

# Efficacy and Safety of Chemo/Radio Therapy combined with Mistletoe in Breast Cancer

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**Gemeinschaftskrankenhaus Herdecke**  
**Germany**



# Agenda

- ❖ Oncology in Germany
- ❖ Gemeinschaftskrankenhaus Herdecke
- ❖ Complimentary medicine in Germany
- ❖ Mistletoe therapy
  - History
  - Studies on mistletoe
  - Side effects & contra indications
  - Case report
  - Conclusion



# Oncology in Germany

## ❖ 2 Oncological disciplines

- Haemato-oncology
- Gynaecological oncology

## ❖ Structure of cancer treatment in Germany

- Cancer centers (certified by the German Cancer Society DKG)
- Breast cancer centers – at least 150 primary diagnoses and about 200 women with metastases each year
- Gynaecological cancer centers – 50 primary diagnoses



# Gemeinschaftskrankenhaus Herdecke

## ❖ About the Hospital

- 12 departments
- 450 beds
- Around 1200 staff-members
- Run by a private non-profit organisation



# Gemeinschaftskrankenhaus Herdecke

## ❖ Anthroposophic Medicine

- We are an integrative health centre that combines cutting-edge skills and resources of a modern emergency hospital
- We have more than 40 years of experience in anthroposophic medicine
- We focus on the patient's individuality and her biography
- *We work on the basis of special cures, art therapy and provide distinctively humane care*

## ❖ Extended Therapy

- Rhythmic massage
- Rhythmic embrocations
- Wet packings
- Eurythmic therapy
- Full bath immersions with essential oils



# Gemeinschaftskrankenhaus Herdecke

- ❖ Set up to combine academic and practical experience:



**Witten/Herdecke University,**  
Faculty of Health,  
School of Medicine,  
Germany



**Department of Integrated Curriculum  
for Anthroposophic Medicine,**  
Gemeinschaftskrankenhaus Herdecke,  
University's academic hospital  
specialized on Integrative Medicine



# Anthroposophic Medicine

- ❖ Set up by R. Steiner and I. Wegmann in the early 20th century
- ❖ Physician-based complementary therapy
- ❖ Human beings are considered in their physical, emotional and spiritual dimensions
- ❖ Acknowledging pre-existential and post-mortal dimensions of spiritual existence
- ❖ Illness as an opportunity for personal growth
- ❖ Therapy based on self-healing processes
- ❖ Curative relationship between nature and man



# Gemeinschaftskrankenhaus Herdecke

## ❖ Interdisciplinary teams:

- Eurythmy Therapists
- Art therapists
- Massage therapists
- Surgeons
- Oncologists
- Anthroposophic nurses



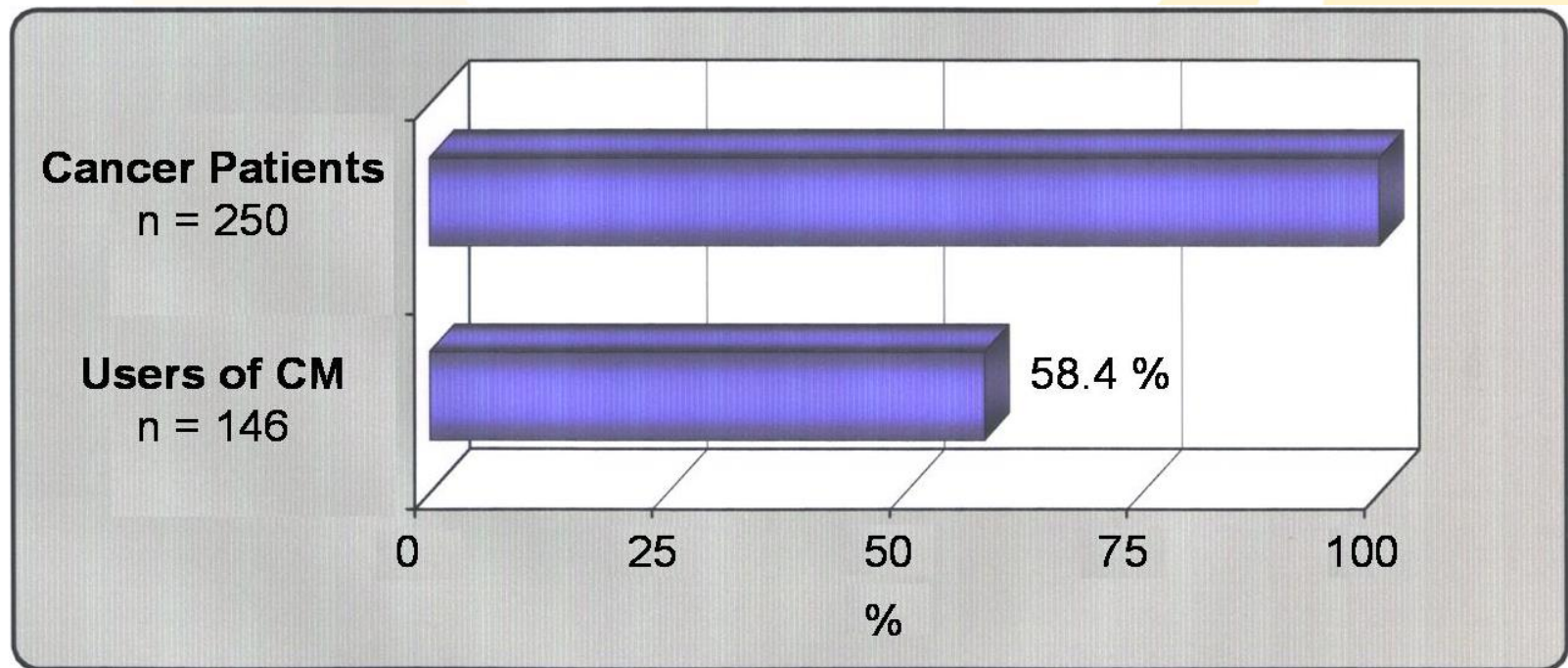


# Complementary Medicine in Germany



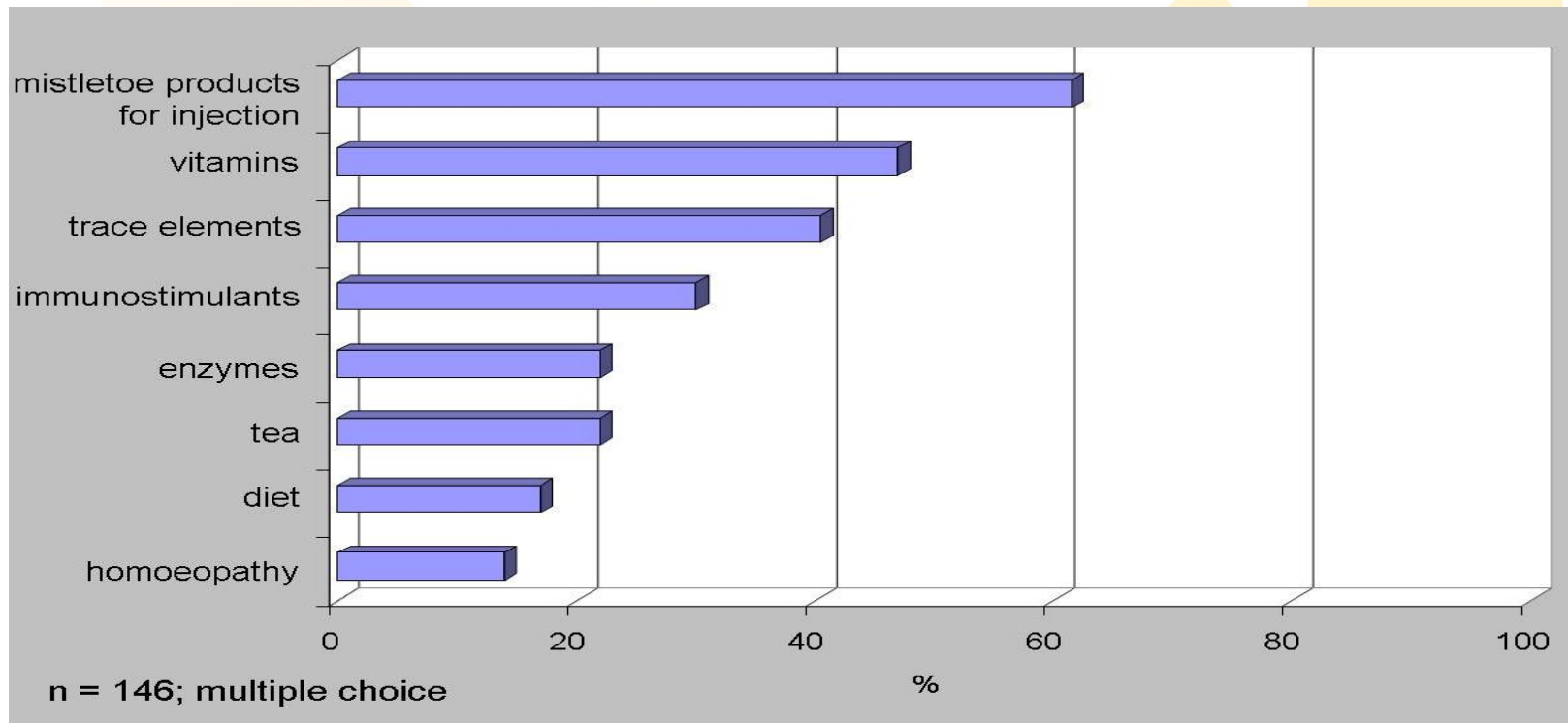
# Use of Complementary Medicine in Cancer patients

- ❖ A cross-sectional study in four German rehabilitation centers



# Use of Complementary Medicine in Cancer patients

## ❖ The most frequently used methods



# Mistletoe Therapy



# Mistletoe Therapy



# Mistletoe as method for healing

## ❖ Set up to combine academic and practical experience:

- 4th C. BCE: „spleen disease“, menstrual complaints (Hippocrates)
- 1st C. CE: epilepsy, infertility, ulcers (Plinius)
- 2nd C. CE: swelling, „tumors“ (Celsus)
- 16th C. CE: epilepsy, spleen/kidney disease, compresses to treat ulcers, fractures and labour pains
- 18th C. CE: labour pain, sore throat, pulmonary & hepatic diseases, lepra, fractures, mumps, hepatitis (Tabernaemontanus 1731)
- 19th C. CE: viscin ointment to treat eczema, ulcers, burns and initiate secondary wound healing (Riehl 1900; Klug 1906)

„ineffectual popular medicine“



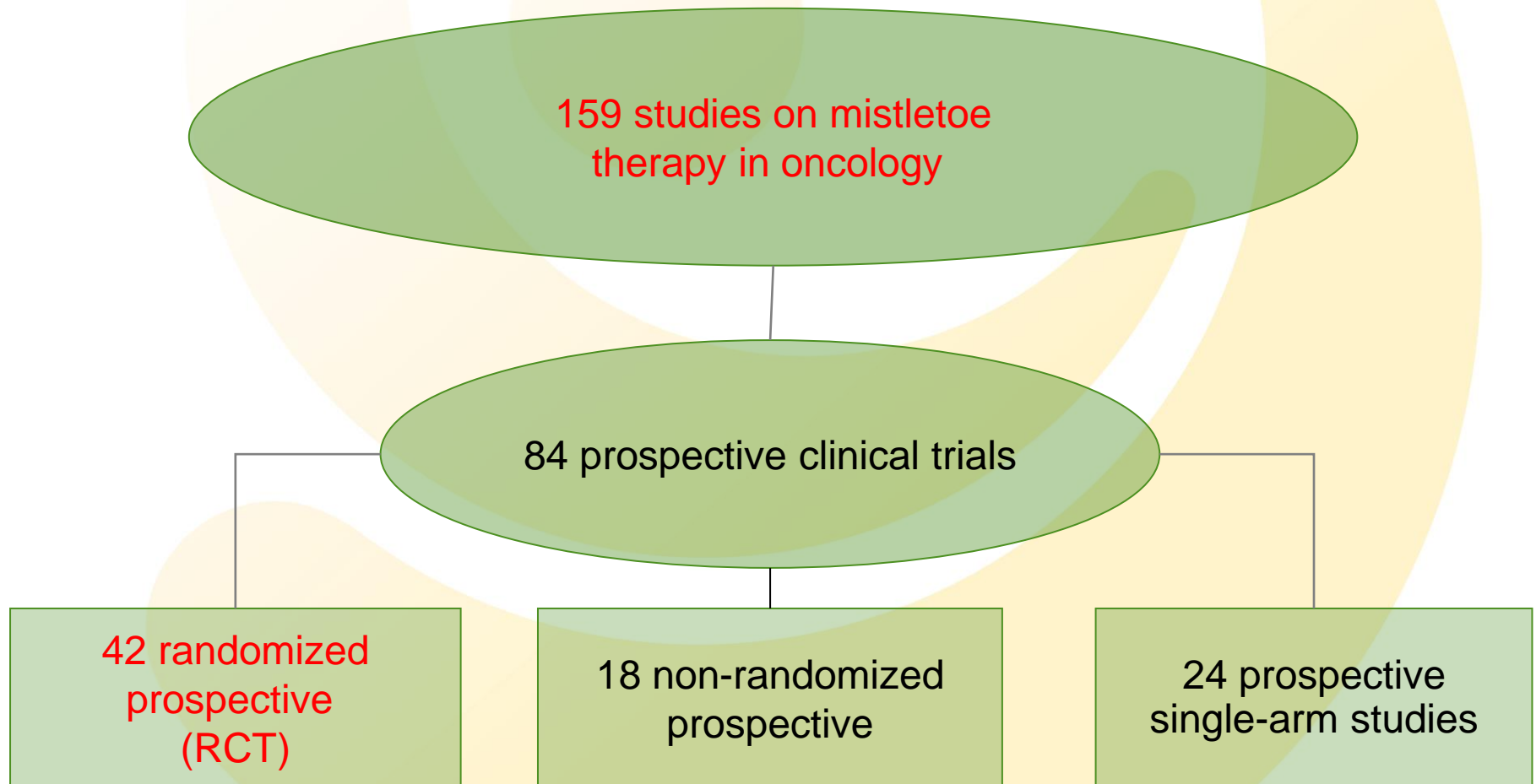
# Mistletoe

## ❖ One of the best investigated herbal drugs:

- Kienle & Kiene 2003: Die Mistel in der Onkologie, Schattauer Stuttgart, New York: *749 pages, 3261 references*
- Büssing 2000 (ed.): Mistletoe – The Genus *Viscum*, Harwood Academic Publishers: *265 pages, 959 references*
- Three reviews available:
  - ✓ Influence of *Viscum album* L (European Mistletoe) Extracts on Quality of Life in Cancer Patients: A Systematic Review of Controlled Clinical Studies (2010)
  - ✓ *Viscum album* L. extracts in breast and gynaecological cancers: a systematic review of clinical and preclinical research (2009)
  - ✓ Complementary cancer therapy: a systematic review of prospective clinical trials on anthroposophic mistletoe extracts (2007)

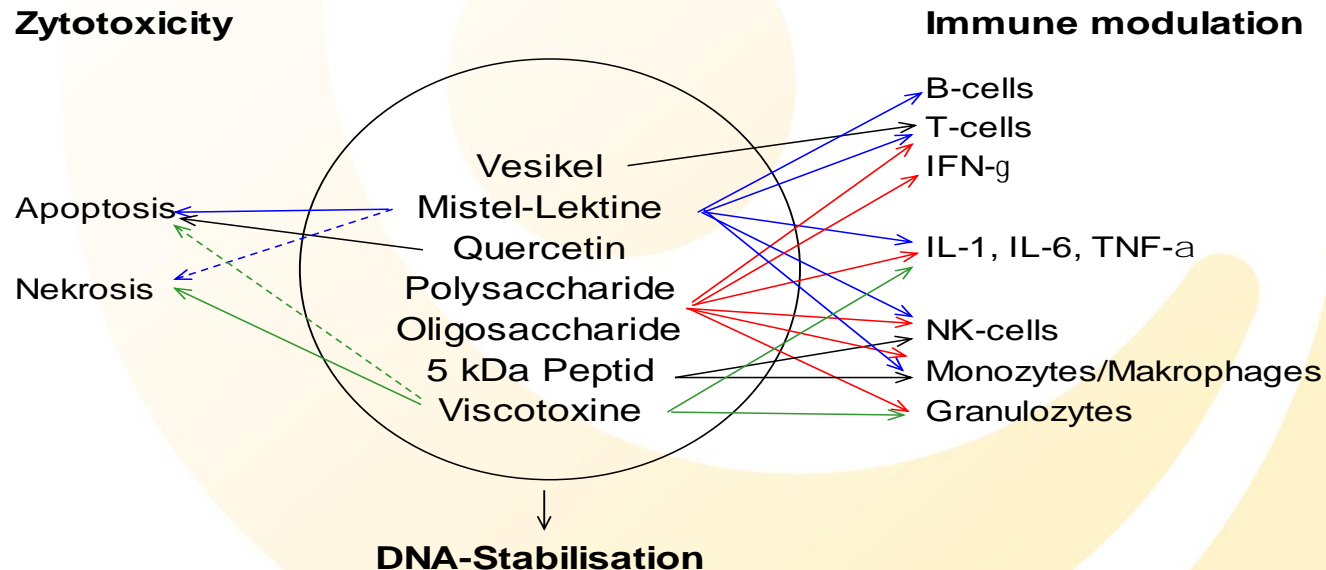


# Mistletoe treatment in oncology





# Active ingredients of viscum album



- **Flavonoide** (Homoeriodyctiol, Sakuranetin und verschiedene Quercetinmethyläther),
- **Phenylpropanoide** (Kaffee-, Sinapin-, Ferula-, Protocatechyl-, Syringin-, Vanillin-, Anis-, Gentisinsäure u.a.),
- **Triterpene** ( $\beta$ -Amyrin,  $\beta$ -Amyrinacetat, Betulinsäure, Oleanolsäure, Ursolsäure),
- **Phytosterole** ( $\beta$ -Sitosterol, Stigmasterol und ihre entsprechenden Glukoside),
- **Cyclitole** (Mannitol, myo-Inositol, Quebrachitol, Pinitol, Viscumitol),
- **Polysaccharide** (Methylester der Galacturonsäure, Rhamno-galacturonane u.a.),
- **Peptide** (Viscotoxine, Viscumamid),
- **Glykoproteine** (ML I [64,0 kDa], ML II [62,2 kDa], ML III [56,2 kDa], ViscalbCBA [10,8 kDa])



# Phase I Study (NCCAM, NIH, USA)

- Indication: Far advanced solid tumours (stage IV) (pancreas, colorectal, NSCLC and breast cancer)
- Objectives: Impact of Helixor<sup>®</sup> A on pharmacokinetics, pharmacodynamics and safety of gemcitabine (Gemzar<sup>®</sup>)
- Study design: monocentric phase I dose escalation study with 2 stages
- Patient numbers: 44 patients (21 f, 23 m, 29 - 81 years)
- Study centre: National Naval Medical Center, Bethesda, Maryland
- Study period: 09/2003 – 07/2007

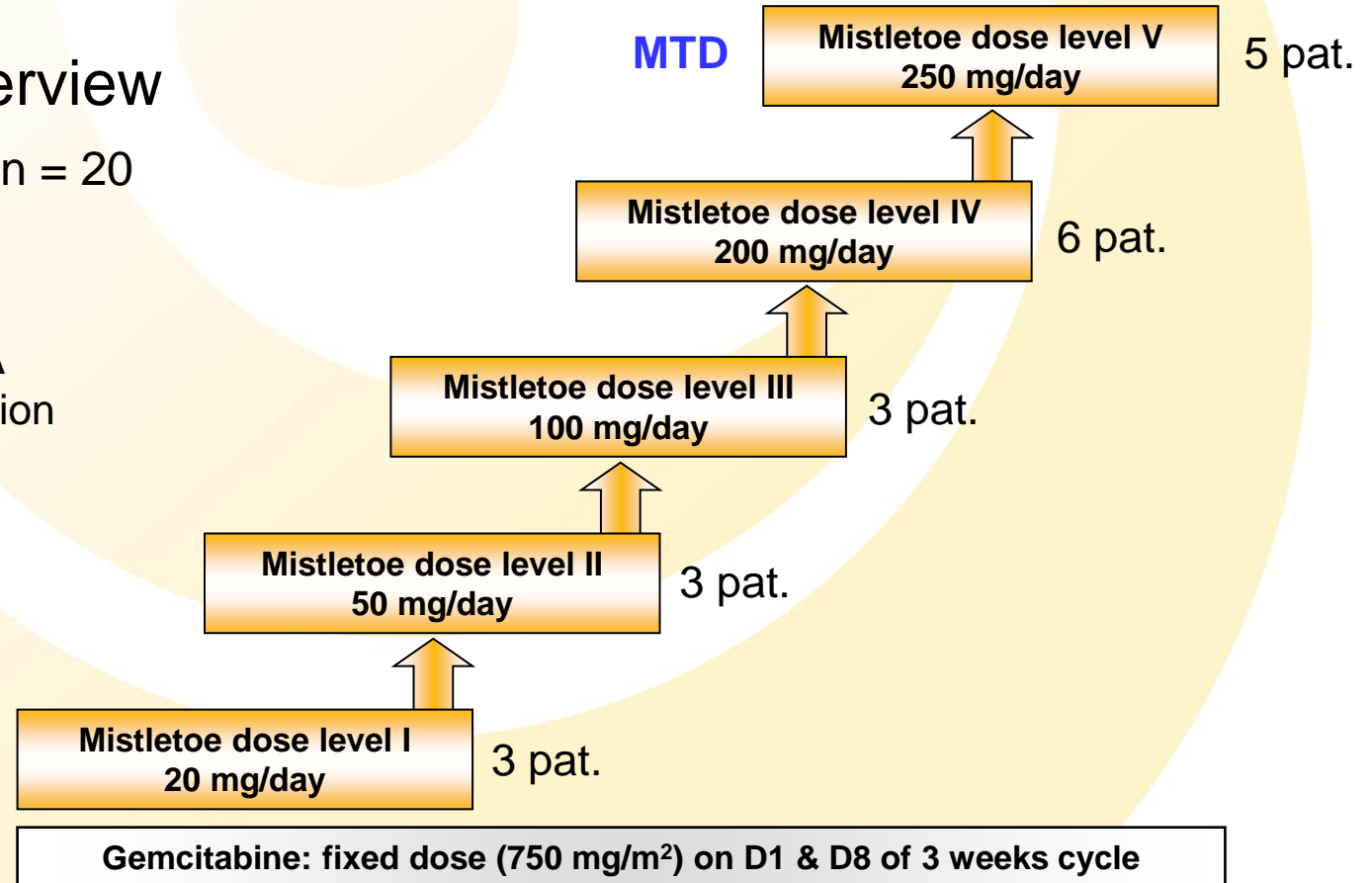


# Phase I Study (NCCAM, NIH, USA)

## ❖ Stage I overview

- enrolled: n = 20

**Helixor® A**  
dose escalation



Mansky, P. J. et al.: Onkologie 31: 200S, 2008; J Clin Oncol 28: 15S, 2010

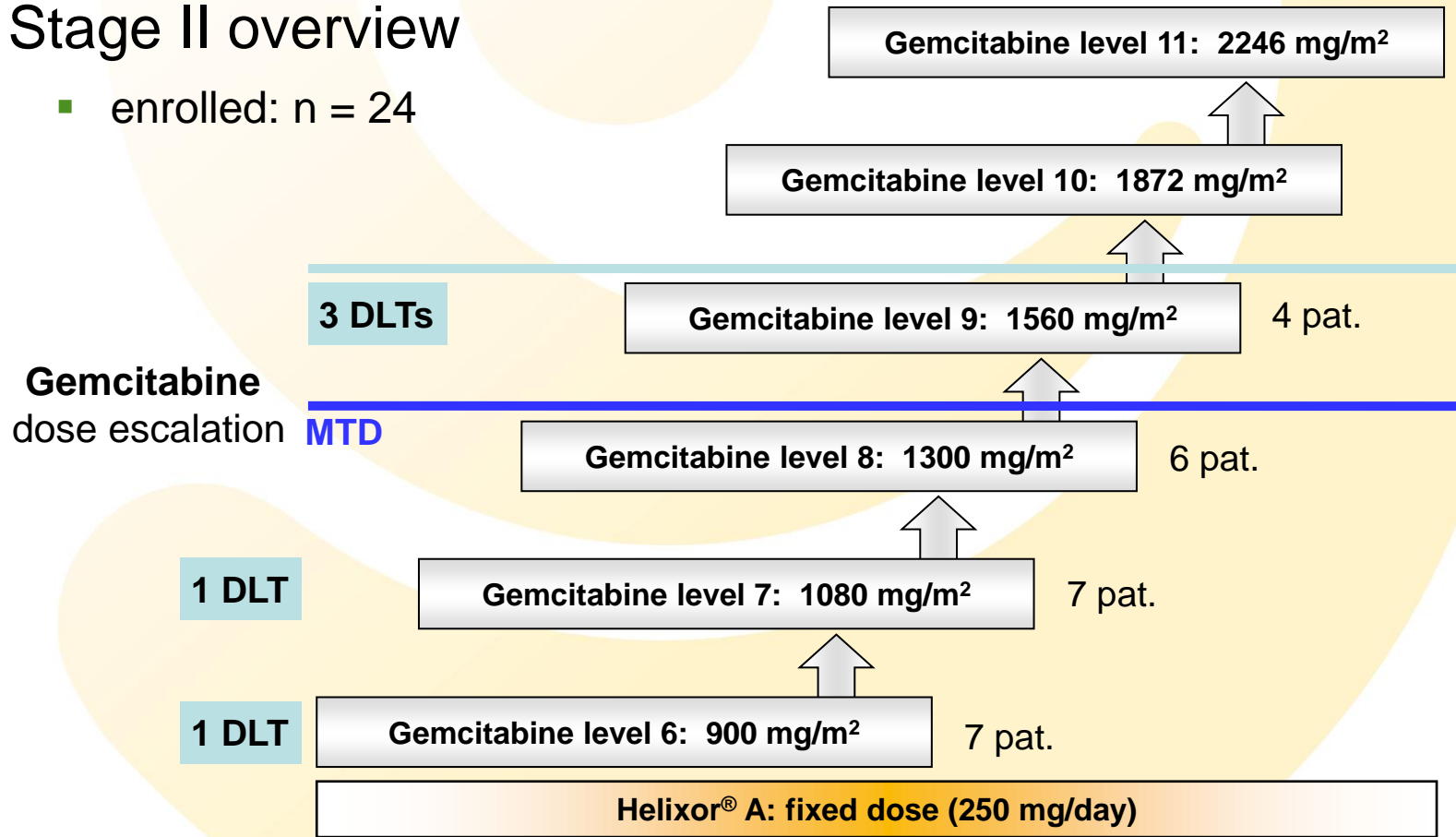
DLT: dose-limiting toxicity, MTD: maximum tolerated dose



# Phase I Study (NCCAM, NIH, USA)

## ❖ Stage II overview

- enrolled: n = 24



# Phase I Study (NCCAM, NIH, USA)

## ❖ Results

- No impact of Helixor<sup>®</sup> A on pharmacokinetics of gemcitabine
- Helixor<sup>®</sup> A: good tolerance and excellent compliance
- Gemcitabine: MTD 1,300 mg/m<sup>2</sup> (usually: 1,000 mg/m<sup>2</sup>)  
→ **dose increase of 30% during Helixor<sup>®</sup> A treatment possible**



# Phase I Study (NCCAM, NIH, USA)

## ❖ Conclusion

- Helixor<sup>®</sup> A enables a better tolerance of chemotherapy, allowing a 30 % higher dose of gemcitabine.
- In this way, a higher efficiency of chemotherapy might be expected.



# Influence of Complementary Mistletoe Therapy on Quality of Life in Breast, Ovarian, and Lung Cancer

## ❖ Question

- Influence of Helixor® on quality of life of cancer patients and on side effects of chemotherapy compared with Lentinan® (immunostimulating injection preparation made of basidiomycetes)
- Safety of Helixor®

## ❖ Study

- Multicentric (3), prospective, randomised, open

## ❖ Indication

- Non-small cell lung, breast, ovarian cancer



# Influence of Complementary Mistletoe Therapy on Quality of Life in Breast, Ovarian, and Lung Cancer

## ❖ Patients and method

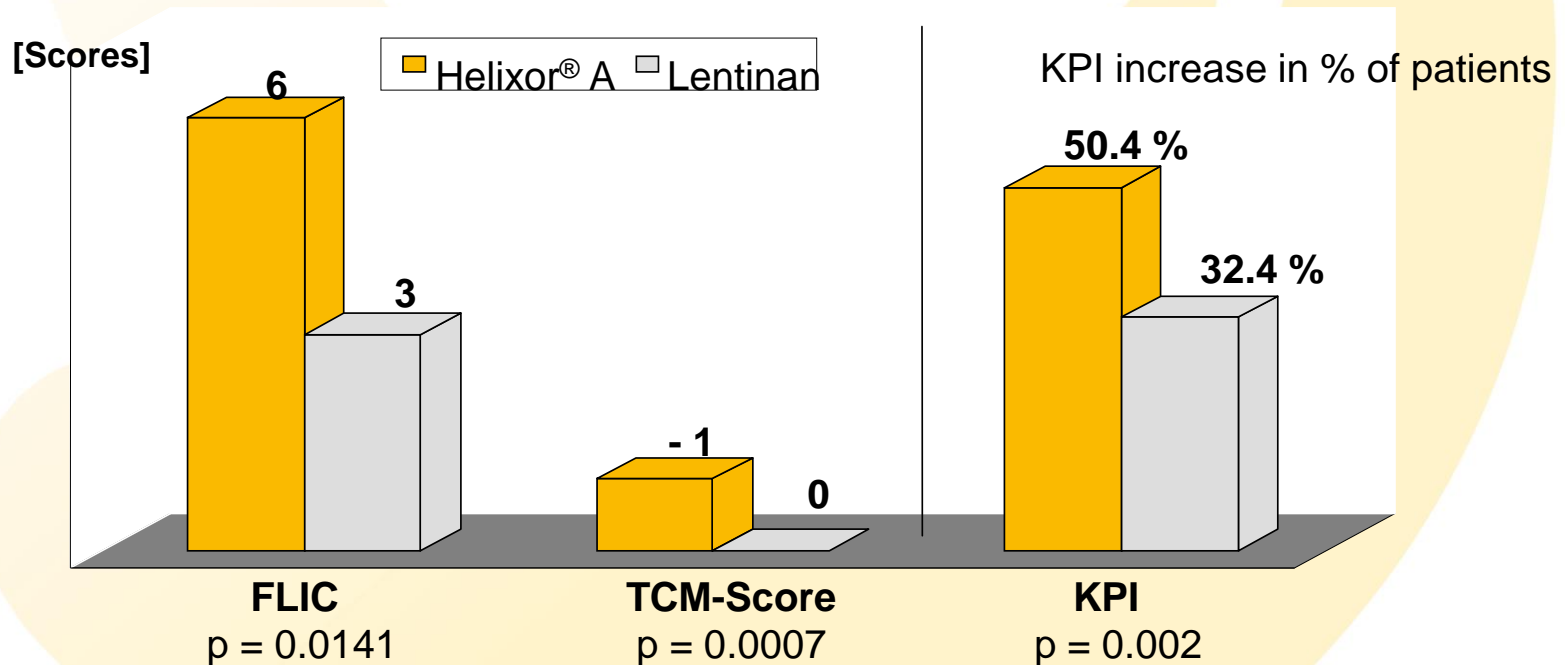
- 233 patients treated with standard chemotherapy
- Verum group:
  - ✓ additionally Helixor® A 3x/week s.c.
  - ✓ progressive dose increase 1 mg → 200 mg
- Control group: additionally Lentinan® 4 mg daily i.m.
- Recording of quality of life through 3 different measuring systems:
  - ✓ Karnofsky Performance Index = KPI
  - ✓ Functional Living Index Cancer = FLIC
  - ✓ Traditional Chinese Medicine Index = TCM Index
- Statistical analysis: Institute for Biometrics and Informatics of the Heidelberg University





# Influence of Complementary Mistletoe Therapy on Quality of Life in Breast, Ovarian, and Lung Cancer

## ❖ General Results / Quality of life



**FLIC** = Functional Living Index Cancer, **TCM-Score** = Traditional Chinese Medicine Score, **KPI** = Karnofsky Performance Index  
Piao, B.K. et al.: Anticancer Research 24, 2004, 303-310

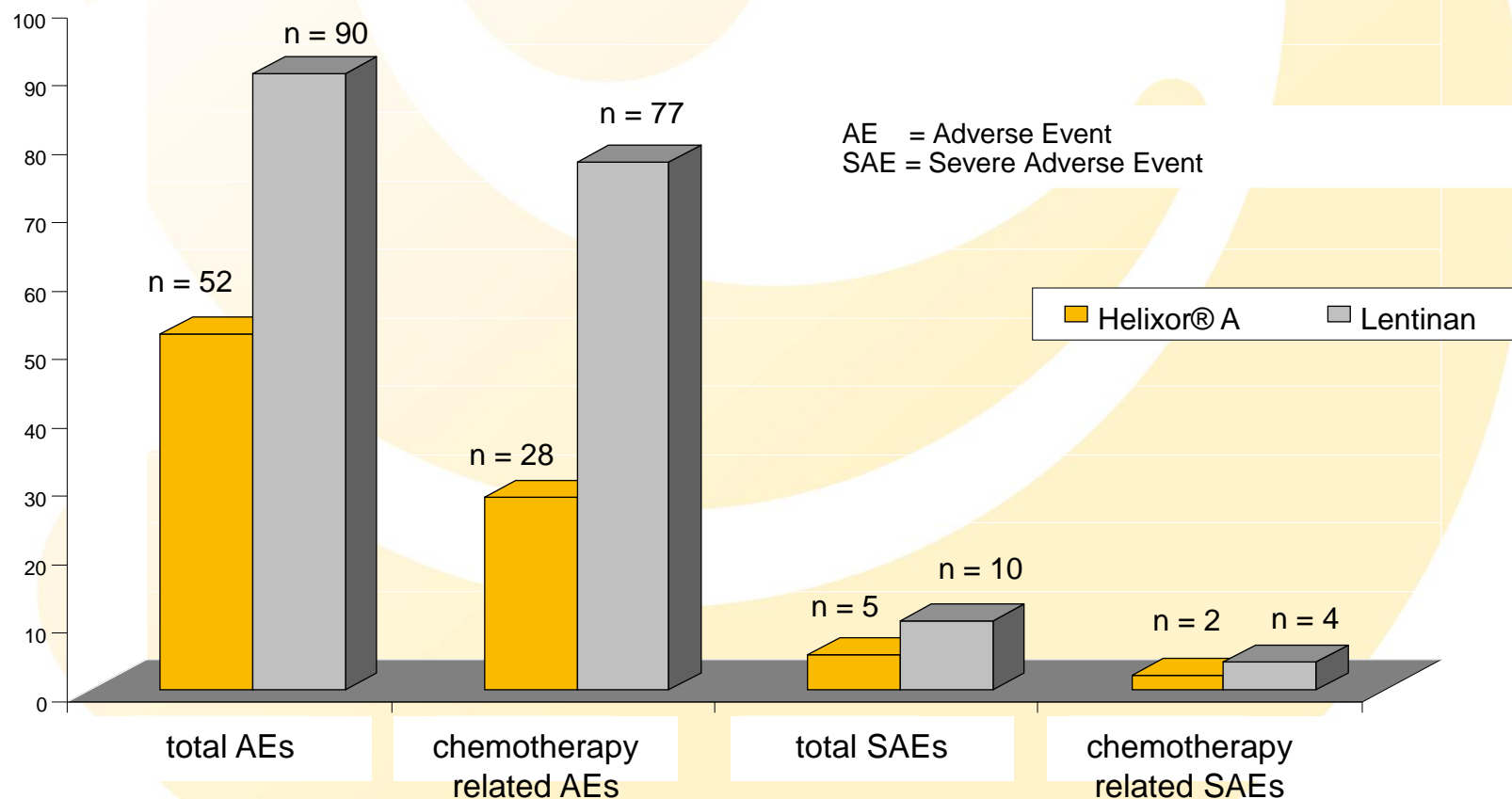


# Influence of Complementary Mistletoe Therapy on Quality of Life in Breast, Ovarian, and Lung Cancer

- ❖ Which QoL variables are significantly improved with mistletoe therapy?
  - Fatigue
  - Insomnia
  - Anorexia
  - Nausea
  - Pain
  - Physical activity



# Influence of Complementary Mistletoe Therapy on Quality of Life in Breast, Ovarian, and Lung Cancer



# Influence of Complementary Mistletoe Therapy on Quality of Life in Breast, Ovarian, and Lung Cancer

## ❖ Results

- *Significant increase of quality of life*
  - ✓ Results compliant within 3 indices for recording quality of life
- *Significantly fewer side effects of chemotherapy (i. a. nausea, vomiting, bone marrow depression, infections)*
- *Good tolerance and low rate of side effects with Helixor® A*
  - ✓ 7 x local reaction > 5 cm Ø at s.c. injection site
  - ✓ 4 x fever
  - ✓ 1 x angioedema and nettle rash



# Other modes of mistletoe therapy (Off-label)

Mode of Application	Indication
Intrapleural instillation	Malignant pleural effusion
Intraperitoneal instillation	Malignant ascites
Intralesional infiltration	Inoperable cancer
Intravenous infusion	Progressive cancer without response to standard treatment and Mistletoe Therapy s.c.



# Mistletoe Treatment in Clinical Setting Patient-centred individualised treatment

- ❖ Type of administration
- ❖ Frequency and intervals of administration
- ❖ Dosing of mistletoe
- ❖ Duration of administration



# Injection Frequency

Induction phase:

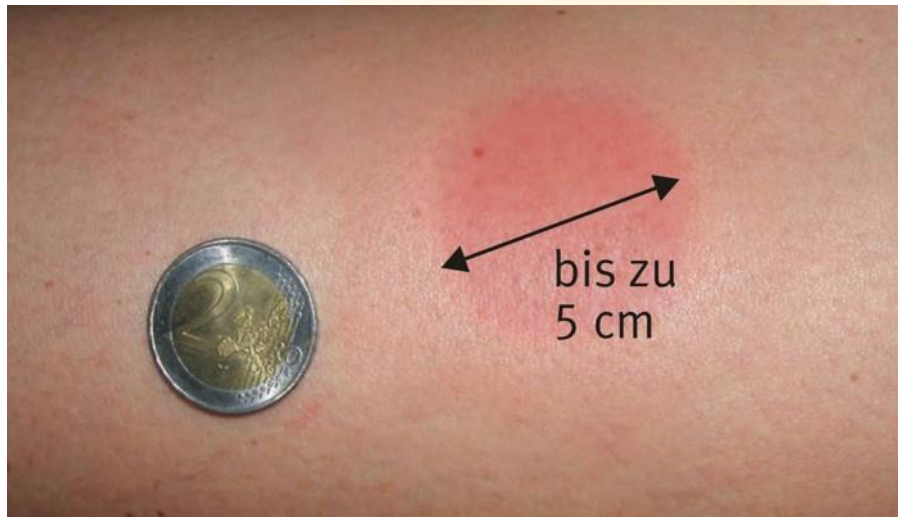
- Start with a low dosis
- Increase dosis gradually until positive patient response sets in

	Injections/Week
Adjuvant Therapy	3 x 1 Amp. s.c./week
Palliative Therapy	<i>Good general condition:</i> 3 x 1 Amp./week  <i>Week general condition, fast disease progrss:</i> daily injection

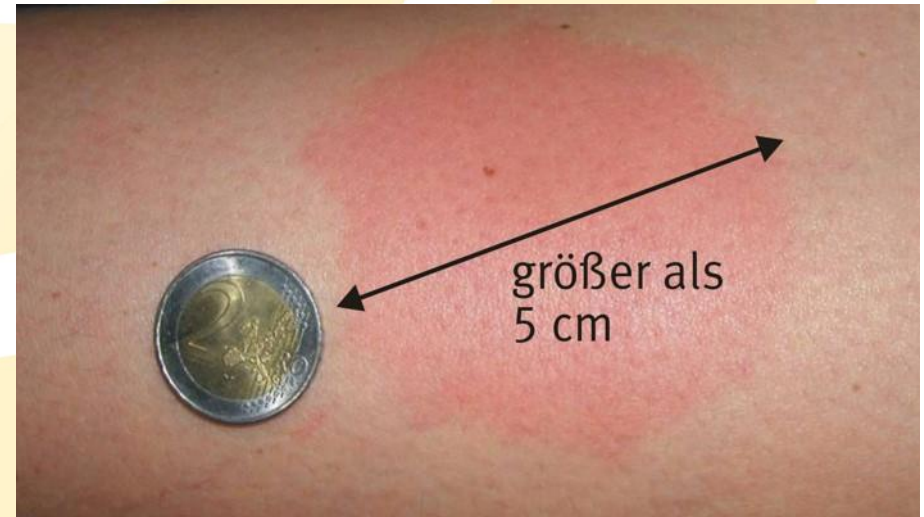


# Local Reaction to Mistletoe Therapy

Desired local reaction



Excessive local reaction





# Temperature rise following subcutaneous mistletoe injection

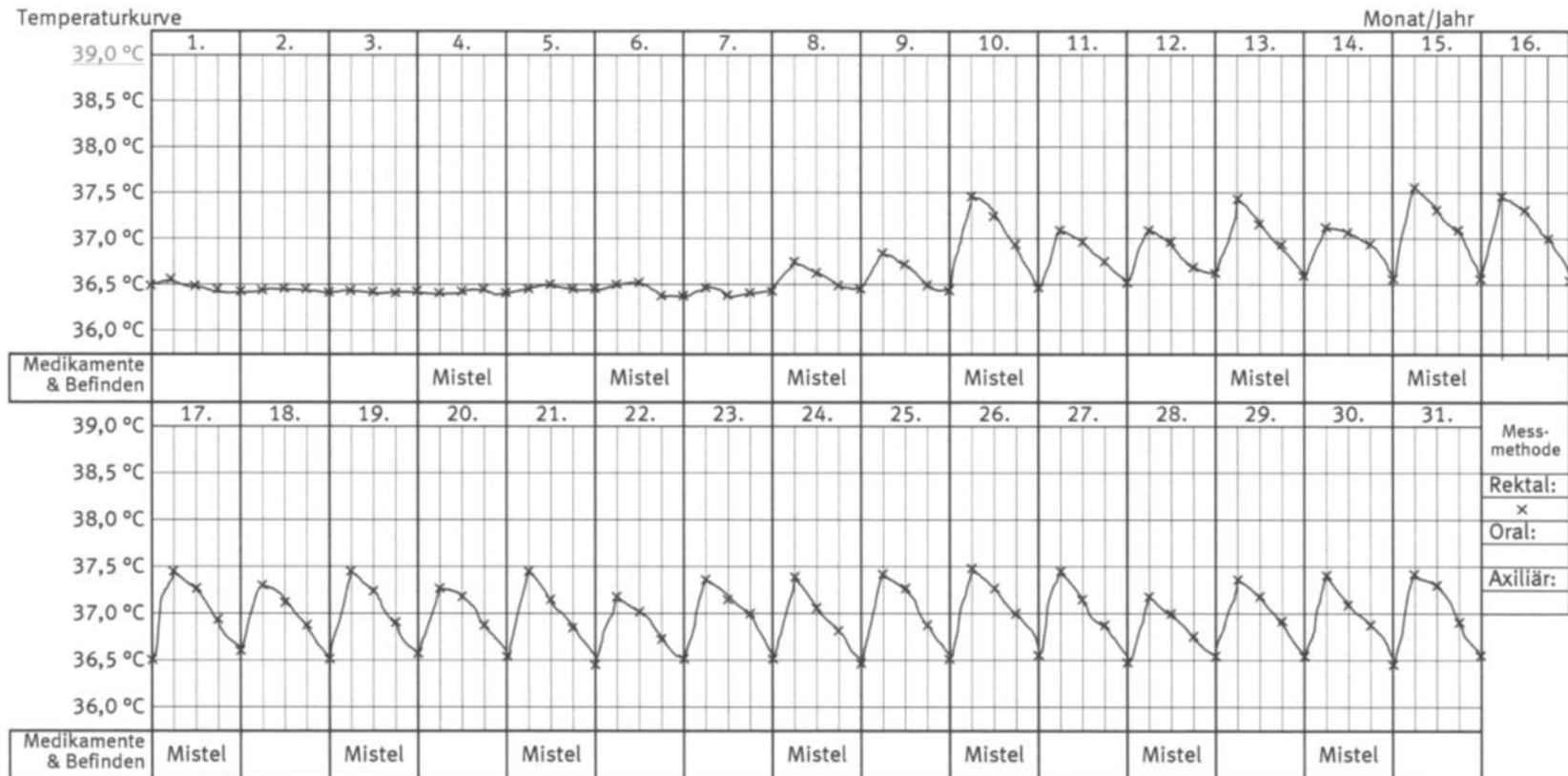


Abb. 1: 56 jährige Patientin S.K. mit Mammakarzinom und circadianer Temperaturstarre. Unter den 3 x pro Woche durchgeführten Mistelinjektionen (HELIXOR® M) kommt es zu einer ausgeprägten circadianen Temperaturregulation mit Temperaturdifferenzen von 1 °C.

Quelle: Matthes, H.: in Scheer, R. et al. (Hrsg.) Die Mistle in der Tumorthherapie, Grundlagenforschung und Klinik. KVC-Verlag Essen 2001, 253 - 274



# Recommended Follow-Up

- ❖ A MUST: Talk to the patient about her mistletoe therapy and what effects she experiences
- ❖ Communication will make or break the therapy
- ❖ There is no therapeutic effect without communication



# Case report



# Case report

- ❖ 08/1994 ED Mammakarzinom links; BET und Axilladiss. links: pT1c, pN1bi (1/14), G3, M0, R0
- ❖ 04/1997 **1. Rezidiv**
- ❖ 04/1997 Mamma TE links, Ablatio Mammae links, multifokales duktales Mammakarzinom rpT4b, G3, **Immunhistochemie status idem**
- ❖ 05/1997 **Mistletoe mali, jeden 2. Tag 1 Amp. sc.**
- ❖ 01/1999 **2. Lokoregionäres Rezidiv Axilla** invasiv duktal, ER positiv, PR positiv, HER-2/neu negativ
- ❖ 01/2001 **3. Lokalrezidiv der Axillanarbe.** Invasiv duktal G2
- ❖ 04/2002 **4. Pektorales Rezidiv** rpT1b, G2, ER positiv, PR positiv



# Case report

- ❖ 2003 5. Rezidiv im Bereich der Ablationarbe.
- ❖ rpT1c, G2,ER positiv, PR positiv, HER-2/neu neg.
- ❖ 07/2005 Maligner Pleuraerguß
- ❖ Immunhistochemie bleibt gleich
- ❖ 07/2005 Pleurodese mit 10 mg Mistletoe M
- ❖ 8/200 Sicherung der ossären Metastasierung (rechter Humerus, rechter Femur, Becken und und BWS)
- ❖ 07/2005 Antihormonelle Therapie mit Zoladex und Tamoxifen (Umstellung nach 2 Monaten auf Zoladex + Arimidex) und Zometa-Infusionen



# Case report

- ❖ 2009 Umstellung von Zoladex+Arimidex auf Faslodex+Femara  
Umstellung von Aredia auf Bondronat i.v.
- ❖ 01/2010 **6. Rezidiv** im Narbenbereich Thoraxwand links,  
Immunhistochemie idem, (0,4cm)
- ❖ 06/10 Bei vergrößerten Ovarien bds.  
V. a. Ovarialmetastasen DD Ovarial NPL.
- ❖ 28.06.2010: **7. Rezidiv Thoraxwand**  
Laparoskopische Adnexektomie bds. mit SSU.Histologie: Adnexe links und rechts, beidseits mit je einer **Metastase eines mäßig differenzierten Adenokarzinoms im Ovar.**  
Aszites ohne Nachweis maligner Zellen; ER 100% pos., IRS 12, PR 100% pos., IRS. 12, HER-2/neu Score 1+



# Conclusion

## ❖ Mistletoe therapy

- Improves the quality of life in cancer patients
- Increases the tolerance to chemo/radiotherapy
- Is safe



# Greetings from Germany





# Annex



GEMEINSCHAFTSKRANKENHAUS  
HERDECKE

Quelle: Melzer, J. et al.: Efficacy and Safety of Mistletoe Preparations, Forschende Komplementärmedizin 2009; 16: 217 - 26

# Side effects of mistletoe therapy

## ❖ Excellent side effect profile

Side effects	Occurrence	Measures
Local inflammation at s.c. site of injection > 5 cm	very often (induction phase)	→ Interruption of therapy until ease-off of symptoms
fever > 38 ° C, flu-like concomitant symptoms	often	→ Dose reduction
Swelling of regional lymph nodes	rarely	→ No antiphlogistic or antipyretic agents
Allergic reactions (urticaria > drug-induced exanthema > Quincke oedema > dyspnoea)	occasionally	→ Common antiallergic therapy
Anaphylactic reaction	isolated cases	
Activation of inflammation	isolated cases	→ Interruption of therapy until ease-off of symptoms. Clean up site



# Mistletoe contraindications

Contra-Indications	Measures
Allergy to mistletoe preparations	Anti-ML-IgE*-pos.: Helixor® to be stopped; no further therapy with ML-containing mistletoe preparations Anti-ML-IgE*-neg.: Start again with ½ Amp. Helixor® A 0,01 mg
Acute inflammatory disease, disease involving high fever	Interrupt therapy until ease-off of symptoms
Acute hyperthyreosis with tachycardia	Hyperthyreosis to be controlled with drugs, then Helixor® A in prudent dosage
Chronically granulomatous disease and florid auto-immune disease, also when under immuno-suppressive therapy	Helixor® A in prudent dosage (only if disease is stable and if no more immuno-suppressive therapy is required)

