Dose-finding and pharmacokinetic study of an all-oral combination regimen of oral vinorelbine and capecitabine for patients with metastatic breast cancer

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Purpose: A phase I study was performed to determine the maximal tolerated dose, recommended doses (RDs), safety and efficacy of oral vinorelbine when combined with capecitabine in an all-oral chemotherapy regimen in patients with metastatic breast cancer (MBC), with pharmacokinetic blood sampling to investigate potential drug–drug interactions.

Patients and methods: Forty-four patients with MBC received as first- or second-line chemotherapy, oral vinorelbine at a dose of 60 or 80 mg/m² on days 1 and 8 (and 15) with escalating doses of capecitabine from 1650 to 2500 mg/m²/day days 1–14 every 3 or 4 weeks. Three schedules were tested: day 1, day 8 and weekly regimens of oral vinorelbine with a 14-day course of capecitabine every 3 weeks; and a days 1 and 8 regimen of oral vinorelbine with a 14-day course of capecitabine every 4 weeks.

Results: With oral vinorelbine at 60 mg/m², the RDs were established as oral vinorelbine 60 mg/m² on days 1 and 8 plus capecitabine 2250 mg/m²/day days 1–14 and oral vinorelbine 60 mg/m²/week plus capecitabine 2000 mg/m²/day days 1–14. With oral vinorelbine at 80 mg/m², the RD was oral vinorelbine 80 mg/m² on days 1 and 8 plus capecitabine 2000 mg/m²/day days 1–14. Neutropenia was the main dose-limiting toxicity of the combination; it was reported in 40 patients (90.9%), with grade 3 in 14 patients (31.8%) and 6.2% of cycles, and grade 4 in 12 patients (27.3%) and 4.3% of cycles. Complications were rare with only three patients experiencing febrile neutropenia (one episode each). The most frequent non-haematological toxicity was gastrointestinal; however, the incidence of grade 3 was low, with no episode of grade 4. Hand–foot syndrome was reported in 14 patients (31.8%) and 22.6% of cycles, with grade 2 in two patients (4.5%) and 1.2% of cycles (two episodes each). No episode of grade 3 was observed. Objective responses were reported in 18 patients (three complete responses and 15 partial responses), yielding a response rate of 40.9% in the intention-to-treat population according to the investigator assessment. Results from the pharmacokinetic study demonstrated the absence of mutual pharmacokinetic interactions when both drugs were co-administered.

Conclusions: The combination of oral vinorelbine and capecitabine is safe and easy to administer in an outpatient setting. This all-oral combination chemotherapy may offer a good alternative to the intravenous route for patients with MBC. Based on these promising results, a phase II study has started using oral vinorelbine 60 mg/m²/week with capecitabine 2000 mg/m²/day days 1–14 every 3 weeks as first-line chemotherapy in patients with MBC.

Key words: metastatic breast cancer, navelbine, oral chemotherapy

introduction

Oral vinorelbine is a new formulation of intravenous (i.v.) vinorelbine. Reliable dose equivalence with the i.v. vinorelbine formulation has been demonstrated. The bioavailability is about 40%. The oral form administered at 60 and 80 mg/m² was proven to provide equivalent blood exposure to i.v. vinorelbine at 25 and 30 mg/m², respectively [1, 2]. The activity of single-agent oral vinorelbine was assessed in two multicentre phase II studies as first-line treatment of patients with metastatic breast cancer (MBC) [3, 4]. Vinorelbine was given orally at 60 mg/m²/week for the first three administrations and then increased to 80 mg/m²/week for subsequent administrations according to haematological tolerance. In these studies the efficacy of oral vinorelbine was comparable to that previously reported for i.v. vinorelbine with a similar safety profile [5–13]. The dose-limiting toxicity (DLT) of both formulations is
neutropenia, which is non-cumulative with a nadir between 7 and 14 days after administration and is rapidly reversible within 5–7 days. In combination, i.v. vinorelbine is generally administered at 25–30 mg/m² with reduced frequency, e.g. days 1 and 8 every 3 weeks.

Vinorelbine is active in advanced breast cancer in combination with other cytotoxic agents including 5-fluorouracil (5-FU) [14–21]. Owing to rapid degradation and highly variable gastrointestinal absorption, 5-FU was not suitable for oral administration. This was solved by the development of oral fluoropyrimidines such as capecitabine, which is converted to 5-FU, and mimics continuous 5-FU infusion [22]. Single-agent capecitabine is indicated for the treatment of patients with MBC after anthracyclines and taxanes failure [23]. The recommended schedule is an intermittent regimen using 2500 mg/m²/day for 2 weeks with 1 week off [24, 25]. Combination of i.v. vinorelbine and capecitabine has been investigated through several phase I–II studies in chemotherapy naïve or pretreated MBC patients [26–31]. Preliminary results from these studies showed that the combination is feasible and active, with response rates of 33–68%.

Based on this clinical experience, we investigated the combination of oral vinorelbine and capecitabine regimen to establish the optimal doses and schedules for phase II trial, and to investigate potential drug–drug interactions when co-administered.

patients and methods

The study protocol and its amendments were reviewed and approved by the ethics committee of the European Institute of Oncology, Milan, Italy. The trial was designed according to the current revised Declaration of Helsinki and conducted in accordance with Good Clinical Practice guidelines. Written informed consent was obtained from each participating patient before entry into the study. The cut-off date for analysis was 24 September 2004.

patient selection

The study was initiated in June 2001 and closed to accrual in February 2004. All enrolled patients had histologically confirmed MBC with a maximum of one previous chemotherapy. Adjuvant chemotherapy, which could have contained anthracycline and/or taxanes, was allowed provided that an interval of at least 1 month had elapsed between the end of chemotherapy and study entry. Other eligibility criteria were: age ≥18 and ≤75 years; Karnofsky performance status ≥70; initial blood parameters of haemoglobin ≥10 g/dl, granulocytes (absolute neutrophil count) ≥2 × 10⁹/l, platelets ≥100 × 10⁹/l; bilirubin ≤1.5 x the upper limit of normal (ULN); transaminases ≤2.5 × ULN; calculated creatinine ≤250 ml/min (Cockcroft–Gault formula); and presence of at least one evaluable or measurable lesion according to WHO criteria.

Exclusion criteria were: inflammatory breast cancer, male, prior adjuvant treatment by vinca alkaloids, concurrent treatment with experimental agents, previous or current malignancies (except adequately treated in situ carcinoma of the cervix or basal or squamous cell carcinoma of skin), known cerebral metastases, pre-existing peripheral neuropathy (grade ≥2) according to National Cancer Institute Common Toxicity Criteria, uncontrolled infection, pregnancy or lactation, uncontrolled coronary disease, medically unstable conditions, and malabsorption or prior bowel resection that could affect absorption of oral vinorelbine and capecitabine.

study design and dose escalation scheme

Three schedules were investigated: days 1 and 8 every 3 weeks, weekly, and days 1 and 8 every 4 weeks. Oral vinorelbine was given at 60 or 80 mg/m² and capecitabine from 1650–2500 mg/m²/day for 14 days in each schedule. Maximal tolerated doses (MTDs) were defined as the dose level (DL) at which two or more out of three or two or more out of six patients developed a DLT during the first cycle. The recommended dose (RD) for the phase II part of the study was defined as the DL below the MTD.

DLTs were one of the following: grade 4 neutropenia lasting 7 days or more, febrile neutropenia defined as a single elevation in oral temperature to >38.5°C or three elevations to >38°C during a 24-h period concomitant with grade 4 neutropenia, according to Pizzo’s definition [32], neutropenic infection (grade 3 or 4 infection concomitant with grade ≥3 neutropenia), grade 3 thrombocytopenia, any grade ≥3 non-haematological toxicity, except asthenia, inadequately treated nausea, vomiting or diarrhoea and grade ≥3 increase of total serum bilirubin, and delay of 1 week in starting the second cycle because of toxicity.

The RD was defined as the dose below the MTD, whatever the schedule used.

study drug administration

Oral vinorelbine (NAVELBINE ORAL; Pierre Fabre Médicament, France) was supplied as soft gelatine capsules in two dose strengths (30 and 40 mg). The capsules had to be swallowed rapidly without chewing or sucking them in the presence of a physician or a nurse from the department. Capecitabine (Xeloda; Hoffman-La Roche, Italy) was supplied as 150 and 500 mg tablets, and administered twice daily orally at home within 30 min after the end of a meal (breakfast, dinner) with water (and not fruit juices). Individual doses for both drugs were determined as the product of the patient’s body surface area times the dosage, rounded to the closest multiple of 10 mg for oral vinorelbine and to the nearest 100 mg of the total daily dose for capecitabine. Prophylaxis with 5-HT3 was recommended before each administration of oral vinorelbine. No antiemetic prophylaxis was recommended with capecitabine intake. If nausea/vomiting occurred during home-based capecitabine treatment, symptomatic treatment was initiated (alizaprid or metoclopramide).

On the day of treatment administration, neutrophils had to be ≥1.5 × 10⁹/l and platelets ≥25 × 10⁹/l. If a patient required a cycle delay both drugs were delayed for a maximum of 2 weeks.

The day 8 and/or 15 administrations of oral vinorelbine was skipped if grade ≥2 toxicity occurred within a cycle and the dose was reduced for subsequent cycles if the highest grade was ≥3. Capecitabine was withheld in case of grade 3 neutropenia and/or grade 3 thrombocytopenia. If grade 4 neutropenia or grade 3 neutropenia concomitantly with documented infection grade ≥3 or grade 4 thrombocytopenia occurred, capecitabine was discontinued until the next cycle and the dose reduced by 25% for subsequent cycles.

If grade ≥2 nausea or vomiting occurred despite adequate prophylaxis, oral vinorelbine was skipped and capecitabine held until resolution. For subsequent cycles, capecitabine was reduced by 25% if nausea/vomiting was grade 3 and by 50% if grade 4.

In the event of grade ≥2 diarrhoea, capecitabine was held until resolution and the dose reduced by 25% or 50% for subsequent cycles if grade 3 or grade 4, respectively.

In case of grade ≥2 hand–foot syndrome, capecitabine was withheld until resolution to grade ≤1 and the dose reduced by 25% for subsequent cycles if grade 3 hand–foot syndrome or on second appearance of grade 2.

pretreatment evaluation and follow up

At baseline, physical examination and routine laboratory tests were performed and Karnofsky performance status was determined. Complete...
Pharmacokinetics
Pharmacokinetics of vinorelbine and of capecitabine were studied during the first cycle of treatment in all patients.

Pharmacokinetics of vinorelbine were evaluated on day 1, when co-administered with capecitabine, using a limited sampling strategy over the first 24 h following treatment administration. Vinorelbine was assayed in blood by the LC-MS/MS method [35]; Bayesian pharmacokinetic parameters of vinorelbine were calculated using NONMEM program.

The normalised exposure to vinorelbine (AUC/dose) was compared with reference data (n = 121) from the vinorelbine population database obtained from the day 1, cycle 1 of oral vinorelbine in monotherapy phase I studies [2].

Pharmacokinetics of capecitabine were evaluated on day 1, when capecitabine was combined to vinorelbine, and on day 7 when administered alone, according to a detailed sampling scheme over the first 10 h post-dosing. The parent drug and all successive metabolites of capecitabine were studied: 5′-deoxy-5-fluorocytidine (5′DFCR), 5′-deoxy-5-fluorouridine (5′DFUR) and the final active compound, 5-FU. Plasma concentrations of capecitabine and its metabolites were quantified by HPLC/UV [25]. Model-independent pharmacokinetic parameters were determined using Kinetics® software (Innaphase Corp., Philadelphia, PA, USA). The normalised exposure (AUC/dose) was compared between day 1 and day 7.

Statistical analysis
The primary objective of the study was to analyse the DLTs during the first cycle of treatment in each DL and to determine the MTD. The secondary objectives were to determine the recommended DL(s) for the phase II part of the study, the safety profile and the antitumour activity of the combination. For response rate, exact 95% confidence intervals (CIs) were provided. The Kaplan–Meier method was used to estimate the time-dependent parameters.

Statistical analysis was performed using SAS software version 8.02 (SAS Institute Inc., Cary, NC, USA).

Results
Patient characteristics
Characteristics of the 44 patients are listed in Table 1. Median time from diagnosis of the primary tumour to study entry was 45.8 months (range 7 months to 21.5 years). Chemotherapy was given to 29 patients (65.9%) in the (neo)adjuvant setting and to nine patients (20.4%) in the metastatic setting. It consisted mainly of anthracyclines (86.4%) ± taxanes (15.9%) and/or CMF (56.8%). The most frequent sites of metastases were liver (59.1%), lymph nodes (50%), bone (38.6%), lung (36.4%), soft tissue (13.6%) and skin (9.1%).

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of registered and treated patients</td>
<td>44</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Median: 53.6; Range: 31.6–73.8</td>
</tr>
<tr>
<td>Karnofsky performance status (%)</td>
<td>100: 9 (88.6); 90: 5 (11.4)</td>
</tr>
<tr>
<td>Premenopausal status</td>
<td>27 (61.4)</td>
</tr>
<tr>
<td>Oestrogen receptor positive</td>
<td>29 (65.9)</td>
</tr>
<tr>
<td>Number of involved organs</td>
<td>1: 15 (34.1); 2: 13 (29.5); 2≥: 16 (36.4)</td>
</tr>
<tr>
<td>Visceral involvement</td>
<td>Yes: 34 (77.3); No: 10 (22.7)</td>
</tr>
</tbody>
</table>

Drug delivery
A total of 323 cycles were given with a median number of seven cycles per patient (range one to 17). DLs are depicted in Table 2.

Cycle delay occurred in 27 patients (61.4%) and 26.1% of cycles. The highest proportion of cycle delay was observed at DL III (88.9%) and IV (46.9%). Day 8 oral vinorelbine administrations were cancelled in 17 patients (38.6%) and 7.7% of cycles. Day 15 was cancelled in 20.2% of the cycles. Dose reduction of oral vinorelbine occurred in 22 patients (50%) and 7.4% of cycles. The highest proportion of dose reduction occurred at DL III (25%) and VII (13.3%). Reasons for cycle delay and/or dose cancellation/modifications were mainly haematological toxicity. Capecitabine was cancelled or missed in 39 cycles among the 323 given cycles (12.1%).

Similar median dose intensity of oral vinorelbine was achieved when using the days 1 and 8 schedule and the weekly schedule, as shown in Table 3. However, the median number of cycles tended to be higher for the weekly schedule: 10 versus 5 for DLs I bis and I, 7 versus 5.5 for DL II bis and II, respectively.

Determination of the MTDs
Four patients were not evaluable for determination of MTD. One patient at DL IV experienced grade 2 neutropenia during cycle 1; because the patient had grade 1 neutrophils at baseline, the shift by one grade could not be assessed as a DLT. At DL V one patient did not undergo biochemical assessment during the first cycle, another received oral vinorelbine on day 8 despite grade 3 neutropenia. One patient treated at DL VI received growth factor during cycle 1.

Neutropenia was the main limiting toxicity of the combination. Table 4 describes the DLTs. Oral vinorelbine was given at the starting dose of 60 mg/m² on days 1 and 8 with...
escalated doses of capecitabine of 2000 (DL I), 2250 (DL II) and 2500 (DL III) mg/m²/day days 1–14 every 3 weeks. When using this schedule, the MTD was reached at DL III (oral vinorelbine 60 mg/m² on days 1 and 8/capecitabine 2500 mg/m²/day days 1–14); three out of three patients experienced neutropenia, which resulted in delay in starting cycle two. DL II (oral vinorelbine 60 mg/m² on days 1 and 8/capecitabine 2250 mg/m²/day days 1–14) was considered as the RD using this schedule. Once this RD was established, oral vinorelbine was investigated at 60 mg/m²/week with capecitabine at 2250 mg/m²/day (DL II bis). Two patients out of six experienced a DLT; one patient had a delay in starting day 1, cycle 2 because of grade 3 neutropenia, and another had grade 3 neutropenia and thrombocytopenia. This DL reached the criteria for MTD. To define the RD with the weekly schedule, six additional patients were treated at a lower DL with capecitabine at 2000 mg/m²/day (DL I bis); none of the patients experienced a DLT. Therefore, DL I bis (oral vinorelbine 60 mg/m²/week and capecitabine 2000 mg/m²/day days 1–14 every 3 weeks) was considered as the RD when using the weekly schedule.

At 80 mg/m², oral vinorelbine was given on days 1 and 8 with capecitabine 1650 mg/m²/day days 1–14 every 3 weeks (DL IV). Four patients out of five evaluable experienced a DLT; the MTD was reached at this DL. Thereafter, additional DLs were tested with an every 4-weeks schedule using capecitabine at 1650 (DL V), 1850 (DL VI) and 2000 (DL VII) mg/m²/day days 1–14. None of the patients treated at these DLs experienced a DLT, except one patient at DL VII, who presented a transient febrile neutropenia.

**safety results**

All patients were evaluable for safety analysis. The haematological and main non-haematological events by cycle are depicted in Tables 5 and 6. Neutropenia occurred in 40 patients (90.9%), with grade 3 and 4 in 14 patients (31.8%) and 12 patients (27.3%), respectively. At the RDs (I bis, II and VII), grade 3/4 neutropenia was observed in 8.2%, 6.5% and 16.7% of the cycles, respectively. Complications were rare; only three episodes of febrile neutropenia were reported at DLs IV, V and VII (one each) and no neutropenic infection was observed.

The most frequent non-haematological toxicity was gastrointestinal. However, the incidence of grade 3 was low and there were no episodes of grade 4. Diarrhoea occurred in 37 patients (84.1%) and 28.8% of the cycles, and grade 3 was reported in two patients (one cycle each) at DL II; grade 3 nausea was reported in one patient (one episode) at DL II; and grade 3 vomiting in two patients at DLs VI and VII (one episode each). Grade 2 hand–foot syndrome was observed in two patients at DLs II and II bis (two cycles each), with no grade 3. Peripheral neuropathy was mild and of low incidence; no episode of grade ≥2 occurred. Alopecia was reported in 15.9% of patients. During study treatment three patients experienced serious dermatological events: one patient presented grade 2 pigmentation change and grade 3 purpura at DL II bis, which were assessed as related to study drugs. At DL III, one patient experienced grade 3 vasculitis (cycle 3) and another one episode of grade 3 erythematous plaque (cycle 3). An independent expert assessed both events as not related to the study drugs. No toxic death occurred during study treatment.

**pharmacokinetics results**

All patients were evaluable for vinorelbine pharmacokinetics. For capecitabine and its metabolites, the number of evaluable patients on both day 1 and day 7 was 42 for capecitabine, 43 for 5’DFCR and 5’DFUR, and 39 for 5-FU.

The potential effect of capecitabine co-administration on vinorelbine pharmacokinetics was assessed by comparing the study data with reference values for vinorelbine monotherapy. Analysis showed normalised exposure (AUC/dose) to vinorelbine in patients (1.51 ± 0.481 ng·ml⁻¹·h), which was similar to the reference data (1.49 ± 0.786 ng·ml⁻¹·h).

Plasma concentrations of capecitabine and its metabolites were highly variable whatever the DL. Capecitabine was absorbed rapidly, with peak plasma levels occurring at ~1 h either on day 1 or on day 7. The metabolites appeared rapidly in plasma. The main circulating compound was either 5’DFCR or 5’DFUR, depending on the patient. Plasma concentrations of 5-FU were low when compared with other compounds and were detected for no longer than 3 h after dosing in most patients, either on day 1 or on day 7. The comparison of normalised exposure (AUC/dose) of capecitabine and its metabolites between day 1 (capecitabine combined with vinorelbine) and day 7 (capecitabine administered alone) did not show any statistically significant difference except for 5-FU. There was significant increase of the 5-FU exposure from day 1 to day 7.

**efficacy**

Responses were assessed by the investigator in all enrolled and treated patients. Two patients discontinued study treatment.
before the first tumour assessment (cycle 2). Twenty-six patients
had at least one measurable lesion. Responses were seen at
DLs I bis, II bis, IV, V, VI and VII. Table 7 gives the responses by
DL. Eighteen objective responses were reported by the
investigator among the 44 treated patients. There were 3
complete responses (6.8%), 15 partial responses (34.1%) and
18 stabilisations (40.9%), yielding a response rate of 40.9%
(95% CI 26.3% to 56.7%). Median duration of follow up was
21.7 months (95% CI 16.3–24.9). Median progression-free
survival was 7.7 months (95% CI 5–11.6). Median survival
had not been reached at the time of this analysis.

**discussion**

Anthracyclines and taxanes are becoming standard adjuvant
treatment for early breast cancer. In the palliative setting of
MBC, there is a need for new treatment options. Although
several chemotherapeutic agents are active, only few are
available in oral form. The development of an ‘all-oral regimen’
may not only improve access to chemotherapy, but also offer
better comfort and convenience for patients. Recently, patients’
interest in oral chemotherapy has increased [36, 37]. Liu et al.
[37] indicated that 90% of cancer patients would prefer oral
versus intravenous chemotherapy because of the convenience of
administration outside a clinical setting, provided that its
efficacy is maintained versus the i.v. route.

The present study is the most extensive prospective phase I
trial to date that has combined the oral formulation of
vinorelbine with capecitabine in MBC patients. The range of
selected doses of oral vinorelbine was derived from the
established bioequivalence between the i.v. and the oral
formulation [2]. When using 60 mg/m² of oral vinorelbine, two
RDs were established: a weekly schedule of vinorelbine with
capecitabine 2000 mg/m²/day days 1–14 every 3 weeks (DL I bis)
and a days 1 and 8 schedule of oral vinorelbine with capecitabine
2250 mg/m²/day days 1–14 every 3 weeks (DL II). At 80 mg/m²,
four DLs were tested with oral vinorelbine days 1 and 8 every
3 weeks (DL IV), and oral vinorelbine days 1 and 8 every 4 weeks
(DL V, VI and VII). The criteria for MTD was reached at DL IV
using the every 3 weeks schedule, while the MTD was not
reached with DLs V, VI and VII using the every 4 weeks
schedule. DL VII (oral vinorelbine 80 mg/m² days 1 and 8/
capecitabine 2000 mg/m²/day days 1–14) displayed the highest
doses intensities for both oral vinorelbine and capecitabine and

### Table 3. Median DI during the first cycle and overall cycles per dose level

<table>
<thead>
<tr>
<th>DL</th>
<th>Oral vinorelbine (mg/m²)</th>
<th>Capecitabine mg/m²/day</th>
<th>No. of cycles [median (range)]</th>
<th>Median DI (range)</th>
<th>Overall cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (n = 3)</td>
<td>60 days 1 and 8</td>
<td>2000 days 1–14 every 3 weeks</td>
<td>5 (2–6)</td>
<td>38.1 (37.8–39.1)</td>
<td>37.9 (34–39.1)</td>
</tr>
<tr>
<td></td>
<td>60 days 1, 8, 15</td>
<td>2000 days 1–14 every 3 weeks</td>
<td>10 (2–17)</td>
<td>57.4 (34.8–60.7)</td>
<td>38.6 (30.9–51.5)</td>
</tr>
<tr>
<td>II (n = 6)</td>
<td>60 days 1 and 8</td>
<td>2250 days 1–14 every 3 weeks</td>
<td>5.5 (3–7)</td>
<td>38.9 (28.8–39.8)</td>
<td>34.6 (25.2–37.9)</td>
</tr>
<tr>
<td>II bis (n = 6)</td>
<td>60 days 1 and 8</td>
<td>2250 days 1–14 every 3 weeks</td>
<td>7 (3–17)</td>
<td>54.2 (27.8–59.7)</td>
<td>38.5 (23.2–61.2)</td>
</tr>
<tr>
<td>III (n = 3)</td>
<td>60 days 1 and 8</td>
<td>2500 days 1–14 every 3 weeks</td>
<td>3 (3–6)</td>
<td>28.8 (26.5–29.7)</td>
<td>25.2 (24–28)</td>
</tr>
<tr>
<td>IV (n = 6)</td>
<td>80 days 1 and 8</td>
<td>1650 days 1–14 every 3 weeks</td>
<td>9.5 (4–13)</td>
<td>40.7 (35.9–54.8)</td>
<td>37.5 (28.9–47)</td>
</tr>
<tr>
<td>V (n = 5)</td>
<td>80 days 1 and 15</td>
<td>1650 days 1–14 every 4 weeks</td>
<td>8 (1–13)</td>
<td>39.8 (36.9–41.3)</td>
<td>31.5 (26.9–39.5)</td>
</tr>
<tr>
<td>VI (n = 3)</td>
<td>80 days 1 and 8</td>
<td>1850 days 1–14 every 4 weeks</td>
<td>12 (10–13)</td>
<td>41.5 (38.4–41.9)</td>
<td>27.4 (24.9–38.4)</td>
</tr>
<tr>
<td>VII (n = 6)</td>
<td>80 days 1 and 8</td>
<td>2000 days 1–14 every 4 weeks</td>
<td>4.5 (1–9)</td>
<td>38.9 (19.3–42.7)</td>
<td>35 (16.7–41.2)</td>
</tr>
</tbody>
</table>

*Oral vinorelbine: mg/m²/w; capecitabine: mg/m²/day.

before the first tumour assessment (cycle 2). Twenty-six patients
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21.7 months (95% CI 16.3–24.9). Median progression-free
survival was 7.7 months (95% CI 5–11.6). Median survival
had not been reached at the time of this analysis.

### Table 4. DLTs during the first cycle, per dose level

<table>
<thead>
<tr>
<th>Dose levels</th>
<th>No. of DLTs</th>
<th>Type of DLT (No. of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0/3</td>
<td></td>
</tr>
<tr>
<td>I bis</td>
<td>0/6</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>1/6</td>
<td>Cycle 2 delay: grade 2 neutropenia (1 patient)</td>
</tr>
<tr>
<td>II bis</td>
<td>2/6</td>
<td>Cycle 2 delay: grade 3 neutropenia and thrombocytopenia (1 patient)</td>
</tr>
<tr>
<td>III</td>
<td>3/3</td>
<td>Cycle 2 delay: grade 2 neutropenia (3 patients)</td>
</tr>
<tr>
<td>IV</td>
<td>4/6a</td>
<td>Cycle 2 delay: grade 2 neutropenia (3 patients)</td>
</tr>
<tr>
<td>V</td>
<td>0/5b</td>
<td>Febrile neutropenia (1 patient)</td>
</tr>
<tr>
<td>VI</td>
<td>0/3a</td>
<td></td>
</tr>
<tr>
<td>VII</td>
<td>1/6</td>
<td>Febrile neutropenia (1 patient)</td>
</tr>
</tbody>
</table>

*One patient non-evaluable in each of these dose levels.

Two patients non-evaluable at this dose level.

**Dose-limiting toxicity.**
was therefore considered as the RD when using oral vinorelbine at 80 mg/m². Results from our study have shown that the combination is safe and feasible. No episode of grade 4 non-haematological toxicity occurred during study treatment. Neutropenia was the main DLT, but the incidence of severe neutropenia and complications was low. When considering all the cycles, the nadir of neutrophils occurred after day 15 and lasted no more than 7 days in most of the patients having experienced severe neutropenia. Median number of cycles received by the patients was higher in the weekly schedule (DLs I bis and II bis) in comparison with the days 1 and 8 schedule. Dose cancellation of day 15 occurred in only 16.4% and 25% of the cycles at DL I bis and II bis, respectively. During the first cycles, the weekly schedule displayed highest dose intensities for oral vinorelbine and capecitabine in comparison with the days 1 and 8 schedule. When considering all of the cycles, equivalent dose intensities of oral vinorelbine were achieved with either the weekly schedule (i.e. DL I bis) or the days 1 and 8 schedule ( i.e. DL I). Clinical responses were observed with the weekly schedule (DL I bis and DL II bis) and with oral vinorelbine given at 80 mg/m². In the present study, a total of three complete and 15 partial responses were seen, yielding a response rate of 40.9% (95% CI 26.3% to 56.8%) in the intention-to-treat population. These results fall in the range of what was published in the previous phase I/II studies with i.v. vinorelbine and capecitabine [26–31].

Table 5. Incidence of haematological toxicity by cycle

<table>
<thead>
<tr>
<th>DLs</th>
<th>No. of cycles</th>
<th>NCI CTC grading</th>
<th>WBC</th>
<th>ANC</th>
<th>Platelets</th>
<th>Haemoglobin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>All grades [n (%)]</td>
<td>Grade 3/4 [n (%)]</td>
<td>All grades [n (%)]</td>
<td>Grade 3/4 [n (%)]</td>
</tr>
<tr>
<td>I</td>
<td>13</td>
<td>6 (46.2) –</td>
<td>6 (46.2) –</td>
<td>3 (23.1) –</td>
<td>5 (38.5) –</td>
<td></td>
</tr>
<tr>
<td>I bis</td>
<td>61</td>
<td>23 (37.7) 1 (1.6)</td>
<td>26 (42.6) 5 (8.2)</td>
<td>3 (4.9) –</td>
<td>30 (49.2) –</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>31</td>
<td>16 (51.6) 1 (3.2)</td>
<td>15 (48.4) 2 (6.5)</td>
<td>6 (19.4) 1 (3.2)</td>
<td>14 (45.2) –</td>
<td></td>
</tr>
<tr>
<td>II bis</td>
<td>48</td>
<td>15 (31.3) 5 (10.5)</td>
<td>17 (35.4) 6 (12.6)</td>
<td>8 (16.7) 1 (2.1)</td>
<td>3 (62.5) –</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>12</td>
<td>11 (91.7) 4 (33.3)</td>
<td>10 (83.3) 4 (33.4)</td>
<td>2 (16.7) –</td>
<td>6 (50) –</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>54</td>
<td>20 (37.0) 2 (3.7)</td>
<td>27 (50.0) 5 (9.2) –</td>
<td>– 20 (37) –</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>38</td>
<td>14 (36.8) 1 (2.6)</td>
<td>7 (18.4) 3 (7.9)</td>
<td>4 (10.5) –</td>
<td>27 (71.1) 1 (2.6)</td>
<td></td>
</tr>
<tr>
<td>VI</td>
<td>35</td>
<td>28 (80.0) 3 (8.6)</td>
<td>19 (54.3) 4 (11.5)</td>
<td>2 (5.7) –</td>
<td>16 (45.7) –</td>
<td></td>
</tr>
<tr>
<td>VII</td>
<td>30</td>
<td>8 (28.7) 3 (10.0)</td>
<td>7 (23.3) 5 (16.7)</td>
<td>3 (10.0) –</td>
<td>8 (26.7) –</td>
<td></td>
</tr>
</tbody>
</table>

DL, dose level; NCI CTC, National Cancer Institute Common Toxicity Criteria; WBC, white blood cell count; ANC, absolute neutrophil count; bis, weekly schedule; V, VI and VII, every 4 weeks regimens.

Table 6. Incidence of most common related non-haematological adverse events by cycle, overall cycles

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>NCI CTC grading</th>
<th>Grade 1 [n (%)]</th>
<th>Grade 2 [n (%)</th>
<th>Grade 3 [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>39 (12.1)</td>
<td>37 (11.5)</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>93 (28.8)</td>
<td>78 (24.1)</td>
<td>13 (4.0)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>147 (45.5)</td>
<td>130 (40.2)</td>
<td>16 (5.0)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>62 (19.2)</td>
<td>54 (16.7)</td>
<td>6 (1.9)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>24 (7.4)</td>
<td>22 (6.8)</td>
<td>2 (0.6)</td>
<td>–</td>
</tr>
<tr>
<td>Anorexia</td>
<td>7 (2.2)</td>
<td>6 (1.9)</td>
<td>1 (0.3)</td>
<td>–</td>
</tr>
<tr>
<td>Hand–foot syndrome</td>
<td>73 (22.6)</td>
<td>69 (21.4)</td>
<td>4 (1.2)</td>
<td>–</td>
</tr>
<tr>
<td>Desquamation</td>
<td>4 (1.2)</td>
<td>2 (0.6)</td>
<td>–</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2 (0.6)</td>
<td>–</td>
<td>2 (0.6)</td>
<td>–</td>
</tr>
<tr>
<td>Wound infection (cellulitis)</td>
<td>1 (0.3)</td>
<td>–</td>
<td>–</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Sensory-neuropathy</td>
<td>4 (1.2)</td>
<td>4 (1.2)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Fatigue</td>
<td>82 (25.4)</td>
<td>68 (21.1)</td>
<td>11 (3.4)</td>
<td>3 (0.9)</td>
</tr>
<tr>
<td>Phlebitis/thrombosis</td>
<td>5 (1.5)</td>
<td>–</td>
<td>4 (1.2)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Petechiae/purpura</td>
<td>1 (0.3)</td>
<td>–</td>
<td>–</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>35 (10.8)</td>
<td>32 (9.9)</td>
<td>2 (0.6)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>44 (13.6)</td>
<td>29 (9.0)</td>
<td>15 (4.6)</td>
<td>NA</td>
</tr>
</tbody>
</table>

NCI CTC, National Cancer Institute Common Toxicity Criteria; NA, not applicable.

was therefore considered as the RD when using oral vinorelbine at 80 mg/m². Results from our study have shown that the combination is safe and feasible. No episode of grade 4 non-haematological toxicity occurred during study treatment. Neutropenia was the main DLT, but the incidence of severe neutropenia and complications was low. When considering all the cycles, the nadir of neutrophils occurred after day 15 and lasted no more than 7 days in most of the patients having experienced severe neutropenia. Median number of cycles received by the patients was higher in the weekly schedule (DLs I bis and II bis) in comparison with the days 1 and 8 schedule. Dose cancellation of day 15 occurred in only 16.4% and 25% of the cycles at DL I bis and II bis, respectively. During the first cycles, the weekly schedule displayed highest dose intensities for oral vinorelbine and capecitabine in comparison with the days 1 and 8 schedule. When considering all of the cycles, equivalent dose intensities of oral vinorelbine were achieved with either the weekly schedule (i.e. DL I bis) or the days 1 and 8 schedule ( i.e. DL I). Clinical responses were observed with the weekly schedule (DL I bis and DL II bis) and with oral vinorelbine given at 80 mg/m². In the present study, a total of three complete and 15 partial responses were seen, yielding a response rate of 40.9% (95% CI 26.3% to 56.8%) in the intention-to-treat population. These results fall in the range of what was published in the previous phase I/II studies with i.v. vinorelbine and capecitabine combination [26–31]. Taking into consideration all these data and based on the highest dose intensity delivered during the first cycle with the

Table 6. Incidence of most common related non-haematological adverse events by cycle, overall cycles
weekly schedule, DL I bis was selected for the first phase II trial conducted with this oral combination.

A common metabolic pathway through carboxylesterases is involved in biotransformation and elimination process of both vinorelbine and capecitabine. Thus, potential drug–drug interaction might theoretically occur when the drugs are combined, and this was assessed in the present study. No change of vinorelbine pharmacokinetics occurred when capecitabine was co-administered.

The exposure to capecitabine and its metabolites was comparable on day 1 (when combined with vinorelbine) and on day 7 (when administered alone), except for 5-FU. The exposure to 5-FU was increased on day 7, and is consistent with the high variability observed for pharmacokinetics of 5-FU exposure after repeated dosing of capecitabine, resulting in AUC increase over a week of treatment [25, 38, 39].

The high variability observed for pharmacokinetics of capecitabine and its metabolites was also consistent with published literature on patients treated with capecitabine as a single agent [38, 40]. It was concluded from this study that drug–drug pharmacokinetic interaction is unlikely to occur when vinorelbine and capecitabine are combined.

In conclusion, oral vinorelbine is a good alternative to the i.v. combination for treatment of MBC patients. The safety profile of this all-oral combination regimen compares favourably with those previously reported with the i.v. vinorelbine and capecitabine combination studies, with no drug–drug interaction.

Based on these promising results, a multicentre phase II study has started with the selected schedule of oral vinorelbine 60 mg/m²/week with capecitabine 2000 mg/m²/day days 1–14 every 3 weeks as first-line chemotherapy in patients with MBC.

### Table 7. Overall response according to the investigator in the intention-to-treat population, per dose level

<table>
<thead>
<tr>
<th>Dose level</th>
<th>I (n)</th>
<th>II (n)</th>
<th>III (n)</th>
<th>IV (n)</th>
<th>V (n)</th>
<th>VI (n)</th>
<th>VII (n)</th>
<th>All (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>3</td>
<td>6</td>
<td>6</td>
<td>3</td>
<td>6</td>
<td>5</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>CR</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PR</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>NC</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>Disease control, CR + PR + NC (&gt;6 months)</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td>Progression</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

CR, complete response; PR, partial response; NC, no change.

### References