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An EORTC phase I study of capecitabine (Xeloda®) in combination with fixed doses of cyclophosphamide and epirubicin (cex) as primary treatment for large operable or locally advanced/inflammatory breast cancer

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Abstract

In breast cancer, chemotherapy regimens that include infusional 5-fluorouracil (5-FU) lead to high response rates, but require central venous access and pumps. To avoid these inconveniences, we substituted infusional 5-FU with capecitabine. The main objective of this study was to determine the maximum tolerated dose (MTD) of capecitabine when given in combination with fixed doses of epirubicin and cyclophosphamide (100 and 600 mg/m^2 day 1 every (q) 3 weeks) as primary treatment for large operable or locally advanced/inflammatory breast cancer without distant metastasis. Capecitabine was escalated from 750 mg/m^2 twice a day (bid) to 1250 mg/m^2 bid from day 1 to day 14 in four dose levels. Dose escalation was permitted if 0/3 or 1/6 patients experienced dose-limiting toxicity (DLT). A total of 23 patients were included and 117 courses were administered. At dose level 4, 2 of 2 patients presented DLTs defining the MTD. A high rate of capecitabine treatment modification was required with capecitabine 1050 mg/m^2 bid (dose level 3). 19 patients achieved an objective response (83%). In conclusion, we believe that capecitabine 900 mg/m^2 bid (dose level 2) is the recommended dose in combination with epirubicin 100 mg/m^2 and cyclophosphamide 600 mg/m^2. The acceptable toxicity profile and encouraging activity of this regimen warrant further evaluation.

Keywords: Breast cancer; Capecitabine; Neoadjuvant chemotherapy; Phase I

1. Introduction

In both large operable and locally advanced/inflammatory breast cancer, the optimal neoadjuvant chemotherapy regimen remains unknown. High response rates have been reported in patients with locally advanced/inflammatory breast cancer either treated with infusional 5-fluorouracil (5-FU) in combination with epirubicin and cisplatin (ECisF regimen) [1] or with carboplatin instead of cisplatin (ECarboF regimen) [2,3]. Interestingly, a 98% response rate was reported in patients with large operable breast cancers on the ECisF regimen [4]. A phase II-III study was then performed to compare the ECisF regimen with the ECycloF regimen (epirubicin, cyclophosphamide and infusional 5-FU) in patients with locally advanced/inflammatory or metastatic breast cancer [5]. In this trial, no difference in terms of response rate, response duration and toxicity were shown [5]. However, the low dose of epirubicin (50–60 mg/m^2 day 1, every (q) 3 weeks) in all of the above regimens has been a concern [1–5], given the dose–response effect of anthracyclines suggested by several trials conducted in the adjuvant setting [6,7]. With the aim of identifying the maximum tolerated dose

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(MTD) of epirubicin to be given together with fixed doses of cyclophosphamide and infusional 5-FU (CEF-infu regimen) in patients with large operable or locally advanced/inflammatory breast cancer, we conducted a phase I study (EORTC 10972). This study demonstrated that epirubicin could be safely escalated up to the dose of 120 mg/m^2 [8].

The next step was to activate a multicentre trial within the European Organization for Research and Treatment of Cancer (EORTC) Breast Cancer Group comparing a standard anthracycline-based chemotherapy regimen with the above CEF-infu regimen in the neoadjuvant setting. Unfortunately, we failed to activate this trial. Many centres found it difficult to accept the related inconveniences, costs and possible complications with continuous infusion of 5-FU, requiring both central venous access and an infusion pump.

At the same time, new oral 5-FU prodrugs and oral 5-FU combined with 5-ethynyluracil became available. Capecitabine is one of these rationally synthesised 5-FU prodrugs that is converted into its active metabolite fluorouracil through a three-step enzymatic metabolic process [9]. It is an orally administered drug that mimics 5-FU continuous infusion without its associated complications and inconveniences. In addition to its oral administration, capecitabine may have other advantages over infusional 5-FU: it can achieve higher tumour concentrations of 5-FU than 5-FU when given intravenously (i.v.) [10], and *in vitro* it has been shown to be active in a colon xenograft resistant to 5-FU [11]. In phase II studies, capecitabine showed a high antitumour activity when used as a single agent in the treatment of metastatic breast cancers [12–14].

From these preclinical and clinical data, we hypothesised that capecitabine should be at least as active as infusional 5-FU, and we decided to perform, as a natural progression of the CEF-infu study, a phase I trial replacing the infusional 5-FU with capecitabine. In this trial, we escalated the dose of capecitabine in combination with fixed doses of epirubicin and cyclophosphamide as the primary treatment for large operable or locally advanced/inflammatory breast cancers. We chose an intermittent schedule of capecitabine (2 weeks on, 1 week off). We refer to our regimen given every 21 days as CEX.

2. Patients and methods

2.1. Eligibility criteria

Patients eligible for the study were female, aged 18–70 years, with a histological or cytological (fine needle aspiration (FNA), incisional biopsy or Trucut biopsy) diagnosis of locally-advanced/inflammatory breast cancer (T4, any N or any T, N2 or N3 or T4d) or large operable breast cancer (large T2 or T3 breast cancers for which a tumour shrinkage was needed before considering breast-conservative surgery as a valid treatment option). Other requirements were a World Health Organization (WHO) Performance Status of 0-1, adequate marrow function (absolute neutrophil count $\geqslant 1.5\times10^9$/l, platelets $\geqslant 100\times10^9$/l), renal function (serum creatinine $\leqslant 1.5\times$upper normal limit) and hepatic function (total bilirubin $\leqslant 1.25\times$upper normal limit, aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) $\leqslant 2\times$upper normal limit) and left ventricular fraction (LVEF) measured either by echocardiography or by radionuclide angiocardiography (MUGA) within normal institutional limits. Distant metastasis other than ipsilateral supraclavicular nodes and previous chemotherapy or radiation therapy were exclusion criteria. All patients gave their written informed consent.

2.2. Study parameters and response criteria

The prestudy evaluation included taking the patient's history, physical examination, weight, WHO performance status, measurement of breast mass and nodes (when possible), complete blood count, serum electrolytes, urea, creatinine, bilirubin, alkaline phosphatase, transaminases, chest X-ray, abdominal ultrasound, bone scintigraphy, electrocardiogram (ECG), and LVEF. Complete blood counts were repeated weekly. A history, physical examination, monitoring of toxicity, and tumour measurements (when possible) were repeated before each cycle (21 days) or as clinically indicated. Toxicity was assessed according to Common Toxicity Criteria (CTC) [15], and tumour response was evaluated according to WHO criteria [16]. LVEF was repeated at completion of the chemotherapy programme.

2.3. Treatment

Patients were centrally registered at the IDBBC data center in Brussels. The treatment consisted of fixed doses of cyclophosphamide (600 mg/m^2) and epirubicin (100 mg/m^2) i.v. bolus on day 1 and oral capecitabine twice daily (bid) from day 1 to day 14, every 3 weeks. We chose a dose of 1500 mg/m^2/day for the first level. The defined dose levels of capecitabine were 750, 900, 1050 and 1250 mg/m^2 bid. A maximum of six cycles of therapy was planned.

Antiemetics were given according to each centre's policy. We did not recommend prophylactic antibiotics; however, in cases of febrile neutropenia, the use of trimethoprim-sulphamethoxazole or ciprofloxacine was recommended in subsequent cycles. All patients received prophylactic mouthcare using antiseptic mouthwash and nystatin four times a day to decrease the risk of mucositis and/or oral fungal infection. Pyridoxine 50

mg orally three times per day was given to treat the palmar–plantar syndrome (PPE).

2.4. Procedure for dose escalation, definition of MTD and recommended dose

An initial cohort of 3 patients had to be treated at each dose level, with a minimum of four cycles in total to be completed by these 3 patients before including new patients at the next dose level. Dose escalation to the next dose level was allowed when no dose-limiting toxicity (DLT) for 3 patients or no more than one DLT for 6 patients was registered. If $\geqslant 2$ patients developed a DLT, the MTD was reached, and the previous dose was defined as the recommended dose for phase II studies.

DLT was defined as (1) febrile neutropenia absolute neutrophil count (ANC) $< 1.0 \times 10^9$/l and a single oral temperature $\geqslant 38.5$ °C); (2) grade 4 neutropenia lasting $\geqslant 7$ days; (3) grade 4 thrombocytopenia; (4) grade 3-4 non-haematological toxicity other than inadequately prevented vomiting; and (5) discontinuation of capecitabine for more than eight doses due to toxicity (other than a grade 3 or 4 non-haematological toxicity already counted as a DLT).

2.5. Protocol review

This was an international multicentre phase I study, conducted in accordance with the Declaration of Helsinki and the European Guidelines on Good Clinical Practice. The protocol was reviewed and approved by the Protocol Review Committee of the EORTC and by the Institutional Review Board of each participating institution. Patients were recruited at four centres, in Bordeaux (France), Brussels (Belgium), Geneva (Switzerland) and Ljubljana (Slovenia). Data were collected on standard case report forms and analysed at the EORTC-Investigational Drug Branch in Breast Cancer (IDBBC) Data Center.

3. Results

3.1. Patient characteristics

A total of 23 patients were enrolled in the study from February to December 2000, and their characteristics are reported in Table 1. All patients were eligible for the study and evaluable for toxicity and response.

3.2. Treatment administration

A total of 117 cycles were delivered (Table 2). The median delivered number of cycles was 6 (range 1–6), and the median time on study was 18 weeks (range 3–24 weeks). All the planned dose levels were evaluated. The number of patients entered at dose levels 1, 2, 3 and 4 were 3, 3, 15 and 2, respectively.

Table 1
Patient characteristics ($n = 23$)

Median age (range) (years)	48 (33–68)
Performance status 0	23
Disease characteristics	
Large operable	5
Locally advanced	9[a]
Inflammatory	9

[a] Including 1 patient with ipsilateral supraclavicular nodes involved, but no distant metastasis.

3.3. Toxicities

No DLT occurred at dose levels 1, 2 and 3. At dose level 4, 2 out of 2 patients presented DLTs (Table 3). The first patient presented grade 3 fatigue requiring capecitabine treatment interruption for more than eight doses. The second patient developed grade 3 mucositis, grade 3 nausea and grade 3 febrile neutropenia after the first cycle. This case deserves some comment. Grade 4 neutropenia lasted for 21 days despite early initiation of granulocyte-colony stimulating factor (G-CSF), and grade 3 stomatitis lasted for 5 days followed by grade 4 stomatitis for 9 days. A dihydropyrimidine dehydrogenase (DPD) deficiency was suspected, and capecitabine treatment was not reinitiated for the subsequent courses. At dose level 4, no additional patients were entered and dose level 3 was considered as a possible recommended dose for phase II studies. A total of 15 patients were entered, and 80 cycles were delivered at this dose level.

During the entire treatment period, a total of 32 DLTs were encountered (Table 4). DLTs that occurred more than once were grade 3 febrile neutropenia, fatigue, PPE, nausea, stomatitis and hypokalaemia.

Details of haematological and non-haematological toxicity in 117 courses at all levels are listed in Table 5. Grade 3 PPE was reported only at dose level 3 (Table 6).

3.4. Treatment compliance

Capecitabine treatment had to be interrupted in 12 patients (52%) and in 16 cycles (14%) (Table 7). The vast majority of treatment interruptions occurred at dose level 3 (7 patients or 47% of patients at this dose level; 12 cycles or 15% of cycles given at this level). The median duration of treatment interruption was 4.5 days (range 0.5–14 days), and the median number of cycles interrupted per patient was 2 (range 1–3). Capecitabine treatment dose reductions were required in 4 patients (27%) and nine cycles (11%) at dose level 3 (Table 7). Overall, at dose level 3, 8 patients (53%) and 21 cycles (26%) required a capecitabine treatment modification (interruption and/or reduction). The most common reasons for capecitabine treatment modification at dose

Table 2
Treatment administration

	Level 1	Level 2	Level 3	Level 4	Total
No. of patients	3	3	15	2	23
No. of cycles	17	17	80	3	117
Median no. cycles (range)	6 (5–6)	6 (5–6)	6 (2–6)	1.5 (1–2)	6 (1–6)
Median time on study					
Weeks (range)	18 (15–18)	18 (15-18)	18 (6–24)	4.5 (3–6)	18 (3–24)
Capecitabine planned dose intensity (DI) (mg/m^2/week)	7000	8400	9800	11 200	
Capecitabine median delivered DI (mg/m^2/week) (range)	7025 (6794–7025)	8622 (8302–8670)	8394 (3615–10173)	9003 (8422–9583)	8394 (3615–10173)
Median relative dose intensity (%)					
Cyclophosphamide (range)	101 (99–103)	101.5 (101–102)	98.0 (69–104)	100.5 (99–102)	100 (69–104)
Epirubicin (range)	100 (97–103)	100 (97–103)	100 (66–104)	100 (100–100)	100 (66-104)
Capecitabine (range)	100 (97–100)	103 (98–103)	85.7 (36–104)	78.6 (75–85.6)	85.7 (36–104)

Table 3
Incidence of dose-limiting toxicities (DLTs) while defining the MTD (minimum of four cycles among 3 patients)

	Level 1	Level 2	Level 3	Level 4
No. of evaluable patients	3	3	3	2
No. of patients experiencing any DLT	0	0	0	2
No. of evaluated cycles at dose level	4	4	4	3
No. of cycles with DLT	0	0	0	2
Dose-limiting toxicity (episodes)	0	0	0	4
Grade 3 febrile neutropenia	–	1	–	1[a]
Grade 4 stomatitis	–	–	–	1[a]
Grade 3 fatigue	–	–	–	1[b]
Grade 3 nausea	–	–	–	1[a]

MTD, maximum tolerated dose.
[a] One patient had 3 DLTs at course 1: grade 3 febrile neutropenia, grade 4 stomatitis and grade 3 nausea.
[b] One patient had 1 DLT at course 2: grade 3 fatigue (capecitabine was stopped during 5 days due to grade 3 fatigue).

level 3 were nausea/vomiting ($n=5$), mucositis ($n=2$), diarrhoea ($n=2$) and PPE ($n=2$).

Epirubicin was reduced by 25% in 5 patients and 17 cycles; cyclophosphamide was reduced by the same amount in 4 patients and 16 cycles. All the dose reductions were performed at dose level 3. Treatment delay (5 patients; seven cycles) was exclusively required at dose level 3.

CEX median relative dose intensities are reported in Table 2. Only 47% of the patients treated at dose level 3 received 90% or more of the planned capecitabine dose intensity. The high rate of capecitabine treatment modification at level 3 led to a median relative dose intensity of 85.7% (Table 2). The median delivered dose intensity was slightly higher at dose level 2 than at dose levels 3 and 4. Therefore, we believe that level 2 is the recommended dose level.

Reasons for stopping study treatment were treatment completion (18 patients, 78%), excessive toxicity (3 patients) and patient's request (2 patients).

Table 4
Incidence of dose-limiting toxicities (DLTs) (all cycles)

	Level 1	Level 2	Level 3	Level 4
No. of evaluable patients	3	3	15	2
No. of patients experiencing DLT	1	1	9	2
No. of cycles at dose level	17	17	80	3
Dose-limiting toxicity (episodes)	2	1	25	4
Grade 3 febrile neutropenia	1[a]	1	2[b,c]	1[g]
Grade 3 PPE	–	–	4[b,d]	–
Grade 3 fatigue	–	–	4[f]	1
Grade 3 infection with neutropenia	–	–	1[f]	–
Grade 3 conjunctivitis	–	–	1[d]	–
Grade 3 or 4 stomatitis	1[a]	–	–	1[g]
Grade 3 oesophagitis	–	–	1[b]	
Grade 3 nausea	–	–	2[d,e]	1[g]
Grade 3 vomiting	–	–	1[e]	–
Grade 3 diarrhoea	–	–	1	–
Grade 3 neurological mood	–	–	1	–
Grade 3 myalgia	–	–	1	–
Grade 3 back pain	–	–	1[d]	–
Grade 3 deep vein thrombosis	–	–	1[b]	–
Grade 3 alkaline phosphatase	–	–	1[c]	–
Grade 3 hypokalaemia	–	–	2[c]	–
Discontinuation of capecitabine for more than eight doses due to toxicity (other than a grade 3-4 non haematological toxicity already counted as a DLT)	–	–	1	–

PPE, plantar–palmar erythrodysesthesia.
Patients who presented more than one DLT:
[a] Patient 1 had 2 DLTs at course 6: grade 3 febrile neutropenia and grade 3 stomatitis.
[b] Patient 17 had 3 DLTs at course 2: grade 3 febrile neutropenia, PPE and oesophagitis and 1 DLT at course 6: grade 3 deep vein thrombosis.
[c] Patient 22 had 3 DLTs at course 1: grade 3 febrile neutropenia, ↑ alkaline phosphatase and hypokalaemia.
[d] Patient 9 had 1 DLT at course 2: grade 3 nausea, 1 DLT at course 3: grade 3 pain (lumbago), 2 DLTs at course 4: grade 3 PPE and conjunctivitis, and 1 DLT at courses 5 and 6: grade 3 PPE.
[e] Patient 18 had 2 DLTs at course 1: grade 3 nausea and vomiting.
[f] Patient 19 had 1 DLT at course 1: grade 3 infection, and 1 DLT at courses 3, 4, 5, 6: grade 3 fatigue.
[g] Patient 11 had 3 DLTs at course 1: grade 3 febrile neutropenia, grade 4 stomatitis and grade 3 nausea.

Table 5
Haematological and non-haematological toxicity in 117 courses (all levels)

	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia[a]	7	16	37	43
Thrombocytopenia	32	4	–	–
Haemoglobin drop	66	37	–	–
Febrile neutropenia	x	x	5	–
PPE	25	5	4	–
Alopecia	11	95	x	x
Fatigue	40	16	5	–
Infection	9	7	1	–
Conjunctivitis	11	2	1	–
Stomatitis	31	8	1	1
Oesophagitis	–	–	1	–
Anorexia	2	3	–	–
Taste alteration	1	–	–	–
Nausea	27	29	3	–
Vomiting	9	20	1	–
Diarrhoea	7	8	1	–
Constipation	9	–	–	–
Haemorrhoids	3	5	–	–
Neurological mood	6	1	1	–
Insomnia	2	–	–	–
Myalgia	2	1	1	–
Back pain	5	1	1	–
Deep vein thrombosis	–	–	1	–
Cough	4	–	–	–
AST[a]	17	1	–	–
ALT[a]	19	3	–	–
Alkaline phosphatase[b]	8	1	1	–
Hypokalaemia[c]	13	x	2	–

ALT, alanine aminotransferase; AST, aspartate aminotransferase; x, grade not existing according to CTC version 2.0.
[a] Missing values for 16 cycles.
[b] Missing values for 11 cycles.
[c] Missing values for 15 cycles.

Table 6
Palmar–plantar erythrodysesthesia: grade experienced per cycle

	No. of cycles	Grade 1	Grade 2	Grade 3
Level 1	17	7	–	–
Level 2	17	2	–	–
Level 3	80	15	4	4
Level 4	3	1	1	–

3.5. Antitumour activity

Objective tumour responses are reported in Table 8. 19 patients (83%) achieved an objective response. The median time to response was 35 days (range 30–42 days).

4. Discussion

According to the results of this phase I study, capecitabine can be safely given in combination with epirubicin 100 mg/m^2 and cyclophosphamide 600 mg/m^2 up to the dose of 1050 mg/m^2 bid for 14 consecutive days every 3 weeks (dose level 3). However, escalation to dose level 3 did not translate into a superior delivered dose intensity of capecitabine (8622 mg/m^2/week at dose level 2 versus 8394 mg/m^2/week at dose level 3) due to a greater incidence of dose modifications at the higher level. In particular, 9 of 15 patients (60%) treated at dose level 3 experienced a toxicity that fit the criteria for DLT.

The most frequent DLT observed in our trial was grade 3 febrile neutropenia, with 22% (5/23) of patients experiencing such an episode while being treated with the CEX regimen (Table 4). In a recent publication, 2.6% (7/268) of patients with breast cancer treated in the adjuvant setting with the combination of cyclophosphamide 600 mg/m^2, epirubicin 100 mg/m^2 and 5-FU 600 mg/m^2 (CEF100 regimen), experienced a febrile neutropenia episode [7]. The only difference between the CEF100 and CEX regimens is the substitution of 5-FU administered as a single bolus injection on day 1, with

Table 7
Capecitabine dose reduction/cycle interruption 117 cycles ($n=23$ patients)

Dose level	Cycle 1 No. pts	Cycle 2 No. pts	Cycle 3 No. pts	Cycle 4 No. pts	Cycle 5 No. pts	Cycle 6 No. pts
Level 1	3	3	3	3	3	2
Reduced dose	0	0	0	0	0	0
Interrupted cycle	0	0	0	0	0	1
Off study	0	0	0	0	0	1
Level 2	3	3	3	3	3	2
Reduced dose	0	0	0	0	0	0
Interrupted cycle	0	0	0	0	0	1
Off study	0	0	0	0	0	1
Level 3	15	15	14	13	12	11
Reduced dose	0	0	1	3	3	2
Interrupted cycle	3	4	1	1	1	2
Off study	0	0	1	2	3	4
Level 4	2	1	0	0	0	0
Reduced dose	0	0	–	–	–	–
Interrupted cycle	1	1	–	–	–	–
Off study	0	1	2	2	2	2

pts, patients.

Table 8
Tumour response

	Level 1	Level 2	Level 3	Level 4	Total (%)
No. of patients	3	3	15	2	23
CR	1	–	3	–	4 (17)
PR	2	3	9	1	15 (66)
NC	–	–	3[a]	1	4 (17)

CR, complete response; PR, partial response; NC, no change.
[a] One patient had a PR evaluated at course two, but went off study after two courses due to toxicity (the tumour remained in PR, but could not be confirmed strictly as a PR one month later because the patient was no longer in the trial).

capecitabine given orally from day 1 to day 14. Myelosuppression is uncommon when capecitabine is used as a single agent, for example, as an intermittent schedule with capecitabine given for 2 weeks followed by a 1-week rest [12,13]. Therefore, the apparent difference in the febrile neutropenia rate between CEF100 and CEX is difficult to explain. One possible explanation could be in the way in which febrile neutropenia is defined and reported. In the French Adjuvant Study Group trial, toxicity was assessed using the WHO grading definition [16]. According to this definition, febrile neutropenia is not defined separately, but as an infection. In this trial, 7 cases were reported as major infections (grade 3), and the information 'neutropenic fever' was added in the results section. The number of minor and moderate episodes of infection was reported (grades 1–2), but the information regarding the neutrophile count was not. In our trial, toxicity was assessed according to CTC criteria [15]. Here, febrile neutropenia is clearly defined and scaled as grade 3 when present or grade 4 when life-threatening. With this classification, an episode of febrile neutropenia cannot be reported as grade 2. Thus, the CTC toxicity scale tends to overestimate the febrile neutropenia rate, while the WHO scale tends to underestimate it.

The second most common DLT was grade 3 fatigue, of which there were five episodes. Of note, four episodes occured in the same patient treated at level 3 (Table 4).

Another toxicity in this study was PPE, with four episodes reported as DLTs. However, it should be emphasised that PPE was not a great concern with the CEX regimen. First, grade 3 PPE occurred in 3.4% (4/117) of the cycles, which is very similar to the rate reported with infusional 5-FU regimens (ECisF or ECycloF) [5]. Second, all grade 3 PPE and the vast majority of grade 2 PPE occurred at dose level 3 and none at dose level 2, which is the recommended level for further studies (Table 6).

Nausea and/or vomiting were the most common reasons for capecitabine treatment modification at dose level 3. This specific side-effect contributed largely to the decrease in the capecitabine dose intensity at level 3. Interestingly, no grade 3 nausea or vomiting toxicity was reported at dose level 2, which is the recommended level.

How should the CEX regimen be developed in the future? The first option could be to replace infusional 5-FU regimens in the neoadjuvant or adjuvant setting. The interim results of a randomised study comparing ECisF ($n=211$) versus conventional AC (doxorubicin, cyclophosphamide) ($n=215$) have shown a significant overall survival benefit in patients who received ECisF ($P=0.04$), despite comparable relapse-free survival [17]. If this survival advantage is confirmed with a longer follow-up, the CEX regimen could become an attractive experimental arm to be compared with the infusional regimen. The second possibility could be to correlate the activity of this regimen with pharmacological parameters at the tumour level. Capecitabine is an ideal candidate for such an approach. Thymidine phosphorylase (TP), thymidylate synthase (TS), thymidine kinase (TK) and DPD are key enzymes among the list of biomarkers involved in the fluoropyrimidine pathway [9,18,19].

In conclusion, the present study establishes that oral capecitabine 900 mg/m^2 bid from day 1 to day 14 given in association with cyclophosphamide 600 mg/m^2 and epirubicin 100 mg/m^2 i.v. day 1, q 3 weeks is the recommended dose level. Given the encouraging response rate with this regimen (RR 83%), we believe that it would be worth further examining the activity of this regimen in the neoadjuvant setting and also evaluating specific biomarkers of response to capecitabine.

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