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Documentation
of published clinical studies
with Iscador®

August 2014
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.

This documentation will be updated from time to time. The newest version of can be found on our website: www.vfk.ch/forschung/klinische_forschung/dokumentation

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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-Matricek. 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 data 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
1.2 Natural Killer Cells and Lymphokine-activated Killer Cells
1.3 Lymphocytes and T-Lymphocytes
1.4 B-Lymphocytes
1.5 Neutrophil Granulocytes
1.6 Eosinophil Granulocytes
1.7 Cytokines
1.8 Reduced Incidence of Common Cold
1.1 Monocytes and Macrophages

References

- Salzer G. (1986) Pleura Carcinosis; Cytomorphological findings with the mistletoe preparation Iscador and other pharmaceuticals. Oncology 43 (suppl. 1), 66–70.
1.2 Natural Killer Cells and Lymphokine-activated Killer Cells

References


Review

1.3 Lymphocytes and T-Lymphocytes

References

- Salzer G. (1986) Pleura Carcinosis; Cytomorphological findings with the mistletoe preparation Iscador and other pharmaceuticals. Oncology 43 (suppl. 1), 66–70.
- Chernyshov V. P., Heusser P., Omelchenko L. I., Chernyshova L. I, Vodyanik M. A., Vykhovanets E. V., Gala-
  with recurrent respiratory infections as a result of the Chernobyl nuclear accident. American Journal of Thera-
  peutics 7 (3), 195–203.

  domisierte Machbarkeits-Studie zu einer postoperativen simultanen Mistel-/Chemotherapie bei Patientinnen 
  mit Mammakarzinom – Ergebnisse zu Rekrutier- und Randomisierbarkeit, Immunparametern, Lebensqualität 
  Fortschritte in der Misteltherapie: Aktueller Stand der Forschung und klinische Anwendung, Essen: KVC Ver-
  lag 2005, 567–578.


- Loewe-Mesch A., Kuehn J. J., Borho K., Abel U., Bauer C., Gerhard I., Schneeweiss A., Sohn C., Strowitzki 
1.4 B-Lymphocytes

References

1.5 Neutrophil Granulocytes

References

1.6 Eosinophil Granulocytes

References

- Salzer G. (1986) Pleura Carcinosis; Cytomorphological findings with the mistletoe preparation Iscador and other pharmaceuticals. Oncology 43 (suppl. 1), 66–70.
1.7 Cytokines

References

1.8 Reduced Incidence of Common Cold

References


2 DNA – Repair

References


In Vitro-Studies


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

3.1.1 Genitourinary Cancer
3.1.2 Breast Cancer
3.1.3 Gastrointestinal Cancer
3.1.4 Cancer of the Respiratory Tract
3.1.5 Melanoma
3.1.6 Various Solid Tumours
   (3.1.7 Lymphomas and Leukaemias)
   (3.1.8 Endocrine Tumours)
   (3.1.9 Central Nervous System Tumours)
   (3.1.10 Sarcomas)
3.1 Validated Questionnaires for Quality of Life

3.1.1 Genitourinary Cancer

References


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


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.
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

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.

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

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


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

**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).](image-url)
Questionnaires for Quality of Life: Breast Cancer

3.1.2.2


### 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**

**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.
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 x 38 primary breast cancer patients.
(2) Mamma: 2 x 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

Measurement
Self-regulation (Score 1 to 6) according to Grossarth-Maticzek 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.
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.


Measurements Self-regulation (Score 1 to 6) according to Grossarth-Matichek 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.
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.


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.
Questionnaires for Quality of Life: Breast Cancer

3.1.2.6

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**

**Measurements**
Quality of life according to EORTC QLQ-C30, incidence of neutropenia: neutrophil granulocytes < 1000 µl 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


The references marked with ☆ are included in abstract form in this documentation.
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).
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.
Questionnaires for Quality of Life: Pancreatic Cancer

3.1.3.1

Global Health Status / QoL difference to baseline

Physical Functioning difference to baseline

Role Functioning difference to baseline

Emotional Functioning difference to baseline

Social Functioning difference to baseline

Cognitive Functioning difference to baseline

Fatigue difference to baseline

Nausea/Vomiting difference to baseline

Pain difference to baseline

Dyspnoea difference to baseline

Insomnia difference to baseline

Appetite Loss difference to baseline

Constipation difference to baseline

QLQ-C30 Diarrhoea difference to baseline

QLQ-C30 Financial Problems difference to baseline
3.1.4 Cancer of the Respiratory Tract

References


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

References


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

**Study design**

**Design**
Randomised, prospective long-term, matched-pair technique.

**Patients**
MelanomRand: $2 \times 22$ 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**

**Measurements**
Self-regulation (Score 1 to 6) according to Grossarth-Maticuk 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


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


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 = 0.005).

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](image-url): 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).
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 medications from plants or minerals given as injections, orally or external applications, baths, massage, therapeutic eurythmy, art therapy (e.g. painting, music), counselling and lacto-vegetarian 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 interview.


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


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


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


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

**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.
- **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).
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).
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).
Pain, Fatigue and Disease Symptoms: Pancreatic Cancer


**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**

**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.
Patients with disease-related symptoms

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.

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-IIl, 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-IIl 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.
**Study design**

<table>
<thead>
<tr>
<th>Design</th>
<th>Original Study: Cohort study with retrospective collection of data («retrolective Study»), study 3.2.3.1.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centres</td>
<td>Data base: 26 centres in Germany and Switzerland.</td>
</tr>
<tr>
<td>Patients</td>
<td>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.</td>
</tr>
<tr>
<td>Treatment</td>
<td>Median length of treatment after chemo- and radiotherapy and with supportive mistletoe therapy Iscador Qu: 8.6 months.</td>
</tr>
<tr>
<td>Study aim</td>
<td>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.</td>
</tr>
</tbody>
</table>

**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


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


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.

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.


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


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

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).

**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**

**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.

![Quality of Life Index](image)

**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


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

**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 Iscador 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
4.2 Breast Cancer
(4.3 Gastrointestinal Cancer)
4.4 Cancer of the Respiratory Tract
(4.5 Melanoma)
4.6 Various Solid Tumours
4.7 Lymphomas and Leukaemias
(4.8 Endocrine Tumours)
(4.9 Central Nervous System Tumours)
(4.10 Sarcomas)
4.1 Genitourinary Cancer

References

  See 4.6.2.

The references marked with ☆ are included in abstract form in this documentation.
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 1 ng mistletoe lectin/kg bodyweight.
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


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


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

**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**

**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

<table>
<thead>
<tr>
<th>Tumour behaviour</th>
<th>Iscador</th>
<th>Polyerga</th>
<th>Placebo</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>uncertain remission</td>
<td>3</td>
<td>6</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>regression</td>
<td>12</td>
<td>6</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>uncertain regression</td>
<td>11</td>
<td>7</td>
<td>10</td>
<td>28</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>30</td>
<td>21</td>
<td>22</td>
<td>73</td>
</tr>
</tbody>
</table>

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 wirken-
den 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–

The references marked with ☆ are included in abstract form in this documentation.
Tumour remissions: Solid Tumours

4.6.1


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.


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

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


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


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.

Study design

<table>
<thead>
<tr>
<th>Design</th>
<th>Case Series.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>24 patients with follicular non-hodgkin's lymphoma.</td>
</tr>
<tr>
<td>Treatment</td>
<td>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.</td>
</tr>
<tr>
<td>Measurements</td>
<td>Remissions (clinical examination, laboratory parameters, medical imaging) and duration of remission.</td>
</tr>
</tbody>
</table>

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.
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.
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
5.2 Breast Cancer
5.3 Gastrointestinal Cancer
5.4 Cancer of the Respiratory Tract
5.5 Melanoma
5.6 Various Solid Tumours
  (5.7 Lymphomas and Leukaemias)
  (5.8 Endocrine Tumours)
  (5.9 Central Nervous System Tumours)
  (5.10 Sarcomas)
5.1 Genitourinary Cancer

5.1.1 Cancer of the Urinary Bladder
5.1.2 Cancer of the Ovary
5.1.3 Cancer of the Body of the Uterus
5.1.4 Cancer of the Uterine Cervix
5.1.5 Cancer of the Kidney
5.1.1 Cancer of the Urinary Bladder

References


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

**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.


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.

![Graph](image)

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


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


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

**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**

**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).](image-url)
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.


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.
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.

### Study design

**Design**

(1) Randomised, prospective long-term, matched-pair technique.

(2) Prospective epidemiological long-term cohort study, matched-pair technique.

**Patients**

(1a) *OvarRand*: $2 \times 21$ patients with ovarian cancer having no metastases.

(1b) *OvarMetRand*: $2 \times 20$ patients with ovarian cancer, with metastases.

(2a) *Ovar*: $2 \times 75$ patients with ovarian cancer having no metastases.

2b) *OvarMet*: $2 \times 62$ 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**


**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 compared to control patients without Iscador (according Grossarth-Maticek/Ziegler 2007).

Fig. 2: Nonrandomised studies Ovar (1 missing value) and 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


The references marked with ☆ are included in abstract form in this documentation.
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 x 30 patients with corpus uteri cancer, without metastases.
(1b) CorpusMetRand: 2 x 26 patients with corpus uteri cancer, with metastases.
(2a) Corpus: 2 x 103 patients with corpus uteri cancer, without metastases.
(2b) CorpusMet: 2 x 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.

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-Matricek/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-Matricek/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


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

**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

<table>
<thead>
<tr>
<th>Stage of disease</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>I–III</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>9</td>
<td>45</td>
<td>334</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>92</td>
<td>37</td>
<td>274</td>
<td>709</td>
</tr>
<tr>
<td>3-year survival rate</td>
<td>100%</td>
<td>87%</td>
<td>81%</td>
<td>86%</td>
</tr>
<tr>
<td>4-year survival rate</td>
<td>100%</td>
<td>77%</td>
<td>70%</td>
<td>83%</td>
</tr>
<tr>
<td>significance</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>yes (p = 0.015)</td>
</tr>
</tbody>
</table>
Survival: Genitourinary Cancer: Uterine Cervix

5.1.4.2


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

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.

![Graph showing survival rates with and without Iscador therapy](image)

**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).

![Graphs showing survival rates combined studies](image)

**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


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

References


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


The distribution of the stages of disease within the groups is comparable.


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.
Survival: Breast Cancer


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).


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

<table>
<thead>
<tr>
<th>Stage of disease</th>
<th>I</th>
<th>II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>n</td>
<td>149</td>
<td>107</td>
</tr>
<tr>
<td>5-year survival rate</td>
<td>84%</td>
<td>63%</td>
</tr>
<tr>
<td>Significance</td>
<td>yes (p&lt;0.002)</td>
<td>yes (p&lt;0.002)</td>
</tr>
<tr>
<td>Patients, who were observed for more than 10 years</td>
<td>36</td>
<td>31</td>
</tr>
<tr>
<td>10-year survival rate</td>
<td>61%</td>
<td>33%</td>
</tr>
<tr>
<td>Significance</td>
<td>yes (p&lt;0.002)</td>
<td>yes (p&lt;0.01)</td>
</tr>
</tbody>
</table>
Survival: Breast Cancer

5.2.3


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

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.
Survival: Breast Cancer

5.2.4

Study design

Design  Retrospective study with 2 groups.
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.
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 \((n = 89, \text{ mean survival} = 67 \text{ months, median 74 months})\) and without \((n = 141, \text{ mean survival} = 46 \text{ months, median 50 months})\) treatment with mistletoe (according to Hellan et al. 1990).

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

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).

![Survival curve](image)

**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-Maticke et al. 2001a).

For further results of this study concerning survival see also 5.6.1 and concerning quality of life see 3.1.2.4 and 3.1.6.1.
Survival: Breast Cancer


**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**

**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).](image-url)
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.

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.


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.

### Study design

**Design**

1. Randomised, prospective long-term, matched-pair technique.
2. Prospective epidemiological long-term cohort study, matched-pair technique.

**Patients**

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**


**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 or 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.

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-Fluorouracil (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


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

**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**

**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).](image)
Table 1: Distribution of tumour stages and results

<table>
<thead>
<tr>
<th></th>
<th>Lymph node positive</th>
<th>Lymph node negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Iscador</td>
<td>Control</td>
</tr>
<tr>
<td>Stage II</td>
<td></td>
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</tr>
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<td></td>
<td>$T_{1,2}$, $N_1$, $M_0$</td>
<td>$T_2$, $N_0$, $M_0$</td>
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<tr>
<td></td>
<td>$n=5$</td>
<td>$n=10$</td>
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<tr>
<td>Stage III</td>
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<td>$T_{1-3}$, $N_{1-2}$, $M_0$</td>
<td>$T_3$, $N_0$, $M_0$</td>
</tr>
<tr>
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<tr>
<td>Total</td>
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<td>$n=37$</td>
</tr>
<tr>
<td>Mean survival</td>
<td>749 days</td>
<td>540 days</td>
</tr>
<tr>
<td>Median survival</td>
<td>660 days</td>
<td>324 days</td>
</tr>
<tr>
<td>Significant</td>
<td>yes ($p&lt;0.05$)</td>
<td>no</td>
</tr>
</tbody>
</table>

### 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**

**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)](image)

For results of this study concerning survival see also 5.6.2.
5.3.2 Cancer of the Pancreas

References


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


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

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

<table>
<thead>
<tr>
<th>Description</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Cohort study with retrospective collection of data («retroactive Study»).</td>
</tr>
<tr>
<td><strong>Centres</strong></td>
<td>17 centres in Germany and Switzerland.</td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td>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).</td>
</tr>
<tr>
<td><strong>Comparability</strong></td>
<td>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).</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Length of study</strong></td>
<td>Diagnosis time from 1993 – 2002.</td>
</tr>
<tr>
<td><strong>Measurements</strong></td>
<td>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).</td>
</tr>
<tr>
<td></td>
<td>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.</td>
</tr>
</tbody>
</table>

### 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 and 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).
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).
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


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

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.


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.

![Graph showing 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).](image)

**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

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inoperable colon cancer</td>
<td>66</td>
<td>25</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Significant</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Inoperable cancer of the rectum</td>
<td>35</td>
<td>29</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>16</td>
<td>8.5</td>
</tr>
<tr>
<td>Significant</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>101</td>
<td>54</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Significant</td>
<td>no</td>
<td></td>
</tr>
</tbody>
</table>
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.


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

<table>
<thead>
<tr>
<th>Stage</th>
<th>Colon cancer</th>
<th>Cancer of the rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Iscador</td>
<td>No therapy</td>
</tr>
<tr>
<td><strong>Stage I:</strong> T1-2 N0 M0</td>
<td>23</td>
<td>12</td>
</tr>
<tr>
<td>Median survival in days</td>
<td>2942</td>
<td>2488</td>
</tr>
<tr>
<td>Significance</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Number of relapses</td>
<td>5 (21.7%)</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>Significance</td>
<td>no</td>
<td>yes (p &lt; 0.05)</td>
</tr>
<tr>
<td><strong>Stage II:</strong> T3-4 N0 M0</td>
<td>41</td>
<td>43</td>
</tr>
<tr>
<td>Median survival in days</td>
<td>2346</td>
<td>2736</td>
</tr>
<tr>
<td>Significance</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Number of relapses</td>
<td>15 (36.6%)</td>
<td>18 (41.9%)</td>
</tr>
<tr>
<td>Significance</td>
<td>no</td>
<td>yes (p &lt; 0.05)</td>
</tr>
<tr>
<td><strong>Stage III:</strong> T1-4 N+, M0</td>
<td>51</td>
<td>23</td>
</tr>
<tr>
<td>Median survival in days</td>
<td>929</td>
<td>580</td>
</tr>
<tr>
<td>Significance</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Number of relapses</td>
<td>23 (45.1%)</td>
<td>18 (78.3%)</td>
</tr>
<tr>
<td>Significance</td>
<td>yes (p &lt; 0.05)</td>
<td>yes (p &lt; 0.05)</td>
</tr>
<tr>
<td><strong>Stage IV:</strong> T1-4 N+, M0-1</td>
<td>43</td>
<td>25</td>
</tr>
<tr>
<td>Median survival in days</td>
<td>347</td>
<td>425</td>
</tr>
<tr>
<td>Significance</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Number of patients</td>
<td>158</td>
<td>103</td>
</tr>
<tr>
<td></td>
<td>282</td>
<td>658</td>
</tr>
<tr>
<td>Total</td>
<td>940</td>
<td></td>
</tr>
</tbody>
</table>
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).
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.


**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-Maticzek 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.
Survival: Gastrointestinal Cancer: Colon and Rectum 5.3.3.4


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**

**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).

**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), \(p = 0.002\). 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


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

**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**  

**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**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Cytostatics</th>
<th>Mistletoe</th>
<th>Cytostatics + mistletoe</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>14</td>
<td>14</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>Median survival (days)</td>
<td>49</td>
<td>78</td>
<td>120</td>
<td>197</td>
</tr>
<tr>
<td>Mean survival (days)</td>
<td>64</td>
<td>120</td>
<td>186</td>
<td>380</td>
</tr>
<tr>
<td>Significant</td>
<td>no</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
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


The references marked with ♦ are included in abstract form in this documentation.
Survival: Respiratory Tract: Lung Cancer

5.4.1.1


**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.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Iscador</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 N0</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Survivors after 80 months</td>
<td>6 (50%)</td>
<td>3 (33%)</td>
</tr>
<tr>
<td>Significant</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>T2 N0, T1 N1, T2 N1</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>Survivors after 80 months</td>
<td>5 (33%)</td>
<td>2 (18%)</td>
</tr>
<tr>
<td>Significant</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>T3 N0 to T3 N2, T1 N2, T2 N2</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>Survivors after 80 months</td>
<td>3 (33%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Significant</td>
<td>yes (p &lt; 0.01)</td>
<td></td>
</tr>
<tr>
<td>Stage I – III</td>
<td>37</td>
<td>40</td>
</tr>
<tr>
<td>Survivors after 80 months</td>
<td>14 (38%)</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>Significant</td>
<td>yes (p &lt; 0.01)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2:** Results according to lymph node metastases.

<table>
<thead>
<tr>
<th>Lymph node</th>
<th>Iscador</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Survivors after 80 months</td>
<td>10 (45%)</td>
<td>5 (23%)</td>
</tr>
<tr>
<td>Significant</td>
<td>yes (p &lt; 0.01)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>Survivors after 80 months</td>
<td>4 (27%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Significant</td>
<td>yes (p &lt; 0.01)</td>
<td></td>
</tr>
</tbody>
</table>

**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).

![Figure 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).](image-url)

**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**

**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

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of Patients</th>
<th>Iscador</th>
<th>Polyerga</th>
<th>Placebo</th>
<th>Total</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>T₁ N₀ M₀</td>
<td>12</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td></td>
<td>3.6</td>
</tr>
<tr>
<td>T₂ N₀ M₀</td>
<td>58</td>
<td>18</td>
<td>21</td>
<td>19</td>
<td></td>
<td>17.2</td>
</tr>
<tr>
<td>T₁ N₁ M₀</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>6</td>
<td>1.8</td>
</tr>
<tr>
<td>T₂ N₁ M₀</td>
<td>39</td>
<td>12</td>
<td>11</td>
<td>16</td>
<td></td>
<td>11.6</td>
</tr>
<tr>
<td>T₁-2 N₂ M₀</td>
<td>11</td>
<td>2</td>
<td>4</td>
<td>5</td>
<td>11</td>
<td>3.3</td>
</tr>
<tr>
<td>T₃ N₀ M₀</td>
<td>34</td>
<td>11</td>
<td>10</td>
<td>13</td>
<td></td>
<td>10.1</td>
</tr>
<tr>
<td>T₃ N₁-2 M₀</td>
<td>54</td>
<td>20</td>
<td>17</td>
<td>17</td>
<td></td>
<td>16.0</td>
</tr>
<tr>
<td>T₁ N₀-2 M₁</td>
<td>6</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>6</td>
<td>1.8</td>
</tr>
<tr>
<td>T₂ N₀ M₁</td>
<td>14</td>
<td>5</td>
<td>6</td>
<td>3</td>
<td>14</td>
<td>4.2</td>
</tr>
<tr>
<td>T₂ N₁-2 M₁</td>
<td>29</td>
<td>13</td>
<td>7</td>
<td>9</td>
<td>29</td>
<td>8.6</td>
</tr>
<tr>
<td>T₃ N₀ M₁</td>
<td>22</td>
<td>9</td>
<td>8</td>
<td>5</td>
<td>22</td>
<td>6.5</td>
</tr>
<tr>
<td>T₃ N₁-2 M₁</td>
<td>44</td>
<td>10</td>
<td>17</td>
<td>17</td>
<td></td>
<td>13.1</td>
</tr>
<tr>
<td>NX / MX</td>
<td>8</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td></td>
<td>2.4</td>
</tr>
<tr>
<td>Total</td>
<td>337</td>
<td>114</td>
<td>110</td>
<td>113</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Distribution of the patients according to tumour stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Number of Patients</th>
<th>Iscador</th>
<th>Polyerga</th>
<th>Placebo</th>
<th>Total</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>77</td>
<td>26</td>
<td>26</td>
<td>25</td>
<td></td>
<td>23.4</td>
</tr>
<tr>
<td>II</td>
<td>38</td>
<td>11</td>
<td>11</td>
<td>16</td>
<td></td>
<td>11.6</td>
</tr>
<tr>
<td>III</td>
<td>100</td>
<td>35</td>
<td>30</td>
<td>35</td>
<td></td>
<td>30.4</td>
</tr>
<tr>
<td>IV</td>
<td>114</td>
<td>41</td>
<td>39</td>
<td>34</td>
<td></td>
<td>34.6</td>
</tr>
<tr>
<td>Total</td>
<td>329</td>
<td>113</td>
<td>106</td>
<td>110</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For results of this study concerning quality of life see 3.2.4.1 and concerning remissions see 4.4.1.
Survival: Respiratory Tract: Lung Cancer

5.4.1.4


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).
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

<table>
<thead>
<tr>
<th>Stage I – II: Lymph node negative, T₁–T₃ N₀</th>
<th>Iscador</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died</td>
<td>59</td>
<td>65</td>
</tr>
<tr>
<td>Post-mortem</td>
<td>30</td>
<td>43</td>
</tr>
<tr>
<td>Tumour-free</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>Relapse/metastases (cases)</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>29 (49%)</td>
<td>33 (50%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage II – III: Lymph node positive, T₁–T₃ N₁–N₂</th>
<th>Iscador</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died</td>
<td>16</td>
<td>27</td>
</tr>
<tr>
<td>Post-mortem</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Tumour-free</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Relapse/metastases (cases)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>8 (50%)</td>
<td>20 (74%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage IV: T₄ N₀, T₁–T₄ N₃</th>
<th>Iscador</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Post-mortem</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Tumour-free</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Relapse/metastases (cases)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>16.5</td>
<td>17</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total</th>
<th>Iscador</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died</td>
<td>86</td>
<td>97</td>
</tr>
<tr>
<td>Post-mortem</td>
<td>51</td>
<td>67</td>
</tr>
<tr>
<td>Tumour-free</td>
<td>22</td>
<td>24</td>
</tr>
<tr>
<td>Relapse/metastases (cases)</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>44 (50%)</td>
<td>53 (55%)</td>
</tr>
</tbody>
</table>

Significant: no

**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**

**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).

![Graph](image)

**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-Matick 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. Österrei-


- Böck D., Salzer G. (1980a) Morphologischer Nachweis einer Wirksamkeit der Iscadorbehandlung maligener

   Pleuraergüsse und ihre klinischen Ergebnisse. Krebsgeschehen 12 (3), 49–53. [Bericht aus einem Kollektiv]

- Böck D., Salzer G. (1980b) Iscadorbehandlung maliger 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]


   Kollektiv]

- Böck D. (1983) Neue zytomorphologische Ergebnisse bei lokaler Behandlung des karzinomatösen Pleuraer-


- 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]


   (Hrsg.) Krebs und Alternativmedizin II. Springer Verlag, Berlin, Heidelberg, 36–49.

The references marked with ☆ are included in abstract form in this documentation.
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.
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.
Survival: Respiratory Tract: Carcinosis of the Pleura

5.4.2.2


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.
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

<table>
<thead>
<tr>
<th>Required punctures</th>
<th>Number of patients</th>
<th>[%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23</td>
<td>10.9</td>
</tr>
<tr>
<td>2</td>
<td>77</td>
<td>36.5</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>21.3</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>14.4</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>4.7</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>5.7</td>
</tr>
<tr>
<td>7</td>
<td>6</td>
<td>2.8</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>1.4</td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>13</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>17</td>
<td>1</td>
<td>0.5</td>
</tr>
</tbody>
</table>

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


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

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.
- **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

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

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).


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).

**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**  

**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

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

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

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  

Measurements  
Survival since first diagnosis, 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
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.
Survival: Melanoma

Fig. 1: Randomised study MelanomRand and 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


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


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.


Measurement Survival.

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.
Survival: Solid Tumours


**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.


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**  

**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


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

References


The references marked with ☆ are included in abstract form in this documentation.
Survival: Solid Tumours


**Study design**

<table>
<thead>
<tr>
<th>Design</th>
<th>Prospective, randomized, open label.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>Histological confirmed diagnosis of osteosarcoma or spindle cell sarcoma, after a second metastatic relapse, age equal or older than 10.</td>
</tr>
<tr>
<td>Treatment</td>
<td>Iscador or Etoposide.</td>
</tr>
<tr>
<td>Measurement</td>
<td>Post relapse disease free survival, Quality of Life.</td>
</tr>
</tbody>
</table>

**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 immunomodulatory 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 immunomodulatory 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


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

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.


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.
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.
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.
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.


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.

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.
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 pre-specified 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).
**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

References


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

### 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 angioedema [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.
Safety and Tolerance: Systematic Review

6.2.2


**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 > 1 mg; 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

7.2 Systematic Reviews for all Types of Cancer

7.3 Systematic Reviews for Selected Clinical Questions
7.1 Review Papers

7.1.1 Reviews for all Types of Cancer

References

7.1.2 Reviews for Selected Types of Cancer

References


7.2 Systematic Reviews for all Types of Cancer

References


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

**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

<table>
<thead>
<tr>
<th>Publication(s)</th>
<th>Study aim, Diagnosis</th>
<th>Study type</th>
<th>Chapter in this documentation</th>
<th>No. of study</th>
<th>Quality (1989)</th>
<th>Advantage for Iscador (Trend)</th>
<th>Validity of the study</th>
<th>Significant advantage for Iscador</th>
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<td>prospective</td>
<td>5.2</td>
<td>18</td>
<td>52</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Salzer (1987)</td>
<td>breast cancer</td>
<td>retrospective</td>
<td>5.2</td>
<td>20</td>
<td>47</td>
<td>yes</td>
<td>no</td>
<td>–</td>
</tr>
</tbody>
</table>

No. of the study (1989): according to Kiene (1989a, 1989b),
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: –
<table>
<thead>
<tr>
<th>Publication(s)</th>
<th>Study aim, Diagnosis</th>
<th>Study type</th>
<th>Chapter in this documentation</th>
<th>No. of study</th>
<th>Advantage for Iscador (Trend)</th>
<th>Validity of the study</th>
<th>Significant advantage for Iscador</th>
</tr>
</thead>
<tbody>
<tr>
<td>Günczler et al. (1968), Günczler (1968, 1969)</td>
<td>stomach</td>
<td>retrospective</td>
<td>5.3.1</td>
<td>22</td>
<td>11</td>
<td>yes</td>
<td>?</td>
</tr>
<tr>
<td>Salzer/Havelec (1983), Salzer/Denk (1979)</td>
<td>stomach</td>
<td>prospective</td>
<td>5.3.1</td>
<td>23</td>
<td>12</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Salzer et al. (1990)</td>
<td>stomach</td>
<td>retrospective</td>
<td>5.3.1</td>
<td>–</td>
<td>13</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Delius-Müller (1979)</td>
<td>pancreas</td>
<td>retrospective</td>
<td>5.3.2</td>
<td>24</td>
<td>15</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Günczler/Salzer (1969)</td>
<td>rectum</td>
<td>retrospective</td>
<td>5.3.3</td>
<td>25</td>
<td>18</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Leroi (1979)</td>
<td>colorectal</td>
<td>retrospective</td>
<td>5.3.3</td>
<td>26</td>
<td>19</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Hoffmann/Hajto (1984)</td>
<td>colorectal</td>
<td>retrospective</td>
<td>5.3.3</td>
<td>27</td>
<td>20</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Salzer et al. (1992)</td>
<td>colorectal</td>
<td>retrospective</td>
<td>5.3.3</td>
<td>–</td>
<td>24</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Hoffmann (1979)</td>
<td>liver metastases</td>
<td>retrospective</td>
<td>5.3.4</td>
<td>31</td>
<td>70</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Salzer (1984)</td>
<td>liver metastases</td>
<td>retrospective</td>
<td>5.3.4</td>
<td>33</td>
<td>72</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Salzer/Frey (1990)</td>
<td>liver metastases</td>
<td>retrospective</td>
<td>5.3.4</td>
<td>–</td>
<td>73</td>
<td>yes</td>
<td>no</td>
</tr>
</tbody>
</table>

**Survival: Cancer of the Respiratory Tract: Lung Cancer 5.4.1**

<table>
<thead>
<tr>
<th>Publication(s)</th>
<th>Study aim, Diagnosis</th>
<th>Study type</th>
<th>Chapter in this documentation</th>
<th>No. of study</th>
<th>Advantage for Iscador (Trend)</th>
<th>Validity of the study</th>
<th>Significant advantage for Iscador</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salzer/Havelec (1978), Salzer (1980a)</td>
<td>lung cancer</td>
<td>prospective</td>
<td>5.4.1.1</td>
<td>34</td>
<td>32</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Salzer (1987)</td>
<td>lung cancer</td>
<td>prospective</td>
<td>5.4</td>
<td>35</td>
<td>–</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Krause/Erkan (1983)</td>
<td>lung cancer</td>
<td>prospective</td>
<td>5.4</td>
<td>36</td>
<td>–</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Salzer (1980b, 1987)</td>
<td>lung cancer</td>
<td>prospective randomised</td>
<td>5.4.1.2</td>
<td>37</td>
<td>33</td>
<td>yes</td>
<td>?</td>
</tr>
<tr>
<td>Hellan (1983), Salzer (1987)</td>
<td>lung cancer</td>
<td>retrospective</td>
<td>5.4</td>
<td>38</td>
<td>–</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Salzer et al. (1991), Salzer (1987)</td>
<td>lung cancer</td>
<td>prospective randomised</td>
<td>5.4.1.4</td>
<td>–</td>
<td>34</td>
<td>yes</td>
<td>yes</td>
</tr>
</tbody>
</table>

**Survival: Cancer of the Respiratory Tract: Carcinosis of the Pleura 5.4.2**

<table>
<thead>
<tr>
<th>Publication(s)</th>
<th>Study aim, Diagnosis</th>
<th>Study type</th>
<th>Chapter in this documentation</th>
<th>No. of study</th>
<th>Advantage for Iscador (Trend)</th>
<th>Validity of the study</th>
<th>Significant advantage for Iscador</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salzer (1977, 1983, 1986), Böck/Salzer (1980a,b), Böck (1983), Salzer/Popp (1990)</td>
<td>carcinosis of the pleura</td>
<td>Case series</td>
<td>5.4.2.1, 5.4.2.2</td>
<td>39</td>
<td>78</td>
<td>yes</td>
<td>–</td>
</tr>
</tbody>
</table>

**Survival: Melanoma 5.5**

<table>
<thead>
<tr>
<th>Publication(s)</th>
<th>Study aim, Diagnosis</th>
<th>Study type</th>
<th>Chapter in this documentation</th>
<th>No. of study</th>
<th>Advantage for Iscador (Trend)</th>
<th>Validity of the study</th>
<th>Significant advantage for Iscador</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feuchtinger (1979)</td>
<td>melanoma</td>
<td>retrospective</td>
<td>5.5.1</td>
<td>40</td>
<td>64</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Leroi (1985)</td>
<td>melanoma</td>
<td>retrospective</td>
<td>5.5</td>
<td>42</td>
<td>65</td>
<td>yes</td>
<td>?</td>
</tr>
<tr>
<td>Schuppeli (1990)</td>
<td>melanoma</td>
<td>retrospective</td>
<td>5.5.2</td>
<td>43</td>
<td>66</td>
<td>yes</td>
<td>?</td>
</tr>
</tbody>
</table>

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

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

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

<table>
<thead>
<tr>
<th>Publication</th>
<th>Diagnosis</th>
<th>Chapter in this documentation</th>
<th>No. of study according to Edler (1996)</th>
<th>No. of study according to Kienle/Kiene 2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salzer/Denk (1979)</td>
<td>stomach</td>
<td>5.3.1.1</td>
<td>2</td>
<td>32</td>
</tr>
<tr>
<td>Salzer (1987)</td>
<td>breast cancer</td>
<td>5.2</td>
<td>4</td>
<td>47</td>
</tr>
<tr>
<td>Dold et al. (1991)</td>
<td>lung cancer</td>
<td>3.2.4.1, 4.4.1, 5.4.1.3</td>
<td>5</td>
<td>35</td>
</tr>
<tr>
<td>Salzer et al. (1991)</td>
<td>lung cancer</td>
<td>5.4</td>
<td>1</td>
<td>34</td>
</tr>
</tbody>
</table>
Systematic Reviews: All Types of Cancer


**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

<table>
<thead>
<tr>
<th>Publication</th>
<th>Diagnosis</th>
<th>Chapter in this documentation</th>
<th>No. of study according to Kienle/Kiene 2003</th>
<th>Results with an advantage for the Iscador group</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Majewski/Bentele (1963)</td>
<td>uterus and ovary</td>
<td>5.1.3</td>
<td>40</td>
<td>trend (survival)</td>
<td>NA</td>
</tr>
<tr>
<td>Salzer (1987)</td>
<td>breast cancer</td>
<td>5.2</td>
<td>33</td>
<td>trend (survival)</td>
<td>50</td>
</tr>
<tr>
<td>Salzer/Denk (1979), Salzer/Havelec (1983), Salzer (1988)</td>
<td>stomach</td>
<td>5.3.1</td>
<td>12</td>
<td>significant (survival)</td>
<td>137</td>
</tr>
<tr>
<td>Dold et al. (1991)</td>
<td>lung cancer</td>
<td>3.2.4.1, 4.4.1, 5.4.1.3</td>
<td>35</td>
<td>Significant (quality of life), trend (survival), trend (tumour remission)</td>
<td>337</td>
</tr>
<tr>
<td>Salzer et al. (1991)</td>
<td>lung cancer</td>
<td>5.4.1.4</td>
<td>34</td>
<td>trend (survival for lymph node positive)</td>
<td>183</td>
</tr>
<tr>
<td>Grossarth-Maticek et al. (2001a)</td>
<td>breast cancer</td>
<td>3.1.2.4, 5.2.5</td>
<td>56</td>
<td>significant (survival), trend (quality of life)</td>
<td>34</td>
</tr>
<tr>
<td>Grossarth-Maticek et al. (2001a)</td>
<td>various solid tumours</td>
<td>3.1.6.1, 5.6.1</td>
<td>10</td>
<td>significant (survival), significant (quality of life)</td>
<td>78</td>
</tr>
</tbody>
</table>

Table 2: Results of quasi randomised studies with Iscador

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

Table 3: Results of non-randomised studies with Iscador

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

**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

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

**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**

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

**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.

**Study design**

Type  
Systematic review with predefined search strategy and quality criteria.

Inclusion 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)

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

**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 trials.
Table 1: Results of studies with Iscador

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

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 systemically 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

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

References


The references marked with ♠ are included in abstract form in this documentation.
Systematic Reviews: Gynaecological Cancer

7.3.1


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

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

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

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

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

<table>
<thead>
<tr>
<th>Publication</th>
<th>Design</th>
<th>Diagnosis</th>
<th>Chapter in this documentation</th>
<th>Most important results with an advantage for the Iscador group</th>
<th>Number of patients analysed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portalupi 1995</td>
<td>prospective 1-arm</td>
<td>CIN-HPV</td>
<td>4.1.1</td>
<td>remissions</td>
<td>22</td>
</tr>
<tr>
<td>Bar-Sela 2006</td>
<td>prospective 1-arm</td>
<td>ascites</td>
<td>3.3.1</td>
<td>longer interval between successive punctures</td>
<td>23</td>
</tr>
</tbody>
</table>
Systematic Reviews: Survival

7.3.2


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 or 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 considerable 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**

<table>
<thead>
<tr>
<th>Year</th>
<th>Tumour localization</th>
<th>Study design of all studies</th>
<th>design of studies enrolled for statistical analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>control</td>
<td>design</td>
</tr>
<tr>
<td>2005</td>
<td>Skin</td>
<td>PLG</td>
<td>retrolec.</td>
</tr>
<tr>
<td>2004</td>
<td>Breast</td>
<td>PLG</td>
<td>retrolec.</td>
</tr>
<tr>
<td>1991</td>
<td>Lung</td>
<td>PLG</td>
<td>prosp.</td>
</tr>
<tr>
<td>2001</td>
<td>Skin</td>
<td>PLG</td>
<td>prosp.</td>
</tr>
<tr>
<td>1966</td>
<td>Cervix</td>
<td>PLG</td>
<td>prosp.</td>
</tr>
<tr>
<td>1977</td>
<td>Skin</td>
<td>Lit</td>
<td>retro.</td>
</tr>
<tr>
<td>2004</td>
<td>Various</td>
<td>PLG</td>
<td>prosp.</td>
</tr>
<tr>
<td>2006</td>
<td>Breast</td>
<td>PLG</td>
<td>prosp.</td>
</tr>
<tr>
<td>2006</td>
<td>Breast</td>
<td>PLG</td>
<td>prosp.</td>
</tr>
<tr>
<td>2006</td>
<td>Breast</td>
<td>PLG</td>
<td>prosp.</td>
</tr>
<tr>
<td>2006</td>
<td>Breast</td>
<td>PLG</td>
<td>prosp.</td>
</tr>
<tr>
<td>2007</td>
<td>Ovary</td>
<td>PLG</td>
<td>prosp.</td>
</tr>
<tr>
<td>2007</td>
<td>Ovary</td>
<td>PLG</td>
<td>prosp.</td>
</tr>
<tr>
<td>2007</td>
<td>Breast</td>
<td>PLG</td>
<td>prosp.</td>
</tr>
<tr>
<td>2007</td>
<td>Breast</td>
<td>PLG</td>
<td>prosp.</td>
</tr>
<tr>
<td>2007</td>
<td>Skin</td>
<td>PLG</td>
<td>prosp.</td>
</tr>
<tr>
<td>2007</td>
<td>Skin</td>
<td>PLG</td>
<td>prosp.</td>
</tr>
<tr>
<td>2007</td>
<td>Corpus uteri</td>
<td>PLG</td>
<td>prosp.</td>
</tr>
<tr>
<td>2008</td>
<td>Corpus uteri</td>
<td>PLG</td>
<td>prosp.</td>
</tr>
<tr>
<td>1962</td>
<td>Breast</td>
<td>Lit</td>
<td>retro.</td>
</tr>
<tr>
<td>1968</td>
<td>Stomach</td>
<td>PLG</td>
<td>retro.</td>
</tr>
<tr>
<td>1969</td>
<td>Breast</td>
<td>historic</td>
<td>retro.</td>
</tr>
<tr>
<td>1979</td>
<td>Ovary</td>
<td>Lit</td>
<td>retro.</td>
</tr>
<tr>
<td>1995</td>
<td>Colorectal</td>
<td>PLG</td>
<td>retro.</td>
</tr>
<tr>
<td>1979</td>
<td>Liver</td>
<td>PLG</td>
<td>retro.</td>
</tr>
<tr>
<td>1980</td>
<td>bladder</td>
<td>PLG</td>
<td>retro.</td>
</tr>
<tr>
<td>1982</td>
<td>Breast</td>
<td>Lit</td>
<td>retro.</td>
</tr>
<tr>
<td>1984</td>
<td>Kidney</td>
<td>historic</td>
<td>prosp.</td>
</tr>
<tr>
<td>2004</td>
<td>Skin</td>
<td>PLG</td>
<td>prosp.</td>
</tr>
<tr>
<td>1983</td>
<td>Lung</td>
<td>historic</td>
<td>retro.</td>
</tr>
<tr>
<td>1980</td>
<td>Breast</td>
<td>Lit</td>
<td>retro.</td>
</tr>
<tr>
<td>1977</td>
<td>Breast</td>
<td>PLG</td>
<td>retro.</td>
</tr>
<tr>
<td>1978</td>
<td>Colorectal</td>
<td>PLG</td>
<td>retro.</td>
</tr>
<tr>
<td>1979</td>
<td>Colorectal</td>
<td>PLG</td>
<td>retro.</td>
</tr>
<tr>
<td>1975</td>
<td>Breast</td>
<td>PLG</td>
<td>retro.</td>
</tr>
<tr>
<td>1982</td>
<td>Ovary</td>
<td>Lit</td>
<td>retro.</td>
</tr>
<tr>
<td>1963</td>
<td>Ovary</td>
<td>PLG</td>
<td>retro.</td>
</tr>
<tr>
<td>1975</td>
<td>Lung</td>
<td>PLG</td>
<td>retro.</td>
</tr>
<tr>
<td>1978</td>
<td>Lunget</td>
<td>PLG</td>
<td>retro.</td>
</tr>
<tr>
<td>1983</td>
<td>Stomach</td>
<td>PLG</td>
<td>prosp.</td>
</tr>
<tr>
<td>1991</td>
<td>Lung</td>
<td>PLG</td>
<td>prosp.</td>
</tr>
<tr>
<td>1998</td>
<td>Pancreas</td>
<td>Lit</td>
<td>retro.</td>
</tr>
<tr>
<td>1984</td>
<td>Ovary</td>
<td>Lit</td>
<td>retro.</td>
</tr>
<tr>
<td>1984</td>
<td>Ovary</td>
<td>PLG</td>
<td>retro.</td>
</tr>
<tr>
<td>1990</td>
<td>Skin</td>
<td>PLG</td>
<td>retro.</td>
</tr>
<tr>
<td>1996</td>
<td>Ovary</td>
<td>Lit</td>
<td>retro.</td>
</tr>
</tbody>
</table>

**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
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)

<table>
<thead>
<tr>
<th>Publication</th>
<th>Qol measure</th>
<th>Chapter in this documentation</th>
<th>Most important results with an advantage for the Iscador group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longhi 2009</td>
<td>EORTC QLQ-C30, ADR</td>
<td>5.10</td>
<td>EORTC QLQ-C30</td>
</tr>
<tr>
<td>Tröger 2009</td>
<td>EORTC QLQ-C30</td>
<td>3.1.2</td>
<td>EORTC QLQ-C30: pain, diarrhea, role, insomnia, nausea/vomiting.</td>
</tr>
<tr>
<td>Büssing 2008</td>
<td>EORTC QLQ-C30, ADR</td>
<td>1.5</td>
<td>ADR: nausea, constipation, pain, stomatitis, appetite</td>
</tr>
</tbody>
</table>

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

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

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

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

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

<table>
<thead>
<tr>
<th>Publication</th>
<th>Qol measure</th>
<th>Chapter in this documentation</th>
<th>Most important results with an advantage for the Iscador group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grossarth 2008 (corpus uteri)</td>
<td>self-regulation questionnaire</td>
<td>3.1.1.3, 5.1.3.1</td>
<td>self-regulation</td>
</tr>
<tr>
<td>Grossarth 2007 (cervix)</td>
<td>self-regulation questionnaire</td>
<td>3.1.1.1, 5.1.4.2</td>
<td>self-regulation</td>
</tr>
<tr>
<td>Grossarth 2007 (ovary)</td>
<td>self-regulation questionnaire</td>
<td>3.1.1.2, 5.1.2.4</td>
<td>self-regulation</td>
</tr>
<tr>
<td>Grossarth 2006 (breast)</td>
<td>self-regulation questionnaire</td>
<td>3.1.2.3, 5.2.8</td>
<td>self-regulation</td>
</tr>
</tbody>
</table>
8 Meta-Analyses

References


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

**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: Overall survival and self-regulation.

**Most important results**

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

<table>
<thead>
<tr>
<th>Table 1: Results of studies with Iscador</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Reference</strong></td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>MammaRand Grossarth 2006a</td>
</tr>
<tr>
<td>MammaLymRand Grossarth 2001a, 2006b</td>
</tr>
<tr>
<td>Mamma Grossarth 2006a</td>
</tr>
<tr>
<td>MammaRec Grossarth 2001a, 2001b, 2006b</td>
</tr>
<tr>
<td>MammaLym Grossarth 2001a, 2001b, 2006b</td>
</tr>
<tr>
<td>MammaMet Grossarth 2001a, 2001b, 2006b</td>
</tr>
</tbody>
</table>

**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).

<table>
<thead>
<tr>
<th>Randomized Study</th>
<th># Pairs</th>
<th>Estimate</th>
<th>95% Confidence Interval</th>
<th>Wald test p-value</th>
<th>Model fit</th>
</tr>
</thead>
<tbody>
<tr>
<td>MammaRand</td>
<td>38</td>
<td>0.65</td>
<td></td>
<td>0.20</td>
<td>moderately</td>
</tr>
<tr>
<td>MammaLymRand</td>
<td>17</td>
<td>0.46</td>
<td></td>
<td>0.14</td>
<td>no</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-Randomized Study</th>
<th>Model</th>
<th># Pairs</th>
<th>Estimate</th>
<th>95% Confidence Interval</th>
<th>Wald test p-value</th>
<th>Model fit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mamma</td>
<td>unadjusted</td>
<td>84</td>
<td>0.42</td>
<td></td>
<td>0.0003</td>
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</tr>
<tr>
<td></td>
<td>adjusted</td>
<td>83</td>
<td>0.0823</td>
<td></td>
<td>0.0017</td>
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<tr>
<td>MammaRec</td>
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<td>47</td>
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<td>0.0012</td>
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</tr>
<tr>
<td></td>
<td>adjusted</td>
<td>43</td>
<td>0.52</td>
<td></td>
<td>0.118</td>
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</tr>
<tr>
<td>MammaLym</td>
<td>unadjusted</td>
<td>55</td>
<td>0.37</td>
<td></td>
<td>0.0009</td>
<td>no</td>
</tr>
<tr>
<td></td>
<td>adjusted</td>
<td>53</td>
<td>0.27</td>
<td></td>
<td>&lt;0.0005</td>
<td>moderately</td>
</tr>
<tr>
<td>MammaMet</td>
<td>unadjusted</td>
<td>83</td>
<td>0.46</td>
<td></td>
<td>0.0009</td>
<td>yes</td>
</tr>
<tr>
<td></td>
<td>adjusted</td>
<td>83</td>
<td>0.33</td>
<td></td>
<td>0.013</td>
<td>no</td>
</tr>
</tbody>
</table>

| MAMMARAND            | unadjusted | 264  | 0.42     |                         | <0.0005           | yes       |
|                      | adjusted   | 263  | 0.43     |                         | <0.0005           | moderately |

### 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).

<table>
<thead>
<tr>
<th>Randomized Study</th>
<th># Pairs</th>
<th>Median Diff.</th>
<th>95% Confidence Interval</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MammaRand</td>
<td>38</td>
<td>0.35</td>
<td></td>
<td>0.034</td>
</tr>
<tr>
<td>MammaLymRand</td>
<td>17</td>
<td>0.9</td>
<td></td>
<td>0.066</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-Randomized Study</th>
<th>Set</th>
<th># Pairs</th>
<th>Median Diff.</th>
<th>95% Confidence Interval</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mamma</td>
<td>full set</td>
<td>83</td>
<td>0.2</td>
<td></td>
<td>0.031</td>
</tr>
<tr>
<td></td>
<td>balanced set</td>
<td>72</td>
<td>0.15</td>
<td></td>
<td>0.056</td>
</tr>
<tr>
<td></td>
<td>strict matching</td>
<td>24</td>
<td>0.3</td>
<td></td>
<td>0.014</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Number of patients</th>
<th>Tumour localization</th>
<th>Study Design</th>
<th>Quality of life instrument</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Iscador</td>
<td>control</td>
<td>control</td>
<td>design</td>
</tr>
<tr>
<td>Grossarth-Maticek, 3.1.6.1</td>
<td>2001</td>
<td>39</td>
<td>39</td>
<td>Multiple</td>
<td>PLG</td>
</tr>
<tr>
<td>Grossarth-Maticek, 3.1.6.1</td>
<td>2001</td>
<td>17</td>
<td>17</td>
<td>Breast</td>
<td>PLG</td>
</tr>
<tr>
<td>Grossarth-Maticek, 3.1.2.4</td>
<td>2006</td>
<td>17</td>
<td>17</td>
<td>Breast</td>
<td>PLG</td>
</tr>
<tr>
<td>Grossarth-Maticek, 3.1.2.3</td>
<td>2006</td>
<td>38</td>
<td>38</td>
<td>Breast</td>
<td>PLG</td>
</tr>
<tr>
<td>Grossarth-Maticek, 3.1.2.3</td>
<td>2006</td>
<td>84</td>
<td>84</td>
<td>Breast</td>
<td>PLG</td>
</tr>
<tr>
<td>Grossarth-Maticek, 3.1.1.2</td>
<td>2007</td>
<td>21 + 20</td>
<td>21 + 20</td>
<td>Ovary</td>
<td>PLG</td>
</tr>
<tr>
<td>Grossarth-Maticek, 3.1.1.2</td>
<td>2007</td>
<td>75 + 62</td>
<td>75 + 62</td>
<td>Ovary</td>
<td>PLG</td>
</tr>
<tr>
<td>Grossarth-Maticek, 3.1.1.1</td>
<td>2007</td>
<td>19</td>
<td>19</td>
<td>Cervix</td>
<td>PLG</td>
</tr>
<tr>
<td>Grossarth-Maticek, 3.1.1.1</td>
<td>2007</td>
<td>102</td>
<td>102</td>
<td>Cervix</td>
<td>PLG</td>
</tr>
<tr>
<td>Grossarth-Maticek, 3.1.5.1</td>
<td>2007</td>
<td>22</td>
<td>22</td>
<td>Melanoma</td>
<td>PLG</td>
</tr>
<tr>
<td>Grossarth-Maticek, 3.1.1.3</td>
<td>2008</td>
<td>198</td>
<td>198</td>
<td>Corpus uter</td>
<td>PLG</td>
</tr>
<tr>
<td>Grossarth-Maticek, 3.1.1.3</td>
<td>2008</td>
<td>56</td>
<td>56</td>
<td>Corpus uter</td>
<td>PLG</td>
</tr>
<tr>
<td>Hagens et al., 3.1.2.5</td>
<td>2005</td>
<td>33</td>
<td>33</td>
<td>Breast</td>
<td>PLG</td>
</tr>
</tbody>
</table>

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

**Study design**

<table>
<thead>
<tr>
<th>Type</th>
<th>Systematic review and meta-analysis of retrolective clinical studies on cancer patients treated with a Viscum album preparation, using pre-defined search strategies and quality criteria.</th>
</tr>
</thead>
</table>
| 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
Table 1: Characteristics of retrospective mistletoe studies

<table>
<thead>
<tr>
<th></th>
<th>Bock 2004(^{21})</th>
<th>Augustin 2005(^{22})</th>
<th>Friedel 2009(^{23})</th>
<th>Matthes 2010(^{24})</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (VA-E vs control)</td>
<td>1442 (710/732)</td>
<td>686 (329/357)</td>
<td>804 (429/375)</td>
<td>396 (201/195)</td>
</tr>
<tr>
<td>Number of centers</td>
<td>16</td>
<td>35</td>
<td>26</td>
<td>17</td>
</tr>
<tr>
<td>Type of cancer</td>
<td>Breast</td>
<td>Melanoma</td>
<td>Colorectal</td>
<td>Pancreatic</td>
</tr>
<tr>
<td>Intervention (iscador/control), %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiation</td>
<td>43.9/75.7</td>
<td>7.9/5.9</td>
<td>17.6/16.5%</td>
<td>4.5/18.5</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>32.8/23.2</td>
<td>10.0/5.9</td>
<td>53.3/53.6</td>
<td>71.6/43.6</td>
</tr>
<tr>
<td>Surgery</td>
<td>All</td>
<td>All</td>
<td>All</td>
<td>69.2/48.2</td>
</tr>
<tr>
<td>Others</td>
<td>50.1/50.3 (hormones)</td>
<td>12.1/19.8 (immunotherapy)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>UICC</td>
<td>I-III</td>
<td>II-III</td>
<td>I-III</td>
<td>I-IV</td>
</tr>
<tr>
<td>Follow-up, mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iscador</td>
<td>66</td>
<td>81</td>
<td>58</td>
<td>15</td>
</tr>
<tr>
<td>Control</td>
<td>60</td>
<td>51</td>
<td>51</td>
<td>10</td>
</tr>
<tr>
<td>Iscador (host tree), %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pinus</td>
<td>31.4</td>
<td>83.3</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Quercus</td>
<td>—</td>
<td>—</td>
<td>52.7</td>
<td>37.3</td>
</tr>
<tr>
<td>Malus</td>
<td>44.9</td>
<td>—</td>
<td>37.8</td>
<td>36.8</td>
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<tr>
<td>Combinations</td>
<td>23.7</td>
<td>16.7</td>
<td>9.5</td>
<td>25.9</td>
</tr>
<tr>
<td>Median duration, mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iscador</td>
<td>52</td>
<td>30</td>
<td>52</td>
<td>15</td>
</tr>
<tr>
<td>Control</td>
<td>63.1</td>
<td>—</td>
<td>48.3</td>
<td>48.9</td>
</tr>
</tbody>
</table>

Fig. 1: Numerical results and forest plot of meta-analysis of retrospective mistletoe studies
9 Single Case Documentation

References