



## Quality of life in breast cancer patients during chemotherapy and concurrent therapy with a mistletoe extract

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### ABSTRACT

**Background:** The effects of standardized aqueous mistletoe extracts on Health Related Quality of Life (HRQoL) of tumor patients needs further evaluation.

**Methods:** In this non-interventional, prospective clinical investigation the longitudinal course of Quality of Life of 270 breast cancer patients during adjuvant chemotherapy and mistletoe therapy with abnobaVISCUM® Mali was investigated. HRQoL was measured 4 times by self-assessment with the QLQ-C30 and QLQ-BR23 questionnaire of the European Organization for Research and Treatment of Cancer (EORTC): at the beginning of mistletoe- and chemotherapy, 4 weeks later, at the end of the chemotherapy and 4 weeks after finishing chemotherapy. Secondary objectives were the tolerability and safety of mistletoe therapy in combination with chemotherapy under conditions of daily practice.

**Results:** After an initial deterioration the average range of all obtained QLQ-C30 function scales ( $n = 262$ , 48.9–71.5) remained stable even at the last chemotherapy cycle and improved significantly ( $p < 0.0001$ ) to 66.9–80.7 4 weeks later, compared to the initial visit. Also the QLQ-BR23 function scales significantly improved ( $p < 0.0001$ ) 4 weeks later. The symptom scales of the QLQ-C30 remained stable under chemotherapy even at the final chemotherapy cycle and decreased from 16.2 to 44.1 at the initial visit to 11.2–29.9 ( $p < 0.001$ ) at the final visit. These results were comparable to the subgroup with initial visit before chemotherapy ( $n = 114$ ) in which rather stable function scales during chemotherapy (difference of the mean values: 9.6 to –3.7) and only little increase of symptoms (difference: 13.2 to –4.9) was measured. The tolerability of the therapy was judged by the physicians as good or very good for 91% of the patients and the efficacy was rated as good or very good for 94%. 89% of the patients reported about a good or very good benefit.

**Conclusion:** The overall results point to a relevant stabilisation of Health Related Quality of Life during various chemotherapy regimes, possibly due to a reduction of chemotherapy caused side effects with an excellent tolerability of the mistletoe therapy.

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### Introduction

Health Related Quality of Life (HRQoL) and reduction of side effects play more and more an accepted and important role for the treatment of cancer patients (Bottomley and Therasse 2002) (<http://www.uni-duesseldorf.de/AWMF/awmfleit.htm>). To objectify and standardize HRQoL numerous questionnaires have been developed (Shimozuma 2002). Several studies support the often-reported clinicians' finding that mistletoe therapy can improve HRQoL and reduce side effects in cancer patients (Kröz et al. 2002; Horneber et al. 2008). They are attributed to effects of mistletoe preparations on parameters of the cellular immune system and

endorphin levels (Heiny et al. 1998; Büssing et al. 2007; Schink et al. 2007). Data about HRQoL during daily practice are lacking.

In this non-interventional, prospective clinical investigation the effects of a mistletoe therapy with abnobaVISCUM® Mali in HRQoL of breast cancer patients during chemotherapy was evaluated under conditions of daily practice. It also yields data of the tolerability of abnobaVISCUM® Mali, the compliance of the patients and the possible clinical relevance of the effects on HRQoL.

### Patients and methods

#### Study design

A multicenter, prospective, non-interventional investigation according to § 4 Section 23 of the German Medicines Act was performed in the whole area of Germany according to the recom-

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recommendations of the **Federal Institute for Drugs and Medical Devices** (1998). Data were analysed with the statistical program SAS® (V. 9.1). Completeness and plausibility of the data were automatically checked and, in case of questions, clarified by contact with the responsible physician. Concomitant diseases and adverse events were coded according to MedDRA® (V. 9.0).

Patients should be included and start mistletoe therapy with beginning of chemotherapy. Baseline investigations were the comprehensive patient history, Karnofsky index (KPI) (Karnofsky et al. 1948), age, body mass index (BMI) and HRQoL measured with the validated questionnaires EORTC QLQ-C30 and EORTC QLQ-BR23 (Aaronson et al. 1993; Sprangers et al. 1993).

HRQoL was measured again 4 weeks after the initial visit (1. control visit) and at the end of chemotherapy (2. control visit). The final examination, which included in addition to the baseline investigations dosing of the mistletoe preparation, adverse events as well as tolerability and efficacy from the view of the patient and physician, was terminated 4 weeks after the end of chemotherapy. Tolerability and efficacy were measured on a rating scale (1 = extremely bad, 2 = moderate, 3 = good, 4 = excellent).

#### Patients

18–70-year-old patients with breast cancer stages I–III and planned adjuvant chemotherapy after surgery were included in the observational study. Patients with stage IV disease, KPI < 60%, neo-adjuvant chemotherapy, severe concomitant diseases, inability to answer the questionnaires and previous mistletoe treatment were excluded.

#### Medication

Patients should receive subcutaneous injections with abnobaVISCUM® Mali 3 times a week one ampoule (=1 ml) according to the product information of the manufacturer (Abnoba GmbH 2003)<sup>1</sup> in parallel to adjuvant chemotherapy. AbnobaVISCUM® Mali is admitted as adjuvant cancer treatment in Germany. The initial dose was 0.02 mg (2.5 weeks), which should be increased to 0.2 mg for 5 weeks thereafter and could, according to tolerability and local reactions at the site of injection, be further increased to 2–20 mg. AbnobaVISCUM® Mali 0.2 mg contains about 90 ng mistletoe lectin (ML)/ml, the ML-concentrations in higher doses are respective. The injections were documented in the case report forms. All kinds of adjuvant chemotherapies were allowed.

By the marketing authorisation in Germany abnobaVISCUM® is classified according to the Ph. Eur. monograph 01/2008:0765 EXTRACTS as “other extract”. For “other extracts” the therapeutic active principle is the whole extract. Thus, it is not allowed to declare a certain content of a single constituent. “Other extracts” are determined by the production process with meticulously defined specifications resulting in pharmaceutically comparable extracts. For further information please contact Abnoba GmbH (Dr. J. Eisenbraun, e-mail address: [info@abnoba.de](mailto:info@abnoba.de)).

#### Outcome parameters and questionnaires

Main outcome parameter was the course of HRQoL. The EORTC QLQ-C30 questionnaire is standardized and validated for cancer patients during chemotherapy (McLachlan et al. 1998). The QLQ-BR23 questionnaire is specifically designed for breast cancer patients (Nagel et al. 2001) and is used complementary to the QLQ-C30. The questionnaires were filled out from the patients during the

visits. The QLQ-C30 questions comprise the current condition of the patient (questions 1–5) or the last week (questions 6–30), the BR-23 the last week (questions 31–43) or the last 4 weeks (questions 44–53).

Further parameters were: efficacy and tolerability from the view of the patients and physicians, adverse events, accordance of practical treatment with recommendations of the manufacturer and compliance. Characteristics of the patients and the tumor, antitumoral therapies, concomitant diseases and concomitant medication were meticulously documented.

#### Statistics

Due to the explorative character of the study descriptive statistics was used. Quantitative parameters were described by mean, standard deviation, minima and maxima. For qualitative and ordinal data, absolute and relative frequencies were calculated. HRQoL baseline scores were compared to HRQoL scores at the final visit with the Wilcoxon test for connected samples. In subgroup analyses the impact of the variables tumor stage, KPI and time interval between inclusion in the study and start of chemotherapy on HRQoL was analysed with covariance analysis (ANCOVA). For this purpose, baseline adjusted differences between baseline and final examination were tested two sided with a 95% interval of confidence. To describe the change of the HRQoL-parameters during the period of chemotherapy the mean value with upper and lower limit of the 95% confidence interval was calculated.

270 patients were planned for this study. This number enables with 95% probability the detection of adverse events with an incidence of 1.2% and allows robust statements about effects of abnobaVISCUM on HRQoL.

#### Results

Between March 2004 and June 2006 271 patients were included in the study. In 1 patient only baseline was documented and she was therefore excluded from analysis. 270 data sets were obtained, analysed and included in the evaluation. 84 physicians from hospital outpatient centres and own practice as oncologists, internists or gynaecologists participated in the study. Patient characteristics are shown in Table 1.

Mean time interval between initial diagnosis and baseline investigation was 10.8 weeks. 68.1% had an invasive carcinoma. 123 patients (45.6%) had concomitant diseases. Most frequently vascular diseases (16.3%) were documented, followed by arterial hypertension (14.4%) and metabolic diseases (10.7%). 113 patients (41.9%) had concomitant medication, most frequently ( $n=44$ , 16.3%) for the treatment of cardiovascular disease and hypertension (beta blockers, calcium channel blockers, angiotensin inhibitors).

First follow up (1, control visit) was  $4.6 \pm 1.3$  weeks, second control visit (end of chemotherapy)  $16.9 \pm 6.9$  weeks and the final investigation  $22.1 \pm 7.8$  weeks after the baseline investigation. The KPI remained stable throughout the observation period (baseline = 84.1%, final investigation = 85.4%).

#### Chemo- and mistletoe therapy

59.6% of the patients were included at the beginning of chemotherapy ( $\pm 1$  week), 18.5% had chemotherapy >1 week prior to inclusion and in 16.3% chemotherapy started >1 week after inclusion with chemo- and mistletoe therapy. Mean duration of chemotherapy was  $17.7 \pm 7.1$  weeks. Most frequently CMF (cyclophosphamide, methotrexate, 5-fluorouracil) was used (49.3%). EC (epirubicin, cyclophosphamide) was used in 25.6%, AC (adriamycin, cyclophosphamide) in 8.5%, FEC (5-fluorouracil,

<sup>1</sup> AbnobaVISCUM.

**Table 1**

Characteristics of the patients (percentage or mean  $\pm$  standard deviation, maxima, minima,  $n = 270$ ).

Age (years)	55.3 $\pm$ 10.1 31–80
BMI (kg/m <sup>2</sup> )	26.6 $\pm$ 4.8 18.1–58.5
Karnofsky index (%)	84 $\pm$ 11 60–100
UICC stage (%)	
I	18.5
II	42.6
III	10.4
IV	4.4
Estrogen receptor status (%)	
Positive, negative, not known	60.7, 29.6, 9.6
Progesterone receptor status (%)	
Positive, negative, not known	40.7, 41.5, 17.8
HER-2 receptor status (%)	
Positive, negative, not known	15.6, 49.3, 35.2
Operation (%)	
Quadrant resection	52.6
Radical mastectomy	37.4
Thylektomie	4.4
No operation	4.8
Unknown	1.9

epirubicin, cyclophosphamide) in 11.1% and FAC (5-fluorouracil, adriamycin, cyclophosphamide) in 1.1%. Paclitaxel was added or was part of 7.4% of the chemotherapy schedules. Most patients received 4 (20.0%) or 6 (54.8%) cycles. 54.4% ( $n = 147$ ) reported about good or excellent tolerability of chemotherapy. During the study period 53.3% of the patients received an additional radiotherapy, 48.5% an antihormonal therapy.

Concomitant mistletoe therapy with abnobaVISCUM<sup>®</sup> Mali started  $1.4 \pm 6.4$  weeks after start of the chemotherapy. The mean duration was  $20.3 \pm 10.3$  weeks, reflecting the time between inclusion and final investigation ( $22.1 \pm 7.8$  weeks). Injection of abnobaVISCUM<sup>®</sup> Mali complied in most cases to the recommendations of the manufacturer: it was injected subcutaneously 3 times a week (76.5%, no information 17.6%) and 96.7% (260 patients) were treated according to the recommendation to start with dosage 0.02 mg. An increase to 0.2 mg was performed in 92.2% (249 patients). A second increase of dosage was performed in 192 (71.1%) of these patients; in 84.9% to 2 mg. All in all 60.2% (167 patients) had the recommended dose escalation from 0.02 mg to 0.2 mg to 2 mg, 17.8% followed only the first dose escalation from 0.02 mg to 0.2 mg.

#### Tolerability

Local reactions at the site of injection, which are typical for mistletoe lectin containing mistletoe preparations (Huber et al. 2005) were documented in 235 patients (87%). They were in 182 patients (77.4%) smaller than 5 cm in diameter. Physician-reported systemic side effects were lassitude in 33%, headache in 24.1% and unspecific malaise in 18.9%. These side effects were expected. Furthermore, 1 case of dizziness and 1 case of dermatitis were documented as adverse event, which are also known as possible side effects (Abnoba GmbH 2003). All these symptoms were mild and disappeared in most cases 1 day (56.3%) or 2 days (20%) after injection (19.6% not specified). Only 4.1% of the patients reported symptoms for more than 2 days. Tolerability of the mistletoe therapy was therefore estimated as good or excellent in 91.1%.

One severe adverse event, a patient who developed necrotizing colitis, occurred. The relation to mistletoe therapy was, how-

ever, regarded as unlikely from the treating physician, because it was a typical adverse event of the chemotherapy (Doxetaxel). 47.8% of the patients indicated no, 40.4% indicated occasional limitations due to the mistletoe treatment. Only 8.5% indicated confinements due to this therapy. 17 patients (6.3%) stopped therapy with abnobaVISCUM<sup>®</sup> Mali before the final examination. The most frequent reason was the discomfort due to regular injections.

#### Physician and patient rated efficacy, immunological parameters

Physicians' rated general well being was improved (final investigation compared to baseline) in 235 patients (87%), mental health in 191 patients (70.7%) and disease coping was improved in 135 patients (50%). 121 patients (44.8%) had improved appetite, 96 (35.6%) improved sleep and 93 (34.4%) less pain. Immunological parameters, obtained within the scope of regular therapy, were documented for 130 patients. 70% of these patients had an increase of leukocyte counts, 45.5% an increase of lymphocyte counts and 26.2% an increase of eosinophils, which is typical for treatment with mistletoe lectin containing mistletoe preparations (16). Physicians' rated efficacy was good or excellent in 93.7% of the patients.

The majority of the patients (88.9%) estimated efficacy of the mistletoe therapy as good or excellent. 65.6% would definitely recommend the therapy to other patients, 19.3% probably, 7% only in certain conditions and 3% probably not. One patient would not recommend the therapy, 4.8% of the patients did not specify.

#### Quality of life

262 complete QLQ-C30 and 260 complete QLQ-BR23 questionnaires were obtained from the patients and included into analysis. QLQ-C30 and QLQ-BR23 function scores at the 4 examinations are shown in Table 2. Higher values (range between 0 and 100) indicate improvement. Most parameters deteriorated during chemotherapy 4 weeks after baseline investigation but improved at the end of therapy to above baseline levels. This improvement at the final examination was, compared to baseline, significant for all parameters of the QLQ-C30 and QLQ-BR23 function scales ( $p < 0.0001$ , Table 2). Symptom scales showed a similar course. A decrease indicates amelioration of the symptoms. All QLQ-C30 symptom scales improved significantly ( $p < 0.0001$ , Table 3), as well as symptoms of breast and arm. Sexual interest was, however, not improved. A part of the patients started chemotherapy before the first visit. The baseline scores of these patients thus were influenced by chemotherapy. In Tables 2 and 3 additionally the values of the subgroup with unaffected baseline scores are listed.

In Tables 4 and 5 the changes between beginning and end of chemotherapy are displayed. The physical function scale deteriorated only minimal during chemotherapy, the global health status and the other functional scales remained stable with a trend to improved scores, especially the emotional functioning and the future perspective (Table 4). The symptom levels of the general questionnaire C30 mostly remained stable with a trend to improved scores (Table 5). The symptoms directly affected by chemotherapy (nausea/vomiting and diarrhoea) aggravated slightly. The systemic therapy symptoms- and hair loss-scale of the BR23 were clearly influenced by chemotherapy and aggravated, especially in the subgroup with the unaffected baseline, whereas the breast and arm symptoms improved distinctly. The improvements of the subgroup with baseline values unaffected from chemotherapy generally were smaller and the deteriorations were larger compared to the whole study population, but in the same range.

**Table 2**  
QLQ-C30 and QLQ-BR23 function scales, comparison between initial visit and final visit.

	Function scores $\pm$ standard deviation subgroup with initial visit before chemotherapy				Wilcoxon-significance-test	
	Initial visit	1. Control visit	2. Control visit	Final visit	n	p-value
EORTC QLQ-C30						
Global health	48.9 $\pm$ 21.9	45.8 $\pm$ 20.4	55.9 $\pm$ 20.4	66.9 $\pm$ 19.6	262	<0.0001
Status	52.3 $\pm$ 21.8	41.7 $\pm$ 19.9	53.5 $\pm$ 20.3	66.2 $\pm$ 18.2	114	<0.0001
Physical	71.5 $\pm$ 22.6	65.2 $\pm$ 21.4	70.9 $\pm$ 20.7	80.3 $\pm$ 21.1	262	<0.0001
Functioning	74.6 $\pm$ 22.6	62.5 $\pm$ 20.3	70.6 $\pm$ 20.1	81.6 $\pm$ 19.0	114	0.0012
Role	58.6 $\pm$ 30.6	52.8 $\pm$ 25.3	61.8 $\pm$ 24.9	73.4 $\pm$ 23.6	262	<0.0001
Functioning	64.2 $\pm$ 31.1	49.9 $\pm$ 24.9	60.0 $\pm$ 26.2	76.6 $\pm$ 22.8	114	<0.0001
Emotional	49.3 $\pm$ 27.5	47.8 $\pm$ 25.2	59.0 $\pm$ 24.4	69.8 $\pm$ 24.9	262	<0.0001
Functioning	51.9 $\pm$ 26.7	45.8 $\pm$ 24.2	60.9 $\pm$ 23.3	73.4 $\pm$ 23.8	114	<0.0001
Cognitive	70.0 $\pm$ 26.1	64.4 $\pm$ 26.5	73.3 $\pm$ 26.0	80.7 $\pm$ 22.4	262	<0.0001
Functioning	73.9 $\pm$ 23.9	62.7 $\pm$ 25.6	74.8 $\pm$ 25.3	83.8 $\pm$ 21.2	114	<0.0001
Social	58.1 $\pm$ 29.8	55.6 $\pm$ 28.7	65.3 $\pm$ 28.0	74.9 $\pm$ 25.4	262	<0.0001
Functioning	60.3 $\pm$ 31.1	51.8 $\pm$ 30.0	64.5 $\pm$ 30.1	77.3 $\pm$ 25.8	114	<0.0001
EORTC QLQ-BR23						
Body	58.8 $\pm$ 30.4	54.1 $\pm$ 29.4	60.7 $\pm$ 30.5	69.1 $\pm$ 31.0	260	<0.0001
Image	61.5 $\pm$ 31.2	51.4 $\pm$ 31.0	60.6 $\pm$ 29.9	72.8 $\pm$ 28.9	112	<0.0001
Future	34.6 $\pm$ 34.0	40.8 $\pm$ 32.2	50.4 $\pm$ 34.9	58.6 $\pm$ 35.9	260	<0.0001
Perspective	36.5 $\pm$ 36.0	37.3 $\pm$ 31.9	48.7 $\pm$ 35.5	62.8 $\pm$ 34.7	112	<0.0001

n: number of samples; p-value for  $\alpha = 0.05$ .

### Subgroup analyses

In the first subgroup analysis, all patients were grouped either to UICC stage I/II or III. Comparison of adjusted means of QLQ-C30 and QLQ-BR23 function and symptom scales revealed, except “depression because of hair loss” no significant differences. Because loss of hairs is associated to the chemotherapy an influence of mistletoe therapy is unlikely.

In the second subgroup analysis patients were either grouped to KPI  $\leq 80\%$  or  $>80\%$ . As a trend all function and symptom scales improved more in the group with KPI  $\leq 80\%$ . For sleeplessness, financial difficulties, body image and future perspective these differences were significant ( $p < 0.02$ ).

As the point of baseline recording had a significant influence on the degree of improvement of the HRQoL-parameters patients were grouped in a third subgroup analysis into the following 3 groups:

**Table 3**  
QLQ-C30 and QLQ-BR23 symptom scales, comparison between initial visit and final visit.

	Symptom scores $\pm$ standard deviation subgroup with initial visit before chemotherapy				Wilcoxon-significance-test	
	Initial visit	1. Control visit	2. Control visit	Final visit	n	p-value
EORTC QLQ-C30						
Fatigue	43.6 $\pm$ 27.2	52.5 $\pm$ 25.3	43.3 $\pm$ 25.0	29.9 $\pm$ 23.1	262	<0.0001
	39.7 $\pm$ 26.8	57.6 $\pm$ 25.3	45.0 $\pm$ 25.0	28.1 $\pm$ 23.1	114	<0.0001
Nausea and vomiting	19.8 $\pm$ 24.6	36.3 $\pm$ 27.1	24.1 $\pm$ 26.0	10.2 $\pm$ 19.7	262	<0.0001
	12.5 $\pm$ 21.3	42.3 $\pm$ 28.6	25.9 $\pm$ 27.3	8.9 $\pm$ 18.6	114	<b>0.0651 n.s.</b>
Pain	36.1 $\pm$ 27.4	38.7 $\pm$ 24.7	29.6 $\pm$ 23.4	19.6 $\pm$ 22.5	262	<0.0001
	33.3 $\pm$ 27.5	42.9 $\pm$ 26.2	30.6 $\pm$ 24.1	17.5 $\pm$ 21.1	114	<0.0001
Dyspnoea	25.6 $\pm$ 30.9	29.4 $\pm$ 28.7	25.2 $\pm$ 27.5	15.8 $\pm$ 22.9	262	<0.0001
	21.9 $\pm$ 29.1	32.5 $\pm$ 31.1	25.2 $\pm$ 28.8	13.1 $\pm$ 22.0	114	0.0003
Insomnia	44.1 $\pm$ 32.9	50.4 $\pm$ 29.6	36.9 $\pm$ 29.8	26.0 $\pm$ 28.4	260	<0.0001
	40.7 $\pm$ 33.4	53.0 $\pm$ 30.4	36.5 $\pm$ 29.0	21.5 $\pm$ 26.7	113	<0.0001
Appetite loss	35.6 $\pm$ 32.0	44.5 $\pm$ 29.1	32.1 $\pm$ 29.6	19.5 $\pm$ 26.7	262	<0.0001
	29.3 $\pm$ 32.2	46.2 $\pm$ 30.9	33.3 $\pm$ 31.2	19.0 $\pm$ 25.8	114	0.0013
Constipation	21.6 $\pm$ 29.2	20.6 $\pm$ 26.1	17.9 $\pm$ 24.3	13.5 $\pm$ 22.9	261	<0.0001
	17.1 $\pm$ 26.1	16.2 $\pm$ 24.2	16.5 $\pm$ 23.5	10.8 $\pm$ 20.6	114	0.0033
Diarrhoea	16.2 $\pm$ 25.2	26.6 $\pm$ 27.8	19.3 $\pm$ 24.4	11.2 $\pm$ 21.7	262	0.0010
	10.8 $\pm$ 21.4	26.5 $\pm$ 28.9	18.3 $\pm$ 23.5	8.2 $\pm$ 17.5	114	<b>0.1579 n.s.</b>
Financial difficulties	27.3 $\pm$ 28.8	31.8 $\pm$ 30.4	27.2 $\pm$ 29.2	21.0 $\pm$ 27.6	262	0.0003
	22.2 $\pm$ 25.1	34.2 $\pm$ 30.8	24.6 $\pm$ 26.5	17.5 $\pm$ 25.6	114	0.0487
EORTC QLQ-BR23						
Systemic therapy symptoms	29.4 $\pm$ 22.2	40.5 $\pm$ 19.1	32.8 $\pm$ 21.3	21.2 $\pm$ 20.4	262	<0.0001
	22.0 $\pm$ 19.3	42.0 $\pm$ 20.2	33.1 $\pm$ 22.8	18.6 $\pm$ 20.3	114	0.0178
Breast symptoms	32.5 $\pm$ 24.7	28.3 $\pm$ 22.3	21.2 $\pm$ 22.8	14.8 $\pm$ 18.4	261	<0.0001
	30.1 $\pm$ 22.7	29.9 $\pm$ 22.1	21.5 $\pm$ 23.3	14.8 $\pm$ 17.8	113	<0.0001
Arm symptoms	35.8 $\pm$ 26.8	33.4 $\pm$ 24.0	24.3 $\pm$ 22.3	18.6 $\pm$ 21.2	261	<0.0001
	32.3 $\pm$ 25.7	34.2 $\pm$ 25.3	22.6 $\pm$ 22.6	16.5 $\pm$ 20.3	113	<0.0001
Hair loss	37.4 $\pm$ 37.0	54.5 $\pm$ 33.9	46.6 $\pm$ 34.3	34.7 $\pm$ 36.2	145	<0.0098
	21.7 $\pm$ 32.8	54.7 $\pm$ 35.9	45.8 $\pm$ 33.5	27.0 $\pm$ 32.9	60	<b>0.9010 n.s.</b>
Sexual function	28.5 $\pm$ 26.4	18.6 $\pm$ 21.7	22.3 $\pm$ 24.0	27.8 $\pm$ 27.6	260	0.8739
	30.3 $\pm$ 27.3	18.5 $\pm$ 22.9	25.5 $\pm$ 25.3	30.5 $\pm$ 27.5	113	0.6166
Sexual enjoyment	39.2 $\pm$ 30.3	30.0 $\pm$ 28.0	33.9 $\pm$ 28.7	42.5 $\pm$ 33.9	166	0.0531
	41.4 $\pm$ 31.7	30.1 $\pm$ 29.7	34.9 $\pm$ 28.0	45.1 $\pm$ 31.6	78	0.1501

n: number of samples; p-value for  $\alpha = 0.05$ ; bold: difference for total and subgroup/n.s.: not significant.

**Table 4**

Mean and 95% confidence interval of the difference between initial visit and 2nd control visit (period of chemotherapy treatment) of the QLQ-C30 and QLQ-BR23 function scales. Negative values indicate deterioration at the 2nd control visit.

	Mean subgroup with initial visit before chemotherapy	Lower limit	Upper limit
<b>EORTC QLQ-C30</b>			
Global health	7.0	4.2	9.7
Status	1.2	-2.7	5.2
Physical Functioning	-0.3	-3.2	2.5
Role Functioning	-3.8	-8.5	0.9
Emotional Functioning	3.5	-0.6	7.6
Cognitive Functioning	-3.9	-10.3	2.5
Social Functioning	10.1	7.0	13.3
Functional status	9.6	5.4	13.9
Cognitive Functioning	3.8	0.5	7.1
Social Functioning	1.2	-3.4	5.7
Social Functioning	7.6	4.0	11.3
Functional status	4.6	-1.0	10.3
<b>EORTC QLQ-BR23</b>			
Body Image	1.9	-1.2	5.1
Future Perspective	-1.1	-5.9	3.8
Body Image	15.7	11.5	19.9
Future Perspective	12.3	5.8	18.8

initial visit after, before and at the same time as beginning of the chemotherapy. The scores of the subgroup in which the initial visit was performed before chemotherapy started (for most parameters  $n = 114$ ) are listed additionally in Tables 2 and 3. In these subgroup-data baseline is unaffected by chemotherapy, so the baseline scores of the function scales were between 1.9% and 5.6% higher than in the overall group.

**Table 5**

Mean and 95% confidence interval of the difference between initial visit and 2nd control visit (period of chemotherapy treatment) of the QLQ-C30 and QLQ-BR23 symptom scales. Positive values indicate deterioration at the 2nd control visit.

	Mean subgroup with initial visit before chemotherapy	Lower limit	Upper limit
<b>EORTC QLQ-C30</b>			
Fatigue	-0.7	-4.1	2.8
Nausea and vomiting	5.1	0.2	10.1
Pain	13.2	7.6	18.7
Dyspnoea	-6.5	-10.3	-2.7
Insomnia	-2.5	-8.2	3.3
Appetite loss	-0.8	-4.7	3.2
Constipation	2.9	-3.0	8.8
Diarrhoea	-8.0	-12.4	-3.5
Financial difficulties	-4.9	-11.5	1.6
	-3.9	-8.6	0.8
	3.8	-3.5	11.1
	-3.7	-7.1	-0.3
	-0.9	-5.7	4.0
	2.8	-0.6	6.2
	7.5	2.6	12.5
	-0.3	-3.8	3.3
	2.6	-2.6	7.8
<b>EORTC QLQ-BR23</b>			
Systemic therapy symptoms	3.1	-0.0	6.3
Breast symptoms	10.9	6.6	15.2
Arm symptoms	-11.5	-14.6	-8.3
Hair loss	-8.4	-13.4	-3.4
Sexual function	-11.6	-14.9	-8.4
Sexual enjoyment	-9.4	-14.8	-4.0
	3.0	-3.7	9.7
	19.4	9.4	29.4
	-5.8	-8.8	-2.8
	-4.1	-8.2	-0.0
	-5.0	-9.2	-0.7
	-5.2	-10.6	0.2

In the covariance analysis these patients exhibited significant stronger improvements ( $p < 0.04$ ) of role functioning, emotional functioning and social functioning compared to patients who already had started their chemotherapy at baseline examination with reduced values. However, at the final visit the differences of the functional scores in the 2 groups were reduced from -0.7% (global health status) to 3.6% (emotional functioning). Even if the HRQoL-parameters in the subgroup with unaffected baseline remained stable until the second visit at the end of the chemotherapy, their HRQoL improved after finishing chemotherapy and was comparable at the final visit with the whole group.

Significant influences could also be detected by covariance analysis in some of the QLQ-C30 symptom scores between these 2 groups. Improvement of the symptom scales was significant smaller for patients of the subgroup. Their symptom scores were at a low level at the initial visit because chemotherapy has not yet been started. This baseline level was reached again at the final visit without an appreciable change. These results coincide with the comparison between initial visit and final visit of the subgroup symptom scores. Typical chemotherapy influenced symptoms like nausea/vomiting, diarrhoea and hair loss did not show a significant difference.

## Discussion

This prospective observational study was performed to learn more about tolerability and efficacy regarding HRQoL of a mistletoe lectin rich mistletoe preparation in breast cancer patients under conditions of daily practice. Statements about efficacy are, however, limited because it had no control group.

The planned number of patients ( $n = 270$ ) was reached and was high enough to detect also rare adverse events (incidence 1.2%) with 95% probability. The recommendations of the manufacturer regarding dosage (frequency and dose escalation according to local reactions and tolerability) were used from the majority of physicians. The majority of patients had, as expected, dose dependent local reactions at the site of injection and temporary mild lassitude after the injection but no therapy related severe adverse reactions or unexpected adverse reactions occurred. The local reactions and mild, temporary lassitude are specified as typical in the product information for physicians (Abnoba GmbH 2003) and indicate immunological reactions (Huber et al. 2002, 2005). Despite these side effects the tolerability of the mistletoe treatment was estimated by the physicians as good or excellent for 91% of the patients. 88.2% of the patients rated correspondingly, indicating that the side effects were only mild.

HRQoL of breast cancer patients is largely affected by chemotherapy. Typical symptoms of the classical CMF chemotherapy are loss of appetite, nausea and fatigue. Fatigue, the most common side effect (65–90%), can be lasting for years (Arndt et al. 2005; Bower 2008) and is regarded as one of the most important therapy burden from the patients' view. 30–60% report about moderate to severe fatigue (Bower 2008). There is beside transfusion and erythropoietin therapy in case of clinical relevant anaemia no effective drug therapy against cancer-related fatigue (Carroll et al. 2007). However, in a meta-analysis with more than 13,000 cancer patients erythropoietin treatment was found to increase mortality by 17% and should therefore be used extremely carefully (Bohlius et al. 2009). And antidepressants and psycho-stimulants showed limited effects in randomized controlled clinical studies (review in Carroll et al. 2007). Actually, the best available evidence for reducing cancer-related fatigue with a pharmacological approach exists out from two positive RCT's for mistletoe therapy (Gutenbrunner et al. 2010). However, in none of these trials CRF (Chronic fatigue syndrome) was the primary outcome. The results were coherent with

our results showing a stable fatigue level of 43% for all patients at the initial and second control visit and a slight elevation from 39% to 45% in the unaffected baseline group. Watters (Watters et al. 2003) reported a fatigue level measured with EORTC QLQ-C30 in younger patients with breast cancer of 29% prior to chemotherapy, 46% at completion and 30% 6-month post-chemotherapy. Another study (Donovan et al. 2004) reported a fatigue level in breast cancer patients undergoing adjuvant chemotherapy measured with the fatigue severity score beginning at 3.6 and at the end of chemotherapy 5.2 (corresponding to 36% resp. 52%). In another German study (Arndt et al. 2005) more than 80% of the women with recurrence-free breast cancer still reported 1 or 3 years after adjuvant chemotherapy a significant CRF (36.7% resp. 37.4%) measured as well with the EORTC QLQ-C30. Compared to these studies the measured fatigue scores in our study of 29.9% for all patients and 28.1% for the subgroup already 4 weeks after end of chemotherapy are surprisingly low. Besides the presumed protective effect of the concomitant mistletoe treatment the high ratio of CMF, AC and EC chemotherapy (83%) with comparatively low toxicity regarding FAC or TAC regimes (Martin et al. 2006) might also have had a beneficial influence on the fast recovery of the patients. Because of the limitation by reason of the missing control group we are unable to distinguish between these different influencing factors.

Alteration of other HRQoL-parameters by chemotherapy could also be found in our patients. After about 4 weeks chemotherapy almost all QLQ-C30 and QLQ-BR23 symptom- and function scores were deteriorated. At the end of chemotherapy, however, the scores were considerably better than after 4 weeks of chemotherapy and more or less stable compared to baseline level. 4 weeks later, at the final examination, the scores further and significantly improved. This is interesting and unexpected because normally the chemotherapy related side effects, especially fatigue, increase as already discussed above (Donovan et al. 2004). Subjectively, from the view of the patients and physicians, treatment with abnobaVISCUM<sup>®</sup> Mali was regarded as beneficial under conditions of daily practice. For a more robust statement, however, a randomized controlled study has to be performed. At least, the estimations of physicians and patients are congruent, speaking for plausibility and the rating of effectiveness was very high: physicians rated effectiveness as good or excellent in 93.7% and patients in 88.9%, speaking for clinical relevance. Also the fact that compliance to treatment, despite side effects, was very high speaks for the notion of a clinical benefit for the patients. Based on these results the present dose recommendations can be regarded as safe and efficacious.

These results on HRQoL are supported by controlled and randomized clinical studies (overview in Horneber et al. 2008; Lange-Lindberg et al. 2006). They found that mistletoe therapy additive to conventional chemotherapy improves HRQoL of women with breast cancer. These studies were not performed with abnobaVISCUM<sup>®</sup> Mali but the doses of mistletoe lectin, which is a main relevant component (Huber et al. 2005) was, at least in the beginning of the treatment, in our study similar to controlled studies (Piao et al. 2004; Semiglasov et al. 2004; Semiglasov et al. 2006), namely about 10 ng per ampoule. Taking all this together, it therefore can be assumed, that abnobaVISCUM<sup>®</sup> Mali has similar effects.

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