EUROPEAN JOURNAL OF CANCER 46 (2010) 3184–3191

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

First-line therapy with moderate dose capecitabine in metastatic breast cancer is safe and active: Results of the MONICA trial

M. Kaufmann [a], N. Maass [b], S.D. Costa [c], A. Schneeweiß [d], S. Loibl [e], M.W. Sütterlin [f], I. Schrader [g], B. Gerber [h], W. Bauer [i], W. Wiest [j], O. Tomé [k], A. Distelrath [l], V. Hagen [m], A. Kleine-Tebbe [n], E. Ruckhaeberle [a], K. Mehta [e], G. von Minckwitz [e,], for the GBG-39 trialists[o]*

[a] *Universitäts-Frauenklinik, Frankfurt, Germany*
[b] *Universitäts-Frauenklinik, Kiel, Germany*
[c] *Universitäts-Frauenklinik, Magdeburg, Germany*
[d] *Frauenklinik im Nationalen Centrum für Tumorerkrankungen, Heidelberg, Germany*
[e] *German Breast Group, Neu-Isenburg, Germany*
[f] *Universitäts-Frauenklinik, Mannheim, Germany*
[g] *Henrietten-Stiftung, Hannover, Germany*
[h] *Universitäts-Frauenklinik, Rostock, Germany*
[i] *Frauenklink, Villigen-Schwenningen, Germany*
[j] *St. Vincenz und Elisabeth-Hospital, Mainz, Germany*
[k] *St. Vincentius Kliniken, Karlsruhe, Germany*
[l] *Tumorklinik, Klinikum Fulda, Germany*
[m] *St. Johannes Hospital, Dortmund, Germany*
[n] *DRK Kliniken, Berlin-Köpenik, Germany*

ARTICLE INFO

Article history:
Received 23 March 2010
Received in revised form 5 July 2010
Accepted 14 July 2010
Available online 24 August 2010

Keywords:
Metastatic breast cancer
Capecitabine
Chemotherapy
Prospective trial

ABSTRACT

Background: To determine activity and safety of capecitabine at a moderate dose of 2000 mg/m^2 as first-line therapy for metastatic breast cancer.

Methods: In this prospective phase II trial, patients with HER2-negative metastatic breast cancer received first-line capecitabine 2000 mg/m^2 on days 1–14 every 3 weeks. The primary aim was to exclude a time to progression (TTP) <6 months. Secondary end-points were overall response rate, overall survival (OS), toxicity and quality of life.

Results: Median age of the 161 included patients was 65 years. Median TTP and OS were 7.3 months [95% (confidence interval) CI: 6.2–8.4] and 17.1 months (95% CI: 14.0–20.3), respectively. An overall response rate of 26.1%, including 13 complete remissions was observed. Patients developing grade I–III hand-foot syndrome had a significantly longer TTP and OS and patients >65 years also achieved a significantly longer TTP. Haematological grade I–IV toxicities were leucopenia (64.0%), anaemia (50.9%) and thrombocytopenia

* *Corresponding author:* Address: German Breast Group, Martin-Behaim-Straße 12, 63263 Neu-Isenburg, Germany. Tel.: +49 0 6102 7480 429; fax: +49 0 6102 7480 111.
E-mail address: Gunter.vonMinckwitz@germanbreastgroup.de (G. von Minckwitz).
[o] GBG 39 trialists (see Appendix).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2010.07.009

(28.0%). Relevant non-haematological toxicities were hand-food-syndrome (37.3%), fatigue (34.2%), nausea (29.8%) and diarrhoea (20.5%). Quality of life assessment revealed an improved emotional function, but worsening of nausea and vomiting from cycle 1–10.
Conclusions: Capecitabine at a dose of 2000 mg/m^2 is active and safe as first-line treatment of patients with metastatic breast cancer.

1. Introduction

As metastatic breast cancer is still considered to be incurable, the leading therapeutic principle is to provide adequate disease and symptom control with low treatment-related toxicity, and consequently improvement and maintenance of the quality of life. The orally available fluoropyrimidine-carbamate capecitabine fulfils these requirements in a convenient manner.[1] Capecitabine at a dose of 2500 mg/m^2 was first approved as monotherapy for the treatment of metastatic breast cancer patients progressing after previous taxane and anthracycline therapy. Overall response rates of 9–36% and a median time to progression (TTP) of 3.1–7.4 months were observed.[2]

First-line capecitabine monotherapy has shown high efficacy in patients with metastatic breast cancer who are older than 65 years. Patients who received a dose reduction from 2500 to 2000 mg/m^2 because of toxicity did not show inferior efficacy in retrospective subgroup analyses.[3] Other trials including low patient numbers have used capecitabine at lower starting doses (1600–2000 mg/m^2) and have suggested similar efficacy but lower toxicity compared with capecitabine at full dose.[4–8] However, confidence intervals were large and confirmatory trials are lacking.

The mono efficacy of capecitabine (MONICA) study was designed to prospectively investigate the activity and safety of capecitabine monotherapy at a dose of 2000 mg/m^2 as first-line treatment in patients with metastatic breast cancer.

2. Patients and methods

2.1. Study design

The MONICA study was a prospective non-randomized phase II trial conducted between 2005 and 2009 in 35 centres in Germany. The aim of the trial was to determine the activity and safety of a moderate dose of capecitabine as first-line treatment for patients with metastatic breast cancer.

2.2. Objectives and end-points

Primary end-point of the study was median time from first study dose to progression. Secondary end-points were overall (complete and partial) response and disease control (complete, partial and stable disease) rate, overall survival (OS), the safety and toxicity of capecitabine and the quality of life. The National Cancer Institute Common Toxicity Criteria (NCI-CTC) Version 2 and the corresponding grading system were used to grade adverse events.

2.3. Patient characteristics

The study enrolled female or male patients with histologically confirmed HER2-negative metastatic breast cancer who had received no prior chemotherapy for advanced disease. Adjuvant chemotherapy (capecitabine excluded), adjuvant or palliative endocrine treatment, bisphosphonates or immunotherapies were allowed. Patients had to have a Karnofsky performance status of $\geqslant$70 and measurable or evaluable target lesions.

2.4. Treatment

After giving informed consent, patients received capecitabine at a total of 2000 mg/m^2 per day (split into two daily doses of 1000 mg/m^2, calculated to be dividable into 500 mg tablets) on days 1–14 every 3 weeks. Treatment was given until disease progression or unacceptable toxicity, patient's request or withdrawal from the study. Dose reduction or interruption for adverse events was performed according to protocol guidelines.

2.5. Study assessments

All patients underwent routine medical and tumour assessment within 2 weeks before treatment start. Laboratory tests were performed every 3 weeks and activity was assessed every second cycle according to the WHO criteria. Safety and quality of life were assessed at baseline and after each cycle. We used the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ)-C30 + BR23. We compared the quality of life information from the baseline assessment with the assessment after cycle 10 or the last cycle received.

2.6. Statistics

The primary analysis used the intent-to-treat (ITT) population, which included all patients who received at least one dose of study medication. Kaplan–Meier was used to estimate the TTP (where three non-breast cancer deaths before progression were censored) and the OS. Cox's proportional hazards logistic regression models were fitted for TTP and OS for age, metastatic site, tumour grade and pre-treatment with adjuvant chemotherapy, steroid hormone receptor status and hand-foot syndrome as a time-dependent covariate.

For sample size calculation we assumed a TTP of 30 weeks for patients treated with capecitabine at 2000 mg/m^2.

Based on reports using 2500 mg/m^2,[2] we wanted to exclude a TTP ⩽25 weeks. With an alpha of 0.05, a beta of 0.8 and assuming a drop-out rate of 5%, the total number of evaluable patients required was 200. Recruitment was stopped after 165 patients were enrolled because of slow enrolment.

The data were analysed using SAS® (Statistical Analysis Software) Version 9.2 and a two-sided significance level of 0.05. No correction for multiple testing was performed.

The protocol was reviewed by all responsible local ethics committees and the study was conducted according to the declaration of Helsinki and GCP guidelines.

3. Results

3.1. Patient characteristics

A total of 165 patients were enrolled in 35 centres in Germany between July 2005 and February 2008. Of these, 161 received at least one dose of capecitabine comprising the ITT population, most of those had a disease-free interval of <2 years (93.3%). Four patients did not start therapy because of disease progression ($n = 1$), withdrawal of consent ($n = 2$) and patient's wish ($n = 1$). A total of 121 patients were treated until disease progression ($n = 119$) or death ($n = 2$). During study treatment, 35 patients discontinued therapy because of adverse events ($n = 24$), investigators decision ($n = 3$), patient's wish ($n = 3$) or withdrawal of consent ($n = 5$). As of August 1, 2009, five patients were still on study treatment.

Table 1 – Demographic data and baseline characteristics.

Patient characteristics	$n = 161$
Age (years)	
Mean	64
Median	65
Range	(37–90)
Karnofsky score	
90–100%	123 (76.4%)
70–80%	38 (23.6%)
Oestrogen receptor status	
ER positive	96 (59.6%)
ER negative	65 (40.4%)
Pre-treatment	
Any adjuvant chemotherapy	87 (54.0%)
Anthracyclines	57 (35.8%)
Taxane	39 (24.5%)
Palliative endocrine therapy	48 (29.8%)
Metastatic site	
Liver	70 (43.5%)
Lung and other	2 (1.2%)
Lung only	52 (32.2%)
Skin	9 (5.6%)
Bone	92 (57.1%)
Lymph nodes	43 (26.7%)

One male patient and 160 female patients were included. The demographic and baseline characteristics for all the patients who received treatment are given in Table 1.

3.2. Efficacy results

At database lock 130 disease progressions and 72 deaths (three without preceding progression) events were reported. The median TTP was 7.9 months (31.6 weeks; 95% confidence interval (CI) 26.9–36.3), which was significantly longer than the hypothesis of a minimum of 25 weeks ($p < 0.05$). The median OS was 18.6 months (74.2 weeks; 95% CI of 60.59–87.85; Fig. 1).

In a post hoc analysis, TTP and OS were determined in subgroups of patients developing hand-food syndrome or not, and in patients older or younger than 65 years. Compared with patients not developing hand-foot syndrome, patients showing this adverse event had a longer median TTP (40.8 [95% CI 28.5–53.0] weeks versus 20.4 [95% CI 10.3–30.5] weeks; $p = 0.0542$) and a longer median OS (99.7 [95% CI 53.0–146.5] weeks versus 61.7 [95% CI 46.5–76.9] weeks; $p = 0.0209$). Compared with younger patients, patients older than 65 years had a longer median TTP (38.0 [95% CI 22.4–53.6] weeks versus 26.8 [95% CI 15.5–38.1] weeks; $p = 0.002$), but no significant difference in median OS (Fig. 1). Univariate and multivariate analyses showed that age >65 years and hand-foot syndrome were the only independent prognostic factors for TTP ($p < 0.05$). Hand-foot syndrome was the only independent prognostic factor for OS ($p = 0.0256$) (Supplementary Table 1).

The overall response rate was 26.1%, 13 (8.1%) patients had a complete response. Disease control rate was 64%. Patients older than 65 years had a response rate of 33.3% compared with 19.8% for patients aged ⩽65 years ($p = 0.0526$). Multivariate analysis revealed that age was the only predictive factor for overall response with borderline significance ($p = 0.0506$).

3.3. Safety results

A total of 1402 cycles of capecitabine were documented with a median of seven cycles per patient. A total of 87 (54.0%) patients had a dose delay or an interruption. Overall, 182 (13.0%) cycles were interrupted and 183 (13.1%) cycles delayed. Cycle delays or interruptions became necessary in 20 (1.4%) cycles due to capecitabine-related haematological toxicity, 200 (13.9%) cycles due to non-haematological toxicity and 49 (3.4%) cycles due to adverse events that were not related to capecitabine.

Two patients died during study treatment due to cerebral bleeding and myocardial infarction. The most common grade III/IV toxicities were thrombocytopenia reported in eight patients (5.0%) and hand-foot syndrome reported in 12 (7.5%) patients (Table 2).

3.4. Quality of life

Results of paired *t*-test comparing the quality of life items assessed at baseline and cycle 10 (or last cycle) showed an improvement of emotional function ($p = 0.005$), whereas

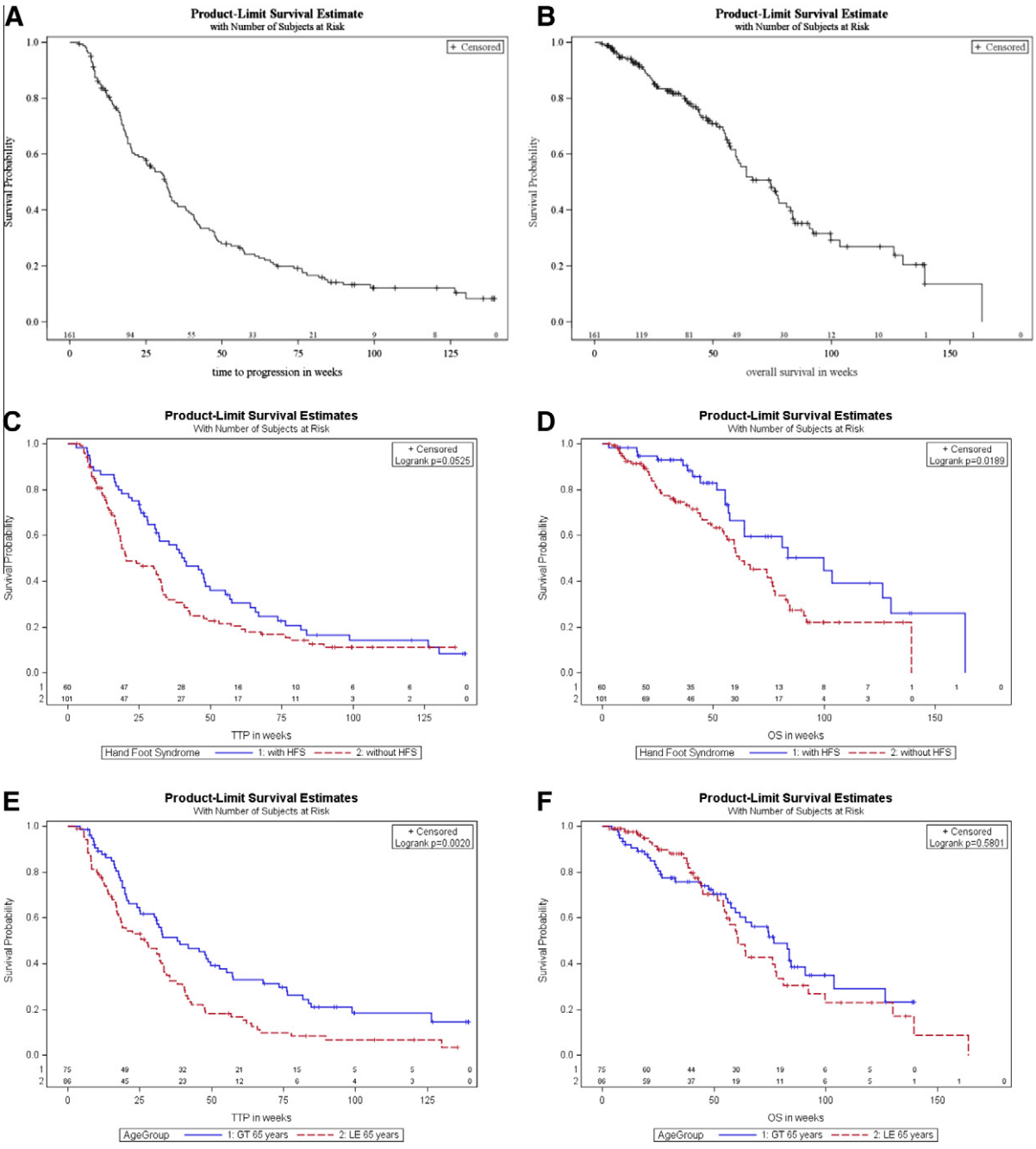


Fig. 1 – Time to progression (A) and overall survival (B) in the whole population and in subgroups defined by the occurrence of hand-foot syndrome (C and D) and by age (E and F). In subgroup analyses of TTP (C) and OS (D) depending on the occurrence of hand-foot-syndrome the blue curve defines patients with hand-foot-syndrome and the red curve patients without hand-foot-syndrome. In the subgroup analyses of TTP (E) and OS (F) depending on age, the red curve represents patients ⩽65 years and the blue curve patients older than 65 years. (GT = greater than; LE = less than). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

nausea/vomiting became worse ($p = 0.011$). The remaining nine items were unchanged.

4. Discussion

This trial represents, to date, the largest open-label, non-randomised, prospective multicentre phase II study with capecitabine monotherapy for the first-line treatment of metastatic breast cancer. We observed a median TTP of 7.9 months, which was significantly longer than our pre-defined hypothesis to exclude inferior activity due to the lower than labelled dosage. Thrombocytopenia and hand-foot syndrome were the only adverse events occurring in more than 5% of patients at grade III/IV. The occurrence of hand-foot syndrome and age

Table 2 – Haematological and non-haematological toxicities with an incidence >5%.

Toxicity	Grade I–IV		Grade III–IV	
	n	%	*n*	%
Anaemia	82	50.9	5	3.1
Leucopoenia	103	64.0	7	4.3
Neutropenia	1	0.6	1	0.6
Febrile neutropenia	0		0	
Thrombopenia	45	28.0	8	5.0
Hand-foot syndrome	60	37.3	12	7.5
Fatigue	55	34.2	8	5
Nausea	48	29.8	0	0
Dyspnoea	33	20.5	7	4.3
Diarrhoea	33	20.5	7	4.3
Alopecia	24	14.9	1	0.6
Stomatitis	23	14.3	2	1.2
Pain	19	11.8	1	0.6
Oedema	18	11.2	1	0.6
Vomiting	17	10.6	2	1.2
Back pain	16	9.9	3	1.9
Thrombosis	13	8	7	4.2
Nail changes	12	7.5	0	0

above 65 years were correlated with improved activity outcomes. Overall, the moderate dose of 2000 mg/m^2 appears to be active and feasible, especially in patients above 65 years of age.

Compared with other first-line trials,[3,9–12] we observed a longer median TTP and median OS. However, only patients with HER2-negative tumours were included in the MONICA study, whereas patients were unselected according to HER2-status in the other cited studies. More recent phase II–III studies have demonstrated for patients with HER2-positive disease that capecitabine in combination with trastuzumab or lapatinib leads to a longer TTP (6.2–8.5 months) compared with capecitabine alone (4.3–5.6 months).[13,14] It is important to note, that capecitabine in combination with lapatinib was evaluated at a dose of 2000 mg/m^2 and compared with capecitabine monotherapy at a dose of 2500 mg/m^2.

In our trial, elderly patients (>65 years) achieved longer TTP than younger patients. This is supported by the study from Bajetta et al., [3] which examined only patients aged ⩾65 years. They found a similar TTP of 4 months but lower toxicity in a second cohort treated with a dose of 2000 mg/m^2 compared with a first cohort treated with 2500 mg/m^2. However, in a recent trial in elderly patients with early breast cancer, six cycles of capecitabine at 2000 mg/m^2 were inferior to four cycles of doxorubicin/cyclophosphamide (AC) or six cycles of CMF with regard to disease-free survival.[15] To determine the baseline activity of adjuvant capecitabine, we have to await the results of the German Ibandronate Capecitabine Elderly (ICE) trial, which is comparing six cycles of capecitabine 2000 mg/m^2 in combination with ibandronate with ibandronate alone.[16]

With a dose of 2000 mg/m^2 we observed less frequent and less severe side-effects compared to trials using capecitabine at 2500 mg/m^2.[9–11,17] This is in line with previous smaller trials using capecitabine at this lower dose.[3,12]

It was suggested that the severity of side-effects like hand-foot syndrome might be an indirect sign of the enzyme over- or under-activity of dihydropyrimidine dehydrogenase (DPD) and thymidine phosphorylase (TP).[18,19] In a recent meta-analysis of 13 retrospective studies including patients with colon, colorectal, gastric and breast cancer, a positive correlation between the occurrence of hand-foot syndrome and longer OS was observed.[20] To our knowledge, we herein report this correlation for the first time for single breast cancer study.

The planned duration of the trial was 18 months and the actual duration, when we decided to close the trial, was 32 months. It would have needed another 9 months to complete accrual. As the sample size was already considerably high for a phase II study, our opinion was that additional 35 patients would not increase the amount of information in a way that would justify such a prolongation.

The MONICA study shows comparable activity of capecitabine 2000 mg/m^2 that is to a higher dose, but with a more favourable safety profile. This dose could therefore be chosen if capecitabine is considered for the first-line treatment of patients with metastatic breast cancer.

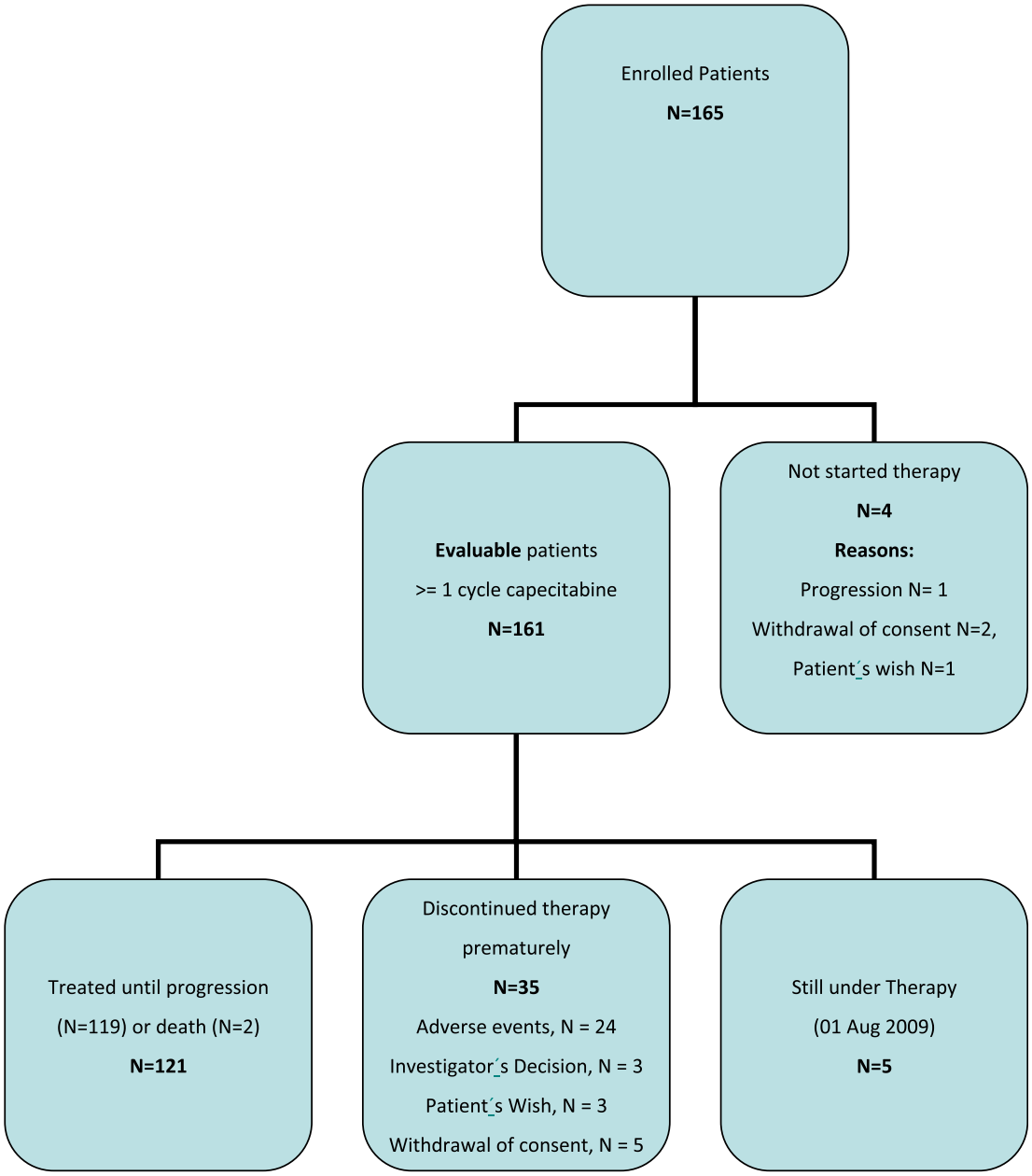
Conflict of interest statement

von Minckwitz G has received research funding from Roche.

Kaufmann M has received honoraria from Roche.

Hagen V has received honoraria from Roche.

Consort


Enrolled Patients
N=165
Evaluable patients
>= 1 cycle capecitabine
N=161
Not started therapy
N=4
Reasons:
Progression N= 1
Withdrawal of consent N=2,
Patient´s wish N=1
Treated until progression
(N=119) or death (N=2)
N=121
Discontinued therapy
prematurely
N=35
Adverse events, N = 24
Investigator´s Decision, N = 3
Patient´s Wish, N = 3
Withdrawal of consent, N = 5
Still under Therapy
(01 Aug 2009)
N=5

Acknowledgement

The study was supported by a grant from Roche AG, Grenzach-Wyhlen, Germany.

Appendix

Investigators of the Monica GBG 39 trial.

Manfred	Kaufmann	Frankfurt
Bernhard	Heinrich	Augsburg
Dietmar	Reichert	Aurich
Jörg	Schreier	Berlin
Winfried	Schoenegg	Berlin
Michael	Braun	Bonn
Volker	Hagen	Dortmund
Thomas	Göhler	Dresden
Daniel	Rein	Düsseldorf
Thorsten	Kühn	Esslingen
Elmar	Stickeler	Freiburg
Heinz-Gert	Höffkes	Fulda
Antje	Belau	Greifswald
Susanna	Hegewisch-Becker	Hamburg
Iris	Schrader	Hannover
Andreas	Schneeweiss	Heidelberg
Oliver	Tomé	Karlsruhe
H.-U.	Ulmer	Karlsruhe
Bettina	Conrad	Kassel
Nicolai	Maass	Kiel
Peter	Scheler	Limburg
Serban Dan	Costa	Magdeburg
Beate	Blümel	Magdeburg
Erika	Kettner	Magdeburg
Wolfgang	Wiest	Mainz
Marc Wolf	Sütterlin	Mannheim
Dimitrios	Chatsiproios	Mannheim
Klaus	Baumann	Marburg
Bernd	Christensen	Neuruppin
Dirk	Kramer	Pforzheim
Olaf	Ortmann	Regensburg
Bernd	Gerber	Rostock
Johannes	Feltz-Süßenbach	Stadthagen
Wolfgang	Bauer	Villingen-Schwenningen
C.	Karg	Waiblingen

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2010.07.009.

REFERENCES

1. Hennessy BT, Gauthier AM, Michaud LB, Hortobagyi G, Valero V. Lower dose capecitabine has a more favorable therapeutic index in metastatic breast cancer: retrospective analysis of patients treated at M.D. Anderson Cancer Center and a review of capecitabine toxicity in the literature. *Ann Oncol* 2005;**16**:1289–96.
2. Ershler WB. Capecitabine monotherapy: safe and effective treatment for metastatic breast cancer. *Oncologist* 2006;**11**:325–35.
3. Bajetta E, Procopio G, Celio L, et al. Safety and efficacy of two different doses of capecitabine in the treatment of advanced breast cancer in older women. *J Clin Oncol* 2005;**23**:2155–61.
4. Sezgin C, Kurt E, Evrensel T, et al. Efficacy of lower dose capecitabine in patients with metastatic breast cancer and factors influencing therapeutic response and outcome. *South Med J* 2007;**100**:27–32.
5. Yap YS, Kendall A, Walsh G, et al. Clinical efficacy of capecitabine as first-line chemotherapy in metastatic breast cancer – how low can you go? *Breast* 2007;**16**:420–4.
6. Saeki T, Kimura T, Toi M, Taguchi T. A pilot phase II study of capecitabine in advanced or recurrent breast cancer. *Breast Cancer* 2006;**13**:49–57.
7. Hennessy BT, Gauthier AM, Michaud LB, Hortobagyi G, Valero V. Lower dose capecitabine has a more favorable therapeutic index in metastatic breast cancer: retrospective analysis of patients treated at M.D. Anderson Cancer Center and a review of capecitabine toxicity in the literature. *Ann Oncol* 2005;**16**:1289–96.
8. El-Helw L, Coleman RE. Reduced dose capecitabine is an effective and well-tolerated treatment in patients with metastatic breast cancer. *Breast* 2005;**14**:368–74.
9. O'Shaughnessy JA, Blum J, Moiseyenko V, et al. 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* 2001;**12**:1247–54.
10. Talbot DC, Moiseyenko V, Van Belle S, et al. Randomised, phase II trial comparing oral capecitabine (Xeloda) with paclitaxel in patients with metastatic/advanced breast cancer pretreated with anthracyclines. *Br J Cancer* 2002;**86**:1367–72.
11. Reynoso N, Torrecillas L, Soto C, et al. Economic evaluation of sequential capecitabine (X) and taxanes vs. the combinations in patients (pts) with advanced/metastatic breast cancer (MBC): a Mexican Oncology Study Group (MOSG) Trial. *Breast Cancer Res Treat* 2005;**94**(Suppl. 1):S219.
12. Stockler MR, Sourjina T, Grimison P, et al. A randomized trial of capecitabine (C) given intermittently (IC) rather than continuously (CC) compared to classical CMF as first-line chemotherapy for advanced breast cancer (ABC). *J Clin Oncol* 2007;**25**(18S):1031.
13. von Minckwitz G, du Bois A, Schmidt M, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a german breast group 26/breast international group 03–05 study. *J Clin Oncol* 2009;**27**:1999–2006.
14. Cameron D, Casey M, Press M, et al. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. *Breast Cancer Res Treat* 2008;**112**:533–43.
15. Muss HB, Berry DA, Cirrincione CT, et al. Adjuvant chemotherapy in older women with early-stage breast cancer. *N Engl J Med* 2009;**360**:2055–65.
16. Reimer T, Nitz U, Potenberg J, et al. A prospective, multicentre, controlled, open-label, randomized phase III trial of ibandronate (I) with or without capecitabine (X) in elderly patients (pts) with early breast cancer (GBG 32). *Eur J Cancer/Suppl* 2009;**7**(2):215 [Abstr # 4003, ECCO/ESMO Berlin].

17. Blum JL, Jones SE, Buzdar AU, et al. Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. *J Clin Oncol* 1999;**17**:485–93.
18. Bronckaers A, Gago F, Balzarini J, Liekens S. The dual role of thymidine phosphorylase in cancer development and chemotherapy. *Med Res Rev* 2009;**29**:903–53.
19. Yen-Revollo JL, Goldberg RM, McLeod HL. Can inhibiting dihydropyrimidine dehydrogenase limit hand-foot syndrome caused by fluoropyrimidines? *Clin Cancer Res* 2008;**14**:8–13.
20. Xeloda® Scientific information (Ro 09-1978), April 2010.