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# Continuing chemotherapy or not after the induction treatment in advanced breast cancer patients: clinical outcomes and oncologists' preferences

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**Abstract**

The optimal duration of cytostatic treatment for metastatic breast cancer is still a matter of debate. Possible gain in the duration of remission has to be weighed against the side-effects of treatment. Our aim was to define the optimal duration of cyclophosphamide, methotrexate, 5-fluorouracil (CMF) treatment by studying the time to treatment failure, overall survival and using a Q-TWiST analysis. The treating physician's opinion was asked. The European Organization for Research and Treatment of Cancer (EORTC) Breast Cancer Group conducted a randomised trial in 204 non-progressing metastatic breast cancer patients after induction chemotherapy (CMF) to stop or continue treatment. Progression-free (PFS) and overall survival (OS) were studied. To gain more insight into the burden of treatment-related side-effects, Q-TWiST was analysed. In addition, we asked for oncologists' preferences as patients are likely to be influenced by their physicians' opinion. Continuation of CMF had a significantly longer time to treatment failure (TTF) 5.2 versus 3.5 months ($P=0.011$). There was no overall survival (OS) difference 14.0 versus 14.4 months ($P=0.77$). Mean quality-adjusted survival time was equal to 8.4 months for no further treatment and decreased to 7.9 months for continuation of CMF (95% Confidence Interval (CI) of difference equals $0.5\pm2.5$ months). Almost half of the oncologists said they would favour continuous treatment for a 3-month gain in time to progression—a difference which was not found in this study. Based on these data, an interruption of chemotherapy (CMF), if this is the wish of the patient, is justified.


*Keywords:* Metastatic breast cancer; Duration of chemotherapy; Q-TwiST; Physicians' preferences

## 1. Introduction

In recent years, several studies have been undertaken to establish the optimal duration of cytostatic treatment in advanced metastatic breast cancer [1–8]. Survival has not been affected in a significant way [1–8], but discussion on the optimal duration of treatment continues. The results of these trials pose a dilemma to clinicians and their patients with advanced breast cancer: a possible gain in time to progression has to be weighed against a loss in quality of life due to the side-effects of therapy.

From December 1985 until March 1992, the European Organization for Research and Treatment of Cancer (EORTC) Breast Cancer Group conducted a trial on the benefit of continuing cyclophosphamide,

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methotrexate, 5-fluorouracil (CMF) after induction with six cycles of CMF. As the opinions of clinicians play an important role in treatment proposals, it was decided to investigate the preferences of medical oncologists participating in this trial as well.

We report on the results of the randomised prospective trial comparing no further treatment with continuation of CMF until progression after induction chemotherapy (six cycles of CMF). Analyses were made for survival, progression-free survival (PFS) and quality-adjusted survival (Q-TWiST). The treatment preferences of medical oncologists involved in the trial are also presented.

## 2. Methods

### 2.1. Clinical investigation

#### 2.1.1. Patients and characteristics

Eligible patients were postmenopausal women (1 year or more after their last period), younger than 71 years, with measurable and/or evaluable biopsy-proven advanced breast cancer, having received no chemotherapy for advanced disease. Previous adjuvant chemotherapy was allowed, provided the time between adjuvant therapy and development of metastases was at least 1 year.

World Health Organization (WHO) performance status had to be 2 or better, white blood cells (WBC) $\geqslant 3\times10^9$/l and platelets $\geqslant 100\times10^9$/l. Patients should have normal liver and kidney functions.

#### 2.1.2. Treatment and modifications

Following six cycles of classical CMF treatment, provided there was no progression, patients were randomised to continue CMF until progression or to no further treatment and the reintroduction of CMF in cases of progression.

Classical CMF (cyclophosfamide 100 mg/m$^2$ day, orally, days 1–15, methotrexate 40 mg/m$^2$, intravenously (i.v.), days 1 and 8, 5-fluorouracil 600 mg/m$^2$, i.v. days 1 and 8) was chosen, as this treatment had proven to be superior to i.v. CMF in EORTC study 10808 [9].

At the first cycle 100% of the dose was given. If at the beginning of further cycles a dose reduction was required, treatment was postponed for 1 week. There was no dose escalation.

During the study neither endocrine treatment nor bisphosphonates were given. Local radiotherapy for symptomatic lesions was allowed provided these were not indicator lesions for response.

The protocol was approved by the Protocol Review Committee of the EORTC and the individual Medical Ethical Committees of the participating centres. Patients were asked for their informed consent.

#### 2.1.3. Evaluation of response

Criteria for evaluation of response and categories of response were those of the International Union Against Cancer (UICC) [10]. All cases were reviewed externally.

#### 2.1.4. Statistical considerations

PFS analysis (time from randomisation to progression or death, whichever comes first) was performed on all randomised patients. However, patients who had already progressed at the time of randomisation after six cycles of CMF were excluded as these patients were never in the risk set. These patients (8 cases) should not have been randomised, but the assessment of the external review with respect to progression was different from the assessment of the local investigator at the time of randomisation.

Survival analysis was first performed on all randomised patients, but again excluding patients who had already progressed at the time of randomisation. A sensitivity analysis was done for survival based on all of the patients regardless of whether they had already progressed or not at the time of randomisation. All survival curves were estimated using the Kaplan–Meier technique [11] and the two treatment arms were compared using the two-sided log rank test [12].

### 2.2. Q-TWiST analysis and oncologists' preferences

#### 2.2.1. Sample and procedure

A mailed survey was conducted among all medical oncologists involved in the EORTC Breast Cancer Group. Those actively participating in the trial were asked to approach other colleagues who had been entering patients in the trial. Reminders were sent out at 6 weeks and 3 months.

#### 2.2.2. Instrument

The instrument was designed (a) to determine utility coefficients to enable a Q-TWiST analysis, (b) to establish clinicians' treatment preferences directly, and (c) to investigate what considerations were considered important in metastatic breast cancer treatment.

The questionnaire therefore contained, first, visual analogue scales (VAS), asking respondents to rate their valuation of overall quality of life on a scale ranging from 0 to 100 during the three relevant outcome states: undergoing palliative CMF, stable disease after CMF without undergoing chemotherapy and having progressive disease. The utilities for each of the three states were then obtained by averaging out the VAS scores over the different respondents. Second, treatment preference was assessed directly with a set of trade-off questions asking preferences for short- or long-term treatment given a certain gain in PFS (e.g. 'If continuous, long-term treatment with CMF would result in a progression-free period of one month longer than the

Table 1
Considerations in enhancing QL in metastatic breast cancer expressed by physicians ($N = 33$)

| | Of no importance (%) | Of little importance (%) | Of considerable importance (%) | Of great importance (%) |
|---|---|---|---|---|
| For the quality of life of patients with metastatic breast carcinoma, I consider: | | | | |
| • The side-effects of the treatment | – | 3 | 63 | 34 |
| • Postponing progression | – | – | 45 | 55 |
| • The treatment of complaints | – | – | 19 | 81 |
| • The fact that I can still offer treatment | 3 | 47 | 44 | 6 |
| • Patient responding to treatment | – | 3 | 41 | 56 |

QL, quality of life.

short-term treatment with CMF, which treatment would you prefer?'). By steadily increasing the gain in time to progression after continuous treatment, the shift in preference could be established.

Third, given the fact that palliative treatment is meant to support the quality of life of the patient, it was asked which factors were considered important to enhance quality of life (see Table 1).

### 2.2.3. Q-TWiST analysis

A Q-TWiST analysis was performed based on all randomised patients, but again excluding patients who had already progressed at the time of randomisation. The Q-TWiST analysis was proposed originally for the evaluation of early breast cancer treatment [13,14]. Different states are given utilities or values in the analysis. Three relevant states with corresponding utilities were

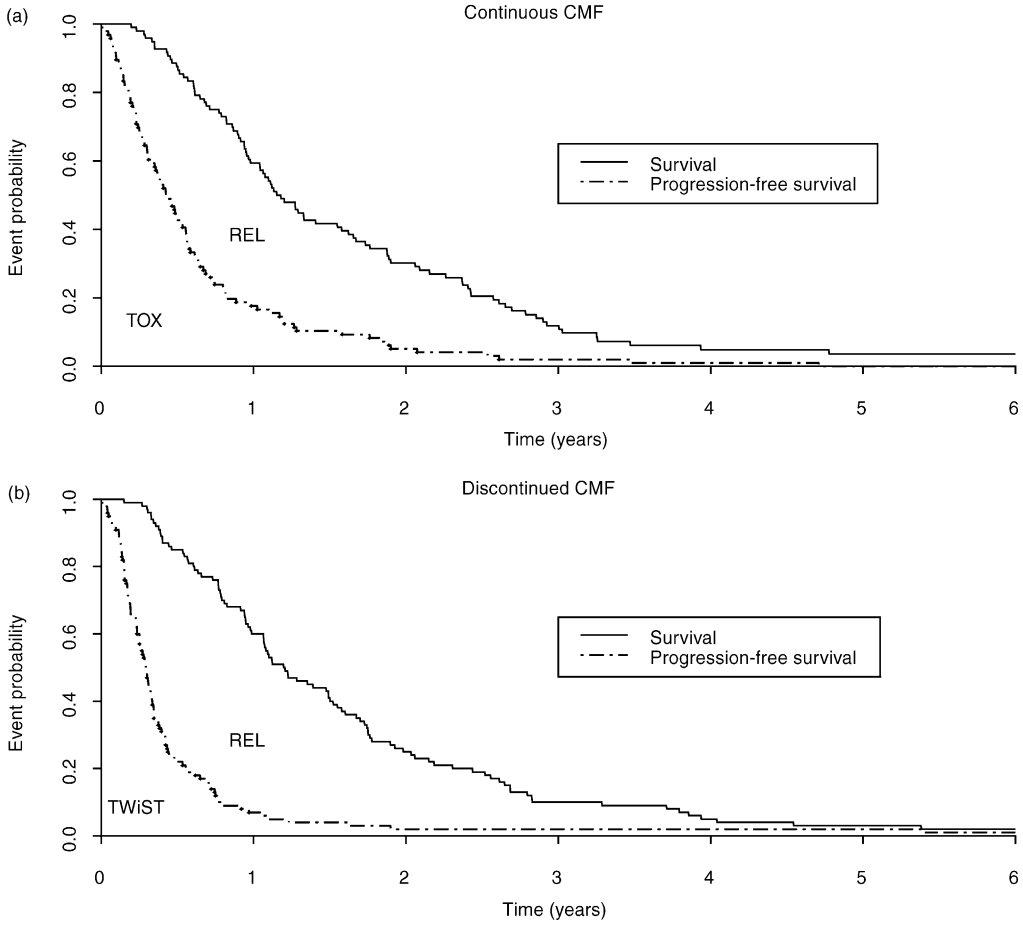


Fig. 1. Kaplan–Meier curves for survival and progression-free survival (PFS) for (a) continuous cyclophosphamide, methotrexate, 5-fluorouracil (CMF) and (b) no further treatment. Time under progression corresponds to the area between the two curves, whereas time between randomisation and progression corresponds to the area under the PFS.

Table 2
Eligibility at randomisation ($N = 204$)

| | Continuation of CMF | No further treatment |
|---|---|---|
| Eligibility | | |
| No | 10 | 10 |
| Yes | 87 | 97 |
| Reason for ineligibility | | |
| Incomplete examination | 0 | 1 |
| Inadequate stage/histology | 2 | 0 |
| Prior treatment for cancer | 1 | 0 |
| Other | 6 | 2 |
| Progression before randomisation | 1 | 7 |

CMF, cyclophosphamide; methotrexate, 5-fluorouracil.

distinguished: undergoing palliative CMF ($U_{CHT}$), stable disease after CMF without undergoing chemotherapy ($U_{STABLE}$) and having progressive disease ($U_{PROG}$). The time spent in each of these states ($T_{CHT}$, $T_{STABLE}$, $T_{PROG}$) for the two treatment groups from the time of randomisation was estimated by the restricted means (with a median follow-up time for survival being used as the limit). The restricted means can be obtained by using the areas under the Kaplan–Meier curves (Fig. 1) [15,16]. The mean quality-adjusted survival time for both groups can then be determined using the restricted means and the utility coefficients and is given by $(U_{CHT} \times T_{CHT}) + (U_{STABLE} \times T_{STABLE}) + (U_{PROG} \times T_{PROG})$. In the continuous arm, stable disease is obviously not entered into the equation as patients are either receiving chemotherapy or have progressed, whereas in the discontinued arm, undergoing palliative CMF is not entered. The bootstrap method was applied to obtain the 95% Confidence Interval (CI) for the difference in mean quality-adjusted survival time for the two groups [16]. Finally, a threshold utility analysis was performed [16].

## 3. Results

### 3.1. Clinical evaluation

Between December 1985 and March 1992, 442 patients were registered for randomisation into the study by 18 institutions. A total of 204 patients were randomised (Table 2) either to continuation of CMF until progression or to no further treatment (Fig. 2). Of these, 20 were not eligible: 10 in the 'continuous treatment' arm and 10 in the 'no further treatment' arm. Characteristics of the randomised patients are shown in Table 3. With respect to overall response in the 'continuous treatment' and 'no further treatment' arms, a similar percentage of patients improved from partial response (PR) to complete response (CR) (2/56 and 2/57, respectively) and from no change (NC) to PR (9/33 and 9/31, respectively).

The 'continuous treatment' arm had a significantly longer median time to progression/death than the 'no further treatment' arm (5.2 versus 3.5 months; log rank $P = 0.011$) (Fig. 3a). 58 patients in the 'no further treatment' arm received additional CMF treatment at first progression after a treatment-free period. The 'continuous treatment' arm and the 'no further treatment' arm had similar median times to death both for an analysis based on all randomised patients (14.0 versus

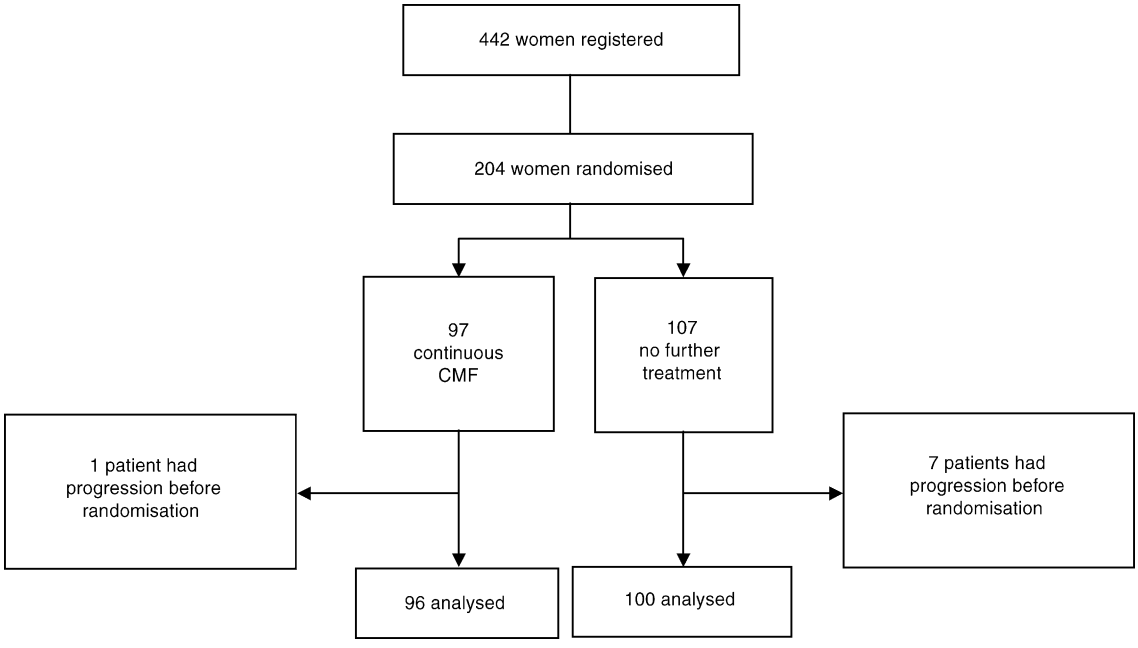


Fig. 2. Trial scheme.

Table 3
Patients' characteristics at randomisation ($N=196$)

| | Continuation of CMF ($n=96$) | | No further treatment ($n=100$) | |
|---|---|---|---|---|
| | *n* | (%) | *n* | (%) |
| Age class (years) | | | | |
| <50 | 12 | (13) | 13 | (13) |
| 50–54 | 16 | (17) | 13 | (13) |
| 55–59 | 19 | (20) | 28 | (28) |
| 60–64 | 21 | (22) | 26 | (26) |
| 65–69 | 23 | (24) | 19 | (19) |
| ⩾70 | 5 | (5) | 1 | (1) |
| Menopause | | | | |
| Natural | 73 | (76) | 70 | (70) |
| Artificial | 22 | (23) | 27 | (27) |
| Unknown | 1 | (1) | 3 | (3) |
| No. of years postmenopause | | | | |
| <1 | 8 | (8) | 3 | (3) |
| 1–4 | 18 | (19) | 30 | (30) |
| 5–9 | 19 | (20) | 17 | (17) |
| 10–14 | 27 | (28) | 19 | (19) |
| 15–19 | 13 | (14) | 17 | (17) |
| 20–24 | 4 | (4) | 1 | (1) |
| ⩾25 | 4 | (4) | 4 | (4) |
| Unknown | 3 | (3) | 9 | (9) |
| Dominant site | | | | |
| Soft tissue | 15 | (16) | 17 | (17) |
| Bone | 21 | (22) | 25 | (25) |
| Visceral | 60 | (63) | 58 | (58) |
| Prior endocrine therapy | | | | |
| No | 23 | (24) | 29 | (29) |
| Yes | 73 | (76) | 71 | (71) |
| Performance status | | | | |
| 0 | 22 | (23) | 31 | (31) |
| 1 | 52 | (54) | 50 | (50) |
| 2 | 21 | (22) | 18 | (18) |
| 3 | 1 | (1) | 0 | (0) |
| Unknown | 0 | (0) | 1 | (1) |
| Primary response | | | | |
| CR | 7 | (7) | 12 | (12) |
| PR | 56 | (58) | 57 | (57) |
| SD | 33 | (34) | 31 | (31) |

CMF, cyclophosphamide, methotrexate, 5-fluorouracil; CR, complete response; PR, partial response; SD, stable disease.

14.4 months; log rank $P=0.77$) and for an analysis based on randomised patients, but excluding the patients that had already progressed at the time of randomisation (14.2 versus 14.5 months; log rank $P=0.64$) (Fig. 3b).

### 3.2. Q-TWiST analysis and preference investigation

Of the 35 medical oncologists involved in the EORTC Breast Cancer Group, 24 (69%) returned the questionnaire. Nine of their colleagues participating in the trial also responded. The 33 oncologists responding came from Belgium, Denmark, Italy, The Netherlands, Poland, Spain and the United Kingdom.

#### 3.2.1. Q-TWiST

The restricted mean time from randomisation to progression was 185 days (6.0 months) if no further treatment was given and 238 days (7.8 months) if continuous treatment was given. Restricted mean time from progression to death was 418 days (13.7 months) for the 'no further treatment' arm and 387 days (12.7 months) for the 'continuous treatment' arm (Fig. 1). The mean utilities corresponded to 0.54 for undergoing palliative CMF, 0.73 for stable disease after CMF without undergoing chemotherapy and 0.29 for time with progressive disease. Therefore, the mean quality-adjusted survival time was equal to 257 days (8.4 months) if no further treatment was given and 241 days (7.9 months) if continuous treatment was given. The 95% CI for the difference in the mean quality-adjusted survival time between the two groups was equal to $0.5\pm2.5$ months. Thus, the difference in mean quality-adjusted survival time is not significant at the 95% confidence level. The threshold analysis (Fig. 4) shows that the utility for time under chemotherapy had to become very small before no further treatment had a significantly better quality-adjusted survival time than continuous CMF. However, no combination of utilities existed where the continuous CMF performed significantly better in terms of quality-adjusted survival time than the no further treatment arm.

#### 3.2.2. Direct preference assessment

All oncologists answered that they would prefer shorter treatment if shorter and continuous treatment would result in an equal time to progression; 3.03% said they would favour continuous treatment given a 1-month gain in the time to progression; 9.09% said they would favour continuous treatment with a 2-month gain in the time to progression; 51.51% said they would favour continuous treatment given a 3-month gain in the time to progression; 18.18% wanted a 4-month gain and 18.18% wanted a longer gain in the time to progression before their preference shifted to continuous chemotherapy. The average gain in time to progression necessary to favour continuous treatment was 3.9 months.

#### 3.2.3. Considerations

Oncologists found the treatment of complaints the most important consideration in the quality of life of metastatic breast cancer patients. Postponing progression and response to treatment were also considered of great importance by most of the oncologists involved. The side-effects of treatment were generally seen as of considerable importance. 'Offering treatment as such'

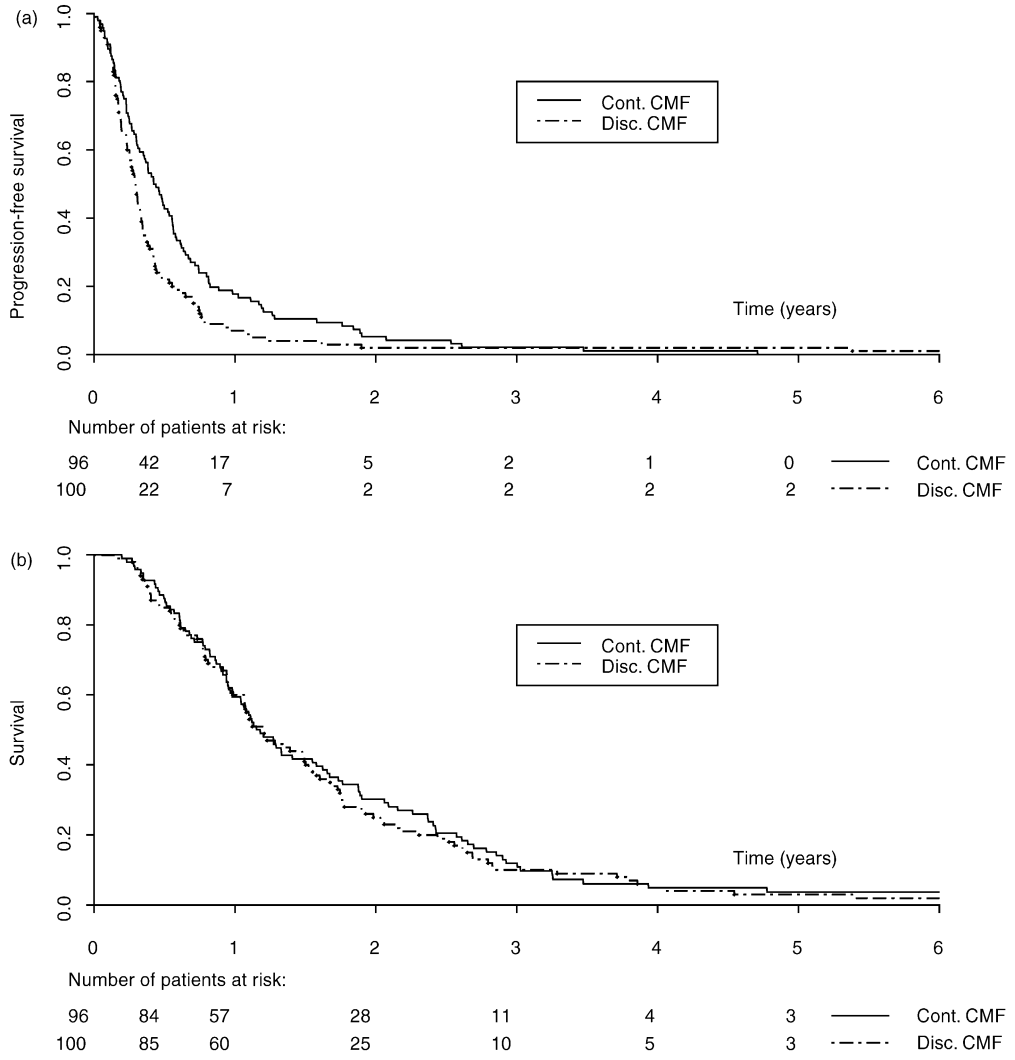


Fig. 3. Kaplan–Meier curves for survival (a) and PFS (b) for all randomised patients, excluding patients that had already progressed at the time of randomisation. Cont, continuous treatment arm; Disc, no further treatment arm; CMF, cyclophosphamide, methotrexate, 5-fluorouracil.

was considered of (some) importance by almost all of the oncologists (97%) (Table 1).

## 4. Discussion

In this multicentre European study, the overall percentage of complete and partial remission is the same as in a comparable American study [3], conducted with cyclophosphamide, doxorubicin, 5-fluorouracil (CAF) chemotherapy. However, the percentage in remission is certainly lower than in other studies [17]. This might be related to patient selection, frequency of assessment or other factors as suggested for the American study. However, it may be that earlier studies were conducted in a more selected patient population and that 36% CR and PR is what can be expected in standard practice. We found a small gain in the median PFS for the patients on 'continuous' treatment. However, this was not translated into a survival difference. In this respect, our results are completely in concordance with other studies [1–8]. Only in a Danish study was a small positive effect on survival found in favour of continuous treatment [4].

Given that there is no survival gain in this study, quality of life issues become very important.

In a former Australian study [1] quality of life was found to be better in the 'continuous treatment' arm. However, the study design of that trial was different from ours: in the 'no further treatment' arm 3 months of treatment was alternated with a treatment-free period until progression, and so on. It might be that the effect of this design for the alternating treatment group is a continuous struggle with disease and side-effects of treatment and does not give the ultimate answer to the question of optimal treatment duration.

Gregory and associates [5] conducted a trial like ours: 107 patients were randomised to stop or continue

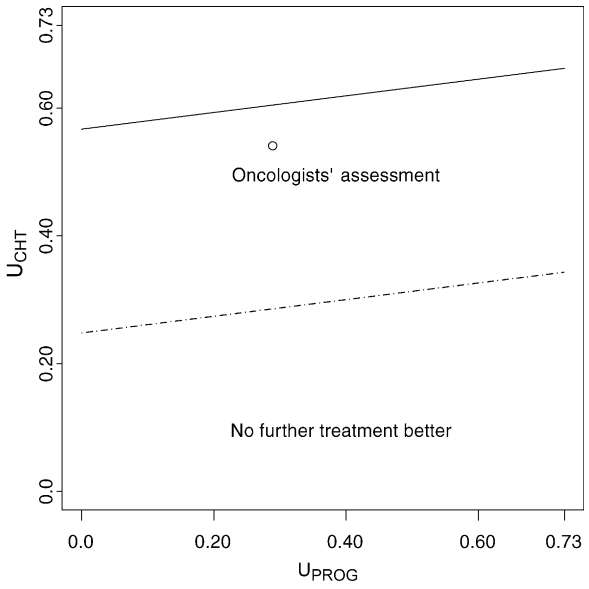


Fig. 4. Threshold utility analysis. The solid line is the threshold (on $U_{PROG}$ and $U_{CHT}$) where the two treatments have equal quality-adjusted survival. The area under the dashed line contains all combinations of utilities ($U_{PROG}$ and $U_{CHT}$) where no further treatment has a significantly longer quality-adjusted survival time than continuous cyclophosphamide, methotrexate, 5-fluorouracil (CMF). $U_{PROG}$ and $U_{CHT}$ only go up to 0.73 as this is the utility supplied by the oncologists for stable disease in advanced breast cancer.

treatment after six cycles of chemotherapy provided there was no progression. PFS and survival were longer in the group continuing treatment, although there was no statistical difference for survival. The authors conclude that discontinuation after six cycles is justified.

In our study, which started in 1985, we tried to gain insight into medical oncologists' treatment preferences retrospectively.

A classical dilemma exists here. The treatment options are equivalent in terms of survival. Which treatment is to be preferred remains to be established. We therefore used, in the first place, a Q-TWiST approach. By looking at the values given to time under chemotherapy, stable disease without such therapy and time after progression, the preferred option could be established, based on the outcomes of the model. The approach is new in the field of palliative cancer treatment, but might be particularly useful [18]. The main objective of such treatment is quality of life [19] and therefore the effects on quality of life within the relevant treatment states have to be weighed. We found no difference between shorter and continuous treatment on the basis of such a Q-TWiST approach.

Therefore, individual preferences become even more important. The clinician usually proposes therapy and patients are likely to be influenced by their physicians' preference. The oncologists involved in the EORTC group did differ in their preferences. Some found a 1-month gain in progression-free survival to be worthwhile. Most found a 3-month gain to be necessary before they said they would favour continuous treatment over shorter chemotherapy. The actual median gain was less than 3 months. Thus, in terms of the Q-TWiST model, both treatment options are equivalent.

These results would indicate that oncologists would favour short-term over continuous chemotherapy. However, daily practice seems to differ. Few oncologists stop at six cycles of chemotherapy. This might partly be explained by the surprising finding that almost all of the oncologists said they considered the fact that they could offer treatment was important for the quality of life of their patients.

However, since median survival is hardly influenced by the continuation of chemotherapy, an interruption of polychemotherapy (such as CMF), if this is the preference of the patient with advanced breast cancer, seems to be fully justified.

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## Appendix. Contributors

Institutions which randomised patients into the study:
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Universital Medical Centre, Nijmegen, The Netherlands
Universitair Medisch Centrum Utrecht, Utrecht, The Netherlands
Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands
Leiden University Medical Centre, Leiden, The Netherlands
Erasmus University Dijkzigt, Rotterdam, The Netherlands
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