Prospective Controlled Cohort Studies on Long-Term Therapy of Breast Cancer Patients with a Mistletoe Preparation (Iscador®)

Ronald Grossarth-Maticek, Renatus Ziegler

Key Words
Breast cancer · Metastases · Quality of life · Complementary and alternative medicine · Anthroposophic medicine · Mistletoe · Iscador®

Summary
Background: Mistletoe preparations such as Iscador® (Weleda, Schwäbisch Gmünd, Germany) are commonly used in complementary and alternative / anthroposophic medicine for many cancer indications, particularly for solid cancers. Efficacy of this complementary therapy is still controversial. Objective: Does long-term therapy with Iscador show any effect on survival, tumor progression and psychosomatic self-regulation of patients with breast cancer? Patients and Methods: Prospective recruitment and long-term follow-up of two controlled cohort studies: (1) Randomized matched-pair study (38 pairs): breast cancer patients without any recurrences or metastases and no mistletoe therapy were matched for prognostic factors. By pairwise random allocation, one of the patients was suggested mistletoe therapy to be applied by the attending physician. (2) Non-randomized matched-pair study (84 pairs): breast cancer patients without recurrences or metastases that already received mistletoe therapy were matched to control patients without Iscador therapy. Results: For overall survival, the non-randomized study shows significant effects in favor of Iscador therapy: hazard ratio HR estimate and 95% confidence interval CI: 0.43 (0.27–0.68). The effect of long-term Iscador therapy on tumor progression as measured by the time to local recurrences, lymphatic or distant metastases is in breast cancer patients without any such events at first diagnosis, is in most cases significant in favor of the Iscador group, in the randomized as well as in the non-randomized study. Psychosomatic self-regulation in the Iscador group improves significantly within 12 months compared with the control group in the randomized as well as in the non-randomized study; estimate of the median difference and 95% CI: 0.35 (0.05–0.60), respectively 0.20 (0–0.35). Conclusion: Iscador shows a clinically relevant effect on breast tumor progression as measured by overall survival as well as by the time to recurrences, lymphatic or distant metastases. In the short term, psychosomatic self-regulation increases more markedly under complementary Iscador therapy than under conventional therapy alone.

Keywords
Breast cancer · Metastases · Quality of life · Complementary and alternative medicine · Anthroposophic medicine · Mistletoe · Iscador®

Zusammenfassung
Hintergrund: Anthroposophische Mistelpräparate wie Iscador® (Weleda, Schwäbisch Gmünd, Deutschland) werden bei verschie denen Krebsindikationen, insbesondere bei soliden Tumoren, verbreitet eingesetzt. Die Wirksamkeit dieser komplementären Therapie wird weiterhin kontrovers diskutiert. Fragestellung: Hat die Langzeitanwendung von Iscador einen Effekt auf Gesamtüberleben, Tumorprogression und psychosomatische Selbstregulation von Patientinnen mit Brustkrebs? Patienten und Methoden: Prospektive Rekrutierung und Langzeit-Verfol gung von zwei kontrollierten Kohortenstudien: (1) Randomisierte Matched-Pair-Studie (84 Paare): Patientinnen mit Brustkrebs ohne Lokalrezidiv oder Metastasen und ohne Misteltherapie wurden gematcht bezüglich prognostischer Faktoren. Durch paarweise Randomisierung wurde je einer Patientin jedes Paares eine Iscador-Therapie empfohlen, die durch ihren behandelnden Arzt durchgeführt werden sollte. (2) Nichtrandomisierte Matched-Pair-Studie (84 Paare): Patientinnen mit Brust krebs ohne Lokalrezidiv oder Metastasen, die bereits Misteltherapie erhielten, wurden nach denselben Kriterien mit Kontrollpatientinnen ohne Iscador-Therapie gematcht. Ergebnisse: Beim Gesamtüberleben zeigt nur die nichtrandomisierte Studie ein signifikantes Resultat zugunsten der Iscador-Therapie: Schätzwert der Hazard Ratio HR und 95%-Konfidenzintervall CI: 0.43 (0.27–0.68). Der Effekt einer Langzeitanwendung von Iscador auf die Progression von Brustkrebs, gemessen anhand der Zeit bis zum Eintreten von Lokalrezidiven, ist in den meisten Fällen signifikant zugunsten von Iscador sowohl in der randomisierten als auch in der nichtrandomisierten Studie. Das Niveau der psychosomatischen Selbstregulation steigt in der Iscadorgruppe innerhalb von 12 Monaten sowohl in der randomisierten als auch in der nichtrandomisierten Studie signifikant gegenüber der Kontrollgruppe (Schätzwert der medianen Differenz mit 95%-CI: 0.35 (0.05–0.60) und 0.20 (0–0.35). Schlussfolgerungen: Iscador zeigt einen klinisch relevanten therapeutischen Effekt auf die Progression von Brustkrebs gemessen anhand der Zeit bis zum Eintreten von Lokalrezidiven oder Metastasen sowie anhand der Gesamtüberlebenszeit. Als Kurzzeitwirkung steigt das Niveau der psychosomatischen Selbstregulation in der Iscador-Gruppe stärker als in der lediglich konventionell behandelten Kontrollgruppe.

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Dr. Renatus Ziegler
Verein für Krebsforschung, Institut Hiscia, Kirschweg 9, 4144 Arlesheim, Schweiz
Tel. +41 61 706 7245, Fax 706 7200
E-mail ziegler@hiscia.ch
Introduction

In Europe, many women with breast cancer use complementary therapies, however, evidence of their efficacy on disease progression and survival is still discussed controversially [1]. Among complementary therapies for breast cancer patients, aqueous extracts of European mistletoe (Viscum album L.) developed on the basis of anthroposophic medicine, are the most frequently used medications, particularly in German-speaking countries [2, 3]. Out of 14 published prospective controlled studies on mistletoe extract (Iscador®, Weleda, Schwäbisch Gmünd, Germany) 7 show positive trends, and 7 show significant results in favor of Iscador [4, 5].

This paper reports on two new data sets concerning long-term therapy with Iscador®: one randomized (‘MammaRand’) and one non-randomized (‘Mamma’) matched-pair study with breast cancer patients without recurrences, lymphatic or distant metastases.

The two special features of these cohort studies are the long-term follow-up and the integration of a prospective controlled cohort study with a randomized trial. The first feature is an important add-on to the existing literature; most of the 14 studies mentioned above were based on rather short terms of therapy (≤12 months) compared with the established long-time use. The second feature might present a solution to a problem well known among investigators of mistletoe therapies, in particular Iscador therapy [6, 7]: At least in German-speaking countries, female patients are well informed about different options of complementary therapy and have often made up their mind concerning these before they are even asked to participate in a study. Furthermore, many patients who use mistletoe therapy are highly motivated and of a different socioeconomic, educational and medical background than patients who use only conventional treatment [8]. Therefore, classical randomized trials cannot be performed easily because of recruitment problems [7, 9], or do not represent the population that uses mistletoe therapy in the first place [10].

Moreover, both studies rely on matching pairs of patients according to important prognostic factors: in ‘Mamma’, at the beginning of the study, available mistletoe-treated patients were matched with control patients, and for every further incoming patient an additional control patient was sought in the data base; in ‘MammaRand’, within the same cohort of control patients (but without intersection with the group of already «used» controls) matched pairs were built and, after randomization, mistletoe therapy was suggested to one of the patients of each pair. This design allows to compare the results of a randomized and a non-randomized matched-pair study. Thus, better internal validity of randomized studies (given comparable results) can be enriched by better generalizability of non-randomized studies [11].

Patients and Methods

Study Objectives

The primary question is: Does long-term therapy with Iscador in addition to conventional oncological treatment influence survival in patients with primary breast cancer of different stages in comparison to standard treatment alone?

The secondary questions are: Does long-term therapy with Iscador in addition to conventional oncological treatment delay the time to recurrences, lymphatic or distant metastases in patients with primary early breast cancer in comparison to standard treatment alone? Does therapy with Iscador in addition to conventional oncological treatment improve psychosomatic self-regulation in patients with breast cancer in comparison to standard treatment alone?

Study Design

Both ‘MammaRand’ and ‘Mamma’ are controlled cohort studies and overall have been prospective by design, that is, breast cancer patients were recruited beginning in 1971, assessed, matched according to prespecified relevant prognostic factors and followed up during the life time of all included patients. However, at each assessment (initial or follow-up) the relevant medical data were retrieved from existing medical records from routine clinical practice (charts) and were then checked for accuracy and consistency for the purpose of these studies. The only intended difference between matched pairs was the presence or absence of treatment with Iscador.

For the record: there was no written study protocol and no initial sample size calculation since both studies started in 1971, i.e. before the mandatory requirements of Good Clinical Practice were issued. Nonetheless, the study objectives, the structure of the initial and follow-up assessments, the parameter to measure (self-regulation), the data to retrieve (medical parameters) and the matching criteria were specified prior to the start of both studies.

Patients

Only patients with sufficiently complete medical records were included in the studies, given that they did not participate in any other clinical study. Every patient of the control and of the therapy group received conventional oncological therapies including, as applicable, surgery, chemotherapy, radiotherapy and hormone therapy. As the matching process included the year of the first diagnosis as a mandatory criterion, it was assured that matched patients received their first diagnosis and baseline treatment in similar times; thus, it is very unlikely that different diagnostic procedures or different modes of conventional therapy due to scientific progress were used between matched pairs.

Consent to participate in the study was assumed after comprehensive information about the study objectives and the study design and the patient’s explicit expression of willingness to participate. There was no written documentation of this process because at that time there was no mandatory requirement for an ethics committee to judge these studies as adequate.

Initial Data Assessment

The personal data were supplied by the patients themselves or their relatives; the medical data were supplied by the attending physicians or retrieved from clinical data records. They were collected during structured personal interviews with standardized checklists and later recorded on cards in patients’ files. There is no electronic data base of these raw data. In most cases, initial data were assessed within 3 years of the first diagnosis with primary breast cancer. The zero point for all time to event data is

the year of first diagnosis. The medical data were then checked and complemented through personal contact with the attending physician. The checklists included the following items:

- personal data: age at first diagnosis, sex, year of first diagnosis;
- tumor data: tumor type and stage at first diagnosis (no histological data);
- conventional treatments (which, when, how often): surgery, chemotherapy, radiotherapy, hormone therapy;
- CAM therapies (which, for how many months: 1–3 / 4–6 / 7–9 / 10–12 / more): Iscador, other mistletoe products, enzyme products, thymus products, multivitamin or mineral products, bacterial (active) pyrotherapy, physical (passive) pyrotherapy, psychotherapy.

Quality of life was assessed by the level of psychosomatic self-regulation using a questionnaire with 16 items [12, 13, 15, 21]. Self-regulation entered our studies as prognostic factor, and, if assessed more than once, also as an endpoint. In the former case self-regulation indicates the status of autonomy at the beginning of the study, in the latter case it reveals how this status changed during various therapeutic performances [12, 13].

**Observed Therapy and Intervention**

In ‘Mamma’, the investigators did not interfere with the treatment decisions (Iscador therapy or not) of the patients or the attending physicians, but only observed the applied treatment. In ‘MammaRand’, one partner of each pair was allocated to the Iscador treatment suggestion. In both studies, Iscador therapy was not administered by study physicians, but by the attending physicians the patients had chosen themselves. The complementary therapy with Iscador that was applied in these studies in addition to conventional oncological treatments is an aqueous extract of the European mistletoe (Viscum album L.) that was first used for cancer therapy in 1922 by Rudolf Steiner and his group. Pharmacological and toxicological properties of mistletoe extracts are documented by various publications on preclinical studies and on immunological and anti-cancer effects in vitro and in vivo [3, 23–26]. Iscador is generally administered subcutaneously 2–3 times a week. There are different doses, different sorts of Iscador depending on the host tree, and different application schemes [24, 27]. Yet, to keep the studies as simple as possible, only the mere fact of Iscador therapy and its duration in months were documented. There is no information concerning doses, variations in dose, breaks in therapy, host trees, etc.

**Matching Process in ‘Mamma’**

The basis for building matched pairs in ‘Mamma’ was formed by those breast cancer patients that had no lymphatic or distant metastases at first diagnosis and already received Iscador (table 2). The difference between the year of first diagnosis which coincides with the year of first operation, and the year of initial data assessment was ±3 years (data not shown). As the patients were consecutively recruited into the data pool from 1971 to 1988 (fig. 1) and met all inclusion criteria, control patients were taken from the pool of already available patients from the data files with no mistletoe therapy and within the same data source. The matching process was performed within 12 months after patient inclusion, too. Excluded pairs were not followed up any more and not used for any other purpose in any mistletoe study. The following criteria were applied to exclude pairs from both studies: (1) if in a randomized matched-pair the allocated suggestion for Iscador therapy is not taken up by the patient or the attending physician; (2) if the control partner of a randomized matched-pair decides to start Iscador therapy or another therapy that modulates the immune system; (3) if in one of the partners of a matched-pair in either kind of study (randomized or non-randomized) a certified non-tumor-related accident or suicide occurs; (4) if after the matching process in either study a patient refuses further participation for any reason, if any partner drops out of the study for any other reason than death, or if a patient cannot be found any more during follow-up. This exclusion of pairs guarantees that random treatment allocation in ‘MammaRand’ is not disturbed. Concerning non-randomized matched-pair studies, this process at least does not favor one of the two therapy groups.

**Outcome Parameters**

The primary outcome parameter was overall survival, i.e. the time from first diagnosis to death for any reason (except certified non-tumor-related...
accidents and suicides). Secondary outcome parameters were tumor progression, i.e. time from first diagnosis to local recurrences, lymphatic metastases or distant metastases, and self-regulation at the second assessment 12 months after initial data assessment.

Follow-Up
Patients without metastases were investigated by a team of scientific researchers of the Institute of Preventive Medicine (Heidelberg). Up to 1998, they made standardized telephone interviews or home visits to make structured interviews at intervals of 1 to several months, using predetermined case report forms in each case. Patients were asked about their well-being, disease progression, other diseases, continuation of conventional treatment, continuation of COM therapy, particularly with Iscador if applicable, and the start of new therapies. Concerning further tumor events (recurrences, lymphatic metastases, distant metastases, death) only the year of occurrence was recorded. Matched patients in the randomized studies were always contacted in the same or two successive weeks. If necessary for precision and validity of the medical follow-up data, the attending physician was contacted.

In the final follow-up in 1998 any dates and causes of death that had not been registered before were determined by the local residents’ registration offices («Einwohnermeldeamts») and the local boards of health («Gesundheitsamt»). The final research of the times and causes of death of the partners of each matched-pair was performed in the same or two successive weeks.

Data Sources and Data Quality
All data were recorded in predetermined report forms and checked for consistency. In cases of doubt or missing data from the initial assessment, the attending physician was contacted personally. A documented monitoring process or audit is not available. At the time these studies were initiated, such mandatory requirements did not yet exist. However, data were checked against errors in the data abstraction process, several times and at different levels. In addition, there were several independent reviews on the overall quality of the data for the whole epidemiological research program [31].

Results
Data Sets and Patient Characteristics
‘MammaRand’: 2 × 38 patients with primary breast cancer without lymphatic or distant metastases (tables 1 and 3). Initial data assessment was performed between 1971 and 1978. Of the available 465 primary breast cancer patients without lymphatic or distant metastases that received no mistletoe therapy, 59 randomized matched-pairs could be formed. 38 pairs entered into the final analysis, 21 pairs were excluded (table 1). 8 patients in each group were still alive at the last status assessment in 1998. Matching was perfect in the variables of stage (FIGO, TNM) and grading, and close to perfect in the conventional therapies (table 3).

‘Mamma’: 2 × 84 primary breast cancer patients without lymphatic or distant metastases (tables 2 and 4). Again, initial data assessment was performed between 1971 and 1978. Of the available 179 primary breast cancer patients without lymphatic or distant metastases that already received mistletoe therapy, 105 non-randomized matched-pairs could be formed using the pool of 670 patients receiving no mistletoe therapy (table 2). 84 matched pairs entered into the final analysis, 21 pairs were excluded (table 2). 6 patients of the Iscador group and 4 patients of the control group were still alive at the last status assessment in 1998. (For details concerning differences in patient characteristics and concerning the matching process, see www.karger.com/doi/10.1159/000095378.)

Overall Survival
Overall survival in both data sets was analyzed in several ways (tables 5 and 6). The results indicate a prolonging effect of Iscador therapy on survival. In ‘MammaRand’ this effect is only a trend in favor of Iscador therapy (hazard ratio estimate and 95% confidence interval: HR = 0.65 (95% CI: 0.34–1.25), p = 0.2; proportional hazard assumption moderately fulfilled). In ‘Mamma’ this effect is highly significant in all cases. The Kaplan-Meier survival curve for ‘MammaRand’ is shown in figure 2. The adjusted survival curve for ‘Mamma’ according to the model from table 6 is shown in figure 3.

Time to Recurrences, Lymphatic Metastases or Distant Metastases
For both data sets, ‘MammaRand’ and ‘Mamma’ the time to first local recurrences, lymphatic metastases or distant metastases was recorded independently. Five types of analyses were performed (tables 7, 8; fig. 4, 5).

In ‘MammaRand’ evidence in favor of Iscador therapy is best regarding lymphatic metastases, less good regarding distant metastases, and unconvincing regarding recurrences (table 7). However, the results over all events are significant: HR = 0.65 (95% CI: 0.47–0.91).

In ‘Mamma’, Iscador therapy seems to delay tumor progression in all cases: the Iscador group fares significantly better than the control group across most analyses (table 8), particularly over all events: HR = 0.66 (95% CI: 0.55–0.79).

Self-Regulation
Psychosomatic self-regulation was assessed twice in both ‘MammaRand’ and ‘Mamma’. The second assessment was 12 months after the initial one. In ‘Mamma’, the Wilcoxon paired-sample test was applied to the full set of pairs, the balanced set and the set with strict matching (table 9). Both studies show significant improvements or at least strong trends indicating that Iscador therapy may help improve the clinical well-being of breast cancer patients at early stages.

Adverse Events
The registration of adverse events of either Iscador therapy or conventional treatment was not part of the study design. Hence no information on such events is available.

Discussion
Design and Analysis
To evaluate the complex interplay of factors that may influence cancer prognosis in real life, an integrative approach was
chosen that combines a non-randomized controlled cohort study with a randomized intervention study within the same population. By this approach, the results of the randomized trial with high internal validity (reliability of study results) can be integrated into the results of the non-randomized study with generally high external validity (generalizability) and vice versa.

The aim of the analysis presented here was explorative in nature, therefore several approaches were studied. The reason for applying different types of analyses was to demonstrate (at best) the robustness of the results against different sets of constraints. Particularly non-randomized studies are susceptible to different types of bias [40] that can be dealt with to a certain extent by comparing the results of different statistical approaches.

The statistical analysis of RCTs according to the principle of intention-to-treat [41, 42] has two aspects which need to be differentiated: (1) to preserve the statistical balance of the baseline factors in the two therapy groups; (2) to present a complete picture of the real-life situation, where non-compliance and dropouts occur and may be associated with the outcome. With respect to ‘MammaRand’, the procedure of exclusion of pairs guaranteed that randomization was not undermined by excluding patients. In other words, internal validity of ‘MammaRand’ is not an issue, as structural comparability was preserved by the pairwise selection and exclusion process. This covers the first aspect of an analysis according to intention-to-treat. However, due to the exclusion process, not all pairs that were randomized were included in the analysis and hence there is a kind of underreporting bias which does not interfere with the randomization but with the completeness of the data sets analyzed. It is important to note, however, that the pairs that were excluded from ‘MammaRand’ were of no clinical relevance, since they were excluded (except for one pair that was lost during follow-up) before Iscador therapy was suggested and started. Thus, these exclusions have no relationship to the therapy, its efficacy or effectiveness, or its side effects.

A blinding process was not applicable to the intervention in ‘MammaRand’, because it did not consist of a therapy as such but of the suggestion to ask for Iscador therapy. In addition, neither the outcome assessors nor the statistician were blinded.

**Self-Regulation**

Quality of life was assessed in terms of the level of psychosomatic self-regulation using a questionnaire with 16 items and response options scaled from 1 through 6 [12, 13, 15, 21]. The test-retest reliability of this questionnaire is 0.80, and Cronbach’s α is 0.82 [18, p. 307]. However, this questionnaire has not yet been checked and validated against any common instrument to evaluate quality of life in cancer patients. The timing of filling out a quality of life questionnaire is important for accuracy and precision of the results [43]. For this reason self-regulation was not simply assessed by handing out the questionnaire to a patient and waiting until it was completed, but after leading a standardized interview session with an open discourse in which the patient could talk about her positive and negative experiences and her reactions to them for half an hour. This introductory session prepared the patient well to look at her specific situation concerning the autonomous regulation of her physical, emotional, social and psychological status [12, p. 98–99; 18, p. 91].

‘MammaRand’

Concerning overall survival, ‘MammaRand’ only indicates a positive trend in favor of long-term complementary Iscador therapy as compared to conventional treatment alone.

Regarding recurrences, lymphatic and distant metastases, the results of ‘MammaRand’ are not convincing in favor of the Iscador group. Conservative analyses of the time to recurrences and distant metastases ignoring censoring of event times, show weak evidence in favor of the Iscador group. Looking at individual Cox models for the different events, the time to distant metastases is close to significant in favor of the Iscador group (HR estimate and 95% CI: 0.50 (0.24–1.03) [values <1 are beneficial for the Iscador group]), and the time to lymphatic metastases is highly significant (HR 0.27 (0.11–0.67)), however limited by the failure of the proportional hazards assumption. These results are corroborated by the log-rank test, stratified according to the matched-pairs in all three cases, proving consistent results across different types of analyses. – The Cox modeling taking into account censoring and all ordered events (first recurrences, then lymphatic and distant metastases) shows significant results (HR: 0.65 (0.47–0.91)). The result with the assumption of unordered events is even better (HR: 0.47 (0.30–0.76)) but limited by the fact that the proportional hazard assumption does not seem adequate for this model.

Several biases might limit these results. First, there is the problem of accuracy and misclassification. In fact, accuracy and precision of the data are poor: exact dates of first diagnosis, operation, initial and follow-up data assessments and matching are not available; yet, this applies to both therapy groups and there is no reason to assume that any consequences of these imprecisions affect one group more than the other. Since matching was accomplished within 12 months of initial data assessment, misclassifications due to shifting criteria are unlikely. Selection bias is neutralized by the randomization process. Performance bias is not a problem, since the main co-therapies were recorded. In addition, it is plausible to assume that the control patients used additional (unconventional and unrecorded) therapies more often, since no such treatment was offered to them by means of study participation; generally speaking, this works in favor of the control group. Detection bias is a minor problem, since objective criteria of clinical diagnosis and survival were used in these studies; there is no reason to assume that either group was watched more closely for the incidence of tumor-related events.
Attrition bias may be a problem in ‘MammaRand’. In all, 21 patients (6 from the Iscador group) dropped out of that study. Along with the elimination of their partners, 21 matched-pairs were eliminated. This does not affect the balance of the compared groups provided by the randomization, since randomization was performed pairwise and both partners were eliminated. In addition, all Iscador partners (except one) dropped out before the start of the therapy. There is no evidence that the reason for dropout may be related to the outcome.

Further limitations of the (internal) validity – apart from the small sample size – might come from the fact that there was no written protocol and no pre-specified formulation of statistical hypotheses and no sample-size calculations in advance. Generalizability (external validity) might be limited by the fact that inclusion and exclusion criteria were not very precise nor were all of them explicitly formulated in advance; in addition, there were no explicit selection criteria for building pairs. In ‘MammaRand’ there might have been a preference for patients with a good prognosis, since patients from both groups that died early could not enter into the study. – Patients with poor compliance with Iscador therapy were not included. If they did not take up the treatment suggestion, they were excluded from the study as well as their matched partners.

Concerning the short-term improvement of psychosomatic self-regulation, the estimate of the median of improvement was well below 0.5; provided there were no significant differences in baseline values, this small improvement with respect to the Iscador group may still be clinically relevant [15].

‘Mamma’
Overall, the results of the non-randomized study ‘Mamma’ (84 pairs) show at least positive trends in favor of the Iscador group and in most cases highly significant results. Particularly, concerning overall survival, the results of the unadjusted evaluations speak significantly in favor of the Iscador group. Concerning the time to local recurrences, lymphatic metastases and distant metastases, the Iscador group fares significantly better than the control group across most types of analyses. The only exception seems to be distant metastases, which are more frequent in the Iscador group than in the control group. However, in the Cox proportional hazards model of this study, taking into account censored and uncensored survival times and no interactions, HR is much weaker in the Iscador group than in the control group (HR: 0.36 (0.21–0.62)).

Pairwise matching was used to reduce selection bias for several known prognostic factors. However, to recruit a relevant number of patients matching could not be performed without some exceptions. In order to deal with biases due to loose matching with up to two deviations from strict matching, several analytic approaches were applied as a kind of sensitivity analysis: within non-adjusted analyses, balanced subsets and sets with strict matching were formed and analyzed separately to compare results. In addition, Cox proportional hazards models were built with and without adjustments of other factors than therapy (including interactions of the first kind, if significant). In an additional sensitivity analysis, the results of all breast cancer patients without recurrences or metastases (n = 2 × 97) were compared with the results of the full set ‘Mamma’ (n = 2 × 84) and no relevant differences were found (data not shown).

Concerning survival, the unadjusted analyses show comparable results for the different subsets, proving that the original sets were fairly well balanced, at least with respect to the prognostic factors used in the matching process. This is corroborated by the fact that the results of the Cox proportional hazards model do not differ very much between the adjusted and the unadjusted analysis.

Concerning the time to recurrences, lymphatic and distant metastases, the different approaches yield similar results (table 8). However, there are two exceptions to this pattern: with respect to recurrences, most of the event times are censored and hence the Wilcoxon paired-sample test cannot give reliable results, in contrast to the stratified log-rank test; in the severely reduced ‘Mamma’ data set with strict matching and only 24 pairs, results are not very strong but at least show a positive trend in favor of the Iscador group, in contrast to the highly significant results in most of the other cases.

Still, several other biases might limit the study results. For the same reason as in the case of ‘MammaRand’, biases due to lack of accuracy and misclassification are of minor importance. The same applies to performance and detection bias. – The single most important sources of bias for non-randomized studies are selection and confounding [40]. More specifically, residual bias might result from (i) non-perfect matching, (ii) non-matched prognostic factors and (iii) not measured (un)known prognostic factors. The first case has already been dealt with. The second and third case are more serious. According to the study design, several important medical prognostic factors were either not recorded throughout all cases, or not recorded at all (i.e. steroid receptor; histopathological type and histopathological grading). In addition, other factors were not deemed relevant for the study objectives at the outset of the study in 1971 and hence are not available for analysis (i.e. exact dates of first diagnosis, operation, initial and follow-up data assessments and matching; socioeconomic status; social support; spirituality). The source of recruitment and the hospital were dropped for reasons of anonymity. This leaves the case of unknown factors open for speculation. Attrition bias, which amounts to 8%, is a minor problem in ‘Mamma’, since with the dropout of any study patient her matching partner was excluded as well and hence, the balance of the groups was not severely affected. There is no evidence that the reason for dropout is related to the outcome. The (internal) validity of the results is, first of all, limited by selection bias and confounding as discussed above. Further limitations of validity might come from the fact that there was no written protocol and hence no pre-specified formulation of sta-
tistical hypotheses; the sample size was small and there were neither sample-size calculations in advance nor adjustments for multiple testing. Still, in many cases the estimated effects are very strong and thus not affected by these limitations.

As in the case of ‘MammaRand’, the generalizability (external validity) of ‘Mamma’ might be limited by the fact that the inclusion and exclusion criteria were neither very precise nor always explicitly formulated in advance. Furthermore, apart from the matching criteria there were no explicit procedures for building pairs. It was simply looking for the best matching partner. In the case of deviations from the main matching criteria there was no rule how to proceed. In ‘Mamma’, too, there might have been a preference for patients with good prognosis, as patients from either group who died shortly after the diagnosis could not enter into the study.

Concerning the short-term improvement of psychosomatic self-regulation in ‘Mamma’, estimated by the median of pairwise differences of self-regulation between second and first evaluation, the analyses of the original set and the subsets show at least trends of improvement (table 9). However, the estimate of the median of improvement is well below 0.5; given the high initial value in the Iscador group and the corresponding significant lower values in the control group, these minor improvements of the Iscador group vs. the control group may still be clinically relevant [15].

Consistency and Generalizability
The baseline values of ‘MammaRand’ and ‘Mamma’ are well comparable, and so are the results. That is, although not in all cases significant, the results of ‘MammaRand’ are consistent with those of ‘Mamma’: they point in the same direction. Together, both studies benefit from each other: ‘MammaRand’ has better internal validity and ‘Mamma’ has better generalizability.

Regarding survival of breast cancer patients of all stages, particularly without metastases, there is evidence from other controlled studies in favor of mistletoe therapy, particularly Iscador [47, 48]. In addition, studies based on archival data show as on survival. In the short run, psychosomatic self-regulation as a measure of autonomous coping with the disease, improves significantly more under Iscador therapy than under conventional therapy alone. Overall, therapy with Iscador seems to delay tumor progression, prolong survival and improve well-being of breast cancer patients of early stages to a clinically relevant extent.

Tolerability and Safety
A documentation of unintended adverse drug reactions to Iscador therapy was not part of the design of these studies. However, there is no evidence for severe adverse effects that can be plausibly related with this therapy [3, 44]. This has also been corroborated by more recent data on the tolerability and safety of complementary therapy with Iscador [45]. In addition, apart from its effects on the prolongation of survival and the delay of tumor progression, mistletoe therapy with Iscador seems to reduce the side effects of conventional chemotherapy [45, 46], i.e. help patients to live better through the impairments of chemotherapy.

Conclusion
The consistency of the results across the randomized and the non-randomized study as well as across different types of analyses give some evidence that long-term therapy with Iscador might have clinically relevant therapeutic effects on the time to recurrences, lymphatic and distant metastases as well as on survival. In the short run, psychosomatic self-regulation as a measure of autonomous coping with the disease, improves significantly more under Iscador therapy than under conventional therapy alone. Overall, therapy with Iscador seems to delay tumor progression, prolong survival and improve well-being of breast cancer patients of early stages to a clinically relevant extent.

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