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Original Paper

The Clinical Relevance of Static Disease (No Change) Category for 6 Months on Endocrine Therapy in Patients with Breast Cancer

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This study reports on the clinical relevance of the static disease (SD) category in 255 breast cancer patients on endocrine therapy. All patients had received first- and second-line endocrine therapy and were assessed for response by the International Union Against Cancer (UICC) criteria. We did not include patients who received first-line endocrine therapy but did not or have not yet proceeded to second-line hormone therapy, e.g. died from rapidly progressive disease, started chemotherapy for rapidly progressive disease, remained in long-term remission on first-line endocrine therapy. We analysed survival from initiation of first-line endocrine therapy by the remission criteria, i.e. complete response (CR), partial response (PR), static disease (SD) or progressive disease (PD), achieved on that therapy. Patients were divided into those with metastatic breast cancer (MBC) and non-metastatic disease. There was no significant difference in survival from starting first-line endocrine therapy between patients who obtained CR, PR or SD: all three groups of patients survived significantly longer than patients who showed PD within 6 months (all $P < 0.0001$ except CR versus PD [MBC] which was $P < 0.002$). Equally, for second-line endocrine therapy there was no difference in survival between patients who obtained CR, PR or SD: all three groups (CR, PR and SD) survived significantly longer than PD (all $P < 0.0003$ except for CR versus PD which was $P < 0.003$ for non-metastatic and $P < 0.059$ for MBC). Durable SD appears to be a clinically useful criteria of therapeutic remission. © **1997 Elsevier Science Ltd.**

Key words: breast cancer, endocrine therapy, static disease
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INTRODUCTION

HORMONE THERAPY is an important therapeutic option in the treatment of patients with advanced breast cancer. However, endocrine agents may take months to induce an objective response (i.e. tumour shrinkage) in endocrine-sensitive tumours with the perception by many clinicians that all other patients (static disease and progression) receive little or no benefit and perhaps are subject to undue delay (for weeks or months) before they receive a change of treatment.

It has previously been reported for endocrine therapy that patients in whom the cancer remains static for at least 6 months have a statistically similar survival to patients whose tumours show a partial response [1, 2]. This has led to the suggestion that the important decision in treating advanced breast cancer patients with endocrine therapy is identification of disease progression as this is the clinically relevant point at which to change treatment.

We have assessed the value of the static disease category on first- and second-line endocrine therapy in patients with advanced breast cancer treated in our unit since 1980.

PATIENTS AND METHODS

Patients treated with endocrine therapy for breast cancer in the Nottingham Breast Unit since 1980 were selected for further evaluation if they fulfilled the following criteria:

1. Histological/cytological confirmation of breast cancer;
2. Endocrine therapies (first- and second-line) were used for treatment of patients with systemic metastases, locally advanced primary tumours or elderly patients with primary operable breast cancer;

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Table 1. First- and second-line endocrine therapies

	First-line *n*	Second-line *n*
Tamoxifen	229	2
Zoladex	7	0
Zoladex + tamoxifen	11	2
Oophorectomy	3	0
Megace	0	240
Aminoglutethamide	0	1
Arimidex	0	2
Onapristone	0	3
Total	250	250

3. Therapeutic response was assessed according to the International Union Against Cancer (UICC) criteria [3].

We have not included in this study patients who received first-line endocrine therapy but did not or have not yet proceeded to second-line hormone therapy, e.g. died from rapidly progressive disease, started chemotherapy for rapidly progressive disease, remained in long-term remission on first-line endocrine therapy.

Two hundred and twenty-five patients were identified. 222 and 250 had lesions which were assessable for therapeutic remission by UICC criteria (i.e. complete response (CR), partial response (PR) or static disease (SD)) for first- and second-line therapy, respectively. The other patients were unassessable for therapeutic remission by UICC and these patients were treated on the basis that the clinician looked for disease progression. The median age was 64 years (range 31–93 years). The majority of patients (92%) had tamoxifen alone as first- line endocrine therapy, while megestrol acetate was used as second-line therapy in 96% of patients (Table 1).

Ninety-eight patients had metastatic breast cancer at the time of commencing first-line endocrine therapy: the remainder having loco-regional disease (i.e. local recurrence, regional recurrence, locally advanced primary cancer, operable breast cancer in elderly patients). The sites of metastases (±loco-regional disease) were as follows: bone only ($n = 48$), lung only ($n = 24$), bone and lung ($n = 12$), bone, lung and liver ($n = 2$), bone, lung and skin ($n = 2$), bone and brain ($n = 1$), skin only ($n = 2$) and supraclavicular fossa lymph nodes ($n = 7$).

Assessment

Assessment of response to therapy was made using the UICC criteria [3] with adherence to the British Breast Group recommendation that any reported objective response (OR), i.e. CR or PR, or SD should be of a minimum duration of 6 months [4]. Patients whose tumour progressed within 6 months of starting endocrine therapy were allocated to a progressive disease (PD) group.

Statistical methods

Survival analysis was carried out by using SPPS for Windows (SPSS U.K. Ltd). Differences in survival between two groups were compared using the Lee–Desu statistic which is a modification of Gehan's Generalised Wilcoxon Test.

The median survival with metastatic disease is 2 years. For first-line therapy, survival analysis between groups was compared up to 5 years. For second-line therapy most patients had died by 3 years: the survival analysis between groups was compared up to 3 years after starting second-line therapy.

RESULTS

One hundred and fifty-nine patients showed a tumour remission (OR + SD) to first-line endocrine therapy (Figure 1). One hundred and thirty-two patients had OR + SD on second-line endocrine therapy (Figure 2).

Survival by remission criteria

We analysed survival by remission criteria (CR, PR, SD and PD) firstly for all patients who had only loco-regional disease (i.e. non-metastatic) and secondly for patients with metastatic breast cancer (MBC).

First-line endocrine therapy

The findings were similar when non-metastatic patients were included in the analysis (Figure 1(a)) or only the patients with metastases (Figure 1(b)). The overall comparison of survival for all four groups showed a significant difference ($P < 0.0001$) with three degrees of freedom. On subsequent pairwise comparisons, there was no significant difference in survival from starting first-line endocrine therapy between patients who obtained CR, PR or SD. All three groups of patients (CR, PR and SD) survived significantly longer than patients who showed PD within 6 months of commencing first-line endocrine therapy (all $P < 0.0001$ except for CR versus PD [MBC] which was $P < 0.002$).

Second-line endocrine therapy

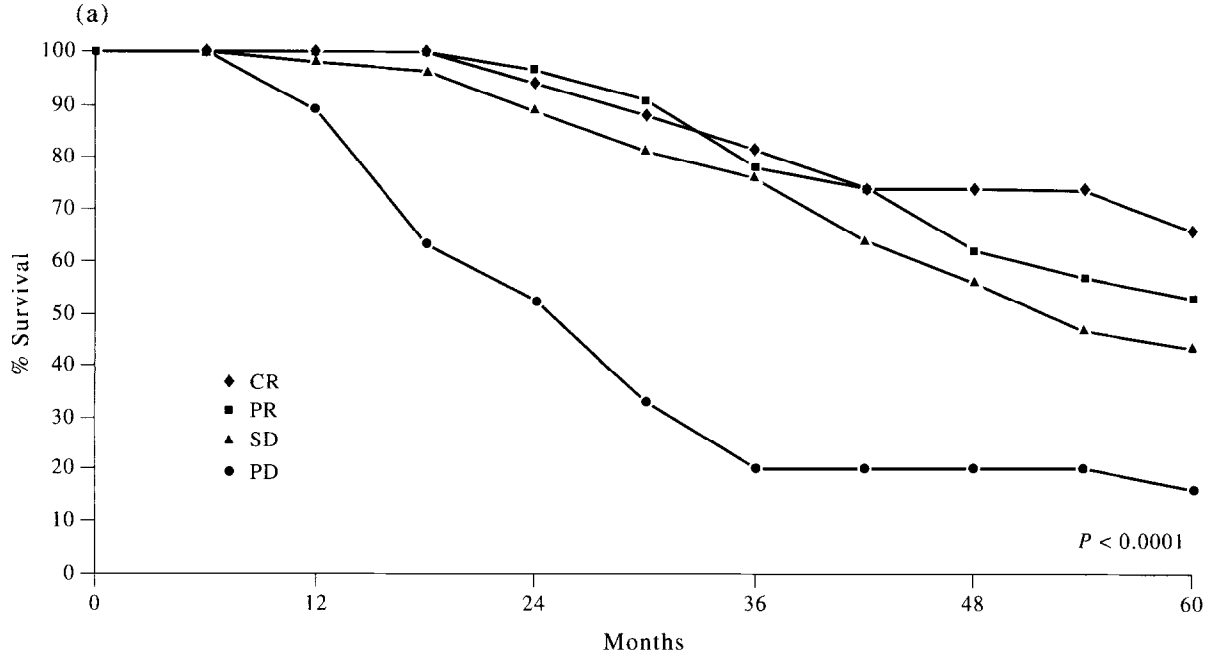
The findings were again similar when non-metastatic patients were included in the analysis (Figure 2(a)) or only the patients with metastases (Figure 2(b)). The overall comparison of survival for all four groups showed a significant difference ($P < 0.0001$) with three degrees of freedom. On subsequent pairwise comparisons, there was no significant difference in survival from starting second-line endocrine therapy between patients who obtained CR, PR or SD. All survived significantly longer compared to patients who showed progressive disease (all at least $P < 0.0003$ except for CR versus PD which was $P < 0.003$ for non-metastatic and $P = 0.059$ for MBC). In the comparison of CR with PD in the non-metastatic group, there were only 3 patients in the CR group (Figure 2(b)).

Third-line endocrine therapy

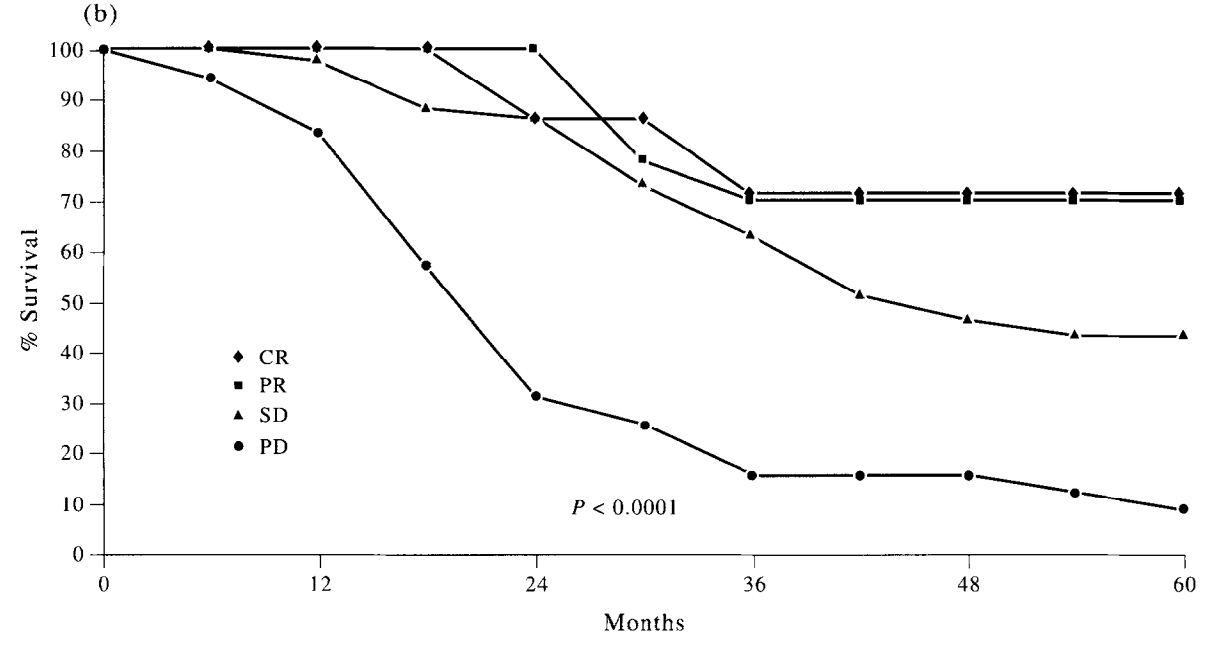
Thirty-four patients went on to receive third-line endocrine therapy. Only 1 patient obtained a partial response. However, again there was a significant difference in survival between patients who obtained SD compared to PD ($P < 0.004$) (Figure 3).

DISCUSSION

Patients who reach SD for at least 6 months on endocrine therapy (first-, second- or third-line) appear to have achieved a worthwhile period of therapeutic remission. It



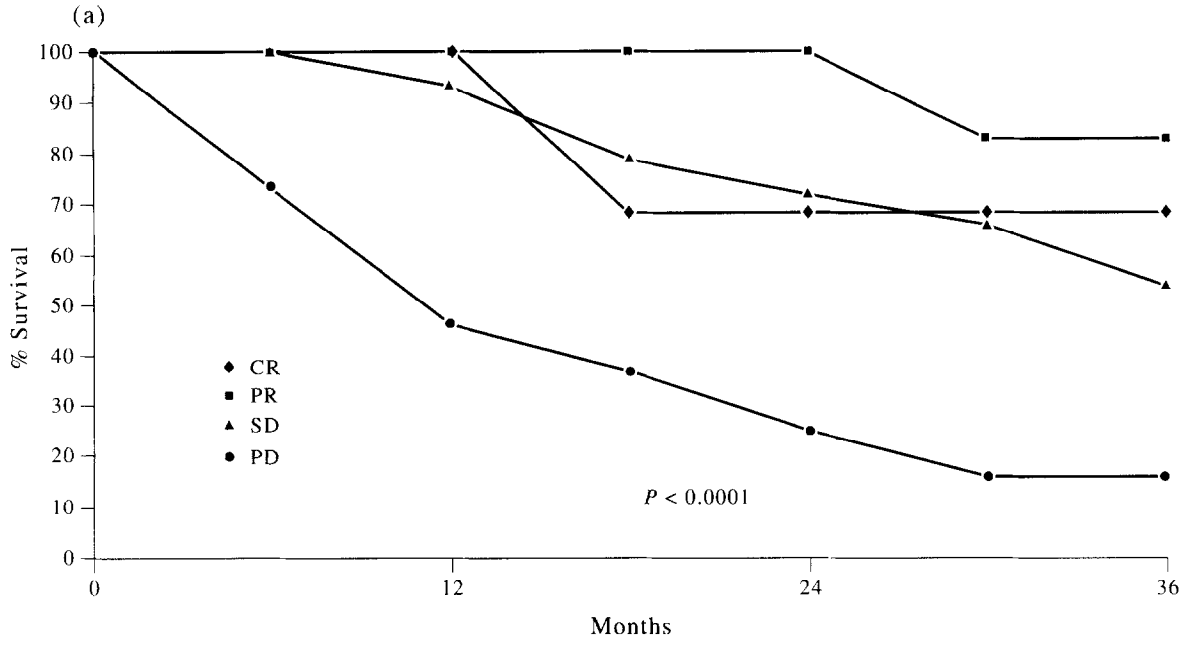
CR (*n*)	16	16	15	12	10	8
PR (*n*)	34	34	32	23	14	10
SD (*n*)	46	45	37	30	20	14
PD (*n*)	28	24	14	5	5	4



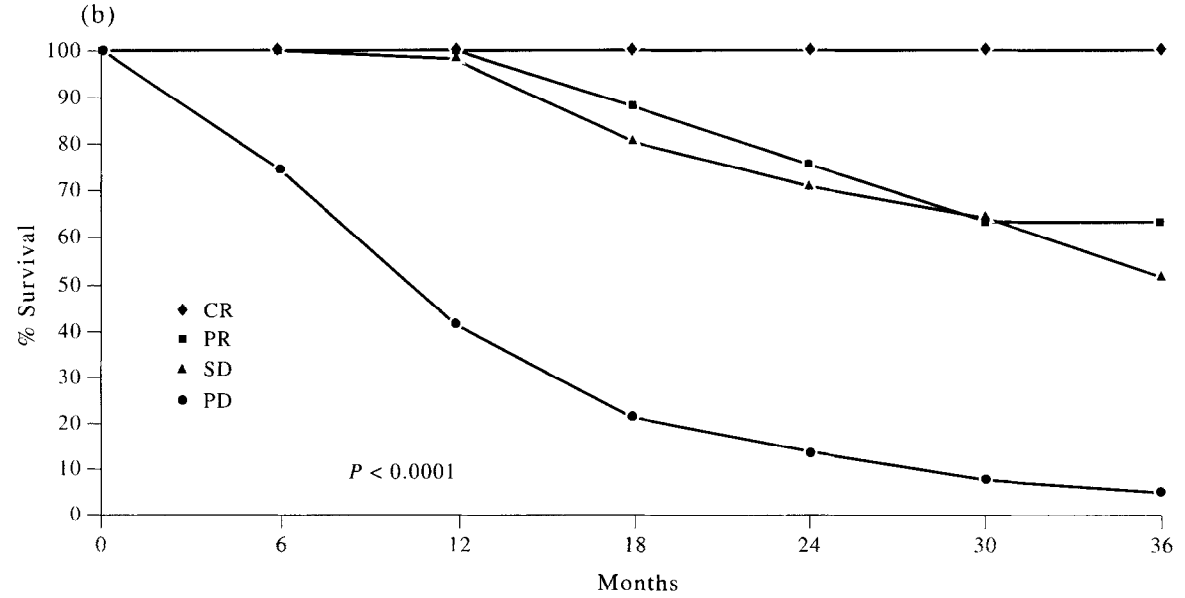
CR (*n*)	7	7	6	5	5	5
PR (*n*)	14	14	14	9	7	7
SD (*n*)	42	41	35	25	17	13
PD (*n*)	35	29	11	4	4	2

Figure 1. (a) Survival from starting first-line endocrine therapy by UICC criteria (non-metastatic). (b) Survival from starting first-line endocrine therapy by UICC criteria (MBC patients).

has previously been pointed out that it is of little or no value to compare survival between groups of patients who show an objective response (OR, CR or PR) and those who show PD, since this difference may reflect differences in the natural biology of the heterogeneous disease in different people [5]. However, it is of clinical value to identify into which category (OR or PD) patients with SD should be grouped. This study has shown that durable SD should be



CR (*n*)	3	3	2	2
PR (*n*)	12	10	6	3
SD (*n*)	62	46	27	16
PD (*n*)	75	31	14	8



CR (*n*)	4	4	4	3		
PR (*n*)	8	8	6	4		
SD (*n*)	43	41	26	14		
PD (*n*)	43	16	5	1		

Figure 2. (a) Survival from starting second-line endocrine therapy by UICC criteria (non-metastatic). (b) Survival from starting second-line endocrine therapy by UICC criteria (MBC patients).

grouped with OR. This finding is true for first-, second- and we believe third-line endocrine therapy.

The clinical importance of this approach is that around 40% of patients on both first- and second-line therapy achieve SD which appears to be a worthwhile remission criteria. Together with OR this means that two thirds of patients benefit from first-line endocrine therapy and half from second-line endocrine therapy. Some clinicians already

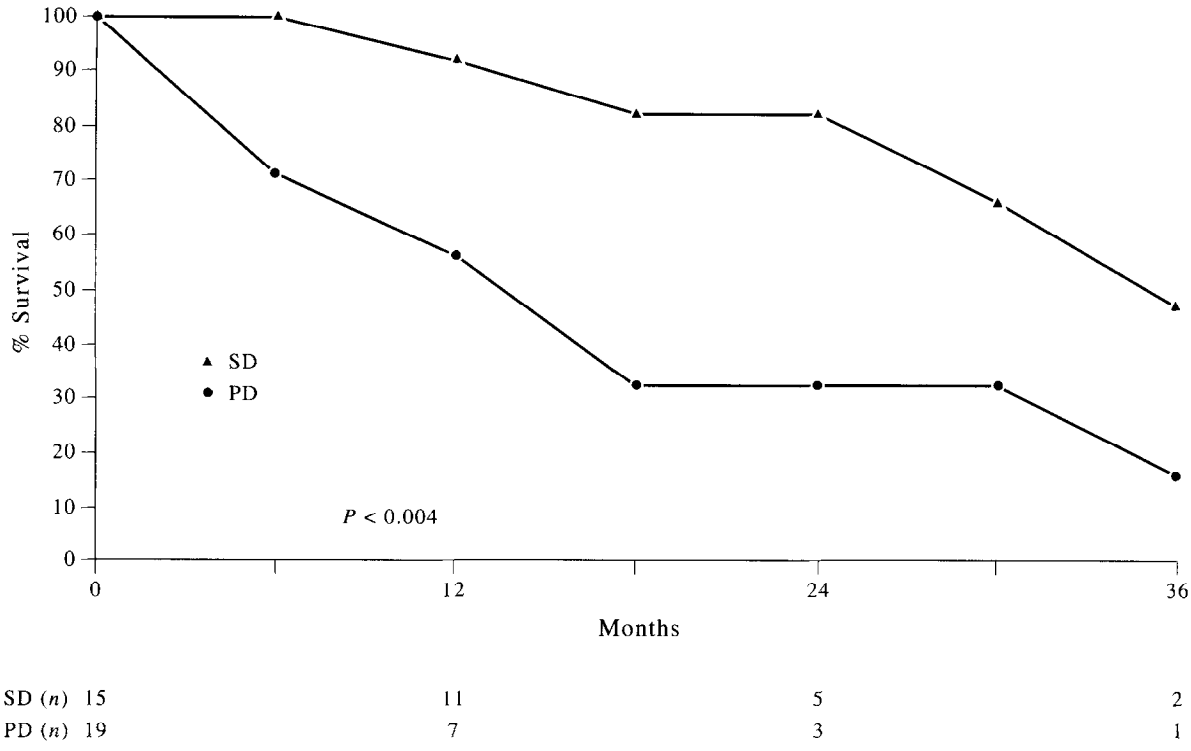


Figure 3. Survival from starting third-line endocrine therapy by UICC criteria.

keep patients achieving SD on endocrine therapy until their disease progresses. The data presented in this paper reassures clinicians that these patients are benefiting from endocrine therapy in similar manner to patients who show objective response. Patients too are often anxious that the tumour has not reduced in size or resolved completely. These data also allow clinicians to reassure these patients that durable SD (i.e. >6 months) is a worthwhile remission criteria.

This study is the first report, to the authors' knowledge, where the value of SD has been reported for first-, second- and third-line endocrine therapies in the same group of patients. Furthermore, the data is a prospective confirmation of the value of SD for at least 6 months which was previously proposed from two separate retrospective studies [1, 2]. It is also of interest that the data relate to the three main classes of additive endocrine agents currently used in breast cancer. The majority of patients on first-line therapy received tamoxifen (anti-oestrogen), on second-line therapy received megestrol acetate (synthetic progestin) and on third-line therapy, aminoglutethamide (aromatase inhibitor). Data from randomised studies shows that the therapeutic efficacy of aromatase inhibitors is similar to tamoxifen [6–8]. Therefore, although the number of patients reported on aromatase inhibitors in this study is smaller, the findings are entirely consistent with other data. However, it would be of interest to compare SD for at least 6 months on an aromatase inhibitor in a larger number of patients—perhaps this would have to be where aromatase inhibitors were used as second-line therapy to achieve a larger patient group.

The number of patients still alive after 2–3 years, particulary on second- and third-line therapies, was small. Most of the events (i.e. deaths) occurred in the first 2 years and this is where the statistical power of the analyses is concentrated. To exclude a Type II error over the latter period of follow-up would require a study starting with 500–1000 patients. To our knowledge our own study will be one of the largest in the literature. The SD and PR curves do not appear to be diverging to suggest a Type II error. Furthermore, even if they were, the number of patients this would involve after 3 years on second- and third-line endocrine therapy is very small. The data therefore supports the view that patients with durable SD have a similar survival to patients with OR (CR or PR).

Unlike the first 2 reports [1, 2] which identified the clinical value of durable SD, this study included patients who did not have advanced breast cancer. The clinician's decision to choose endocrine therapy is based on a number of factors. Some elderly patients in this study received endocrine therapy as initial treatment for primary operable breast cancer. Most were as part of randomised clinical trials comparing tamoxifen with primary surgery (±tamoxifen) which have been reported [9–11], while the remaining elderly patients received initial tamoxifen because they were unfit for surgery. In elderly patients with primary operable breast cancer, the weight of evidence from randomised trials now suggests that primary surgery (±adjuvant therapy if appropriate) should be the initial therapy of choice. This is not surprising since there appears to be no difference in tumour biology (i.e. type or grade) between breast cancers in patients <70 years and >70 years of age [12, 13]. There may still be a small subgroup of elderly patients with very endocrine-sensitive tumours in whom hormone therapy may be the initial treatment of choice, although such a subgroup remains to be fully defined [11]. Nevertheless, in elderly patients unfit for surgery, endocrine therapy is still the initial treatment of choice. In such patients and in patients with advanced breast cancer where endocrine therapy is pre-

scribed, it appears from the results of this study that durable SD should be regarded as a worthwhile criterion.

Previously patients receiving endocrine therapy for breast cancer were grouped as 'responders' (CR + PR) or 'non-responders' (SD + PD). We believe that now patients should be classified in terms of 'non-progression' (CR + PR + SD) or 'progression' (PD). It is our proposal that patients with SD should be continued on endocrine therapy until disease progression as this would appear to be the clinically relevant time to change therapy.

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