Phase I, dose-finding study of capecitabine in combination with docetaxel and epirubicin as first-line chemotherapy for advanced breast cancer

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Purpose: Capecitabine is an oral fluoropyrimidine with considerable activity and minimal myelosuppression and alopecia. This phase I study evaluated the addition of capecitabine to epirubicin/docetaxel combination therapy as first-line treatment for advanced breast cancer.

Patients and methods: Twenty-three female patients with advanced breast cancer received capecitabine (765–1060 mg/m² twice daily on days 1–14 of a 3-week treatment cycle) in combination with epirubicin and docetaxel (75 mg/m² i.v. on day 1).

Results: The maximum tolerated dose of capecitabine was 985 mg/m² and the principal dose-limiting toxicity was febrile neutropenia. No grade 3/4 anemia or thrombocytopenia occurred. There were no grade 4 non-hematological events and grade 3 events other than alopecia were rare. Alopecia occurred in all patients and treatment cycles, and asthenia occurred in all patients and in 84% of treatment cycles. Other frequent adverse events included nausea, vomiting, fever, paresthesia and elevated transaminase levels. An objective response to treatment was observed in 91% (95% confidence interval 72% to 99%) of patients.

Conclusions: The addition of capecitabine to docetaxel/epirubicin combination therapy provides a well-tolerated and active first-line chemotherapy regimen in patients with advanced breast cancer, and merits phase II/III evaluation.

Key words: advanced breast cancer, capecitabine, docetaxel, epirubicin, phase I

Introduction

Breast cancer is the most common cancer in women in Europe and the USA, affecting 8% to 9% of the female population [1–3]. Approximately 50% of all patients treated with curative intent will develop metastatic disease and the average survival time for patients following the diagnosis of metastatic disease is 18–24 months [4]. Systemic cytotoxic chemotherapy is the treatment of choice for patients who are hormone resistant, those who are estrogen-receptor negative and those who have rapidly growing tumors [5]. The choice of first-line treatment is influenced by a wide range of factors, related to both tumor and patient characteristics. Therapy commonly includes an anthracycline and/or 5-fluorouracil (5-FU) in regimens such as CAF (cyclophosphamide, doxorubicin, 5-FU) [6] and CEF (cyclophosphamide, epirubicin, 5-FU) [7]. The taxanes (paclitaxel and docetaxel), however, are increasingly being used as first- and second-line agents for this indication [8].

Capecitabine (Xeloda®, F. Hoffmann-La Roche, Basel, Switzerland) is a novel, oral fluoropyrimidine carbamate, which was rationally designed to mimic continuous infusion 5-FU and generate 5-FU preferentially in tumor tissue through exploitation of high intratumoral concentrations of thymidine phosphorylase (TP) [9, 10]. Human pharmacokinetic studies have shown that capecitabine is rapidly and almost completely absorbed through the gastrointestinal wall, and is metabolized to 5-FU via a three-step enzymatic cascade [11]. The final step in the activation of capecitabine is mediated by TP, an enzyme that is highly active in tumor tissue compared with corresponding normal tissue [9]. The antitumor activity of capecitabine is enhanced by upregulation of TP activity, and preclinical studies have demonstrated synergy when capecitabine is combined with therapies that upregulate TP, including taxanes [12].

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Capecitabine is an important agent for the treatment of patients with metastatic breast cancer who have exhausted all treatment options. In a phase II study of heavily pre-treated patients who had received prior paclitaxel therapy, capecitabine resulted in a 20% response rate and median survival of 12.8 months [13]. Four further studies in patients pre-treated with taxanes confirmed these results [14–17]. Capecitabine has a safety profile that is typical of infused fluoropyrimidines. It is associated with a very low incidence of alopecia and myelosuppression. Promising results from two randomized phase II studies of capecitabine have demonstrated that the drug may also play a role in the first- and second-line treatment of metastatic breast cancer. Capecitabine monotherapy is active in anthracycline-resistant patients [18] and in previously untreated, post-menopausal women [19].

The activity of capecitabine, and the low incidence of myelosuppression, make it an attractive agent for incorporation into combination regimens. Furthermore, there is a clear rationale for combining capecitabine with agents known to upregulate TP activity in tumor tissue. A randomized phase III trial has recently demonstrated that capecitabine combined with docetaxel resulted in significantly superior tumor response rates, time to disease progression or death, and overall survival compared with docetaxel monotherapy in patients with anthracycline pre-treated, advanced breast cancer [20].

Previous studies have demonstrated that doxorubicin/docetaxel combination is an effective first-line treatment for patients with metastatic breast cancer [21, 22]. In a previous study, we demonstrated that epirubicin plus docetaxel, each administered at 75 mg/m², is also a safe and active regimen in advanced breast cancer [23]. The principal dose-limiting toxicity (DLT) with this combination was febrile neutropenia.

The non-overlapping toxicity profiles, together with the observed synergistic activity with docetaxel, suggest that capecitabine is an attractive agent for addition to the epirubicin/docetaxel combination regimen. The current phase I trial was undertaken to evaluate a triple combination of capecitabine, epirubicin and docetaxel as first-line therapy in patients with advanced breast cancer. The objectives of the study were to determine the maximum tolerated dose (MTD) and DLTs of oral capecitabine when administered twice daily according to the standard, intermittent schedule (2 weeks on treatment, 1 week off) in combination with intravenous epirubicin and docetaxel.

**Patients and methods**

This phase I trial of intermittent, oral capecitabine in combination with intravenous epirubicin and docetaxel (TEX regimen) was conducted between July 1998 and May 2000, in accordance with the International Good Clinical Practice principles and local ethical and regulatory requirements. Capecitabine was administered orally, with −200 ml water and within 30 min after a meal (ideally after breakfast and evening meal, −12 h apart). Capecitabine was administered at escalating doses (765, 875, 985 or 1060 mg/m² twice daily) on days 1–14 every 3 weeks, in combination with fixed doses of docetaxel 75 mg/m² and epirubicin 75 mg/m², given intravenously on day 1. The doses of both docetaxel and epirubicin were identified in a dose-finding study we conducted previously [23]. In order to prevent fluid retention related to docetaxel, all patients received prophylactic therapy comprising prednisolone or methylprednisolone (50 and 40 mg, respectively, twice daily, starting 12 h before and continuing until 60 h after docetaxel administration). Additionally, for the prevention of nausea and vomiting, patients received therapy including granisetron (3 mg i.v. 30 min prior to the start of the intravenous chemotherapy, and a 1 mg tablet 24 h after intravenous chemotherapy), and 10 mg metoclopramide tablets (two tablets every 8 h for 3 days). Three patients were recruited at each capecitabine dose level, and at least three patients were to have received at least one cycle and to have been observed for toxicity for at least 3 weeks before dose escalation was permitted. If no patients experienced a DLT, the dose was escalated to the next level in subsequent patients. If one of the three patients developed a DLT, that dose level was expanded to a total of six patients. If an additional patient in the six-patient cohort experienced a DLT, no further dose escalation was allowed and the previous dose level was identified as the MTD. Once the MTD was defined, a total of six patients were to be treated at this dose level. The occurrence of one or more of the following toxicities during the first cycle of chemotherapy was considered dose limiting: any National Cancer Institute Common Toxicity Criteria (NCI CTC) grade 3 or 4 non-hematological toxicity (excluding grade 3 alopecia, grade 3 nausea or vomiting, or grade 3 stomatitis persisting for <3 days), platelet count <25000/µl for >7 days or accompanied by bleeding requiring blood transfusion, neutropenia [absolute neutrophil count (ANC) <500/µl for >7 days, or <100/µl for >3 days], or febrile neutropenia [ANC <500/µl accompanied by a fever ≥38.5°C (single evaluation), or a fever ≥38°C for >12 h]. Short episodes of febrile neutropenia that responded to treatment with oral antibiotics were observed during assessment of the first two dose levels. Accordingly, the defining criteria for febrile neutropenia were amended in the protocol to specify that the fever should persist for >72 h despite adequate empirical antibiotic therapy.

Dose adjustments of capecitabine were based on the observed toxicity, and efforts were made to administer the full dose to all patients entered at the different levels. Patients that experienced higher than grade 1 non-hematological toxicity discontinued capecitabine until recovery to grade S1. Since capecitabine was not expected to worsen or unduly prolong the episode of neutropenia, its administration was continued throughout grade 3 or 4 neutropenic episodes. However, the administration of capecitabine was interrupted if any higher than grade 1 non-hematological toxicity coincided with the neutropenic phase. Doses of capecitabine omitted due to toxicity were not replaced.

Duration of treatment depended on stage (III versus IV) and tumor response. Regardless of the stage, patients with progressive disease discontinued study treatment. Patients with stage III disease were treated with four to six cycles of chemotherapy, before local therapy (surgery and/or radiotherapy). Patients with stage IV disease were treated with up to eight cycles of chemotherapy.

**Eligibility**

The study included female patients with histologically or cytologically confirmed breast cancer with advanced disease (stage III or IV) who had received no prior chemotherapy for metastatic disease. Patients were required to meet the following additional criteria: age 18–75 years, life expectancy >3 months, Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2, ANC ≥2000/µl, platelet count ≥100000/µl, total bilirubin <1.5 times the upper normal limit (UNL), aspartate
transaminase (AST) and/or alanine transaminase (ALT) <1.5 times UNL, alkaline phosphatase <2.5 times UNL (unless bone metastases were present in the absence of any liver disorders), creatinine concentrations <1.6 mg/dl (in cases of borderline concentrations, creatinine clearance ≥60 ml/min), and no evidence of other serious illness, medical condition, or symptomatic peripheral neuropathy with grade 2 (NCI CTC) or greater intensity. A normal left ventricular ejection fraction (LVEF) as measured by multiple gated acquisition (MUGA) scan or echocardiography was also required.

Patients were excluded from the study if they had received prior therapy for metastatic disease, previous docetaxel treatment in any setting, a cumulative epirubicin dose of >360 mg/m², a cumulative doxorubicin dose of >200 mg/m², concurrent treatment with experimental drugs in the 30 days prior to screening or concurrent treatment with corticosteroids used for reasons other than pre-medication (except chronic low-dose corticosteroid treatment: <20 mg/day used for ≥6 months). Other investigational drugs, other anticancer treatments, and prophylactic oral or intravenous antibiotics were prohibited during the study period. Hematopoietic growth factors were not permitted during the first treatment cycle, but during subsequent cycles could be administered as prophylactic treatment following febrile neutropenia or severe neutropenia lasting for >1 week in the previous cycle. All patients provided written informed consent.

Patient evaluation

Safety evaluation included history, physical examination, ECG and blood chemistry, performed every 3 weeks. Complete blood counts were performed at least twice weekly and in case of ANC <500/µl, daily. If clinically indicated, chest X-rays were performed every 3 weeks. An evaluation of LVEF was performed at baseline and every other cycle thereafter. Cardiac toxicity was defined as clinical signs and symptoms of congestive heart failure (CHF), a decrease in LVEF ≤45%, a decrease from baseline LVEF of ≥20 EF units, or a decrease in LVEF ≥10 EF units associated with a decline to a level of LVEF ≤50%. All adverse events were documented, including the nature, severity and outcome of the event. ECOG performance status was assessed every 3 weeks and tumor evaluation was performed at baseline and then every 6 weeks based on WHO criteria. The best overall response was defined as the best response recorded from the start of treatment to disease progression. Complete responses (CR: complete disappearance of all previously detectable disease for a period of at least 28 days, and no new lesions) and partial responses (PR; >50% reduction in the sums of the products of the biperpendicular diameters of all measurable disease for a period of at least 28 days, and no new lesions) were confirmed by a second tumor assessment after 4 weeks. The time to progression (TTP) was defined as the time from treatment initiation to progression, last contact or start of further antitumor therapy.

Results

Patient characteristics and disposition

A total of 23 patients were recruited into the study. The median age was 52 years (range 34–67 years) and the majority of patients (91%) were asymptomatic (ECOG performance status 0). Patients with locally advanced and metastatic disease were equally represented (11 and 12 patients, respectively). Metastatic sites included liver, bone and lung (each documented in four patients). Among patients with metastatic disease, half had disease involvement at more than one metastatic site. The majority of patients (74%) had received no prior hormonal therapy for metastatic disease.

Table 1. Characteristics of patients with metastatic disease (n = 12)

<table>
<thead>
<tr>
<th>Number of metastatic sites (12 patients)</th>
<th>No. of patients, n (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>6 (50)</td>
</tr>
<tr>
<td>2</td>
<td>3 (25)</td>
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<tr>
<td>&gt;2</td>
<td>3 (25)</td>
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<tr>
<th>Predominant site of metastatic disease (12 patients)</th>
<th>No. of patients, n (%)</th>
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<tbody>
<tr>
<td>Visceral</td>
<td>5 (41.7)</td>
</tr>
<tr>
<td>Bone</td>
<td>2 (15.7)</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>5 (41.7)</td>
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<tr>
<th>Previous adjuvant therapy (12 patients)</th>
<th>No. of patients, n (%)</th>
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<tbody>
<tr>
<td>None</td>
<td>7 (58.3)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td>Hormonal</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td>Both</td>
<td>1 (8.3)</td>
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<thead>
<tr>
<th>Prior hormonal therapy for metastatic disease</th>
<th>No. of patients, n (%)</th>
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<td></td>
<td>3 (25)</td>
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A total of 139 cycles of chemotherapy were administered, with a median of six cycles (range three to eight) per patient. All patients were evaluable for toxicity and 22 were evaluable for response. One patient was excluded from the analysis of response because baseline positive mammography was not repeated during the treatment period.
DLTs and MTD

At dose level I, one patient experienced a DLT (according to the original protocol) during the first cycle (Table 2). This patient experienced grade 4 neutropenia on days 11–13, accompanied by fever on days 12 and 13. The fever resolved without treatment modification and was not regarded as a DLT using the amended protocol specifying persistence of fever for >72 h. At dose level II, febrile neutropenia was recorded in two patients during the first cycle. However, in each case, fever persisted for <72 h and the patients continued therapy according to the amended protocol. Febrile neutropenia was also recorded in a patient receiving the first cycle of therapy at dose level III. In this patient, fever (38.2–38.5°C) persisted for 3 days and neutropenia (nadir 20/µl) resolved after 6 days without any adjustments to treatment, thus meeting the amended protocol definition of a DLT. At dose level IV, three patients experienced DLTs during the first treatment cycle. Grade 4 neutropenia (ANC <100/µl) occurred on day 9 in one patient and persisted for 5 days (nadir 9/µl). The patient recovered without capecitabine dose modification. A second patient experienced a grade 3 infection on day 15, which lasted for 8 days. The third patient experienced grade 3 mucositis on day 6 that persisted for 5 days. In this patient, capecitabine therapy was delayed for 2 days. All three patients treated at dose level IV (1060 mg/m² twice daily) required prophylactic granulocyte-colony stimulating factor (G-CSF) and/or capecitabine dose reduction, and all experienced DLTs. Therefore, dose level III (capecitabine 985 mg/m² twice daily, days 1–14, in combination with docetaxel and epirubicin, each administered at 75 mg/m² on day 1 of each 21-day treatment cycle) was identified as the MTD. Five additional patients were treated at this dose level, and no further DLTs were observed. A total of 47 cycles were administered, with a median of six cycles (range three to eight) per patient. At this dose level, one patient received G-CSF starting from the second cycle.

Non-hematological adverse events

The majority of treatment-related, non-hematological adverse events were mild to moderate in intensity (Figure 2) and there were no grade 4 non-hematological adverse events. Alopecia occurred in all patients, but grade 3 adverse events other than alopecia were infrequent (18% of cycles). The most frequent grade 3 non-hematological adverse events other than alopecia

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Table 2. Incidences of DLTs during the first cycle of treatment

<table>
<thead>
<tr>
<th>Twice daily capecitabine dose (mg/m²)</th>
<th>No. of patients</th>
<th>DLT (no. of patients)</th>
</tr>
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<tbody>
<tr>
<td>765</td>
<td>6</td>
<td>Febrile neutropenia (1)²</td>
</tr>
<tr>
<td>875</td>
<td>6</td>
<td>Febrile neutropenia (2)²</td>
</tr>
<tr>
<td>985</td>
<td>8</td>
<td>Febrile neutropenia (1)</td>
</tr>
<tr>
<td>1060</td>
<td>3</td>
<td>Prolonged grade 4 neutropenia (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grade 3 infection (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grade 3 stomatitis (1)</td>
</tr>
</tbody>
</table>

²Does not qualify for DLT according to criteria specified in amended protocol.
were nausea and vomiting, which together accounted for 52% of remaining grade 3 non-hematological adverse events. Asthenia was frequent, occurring in 84% of treatment cycles and in all patients. However, in the majority of patients, asthenia was mild and grade 3 asthenia occurred in only two patients. Other frequent (>20% of treatment cycles) adverse events included stomatitis, fever (usually associated with neutropenia), paresthesia, conjunctivitis and elevated transaminases. Edema occurred in 18% of cycles, and in most cases was accompanied by weight gain. At the fourth and the eighth cycle, the mean ± standard deviation (SD) weight increases were 2% (± 4.5) and 7.5% (± 4.1), respectively. Diarrhoea occurred in 13% of cycles, and hand-foot syndrome in 14% of cycles, but the majority of these events were of grade 1 intensity. In addition, two patients developed a maculopapular rash. In one patient, the rash persisted, despite capecitabine dose reduction, and required discontinuation of therapy. Chemotherapy with epirubicin and docetaxel was administered to this patient for a further two cycles, and the patient then underwent breast surgery.

Clinical cardiac toxicity, e.g. CHF, was not observed and no significant changes in mean LVEF were recorded during study treatment (Figure 3). Only two episodes of asymptomatic cardiotoxicity were reported. One patient, previously treated with adjuvant epirubicin (360 mg/m²) and left chest-wall radiotherapy, experienced a transient drop of LVEF down to 42% after eight cycles of chemotherapy. A subsequent evaluation 1 month later demonstrated an LVEF of 50%. The patient remained completely asymptomatic throughout the study period and did not require specific cardiologic treatment. A fall of 11 EF units, associated with an LVEF value of 49%, was observed in an additional patient. Again the patient remained asymptomatic and continued therapy, and an LVEF of 58% was recorded during a subsequent evaluation at the eighth cycle.

### Hematological adverse events

Myelosuppression (generally neutropenia) was the predominant treatment-related adverse event. Grade 3/4 anemia or thrombocytopenia was never reported. Grade 4 leukopenia was observed in 74% of patients, and all patients experienced grade 4 neutropenia. ANC <500/µl (grade 4 neutropenia) occurred in all patients during the first treatment cycle, with the exception of one patient receiving therapy at dose level I. The mean duration of neutropenia (<500/µl) was 4 days (range 1–7 days). ANC <100/µl was observed in 17 patients (74%) with a mean duration of 2 days (range 1–5 days). In most patients, neutropenia was transient and resolved without capecitabine interruption or dose modification. The mean time for neutrophil nadir was 11 days after treatment initiation and neutrophil levels were typically restored to baseline values by the end of the first 3-week treatment cycle (Figure 4). In general, the severity and duration of neutropenia did not increase during subsequent cycles.

Six patients received concomitant treatment with G-CSF (one at dose level I, two at dose level II, one at dose level III, and two at dose level IV). Administration of G-CSF for one to two cycles prevented the recurrence of febrile neutropenia in all patients, and of neutropenia in all but one patient.

### Activity

An objective response (CR plus PR) to treatment was observed in 21 (95%) of the 22 patients evaluable for response (91% of the intent-to-treat population, 95% confidence interval,
72% to 99%), including one CR. Stable disease was recorded in the remaining evaluable patient. The median duration of follow-up, measured as the first day of treatment to last contact, was 23.2 months (range 2.6–34.2 months). Progressive disease was recorded in seven patients in the follow-up phase. Of these patients, six had metastatic disease at baseline, and only one had stage III disease. The median TTP was 19.5 months (range 2.6–34.2 months) in patients with metastatic disease, and was not meaningfully assessable in patients with locally advanced disease.

Discussion

5-FU has remained an important component of chemotherapy for advanced breast cancer for more than 40 years, and is commonly used in combination with anthracyclines as first-line therapy, e.g. CAF and CEF. The taxanes are also increasingly being used in this setting, and several randomized trials have identified docetaxel as one of the most active single agents in metastatic breast cancer [24–26]. Combinations of anthracyclines and docetaxel have subsequently been investigated in an attempt to improve the outcome further. A report of a phase III study of first-line doxorubicin and docetaxel in patients with metastatic breast cancer reported a statistically significant increase in both response rate and time to progression for doxorubicin/docetaxel (50 and 75 mg/m², respectively) combination therapy compared with standard doxorubicin/cyclophosphamide [22]. We have previously determined the MTD of epirubicin/docetaxel combination therapy and observed that myelosuppression was the most clinically important DLT with this combination [23]. Interestingly, the recommended doses identified in this study (epirubicin 75 mg/m² and docetaxel 80 mg/m²) were similar to those used by Nabholtz et al. [22]: doses of docetaxel were almost identical, and doses of epirubicin and doxorubicin were equimyelotoxic, i.e. doxorubicin 50 mg/m² and epirubicin 75 mg/m².

In the present study, the MTD determined for the TEX regimen was capecitabine 985 mg/m² twice daily for 14 days followed by a 7-day rest period, in combination with docetaxel and epirubicin, each administered at 75 mg/m² on day 1 of each 21-day treatment cycle. As predicted from the known toxicity profile of docetaxel and epirubicin combination therapy, the predominant adverse events associated with this regimen were asthenia, nausea and neutropenia, and the principal DLT was febrile neutropenia. However, neutropenia did not require withdrawal from treatment in any patient, and concomitant administration of G-CSF prevented the recurrence of neutropenia in five of six patients receiving this prophylactic therapy as directed in the protocol. Typically, neutrophil levels were restored to baseline by the end of the 3-week regimen and there were no long-standing or cumulative effects of myelosuppression. There were no treatment-related deaths during the study.

The most frequent non-hematological toxicities were asthenia and nausea. Asthenia is a common complication of docetaxel administration, regardless of the dose used; an incidence of 65% was reported with the use of either 60 mg/m² or 100 mg/m² [27]. Asthenia is also observed with capecitabine monotherapy, and therefore the additive effect with the combination of capecitabine and docetaxel was predictable. In our study, although asthenia was recorded in all patients, the majority of cases were of only grade 1 or 2, with grade 3 asthenia recorded in only two patients. Nausea has also been observed with capecitabine monotherapy [28], and in the present study was reported in nearly 50% of cycles. However, in our study anti-emetic therapy was given for a maximum of 3 days using corticosteroids and metoclopramide, both useful drugs for the prevention of delayed emesis. Therefore, in order to avoid side effects related to a long-term use of corticosteroids, metoclopramide may be a good candidate for the treatment of nausea induced by capecitabine. Adequate supportive care with both pharmacological and non-pharmacological interventions to better control asthenia and nausea may improve the tolerability of the TEX regimen, and should be used in future trials investigating this regimen. Other non-hematological adverse events were generally predictable, and treatment interruption and, if necessary, dose modification were effective in managing the majority of cases. Notably, grade 3 hand-foot syndrome was observed in only one patient. There were no grade 3/4 cardiotoxicities, indicating that anthracycline-induced cardiotoxicity was not potentiated.

The combination also demonstrated high antitumor activity. An objective response was observed in 95% of evaluable patients (91% of the intent-to-treat population). These results compare favorably with those of previous phase I studies, which have demonstrated response rates of 52% to 75% for docetaxel and epirubicin as first-line therapy in patients with advanced breast cancer [23, 29–33].

In conclusion, TEX was shown to be a well-tolerated and active chemotherapy regimen in patients with advanced metastatic breast cancer. The results of this trial support further evaluation of this triple combination in phase II/III studies in patients with advanced/metastatic breast cancer. The dose recommended for further evaluation is intermittent capecitabine 985 mg/m² twice daily for 14 days followed by a 7-day rest period, in combination with docetaxel and epirubicin, each administered at 75 mg/m² on day 1 of each 21-day treatment cycle.

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32. Docetaxel Prescribing Information, Aventis, January 2000.