Documentation of published clinical trials and observational studies with Iscador®

June 2006
Contents

Preface
Introduction
1 Immunology
2 DNA-Repair
3 Quality of Life / Pain
4 Tumour Remissions
5 Survival
   5.1 Urogenital Cancers
       5.1.1 Bladder
       5.1.2 Ovarial
       5.1.3 Body of the Uterus
       5.1.4 Uterus, Cervix
       5.1.5 Kidney
   5.2 Breast Cancer
   5.3 Gastrointestinal Cancer
       5.3.1 Stomach
       5.3.2 Pancreas
       5.3.3 Rectum / Colon
       5.3.4 Liver Metastases
   5.4 Lung Cancer
   5.5 Carcinosis of the Pleura
   5.6 Malignant Melanoma
6 Safety and Tolerance
7 Systematic Reviews

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Preface

This documentation is based on Konrad Urech’s compilation of the preparatory works of Henning Schramm (Medical-scientific department, Weleda AG, Arlesheim). Konrad Urech and Renatus Ziegler revised the original work and brought it up to date. It is intended as a basic 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 50 clinical trials and observational studies with Iscador, as well as 6 systematic reviews of these studies had been carried out by the end of 2005. 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.

The current version of the documentation is not yet complete, especially due to the absence of the first chapter on immunology.

A collection of clinical trials and observational studies which are still in process or have yet to be evaluated is currently being compiled.

It is intended that this documentation will be updated approximately every two years.

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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. 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 medicines can be sorted into two main groups: Clinical trials and observational studies. The latter group includes 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 special cases of this sort will be considered in this documentation, where only little literature was otherwise available, as a concise presentation is unable to go into the details of characteristic individual cases. A bibliography of such case reports structured according to indication is still outstanding.

Clinical trials and observational studies

Clinical trials (RCT, randomised controlled clinical trial) should be understood to be 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 double-blinded.

In many cases not only ethical, but also medical, human and technical problems prevent a complete double-blind 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
With anthroposophical medical therapies, especially with Iscador, the whole surroundings (doctor, clinic, accompanying therapies) as well as the doctor’s and patient’s wishes, beliefs and activities are at least as important as the application of the medication itself. This makes the implementation of RCT type clinical trials with Iscador, especially with double-blinding, very difficult, if not impossible. For these cases multi-arm at best prospective observational studies, with provision for patient and doctor preferences, are usually preferred. Alongside the uncertainty regarding the comparability of the different therapy groups (study arms), which cannot be eliminated, it could be presumed that such studies tend to overestimate the effectiveness; however, they more convincingly reflect clinical practice.
It can be concluded that both study types (RCT with double-blinding and observational studies), assuming the best case, complement each other and should consequently be included in the overall evaluation to an equal degree
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 Grossarth-Maticzek et al. (2001). The difficulty of observing patients over longer periods of time, as necessary for survival in oncological 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 due to Iscador.

**Good clinical practice (GCP)**
The guidelines for good clinical practice in clinical trials which were developed in the 1990s were not considered in the articles published up until 2002 on Iscador. This was probably due to ignorance of these guidelines, but to a large extent due to the tremendous complexity of carrying out a study conforming to GCP guidelines. In many cases, the observing of these standards was dispensed with in order to be able to evaluate and publish the results at all. As a result, the published studies are unfortunately of very differing qualities. The quality of the studies in the following systematic reviews is analysed from various angles (Chapter 7).
If the observation and adherence to the guidelines of GCP from the study design to the implementation of the study up to the evaluation is not explicitly mentioned in our presentation of the studies, then these guidelines were not applied to that study.

**Safety**
Data on the safety of a therapy with Iscador (Chapter 6) are available from only a few controlled studies. 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 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; this is without taking the various time intervals of the studies into account.
In connection with systematic reviews of clinical trials, it must be considered that only very few clinical trials exist even in the field of oncology, which reach all the criteria, set by the oncologists themself. 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 fortgeschrittene 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.

Kiene (1989) and Kleijnen and Knipschild (1994) carried out systematic reviews on most of the early clinical trials on the influence of Iscador and other mistletoe compounds on quality of life (see chapter 7). Kiene then classified 12 studies as valid. Within these 12 were 5 Iscador trials showing a significant advantage for the medication. Kleijnen and Knipschild excluded all retrospective and historical studies and classified 7 Iscador trials according to strict criteria. One of these studies showed a statistical significance, all of the others showed only a trend in favor of Iscador.

In a new review, Kienle et. al. (2003) show that from 14 prospective controlled studies 7 report a significant advantage for Iscador and 7show a positive trend. This result was largely confirmed by a National Cancer Institute (USA) report.

**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 extending length of life and quality of life, 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 •.
I Immunology

(Not yet available)
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 bodyweight) and daily 1 ml Iscador M s.c. 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 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.

![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).](image)

* Difference to 0-value is significant (p < 0.05)
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, urogenital or bronchial.

**Treatment**  123 patients received Iscador s.c. in various concentrations alongside the usual oncological therapies (chemotherapy, radiotherapy, surgery). 124 patients did not receive Iscador.


**Measurements**  Use of medication (analgesics, psychotropic drugs, spasmolitics 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, spasmolitics 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 was 11.3 months longer than the control group (not significant).
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 antitumoural 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 / 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 further results see 5.4.3.

**Study design**

**Design** Prospective, non-controlled study.

**Patients** 16 tumour patients (breast, liver, bladder, colon, tongue, prostate cancer, malignant melanoma and sarcoma) at stage III or IV.

**Treatment** Iscador “dose optimised” (dose equivalent of 1ng mistletoe lectin / kg bodyweight), 2 times a week during 5 to 12 months. 12 patients received only Iscador therapy, without the other therapy modality


**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 to 87 after treatment. The study was not evaluated statistically.

![Graph](image-url)

**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 (graph according to Hajto et al. 1992).

**Study design**

**Design** Randomised, placebo-controlled study.

**Patients** 30 patients with breast cancer with metastases after operation, 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 (graph according to Borrelli 1999).](image-url)
Quality of Life / Pain


**Study design**

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

**Patients**
56 matched pairs of patients with different tumours.

**Treatment**
The patients in the Iscador group received an individual therapy with different doses and types of s.c. applied Iscador. The control group with matched patients did not receive any type of mistletoe treatment.

**Length of study**

**Measurement**
Self-regulation (Score 1 to 6) according to Grossarth-Maticek measured using questionnaires with graded answers.

**Most important results**
The self-regulation index is a measurement of individual activity to achieve well-being, inner balance, adapted motivation, a feeling of competence and safety and overcoming of stress situations. Two separately studied matched-pair groups (39 and 17 pairs), in which the Iscador treatment was prospectively randomly recommended to one partner of the pair, showed an increase in the values for self-regulation after a 3-month treatment with Iscador from 3.41 to 3.87 and 2.92 to 3.70 respectively, whereas the values in the control group sank from 3.85 to 3.62 respectively increased only marginally from 2.87 to 2.99. The change in the value for self-regulation for the Iscador group was significantly different to that of the control group (56 pairs, p = 0005)

For further results see 5.2.5, 5.2.6, 5.3.1.2, 5.3.3.3, 5.4.5.

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

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 (operation, 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.
Measurement Primary (efficacy): Frequency of side-effects from conventional therapy (adverse drug effects, ADE); 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 effects, ADE) 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 ADE-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 further results see 5.2.7, 6.1.
Fig. 1: Frequency of side-effects (adverse drug effects, ADE) from conventional basis therapy, raw data: 152 ADE in 112 Iscador patients vs. 780 ADE in 395 control patients. Multivariate analysis: Proportion of the patients with ADE from conventional therapy: adjusted odds ration OR = 0.47 (95% confidence interval 0.32 – 0.67), p < 0.0001 (graph 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 (graph according to Bock et al. 2004).

**Study design**

**Design**  
1-arm, prospective, longitudinal study concerning quality of life (QoL) of cancer patients before, during and after treatment in an anthroposophic clinic in Switzerland (Lukas Klinik, LK).

**Patients**  
144 in-patients with advanced epithelial cancers. Assessment of tumour-related therapy patterns 4 months prior to admission, during stationary treatment (3 weeks on average) and 4 months after baseline. Assessment of QoL at admission, hospital discharge and 4 months after hospitalisation.

**Treatment**  
Anthroposophic treatment starting at LK consisted of Iscador, other medicaments from plants or minerals given as injections, orally or external applications, baths, massage, therapeutic eurythmy, art therapy (e.g. painting, music), counselling and 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.

**Length of study**  

**Measurements**  
Medical and socio-demographic baseline data, conventional cancer treatments, anthroposophical treatment, 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: hormonotherapy, 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 tumor with alleviation of symptoms and pain. Side effects were only indicated for conventional cancer treatment.

Conclusion: Our 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 tumor focused.
4 Tumour Remissions

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 antitumoural glucosamine) once a week i.m.

**Length of study**

**Measurements**
Survival, tumour remission, symptom-free interval, Karnofsky Index, patients’ subjective well-being, quality of life.

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**Results regarding tumour remissions**

<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>

*Tab. 1: Regression of tumour and metastases during the course of the study*
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.

The total remission rate of 22% (73 cases) is relatively high (see Table 4.1). 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 further results see 3.2 and 5.4.3.

Study design

Design
Prospective observational study without a control group

Patients
16 patients with histologically defined advanced tumours, stage III and IV (see table 4.2).

Treatment
12 patients received only a dose-optimised Iscador therapy (dose equivalent of 1ng mistletoe lectin / kg bodyweight), twice a week during 5 to 12 months. The other 4 also received different conventional treatments.

Length of study

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 further results see 3.3.
<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>Malignant 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>no change</td>
</tr>
<tr>
<td>11</td>
<td>Malignant 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>

**Tab. 1: Clinical results**
Tumour remissions

Study design

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

Results regarding tumour remissions

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

Set 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.

Set 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.
**Tumour remissions**


*Deutsche Medizinische Wochenschrift* 124 (47), 1414–1418.

---

**Study design**

**Design**
Observation of individual case.

**Patient**
Patient with very good general condition, 44 years old, histologically confirmed follicular centroblastic centrocytic non-Hodgkin lymphoma (low grade) stage IVA (Ann Arbor classification), with bone marrow infiltration, normal blood parameters und high Karnofsky Performance status (100%).

**Treatment**
Chemotherapy was not indicated. Out-patient subcutaneous Iscador therapy with Iscador P or Qu 0.1 to 30 mg respectively at two day intervals.

**Length of study**

**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.
5 Survival

5.1 Urogenital Cancers

5.1.1 Bladder
5.1.2 Ovarial
5.1.3 Body of the Uterus
5.1.4 Uterus, Cervix
5.1.5 Kidney
5.1.1 Bladder

References


The references marked with ☆ are included in abstract form in this documentation.
Survival Urogenital Cancer Bladder 5.1.1.1


**Study design**

**Design**
Retrospective study without a comparative group.

**Patients**
62 patients with cancer of the bladder treated between 1963 and 1975 at the Lukas Klinik, stages I to IV.

**Treatment**
Iscador s.c. in different doses.

**Length of study**

**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.

![Pie chart showing the results of the study.](image)

**Fig. 1:** Reaction of patients with cancer of the bladder (stages I–IV, n = 62) to a therapy with Iscador (graph 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: 30.9.1977. Their initial diagnosis was at least 5 years previous and histologically secured.

**Treatment** Iscador s.c. in different doses. One group of 17 patients received inadequate doses of Iscador, for various reasons.

**Length of study** 1963–1977.

**Measurement** Survival.

**Most important results**

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

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, operated; 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).

Treatement  Iscador s.c. in different doses.


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 severe side-effects from the therapy. No such problems were reported in the Iscador group, the reverse was the case, well-being improved and requirements for analgesics decreased.

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

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

**Most important results**

The Iscador patients in stage I (n = 31) achieved a 5-year survival of 73% and those in stage II (n = 18) achieved a 5-year survival of 53%. These survival rates lie above the mean described in the literature (67% and 38% respectively), the differences are however not statistically significant. The median survival of the Iscador patients in stages III and IV (n = 53 + 30), was better, with 11.5 months in comparison with the historical control with 6.6 to 10.3 months (not significant). The positive well-being of the patients, the reduction in side-effects of chemo- and radiotherapy as well the reduction of pain were also mentioned.
*Der Merkurstab* 49 (2), 152–153.

**Study design**

**Design**
Retrospective study with historical control.

**Patients**
36 patients with ovarian cancer in stage III with progression under chemotherapy, registered at the medical practice of R. Wagner, Stuttgart, between 1990 and 1996.

**Treatment**
Iscador s.c. in different doses.

**Length of study**

**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 general 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.
5.1.3 Body of the Uterus

References


The references marked with ★ are included in abstract form in this documentation.
5.1.4 Uterus, 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 3 times a week s.c., over 5 years. The control group did not receive treatment with Iscador.


**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>
<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></td>
<td>Iscador</td>
<td>Control</td>
<td>Iscador</td>
<td>Control</td>
</tr>
<tr>
<td>n</td>
<td>9</td>
<td>92</td>
<td>45</td>
<td>334</td>
</tr>
<tr>
<td>3-year survival rate</td>
<td>100%</td>
<td>89%</td>
<td>87%</td>
<td>82%</td>
</tr>
<tr>
<td>5-year survival rate</td>
<td>100%</td>
<td>79%</td>
<td>87%</td>
<td>77%</td>
</tr>
<tr>
<td>Significance</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>yes ( p = 0.015 )</td>
</tr>
</tbody>
</table>

Tab. 1: Results according to stage of disease.

<table>
<thead>
<tr>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
</tr>
<tr>
<td><strong>Patients</strong></td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td><strong>Measurements</strong></td>
</tr>
</tbody>
</table>

**Most important results**

5 (18.5%) of the 27 patients discontinued the treatment. 9 (40.9%) of the 22 treated patients showed complete remission (secured by biopsy), 6 (27.3%) showed a partial remission (< 50% reduction in the lesion, or regression of the histological level respectively), 6 (27.3%) showed no change and 1 showed progression. This correlates with a response rate of 68.2%.
5.1.5 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 with 35 series, on average a year
- **Group 2**: (n = 79) and
- **Group 3**: (n = 30) were treated, inadequately with 18 and 4 Iscador series respectively.

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  5.2.2


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 operation (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 operations 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) (graph according to Lerori 1977).
<table>
<thead>
<tr>
<th>Stage of disease</th>
<th>I</th>
<th>II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group</td>
<td></td>
<td></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>

Tab. 1: Results according to stage of disease.

**Study design**

**Design**
Retrospective study with 3 groups.

**Patients**
495 operated patients with breast cancer and metastases, from the Lukas Klinik.

**Treatment**

*Group 1 (n = 116):* Received Iscador for at least 3 months after operation, 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 became 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.
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 operation. 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 operation. 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 (graph according to Hellan et al. 1990).
Fig. 2: Course of survival in breast cancer patients, with stage III disease with ($n = 89$, mean survival = 67 months, median 74 months) and without ($n = 141$, mean survival = 46 months, median 50 months) additional treatment with mistletoe (graph according to Hellan et al. 1990).

Fig. 3: Course of survival in breast cancer patients with stage IV disease with ($n = 10$, mean survival = 46.7 months, median 49 months) and without ($n = 28$, mean survival = 21.9, median 21 months) treatment with mistletoe (graph 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  Iscador s.c., individual dosage.


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).

For further results see 3.5, 5.2.6, 5.3.1.2, 5.3.3.3, 5.4.5.

![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) (graph according to Grossarth-Maticek et al. 2001).](image)
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 matched with patients who did not receive treatment with Iscador. 120 pairs could be found after following the strict criteria required for matching.

Treatment Iscador s.c., individual dosage.


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 metastases in the axilla (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). For further results see 3.5, 5.2.5, 5.3.1.2, 5.3.3.3, 5.4.5.

![Graph showing survival of breast cancer patients with and without Iscador therapy](image)

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

**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 (operation, radiotherapy, chemotherapy), 710 of which received additional Iscador therapy (treatment group), 732 only received the conventional basic therapy (control group).

**Comparability**
The patients in the treatment group were more seriously ill and had more pronounced risk factors for progression.

**Treatment**
Median length of observation during aftercare: 66 months (treatment or Iscador group), 60 months (control group). 156 (22%) of the patients in the treatment group and 42 (6%) of the patients in the control group did not receive conventional therapy.

**Length of study**

**Measurements**
Primary (efficacy): Frequency of side-effects from the conventional therapy, symptoms due to the disease and the 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.

For further results see 3.6, 6.1.
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 (graph 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 (graph according to Bock et al. 2004).
5.3 Gastrointestinal Cancer

5.3.1 Stomach
5.3.2 Pancreas
5.3.3 Rectum, Colon
5.3.4 Liver metastases
5.3.1 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 of the patients were operated and 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 operated stomach cancer with (LN-positive) and without (LN-negative) lymph node metastases under therapy with and without Iscador (graph according to Salzer G. et al. 1983).](image-url)
<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></td>
<td>T1,2 N1 M0</td>
<td>T2 N0 M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>n = 5</td>
<td>n = 10</td>
</tr>
<tr>
<td></td>
<td>n = 15</td>
<td>n = 24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>T1-3 N1-2 M0</td>
<td>T3 N0 M0</td>
</tr>
<tr>
<td></td>
<td>n = 30</td>
<td>n = 27</td>
</tr>
<tr>
<td></td>
<td>n = 12</td>
<td>n = 14</td>
</tr>
<tr>
<td>Total</td>
<td>n = 35</td>
<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>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1661 days</td>
<td>1364 days</td>
</tr>
<tr>
<td></td>
<td>–</td>
<td>1201 days</td>
</tr>
</tbody>
</table>

**Tab. 1:** Distribution of tumour stages and results.
Survival  Gastrointestinal Cancer  Stomach


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 an individual therapy s.c applied at different dosages and of different types.


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.

For further results see 3.5, 5.2.5, 5.2.6, 5.3.3.3, 5.4.5.

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

References


The references marked with ☆ are included in abstract form in this documentation.
Survival Gastrointestinal Cancer Pancreas 5.3.2.1


**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% were operable and over 50% had stage IV disease.

**Treatment** Different dosages of Iscador M or Qu s.c..

**Length of study** 1986–1996.

**Measurement** Survival.

**Most important results**

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

<table>
<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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<td>IV</td>
<td>136</td>
<td>60.6</td>
<td>5.2</td>
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<td>76</td>
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<td>292</td>
<td>64.0</td>
<td>7.0</td>
<td>6.6</td>
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<tr>
<td>operable patients</td>
<td>29</td>
<td>55.3</td>
<td>33.6</td>
<td>16.7</td>
</tr>
</tbody>
</table>

Tab. 1: Results according to stage of disease.
5.3.3 Rectum / Colon

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 palliatively operated 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.

![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) (graph according to Leroi 1979).](image-url)
Survival Gastrointestinal Cancer Rectum/Colon

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group</th>
</tr>
</thead>
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<td>Inoperable colon cancer</td>
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</tr>
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<td>Inoperable cancer of the rectum</td>
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<td>Median survival (months)</td>
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</tr>
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<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>

Tab. 1: Results

Study design

Design  Retrospective study with comparative groups.

Patients  991 from 1117 patients with operated colorectal tumours, stage I–IV, who had been transferred to the L. Boltzmann-Institut 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-operative 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.


Measurements  Survival and relapse-free interval.

Most important results

This retrospective evaluation of data from patients with operated colorectal tumours showed that Iscador mainly lead 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 II 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>
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<th>Stage</th>
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<th>Chemoth</th>
<th>Iscador</th>
<th>No therapy</th>
<th>Chemoth</th>
<th>Radiother</th>
<th>Combination therapy</th>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1-2 N0 M0</td>
<td>23</td>
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<td>73</td>
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<td>5</td>
<td>(21.7%)</td>
<td>3</td>
<td>22</td>
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<td>26</td>
<td>(48.1%)</td>
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<td></td>
<td></td>
<td></td>
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<td>1477</td>
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<td></td>
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<td>(36.9%)</td>
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<td>66</td>
<td>65</td>
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<td>580</td>
<td>1251</td>
<td>1083</td>
<td>950</td>
<td>849</td>
<td>1067</td>
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<td></td>
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<td>18</td>
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<td>(47%)</td>
<td>52</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1-4 N+, M0,i</td>
<td>43</td>
<td>25</td>
<td>14</td>
<td>52</td>
<td>59</td>
<td>19</td>
<td></td>
<td>10</td>
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<tr>
<td>Median survival in days</td>
<td>347</td>
<td>425</td>
<td>383</td>
<td>330</td>
<td>536</td>
<td>371</td>
<td>544</td>
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<tr>
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<td></td>
<td>no</td>
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<td></td>
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<td>103</td>
<td>21</td>
<td>294</td>
<td>245</td>
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<td>33</td>
<td>48</td>
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Tab. 1: Results according to stage of disease.
Survival Gastrointestinal Cancer Rectum/Colon 5.3.3.2

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) (graph 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) (graph 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 (graph 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 (graph 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 (graph according to Hellan et al. 1995).
Survival Gastrointestinal Cancer Rectum/Colon


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 One partner from each pair was treated with different dosages of Iscador s.c. The other partner did not receive treatment with Iscador.


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.

For further results see 3.5, 5.2.5, 5.2.6, 5.3.1.2, 5.4.5.

![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) (graph according to Grossarth-Maticek et al. 2001).](image-url)
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) (graph according to Grossarth-Maticek et al. 2001).
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 ($\geq 3$ 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 monotherapy and 15 patients received a combination of cytostatic 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>
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<tr>
<th></th>
<th>Control</th>
<th>Cytostatic</th>
<th>Mistletoe</th>
<th>Cytostatics + mistletoe</th>
</tr>
</thead>
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<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>
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<td>Mean survival (days)</td>
<td>64</td>
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<td></td>
</tr>
</tbody>
</table>

Tab. 1: Results.
5.4 Lung Cancer

References


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

Study design

Design Prospective, controlled study.
Patients 77 patients were divided into two groups after operation for lung cancer. All of the patients who were admitted from further away (n = 37), were treated post-operatively 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..
Measurement Survival.

Most important result

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 operation 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 pulmological centre, Vienna (graph according to Salzer and Havelec 1978).
Survival Lung Cancer

<table>
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<tr>
<th>Stage I: T1 N0</th>
<th>Iscador</th>
<th>Control</th>
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<tr>
<td>Survivors after 80 months</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Significant</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>Survivors after 80 months</td>
<td>6 (50%)</td>
<td>3 (33%)</td>
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<tr>
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<td>no</td>
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<td>11</td>
</tr>
<tr>
<td>Survivors after 80 months</td>
<td>5 (33%)</td>
<td>2 (18%)</td>
</tr>
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<td></td>
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<td>19</td>
</tr>
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<td>3 (33%)</td>
<td>1 (5%)</td>
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<td>6 (15%)</td>
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<td>Significant</td>
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Tab. 1: Results according to stage of disease

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<th>Iscador</th>
<th>Control</th>
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<tr>
<td>Lymph node 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>
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</tbody>
</table>

Tab. 2: Results according to lymph node metastases.
Study design

Design
Prospective, controlled, randomised study.

Patients
26 patients with radically operated 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

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).

![Graph of survival rates](image_url)

**Fig. 1:** Course of survival in patients with operated lung cancer without further treatment (n = 14) and with Iscador therapy (n = 12) (graph according to Salzer 1980).
Study design

Design 3 arm, prospective, randomised, placebo-controlled multi-centre 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 (and antitumoural glucosamine) once a week i.m.


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 also increased by 20% 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.

For further results see 3.2.
### Tab. 1: Distribution of patients according to TNM categories.

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<tr>
<th>Category</th>
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<th>Placebo</th>
<th>Total</th>
<th>Percent</th>
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<td>3</td>
<td>3</td>
<td>12</td>
<td>3.6</td>
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<td>T2 N0 M0</td>
<td>18</td>
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<td>19</td>
<td>58</td>
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</tr>
<tr>
<td>T1 N1 M0</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>6</td>
<td>1.8</td>
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<tr>
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<td>11</td>
<td>16</td>
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</tr>
<tr>
<td>T3 N1-2 M1</td>
<td>10</td>
<td>17</td>
<td>17</td>
<td>44</td>
<td>13.1</td>
</tr>
<tr>
<td>NX / MX</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>8</td>
<td>2.4</td>
</tr>
<tr>
<td>Total</td>
<td>114</td>
<td>110</td>
<td>113</td>
<td>337</td>
<td></td>
</tr>
</tbody>
</table>

### Tab. 2: Distribution of the patients according to tumour stage.

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

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Study design

Design  Controlled, randomised, multi-centre study.

Patients  183 patients with non-small cell lung cancer from the hospitals in Vienna-Lainz, Innsbruck and Grosshansdorf. The patients in both groups were comparable in respect to age, sex, lymph node metastases and histology.

Treatment  The patients were randomised after operation 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.

![Survival Graph](image)

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) (graph according to Salzer et al. 1991).
<table>
<thead>
<tr>
<th>Stages</th>
<th>Iscador</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage I – II:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph node negative, T(_1)–T(_3), N(_0)</td>
<td>59</td>
<td>65</td>
</tr>
<tr>
<td>Died</td>
<td>30</td>
<td>43</td>
</tr>
<tr>
<td>Post-mortem</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>Tumour-free</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Relapse / metastases (cases)</td>
<td>29 (49%)</td>
<td>33 (50%)</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>44</td>
<td>43</td>
</tr>
<tr>
<td>Significant</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td><strong>Stage II – III:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph node positive, T(_1)–T(_3), N(_1)–N(_2)</td>
<td>16</td>
<td>27</td>
</tr>
<tr>
<td>Died</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Post-mortem</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Tumour-free</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Relapse / metastases (cases)</td>
<td>8 (50%)</td>
<td>20 (74%)</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>31</td>
<td>24</td>
</tr>
<tr>
<td>Significant</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td><strong>Stage IV:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T(_4), N(_0), T(_1)–T(_4), N(_3)</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Died</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Post-mortem</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Tumour-free</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Relapse / metastases (cases)</td>
<td>16.5</td>
<td>17</td>
</tr>
<tr>
<td>Significant</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>86</td>
<td>97</td>
</tr>
<tr>
<td>Died</td>
<td>51</td>
<td>67</td>
</tr>
<tr>
<td>Post-mortem</td>
<td>22</td>
<td>24</td>
</tr>
<tr>
<td>Tumour-free</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Relapse / metastases (cases)</td>
<td>44 (50%)</td>
<td>53 (55%)</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>33</td>
<td>31</td>
</tr>
<tr>
<td>Significant</td>
<td>no</td>
<td></td>
</tr>
</tbody>
</table>

Tab. 1: Results according to stage of tumour

**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 treatment groups received Iscador s.c. in different individual dosages.

**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)

For further results see 3.5, 5.2.5, 5.2.6, 5.3.1.2, 5.3.3.3.

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

References

- 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]

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 intrapleural instillations with Iscador lead to pleurodesis. There were only 2 failures among the 89 patients. Mean survival was 6.3 months.
**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>
<thead>
<tr>
<th>Required puncturings</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[n]</td>
</tr>
<tr>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>17</td>
<td>1</td>
</tr>
</tbody>
</table>

*Tab. 1:* The number of puncturings 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).
5.6 Malignant 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) malignant melanoma from the patients at the Lukas Klinik on 31.07.77. 84% or 28% of the stage II patients were operated or operated 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>
<thead>
<tr>
<th></th>
<th>Stage II Regional lymph node befall</th>
<th>Stage III With 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>52%</td>
<td>13%</td>
</tr>
<tr>
<td>2 years</td>
<td>24%</td>
<td>6%</td>
</tr>
<tr>
<td>5 years</td>
<td>20%</td>
<td>–</td>
</tr>
<tr>
<td>10 years</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tab. 1: Results according to stage of disease
Study design

Design  Controlled study.

Patients  198 patients with malignant 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 malignant melanoma with (n = 84) and without (n = 114) treatment with Iscador over the course of 8 years (graph 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 malignant 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 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.
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 (Tab. 1).
For further results see 6.2.
Fig. 1: Multivariate analysis of tumour-related survival (TS) with a Cox proportional hazard regression adjusted hazard ratio $HR = 0.41$ (95% confidence interval, $0.23 – 0.71$), $p = 0.002$ (graph according to Augustin et al. 2005). FME = fermented mistletoe extract = Iscador.

<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>

Tab. 1: Multivariate analysis of different lengths of survival using Cox proportional hazard regression.
6 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 (operation, 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 effects (ADE) due to the Iscador therapy, every occurrence of tumour enhancement.

Most important results

Systemic ADE 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 ADE mainly only continued for one day. Serious systemic ADE 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».

Summarising, this demonstrates that the application of Iscador can be associated with good tolerance and safety.
For further results see 3.6, 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 malignant 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.

Length of study  

Measurements  
Primary (safety): Incidence of systemic and localised adverse drug effects (ADE), 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 ADE in connection with the Iscador therapy were recorded in 11 (3.3%) of the 686 patients in the Iscador group. The ADE 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 ADE did not occur.
Localised ADE 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 ADE were erythema (41), oedema (12), itching or local pain (3) or other localised reactions (3). The level of ADE 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.
To summarise, the results of this safety analysis indicate that a therapy with Iscador is safe and well-tolerated.
For further results see 5.6.3.
7 Systematic Reviews

References

A) Systematic Reviews


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


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:

- *(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:

- *(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:

- *(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 studies with mistletoe**

35 of the 46 analysed studies with mistletoe fulfil the inclusion criteria and at the same time do not fulfil 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 has 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>
<thead>
<tr>
<th>Publication(s)</th>
<th>Study aim.</th>
<th>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>
</tr>
</thead>
<tbody>
<tr>
<td>Buchner (1984)</td>
<td>pain</td>
<td>retrospective</td>
<td>3 46</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td></td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Dold et al. (1991)</td>
<td>quality of life</td>
<td>prospective randomised</td>
<td>3 35</td>
<td>yes</td>
<td>yes</td>
<td>partially</td>
<td></td>
<td>yes</td>
<td></td>
</tr>
</tbody>
</table>

| Urogenital Cancers 5.1 |
|------------------------|------------|---------------|------------------|-------------------------------|--------------|----------------|-----------------------------|-------------------|----------------------------------|
| Leroi (1978, 1980)     | bladder    | case series   | 5.1.1 1 57 | yes                           | –            | –              |                             | –                 | –                                |
| Hoffmann (1978, 1980)  | bladder    | retrospective | 5.1.1 2 58 | yes                           | no           | no             |                             | –                 | –                                |
| Leroi (1969, 1980)     | ovary      | case series   | 5.1.2 5 41 | yes                           | –            | –              |                             | –                 | –                                |
| Leroi/Hajto (1982)     | ovary      | retrospective | 5.1.2 6 42 | yes                           | ?            | no             |                             | –                 |                                   |
| Schreiber/Stumpf (1984)| ovary      | retrospective | 5.1.2 7 42 | yes                           | no           | –              |                             | –                 |                                   |
| Majewski/Bentele (1963)| ovary      | prospective   | 5.1.2 9 40 | no                            | no           | –              |                             | –                 |                                   |
| Hassauer et al. (1979) | ovary      | retrospective | 5.1.2 10 43 | yes                           | yes          | yes            |                             | yes               | yes                              |
| Leroi (1969)           | uterus, corpus | case series   | 5.1.3 5 41 | yes                           | –            | –              |                             | –                 | –                                |
| Majewski/Bentele (1963)| uterus, corpus | prospective  | 5.1.3 9 40 | yes                           | no           | –              |                             | –                 | –                                |
| Leroi (1969)           | uterus, cervix | case series   | 5.1.4 5 41 | yes                           | –            | –              |                             | –                 | –                                |
| Fellmer/Fellmer (1966), Fellmer (1968) | uterus, cervix | prospective  | 5.1.4 8 44 | yes                           | yes          | yes            |                             | yes               | yes                              |
| Majewski/Bentele (1963)| uterus, cervix | prospective  | 5.1.4 9 40 | no                            | no           | –              |                             | –                 | –                                |
| Kjaer (1989)           | kidney     | prospective   | 5.1.5  61  | no                            | no           | no             |                             | –                 | –                                |

| Breast Cancer 5.2 |
|-------------------|------------|---------------|------------------|-------------------------------|--------------|----------------|-----------------------------|-------------------|----------------------------------|
| Majewski/Bentele (1963) | breast cancer | prospective | 5.2 9 40 | yes                           | no           | –              |                             | –                 | –                                |
| Gänzler/Salzer (1962)| breast cancer | retrospective | 5.2 11 47 | yes                           | –            | –              |                             | –                 | –                                |
| Gänzler/Salzer (1969)| breast cancer | retrospective | 5.2 12 48 | yes                           | –            | –              |                             | –                 | –                                |
| Koch/Voss (1980)    | breast cancer | retrospective | 5.2 14 49 | yes                           | –            | –              |                             | –                 | –                                |
| Leroi (1977)        | breast cancer | retrospective | 5.2 15 50 | yes                           | ?            | yes            |                             | –                 | –                                |
| Leroi (1977)        | breast cancer | retrospective | 5.2 16 50 | yes                           | no           | –              |                             | –                 | –                                |
| Hoffmann/Hajto (1982)| breast cancer | retrospective | 5.2 17 51 | yes                           | no           | yes            |                             | –                 | –                                |
| Salzer (1987)       | breast cancer | prospective   | 5.2 18 52 | yes                           | no           | no             |                             | –                 | –                                |
| Salzer (1987)       | breast cancer | retrospective | 5.2 20 47 | yes                           | no           | –              |                             | –                 | –                                |

Tab. 1a: Results of studies with Iscador.

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: –
### Systematic Reviews 7.1

#### Gastrointestinal Cancers 5.3

<table>
<thead>
<tr>
<th>Publication(s)</th>
<th>Study aim, Diagnosis</th>
<th>Study type</th>
<th>Chapter in this documentation</th>
<th>1989</th>
<th>2003</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>
<td>yes</td>
</tr>
<tr>
<td>Salzer/Havelec (1983), Salzer/Denk (1979)</td>
<td>stomach</td>
<td>prospective randomised</td>
<td>5.3.1</td>
<td>23</td>
<td>12</td>
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<td>yes</td>
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<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>
<td>–</td>
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<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>
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<tr>
<td>Günczler/Salzer (1983)</td>
<td>rectum</td>
<td>retrospective</td>
<td>5.3.3</td>
<td>25</td>
<td>18</td>
<td>yes</td>
<td>no</td>
<td>–</td>
</tr>
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<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>
<td>–</td>
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<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>
<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>
<td>–</td>
</tr>
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<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>
<td>–</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>
<td>no</td>
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<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>
<td>–</td>
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<td>lung cancer</td>
<td>5.4</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salzer/Havelec (1978), Salzer (1980a)</td>
<td>lung cancer</td>
<td>prospective</td>
<td>5.4</td>
<td>34</td>
<td>32</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
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<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>
<td>yes</td>
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<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>
<td>–</td>
</tr>
<tr>
<td>Salzer (1980b, 1987)</td>
<td>lung cancer</td>
<td>prospective randomised</td>
<td>5.4</td>
<td>37</td>
<td>33</td>
<td>yes</td>
<td>?</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>
<td>–</td>
</tr>
<tr>
<td>Salzer et al. (1991), Salzer (1987)</td>
<td>lung cancer</td>
<td>prospective randomised</td>
<td>5.4</td>
<td>–</td>
<td>34</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
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</table>

#### Carcinosis of the Pleura 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>1989</th>
<th>2003</th>
<th>Advantage for Iscador (Trend)</th>
<th>Validity of the study</th>
<th>Significant advantage for Iscador</th>
</tr>
</thead>
<tbody>
<tr>
<td>carcinosis of the pleura</td>
<td>Case series</td>
<td>5.5</td>
<td>39</td>
<td>78</td>
<td>yes</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>malignant melanoma</td>
<td>5.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feuchtinger (1979)</td>
<td>malignant melanoma</td>
<td>retrospective</td>
<td>5.6</td>
<td>40</td>
<td>64</td>
<td>yes</td>
<td>no</td>
<td>–</td>
</tr>
<tr>
<td>Leroi (1985)</td>
<td>malignant melanoma</td>
<td>retrospective</td>
<td>5.6</td>
<td>42</td>
<td>65</td>
<td>yes</td>
<td>?</td>
<td>no</td>
</tr>
<tr>
<td>Schuppli (1990)</td>
<td>malignant melanoma</td>
<td>retrospective</td>
<td>5.6</td>
<td>43</td>
<td>66</td>
<td>yes</td>
<td>?</td>
<td>–</td>
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</table>

Tab. 1b: Results of studies with Iscador.

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: –
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) prestratification (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 studies with mistletoe

11 of the analysed studies fulfilled the inclusion criteria and at the same time did not fulfil 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>
<thead>
<tr>
<th>Publication</th>
<th>Diagnosis</th>
<th>Chapter in this documentation</th>
<th>No. of study in Klene/Kiene 2003</th>
<th>Result to the advantage of the Iscador group</th>
<th>Quality Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fellmer (1966, 1968)</td>
<td>uterus, cervix</td>
<td>5.1.3</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</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</td>
<td>32</td>
<td>trend</td>
<td>4.5</td>
</tr>
<tr>
<td>Dold et al. (1991)</td>
<td>lung cancer</td>
<td>5.4</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</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</td>
<td>32</td>
<td>significant</td>
<td>5.0</td>
</tr>
</tbody>
</table>

**Tab. 1:** Results of studies with Iscador

**Study design**

**Type** Systematic review

**Inclusion criteria** Prospective clinical trials with mistletoe extracts and with control and/or comparative groups.

**Exclusion criteria** Absence of, unclear or non-description of randomisation in the group allocation.

**Results pertaining to studies with mistletoe**

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

<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</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>5.4</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>

**Tab. 1:** Results of studies with Iscador
Study design

Type Systematic review with defined initial search strategy and quality criteria.

Inclusion criteria 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 is patients who do not have cancer.

Judgement criteria A) protection against selection bias;
B) minimisation of heterogeneity by prestratification 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 studies with mistletoe, especially 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.
### Tab. 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>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>
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<td>Dold et al. (1991)</td>
<td>lung cancer</td>
<td>3, 4, 5.4</td>
<td>35</td>
<td>Significant (quality of life), trend (survival), trend (tumour remission)</td>
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<tr>
<td>Salzer et al. (1991)</td>
<td>lung cancer</td>
<td>5.4</td>
<td>34</td>
<td>trend (survival for lymph node positive)</td>
<td>183</td>
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<tr>
<td>Grossarth-Maticek et al. (2001)</td>
<td>breast cancer</td>
<td>3, 5.2</td>
<td>56</td>
<td>significant (survival), trend (quality of life)</td>
<td>34</td>
</tr>
<tr>
<td>Grossarth-Maticek et al. (2001)</td>
<td>diverse carcinomas</td>
<td>3</td>
<td>10</td>
<td>significant (survival), significant (quality of life)</td>
<td>78</td>
</tr>
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</table>

### Tab. 2: Result 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 (1963)</td>
<td>uterus and ovary</td>
<td>5.1</td>
<td>40</td>
<td>trend (survival)</td>
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</tr>
<tr>
<td>Salzer (1987)</td>
<td>breast cancer</td>
<td>5.2</td>
<td>52</td>
<td>trend (survival)</td>
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</tr>
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</table>

### Tab. 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>Fellner (1966, 1968)</td>
<td>uterus, cervix</td>
<td>5.1.3</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</td>
<td>32</td>
<td>significant (survival)</td>
<td>77</td>
</tr>
<tr>
<td>Schuppil (1990)</td>
<td>malignant melanoma</td>
<td>5.6</td>
<td>66</td>
<td>trend (survival)</td>
<td>198</td>
</tr>
<tr>
<td>Grossarth-Maticek et al. (2001)</td>
<td>diverse carcinomas</td>
<td>3, 5.2, 5.3, 5.4</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.

Exclusion 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.

Results pertaining to Iscador

Positive results were reported in 7 randomised studies with Iscador (level Iii). The only study report with a significantly positive result in different gynaecological cancers achieved level 2. The non-randomised controlled studies were allocated level 3iii (non-consecutive case series) or no level at all.
<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>Grossarth-Maticek et al., (2001)</td>
<td>diverse carcinomas</td>
<td>prospective randomised</td>
<td>3</td>
<td>10</td>
<td>survival</td>
<td>ii</td>
</tr>
<tr>
<td>Grossarth-Maticek et al., (2001)</td>
<td>diverse carcinomas</td>
<td>prospective controlled</td>
<td>3</td>
<td>9, 14, 25, 36, 55</td>
<td>survival</td>
<td>iii</td>
</tr>
<tr>
<td>Leroi (1969, 1980)</td>
<td>ovary</td>
<td>case series</td>
<td>5.1.2</td>
<td>57</td>
<td>survival</td>
<td>–</td>
</tr>
<tr>
<td>Majewski/Bentele (1963)</td>
<td>ovary</td>
<td>prospective controlled</td>
<td>5.1.2</td>
<td>40</td>
<td>survival</td>
<td>2</td>
</tr>
<tr>
<td>Leroi (1969)</td>
<td>uterus, corpus</td>
<td>case series</td>
<td>5.1.3</td>
<td>41</td>
<td>survival</td>
<td>–</td>
</tr>
<tr>
<td>Majewski/Bentele (1963)</td>
<td>uterus, corpus</td>
<td>prospective controlled</td>
<td>5.1.3</td>
<td>40</td>
<td>survival</td>
<td>2</td>
</tr>
<tr>
<td>Leroi (1969)</td>
<td>uterus, cervix</td>
<td>case series</td>
<td>5.1.4</td>
<td>41</td>
<td>survival</td>
<td>–</td>
</tr>
<tr>
<td>Fellmer/Fellmer (1966), Fellmer (1968)</td>
<td>uterus, cervix</td>
<td>case series</td>
<td>5.1.4</td>
<td>44</td>
<td>survival</td>
<td>iii</td>
</tr>
<tr>
<td>Majewski/Bentele (1963)</td>
<td>uterus, cervix</td>
<td>prospective controlled</td>
<td>5.1.4</td>
<td>40</td>
<td>survival</td>
<td>2</td>
</tr>
<tr>
<td>Kjaer (1989)</td>
<td>kidney</td>
<td>prospective controlled</td>
<td>5.1.5</td>
<td>61</td>
<td>–</td>
<td>iii</td>
</tr>
<tr>
<td>Majewski/Bentele (1963)</td>
<td>breast cancer</td>
<td>prospective controlled</td>
<td>5.2</td>
<td>40</td>
<td>survival</td>
<td>2</td>
</tr>
<tr>
<td>Leroi (1977)</td>
<td>breast cancer</td>
<td>case series</td>
<td>5.2</td>
<td>50</td>
<td>survival</td>
<td>iii</td>
</tr>
<tr>
<td>Salzer (1987)</td>
<td>breast cancer</td>
<td>prospective randomised</td>
<td>5.2</td>
<td>47</td>
<td>survival</td>
<td>iii</td>
</tr>
<tr>
<td>Grossarth-Maticek et al., (2001)</td>
<td>breast cancer</td>
<td>prospective randomised</td>
<td>3</td>
<td>56</td>
<td>survival</td>
<td>ii</td>
</tr>
<tr>
<td>Schaefermeyer (1998)</td>
<td>stomach</td>
<td>prospective randomised</td>
<td>5.3.1</td>
<td>32</td>
<td>survival</td>
<td>iii</td>
</tr>
<tr>
<td>Salzer (1987)</td>
<td>pancreas</td>
<td>case series</td>
<td>5.3.2</td>
<td>17</td>
<td>survival</td>
<td>iii</td>
</tr>
<tr>
<td>Salzer (1987)</td>
<td>colon</td>
<td>case series</td>
<td>5.3.3</td>
<td>–</td>
<td>survival</td>
<td>iii</td>
</tr>
<tr>
<td>Salzer (1987)</td>
<td>rectal</td>
<td>case series</td>
<td>5.3.3</td>
<td>–</td>
<td>survival for lymph node positive</td>
<td>–</td>
</tr>
</tbody>
</table>

*Tab. 1a: 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>Nr. of studies according to Kienle/Kiene 2003</th>
<th>Strongest reported advantage</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Cancer 5.4</td>
<td>Salzer/Havelec (1978), Salzer (1980a)</td>
<td>lung cancer case series</td>
<td>5.4</td>
<td>32</td>
<td>survival</td>
<td>3iii</td>
</tr>
<tr>
<td></td>
<td>Salzer (1987)</td>
<td>lung cancer case series</td>
<td>5.4</td>
<td>–</td>
<td>survival</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Krause/Erkan (1983)</td>
<td>lung cancer case series</td>
<td>5.4</td>
<td>–</td>
<td>survival</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Salzer (1980b, 1987)</td>
<td>lung cancer prospective randomised</td>
<td>5.4</td>
<td>33</td>
<td>survival</td>
<td>i ii</td>
</tr>
<tr>
<td></td>
<td>Salzer et al. (1991), Salzer (1987)</td>
<td>lung cancer prospective randomised</td>
<td>5.4</td>
<td>34</td>
<td>survival for lymph node positive</td>
<td>i ii</td>
</tr>
<tr>
<td></td>
<td>Dold et al. (1991)</td>
<td>lung cancer prospective randomised</td>
<td>3</td>
<td>35</td>
<td>quality of life</td>
<td>i ii</td>
</tr>
<tr>
<td>Malignant Melanoma 5.6</td>
<td>Kleeberg et al. 2004</td>
<td>malignant melanoma, stages II-III prospective randomised</td>
<td>5.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Augustin et al. 2005</td>
<td>malignant melanoma, stages II-III Cohorts with retrospective data collection</td>
<td>5.6</td>
<td></td>
<td>Tumour-dependent survival</td>
<td></td>
</tr>
</tbody>
</table>

Tab. 1b: Results of clinical studies and case series with Iscador

**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 randomized 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>
<thead>
<tr>
<th>Publication</th>
<th>Diagnosis</th>
<th>Chapter in this documentation</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, 5.4</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</td>
<td>No significant differences between the groups regarding tumour relapse and mortality.</td>
<td>183</td>
<td>2</td>
</tr>
</tbody>
</table>

**Tab. 1:** Results of randomised studies with Iscador