB to 22 mg/m$^2$, as was the case for any other neurotoxicity lasting for at least 21 days or with functional impairment lasting between 1 and 3 weeks. If symptoms persisted the dose could be reduced to a minimum of 85 mg/m$^2$ OXA and 20 mg/m$^2$ VNB. Treatment was discontinued if functional impairment or continuation of symptoms persisted despite maximal dose reduction. No dose re-escalation was permitted.

Using a Simon two-stage minimax design (10% lowest response rate, 25% optimal response rate, 5% $\alpha$ error, 20% $\beta$ error), 40 patients were required [27]. Twenty-two patients were planned in a first step. If three or more responses were observed in this cohort, at least 18 additional patients were planned.

Safety was assessed according to NCI-CTC version 2, except for neurotoxicity, which was assessed according to an OXA-specific scale adapted from Lévi *et al.* [28]. Tumor response was assessed by the investigator using RECIST criteria [29]. To be considered evaluable for

efficacy patients had to have received at least 2 treatment cycles or have early disease progression. Efficacy was analyzed only in eligible patients, and according to clinical resistance status with respect to anthracyclines and taxanes. Several definitions of clinical resistance have been proposed [8,11,21,30–32], but none is universally accepted or prospectively validated, and all are arbitrary and exploratory. For this study, patients were considered to be refractory/resistant when disease progression could be reliably established within 6 months of the last drug administration in adjuvant treatment and/or within 3 months of last administration for metastatic disease. All other patients were assessed as potentially sensitive (modified from [30]).

Median time to progression (TTP) and overall survival were calculated using the Kaplan–Meier method, based on all eligible patients. The data acquisition cut-off date was 26 February 2003.

## Results

Forty-two patients were treated between August 2000 and July 2002 in a total of nine centers in France and Morocco. One patient was considered ineligible after being identified as having documented disease progression 45 months after taxane-based therapy.

Table 1 shows the characteristics of all treated patients. The median age was 54 years (range 32–72) and 90% of patients had a WHO PS of 0–1. All patients were metastatic at study entry, with liver involvement in 64% of cases.

Resistance rates to anthracyclines and more particularly taxanes were high, with 28 patients (67%) being assessed as taxane refractory/resistant and 16 patients (38%) as anthracycline refractory/resistant. Overall, 13 patients (31%) were assessed as refractory/resistant to both agents.

Of the 41 eligible patients, three had no evaluation of response because they withdrew due to toxicity after 1 cycle; one patient experienced grade 2 cold-related dysesthesia and pharyngo-laryngeal spasm, another had grade 2 asthenia with nausea and vomiting, and the third had grade 3 vomiting with dehydration, weight loss and persistent grade 2 paresthesia.

Eleven partial responses were reported in the 41 eligible patients, giving an overall response rate of 26.8% [95% confidence interval (CI) 14.2–42.9; Table 2]. Sixteen patients had stable disease, lasting 4 months or more in five patients. The primary site of metastatic disease for the majority of responders (82%) was the liver, with bone 45% and lymph nodes 45%. These responding patients received a median of 6 cycles of treatment (range 3–9).

**Table 1 Patient characteristics at study entry**

| | Total ($n=42$) |
|---|---|
| Age (years) [median (range)] | 54 (32–72) |
| WHO PS 0/1/2 | 26/12/4 |
| Disease characteristics at diagnosis [*n* (%)] | |
| local or locally advanced | 36 (82) |
| metastatic | 8 (18) |
| No. involved organs [median (range)] | 2.5 (1–7) |
| Site of involved organs [*n* (%)] | |
| liver | 27 (64) |
| lymph nodes | 17 (41) |
| bone | 17 (41) |
| lung | 17 (41) |
| pleural | 10 (24) |
| breast ipsilateral | 10 (24) |
| skin | 6 (14) |
| Abnormal laboratory parameters [*n* (%)] | |
| LDH elevated | 21 (50) |
| CA 15-3 50–299 IU/ml | 16 (38) |
| CA 15-3 $\geq$ 300 IU/ml | 6 (14) |
| Prior surgery [*n* (%)] | 39 (93) |
| Prior radiotherapy [*n* (%)] | 34 (81) |
| No. prior lines chemotherapy [*n* (%)] | |
| 1 | 4 (10) |
| 2 | 25 (60) |
| 3 | 13 (31) |
| Time since last chemotherapy (months) [*n* (%)] | |
| $<2$ | 20 (48) |
| 2–8 | 13 (31) |
| $\geq 8$ | 9 (21) |
| Status after prior chemotherapy [*n* (%)] | |
| taxane refractory/resistant | 28 (67) |
| anthracycline refractory/resistant | 16 (38) |
| refractory/resistant to both | 13 (31) |
| Median time between last chemotherapy and study treatment (months) [*n* (%)] | 2.23 |
| Prior hormone therapy [*n* (%)] | 28 (67) |
| Positive hormonal receptors [*n* (%)] | 15 (36) |

**Table 2 Patient response in eligible patients**

| | Total ($n=41$) |
|---|---|
| Partial response | 11 |
| Stable disease[a] | 16 |
| Progressive disease | 11 |
| No effect | 3 |
| Overall response rate (95% CI) | 26.8% (14.2–42.9) |

[a]Including three patients with unconfirmed partial response/five patients lasting 4 months or more.

A response was observed in three of 15 (20%) patients refractory/resistant to taxanes, and two of 13 (15%) patients refractory/resistant to anthracycline and taxanes (Table 3).

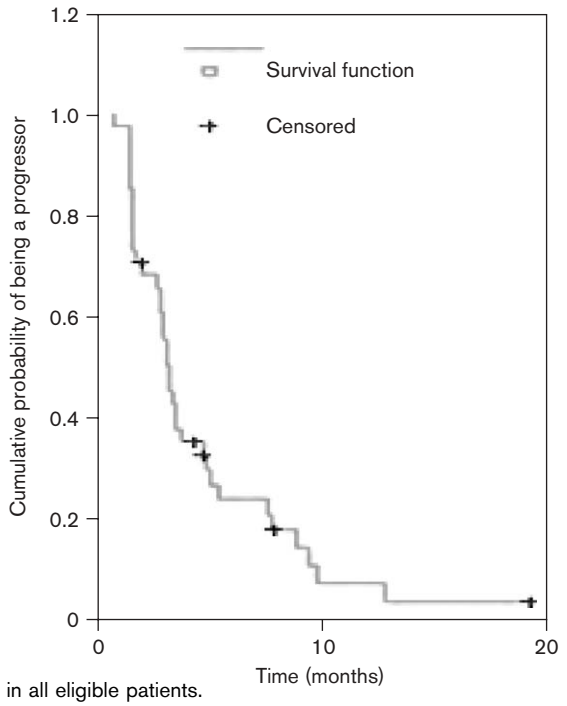
The median response duration for the 27 eligible patients with either a partial response or stable disease was 3.1 months (95% CI 2.8–3.4); seven patients had responses lasting 6 months or more (6.3, 7.9, 8.2, 10.7, 6.1 + , 8.3 + and 17.0 + months). Median TTP in the 41 eligible patients was 3.4 months (95% CI 2.0–4.8; Fig. 1). As of 26 February 2003, with a median follow-up of 15.9 months (7.2–30.6), 22 patients (54%) were still alive and the median overall survival was estimated at 12.7 months (95% CI 7.7–17.6).

**Table 3 Resistance status of responding patients compared with all eligible patients (responders/eligible)**

| Anthracycline status | Taxane status | |
|---|---|---|
| | Sensitive ($n=13$) | Resistant/refractory ($n=28$) |
| Sensitive ($n=26$) | 6/11 | 3/15 |
| Resistant/refractory ($n=15$) | 0/2 | 2/13 |

Includes all the responders at dose level 2.

**Fig. 1**




TTP in all eligible patients.

In 29 of the 42 treated patients (69%), the dose of VNB was not increased at cycle 2, due to neutropenia (21 patients), nausea/vomiting (five patients), asthenia (four patients) and neuro-constipation (two patients). In two patients, the dose was not increased despite the absence of toxicity after cycle 1.

In total, 189 cycles were administered with a median of 4 cycles per patient (range 1–9). Thirteen patients (31%) received 6 cycles or more. While the relative dose intensity for patients receiving fewer than 4 cycles was 0.98 for OXA and 0.82 for VNB, these figures fell to 0.84 and 0.77, respectively, for patients receiving more than 6 cycles. Twenty-nine patients experienced delay of at least 1 cycle, with 11 patients (28%) experiencing 3 or more. In total, 65 cycles were delayed, although only 15 were for more than 1 week. Cycle delays were mainly due to hematological toxicity (69%), particularly neutropenia and neurotoxicity.

**Table 4 Worst toxicities per patient (NCI-CTC) ($n=42$)**

| | Grade 3 [*n* (%)] | Grade 4 [*n* (%)] | Grade 3/4 [*n* (%)] |
|---|---|---|---|
| Neutropenia | 13 (31) | 20 (48) | 33 (79) |
| Anemia | 2 (5) | 1 (2) | 3 (7) |
| Thrombocytopenia | 7 (17) | – | 7 (17) |
| Constipation | 2 (5) | 1 (2) | 3 (7) |
| Nausea | 3 (7) | – | 3 (7) |
| Vomiting | 2 (5) | – | 2 (5) |
| Neurological toxicities[a] | 9 (21) | | |

[a]According to the OXA-specific scale [28]

Sixteen patients (38%) experienced at least one dose reduction accounting for a total of 22 dose reductions – eight involving both agents, nine OXA alone and five VNB alone. Dose reductions were due to neurotoxicity (seven patients), hematotoxicity (five patients) and gastrointestinal toxicity (four patients). The administration of VNB on day 8 was delayed for more than 3 days in five instances and was canceled 39 times (21% of cycles).

The most common toxicities were hematological and neurological (Table 4). Thirty-three patients (79%) experienced grade 3–4 neutropenia including 20 (48%) with grade 4 neutropenia, although there was only one case of febrile neutropenia. Three patients experienced grade 3–4 neuro-constipation requiring hospitalization a total of 5 times. Peripheral neurotoxicity (OXA-specific scale) was mostly mild to moderate with nine patients (21%) experiencing grade 3 toxicity. The median cumulative OXA dose for these nine patients was 731.3 mg/m$^2$ – almost 50% higher than the median cumulative OXA dose in all treated patients (501.3 mg/m$^2$; Table 5).

## Discussion

Finding an appropriate treatment for MBC in patients who have already exhausted standard options of taxanes and anthracyclines is currently critical. The problem of cumulative toxicity is compounded by drug cross-resistance. As long-term survival prospects are relatively poor, it is essential to provide palliative treatment, reducing the tumor burden without excessive toxicity. The single-agent versus combination question in this setting is still a matter of controversy. In the absence of randomized trials, combination therapy could be proposed to and patients with high-volume visceral or symptomatic disease. The present OXA/VNB combination was conceived in this light, and the study aimed to determine the safety profile and the activity of the combination in this particular setting.

The response rate of 27%, the median TTP of 3.4 months and the median overall survival of 12.7 months achieved in this study fall within the range of a number of other single-agent and combination regimens that have been evaluated in this indication [5,6,8–11,24,33–36], although higher response rates and/or median TTP have been

**Table 5 Neurological clinical toxicity according to OXA cumulative dose[a]**

| | Grade 0 | Grade 1 | Grade 2 | Grade 3 | Total |
|---|---|---|---|---|---|
| Cumulative OXA dose (mg/m$^2$) | | | | | |
| median | 128.9 | 487.4 | 490.6 | 731.3 | 501.3 |
| range | – | 226.4–1173.4 | 128.5–1195.9 | 257.4–1061.0 | 128.5–1195.9 |
| Cumulative VNB dose (mg/m$^2$) | | | | | |
| median | 23.6 | 165.3 | 183.6 | 211.5 | 172.9 |
| range | – | 90.6–392.6 | 48.1–386.8 | 45.2–416.1 | 23.6–416.1 |

[a]According to the OXA-specific scale [28]

reported in regimens incorporating 5-FU or capecitabine in two- or three-agent combinations with OXA, VNB or gemcitabine or cisplatin. Single-agent capecitabine has been demonstrated to be effective in this setting with an overall response rate of 9–28%, a median TTP of 3.5–4.9 months and an overall survival of 9.4–15.2 months in several phase II–III trials [6,7,37,38]. The main drawback observed with capecitabine monotherapy is the 10–20% rate of discontinuation and up to 40% reduction of the recommended dose, mostly due to gastrointestinal toxicity and hand–foot syndrome.

The response rate reported for the combination of cisplatin and VNB in a phase II trial in 36 patients [11] (47.2% including 5.6% complete responses) is among the highest ever in this setting. However, the median TTP and overall survival (3.7 and 8.3 months, respectively) observed are in line with those observed in our study. With the combination of OXA and 5-FU [8], a response rate of 27% (95% CI 16.3–39.1) with a median TTP of 4.8 months and median overall survival of 11.9 months were reported. Interesting preliminary results of a randomized trial comparing 5-FU combined with either OXA or VNB have recently been presented in an abstract [39]. Response rates observed in both arms compare well with our study (5-FU-VNB: 27.5%; 5-FU-OXA: 23.5%) although both arms had slightly higher TTP and overall survival (5-FU-VNB: TTP: 5.3 months, overall survival: 16.4 months; 5-FU-OXA: TTP: 4.4 months, overall survival: 14.1 months). Another trial using the triple combination of OXA/VNB/5-FU in the same indication has also been recently reported in an abstract with an overall response rate of 34.8% (95% CI 21.3–50.3%), a TTP of 5.67 months and an estimated overall survival of 18.75 months. Of interest, an unpublished pilot phase II trial of single-agent OXA in the same indication was stopped early due to a lack of objective response among patients before the interim analysis (four of 16 patients with stable disease).

It should be noted that in the present study four of the 11 partial responses lasted for at least 6 months, while 82% of responders had liver metastases. Indeed, patients had multiple disease sites including a prevalence of visceral metastases and a significant number had evidence of high tumor burden, including 50% with elevated lactate dehydrogenase and 52% with more than 50 IU/ml CA15-3 at baseline. In addition, 67% were resistant or refractory to taxanes and 38% were resistant or refractory to anthracyclines, with 31% resistant and/or refractory to both. Interestingly, responses were observed within all categories of resistance status.

Taking into account the prior exposure of the cohort, the treatment was reasonably well tolerated. Overall, 30% of patients received at least 6 cycles of treatment, although the relative dose intensity of both agents decreased in patients receiving more than 3 cycles due to treatment delay, mainly hemato- and neurotoxicity. Neutropenia was widespread and often grade 3–4, as expected with VNB considering the population's pre-treatment profile. However, grade 3–4 neutropenia was complicated with fever in only one patient (2%). This compares well with other combinations such as 5-FU/OXA (0–2%) or cisplatin/VNB (0%) and is lower than with the 5-FU/VNB combination (up to 33%) in this setting [8,11,36,39,40]. No hematological growth factors were administered during this trial, required in almost 50% of patients treated with cisplatin/VNB [11].

Neurotoxicity, as expected, was linked to the cumulative dose of both compounds. All patients who received more than 600 mg/m$^2$ OXA and more than 140 mg/m$^2$ VNB experienced at least grade 1 toxicity. The level of grade 3 OXA-specific scale neuropathy observed (21%) is higher than observed with the 5-FU/OXA combination (6–8%) and with the cisplatin/NVB combination (3%). It should be noted, however, that in the trial with the cisplatin/NVB combination [11], the number of cycles was limited to 6 and the evaluation of neuropathy was performed using a different scale (WHO scale), which makes observations difficult to compare. The occurrence of five cases in three patients of grade 3–4 neuro-constipation requiring hospitalization is of concern. This severe constipation is thought to be related to VNB, but may be aggravated by its combination with OXA. Otherwise, most toxicities were mild to moderate. As the majority of patients did not have an increased VNB dose at cycle 2 due to toxicity experienced during the first cycle, 24 mg/m$^2$ VNB should be retained as the recommended dose for this combination. It should be noted, however, that in 11% of cycles at the recommended dose one of

the two agents was reduced and in 21% of cycles the day 8 infusion of VNB was canceled.

This OXA (130 mg/m$^2$ 2-h infusion day 1) and VNB (24 mg/m$^2$/day, days 1 and 8) combination, administered every 3 weeks, is active and can be safely administered to MBC patients previously treated with taxanes and anthracyclines, and who have relapsed within 12 months of taxane chemotherapy. Other combinations including both study compounds are being investigated for use in this difficult clinical context.

## References


1 American Cancer Society. *Cancer facts and figures*. Washington, DC: ACS; 2004.

2 Insa A, Lluch A, Prosper F, Marugan I, Martinez-Agullo A, Garcia-Conde J. Prognostic factors predicting survival from first recurrence in patients with metastatic breast cancer: analysis of 439 patients. *Breast Cancer Res Treat* 1999; **56**:67–78.

3 Sledge GW, Neuberg D, Bernardo P, Ingle JN, Martino S, Rowinsky E, *et al.* Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: an intergroup trial (E1193). *J Clin Oncol* 2003; **21**:588–592.

4 Livingston R, Ellis G, Gralow J, Williams MA, White R, McGuirt C, *et al.* Dose-intensive vinorelbine with current granulocyte colony-stimulating factor support in paclitaxel-refractory metastatic breast cancer. *J Clin Oncol* 1997; **15**:1395–400.

5 Spielmann M, Martin M, Namer M, duBois A, Unger C, Dodwell DJ. Activity of pemetrexed (ALIMTA, multitargeted antifolate, LY231514) in metastatic breast cancer patients previously treated with an anthracycline and a taxane: an interim analysis. *Clin Breast Cancer* 2001; **2**:47–51.

6 Fumoleau P, Largiller R, Clippe C, Dieras V, Orfeuvre H, Lesimple T, *et al.* Multicentre, phase II study evaluating capecitabine monotherapy in patients with anthracycline- and taxane-pretreated meastatic breast cancer. *Eur J Cancer* 2004; **40**:536–542.

7 Reichardt P, von Minckwitz G, Thuss-Patience PC, Jonat W, Kolbl H, Janicke F, *et al.* Multicenter phase II study of oral capecitabine (Xeloda) in patients with metastatic breast cancer relapsing after treatment with a taxane-containing therapy. *Ann Oncol* 2003; **14**:1227–1233.

8 Zelek L, Cottu P, Tubiana-Hulin M, Vannetzel JM, Chollet P, Misset JL, *et al.* Phase II study of oxaliplatin and fluorouracil in taxane- and anthracycline-pretreated breast cancer patients. *J Clin Oncol* 2002; **20**:2551–2558.

9 Razis E, Kosmidis P, Aravantinos G, Bakoyiannis C, Janinis J, Timotheadou H, *et al.* Second line chemotherapy with 5-fluorouracil and vinorelbine in anthracycline and taxane pretreated patients with metastatic breast cancer. *Cancer Invest* 2004; **22**:10–15.

10 Frasci G, D'Aiuto G, Comella P, Thomas R, Capasso I, Botti G, *et al.* A phase I–II study on a gemcitabine–cyclophosphamide–fluorouracil/folinic acid triplet combination in anthracycline- and taxane-refractory breast cancer patients. *Oncology (Huntingt)* 2002; **62**:25–32.

11 Vassilomanolakis M, Koumakis G, Demiri M, Missitzis J, Barbounis V, Efremidis AP. Vinorelbine and cisplatin for metastatic breast cancer: a salvage regimen in patients progressing after docetaxel and anthracycline treatment. *Cancer Invest* 2003; **21**:497–504.

12 Weber B, Vogel C, Jones S, Harvey H, Hutchins L, Bigley J, *et al.* Intravenous vinorelbine as first-line and second-line therapy in advanced breast cancer. *J Clin Oncol* 1995; **13**:2722–2730.

13 Jones S, Winer E, Vogel C, Laufman L, Hutchins L, O'Rourke M, *et al.* Randomized comparison of vinorelbine and melphalan in anthracycline-refractory advanced breast cancer. *J Clin Oncol* 1995; **13**:2567–2574.

14 Kornek G, Ullrich-Pur H, Penz M, Haider K, Kwasny W, Depisch D, *et al.* Treatment of advanced breast cancer with vinorelbine and docetaxel with or without human granulocyte colony-stimulating factor. *J Clin Oncol* 2001; **19**:621–627.

15 Berruti A, Sperone P, Bottini A, Gorzegno G, Lorusso V, Brunelli A, *et al.* Phase II study of vinorelbine with protracted fluorouracil infusion as a second- or third-line approach for advanced breast cancer patients previously treated with anthracyclines. *J Clin Oncol* 2000; **18**:3370–377.

16 Dieras V, Extra JM, Bellissant E, Espie M, Morvan F, Pierga JY, *et al.* Efficacy and tolerance of vinorelbine and fluorouracil combination as first-line chemotherapy of advanced breast cancer: results of a phase II study using a sequential group method. *J Clin Oncol* 1996; **14**:3097–3104.

17 Woynarowski J, Faivre S, Herzig M, Arnett B, Chapman W, Trevino AV, *et al.* Oxaliplatin-induced damage of cellular DNA. *Mol Pharmacol* 2000; **58**:920–927.

18 Raymond E, Faivre S, Woynarowski J, Chaney S. Oxaliplatin: mechanism of action and antineoplastic activity. *Semin Oncol* 1998; **25**:4–12.

19 Rixe O, Ortuzar W, Alvarez M, Parker R, Reed E, Paull K, *et al.* Oxaliplatin, tetraplatin, cisplatin, and carboplatin: spectrum of activity in drug-resistant cell lines and in the cell lines of the National Cancer Institute's Anticancer Drug Screen panel. *Biochem Pharmacol* 1996; **52**:1855–1865.

20 MacKay H, Cameron D, Rawhilly D, McKean M, Paul J, Kaye S, *et al.* Reduced MLH1 expression in breast tumors after primary chemotherapy predicts disease free survival [abstract]. *Proc Am Assoc Cancer Res* 1999; **40**:492.

21 Garufi C, Nistico C, Brienza S, Vaccaro A, D'Ottavio A, Zappala A, *et al.* Single-agent oxaliplatin in pretreated advanced breast cancer patients: a phase II study. *Ann Oncol* 2001; **12**:1791–1782.

22 Raymond E, Chaney S, Taamma A, Cvitkovic E. Oxaliplatin: a review of preclinical and clinical studies. *Ann Oncol* 1998; **9**:1053–1071.

23 Ashizawa T, Asada M, Kobayashi E, Okabe M, Gomi K, Hirata T. Combination effect of navelbine (vinorelbine ditartrate) with cisplatin against murine P388 leukemia and human lung carcinoma xenografts in mice. *Anticancer Drugs* 1993; **4**:577–583.

24 Guastalla JP, Delozier T, Chollet P, Mousseau M, Delva R, Vannetzel JM, *et al.* Phase II study of a 5-fluorouracil (5-FU), oxaliplatin (OXA) and navelbine (NVB) combination (FON) in patients (pts) with advanced/metastatic breast cancer (AMBC) previously treated with anthracyclines (A) and Taxanes (T) [abstract]. *Proc Am Soc Clin Oncol* 2002; **21** (**2**): 58b.

25 Monnet I, de Cremoux CH, Soulie P, Saltiel-Voisin S, Bekradda M, Saltiel JC, *et al.* Oxaliplatin plus vinorelbine in advanced non-small-cell lung cancer: final results of a multicenter phase II study. *Ann Oncol* 2002; **13**:103–107.

26 Robieux I, Sorio R, Borsatti E, Cannizzaro R, Vitali V, Aita P, *et al.* Pharmacokinetics of vinorelbine in patients with liver metastases. *Clin Pharmacol Ther* 1996; **59**:32–40.

27 Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials* 1989; **10**:1–10.

28 Levi F, Misset JL, Brienza S, Adam R, Metzger G, Itzhaki M, *et al.* A chronopharmacologic phase II clinical trial with 5-fluorouracil, folinic acid, and oxaliplatin using an ambulatory multichannel programmable pump. High antitumor effectiveness against metastatic colorectal cancer. *Cancer* 1992; **69**:893–900.

29 Therasse P, Arbuck SG, Eisenhauer E. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 2000; **92**: 205–216.

30 Piccart M, Raymond E, Aapro M, Eisenhauer EA, Cvitkovic E. Cytotoxic agents with activity in breast cancer patients previously exposed to anthracyclines: current status and future prospects. *Eur J Cancer* 1995; **31A**:S1–S10.

31 Pivot X, Asmar L, Buzdar A, Valero V, Hortobagyi G. A unified definition of clinical anthracycline resistance breast cancer. *Br J Cancer* 2000; **82**:529–534.

32 Ravdin P. Anthracycline resistance in breast cancer: clinical applications of current knowledge. *Eur J Cancer* 2002; **31A**:S11–S14.

33 Kalbakis K, Kourousis C, Kakolyris S, Mavroudis D, Souglakos J, Agelaki S, *et al.* Salvage chemotherapy with high-dose leucovorin (LV) and 48-hour continuous infusion (CI) of 5-fluorouracil (5-FU) in combination with conventional doses of cyclophosphamide (CPM) in patients with metastatic breast cancer (MBC) pretreated with anthracycline and taxanes. *Br J Cancer* 2001; **85**:798–802.

34 Udom DI, Vigushin DM, Linardou H, Graham H, Palmieri C, Coombes R. Two weekly vinorelbine: administration in patients who have received at least two prior chemotherapy regimes for advanced breast cancer. *Eur J Cancer* 2000; **36**:177–182.

35 Campone M, Vorobiof D, Cotes-Funes H, Verrill MW, Khoo K, Slabber C, *et al.* Preliminary results of a phase II study of intravenous vinflunine as second line therapy in patients with metastatic breast cancer after anthracycline-taxane based regimen failure [abstract]. *Breast Cancer Res Treat* 2003; **82**: S85.

36 Girre V, Dalenc F, Laurence V, Jouve M, Dieras V, Pierga JY, *et al.* Vinorelbine–5-fluorouracil combination as second line chemotherapy in metastatic breast cancer (MBC) after anthracycline–taxanes combination (AT) [abstract]. *Ann Oncol* 2000; **11**:24.

37 Wist E, Sommer HH, Ostenstad B, Risberg T, Bremnes Y, Mjaaland I. Oral capecitabine in anthracycline- and taxane-pretreated advanced/metastatic breast cancer. *Acta Oncol* 2004; **43**:186–189.

38 Miller KD, Chap LI, Holmes F, Cobleigh MA, Marcom PK, Fehrenbacher L, *et al.* Randomized phase III trial of capecitabine compared with bevacizumab

plus capecitabine in patients with previously treated metastatic breast cancer. *J Clin Oncol* 2005; **23**:792–799.

39 Delaloge S, Tubiana-Hulin M, Wardley A, Del Mastro L, Santoro A, Zambelli A, *et al.* A multistep randomized phase II/III trial comparing oxaliplatin (OXA) + 5fluorouracil (FU) to vinorelbine (VIN) + FU (FUN) after taxane (T)/anthracycline (A) failure in advanced/metastatic breast cancer (MBC) patients (pts): Final results [abstract]. *Proc Am Soc Clin Oncol* 2004; **23**:41.

40 Pienkowski T, Jagiello-Gruszfeld A. Five-day infusion of fluorouracil and vinorelbine for advanced breast cancer patients treated previously with anthracyclines. *Int J Clin Pharmacol Res* 2001; **21**: 111–117.