Cancer Chemother Pharmacol (2008) 61:989–995
DOI 10.1007/s00280-007-0555-z

ORIGINAL ARTICLE

Capecitabine and paclitaxel combination chemotherapy for inoperable or recurrent breast cancer: a phase I dose-finding study by the Kinki Breast Cancer Study Group

Norikazu Masuda · Tetsuya Taguchi · Takahiro Nakayama · Eiichi Shiba · Masahiro Watatani · Junichi Kurebayashi · Yuichi Takatsuka · Junichi Sakamoto · Shinzaburo Noguchi · Kinki Breast Cancer Study Group (KBCSG)

Received: 14 March 2007 / Accepted: 27 June 2007 / Published online: 20 July 2007

Abstract
Background The combination of capecitabine and paclitaxel (XP) has demonstrated synergistic antitumor activity in preclinical models. Three-weekly XP regimens have demonstrated excellent efficacy in phase II and III trials in metastatic breast cancer. We conducted a dose-finding study to identify the recommended 4-weekly XP regimen in patients with inoperable or recurrent breast cancer for phase II evaluation.
Methods Eligible patients had inoperable or recurrent breast cancer previously treated with chemotherapy (but not capecitabine or paclitaxel) in the (neo)adjuvant or metastatic setting. Each 4-week treatment cycle consisted of escalating doses of capecitabine (628 or 829 mg/m^2 twice daily [b.i.d.] on days 1–21) and paclitaxel (80 or 90 mg/m^2 on days 1, 8, and 15). Dose-limiting toxicities (DLT) were evaluated during the first two cycles.
Results Nine patients were treated. At dose level 1 (capecitabine 628 mg/m^2 b.i.d. plus paclitaxel 80 mg/m^2), one patient experienced a DLT (grade 3 non-hematologic toxicity). There were no further DLTs at dose level 1 or 2. Although the MTD was not reached, dose level 2 (capecitabine 829 mg/m^2 b.i.d., days 1–21, plus paclitaxel 80 mg/m^2, days 1, 8, and 15, every 28 days) is recommended for phase II evaluation, taking into consideration the single-agent doses used in Japan and the doses identified in Western studies of 3-weekly XP. The overall response rate was 44%; all patients treated at dose level 2 achieved a partial response.
Conclusions This 4-weekly XP regimen was well tolerated, active in patients with pretreated advanced breast cancer, and could be given as outpatient treatment. These results are consistent with findings of phase II and III trials evaluating 3-weekly regimens, and indicate that further investigation of a 4-weekly XP regimen is warranted.

Keywords Metastatic breast cancer · Capecitabine · Weekly · Paclitaxel · Phase I

N. Masuda (✉)
Department of Surgery, Breast Oncology Group,
Osaka National Hospital, 2-1-14, Honenzaka,
Chuou-ku, Osaka city, Osaka 540-0006, Japan
e-mail: nmasuda@alpha.ocn.ne.jp

T. Taguchi · S. Noguchi
Graduate School of Medicine,
Department of Breast and Endocrine Surgery,
Osaka University, Osaka city, Osaka, Japan

T. Nakayama
Department of Surgery, Sakai Municipal Hospital,
Sakai, Osaka, Japan

E. Shiba
Department of Breast and Endocrine Surgery,
Osaka Koseinenkin Hospital (Osaka Breast Clinic), Osaka, Japan

M. Watatani
Department of Surgery, Kinki University Hospital,
Osakasayama, Osaka, Japan

J. Kurebayashi
Department of Breast and Thyroid Surgery,
Kawasaki Medical School,
Kurashiki, Okayama, Japan

Y. Takatsuka
Department of Surgery, Kansai Rosai Hospital,
Amagasaki, Hyogo, Japan

J. Sakamoto
Graduate School of Medicine, Social Life Science,
Young Leaders' Program, Nagoya University,
Nagoya, Japan

Introduction

Anthracycline-containing regimens, such as doxorubicin and cyclophosphamide (AC), cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF), and 5-fluorouracil, epirubicin, and cyclophosphamide (FEC), are highly active and widely used as primary systemic therapy (neoadjuvant or adjuvant), reducing the risks of recurrence and death compared with non-anthracycline-containing regimens [1]. Nevertheless, most patients develop metastatic disease. Further anthracycline therapy is frequently not possible because of the increased risk of cardiotoxicity, and the benefit of re-exposure to anthracyclines is unclear. Consequently, the search for new, more effective treatments for metastatic breast cancer (MBC) is ongoing.

The taxanes, including paclitaxel, are among the most active agents for the treatment of MBC [2–6] and are increasingly being used in the adjuvant setting for high-risk patients. In a Japanese study, paclitaxel produced a 33% response rate in anthracycline-pretreated patients with advanced or metastatic disease [7]. Results of the CALGB 9840 trial indicate that weekly paclitaxel is more effective than a 3-weekly schedule, resulting in a significantly higher response rate (40 vs. 28%, respectively; OR = 1.61, $P = 0.017$) and longer time to progression (adjusted hazard ratio = 1.45, $P = 0.0008$; median = 9 vs. 5 months, respectively), although the trend towards improved overall survival with the weekly regimen did not reach statistical significance [8]. Early results from the Anglo-Celtic IV trial, presented at ASCO 2007, support these findings [9]. The administration schedule of paclitaxel also affects the safety profile, with less myelosuppression but more neurotoxicity seen with the weekly regimen [8, 10]. In Japan, weekly taxane monotherapy is currently introduced as the standard therapy after anthracycline failure. We have previously reported the antitumor activity of weekly paclitaxel in docetaxel-resistant MBC [11].

The oral fluoropyrimidine capecitabine, which was created in the Chugai Pharmaceutical Kamakura Research Laboratories (at that time the Nippon Roche KK, Research Center), generates 5-fluorouracil preferentially at the tumor site through exploitation of the significantly higher concentration of thymidine phosphorylase (TP) in tumor versus normal tissue [12]. Capecitabine monotherapy has demonstrated consistently high activity and excellent tolerability in anthracycline- and/or taxane-pretreated MBC [13–17] and in the first-line setting [18–21]. The high single-agent activity and good tolerability of capecitabine make it an attractive combination partner. Furthermore, in preclinical models, upregulation of TP by agents such as docetaxel, paclitaxel, and cyclophosphamide results in synergistic antitumor activity when co-administered with capecitabine [22, 23]. In the clinical setting, the combination of capecitabine and docetaxel in anthracycline-pretreated MBC significantly improves response rate, time to progression, and overall survival compared with docetaxel alone [24]. In addition, results of a randomized, phase II trial presented at ASCO 2006 indicated that in the first-line setting, the combination of capecitabine and docetaxel significantly improved response rate, time to progression, and overall survival compared with sequential docetaxel followed at progression by capecitabine [25]. Several phase II and III trials have demonstrated that the combination of capecitabine and paclitaxel (XP, with paclitaxel administered using a weekly or a 3-weekly schedule) is also highly active [26–30]. In a recently reported randomized, phase III trial, XP demonstrated similar efficacy to epirubicin plus paclitaxel, with median overall survival of 25.6 months and median progression-free survival of 12.0 months at interim analysis [30].

Previously reported clinical trials have evaluated XP administered using 3-weekly cycles, with capecitabine given according to the standard schedule used in Europe and the USA (capecitabine twice daily (b.i.d.) for 14 days followed by a 7-day rest period). In Japan, however, a 4-weekly regimen with capecitabine given on days 1–21 followed by a 7-day rest period has been investigated [31–33]. This regimen was selected for further development based on cutaneous effects observed in an early dose-finding study of a continuous regimen in Japanese patients [34]. Treatment with capecitabine monotherapy is covered by National Health Insurance only if administered using this 4-weekly schedule at a dose of 829 mg/m^2 b.i.d. As a result, a 4-weekly schedule is commonly adopted in clinical practice in Japan. Similarly, paclitaxel treatment for MBC typically consists of weekly administration of 80 mg/m^2 on days 1, 8, and 15 every 28 days. Therefore a 28-day XP combination regimen may be a valid alternative to the 21-day regimen developed in most Western countries.

Patients and methods

Study design

The primary objective of this multicenter, phase I, dose-finding study conducted by the Kinki Breast Cancer Study Group (KBCSG) was to identify the maximum tolerated dose of a 28-day regimen of capecitabine in combination with weekly paclitaxel in patients with advanced or recurrent breast cancer, and determine the recommended dose for a phase II study. Secondary objectives included estimation of the proportion of patients achieving a response or stable disease 6 months after treatment initiation and assessment of the safety profile. A standard 3 + 3 dose–escalation design was used.

The protocol was approved by the institutional review board at each center. The study was conducted in accordance with Good Clinical Practice Guidelines (Sixth International Conference on Harmonisation and the Declaration of Helsinki). All patients provided written informed consent.

Eligibility criteria

Female patients with histologically or cytologically confirmed breast cancer and evidence of measurable metastatic disease using Response Evaluation Criteria in Solid Tumors (RECIST) were eligible for this study. Main inclusion criteria were: age 20–75 years, ECOG performance status 0 or 1, normal renal, hepatic, and hematologic function confirmed by a prestudy examination (white blood cell count $\geq$ 4,000/mm^3 and $\leq$12,000/mm^3, neutrophil count $\geq$ 2,000/mm^3, platelet count $\geq$ 100,000/mm^3, hemoglobin $\geq$ 9.0 g/dl, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq$ 2.5 $\times$ upper limit of clinic normal (ULN), total bilirubin < 1.25 $\times$ ULN, serum creatinine < 1.5 $\times$ ULN, creatinine clearance > 50 ml/min), and no prior radiotherapy to the target lesion. At least 2 weeks must have elapsed since completing previous endocrine therapy and 4 weeks must have elapsed since completion of previous chemotherapy, radiotherapy, surgery, or treatment with an investigational new drug. Patients were ineligible if they had previously received a taxane or capecitabine.

Treatment

Capecitabine was administered orally at a twice-daily dose of 628 mg/m^2 (dose level 1) or 829 mg/m^2 (dose levels 2 and 3) taken within 30 min after morning and evening meals, for 21 consecutive days. Paclitaxel was administered intravenously as a 60-minute infusion at a dose of 80 mg/m^2 (levels 1 and 2) or 90 mg/m^2 (level 3) on days 1, 8, and 15. These initial doses were selected based on the anticipated increase in both efficacy and toxicity compared with single-agent administration, as is usual in combination studies. Table 1 shows the dose–escalation scheme. Premedication prior to paclitaxel administration was mandatory and consisted of i.v. dexamethasone 20 mg, oral diphenhydramine hydrochloride 50 mg, and i.v. ranitidine 50 mg. If no hypersensitivity reactions occurred after the first dose of paclitaxel, the dexamethasone dose could be reduced to 8 mg from cycle 2 onwards at the discretion of the treating physician. If the first two cycles of XP combination therapy were well tolerated, patients could continue to receive combination therapy until disease progression or unacceptable toxicity.

Table 1 Dose-escalation scheme

Dose level	Paclitaxel days 1, 8.15 (mg/m^2)	Capecitabine days 1–21 (mg/m^2) b.i.d
−1	70	628
1	80	628
2	80	829
3	90	829

b.i.d. twice daily

Dose–escalation scheme

The first cohort of three patients was treated at dose level 1. Dose-escalation decisions were based on the occurrence of dose-limiting toxicities (DLT) during the first two cycles. DLTs were defined as any of the following during the first two cycles of chemotherapy: (1) grade 4 leukopenia (<1,000/mm^3) or neutropenia (<500/mm^3) lasting for >4 days; (2) toxicity resulting in omission of two or more paclitaxel doses; (3) fever (>38.0°C) associated with grade 3 or 4 neutropenia (<1,000/mm^3) or clinical infection; (4) grade 4 thrombocytopenia (<25,000/mm^3); (5) grade 3 hand–foot syndrome [12]; (6) other grade 4 non-hematologic toxicity (excluding hair loss, nausea/vomiting, and anorexia); (7) toxicity resulting in a delay of >7 days before administration of the second or third cycle. Any events other than those described above could be classified as a DLT at the discretion of the data and safety monitoring committee.

If none of the three patients in a cohort experienced a DLT, three patients were to be treated at the next dose level. If one of the three patients experienced a DLT, three additional patients were to be treated at the same dose level. If no further DLTs occurred, three patients were to be treated at the next dose level. If a DLT occurred in two or more of a cohort of six patients, or two or more of a cohort of three patients, that dose level was to be defined as the maximum tolerated dose and the previous dose level was to be defined as the recommended dose.

Study assessments

Adverse events were graded using the National Cancer Institute Common Toxicity Criteria (CTCAE v3.0). Details of all adverse events and laboratory abnormalities and their relationship to study treatment were to be recorded on the Case Report Form. Tumor lesions were measured at baseline and after every second cycle using RECIST.

Results

Patient characteristics

Between November 2003 and June 2005, nine women were enrolled, all of whom had previously received chemotherapy. Six received dose level 1 and three received dose level 2. Baseline characteristics are summarized in Table 2. XP was given as first-line chemotherapy for MBC in three patients, second-line therapy in five patients and third-line therapy in one patient.

Tolerability

Table 3 shows all adverse events occurring in more than one patient during the first two cycles of therapy. Among the first cohort of three patients treated at dose level 1 (capecitabine 628 mg/m^2 b.i.d., paclitaxel 80 mg/m^2), one experienced grade 3 non-hematologic toxicity (peripheral neuropathy, malaise, muscle pain, difficulty in walking due to pelvic pain), meeting the criteria for DLT. Therefore, three additional patients were recruited to dose level 1. There were no further DLTs at this dose level. Three patients were enrolled to dose level 2, none of whom experienced any DLT. Hand-foot syndrome was observed at grade 1 intensity in two patients and grade 2 intensity in four patients. There were no grade 3 cases in any of the patients treated in this study and there was no evidence that concomitant use of paclitaxel exacerbated hand-foot syndrome.

When all three patients had completed combination treatment at level 2, tolerability was evaluated by the data and safety monitoring committee. The panel decided that as both capecitabine and paclitaxel had been administered at their full, Japanese regimen, single-agent doses (capecitabine 829 mg/m^2 b.i.d., paclitaxel 80 mg/m^2), and the dose intensity of level 2 exceeded the doses adopted in clinical trials of this combination in the USA, escalation to dose level 3 should not proceed. Consequently, the recommended regimen for phase II evaluation is capecitabine 829 mg/m^2 b.i.d. on days 1–21 in combination with paclitaxel 80 mg/m^2 on days 1, 8, and 15, both repeated every 28 days.

Table 2 Baseline characteristics (n = 9)

Median age, years (range)	55 (47–66)
ECOG performance status	
0	4
1	5
Menopausal status	
Premenopausal	1
Postmenopausal	8
Sites of metastases	
Liver	6
Lung	3
Pleura	1
Bone	5
Skin	1
Lymph node	4
Prior adjuvant chemotherapy	
None	4
CMF	2
Anthracycline	2
Oral 5-fluorouracil	1
Prior chemotherapy for MBC	
None	3
Anthracycline	5
Docetaxel	1

CMF cyclophosphamide methotrexate 5-fluorouracil, *MBC* metastatic breast cancer

Table 3 Adverse events occurring in more than one patient during the first two cycles of therapy

	Level 1 (n = 6)		Level 2 (n = 3)	
Capecitabine (mg/m^2 b.i.d., days 1–21)	628		829	
Paclitaxel (mg/m^2, days 1, 8,15)	80		80	
Grade	2	3	2	3
Hematologic				
Leukopenia	3	0	3	0
Neutropenia	0	1	3	0
Non-hematologic				
Anorexia	0	0	1	0
Nausea	0	0	1	0
Vomiting	1	0	2	0
Diarrhea	0	0	2	0
Constipation	1	0	1	0
Neurotoxicity (sensory)	1	1	0	0
Fatigue	1	1	0	0
Muscle pain	0	1	0	0
Arthralgia	1	0	0	0
Hand–foot syndrome	3	0	1	0
Alopecia	2	0	0	0
Dysgeusia	0	0	2	0
Hypertension	0	0	1	0
Desquamation	0	0	2	0
Laboratory				
AST	1	0	0	0
ALT	0	0	1	0

ALT alanine aminotransferase, *AST* aspartate aminotransferase

Antitumor efficacy

Partial responses were confirmed in all three patients receiving dose level 2 and one of the two patients receiving dose level 1 as first-line therapy, giving an overall response rate of 44% (4/9 patients). The other patient receiving dose level 1 as first-line therapy achieved stable disease. Among the remaining four patients receiving dose level 1 as second- ($n = 3$) or third-line ($n = 1$) therapy, three-showed disease progression and one was not evaluable.

Discussion

The 4-weekly XP schedule investigated in this study is well tolerated and active. We recommend a regimen of capecitabine 829 mg/m^2 b.i.d. on days 1–21 plus paclitaxel 80 mg/m^2 on days 1, 8, and 15, both repeated every 28 days, for phase II evaluation. Our results provide an early indication that our 4-weekly XP regimen is a valid alternative to the 3-weekly regimen used in other parts of the world.

In patients with less aggressive, asymptomatic, small-volume breast cancer following anthracycline- and/or taxane-containing (neo)adjuvant therapy, oral capecitabine monotherapy is considered an acceptable first-line therapy, enabling patients to maintain good quality of life. At disease progression, more intensive chemotherapy, including intravenous taxane therapy, may be considered.

In patients with more aggressive disease who require rapid reduction in tumor burden, the regimen offering the highest response rate should be considered. This strategy is important because if first-line therapy is ineffective, resulting in increased tumor volume, further treatment may be compromised because of extensive tumor growth, deterioration in general health, or worsening symptoms. This concept is supported by results of the randomized, phase III trial reported by O'Shaughnessy et al. [24], in which 35% of patients initially randomized to docetaxel received no further chemotherapy at progression, thus denying them the opportunity to benefit from other agents [35]. Further support comes from a randomized clinical trial comparing capecitabine and docetaxel combination treatment versus sequential administration of these two agents [25]. In this trial, response rate, progression-free survival, and overall survival were significantly superior in patients receiving combination versus sequential treatment. Similarly, the authors of the Mexican Oncology Group Study concluded that "when rapid response is the primary goal, patients should receive combination therapy (capecitabine plus taxane). If long-term outcomes and quality of life are more important, capecitabine followed by a taxane is an equally appropriate choice" [21].

The value of capecitabine/taxane combination regimens has been seen in numerous clinical trials [24–30, 36–38]. Phase I and II studies conducted in Europe and North and South America have explored different doses and schedules of XP. In several of these studies [28, 36, 38], a capecitabine dose of 1,000 mg/m^2 b.i.d., days 1–14 every 21 days, has been adopted. This dose was also used in combination with 3-weekly paclitaxel in the randomized phase III trial versus epirubicin/paclitaxel as first-line therapy for MBC [30]. The capecitabine dose recommended based on results of the present study provides a dose intensity of 8,699 mg/m^2/week, very similar to the 9,333 mg/m^2/week intensity in the studies using 1,000 mg/m^2 b.i.d. in a 3-weekly regimen. Interestingly, in the US Oncology phase II study reported by Blum et al. [29], the US phase II study reported by Gradishar et al. [27], and the randomized trial by the Mexican Oncology Study Group [21], the dose intensity was only 7,700 mg/m^2/week. This difference can probably be explained by regional differences in the tolerability of fluoropyrimidines that have recently become apparent. In an analysis of more than 3,000 patients treated with 5-fluorouracil- or capecitabine-based regimens for colorectal cancer, fluoropyrimidine therapy was least well tolerated in US patients and best tolerated in Asian patients [39]. Tolerability in European patients was intermediate. Thus, subtle differences in dose intensity may be appropriate when these differences are taken into account. Recently, a 2-weekly regimen with capecitabine given on days 1–7 every 14 days has been investigated in the USA [40], based on preclinical findings and mathematical modeling [41]. Although the average weekly dose delivered using this 7/7 schedule is no higher than with the conventional schedule, it is attracting some interest in the USA. Hand–foot syndrome and diarrhea remain the DLTs. The paclitaxel dose intensity in our study was identical to that used in the study by Susnjar et al. [36].

Both the randomized phase III trial of capecitabine plus 3-weekly paclitaxel [30] and the US phase II study investigating capecitabine plus paclitaxel on days 1 and 8 [29] demonstrated remarkable efficacy. Response rates were 52 and 55%, respectively, and median overall survival was 25.6 and 17 months, respectively. The slightly lower response rate in the present small study was to be expected given that most patients received XP in the second- or third-line setting in our study, contrasting with the first-line setting in the larger studies. Moreover, this Japanese study included only nine patients and was not designed to assess efficacy. Nevertheless, antitumor activity was evident.

To further assess the efficacy and tolerability of a 4-weekly XP schedule in Japanese patients, a multicenter, phase II trial (KBCSG 0609) has been initiated using the regimen identified in the present study.

Acknowledgments This work is supported in part by the non-profit organization, Epidemiological and Clinical Research Information Network (ECRIN). We would like to thank Ms Kanae Nakamura, Nahomi Iwahori, and Chieko Takeuchi for their devoted logistical support for this clinical trial.

References

1. Early Breast Cancer Trialists' Collaborative Group (1998) Polychemotherapy for early breast cancer: an overview of the randomised trials. Lancet 352:930–942
2. Nabholtz JM, Gelmon K, Bontenbal M, Spielmann M, Catimel G, Conte P, Klaassen U, Namer M, Bonneterre J, Fumoleau P, Winograd B (1996) Multicenter, randomized comparative study of two doses of paclitaxel in patients with metastatic breast cancer. J Clin Oncol 14:1858–1867
3. Biganzoli L, Cufer T, Bruning P, Coleman R, Duchateau L, Calvert AH, Gamucci T, Twelves C, Fargeot P, Epelbaum R, Lohrisch C, Piccart MJ (2002) Doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide as first-line chemotherapy in metastatic breast cancer: the European Organization for Research and Treatment of Cancer 10967 multicenter phase III trial. J Clin Oncol 20:3114–3121
4. Jassem J, Pienkowski T, Pluzanska A, Jelic S, Gorbunova V, Mrsic-Krmpotic Z, Berzins J, Nagykalnai T, Wigler N, Renard J, Munier S, Weil C, Central & Eastern Europe, Israel Pacitaxel Breast Cancer Study Group (2001) Doxorubicin and paclitaxel versus fluorouracil, doxorubicin, and cyclophosphamide as first-line therapy for women with metastatic breast cancer: final results of a randomized phase III multicenter trial. J Clin Oncol 19:1707–1715
5. Smith RE, Brown AM, Mamounas EP, Anderson SJ, Lembersky BC, Atkins JH, Shibata HR, Baez L, DeFusco PA, Davila E, Tipping SJ, Bearden JD, Thirlwell MP (1999) Randomized trial of 3-hour versus 24-hour infusion of high-dose paclitaxel in patients with metastatic or locally advanced breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-26. J Clin Oncol 17:3403–3411
6. Jones SE, Erban J, Overmoyer B, Budd GT, Hutchins L, Lower E, Laufman L, Sundaram S, Urba WJ, Pritchard KI, Mennel R, Richards D, Olsen S, Meyers ML, Ravdin PM (2005) Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. J Clin Oncol 23:5542–5551
7. Ito Y, Horikoshi N, Watanabe T, Sasaki Y, Tominaga T, Okawa T, Tabei T, Kuraishi Y, Tamura K, Abe R, Kitajima M, Yamaguchi S, Kobayashi T, Koyama H, Orita K, Takashima S, Nomura Y, Ogawa M (1998) Phase II study of paclitaxel (BMS-181339) intravenously infused over 3 hours for advanced or metastatic breast cancer in Japan. BMS-181339 Breast Cancer Study Group. Invest New Drugs 16:183–190
8. Seidman AD, Berry D, Cirrincione C, Harris L, Dressler L, Muss H, Naughton M, Norton L, Winer E, Hudis C (2004) CALGB 9840: phase III study of weekly (W) paclitaxel via 1-hour(h) infusion versus standard (S) 3 hr infusion every third week in the treatment of metastatic breast cancer (MBC), with trastuzumab (T) for HER2 positive MBC and randomized for T in HER2 normal MBC. J Clin Oncol 22(14S):512
9. Verrill MW, Lee J, Cameron D, Agrawal R, Coleman RE, McAdam K, Wardley A, Bowman A, Ferrigan L, Yellowlees A (2007) Anglo-Celtic IV: first results of a UK National Cancer Research Network randomised phase 3 pharmacogenetic trial of weekly versus 3 weekly paclitaxel in patients with locally advanced or metastatic breast cancer (ABC). J Clin Oncol 25(18S):LBA1005
10. Seidman AD, Hudis CA, Albanell J, Tong W, Tepler I, Currie V, Moynahan ME, Theodoulou M, Gollub M, Baselga J, Norton L (1998) Dose-dense therapy with weekly 1-hour paclitaxel infusions in the treatment of metastatic breast cancer. J Clin Oncol 16:3353–3361
11. Taguchi T, Aihara T, Takatsuka Y, Shin E, Motomura K, Inaji H, Noguchi S, Kinki Breast Cancer Study Group (2004) Phase II study of weekly paclitaxel for docetaxel-resistant metastatic breast cancer in Japan. Breast J 10:509–513
12. Miwa M, Ura M, Nishida M, Sawada N, Ishikawa T, Mori K, Shimma N, Umeda I, Ishitsuka H (1998) Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. Eur J Cancer 34:1274–1281
13. Blum JL, Jones SE, Buzdar AU, LoRusso PM, Kuter I, Vogel C, Osterwalder B, Burger HU, Brown CS, Griffin T (1999) Multicenter phase II study of capecitabine in paclitaxel refractory metastatic breast cancer. J Clin Oncol 17:485–493
14. Blum JL, Dieras V, Lo Russo PM, Horton J, Rutman O, Buzdar A, Osterwalder B (2001) Multicenter, phase II study of capecitabine in taxane-pretreated metastatic breast carcinoma patients. Cancer 92:1759–1768
15. Fumoleau P, Largillier R, Clippe C, Dieras V, Orfeuvre H, Lesimple T, Culine S, Audhuy B, Serin D, Cure H, Vuillemin E, Morere JF, Montestruc F, Mouri Z, Namer M (2004) Multicentre, phase II study evaluating capecitabine monotherapy in patients with anthracycline- and taxane-pretreated metastatic breast cancer. Eur J Cancer 40:536–542
16. Talbot DC, Moiseyenko V, Van Belle S, O'Reilly SM, Alba Conejo E, Ackland S, Eisenberg P, Melnychuk D, Pienkowski T, Burger HU, Laws S, Osterwalder B (2002) Randomised, phase II trial comparing oral capecitabine (Xeloda®) with paclitaxel in patients with metastatic/advanced breast cancer pretreated with anthracyclines. Br J Cancer 86:1367–1372
17. Reichardt P, Von Minckwitz G, Thuss-Patience PC, Jonat W, Kolbl H, Janicke F, Kieback DG, Kuhn W, Schindler AE, Mohrmann S, Kaufmann M, Luck HJ (2003) Multicenter phase II study of oral capecitabine (Xeloda®) in patients with metastatic breast cancer relapsing after treatment with a taxane-containing therapy. Ann Oncol 14:1227–1233
18. Stockler MR, Sourjina T, Harvey V, Frances P, Byrne M, van Hazel G, Fitzharris B, Ackland S, Finch K, Lindsay D, Kato-Fong A, Paksec L, Gebski V, Simes RJ, Coates AS, Forbes J (2006) A randomized trial of capecitabine given intermittently versus continuously versus classical CMF as first line chemotherapy for women with advanced breast cancer unsuited to more intensive treatment. Breast Cancer Res Treat 100(Suppl 1):S278
19. O'Shaughnessy JA, Blum J, Moiseyenko V, Jones SE, Miles D, Bell D, Rosso R, Mauriac L, Osterwalder B, Burger HU, Laws S (2001) Randomized, open-label, phase II trial of oral capecitabine (Xeloda) vs. a reference arm of intravenous CMF (cyclophosphamide, methotrexate and 5-fluorouracil) as first-line therapy for advanced/metastatic breast cancer. Ann Oncol 12:1247–1254
20. Bajetta E, Procopio G, Celio L, Gattinoni L, Della Torre S, Mariani L, Catena L, Ricotta R, Longarini R, Zilembo N, Buzzoni R (2005) Safety and efficacy of two different doses of capecitabine in the treatment of advanced breast cancer in older women. J Clin Oncol 23:2155–2161
21. Soto C, Torrecillas L, Reyes S, Ramirez M, Perez L, Cervantes G, González F, Tellez E, Benitez H (2006) Capecitabine (X) and taxanes in patients (pts) with anthracycline-pretreated metastatic breast cancer (MBC): sequential vs. combined therapy results from a MOSG randomized phase III trial. J Clin Oncol 24(18S):570
22. Endo M, Shinbori N, Fukase Y, Sawada N, Ishikawa T, Ishitsuka H, Tanaka Y (1999) Induction of thymidine phosphorylase expression and enhancement of efficacy by cyclophosphamide in mammary tumor models. Int J Cancer 83:127–134

23. Sawada N, Ishikawa T, Fukase Y, Nishika M, Yoshikubo T, Ishitsuka H (1998) Induction of thymidine phosphorylase activity and enhancement of capecitabine efficacy by Taxol/Taxotere in human cancer xenografts. Clin Cancer Res 4:1013–1019
24. O'Shaughnessy J, Miles D, Vukelja S, Moiseyenko V, Ayoub JP, Cervantes G, Fumoleau P, Jones S, Lui WY, Mauriac L, Twelves C, Van Hazel G, Verma S, Leonard R (2002) Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. J Clin Oncol 20:2812–2823
25. Beslija S, Obralic N, Basic H, Tatarevic A, Naila M, Banjin M, Cardzic A, Sosevic A, Pasic A, Ceric T, Salkic B (2006) Randomized trial of sequence vs. combination of capecitabine (X) and docetaxel (T): XT vs. T followed by X after progression as first-line therapy for patients (pts) with metastatic breast cancer (MBC). J Clin Oncol 24(18S):571
26. Batista N, Perez-Manga G, Constenla M, Ruiz A, Carabantes F, Castellanos J, Gonzalez Baron M, Villman K, Soderberg M, Ahlgren J, Casinello J, Regueiro P, Murias A (2004) Phase II study of capecitabine in combination with paclitaxel in patients with anthracycline-pretreated advanced/metastatic breast cancer. Br J Cancer 90:1740–1746
27. Gradishar WJ, Meza LA, Amin B, Samid D, Hill T, Chen YM, Lower EE, Marcom PK (2004) Capecitabine plus paclitaxel as front-line combination therapy for metastatic breast cancer: a multicenter phase II study. J Clin Oncol 22:2321–2327
28. Bari M, D'Andrea MR, Azzarello G, Pappagallo G, Sartori D, Iop A, Gaion F, Rosetti F, Silvestri B, Bonura S, D'Alessio A, Vinante O (2005) Salvage therapy with capecitabine plus weekly paclitaxel in heavily pretreated advanced breast cancer. A multicenter phase II study. Am J Cancer 4:307–313
29. Blum JL, Dees EC, Chacko A, Doane L, Ethirajan S, Hopkins J, McMahon R, Merten S, Negron A, Neubauer M, Ilegbodu D, Boehm KA, Asmar L, O'Shaughnessy JA (2006) Phase II trial of capecitabine and weekly paclitaxel as first-line therapy for metastatic breast cancer. J Clin Oncol 24:4384–4390
30. Lück HJ, Thomssen C, Untch M, Kuhn W, Eidtmann H, du Bois A, Olbricht S, Moebus V, Steinfeld D, Bauknecht T, Schroeder W, Jackisch C (2000) Multicentric phase III study in first line treatment of advanced metastatic breast cancer (ABC). Epirubicin/paclitaxel (ET) vs. epirubicin/cyclophosphamide (EC). A study of the AGO breast cancer group. Proc Am Soc Clin Oncol 19:abstract 280
31. Saeki T, Kimura T, Toi M, Taguchi T (2006) A pilot phase II study of capecitabine in patients with advanced or recurrent breast cancer. Breast Cancer 13:49–57
32. Kusama M, Sano M, Ikeda T, Sonoo H, Takashima S (2001) A phase II study of Xeloda (capecitabine) in patients with advanced/metastatic breast carcinoma—the Cooperative Study Group of Capecitabine for Breast Carcinoma. Proc Am Soc Clin Oncol 20:abstract 1924
33. Watanabe T, Katsumata N, Saski Y, Saeki T, Aogi K, Toi M, Holdener E (2001) A multicenter phase II trial of Xeloda (capecitabine) in patients with docetaxel-refractory advanced/metastatic breast cancer. Proc Am Soc Clin Oncol 20:abstract 1991
34. Saeki T, Takashima S, Terashima S, Satoh A, Toi M, Osaki A, Toge T, Ohno S, Nomura N, Fukuyama Y, Koizumi W, Taguchi T (2005) A Japanese phase I study of continuous oral capecitabine in patients with malignant solid tumors. Int J Clin Oncol 10:51–57
35. Miles D, Vukelja S, Moiseyenko V, Cervantes G, Mauriac L, Van Hazel G, Liu WY, Ayoub JP, O'Shaughnessy JA (2004) Survival benefit with capecitabine/docetaxel versus docetaxel alone: analysis of therapy in a randomized phase III trial. Clin Breast Cancer 5:273–278
36. Susnjar S, Bosnjak S, Radulovic S, Stefanovic J, Gajic-Dobrosavljevic M, Kreacic M (2005) Weekly paclitaxel (TAX) and capecitabine (CAP) for metastatic breast cancer (MBC) patients (PTS) previously treated with anthracycline-containing therapy: a phase I dose-finding study. J Clin Oncol 23(16S):851
37. Di Costanzo F, Gasperoni S, Papaldo P, Bilancia D, Manzione L, Landucci E, Mazzoni F, Cognetti F, Gruppo Oncologico Italiano di Ricerca clinica, Gruppo Oncologico del Lazio (2006) Weekly paclitaxel plus capecitabine in advanced breast cancer patients: dose-finding trial of GOIRC and GOL. Ann Oncol 17:79–84
38. Uhlmann C, Ballabeni P, Rijken N, Brauchli P, Mingrone W, Rauch D, Pestalozzi BC, Rochlitz C, Aebi S, Swiss Group for Clinical Cancer Research, Swiss Institute for Applied Cancer Research (2004) Capecitabine with weekly paclitaxel for advanced breast cancer: a phase I dose-finding trial. Oncology 67:117–122
39. Haller DG, Cassidy J, Clarke S, Cunningham D, Van Cutsem E, Hoff P, Rothenberg M, Saltz L, Schmoll HJ, Twelves C (2006) Tolerability of fluoropyrimidines appears to differ by region. J Clin Oncol 24(18S):3514
40. Theodoulou M, Traina TA, Dugan U, Lake D, Fornier M, Feigin K, Patil S, Edwards C, Norton L, Hudis C (2007) Phase I study of a novel capecitabine schedule based on Norton-Simon mathematical modeling. J Clin Oncol 25(18S):1045
41. Norton L, Dugan U, Young D, Farrell C, Tanaka Y, Theodoulou M, Traina T, Hudis C (2005) Optimizing chemotherapeutic dose-schedule (CDS) by Norton-Simon modeling: capecitabine (Xeloda® = X) Proc Am Assoc Cancer Res (abstract 5007)