Renatus Ziegler, Konrad Urech

Documentation of published clinical studies with Iscador®

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Preface

This documentation is intended as a basic working tool for specialised staff and medical doctors to provide an orientation on the effectiveness of an Iscador therapy in cancer patients, based on published clinical trials and observational studies.

More than 66 clinical trials and observational studies with Iscador, as well as over 10 systematic reviews and 2 meta-analyses of these studies had been carried out by now. Several further studies are currently intended or being carried out. Reports on these studies will be given here, as soon as citable publications are available.

Chapters or sections in parentheses (…) indicate that there are up to now no clinical studies available for these indications.

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Dr. rer. nat. Renatus Ziegler
Dr. sc. nat. Konrad Urech
Institut Hiscia
Verein für Krebsforschung, Arlesheim

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Introduction

Documentation Content

The aim of this documentation is to provide, as far as possible, a comprehensive registration of every reference of clinical trials and observational studies with Iscador concerning immunology, DNA-repair, quality of life/pain, tumour remission and survival. Systematic reviews, meta-analyses and exceptionally well documented case reports are also included. Summaries of chosen works will be used to provide an insight into the relevant clinical and pharmacological effectiveness of Iscador.

We have generally not included studies which have not appeared in the publicly available journals, meaning those which have been documented as internal reports. Such studies are only included in this documentation when the topic is not otherwise represented in the literature, or the study has other notable attributes. Studies which have been published several times are generally only included once. A multiple citation only occurs when different facets are reported, when the consistency of the study is unclear or when the specialised literature on mistletoe therapy especially refers to these works.

The studies on the clinical and pharmacological effectiveness of drugs can be roughly sorted into two main groups: Clinical trials and observational studies. The latter group includes mainly observation of individual cases, case reports and series of cases or collective reports, culminating in treatment observations, which make up a large part of the studies with Iscador.

The beneficial effect of Iscador is often immediately experienced by the patient as well as the treating doctor. Many case reports have been published that have been the result of such an experience, as well as those which could show a convincing intra-individual effect of the treatment with Iscador. Only exceptional well documented cases of this sort will be considered in this documentation, or special cases, where only little literature was otherwise available.

In recent times, the culture of thorough representation of case reports is gaining again terrain. Some outstanding and well documented case reports will be mentioned in Chapter 9.

Chapters or sections in parentheses (…) indicate that there are up to now no clinical studies available for these indications.

Clinical Trials and Observational Studies

Clinical trials (RCT, randomised controlled clinical trial) should be understood to be clinical studies in which the patients are divided into different, mostly two, therapy groups. The allocation of the patients to the groups is controlled by the study leader and not the treating doctor or the patient. Randomisation is the technical instrument for this allocation. This method guarantees, by a large enough number of patients, the comparability of the therapy groups in regards to known and unknown risk factors. The design of RCT type clinical studies minimises the influence of doctor and patient preferences, as well as the personal relationship involving therapeutic care and trust between doctor and patient.

In order to prove the effectiveness of a medication within a patient collective, independent of the knowledge and actions of the doctor or patient and without subjective bias, RCT type placebo-controlled studies should be, if at all possible, double-blinded.

In many cases not only ethical, but also medical, human and technical problems prevent a complete double-blinding in studies with Iscador. For example, a therapy with Iscador is usually accompanied by a visible local reaction, which cannot be imitated by a neutral placebo, thus invalidating the double-blinding. In addition, when applying this treatment for cancer the doctor has to be able to treat therapy-dependent reactions; this is not possible when the medication is unknown.

Type RCT clinical trials, where necessary with double-blinding, are especially conclusive when regarding an unadulterated medication effect, excluding almost all other factors. They therefore tend to underestimate the effectiveness of the studied therapy; they are also quite removed from day-to-day clinical practice.

An approved method in order to achieve the comparability of two groups in prospective observational studies is the forming of matched pairs, as used in the epidemiological studies by Ronald Grossarth-Maticek. The difficulty of observing patients over longer periods of time, as necessary for survival in oncologic patients, was overcome in this study. The reliability of the results was not only due to the accurate matching of the patients at the outset of the prospective data collection, but also due to accompanying prospective randomised intervention studies which confirmed a prolonging of life as well as improved quality of life due to Iscador.

Safety and Tolerance

Data on tolerability and safety of a therapy with Iscador (Chapter 6) are available from only a few controlled studies and systematic reviews. Please refer to the relevant literature summary for data on case reports.

Systematic Reviews

Qualitative systematic reviews assess the quality and validity of studies within a certain area of research using previously defined criteria and according to the data published as well as the description of the study. There are, of course, very different aspects according to which general quality can be accessed. These principles are in currently in the process of being standardised (Cochrane Collaboration, EBM). This standardisation is mainly orientated on conventional studies, of the RCT type, which most Iscador therapy studies cannot adhere to. Accordingly, both of the articles included, as well as the levels of quality of the systematic reviews presented in chapter 7 are very different.

In connection with systematic reviews of clinical trials, it must be considered as well that only very few clinical trials exist even in the field of oncology, which reach all the criteria, set by the oncologists themselves. Systematic reviews and meta-analyses of clinical trials with chemotherapies within oncology often show methodological deficits in the primary studies, several of these studies could not produce the same results when repeated (see: Ulrich Abel, «Chemotherapie fortgeschrittener Karzinome – Eine kritische Bestandsaufnahme», Stuttgart: Hippocrates, 2. Auflage 1995). This is an important factor when assessing clinical trials with Iscador, as it is often incorrectly assumed that clinical trials with other medication in oncology fulfil the required criteria.

Meta-Analyses

Meta-analyses are systematic reviews with a quantitative and comparative analysis of published date across different studies, preferably based on the same interventions and indications.

If the whole data set is available for analysis, then raw patient data can be used instead of statistical summaries from individual studies. This gives then an individual patient data meta-analysis.

Conclusion

When all of the various aspects are taken into consideration, the evaluation of clinical trials with Iscador can establish a therapeutic advantage for Iscador in regards to life extension, quality of life and reducing chemotherapy related symptoms, as well as good tolerance and sufficient safety.

Description of Symbols

The studies which are more comprehensively presented in this documentation are marked with a ☆, the others are marked with a ●.

1 Immunology

1.1 Monocytes and Macrophages

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1.2 Natural Killer Cells and Lymphokine-activated Killer Cells

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1.6 Eosinophil Granulocytes

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1.7 Cytokines

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1.8 Reduced Incidence of Common Cold

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2 DNA – Repair

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Kovacs E., Hajto T., Hostanska K. (1991) Improvement of DNA repair in lymphocytes of breast cancer patients treated with *Viscum album* extracts (Iscador). *European Journal of Cancer* 27 (12): 1672–1676.

Study design

Design	Prospective, partially controlled study.
Subjects	14 breast cancer patients (stage II-IV) and 92 control subjects.
Treatment	Intravenous infusion of Iscador M on day 0 (0.33 ± 0.07 mg/kg body-weight) and 1ml Iscador M s.c. daily on days 2 to 7.
Measurements	The DNA from lymphocytes isolated from patient blood was damaged in vitro using UV-C. The integration of ^{3}H-Thymidin into the cells' DNA was used as a measurement parameter for DNA repair.

Results

DNA-repair in patient lymphocytes was 84% lower than in the healthy subjects at the beginning of the therapy. The DNA-repair after 7 to 9 days therapy with Iscador increased on average by a factor of 2.7.

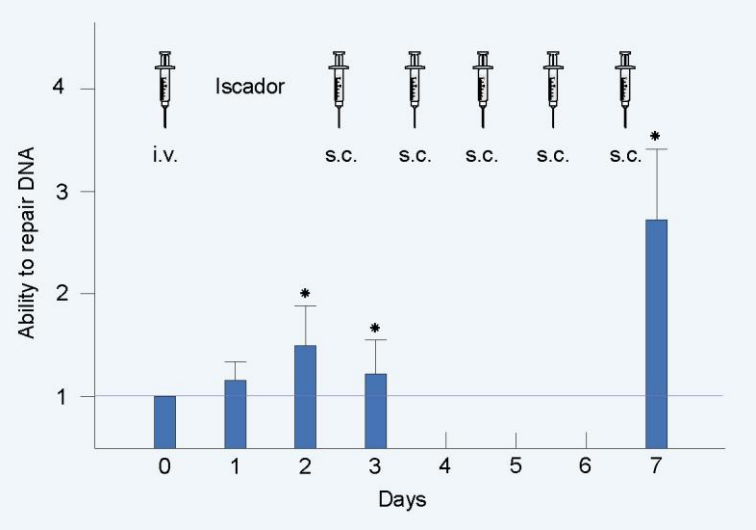

Fig. 1: DNA-repair in breast cancer patients' lymphocytes during the course of therapy with Iscador. The values were calculated relative to the values before beginning the therapy (Day 0).

* Difference to 0-value is significant ($p < 0.05$)

3 Quality of Life/Pain

3.1 Validated Questionnaires for Quality of Life (QoL)

3.1 Validated Questionnaires for Quality of Life

3.1.1 Genitourinary Cancer

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Grossarth-Maticek R., Ziegler R. (2007a) Prospective controlled cohort studies on long-term therapy of cervical cancer patients with a mistletoe preparation (Iscador). *Forschende Komplementärmedizin* 14 (3), 140–147.

Study design

Design	(1) Randomised, prospective long-term, matched-pair technique.
	(2) Prospective epidemiological long-term cohort study, matched-pair technique.
Patients	(1) *CervixMetRand:* 2 × 19 cervical cancer patients with metastases.
	(2) *Cervix:* 2 × 102 cervical cancer patients without metastases.
Treatment	The patients in the Iscador group received in addition to conventional cancer treatment an individual therapy with different doses and types of s.c. applied Iscador. The control group with matched patients received only conventional cancer treatment and did not receive any type of mistletoe treatment.
Length of study	1973 – 2002.
Measurements	Self-regulation (Score 1 to 6) according to Grossarth-Maticek measured using questionnaires with graded answers.

Most important results

The self-regulation index is a measurement of individual activity to achieve well-being, inner balance, adapted motivation, a feeling of competence and safety and overcoming of stress situations.

(1) *CervixMetRand:* Improvement of self-regulation within 12 months, with the median of differences (based on pairwise differences between Iscador and control patients) of 0.70 score-points and a 95% confidence interval of 0.15 – 1.05 ($p = 0.014$).

(2) *Cervix:* Improvement of self-regulation within 12 months, with the median of differences (based on pairwise differences between Iscador and control patients) of 0.25 score-points and a 95% confidence interval of 0.15 – 0.35 ($p < 0.0005$) for the complete set (102 pairs) and the strictly matched subset (73 pairs).

For results of this study concerning survival see 5.1.4.3.

Grossarth-Maticek R., Ziegler R. (2007b) Prospective controlled cohort studies on long-term therapy of ovarian cancer patients with a mistletoe (*Viscum album* L.) extracts Iscador. *Arzneimittel-Forschung/Drug Research* 57 (10), 665–678.

Study design

Design	(1) Randomised, prospective long-term, matched-pair technique.
	(2) Prospective epidemiological long-term cohort study, matched-pair technique.
Patients	(1) *OvarRand:* 2 × 21 ovarian cancer patients with metastases.
	(2) *Ovar:* 2 × 75 ovarian cancer patients without metastases.
Treatment	The patients in the Iscador group received in addition to conventional cancer treatment an individual therapy with different doses and types of s.c. applied Iscador. The control group with matched patients received only conventional cancer treatment and did not receive any type of mistletoe treatment.
Length of study	1973 – 2002.
Measurements	Self-regulation (Score 1 to 6) according to Grossarth-Maticek measured using questionnaires with graded answers.

Most important results

The self-regulation index is a measurement of individual activity to achieve well-being, inner balance, adapted motivation, a feeling of competence and safety and overcoming of stress situations.

(1) *OvarRand:* Improvement of self-regulation within 12 months, with the median of differences (based on pairwise differences between Iscador and control patients) of 0.58 score-points and a 95% confidence interval of 0.30 – 0.90 (p = 0.0002).

(2) *Ovar:* Improvement of self-regulation within 12 months, with the median of differences (based on pairwise differences between Iscador and control patients) of 0.30 score-points and a 95% confidence interval of 0.05 – 0.65 (p = 0.026) for the strictly matched subset (29 pairs). The corresponding results for the complete set (75 pairs) are: 0.30 (0.10 – 0.60), p = 0.0054.

For results of this study concerning survival see 5.1.2.4.

Grossarth-Maticek R., Ziegler R. (2008) Randomized and non-randomized prospective controlled cohort studies in matched pair design for the long-term therapy of corpus uteri cancer patients with a mistletoe preparation (Iscador). *European Journal of Medical Research* 13 (3), 107–120.

Study design

Design	(1) Randomised, prospective long-term, matched-pair technique.
	(2) Prospective epidemiological long-term cohort study, matched-pair technique.
Patients	(1) *CorpusRand:* 2 × 30 corpus uteri cancer patients without metastases.
	(2) *Corpus:* 2 × 103 corpus uteri cancer patients without metastases.
Treatment	The patients in the Iscador group received in addition to conventional cancer treatment an individual therapy with different doses and types of s.c. applied Iscador. The control group with matched patients received only conventional cancer treatment and did not receive any type of mistletoe treatment.
Length of study	1973 – 2002.
Measurements	Self-regulation (Score 1 to 6) according to Grossarth-Maticek measured using questionnaires with graded answers.

Most important results

The self-regulation index is a measurement of individual activity to achieve well-being, inner balance, adapted motivation, a feeling of competence and safety and overcoming of stress situations.

(1) *CorpusRand:* Improvement of self-regulation within 12 months, with the median of differences (based on pairwise differences between Iscador and control patients) of 0.40 score-points and a 95% confidence interval of 0.15 – 0.70 ($p = 0.0012$).

(2) *Corpus:* Improvement of self-regulation within 12 months, with the median of differences (based on pairwise differences between Iscador and control patients) of 0.70 score-points and a 95% confidence interval of 0.25 – 1.15 ($p = 0.0037$) for the strictly matched subset (34 pairs). The corresponding results for the complete set (103 pairs) are: 0.65 (0.40 – 0.95), $p < 0.0005$.

For results of this study concerning survival see 5.1.3.1.

3.1.2 Breast Cancer

References

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☆ Grossarth-Maticek R., Ziegler R. (2006a) Prospective controlled cohort studies on long-term therapy of breast cancer patients with a mistletoe preparation (Iscador). Forschende Komplementärmedizin 13 (5), 285–292.

☆ Grossarth-Maticek R., Ziegler R. (2006b) Randomised and non-randomised prospective controlled cohort studies in matched pair design for the long-term therapy of breast cancer patients with a mistletoe preparation (Iscador): A re-analysis. European Journal of Medical Research 11 (11): 485–495.

☆ Loewe-Mesch A., Kuehn J. J., Borho K., Abel U., Bauer C., Gerhard I., Schneeweiss A, Sohn C., Strowitzki T., Von Hagens C. (2008) Adjuvante simultane Mistel-/Chemotherapie bei Mammakarzinom – Einfluss auf Immunparameter, Lebensqualität und Verträglichkeit. Forschende Komplementärmedizin 15 (1), 22–30.

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☆ Tröger W., Jezdić S., Ždrale Z., Tišma N., Hamre H., Matijašević M. (2009) Quality of life and neutropenia in patients with early stage breast cancer: a randomized pilot study comparing additional treatment with mistletoe extract to chemotherapy alone. Breast Cancer: Basic and Clinical Research 3, 35–45.

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The references marked with ☆ are included in abstract form in this documentation.

Borrelli E. (1999) Valutazione della qualità di vita in pazienti affette da adenocarcinoma mammario sottoposte a terapia con Viscum album. [Evaluation of the quality of life in patients with metastatic breast cancer treated by Viscum album.] *La Medicina Biologica,* luglio-settembre, 27–30.

Study design

Design	Randomised, placebo-controlled study.
Patients	30 patients with breast cancer with metastases after surgery, radiotherapy or chemotherapy.
Treatment	20 patients were treated with Iscador M s.c. (3 times a week, dose equivalent of 1ng mistletoe lectin/kg bodyweight) and 10 patients with physiological sodium chloride solution (3 times a week). Treatment allocation for both groups was randomised.
Length of study	1997 – 1998.
Measurement	Quality of Life index according to Spitzer.

Most important results

Quality of life marginally significantly increased in the Iscador group after 2 months (p = 0.05) in contrast to the control group, where quality of life decreased slightly. An improvement in quality of life could even be shown in cases with progressive disease in the Iscador group, this improvement was however not statistically significant.

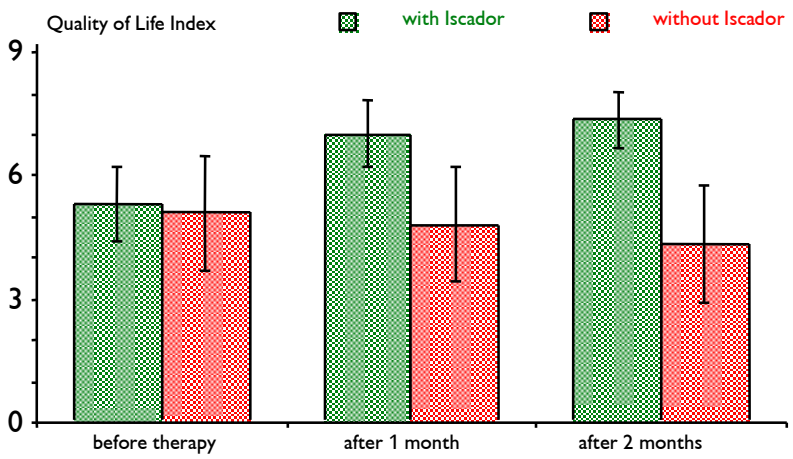

Fig. 1: Course of quality of life of patients with breast cancer during a 2 month Iscador therapy in comparison with those not treated with Iscador. Quality of life was measured according to Spitzer (according to Borrelli 1999).

Carlsson M. et al. (2006) A five-year follow-up of quality of life in women with breast cancer in anthroposophic and conventional care. *eCAM Evidence-based Complementary and Alternative Medicine*, 3 (4), 523–531.

Study design

Design	Prospective, open, 2-arm non-randomised study, matched-pair technique.
Patients	60 breast cancer patients treated with anthroposophic medicine from the Vidar clinic in Järna were matched with 60 breast cancer patients treated conventionally from clinics within the same district (matching criteria included: cancer stage at admission by the clinic, age, prior conventional treatment within 3 months, prognosis).
Treatment	The 60 breast cancer patients treated with anthroposophic medicine also received mistletoe therapy with Iscador.
Length of study	Admission by the Vidar clinic November 1995 – January 1999. 5-year follow-up until 2004.
Measurement	Quality of life according to EORTC QLQ-C30 and LSQ (Life Satisfaction Questionnaire), measured at admission, after 1, 3, 6, 12 months and after 5 years.

Most important results

Within the group that received anthroposophic treatment, including Iscador, there were improvements (analyzable: n = 21) with respect to quality of life measured by EORTC QLQ-C30 during the whole treatment period. In particular, the improvements were significant within four functional scales (emotional functioning, cognitive functioning, social functioning, global quality of life) and four symptom scales (fatigue, nausea/vomiting, pain, dyspnoea). With respect to LSQ there were improvements in four factors (physical symptoms, sickness impact, quality of daily activities, socioeconomic situation) and in the overall score. In both scales, the highest improvements showed up during the first year.

In both scales, further improvements did not show up during the following years. Within the group that received only conventional treatment (analyzable: n = 23), with the exception of one factor from LSQ, no improvements were detected.

The difference in overall 5-year survival between the Iscador and the control group was not significant.

Grossarth-Maticek R., Ziegler R. (2006a) Prospective controlled cohort studies on long-term therapy of breast cancer patients with a mistletoe preparation (Iscador). *Forschende Komplementärmedizin* 13 (5), 285–292.

Study design

Design	(1) Randomised, prospective long-term, matched-pair technique.
	(2) Prospective epidemiological long-term cohort study, matched-pair technique.
Patienta	(1) *MammaRand:* 2 × 38 primary breast cancer patients.
	(2) *Mamma:* 2 × 84 primary breast cancer patients.
Treatment	The patients in the Iscador group received in addition to conventional cancer treatment an individual therapy with different doses and types of s.c. applied Iscador. The control group with matched patients received only conventional cancer treatment and did not receive any type of mistletoe treatment.
Length of study	1971 – 1998.
Measurement	Self-regulation (Score 1 to 6) according to Grossarth-Maticek measured using questionnaires with graded answers.

Most important results

The self-regulation index is a measurement of individual activity to achieve well-being, inner balance, adapted motivation, a feeling of competence and safety and overcoming of stress situations.

(1) *MammaRand:* Improvement of self-regulation within 12 months, with the median of differences (based on pairwise differences between Iscador and control patients) of 0.35 score-points and a 95% confidence interval of 0.05 – 0.60 (p = 0.034).

(2) *Mamma:* Improvement of self-regulation within 12 months, with the median of differences (based on pairwise differences between Iscador and control patients) of 0.30 score-points and a 95% confidence interval of 0.05 – 0.60 (p = 0.014) for the strictly matched subset (24 pairs). The corresponding results for the complete set (83 pairs, 1 missing value) are: 0.20 (0.00 – 0.35), p = 0.031.

For results of this study concerning survival see 5.2.8.

Grossarth-Maticek R., Kiene H., Baumgartner S.M., Ziegler R. (2001a) Use of Iscador, an extract of European mistletoe (*Viscum album*), in cancer treatment: prospective nonrandomized and randomized matched-pair studies nested within a cohort study. *Alternative Therapies* 7 (3), 57–78.

Grossarth-Maticek R., Ziegler R. (2006b) Randomised and non-randomised prospective controlled cohort studies in matched pair design for the long-term therapy of breast cancer patients with a mistletoe preparation (Iscador): A re-analysis. *European Journal of Medical Research* 11 (11): 485–495.

Study design

Design	Randomised, prospective long-term, matched-pair technique.
Patients	17 matched pairs of breast cancer patients with lymphatic metastases, but without distant metastases.
Treatment	The patients in the Iscador group received in addition to conventional cancer treatment an individual therapy with different doses and types of s.c. applied Iscador. The control group with matched patients received only conventional cancer treatment and did not receive any type of mistletoe treatment.
Length of study	1971 – 1998.
Measurements	Self-regulation (Score 1 to 6) according to Grossarth-Maticek measured using questionnaires with graded answers.

Most important results

The self-regulation index is a measurement of individual activity to achieve well-being, inner balance, adapted motivation, a feeling of competence and safety and overcoming of stress situations.

In this randomised matched pair study with 17 pairs of breast cancer patients, the suggestion to use Iscador treatment was implemented for one partner of each pair after pairwise randomization. After 3 months of Iscador treatment, self-regulation improved on average from 2.92 to 3.70 (+ 0.78), and in the control group from 2.87 to 2.99 (+ 0.12). The estimate for the variation of self-regulation in the Iscador group, measured by the median of pairwise differences, yielded 0.90 with the 95% confidence interval 0.00 – 1.75. This variation missed significance marginally in favour of the Iscador group ($p = 0.055$).

For results of this study concerning quality of life see also 3.1.6.1 and for survival see 5.2.5.

Loewe-Mesch A., Kuehn J. J., Borho K., Abel U., Bauer C., Gerhard I., Schneeweiss A, Sohn C., Strowitzki T., Von Hagens C. (2008) Adjuvante simultane Mistel-/Chemotherapie bei Mammakarzinom – Einfluss auf Immunparameter, Lebensqualität und Verträglichkeit. [Simultaneous Adjuvant Treatment with Mistletoe during Chemotherapy for Breast Cancer – Influence on Immune Parameters, Quality of Life and Tolerability.] *Forschende Komplementärmedizin* 15, 22–30.

Study design

Design	Prospective, open, 2-arm non-randomised feasibility study.
Patients	66 primary breast cancer patients after surgery, with adjuvant chemotherapy with CMF or EC.
Treatment	33 patients were treated by their own will with Iscador M 5 mg pezial, complementary with adjuvant chemotherapy. The 33 patients from the control group were treated only with chemotherapy.
Length of study	Recruitment May 1999 – August 2001, Follow-up until 2002.
Measurements	Quality of life according EORTC QLQ-C30 and QLQ-BR23.

Most important results

A significant smaller impairment due to side effects of chemotherapy (in particular with respect to the symptom scales nausea and vomiting from the EORTC QLQ-C30, $p = 0.02$) brought some improvement in the quality of life. In addition, systemic side effects (EORTC QLQ-BR23) were significant smaller ($p = 0.02$). The remaining symptom scales showed a beneficial tendency for the Iscador group.

For results of this study concerning safety and tolerance see 6.1.3.

Tröger W., Jezdić S., Ždrale Z., Tišma N., Hamre H., Matijašević M. (2009) Quality of life and neutropenia in patients with early stage breast cancer: a randomized pilot study comparing additional treatment with mistletoe extract to chemotherapy alone. Breast Cancer: Basic and Clinical Research 3, 35–45.

Study design

Design	Randomised, open, 3-arm pilot study
Patients	95 primary breast cancer patients after surgery and with adjuvant chemotherapy.
Treatment	30 patients received in addition to conventional therapies Iscador M spezial and 34 patients received in addition Helixor. The 31 patients from the control group were treated only conventionally.
Length of study	Recruitment December 2005 – February 2007.
Measurements	Quality of life according to EORTC QLQ-C30, incidence of neutropenia: neutrophil granulocytes < 1000µl within the peripheral blood.
Analysis	Only control group vs. Iscador group.

Most important results

The descriptive analysis showed in all 15 symptom scores of quality of life from the EORTC QLQ-C30 improvements; 12 scores were significant ($p < 0.02$); for 9 scores these differences were clinical relevant (difference at least 5 score points).

Neutropenia was found in 3 cases within the Iscador group and in 8 cases within the control group ($p = 0.182$).

For the 5-year follow-up of this study see 5.2.9.

3.1.3 Gastrointestinal Cancer

References

☆ Tröger W., Galun D., Reif M., Schumann A., Stanković N., Milićević M. (2014) Lebensqualität von Patienten mit fortgeschrittenem Pankreaskarzinom unter Misteltherapie. Deutsches Ärzteblatt 2014; 111 (29–30): 493–502. DOI: 10.3238/arztebl.2014.0493.

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Tröger W., Galun D., Reif M., Schumann A., Stanković N., Milićević M. (2014) Quality of Life of Patients With Advanced Pancreatic Cancer During Treatment With Mistletoe: A randomized controlled trial. Deutsches Ärzteblatt 2014; 111 (29–30): 493–502. DOI: 10.3238/arztebl.2014.0493.

Study design

Design	Randomised, open label, group sequential, clinical phase III trial.
Centre	HPB Surgical Department, First Surgical Department, Clinical Centre of Serbia, Belgrade.
Patients	220 patients with locally advanced or metastatic adenocarcinoma of the pancreas with best supportive care.
Treatment	Iscador Qu special, three times a week or no antineoplastic therapy (control).
Recruitment	January 2009 until December 2010.
Measurements	12-month overall survival (OS), QoL dimensions from the EORTC Questionnaire.

Summary: Quality of Life

Background: The treatment of cancer patients with mistletoe extract is said to prolong their survival and, above all, improve their quality of life. We studied whether the quality of life of patients with advanced pancreatic cancer could be improved by mistletoe extract.

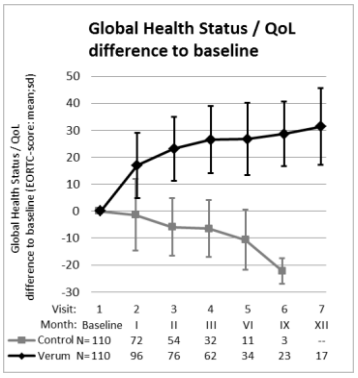
Method: An open, single-center, group-sequential, randomized phase III trial (ISRCTN70760582) was conducted. From January 2009 to December 2010, 220 patients with locally advanced or metastatic pancreatic cancer who were receiving no further treatment for pancreatic cancer other than best supportive care were included in this trial. They were stratified by prognosis and randomly allocated either to a group that received mistletoe treatment or to one that did not. Mistletoe extract was given in escalating doses by subcutaneous injection three times a week. The planned interim evaluation of data from 220 patients indicated that mistletoe treatment was associated with longer overall survival, and the trial was terminated prematurely. After termination of the study, the results with respect to quality of life (assessed with the QLO-C30 scales of the European Organisation for Research and Treatment of Cancer) and trends in body weight were evaluated.

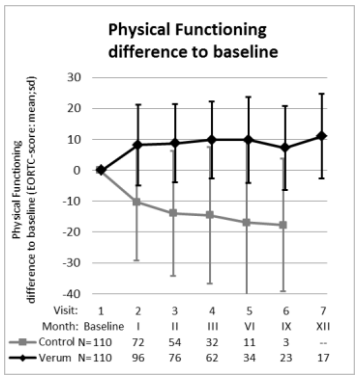
Results: Data on quality of life and body weight were obtained from 96 patients treated with mistletoe and 72 control patients. Those treated with mistletoe did better on all 6 functional scales and on 7 of 9 symptom scales, including pain (95% confidence interval [CI] −29 to –17), fatigue (95% CI –36.1 to –25.0), appetite loss (95% CI −51 to −36.7), and insomnia (95% CI –45.8 to –28.6). This is reflected by the trend in body weight during the trial.

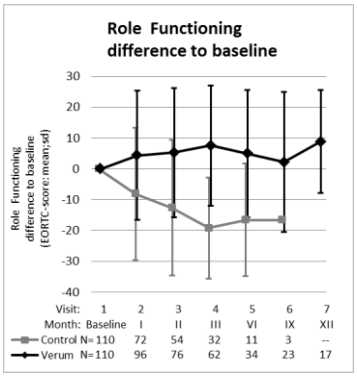
Conclusion: In patients with locally advanced or metastatic pancreatic carcinoma, mistletoe treatment significantly improves the quality of life in comparison to best supportive care alone. Mistletoe is an effective second-line treatment for this disease.

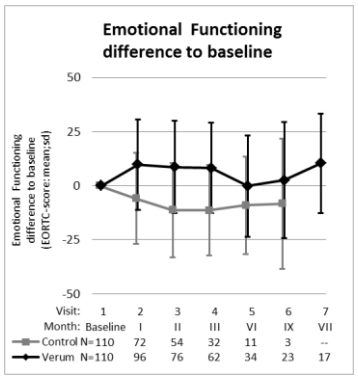
For results concerning body weight and disease related symptoms see 3.2.3.3 and for survival see 5.3.2.3.

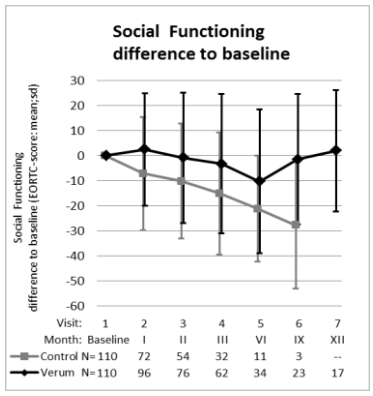
Fig. 1 (next page): Quality of life (QoL): EORTC QLQ-C30, differences to baseline (Verum = Iscador Qu special). Questionnaires were filled in at baseline and at months I, II, III, VI, IX, and XII. Baseline data were well balanced or worse (emotional functioning, financial impact) for the Iscador group; the graphs should be interpreted with caution due to the decreasing patient numbers.

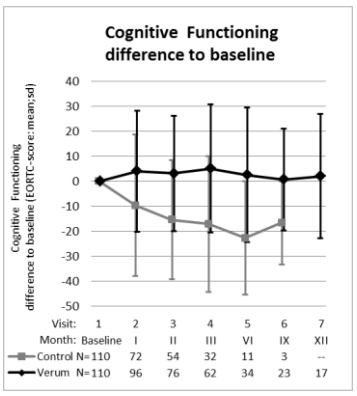


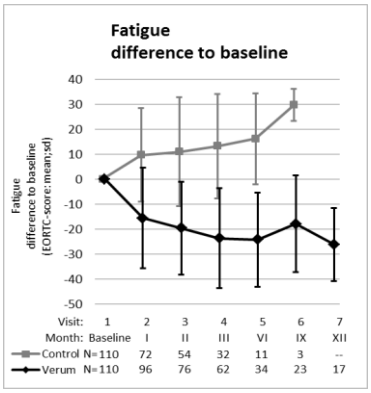


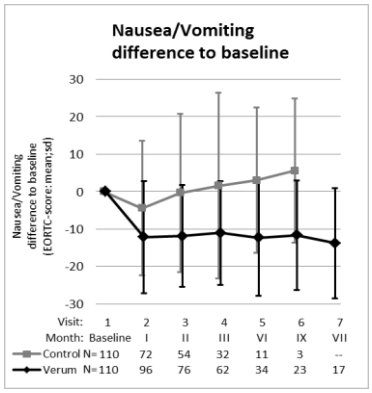


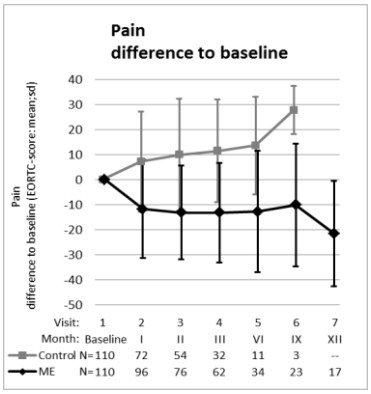


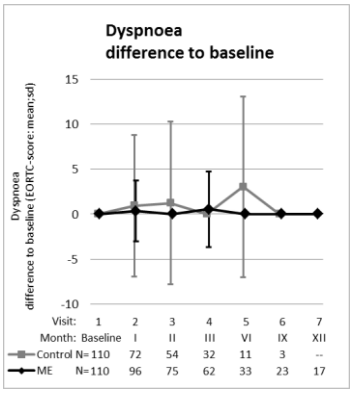


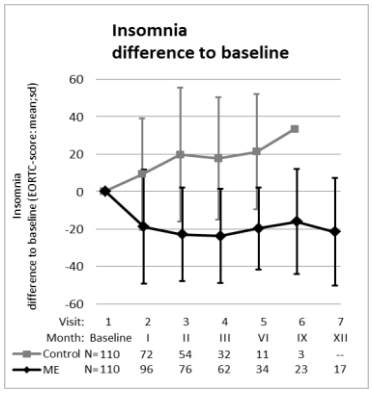


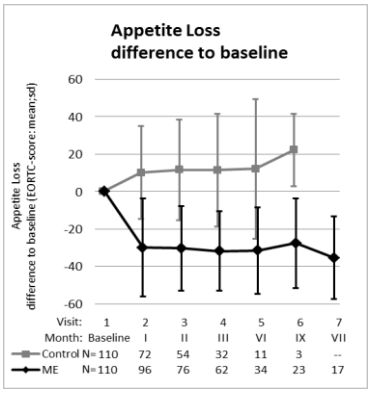


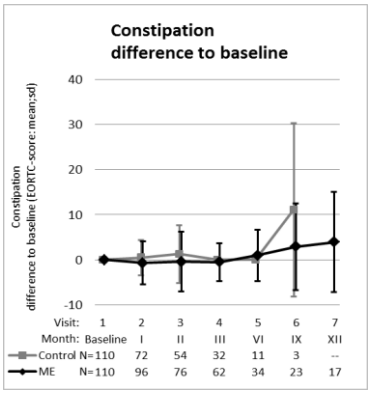


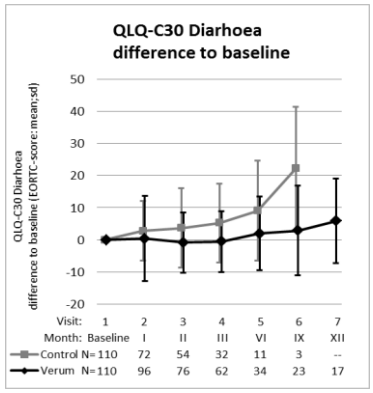


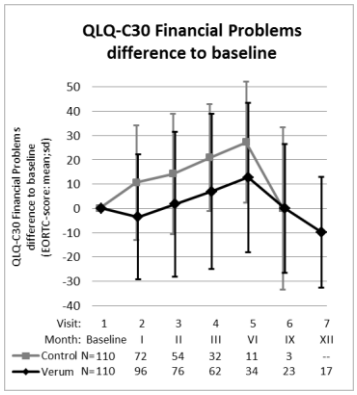












3.1.4 Cancer of the Respiratory Tract

References

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- Grah C., Matthes B., Happel H. (2010) Mistletoe therapy for non-small cell bronchial carcinoma. Der Merkurstab 63(6): 588.

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3.1.5 Melanoma

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The references marked with ☆ are included in abstract form in this documentation.

Grossarth-Maticek R., Ziegler R. (2007) Wirksamkeit und Unbedenklichkeit einer Langzeitbehandlung von Melanompatienten mit einem Mistelpräparat (Iscador). [Efficacy and Tolerance of a Long-term Treatment of Melanoma Cancer Patients with a Mistletoe Preparation (Iscador).] *Schweizerische Zeitschrift für GanzheitsMedizin* 19 (6), 325–332.

Study design

Design	Randomised, prospective long-term, matched-pair technique.
Patients	*MelanomRand:* 2 × 22 melanoma patients.
Treatment	The patients in the Iscador group received in addition to conventional cancer treatment an individual therapy with different doses and types of s.c. applied Iscador. The control group with matched patients received only conventional cancer treatment and did not receive any type of mistletoe treatment.
Length of study	1973 – 2001.
Measurements	Self-regulation (Score 1 to 6) according to Grossarth-Maticek measured using questionnaires with graded answers.

Most important results

The self-regulation index is a measurement of individual activity to achieve well-being, inner balance, adapted motivation, a feeling of competence and safety and overcoming of stress situations.

Improvement of self-regulation within 12 months, with the median of differences (based on pairwise differences between Iscador and control patients) of 0.55 score-points and a 95% confidence interval of 0.15 – 0.85 ($p = 0.0048$).

For results of this study concerning survival see 5.5.4.

3.1.6 Various Solid Tumours

References

- Clover A. et al. (1995) Complementary cancer therapy: a pilot study of patients, therapies and quality of life. Complementary Therapies in Medicine 3, 129–133.
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- ✯ Heusser P., Berger Braun S., Ziegler R., Bertschy M., Helwig S., Van Wegberg B., Cerny Th. (2006) Palliative in-patient cancer treatment in an anthroposophic hospital: I. Treatment patterns and compliance with anthroposophic medicine. Forschende Komplementärmedizin 13 (2): 94–100.
- ✯ Heusser P., Berger Braun S., Bertschy M., Burkhard R., Ziegler R., Helwig S., Van Wegberg B., Cerny Th. (2006) Palliative in-patient cancer treatment in an anthroposophic hospital: II. Quality of live during and after stationary treatment, and subjective treatment benefits. Forschende Komplementärmedizin 13 (3): 156–166.
- Brandenberger M., Simões-Wüst A. P. H., Rostock M., Rist L., Saller R. (2011) An exploratory study on the quality of life and individual coping of cancer patients during mistletoe therapy. Integrative Cancer Therapies 11(2): 90–100.

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Grossarth-Maticek R., Kiene H., Baumgartner S.M., Ziegler R. (2001a) Use of Iscador, an extract of European mistletoe (*Viscum album*), in cancer treatment: prospective nonrandomized and randomized matched-pair studies nested within a cohort study. *Alternative Therapies* 7 (3), 57–78.

Study design

Design	Randomised, prospective long-term, matched-pair technique.
Patients	56 matched pairs of patients with different tumours (17 pairs: breast cancer with lymphatic metastases and no distant metastases; 39 pairs: various solid tumours).
Treatment	The patients in the Iscador group received in addition to conventional cancer treatment an individual therapy with different doses and types of s.c. applied Iscador. The control group with matched patients received only conventional cancer treatment and did not receive any type of mistletoe treatment.
Length of study	1973 – 1998.
Measurement	Self-regulation (Score 1 to 6) according to Grossarth-Maticek measured using questionnaires with graded answers.

Most important results

The self-regulation index is a measurement of individual activity to achieve well-being, inner balance, adapted motivation, a feeling of competence and safety and overcoming of stress situations.

Two separately studied matched-pair groups (39 and 17 pairs), in which the Iscador treatment was prospectively randomly recommended to one partner of the pair, showed an increase in the values for self-regulation after a 3-month treatment with Iscador from 3.41 to 3.87 and 2.92 to 3.70 respectively, whereas the values in the control group sank from 3.85 to 3.62 respectively increased only marginally from 2.87 to 2.99. The change in the value for self-regulation for the Iscador group was significantly different to that of the control group (56 pairs, p = 0005).

For results of this study concerning quality of life see also 3.1.2.4 and for survival see 5.2.5, 5.6.1.

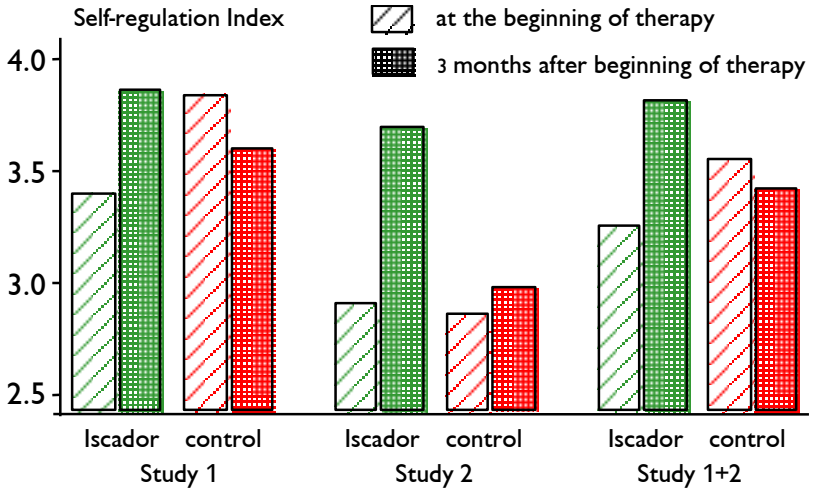

Fig. 1: Changes in the values for the self-regulation index for tumour patients due to a 3-month treatment with Iscador in comparison to matched control patients without Iscador (Study 1: 39 matched pairs, Study 2: 17 matched pairs) (according to Grossarth-Maticek et al. 2001a).

Heusser P. et al. (2006) Palliative in-patient cancer treatment in an anthroposophic hospital: Part I / Part II. *Forschende Komplementärmedizin* 13 (2): 94–100, 13 (3): 156–166.

Study design

Design	1-arm, prospective, longitudinal study concerning quality of life (QoL) of cancer patients before, during and after treatment in an anthroposophic clinic in Switzerland (Lukas Klinik, LK).
Patients	144 in-patients with advanced epithelial cancers. Assessment of tumour-related therapy patterns 4 months prior to admission, during stationary treatment (3 weeks on average) and 4 months after baseline. Assessment of QoL at admission, hospital discharge and 4 months after hospitalisation.
Treatment	Anthroposophic treatment starting at LK consisted of Iscador, other medicaments from plants or minerals given as injections, orally or external applications, baths, massage, therapeutic eurythmy, art therapy (e.g. painting, music), counselling and lactovegetarian diet. They were applied in addition to already started or finished conventional cancer treatments. At month 4, the subjectively perceived benefit from anthroposophic therapies at LK and from conventional cancer therapy was assessed retrospectively by telephone inteview.
Length of study	1995 – 1998.
Measurements	Medical and socio-demographic baseline data, conventional cancer treatments, anthroposophic treatments, treatment compliance, quality of life (EORTC, QLQ-C30, HADS, SELT-M).

Most important results

As compared to before admission, at LK some conventional treatments appeared reduced, and after discharge either reascended again (chemotherapy, radiotherapy, sleeping drugs, psychoactive drugs), or remained constant (pain medication WHO I and II). Other treatments remained about the same for all three periods: hormone therapy, corticosteroids, pain medication WHO III (opiates), antidepressants. As for anthroposophic treatment starting at LK compliance after discharge was highest with Iscador (90%), lowest with art therapy (14%); many patients remained primarily in the care of AM physicians. Compliance with anthroposophic therapies remained high and the use of other complementary therapies (CAM) low.

From admission to discharge, QoL improvements were observed in all 20 dimensions, 12 of which were significant. This concerned global health status/QoL, 5 of 11 physical, all of 4 emotional, both of 2 cognitive-spiritual and 1 of 2 social dimensions. In the context of related studies, the improvements appear fairly high. After discharge, at month 4, QoL scores had decreased again, but in all 20 dimensions they were still above baseline levels, in 10 dimensions significant.

Retrospectively, both, anthroposophic therapy at LK and conventional cancer treatment were perceived as beneficial: anthroposophic treatment mainly through effects on physical recovery and well-being, emotional and cognitive-spiritual QoL, quality of human relations and care; conventional cancer treatment mainly through effects on the tumour with alleviation of symptoms and pain. Side effects were only indicated for conventional cancer treatment.

Conclusion

The data provide descriptive evidence that a comprehensive stationary therapy program at an anthroposophic hospital can lead to significant QoL improvements, especially in emotional, but also global, physical, cognitive-spiritual and social aspects of QoL dimensions. After 4 months, QoL was still above baseline. Benefits of anthroposophic therapies were experienced on the physical, emotional, cognitive-spiritual and relational level; benefits of conventional cancer treatment were more tumour focused.

(3.1.7 Lymphomas and Leukaemias)

No studies available

(3.1.8 Endocrine Tumours)

No studies available

(3.1.9 Central Nervous System Tumours)

No studies available

(3.1.10 Sarcomas)

No studies available

3.2 Pain, Fatigue and Disease Symptoms

(3.2.1 Genitourinary Cancer)

3.2.2 Breast Cancer

3.2.3 Gastrointestinal Cancer

3.2.4 Cancer of the Respiratory Tract

(3.2.5 Melanoma)

3.2.6 Various Solid Tumours

(3.2.7 Lymphomas and Leukaemias)

(3.2.8 Endocrine Tumours)

(3.2.9 Central Nervous System Tumours)

(3.2.10 Sarcomas)

(3.2.1 Genitourinary Cancers)

No studies available

3.2.2 Breast Cancer

References

- ☆ Bock P. R., Friedel W. E., Hanisch J., Karasmann M., Schneider B. (2004) Wirksamkeit und Sicherheit der komplementären Langzeitbehandlung mit einem standardisierten Extrakt aus Europäischer Mistel (Viscum album L.) zusätzlich zur konventionellen adjuvanten onkologischen Therapie bei primärem, nicht metastasiertem Mammakarzinom. Ergebnisse einer multizentrischen, komparativen, retrolektiven, epidemiologischen Kohortenstudie in Deutschland und der Schweiz. Arzneimittel-Forschung/Drug Research 54 (8): 456–466.
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Bock P. R., Friedel W. E., Hanisch J., Karasmann M., Schneider B. (2004) Wirksamkeit und Sicherheit der komplementären Langzeitbehandlung mit einem standardisierten Extrakt aus Europäischer Mistel (*Viscum album* L.) zusätzlich zur konventionellen adjuvanten onkologischen Therapie bei primärem, nicht metastasiertem Mammakarzinom. [Efficacy and Safety of Long-term Complementary Treatment with Standardised European Mistletoe Extract (*Viscum album* L.) in Addition to the Conventional Adjuvant Oncological Therapy in Patients with Primary Non-metastatic Breast Cancer.] *Arzneimittel-Forschung/Drug Research* 54 (8): 456–466.

Study design

Design	Cohort study with retrospective collection of data («retrolective Study»).
Centres	16 centres in Germany and Switzerland.
Patients	1442 patients with primary breast cancer, without metastases, with conventional basic therapy (surgery, radiotherapy, chemotherapy), 710 of which received additional Iscador therapy (treatment group), 732 only received conventional basic therapy (control group).
Comparability	The patients in the treatment group were more seriously ill and had more pronounced risk factors for progression.
Treatment	Median length of observation during aftercare: 66 months (treatment group), 60 months (control group). 156 patients (22%) were in the treatment group and the 42 patients (6%) in the control group did not receive any conventional therapy.
Length of study	1988 – 2000.
Measurements	Primary (efficacy): Frequency of side-effects from conventional therapy (adverse drug reactions, ADR); symptoms due to illness and therapy, tumour-related and overall survival. Secondary (safety): Frequency and level of severity of adverse drug effects due to Iscador therapy, possible tumour enhancement.

Most important results

There was a significant difference between the groups regarding the frequency of side-effects (adverse drug reactions, ADR) due to the conventional therapy (fig. 1). 152 adverse drug effects, which were related to the conventional therapy, were recorded in 112 patients in the Iscador group (16% of the whole, 20% of those who received conventional therapy). 780 adverse drug effects, which were related to the conventional therapy, were recorded in 395 patients in the control group (54% of the whole, 57% of those who received conventional therapy). The ADR-rate in the Iscador group was therefore considerable and statistically significantly lower than in the control group. A sub-group analysis, which was intended according to the protocol, showed that this effect in patients with or without Iscador therapy, who had only received either radiotherapy, chemotherapy or a combined therapy, was similarly pronounced.

For results of this study concerning survival see 5.2.7 and concerning safety and tolerance see 6.1.1.

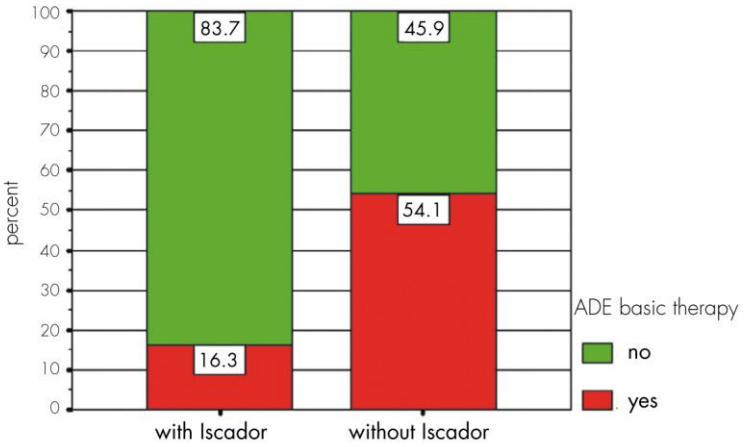

Fig. 1: Frequency of side-effects (adverse drug reactions, ADE = ADR) from conventional basis therapy, raw data: 152 ADR in 112 Iscador patients vs. 780 ADR in 395 control patients. Multivariate analysis: Proportion of the patients with ADR from conventional therapy: adjusted odds ration OR = 0.47 (95% confidence interval 0.32 – 0.67), $p < 0.0001$ (according to Bock et al. 2004).

The effectiveness regarding symptoms due to illness and therapy were studied as secondary parameters, to determine whether the symptoms occurring at the beginning of aftercare were still apparent at the end of aftercare. The respective symptoms are listed in Fig. 2. The adjusted relative quotas (odds ratio) for freedom from symptoms between the Iscador group and the control group are shown with their 95% confidence interval. The estimated values show a value larger than 1 in all symptoms. This means that the quota of patients without symptoms in the Iscador group is larger than that of the control group at the end of aftercare. The confidence interval is greater than 1 for many of the symptoms, which shows a significantly higher quota of patients in the Iscador group who were free of symptoms.

The frequency of symptoms, of all types, could therefore be significantly reduced during the course of aftercare due to additional therapy with Iscador.

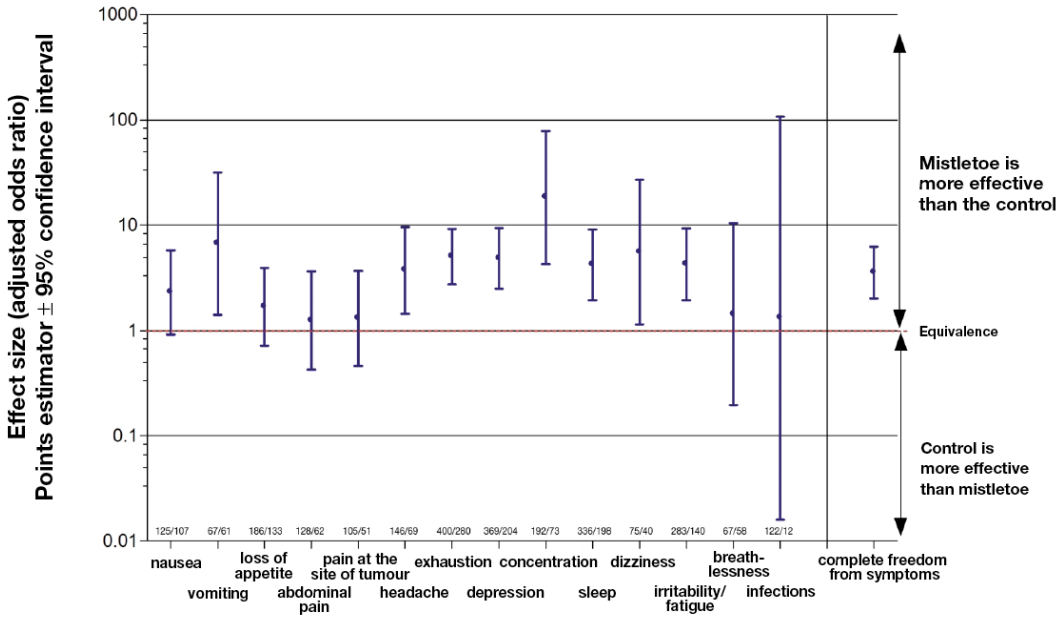

Fig. 2: Symptoms due to illness and therapy. Multivariate analysis of symptom frequencies: adjusted relative quota (odds ratio) and 95% confidence interval for complete recovery (cure) from each symptom present at the beginning of aftercare by the end of aftercare (according to Bock et al. 2004).

3.2.3 Gastrointestinal Cancer

References

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Study design

Design	Cohort study with retrospective collection of data («retrolective Study»).
Centres	26 centres in Germany and Switzerland.
Patients	804 patients with colorectal cancer without metastases, with conventional basic therapy (surgery, radiotherapy, chemotherapy), 429 of which received additional Iscador therapy (treatment group), 375 only received conventional basic therapy (control group).
Comparability	The patients in the treatment group were younger, more advanced disease with more symptoms but less comorbidity.
Treatment	Median length of observation during aftercare: 58 months (treatment group), 51 months (control group). Median length of Iscador treatment: 52 months.
Length of study	1990 – 2004.
Measurements	Efficacy: (1) rate and adjusted risk of documented AT-ADRs (adjuvant therapy-related adverse drug reactions), assessed by adapting the National Institutes of Health Common Toxicity Criteria (CTC) in oncology; (2) predefined QoL surrogate criteria adapted from the symptom scales of the EORTC QLQ-C30 questionnaire, consisting of rate and adjusted risk of persistence of prespecified disease- and treatment-associated symptoms, particularly pain, skin, mucosal, gastrointestinal, and CNS symptoms; and (3) adjusted disease-free survival (DFS) calculated by the Cox proportional hazard regression method. Safety: Number of patients with documented systemic and local ADRs attributed to the Iscador therapy. The number and severity of ADRs were evaluated according to CTC. Any evidence of possible tumour enhancement in the Iscador group was also documented.

Most important results

Among the 443 patients treated with adjuvant therapy, significantly fewer in the Iscador group than in the control group experienced AT-ADR (incidence rate 19.1% vs. 48.3%, $p < 0.001$) (Figure 1). Particularly common AT-ADR had a lower absolute incidence in the Iscador group, such as diarrhoea (20 vs. 47), nausea (8 vs. 42), loss of appetite (1 vs. 22), dermatitis (1 vs. 13), fatigue (1 vs. 9), and mucositis (2 vs. 8). The adjusted odds ratio (OR) estimating the risk (odds) of developing any AT-ADR during the therapy was lower by 54% in the Iscador group than in the control group (OR [95% CI] = 0.46 [0.28–0.77]), $p = 0.003$). This difference is significant and clinically relevant.

For results of this study concerning survival see 5.3.3.4 und concerning safety and tolerance see 6.1.4. For the results of a subgroup analysis concerning Iscador Qu see 3.2.3.4 (disease- and therapy-induced symptoms) and 5.3.3.5 (disease-free survival).

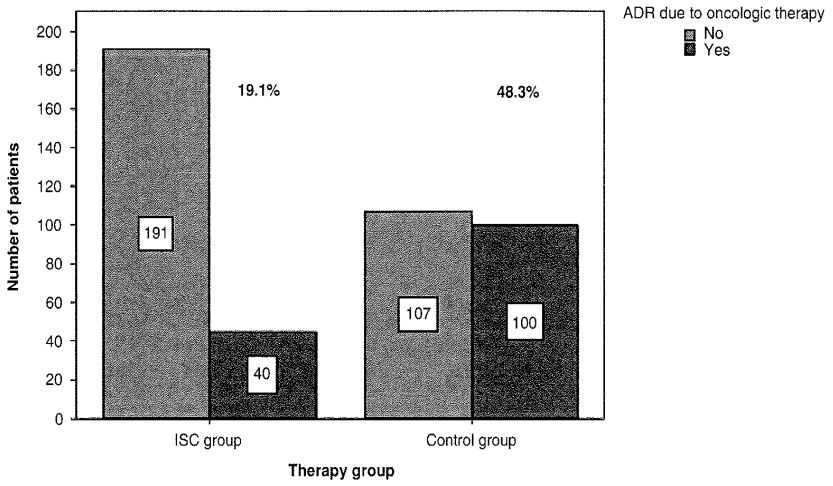


Fig. 1: Adjuvant therapy adverse reaction (ADR) incidence and adjusted odds ratio (OR) in the mistletoe extract Iscador (ISC) versus the control group (incidence calculated in contingency tables using the Fisher exact test; adjusted OR calculated by logistic regression with the Wald test; according to Friedel et al. 2009).

Symptom persistence risk estimates adjusted for single symptom persistence and total symptom score calculated by logistic regression and Wald test (Fig. 2). The x-axis nominates the singly symptoms and the total number of patients and percentages who experienced the different symptoms. The logarithmic y-axis denominates the multi-variable adjusted odds ratios (OR). OR > 1 means treatment in the control group is more effective, OR < 1 means the Iscador group is superior. The bars show the 95% confidence intervals of OR and the statistical significance is listed (p-values) above.

Significantly fewer patients in the Iscador than in the control group showed a persistence of individual symptoms at the end of adjuvant therapy (AT) (after a mean AT duration of 8 months in both groups) or conventional aftercare. The adjusted total symptom status (TSS), that is, status not free of any persisting symptom, revealed an OR of 0.30, $p < 0.001$. Particularly, the gastrointestinal and CNS symptoms, mucositis, and TSS showed consistently better results in the Iscador group during and after the therapy course (Fig. 2).

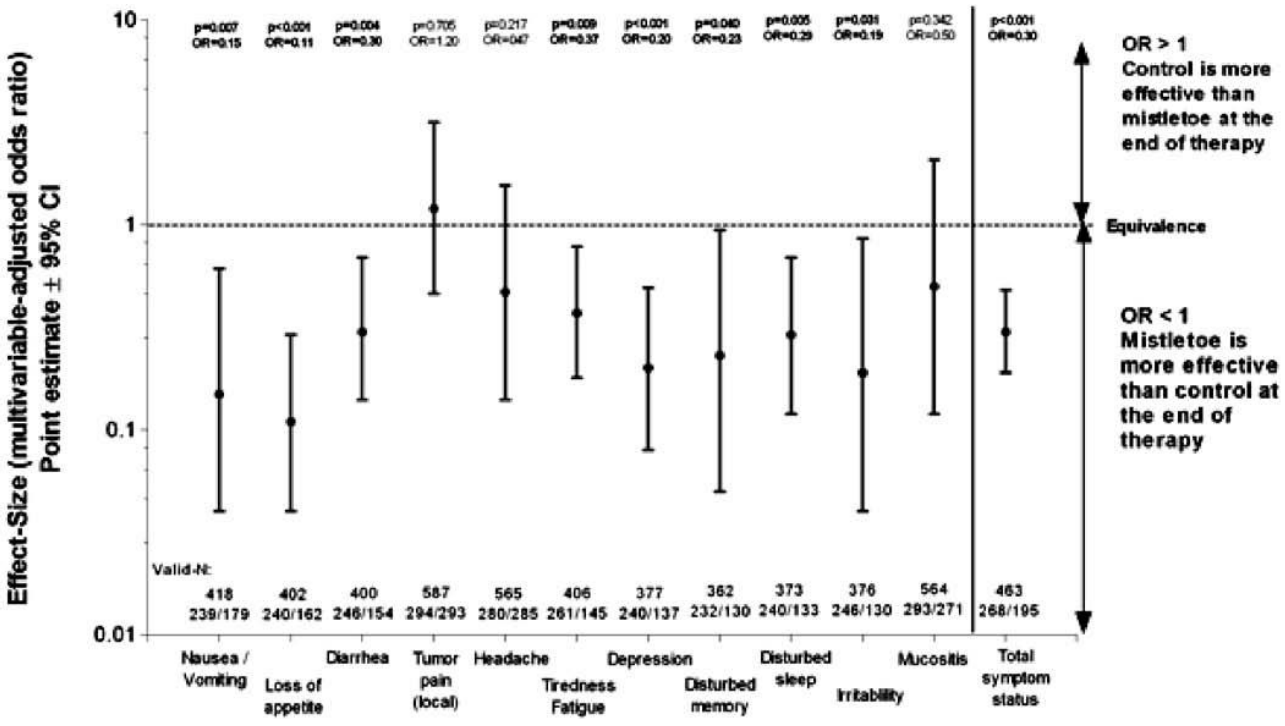


Fig. 2: Symptom persistence odds ratio (OR) in the mistletoe extract Iscador group versus the control group; adjusted OR for single symptom persistence; and total symptom status, that is, persistence of any symptom, calculated by logistic regression and Wald test. Bars = 95% confidence interval (CI) of OR; points = OR point estimate (according to Friedel et al. 2009).

Matthes H., Friedel W. E., Bock P. R., Zänker K. S. (2010) Molecular Mistletoe Therapy: Friend or Foe in Established Anti-Tumor Protocols? A Multicenter, Controlled, Retrospective Pharmaco-Epidemiological Study in Pancreas Cancer. Current Molecular Medicine 10(4): 430–439.

Study design

Design	Cohort study with retrospective collection of data («retrolective Study»).
Centres	17 centres in Germany and Switzerland.
Patients	396 patients with histologically verified pancreatic tumour who had macroscopic complete resection and not prior radiation or neoadjuvant chemotherapy were eligible for the study. 201 of which received additional Iscador therapy (ISC = treatment group), 195 only received conventional basic therapy (control group).
Comparability	Within the overall control group (chemotherapy without ISC but with/without best of care) more patients were at high risk (T3/T4) tumour stage: 71.3% of the patients), but less patients in this group had regional lymphnode involvement (37.4% vs. 66.7%); most of the patients in the chemotherapy/ISC group had extended disease in respect to tumour size (more than 2 cm in diameter) involving extrapancreatic structures.
Treatment	Median length of observation during aftercare: 15.2 months (treatment group), 10.1 months (control group). Median/mean length of Iscador treatment: 15.0/20.5 months.
Length of study	Diagnosis time from 1993 – 2002.
Measurements	Efficacy: (1) rate and adjusted risk of documented AT-ADR (adjuvant therapy-related adverse drug reactions), assessed by adapting the National Institutes of Health Common Toxicity Criteria (CTC) in oncology; (2) predefined QoL surrogate criteria adapted from the symptom scales of the EORTC QLQ-C30 questionnaire, consisting of rate and adjusted risk of persistence of prespecified disease- and treatment-associated symptoms, particularly pain, skin, mucosal, gastrointestinal, and CNS symptoms; (3) adjusted overall survival (OS). Safety: Number of patients with documented systemic and local ADRs attributed to the Iscador therapy. Any evidence of possible tumour enhancement in the Iscador group was also documented.

Most important results

Among the patients treated with adjuvant therapy, significantly fewer in the Iscador group than in the control group experienced AT-ADR (Figure 1). The incidence was 13.7% vrs. 48.9% with $p < 0.001$. The adjusted odds ratio (OR) estimating the risk (odds) of developing any AT-ADR during the therapy was lower by 74% in the Iscador group than in the control group (OR [95% CI] = 0.26 [0.12–0.61]), $p = 0.001$). This difference is significant and clinically relevant.

For results of this study concerning survival see 5.3.2.2 und concerning safety and tolerance see 6.1.5.

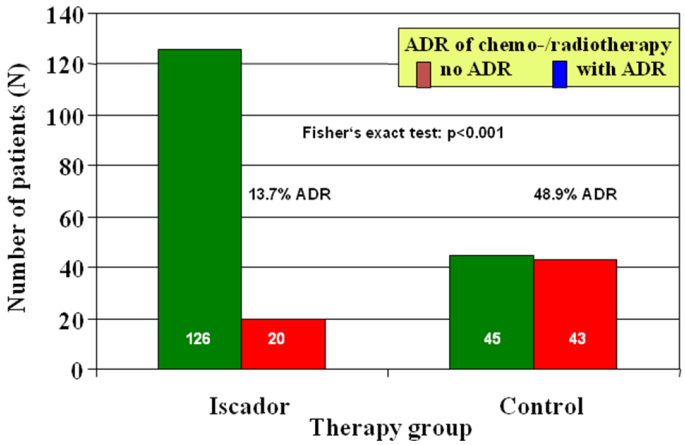


Fig. 1: Adjuvant therapy adverse reaction (ADR) incidence and adjusted odds ratio (OR) in the mistletoe extract Iscador (ISC) versus the control group; incidence calculated in contingency tables using the Fisher exact test; adjusted OR calculated by logistic regression with the Wald test (according to Matthes et al. 2010).

Symptom persistence risk estimates adjusted for single symptom persistence and total symptom score calculated by logistic regression and Wald test (Fig. 2). The x-axis nominates the singly symptoms and the total number of patients and percentages who experienced the different symptoms. The logarithmic y-axis denominates the multi-variable adjusted odds ratios (OR). OR > 1 means treatment in the control group is more effective, OR < 1 means the Iscador group is superior. The bars show the 95% confidence intervals of OR and the statistical significance is listed (p-values) above.

Significantly fewer patients in the Iscador than in the control group showed a persistence of individual symptoms at the end of adjuvant therapy (AT) (after a mean AT duration of 8 months in both groups) or conventional aftercare. The adjusted total symptom scale revealed an OR of 0.43, statistically not significant, but a prominent trend to more symptom-free patients in the ISC group (Fig. 2).

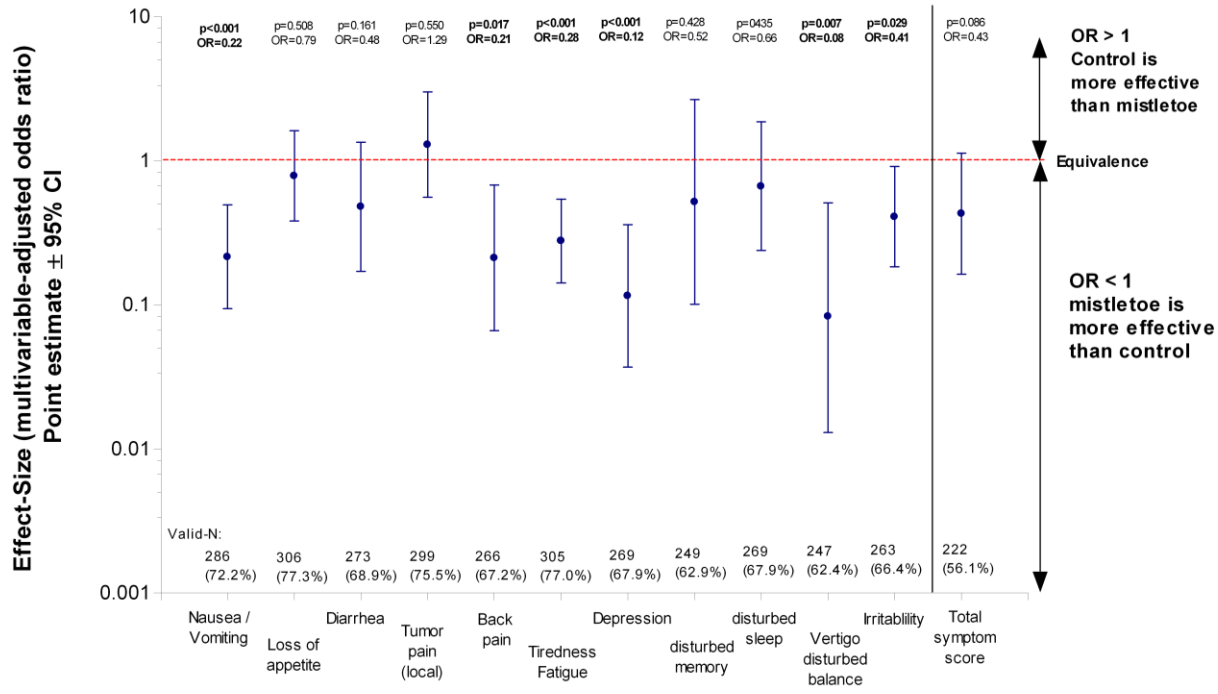


Fig. 2: Symptom persistence odds ratio (OR) in the mistletoe extract Iscador group versus the control group; adjusted OR for single symptom persistence; and total symptom status, that is, persistence of any symptom, calculated by logistic regression and Wald test. Bars = 95% confidence interval (CI) of OR; points = OR point estimate (according to Matthes et al. 2010).

Galun D., Tröger W., Reif M., Schumann A., Stanković N., Milićević M. (2012) Phase III trial on mistletoe extract versus no anti-neoplastic therapy in patients with inoperable locally advanced or metastatic pancreatic cancer. Annals of Oncology 2012, 23 (suppl. 9), ESMO Congress, Vienna, Austria, 28.09–02.10.2012, Abstract 712P.

Tröger W., Galun D., Reif M., Schumann A., Stanković N., Milićević M. (2014) Quality of Life of Patients With Advanced Pancreatic Cancer During Treatment With Mistletoe: A randomized controlled trial. Deutsches Ärzteblatt 2014; 111 (29–30): 493–502. DOI: 10.3238/arztebl.2014.0493.

Study design

Design	Randomised, open label, group sequential, clinical phase III trial.
Centre	HPB Surgical Department, First Surgical Department, Clinical Centre of Serbia, Belgrade.
Patients	220 patients with locally advanced or metastatic adenocarcinoma of the pancreas with best supportive care.
Treatment	Iscador Qu special, three times a week or no antineoplastic therapy (control).
Recruitment	January 2009 until December 2010.
Measurements	12-month overall survival, QoL dimensions from the EORTC Questionnaire.

Summary: Body weight, disease-related symptoms

Purpose: To compare body weight and disease-related symptoms of advanced pancreatic cancer patients receiving Iscador therapy or no antineoplastic therapy.

Patients and Methods: In this prospective, parallel, open label, monocenter, group-sequential, randomized phase III study patients with locally advanced or metastatic adenocarcinoma of the pancreas were stratified according to their prognosis index, a binary composite of age, tumor stage and performance status, and were evenly randomized to s.c. injections of Iscador Qu special in a dose-escalating manner from 0.01 mg up to 10 mg three times per week (n = 110), or no antineoplastic therapy (control, n = 110). All patients received best supportive care. Measure of body weight and disease-related symptoms.

Results: This first interim analysis includes data from 220 patients. Baseline characteristics were well balanced between the Iscador and control groups. Body weight showed converse trends during the course of studies; disease-related symptoms were significantly less/milder in the Iscador group. No Iscador-related serious or non-serious adverse events were observed.

Conclusion: In this analysis Iscador therapy showed a significant and clinically relevant increase of body weight and improvement of disease-related symptoms. The independent data monitoring committee recommended the termination of the trial due to proven efficacy. Iscador may provide an effective second-line therapy for patients with locally advanced or metastatic pancreatic cancer after failure of, or ineligibility for, first-line therapies.

For results concerning quality of life (QoL) see 3.1.3.1 (EORTC questionnaire) and for survival see 5.3.2.3.

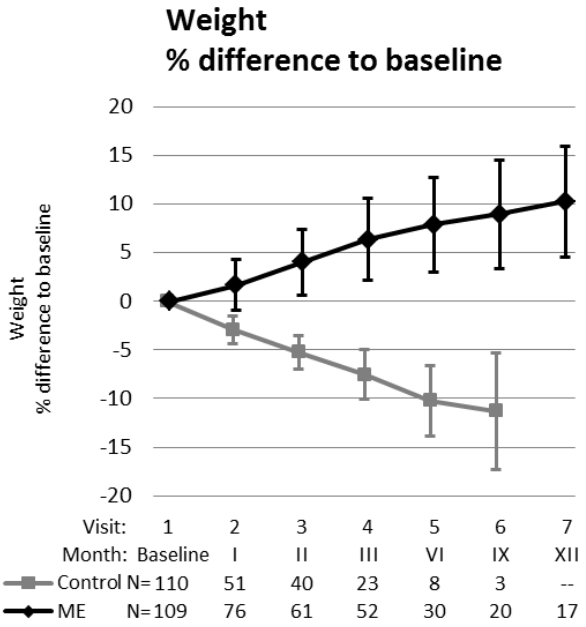


Fig. 1: Weight in percent differences to baseline. Both groups had a mean body weight of 69 kg at baseline.
ME = Iscador group.

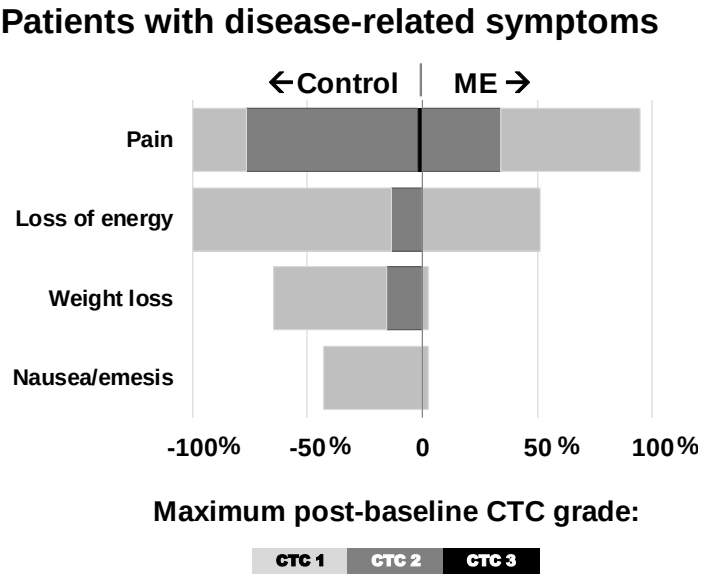


Fig. 2: Patients with disease-related symptoms.
ME = Iscador group.

Zänker K. S., Matthes H., Bock P. R., Hanisch J. (2012) A Specific Mistletoe Preparation (Iscador-Qu) in Colorectal Cancer (CRC) Patients: More than Just Supportive Care? Journal of Cancer Science and Therapy 4(9): 264–270.

Study design

Design	Original Study: Cohort study with retrospective collection of data («retrolective Study»).
Centres	Data base: 26 centres in Germany and Switzerland.
Patients	318 patients with colorectal cancer without metastases, with conventional basic therapy (surgery, radiotherapy, chemotherapy), 106 of which received additional Iscador Qu therapy (treatment group), 212 received conventional basic therapy (control group) only.
Treatment	Median length of observation: 59 months (treatment group), 43 months (control group). Median length of Iscador treatment: 54 months.
Study aim	Secondary and confirmatory analysis of the original data set from study 3.2.3.1/5.3.3.4 with respect to Iscador Qu concerning disease-free survival and disease- and therapy-induced symptoms.

Summary: Disease- and therapy-induced symptoms

Rationale: In the study 3.2.3.1 the results were reported from a pharmaco-epidemiological, retrospective observational cohort study in colorectal carcinoma (CRC) patients UICC stage I-III, receiving chemo- and/or radiotherapy together with Iscador as supportive care versus conventional treatment. The endpoints have been therapy-induced adverse effects and disease symptoms.

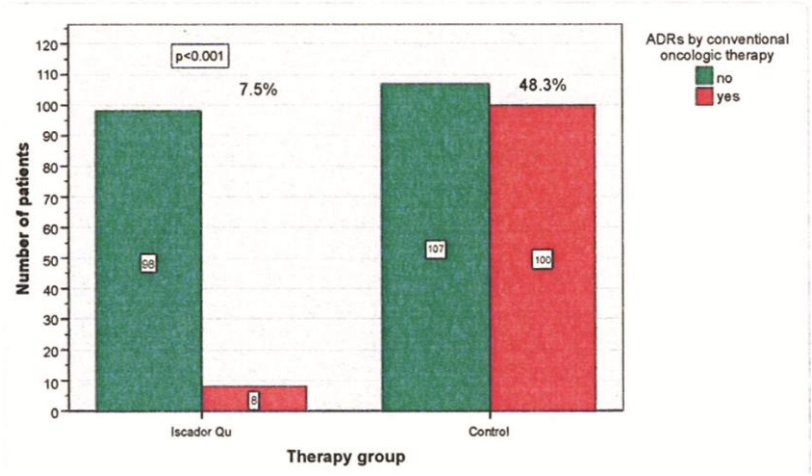
Objective: Secondary and confirmatory analysis with respect to Iscador Qu.

Results: Patients receiving Iscador Qu in a supportive care mode simultaneously with chemo- and/or radiotherapy (n = 106) showed a significant improvement in therapy induced adverse effects compared to conventionally treated patients (n = 212) (control). To make the analysis more robust, patients treated by the chemo- and/or radiotherapy protocols were also analyzed and stratified for the UICC I-III stages. Patients concomitantly treated by Iscador Qu showed fewer persisting disease- and therapy-induced symptoms.

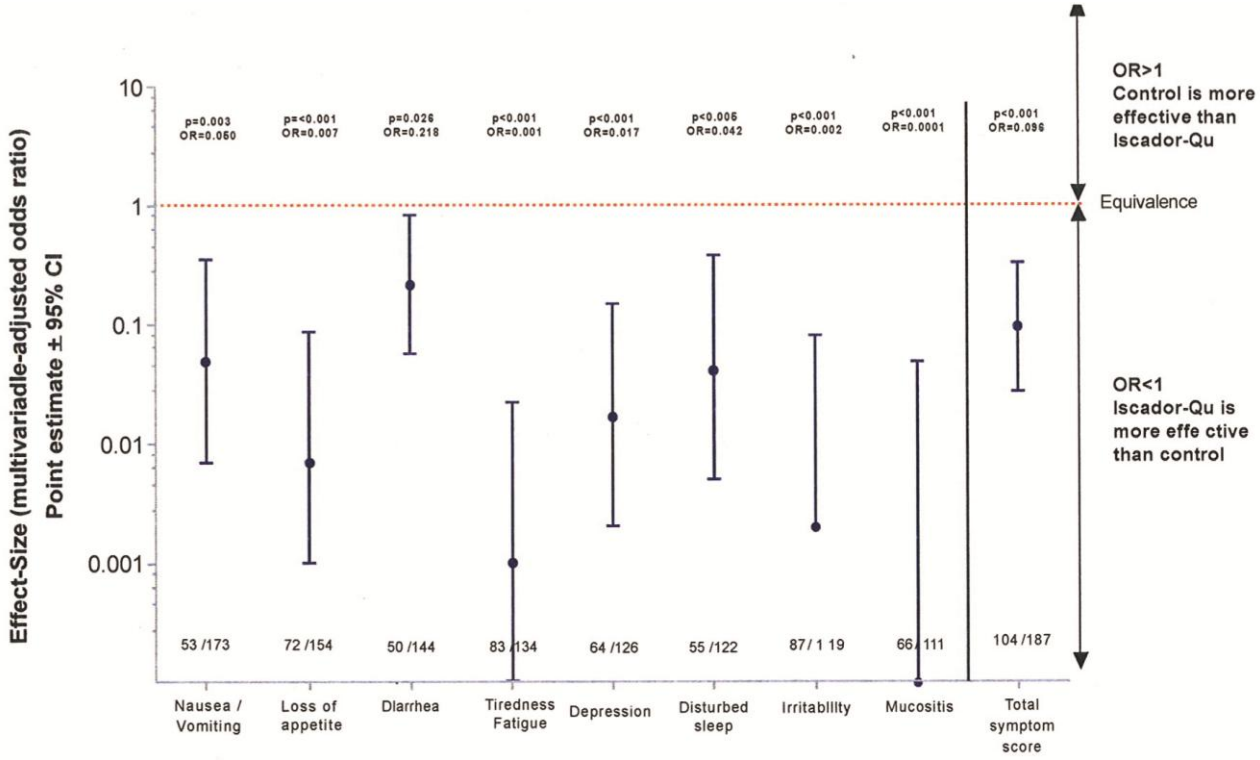
Clinical implication: This secondary analysis of the original data set suggests that Iscador Qu appears to be a naturally tailored molecular composition to target CRC patients by reducing therapy-related adverse effects and improving the cancer-related symptoms.

Limitations: The effects should be interpreted with some caution because the applied study design shares some potential risk for bias common to all non-randomized observational studies. However, potential biases were tried to minimize by systematic multivariable adjusting.

For the overall results of this study see 3.2.3.1 (disease- and therapy-induced symptoms), 5.3.3.4 (survival), 6.1.4 (safety and tolerance); for this subgroup analysis particularly concerning disease-free survival see 5.3.3.5.



Figur 1: Comparison of conventional treatment group obtaining supportive Iscador Qu care (left) with conventional therapy only (right) in respect to the number of patients with therapy-induced adverse reactions (ADR).
Green: without ADRs, Red: with ADRs.



Figur 2: Detailed symptom persistence analysis after a median 5 months therapy course. The horizontal axis nominates the single symptoms and the total number of patients evaluated with the different symptoms. The logarithmic vertical axis nominates the multivariable-adjusted odds ratio (OR). The dots show the OR point estimate and the bars the 95% confidence interval of OR.

Bock P. R., Hanisch, J., Matthes H., Zänker K. S. (2014) Targeting inflammation in cancer-related-fatigue: a rationale for mistletoe therapy as supportive care in colorectal cancer patients. Inflammation & Allergy – Drug Targets 13: 105–111.

Study design

Design	Original Study: Cohort study with retrospective collection of data («retrolective Study»), study 3.2.3.1.
Centres	Data base: 26 centres in Germany and Switzerland.
Patients	324 patients with colorectal cancer without metastases (stage I – III), with conventional basic therapy (surgery, radiotherapy, chemotherapy), 181 of which received additional Iscador Qu therapy (treatment group), 143 received conventional basic therapy (control group) only.
Treatment	Median length of treatment after chemo- and radiotherapy and with supportive mistletoe therapy Iscador Qu: 8.6 months.
Study aim	Secondary analysis of the original data set from study 3.2.3.1/5.3.3.4 with respect to Iscador Qu and cancer-related fatigue.

Summary

Background: The study 3.2.3.1 includes the results of a pharmaco-epidemiologic, retrospective observational cohort study with colorectal cancer patients (stage I – III). The patients received chemo- or radiochemotherapy either together with Iscador as supportive therapy or conventional therapy alone. The measurements included therapy-related side effects and disease-related symptoms. In this secondary analysis at hand cancer-related fatigue ist the main issue. – Cancer-related fatigue (CRF) affects a majority of patients with symptoms lasting up to several years after finishing therapy. These symptoms lead to decreased health related quality of life. Fatigue during treatment for colorectal cancer is common, but poorly understood and can affect compliance with post-surgical cancer therapy. We examined the fatigue levels during first-line chemo- or radiochemotherapy protocols, which were supported by a pharmaceutical mistletoe preparation (Iscador Qu) (181 patients). We compared the outcome to a parallel control group (143 patients), which did not receive this supportive care treatment.

Methods: The medical records of 324 patients with non-metastasized colorectal cancer (UICC stage I – III), which were obtained from hospitals and resident physicians, were assessed. The documented treatment decision by chemo- or radiochemotherapy supported by mistletoe interventions was followed for a median treatment period of 8.6 months. During the post-surgical treatment period the patients were diagnosed twice for the presence of fatigue symptoms by structural interviews carried out by physicians.

Results: At the end of the median treatment period, 16/181 patients (8.8%) were diagnosed with CRF in the supportive care group and 86/143 (60.1%) in the chemo- or radiochemotherapy group without supportive mistletoe medication. Multivariable-adjusted ORs provided evidence for a chance to improve CRF by supportive mistletoe medication compared to chemo- or radiochemotherapy alone over the time of treatment. The OR = 10.651 (95% CI 5.09 – 22.28; $p < 0.001$) declined from the first visit to OR = 0.054 (95 CI 0.02 – 0.13; $p < 0.001$) at the end of therapy. Furthermore, 14 confounding factors for risk assessment of CRF were compared by means of forest plots. It turned out that the hospital versus office-based treatment and the co-morbidity/inflammation represent independent but important determinants for fatigue levels.

Conclusion: The clinically used mistletoe medication (Iscador Qu) is the first candidate to be included in a supportive care modus into chemo- or radiochemotherapy protocols for colorectal patients to improve CRF without discernable toxicities.

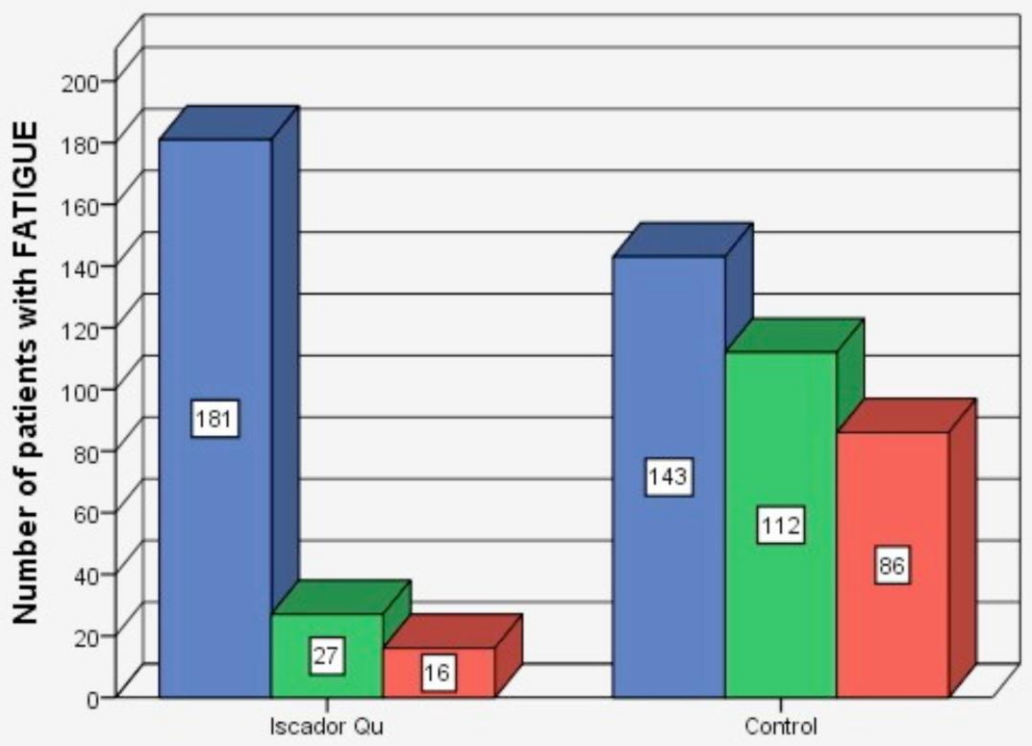


Figure 1: The columns depict the number of patients diagnosed with symptoms of cancer-related fatigue at the time of diagnosis or surgical intervention (blue), in the midst of the chemo- or radiochemotherapy protocol with and without Iscador Qu (green) and at the end of the chemo- or radiochemotherapy with or without Iscador Qu (red). The left three columns present the data of the supportive care group (Iscador Qu), the right three columns the control group (without Iscador Qu).

3.2.4 Cancer of the Respiratory Tract

References

- ✯ Dold U. et al. (1991) Krebszusatztherapie beim fortgeschrittenen nicht-kleinzelligen Bronchialkarzinom. Thieme Verlag, Stuttgart, New York.
- ✯ Bar-Sela G., Wollner M., Hammer L., Agbarya A., Dudnik E., Haim N. (2013): Mistletoe as complementary treatment in patients with advanced non-small-cell lung cancer treated with carboplatin-based combinations: A randomised phase II study. European Journal of Cancer 49: 1058–1064.

The references marked with ✯ are included in abstract form in this documentation.

Dold U. et al. (1991) Krebszusatztherapie beim fortgeschnittenen nicht-kleinzelligen Bronchialkarzinom. [Complementary cancer therapy by advanced non-small cell lung cancer.] *Thieme Verlag, Stuttgart, New York*.

Study design

Design	3-arm, prospective, randomised, placebo-controlled, multicentre study.
Patients	337 patients with advanced non-small cell lung cancer, who could not be operated and were without justified indication for an initial radiotherapy or chemotherapy were evaluated.
Treatment	Iscador U c Hg or Qu c Hg s.c. 3 times a week at various doses over more than 6 months (n = 114). Placebo was a multivitamin supplement (BVK Roche) with 7 vitamins, once a week i.m. (n = 113). The third group (n = 110) received Polyerga (an anti-tumour glucosamine) once a week i.m.
Length of study	1978 – 1986.
Measurements	Length of survival, tumour remission, symptom-free interval, Karnofsky Index, patient's subjective condition, quality of life.

Results regarding Quality of life and pain

The patients' subjective condition, as documented by the doctor, improved by 59% in the Iscador patients and by 45% in the placebo patients. The difference is statistically significant. (p = 0.018, single sided test).

The Karnofsky Index did not show a significant difference between the Iscador group and the placebo group.

Quality of life was measured in 5 levels according to reduction in physical capacity, pain, coughing, loss of appetite, shortness of breath and blood in sputum.

There was no notable difference between the therapy groups.

For results of this study concerning tumour remission see 4.4.1 und concerning survival see 5.4.1.3.

Bar-Sela G., Wollner M., Hammer L., Agbarya A., Dudnik E., Haim N. (2013): Mistletoe as complementary treatment in patients with advanced non-small-cell lung cancer treated with carboplatin-based combinations: A randomised phase II study. European Journal of Cancer 49: 1058–1064.

Study design

Design	2-arm, prospective, randomised, single centre study.
Patients	79 patients with advanced non-small cell lung cancer receiving chemotherapy entered the study; seven patients were excluded before randomisation.
Treatment	*Control group* (n = 39): up to 6 21-day cycle of carboplatin, combined with gemcitabine or pemetrexed. *Treatment group* (n = 33): Additional to chemotherapy, thrice weekly until tumour progression Iscador Qu.
Length of study	Recruitment February 2007 – December 2010.
Measurements	Chemotherapy-related side effects and Quality of Life.

Results

Introduction*:* This randomised phase II study of Iscador combined with carboplatin-containing regimens was conducted in chemotherapy-naive advanced non-small-cell lung cancer (NSCLC) patients to assess its influence on chemotherapy-related side-effects and Quality of Life.

Methods*:* Patients with advanced NSCLC were randomised to receive chemotherapy alone or chemotherapy plus Iscador thrice weekly until tumour progression. Chemotherapy consisted of 21-day cycles of carboplatin combined with gemcitabine or pemetrexed.

Results*:* Seventy-two patients (control: 39; Iscador: 33) were enrolled in the study. Most (65%) were in stage IV, and 62% had squamous histology. Median overall survival in both groups was 11 months. Median time to tumour progression was 4.8 months for the controls and 6 months in the Iscador arm (p = not significant). Differences in grade 3-4 haematological toxicity were not significant but more control patients had chemotherapy dose reductions (44% versus 13%, $p = 0.005$), grade 3-4 non-haematological toxicities (41% versus 16%, $p = 0.043$) and hospitalisations (54% versus 24%, $p = 0.016$) due to side effects.

Conclusion*:* No effect of Iscador could be found on Quality of Life or total adverse events. Nevertheless, chemotherapy dose reductions, severe non-haematological side-effects and hospitalisations due to side effects were less frequent in patients treated with Iscador.

(3.2.5 Melanoma)

No studies available

3.2.6 Various Solid Tumours

References

- ✯ Buchner C. (1984) Über den Verbrauch von Analgetika und Psychopharmaka von Malignompatienten mit und ohne adjuvante Misteltherapie. Unveröffentlichtes Manuskript, Stuttgart/Herdecke.
- ✯ Hajto T., Hostanska K., Fornalski M., Kirsch A. (1992) Eine neue Alternative zur Erhöhung der antitumoralen Wirkung eines klinisch angewandten Mistelextraktes durch Lektinoptimierung. Erfahrungsheilkunde 41 (6), 406–408.
- Toelg M., Antonu H., Reiss B., Ramos M. H. (2005) Lebensqualität von Tumorpatientinnen unter begleitender Misteltherapie. Schweizerische Zeitschrift für GanzheitsMedizin 17 (5): 294–299.
- Toelg M., Reiss B., Antonu H. (2005) Chemotherapie mit begleitender Misteltherapie – Prospektive, nicht randomisierte, kontrollierte, offene Studie (AWB) zur Lebensqualität. CO'MED 11 (8): 18–22.
- Büssing A., Tröger W., Stumpf C., Schietzel M. (2008) Local reactions to treatments with Viscum album L. extracts and their association with T-lymphocyte subsets and quality of life. Anticancer Research 28: 1893–1898.

The references marked with ✯ are included in abstract form in this documentation.

Buchner C. (1984) Über den Verbrauch von Analgetika und Psychopharmaka von Malignompatienten mit und ohne adjuvante Misteltherapie. [On the use of analgesics and psychotropic drugs in malignant neoplasm patients with and without mistletoe therapy.] *Unveröffentlichtes Manuskript [unpublished manuscript],Stuttgart/Herdecke.*

Study design

Design	Retrospective study with 2 groups.
Patients	247 patients with malignant neoplasm, who were hospitalised in the medical clinic of the town hospital, Stuttgart- Bad Cannstadt in the time from 1970 – 1973. Most of the patients had advanced tumours; main localisations were gastro-intestinal, genitourinary or bronchial.
Treatment	123 patients received Iscador s.c. in various concentrations alongside the usual oncologic therapies (chemotherapy, radiotherapy, surgery). 124 patients did not receive Iscador.
Length of Study	1970 – 1973.
Measurements	Use of medication (analgesics, psychotropic drugs, spasmolytics etc.) during the terminal phase of illness.

Most important results

The group of patients, who additionally received Iscador, required significantly less palliative medication with medium and strong opiates, spasmolytics and tranquilisers during the terminal phase of illness in comparison with the control group. The measurement of medication dose did not occur in mg per period of time, but in very rough groups. The Iscador group generally showed a small disadvantage when regarding prognosis factors (distribution of stages of disease, age and forms of additional therapy). The mean survival in the Iscador group however was 11.3 months longer than the control group (not significant).

Hajto T., Hostanska K., Fornalski M., Kirsch A. (1992) Eine neue Alternative zur Erhöhung der antitumoralen Wirkung eines klinisch angewandten Mistelextraktes durch Lektin-Optimierung. [A new alternative to increase the anti-tumour effect of clinically applied mistletoe extract using lectin optimisation.] *Erfahrungsheilkunde* 41 (6), 406–408.

Study design

Design	Prospective, non-controlled study.
Patients	16 tumour patients (breast, thyroid, liver, bladder, colon, tongue, prostate cancer, melanoma and sarcoma) at stage III or IV.
Treatment	Iscador «dose optimised» (dose equivalent of 1ng mistletoe lectin/kg body weight), 2 times a week during 5 to 12 months. 12 patients received only Iscador therapy, without the other therapy modality.
Length of study	1989 – 1991.
Measurements	Karnofsky Index, tumour remission.

Most important results

Quality of life improved in 14 of the 16 patients. The Karnofsky Index improved on average from 70 before to 87 after treatment. The study was not evaluated statistically.

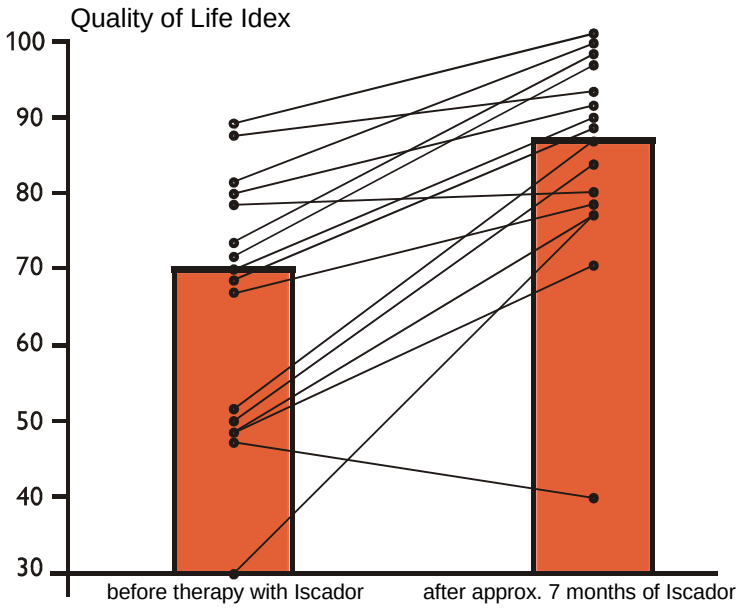


Fig. 1: The patients' quality of life was ascertained using the Karnofsky Index before and after, on average, 7 months of treatment. The points show the individual measurement values and the bars show the mean values (according to Hajto et al. 1992).

For results of this study concerning tumour remission see 4.6.1

(3.2.7 Lymphomas and Leukaemias)

No studies available

(3.2.8 Endocrine Tumours)

No studies available

(3.2.9 Central Nervous System Tumours)

No studies available

(3.2.10 Sarcomas)

No studies available

3.3 Malignant Ascites

References

✯ Bar-Sela G., Goldberg H., Beck D., Amit A., Kuten A (2006) Reducing malignant ascites accumulation by repeated intraperitoneal administration of a Viscum album extract. Anticancer Research 26: 709–713.

The references marked with ✯ are included in abstract form in this documentation.

Bar-Sela G., Goldberg H., Beck D., Amit A., Kuten A. (2006) Reducing malignant ascites accumulation by repeated intraperitoneal administration of a *Viscum album* extract. *Anticancer Research* 26: 709–713.

Study design

Design	1-arm study, phase II.
Patients	25 cancer patients in final stage with malignant ascites, repeated peritoneal punctures for symptom relief required.
Treatment	Following each of the abdominal punctures, Iscador M 10 mg (diluted in 10 – 15 ml of normal saline) was injected into the peritoneal cavity via the same catheter used for drainage.
Study length	Februar 2000 – April 2003.
Measurements	The time intervals between the required punctures following Icador M administration were measured and compared to the previous intervals as an indicator of change in the rate of accumulation of ascitic fluid.

Most important results

2 patients died after the first puncture without Iscador treatment. 23 patients could be analysed.

The median duration of the time interval between punctures was significantly higher after the first injection of Iscador: it rised from 7 to 12 days ($p = 0.001$) and after the second injection to 13 days ($p = 0.03$). In the first case the time interval was longer for 20 of 23 patients and in the second case for 10 of 14 patients. There were no events related to safety.

4 Tumour Remissions

4.1 Genitourinary Cancer

References

- Leroi R. (1978) Viscum album therapy of cancer. The British Homoeopathic Journal 67(3), 167–184, in particular p. 175.

☆ Wagner R. F. (1996) Ovarial Ca und Misteltherapie. Der Merkurstab 49 (2), 152–153.

See 4.6.2.

☆ Portalupi E. (1995) Neoadjuvant treatment in HPV-related CIN with a mistletoe preparation (Iscador). Scuola die specializzazione in oncologia (Dir. Leonida Santamaria). Pavia: Università degli Studi di Pavia, 1995.

The references marked with ☆ are included in abstract form in this documentation.

Portalupi E. (1995) Neoadjuvant treatment in HPV-related CIN with a mistletoe preparation (Iscador). Scuola die specializzazione in oncologia (Dir. Leonida Santamaria). Pavia: Università degli Studi di Pavia, 1995.

Study design

Design	Prospective, non-controlled study.
Patients	27 patients with cytological colposcopical and histological results for CIN-HPV (4 patients at stage CIN I, 6 at CIN II and 17 at CIN III).
Treatment	Iscador s.c. twice a week, over 16 weeks. Dose equivalent of 1ng mistletoe lectin/kg bodyweight.
Length of study	July 1992 – January 1994.
Measurements	Degree of lesions and histological level of dysplasia.

Most important results

5 (18.5%) of the 27 patients discontinued the treatment.

9 (40.9%) of the 22 treated patients showed complete remission (CR, secured by biopsy), 6 (27.3%) showed a partial remission (PR: < 50% reduction in the lesion, or regression of the histological level respectively), 6 (27.3%) showed no change (NC) and 1 (5%) showed progression (P). This correlates with a response rate of 68.2%.

4.2 Breast Cancer

References

☆ Wagner R. F. (1996a) Iscador M 5 mg spezial und Iscador Qu 5 mg spezial – Eine Praxisbeobachtung 1993–1996. *Iscador Informationen*, Heft 4, pp. 3–42, in particular pp. 5–7, 26–27.

See 4.6.2.

The references marked with ☆ are included in abstract form in this documentation.

(4.3 Gastrointestinal Cancer)

No studies available

4.4 Cancer of the Respiratory Tract

References

- Bradley G. W., Clover A. (1989) Apparent response of small cell lung cancer to an extract of mistletoe and homoeopathic treatment. Thorax 44, 1047–1048. [single case report]
- ☆ Dold U. et al. (1991) Krebszusatztherapie beim fortgeschrittenen nicht-kleinzelligen Bronchialkarzinom. Thieme Verlag, Stuttgart-New York.

The references marked with ☆ are included in abstract form in this documentation.

Dold U. et al. (1991) *Krebszusatztherapie beim fortgeschnittenen nicht-kleinzelligen Bronchialkarzinom*. [Complementary cancer therapy by advanced non-small cell lung cancer.] Thieme Verlag, Stuttgart, New York, pp. 61–62.

Study design

Design	3-arm, prospective, randomised, placebo-controlled, multicentre study.
Patients	337 patients with advanced non-small cell lung cancer could be evaluated, who could not be operated on and were without a justified indication for initial radiotherapy or chemotherapy.
Treatment	Iscador U c Hg or Qu c Hg s.c. 3 times a week at various doses over more than 6 months (n = 114). Placebo was a multivitamin supplement (BVK Roche) with 7 vitamins, once a week i.m. (n = 113). The third group (n = 110) received Polyerga (an anti-tumour glucosamine) once a week i.m.
Length of study	1978 – 1986.
Measurements	Survival, tumour remission, symptom-free interval, Karnofsky Index, patients' subjective condition, quality of life.

Results regarding tumour remissions

The regression of tumours or metastases can be classified into 4 categories, based on documented observations of the course of disease. (1) Remission: Cases where a tumour could not be found at the localisation of the primary tumour at least twice, or the disappearance of distant metastases. (2) Uncertain remission: Cases where a tumour could not be found at the localisation of the primary tumour once and possibly the disappearance of distant metastases. (3) Regression: Cases where regression of the primary tumour could be documented, independent of the development of distant metastases, without a previous increase in the primary tumour. (4) Uncertain regression: Cases with regression of the primary tumour after initial increase and cases with a documented disappearance of distant metastases with a previous or simultaneous increase in the primary tumour.

Table 1: Regression of tumour and metastases during the course of the study

Tumour behaviour	Iscador	Polyerga	Placebo	TOTAL
Remission	4	2	3	9
uncertain remission	3	6	5	14
regression	12	6	4	22
uncertain regression	11	7	10	28
Total	30	21	22	73

The total remission rate of 22% (73 cases) is relatively high (see Table 1). But a statistically significant difference cannot be shown either between Iscador and placebo (single sided test, p = 0.10) or between Iscador and Polyerga (single sided test, p = 0.2). However, considering the strict conditions of the study, it is remarkable that the rate of remission was approximately a third higher under Iscador therapy and can be interpreted as a distinct trend.

The situation is more or less the same, when the questionable category of uncertain reduction is omitted. The difference between the three therapy groups then becomes even less.

For results of this study concerning quality of life see 3.2.4.1 and for survival see 5.4.1.3.

(4.5 Melanoma)

No studies available

4.6 Various Solid Tumours

References

- ✯ Hajto T., Hostanska K., Fornalski M., Kirsch A. (1992) Antitumorale Aktivität des immunmodulatorisch wirkenden Beta-galaktosidspezifischen Mistellektins bei der klinischen Anwendung von Mistelextrakten (Iscador). Deutsche Zeitschrift für Onkologie 23 (1), 1–6.
- ✯ Wagner R. F. (1996a) Iscador M 5 mg spezial und Iscador Qu 5 mg spezial – Eine Praxisbeobachtung 1993–1996. Iscador Informationen, Heft 4, pp. 3–42, in particular pp. 5–7, 26–27.

The references marked with ✯ are included in abstract form in this documentation.

Hajto T., Hostanska K., Fornalski M., Kirsch A. (1992) Antitumorale Aktivität des immunmodulatorisch wirkenden Beta-galaktosidspezifischen Mistellektins bei der klinischen Anwendung von Mistelextrakten (Iscador). [Anti-tumour activity of immunomodulatory beta-galactoside specific mistletoe lectin in the clinical application of mistletoe extracts Iscador®] *Deutsche Zeitschrift für Onkologie* 23 (1), 1–6.

Study design

Design	Prospective observational study without a control group.
Patients	16 patients with histological defined advanced tumours, stage III and IV (see Table 1).
Treatment	12 patients received only a dose-optimised Iscador therapy (dose equivalent of 1ng mistletoe lectin/kg bodyweight), twice a week during 5 to 12 months. The other 4 also received different conventional treatments.
Length of study	1989 – 1991.
Measurements	Immunomodulation, course of growth of the tumour, quality of life.

Results regarding tumour remissions

In all but one patient with colon cancer (who died after 3 months), the course of illness was observed for at least 5 months after beginning the therapy.

Complete remission was defined as the disappearance of all clinical tumour symptoms. Partial remission was defined as a 50% or more reduction in the diameter of all measurable tumour manifestations, without a simultaneous increase in other existing symptoms or the development of new damage. Minimal tumour remission was defined as an objective reduction of less than 50% of the measurable events. An improvement over at least 8 weeks was defined as remission. Progressive disease was defined as an increase in measurable tumour manifestation or as the appearance of new lesions.

One complete remission, three partial remissions and three minimal remissions were recorded in the group which was treated only with Iscador; this corresponds with a remission rate of 58%. Until the end of the observation, no relapses were recorded in any of the patients in remission, so that the duration of the tumour regression lasted 2 to 9 months.

For results of this study concerning quality of life see 3.2.6.2.

Table 1: Clinical results

Nr.	Type of tumour	Metastases	Stage	Length of observation	Treatment	Clinical reaction
1	Breast cancer	Local relapse, Skin	IV	9	Iscador	complete remission
2	Breast cancer	Bones	IV	8	Iscador	partial remission
3	Cancer of the thyroid gland	Bones, Lung	IV	6	Iscador	partial remission
4	Sarcoma	Peritoneum	IV	8	Iscador	partial remission
5	Liver cancer	Spleen, Stomach	IV	4	Iscador	minimal remission
6	Sarcoma	Lymph nodes	III	5	Iscador	minimal remission
7	Sarcoma	Lungs	IV	9	Iscador	minimal remission
8	Bladder cancer	Local relapse	IV	7	Iscador	no change
9	Melanoma	Skin	IV	5	Iscador	no change
10	Breast cancer	Skin	IV	5	Iscador	no change
11	Melanoma	Skin	IV	5	Iscador	progression
12	Colon cancer	Liver	IV	3	Iscador	progression
13	Cancer of the tongue	Lymph nodes	III	12	Iscador + radiotherapy	complete remission
14	Prostate cancer	Bones	IV	12	Iscador + hormone therapy	partial remission
15	Breast cancer	Pleura	IV	5	Iscador + chemotherapy	partial remission
16	Breast cancer	Bones	IV	6	Iscador + hormone therapy	minimal remission

Wagner R. F. (1996a) Iscador M 5 mg spezial und Iscador Qu 5 mg spezial – Eine Praxisbeobachtung 1993–1996. [Iscador M 5 mg special and Iscador Qu 5 mg special – a practical observation 1993-1996.] *Iscador Informationen*, Issue 4, pp. 3–42, in particular pp. 5–7, 26–27 [Case Report 1 and 2].

Wagner R. F. (1996b) Ovarial Ca und Misteltherapie. [Ovarian cancer and mistletoe therapy.] *Der Merkurstab* 49 (2), 152–153. [Case Report 3]

Study design

Design	Observation of 3 sets of cases.
Patients	Case Report 1: 15 patients with breast cancer with metastases, the metastases mainly in the bones and liver.
	Case Report 2: 66 patients with different cancers (prostate, breast, ovarian, rectum, parotid mixed tumour).
	Case Report 3: 36 patients with advanced (stage III) ovarian cancer. Previous chemotherapeutic treatment: no more therapy options by tumour progression.
Treatment	Case Report 1: Treatment with Iscador M 5 mg special s.c., 2 to 3 times a week.
	Case Report 2: Treatment with Iscador Qu 5 mg special s.c., 2 to 3 times a week.
	Case Report 3: Treatment with Iscador.
Length of study	1990 – 1996.
Measurements	Immunomodulation, temperature reaction, chromosome breaks, tumour remission, quality of life.

Results regarding tumour remissions

Case Report 1: Therapeutic success (stable disease for at least 6 months) in 9 of the 15 patients. In two of these patients a regression in scintigraphic presented bone metastases was recorded. Previous chemotherapy and adjuvant hormone therapy had not been able to produce these changes.

Case Report 2: 43 of the 66 patients had a positive reaction to the Iscador therapy (immune status). A tumour reduction was observed in 6 of these patients.

Case Report 3: A state of no change was reached in 15 of the 36 patients, meaning that a stable situation could be seen for 6 months (sonographic control, tumour marker). 8 patients went into partial remission (e.g. reduction of existing ascites) for more than 6 months and 3 patients went into remission (regression of peritoneal lymph nodes, reduction of ascites) for more than 6 months.

For results of this study [Case Report 3] concerning survival see 5.1.2.3.

4.7 Lymphomas and Leukaemias

References

✯ Kuehn J. J. (1999) Langfristig guter Verlauf unter Misteltherapie bei einem Patienten mit einem zentroblastisch-zentrozytischen Non-Hodgkin-Lymphom. Deutsche Medizinische Wochenschrift 124 (47), 1414–1418. [single case report]

- Kuehn J. J. (2000) [Erwiderung zu Leserbriefen zu Kuehn 1999] Deutsche Medizinische Wochenschrift 125 (31-32), 958–960.

✯ Kuehn J J. (2005) Misteltherapie bei malignen Lymphomen – Neue Erkenntnisse und Erfahrungen im Rahmen einer prospektiven Kasuistikserie bei Patienten mit follikulärem Non-Hodgkin-Lymphom. In: Scheer R., Bauer R., Becker H., Fintelmann V., Kemper F. H., Schilcher H. (Hrsg.), Fortschritte in der Misteltherapie: Aktueller Stand der Forschung und klinische Anwendung, Essen: KVC Verlag, pp. 477–489.

- Kuehn J. J. (2006) Ergebnisse bei der Behandlung von malignen Lymphomen mit dem Mistelpräparat Iscador. In: Streit E., Rist L. (Hrsg), Ethik und Wissenschaft in der anthroposophischen Medizin, Bern: Peter Lang, pp. 85–94.

✯ Kuehn J. J. (2007) Treatment responses to viscum album pini (Iscador P) in non-hodgkin's lymphoma exploring a new therapeutic route. Medicina 67 (Supl. II), 107–114.

- Kuehn J. J. (2009) Viscum album L. Pini in der Behandlung des Non-Hodgkin-Lymphoms – Wirksamkeit und Risikoeinschätzung einer subkutanen Misteltherapie im Rahmen einer retrospektiven Fallkontrollstudie. In: Scheer R., Alban S., Becker H., Holzgrabe U., Kemper F. H., Kreis W., Matthes H., Schilcher H. (Hrsg.) Die Mistel in der Tumortherapie 2: Aktueller Stand der Forschung und klinische Anwendung. Essen: KVC Verlag, 353–373.

The references marked with ✯ are included in abstract form in this documentation.

Kuehn J. J. (1999) Langfristig guter Verlauf unter Misteltherapie bei einem Patienten mit einem zentroblastisch-zentrozytischen Non-Hodgkin-Lymphom. [Long term good course of events under mistletoe therapy by patients with centroblastic centrocytic non-Hodgkin lymphoma.] *Deutsche Medizinische Wochenschrift* 124 (47), 1414–1418.

Study design

Design	Observation of individual case.
Patient	Patient with very good general condition, 44 years old, histological confirmed follicular centroblastic centrocytic non-Hodgkin lymphoma (low grade) stage IVA (Ann Arbor classification), with bone marrow infiltration, normal blood parameters und high Karnofsky Performance status (100%).
Treatment	Chemotherapy was not indicated. Out-patient subcutaneous Iscador therapy with Iscador P or Qu 0.1 to 30 mg respectively at two day intervals.
Length of study	1983 – 1999.
Measurements	Immunomodulation, tumour remission, quality of life (Karnofsky Index).

Results regarding tumour remissions

Phases of continuous therapy lead to lymphoma regression (regionally complete), whereas breaks in the therapy, without medical consultation, lead to progression. The patient remained free of symptoms and retained a Karnofsky performance status of 100% for the whole course of the treatment.

As the remissions and progressions occurred several times (3 phases) and were definitely in connection with the Iscador therapy or a break in the therapy, it stands to reason that the remissions were due to the Iscador therapy.

Kuehn J. J. (2005) Misteltherapie bei malignen Lymphomen – Neue Erkenntnisse und Erfahrungen im Rahmen einer prospektiven Kasuistikserie bei Patienten mit follikulärem Non-Hodgkin-Lymphom. [Mistletoe therapy for lymphoma patients – new results and experiences within a prospective case series of patients with follicular non-hodgkin's lymphoma.] In: Scheer R., Bauer R., Becker H., Fintelmann V., Kemper F. H., Schilcher H. (Hrsg.), *Fortschritte in der Misteltherapie: Aktueller Stand der Forschung und klinische Anwendung*, Essen: KVC Verlag, pp. 477–489.

Study design

Design	Case Series.
Patients	24 patients with follicular non-hodgkin's lymphoma.
Treatment	All patients received on their own will Iscador (P 0.01 mg up to 20 mg, 3 times weekly s.c.), in addition to chemotherapy or watchful waiting.
Length of study	1999 – 2003.
Measurements	Remissions (clinical examination, laboratory parameters, medical imaging) and duration of remission.

Results regarding tumour remissions

4 patients had a complete remission (duration between 1.5 and 27.5 months), 6 patients a partial remission (duration between 2.5 and 34 months).

A preservation of a remission with Iscador after the initiation of this remission due to chemotherapy or surgery could be observed in 3 cases (2 complete remissions longer than 18 or 20 months respectively, 1 partial remission longer than 10 months).

Combined chemotherapy and mistletoe therapy yielded 2 complete and 7 partial remissions with a duration between 3 and 24 months.

A stimulation of cytokines (including interleukin-6) was not observed during the complete study period.

Kuehn J. J. (2007) Treatment responses to viscum album pini (Iscador P) in non-hodgkin's lymphoma exploring a new therapeutic route. *Medicina* 67 (Supl. II), 107–114.

Study design

Design	Case series.
Patients	191 patients with non-hodgkin's lymphoma (61 follicular, 130 not follicular); 36 patients received no Iscador therapy or were excluded before they received their minimal dose (14 follicular, 22 not follicular).
Treatment	155 patients (47 follicular, 108 not follicular) were treated long-term with Iscador (P, 0.01 mg up to 20 mg, 3 times weekly s.c.).
	Group A: Single treatment regimen with mistletoe without prior chemotherapy.
	Group B: Single treatment regimen with mistletoe after completion of chemotherapy, and after complete or partial remission.
	Group C: Combined treatment with mistletoe and chemotherapy.
Length of study	1999 – 2007.
Measurements	Remissions (clinical examination, laboratory parameters, medical imaging) and duration of remission.

Results regarding tumour remissions

Group A: 5 complete and 3 partial remissions with a duration between 3 and 80 months

Group B: Progression-free intervals with durations from 11 to 95 months. Some transitions from partial to complete remission under Iscador therapy.

All patients showed without exception good local and systemic tolerance of Iscador therapy No potential clinical risk concerning the treatment with Iscador of patients with non-hodgkin's lymphoma could be observed. A difference in survival was not manifest.

(4.8 Endocrine Tumours)

No studies available

(4.9 Central Nervous System Tumours)

No studies available

(4.10 Sarcomas)

No studies available

5 Survival

5.1 Genitourinary Cancer

5.1.1 Cancer of the Urinary Bladder

References

- ☆ Leroi R. (1978) The viscum album therapy of cancer. British Homoeopathic Journal 67 (3), 167–184.
- ☆ Hoffmann J. (1978) Behandlungsergebnisse bei den Blasenkarzinomen der Lukas Klinik. Mitteilungen aus der Behandlung maligner Tumoren mit Viscum album 10 (2), 6–11.
- Hoffmann J. (1980) Behandlungsergebnisse bei den Blasenkarzinomen der Lukas Klinik. In: Rilling S. (Hrsg.), Blasenkarzinom, Verlag Medizin Fischer, Heidelberg, 172–175.
- Schaefermeyer H. (1996) Zur Therapie des Blasenkarzinoms. Merkurstab 53 (2), 131.

The references marked with ☆ are included in abstract form in this documentation.

Leroi R. (1978) The viscum album therapy of cancer. *British Homoeopathic Journal* 67 (3), 167–184.

Study design

Design	Retrospective study without control group.
Patients	62 patients with cancer of the bladder treated between 1963 and 1975 at the Lukas Klinik, stages I to IV.
Treatment	Iscador s.c. in different doses.
Length of study	1963 – 1975.
Measurements	Survival and growth of tumour.

Most important results

13 (21%) of the 62 patients showed tumour remission of 25–100% under therapy with Iscador. A statistical evaluation is not available.

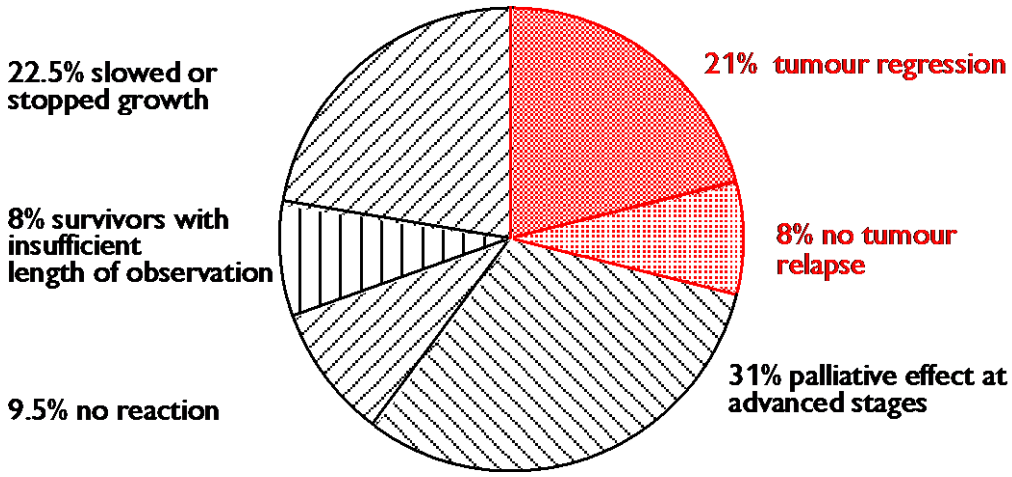


Fig. 1: Reaction of patients with cancer of the bladder (stages I–IV, n = 62) to a therapy with Iscador (according to Leroi 1978).

Hoffmann J. (1978) Behandlungsergebnisse bei den Blasenkarzinomen der Lukas Klinik. [Results of treatment of cancer of the bladder in the Lukas Clinic.] *Mitteilungen aus der Behandlung maligner Tumoren mit Viscum album* 10 (2), 6–11.

Study design

Design	Retrospective study with 2 groups.
Patients	103 patients with cancer of the bladder, who were being treated on the reference date of 30.9.1977. Their initial diagnosis was at least 5 years previous and histological secured.
Treatment	Iscador s.c. in different doses. One group of 17 patients received inadequate doses of Iscador, for various reasons.
Length of study	1963 – 1977.
Measurement	Survival.

Most important results

The 5- and 10-year rates of survival were 35% and 30% respectively. The mean survival of the patients who died during the treatment, whose disease had been diagnosed as stage IV, was better under Iscador therapy. These patients survived 23.6 months in comparison to 9.2 months in the group of the 17 patients, with stage II-IV, who received inadequate Iscador doses. The differences are not statistically significant.

5.1.2 Cancer of the Ovary

References

- Majewsky A., Bentele W. (1963) Über Zusatzbehandlung beim weiblichen Genitalkarzinom. Zentralblatt für Gynäkologie 85 (20), 696–700.
- Leroi R. (1969) Beobachtungen über die zusätzliche Iscador-Therapie in der Behandlung der Frauen mit operiertem und bestrahltem Genitalkarzinom. Gynaecologia 167 (3), 158–170.
- ☆ Hassauer W., Gutsch J., Burkhardt R. (1979) Welche Erfolgsaussichten bietet die Iscador-Therapie beim fortgeschrittenen Ovarialkarzinom? Onkologie 2 (1), 28–36.
- Leroi R. (1980) Klinische Erfahrungen mit dem Mistelpräparat Iscador. In: Wolff O. (Hrsg.), Die Mistel in der Krebsbehandlung, Vittorio Klostermann (2. Auflage), Frankfurt, 58–100.
- ☆ Leroi R., Hajto T. (1982) Die Iscadortherapie beim Ovarialkarzinom. Krebsgeschehen 14 (2), 38–44.
- Schreiber K., Stumpf C. (1984) Iscador in der postoperativen Therapie des Ovarialkarzinoms, Ergebnisse 24jähriger Therapie. Erfahrungsheilkunde 33 (6), 349–358.
- ☆ Wagner R. (1996) Ovarial-Karzinom und Misteltherapie. Merkurstab 49 (2), 152–153.
- Grossarth-Maticek R., Ziegler R. (2005) Randomisierte Kohortenstudien im Matched-Pair-Design zur Misteltherapie (Iscador) bei gynäkologischen Karzinomen. In: Scheer R., Bauer R., Becker H., Fintelmann V., Kemper F. H., Schilcher H. (Hrsg.), Fortschritte in der Misteltherapie: Aktueller Stand der Forschung und klinische Anwendung. Essen: KVC Verlag 2005, 611–623.
- ☆ Grossarth-Maticek R., Ziegler R. (2007) Prospective controlled cohort studies on long-term therapy of ovarian cancer patients with mistletoe (Viscum album L.) extracts Iscador. Arzneimittel-Forschung/Drug Research 57 (10), 665–678.

The references marked with ☆ are included in abstract form in this documentation.

Hassauer W., Gutsch J., Burkhardt R. (1979) Welche Erfolgsaussichten bietet die Iscador-Therapie beim fortgeschrittenen Ovarialkarzinom? [How much success can an Iscador therapy by advanced ovarian cancer offer?] *Onkologie* 2 (1), 28–36.

Study design

Design	Retrospective study with historical control.
Patients	25 patients with primary ovarian neoplasms, underwent surgery; 22 control patients. After accounting for comparability of the two groups, 12 Iscador patients remained (7 with stage III disease, 5 with stage IV disease) and 18 control patients (13 with stage III disease, 5 with stage IV disease).
Treatment	Iscador s.c. in different doses.
Length of study	1969 – 1976.
Measurement	Survival.

Most important results

The 5-year survival rate was 100% in patients with disease at stages I and II, 28% with patients at stage II and 0% in patients at stage IV. In a historical comparison with a collective of patients with ovarian cancer, treated with the cytostatic Cytoval, the Iscador group (stage III and IV) achieved a longer mean survival of 16.2 months compared with 5.2 months in the Cytoval group, despite disadvantageous prognostic conditions. The patients with stage III disease lived 4.2 times longer under treatment with Iscador, and in stage IV 1.6 times longer. The difference was statistically significant ($p < 0.018$).

7 patients in the Cytoval group suffered from severe side-effects by the therapy. No such findings were reported in the Iscador group, in contrast well-being improved and the demand for analgesics decreased.

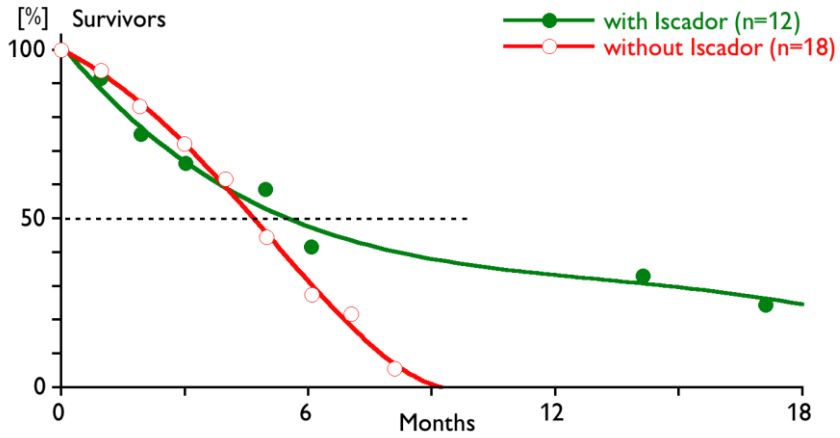


Fig. 1: Course of survival of patients with ovarian cancer under therapy with Cytoval and Iscador respectively (according to Hassauer et al. 1979).

Leroi R., Hajto T. (1982) Die Iscadortherapie beim Ovarialkarzinom. [Iscador therapy of ovarian cancer.] *Krebsgeschehen* 14 (2), 38–44.

Study design

Design	Retrospective study with historical control.
Patients	132 patients with ovarian cancer at stage I–IV from a pool of 388 patients with ovarian cancer.
Treatment	Iscador s.c. in different doses.
Length of study	1963 – 1981.
Measurement	Survival.

Most important results

The Iscador patients in stage I (n = 31) achieved a 5-year survival of 73% and those in stage II (n = 18) achieved a 5-year survival of 53%. These survival rates lie above the mean described in the literature (67% and 38% respectively), the differences are however not statistically significant. The median survival of the Iscador patients in stages III and IV (n = 53 + 30), was better, with 11.5 months in comparison with the historical control with 6.6 to 10.3 months (not significant). The positive well-being of the patients, the reduction in side-effects of chemo- and radiotherapy as well as the reduction of pain were also positively highlighted.

Wagner R. (1996) Ovarial-Karzinom und Misteltherapie. [Ovarian cancer and mistletoe therapy.] *Der Merkurstab* 49 (2), 152–153.

Study design

Design	Retrospective study with historical control.
Patients	36 patients with ovarian cancer in stage III with progression under chemotherapy, registered at the medical practice of R. Wagner, Stuttgart, between 1990 and 1996.
Treatment	Iscador s.c. in different doses.
Length of study	1990 – 1996.
Measurements	Tumour status (sonography, tumour markers) and survival.

Most important results

Under treatment with Iscador: the tumour could be kept stable in 15 cases, progression arose in 10 cases, partial remission was achieved in 8 cases and a remission was achieved over 6 months in 3 cases. Iscador lead to a survival rate which corresponds with the best results in the literature. The improvement in quality of life due to Iscador is also emphasized. A statistical analysis is not available.

For results of this study concerning tumour remission see 4.6.2.

Grossarth-Maticek R., Ziegler R. (2007) Prospective controlled cohort studies on long-term therapy of ovarian cancer patients with mistletoe *(Viscum album* L.*)* extracts *Isca*dor. *Arzneimittel-Forschung/Drug Research* 57 (10), 665–678.

Study design

Design	(1) Randomised, prospective long-term, matched-pair technique.
	(2) Prospective epidemiological long-term cohort study, matched-pair technique.
Patients	(1a) *OvarRand*: 2 × 21 patients with ovarian cancer having no metastases.
	(1b) *OvarMetRand:* 2 × 20 patients with ovarian cancer, with metastases.
	(2a) *Ovar*: 2 × 75 patients with ovarian cancer having no metastases.
	2b) *OvarMet*: 2 × 62 patients with ovarian cancer, with metastases.
Treatment	The patients in the Iscador group received in addition to conventional cancer treatment an individual therapy with different doses and types of s.c. applied Iscador. The control group with matched patients received only conventional cancer treatment and did not receive any type of mistletoe treatment.
Length of study	1973 – 2002.
Measurement	Survival since first diagnosis with cancer.

Most important results

Results are (in the case of non-randomised studies: adjusted) statistical estimates of the hazard rate (HR), the 95% confidence interval (in parentheses) and the p-value. For values of the HR below 1, mortality in the Iscador group is lower than in the control group; for HR above 1, mortality is higher in the Iscador group and for HR = 1 there is no difference.

OvarRand (Fig. 1): Estimated trend for higher survival in the Iscador group:
HR 0.40 (0.15 – 1.03), p = 0.058.

OvarMetRand (Fig. 1): Significant higher survival in the Iscador group:
HR 0.33 (0.12 – 0.92), p = 0.033.

OVARRAND = *OvarRand* + *OvarMetRand* (Fig. 1): Significant higher survival in the Iscador group: HR 0.37 (0.18 – 0.73), p = 0.0044.

Ovar (Fig. 2): Significant higher survival in the Iscador group:
HR 0.47 (0.31 – 0.69), p = 0.0002 (Note: Some requirements for the statistical model are not fulfilled).

OvarMet (Fig. 2): Estimated trend for higher survival in the Iscador group:
HR 0.62 (0.37 – 1.05), p = 0.077.

OVAR = *Ovar* + *OvarMet* (Fig. 2): Significant higher survival in the Iscador group:
HR 0.46 (0.34 – 0.62), p < 0.0001.

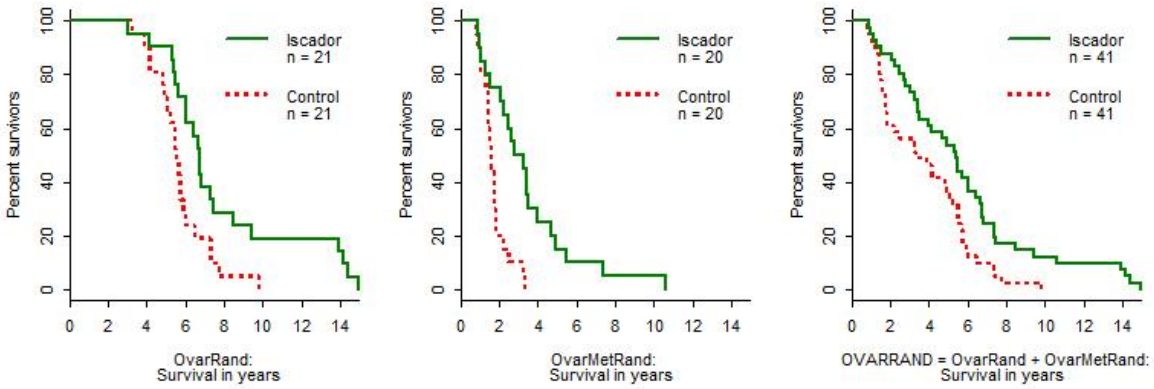


Fig. 1: Randomised studies *OvarRand* and *OvarMetRand*: Survival of patients with ovarian cancer without and with metastases, both studies combined in *OVARRAND*, during ca. 15 years of therapy with Iscador compard to control patients without Iscador (according Grossarth-Maticek/Ziegler 2007)

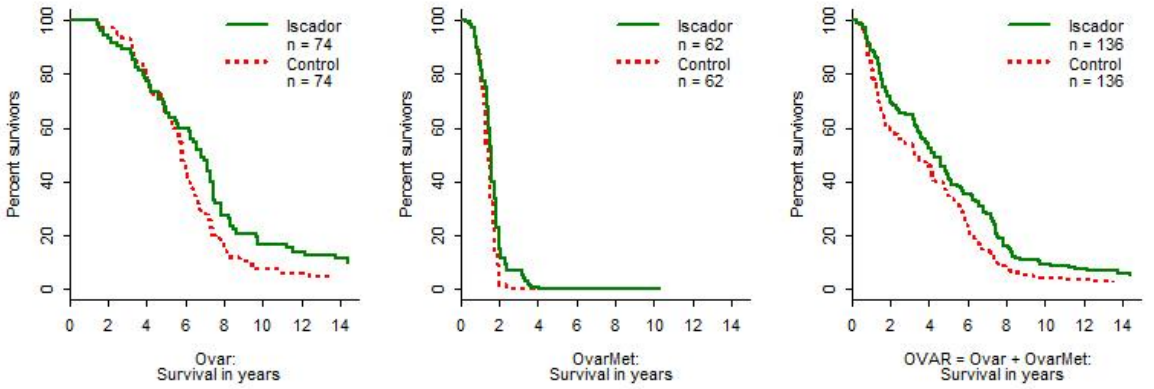


Fig. 2: Nonrandomised studies *Ovar* (1 missing value) *a*nd *OvarMet*: Survival of patients with ovarian cancer without and with metastases, both studies combined in *OVAR*, during ca. 15 years of therapy with Iscador compared to control patients without Iscador (according Grossarth-Maticek/Ziegler 2007).

For results of this study concerning quality of life see 3.1.1.2.

5.1.3 Cancer of the Body of the Uterus

References

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- ☆ Grossarth-Maticek R., Ziegler R. (2008) Randomized and non-randomized prospective controlled cohort studies in matched pair design for the long-term therapy of corpus uteri cancer patients with a mistletoe preparation (Iscador). European Journal of Medical Research 13: 107–120.

The references marked with ☆ are included in abstract form in this documentation.

Grossarth-Maticek R., Ziegler R. (2008) Randomized and non-randomized prospective controlled cohort studies in matched pair design for the long-term therapy of corpus uteri cancer patients with a mistletoe preparation (Iscador). *European Journal of Medical Research* 13: 107–120.

Study design

Design	(1) Randomised, prospective long-term, matched-pair technique.
	(2) Prospective epidemiological long-term cohort study, matched-pair technique.
Patients	(1a) *CorpusRand*: 2 × 30 patients with corpus uteri cancer, without metastases.
	(1b) *CorpusMetRand*: 2 × 26 patients with corpus uteri cancer, with metastases.
	(2a) *Corpus*: 2 × 103 patients with corpus uteri cancer, without metastases.
	(2b) *CorpusMet*: 2 × 95 patients with corpus uteri cancer, with metastases.
Treatment	The patients in the Iscador group received in addition to conventional cancer treatment an individual therapy with different doses and types of s.c. applied Iscador. The control group with matched patients received only conventional cancer treatment and did not receive any type of mistletoe treatment.
Length of study	1973 – 1998.
Measurement	Survival since first diagnosis with cancer.

Most important results

Results are (in the case of non-randomised studies: adjusted) statistical estimates of the hazard rate (HR), the 95% confidence interval (in parentheses) and the p-value. For values of the HR below 1, mortality in the Iscador group is lower than in the control group; for HR above 1, mortality is higher in the Iscador group and for HR = 1 there is no difference.

CorpusRand (Fig. 1): Significant higher survival in the Iscador group:
HR 0.36 (0.16 – 0.82), p = 0.014.

CorpusMetRand (Fig. 1): No significant difference in survival:
HR 1.0 (0.46 – 2.16), p = 0.99 (Note: Some requirements for the statistical model are not fulfilled).

CORPUSRAND = *CorpusRand* + *CorpusMetRand* (Fig. 1): Estimated trend for higher survival in the Iscador group: HR 0.60 (0.35 – 1.03), p = 0.061 (Note: Some requirements for the statistical model are not fulfilled).

Corpus (Fig. 2): Significant higher survival in the Iscador group:
HR 0.41 (0.26 – 0.63), p < 0.0001.

CorpusMet (Fig. 2): Significant higher survival in the Iscador group:
HR 0.61 (0.39 – 0.93), p = 0.023.

CORPUS = *Corpus* + *CorpusMet* (Fig. 2): Significant higher survival in the Iscador group: HR 0.46 (0.35 – 0.60), p < 0.0001.

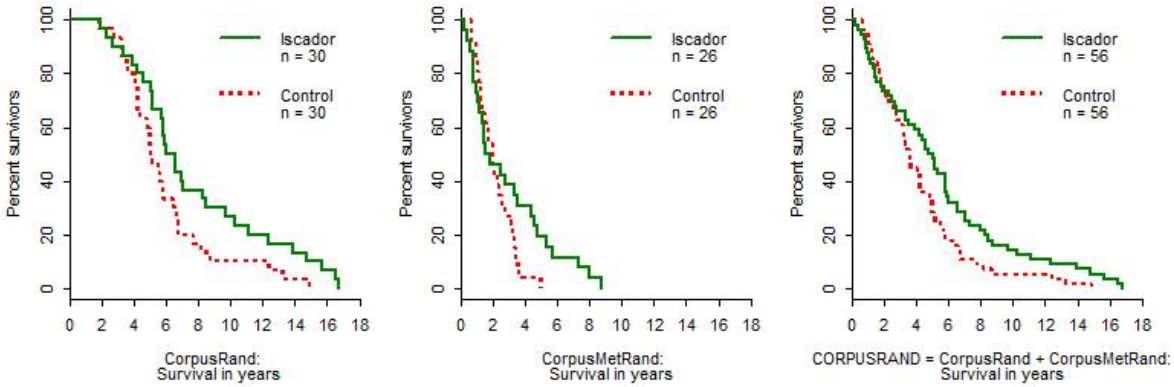

Fig. 1: Randomised studies *CorpusRand* and *CorpusMetRand*: Survival of corpus uteri cancer patients without and with metastases and both studies combined in *CORPUSRAND* during ca. 17 years therapy with Iscador compared to control patients without Iscador (according to Grossarth-Maticek/Ziegler 2008).

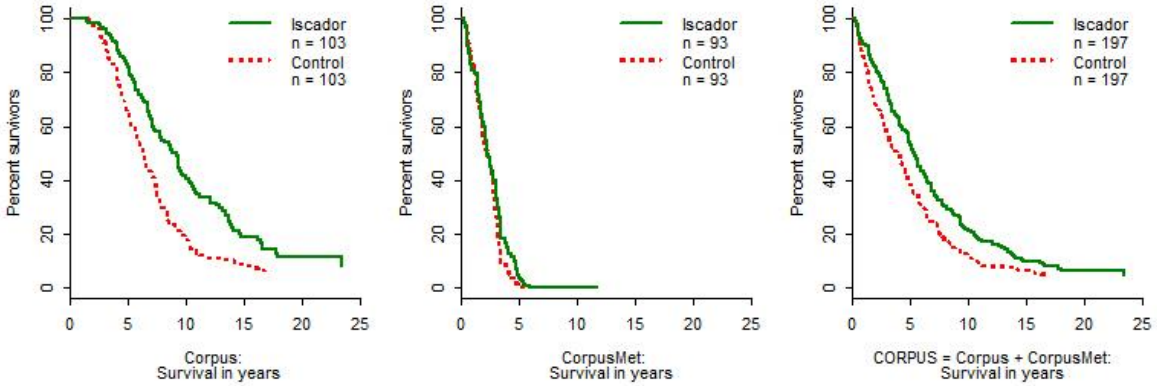

Fig. 2: Nonrandomised studies *Corpus* and *CorpusMed* (missing values in 2 pairs): Survival of corpus uteri cancer patients without and with metastases and both studies combined in *CORPUS* during ca. 23 years therapy with Iscador compared to control patients without Iscador (according to Grossarth-Maticek/Ziegler 2008).

For results of this study concerning quality of life see 3.1.1.3.

5.1.4 Cancer of the Uterine Cervix

References

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- ☆ Grossarth-Maticek R, Ziegler R. (2007) Prospective controlled cohort studies on long-term therapy of cervical cancer patients with a mistletoe preparation (Iscador). Forschende Komplementärmedizin 14 (3), 140–147.

The references marked with ☆ are included in abstract form in this documentation.

Fellmer Ch., Fellmer K.E. (1966) Nachbehandlung bestrahlter Genitalkarzinome mit dem *Viscum album* Präparat „Iscador“. [Aftercare of genital cancer after radiotherapy with the Viscum album compound „Iscador”.] *Krebsarzt* 21 (3), 174–185.

Study design

Design	Prospective, controlled study.
Patients	790 patients with cancer of the cervix from the "I. Universitäts-Frauenklinik München" were divided, after radiotherapy into two groups: an Iscador group (81 patients) and a control group (709 patients).
Treatment	Iscador M c Arg, at different doses, twice respectively three times a week s.c., over 5 years. The control group did not receive treatment with Iscador.
Length of study	1956 – 1961.
Measurement	Survival rate.

Most important results

82.7% of the Iscador group survived the 5 years in comparison with 69.1% in the control group. This difference is statistically secured with p = 0.015. The comparability of the groups was recorded. A positive trend in the quality of life in the Iscador group was emphasized.

Table 1: Results according to stage of disease

Stage of disease	**I**		**II**		**III**		**I–III**	
	Iscador	Control	Iscador	Control	Iscador	Control	Iscador	Control
n	9	92	45	334	27	283	81	709
3-year survival rate	100%	89%	87%	82%	81%	65%	86%	76%
4-year survival rate	100%	79%	87%	77%	70%	56%	83%	69%
significance	no		no		no		yes (p = 0.015)	

Grossarth-Maticek R, Ziegler R. (2007) Prospective controlled cohort studies on long-term therapy of cervical cancer patients with a mistletoe preparation (Iscador). *Forschende Komplementärmedizin* 14 (3), 140–147.

Study design

Design	(1) Randomised, prospective long-term, matched-pair technique.
	(2) Prospective epidemiological long-term cohort study, matched-pair technique.
Patients	(1) *CervixMetRand*: 2 × 19 patients with cancer of the uterine cervix, with metastases.
	(2a) *Cervix*: 2 × 102 patients with cancer of the uterine cervix, without metastases
	(2b) *CervixMet*: 2 × 66 patients with cancer of the uterine cervix, with metastases.
Treatment	The patients in the Iscador group received in addition to conventional cancer treatment an individual therapy with different doses and types of s.c. applied Iscador. The control group with matched patients received only conventional cancer treatment and did not receive any type of mistletoe treatment.
Length of study	1973 – 1998.
Measurements	Survival since first diagnosis with cancer, time to relapse, lymphatic metastases or distant metastases (only for *Cervix*).

Most important results

Results are (in the case of non-randomised studies: adjusted) statistical estimates of the hazard rate (HR), the 95% confidence interval (in parentheses) and the p-value. For values of the HR below 1, mortality in the Iscador group is lower than in the control group; for HR above 1, mortality is higher in the Iscador group and for HR = 1 there is no difference.

Survival

CervixMetRand (Fig. 1): Estimated trend for higher survival in the Iscador group:
HR 0.46 (0.18 – 1.21), p = 0.12.

Cervix (Fig. 2): Significant higher survival in the Iscador group:
HR 0.23 (0.14 – 0.39), p < 0.0005.

CervixMet (Fig. 2): Significant higher survival in the Iscador group:
HR 0.37 (0.17 – 0.80), p = 0.011.

CERVIX = *Cervix* + *CervixMet* (Fig. 2): Significant higher survival in the Iscador group:
HR 0.38 (0.28 – 0.52), p < 0.0005.

Time to relapse, lymphatic or distant metastases

The study *Cervix* showed no significant differences in time to relapse and distant metastases in the Iscador group compared to the control group (lymphatic metastases did not occur). Together with the time to death, the combined analysis yielded a significant benefit for the Iscador group: HR 0.32 (0.22 – 0.48), $p < 0.0005$.

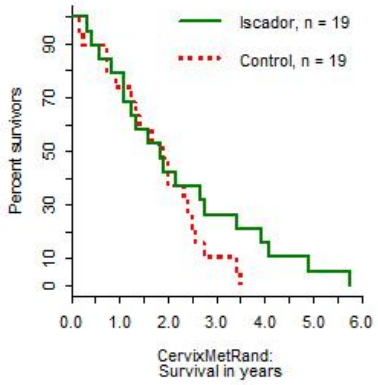

Fig. 1: Randomised study *CervixMetRand*: Survival of uterine cervix cancer patients with metastases during ca. 6 years with Iscador therapy compared to control patients without Iscador (according to Grossarth-Maticek/Ziegler 2007).

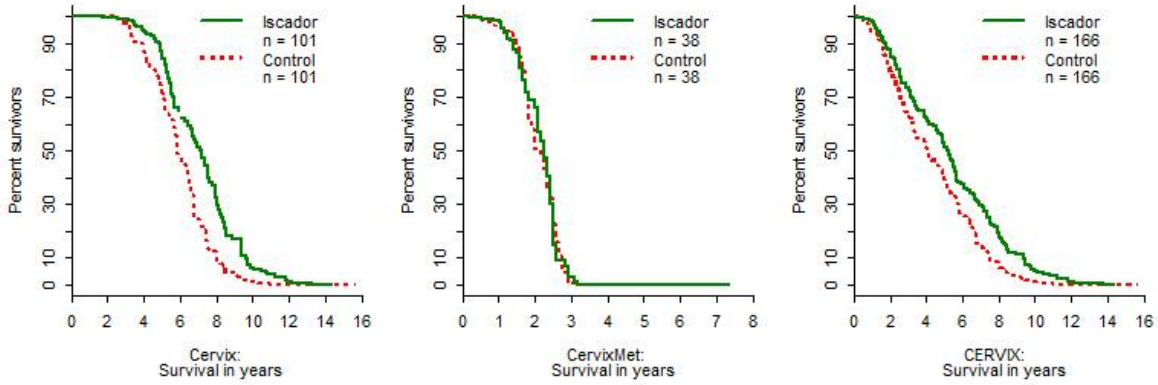

Fig. 2: Nonrandomised studies *Cervix* and *CervixMet*: Survival of uterine cervix cancer patients without and with metastases and both studies combined in *CERVIX* during ca. 16 years with Iscador therapy compared to control patients without Iscador (according to Grossarth-Maticek/Ziegler 2007).

For results of this study concerning quality of life see 3.1.1.1.

5.1.5 Cancer of the Kidney

References

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5.2 Breast Cancer

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- ☆ Hoffmann J., Hajto T. (1982) Iscadorbehandlung beim metastasierenden Mammakarzinom. Krebsgeschehen 14 (3), 71–75.
- Hajto T., Lanzrein Ch. (1986) Natural Killer- and Antibody-Dependent Cell Mediated Cytotoxicity Activities and large Granular Lymphocyte Frequencies in Viscum album-Treated Breast Cancer Patients. Oncology 43, 93–97.
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Leroi R. (1975) Malignomtherapie mit neuen Iscadorpräparaten. [Therapy of malignant neoplasms with a new Iscador medication.] *Krebsgeschehen* 7 (5), 124–126.

Study design

Design	Retrospective study with 3 groups.
Patients	315 patients with breast cancer, stage I and II from the Lukas Klinik, who could be observed between 1962 and 1972 over 5 years.
Treatment	*Group 1* (n = 81): received an optimal treatment with Iscador on average 35 series in the first 5 years.
	Group 2 (n = 79): treated inadequately with 18 Iscador series.
	Group 3 (n = 30): treated inadequately with 4 Iscador series.
	The distribution of the stages of disease within the groups is comparable.
Length of study	1962 – 1972.
Measurements	Survival, 5-year survival.

Most important results

The 5-year rate of survival in group 1, who received an optimal Iscador therapy, was considerably better, with 74%, than the other groups, 67% in group 2 and 46% in group 3. The difference between groups 1 and 3 is statistically significant.

Leroi R. (1977) Nachbehandlung des operierten Mamma-Karzinoms mit *Viscum album*. [Aftercare of breast cancer after surgery with Viscum Album.] *Helvetica Chirurgica Acta* 44, 403–414.

Study design

Design	Retrospective study with 2 groups.
Patients	547 patients with breast cancer, stage I and II from the Lukas Klinik, chosen according to criteria noted below. The first diagnosis was at least 5 years previous.
Treatment	*Group 1*: Iscador treatment began within 1 year after surgery (on average 25 Iscador series in the first 5 years) and observed for at least 5 years. *Group 2*: Patients without Iscador or patients that discontinued therapy after only a few Iscador series (on average 3 Iscador series in the first 5 years), observation over at least 5 years (n = 228).
Length of study	1963 – 1975.
Measurement	Survival.

Most important results

The 5-year survival rate in the Iscador group 1 with stage I disease is 84% in comparison with 63% in group 2 and in the patients with stage II disease 59% in comparison with 41% (both differences are statistically significant, p = 0.002). Age distribution and histology were comparable in both groups. However, there were more patients in group 2 who had received radical mastectomy and radiotherapy. The good general condition, longer ability to work, good psychological condition and reduced use of analgesics in the Iscador group 1 were emphasized.

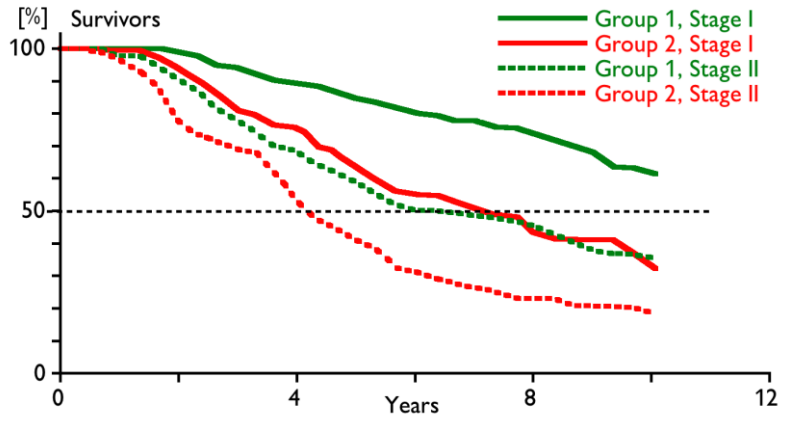

Fig. 1: Course of survival of breast cancer patients with stage I and II disease with adequate (group 1) and inadequate therapy with Iscador (group 2) (according to Leroi 1977).

Table 1: Results according to stage of disease

Stage of disease	**I**		**II**	
Treatment group	1	2	1	2
n	149	107	170	121
5-year survival rate	84%	63%	59%	41%
Significance	yes ($p < 0.002$)		yes ($p < 0.002$)	
Patients, who were observed for more than 10 years	36	31	47	35
10-year survival rate	61%	33%	34%	18%
Significance	yes ($p < 0.002$)		yes ($p < 0.01$)	

Hoffmann J., Hajto T. (1982) Iscadorbehandlung beim metastasierenden Mamma-Karzinom. [Iscador treatment of breast cancer with metastases.] *Krebsgeschehen* 14 (3), 71–75.

Study design

Design	Retrospective study with 3 groups.
Patients	495 patients underwent surgery with breast cancer and metastases, from the Lukas Klinik.
Treatment	*Group 1* (n = 116): Received Iscador for at least 3 months after surgery, and after diagnosis of metastases, 8 series of Iscador a year for at least one year. *Group 2* (n = 138): Did not receive adequate Iscador until after diagnosis of metastases (8 series a year for at least one year). *Group 3* (n = 241): Did not receive any adequate treatment with Iscador. All patients of the groups received chemotherapy, radiotherapy and hormone therapy to similar degrees.
Length of study	1963 – 1980.
Measurement	Survival.

Most important results

Group 1 and group 2 achieved a median survival of 29 and 23.5 months respectively, in comparison with 17 months in group 3. The differences from groups 1 and 2 to group 3 are statistically significant ($p = 0.001$ and $p = 0.03$ respectively). When comparing the patients with localised relapse, the median survival in the Iscador groups 1 and 2 (48.5 months) was significantly higher than in group 3 (27.5 months), with $p = 0.008$.

Hellan J., Salzer G., Wutzlhofer F. (1990) Das operierte Mammakarzinom – Retrospektive Auswertung. [Extirpated breast cancer – retrospective evaluation.] In: Jungi W. F., Senn H. J. (Hrsg.) *Krebs und Alternativmedizin* II, Springer Verlag, Berlin, Heidelberg, 29–35.

Study design

Design	Retrospective study with 2 groups.
Patients	A pool of 794 patients underwent surgery for breast cancer, stages II-IV, from 1979–1982.
Treatment	244 patients were treated with Iscador or Helixor s.c. for at least 3 months after surgery. The other patients did not receive mistletoe therapy.
Length of study	1979 – 1982.
Measurement	Survival.

Most important results

The mean survival in the mistletoe patients was 86.8 months (median 101 months) in comparison with 79.9 months (median 99 months) in the group who did not receive treatment with mistletoe. In the groups with stage II tumours, an advantage for the mistletoe patients could only be seen 10 years after surgery. Treatment with mistletoe increased survival significantly in stage III disease and tends to increase survival in stage IV disease.

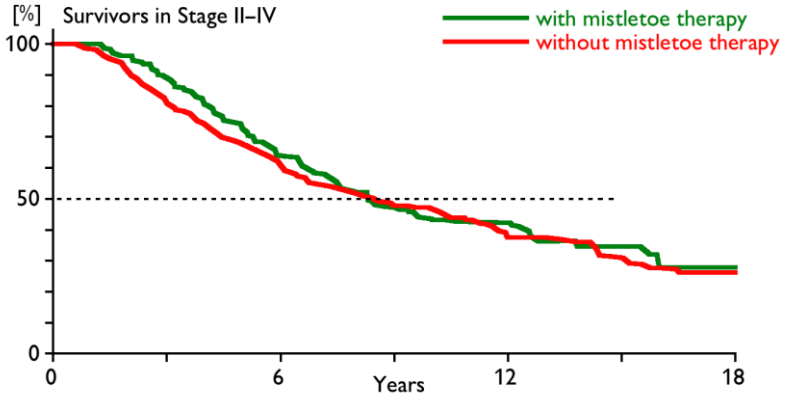

Fig. 1: Course of survival of breast cancer patients (stages I–IV) with and without treatment with mistletoe (according to Hellan et al. 1990).

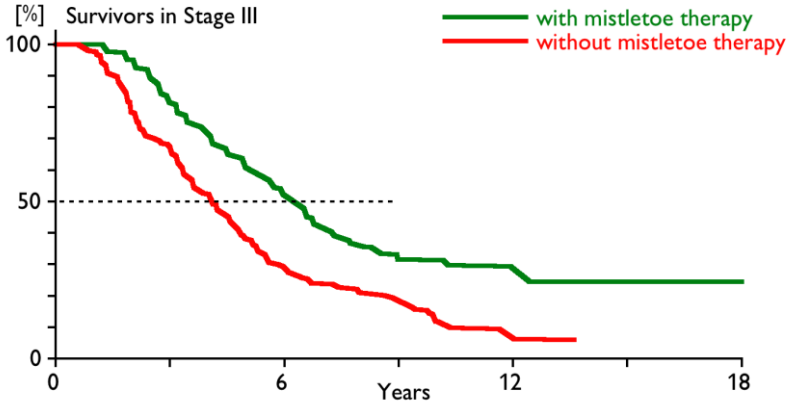

Fig. 2: Course of survival in breast cancer patients, with stage III disease with (n = 89, mean survival = 67 months, median 74 months) and without (n = 141, mean survival = 46 months, median 50 months) treatment with mistletoe (according to Hellan et al. 1990).

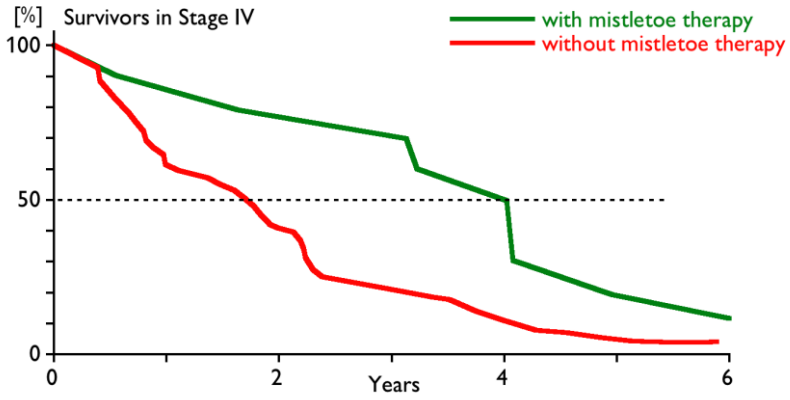

Fig. 3: Course of survival in breast cancer patients with stage IV disease with (n = 10, mean survival = 46.7 months, median 49 months) and without (n = 28, mean survival = 21.9, median 21 months) treatment with mistletoe (according to Hellan et al 1990).

Grossarth-Maticek R., Kiene H., Baumgartner S.M., Ziegler R. (2001a) Use of Iscador, an extract of European mistletoe (*Viscum album*), in cancer treatment: prospective nonrandomized and randomized matched-pair studies nested within a cohort study. *Alternative Therapies* 7 (3), 57–78.

Study design

Design	Randomised prospective long-term study, matched-pair technique.
Patients	17 matched pairs of patients with breast cancer and lymph node metastases, without distant metastases.
Treatment	The patients in the Iscador group received in addition to conventional cancer treatment an individual therapy with different doses and types of s.c. applied Iscador. The control group with matched patients received only conventional cancer treatment and did not receive any type of mistletoe treatment.
Length of study	1971 – 1998.
Measurement	Survival.

Most important results

The patients treated with Iscador lived significantly longer than the controls. Breast cancer with lymph node metastases (17 pairs): Mean survival in the Iscador group was 4.79 years and in the control group 2.41 years, a difference of 2.38 years (log-rank test, p = 0.02).

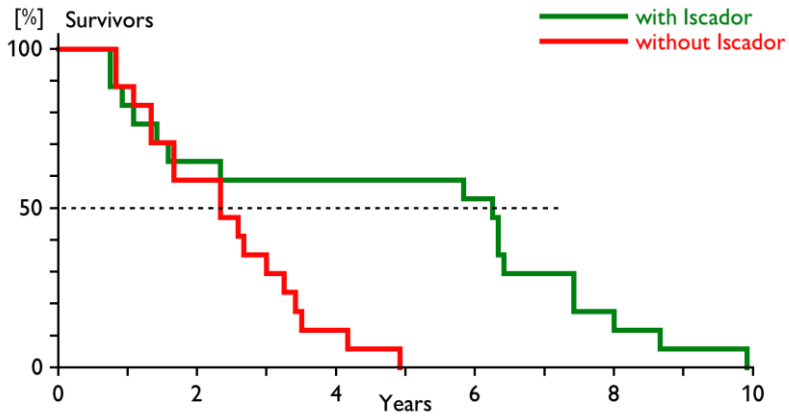

Fig. 1: Survival of breast cancer patients with lymph node metastases and without distant metastases over the course of 10 years with an Iscador therapy (n = 17) and without an Iscador therapy (n = 17) (according to Grossarth-Maticek et al. 2001a).

For further results of this study concerning survival see also 5.6.1 und concerning quality of life see 3.1.2.4 und 3.1.6.1.

Grossarth-Maticek R., Kiene H., Baumgartner S.M., Ziegler R. (2001a) Use of Iscador, an extract of European mistletoe (*Viscum album*), in cancer treatment: prospective nonrandomized and randomized matched-pair studies nested within a cohort study. *Alternative Therapies* 7 (3), 57–78.

Study design

Design	Prospective, epidemiological long-term study, matched-pair-technique.
Patients	Within a collective of breast cancer patients, patients who received treatment with Iscador were strictly matched with comparable patients who did not receive treatment with Iscador. 120 pairs could be found: breast cancer metastases (29 pairs), breast cancer with lymphatic metastases (38 pairs) and breast cancer with distant metastases (53 pairs).
Treatment	The patients in the Iscador group received in addition to conventional cancer treatment an individual therapy with different doses and types of s.c. applied Iscador. The control group with matched patients received only conventional cancer treatment and did not receive any type of mistletoe treatment.
Length of study	1973–1998.
Measurement	Survival.

Most important results

The patients treated with Iscador lived, on average, significantly longer than the controls. Breast cancer without metastases (29 pairs): Iscador 6.08 years vs. control 4.44 years ($p = 0.0127$); with lymphatic metastases (38 pairs): Iscador 3.86 years vs. control 2.97 years ($p = 0.0002$); with distant metastases (53 pairs): Iscador 3.42 years vs. control 2.38 years ($p = 0.00003$).

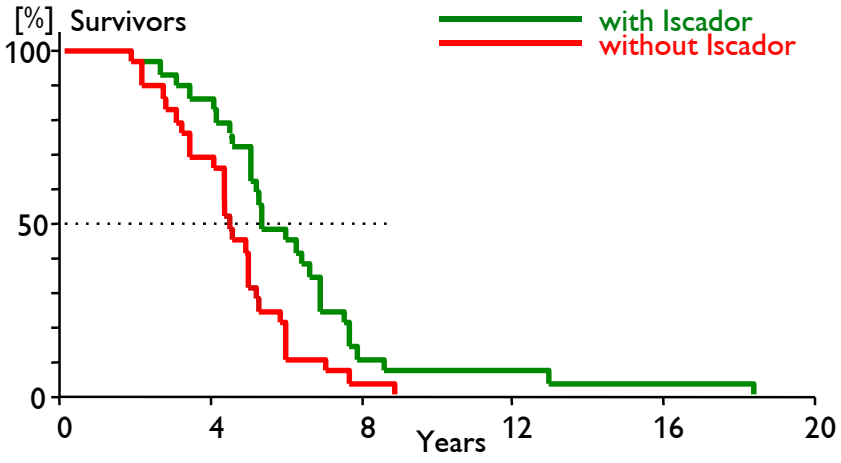

Fig. 1: Survival of breast cancer patients without metastases over the course of 18 years with an Iscador therapy (n = 29) and without an Iscador therapy (n = 29) (according to Grossarth-Maticek et al. 2001).

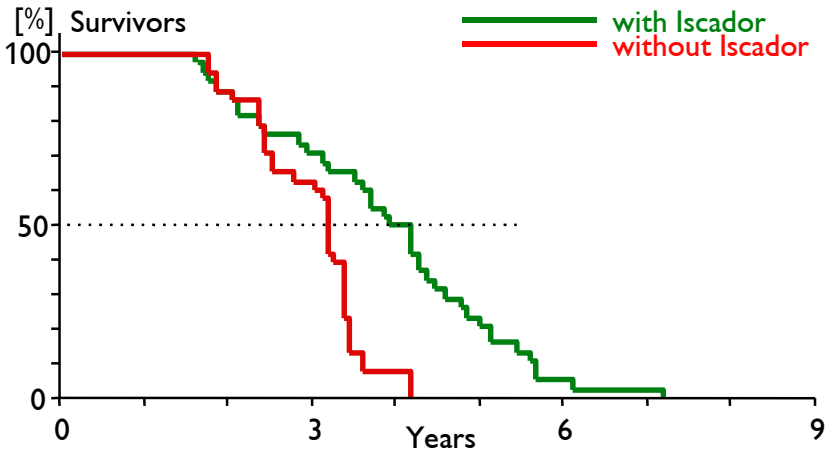

Fig. 2: Survival of breast cancer patients with lymphatic metastases over the course of 7 years with Iscador therapy (n = 38) and without Iscador therapy (n = 38) (according to Grossarth-Maticek et al. 2001).

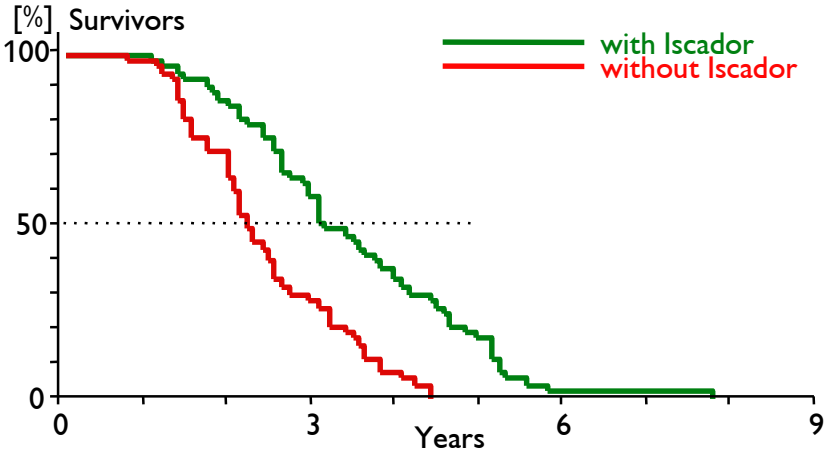

Fig. 3: Survival of breast cancer patients with distant metastases over the course of 8 years with Iscador therapy (n = 53) and without Iscador therapy (n = 53) (according to Grossarth-Maticek et al. 2001).

For further results of this study concerning survival see also 5.6.2.

Bock P. R., Friedel W. E., Hanisch J., Karasmann M., Schneider B. (2004) Wirksamkeit und Sicherheit der komplementären Langzeitbehandlung mit einem standardisierten Extrakt aus Europäischer Mistel (*Viscum album* L.) zusätzlich zur konventionellen adjuvanten onkologischen Therapie bei primärem, nicht metastasiertem Mammakarzinom. [Efficacy and safety of long-term complementary treatment with standardised European mistletoe extract (*Viscum album* L.) in addition to the conventional adjuvant oncological therapy in patients with primary non-metastatic breast cancer] *Arzneimittel-Forschung/Drug Research* 54 (8): 456–466.

Study design

Design	Cohort study with retrospective collection of data («retrolective study»).
Centres	16 centres in Germany and Switzerland.
Patients	1442 patients with primary breast cancer without metastases with conventional basic therapy (surgery, radiotherapy, chemotherapy), 710 thereof received additional Iscador therapy (treatment group), 732 only received the conventional basic therapy (control group).
Comparability	The patients in the treatment group were more seriously ill and had more pronounced risk factors for progression.
Treatment	Median length of observation during aftercare: 66 months (treatment or Iscador group), 60 months (control group). 156 (22%) of the patients in the treatment group and 42 (6%) of the patients in the control group did not receive conventional therapy.
Length of study	1988 – 2000.
Measurements	Primary (efficacy): Frequency of side-effects from the conventional therapy, symptoms due to the disease and therapy, tumour-related survival and overall survival. Secondary (safety): Frequency and level of severity of adverse drug effects due to Iscador therapy, any occurrence of tumour enhancement.

Most important results

97 (13.7%) of the 710 patients in the Iscador group and 49 (6.7%) of the 732 patients in the control group died over the course of the observation. This difference can mainly be attributed to the fact that the Iscador group were initially in a considerably worse position, regarding their prognosis. Figures 1 and 2 show the survival curves modelled according to the “Cox proportional hazards model” (tumour-related survival and overall survival). The factors relevant to prognosis were adjusted using Cox regression in order to reduce the influence of the biased initial position on the estimation of effect to a minimum.

A statistically significant advantage could be seen in overall survival in the Iscador group. A trend in favour of the Iscador group could be seen in tumour-related survival.

A planned sub-group analysis showed that, in the study described, optimal results for survival can only be expected after three or more years of treatment with Iscador.

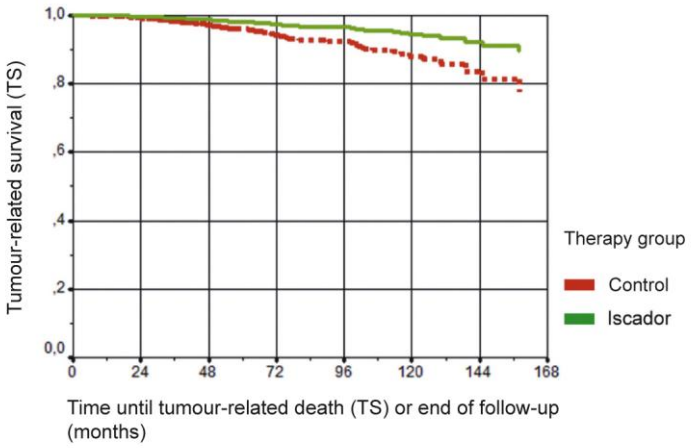

Fig. 1: Multivariate analysis of **tumour-related survival (TS)** using the Cox proportional hazard regression; adjusted hazard ratio HR = 0.44 (95% confidence interval 0.17 – 1.15), p = 0.093 (according to Bock et al. 2004).

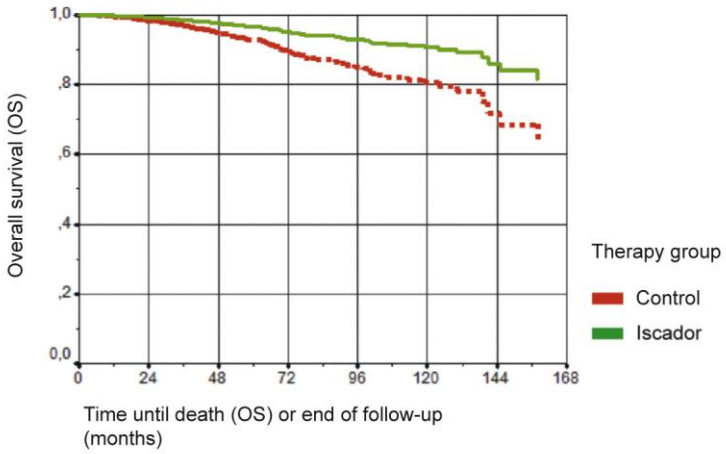

Fig. 2: Multivariate analysis of **overall survival (OS)** using the Cox proportional hazard regression; adjusted hazard ratio HR = 0.46 (95% confidence interval 0.22 – 0.96), p = 0.038 (according to Bock et al. 2004).

For results of this study concerning quality of life see 3.2.2.1 and concerning safety and tolerance see 6.1.1.

Grossarth-Maticek R., Ziegler R. (2006a) Prospective controlled cohort studies on long-term therapy of breast cancer patients with a mistletoe preparation (Iscador). *Forschende Komplementärmedizin* 13, 285–292.

Study design

Design	(1) Randomised, prospective long-term, matched-pair technique.
	(2) Prospective epidemiological long-term cohort study, matched-pair technique.
Patients	(1) *MammaRand*: 2 × 38 breast cancer patients without lymphatic and distant metastases.
	(2) *Mamma*: 2 × 84 breast cancer patients without lymphatic and distant metastases.
Treatment	The patients in the Iscador group received in addition to conventional cancer treatment an individual therapy with different doses and types of s.c. applied Iscador. The control group with matched patients received only conventional cancer treatment and did not receive any type of mistletoe treatment.
Length of study	1971 – 1998.
Measurements	Survival since first diagnosis with cancer, time to relapse, lymphatic or distant metastases.

Most important results

Results are (in the case of non-randomised studies: adjusted) statistical estimates of the hazard rate (HR), the 95% confidence interval (in parentheses) and the p-value. For values of the HR below 1, mortality in the Iscador group is lower than in the control group; for HR above 1, mortality is higher in the Iscador group and for HR = 1 there is no difference.

Survival

MammaRand (Fig. 1): Estimated trend for higher survival in the Iscador group:
HR 0.65 (0.34 – 1.25), p = 0.2.

Mamma (Fig. 1): Significant higher survival in the Iscador group:
HR 0.43 (0.27 – 0.68), p = 0.0003.

Time to relapse, lymphatic or distant metastases

For the randomised study *MammaRand* the differences in the time to relapse, lymphatic or distant metastases in the Iscador group compared to the control group were only significant for lymphatic metastases (Fig. 2), however, the requirements for the statistical model were not fulfilled. The combined analysis including death yields a significant benefit for the Iscador group: HR 0.65 (0.47 – 0.91), p = 0.012.

For the study *Mamma* all individual differences in time to relapse, lymphatic or distant metastases in the Iscador group compared to the control group were significant (Fig. 3). The combined analysis including death yielded a highly significant benefit for the Iscador group: HR 0.66 (0.55 – 0.79), p < 0.0001.

Fig. 1: Randomised study *MammaRand* and nonrandomised study *Mamma* (1 missing value): Survival of breast cancer patients without lymphatic or distant metastases during ca. 24 or 19 years respectively with Iscador therapy compared to control patients without Iscador (according to Grossarth-Maticek/Ziegler 2006a).

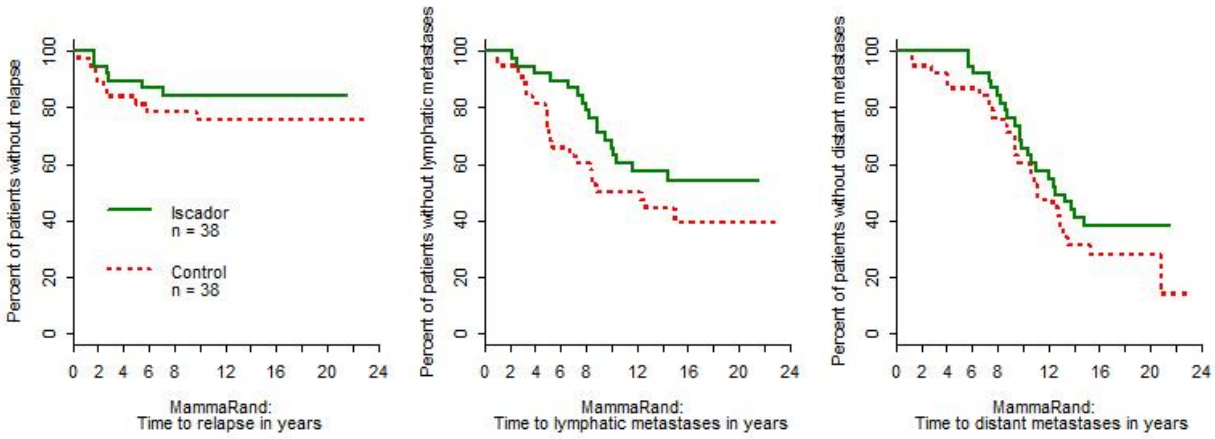

Fig. 2: Randomised study *MammaRand* : Time to relapse, lymphatic or distant metastases of breast cancer patients without lymphatic or distant metastases during ca. 24 years with Iscador therapy compared to control patients without Iscador (according to Grossarth-Maticek/Ziegler 2006a).

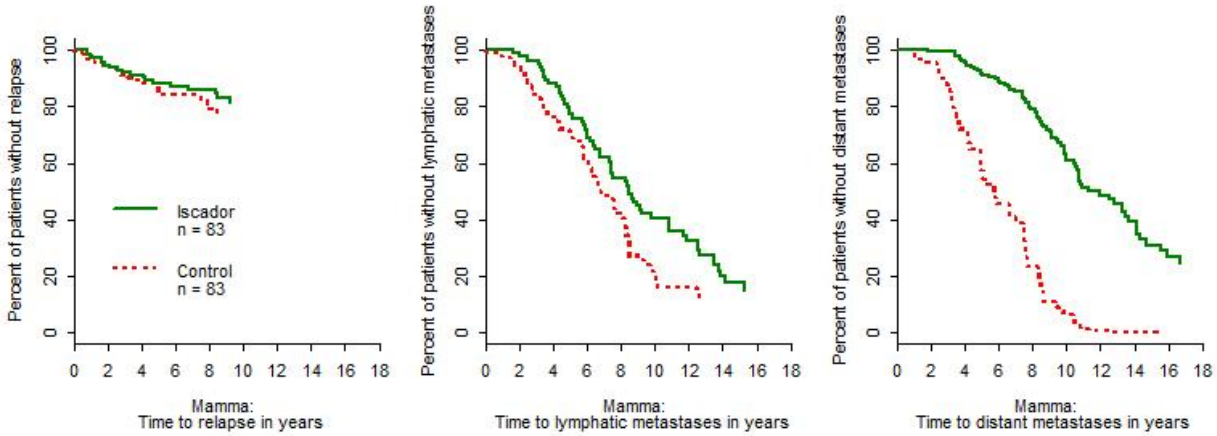

Fig. 3: Nonrandomised study *Mamma* (1 missing value): Time to relapse, lymphatic or distant metastases of breast cancer patients without lymphatic of distant metastases during ca. 16 years with Iscador therapy compared to control patients without Iscador (according to Grossarth-Maticek/Ziegler 2006a).

For results of this study concerning quality of life see 3.1.2.3.

Tröger W., Ždrale Z., Stanković N., Matijašević M. (2012) Five-Year Follow-up of Patients with Early Breast Cancer after a Randomized Study Comparing Additional Treatment with Viscum album (L.) Extract to Chemotherapy alone. Breast Cancer: Basic and Clinical Research 6, 173–180.

Study design

Design	Prospective non-interventional follow-up study of two patient groups after participation in a randomized clinical trial
Patients	57 primary breast cancer patients after surgery and with adjuvant chemotherapy.
Treatment	28 patients received Iscador M spezial in addition to conventional therapies. The 29 patients from the control group were treated only conventionally.
Length of study	Follow-up from June 2006 until May 2012.
Measurements	Frequency of relapse and/or metastases.

Abstract

Background: Additional therapy with Iscador M spezial increases the quality of life of patients suffering from early stage breast cancer during chemotherapy. Usually Iscador therapy is continued after the end of chemotherapy for several years, and by now no long term follow up of the use of Iscador limited to the duration of chemotherapy and regarding relapse and metastasis was feasible. The results of this study shall contribute to the discussion whether additional Iscador during chemotherapy is beneficial in the long run.

Patients and Methods: In a prospective randomized clinical trial 95 patients suffering from early stage breast cancer were evenly randomized into three groups. All patients received chemotherapy, consisting of six cycles of cyclophosphamide, anthracycline, and 5-Fluoro-Uracil (CAF). Two groups received one of two mistletoe extracts from two different manufacturers as subcutaneous injection three times per week additionally to a chemotherapy of six cycles of CAF. These patients did not continue mistletoe therapy after the end of chemotherapy. The control group received CAF with no additional therapy. In this non-interventional 5-year follow-up study the total frequency of relapses and metastases of the control and Iscador groups is compared.

Results: 28 of 30 Iscador patients and 29 of 30 control patients could be analysed. Six of 28 patients in the Iscador group and eight of 29 patients in the control group developed relapse or metastasis within 5 years ($p = 0.551$, log-rank test). Subgroup analysis for hormone- and radiotherapy also showed no difference between the groups.

Conclusion: Additional Iscador therapy during chemotherapy of early stage breast cancer patients seem not to influence the frequency of relapse or metastasis within 5 years.

For the original randomized study see 3.1.2.6.

5.3 Gastrointestinal Cancer

5.3.1 Cancer of the Stomach
5.3.2 Cancer of the Pancreas
5.3.3 Cancer of the Colon and Rectum
5.3.4 Liver Metastases

5.3.1 Cancer of the Stomach

References

- Günczler M., Osika Ch., Salzer G. (1968) Ergebnisse von Resektion und Nachbehandlung beim Magenkarzinom. Wiener klinische Wochenschrift 80 (6), 105–106.
- Günczler M. (1968) Ergebnisse und Erfahrungen in der Krebstherapie mit Iscador. Das Magencarcinom. 1. Teil. Beiträge zur Erweiterung der Heilkunst 21 (6), 188–195.
- Günczler M. (1969) Ergebnisse und Erfahrungen in der Krebstherapie mit Iscador. Das Magencarcinom. 2. Teil. Beiträge zur Erweiterung der Heilkunst 22 (1), 6–12.
- Salzer G., Denck H. (1979) Randomized study of prophylactic 5-Fluorouracil and Iscador treatment of patients with respected gastric carcinoma. Interim results. Krebsgeschehen 11 (5), 130–131.

☆ Salzer G., Havelec L. (1983) Adjuvante Iscadorbehandlung nach operiertem Magen-Karzinom. Ergebnisse einer randomisierten Studie. Krebsgeschehen 15 (4), 106–110.

- Salzer G., Frey S., Danmayr E. (1990) Die Behandlung des operierten Magenkarzinoms am L. Boltzmann Institut für klinische Onkologie. Deutsche Zeitschrift für Onkologie 22, 21–25.

☆ Grossarth-Maticek R., Kiene H., Baumgartner S.M., Ziegler R. (2001a) Use of Iscador, an extract of European mistletoe (Viscum album), in cancer treatment: prospective nonrandomized and randomized matched-pair studies nested within a cohort study. Alternative Therapies 7 (3), 57–78. – Addendum to Iscador article : Alternative Therapies 7 (4), 26. – Deutsche Übersetzung: Der Merkurstab 2001, 54 (3), 171–189.

- Grossarth-Maticek R., Kiene H., Baumgartner S.M., Ziegler R. (2001b) Verlängerung der Überlebenszeit von Krebspatienten unter Misteltherapie (Iscador). Ergebnisse einer epidemiologischen Langzeitstudie. Schweizerische Zeitschrift für Ganzheitsmedizin 13 (4), 217–225.

The references marked with ☆ are included in abstract form in this documentation.

Salzer G., Havelec L. (1983) Adjuvante Iscadorbehandlung nach operiertem Magenkarzinom. Ergebnisse einer randomisierten Studie. [Treatment with Iscador after extirpated stomach cancer – Results of a randomised study.] *Krebsgeschehen* 15 (4), 106–110.

Study design

Design	Randomised, controlled study.
Patients	137 patients with stage II and III stomach cancer from three different surgical centres in Vienna. 72 were lymph node positive and 65 were lymph node negative. There were no significant differences between the Iscador and the control group regarding age, distribution of tumour stage and frequency of different histological types.
Treatment	All patients underwent surgery and were then randomised into a group without further tumour specific treatment (n = 75) and a group who received different dosages of Iscador therapy s.c.
Length of study	1974 – 1979.
Measurement	Survival.

Most important results

The mean survival of the lymph node positive cases in the group treated with Iscador was significantly longer (749 days, $p < 0.05$) than in the control group (540 days). The lymph node negative cases showed the same tendency with a difference of 1661 days versus 1364 days; however this difference was not significant.

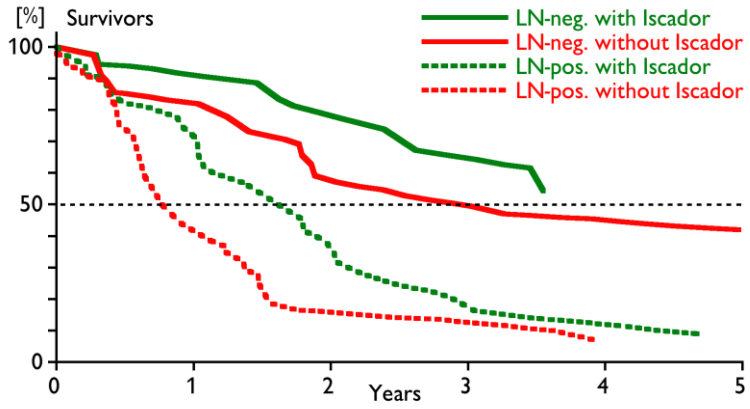

Fig. 1: Course of survival in patients with extirpated stomach cancer with (LN-positive) and without (LN-negative) lymph node metastases under therapy with and without Iscador (according to Salzer G. et al. 1983).

Table 1: Distribution of tumour stages and results

	Lymph node positive		Lymph node negative	
	Iscador	**Control**	**Iscador**	**Control**
Stage II	$T_{1,2}$ N_1 M_0		T_2 N_0 M_0	
	n = 5	n = 10	n = 15	n = 24
Stage III	$T_{1–3}$ $N_{1–2}$ M_0		T_3 N_0 M_0	
	n = 30	n = 27	n = 12	n = 14
Total	n = 35	n = 37	n = 27	n = 38
Mean survival	749 days	540 days	1661 days	1364 days
Median survival	660 days	324 days	–	1201 days
Significant	yes ($p < 0.05$)		no	

Grossarth-Maticek R., Kiene H., Baumgartner S.M., Ziegler R. (2001a) Use of Iscador, an extract of European mistletoe (*Viscum album*), in cancer treatment: prospective nonrandomized and randomized matched-pair studies nested within a cohort study. *Alternative Therapies* 7 (3), 57–78.

Study design

Design	Prospective, epidemiological long-term study, matched-pair-technique.
Patients	Within a collective of stomach cancer patients, patients who received treatment with Iscador were matched as closely as possible with patients who did not receive treatment with Iscador. 44 pairs could be found after following the strict criteria required for matching.
Treatment	The patients in the Iscador group received in addition to conventional cancer treatment an individual therapy with different doses and types of s.c. applied Iscador. The control group with matched patients received only conventional cancer treatment and did not receive any type of mistletoe treatment.
Length of study	1973 – 1998.
Measurement	Survival.

Most important results

The patients treated with Iscador showed a 46% longer survival than the control patients (Iscador group: 2.06 years; control group: 1.41 years). The difference with $p = 0.06$ is not statistically significant.

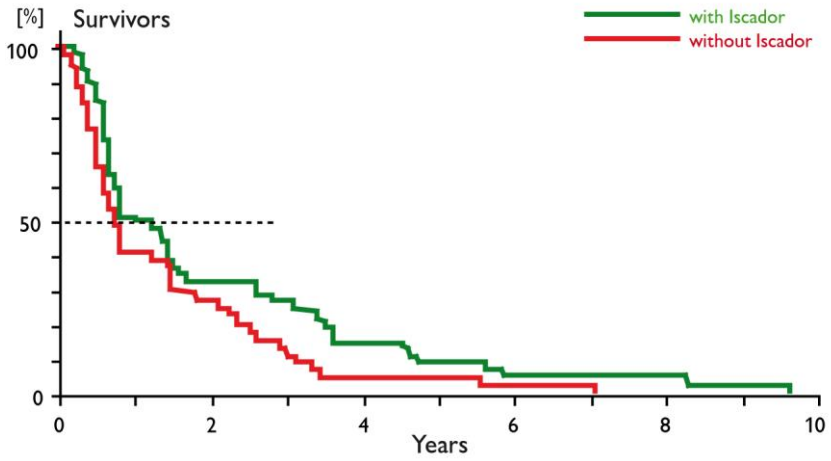

Fig. 1: Survival of stomach cancer patients over the course of 10 years with (n = 44) and without Iscador therapy (n=44) (according to Grossarth-Maticek et al. 2001a)

For results of this study concerning survival see also 5.6.2.

5.3.2 Cancer of the Pancreas

References

- Delius-Müller U. (1979) Ergebnisse der Iscadortherapie bei der Behandlung des Pankreaskarzinoms in der Lukas Klinik. Behandlung maligner Tumoren mit Viscum Album (Verein für Krebsforschung, Arlesheim): Mitteilungen 11 (2), 5–8.
- ✯ Schaefermeyer G., Schaefermeyer H. (1998) Treatment of pancreatic cancer with Viscum album (Iscador): a retrospective study of 292 patients 1986–1996. Complementary Therapies in Medicine 6, 172–177.
- ✯ Matthes H., Friedel W. E., Bock P. R., Zänker K. S. (2010) Molecular Mistletoe Therapy: Friend or Foe in Established Anti-Tumor Protocols? A Multicenter, Controlled, Retrospective Pharmaco-Epidemiological Study in Pancreas Cancer. Current Molecular Medicine 10(4): 430–439.
- ✯ Tröger W., Galun D., Reif M., Schumann A., Stanković N., Milićević M. (2013) *Viscum album* [L.] extract therapy with locally advanced or metastatic pancreatic cancer: a randomized clinical trial on overall survival. European Journal of Cancer 49: 3788–3797, DOI information: 10.1016/j.ejca.2013.06.043.
- Schad F., Axtner J., Buchwald D., Happe A., Popp S., Kröz M., Matthes H. (2014) Intratumoral mistletoe (*Viscum album* L.) therapy in patients with unresectable pancreas carcinomas: a retrospective study. Integrative Cancer Therapies 13(4): 332–340, doi:10.1177/1534735413513637

The references marked with ✯ are included in abstract form in this documentation.

Schaefermeyer G., Schaefermeyer H. (1998) Treatment of pancreatic cancer with Viscum album (Iscador): a retrospective study of 292 patients 1986–1996. *Complementary Therapies in Medicine* 6, 172–177.

Study design

Design	Retrospective study with historical controls.
Patients	All patients with pancreatic cancer, who were treated with Iscador at the Lukas Klinik in Arlesheim from 1986 to 1996 either as in- or out-patients (n = 320). 292 patients fulfilled the criteria for inclusion. Less than 10% of the patients underwent surgery and over 50% had stage IV disease.
Treatment	Different dosages of Iscador M or Qu s.c.
Length of study	1986 – 1996.
Measurement	Survival.

Most important results

26.3% of the patients survived one year, which is remarkable in comparison with the values in the literature of approximately 10% survival. Median survival in the Iscador patients was high (6.58 months) in comparison with the published data with similar patient collectives (2.85 and 3.95 months respectively). Extraordinary improvements in quality of life, in association with the Iscador treatment were observed in particular patients. A statistical analysis was not carried out.

Table 1: Results according to stage of disease

Stage at initial diagnosis	n	Age (mean)	Time in weeks from initial diagnosis until first therapy with Iscador (median)	Survival in months (median)
I	15	59.0	38.1	17.0
II	26	62.7	8.6	10.9
III	39	59.7	7.4	9.3
IV	136	60.6	5.2	5.2
uncertain	76	61.8	9.1	7.2
total	292	64.0	7.0	6.6
operable patients	29	55.3	33.6	16.7

Matthes H., Friedel W. E., Bock P. R., Zänker K. S. (2010) Molecular Mistletoe Therapy: Friend or Foe in Established Anti-Tumor Protocols? A Multicenter, Controlled, Retrospective Pharmaco-Epidemiological Study in Pancreas Cancer. Current Molecular Medicine 10(4): 430–439.

Study design

Design	Cohort study with retrospective collection of data («retrolective Study»).
Centres	17 centres in Germany and Switzerland.
Patients	396 patients with histologically verified pancreatic tumour who had macroscopic complete resection and not prior radiation or neoadjuvant chemotherapy were eligible for the study. 201 of which received additional Iscador therapy (treatment group), 195 only received conventional basic therapy (control group).
Comparability	Within the overall control group (chemotherapy without Iscador but with/without best of care) more patients were at high risk (T3/T4 tumour stage: 71.3% of the patients), but less patients in this group had regional lymphnode involvement (37.4% vs. 66.7%); most of the patients in the chemotherapy/Iscador group had extended disease in respect to tumour size (more than 2 cm in diameter).
Treatment	Median length of observation during aftercare: 15.2 months (treatment group), 10.1 months (control group). Median/mean length of Iscador treatment: 15.0/20.5 months.
Length of study	Diagnosis time from 1993 – 2002.
Measurements	Efficacy: (1) rate and adjusted risk of documented AT-ADR (adjuvant therapy-related adverse drug reactions), assessed by adapting the National Institutes of Health Common Toxicity Criteria (CTC) in oncology; (2) predefined QoL surrogate criteria adapted from the symptom scales of the EORTC QLQ-C30 questionnaire, consisting of rate and adjusted risk of persistence of prespecified disease- and treatment-associated symptoms, particularly pain, skin, mucosal, gastrointestinal, and CNS symptoms; (3) adjusted overall survival (OS). Safety: Number of patients with documented systemic and local ADRs attributed to the Iscador therapy. Any evidence of possible tumour enhancement in the Iscador group was also documented.

Most important results

Among 396 evaluable patients a total number of 315 patients (79.5%) died during the study period. The adjusted relative hazard to die from any cause during the onset of aftercare and within the follow-up period was significantly lower in the Iscador group than in the overall control group. The adjusted hazard ratio (HR, 95% CI) was HR = 0.52 (0.40 – 0.68), $p < 0.001$, suggesting a relevant overall (OS) survival benefit for patients treated concomittantly with chemotherapy and Iscador (Fig. 1).

For results of this study concerning quality of life see 3.2.3.2 und concerning safety and tolerance see 6.1.5.

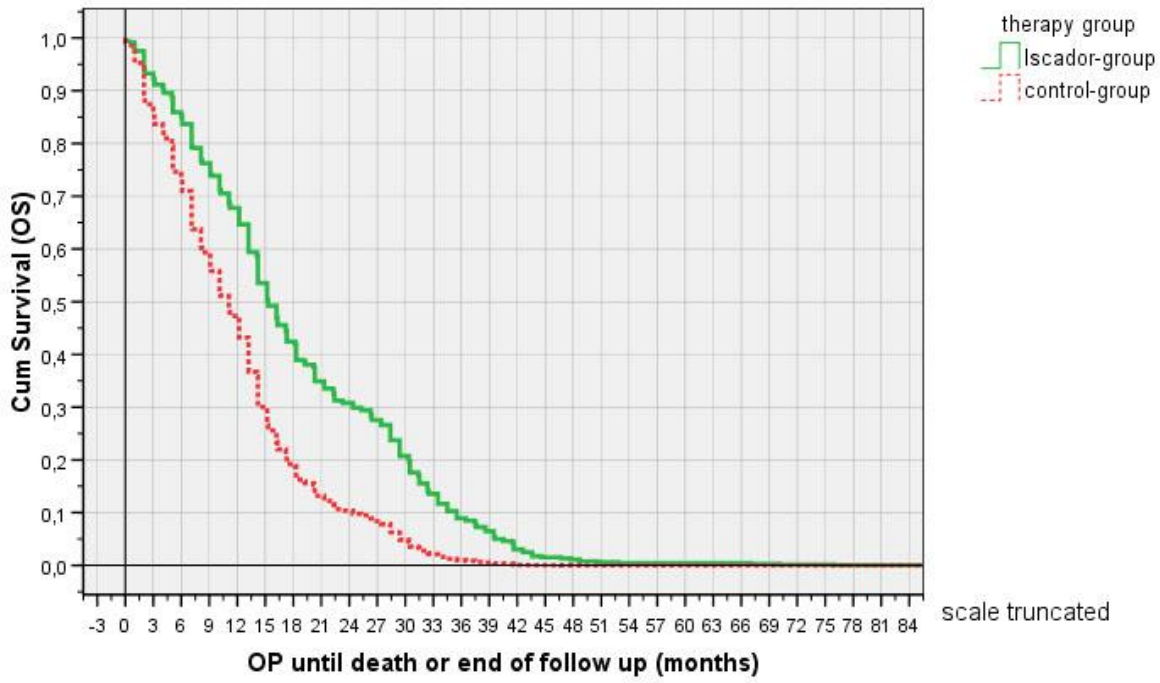

Fig. 1: Overall survival hazard ratio (OS-HR) estimated in the mistletoe extract Iscador group (n = 201, *full green line*) versus the control group (n = 195, *dotted red line*); adjusted OS-HR calculated by Cox proportional hazard regression method (Wald test) and confirmed in sensitivity analyses (according to Matthes et al. 2010).

Tröger W., Galun D., Reif M., Schumann A., Stanković N., Milićević M. (2013) *Viscum album* [L.] extract therapy with locally advanced or metastatic pancreatic cancer: a randomized clinical trial on overall survival. European Journal of Cancer 49: 3788–3797, DOI information: 10.1016/j.ejca.2013.06.043.

Study design

Design	Randomised, open label, group sequential, clinical phase III trial.
Centre	HPB Surgical Department, First Surgical Department, Clinical Centre of Serbia, Belgrade.
Patients	220 patients with locally advanced or metastatic adenocarcinoma of the pancreas with best supportive care.
Treatment	Iscador Qu special, three times a week or no antineoplastic therapy (control).
Recruitment	January 2009 until December 2010.
Measurements	12-month overall survival.

Summary

Purpose: To compare the 12-month overall survival (OS) of advanced pancreatic cancer patients receiving Iscador therapy or no antineoplastic therapy.

Patients and Methods: In this prospective, parallel, open label, monocenter, group-sequential, randomized phase III study patients with locally advanced or metastatic adenocarcinoma of the pancreas were stratified according to their prognosis index, a binary composite of age, tumor stage and performance status. «Poor» prognosis was defined as presenting at least two out of the three following criteria: UICC class = IV, age > 65, ECOG ≥ 2. Otherwise, patients were classified into «good» prognosis. Within each stratum, patients were evenly randomized to s.c. injections of Iscador Qu special in a dose-escalating manner from 0.01 mg up to 10 mg three times per week (n = 110), or no antineoplastic therapy (control, n = 110). All patients received best supportive care. The primary endpoint was 12-month OS to be repeatedly assessed in three subsequent group-sequential analyses.

Results: This first interim analysis includes data from 220 patients. Baseline characteristics were well balanced between the Iscador and control groups. Median OS for the Iscador versus control patients was 4.8 vs. 2.7 months (prognosis-group adjusted hazard ratio, HR = 0.49; p < 0.0001); within the «good» prognosis subgroup 6.6 vs. 3.2 months (HR = 0.43; p < 0.0001); within the «poor» prognosis subgroup 3.4 vs. 2.0 months (HR = 0.55; p = 0.0031). No Iscador-related serious or non-serious adverse events were observed.

Conclusion: In this analysis Iscador therapy shows a significant and clinically relevant increase of OS. The independent data monitoring committee recommended the termination of the trial due to proven efficacy. Iscador may provide an effective second-line therapy for patients with locally advanced or metastatic pancreatic cancer after failure of, or ineligibility for, first-line therapies.

For results concerning Quality of Life (QoL) see 3.1.3.1 (EORTC questionnaire) und 3.2.3.3 (body weight, disease-related symptoms).

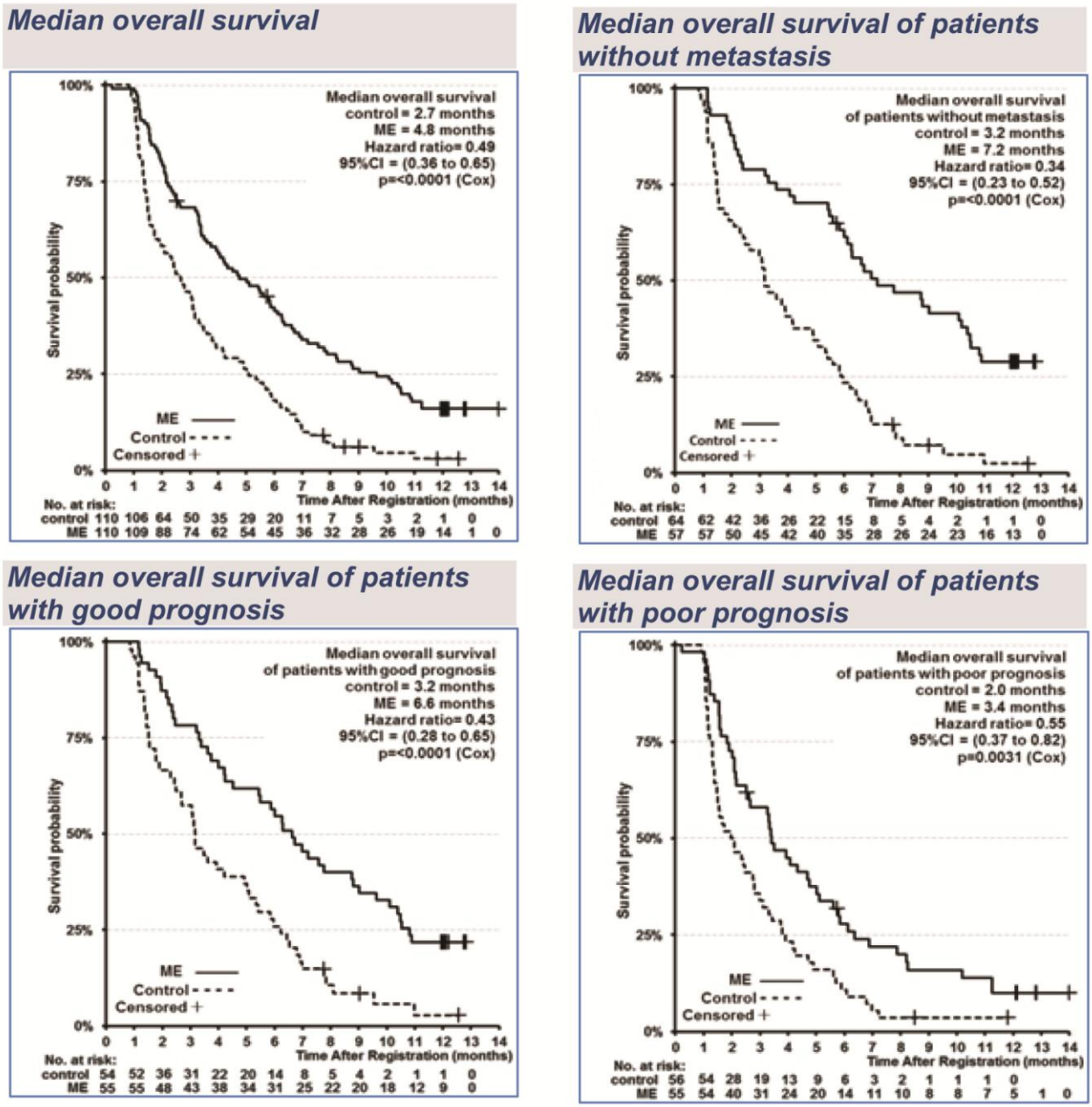

Fig. 1: Survival graphs for median overall survival for all patients, patients without metastases, patients with good and with poor prognosis.

5.3.3 Cancer of the Colon and Rectum

References

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The references marked with ✯ are included in abstract form in this documentation.

Leroi R. (1979) Die Iscadorbehandlung bei inoperablen kolorektalen Tumoren. [Iscador treatment of inoperable colorectal tumours.] *Krebsgeschehen* 11 (6), 163–165.

Study design

Design	Retrospective study with 2 groups.
Patients	155 patients with primary inoperable or primary only with palliative surgery colorectal cancer from the Lukas Klinik.
Treatment	*Group 1:* 101 patients received an adequate treatment with different dosages of Iscador (s.c., average of 128 injections per patient).
	Group 2: 54 patients either were not treated with Iscador or the treatment was discontinued after a short time (on average 19 injections per patient). Both groups were comparable regarding distribution of age, sex and histology.
Length of study	1962 – 1977.
Measurement	Survival.

Most important results

The median survival in group 1, Iscador patients, was 14 months versus 7 months in group 2. A statistical analysis was not carried out.

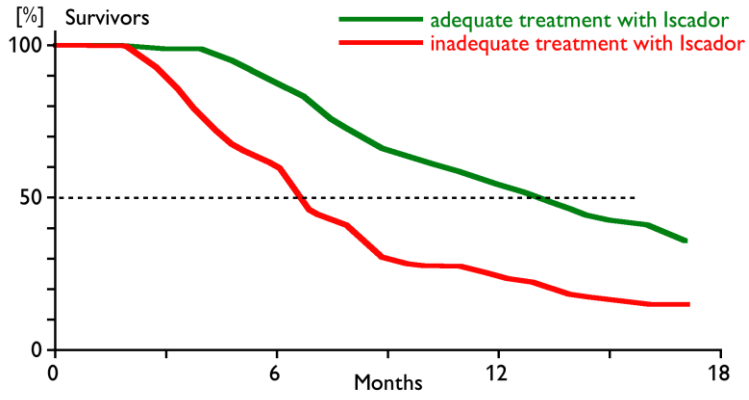

Fig. 1: Survival of patients with inoperable colorectal cancer over the course of 17 years with adequate treatment with Iscador (n = 101, median survival: 14 months) and without or with inadequate treatment with Iscador (n = 54, median survival: 7 months) (according to Leroi 1979).

Table 1: Results

	Group 1	Group
Inoperable colon cancer	66	25
Median survival (months)	12	5
Significant	yes	
Inoperable cancer of the rectum	35	29
Median survival (months)	16	8.5
Significant	yes	
Total	101	54
Median survival (months)	14	7
Significant	no	

Hellan J., Danmayr E., Hellan M. (1995) Stellenwert der Komplementärmedizin in der Behandlung onkologischer Patienten – dargestellt anhand des kolorektalen Karzinoms. [Value of complementary medicine in the treatment of oncologic patients – presented using colorectal cancer.] *Onkologie* 27 (4), 85–94.

Study design

Design	Retrospective study with comparative groups.
Patients	991 from 1117 patients who underwent surgery of their colorectal tumours, stage I–IV, who had been transferred to the L. Boltzmann-Institute for follow-up treatment could be evaluated. Concrete data from 940 patients are presented in this publication. 658 patients (70%) had cancer of the rectum and 282 patients (30%) had colon cancer.
Treatment	From the patients with colorectal cancer, one group received different dosages of Iscador s.c. as a post-surgery therapy (n = 158 and n = 294 respectively), a second group did not receive any therapy (n = 103 and n = 245 respectively) and a third group only received chemotherapy (n = 21 and n = 38 respectively). A group with only radiotherapy (n = 33) and a group with a combination therapy (n = 48) were formed from the patients with cancer of the rectum.
Length of study	1975 – 1990.
Measurement	Survival and relapse-free interval.

Most important results

This retrospective evaluation of data from patients who underwent surgery of their colorectal tumours showed that Iscador mainly led to an increase in median survival and delayed relapse.

Statistically significant differences could be seen between the Iscador and control groups in lymph node negative cancer of the rectum patients. The rate of relapse decreased by 18% in patients with stage I disease and by 30.2% in patients with stage II disease. In stage III lymph node positive cancer of the rectum, Iscador significantly decreased the rate of relapse by 33%. In stage III lymph node positive cancer of the rectum, Iscador significantly decreased the rate of relapse by 33.2%.

Patients under 75 years of age and those without stage IV disease responded better to the therapy with Iscador than older patients and those with stage IV disease.

Table 1: Results according to stage of disease

	Colon cancer			Cancer of the rectum				
	Iscador	**No therapy**	**Chemotheray**	**Iscador**	**No therapy**	**Chemotherapy**	**Radiotherapy**	**Combination therapy**
Stage I: T_{1-2} N_0 M_0	23	12		73	54			
Median survival in days	2942	2488		3210	2268			
Significance	no			no				
Number of relapses	5 (21.7%)	3 (25%)		22 (30.2%)	26 (48.1%)			
Significance	no			yes ($p < 0.05$)				
Stage II: T_{3-4} N_0 M_0	41	43	7	103	67	12	19	19
Median survival in days	2346	2736		2163	1477			
Significance	no			no				
Number of relapses	15 (36.6%)	18 (41.9%)		38 (36.9%)	45 (67.2%)			
Significance	no			yes ($p < 0.05$)				
Stage III: T_{1-4} N_+ M_0	51	23	–	66	65	7	14	19
Median survival in days	929	580		1251	1083	950	849	1067
Significance	no			no				
Number of relapses	23 (45.1%)	18 (78.3%)		31 (47%)	52 (80%)	–	8 (58%)	13 (48%)
Significance	yes ($p < 0.05$)			yes ($p < 0.05$)				
Stage IV: T_{1-4} N_x M_{0-1}	43	25	14	52	59	19		10
Median survival in days	347	425	383	330	536	371		544
Significance	no			no				
Number of patients	158	103	21	294	245	38	33	48
	282			658				
	940							

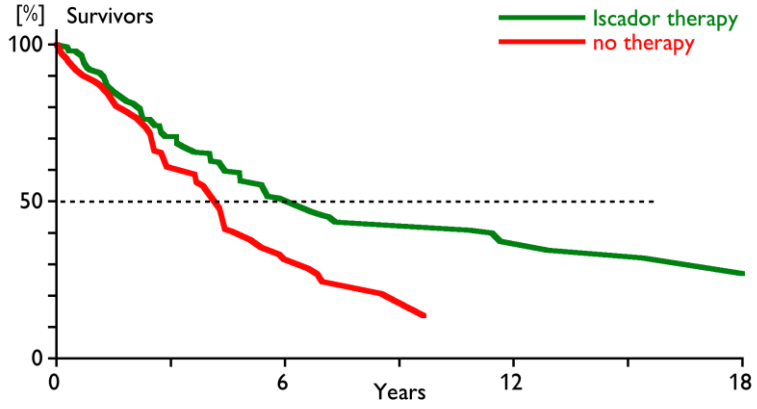

Fig. 1: Course of survival of patients with operated cancer of the rectum in stage II and lymph node negative without further therapy (n = 67, median survival: 1477 days) and with Iscador therapy (n = 103, median survival: 2163 days) (according to Hellan et al. 1995).

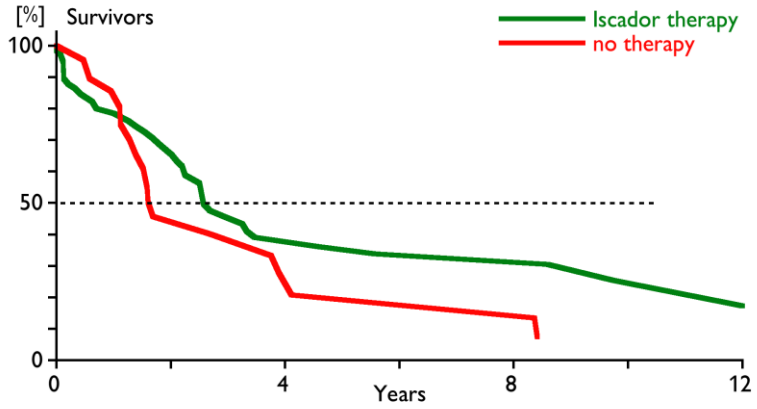

Fig. 2: Course of survival of patients with operated colon cancer in stage III and lymph node negative without further therapy (n = 23, median survival: 580 days) and with Iscador therapy (n = 51, median survival: 929 days) (according to Hellan et al. 1995).

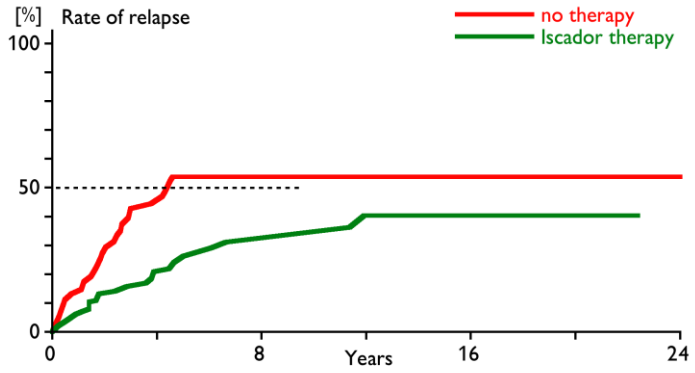

Fig. 3: Rate of relapse in patients with operated cancer of the rectum in stage I and lymph node negative without further therapy (n = 54, number of patients with relapse: 26 (48%)) and with Iscador therapy (n = 73, number of patients with relapse: 22 (30%)). The difference is statistically significant (according to Hellan et al. 1995).

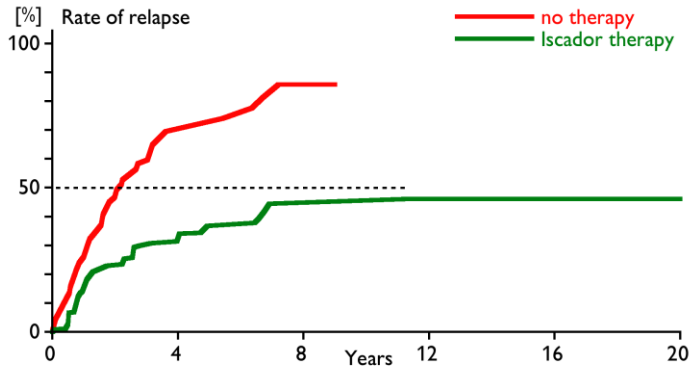

Fig. 4: Rate of relapse in patients with operated cancer of the rectum in stage II and lymph node negative without further therapy (n = 67, number of patients with relapse: 45 (67%)) and with Iscador therapy (n = 103, number of patients with relapse: 38 (37%)). The difference is statistically significant (according to Hellan et al. 1995).

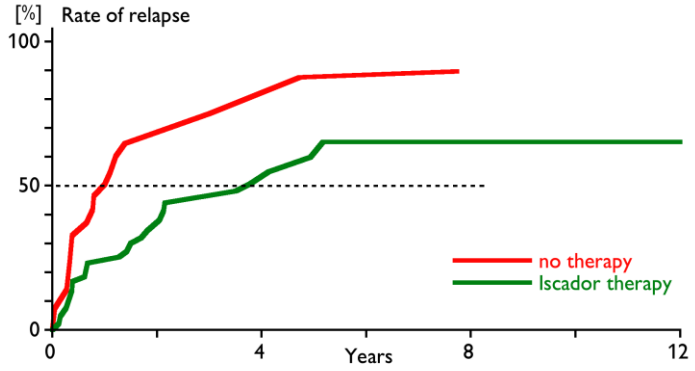

Fig. 5: Rate of relapse in patients with operated colon cancer in stage III and lymph node positive without further therapy (n = 23, number of patients with relapse: 18 (78%)) and with Iscador therapy (n = 51, number of patients with relapse: 23 (45%)). The difference is statistically significant (according to Hellan et al. 1995).

Grossarth-Maticek R., Kiene H., Baumgartner S.M., Ziegler R. (2001a) Use of Iscador, an extract of European mistletoe (*Viscum album*), in cancer treatment: prospective nonrandomized and randomized matched-pair studies nested within a cohort study. *Alternative Therapies* 7 (3), 57–78.

Study design

Design	Prospective, epidemiological long-term study, matched-pair-technique.
Patients	Within a collective of patients with colorectal tumours, patients who received treatment with Iscador were matched as closely as possible with patients who did not receive treatment with Iscador. 69 pairs of patients with cancer of the rectum and 90 pairs of patients with colon cancer could be found after following the strict criteria required for matching.
Treatment	The patients in the Iscador group received in addition to conventional cancer treatment an individual therapy with different doses and types of s.c. applied Iscador. The control group with matched patients received only conventional cancer treatment and did not receive any type of mistletoe treatment.
Length of study	1973 – 1998.
Measurement	Survival.

Most important results

The patients who were treated with Iscador showed an increase in mean survival. Those with cancer of the rectum showed an increase of 54% from 3.04 years in the control group to 4.68 years in the Iscador group. Those with colon cancer showed an increase of 39% from 4.46 years in the control group to 6.18 years in the Iscador group. The differences with $p = 0.002$ and $p < 0.001$ respectively are statistically highly significant.

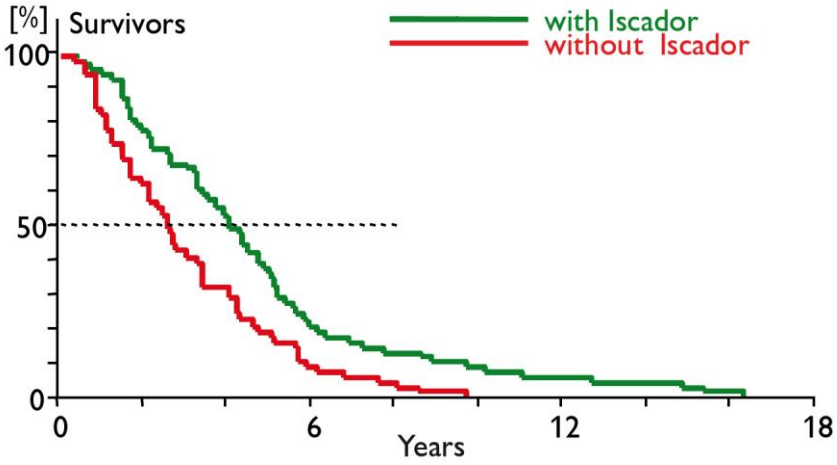

Fig. 1: Survival of patients with cancer of the rectum over the course of 16 years under therapy with Iscador (n = 69) or without Iscador therapy (n = 69) (according to Grossarth-Maticek et al. 2001).

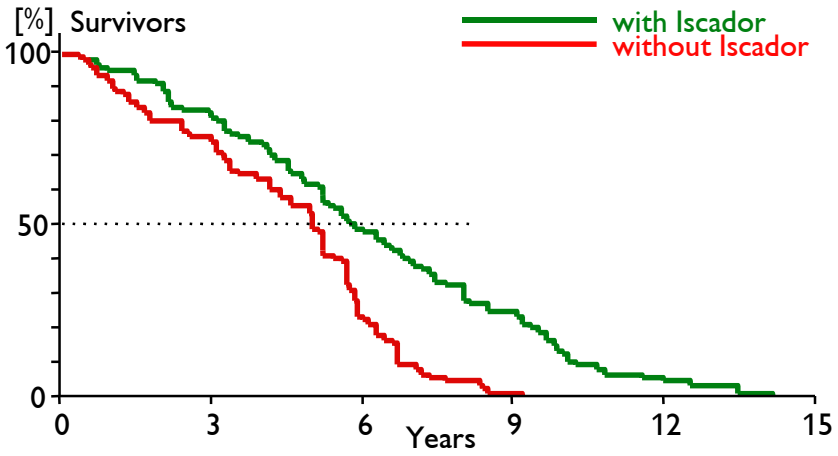

Fig. 2: Survival of patients with colon cancer over the course of 14 years under therapy with Iscador (n = 90) or without Iscador therapy (n = 90) (according to Grossarth-Maticek et al. 2001).

For further results of this study concerning survival see 5.6.2.

Friedel W. E., Matthes H., Bock P. R., Zänker K. S. (2009) Systematic Evaluation of the Clinical Effects of Supportive Mistletoe Treatment within Chemo- and/or Radiotherapy Protocols and Long-Term Mistletoe Application in Non-metastatic Colorectal Carcinoma: Multicenter, Controlled, Observational Cohort Study. Journal of the Society for Integrative Oncology 7(4): 137–145.

Study design

Design	Cohort study with retrospective collection of data («retrolective Study»).
Centres	26 centres in Germany and Switzerland.
Patients	804 patients with colorectal cancer without metastases, with conventional basic therapy (surgery, radiotherapy, chemotherapy), 429 of which received additional Iscador therapy (treatment group), 375 only received conventional basic therapy (control group).
Comparability	The patients in the treatment group were younger, in more advanced disease with more symptoms but less comorbidity.
Treatment	Median length of observation during aftercare: 58 months (treatment group), 51 months (control group). Median length of Iscador treatment: 52 months.
Length of study	1990 – 2004.
Measurements	Efficacy: (1) rate and adjusted risk of documented AT-ADR (adjuvant therapy-related adverse drug reactions), assessed by adapting the National Institutes of Health Common Toxicity Criteria (CTC) in oncology; (2) predefined QoL surrogate criteria adapted from the symptom scales of the EORTC QLQ-C30 questionnaire, consisting of rate and adjusted risk of persistence of pre-specified disease- and treatment-associated symptoms, particularly pain, skin, mucosal, gastrointestinal, and CNS symptoms; and (3) adjusted disease-free survival (DFS) calculated by the Cox proportional hazard regression method. Safety: Number of patients with documented systemic and local ADRs attributed to the Iscador therapy. The number and severity of ADRs were evaluated according to CTC. Any evidence of possible tumour enhancement in the Iscador group was also documented.

Most important results concerning disease-free survival

The adjusted relative hazard to experience a first tumour related event (i.e., recurrence, distant metastasis, or death) during the therapy and follow-up period was significantly lower in the Iscador group than in the controls, despite the more advanced disease in the Iscador group at baseline. The adjusted HR (95% CI) of 0.68 (0.51–0.92), p = .013, suggests a longer disease-free period and a survival benefit in ISC-treated patients (Fig. 1).

For results of this study concerning quality of life (disease- and therapy-induced symptoms) see 3.2.3.1 and concerning safety and tolerance see 6.1.4. For the results of a subgroup analysis concerning Iscador Qu see 3.2.3.4 (disease- and therapy-induced symptoms) and 5.3.3.5 (disease-free survival).

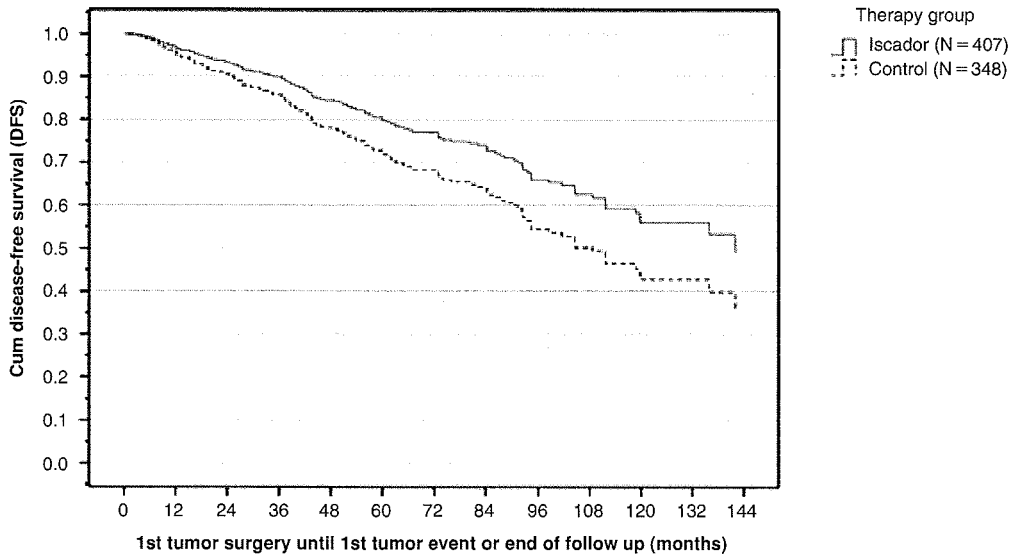

Fig. 1: Disease-free survival hazard ratio (DFS-HR) estimated in the mistletoe extract Iscador group (n = 407, *full line*) versus the control group (n = 348, *dotted line*); adjusted DFS-HR calculated by Cox proportional hazard regression method (Wald test) and confirmed in sensitivity analyses (according to Friedel et al. 2009).

Zänker K. S., Matthes H., Bock P. R., Hanisch J. (2012) A Specific Mistletoe Preparation (Iscador-Qu) in Colorectal Cancer (CRC) Patients: More than Just Supportive Care? Journal of Cancer Science and Therapy 4(9): 264–270.

Study design

Design	Cohort study with retrospective collection of data («retrolective Study»).
Centres	26 centres in Germany and Switzerland.
Patients	318 patients with colorectal cancer without metastases, with conventional basic therapy (surgery, radiotherapy, chemotherapy), 106 of which received additional Iscador Qu therapy (treatment group), 212 received conventional basic therapy (control group) only.
Treatment	Median length of observation: 59 months (treatment group), 43 months (control group). Median length of Iscador treatment: 54 months.
Study aim	Secondary and confirmatory analysis of the original data set from study 3.2.3.1/5.3.3.4 with respect to Iscador Qu concerning disease-free survival and disease- and therapy-induced symptoms.

Summary: Disease-free survival

Rationale: In the study 5.3.3.4 the results were reported from a pharmaco-epidemiological, retrospective observational cohort study in colorectal carcinoma (CRC) patients UICC stage I-III, receiving chemo- and/or radiotherapy together with Iscador as supportive care versus conventional treatment. The endpoint has been disease-free survival.

Objective: Secondary and confirmatory analysis with respect to Iscador Qu.

Results: Patients receiving Iscador Qu in a supportive care mode simultaneously with chemo- and/or radiotherapy (n = 106) showed a significant delay of metastasis formation and longer disease-free survival compared to conventionally treated patients (n = 212) (control). To make the analysis more robust, patients treated by the chemo- and/or radiotherapy protocols were also analyzed and stratified for the UICC I-III stages. Accordingly to the overall Kaplan-Meier analysis result, patients receiving Iscador Qu as supportive care presented significantly longer median time to distant metastases formation (metastasis-free survival) within the course of the observational cohort study (133+ months, Iscador Qu) versus 94 months (control), p (Log Rank) = 0.002. In the Cox regression analysis, the confounder-adjusted hazard ratio, HR, (95% confidence interval) came up to HR (metastasis) = 0.31 (0.13 – 0.711), p = 0.006. This result indicates an estimated 69% metastasis-hazard-reduction in the Iscador Qu group relative to the controls.

Clinical implication: This secondary analysis of the original data set suggests that Iscador Qu appears to be a naturally tailored molecular composition to target CRC patients by showing a potential to increasing the metastases-free survival.

Limitations: The effects should be interpreted with some caution because the applied study design shares some potential risk for bias common to all non-randomized observational studies. However, potential biases were tried to minimize by systematic multivariable adjusting.

For the overall results of this study see 3.2.3.1 (disease- and therapy-induced symptoms), 5.3.3.4 (survival), 6.1.4 (safety and tolerance); for this subgroup analysis particularly concerning disease- and therapy-induced symptoms see 3.2.3.4.

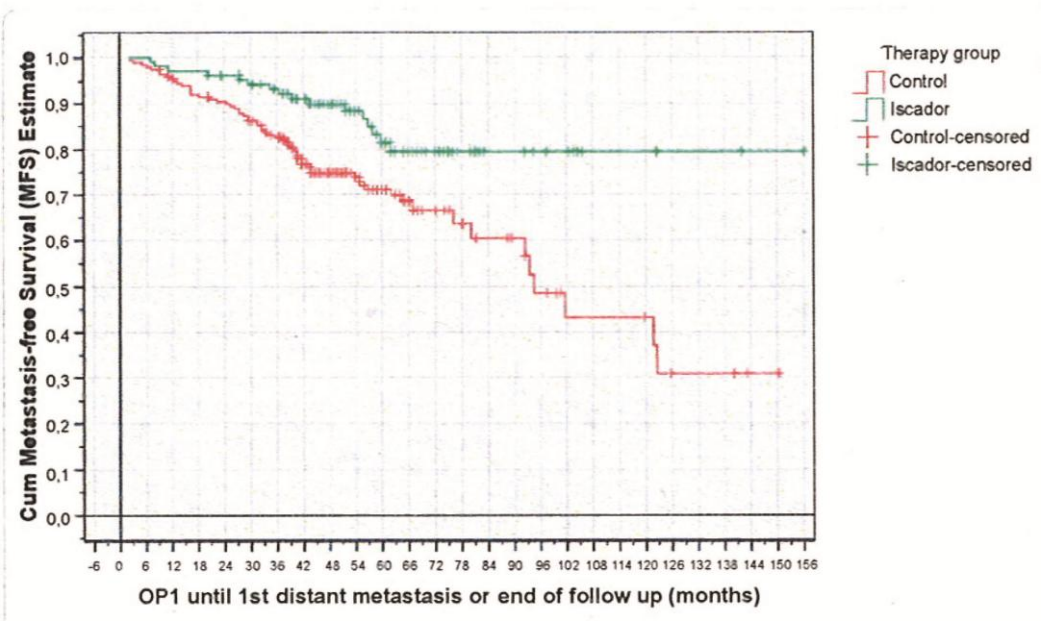

Fig. 1: Kaplan-Meier analysis of metastases free survival of all patients (n = 318, UICC stages I-III). Green: Iscador Qu group, red: control group.

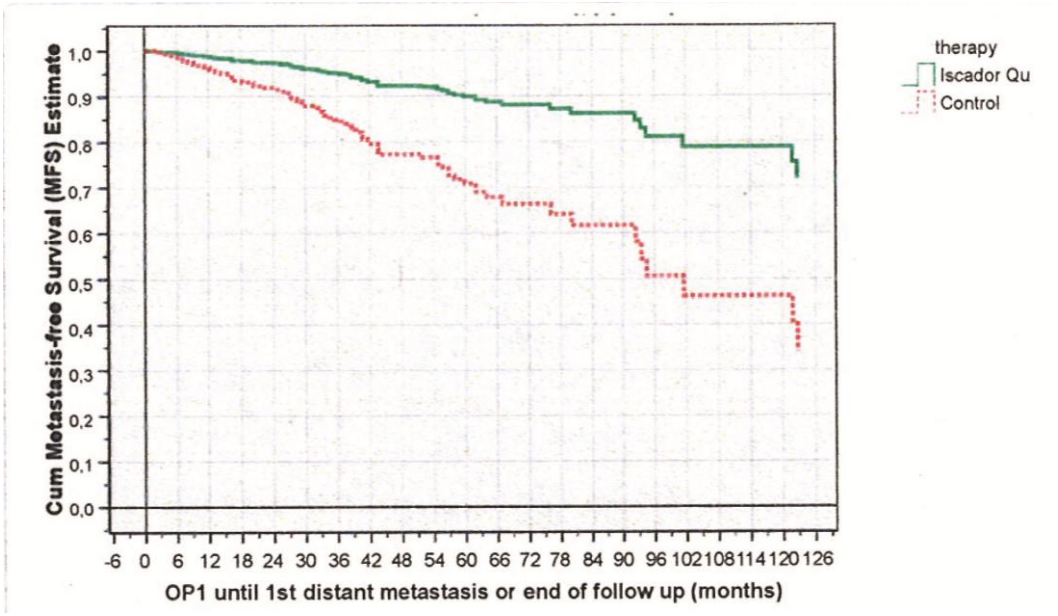

Fig. 2: Confounder-adjusted Cox proportional hazard regression analysis of metastases free survival in all patients (n = 318, UICC stages I-III). Green: Iscador Qu group, red: control group.

5.3.4 Liver Metastases

References

- ☆ Hoffmann J. (1979) Die Iscadorbehandlung bei Lebermetastasen. Krebsgeschehen 11 (6), 172–175.
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- Salzer G., Frey S. (1990) Ergebnisse der Behandlung von Lebermetastasen nach kolorektalen Karzinomen. Erfahrungsheilkunde 2, 109–112.

The references marked with ☆ are included in abstract form in this documentation.

Hoffmann J. (1979) Die Iscadorbehandlung bei Lebermetastasen. [Iscador treatment of liver metastases.] *Krebsgeschehen* 11 (6), 172–175.

Study design

Design	Retrospective study with 2 groups.
Patients	310 patients from the Lukas Klinik seen on the 31.07.1978. 188 of those received a longer treatment with Iscador (≥ 3 Iscador series, on average 8.6 series) and 122 received an obviously inadequate treatment with Iscador (< 3 Iscador series, on average 1.2 series). Distribution of age and sex, as well as the position of the primary tumour were comparable in the two groups.
Treatment	Different dosages of Iscador s.c.
Length of study	1962 – 1978.
Measurement	Survival.

Most important results

The mean survival of the Iscador patients was 14.1 months in comparison with 7.9 months in the control group. By dividing the patients into groups according to position of the primary tumour, an increase in mean survival due to Iscador could be seen in all the sub-groups. A statistical analysis is not available.

Salzer G. (1984) Ergebnisse onkologischer Behandlungsversuche bei Lebermetastasen. [Results from observations of treatments of liver metastases.] *Krebsgeschehen* 16 (2), 46–51.

Study design

Design	Retrospective study with 4 groups.
Patients	All of the 63 patients who were treated for liver metastases at the Boltzmann Institute in Vienna, between 1979 and the end of 1982.
Treatment	14 patients did not receive any tumour specific therapy, 14 patients received cytostatics (5-FU), 20 patients received mistletoe (14 Iscador, 6 Helixor) as a single treatment regimen and 15 patients received a combination of cytostatics and mistletoe. Iscador application was s.c and in different dosages.
Length of study	1979 – 1982.
Measurement	Survival.

Most important results

The highest mean survival of 380 days was reached in the group with combined mistletoe-cytostatic therapy. The mean survival in the mistletoe group was 186 days, in the cytostatics group 120 days and in the untreated controls 64 days. The differences are not statistically significant. An improvement in quality of life due to Iscador is indicated and was documented according to case**.**

Table 1: Results

	Control	Cytostatics	Mistletoe	Cytostatics + mistletoe
n	14	14	20	15
Median survival (days)	49	78	120	197
Mean survival (days)	64	120	186	380
Significant			no	

5.4 Cancer of the Respiratory Tract

5.4.1 Lung Cancer

5.4.2 Carcinosis of the Pleura

5.4.1 Lung Cancer

References

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☆ Salzer G., Danmayr E., Wutzlhofer F., Frey S. (1991) Adjuvante Iscador-Behandlung operierter nicht-kleinzelliger Bronchuskarzinome. Ergebnisse einer randomisierten Studie. Onkologie 23 (4), 93–98.

☆ Dold U. et al. (1991) Krebszusatztherapie beim fortgeschrittenen nicht-kleinzelligen Bronchialkarzinom. G. Thieme Verlag, Stuttgart, New York.

☆ Grossarth-Maticek R., Kiene H., Baumgartner S.M., Ziegler R. (2001a) Use of Iscador, an extract of European mistletoe (Viscum album), in cancer treatment: prospective nonrandomized and randomized matched-pair studies nested within a cohort study. Alternative Therapies 7 (3), 57–78. – Addendum to Iscador article : Alternative Therapies 7 (4), 26. – Deutsche Übersetzung: Der Merkurstab 2001, 54 (3), 171–189.

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Salzer G., Havelec L. (1978) Rezidivprophylaxe bei operierten Bronchuskarzinom-Patienten mit dem Mistelpräparat Iscador. Ergebnisse eines klinischen Versuchs aus dem Jahre 1969-1971. [Relapse prophylaxis with the mistletoe compound Iscador in patients with operated lung cancer. Results of a clinical trial from 1969-1971.] *Onkologie* 1 (6), 264–267.

Study design

Design	Prospective, controlled study.
Patients	77 patients were divided into two groups after surgery for lung cancer. All of the patients who were admitted from further away (n = 37), were treated post-surgically with Iscador. Patients from the local area were the control group (n = 40). Both of the groups were comparable regarding age, and tumour stage and histological type.
Treatment	Different dosages of Iscador s.c.
Length of study	1969 – 1971.
Measurement	Survival.

Most important results

38% of the Iscador patients and 15% of the control group were alive 6 years after lung resection ($p < 0.01$). The difference between Iscador treatment and the control was statistically significant in both the lymph node positive and the lymph node negative groups.

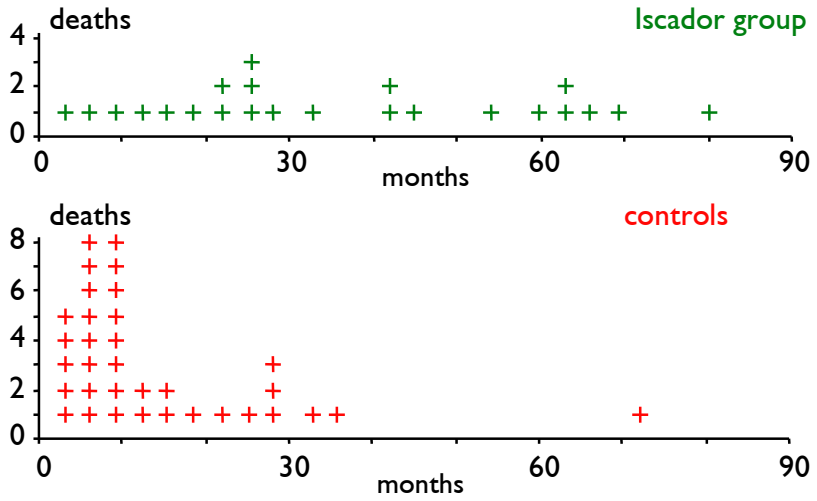

Fig. 1: Deaths (+ = 1 death) within 80 months after lung cancer surgery in a group of 37 patients who were post-operatively treated with Iscador (above), and in a group of 40 patients who did not receive Iscador (below). All of the patients were operated on at the same surgical ward in the pneumologic centre, Vienna (according to Salzer and Havelec 1978).

Table 1: Results according to stage of disease.

	Iscador	Control
Stage I: T_1 N_0	12	10
Survivors after 80 months	6 (50%)	3 (33%)
Significant	no	
Stage II: T_2 N_0, T_1 N_1, T_2 N_1	15	11
Survivors after 80 months	5 (33%)	2 (18%)
Significant	no	
Stage III: T_3 N_0 to T_3 N_2, T_1 N_2, T_2 N_2	10	19
Survivors after 80 months	3 (33%)	1 (5%)
Significant	yes ($p < 0.01$)	
Stage I – III	37	40
Survivors after 80 months	14 (38%)	6 (15%)
Significant	yes ($p < 0.01$)	

Table 2: Results according to lymph node metastases.

	Iscador	Control
Lymph node negative	22	22
Survivors after 80 months	10 (45%)	5 (23%)
Significant	yes ($p < 0.01$)	
Lymph node positive	15	18
Survivors after 80 months	4 (27%)	1 (6%)
Significant	yes ($p < 0.01$)	

Salzer G. (1980) *Kleine randomisierte Bronchus-Studie*. [Small randomised lung study.] Interner Bericht, L. Boltzmann-Institut für klinische Onkologie im Krankenhaus der Stadt Wien-Lainz.

Study design

Design	Prospective, controlled, randomised study.
Patients	26 patients who underwent radically surgery of lung cancer (lymph node negative), presented as case studies, were randomised by the surgical ward, irrelevant of stage of disease. The comparability of the groups after randomisation was not assessed or documented.
Treatment	12 patients were treated as out-patients with different dosages of Iscador s.c. and 14 patients without further therapy were regularly controlled.
Length of study	1974 – 1980.
Measurement	Survival.

Most important results

The Iscador patients showed a 5-year survival of 67% in comparison with 37% in the control group ($p < 0.05$).

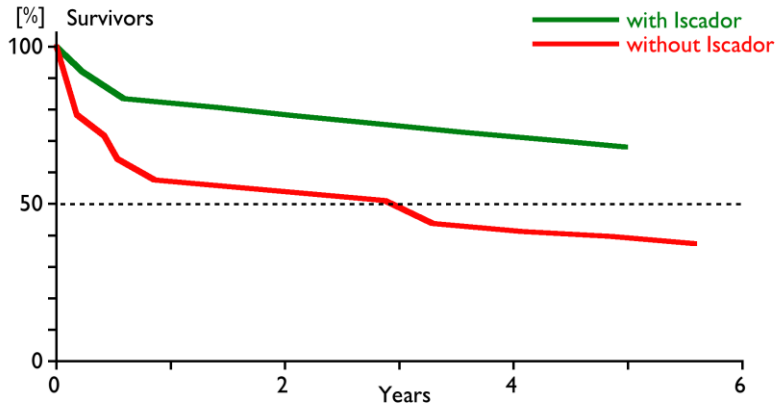

Fig. 1: Course of survival in patients who underwent surgery of lung cancer without further treatment (n = 14) and with Iscador therapy (n = 12) (according to Salzer 1980).

Dold U. et al. (1991) *Krebszusatztherapie beim fortgeschrittenen nicht-kleinzelligen Bronchialkarzinom*. [Complementary cancer therapy of advanced non-small cell lung cancer.] G. Thieme Verlag, Stuttgart, New York.

Study design

Design	3 arm, prospective, randomised, placebo-controlled multi-centre study.
Patients	337 patients with advanced non-small cell inoperable lung cancer and were without justified indication for an initial radiotherapy or chemotherapy were evaluated.
Treatment	Iscador U c Hg or Qu c Hg s.c. 3 times a week at various doses over more than 6 months (n = 114). Placebo was a multivitamin supplement (BVK Roche) with 7 vitamins, once a week i.m. (n = 113). The third group (n = 110) received Polyerga (and anti-tumour glucosamine) once a week i.m.
Length of study	1978 – 1986.
Measurements	Survival, tumour remission, symptom-free interval, Karnofsky Index, patients' subjective condition, quality of life.

Most important results

The distribution of the patients according to TNM categories is shown in Table 1 (test for inhomogeneity not significant: p = 0.62) and according to tumour stage in Table 2 (test for inhomogeneity between the three therapy arms not significant: p = 0.89).

The median survival in the Iscador group was 9.1 months and only tended to differ from the median survival in the placebo group with 7.6 months (p = 0.24, one-sided test). The median survival in the Iscador group was increased by 20% however in comparison with the placebo.

The diagnostic findings referring to the tumour and documented by the doctor improved in the Iscador group by 27% in comparison with an improvement of 19% in the placebo group (narrowly not significant, p = 0.08, one-sided test).

Remission was observed in 30 cases in the Iscador group and in the placebo group in 22 cases (p = 0.10, one-sided test).

The subjective condition documented by the doctor improved by 59% in the Iscador patients and by 45% in the placebo patients. The difference is statistically significant (p = 0.018, one-sided test).

The Karnofsky Index did not show significant differences between the Iscador group and the placebo group.

Quality of life was measured at 5 levels, using categories on reduced performance, pain, coughing, loss of appetite, shortness of breath and sputum containing blood. There were not any notable differences between the therapy groups.

Table 1: Distribution of patients according to TNM categories

Category	Number of Patients				
	Iscador	Polyerga	Placebo	Total	Percentage
T_1 N_0 M_0	6	3	3	12	3.6
T_2 N_0 M_0	18	21	19	58	17.2
T_1 N_1 M_0	2	1	3	6	1.8
T_2 N_1 M_0	12	11	16	39	11.6
T_{1-2} N_2 M_0	2	4	5	11	3.3
T_3 N_0 M_0	11	10	13	34	10.1
T_3 N_{1-2} M_0	20	17	17	54	16.0
T_1 N_{0-2} M_1	5	1	0	6	1.8
T_2 N_0 M_1	5	6	3	14	4.2
T_2 N_{1-2} M_1	13	7	9	29	8.6
T_3 N_0 M_1	9	8	5	22	6.5
T_3 N_{1-2} M_1	10	17	17	44	13.1
NX / MX	1	4	3	8	2.4
Total	114	110	113	337	

Table 2: Distribution of the patients according to tumour stage

Stage	Number of Patients				
	Iscador	Polyerga	Placebo	Total	Percentage
I	26	26	25	77	23.4
II	11	11	16	38	11.6
III	35	30	35	100	30.4
IV	41	39	34	114	34.6
Total	113	106	110	329	

For results of this study concerning quality of life see 3.2.4.1 and concerning remissions see 4.4.1.

Salzer G., Danmayr E., Wutzlhofer F., Frey S. (1991) Adjuvante Iscador-Behandlung operierter nicht-kleinzelliger Bronchuskarzinome. [Adjuvant treatment of non-small cell lung cancer after surgery with Iscador.] *Onkologie* 23 (4), 93–98.

Study design

Design	Controlled, randomised, multi-centre study.
Patients	183 patients with non-small cell lung cancer from the hospitals in Vienna-Lainz, Innsbruck, Grosshansdorf and Wöllershof. The patients in both groups were comparable in respect to age, sex, lymph node metastases and histology.
Treatment	The patients were randomised after surgery into a group with treatment with Iscador (n = 86) and a group without tumour specific therapy (n = 97).
Length of study	1981 – 1990.
Measurement	Survival.

Most important results

Mean survival was 2.5 months longer in the group treated with Iscador (40 months) than in the control group (37.5 months). After 8 years, 40% of the Iscador group and 25% of the control group were still alive. A statistical significance could not be achieved.

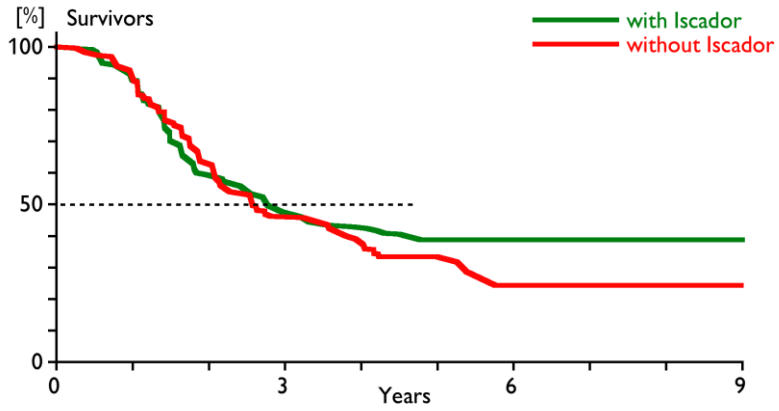

Fig. 1: Course of survival in patients with operated non-small cell lung cancer without further therapy (n = 97, mean survival: 37.5 months) and with treatment with Iscador (n = 51, mean survival: 40 months) (according to Salzer et al. 1991).

Table 1: Results according to stage of tumour

	Iscador	Control
Stage I – II: Lymph node negative, T_1–T_3 N_0	59	65
Died	30	43
Post-mortem	17	18
Tumour-free	6	2
Relapse/metastases (cases)	29 (49%)	33 (50%)
Median survival (months)	44	43
Significant	no	
Stage II – III: Lymph node positive, T_1–T_3 N_1–N_2	16	27
Died	10	20
Post-mortem	1	4
Tumour-free	1	1
Relapse/metastases (cases)	8 (50%)	20 (74%)
Median survival (months)	31	24
Significant	no	
Stage IV: T_4 N_0 ,T_1–T_4 N_3	11	5
Died	11	4
Post-mortem	4	2
Tumour-free	0	0
Relapse/metastases (cases)	16.5	17
Significant	no	
Total	86	97
Died	**51**	67
Post-mortem	22	24
Tumour-free	7	3
Relapse/metastases (cases)	44 (50%)	53 (55%)
Median survival (months)	33	31
Significant	no	

Grossarth-Maticek R., Kiene H., Baumgartner S.M., Ziegler R. (2001a) Use of Iscador, an extract of European mistletoe (*Viscum album*), in cancer treatment: prospective nonrandomized and randomized matched-pair studies nested within a cohort study. *Alternative Therapies* 7 (3), 57–78.

Study design

Design	Prospective, epidemiological long-term study, matched-pair-technique.
Patients	Within a collective of patients with non-small and small cell lung cancer, patients who received treatment with Iscador were matched as closely as possible with patients who did not receive treatment with Iscador. 52 pairs of patients with non-small cell lung cancer and 21 pairs of patients with small cell lung cancer could be found after following the strict criteria required for matching.
Treatment	The patients in the Iscador group received in addition to conventional cancer treatment an individual therapy with different doses and types of s.c. applied Iscador. The control group with matched patients received only conventional cancer treatment and did not receive any type of mistletoe treatment.
Length of study	1973 – 1998.
Measurement	Survival.

Most important results

The Iscador therapy increased survival in the patients with non-small cell lung cancer by 18% from 2.60 years (control group) to 3.08 years (Iscador group). The Iscador therapy increased survival in the patients with small cell lung cancer by 38% from 1.44 years (control group) to 1.99 years (Iscador group). The differences are significant (p = 0.05 and p = 0.02).

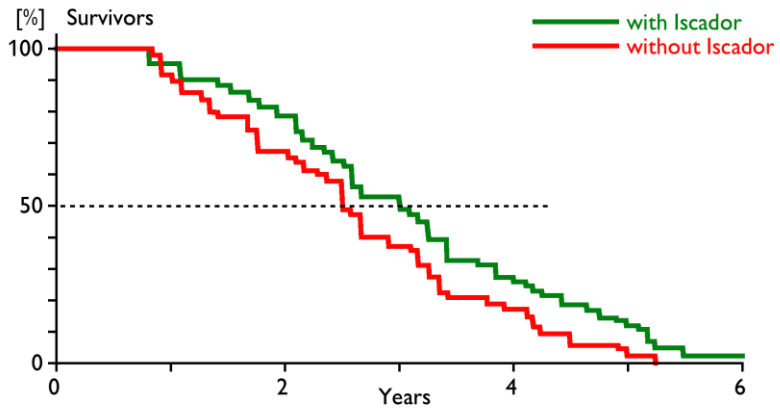

Fig. 1: Survival of patients with non-small cell lung cancer over the course of 7 years with Iscador therapy (n = 52) and without Iscador therapy (n = 52) (according to Grossarth-Maticek et al. 2001a).

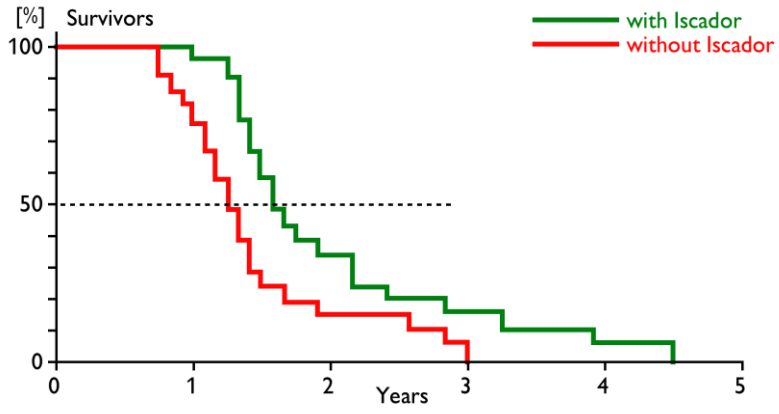

Fig. 2: Survival of patients with small cell lung cancer with Iscador therapy (n = 21) and without Iscador therapy (n = 21) (according to Grossarth-Maticek et al. 2001a).

For further results of this study concerning survival see 3.6.2.

5.4.2 Carcinosis of the Pleura

References

- Salzer G. (1977) Die lokale Behandlung carcinomatöser Pleuraergüsse mit dem Mistelpräparat Iscador. Österreichisches Kneipp Magazin 4 (1), 13–14.
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- Böck D., Salzer G. (1980b) Iscadorbehandlung maligner Pleuraergüsse, cytologische Befunde und klinische Ergebnisse. In: Wolff O., Die Mistel in der Krebsbehandlung, Vittorio Klostermann (2. Auflage), Frankfurt, 111–123. [Bericht aus einem Kollektiv]

☆ Salzer G. (1983) Lokalbehandlung der Pleurakarzinose. Krebsgeschehen 15 (2), 52–53. [Bericht aus einem Kollektiv]

- Böck D. (1983) Neue zytomorphologische Ergebnisse bei lokaler Behandlung des karzinomatösen Pleuraergusses. Krebsgeschehen 15 (2), 33–34. [Bericht aus einem Kollektiv]
- Salzer G. (1986) Pleura Carcinosis; Cytomorphological findings with the mistletoe preparation Iscador and other pharmaceuticals. Oncology 43 (Suppl. 1), 66–70. [Bericht aus einem Kollektiv]

☆ Salzer G., Popp W. (1990) Die lokale Iscadorbehandlung der Pleurakarzinose. In: Jungi W.F., Senn H.J. (Hrsg.) Krebs und Alternativmedizin II. Springer Verlag, Berlin, Heidelberg, 36–49.

The references marked with ☆ are included in abstract form in this documentation.

Salzer G. (1983) Lokalbehandlung der Pleurakarzinose. [Localised treatment of carcinosis of the pleura.] *Krebsgeschehen* 15 (2), 52–53.

Study design

Design	Retrospective study.
Patients	89 patients (75% of which with breast cancer) with carcinomatous pleural effusion.
Treatment	After puncturing the pleural effusion, instillation of 1 ml 5% Iscador in the pleural cavity.
Length of study	1976 – 1981.
Measurements	Number of instillations until pleurodesis and survival.

Most important results

An average of 3.5 intra-pleural instillations with Iscador lead to pleurodesis. There were only 2 failures among the 89 patients. Mean survival was 6.3 months.

Salzer G., Popp W. (1990) Die lokale Iscadorbehandlung der Pleurakarzinose. [Localised treatment of carcinosis of the pleura with Iscador.] In: Jungi, Senn H.J. (Hrsg.) *Krebs und Alternativmedizin* II. Springer Verlag, Heidelberg, Wien, 70–83.

Study design

Design	Retrospective study.
Patients	192 patients with carcinosis of the pleura, where tumour cells could be found in the pleural effusion.
Treatment	Intrapleural instillation of Iscador at weekly intervals.
Length of study	1976 – 1988.
Measurements	Number of instillations until pleurodesis; cytological observations.

Most important results

A pleurodesis was achieved in 92% of the patients. An average of 3.2 instillations were required to achieve this result.

Table 1: The number of punctures per patient

Required punctures	Number of patients	
	[n]	[%]
1	23	10.9
2	77	36.5
3	45	21.3
4	30	14.4
5	10	4.7
6	12	5.7
7	6	2.8
8	3	1.4
9	2	1.0
10	1	0.5
13	1	0.5
17	1	0.5

Punctures necessary to dry up the pleural effusion following instillation with Iscador in 192 patients (19 of which had double-sided effusions, calculated double in the Table) (table according to Salzer und Popp 1990).

5.5 Melanoma

References

☆ Feuchtinger T. (1979) Ergebnisse der Internistischen Therapie des malignen Melanoms (Stadium II und III) mit Iscador. In: Rilling S. (Hrsg.), Malignes Melanom. Verlag für Medizin Fischer, Heidelberg, Band 14, 51–58.

- Leroi R. (1985) Klinische Erfahrung mit Iscador. In: Wolf O., Die Mistel in der Krebsbehandlung (3. Auflage), Frankfurt, 58–101.

☆ Schuppli R. (1990) Die adjuvante Behandlung des malignen Melanoms mit Iscador c Hg. In: Jungi W.F., Senn H.J. (Hrsg.), Krebs und Alternativmedizin, Springer Verlag, Berlin, Heidelberg, 50–53.

- Kleeberg U., Suciu S., Bröcker E. B., Ruiter D. J., Chartier C., Liénard D., Marsden J., Schadendorf D, Eggermont A. M. M. for the EORTC Melanoma Group in cooperation with the German Cancer Society (DKG) (2004) Final results of the EORTC 18871/DKG 80-1 randomised phase III trial: rIFN-α2b versus rIFN-γ versus ISCADOR M versus observation after surgery in melanoma patients with either high-risk primary (thickness > 3 mm) or regional lymph node metastasis. European Journal of Cancer 40: 390–402.

☆ Augustin M., Bock P. R., Hanisch J., Karasmann M., Schneider B. (2005) Safety and efficacy of the long-term adjuvant treatment of primary intermediate- to high-risk malignant melanoma (UICC/AJCC stage II and III) with a standardized fermented European mistletoe (Viscum album L.) extract: Results from a multicenter, comparative, epidemiological cohort study in Germany and Switzerland. Arzneimittel-Forschung/Drug Research 55 (1): 38–49.

☆ Grossarth-Maticek R., Ziegler R. (2007) Wirksamkeit und Unbedenklichkeit einer Langzeitbehandlung von Melanompatienten mit einem Mistelpräparat (Iscador). Schweizerische Zeitschrift für GanzheitsMedizin 19 (6), 325–332.

The references marked with ☆ are included in abstract form in this documentation.

Feuchtinger T. (1979) Ergebnisse der internistischen Therapie des malignen Melanoms (Stadium II und III) mit Iscador. [Results of an internistic therapy of malignant melanoma (stage II and III) with Iscador.] In: Rilling S. (Hrsg.) *Malignes Melanom*, Band 14, Verlag für Medizin E. Fischer, Heidelberg, 51–58.

Study design

Design	Retrospective study with historical controls.
Patients	For each 25 patients with stage II (with regional lymph nodes) and III (with distant metastases) melanoma from the patients at the Lukas Klinik on 31.07.77. 84% or 28% of the stage II patients only underwent surgery or underwent surgery and received radiotherapy respectively. The ratio was 36% to 8% in the stage III patients respectively and 16% received only radiotherapy.
Treatment	Iscador in different dosages, at least 2 series.
Length of study	1963 – 1977.
Measurement	Survival.

Most important results

Median survival in the stage II patients was 22 months. Corresponding values from the literature were 15 months in the controls and 18 months in the patients who received BCG therapy. The 2-year survival in the Iscador patients was 52% in comparison with 32% from a historical control in the literature. The survival of Iscador patients was also higher than the controls in the literature. A statistical analysis was not carried out.

Table 1: Results according to stage of disease

	Stage II **Regional lymph nodes**	**Stage III** **Distant metastases**
Number	25	25
Stage I at OP	92%	72%
Mean time from OP until occurrence of metastases	17 months	25 months
Median survival	22 months	10 months
Mean survival	40 months	16 months
Probability of survival for at least:		
2 years	52%	13%
5 years	24%	6%
10 years	20%	–

Schuppli R. (1990) Die adjuvante Behandlung des malignen Melanoms mit Iscador P c Hg. [Adjuvant treatment of malignant melanoma with Iscador P c Hg.] In: Jung H. W., Senn H. J. (Hrsg.) *Krebs und Alternativmedizin* II, Springer Verlag, Berlin, Heidelberg, 50–53.

Study design

Design	Controlled study.
Patients	198 patients with melanoma at the dermatological University Hospital, Basel. A risk factor of 3.4 was calculated for the Iscador patients and 2.3 for the control group.
Treatment	All of the patients were operated. 114 patients were treated with BCG (1st year: monthly, then for at least 8 years every 6 months) and 84 patients were treated with BCG and Iscador P c Hg 1% and 2% s.c. (several cycles of 7 injections, each with 2 injections/week over months or years).
Length of study	1982 – 1985.
Measurement	Survival.

Most important results

The 7-year survival rate was 80% in the Iscador patients versus 65% in the control group, although the patients with a higher risk were assigned to the Iscador group. The study does not include a statistical evaluation.

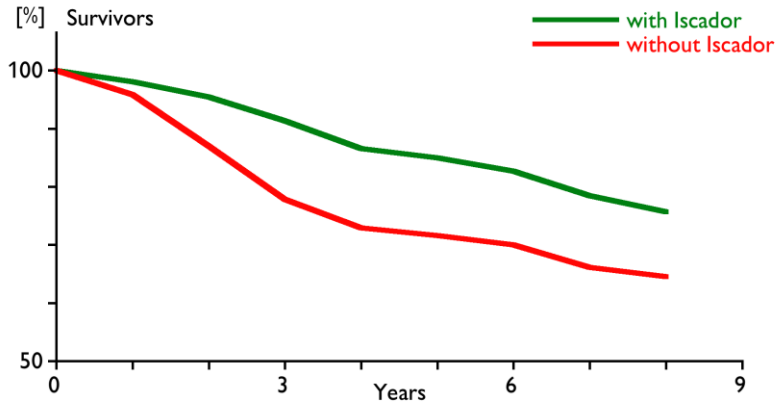

Fig. 1: Survival of patients with melanoma with (n = 84) and without (n = 114) treatment with Iscador over the course of 8 years (according to Schuppli 1990).

Augustin M., Bock P. R., Hanisch J., Karasmann M., Schneider B. (2005) Safety and efficacy of the long-term adjuvant treatment of primary intermediate- to high-risk malignant melanoma (UICC/AJCC stage II and III) with a standardized fermented European mistletoe (*Viscum album* L.) extract. *Arzneimittel-Forschung/Drug Research* 55 (1): 38–49.

Study design

Design	Cohort study with retrospective data collection («retrolective study»).
Centres	35 centres in Germany and Switzerland.
Patients	686 patients with primary melanoma with a middle to high risk (UICC/AJCC-stage II and III) were evaluated. 329 of which received aftercare with additional therapy with Iscador (Iscador group), 357 did not receive a therapy with mistletoe (control group).
Comparability	Demographic data and initial tumour findings, as well as prognostic factors are balanced between the groups.
Treatment	Median duration of observation of aftercare in months: 81 (Iscador group), 52 (control group). Median duration of therapy with Iscador: 30 months.
Period of study	1985 – 2001.
Measurements	Primary (safety): Incidence of systemic and locally adverse drug effects, which the doctor explicitly connects with the Iscador therapy; every occurrence of tumour enhancement, especially the occurrence of brain metastases. Secondary (efficacy): tumour-related survival, overall survival, tumour-free survival, survival without occurrence of brain metastases.

Most important results

A summary of the results indicates a significant and clinically relevant reduction in the Hazard Ratio for tumour-related mortality in the Iscador group in comparison with the control group (Fig. 1).

The results of the evaluation of overall survival, tumour-free survival and survival without the occurrence of brain metastases also showed significant advantages for the Iscador group with Iscador therapy (Table 1).

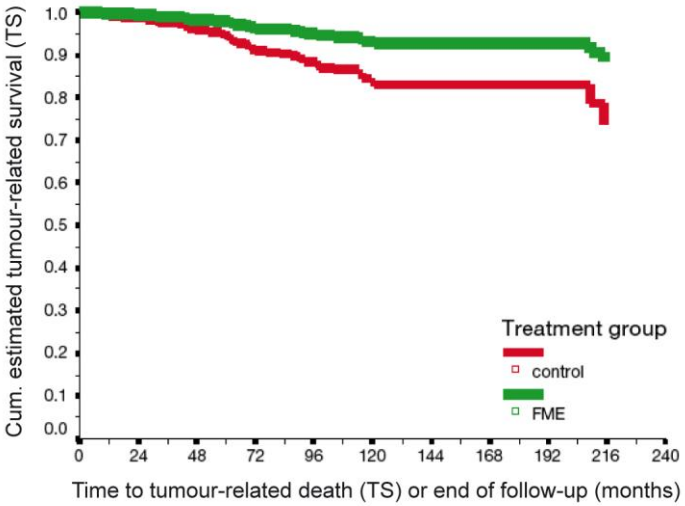

Fig. 1: Multivariate analysis of tumour-related survival (TS) with a Cox proportional hazard regression adjusted hazard ratio HR = 0.41 (95% confidence interval, 0.23 – 0.71), p = 0.002 (according to Augustin et al. 2005). FME = fermented mistletoe extract = Iscador.

Table 1: Multivariate analysis of different lengths of survival using Cox proportional hazard regression

Efficacy: Analysis of survival	**Adjusted Hazard Ratio (test group vs. control group)**	**95% confidence interval**	**p-value for the Cox-Regression**
Tumour-related survival	0.41	0.23 – 0.71	0.002
Overall survival	0.64	0.42 – 0.96	0.033
Tumour-free survival	0.73	0.55 – 0.97	0.029
Survival without the occurrence of brain metastases	0.33	0.13 – 0.86	0.024

For results of this study concerning safety and tolerance see 6.1.2.

Grossarth-Maticek R., Ziegler R. (2007) Wirksamkeit und Unbedenklichkeit einer Langzeitbehandlung von Melanompatienten mit einem Mistelpräparat (Iscador). [Efficacy and safety of long-term mistletoe (Iscador) treatment in melanoma cancer patients.] *Schweizerische Zeitschrift für GanzheitsMedizin* 19 (6), 325–332.

Study design

Design	(1) Randomised, prospective long-term, matched-pair technique.
	(2) Prospective epidemiological long-term cohort study, matched-pair technique.
Patients	(1) *MelanomRand*: 2 × 22 patients with melanoma without relapse, and without lymphatic or distant metastases.
	(2) *Melanom*: 2 × 32 patients with melanoma without relapse, and without lymphatic or distant metastases.
Treatment	The patients in the Iscador group received in addition to conventional cancer treatment an individual therapy with different doses and types of s.c. applied Iscador. The control group with matched patients received only conventional cancer treatment and did not receive any type of mistletoe treatment.
Length of study	1973 – 1998.
Measurements	Survival since first diagnosis, time to relapse, lymphatic or distant mestases.

Most important results

Results are (in the case of non-randomised studies: adjusted) statistical estimates of the hazard rate (HR), the 95% confidence interval (in parentheses) and the p-value. For values of the HR below 1, mortality in the Iscador group is lower than in the control group; for HR above 1, mortality is higher in the Iscador group and for HR = 1 there is no difference.

Survival

MelanomRand (fig. 1): Estimated trend for higher survival in the Iscador group:
HR 0.47 (0.19 – 1.14), p = 0.096.

Melanom (fig. 1): Estimated trend for higher survival in the Iscador group:
HR 0.76 (0.43 – 1.33), p = 0.33.

Time to relapse, lymphatic or distant metastases

For the randomised study *MelanomRand* the difference between the Iscador group and the control group concerning time to relapse, lymphatic or distant metastases were only significant for relapses: HR 0.31 (0.10 – 0.94), p = 0.039. Together with time to death the combined analyses yielded a significant benefit for the Iscador group: HR 0.49 (0.32 – 0.75), p = 0.001.

For the randomised study *Melanom* all differences between the Iscador group and the control group concerning time to relapse, lymphatic or distant metastases were not significant. Together with time to death the combined analyses yielded a significant benefit for the Iscador group: HR 0.72 (0.54 – 0.97), p = 0.03.

Fig. 1: Randomised study *MelanomRand a*nd nonrandomised study *Melanom:* Survival of patients with melanoma without relapse, lymphatic or distant metastases during ca. 20 or 25 years respectively of therapy with Iscador compared to control patients without Iscador (according to Grossarth-Maticek/Ziegler 2007).

Time to brain metastases

Concerning time to brain metastases there was no negative effect on behalf of the Iscador group (fig. 2). For *MelanomRand* as well as for *Melanom* the difference between the Iscador and the control group was not significant: HR 0.50 (0.09 – 2.73), p = 0.42, bzw. HR 0.79 (0.35 – 1.77), p = 0.56.

Fig. 2: Randomised study *MelanomRand* and nonrandomised study *Melanom*: Time to brain metastases of patients with melanoma without relapse, lymphatic or distant metastases during ca. 20 or 16 years respectively of therapy with Iscador compared to control patients without Iscador (according to Grossarth-Maticek/Ziegler 2007).

For results of this study concerning quality of life see 3.1.5.1.

5.6 Various Solid Tumours

References

- ✯ Grossarth-Maticek R., Kiene H., Baumgartner S.M., Ziegler R. (2001a) Use of Iscador, an extract of European mistletoe (Viscum album), in cancer treatment: prospective nonrandomized and randomized matched-pair studies nested within a cohort study. Alternative Therapies in Health and Medicine 7 (3), 57–78. – Deutsche Übersetzung: Merkurstab 2001, 54 (3), 171–189. – Addendum to Iscador article: Alternative Therapies in Health and Medicine 2001, 7 (4):26.
- ✯ Grossarth-Maticek R., Kiene H., Baumgartner S., Ziegler R. (2001b) Verlängerung der Überlebenszeit von Krebspatienten unter Misteltherapie (Iscador) - Ergebnisse einer epidemiologischen Langzeitstudie. Schweizerische Zeitschrift für GanzheitsMedizin 2001, 13 (4): 217–225.

The references marked with ✯ are included in abstract form in this documentation.

Grossarth-Maticek R., Kiene H., Baumgartner S.M., Ziegler R. (2001a) Use of Iscador, an extract of European mistletoe (Viscum album), in cancer treatment: prospective nonrandomized and randomized matched-pair studies nested within a cohort study. Alternative Therapies in Health and Medicine 7 (3), 57–78.

Grossarth-Maticek R., Kiene H., Baumgartner S., Ziegler R. (2001b) Verlängerung der Überlebenszeit von Krebspatienten unter Misteltherapie (Iscador) – Ergebnisse einer epidemiologischen Langzeitstudie. [Longer survival of cancer patients with mistletoe therapy (Iscador) – results of an epidemiologic long-term study.] Schweizerische Zeitschrift für GanzheitsMedizin 2001, 13 (4): 217–225.

Study design

Design	Randomised, prospective long-term, matched-pair technique.
Patients	56 matched pairs of patients with different solid cancers (17 pairs: breast cancer patients with lymphatic metastases and no distant metastases; 39 pairs: various solid tumours of different stages).
Treatment	The patients in the Iscador group received in addition to conventional cancer treatment an individual therapy with different doses and types of s.c. applied Iscador. The control group with matched patients received only conventional cancer treatment and did not receive any type of mistletoe treatment.
Length of study	1973 – 1998.
Measurement	Suvival.

Most important results

The mean survival time of the Iscador group was with 3.89 years significant (p = 0.0014) longer (+ 1.45) than the mean survival with 2.44 years of the control patients.

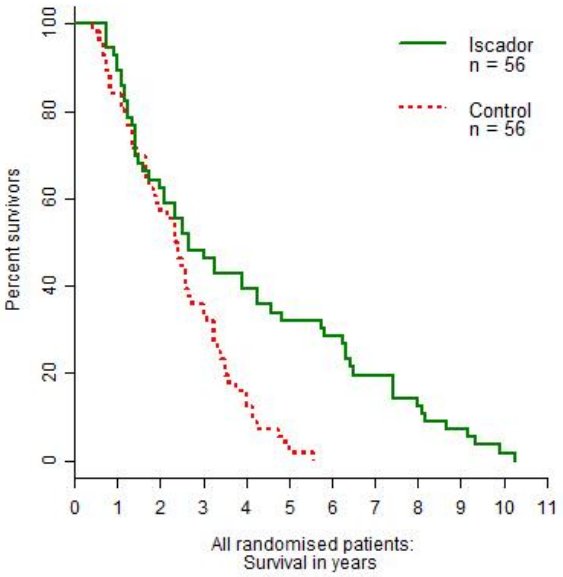

Fig. 1: Randomised study with 56 matched pairs*:* Survival of patients with various solid tumours during ca. 10 years of therapy with Iscador compared to control patients without Iscador (new graph).

For more results of this study concerning survival see 5.2.5 and for quality of life see 3.1.2.4, 3.1.6.1.

Grossarth-Maticek R., Kiene H., Baumgartner S.M., Ziegler R. (2001a) Use of Iscador, an extract of European mistletoe (Viscum album), in cancer treatment: prospective nonrandomized and randomized matched-pair studies nested within a cohort study. Alternative Therapies in Health and Medicine 7 (3), 57–78.

Grossarth-Maticek R., Kiene H., Baumgartner S., Ziegler R. (2001b) Verlängerung der Überlebenszeit von Krebspatienten unter Misteltherapie (Iscador) – Ergebnisse einer epidemiologischen Langzeitstudie. [Longer survival of cancer patients with mistletoe therapy (Iscador) – results of an epidemiologic long-term study.] Schweizerische Zeitschrift für GanzheitsMedizin 2001, 13 (4): 217–225.

Study design

Design	Prospective, epidemiologic, long-term, matched-pair technique.
Patients	In a set of cancer patients treated or not treated with Iscador, for every Iscador patient a matched pair was selected according to strong and loose matching criteria. In the first case 396 pairs emerged and in the second 622 pairs. 622 loosely matched pairs of patients with various solid tumours: 93 cancer of the rectum, 130 cancer of the colon, 42 breast cancer without distant metastases, 55 breast cancer with lymphatic metastases, 83 breast cancer with distant metastases, 85 cancer of the stomach, 109 non small-cell lung cancer, 25 small-cell lung cancer. 396 strongly matched pairs of patients with various solid tumours: 69 cancer of the rectum, 90 cancer of the colon, 29 breast cancer without distant metastases, 38 breast cancer with lymphatic metastases, 53 breast cancer with distant metastases, 44 cancer of the stomach, 52 non small-cell lung cancer, 21 small-cell lung cancer.
Treatment	The patients in the Iscador group received in addition to conventional cancer treatment an individual therapy with different doses and types of s.c. applied Iscador. The control group with matched patients received only conventional cancer treatment and did not receive any type of mistletoe treatment.
Length of study	1973 – 1998.
Measurement	Survival.

Most important results

For the 622 loosely matched patient the mean survival time of the Iscador group was 4.26 years and for the control group 3.05 years; the difference (+ 1.21) was significant: $p < 0.001$.

For the 396 strongly matched patient the mean survival time of the Iscador group was 4.23 years and for the control group 3.05 years; the difference (+ 1.18) was significant: $p < 0.001$.

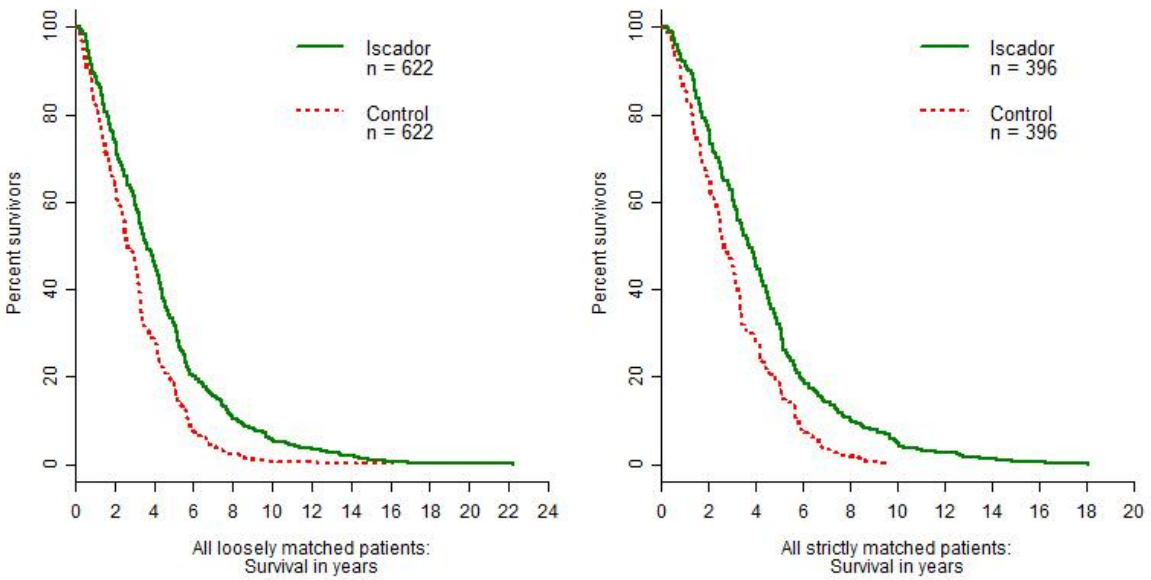

Fig. 1: Nonrandomised studies with 622 loosely and 396 strongly matched pairs*:* Survival of patients with various solid tumours during ca. 22 or 18 years respectively with Iscador therapy compared to control patients without Iscador (according to Grossarth-Maticek et al. 2001a, 2001b).

For more results of this study concerning survival see 5.2.6 (breast cancer), 5.3.1.2 (cancer of the stomach), 5.3.3.3 (cancer of the rectum and colon), 5.4.1.5 (lung cancer).

(5.7 Lymphomas and Leukaemias)

No studies available

(5.8 Endocrine Tumours)

No studies available

5.9 Central Nervous System Tumours

References

- Seifert G., Rutkowski S., Jesse P., Madeleyn R., Reif M., Henze G., Länger A. (2011) Anthroposophic supportive treatment in children with medulloblastoma receiving first-line therapy. Journal of Pediatric Hematology/Oncology 33(3): e105-e108

The references marked with ☆ are included in abstract form in this documentation.

5.10 Sarcomas

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- ☆ Longhi A., Reif M., Mariani E., Ferrari S. (2014) A randomized study on postrelapse disease-free survival with adjuvant mistletoe versus oral Etoposide in osteosarcoma patients. Evidence-Based Complementary and Alternative Medicine, Article ID 210198, http://dx.doi.org/10.155/2014/210198

The references marked with ☆ are included in abstract form in this documentation.

Longhi A., Reif M., Mariani E., Ferrari S. (2014) A randomized study on postrelapse disease-free survival with adjuvant mistletoe versus oral Etoposide in osteosarcoma patients. Evidence-Based Complementary and Alternative Medicine, Article ID 210198, http://dx.doi.org/10.155/2014/210198

Study design

Design	Prospective, randomized, open label.
Patients	Histological confirmed diagnosis of osteosarcoma or spindle cell sarcoma, after a second metastatic relapse, age equal or older than 10.
Treatment	Iscador or Etoposide.
Length of study	2007 – 2011.
Measurement	Post relapse disease free survival, Quality of Life.

Results

Background. Osteosarcoma is a highly malignant bone tumour. After the second relapse, the 12-month postrelapse disease-free survival (PRDFS) rate decreases below 20%. Oral Etoposide is often used in clinical practice after surgery as an "adjuvant" outside any protocol and with only limited evidence of improved survival. *Viscum album fermentatum Pini (Viscum)* is an extract of mistletoe plants grown on pine trees for subcutaneous (sc) injection with immunodmodulatory activity.

Methods. Encouraged by preliminary findings, we conducted a study where osteosarcoma patients free from disease after second metastatic relapse were randomly assigned to *Viscum* sc or Oral Etoposide. Our goal was to compare 12-month PRDFS rates with an equivalent historical control group.

Results. Twenty patients have been enrolled, with a median age of 34 years (range 11–65) and a median follow-up time of 38.5 months (3-73). The median PRDSF is currently 4 months (1-47) in the Etoposide and 39 months (2-73) in the *Viscum* group. Patients getting *Viscum* reported a higher quality of life due to lower toxicity.

Conclusion: *Viscum* shows promise as adjuvant treatment in prolonging PRDFS after second relapse in osteosarcoma patients. A larger study is required to conclusively determine efficacy and immunodmodulatory mechanism of Viscum therapy in osteosarcoma patients.

6 Safety and Tolerance

6.1 Clinical studies: safety and tolerance

6.2 Reviews and systematic reviews

6.1 Clinical studies: safety and tolerance

References

- ✯ Bock P. R., Friedel W. E., Hanisch J., Karasmann M., Schneider B. (2004) Wirksamkeit und Sicherheit der komplementären Langzeitbehandlung mit einem standardisierten Extrakt aus Europäischer Mistel (*Viscum album* L.) zusätzlich zur konventionellen adjuvanten onkologischen Therapie bei primärem, nicht metastasiertem Mammakarzinom. Ergebnisse einer multizentrischen, komparativen, retrolektiven, epidemiologischen Kohortenstudie in Deutschland und der Schweiz. Arzneimittel-Forschung/Drug Research 54 (8): 456–466.
- ✯ Augustin M., Bock P. R., Hanisch J., Karasmann M., Schneider B. (2005) Safety and efficacy of the long-term adjuvant treatment of primary intermediate-to high-risk malignant melanoma (UICC/AJCC stage II and III) with a standardized fermented European mistletoe (Viscum album L.) extract: Results from a multicenter, comparative, epidemiological cohort study in Germany and Switzerland. Arzneimittel-Forschung/Drug Research 55 (1): 38–49.
- Von Hagens C., Loewe-Mesch A., Kuehn J. J., Abel U., Gerhard I. (2005) Prospektive kontrollierte nicht randomisierte Machbarkeits-Studie zu einer postoperativen simultanen Mistel-/Chemotherapie bei Patientinnen mit Mammakarzinom – Ergebnisse zu Rekrutier- und Randomisierbarkeit, Immunparametern, Lebensqualität und Verträglichkeit. In: Scheer R., Bauer R., Becker H., Fintelmann V., Kemper F. H., Schilcher H. (Hrsg.), Fortschritte in der Mistletherapie: Aktueller Stand der Forschung und klinische Anwendung, Essen: KVC Verlag, S. 567–578.
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- ✯ Friedel W. E., Matthes H., Bock P. R., Zänker K. S. (2009) Systematic Evaluation of the Clinical Effects of Supportive Mistletoe Treatment within Chemo- and/or Radiotherapy Protocols and Long-Term Mistletoe Application in Non-metastatic Colorectal Carcinoma: Multicenter, Controlled, Observational Cohort Study. Journal of the Society for Integrative Oncology 7(4): 137–145.
- ✯ Matthes H., Friedel W. E., Bock P. R., Zänker K. S. (2010) Molecular Mistletoe Therapy: Friend or Foe in Established Anti-Tumor Protocols? A Multicenter, Controlled, Retrospective Pharmaco-Epidemiological Study in Pancreas Cancer. Current Molecular Medicine 10(4): 430–439.
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Bock P. R., Friedel W. E., Hanisch J., Karasmann M., Schneider B. (2004) Wirksamkeit und Sicherheit der komplementären Langzeitbehandlung mit einem standardisierten Extrakt aus Europäischer Mistel (*Viscum album* L.) zusätzlich zur konventionellen adjuvanten onkologischen Therapie bei primärem, nicht metastasiertem Mammakarzinom. [Efficacy and safety of long-term complementary treatment with standardised European mistletoe extract (*Viscum album* L.) in addition to the conventional adjuvant oncologic therapy in patients with primary non-metastatic breast cancer] *Arzneimittel-Forschung/Drug Research* 54 (8): 456–466.

Study design

Design	Cohort study with retrolective data collection (“retrolective study”).
Centres	16 centres in Germany and Switzerland.
Patients	1442 patients with primary breast cancer without metastases and with conventional basic therapy (surgery, radiotherapy, chemotherapy), 710 of whom received an additional therapy with Iscador (Iscador group) and 732 only received the conventional basic therapy (control group).
Comparability	The patients in the Iscador group were more seriously ill and had pronounced risk factors for progression.
Treatment	Median duration of observation: 66 months (Iscador group), 60 months (control group). 156 of the patients in the Iscador group (22%) and 42 patients in the control group (6%) did not have any form of conventional therapy.
Study period	1988 – 2000.
Measurements	Primary (efficacy): Frequency of side-effects from the conventional therapy, symptoms due to disease and therapy, tumour-related survival and overall survival. Secondary (safety): Frequency and level of severity of adverse drug reactions (ADR) due to the Iscador therapy, every occurrence of tumour enhancement.

Most important results

Systemic ADR were recorded in 6 (0.8%) of the 710 patients in the Iscador group, with a secured or probable connection with the Iscador therapy. The level of severity was graded as «light» or «middle». The ADR mainly only continued for one day. Serious systemic ADR did not occur. The known localised reactions were recorded in 123 (17.3%) of the patients. 71% of which were only light and soon went away. A change in the therapy (dose adaptation) was necessary in 7 patients and 4 discontinued the therapy with Iscador.

Signs of tumour enhancement were not observed. When comparing the Iscador group with the control group, no significant and/or clinically relevant differences in progression of the primary tumour (especially relapse), in metastases with a new localisation and in new tumours in new localisations were observed. The doctor treating the patients recorded that 78.9% of the patients tolerated the Iscador therapy «very well».

For results of this study concerning quality of life see 3.2.2.1 and for survival see 5.2.7.

Augustin M., Bock P. R., Hanisch J., Karasmann M., Schneider B. (2005) Safety and efficacy of the long-term adjuvant treatment of primary intermediate to high-risk malignant melanoma (UICC/AJCC stage II and III) with a standardized fermented European mistletoe (*Viscum album* L.) extract. *Arzneimittel-Forschung/Drug Research* 55 (1): 38–49.

Study design

Design	Cohort study with retrolective data collection (“retrolective study”).
Centres	35 centres in Germany and Switzerland.
Patients	686 patients with primary melanoma with a middle to high risk (UICC/AJCC stage II und III) were evaluated. 329 of whom received an additional therapy with Iscador in aftercare (Iscador group) and 357 did not receive any form of mistletoe therapy (control group).
Treatment	Median duration of observation in months in aftercare: 81 (Iscador group) and 52 (control group). Median duration of therapy with Iscador: 30 months.
Study period	1985 – 2001.
Measurements	Primary (safety): Incidence of systemic and localised adverse drug reactions (ADR), which are explicitly described by the doctor as being due to the Iscador therapy; every occurrence of tumour enhancement, especially the occurrence of brain metastases. Secondary (efficacy): tumour-related survival, overall survival, tumour-free survival, survival without the occurrence of brain metastases.

Most important results

Systematic ADR in connection with the Iscador therapy were recorded in 11 (3.3%) of the 686 patients in the Iscador group. The ADR were unspecific and were graded as «light» to «middle». The reactions went away of their own accord within a week in most of the cases. Only one case prematurely discontinued the treatment. Life-threatening ADR did not occur.

Localised ADR at the point of injection were often mentioned. At least one localised reaction was recorded in 42 (12.8%) of the patients treated with Iscador. The main ADR were erythema (41), oedema (12), itching or local pain (3) or other localised reactions (3). The level of ADR were mainly «light» to «middle» and in most cases went away of their own accord. Iscador therapy was discontinued in 5 cases due to localised reactions.

Signs of tumour enhancement were not observed. When comparing the Iscador group with the control group, no significant and/or clinically relevant differences in progression of the primary tumour (especially relapse), in metastases with a new localisation and in new tumours in new localisations were observed. There were also no signs of more frequent or of earlier occurrence of brain metastases in the Iscador group.

For results of this study concerning survival see 5.5.3.

Loewe-Mesch A., Kuehn J. J., Borho K., Abel U., Bauer C., Gerhard I., Schneeweiss A, Sohn C., Strowitzki T., Von Hagens C. (2008) Adjuvante simultane Mistel-/Chemotherapie bei Mammakarzinom – Einfluss auf Immunparameter, Lebensqualität und Verträglichkeit. [Adjuvant simultaneous mistletoe/chemotherapy in breast cancer patients – influence on immune parameters, quality of life and tolerance.] *Forschende Komplementärmedizin* 15, 22–30.

Study design

Design	Prospective, open, 2-arm nonrandomised study.
Patients	66 patients with primary breast cancer after surgery, with adjuvant chemotherapy with CMF or EC.
Treatment	33 patients received Iscador M spezial on their own will, in addition to adjuvant chemotherapy. The 33 patients of the control group had only chemotherapy.
Length of study	Recruitment: Mai 1999 – August 2001, Follow-up until 2002.
Measurements	Nausea and vomiting (EORTC-QLQ-C30) and systemic adverse effects (BR23) due to chemotherapy; local reactions at the injection site, dose adjustments and adverse effects of mistletoe therapy.

Most important results

Nausea and vomiting (EORTC-QLQ-C30) as well as systemic adverse effects (BR23) due to chemotherapy were significantly lower in the Iscador group compared to the control group ($p = 0.02$). In general, Iscador patients had fewer impairments from chemotherapy.

Ahead of the start of chemotherapy, 15 patients (45%) showed typical signs of local reactions, in 6 patients (18%) bigger(> 5 cm) than usual. After begin of chemotherapy, more and bigger local reactions showed up: within the group of 31 patients (94%) having local reactions, 24 patients (73%) had bigger than usual reactions (> 5 cm). In 29 patients (88%) the dose had to be reduced or the mistletoe therapy temporarily interrupted. There were no drop-outs or dose reductions due to chemotherapy in the mistletoe group.

General reactions like higher temperature, influenza-like feeling, fatigue, headache, nausea and general skin reactions were fewer in the mistletoe group, the sum of all medical conditions was smaller during all periods in the Iscador group.

Serious adverse effects were not seen in the mistletoe group.

For results of this study concerning quality of life see 3.1.2.5.

Friedel W. E., Matthes H., Bock P. R., Zänker K. S. (2009) Systematic Evaluation of the Clinical Effects of Supportive Mistletoe Treatment within Chemo- and/or Radiotherapy Protocols and Long-Term Mistletoe Application in Non-metastatic Colorectal Carcinoma: Multicenter, Controlled, Observational Cohort Study. Journal of the Society for Integrative Oncology 7(4): 137–145.

Study design

Design	Cohort study with retrospective collection of data («retrolective Study»).
Centres	26 centres in Germany and Switzerland.
Patients	804 patients with colorectal cancer without metastases, with conventional basic therapy (surgery, radiotherapy, chemotherapy), 429 of which received additional Iscador therapy (treatment group), 375 only received conventional basic therapy (control group).
Comparability	The patients in the treatment group were younger, had more advanced disease with more symptoms but less comorbidity.
Treatment	Median length of observation during aftercare: 58 months (treatment group), 51 months (control group). Median length of Iscador treatment: 52 months.
Length of study	1990 – 2004.
Measurements	Efficacy: (1) rate and adjusted risk of documented AT-ADR (adjuvant therapy-related adverse drug reactions), (2) predefined QoL surrogate criteria adapted from the symptom scales of the EORTC QLQ-C30 questionnaire, consisting of rate and adjusted risk of persistence of prespecified disease- and treatment-associated symptoms; and (3) adjusted disease-free survival (DFS). Safety: Number of patients with documented systemic and local ADR attributed to the Iscador therapy. The number and severity of ADR were evaluated according to CTC. Any evidence of possible tumour enhancement in the Iscador group was also documented.

Most important results

Systemic ADR attributed to the Iscador therapy were documented in 10 (2.3%) patients. All systemic Iscador ADR were mild to medium (grades 1–2) unspecific reactions such as dizziness, fatigue, depression, tinnitus, nausea, itching, pain, low-grade fever, and one case of acute allergic reaction. In five cases (1.2%), the Iscador therapy was prematurely terminated owing to systemic Iscador ADR.

Local Iscador ADR at the injection site of mild to medium severity, such as induration, oedema, erythema, itching, and local pain, occurred in 100 (23.3%) patients, with two therapy discontinuations (0.5%).

Severe life-threatening or persisting Iscador ADR and interactions between Iscador and other therapy were not observed. Particularly, an Iscador-related tumour enhancement (progression) did not occur. This means, that when comparing the Iscador group with the control group, no significant and/or clinically relevant differences in progression of the primary tumour (especially relapse), in metastases with a new localisation and in new tumours in new localisations were observed.

For results of this study concerning quality of life (disease- and therapy-induced symptoms) see 3.2.3.1 and concerning survival see 5.3.3.4. For the results of a subgroup analysis concerning Iscador Qu see 3.2.3.4 (disease- and therapy-induced symptoms) and 5.3.3.5 (disease-free survival).

Matthes H., Friedel W. E., Bock P. R., Zänker K. S. (2010) Molecular Mistletoe Therapy: Friend or Foe in Established Anti-Tumor Protocols? A Multicenter, Controlled, Retrospective Pharmaco-Epidemiological Study in Pancreas Cancer. Current Molecular Medicine 10(4): 430–439.

Study design

Design	Cohort study with retrospective collection of data («retrolective Study»).
Centres	17 centres in Germany and Switzerland.
Patients	396 patients with histologically verified pancreatic tumour who had macroscopic complete resection and not prior radiation or neoadjuvant chemotherapy were eligible for the study. 201 of which received additional Iscador therapy (treatment group), 195 only received conventional basic therapy (control group).
Comparability	Within the control group (chemotherapy without Iscador but with/without best of care) more patients were at high risk (T3/T4) tumour stage: 71.3% of the patients), but less patients in this group had regional lymphnode involvement (37.4% vs. 66.7%); most of the patients in the chemotherapy/Iscador group had extended disease in respect to tumour size (more than 2 cm in diameter) involving extrapancreatic structures.
Treatment	Median length of observation during aftercare: 15.2 months (treatment group), 10.1 months (control group). Median/mean length of Iscador treatment: 15.0/20.5 months.
Length of study	Diagnosis time from 1993 – 2002.
Measurements	Efficacy: (1) rate and adjusted risk of documented AT-ADR (adjuvant therapy-related adverse drug reactions), assessed by adapting the National Institutes of Health Common Toxicity Criteria (CTC) in oncology; (2) predefined QoL surrogate criteria adapted from the symptom scales of the EORTC QLQ-C30 questionnaire, consisting of rate and adjusted risk of persistence of prespecified disease- and treatment-associated symptoms, particularly pain, skin, mucosal, gastrointestinal, and CNS symptoms; (3) adjusted overall survival (OS). Safety: Number of patients with documented systemic and local ADR attributed to the Iscador therapy. Any evidence of possible tumour enhancement in the Iscador group was also documented.

Most important results

Systemic adverse drug reactions attributed to Iscador were documented in 3 patients (1.5%). All systemic Iscador-related ADR were mild to medium (toxicity grade 1-2) and clinically relevant as fatigue, low-grade fever and Iscador immune intolerance. Local Iscador-related adverse drug reactions at the site of subcutaneous injection were of toxicity grade 1-3, like induration, edema, erythema, itching and local pain and occured in 45 patients (22.4%).

Life-threatening or persisting Iscador related ADR, clinically relevant interations between Iscador and other medications, or even tumour enhancement were not observed. Particularly, an Iscador-related tumour enhancement (progression) did not occur. This means, that when comparing the Iscador group with the control group, no significant and/or clinically relevant differences in progression of the primary tumour (especially relapse), in metastases with a new localisation and in new tumours in new localisations were observed.

For results of this study concerning quality of life see 3.2.3.2 und concerning survival see 5.3.2.2.

6.2 Reviews and systematic reviews

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☆ Melzer J., Iten F., Hostanska K., Saller R. (2009) Efficacy and Safety of mistletoe preparations (Viscum album) for patients with cancer diseases. A systematic review. Forschende Komplementärmedizin 16, 17–26.

☆ Kienle G. S., Grugel R., Kiene H. (2011) Safety of higher dosages of *Viscum album* L. in animals and humans – systematic review of immune changes and safety parameters. BMC Complementary and Alternativ Medicine 2011, 11: 72.

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The references marked with ☆ are included in abstract form in this documentation.

Melzer J., Iten F., Hostanska K., Saller R. (2009) Efficacy and Safety of mistletoe preparations (Viscum album) for patients with cancer diseases. A systematic review. Forschende Komplementärmedizin 16, 17–26.

Study design

Type	Systematic review with predefined search strategy and quality criteria.
Inclusion criteria	Prospective controlled randomised or comparative cohort studies with process standardised mistletoe preparations in cancer patients with systemic interventions (subcutaneous or per infusion).
Exclusion criteria	Phase I and II studies, other types of interventions, incomplete documentation, other languages than German, English, French.
Judgement criteria	Multidimensional quality judgement using tables but without a formal rating procedure.

Results pertaining to studies with mistletoe

In terms of safety, the available studies indicate that mistletoe therapy is well tolerated although a systematic evaluation is lacking in some trials. Serious adverse events (AEs) definitely related to mistletoe therapy were not reported except for 1 patient with angiooedema [not from an Iscador study].

AEs related to mistletoe therapy were: (a) local (at the injection site): e.g. pruritus, erythema, induration; (b) systemic: e.g. flu-like syndrome, fatigue, fever, and headache. The data about the incidence of AEs ranges widely. Especially in mistletoe therapy it is a matter of ongoing debate whether some of the most common AEs, the local ones are considered or interpreted as undesired or actually desired (e.g. kind of surrogate for general physiological response). According to this, the data about the incidence of side effects ranges widely.

Only a few of the studies reviewed here [6.1.1, 6.1.2] explicitly differentiate between local and systemic side-effects. The cumulated numbers are 17.5% for total side-effects, 15.9% for local, and 1.6% for systemic side-effects. These data are more or less comparable to the result of a previous systematic review on AEs under mistletoe therapy which showed local reactions between 0.9–43% and systemic reactions between 0.8–4% depending on the interpretation whether being desirable or undesirable [Saller/Kramer/Iten/Melzer 2005]. Allergic reactions occurred but the frequency was approximately <1%.

These results were confirmed by the data of authorities and manufacturers, as far as they were available [Saller/Kramer/Iten/Melzer 2005].

For results of this systematic review concerning efficacy see 7.2.10.

Kienle G. S., Grugel R., Kiene H. (2011) Safety of higher dosages of *Viscum album* L. in animals and humans – systematic review of immune changes and safety parameters. BMC Complementary and Alternativ Medicine 2011, 11: 72.

Study design

Type	Systematic review with predefined search strategy and eligibility criteria.
Inclusion criteria	Clinical studies with humans or animals; study population with/without disease; intervention group treated with *Viscum album* L. dosed at > 1mg; outcome measure: immune parameter; completion of study/report.
Exclusion criteria	Unpublished animal studies; purely toxological tests.
Judgement criteria	Multidimensional quality judgement using tables but without a formal rating procedure.

Results pertaining to studies with mistletoe

Background: *Viscum album* L extracts (VAE, mistletoe) and isolated mistletoe lectins (ML) have immunostimulating properties and a strong dose-dependent cytotoxic activity. They are frequently used in complementary cancer treatment, mainly to improve quality of life, but partly also to influence tumour growth, especially by injecting VAE locally and in high dosage. The question is raised whether these higher dosages can induce any harm or immunosuppressive effects.

Methods: Systematic review of all experiments and clinical studies investigating higher dosages of VAE in animals and humans (*Viscum album* > 1 mg in humans corresponding to > 0.02 mg/kg in animals or ML > 1 ng/kg) and assessing immune parameters or infections or adverse drug reactions.

Results: 69 clinical studies and 48 animal experiments reported application of higher doses of VAE or ML and had assessed immune changes and/or harm. In these studies, *Viscum album* was applied in dosages up to 1500 mg in humans and 1400 mg/kg in animals, ML was applied up to 6.4 µg/kg in humans and in animals up to 14 µg/kg subcutaneously, 50 µg/kg nasally and 500 µg/kg orally. A variety of immune parameters showed fluctuating or rising outcomes, but no immunosuppressive effect. Side effects consisted mainly of dose-dependent flu-like symptoms (FLS), fever, local reactions at the injection site and various mild unspecific effects. Occasionally, allergic reactions were reported. After application of high doses of recombinant ML, reversible hepatotoxicity was observed in some cases.

Conclusions: Application of higher dosages of VAE or ML is not accompanied by immunosuppression; altogether VAE seems to exhibit low risk but should be monitored by clinicians when applied in high dosages.

7 Systematic Reviews

7.1 Review Papers

7.1.1 Reviews for all Types of Cancer

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7.1.2 Reviews for Selected Types of Cancer

References

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7.2 Systematic Reviews for all Types of Cancer

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The references marked with ☆ are included in abstract form in this documentation.

Kiene H. (1989a, 1989b, 1991, 1996) Klinische Studien zur Misteltherapie karzinomatöser Erkrankungen. [Clinical studies on the mistletoe therapy of carcinomatous disease.]

Study design

Type	Systematic Review.
Inclusion criteria	Clinical trials and observational studies with mistletoe extracts.
Exclusion criteria	Case series, collective reports, case reports, uncertain grouping, mistletoe therapy not as single test therapy, different measurement parameters in the groups.
Judgement criteria	The validity of a study is judged as *granted* when one of the following conditions applies:
„granted“	(1) When the analysis of the prognostic factors shows a convincingly disadvantageous prognosis structure in the mistletoe group.
	(2) When the analysis of the prognostic factors shows a balanced prognosis structure in both groups and there is *no* reason to believe that a prognostic advantage exists due to the manner of allocation to the mistletoe group.
	The validity of a study is judged as *uncertain* when one of the following conditions applies:
„uncertain“	(1) When the analysis of the prognostic factors shows a balanced prognosis structure, but there is reason to believe that a prognostic advantage exists due to the manner of allocation to the mistletoe group.
	(2) When the analysis of the prognostic factors was neglected, but there is not necessarily reason to believe that a prognostic advantage exists due to the manner of allocation to the mistletoe group.
	The validity of a study is judged as *not granted* when one of the following conditions applies:
„not granted“	(1) When the analysis of the prognostic factors was neglected, and there is reason to believe that a prognostic advantage exists due to the manner of allocation to the mistletoe group.
	(2) When the analysis of the prognostic factors convincingly shows an advantageous prognosis structure in the mistletoe group.

Results pertaining to all studies with mistletoe, in particular Iscador

35 of the 46 analysed studies with mistletoe fulfill the inclusion criteria and at the same time do not fulfill the exclusion criteria. The validity is granted in 12 of the studies, 9 of which show significantly positive results for the Iscador group. The validity is uncertain for 9 of the studies, 3 of which have significantly positive results in the Iscador group. 14 studies are not valid, one of which had a significantly positive result in the Iscador group.

The results for each of the Iscador studies are summarised in the following table. There are only 5 studies with Iscador which are granted as valid and show a significant advantage for a therapy with Iscador.

Table 1 (2 pages): Results of studies with Iscador

Publication(s)	Study aim , Diagnosis	Study type	Chapter in this documentation	No. of study		Quality (1989)		
				1989	2003	Advantage for Iscador (Trend)	Validity of the study	Significant advantage for Iscador
Pain/Quality of Life 3								
Buchner (1984)	pain	retrospective	3.2.6.1	46	–	yes	yes	yes
Dold et al. (1991)	quality of life	prospective randomised	3.2.4.1, 4.4.1, 5.4.1.3	–	35	yes	yes	partially
Survival: Genitourinary Cancer 5.1								
Leroi (1978, 1980)	bladder	case series	5.1.1.1	1	57	yes	–	–
Hoffmann (1978, 1980)	bladder	retrospective	5.1.1.2	2	58	yes	no	no
Leroi (1969, 1980)	ovary	case series	5.1.2	5	41	yes	–	–
Leroi/Hajto (1982)	ovary	retrospective	5.1.2.2	6	42	yes	?	no
Schreiber/Stumpf (1984)	ovary	retrospective	5.1.2	7	42	yes	no	–
Majewski/Bentele (1963)	ovary	prospective	5.1.2	9	40	no	no	–
Hassauer et al. (1979)	ovary	retrospective	5.1.2.1	10	43	yes	yes	yes
Leroi (1969)	uterus, corpus	case series	5.1.3	5	41	yes	–	–
Majewski/Bentele (1963)	uterus, corpus	prospektive	5.1.3	9	40	yes	no	–
Leroi (1969)	uterine cervix	case series	5.1.4	5	41	yes	–	–
Fellmer/Fellmer (1966), Fellmer (1968)	uterine cervix	prospective	5.1.4.1	8	44	yes	yes	yes
Majewski/Bentele (1963)	uterine cervix	prospective	5.1.4	9	40	no	no	–
Kjaer (1989)	kidney	prospective	5.1.5	–	61	no	no	no
Survival: Breast Cancer 5.2								
Majewski/Bentele (1963)	breast cancer	prospective	5.2	9	40	yes	no	–
Günczler/Salzer (1962)	breast cancer	retrospective	5.2	11	47	yes	–	–
Günczler/Salzer (1969)	breast cancer	retrospective	5.2	12	48	yes	–	–
Koch/Voss (1980)	breast cancer	retrospective	5.2	14	49	yes	–	–
Leroi (1975)	breast cancer	retrospective	5.2.1	15	50	yes	?	yes
Leroi (1977)	breast cancer	retrospective	5.2.2	16	50	yes	no	–
Hoffmann/Hajto (1982)	breast cancer	retrospective	5.2.3	17	51	yes	no	yes
Salzer (1987)	breast cancer	prospective	5.2	18	52	yes	no	no
Salzer (1987)	breast cancer	retrospective	5.2	20	47	yes	no	–

No. of the study (1989): according to Kiene (1989a, 1989b),
No. of the study (2003): according to Kienle/Kiene (2003).
Validity granted: yes
Validity uncertain: ?
Validity not granted: no
Validity not determined: –.
Significant advantage exists: yes
Significant advantage does not exist: no
Significant disadvantage for Iscador therapy: disadvantage
Without calculating statistical significance: –

Publication(s)	Study aim, Diagnosis	Study type	Chapter in this documentation	No. of study		Quality (1989)		
				1989	2003	Advantage for Iscador (Trend)	Validity of the study	Significant advantage for Iscador
Survival: Gastrointestinal Cancer 5.3								
Günczler et al. (1968), Günczler (1968, 1969)	stomach	retrospective	5.3.1	22	11	yes	?	yes
Salzer/Havelec (1983), Salzer/Denk (1979)	stomach	prospective randomised	5.3.1.1	23	12	yes	yes	yes
Salzer et al. (1990)	stomach	retrospective	5.3.1	–	13	yes	no	–
Delius-Müller (1979)	pancreas	retrospective	5.3.2	24	15	yes	no	–
Günczler/Salzer (1969)	rectum	retrospective	5.3.3	25	18	yes	no	–
Leroi (1979)	colorectal	retrospective	5.3.3.1	26	19	yes	no	–
Hoffmann/Hajto (1984)	colorectal	retrospective	5.3.3	27	20	yes	no	no
Salzer et al. (1992)	colorectal	retrospective	5.3.3	–	24	yes	no	–
Hoffmann (1979)	liver metastases	retrospective	5.3.4.1	31	70	yes	yes	–
Salzer (1984)	liver metastases	retrospective	5.3.4.2	33	72	yes	no	no
Salzer/Frey (1990)	liver metastases	retrospective	5.3.4	–	73	yes	no	–
Survival: Cancer of the Respiratory Tract: Lung Cancer 5.4.1								
Salzer/Havelec (1978), Salzer (1980a)	lung cancer	prospective	5.4.1.1	34	32	yes	yes	yes
Salzer (1987)	lung cancer	prospective	5.4	35	–	yes	yes	yes
Krause/Erkan (1983)	lung cancer	prospective	5.4	36	–	yes	no	–
Salzer (1980b, 1987)	lung cancer	prospective randomised	5.4.1.2	37	33	yes	?	–
Hellan (1983), Salzer (1987)	lung cancer	retrospective	5.4	38	–	yes	no	–
Salzer et al. (1991), Salzer (1987)	lung cancer	prospective randomised	5.4.1.4	–	34	yes	yes	no
Survival: Cancer of the Respiratory Tract: Carcinosis of the Pleura 5.4.2								
Salzer (1977, 1983, 1986), Böck/Salzer (1980a,b), Böck (1983), Salzer/Popp (1990)	carcinosis of the pleura	Case series	5.4.2.1, 5.4.2.2	39	78	yes	–	–
Survival: Melanoma 5.5								
Feuchtinger (1979)	melanoma	retrospective	5.5.1	40	64	yes	no	–
Leroi (1985)	melanoma	retrospective	5.5	42	65	yes	?	no
Schuppli (1990)	melanoma	retrospective	5.5.2	43	66	yes	?	–

No. of the study (1989): according to Kiene (1989a, 1989b),
No. of the study (2003): according to Kienle/Kiene (2003).
Validity granted: yes
Validity uncertain: ?
Validity not granted: no
Validity not determined: –.
Significant advantage exists: yes
Significant advantage does not exist: no
Significant disadvantage for Iscador therapy: disadvantage
Without calculating statistical significance: –

Kleijnen J., Knipschild P. (1994) Mistletoe treatment for cancer. Review of controlled trials in humans. *Phytomedicine* 1, 255–260.

Study design

Type	Systematic review.
Inclusion criteria	Prospective clinical trials with mistletoe extracts, with control groups and clinical outcome measurement, not necessarily randomised allocation to groups.
Exclusion criteria	No comparative group, incomplete or only preliminary results, comparative group with refusal of Iscador therapy.
Judgement criteria	A) well described disease (diagnosis, stage, duration) and previous therapy; B) at least 50 patients per group; C) pre-stratification (matching) on relevant prognostic indicators; D) random allocation; E) presentation of relevant baseline characteristics; F) less than 10% dropout, and dropouts described; G) intervention well described; H) double-blinding; I) effect measurement relevant and well described (at least survival time); J) presentation of the data in such a manner that the analysis can be checked by the reader Each study was analysed according to these 10 criteria and allocated a cumulative score (0 for unfulfilled, 1 for fulfilled and a value between 0 and 1 for partially fulfilled criteria). On this basis, each study received a total score between 0 and 10.

Results pertaining to all studies with mistletoe, in particular Iscador

11 of the analysed studies fulfilled the inclusion criteria and at the same time did not fulfill the exclusion criteria. None of these studies reached the highest possible score, only one study achieved a score of 8.5; all of the other studies had a score of 6.0 or less. Under the 11 studies with mistletoe were 7 studies with Iscador. Only one of these studies showed a statistically significant advantage for Iscador, the others only showed a positive trend for Iscador.

Table 1: Results of studies with Iscador

Publication	Diagnosis	Chapter in this documentation	No. of study in Kienle/Kiene 2003	Result with an advantage for the Iscador group	Quality Score
Fellmer (1966, 1968)	uterine cervix	5.1.4.1	44	trend	4.0
Majewski/Bentele (1963)	uterus and ovary	5.1.4	40	trend	1.0
Salzer (1987)	breast cancer	5.2	47	trend	3.0
Salzer/Denk (1979), Salzer/Havelec (1983), Salzer (1988)	stomach	5.3.1.1	32	trend	4.5
Dold et al. (1991)	lung cancer	3.2.4.1, 4.4.1, 5.4.1.3	35	mostly not significant	8.5
Salzer et al. (1991)	lung cancer	5.4.1.4	34	trend	5.5
Salzer/Havelec (1978)	lung cancer	5.4.1.1	32	significant	5.0

Edler L. (1996) Randomisierte klinische Studien zur Misteltherapie bei Krebs: Ergebnisse, Erfahrungen und Perspektiven. [Randomised clinical trials on mistletoe therapy of cancer, experiences and perspectives.] In: Scheer R., Becker H., Berg P.A. (Hrsg.) *Grundlagen der Misteltherapie – Aktueller Stand der Forschung und klinische Anwendung*, Hippokrates Verlag, Stuttgart, 508–518.

Study design

Type	Systematic review.
Inclusion criteria	Prospective clinical trials with mistletoe extracts and with control and/or comparative groups.
Exclusion criteria	Absence, unclear or non-description of randomisation in the group allocation.

Results pertaining to all studies with mistletoe, in particular Iscador

5 of the analysed studies with mistletoe fulfilled the inclusion criteria and at the same time did not fulfill the exclusion criteria. 4 of the studies are with Iscador.

Table 1: Results for Iscador studies

Publication	Diagnosis	Chapter in this documentation	No. of study according to Edler (1996)	No. of study according to Kienle/Kiene 2003
Salzer/Denk (1979)	stomach	5.3.1.1	2	32
Salzer (1987)	breast cancer	5.2	4	47
Dold et al. (1991)	lung cancer	3.2.4.1, 4.4.1, 5.4.1.3	5	35
Salzer et al. (1991)	lung cancer	5.4	1	34

Kienle G. S., Berrino F., Büssing A., Portalupi S., Rosenzweig S., Kiene H. (2003) Mistletoe in cancer: a systematic review on controlled clinical trials. *European Journal of Medical Research* 8, 109–119.

Study design

Type	Systematic review with defined initial search strategy and quality criteria.
Inclusion criteria	Study with mistletoe preparations: 1) prospective controlled clinical trial, either randomised or non- randomised. 2) study population with cancer, 3) intervention group treated with mistletoe preparation, 4) measurement of clinically relevant outcomes, 5) completion of study, 6) publication as manuscript or abstract, 7) all languages.
Exclusion criteria	Phase I studies on tolerance and toxicity, purely immunological studies; study population with patients who do not have cancer.
Judgement criteria	A) protection against selection bias; B) minimisation of heterogeneity by pre-stratification or matching; C) protection against observer bias by blinding patients, care providers, and outcome assessors; D) protection against performance (treatment) bias by standardisation of care protocol, documentation of all co-interventions, blinding of patients and care providers; E) protection against measurement (detection) bias by standardisation of outcome assessment; F) protection against attrition (exclusion) bias (loss to follow-up); G) effect measurement relevant and well described; H) well described intervention, patient characteristics, disease and previous therapy; I) well described study design; J) well described results; K) data quality assured by GCP-ICH guidelines.

Results pertaining to all studies with mistletoe, in particular Iscador

23 of the 138 clinical therapy studies found with mistletoe compounds fulfilled all of the inclusion criteria and none of the exclusion criteria (14 of which were with Iscador). 16 of the 23 studies were randomised (8 of which were with Iscador), 2 quasi-randomised with alternative allocation and 5 studies were not randomised (4 of which were with Iscador).

12 of the 23 controlled studies showed significantly positive results with clinically relevant outcomes, e.g. survival and quality of life (7 of which were with Iscador); there was a positive trend in 8 studies (6 of which were with Iscador). 6 of the 16 randomised studies showed significantly positive results (4 of which were with Iscador) and 4 a positive trend (3 of which were with Iscador).

Two of the randomised studies with Iscador have not yet been published at the time of the review. They will not be considered in the following summaries.

Table 1: Results of randomised studies with Iscador

Publication	Diagnosis	Chapter in this documentation	No. of study according to Kienle/Kiene 2003	Results with an advantage for the Iscador group	Number of patients
Salzer (1987)	breast cancer	5.2	33	trend (survival)	50
Salzer/Denk (1979), Salzer/Havelec (1983), Salzer (1988)	stomach	5.3.1	12	significant (survival)	137
Dold et al. (1991)	lung cancer	3.2.4.1, 4.4.1, 5.4.1.3	35	Significant (quality of life), trend (survival), trend (tumour remission)	337
Salzer et al. (1991)	lung cancer	5.4.1.4	34	trend (survival for lymph node positive)	183
Grossarth-Maticek et al. (2001a)	breast cancer	3.1.2.4, 5.2.5	56	significant (survival), trend (quality of life)	34
Grossarth-Maticek et al. (2001a)	various solid tumours	3.1.6.1, 5.6.1	10	significant (survival), significant (quality of life)	78

Table 2: Results of quasi randomised studies with Iscador

Publication	Diagnosis	Chapter in this documentation	No. of study according to Kienle/Kiene 2003	Results with an advantage for the Iscador group	Number of patients
Majewski/Bentele (1963)	uterus and ovary	5.1.3	40	trend (survival)	NA
Salzer (1987)	breast cancer	5.2	52	trend (survival)	155

Table 3: Results of non-randomised studies with Iscador

Publication	Diagnosis	Chapter in this documentation	No. of study according to Kienle/Kiene 2003	Results with an advantage for the Iscador group	Number of patients
Fellmer (1966, 1968)	uterine cervix	5.1.4	44	significant (survival)	790
Salzer/Havelec (1978)	lung cancer	5.4.1.1	32	significant (survival)	77
Schuppli (1990)	melanoma	5.5.2	66	trend (survival)	198
Grossarth-Maticek et al. (2001a)	various solid tumours	5.2.6, 5.6.2, 5.3.1.2, 5.3.3.3, 5.4.1.5	9, 14, 25, 36, 55	significant (survival)	792

National Cancer Institute (USA), Mistletoe Extracts (Version vom 23.04.2014): http://www.cancer.gov/cancertopics/pdq/cam/mistletoe/HealthProfessional, Zugriff am 13.08.2014)

Study design

Type	Systematic summary with judgement of the studies according to Levels of Evidence for Human Studies of Cancer.
Inclusion criteria	All clinical trials and case series with mistletoe compounds for all types of carcinoma without any limit for language.
Criteria	Levels of Evidence for Humans Studies of Cancer: Complementary and Alternative Medicine (link at website above): 1 randomised clinical studies, (i blinded, ii not blinded), 2 non-randomised controlled clinical trials, 3 case series (i population-based consecutive case series, ii consecutive case series, iii non-consecutive case series), 4 series of good cases. Strength of endpoints measured: A total mortality, B cause-specific mortality, C carefully assessed quality of life, D indirect surrogates (i disease-free survival, ii progression-free survival, iii tumor response rate).

General summary

Mistletoe is a semiparasitic plant that has been used for centuries to treat numerous human ailments.

Mistletoe is used commonly in Europe, where a variety of different extracts are manufactured and marketed as injectable drugs. These injectable drugs are not available commercially in the United States and are not approved as a cancer treatment.

Mistletoe is one of the most widely studied CAM therapies for cancer. In certain European countries, the preparations made from European mistletoe (*Viscum album* L.) are among the most prescribed drugs offered to cancer patients.

Although mistletoe plants and berries are considered poisonous to humans, few serious side effects have been associated with mistletoe extract use.

The use of mistletoe as a treatment for cancer has been investigated in clinical studies. Reports of improved survival and/or quality of life have been common, but nearly all of the studies had major weaknesses that raise doubts about the reliability of the findings.

At present, the use of mistletoe cannot be recommended outside the context of well-designed clinical trials. Such trials will be valuable to determine more clearly whether mistletoe can be useful in the treatment of specific subsets of cancer patients.

Results pertaining to Iscador

Positive results were reported in 4 randomised studies with Iscador (level 1ii). The non-randomised controlled studies were allocated level 2 or level 3iii (non-consecutive case series).

Table 1: Reported results of clinical studies and case studies with Iscador

Publication(s)	Diagnosis	Study type	Chapter in this documentation	No. of study according to Kienle/Kiene 2003	Strongest reported advantage	Level of Evidence
Various Solid Tumours						
Grossarth-Maticek et al., (2001a)	various solid tumours	prospective randomised	3.1.6.1, 5.6.1	10	survival	1iiA
Grossarth-Maticek et al., (2001a)	various solid tumours	prospective controlled	5.2.6, 5.6.2, 5.3.1.2, 5.3.3.3, 5.4.1.5	9, 14, 25, 36, 55	survival	3iiiA
Survival: Breast Cancer 5.2						
Grossarth-Maticek et al., (2001a)	breast cancer	prospective randomised	3.1.2.4 5.2.5	56	survival	1iiA
Bock et al. (2004)	breast cancer	cohorts with retrospective data collection	3.2.2.1, 5.2.7, 6.1.1	–	survival	2B
Survival: Gastrointestinal Cancer 5.3						
Schaefermeyer (1998)	pancreas	case series	5.3.2.1	17	survival	3iiiA
Friedel et al. (2009)	colorectal carcinoma	cohorts with retrospective data collection	3.2.3.1, 5.3.3.4, 6.1.4	–	survival	2C
Survival: Respiratory Tract: Lung Cancer 5.4.1						
Dold et al. (1991)	lung cancer	prospective randomised	3.2.4.1, 4.4.1, 5.4.1.3	35	subjective quality of life	1iiA
Salzer et al. (1991)	lung cancer	prospective randomised	5.4.1.4	34	survival for lymph node positive	1iiA
Bradley/Clover (1989)	lung cancer	case series	4.4	–	partial tumour response	none
Survival: Melanoma 5.5						
Kleeberg et al. (2004)	melanoma, stages II-III	prospective randomised	5.5	–	none	none
Augustin et al.(2005)	melanoma, stages II-III	cohorts with retrospective data collection	5.5.3, 6.1.2	–	survival	2A

Ernst E., Schmidt K., Steuer-Vogt M. K. (2003) Mistletoe for cancer: a systematic review of randomized clinical trials. *International Journal of Cancer* 107, 262–267.

Study design

Type	Systematic review with defined initial search strategy and quality criteria.
Inclusion criteria	All randomised clinical trials with mistletoe preparation for all types of carcinoma without any limit for language.
Exclusion criteria	No clinically relevant outcome (i.e. purely immunological parameters), no adequate control group (i.e. testing one mistletoe preparation with another).
Judgement criteria	Study design, number of patients, patient description, description of intervention, presentation of primary outcomes and results. The Jadad score was implemented to judge the methodical quality of the studies (see: Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, McQuay HJ (1996): Assessing the quality of reports of randomised clinical trials: Is blinding necessary? *Controlled Clinical Trials* 17: 1–12).

Results pertaining to studies with mistletoe, especially Iscador

10 randomised studies fulfilled all of the inclusion criteria and none of the exclusion criteria, 3 of which were with Iscador (see Table 1).

One of the randomised studies with Iscador has not yet been published at the time of the review and is not considered in the following summary.

Table 1: Results of randomised studies with Iscador

Publication	Diagnosis	Chapter in this documentation	No. of study according to Kienle/Kiene 2003	Main results	Number of patients	Jadad score
Dold et al. (1991)	lung cancer	3.2.4.1, 4.4.1, 5.4.1.3	35	Quality of life with Iscador significantly better. No significant differences between the groups regarding survival and growth of tumour	337	3
Salzer et al. (1991)	lung cancer	5.4.1.4	34	No significant differences between the groups regarding tumour relapse and mortality.	183	2

Lange-Lindberg A.-M., Velasco-Garrido M., Busse R. (2006) *Misteltherapie als begleitende Behandlung zur Reduktion der Toxizität der Chemotherapie maligner Erkrankungen*. [Mistletoe as complementary therapy for the reduction of the toxicity of chemotherapy for malignant diseases.] Köln: Deutsche Agentur für Health Technology Assessment des Deutschen Instituts für Medizinische Dokumentation und Information (DAHTA-DIMDI).

Study design

Type	Systematic literature search based on a protocol with narrative presentation of results.
Questions	Main questions: (1) Does the addition of mistletoe therapy to conventional chemotherapy for malignant diseases reduce the chemotherapy-induced toxicity? (2) Does the addition of mistletoe therapy to conventional chemotherapy for malignant diseases lead to higher quality of life compared to chemotherapy alone? Additional questions: Has the addition of mistletoe therapy to conventional chemotherapy for malignant diseases effects on survival and/or the remission of tumours in oncologic patients?
Inclusion criteria	Systematic literature search for mistletoe studies according to the standards of the German Agency for Health Technology Assessment (DAHTA) in the data bases The Cochrane Library, DIMDI-superbase and Dissertation Abstracts. All systematic reviews and randomised controlled trials (RCT) with primary end points were included to answer the study questions (1) and (2).
Judgement criteria	The studies were judged according to check lists. The study quality was quantified using the Jadad-Score.

Results pertaining to studies with mistletoe

After the selection procedure, 3 published reviews remained (7.2.2, 7.2.4, 7.2.6), together with 6 published and 3 unpublished RCTs. The reviews were not sufficient to answer the main questions. Not one of the RCTs had incidence and severity of chemotherapy-induced side effects as their primary endpoints; the results of these studies concerning these parameters were inconsistent. Only quality of life of breast cancer patients can be enhanced with mistletoe therapy. The evidence is not sufficient to answer the question of efficacy of mistletoe therapy concerning survival and the remission of tumours respectively.

Results pertaining to studies with Iscador

No Iscador study fulfilled the inclusion criteria.

Kienle G. S., Kiene H. (2007) Complementary cancer therapy: a systematic review of prospective clinical trials on anthroposophic mistletoe extracts. *European Journal of Medical Research* 12, 103–119.

Study design

Type	Systematic review with predefined search strategy and quality criteria.
Incluscion criteria	Clinical studies with mistletoe therapy: 1) Prospective controlled clinical studies, randomised or nonrandomised, prospective one-arm cohort studies (phase II studies) 2) Study population with cancer patients, including CIN (Cervical Intraepithelial Neoplasia) 3) Intervention group with anthroposophic mistletoe preparations 4) Measurement of clinical relevant parameters 5) Study completed.
Exclusion criteria	1) Only measurement of toxicity or tolerance (phase I studies) 2) Only measurement of immunological parameters 3) Studies not with cancer patients.
Judgement criteria	See 7.2.4.

Results pertaining to studies with mistletoe, especially Iscador

37 of the final 197 studies with anthroposophic mistletoe preparations fulfilled the inclusion criteria (20 with Iscador). 16 studies were randomised (8 with Iscador), 9 studies nonrandomised cohort studies (8 with Iscador) and 12 studies only with one arm (4 with Iscador).

Within the 8 randomised studies as well as within the 8 nonrandomised studies with Iscador 5 studies each showed statistical significant results in favour of the Iscador group

This review is an update of the review 7.2.4 concerning anthroposophic mistletoe preparations. The following table 1 shows only those studies that were not present in the previous tables 1–3 in 7.2.4.

Table 1: Results of studies with Iscador (in addition to the studies from tables 1–3 in 7.2.4)

Publication	Design	Diagnosis	Chapter in this documentation	Results with an advantage for the Iscador group	Number of patients
Borrelli 1999	RCT	breast cancer	3.1.2.1	significant improvement of quality of life	30
Kleeberg 2004	RCT	melanoma	5.5	no significant difference concerning overall survival and disease-free interval	407
Büssing 2004	2-arm	breast cancer	1.5	significant prevention of surgery-induced inhibition of granulocytes (oxidative burst)	103
Von Hagens 2005	2-arm	breast cancer	1.3, 3.1.2	significant reduction of chemotherapy-induced side effects	66
Kuehn 2005	1-arm	follicular lymphoma	4.7.2	remissions	24
Kjaer 1989	1-arm	kidney	5.1.5	–	14
Portalupi 1995	1-arm	CIN	4.1.1	remissions	27
Bar-Sela 2006	1-arm	ascites, malignant effusion	3.3.1	longer intervals between punctures	23

Horneber M. A., Bueschel G., Huber R., Linde K., Rostock M. (2008) Mistletoe therapy in oncology. Cochrane Database of Systematic Reviews 2008, Issue 2. No. CD003297.

Study design

Typ	Systematic review with predefined search strategy and quality criteria.
Inclusion criteria	Prospective controlled randomised clinical studies with adult cancer patients and mistletoe therapy
Exclusion criteria	Only measurement of physiological, in particular immunological parameters.
Judgement criteria	Methodological quality was assessed by narrative using a delphi-list and the Jadad-score (see 7.2.4). High methodological quality was defined by fulfilling at least 6 to 9 delphi-criteria and at least 4 to 5 Jadad-criteria.

Results pertaining to studies with mistletoe

80 studies were identified. 58 were excluded for various reasons, usually as there was no prospective trial design with randomised treatment allocation. Of the 21 included studies 13 provided data on survival, 7 on tumour response, 16 on measures of QoL or psychological outcomes, or prevalence of chemotherapy-related adverse effects and 12 on side effects of mistletoe treatment; overall comprising 3484 randomised cancer patients. Interventions evaluated were 5 preparations of mistletoe extracts from 5 manufacturers and one commercially not available preparation. The general reporting of RCTs was poor.

Of the 13 trials investigating survival, 6 showed some evidence of a benefit, but none of them was of high methodological quality. The results of two trials in patients with melanoma and head and neck cancer gave some evidence that the used mistletoe extracts are not effective for improving survival.

Of the 16 trials investigating the efficacy of mistletoe extracts for either improving QoL, psychological measures, performance index, symptom scales or the reduction of adverse effects of chemotherapy, 14 showed some evidence of a benefit, but only 2 of them including breast cancer patients during chemotherapy were of higher methodological quality.

Data on side effects indicated that, depending on the dose, mistletoe extracts were usually well tolerated and had few side effects.

Authors' conclusions

The evidence from RCTs to support the view that the application of mistletoe extracts has impact on survival or leads to an improved ability to fight cancer or to withstand anticancer treatments is weak. Nevertheless, there is some evidence that mistletoe extracts may offer benefits on measures of QoL during chemotherapy for breast cancer, but these results need replication. Overall, more high quality, independent clinical research is needed to truly assess the safety and effectiveness of mistletoe extracts. Patients receiving mistletoe therapy should be encouraged to take part in future trails.

Table 1: Results of studies with Iscador

Publication	Number of patients/ analysed	Diagnosis	Chapter in this documentation	Results with an advantage for the Iscador group	Quality: Delphi/ Jadad
Borrelli 1999	30 / 30	breast cancer, with metastases	3.1.2.1	quality of life (Spitzer): significant improvement tumour response: no significant difference	4 / 3
Dold 1991	408 / 337	non small-cell lung cancer	3.2.4.1, 4.4.1, 5.4.1.3	subjective well-being: significant improvement tumour response: no significant difference overall survival: no significant difference	6 / 3
Grossarth 2001a	98 / 78	various solid tumours	3.1.6.1, 5.6.1	self-regulation: significant improvement overall survival: significant improvement	3 / 2
Grossarth 2001b	34 /34	breast cancer	3.1.2.4, 5.2.5	self-regulation: positive trend overall survival: significant improvement	4 / 2
Kleeberg 2004	407 / 407	primary melanoma	5.5	disease-free interval: no significant difference overall survival: no significant difference	6 / 3
Salzer 1983	271 / 238 359 / 137	cancer of the stomach	5.3.1.1	overall survival: significant improvement for patients with lymphatic metastases	4 / 3
Salzer 1991	218 / 183	non small-cell lung cancer	5.4.1.4	overall survival: significant improvement for patients with and without lymphatic metastases	4 / 3

Melzer J., Iten F., Hostanska K., Saller R. (2009) Efficacy and Safety of mistletoe preparations (Viscum album) for patients with cancer diseases. A systematic review. Forschende Komplementärmedizin 16, 17–26.

Study design

Type	Systematic review with predefined search strategy and quality criteria.
Inclusion criteria	Prospective controlled randomised or comparative cohort studies with process standardised mistletoe preparations in cancer patients with systemic interventions (subcutaneous or per infusion).
Exclusion criteria	Phase I and II studies, other types of interventions, incomplete documentation, other languages than German, English, French.
Judgement criteria	Multidimensional quality judgement using tables but without a formal rating procedure.

Results pertaining to studies with mistletoe

18 clinical trials (>6,800 participants) were included, 7 concerning Iscaodor (Table 1). Their internal quality was mostly low. Due to heterogeneity between trials a meta-analysis was impossible. Regarding efficacy, findings were inconsistent regarding life expectancy, relation to tumour entity, dosing and treatment duration. Yet, studies indicate that quality of life (QoL) is improved. As these findings do not seem to be limited to one of the different parenteral mistletoe preparations reviewed the treatment may be summarised under the umbrella term ‘mistletoe therapy’. Regarding safety, 1 serious adverse drug reaction (ADR) related to mistletoe was described; non-serious ADR were local reactions at injection site. Allergic reactions were rare.

Author's Conclusions

Supportive ‘mistletoe therapy’ seems safe and beneficial for QoL in adult patients with solid tumours. But there is an urgent need to confirm its efficacy in patient-centred care in a complex oncologic setting. This has to be evaluated systematically in prospective observational trials with validated, multidimensional patient-rated QoL questionnaires and comparisons of different preparations and dosages.

For results of this systematic review concerning safety see 6.2.1

Table 1: Results of studies with Iscador

Publication	Number of patients/ analysed	Diagnosis	Chapter in this documentation	Results with an advantage for the Iscador group
Kleeberg et al. 2004	407 / 407	primary melanoma	5.5	disease-free interval: no significant difference overall survival: no significant difference
Dold et al. 1991	408 / 337	non small-cell lung cancer	3.2.4.1 4.4.1 5.4.1.3	overall survival: no significant difference tumour response: no significant difference subjective well-being: significant improvement physical indisposition: no significant difference
Toelg et al. 2005	128	gynaecological cancers	3.1.1	improvement of overall health improvement of mental well-being improvement of quality of life
Augustin et al. 2005	783 / 686	melanoma	5.5.3 6.1.2	tumour-related survival: significant improvement overall survival: significant improvement
Bock et al. 2004	98 / 78	breast cancer	3.2.2.1 6.1.1	disease symptoms: significant improvement overall survival: significant improvement
Grossarth et al. 2001	98 / 78	various solid tumours	3.1.6.1 5.6.1	self-regulation: significant improvement overall survival: significant improvement
Grossarth et al. 2001	34 /34	breast cancer	3.1.2.4 5.2.5	self-regulation: no significant difference overall survival: significant improvement

7.3 Systematic Reviews Concerning Selected Clinical Questions

References

- Melzer J., Saller R. (2009) Lebensqualität onkologischer Patienten unter supportiver Behandlung mit Viscum album (parenterale Mistelpräparate). Schweizerische Zeitschrift für GanzheitsMedizin 21 (3):157–161 [keine Studien mit Iscador erfüllten die Einschlusskriterien].

☆ Kienle G.S., Glockmann A., Schink M., Kiene H. (2009) Viscum album L. extracts in breast and gynaecological cancers: a systematic review of clinical and preclinical research. Journal of Experimental & Clinical Cancer Research 28: 79.

☆ Ostermann T., Raak C., Büssing A. (2009) Survival of cancer patients treated wih mistletoe extract (Iscador): a systematic literature review. BMC Cancer 9: 451.

☆ Kienle G. S., Kiene H. (2010) Influence of *Viscum album* L (European mistletoe) extracts on quality of life in cancers patients: a systematic review of controlled clinical studies. Integrative Cancer Therapies 9(2): 142–157.

The references marked with ☆ are included in abstract form in this documentation.

Kienle G. S., Glockmann A., Schink M., Kiene H. (2009) Viscum album L. extracts in breast and gynaecological cancers: a systematic review of clinical and preclinical research. Journal of Experimental & Clinical Cancer Research 28: 79.

Study design

Type	Systematic review of clinical and preclinical studies concerning breast cancer and gynaecological tumours with predefined search strategy and quality criteria.
Inclusion criteria	Clinical and preclinical studies about the therapeutic efficacy and biological effects of mistletoe preparations: 1) prospective controlled clinical studies, randomised or nonrandomised, prospective 1-arm cohort studies (phase II studies), pharmaco-epidemiological cohort studies 2) study population with breast cancer or gynaecological cancer, including CIN (Cervical Intraepithelial Neoplasia) 3) intervention group with mistletoe preparations 4) measurement of clinical relevant parameters 5) study completed
Exclusion criteria	1) only measurement of toxicity or tolerance (phase I studies) 2) only measurement of immunological parameters 3) studies not with cancer patients 4) retrospective studies (excluding pharmaco-epidemiological cohort studies)
Judgement criteria	See 7.2.4.

Results pertaining to studies with mistletoe, especially Iscador

Results: 46 clinical studies with mistletoe preparations fulfilled the inclusion criteria (27 with Iscador). 19 studies were randomised (RCT) (11 with Iscador, table 1), 16 non-randomised (non-RCT) controlled studies (14 with Iscador, table 2), and 11 single-arm cohort studies (2 with Iscador, table 3) were identified that investigated viscum album extracts (VAE) treatment of breast or gynaecological cancer. They included 2420, 6399 and 1130 patients respectively. 8 RCTs and 8 non-RCTs were embedded in the same large epidemiological cohort study. 9 RCTs and 13 non-RCTs assessed survival; 12 reported a statistically significant benefit, the others either a trend or no difference. 3 RCTs and 6 non-RCTs assessed tumour behaviour (remission or time to relapse); 3 reported statistically significant benefit, the others either a trend, no difference or mixed results. Quality of life (QoL) and tolerability of chemotherapy, radiotherapy or surgery was assessed in 15 RCTs and 9 non-RCTs. 21 reported a statistically significant positive result, the others either a trend, no difference, or mixed results. Methodological quality of the studies differed substantially; some had major limitations, especially RCTs on survival and tumour behaviour had very small sample sizes. Some recent studies, however, especially on QoL were reasonably well conducted. Single-arm cohort studies investigated tumour behaviour, QoL, pharmacokinetics and safety of VAE. Tumour remission was observed after high dosage and local application. VAE application was well tolerated.

Conclusion: VAE shows some positive effects in breast and gynaecological cancer. More research into clinical efficacy is warranted.

Table 1: Results of randomised studies with Iscador

Publication	Design	Diagnosis	Chapter in this documentation	Most important results with an advantage for the Iscador group	Number of patients analysed
Tröger 2009	RCT	breast	3.1.2	–	95
Büssing 2008	RCT	breast	1.5	–	65
Grossarth 2008	RCT	uterus, corpus	3.1.1.3, 5.1.3.1	survival significant	60
Grossarth 2008	RCT	uterus, corpus	5.1.3.1	–	52
Grossarth 2007	RCT	ovary	3.1.1.2, 5.1.2.4	trend in survival	42
Grossarth 2007	RCT	ovary	5.1.2.4	survival significant	40
Grossarth 2007	RCT	uterine cervix	3.1.1.1, 5.1.4.2	trend in survival	38
Grossarth 2006	RCT	breast	3.1.2.3, 5.2.8	survival significant	76
Borrelli 2001	RCT	breast	3.1.2.1	quality of life significant	30
Grossarth 2001	RCT	breast	3.1.2.4, 3.1.6.1, 5.2.5	survival significant	34
Grossarth 2001	RCT	breast and other sites	3.1.6.1, 5.6.1	survival significant	78

Table 2: Results of prospective 2-arm nonrandomised studies with Iscador

Publication	Design	Diagnosis	Chapter in this documentation	Most important results with an advantage for the Iscador group	Number of patients analysed
Grossarth 2008	prospective 2-arm	uterus, corpus	3.1.1.3, 5.1.3.1	survival significant	206
Grossarth 2008	prospective 2-arm	uterus, corpus	5.1.3.1	survival significant	190
Loewe-Mesch 2008	prospective 2-arm	breast	1.3, 3.1.2.5	quality of life significant	66
Grossarth 2007	prospective 2-arm	ovary	3.1.1.2, 5.1.2.4	survival significant	150
Grossarth 2007	prospective 2-arm	ovary	5.1.2.4	trend in survival	124
Grossarth 2007	prospective 2-arm	uterine cervix	3.1.1.1, 5.1.4.2	survival significant	204
Grossarth 2007	prospective 2-arm	uterine cervix	5.1.4.2	survival significant	132
Grossarth 2006	prospective 2-arm	breast	3.1.2.3, 5.2.8	survival significant	168
Büssing 2005	prospective 2-arm	breast	1.5	–	105
Grossarth 2001	prospective 2-arm	breast and other sites	5.6.2	survival significant	622
Salzer 1987	prospective 2-arm	breast	5.2	trend in survival	155
Fellmer 1966	prospective 2-arm	uterine cervix	5.1.4.1	survival significant	790
Majewski 1963	prospective 2-arm	genital	5.2	trend in survival	–
Bock 2004	retrospective 2-arm	breast	3.2.2.1, 5.2.7, 6.1.1	survival significant	1442

Table 3: Results of prospective 1-arm studies with Iscador

Publication	Design	Diagnosis	Chapter in this documentation	Most important results with an advantage for the Iscador group	Number of patients analysed
Portalupi 1995	prospective 1-arm	CIN-HPV	4.1.1	remissions	22
Bar-Sela 2006	prospective 1-arm	ascites	3.3.1	longer interval between successive punctures	23

Ostermann T., Raak C., Büssing A. (2009) Survival of cancer patients treated wih mistletoe extract (Iscador): a systematic literature review. BMC Cancer 9: 451.

Study design

Type	Systematic review of controlled clinical studies on parameters associated with survival in cancer patients treated with the Viscum album preparation Iscador, using predefined search strategies and quality criteria.
Inclusion criteria	1) Controlled clinical studies, randomised oder non-randomised, in English or German language journals 2) Study population with cancer 3) Treatment group with mistletoe preparation Iscador 4) Measurement of parameters associated with survival
Exclusion criteria	1) Field reports 2) Case series or case reports 3) Studies without any control group 4) Abstracts which proceeded a full length publication 5) Double publication of similar data 6) Internal reports and unpublished manuscripts
Judgement criteria	1) Adequate description of the study design 2) Subject assembly process 3) Comparability of groups 4) Allocation concealment 5) Description of the intervention 6) Description of statistical analysis 7) External validity

Results

There were 49 publications on the clinical effects of Iscador usage on survival of cancer patients which met the inclusion/exclusion criteria. Among them, 41 studies provided enough data to extract hazard ratios (HR) and their standard errors (Iscador versus no extra treatment). The majority of studies reported positive effects in favour of the Iscador application. Heterogeneity of study results was moderate. The analysis of the studies by funnel plots showed considerabls skewness, indicating a publication bias. A random effect meta-analysis estimated the overall hazard ratio at HR = 0.59 with a confidence interval (CI) of 0.53 – 0.66 and $p < 0.0001$. Randomised studies showed less effects than non-randomised studies (ratio of HRs: 1.24, CI: 0.79 – 1.92, $p = 0.35$), and matched-pair studies gave significantly better results than others (ratio of HRs: 0.33; CI: 0.17 – 0.65, $p = 0.0012$).

Conclusions

Pooled analysis of clinical studies suggests that adjuvant treatment of cancer patients with the mistletoe extract Iscador is associated with a better survival. Despite obvious limitations, and strong hints for a publication bias which limits the evidence found in this meta-analysis, one cannot ignore the fact that studies with positive effects of Viscum album preparations on survival of cancer patients are accumulating. Future studies evaluating the effects of Iscador should focus on a transparent design and description of endpoints in order to provide greater insight into a treatment often being depreciated as ineffective, but highly valued by cancer patients.

Table 1: Clinical studies on survival with Iscador

			Study design of all studies			design of studies enrolled for statistical analysis			
	Year	Tumour localization	control	design	random.	matched pairs	Blinding	Multi-center	Description Drop-outs
*Augustin, 5.5.3	2005	Skin	PLG	retrolec.	NR	N-MP	no	**yes**	**yes**
*Bock, 5.2.7	2004	Breast	PLG	retrolect.	NR	N-MP	no	**yes**	unclear
Dold, 5.4.1.3	1991	Lung	PLG	prosp.	**rand**	N-MP	-	-	-
Eggermont, 5.5	2001	Skin	PLG	prosp.	**rand**	N-MP	-	-	-
*Fellmer, 5.1.4.1	1966	Cervix	PLG	prosp.	NR	N-MP	no	no	no
Feuchtinger, 5.5.1	1977	Skin	Lit	retro.	-	-	-	-	-
*Grossart-Maticek, 5.6.2	2004	Various	PLG	prosp.	NR	**MP**	no	**yes**	unclear
*Grossart-Maticek, 5.2.5	2006	Breast	PLG	prosp.	**rand**	**MP**	no	**yes**	yes
Grossart-Maticek, 5.2.6	2006	Breast	PLG	prosp.	NR	**MP**	-	-	-
Grossart-Maticek, 5.2.8	2006	Breast	PLG	prosp.	**rand**	**MP**	-	-	-
Grossart-Maticek, 5.2.8	2006	Breast	PLG	prosp.	NR	**MP**	-	-	-
Grossart-Maticek, 5.1.2.4	2007	Ovary	PLG	prosp.	**rand**	**MP**	-	-	-
Grossart-Maticek, 5.1.2.4	2007	Ovary	PLG	prosp.	NR	**MP**	-	-	-
*Grossart-Maticek, 5.1.4.2	2007	Cervix	PLG	prosp.	NR	**MP**	no	**yes**	yes
*Grossart-Maticek, 5.1.4.2	2007	Cervix	PLG	prosp.	**rand**	**MP**	no	**yes**	yes
Grossart-Maticek, 5.5.4	2007	Skin	PLG	prosp.	**rand**	**MP**	-	-	-
*Grossart-Maticek, 5.5.4	2007	Skin	PLG	prosp.	NR	**MP**	no	**yes**	yes
*Grossart-Maticek, 5.1.3.1	2008	Corpus uteri	PLG	prosp.	NR	**MP**	no	**yes**	no
*Grossart-Maticek, 5.1.3.1	2008	Corpus uteri	PLG	prosp.	**rand**	**MP**	no	**yes**	**yes**
Günczler, 5.2	1962	Breast	Lit	retro.	-	-	-	-	-
*Günczler, 5.3.1	1968	Stomach	PLG	retro.	NR	N-MP	no	no	yes
*Günczler, 5.2	1969	Breast	historic	retro.	-	-	no	no	unclear
*Hassauer, 5.1.2.1	1979	Ovary	Lit	retro.	-	-	no	no	unclear
Hellan, 5.3.3.2	1995	Colorectal	PLG	retro.	NR	N-MP	-	-	-
Hoffmann, 5.3.4.1	1979	Liver	PLG	retro.	NR	N-MP	-	-	-
*Hoffmann, 5.1.1	1980	bladder	PLG	retro.	NR	N-MP	-	-	-
Hoffmann, 5.2.3	1982	Breast	Lit	retro.	-	-	no	no	no
Kjaer, 5.1.5	1984	Kidney	historic	prosp.	-	-	-	-	-
Kleeberg, 5.5	2004	Skin	PLG	prosp.	**rand**	N-MP	-	-	-
Krause, 5.4.1	1983	Lung	historic	retro.	-	-	-	-	-
Koch, 5.2	1980	Breast	Lit	retro.	-	-	-	-	-
*Leroi, 5.2.2	1977	Breast	PLG	retro.	NR	N-MP	no	no	no
Leroi, 5.3.3	1978	Colorectal	PLG	retro.	NR	N-MP	-	-	-
Leroi, 5.3.3.1	1979	Colorectal	PLG	retro.	NR	N-MP	-	-	-
Leroi, 5.2.1	1975	Breast	PLG	retro.	NR	N-MP	-	-	-
*Leroi, 5.1.2.2	1982	Ovary	Lit	retro.	-	-	no	no	no
*Majewski, 5.1.2	1963	Ovary	PLG	retro.	NR	N-MP	no	no	yes
*Salzer, 5.4.1	1975	Lung	PLG	retro.	NR	N-MP	no	no	yes
*Salzer, 5.4.1.1	1978	Lung	PLG	retro.	NR	N-MP	no	no	no
*Salzer, 5.3.1.1	1983	Stomach	PLG	prosp.	**rand**	N-MP	no	no	unclear
Salzer, 5.4.1.4	1991	Lung	PLG	prosp.	**rand**	N-MP	-	-	-
Schaefermeyer, 5.3.2.1	1998	Pancreas	Lit	retro.	-	-	-	-	-
*Schreiber, 5.1.2	1984	Ovary	Lit	retro.	-	-	no	no	unclear
*Schreiber, 5.1.2	1984	Ovary	PLG	retro.	NR	N-MP	no	no	unclear
Schuppli, 5.5.2	1990	Skin	PLG	retro.	NR	N-MP	-	-	-
Wagner, 5.1.2.3	1996	Ovary	Lit	retro.	-	-	-	-	-

Abbreviations: PLG – parallel group; Lit – literature control; NR – no randomization; rand – randomization; MP – matched pairs; N-MP – no matched pairs; prosp. – prospective; retro. – retrospective; retrolec. – retrolective.

* study suited for data extraction

Kienle G. S., Kiene H. (2010) Influence of *Viscum album* L (European mistletoe) extracts on quality of life in cancers patients: a systematic review of controlled clinical studies. Integrative Cancer Therapies 9(2): 142–157.

Study design

Type	Systematic review of clinical studies concerning quality of life (QoL) of cancer patients with predefined search strategy and quality criteria.
Inclusion criteria	Clinical studies about effects in quality of life of mistletoe preparations: 1) prospective controlled clinical studies, randomised or nonrandomised, prospective, pharmaco-epidemiological cohort studies 2) including control group 3) study population with cancer 4) intervention group treated with VAE (mistletoe) preparation 5) QoL outcome 6) study completed 7) published or unpublished
Exclusion criteria	1) only measurement of toxicity or tolerance (phase I studies) 2) only measurement of stimulation of immunological parameters 3) studies not with cancer patients
Judgement criteria	See 7.2.4.

Results pertaining to studies with mistletoe, in particular Iscador

Objective: To evaluate controlled clinical studies on the efficacy and effectiveness of *Viscum album* for quality of life (QoL) in cancer.

Materials and methods: The authors conducted a search of 7 electronic databases and reference lists and had extensive consultations with experts. They carried out a criteria-based assessment of methodological study quality.

Results: The authors identified 26 randomized controlled trials (RCTs) and 10 non-RCTs that investigated the influence of *Viscum album* extracts (VAEs) on QoL in malignant diseases [13 and 8 respectively with Iscador]; 26 studies assessed patient-reported QoL. Questionnaires were mostly well established and validated. Half of the studies investigated VAEs concomitant with chemotherapy, radiotherapy, or surgery. Some studies were well designed, whereas others had minor or major methodological weaknesses. Among the 26 RCTs, 22 reported a QoL benefit [12 with Iscador], 3 indicated no difference [none with Iscador], and 1 did not report any result [1 with Iscador]. All the non-RCTs reported a QoL benefit. Of the studies with higher methodological quality, most reported a benefit, whereas 1 found no difference [1 with Iscador]. Improvements were mainly in regard to coping, fatigue, sleep, exhaustion, energy, nausea, vomiting, appetite, depression, anxiety, ability to work, and emotional and functional well-being in general and, less consistently, in regard to pain, diarrhea, general performance, and side effects of conventional treatments. VAEs were well tolerated.

Conclusions: VAE treatment seems to have an impact on QoL and reduces side effects of conventional therapies (chemotherapy, radiation) in experimental trials as well as in daily routine application. Fatigue, a debilitating symptom of cancer, seems to improve. The studies vary in the degree of methodological quality. Some of the weaknesses could be avoided by designing and conducting the studies carefully, whereas others represent typical and widely discussed problems of QoL research.

Table 1: Results of randomised studies on Iscador with concomitant chemotherapy (ADR = adverse drug reaction)

Publication	QoI measure	Chapter in this documentation	Most important results with an advantage for the Iscador group
Longhi 2009	EORTC QLQ-C30, ADR	5.10	EORTC QLQ-C30
Tröger 2009	EORTC QLQ-C30	3.1.2	EORTC QLQ-C30: pain, diarrhea, role, insomnia, nausea/vomiting,
Büssing 2008	EORTC QLQ-C30, ADR	1.5	ADR: nausea, constipation, pain, stomatitis, appetite

Table 2: Results of prospective 2-arm nonrandomised studies with Iscador with concomitant chemotherapy (ADR = adverse drug reaction)

Publication	QoI measure	Chapter in this documentation	Most important results with an advantage for the Iscador group
Loewe-Mesch 2008	EORTC QLQ-C30, ADR	1.3, 3.1.2.5	EORTC QLQ-C30: nausea/vomiting
Matthes 2009	disease- or treatment-associated symptoms	3.2.3.2, 5.3.2.2, 6.1.5	nausea/vomiting, appetite, back pain, tiredness, depression, irritability, total symptom score Karnofsy Performance Status
Friedel 2009	disease- or treatment-associated symptoms	3.2.3.1, 5.3.3.4, 6.1.4	nausea/vomiting, appetite, diarrhea, tiredness, depression, memory, sleep, irritability, total symptom score Karnofsy Performance Status
Bock 2004	disease-associated symptoms	3.2.2.1, 5.2.7, 6.1.1	symptom-free: vomiting, headache, exhaustion, depression, concentration, sleep, dizziness, irritability

Table 3: Results of randomised studies on Iscador independent of concomitant conventional cancer treatment

Publication	QoI measure	Chapter in this documentation	Most important results with an advantage for the Iscador group
Grossarth 2008 (corpus uteri)	self-regulation questionnaire	3.1.1.3, 5.1.3.1	self-regulation
Grossarth 2007 (cervix)	self-regulation questionnaire	3.1.1.1, 5.1.4.2	self-regulation
Grossarth 2007 (melanoma)	self-regulation questionnaire	5.5.4	self-regulation
Grossarth 2007 (ovary)	self-regulation questionnaire	3.1.1.2, 5.1.2.4	self-regulation
Grossarth 2006 (breast)	self-regulation questionnaire	3.1.2.3, 5.2.8	self-regulation
Kleeberg 2004	QoL evalution	5.5	no data
Borrelli 1999	Spitzer Score	3.1.2.1	well being, daily life
Grossarth 2001 (breast)	self-regulation questionnaire	3.1.2.4, 3.1.6.1, 5.2.5	self-regulation
Grussarth 2001 (diverse)	self-regulation questionnaire	3.1.6.1, 5.6.1	self-regulation
Dold 1991	subjective improvement of QoL	3.2.4.1, 4.4.1, 5.4.1.3	subjective improvement of QoL

Table 4: Results of prospective 2-arm nonrandomised studies on Iscador independent of concomitant conventional cancer treatment

Publication	QoI measure	Chapter in this documentation	Most important results with an advantage for the Iscador group
Grossarth 2008 (corpus uteri)	self-regulation questionnaire	3.1.1.3, 5.1.3.1	self-regulation
Grossarth 2007 (cervix)	self-regulation questionnaire	3.1.1.1, 5.1.4.2	self-regulation
Grossarth 2007 (ovary)	self-regulation questionnaire	3.1.1.2, 5.1.2.4	self-regulation
Grossarth 2006 (breast)	self-regulation questionnaire	3.1.2.3, 5.2.8	self-regulation

8 Meta-Analyses

References

- ✭ Ziegler R., Grossarth-Maticek R. (2008) Individual Patient Data Meta-analysis of Survival and Psychosomatic Self-regulation from Published Prospective Controlled Cohort Studies for Long-term Therapy of Breast Cancer Patients with a Mistletoe Preparation (Iscador). eCAM 2008;doi: 10.1093/ecam/nen025.
- ✭ Ostermann T., Raak C., Büssing A. (2009) Survival of cancer patients treated wih mistletoe extract (Iscador): a systematic literature review. BMC Cancer 9: 451. [see 7.3.2]
- ✭ Büssing A., Raak C., Ostermann T. (2012) Quality of life and related dimensions in cancer patients treated wih mistletoe extract (Iscador): a meta-analysis. Evidence Based Complementary and Alternative Medicine 2012, Article ID 219402, 8 pages.
- ✭ Ostermann T., Büssing A., (2012) Retrolective studies on the survival of cancer patients treated wih mistletoe extracts: a meta-analysis. Explore 8(5): 277–281.

The references marked with ✭ are included in abstract form in this documentation.

Ziegler R., Grossarth-Maticek R. (2008) Individual Patient Data Meta-analysis of Survival and Psychosomatic Self-regulation from Published Prospective Controlled Cohort Studies for Long-term Therapy of Breast Cancer Patients with a Mistletoe Preparation (Iscador). eCAM 2008;doi: 10.1093/ecam/nen025.

Study design

Type	Systematic review with predefined search strategy.
Inclusion criteria	Prospective controlled clinical studies in breast cancer patients with Iscador therapy in matched-pair-design, randomised or nonrandomised. End Points: Overalls survival and self-regulation.

Most important results

There were 2 randomised and 4 nonrandomised studies with Iscador (table 1).

Table 1: Results of studies with Iscador

Study Reference	**Pairs**	**Design: matched pairs**	**Cancer**	**End points**	**Chapter in this documentation**
MammaRand Grossarth 2006a	38	randomised	primary breast cancer without relapse or metastases	self-regulation, overall survival	3.1.2.3, 5.2.8
MammaLymRand Grossarth 2001a, 2006b	17	randomised	breast cancer with lymphatic metastases	self-regulation, overall survival	3.1.2.4, 5.2.5
Mamma Grossarth 2006a	84	non-randomised	breast cancer without relapse or metastases	self-regulation, overall survival	3.1.2.3, 5.2.8
MammaRec Grossarth 2001a, 2001b, 2006b	42	non-randomised	breast cancer with relapse and without metastases	overall survival	5.2.6 (strict matching: 29 pairs)
MammaLym Grossarth 2001a, 2001b, 2006b	55	non-randomised	breast cancer with lymphatic metastases	overall survival	5.2.6 (strict matching: 38 pairs)
MammaMet Grossarth 2001a, 2001b, 2006b	83	non-randomised	breast cancer with distant metastases	overall survival	5.2.6 (strict matching: 53 pairs)

Results of meta-analysis: Overall survival (fig. 1) was almost significant in favour of the Iscador group in the combined data set of the randomised studies: estimate of the hazard ratio with 95% confidence interval 0.59 (0.34, 1.02). Overall survival was highly significant in the combined data set of the non-randomised studies: 0.43 (0.34, 0.56).

In the combined analysis of the randomised studies, improvement of psychosomatic self-regulation (fig. 2), as a measure of autonomous coping with the disease, was also highly significant in favour of the Iscador group: estimate of the median difference with 95% confidence interval 0.45 (0.15, 0.80), p = 0.0051.

Conclusions: The analysed studies show that therapy with Iscador might prolong overall survival and improve psychosomatic self-regulation of breast cancer patients.

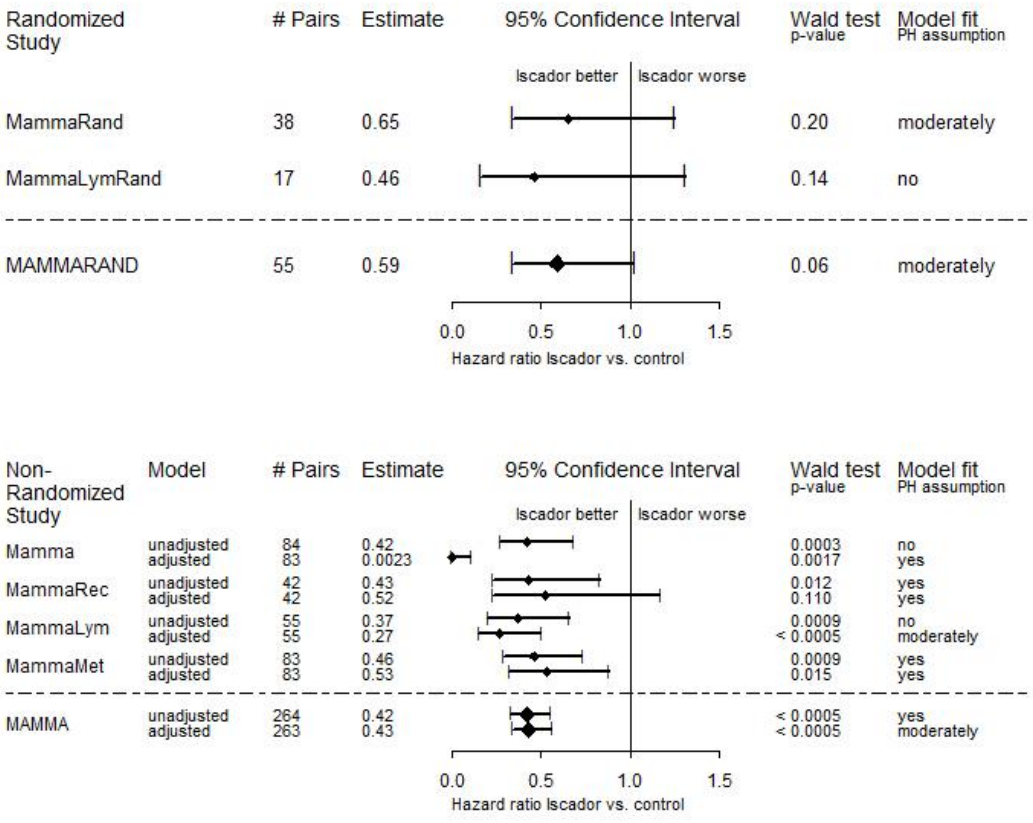

Fig. 1: Meta-analysis of final Cox models for overall survival in the data sets with randomised matched-pairs: *MammaRand*, *MammaLymRand* and their combination into *MAMMARAND* and with non-randomised matched pairs: *Mamma*, *MammaRec*, *MammaLym*, *MammaMet* and their combination into *MAMMA* (according to Ziegler/Grossarth-Maticek 2008).

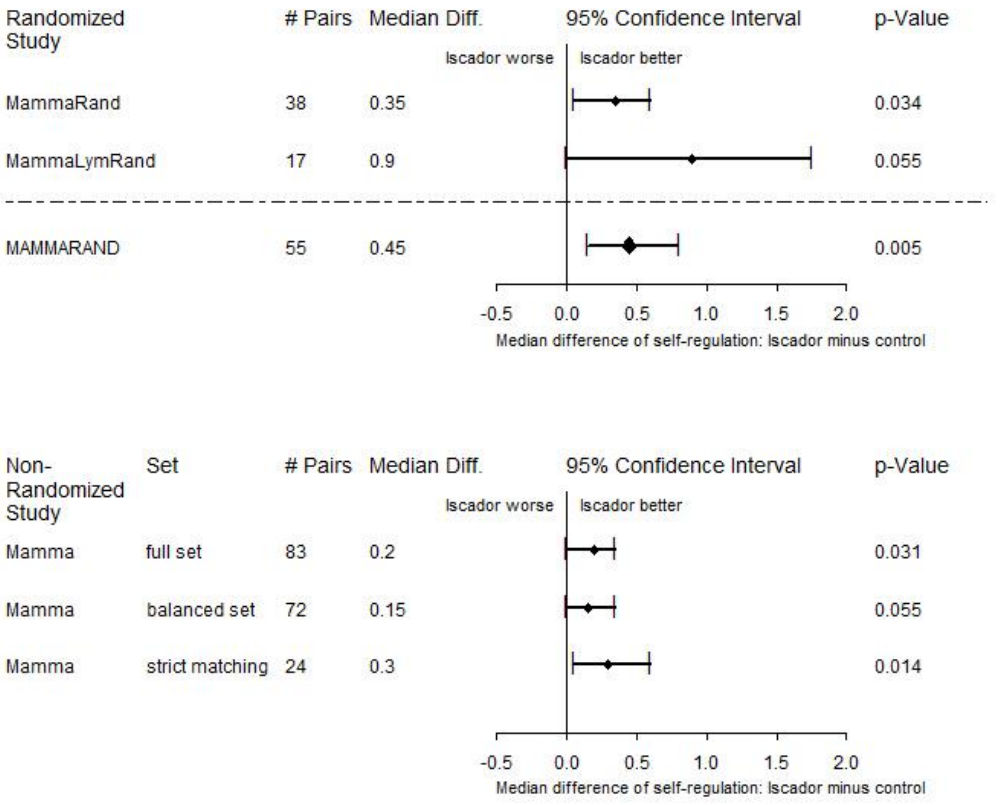

Fig. 2: Meta-analysis of self-regulation for the randomised studies *MammaRand* and *MammaLymRand* and their combination into *MAMMARAND*. Self-regulation for the study *Mamma* according to the complete with respect to risk factors balanced and strictly matched data set (according to Ziegler/Grossarth-Maticek 2008).

Büssing A., Raak C., Ostermann T. (2012) Quality of life and related dimensions in cancer patients treated wih mistletoe extract (Iscador): a meta-analysis. Evidence Based Complementary and Alternative Medicine 2012, Article ID 219402, 8 pages.

Study design

Type	Systematic review and meta-analysis of controlled clinical studies on parameters associated with quality of life in cancer patients treated with the Viscum album preparation Iscador, using predefined search strategies and quality criteria.
Inclusion criteria	1) Controlled clinical studies, randomised oder non-randomised, in English or German language journals 2) Study population with cancer 3) Treatment group with mistletoe preparation Iscador 4) Measurement of parameters associated with survival
Exclusion criteria	1) Field reports 2) Case series or case reports 3) Studies without any control group 4) Abstracts which proceeded a full length publication 5) Double publication of similar data 6) Internal reports and unpublished manuscripts
Judgement criteria	1) Adequate description of the study design 2) Subject assembly process 3) Equality of comparison groups 4) Description of drop outs 5) Allocation concealment 6) Description of the intervention 7) Description of statistical analysis 8) External validity

Results

There were 16 studies described in 11 publications; 13 met the inclusion/exclusion criteria. All of them were controlled and prospective studies. 9 studies were randomised, 4 non-randomised; all included studies were published 2001 or later. All studies reported positive effects in favour of the Iscador application; study quality was generally poor. Standardized mean difference ranged from 0.41 to 0.71 (confidence interval) with a mean of 0.56 ($p < 0.0001$). However, funnel plot analysis of the trials indicated selective publication of positive trials.

Conclusions

The analyzed studies give some evidence that Iscador treatment might have beneficial short time effects on quality of life associated dimensions and psychosomatic self regulation. The results encourage large and well designed randomised controlled trials.

Table 1: Included clinical studies on quality of life with Iscador

Reference	Year	Number of patients		Tumour localization	Study Design				Quality of life instrument
		Iscador	control		control	design	random.	matched pairs	(uni-/multi-dimensionality)
Grossarth-Maticek, 3.1.6.1	2001	39	39	Multiple	PLG	prosp.	rand	MP	Self Regulation (unidimensional)
Grossarth-Maticek, 3.1.6.1	2001	17	17	Breast	PLG	prosp.	rand	MP	Self Regulation (unidimensional)
Grossarth-Maticek, 3.1.2.4	2006	17	17	Breast	PLG	prosp.	rand	MP	Self Regulation (unidimensional)
Grossarth-Maticek, 3.1.2.3	2006	38	38	Breast	PLG	prosp.	rand	MP	Self Regulation (unidimensional)
Grossarth-Maticek, 3.1.2.3	2006	84	84	Breast	PLG	prosp.	NR	MP	Self Regulation (unidimensional)
Grossarth-Maticek, 3.1.1.2	2007	21 + 20	21 + 20	Ovary	PLG	prosp.	rand	MP	Self Regulation (unidimensional)
Grossarth-Maticek, 3.1.1.2	2007	75 + 62	75 + 62	Ovary	PLG	prosp.	NR	MP	Self Regulation (unidimensional)
Grossarth-Maticek, 3.1.1.1	2007	19	19	Cervix	PLG	prosp.	rand	MP	Self Regulation (unidimensional)
Grossarth-Maticek, 3.1.1.1	2007	102	102	Cervix	PLG	prosp.	NR	MP	Self Regulation (unidimensional)
Grossarth-Maticek, 3.1.5.1	2007	22	22	Melanoma	PLG	prosp.	rand	MP	Self Regulation (unidimensional)
Grossarth-Maticek, 3.1.1.3	2008	198	198	Corpus uteri	PLG	prosp.	NR	MP	Self Regulation (unidimensional)
Grossarth-Maticek, 3.1.1.3	2008	56	56	Corpus uteri	PLG	prosp.	rand	MP	Self Regulation (unidimensional)
Hagens et al., 3.1.2.5	2005	33	33	Breast	PLG	prosp.	rand	N-MP	EORTC-QLQ C30, BR 23 (multidimensional)

Abbreviations: PLG – parallel group; NR – no randomization; rand – randomization; MP – matched pairs; N-MP – no matched pairs; prosp. – prospective; retro. – retrospective; retrolec. - retrolective

Ostermann T., Büssing A., (2012) Retrolective studies on the survival of cancer patients treated wih mistletoe extracts: a meta-analysis. Explore 8(5): 277–281.

Study design

Type	Systematic review and meta-analysis of retrolective clinical studies on cancer patients treated with a Viscum album preparation, using predefined search strategies and quality criteria.
Inclusion criteria	1) Retrolective clinical studies in English or German language journals 2) Study population with cancer 3) Treatment group with mistletoe preparation
Exclusion criteria	1) Abstracts which proceeded a full length publication 2) Double publication of similar data

Results

Background: Studies reveal that patients with cancer are actively seeking supportive treatments and may use distinct coping strategies that might be helpful to extend survival time. In this respect, retrolective studies have been applied to examine the therapeutic potential of adjuvant mistletoe treatment.

Material and Methods: The databases PubMed, EMBASE, AMED, and CAMbase were used to identify retrolective studies in mistletoe treatment. In addition to a review, we also performed a meta-analysis with respect to cancer patients' survival time by a random effects model. Overall estimates of treatment effects were displayed with a forest plot.

Results: A total of 17 articles met the inclusion criteria. From these, 10 duplicates and 3 descriptive literature and popular articles had to be removed, leaving 4 retrolective studies on mistletoe preparations (Iscador) and patients' survival conducted between 1985 and 2002, with a total of 3.324 patients (2.454 per protocol) recruited in 17 to 35 German and Swiss hospitals, wards, and private practices. Meta-analysis revealed a moderate overall effect of hazard ratios 0.59 (95% confidence interval 0.50–0.70) in favor of mistletoe treatment with Iscador.

Discussion: Although we found a positive treatment effect, there are several methodological limitations with respect to the retrolective study design.

The four retrolective studies can be found in this documentation under the following references:

Bock et al. 2004	3.2.2.1, 5.2.7, 6.1.1
Augustin et al. 2005	5.5.3, 6.1.2
Friedel et al. 2009	3.2.3.1, 5.3.3.4, 6.1.
Matthes et al. 2010	3.2.3.2, 5.3.2.2, 6.1.5

	Bock 2004[21]	Augustin 2005[22]	Friedel 2009[23]	Matthes 2010[24]
N (VA-E vs control)	1442 (710/732)	686 (329/357)	804 (429/375)	396 (201/195)
Number of centers	16	35	26	17
Time frame	1988-2000	1985-2001	1993-2002	1993-2002
Type of cancer	Breast	Melanoma	Colorectal	Pancreatic
Intervention (Iscador/control), %				
Radiation	43.9/75.7	7.9/5.9	17.8/16.5%	4.5/18.5
Chemotherapy	32.8/23.2	10.0/5.9	53.3/53.6	71.6/43.6
Surgery	All	All	All	69.2/48.2
Others	50.1/50.3 (hormones)	12.1/19.8 (immunotherapy)	—	—
UICC	I-III	II-III	I-III	I-IV
Follow-up, mo				
Iscador	66	81	58	15
Control	60	51	51	10
Iscador (host tree), %				
Pinus	31.4	83.3	—	—
Quercus	—	—	52.7	37.3
Malus	44.9	—	37.8	36.8
Combinations	23.7	16.7	9.5	25.9
Median duration, mo	52	30	52	15
Interventional adverse drug reactions, %				
Iscador	25.3	—	19.1	13.7
Control	63.1	—	48.3	48.9

Table 1: Characteristics of retrolective mistletoe studies

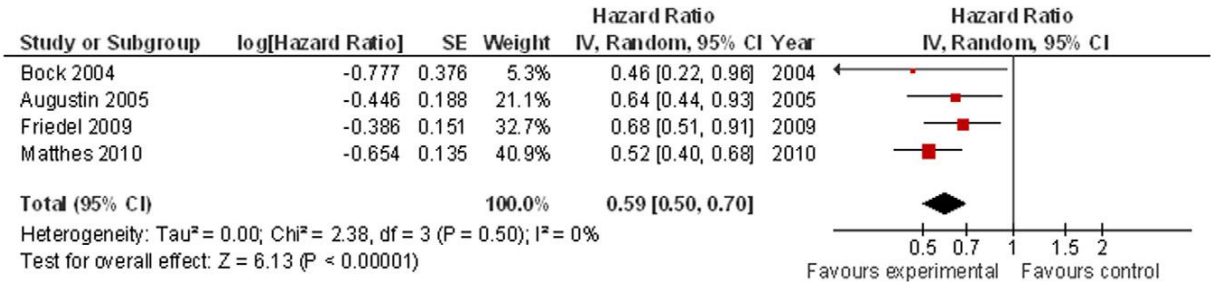

Fig. 1: Numerical results and forest plot of meta-analysis of retrolective mistletoe studies

9 Single Case Documentation

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