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Nr. 45

Multicentric, randomized, open, prospective clinical trial for the investigation of efficacy and tolerance and adverse drug reactions of HELIXOR® A in comparison to Lentinan in patients with non small cell lung cancer, breast cancer or ovarian cancer

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1 Introduction

1.1 Study Objectives

HELIXOR® A, an injection solution of active components extracted from Viscum album is applied for registration in China. Therefore a clinical trial was performed according to the "Chinese Application and Administration Methods for Imported Drugs". The main objectives of the clinical trial are as following:

(1) Observation of the efficacy of the drug to reduce side effects and toxicity of chemotherapy in tumor patients
(2) Observation of the influence of the drug as to immune functions
(3) Observation of safety and side effects of the drug

1.2 Study Design

Multicentric, randomized, open, prospective clinical trial in a total of 210 patients. Patients with lung, breast or ovarian cancer will be randomized to verum group HELIXOR® A or to control group Lentinan. Assigned patients should be comparable as to sex, age, classification of disease and chemotherapy. Patients were recorded from 11/07/00 to 06/06/01 in 3 different centers in China, Beijing, Shenyang, Tianjin.

Inclusion criteria are as following,

(1) Patients with non small cell lung carcinoma, breast or ovarian cancer diagnosed by pathological or cytological methods.
(2) Patients being suitable for a chemotherapeutic treatment after different examinations, and who had not yet been treated by radiotherapy or chemotherapy, or a radiotherapy or chemotherapy is going back at least one month.
(3) Men and women at the age of at least 18 up to maximum 70 years.
(4) Patients reaching a Karnofsky Index between 80 and 50 % with an expected survival time exceeding 3 months and being suitable for chemotherapy.
(5) Voluntary patients agreeing to treatment with clinical trial preparations
(6) Stationary patients
(7) Patients not applying drugs including special healthy food influencing blood count and immune function one month before beginning of the clinical trial treatment

Exclusion criteria are as following,

(1) Patients for whom inclusion criteria are not applicable
(2) Patients with functional damage of heart, liver, kidney or dyshematopoiesis
(3) Advanced seriously ill patients with a life expectancy of less than 3 months
(4) Pregnant or nursing women and mentally handicapped people
(5) Patients with allergy against drugs

(6) Leukocyte counts less than 4.000/mm^3, platelets less than 80.000/mm^3 or serious anaemia with hemoglobin less than 8g/dl

(7) Acute inflammatory disease and/or fever more than 37.5°C.

Treatment plan of verum and control group:

The assignment of patients to verum or control group has to follow the randomization list. Both groups should be comparable as to sex, age, classification of disease and chemotherapy plan.

***Verum group**: Chemotherapy + HELIXOR® A*

HELIXOR® A: subcutaneous injection 3 times /week (day 1, 3, 5).

Table 1 Injection method of HELIXOR® A

HELIXOR® A injections	First time	Second time	Third time
Week 1	1 mg	5 mg	10 mg
Week 2	10 mg	20 mg	20 mg
Week 3	30 mg	30 mg	50 mg
Week 4	50 mg	70 mg	70 mg
Week 5	80 mg	80 mg	100 mg
Week 6 – 8	100 mg	150 mg	200 mg

Patients not having received all injections due to side effects to HELIXOR® A, but having received more than 70 % of the foreseen number of injections, are evaluable.

***Control group**: Chemotherapy + Lentinan injectable solution*

Lentinan injectable solution: 8 mg intramuscular/ application, one application per day. Duration of treatment the same as verum group.

Treatment plan of chemotherapy for non small cell lung cancer: (NVB + PDD) or MVP

NVB+PDD

NVB[1] 25 mg/m^2 iv (infusion) d1, "8 days"

PDD[2] 60-80 mg/m^2, (infusion) dl (or in 2-3 days)

repetition once after 3 weeks x 2

MVP

MMC[5] 6-8 mg/m^2 iv d1

VDS[6] 3 mg/m^2 iv dl, d8

PDD[2] 60-80 mg/m^2 iv d2, (or in 2-3 days)

21 days/ cycle x 2

Treatment plan of chemotherapy for breast cancer: CAP or CAF

CAP

CTX[7] 600 mg/m^2 iv d1, d8

ADM[8] 40-50 mg/m^2 iv d1 (or EADM 50-70 mg/m^2)

PDD[2] 20-30 mg/m^2 iv (infusion) d3, 4, 5

21 days/ cycle x 2

CAF

CTX[7] 600 mg/m^2 iv d1, d8

EADM[9] 50-70 mg, iv d1

5FU[10] 500mg, iv (infusion) d1-5

21 days/ cycle x 2

Treatment plan of chemotherapy for ovarian cancer: CP or (IFO+CBP or PDD)

CP

PDD[2] 70 mg/m^2, d1 hydratation, diuresis

CTX[7] 500 mg/m^2, d2

21 days/ cycle x 2

IFO+CBP or PDD

CBP[3] 300 mg/m^2 or PDD[2] 70mg/m^2, d1

IFO[4] 1,2 g/m^2 ,d1-d4 Mesna[11] 20% of IFO[4] dosage, three times, once at 0, 4 and 8 h after injection of IFO[4], respectively.

28 days/ cycle x 2

1 NVB: Vinorelbin
2 PDD: cis-Diaminodichloroplatinum
3 CBP = C-PPD = Carboplatin
4 IFO: Ifosfamid
5 MMC: Mitomycin
6 VDS: Vindesine
7 CTX: Cyclophosphamid
8 ADM: Adriamycin
9 EADM: Epiadriamycin
10 5-FU: 5-Fluorouracil
11 Mesna: mucolytic agent (given as prophylaxis against urotoxicity of cytostatic drugs)

1.3 Analysis planned according to Protocol

In the clinical trial protocol primary and secondary endpoints as well as an analysis strategy are not specified. However, criteria for the evaluation of efficacy are defined in chapter V of the final clinical trial protocol including analyses of TCM criteria, tumor changes, immune function, blood parameters, liver/ kidney and heart function, quality of life (Karnofsky index) and body weight.

Ancillary to that the quality of life parameters – Karnofsky index (KPI), Functional Living Index of cancer (FLIC) and traditional chinese medicine criteria (TCM) – will be correlated. In addition, a safety evaluation will be performed.

1.4 Statistical Methods

Statistical analysis will be performed using SAS Version 8.02 and StatExact Version 5. The analysis has to be interpreted as explorative and has no confirmative power.

Analysing the trial population and describing the efficacy criteria, safety criteria and quality of life questionnaires at baseline and at final end of treatment binary and categorical data will be evaluated with Fisher's exact test, while continuous data will be compared by means of the Wilcoxon-Mann-Whitney test.

The statistical analysis of the efficacy criteria, safety criteria and quality of life questionnaires follows the *as-treated* principle (AT analysis). For treatment comparison the difference between baseline and final end of treatment are compared for each criterion:

The Karnofsky Index and loss of weight were analysed with a stratified Mantel-Haenszel test with standardized mid-ranks, also known as 'modified ridit scores', in case of the total trial population or a simple Mantel-Haenszel test in case of different tumor entities. The p-values of separate tumor entities have to be regarded under the problem of multiple testing. Here, the Bonferroni-Holm procedure was applied: P-values for the three entities have to be put in ascending order if the test for the total study population was significant at the 5% level; one after another the p-values have to be compared with the adjusted p-values 0.017 ($\alpha/3$), 0.025 ($\alpha/2$) and 0.05 (α).

For the other quality of life criteria – TCM (Traditional Chinese Medicine) and FLIC (Functional Living Index of cancer) – as well as the Body Mass Index the stratified Wilcoxon-Mann-Whitney test was used for the overall population and the simple Wilcoxon-Mann-Whitney test for the subgroups of different tumor types. In addition, the 95% confidence limits for the difference in medians between the treatment groups Helixor® A and Lentinan is given (the confidence limits are based on the asymptotic method by Conover (1980)). Please note here, that confidence limits of discrete data in case of ordered categorical data have to be considered with caution (both, if the corresponding p-value is significant and if the corresponding p-value is non-significant zero may be confidence limit; here, the confidence interval only gives information about precision).

The data of urine examination are analysed with McNemar test, the data of stool examination with the Fisher's exact test.

For evaluation of efficacy (tumour response) the multiple logistic regression was used in order to adjust for possible confounding parameters.

Comparison analyses of quality of life parameters are evaluated with weighted Kappa statistics as measure of agreement and graphically depicted with regression lines and respective confidence intervals (linear regression analysis).

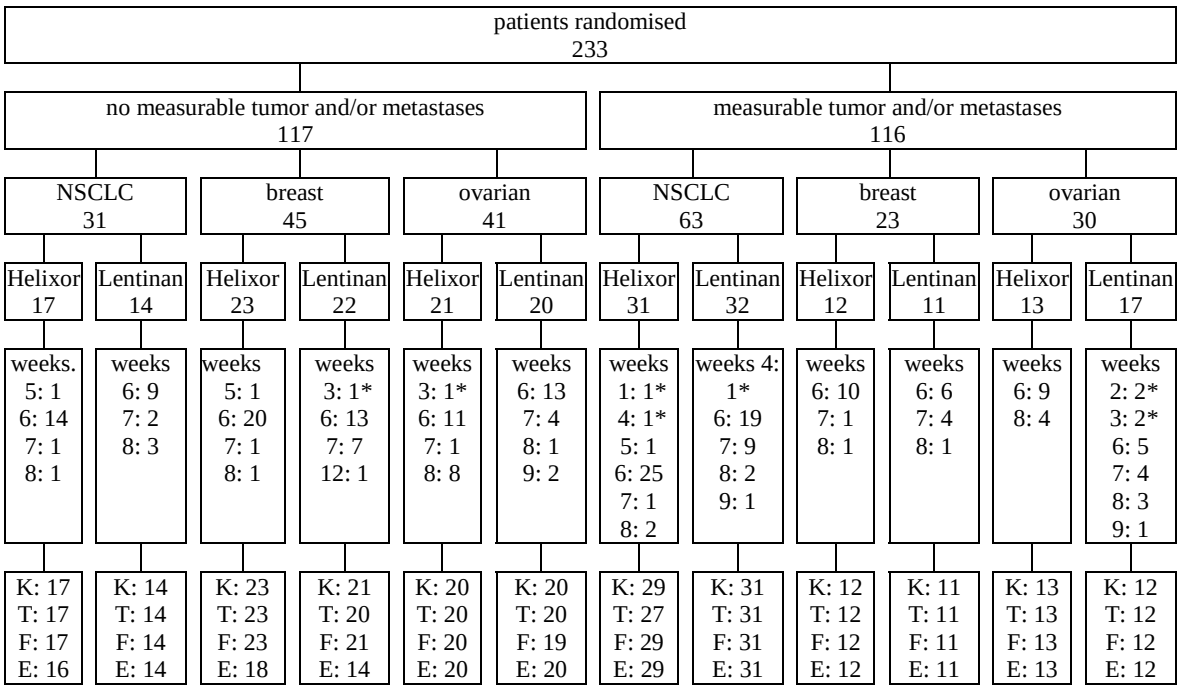
Box-and-whisker plots have been added to several tables (e.g. Figure 1, Figure 11 or Figure 12). The box in a box-and-whisker plot indicates the lower and upper quartiles (25^{th} and 75^{th} percentiles) and the central line is the median. The mean is represented by a '+'. The points at the ends of the 'whiskers' are drawn to the most extreme points that lie within so-called "fences". The upper fence is defined as the third quartile (represented by the upper edge of the box) plus 1.5 times the interquartile range. The lower fence is defined as the first quartile (represented by the lower edge of the box) minus 1.5 times the interquartile range. Observations outside the fences are identified with a dot.

2 Analysis of Trial Population

The number of patients entering the study added up to 233 randomized patients. This is presented as flow chart in **Table 2**. A group of 117 patients had no measurable tumor and/or metastases, while a group of 116 patients were classified with measurable tumor and/or metastases. Three different tumor types were considered in the survey – 94 patients were diagnosed with non small cell lung carcinoma (NSCLC), 68 patients with breast cancer and 71 patients with ovarian cancer. Moreover, patients were recruited in 3 different centres, namely, in Beijing, Shenyang, Tianjin with 46, 129 and 58 patients respectively.

A total of 117 patients of the trial population were treated with HELIXOR® A and 116 with Lentinan. This distribution contains 1 patient who was randomised to HELIXOR® A, but was treated with Lentinan by mistake. This was a protocol violation. For this reason the following analysis was accomplished 'as treated' instead of 'intention to treat'.

Table 2 Patient flow chart



Treatment scheme described in weeks.
Weeks of trial med. enlists the weeks of medication : number of patients treated.
K: Karnofsky index; T: TCM; F: FLIC
E tumor evaluation
* patients with less than 4 weeks of treatment

The treatment duration with HELIXOR® A was arranged according to the scheme of the chemotherapy which means HELIXOR® A injection was given 3 times per week during 6 – 8 weeks. In contrast Lentinan was given for the same period of time but was injected daily. As further determined in the trial protocol patients that terminated therapy early, are evaluable only if more than 70 % of foreseen number of injections were received - corresponding to 12 injections of HELIXOR® A or 4 weeks of treatment. As seen in **Table 2**, several patients obtained therapy for less than 4 weeks. Out of 9 patients, 3 patients treated with HELIXOR® A and 6 patients treated with Lentinan had to be excluded from the statistical analysis. One reason was for short-term and the other reason was a most likely ineffective therapy. None of these 9 patients finished the clinical trial with the final investigation.

Therefore, **224 out of the 233 patients are considered in the present analysis (114 treated with HELIXOR® A, 110 treated with Lentinan),** excluding only patients who were treated with verum or control medication for less than 4 weeks.

Out of these 224 patients only 223 patients reached the final investigation. In addition to the above-mentioned 9 patients, one patient who received the complete therapy, was not reachable for the final investigation. **Table 3** lists the various reasons for early termination.

Table 3 Reasons for termination (N=233)

	Helixor	Lentinan
Regularly terminated	**112**	**108**
Informed consent	2	3
Not reachable	0	1
Chemotherapy not according to protocol	**1**	**1**
Possible side effect of test drug	1	1
Other adverse events incl. death	0	1
Other	**1**[a]	1 [b]

Patients in bold are included in analysis for the final investigation. (N=223)
a diagnosed heart disease after final investigation
b multiple organ failure

Beside the patient who was allocated to the HELIXOR® A group but treated with Lentinan several violations against inclusion/exclusion criteria and trial plan happened and are summarized as follows.

Violations against inclusion and exclusion criteria,

(1) 64 patients have a Karnofsky index > 80 %
(2) 1 patient has a Karnofsky index < 50 %
(3) 1 patient (patient no.181) did not stay at the hospital for the complete duration of the clinical trial, but was under permanent supervision of the investigator
(4) 1 patient (patient no.212) has a Hb value of 6.9, violating the exclusion criteria of Hb < 8

Violations against the trial protocol,

(1) At the beginning of the study Lentinan was administered at a dosage of 8 mg instead of 4 mg as determined in the trial protocol. Patients starting therapy from 16/8/00 to 19/12/00, and another 3 patients from the 1/04/01, 10/04/01 and 6/06/01 received a dosage of 8 mg Lentinan. Patients entering the study after the 20/12/00 were given Lentinan at the originally assigned dosage of 4 mg.

2.1 Demographic characteristics and general anamnesis

2.1.1.1 Total study population

The demography and general anamnesis of the total study population are summarized in **Table 4** and **Table 5**. The explorative analysis shows that HELIXOR® A and Lentinan are comparable for most parameters including center, sex, diagnosis, ECG, physical examination, age, body mass index, blood pressure and pulse. Exceptions are body height and body weight with the respective p-values of p = 0.039 and p = 0.035.

Table 4 Total study population – demographic characteristics and general anamnesis

ALL		Helixor N=114		Lentinan N=110		Total N=224		p-value
		N	%	N	%	N	%	
Center	Beijing	22	19.3	23	20.9	45	20.1	0.858
	Shenyang	62	54.4	62	56.4	124	55.4	
	Tianjin	30	26.3	25	22.7	55	24.6	
Sex	male	26	22.8	23	20.9	49	21.9	0.749
	female	88	77.2	87	79.1	175	78.1	
Diagnosis	NSCLC	46	40.4	45	40.9	91	40.6	0.971
	breast	35	30.7	32	29.1	67	29.9	
	ovarian	33	28.9	33	30.0	66	29.5	
ECG	missing	0	0.0	1	0.9	1	0.4	0.862
	normal	94	82.5	89	80.9	183	81.7	
	abnormal	20	17.5	20	18.2	40	17.9	
Physical examination	missing	1	0.9	0	0.0	1	0.4	0.354
	normal	105	92.1	98	89.1	203	90.6	
	abnormal	8	7.0	12	10.9	20	8.9	

Table 5 Total study population – demographic characteristics and general anamnesis (continued)

ALL	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
Age	Helixor	114	0	52.5	9.3	31.0	46.0	50.0	60.0	70.0	0.757
	Lentinan	110	0	52.0	9.6	30.0	45.0	51.0	59.0	70.0	
	Total	224	0	52.2	9.5	30.0	45.0	51.0	60.0	70.0	
Height [cm]	Helixor	114	0	163.0	6.8	145.0	158.0	162.0	167.0	180.0	0.039
	Lentinan	110	0	161.3	7.4	145.0	156.0	160.0	164.0	184.0	
	Total	224	0	162.2	7.1	145.0	158.0	162.0	166.0	184.0	
Weight [kg]	Helixor	114	0	62.9	10.3	39.0	56.0	62.0	70.0	89.0	0.035
	Lentinan	110	0	60.9	10.3	42.0	55.0	59.0	65.0	100.0	
	Total	224	0	61.9	10.3	39.0	55.0	60.0	67.0	100.0	
Body Mass Index	Helixor	114	0	23.6	3.3	15.8	21.0	23.4	26.4	30.5	0.543
	Lentinan	110	0	23.4	3.2	16.5	20.8	23.0	25.5	31.2	
	Total	224	0	23.5	3.3	15.8	20.9	23.4	25.8	31.2	
RRsyst [mmHg]	Helixor	113	1	123.6	15.4	90.0	112.0	120.0	130.0	180.0	0.613
	Lentinan	110	0	124.7	16.1	90.0	112.0	120.0	135.0	180.0	
	Total	223	1	124.1	15.7	90.0	112.0	120.0	135.0	180.0	
RRdiast [mmHg]	Helixor	113	1	79.4	8.3	60.0	75.0	80.0	85.0	100.0	0.308
	Lentinan	110	0	78.0	8.8	60.0	70.0	80.0	80.0	100.0	
	Total	223	1	78.7	8.6	60.0	75.0	80.0	85.0	100.0	
Pulse [beats/min.]	Helixor	113	1	82.5	6.1	64.0	80.0	82.0	84.0	110.0	0.507
	Lentinan	110	0	82.7	7.0	56.0	80.0	84.0	86.0	110.0	
	Total	223	1	82.6	6.6	56.0	80.0	82.0	85.0	110.0	

2.1.1.2 Non small cell lung cancer

In the following the study population was separated by tumor types to gain more detailed information about different subgroups. Analyses of demography and general anamnesis of non small cell lung cancer patients are listed in **Table 6** and **Table 7**. There is no significant difference between the treatment groups HELIXOR® A and Lentinan for the listed parameters. Therefore, the two treatment groups are comparable in the subgroup of patients with non small cell lung cancer.

Table 6 Non small cell lung cancer – demographic characteristics and general anamnesis

NSCLC		Helixor N=46		Lentinan N=45		Total N=91		p-value
		N	%	N	%	N	%	
Center	Beijing	16	34.8	16	35.6	32	35.2	0.964
	Shenyang	20	43.5	18	40.0	38	41.8	
	Tianjin	10	21.7	11	24.4	21	23.1	
Sex	Male	26	56.5	23	51.1	49	53.8	0.676
	Female	20	43.5	22	48.9	42	46.2	
ECG	Missing	0	0.0	1	2.2	1	1.1	0.711
	Normal	36	78.3	33	73.3	69	75.8	
	Abnormal	10	21.7	11	24.4	21	23.1	
Physical examination	Missing	1	2.2	0	0.0	1	1.1	1.000
	Normal	40	87.0	39	86.7	79	86.8	
	Abnormal	5	10.9	6	13.3	11	12.1	

Table 7 Non small cell lung cancer – demographic characteristics and general anamnesis (continued)

NSCLC	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
Age	Helixor	46	0	56.8	9.4	35.0	48.0	59.0	64.0	70.0	0.773
	Lentinan	45	0	56.0	10.0	30.0	48.0	58.0	63.0	70.0	
	Total	91	0	56.4	9.7	30.0	48.0	58.0	64.0	70.0	
Height [cm]	Helixor	46	0	166.4	8.1	150.0	160.0	169.0	172.0	180.0	0.228
	Lentinan	45	0	164.5	9.0	151.0	157.0	163.0	170.0	184.0	
	Total	91	0	165.5	8.6	150.0	158.0	165.0	172.0	184.0	
Weight [kg]	Helixor	46	0	65.4	11.5	39.0	60.0	64.5	75.0	89.0	0.069
	Lentinan	45	0	63.0	11.7	46.0	56.0	60.0	65.0	100.0	
	Total	91	0	64.2	11.6	39.0	57.0	62.0	72.0	100.0	
Body Mass Index	Helixor	46	0	23.5	3.5	15.8	20.8	23.3	26.9	29.7	0.672
	Lentinan	45	0	23.3	3.5	16.5	20.7	23.7	25.6	29.5	
	Total	91	0	23.4	3.5	15.8	20.8	23.4	26.2	29.7	
RR syst [mmHg]	Helixor	46	0	124.8	14.3	90.0	120.0	120.0	135.0	170.0	0.896
	Lentinan	45	0	125.9	17.9	90.0	110.0	120.0	135.0	180.0	
	Total	91	0	125.4	16.1	90.0	120.0	120.0	135.0	180.0	
RR diast [mmHg]	Helixor	46	0	79.7	7.5	60.0	75.0	80.0	82.0	95.0	0.653
	Lentinan	45	0	78.9	8.5	60.0	75.0	80.0	80.0	95.0	
	Total	91	0	79.3	7.9	60.0	75.0	80.0	82.0	95.0	
Pulse [beats/min.]	Helixor	46	0	82.7	4.5	72.0	80.0	82.0	84.0	95.0	0.361
	Lentinan	45	0	83.4	7.2	60.0	80.0	84.0	86.0	104.0	
	Total	91	0	83.1	6.0	60.0	80.0	82.0	85.0	104.0	

2.1.1.3 Breast cancer

Analysis of demography and general anamnesis of breast cancer patients are shown in **Table 8** and **Table 9**. The treatment groups HELIXOR® A and Lentinan are comparable for all parameters. The parameter sex is not listed in this table since breast cancer patients of the trial population are exclusively women.

Table 8 Breast cancer – demographic characteristics and general anamnesis

BREAST		Helixor N=35		Lentinan N=32		Total N=67		p-value
		N	%	N	%	N	%	
Center	Beijing	6	17.1	6	18.8	12	17.9	0.474
	Shenyang	18	51.4	20	62.5	38	56.7	
	Tianjin	11	31.4	6	18.8	17	25.4	
ECG	Normal	30	85.7	27	84.4	57	85.1	1.000
	Abnormal	5	14.3	5	15.6	10	14.9	
Physical examination	Normal	33	94.3	29	90.6	62	92.5	0.664
	Abnormal	2	5.7	3	9.4	5	7.5	

Table 9 Breast cancer – demographic characteristics and general anamnesis (continued)

BREAST	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
Age	Helixor	35	0	47.6	8.1	31.0	42.0	49.0	54.0	64.0	0.822
	Lentinan	32	0	47.0	8.0	31.0	41.5	46.5	52.0	67.0	
	Total	67	0	47.3	8.0	31.0	42.0	47.0	52.0	67.0	
Height [cm]	Helixor	35	0	161.9	3.6	155.0	158.0	162.0	166.0	167.0	0.101
	Lentinan	32	0	160.0	4.3	150.0	159.0	160.0	163.0	170.0	
	Total	67	0	161.0	4.0	150.0	159.0	161.0	164.0	170.0	
Weight [kg]	Helixor	35	0	63.1	8.2	48.0	58.0	62.0	70.0	78.0	0.286
	Lentinan	32	0	61.3	8.6	43.0	55.0	60.0	66.0	85.0	
	Total	67	0	62.3	8.4	43.0	57.0	60.0	70.0	85.0	
Body Mass Index	Helixor	35	0	24.1	3.1	17.4	21.8	24.0	26.4	29.7	0.595
	Lentinan	32	0	23.9	2.9	17.7	21.6	23.4	25.7	31.2	
	Total	67	0	24.0	3.0	17.4	21.6	23.4	26.2	31.2	
RR syst [mmHg]	Helixor	34	1	119.4	12.9	90.0	110.0	120.0	130.0	140.0	0.259
	Lentinan	32	0	124.7	13.7	105.0	120.0	120.0	130.0	165.0	
	Total	66	1	122.0	13.5	90.0	110.0	120.0	130.0	165.0	
RR diast [mmHg]	Helixor	34	1	78.4	7.7	60.0	75.0	80.0	85.0	90.0	0.819
	Lentinan	32	0	78.8	9.4	60.0	75.0	80.0	82.5	100.0	
	Total	66	1	78.6	8.5	60.0	75.0	80.0	85.0	100.0	
Pulse [beats/min.]	Helixor	34	1	81.5	6.1	64.0	80.0	81.5	84.0	100.0	0.979
	Lentinan	32	0	81.7	5.5	70.0	78.5	82.0	84.0	98.0	
	Total	66	1	81.6	5.8	64.0	80.0	82.0	84.0	100.0	

2.1.1.4 Ovarian cancer

Analysis of demography and general anamnesis of ovarian cancer patients are shown in **Table 10** and **Table 11**. There is no significant difference for any of the quoted parameters between treatment group HELIXOR® A and Lentinan. The parameter sex is not listed in this table since ovarian cancer patients of the trial population are exclusively women.

Table 10 Ovarian cancer – demographic characteristics and general anamnesis

OVARIAN		Helixor N=33		Lentinan N=33		Total N=66		p-value
		N	%	N	%	N	%	
Center	Beijing	0	0.0	1	3.0	1	1.5	1.000
	Shenyang	24	72.7	24	72.7	48	72.7	
	Tianjin	9	27.3	8	24.2	17	25.8	
ECG	Normal	28	84.8	29	87.9	57	86.4	1.000
	Abnormal	5	15.2	4	12.1	9	13.6	
Physical examination	Normal	32	97.0	30	90.9	62	93.9	0.613
	Abnormal	1	3.0	3	9.1	4	6.1	

Table 11 Ovarian cancer – demographic characteristics and general anamnesis (continued)

OVARIAN	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
Age	Helixor	33	0	51.6	7.8	32.0	47.0	50.0	57.0	67.0	0.749
	Lentinan	33	0	51.3	8.1	37.0	45.0	50.0	57.0	67.0	
	Total	66	0	51.5	7.9	32.0	45.0	50.0	57.0	67.0	
Height [cm]	Helixor	33	0	159.4	5.2	145.0	155.0	160.0	163.0	169.0	0.300
	Lentinan	33	0	158.1	5.2	145.0	155.0	158.0	161.0	170.0	
	Total	66	0	158.8	5.2	145.0	155.0	160.0	162.0	170.0	
Weight [kg]	Helixor	33	0	59.2	9.8	39.5	50.0	58.0	65.0	81.0	0.507
	Lentinan	33	0	57.5	8.9	42.0	52.0	55.0	61.0	84.0	
	Total	66	0	58.3	9.3	39.5	52.0	56.5	65.0	84.0	
Body Mass Index	Helixor	33	0	23.2	3.4	17.2	20.8	23.1	24.8	30.5	0.808
	Lentinan	33	0	23.0	3.0	17.5	20.7	22.9	25.1	29.1	
	Total	66	0	23.1	3.2	17.2	20.8	22.9	25.1	30.5	
RR syst [mmHg]	Helixor	33	0	126.1	18.5	95.0	115.0	120.0	135.0	180.0	0.727
	Lentinan	33	0	123.0	16.1	90.0	110.0	120.0	135.0	157.0	
	Total	66	0	124.6	17.3	90.0	110.0	120.0	135.0	180.0	
RR diast [mmHg]	Helixor	33	0	80.1	10.0	60.0	70.0	80.0	90.0	100.0	0.129
	Lentinan	33	0	76.2	8.7	60.0	70.0	80.0	80.0	90.0	
	Total	66	0	78.1	9.5	60.0	70.0	80.0	85.0	100.0	
Pulse [beats/min.]	Helixor	33	0	83.2	7.8	68.0	80.0	82.0	88.0	110.0	0.872
	Lentinan	33	0	82.7	8.2	56.0	80.0	84.0	86.0	110.0	
	Total	66	0	83.0	7.9	56.0	80.0	84.0	86.0	110.0	

2.2 Tumor anamnesis

2.2.1.1 Total study population

The tumor anamnesis of the total trial population is listed in **Table 12**. The variables pT, pN and M characterize the primary tumor, lymph node metastases and distant metastases status respectively and are compared for treatment groups of HELIXOR® A and Lentinan without revealing any significant differences. Furthermore, the variables, like previous treatment, operation, radiotherapy, chemotherapy, other treatment and measurable tumor, are shown to be comparable between treatment groups.

Table 12 Total study population – tumor anamnesis

ALL		Helixor N=114		Lentinan N=110		Total N=224		p-value
		N	%	N	%	N	%	
pT	1	10	8.8	16	14.5	26	11.6	0.127
	2	45	39.5	29	26.4	74	33.0	
	3	34	29.8	30	27.3	64	28.6	
	4	18	15.8	22	20.0	40	17.9	
	X	7	6.1	13	11.8	20	8.9	
pN	0	50	43.9	41	37.3	91	40.6	0.361
	1	18	15.8	18	16.4	36	16.1	
	2	31	27.2	25	22.7	56	25.0	
	3	9	7.9	16	14.5	25	11.2	
	X	6	5.3	10	9.1	16	7.1	
M	0	70	61.4	71	64.5	141	62.9	0.679
	1	44	38.6	39	35.5	83	37.1	
Number of distant metastases	0	70	61.4	71	64.5	141	62.9	0.517
	1	34	29.8	24	21.8	58	25.9	
	2	8	7.0	11	10.0	19	8.5	
	3	1	0.9	3	2.7	4	1.8	
	4	1	0.9	1	0.9	2	0.9	
Distant metastases	None	70	61.4	71	64.5	141	62.9	
	Bones	10	8.8	6	5.5	16	7.1	
	Bones liver	0	0.0	1	0.9	1	0.4	
	Bones liver brain lymphnodes	0	0.0	1	0.9	1	0.4	
	Bones lymphnodes	1	0.9	1	0.9	2	0.9	
	Bones other	1	0.9	0	0.0	1	0.4	
	Liver	4	3.5	4	3.6	8	3.6	
	Liver lymphnodes	1	0.9	0	0.0	1	0.4	
	Liver other	1	0.9	0	0.0	1	0.4	
	Lung	10	8.8	4	3.6	14	6.3	
	Lung bones	1	0.9	2	1.8	3	1.3	
	Lung lymphnodes other	0	0.0	1	0.9	1	0.4	
	Lung lymphnodes skin	0	0.0	1	0.9	1	0.4	
	Lymphnodes	2	1.8	4	3.6	6	2.7	
	Other	3	2.6	1	0.9	4	1.8	
	Peritoneum	1	0.9	1	0.9	2	0.9	
	Peritoneum lymphnodes	1	0.9	1	0.9	2	0.9	
	Peritoneum other	0	0.0	1	0.9	1	0.4	
	Skin	1	0.9	1	0.9	2	0.9	
	Pleura	3	2.6	3	2.7	6	2.7	
	Pleura bones	0	0.0	1	0.9	1	0.4	
	Pleura lung	2	1.8	2	1.8	4	1.8	
	Pleura lung bones	1	0.9	0	0.0	1	0.4	
	Pleura lung bones liver	1	0.9	0	0.0	1	0.4	
	Pleura lymphnodes	0	0.0	2	1.8	2	0.9	
	Pleura peritoneum lymphnodes	0	0.0	1	0.9	1	0.4	
Previous treatment	No	21	18.4	23	20.9	44	19.6	0.737
	Yes	93	81.6	87	79.1	180	80.4	
Operation	No	31	27.2	38	34.5	69	30.8	0.250
	Yes	83	72.8	72	65.5	155	69.2	
Radiotherapy	No	95	83.3	92	83.6	187	83.5	1.000
	Yes	19	16.7	18	16.4	37	16.5	
Chemotherapy	No	63	55.3	63	57.3	126	56.3	0.789
	Yes	51	44.7	47	42.7	98	43.8	
Other treatment	No	112	98.2	110	100.0	222	99.1	0.498
	Yes	2	1.8	0	0.0	2	0.9	
Measurable tumor	No	60	52.6	55	50.0	115	51.3	0.789
	Yes	54	47.4	55	50.0	109	48.7	

In addition, the data for the period of time between cancer diagnosis and screening indicate that both treatment groups are comparable as seen in **Table 13**.

Table 13 Total study population – period of time between diagnosis and screening [months]

ALL	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
Months since	Helixor	114	0	18.9	37.1	0.0	1.0	4.0	19.0	222.0	0.391
diagnosis	Lentinan	110	0	12.1	23.0	0.0	1.0	3.5	14.0	143.0	
	Total	224	0	15.5	31.1	0.0	1.0	4.0	16.0	222.0	

2.2.1.2 Non small cell lung cancer

The tumor anamnesis of non small cell lung cancer patients is listed in **Table 14**. Primary tumor, lymph node metastases and distant metastases status are comparable for patients randomized either in the HELIXOR® A or Lentinan group. However, patients randomized to the treatment group of HELIXOR® A tend to have less invasive primary tumors – major differences are seen for pT2 and pT4 with 37.0% and 28.3% for HELIXOR® A and 13.3 and 42.2% for Lentinan, respectively. The other variables including operation, measurable tumor, tumor treatment – chemotherapy, radiotherapy and other treatment – are similar in both treatment groups.

Table 14 Non small cell lung cancer – tumor anamnesis

NSCLC		Helixor N=46		Lentinan N=45		Total N=91		p-value
		N	%	N	%	N	%	
pT	1	3	6.5	3	6.7	6	6.6	0.074
	2	17	37.0	6	13.3	23	25.3	
	3	11	23.9	11	24.4	22	24.2	
	4	13	28.3	19	42.2	32	35.2	
	X	2	4.3	6	13.3	8	8.8	
pN	0	10	21.7	9	20.0	19	20.9	0.372
	1	5	10.9	6	13.3	11	12.1	
	2	21	45.7	13	28.9	34	37.4	
	3	9	19.6	16	35.6	25	27.5	
	X	1	2.2	1	2.2	2	2.2	
M	0	27	58.7	29	64.4	56	61.5	0.668
	1	19	41.3	16	35.6	35	38.5	
Number of Distant metastases	0	27	58.7	29	64.4	56	61.5	0.839
	1	14	30.4	10	22.2	24	26.4	
	2	4	8.7	4	8.9	8	8.8	
	3	1	2.2	1	2.2	2	2.2	
	4	0	0.0	1	2.2	1	1.1	
Distant metastases	None	27	58.7	29	64.4	56	61.5	
	Bones	5	10.9	3	6.7	8	8.8	
	Bones liver	0	0.0	1	2.2	1	1.1	
	Bones liver brain lymphnodes	0	0.0	1	2.2	1	1.1	
	Bones lymphnodes	1	2.2	0	0.0	1	1.1	
	Liver	1	2.2	1	2.2	2	2.2	
	Lung	5	10.9	3	6.7	8	8.8	
	Lung bones	1	2.2	1	2.2	2	2.2	
	Lung lymphnodes other	0	0.0	1	2.2	1	1.1	
	Lymphnodes	0	0.0	2	4.4	2	2.2	
	Skin	1	2.2	0	0.0	1	1.1	
	Pleura	2	4.3	1	2.2	3	3.3	
	Pleura lung	2	4.3	1	2.2	3	3.3	
	Pleura lung bones	1	2.2	0	0.0	1	1.1	
	Pleura lymphnodes	0	0.0	1	2.2	1	1.1	
Previous treatment	No	16	34.8	16	35.6	32	35.2	1.000
	Yes	30	65.2	29	64.4	59	64.8	
Operation	No	24	52.2	30	66.7	54	59.3	0.202
	Yes	22	47.8	15	33.3	37	40.7	
Radiotherapy	No	40	87.0	37	82.2	77	84.6	0.574
	Yes	6	13.0	8	17.8	14	15.4	
Chemotherapy	No	27	58.7	26	57.8	53	58.2	1.000
	Yes	19	41.3	19	42.2	38	41.8	
Other treatment	No	45	97.8	45	100.0	90	98.9	1.000
	Yes	1	2.2	0	0.0	1	1.1	
Tumor treatment	None	16	34.8	16	35.6	32	35.2	0.414
	Chemo	5	10.9	11	24.4	16	17.6	
	Others	1	2.2	0	0.0	1	1.1	
	Radiatio	1	2.2	1	2.2	2	2.2	
	Radiatio chemo	1	2.2	2	4.4	3	3.3	
	Operation	8	17.4	7	15.6	15	16.5	
	Operation chemo	10	21.7	3	6.7	13	14.3	
	Operation radiatio	1	2.2	2	4.4	3	3.3	
	Operation radiatio chemo	3	6.5	3	6.7	6	6.6	
Measurable tumor	No	17	37.0	14	31.1	31	34.1	0.659
	Yes	29	63.0	31	68.9	60	65.9	

In addition, the data for the period of time between cancer diagnosis and screening indicate that both treatment groups are comparable as seen in **Table 15**.

Table 15 Non small cell lung cancer – period of time between diagnosis and screening [months]

NSCLC	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
Months	Helixor	46	0	9.8	19.0	0.0	1.0	3.5	9.0	99.0	0.747
since	Lentinan	45	0	5.9	6.9	0.0	1.0	4.0	9.0	24.0	
diagnosis	Total	91	0	7.8	14.4	0.0	1.0	4.0	9.0	99.0	

2.2.1.3 Breast cancer

Tumor anamnesis of breast cancer patients is listed in **Table 16.** Treatment groups of HELIXOR® A and Lentinan are comparable for tumor characteristics including primary tumor, lymph node metastases and distant metastases status. The parameters operation, measurable tumor, tumor treatment – chemotherapy, radiotherapy and other treatment – are distributed similarly in both the verum and the control group.

Table 16 Breast cancer – tumor anamnesis

BREAST		Helixor N=35		Lentinan N=32		Total N=67		p-value
		N	%	N	%	N	%	
pT	1	4	11.4	9	28.1	13	19.4	0.183
	2	21	60.0	15	46.9	36	53.7	
	3	3	8.6	1	3.1	4	6.0	
	4	5	14.3	2	6.3	7	10.4	
	X	2	5.7	5	15.6	7	10.4	
pN	0	17	48.6	11	34.4	28	41.8	0.418
	1	8	22.9	8	25.0	16	23.9	
	2	10	28.6	11	34.4	21	31.3	
	X	0	0.0	2	6.3	2	3.0	
M	0	18	51.4	16	50.0	34	50.7	1.000
	1	17	48.6	16	50.0	33	49.3	
Number of distant metastases	0	18	51.4	16	50.0	34	50.7	0.467
	1	13	37.1	9	28.1	22	32.8	
	2	3	8.6	6	18.8	9	13.4	
	3	0	0.0	1	3.1	1	1.5	
	4	1	2.9	0	0.0	1	1.5	
Distant metastases	None	18	51.4	16	50.0	34	50.7	
	Bones	5	14.3	3	9.4	8	11.9	
	Bones lymphnodes	0	0.0	1	3.1	1	1.5	
	Bones other	1	2.9	0	0.0	1	1.5	
	Liver	0	0.0	1	3.1	1	1.5	
	Liver lymphnodes	1	2.9	0	0.0	1	1.5	
	Lung	5	14.3	1	3.1	6	9.0	
	Lung bones	0	0.0	1	3.1	1	1.5	
	Lung lymphnodes skin	0	0.0	1	3.1	1	1.5	
	Lymphnodes	1	2.9	1	3.1	2	3.0	
	Other	1	2.9	1	3.1	2	3.0	
	Peritoneum lymphnodes	1	2.9	1	3.1	2	3.0	
	Skin	0	0.0	1	3.1	1	1.5	
	Pleura	1	2.9	1	3.1	2	3.0	
	Pleura bones	0	0.0	1	3.1	1	1.5	
	Pleura lung	0	0.0	1	3.1	1	1.5	
	Pleura lung bones liver	1	2.9	0	0.0	1	1.5	
	Pleura lymphnodes	0	0.0	1	3.1	1	1.5	
Previous treatment	No	2	5.7	2	6.3	4	6.0	1.000
	Yes	33	94.3	30	93.8	63	94.0	
Operation	No	3	8.6	2	6.3	5	7.5	1.000
	Yes	32	91.4	30	93.8	62	92.5	
Radiotherapy	No	22	62.9	24	75.0	46	68.7	0.307
	Yes	13	37.1	8	25.0	21	31.3	
Chemotherapy	No	20	57.1	22	68.8	42	62.7	0.449
	Yes	15	42.9	10	31.3	25	37.3	
Other treatment	No	34	97.1	32	100.0	66	98.5	1.000
	Yes	1	2.9	0	0.0	1	1.5	
Tumor treatment	None	2	5.7	2	6.3	4	6.0	
	Chemo	1	2.9	0	0.0	1	1.5	
	Operation	13	37.1	17	53.1	30	44.8	
	Operation chemo	6	17.1	5	15.6	11	16.4	
	Operation radiatio	5	14.3	3	9.4	8	11.9	
	Operation radiatio chemo	7	20.0	5	15.6	12	17.9	
	Operation radiatio chemo others	1	2.9	0	0.0	1	1.5	
Measurable tumor	No	23	65.7	21	65.6	44	65.7	1.000
	Yes	12	34.3	11	34.4	23	34.3	

In addition, the data for the period of time between cancer diagnosis and screening indicate that both treatment groups are comparable as seen in **Table 17**.

Table 17 Breast cancer – period of time between diagnosis and screening [months]

BREAST	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
Months since diagnosis	Helixor	35	0	32.4	48.9	0.0	0.0	2.0	59.0	188.0	0.569
	Lentinan	32	0	23.8	37.3	0.0	0.0	3.0	36.5	143.0	
	Total	67	0	28.3	43.6	0.0	0.0	2.0	44.0	188.0	

2.2.1.4 Ovarian cancer

Tumor anamnesis of ovarian cancer patients is listed in **Table 18**. Primary tumor, lymph node and metastases status are comparable for verum and control treatment group. Additional parameters listed, including operation, measurable tumor, tumor treatment – chemotherapy, radiotherapy and other treatment – are also similar distributed in the treatment groups HELIXOR® A and Lentinan.

Table 18 Ovarian cancer – tumor anamnesis

OVARIAN		Helixor N=33		Lentinan N=33		Total N=66		p-value
		N	%	N	%	N	%	
pT	1	3	9.1	4	12.1	7	10.6	0.934
	2	7	21.2	8	24.2	15	22.7	
	3	20	60.6	18	54.5	38	57.6	
	4	0	0.0	1	3.0	1	1.5	
	X	3	9.1	2	6.1	5	7.6	
pN	0	23	69.7	21	63.6	44	66.7	0.809
	1	5	15.2	4	12.1	9	13.6	
	2	0	0.0	1	3.0	1	1.5	
	X	5	15.2	7	21.2	12	18.2	
M	0	25	75.8	26	78.8	51	77.3	1.000
	1	8	24.2	7	21.2	15	22.7	
Number of distant metastases	0	25	75.8	26	78.8	51	77.3	0.873
	1	7	21.2	5	15.2	12	18.2	
	2	1	3.0	1	3.0	2	3.0	
	3	0	0.0	1	3.0	1	1.5	
Distant metastases	None	25	75.8	26	78.8	51	77.3	
	Liver	3	9.1	2	6.1	5	7.6	
	Liver other	1	3.0	0	0.0	1	1.5	
	Lymphnodes	1	3.0	1	3.0	2	3.0	
	Other	2	6.1	0	0.0	2	3.0	
	Peritoneum	1	3.0	1	3.0	2	3.0	
	Peritoneum other	0	0.0	1	3.0	1	1.5	
	Pleura	0	0.0	1	3.0	1	1.5	
	Pleura peritoneum lymphnodes	0	0.0	1	3.0	1	1.5	
Previous treatment	No	3	9.1	5	15.2	8	12.1	0.708
	Yes	30	90.9	28	84.8	58	87.9	
Operation	No	4	12.1	6	18.2	10	15.2	0.733
	Yes	29	87.9	27	81.8	56	84.8	
Radiotherapy	No	33	100.0	31	93.9	64	97.0	0.492
	Yes	0	0.0	2	6.1	2	3.0	
Chemotherapy	No	16	48.5	15	45.5	31	47.0	1.000
	Yes	17	51.5	18	54.5	35	53.0	
Tumor treatment	None	3	9.1	5	15.2	8	12.1	0.777
	Chemo	1	3.0	1	3.0	2	3.0	
	Operation	13	39.4	9	27.3	22	33.3	
	Operation chemo	16	48.5	16	48.5	32	48.5	
	Operation radiatio	0	0.0	1	3.0	1	1.5	
	Operation radiatio chemo	0	0.0	1	3.0	1	1.5	
Measurable tumor	No	20	60.6	20	60.6	40	60.6	1.000
	Yes	13	39.4	13	39.4	26	39.4	

The trial population with ovarian cancer does not reveal any difference in the period of time between cancer diagnosis and screening for both treatment groups as shown in **Table 19**.

Table 19 Ovarian cancer – period of time between diagnosis and screening [months]

OVARIAN	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
Months since diagnosis	Helixor	33	0	17.2	38.7	0.0	0.0	7.0	20.0	222.0	0.510
	Lentinan	33	0	9.3	13.7	0.0	0.0	3.0	13.0	67.0	
	Total	66	0	13.2	29.0	0.0	0.0	5.0	16.0	222.0	

2.3 Treatment

The subdivision of HELIXOR® A and Lentinan patients into different chemotherapy schemes are listed in **Table 20** and **Table 21**. In addition the number of cycles of chemotherapy as well as the duration of trial medication in weeks are depicted with the respective number of patients.

The treatment duration with HELIXOR® A was arranged according to the scheme described in the original protocol. The control Lentinan was given in the same time period but was injected daily.

Table 20 Chemotherapy scheme, number of cycles and duration of HELIXOR® A in weeks

Treatment:	N	Diagnosis:	N	Chemotherapy scheme:	N	Number of cycles:	N	Duration of trial medication (weeks):	N
Helixor:	114	NSCLC:	46	NVB+PDD:	24	2	24	6	23
								7	1
				MVP:	22	2:	22	5:	2
								6:	16
								7:	1
								8:	3
		Breast:	35	CAP:	12	2:	12	6:	9
								7:	2
								8:	1
				CAF:	23	2:	23	5:	1
								6:	21
								8:	1
		Ovarian:	33	CP:	21	1:	1	6:	1
						2:	20	6:	18
								7:	1
								8:	1
				IFO+CBP or PDD:	12	2:	12	6:	1
								8:	11

Table 21 Chemotherapy scheme, number of cycles and duration of Lentinan in weeks

Treatment:	N	Diagnosis:	N	Chemotherapy scheme:	N	Number of cycles:	N	Duration of trial medication (weeks):	N
Lentinan:	110	NSCLC:	45	NVB+PDD:	20	1:	1	6:	1
						2:	19	6:	15
								7:	4
				MVP:	25	2:	25	6:	12
								7:	7
								8:	5
								9:	1
		Breast:	32	CAP:	8	2:	8	6:	4
								7:	3
								12:	1
				CAF:	24	2:	24	6:	15
								7:	8
								8:	1
		Ovarian:	33	CP:	26	2:	26	6:	17
								7:	7
								8:	1
								9:	1
				IFO+CBP or PDD:	7	1:	1	8:	1
						2:	6	6:	1
								7:	1
								8:	2
								9:	2

Each tumor entity was treated with 2 different chemotherapeutics according to the trial protocol (chapter 1.2). Comparison of verum and control groups do not reveal significant differences in chemotherapy plans as shown in **Table 22**.

Table 22 Chemotherapy of tumor entities

		Helixor		Lentinan		Total		p-value
		N	%	N	%	N	%	
NSCLC	NVB+PDD	24	52.2	20	44.4	44	48.4	0.531
	MVP	22	47.8	25	55.6	47	51.6	
Breast	CAP	12	34.3	8	25.0	20	29.9	0.437
	CAF	23	65.7	24	75.0	47	70.1	
Ovarian	CP	21	63.6	26	78.8	47	71.2	0.277
	IFO+CBP or PDD	12	36.4	7	21.2	19	28.8	

2.4 Comparability between the verum and the control group

The verum and the control group are compared in total as well as for each cancer entity. The variables to be looked at are sex, age, classification of disease (TNM) and chemotherapy plan. The variable sex is shown and analysed exclusively for the tumor subgroup of non small cell lung cancer patients since patients with breast and ovarian cancer are all female. Comparison of the chemotherapy plan is carried out only for subgroups of tumor entities and not for the total trial population since every tumor type was treated with different preparations.

2.4.1.1 Total study population

Randomization of the overall trial population resulted in comparable treatment groups of HELIXOR® A and Lentinan as shown in **Table 23** and **Table 24**.

Table 23 Total study population – Comparison of sex and tumor characteristics in treatment groups

ALL		Helixor N=114		Lentinan N=110		Total N=224		p-value
		N	%	N	%	N	%	
Sex	Male	26	22.8	23	20.9	49	21.9	0.749
	Female	88	77.2	87	79.1	175	78.1	
pT	1	10	8.8	16	14.5	26	11.6	0.127
	2	45	39.5	29	26.4	74	33.0	
	3	34	29.8	30	27.3	64	28.6	
	4	18	15.8	22	20.0	40	17.9	
	X	7	6.1	13	11.8	20	8.9	
pN	0	50	43.9	41	37.3	91	40.6	0.361
	1	18	15.8	18	16.4	36	16.1	
	2	31	27.2	25	22.7	56	25.0	
	3	9	7.9	16	14.5	25	11.2	
	X	6	5.3	10	9.1	16	7.1	
M	0	70	61.4	71	64.5	141	62.9	0.679
	1	44	38.6	39	35.5	83	37.1	

Table 24 Total study population – Comparison of age in treatment groups

ALL	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
Age	Helixor	114	0	52.5	9.3	31.0	46.0	50.0	60.0	70.0	0.757
	Lentinan	110	0	52.0	9.6	30.0	45.0	51.0	59.0	70.0	
	Total	224	0	52.2	9.5	30.0	45.0	51.0	60.0	70.0	

2.4.1.2 Non small cell lung cancer

Randomization of the non small cell lung cancer trial population resulted in comparable treatment groups of HELIXOR® A and Lentinan as shown in **Table 25** and **Table 26**. However, patients randomized to the treatment group of HELIXOR® A tend to have less invasive primary tumors.

Table 25 Non small cell lung cancer – Comparison of sex, tumor characteristics and chemotherapy plan in treatment groups

NSCLC		Helixor N=46		Lentinan N=45		total N=91		p-value
		N	%	N	%	N	%	
Sex	Male	26	56.5	23	51.1	49	53.8	0.676
	Female	20	43.5	22	48.9	42	46.2	
pT	1	3	6.5	3	6.7	6	6.6	0.074
	2	17	37.0	6	13.3	23	25.3	
	3	11	23.9	11	24.4	22	24.2	
	4	13	28.3	19	42.2	32	35.2	
	X	2	4.3	6	13.3	8	8.8	
pN	0	10	21.7	9	20.0	19	20.9	0.372
	1	5	10.9	6	13.3	11	12.1	
	2	21	45.7	13	28.9	34	37.4	
	3	9	19.6	16	35.6	25	27.5	
	X	1	2.2	1	2.2	2	2.2	
M	0	27	58.7	29	64.4	56	61.5	0.668
	1	19	41.3	16	35.6	35	38.5	
Chemotherapy	NVB+PDD	24	52.2	20	44.4	44	48.4	0.531
	MVP	22	47.8	25	55.6	47	51.6	

Table 26 Non small cell lung cancer – Comparison of age in treatment groups

NSCLC	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
Age	Helixor	46	0	56.8	9.4	35.0	48.0	59.0	64.0	70.0	0.773
	Lentinan	45	0	56.0	10.0	30.0	48.0	58.0	63.0	70.0	
	Total	91	0	56.4	9.7	30.0	48.0	58.0	64.0	70.0	

2.4.1.3 Breast cancer

Randomization of the trial population diseased with breast cancer is comparable for both treatment groups HELIXOR® A and Lentinan and shown in **Table 27** and **Table 28**.

Table 27 Breast cancer – Comparison tumor characteristics and chemotherapy plan in treatment groups

BREAST		Helixor N=35		Lentinan N=32		Total N=67		p-value
		N	%	N	%	N	%	
pT	1	4	11.4	9	28.1	13	19.4	0.183
	2	21	60.0	15	46.9	36	53.7	
	3	3	8.6	1	3.1	4	6.0	
	4	5	14.3	2	6.3	7	10.4	
	X	2	5.7	5	15.6	7	10.4	
pN	0	17	48.6	11	34.4	28	41.8	0.418
	1	8	22.9	8	25.0	16	23.9	
	2	10	28.6	11	34.4	21	31.3	
	X	0	0.0	2	6.3	2	3.0	
M	0	18	51.4	16	50.0	34	50.7	1.000
	1	17	48.6	16	50.0	33	49.3	
Chemotherapy	CAP	12	34.3	8	25.0	20	29.9	0.437
	CAF	23	65.7	24	75.0	47	70.1	

Table 28 Breast cancer – Comparison of age in treatment groups

BREAST	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
Age	Helixor	35	0	47.6	8.1	31.0	42.0	49.0	54.0	64.0	0.822
	Lentinan	32	0	47.0	8.0	31.0	41.5	46.5	52.0	67.0	
	Total	67	0	47.3	8.0	31.0	42.0	47.0	52.0	67.0	

2.4.1.4 Ovarian cancer

Patients diseased with ovarian cancer are assigned comparable to verum and control treatment groups analysed for the variables tumor characteristics, chemotherapy plan and age as shown in **Table 29** and **Table 30.**

Table 29 Ovarian cancer – Comparison of tumor characteristics and chemotherapy plan in treatment groups

OVARIAN		Helixor N=33		Lentinan N=33		Total N=66		p-value
		N	%	N	%	N	%	
pT	1	3	9.1	4	12.1	7	10.6	0.934
	2	7	21.2	8	24.2	15	22.7	
	3	20	60.6	18	54.5	38	57.6	
	4	0	0.0	1	3.0	1	1.5	
	X	3	9.1	2	6.1	5	7.6	
pN	0	23	69.7	21	63.6	44	66.7	0.809
	1	5	15.2	4	12.1	9	13.6	
	2	0	0.0	1	3.0	1	1.5	
	X	5	15.2	7	21.2	12	18.2	
M	0	25	75.8	26	78.8	51	77.3	1.000
	1	8	24.2	7	21.2	15	22.7	
Chemotherapy	CP	21	63.6	26	78.8	47	71.2	0.277
	IFO+CBP or PDD	12	36.4	7	21.2	19	28.8	

Table 30 Ovarian cancer – Comparison of age in treatment groups

OVARIAN	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
Age	Helixor	33	0	51.6	7.8	32.0	47.0	50.0	57.0	67.0	0.749
	Lentinan	33	0	51.3	8.1	37.0	45.0	50.0	57.0	67.0	
	Total	66	0	51.5	7.9	32.0	45.0	50.0	57.0	67.0	

This is to summarize the results of Tables 23 to 30: The assignment of patients according to the randomization plan resulted in comparable trial groups for both the verum and the control group. Parameters taken into consideration include sex, age, tumor characteristics and chemotherapy plan. The subgroup of non small cell lung cancer patients has to be considered carefully concerning the primary tumor status since patients treated with HELIXOR® A incline to have less invasive primary tumors.

3 Evaluation of Tolerance

3.1 Quality of Life in different Treatment Groups

Three different parameters were used to evaluate the quality of life of patients, namely, the KPI (Karnofsky Performance Index), TCM (Traditional Chinese Medicine) and FLIC (Functional Living Index of cancer). Quality of life parameters are determined at the time of screening and for the final examination. The following analysis presents these measure points separately and shows additionally the change of quality of life parameters during the treatment period (difference between final and screening).

3.1.1 Karnofsky Performance Index

The KPI or Karnofsky Performance Index is evaluating the physical condition of patients on a scale from 0-100%, the higher the percentage the better the performance. Changes over the period of treatment time are analysed as 'reduced', 'stable' or 'increased' quality of life whereas 'reduced' or 'increased' signifies a change of at least 10% and is calculated as difference of the Karnofsky Index at the final investigation minus Karnofsky Index at screening.

3.1.1.1 Total study population

The Karnofsky Index of the total trial population at screening and final investigation is summarized in **Table 31** and **Table 32**. The given p-value (p = 0.170) at screening time indicated comparability of verum and control group at the beginning of the study.

Table 31 Total study population – Karnofsky Performance Index (KPI) at screening

ALL		**Helixor N=114**		**Lentinan N=110**		**Total N=224**		**p-value**
		N	%	N	%	N	%	
KPI	40%	0	0.0	1	0.9	1	0.4	0.170
	50%	4	3.5	1	0.9	5	2.2	
	60%	8	7.0	10	9.1	18	8.0	
	70%	20	17.5	34	30.9	54	24.1	
	80%	47	41.2	37	33.6	84	37.5	
	90%	28	24.6	22	20.0	50	22.3	
	100%	7	6.1	5	4.5	12	5.4	

Table 32 Total study population – Karnofsky Peformance Index at final investigation

ALL		**Helixor N=114**		**Lentinan N=110**		**Total N=224**	
		N	%	N	%	N	%
KPI	Missing	0	0.0	1	0.9	1	0.4
	40%	1	0.9	1	0.9	2	0.9
	50%	1	0.9	0	0.0	1	0.4
	60%	2	1.8	9	8.2	11	4.9
	70%	11	9.6	22	20.0	33	14.7
	80%	23	20.2	39	35.5	62	27.7
	90%	66	57.9	32	29.1	98	43.8
	100%	10	8.8	6	5.5	16	7.1

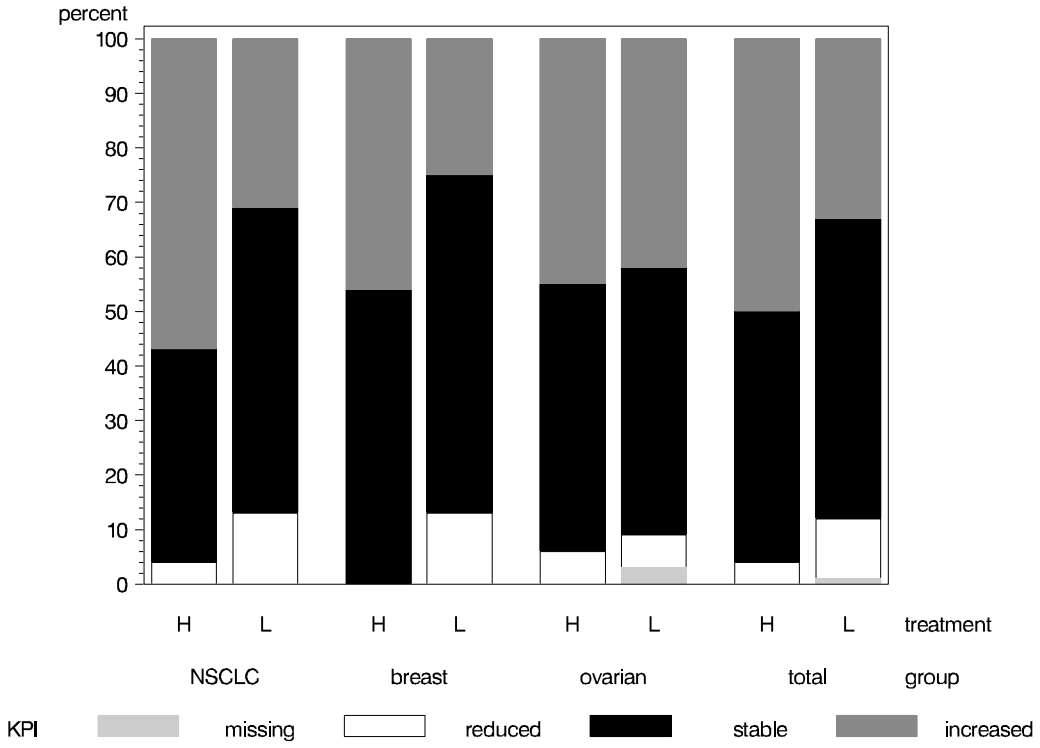
Changes of the KPI during period of treatment are evaluated in **Table 33** as difference of Karnofsky Performance Index between final investigation and screening. The highly significant p-value (p = 0.003) between HELIXOR® A and Lentinan group was calculated by stratification across the different tumor entities. Half of the patients in the HELIXOR® A group show an increase in the KPI in comparison to 33% of patients under control treatment. For further interpretation of this result single tumor subtypes will be considered in detail as follows.

Table 33 Total study population – Karnofsky Performance Index evaluated as reduced, stable and increased

ALL		Helixor N=114		Lentinan N=109		Total N=223		strat. p-value
		N	%	N	%	N	%	
KPI	Reduced	4	3.5	12	11.0	16	7.2	0.003
	Stable	53	46.5	61	56.0	114	51.1	
	Increased	57	50.0	36	33.0	93	41.7	

The graphical presentation of the KPI categorized in 'reduced', 'stable' and 'increased' in cancer subgroups and for the treatment groups HELIXOR® A (H) and Lentinan (L) is shown in **Figure 1**.

Figure 1 Total study population, NSCLC, breast cancer, ovarian cancer – Karnofsky Performance Index evaluated as reduced, stable and increased



3.1.1.2 Non small cell lung cancer

The KPI of the non small cell lung cancer patient population at screening and final investigation are shown in **Table 34** and **Table 35**. Patients in the different treatment groups are comparable at screening time as shown by the p-value 0.353.

Table 34 Non small cell lung cancer – Karnofsky Performance Index at screening

NSCLC		Helixor N=46		Lentinan N=45		Total N=91		p-value
		N	%	N	%	N	%	
KPI	50%	3	6.5	0	0.0	3	3.3	0.353
	60%	4	8.7	5	11.1	9	9.9	
	70%	13	28.3	19	42.2	32	35.2	
	80%	16	34.8	13	28.9	29	31.9	
	90%	10	21.7	8	17.8	18	19.8	

Table 35 Non small cell lung cancer – Karnofsky Performance Index at final investigation

NSCLC		Helixor N=46		Lentinan N=45		Total N=91	
		N	%	N	%	N	%
KPI	40%	1	2.2	0	0.0	1	1.1
	50%	1	2.2	0	0.0	1	1.1
	60%	2	4.3	5	11.1	7	7.7
	70%	6	13.0	13	28.9	19	20.9
	80%	7	15.2	15	33.3	22	24.2
	90%	29	63.0	12	26.7	41	45.1

Changes of KPI during period of treatment are evaluated in **Table 36** as its difference between final investigation and screening. The significant p-value (p = 0.011) between the HELIXOR® A and Lentinan group has to be considered under the problem of multiple testing. However, adjustment after Bonferroni-Holm still provides a significant p-value with 0.011 (adjusted level of 0.017). More than half of the patients (56,5 %) in the HELIXOR® A group show an increase in the Karnofsky Performance Index compared to 31% of patients under control treatment.

Table 36 Non small cell lung cancer – Karnofsky Performance Index evaluated as reduced, stable and increased

NSCLC		Helixor N=46		Lentinan N=45		Total N=91		p-value
		N	%	N	%	N	%	
KPI	Reduced	2	4.3	6	13.3	8	8.8	0.011
	Stable	18	39.1	25	55.6	43	47.3	
	Increased	26	56.5	14	31.1	40	44	

3.1.1.3 Breast cancer

The Karnofsky Performance Index data of the breast cancer patient population at screening and final investigation are listed in **Table 37** and **Table 38**. Breast cancer patients in the group either of HELIXOR® A or Lentinan are comparable at the screening time as shown by the p-value 0.882.

Table 37 Breast cancer – Karnofsky Performance Index at screening

BREAST		Helixor N=35		Lentinan N=32		Total N=67		p-value
		N	%	N	%	N	%	
KPI	40%	0	0.0	1	3.1	1	1.5	0.882
	60%	2	5.7	1	3.1	3	4.5	
	70%	5	14.3	6	18.8	11	16.4	
	80%	18	51.4	17	53.1	35	52.2	
	90%	10	28.6	7	21.9	17	25.4	

Table 38 Breast cancer – Karnofsky Performance Index at final investigation

BREAST		Helixor N=35		Lentinan N=32		Total N=67	
		N	%	N	%	N	%
KPI	40%	0	0.0	1	3.1	1	1.5
	60%	0	0.0	1	3.1	1	1.5
	70%	2	5.7	5	15.6	7	10.4
	80%	11	31.4	16	50.0	27	40.3
	90%	22	62.9	9	28.1	31	46.3

Improvement and deterioration of the Karnofsky Performance Index during period of treatment are evaluated in **Table 39**. The p-value between treatment groups HELIXOR® A and Lentinan is not significant on the $\alpha/3$-level taking into consideration the problem of multiple testing. The p-value of 0.027 just exceeds the Bonferroni-Holm adjusted value of 0.025 and therefore the nullhypothesis of no treatment difference can not be rejected. But the result shows a trend which may have clinical implications.

Table 39 Breast cancer – Karnofsky Index evaluated as reduced, stable and increased

BREAST		Helixor N=35		Lentinan N=32		total N=67		p-value
		N	%	N	%	N	%	
KPI	Reduced	0	0.0	4	12.5	4	6.0	0.027
	Stable	19	54.3	20	62.5	39	58.2	
	increased	16	45.7	8	25	24	35.8	

3.1.1.4 Ovarian cancer

The Karnofsky Index of ovarian cancer patients at screening and final investigation are enlisted in **Table 40** and **Table 41**. Ovarian cancer patient groups are comparable at the screening time in verum and control treatment as shown by the p-value of 0.166.

Table 40 Ovarian cancer – Karnofsky Index at screening

OVARIAN		Helixor N=33		Lentinan N=33		Total N=66		p-value
		N	%	N	%	N	%	
KPI	50%	1	3.0	1	3.0	2	3.0	0.166
	60%	2	6.1	4	12.1	6	9.1	
	70%	2	6.1	9	27.3	11	16.7	
	80%	13	39.4	7	21.2	20	30.3	
	90%	8	24.2	7	21.2	15	22.7	
	100%	7	21.2	5	15.2	12	18.2	

Table 41 Ovarian cancer – Karnofsky Index at final investigation

OVARIAN		Helixor N=33		Lentinan N=33		Total N=66	
		N	%	N	%	N	%
KPI	Missing	0	0.0	1	3.0	1	1.5
	60%	0	0.0	3	9.1	3	4.5
	70%	3	9.1	4	12.1	7	10.6
	80%	5	15.2	8	24.2	13	19.7
	90%	15	45.5	11	33.3	26	39.4
	100%	10	30.3	6	18.2	16	24.2

Improvement and deterioration of the Karnofsky Index over period of treatment are evaluated in **Table 42** as difference of Karnofksy Index between final investigation and screening. Treatment groups HELIXOR® A and Lentinan are comparable for changes of the Karnofsky Index (p = 0.953).

Table 42 Ovarian cancer – Karnofsky Index evaluated as reduced, stable and increased

OVARIAN		Helixor N=33		Lentinan N=32		Total N=65		p-value
		N	%	N	%	N	%	
KPI	Reduced	2	6.1	2	6.3	4	6.2	0.953
	Stable	16	48.5	16	50.0	32	49.2	
	Increased	15	45.5	14	43.8	29	44.6	

3.1.2 TCM criteria

The second quality of life criteria under consideration in this study is the TCM (Traditional Chinese Medicine) index evaluating various symptoms including general fatigue, insomnia, anorexia, nausea/vomiting and pain. All these symptoms are categorized on 4 levels (none=0, slight=1, middle=2, serious=3) and are added up to a single TCM score. The single symptoms are represented as well as the overall TCM score at the time of screening and for the final examination. Moreover, the change of parameters during the treatment period is listed.

3.1.2.1 Total study population

The TCM parameters of the total trial population at screening and final investigation are listed in **Table 43, Table 44, Table 45** and **Table 46**. The symptoms anorexia, general fatigue, insomnia, nausea/vomiting and pain in the total population as well as the total TCM score are comparable in verum and control group at time of screening.

Table 43 Total study population – TCM criteria at screening

ALL		Helixor N=114		Lentinan N=110		Total N=224		p-value
		N	%	N	%	N	%	
Anorexia	Missing	1	0.9	0	0.0	1	0.4	0.976
	None	52	45.6	47	42.7	99	44.2	
	Slight	46	40.4	47	42.7	93	41.5	
	Middle	12	10.5	13	11.8	25	11.2	
	Serious	3	2.6	3	2.7	6	2.7	
General fatigue	None	32	28.1	24	21.8	56	25.0	0.640
	Slight	58	50.9	56	50.9	114	50.9	
	Middle	23	20.2	29	26.4	52	23.2	
	Serious	1	0.9	1	0.9	2	0.9	
Insomnia	None	63	55.3	55	50.0	118	52.7	0.303
	Slight	34	29.8	34	30.9	68	30.4	
	Middle	13	11.4	20	18.2	33	14.7	
	Serious	4	3.5	1	0.9	5	2.2	
Nausea/vomiting	None	90	78.9	92	83.6	182	81.3	0.605
	Slight	20	17.5	16	14.5	36	16.1	
	Middle	4	3.5	2	1.8	6	2.7	
Pain	Missing	1	0.9	0	0.0	1	0.4	0.129
	None	80	70.2	67	60.9	147	65.6	
	Slight	18	15.8	31	28.2	49	21.9	
	Middle	12	10.5	11	10.0	23	10.3	
	Serious	3	2.6	1	0.9	4	1.8	

Table 44 Total study population – TCM total score at screening

ALL	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
TCM score	Helixor	112	2	2.9	2.5	0.0	1.0	2.5	5.0	10.0	0.274
	Lentinan	110	0	3.2	2.4	0.0	1.0	3.0	4.0	10.0	
	Total	222	2	3.0	2.5	0.0	1.0	3.0	5.0	10.0	

Table 45 Total study population – TCM criteria at final investigation

ALL		Helixor N=114		Lentinan N=110		Total N=224	
		N	%	N	%	N	%
Anorexia	Missing	0	0.0	1	0.9	1	0.4
	None	79	69.3	44	40.0	123	54.9
	Slight	31	27.2	46	41.8	77	34.4
	Middle	4	3.5	18	16.4	22	9.8
	Serious	0	0.0	1	0.9	1	0.4
General fatigue	Missing	0	0.0	1	0.9	1	0.4
	None	56	49.1	30	27.3	86	38.4
	Slight	54	47.4	61	55.5	115	51.3
	Middle	4	3.5	15	13.6	19	8.5
	Serious	0	0.0	3	2.7	3	1.3
Insomnia	Missing	0	0.0	2	1.8	2	0.9
	None	89	78.1	57	51.8	146	65.2
	Slight	20	17.5	37	33.6	57	25.4
	Middle	4	3.5	13	11.8	17	7.6
	Serious	1	0.9	1	0.9	2	0.9
Nausea/ vomiting	Missing	0	0.0	1	0.9	1	0.4
	Non	96	84.2	69	62.7	165	73.7
	Slight	13	11.4	33	30.0	46	20.5
	Middle	5	4.4	5	4.5	10	4.5
	Serious	0	0.0	2	1.8	2	0.9
Pain	Missing	0	0.0	1	0.9	1	0.4
	None	91	79.8	78	70.9	169	75.4
	Slight	20	17.5	27	24.5	47	21.0
	Middle	3	2.6	4	3.6	7	3.1

Table 46 Total study population – TCM total score at final investigation

ALL	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX
TCM score	Helixor	114	0	1.6	1.8	0.0	0.0	1.0	3.0	8.0
	Lentinan	108	2	3.1	2.5	0.0	1.0	3.0	4.0	10.0
	Total	222	2	2.3	2.3	0.0	1.0	2.0	3.0	10.0

A graphical presentation of baseline and final end of treatment is presented in **Figure 2** and **Figure 3**.

Figure 2 Total study population – TCM criteria at screening

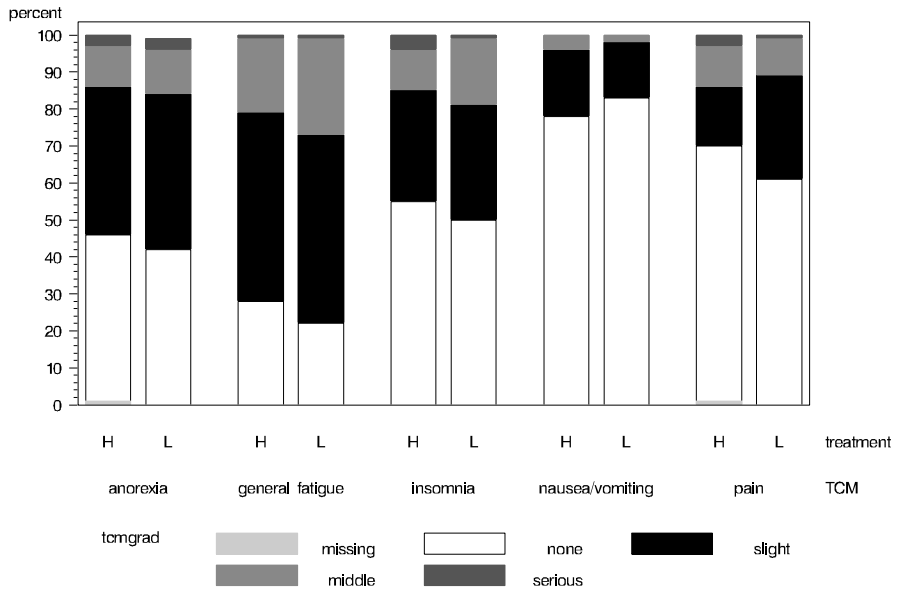
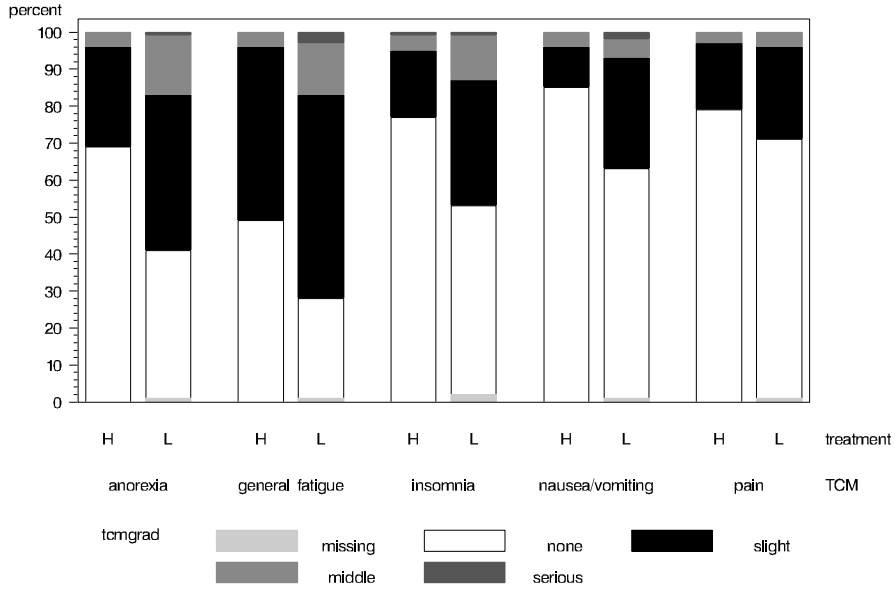


Figure 3 Total study population – TCM criteria at final investigation



Looking at Figure 2 and Figure 3 which illustrate the various symptoms of the TCM score at screening and at final investigation it can be seen that at final investigation the frequency of occurence of the assessment 'middle' and 'serious' were reduced in favour of 'none' and 'slight' in the HELIXOR® A treatment group. Furthermore, the difference of the overall TCM score between screening and final investigation is shown in **Table 47** with a highly significant p-value of 0.0007 between verum and control treatment group. In the HELIXOR® A treatment group there was a reduction of the TCM total score of 1 point in median from screening to final investigation and therefore an improvement of the condition of the patients whereas in the Lentinan treatment group there was no change in median.

Graphically the difference of the TCM score during the period of treatment time is represented in **Figure 4**.

Table 47 Total study population – difference of TCM total score between screening and final investigation

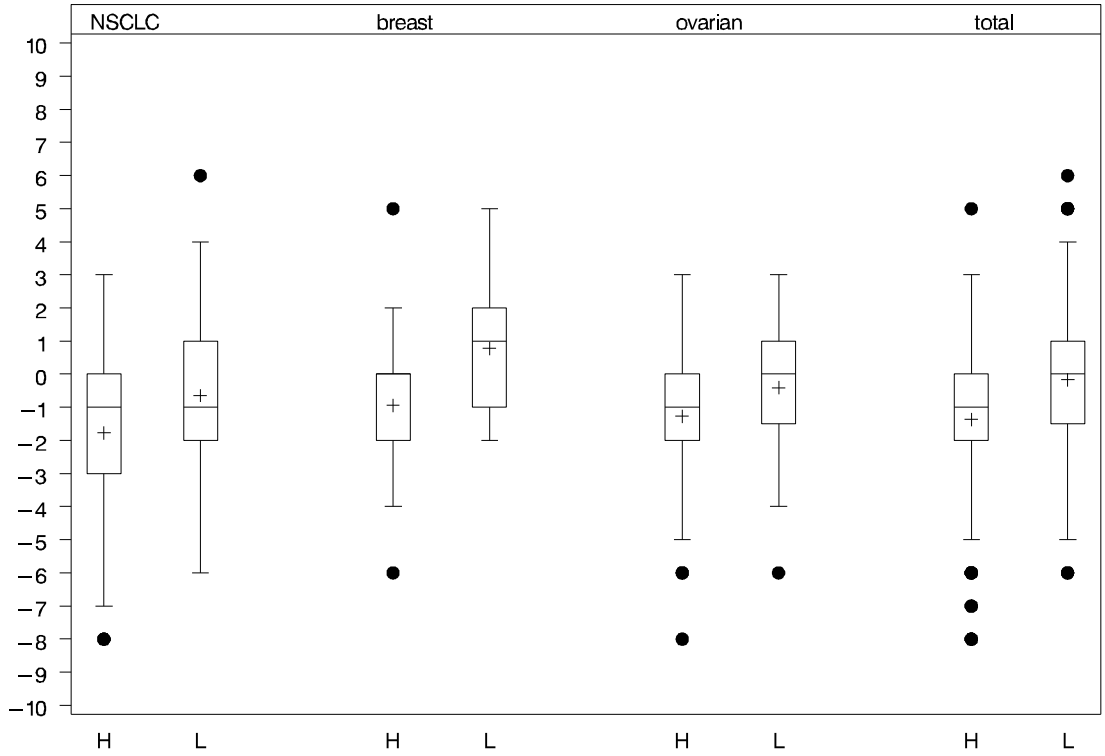
ALL	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	strat. p-value	95%-CI *
TCM score	Helixor	112	2	-1.4	2.4	-8.0	-2.0	-1.0	0.0	5.0	0.0007	-2;0
	Lentinan	108	2	-0.2	2.4	-6.0	-1.5	0.0	1.0	6.0		
	total	220	4	-0.8	2.5	-8.0	-2.0	0.0	1.0	6.0		

Difference: (value of final investigation minus value of screening).
* Because of discrete data, be careful in interpreting the limits of the confidence interval.

Table 48 Total study population – change of TCM items between screening and final investigation

	Helixor	Final investigation								Lentinan	Final investigation							
		None		Slight		Middle		Serious			None		Slight		Middle		Serious	
	Screening	N	%	N	%	N	%	N	%	Screening	N	%	N	%	N	%	N	%
Fatigue	**None**	26	22.8	6	5.3	-	-	-	-	**None**	16	14.7	7	6.4	1	0.9	-	-
	Slight	24	21.1	34	29.8	-	-	-	-	**Slight**	12	11.0	36	33.0	7	6.4	-	-
	Middle	6	5.3	13	11.4	4	3.5	-	-	**Middle**	2	1.8	18	16.5	7	6.4	2	1.8
	Serious	-	-	1	0.9	-	-	-	-	**Serious**	-	-	-	-	-	-	1	0.9
Insomnia	**None**	61	53.5	2	1.8	-	-	-	-	**None**	46	42.6	6	5.6	2	1.9	-	-
	Slight	18	15.8	15	13.2	1	0.9	-	-	**Slight**	9	8.3	22	20.4	2	1.9	-	-
	Middle	9	7.9	2	1.8	2	1.8	-	-	**Middle**	2	1.9	9	8.3	9	8.3	-	-
	Serious	1	0.9	1	0.9	1	0.9	1	0.9	**Serious**	-	-	-	-	-	-	1	0.9
Anorexia	**None**	42	37.2	10	8.8	-	-	-	-	**None**	25	22.9	18	16.5	2	1.8	1	0.9
	Slight	27	23.9	17	15.0	2	1.8	-	-	**Slight**	15	13.8	26	23.9	6	5.5	-	-
	Middle	7	6.2	4	3.5	1	0.9	-	-	**Middle**	3	2.8	2	1.8	8	7.3	-	-
	Serious	3	2.7	-	-	-	-	-	-	**Serious**	1	0.9	-	-	2	1.8	-	-
Nausea	**None**	78	68.4	8	7.0	4	3.5	-	-	**None**	65	59.6	22	20.2	3	2.8	1	0.9
	Slight	16	14.0	3	2.6	1	0.9	-	-	**Slight**	4	3.7	9	8.3	2	1.8	1	0.9
	Middle	2	1.8	2	1.8	-	-	-	-	**Middle**	-	-	2	1.8	-	-	-	-
	Serious	-	-	-	-	-	-	-	-	**Serious**	-	-	-	-	-	-	-	-
Pain	**None**	77	68.1	3	2.7	-	-	-	-	**None**	59	54.1	6	5.5	1	0.9	-	-
	Slight	10	8.8	8	7.1	-	-	-	-	**Slight**	14	12.8	16	14.7	1	0.9	-	-
	Middle	3	2.7	7	6.2	2	1.8	-	-	**Middle**	4	3.7	5	4.6	2	1.8	-	-
	Serious	-	-	2	1.8	1	0.9	-	-	**Serious**	1	0.9	-	-	-	-	-	-

Figure 4 Total study population, NSCLC, breast cancer, ovarian cancer – difference of TCM total score between screening and final investigation



3.1.2.2 Non small cell lung cancer

The TCM parameters of patients diseased with non small cell lung cancer at time of screening and final investigation are listed in **Table 49, Table 50, Table 51** and **Table 52**. The score for each symptom like anorexia, general fatigue, insomnia, nausea/vomiting and pain in the non small cell lung cancer patients as well as the total TCM score are comparable in verum and control group at time of screening.

Table 49 Non small cell lung cancer – TCM criteria at screening

NSCLC		Helixor N=46		Lentinan N=45		Total N=91		p-value
		N	%	N	%	N	%	
Anorexia	Missing	1	2.2	0	0.0	1	1.1	1.000
	None	17	37.0	16	35.6	33	36.3	
	Slight	21	45.7	21	46.7	42	46.2	
	Middle	7	15.2	7	15.6	14	15.4	
	Serious	0	0.0	1	2.2	1	1.1	
General fatigue	None	8	17.4	5	11.1	13	14.3	0.866
	Slight	23	50.0	24	53.3	47	51.6	
	Middle	14	30.4	15	33.3	29	31.9	
	Serious	1	2.2	1	2.2	2	2.2	
Insomnia	None	22	47.8	20	44.4	42	46.2	0.365
	Slight	14	30.4	11	24.4	25	27.5	
	Middle	7	15.2	13	28.9	20	22.0	
	Serious	3	6.5	1	2.2	4	4.4	
Nausea/vomiting	None	38	82.6	40	88.9	78	85.7	0.310
	Slight	5	10.9	5	11.1	10	11.0	
	Middle	3	6.5	0	0.0	3	3.3	
Pain	Missing	1	2.2	0	0.0	1	1.1	0.201
	None	28	60.9	23	51.1	51	56.0	
	Slight	6	13.0	14	31.1	20	22.0	
	Middle	8	17.4	7	15.6	15	16.5	
	Serious	3	6.5	1	2.2	4	4.4	

Table 50 Non small cell lung cancer – TCM total score at screening

NSCLC	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
TCM score	Helixor	44	2	3.5	2.7	0.0	1.0	3.0	5.0	10.0	0.400
	Lentinan	45	0	3.8	2.4	0.0	2.0	4.0	5.0	10.0	
	Total	89	2	3.7	2.6	0.0	2.0	3.0	5.0	10.0	

Table 51 Non small cell lung cancer – TCM criteria at final investigation

NSCLC		Helixor N=46		Lentinan N=45		Total N=91	
		N	%	N	%	N	%
Anorexia	None	31	67.4	20	44.4	51	56.0
	Slight	14	30.4	17	37.8	31	34.1
	Middle	1	2.2	8	17.8	9	9.9
General fatigue	None	20	43.5	10	22.2	30	33.0
	Slight	23	50.0	26	57.8	49	53.8
	Middle	3	6.5	6	13.3	9	9.9
	Serious	0	0.0	3	6.7	3	3.3
Insomnia	None	32	69.6	23	51.1	55	60.4
	Slight	11	23.9	13	28.9	24	26.4
	Middle	2	4.3	8	17.8	10	11.0
	Serious	1	2.2	1	2.2	2	2.2
Nausea/vomiting	None	41	89.1	32	71.1	73	80.2
	Slight	4	8.7	11	24.4	15	16.5
	Middle	1	2.2	2	4.4	3	3.3
Pain	None	31	67.4	33	73.3	64	70.3
	Slight	12	26.1	9	20.0	21	23.1
	Middle	3	6.5	3	6.7	6	6.6

Table 52 Non small cell lung cancer – TCM total score at final investigation

NSCLC	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX
TCM score	Helixor	46	0	1.9	2.1	0.0	0.0	1.0	3.0	8.0
	Lentinan	45	0	3.2	2.7	0.0	1.0	3.0	5.0	10.0
	Total	91	0	2.5	2.4	0.0	0.0	2.0	4.0	10.0

A graphical presentation of baseline and final end of treatment is presented in **Figure 5** and **Figure 6**.

Figure 5 Non small cell lung cancer – TCM criteria at screening

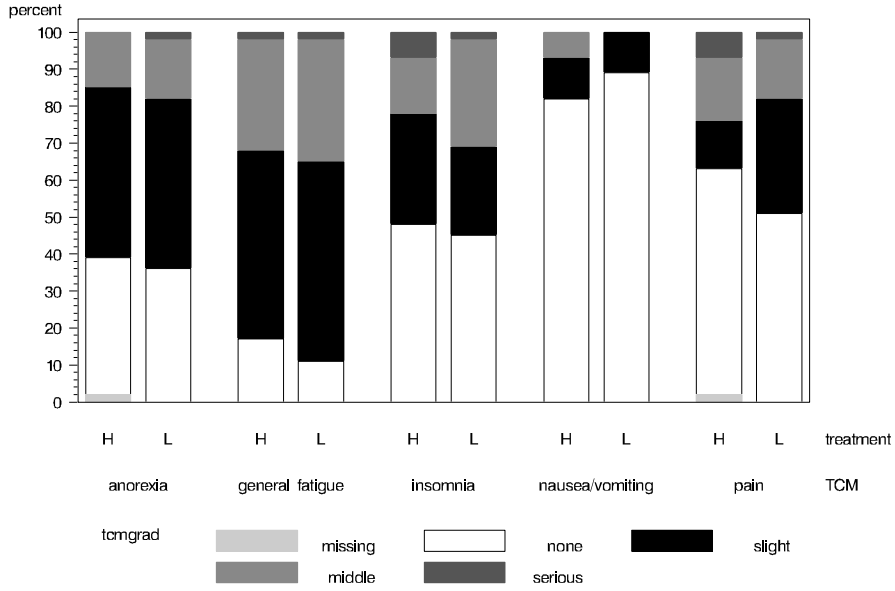


Figure 6 Non small cell lung cancer – TCM criteria at final investigation

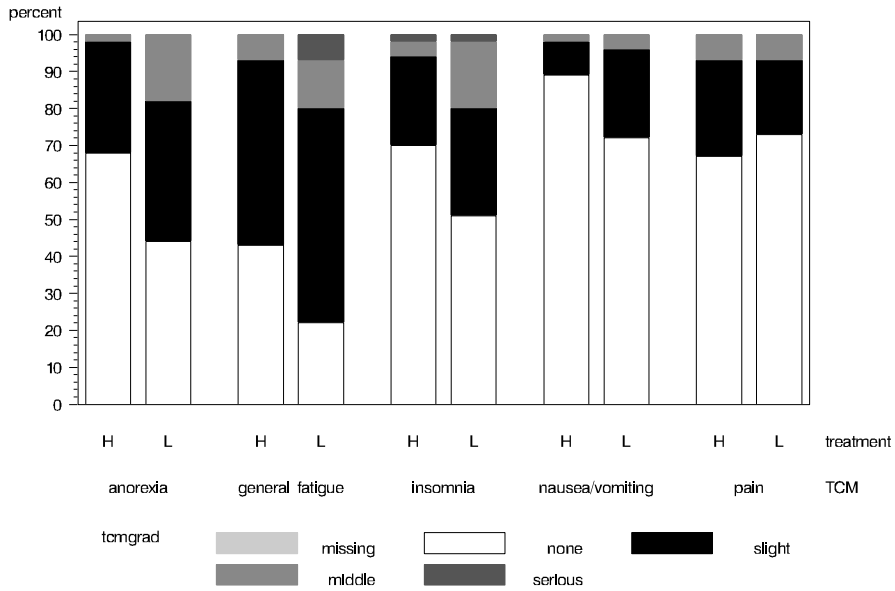


Table 53 Non small cell lung cancer– change of TCM items between screening and final investigation

	Helixor	Final investigation								Lentinan	Final investigation							
		None		Slight		Middle		Serious			None		Slight		Middle		Serious	
	Screening	N	%	N	%	N	%	N	%	Screening	N	%	N	%	N	%	N	%
Fatigue	**None**	6	13.0	2	4.3	-	-	-	-	**None**	4	8.9	1	2.2	-	-	-	-
	Slight	9	19.6	14	30.4	-	-	-	-	**Slight**	6	13.3	14	31.1	4	8.9	-	-
	Middle	5	10.9	6	13.0	3	6.5	-	-	**Middle**	-	-	11	24.4	2	4.4	2	4.4
	Serious	-	-	1	2.2	-	-	-	-	**Serious**	-	-	-	-	-	-	1	2.2
Insomnia	**None**	21	45.7	1	2.2	-	-	-	-	**None**	18	40.0	-	-	2	4.4	-	-
	Slight	6	13.0	8	17.4	-	-	-	-	**Slight**	3	6.7	6	13.3	2	4.4	-	-
	Middle	5	10.9	1	2.2	1	2.2	-	-	**Middle**	2	4.4	7	15.6	4	8.9	-	-
	Serious	-	-	1	2.2	1	2.2	1	2.2	**Serious**	-	-	-	-	-	-	1	2.2
Anorexia	**None**	14	31.1	3	6.7	-	-	-	-	**None**	11	24.4	5	11.1	-	-	-	-
	Slight	12	26.7	9	20.0	-	-	-	-	**Slight**	7	15.6	10	22.2	4	8.9	-	-
	Middle	5	11.1	2	4.4	-	-	-	-	**Middle**	2	4.4	2	4.4	3	6.7	-	-
	Serious	-	-	-	-	-	-	-	-	**Serious**	-	-	-	-	1	2.2	-	-
Nausea	**None**	34	73.9	3	6.5	1	2.2	-	-	**None**	30	66.7	9	20.0	1	2.2	-	-
	Slight	5	10.9	-	-	-	-	-	-	**Slight**	2	4.4	2	4.4	1	2.2	-	-
	Middle	2	4.3	1	2.2	-	-	-	-	**Middle**	-	-	-	-	-	-	-	-
	Serious	-	-	-	-	-	-	-	-	**Serious**	-	-	-	-	-	-	-	-
Pain	**None**	26	57.8	2	4.4	-	-	-	-	**None**	21	46.7	1	2.2	1	2.2	-	-
	Slight	2	4.4	4	8.9	-	-	-	-	**Slight**	9	20.0	4	8.9	1	2.2	-	-
	Middle	2	4.4	4	8.9	2	4.4	-	-	**Middle**	2	4.4	4	8.9	1	2.2	-	-
	Serious	-	-	2	4.4	1	2.2	-	-	**Serious**	1	2.2	-	-	-	-	-	-

The difference of the overall TCM score between screening and final investigation is shown in **Table 54**. There is no statistically significant difference between verum and control group.

Table 54 Non small cell lung cancer – difference of TCM total score between screening and final investigation

NSCLC	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value	95%-CI *
TCM score	Helixor	44	2	-1.8	2.7	-8.0	-3.0	-1.0	0.0	3.0	0.132	-2;0
	Lentinan	45	0	-0.6	2.7	-6.0	-2.0	-1.0	1.0	6.0		
	Total	89	2	-1.2	2.7	-8.0	-3.0	-1.0	0.0	6.0		

Difference: (value of final investigation minus value of screening).
* Because of discrete data, be careful in interpreting the limits of the confidence interval.

3.1.2.3 Breast cancer

The TCM parameters of patients diseased with breast cancer at time of screening and final investigation are listed in **Table 55**, **Table 56**, **Table 57** and **Table 58**. The score for each symptom like anorexia, general fatigue, insomnia, nausea/vomiting and pain in the breast cancer patients as well as the total TCM score are comparable in verum and control treatment at time of screening.

Table 55 Breast cancer – TCM criteria at screening

BREAST		Helixor N=35		Lentinan N=32		Total N=67		p-value
		N	%	N	%	N	%	
Anorexia	None	20	57.1	16	50.0	36	53.7	0.824
	Slight	12	34.3	12	37.5	24	35.8	
	Middle	3	8.6	4	12.5	7	10.4	
General fatigue	None	14	40.0	9	28.1	23	34.3	0.432
	Slight	17	48.6	16	50.0	33	49.3	
	Middle	4	11.4	7	21.9	11	16.4	
Insomnia	None	25	71.4	18	56.3	43	64.2	0.148
	Slight	10	28.6	11	34.4	21	31.3	
	Middle	0	0.0	3	9.4	3	4.5	
Nausea/vomiting	None	28	80.0	26	81.3	54	80.6	1.000
	Slight	6	17.1	5	15.6	11	16.4	
	Middle	1	2.9	1	3.1	2	3.0	
Pain	None	27	77.1	22	68.8	49	73.1	0.333
	Slight	4	11.4	8	25.0	12	17.9	
	Middle	4	11.4	2	6.3	6	9.0	

Table 56 Breast cancer – TCM total score at screening

BREAST	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
TCM score	Helixor	35	0	2.1	2.1	0.0	0.0	2.0	4.0	6.0	0.250
	Lentinan	32	0	2.7	2.2	0.0	0.5	3.0	4.0	7.0	
	Total	67	0	2.4	2.1	0.0	0.0	3.0	4.0	7.0	

Table 57 Breast cancer – TCM criteria at final investigation

BREAST		Helixor N=35		Lentinan N=32		Total N=67	
		N	%	N	%	N	%
Anorexia	None	27	77.1	7	21.9	34	50.7
	Slight	7	20.0	17	53.1	24	35.8
	Middle	1	2.9	7	21.9	8	11.9
	Serious	0	0.0	1	3.1	1	1.5
General fatigue	None	21	60.0	7	21.9	28	41.8
	Slight	13	37.1	19	59.4	32	47.8
	Middle	1	2.9	6	18.8	7	10.4
Insomnia	Missing	0	0.0	1	3.1	1	1.5
	None	31	88.6	16	50.0	47	70.1
	Slight	4	11.4	12	37.5	16	23.9
	Middle	0	0.0	3	9.4	3	4.5
Nausea/vomiting	None	30	85.7	15	46.9	45	67.2
	Slight	3	8.6	14	43.8	17	25.4
	Middle	2	5.7	2	6.3	4	6.0
	Serious	0	0.0	1	3.1	1	1.5
Pain	None	30	85.7	23	71.9	53	79.1
	Slight	5	14.3	9	28.1	14	20.9

Table 58 Breast cancer – TCM total score at final investigation

BREAST	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX
TCM score	Helixor	35	0	1.1	1.4	0.0	0.0	1.0	2.0	6.0
	Lentinan	31	1	3.5	2.1	0.0	2.0	3.0	5.0	8.0
	Total	66	1	2.3	2.2	0.0	1.0	2.0	4.0	8.0

A graphical presentation of baseline and final end of treatment is presented in **Figure 7** and **Figure 8**.

Figure 7 Breast cancer – TCM criteria at screening

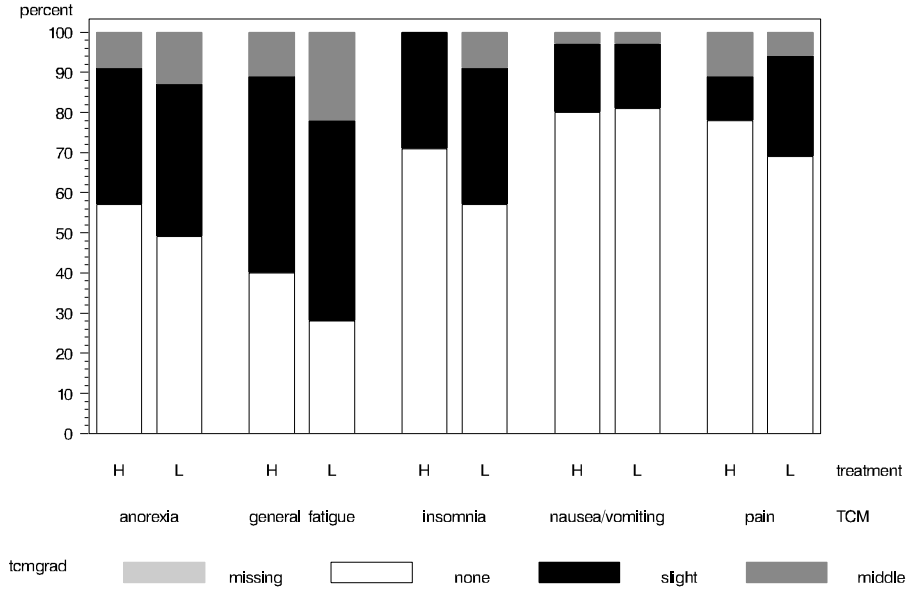


Figure 8 Breast cancer – TCM criteria at final investigation

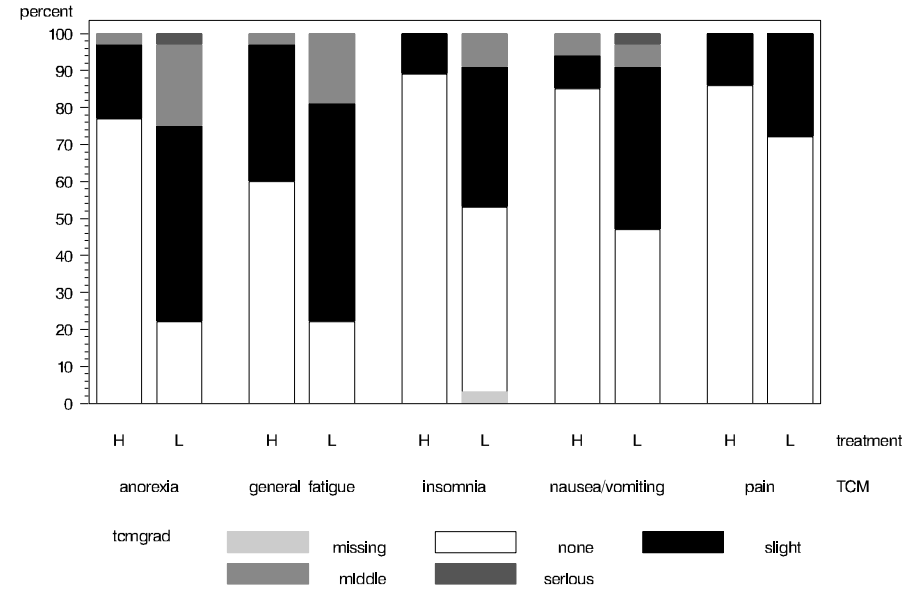


Table 59 Breast cancer – change of TCM items between screening and final investigation

	Helixor	Final investigation								Lentinan	Final investigation							
		None		Slight		Middle		Serious			None		Slight		Middle		Serious	
	Screening	N	%	N	%	N	%	N	%	Screening	N	%	N	%	N	%	N	%
Fatigue	**None**	12	34.3	2	5.7	-	-	-	-	**None**	4	12.5	4	12.5	1	3.1	-	-
	Slight	8	22.9	9	25.7	-	-	-	-	**Slight**	2	6.3	13	40.6	1	3.1	-	-
	Middle	1	2.9	2	5.7	1	2.9	-	-	**Middle**	1	3.1	2	6.3	4	12.5	-	-
	Serious	-	-	-	-	-	-	-	-	**Serious**	-	-	-	-	-	-	-	-
Insomnia	**None**	24	68.6	1	2.9	-	-	-	-	**None**	14	45.2	3	9.7	-	-	-	-
	Slight	7	20.0	3	8.6	-	-	-	-	**Slight**	2	6.5	9	29.0	-	-	-	-
	Middle	-	-	-	-	-	-	-	-	**Middle**	-	-	-	-	3	9.7	-	-
	Serious	-	-	-	-	-	-	-	-	**Serious**	-	-	-	-	-	-	-	-
Anorexia	**None**	17	48.6	3	8.6	-	-	-	-	**None**	4	12.5	9	28.1	2	6.3	1	3.1
	Slight	9	25.7	2	5.7	1	2.9	-	-	**Slight**	2	6.3	8	25.0	2	6.3	-	-
	Middle	1	2.9	2	5.7	-	-	-	-	**Middle**	1	3.1	-	-	3	9.4	-	-
	Serious	-	-	-	-	-	-	-	-	**Serious**	-	-	-	-	-	-	-	-
Nausea	**None**	25	71.4	1	2.9	2	5.7	-	-	**None**	14	43.8	9	28.1	2	6.3	1	3.1
	Slight	5	14.3	1	2.9	-	-	-	-	**Slight**	1	3.1	4	12.5	-	-	-	-
	Middle	-	-	1	2.9	-	-	-	-	**Middle**	-	-	1	3.1	-	-	-	-
	Serious	-	-	-	-	-	-	-	-	**Serious**	-	-	-	-	-	-	-	-
Pain	**None**	26	74.3	1	2.9	-	-	-	-	**None**	20	62.5	2	6.3	-	-	-	-
	Slight	3	8.6	1	2.9	-	-	-	-	**Slight**	1	3.1	7	21.9	-	-	-	-
	Middle	1	2.9	3	8.6	-	-	-	-	**Middle**	2	6.3	-	-	-	-	-	-
	Serious	-	-	-	-	-	-	-	-	**Serious**	-	-	-	-	-	-	-	-

The difference of the overall TCM score between screening and final investigation is shown in **Table 60**. The difference is highly significant between verum and control group (p = 0.003), even after Bonferroni-Holm adjustment for multiple testing. In the breast cancer patients the median for the overall TCM score changes in the HELIXOR® A group for 0 points, in the Lentinan group for 1 point. Latter is the same as an increase of the overall TCM score and therefore a deterioration of the patient condition of 1 point in the median. Because of discrete data, the limits of the confidence intervals have to be interpreted carefully. However, the width of the confidence intervals gives an impression of the magnitude of the change of the overall TCM score in both treatment groups.

Table 60 Breast cancer – difference of TCM total score between screening and final investigation

BREAST	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value	95%-CI *
TCM score	Helixor	35	0	-0.9	2.1	-6.0	-2.0	0.0	0.0	5.0	0.003	-2;-1
	Lentinan	31	1	0.8	2.0	-2.0	-1.0	1.0	2.0	5.0		
	Total	66	1	-0.1	2.2	-6.0	-2.0	0.0	1.0	5.0		

Difference: (value of final investigation minus value of screening).
* Because of discrete data, be careful in interpreting the limits of the confidence interval.

3.1.2.4 Ovarian cancer

The TCM parameters of patients diseased with ovarian cancer at time of screening and final investigation are listed in **Table 61**, **Table 62**, **Table 63** and **Table 64**. The score for each symptom anorexia, general fatigue, insomnia, nausea/vomiting and pain in the ovarian cancer patients as well as the total TCM score are comparable in verum and control treatment at the time of screening.

Table 61 Ovarian cancer – TCM criteria at screening

OVARIAN		Helixor N=33		Lentinan N=33		Total N=66		p-value
		N	%	N	%	N	%	
Anorexia	None	15	45.5	15	45.5	30	45.5	1.000
	Slight	13	39.4	14	42.4	27	40.9	
	Middle	2	6.1	2	6.1	4	6.1	
	Serious	3	9.1	2	6.1	5	7.6	
General fatigue	None	10	30.3	10	30.3	20	30.3	0.850
	Slight	18	54.5	16	48.5	34	51.5	
	Middle	5	15.2	7	21.2	12	18.2	
Insomnia	None	16	48.5	17	51.5	33	50.0	0.795
	Slight	10	30.3	12	36.4	22	33.3	
	Middle	6	18.2	4	12.1	10	15.2	
	Serious	1	3.0	.	.	1	1.5	
Nausea/vomiting	None	24	72.7	26	78.8	50	75.8	0.558
	Slight	9	27.3	6	18.2	15	22.7	
	Middle	.	.	1	3.0	1	1.5	
Pain	None	25	75.8	22	66.7	47	71.2	0.514
	Slight	8	24.2	9	27.3	17	25.8	
	Middle	.	.	2	6.1	2	3.0	

Table 62 Ovarian cancer – TCM total score at screening

OVARIAN	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
TCM score	Helixor	33	0	2.9	2.3	0.0	1.0	3.0	4.0	8.0	0.836
	Lentinan	33	0	2.9	2.5	0.0	1.0	2.0	4.0	10.0	
	Total	66	0	2.9	2.4	0.0	1.0	2.5	4.0	10.0	

Table 63 Ovarian cancer – TCM criteria at final investigation

OVARIAN		Helixor N=33		Lentinan N=33		Total N=66	
		N	%	N	%	N	%
Anorexia	Missing	0	0.0	1	3.0	1	1.5
	None	21	63.6	17	51.5	38	57.6
	Slight	10	30.3	12	36.4	22	33.3
	Middle	2	6.1	3	9.1	5	7.6
General fatigue	Missing	0	0.0	1	3.0	1	1.5
	None	15	45.5	13	39.4	28	42.4
	Slight	18	54.5	16	48.5	34	51.5
	Middle	0	0.0	3	9.1	3	4.5
Insomnia	Missing	0	0.0	1	3.0	1	1.5
	None	26	78.8	18	54.5	44	66.7
	Slight	5	15.2	12	36.4	17	25.8
	Middle	2	6.1	2	6.1	4	6.1
Nausea/vomiting	Missing	0	0.0	1	3.0	1	1.5
	None	25	75.8	22	66.7	47	71.2
	Slight	6	18.2	8	24.2	14	21.2
	Middle	2	6.1	1	3.0	3	4.5
	Serious	0	0.0	1	3.0	1	1.5
Pain	Missing	0	0.0	1	3.0	1	1.5
	None	30	90.9	22	66.7	52	78.8
	Slight	3	9.1	9	27.3	12	18.2
	Middle	0	0.0	1	3.0	1	1.5

Table 64 Ovarian cancer – TCM total score at final investigation

OVARIAN	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX
TCM score	Helixor	33	0	1.6	1.6	0.0	0.0	1.0	2.0	6.0
	Lentinan	32	1	2.5	2.4	0.0	1.0	2.0	4.0	8.0
	Total	65	1	2.1	2.1	0.0	1.0	1.0	3.0	8.0

A graphical presentation of baseline and final end of treatment is presented in **Figure 9** and **Figure 10**.

Figure 9 Ovarian cancer – TCM criteria at screening

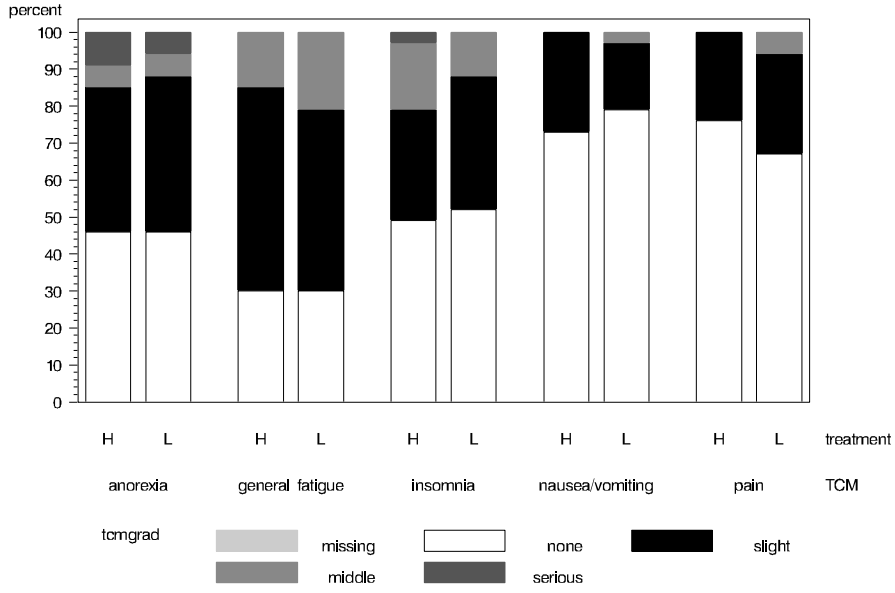


Figure 10 Ovarian cancer – TCM criteria at final investigation

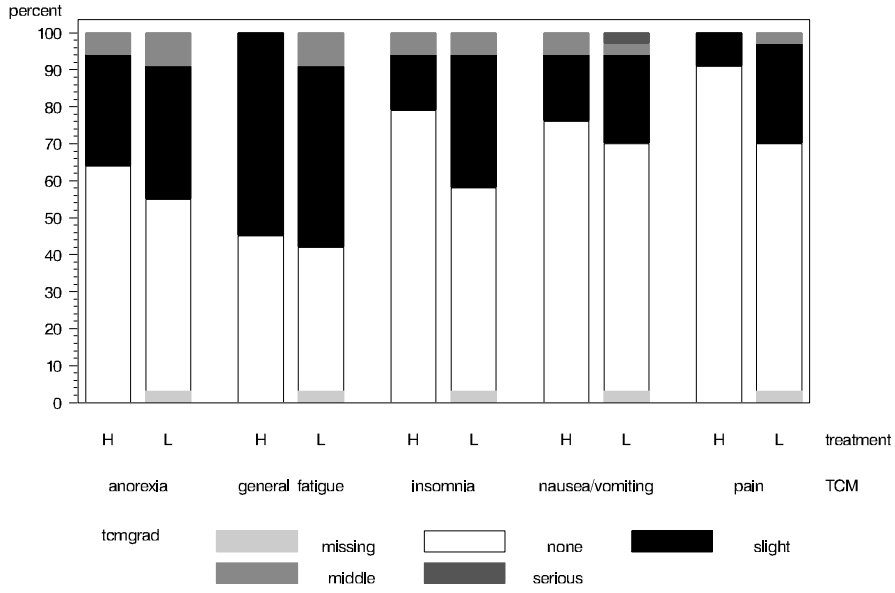


Table 65 Ovarian cancer – change of TCM items between screening and final investigation

	Helixor	Final investigation								Lentinan	Final investigation							
		None		Slight		Middle		Serious			None		Slight		Middle		Serious	
	Screening	N	%	N	%	N	%	N	%	Screening	N	%	N	%	N	%	N	%
Fatigue	**None**	8	24.2	2	6.1	-	-	-	-	**None**	8	25.0	2	6.3	-	-	-	-
	Slight	7	21.2	11	33.3	-	-	-	-	**Slight**	4	12.5	9	28.1	2	6.3	-	-
	Middle	-	-	5	15.2	-	-	-	-	**Middle**	1	3.1	5	15.6	1	3.1	-	-
	Serious	-	-	-	-	-	-	-	-	**Serious**	-	-	-	-	-	-	-	-
Insomnia	**None**	16	48.5	-	-	-	-	-	-	**None**	14	43.8	3	9.4	-	-	-	-
	Slight	5	15.2	4	12.1	1	3.0	-	-	**Slight**	4	12.5	7	21.9	-	-	-	-
	Middle	4	12.1	1	3.0	1	3.0	-	-	**Middle**	-	-	2	6.3	2	6.3	-	-
	Serious	1	3.0	-	-	-	-	-	-	**Serious**	-	-	-	-	-	-	-	-
Anorexia	**None**	11	33.3	4	12.1	-	-	-	-	**None**	10	31.3	4	12.5	-	-	-	-
	Slight	6	18.2	6	18.2	1	3.0	-	-	**Slight**	6	18.8	8	25.0	-	-	-	-
	Middle	1	3.0	-	-	1	3.0	-	-	**Middle**	-	-	-	-	2	6.3	-	-
	Serious	3	9.1	-	-	-	-	-	-	**Serious**	1	3.1	-	-	1	3.1	-	-
Nausea	**None**	19	57.6	4	12.1	1	3.0	-	-	**None**	21	65.6	4	12.5	-	-	-	-
	Slight	6	18.2	2	6.1	1	3.0	-	-	**Slight**	1	3.1	3	9.4	1	3.1	1	3.1
	Middle	-	-	-	-	-	-	-	-	**Middle**	-	-	1	3.1	-	-	-	-
	Serious	-	-	-	-	-	-	-	-	**Serious**	-	-	-	-	-	-	-	-
Pain	**None**	25	75.8	-	-	-	-	-	-	**None**	18	56.3	3	9.4	-	-	-	-
	Slight	5	15.2	3	9.1	-	-	-	-	**Slight**	4	12.5	5	15.6	-	-	-	-
	Middle	-	-	-	-	-	-	-	-	**Middle**	-	-	1	3.1	1	3.1	-	-
	Serious	-	-	-	-	-	-	-	-	**Serious**	-	-	-	-	-	-	-	-

The difference of the overall TCM score between before and after treatment is shown in **Table 66** to be comparable between verum and control group (p = 0.167).

Table 66 Ovarian cancer – difference of TCM total score between screening and final investigation

OVARIAN	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value	95%-CI *
TCM score	Helixor	33	0	-1.3	2.4	-8.0	-2.0	-1.0	0.0	3.0	0.167	-2;0
	Lentinan	32	1	-0.4	2.0	-6.0	-1.5	0.0	1.0	3.0		
	Total	65	1	-0.8	2.2	-8.0	-2.0	0.0	1.0	3.0		

Difference: (value of final investigation minus value of screening).
* Because of discrete data, be careful in interpreting the limits of the confidence interval.

3.1.3 Functional Living Index (FLIC)

The Functional Living Index (FLIC) is the third quality of life parameter which was evaluated in this trial. It consists of 22 questions which can be subgrouped in physical well-being and ability (9 items), psychological well-being (6 items), hardship due to cancer (3 items), social well-being (2 items), nausea (2 items) and pain (2 items). Every question is answered on a continuous scale from 1 to 7 and items of subgroups are arranged as described before. In addition, the total Functional Living Index or FLIC score is listed as follows.

3.1.3.1 Total study population

According to **Table 67** the total study population is comparable concerning the global FLIC score as well as its division into the subgroups of physical well-being, hardship due to cancer, nausea/vomiting, social well-being and pain at time of screening. However, the p-value (0.036) indicates, that at time of screening psychological well-being in patients treated with HELIXOR® A is significantly better than in the control group.

Table 67 Total study population – FLIC total score and FLIC subscales at screening

ALL	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
FLIC score	Helixor	114	0	101.4	19.0	57.0	87.0	103.0	117.5	144.0	0.192
	Lentinan	109	1	98.0	18.7	53.0	85.5	96.0	113.0	138.0	
	Total	223	1	99.7	18.9	53.0	87.0	99.0	115.0	144.0	
Physical well-being	Helixor	114	0	40.3	10.1	16.5	32.5	41.3	49.0	62.5	0.166
	Lentinan	109	1	38.8	9.6	14.5	31.5	39.5	46.5	58.5	
	Total	223	1	39.5	9.9	14.5	31.5	40.5	47.5	62.5	
Psychological well-being	Helixor	114	0	28.2	5.9	12.0	24.0	29.0	33.0	41.5	0.036
	Lentinan	109	1	26.4	6.1	9.0	23.0	26.0	31.0	39.0	
	Total	223	1	27.3	6.0	9.0	23.0	28.0	32.0	41.5	
Hardship due to cancer	Helixor	114	0	11.4	3.6	4.5	9.5	11.5	14.0	19.0	0.628
	Lentinan	109	1	11.3	3.3	4.5	9.0	10.5	13.5	19.5	
	Total	223	1	11.3	3.4	4.5	9.5	11.5	13.5	19.5	
Nausea/ vomiting	Helixor	114	0	10.8	2.2	4.0	10.0	11.0	13.0	14.0	0.462
	Lentinan	109	1	11.0	2.2	5.0	10.0	11.0	13.0	14.0	
	Total	223	1	10.9	2.2	4.0	10.0	11.0	13.0	14.0	
Social well-being	Helixor	114	0	10.7	2.3	3.0	9.5	11.0	13.0	14.0	0.143
	Lentinan	109	1	10.5	1.9	3.0	9.5	11.0	12.0	13.0	
	Total	223	1	10.6	2.1	3.0	9.5	11.0	12.0	14.0	
Pain	Helixor	114	0	8.3	3.0	3.0	6.0	8.0	11.0	14.0	0.622
	Lentinan	109	1	8.2	2.8	3.0	5.5	8.0	11.0	14.0	
	Total	223	1	8.3	2.9	3.0	6.0	8.0	11.0	14.0	

Table 68 Total study population – FLIC total score and FLIC subscales at final investigation

ALL	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX
FLIC score	Helixor	114	0	110.5	17.6	60.0	99.0	113.8	123.5	139.0
	Lentinan	108	2	102.4	18.3	57.0	87.0	103.0	116.5	142.0
	Total	222	2	106.5	18.3	57.0	93.0	108.5	121.5	142.0
Physical well-being	Helixor	114	0	45.2	8.6	14.5	40.5	48.5	51.5	57.5
	Lentinan	108	2	41.1	9.5	17.5	34.0	41.5	48.5	58.5
	Total	222	2	43.2	9.3	14.5	36.5	44.8	50.5	58.5
Psychological well-being	Helixor	114	0	30.1	5.4	13.0	27.0	30.0	34.0	40.5
	Lentinan	108	2	28.0	5.4	13.0	24.0	28.0	32.0	39.0
	Total	222	2	29.1	5.5	13.0	25.0	29.0	33.0	40.5
Hardship due to cancer	Helixor	114	0	13.5	3.3	4.5	11.5	13.5	16.5	19.5
	Lentinan	108	2	12.5	3.0	4.5	10.5	12.5	14.5	19.5
	Total	222	2	13.0	3.2	4.5	10.5	12.5	15.5	19.5
Nausea	Helixor	114	0	10.5	2.3	3.0	9.5	11.0	12.0	14.0
	Lentinan	108	2	9.8	2.5	4.0	8.0	11.0	12.0	13.5
	Total	222	2	10.2	2.4	3.0	9.0	11.0	12.0	14.0
Social well-being	Helixor	114	0	11.1	1.8	5.0	10.0	11.0	13.0	14.0
	Lentinan	108	2	11.0	1.6	6.0	10.0	11.0	12.0	13.0
	Total	222	2	11.1	1.7	5.0	10.0	11.0	13.0	14.0
Pain	Helixor	114	0	9.8	2.6	3.0	8.0	11.0	12.0	14.0
	Lentinan	108	2	8.7	2.6	3.0	7.0	8.0	11.0	14.0
	Total	222	2	9.3	2.6	3.0	7.0	9.0	11.0	14.0

A graphical presentation of baseline and final end of treatment is presented in **Figure 11** and **Figure 12**.

Figure 11 Total study population – FLIC subscales at screening

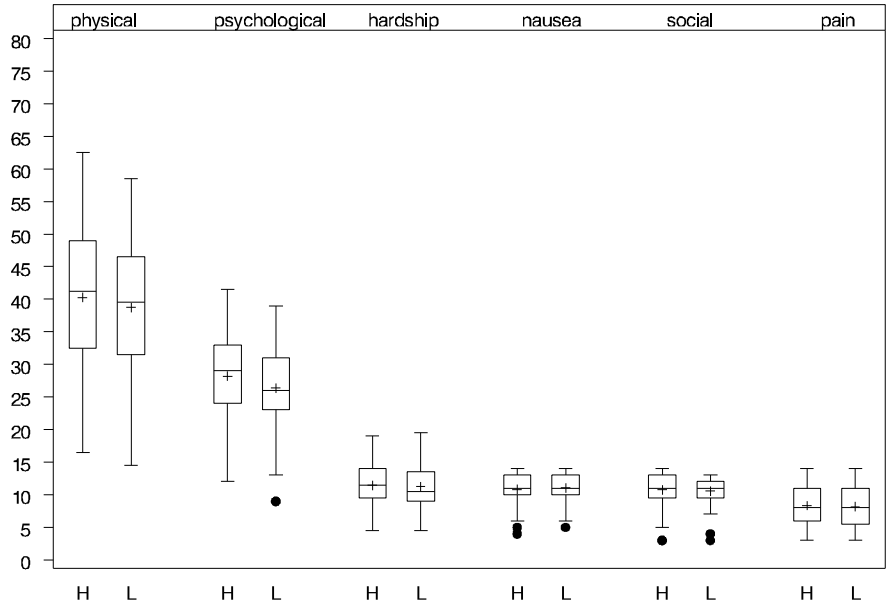
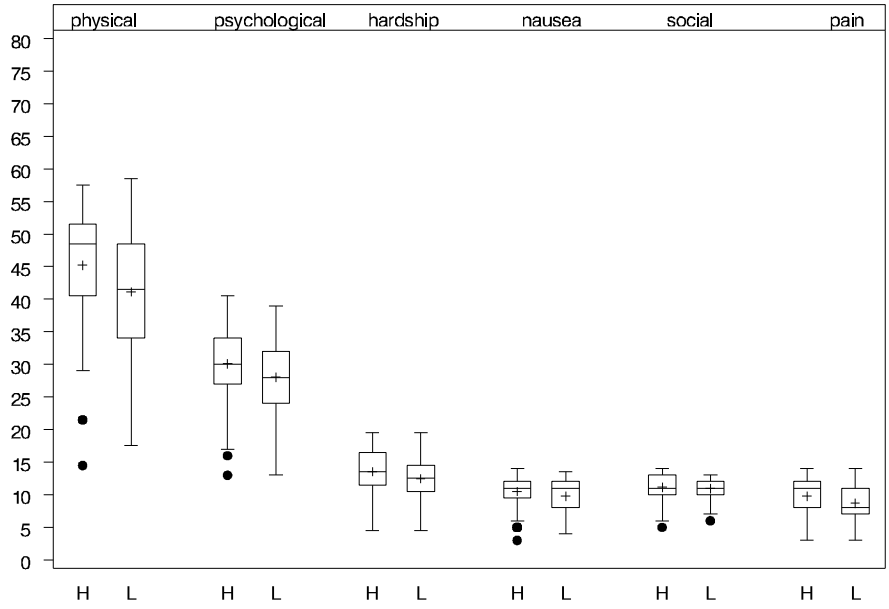


Figure 12 Total study population – FLIC subscales at final investigation



The difference of the global FLIC score as well as the difference of all subscales between screening and final investigation are shown in **Table 69**. The greater the FLIC score, the better quality of life of patients. If the difference final minus screening is positive then the quality of life increased while treatment. The greater the difference final minus screening, the greater the treatment effect. The median in the Helixor treatment group is 5.8 whereas in the Lentinan treatment group 3.5. Therefore, patients under Helixor treatment have a greater increase in life quality. This result is significant with a p-value of 0.0147 between verum and control group.

The difference between the two treatment groups is mainly based on differences for the subscales 'physical well-being', 'hardship due to cancer', 'nausea/vomiting' and 'pain', with only the subscale 'nausea/vomiting' significant to the after Bonferroni-Holm adjusted significance level of $\alpha/6 = 0.05/6 = 0.0083$ ($p = 0.0055$). Graphically the differences of the global FLIC score and of the subscales over the period of treatment time are represented in **Figure 13**.

Table 69 Total study population – difference of FLIC between screening and final investigation

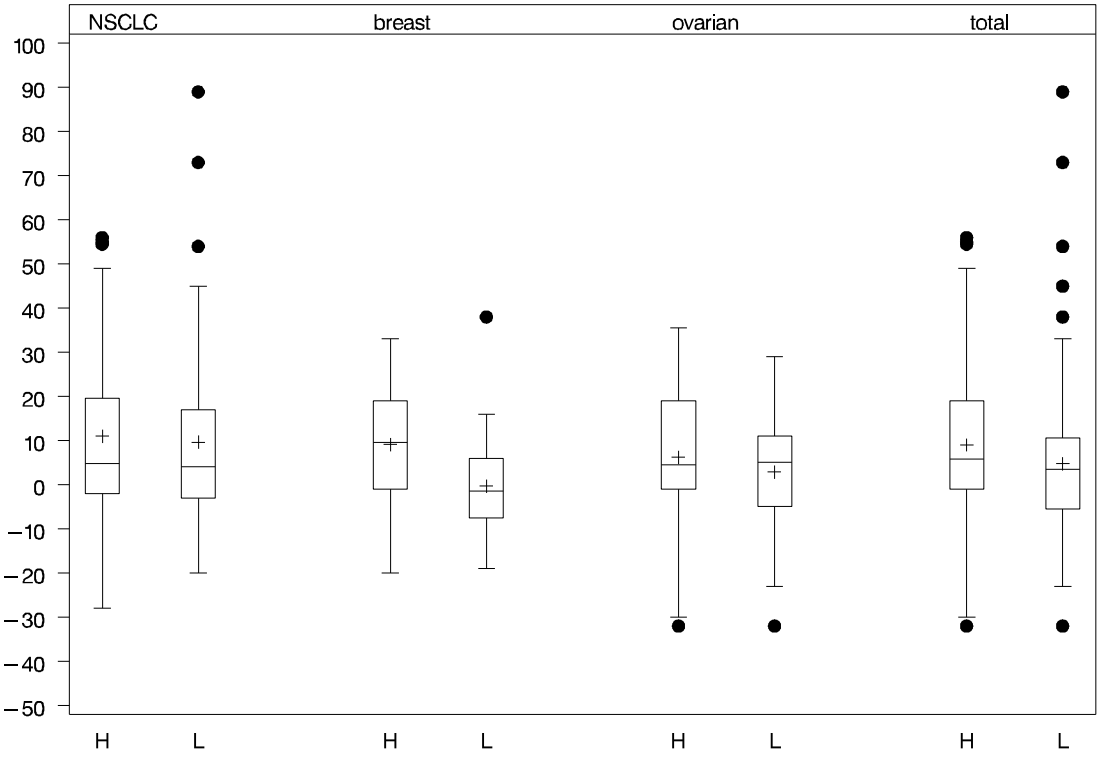
ALL	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	strat. p-value	95%-CI
FLIC score	Helixor	114	0	9.0	16.6	-32.0	-1.0	5.8	19.0	56.0	0.0147	1;8.5
	Lentinan	108	2	4.7	17.5	-32.0	-5.5	3.5	10.5	89.0		
	Total	222	2	6.9	17.1	-32.0	-3.0	4.5	14.5	89.0		
Physical well-being	Helixor	114	0	4.9	9.0	-22.0	0.0	3.0	9.0	31.5	0.0275	0;4
	Lentinan	108	2	2.5	8.2	-14.5	-1.8	2.0	5.0	37.0		
	Total	222	2	3.8	8.7	-22.0	-1.0	2.0	8.0	37.0		
Psycho-logical well-being	Helixor	114	0	1.9	4.5	-12.5	0.0	1.3	4.0	17.0	0.3523	-0.5;1.5
	Lentinan	108	2	1.7	5.4	-9.0	-1.0	1.0	4.0	29.0		
	Total	222	2	1.8	5.0	-12.5	-1.0	1.0	4.0	29.0		
Hardship due to cancer	Helixor	114	0	2.1	3.4	-5.0	0.0	1.0	4.0	14.0	0.0670	0;1.5
	Lentinan	108	2	1.3	3.6	-7.0	-1.0	1.0	3.0	15.0		
	Total	222	2	1.7	3.5	-7.0	0.0	1.0	4.0	15.0		
Nausea/ vomiting	Helixor	114	0	-0.3	2.4	-8.0	-2.0	0.0	1.0	8.0	0.0055	0;1
	Lentinan	108	2	-1.2	2.5	-9.0	-2.0	-1.0	0.0	4.0		
	Total	222	2	-0.8	2.5	-9.0	-2.0	0.0	1.0	8.0		
Social well-being	Helixor	114	0	0.4	2.0	-4.0	-1.0	0.0	1.0	10.0	0.848♣	0;0
	Lentinan	108	2	0.5	2.0	-5.0	-0.5	0.0	1.0	9.0		
	Total	222	2	0.4	2.0	-5.0	-0.5	0.0	1.0	10.0		
Pain	Helixor	114	0	1.4	2.8	-7.0	0.0	1.0	3.0	9.0	0.017♣	0;1
	Lentinan	108	2	0.6	2.4	-6.0	-1.0	0.0	2.0	8.0		
	Total	222	2	1.0	2.7	-7.0	0.0	1.0	2.0	9.0		

Difference: (value of final investigation minus value of screening).

* Because of discrete data, be careful in interpreting the limits of the confidence intervals.

♣ Unstratified Wilcoxon-Mann-Whitney (stratified problem too large for StatExact 5)

Figure 13 Total study population, NSCLC, breast cancer, ovarian cancer – difference of FLIC total score between screening and final investigation



3.1.3.2 Non small cell lung cancer

For the entity non small cell lung cancer the global FLIC score and the subgroups like physical well-being, psychological well-being, hardship due to cancer, nausea/vomiting, social well-being and pain at time of screening are shown in **Table 70**, at time of final investigation in **Table 71**. Some of the p-values are below the level of 0.05, but have only descriptive meaning because they are not adjusted for multiple testing.

Table 70 Non small cell lung cancer – FLIC total score and FLIC subscales at screening

NSCLC	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
FLIC score	Helixor	46	0	98.4	20.0	57.0	84.5	99.5	114.0	140.5	0.104
	Lentinan	45	0	90.9	19.5	53.0	79.0	90.5	106.0	129.0	
	Total	91	0	94.7	20.0	53.0	82.0	92.0	108.0	140.5	
Physical well-being	Helixor	46	0	37.7	10.5	17.5	30.5	39.0	46.5	57.0	0.184
	Lentinan	45	0	35.0	9.7	14.5	28.5	32.5	43.0	54.5	
	Total	91	0	36.4	10.2	14.5	29.5	36.5	44.5	57.0	
Psychological well-being	Helixor	46	0	27.4	6.7	13.0	22.5	27.5	34.0	38.5	0.024
	Lentinan	45	0	23.9	6.5	9.0	20.0	25.0	27.0	36.0	
	Total	91	0	25.7	6.8	9.0	20.0	26.0	30.0	38.5	
Hardship due to cancer	Helixor	46	0	11.2	3.6	4.5	9.5	11.5	13.5	19.0	0.442
	Lentinan	45	0	10.6	3.4	4.5	8.5	10.5	13.0	17.5	
	Total	91	0	10.9	3.5	4.5	8.5	10.5	13.5	19.0	
Nausea/ vomiting	Helixor	46	0	11.2	1.8	6.0	10.0	11.0	13.0	13.0	0.951
	Lentinan	45	0	11.2	2.0	6.0	10.0	12.0	13.0	13.0	
	Total	91	0	11.2	1.9	6.0	10.0	11.5	13.0	13.0	
Social well-being	Helixor	46	0	10.9	2.5	3.0	10.0	11.0	13.0	13.0	0.025
	Lentinan	45	0	10.2	2.0	4.0	9.0	11.0	11.5	13.0	
	Total	91	0	10.5	2.3	3.0	9.5	11.0	12.0	13.0	
Pain	Helixor	46	0	7.8	3.2	3.0	5.0	7.0	11.0	13.0	0.687
	Lentinan	45	0	7.4	2.7	3.0	5.0	7.0	10.0	13.0	
	Total	91	0	7.6	3.0	3.0	5.0	7.0	10.0	13.0	

Table 71 Non small cell lung cancer – FLIC total score and FLIC subscales at final investigation

NSCLC	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX
FLIC score	Helixor	46	0	109.4	20.0	60.0	96.0	112.8	125.0	139.0
	Lentinan	45	0	100.5	19.9	57.0	87.0	102.5	113.5	142.0
	Total	91	0	105.0	20.3	57.0	90.0	106.0	121.0	142.0
Physical well-being	Helixor	46	0	44.0	9.8	14.5	39.0	46.5	50.5	57.5
	Lentinan	45	0	39.9	10.2	17.5	31.5	40.5	46.0	58.5
	Total	91	0	42.0	10.2	14.5	34.5	44.5	49.5	58.5
Psychological well-being	Helixor	46	0	29.6	6.6	13.0	25.0	29.0	35.0	40.5
	Lentinan	45	0	27.0	5.6	13.0	24.0	27.0	31.0	38.0
	Total	91	0	28.3	6.2	13.0	25.0	29.0	33.0	40.5
Hardship due to cancer	Helixor	46	0	13.3	3.4	4.5	11.5	13.5	15.5	19.5
	Lentinan	45	0	12.6	3.1	5.5	10.5	12.5	14.5	19.5
	Total	91	0	12.9	3.3	4.5	10.5	12.5	14.5	19.5
Nausea	Helixor	46	0	11.2	2.2	5.0	11.0	12.0	13.0	14.0
	Lentinan	45	0	10.2	2.4	5.0	9.0	11.0	12.0	13.0
	Total	91	0	10.7	2.3	5.0	10.0	11.0	13.0	14.0
Social well-being	Helixor	46	0	11.3	2.0	6.0	10.0	12.0	13.0	14.0
	Lentinan	45	0	10.8	1.7	6.0	10.0	11.0	12.0	13.0
	Total	91	0	11.0	1.9	6.0	10.0	11.0	13.0	14.0
Pain	Helixor	46	0	9.4	2.7	3.0	8.0	10.5	11.0	13.0
	Lentinan	45	0	8.3	2.5	4.0	6.0	8.0	9.0	13.0
	Total	91	0	8.9	2.6	3.0	7.0	9.0	11.0	13.0

Figure 14 Non small cell lung cancer – FLIC subscales at screening

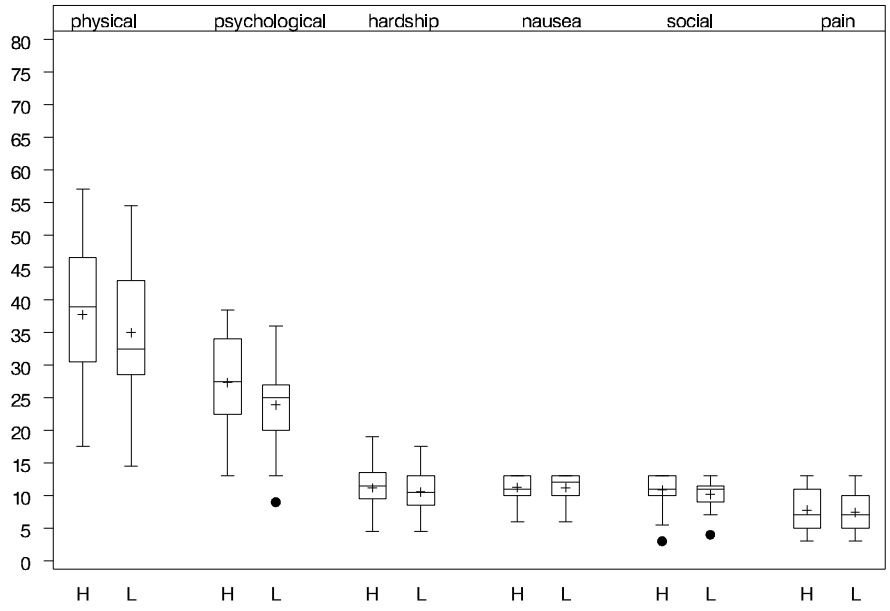
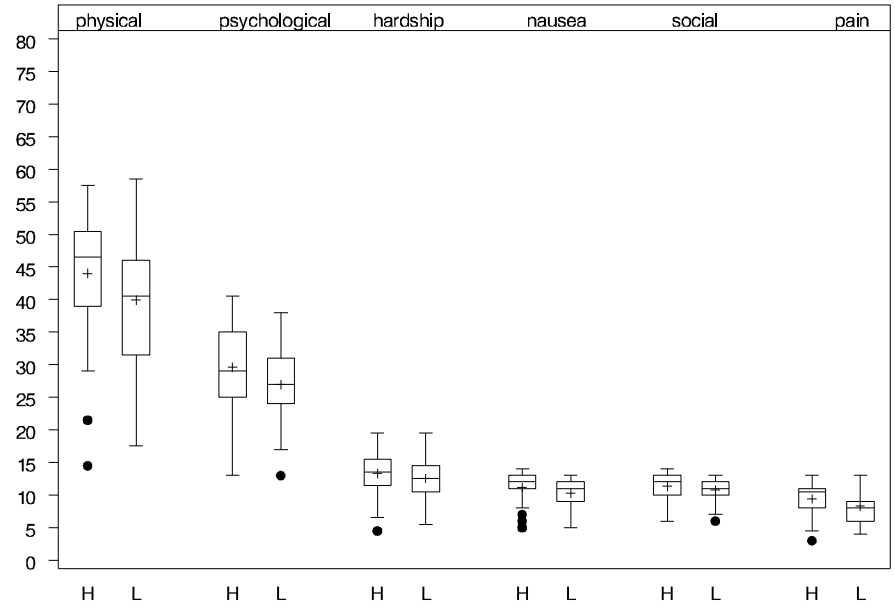


Figure 15 Non small cell lung cancer – FLIC subscales at final investigation



The difference of the global FLIC score as well as the differences of all subscales between screening and final investigation are shown in **Table 72**. Looking at the global FLIC score there is no statistically significant difference between verum and control group.

Table 72 Non small cell lung cancer – difference of FLIC between screening and final investigation

NSCLC	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value	95%-CI
FLIC score	Helixor	46	0	11.0	19.8	-28.0	-2.0	4.8	19.5	56.0	0.529	-4.5;8
	Lentinan	45	0	9.6	21.4	-20.0	-3.0	4.0	17.0	89.0		
	Total	91	0	10.3	20.5	-28.0	-2.0	4.5	17.0	89.0		
Physical well-being	Helixor	46	0	6.3	10.7	-11.0	-1.0	3.0	11.0	31.5	0.689	-2.5;3
	Lentinan	45	0	4.9	9.3	-9.0	0.0	2.0	7.0	37.0		
	Total	91	0	5.6	10.0	-11.0	-1.0	3.0	8.0	37.0		
Psycho-logical well-being	Helixor	46	0	2.2	5.4	-10.0	0.0	1.5	4.0	17.0	0.712	-2;1.5
	Lentinan	45	0	3.0	7.1	-9.0	0.0	2.0	5.0	29.0		
	Total	91	0	2.6	6.2	-10.0	0.0	2.0	4.0	29.0		
Hardship due to cancer	Helixor	46	0	2.1	4.0	-5.0	-1.0	1.0	4.0	14.0	0.821	-1.5;1
	Lentinan	45	0	2.0	4.0	-6.0	0.0	1.5	4.0	15.0		
	Total	91	0	2.0	4.0	-6.0	-0.5	1.0	4.0	15.0		
Nausea/ vomiting	Helixor	46	0	-0.1	1.9	-6.0	-1.0	0.0	1.0	5.0	0.053	0;2
	Lentinan	45	0	-1.0	2.2	-8.0	-2.0	-1.0	0.0	3.0		
	Total	91	0	-0.5	2.1	-8.0	-2.0	0.0	1.0	5.0		
Social well-being	Helixor	46	0	0.4	2.2	-4.0	0.0	0.0	1.0	10.0	0.863	-1;0.5
	Lentinan	45	0	0.6	2.2	-5.0	-0.5	0.0	1.0	9.0		
	Total	91	0	0.5	2.2	-5.0	-0.5	0.0	1.0	10.0		
Pain	Helixor	46	0	1.7	3.1	-5.0	0.0	1.0	4.0	8.0	0.299	-0.5;2
	Lentinan	45	0	0.8	2.4	-4.0	0.0	1.0	2.0	8.0		
	Total	91	0	1.3	2.8	-5.0	0.0	1.0	3.0	8.0		

Difference: (value of final investigation minus value of screening).
* Because of discrete data, be careful in interpreting the limits of the confidence intervals.

3.1.3.3 Breast cancer

For the entity breast cancer the global FLIC score and the subgroups of physical well-being, psychological well-being, hardship due to cancer, nausea/vomiting, social well-being and pain at time of screening are shown in **Table 73**, at time of final investigation in **Table 74**.

Table 73 Breast cancer – FLIC total score and FLIC subscales at screening

BREAST	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
FLIC score	Helixor	35	0	100.6	17.4	69.5	88.0	97.0	117.5	131.0	0.970
	Lentinan	32	0	101.1	13.2	77.0	91.0	101.0	113.5	121.0	
	Total	67	0	100.8	15.4	69.5	90.0	100.0	114.0	131.0	
Physical well-being	Helixor	35	0	40.8	9.1	23.5	32.5	41.5	48.5	54.5	0.817
	Lentinan	32	0	40.6	7.0	26.5	36.5	41.0	46.5	53.5	
	Total	67	0	40.7	8.1	23.5	33.5	41.5	47.5	54.5	
Psychological well-being	Helixor	35	0	27.6	5.3	12.0	24.0	29.0	32.0	37.0	0.652
	Lentinan	32	0	27.3	4.6	17.0	24.0	28.0	30.0	38.0	
	Total	67	0	27.5	5.0	12.0	24.0	28.0	31.0	38.0	
Hardship due to cancer	Helixor	35	0	11.2	3.2	4.5	9.5	10.5	13.5	17.5	0.546
	Lentinan	32	0	11.7	2.8	6.5	9.5	12.0	14.5	16.5	
	Total	67	0	11.4	3.0	4.5	9.5	11.5	13.5	17.5	
Nausea/ vomiting	Helixor	35	0	10.7	2.3	6.0	9.0	11.0	13.0	13.5	0.883
	Lentinan	32	0	11.0	1.9	7.0	10.0	11.0	13.0	13.0	
	Total	67	0	10.9	2.1	6.0	10.0	11.0	13.0	13.5	
Social well-being	Helixor	35	0	10.2	2.3	5.0	9.0	11.0	12.0	13.0	0.823
	Lentinan	32	0	10.6	1.6	7.0	9.3	11.0	11.5	13.0	
	Total	67	0	10.4	2.0	5.0	9.0	11.0	12.0	13.0	
Pain	Helixor	35	0	8.6	2.7	4.0	7.0	9.0	11.0	13.5	0.641
	Lentinan	32	0	8.3	2.3	4.0	7.0	8.0	10.0	13.0	
	Total	67	0	8.5	2.5	4.0	7.0	8.5	11.0	13.5	

Table 74 Breast cancer – FLIC total score and FLIC subscales at final investigation

BREAST	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX
FLIC score	Helixor	35	0	109.7	15.8	80.0	99.0	112.0	123.0	137.0
	Lentinan	32	0	100.8	14.8	73.0	87.5	101.0	112.5	128.0
	Total	67	0	105.5	15.9	73.0	93.0	106.0	118.0	137.0
Physical well-being	Helixor	35	0	45.7	7.9	29.5	39.5	49.5	52.5	57.5
	Lentinan	32	0	40.7	7.8	24.5	35.8	40.5	47.5	53.5
	Total	67	0	43.3	8.2	24.5	37.5	43.5	51.5	57.5
Psychological well-being	Helixor	35	0	29.9	4.4	17.0	28.0	31.0	33.0	37.0
	Lentinan	32	0	28.0	4.1	21.0	24.0	28.0	31.0	36.0
	Total	67	0	29.0	4.3	17.0	26.0	29.0	32.0	37.0
Hardship due to cancer	Helixor	35	0	13.3	3.3	5.5	10.5	12.5	16.5	19.5
	Lentinan	32	0	12.2	2.8	4.5	10.5	12.0	14.5	16.5
	Total	67	0	12.8	3.1	4.5	10.5	12.5	15.5	19.5
Nausea	Helixor	35	0	10.0	2.4	5.0	8.0	11.0	12.0	13.0
	Lentinan	32	0	9.2	2.8	4.0	7.0	10.0	11.0	13.5
	Total	67	0	9.6	2.6	4.0	8.0	10.5	11.0	13.5
Social well-being	Helixor	35	0	10.8	1.8	5.0	10.0	11.0	12.0	13.0
	Lentinan	32	0	10.8	1.6	7.0	10.0	11.0	12.0	13.0
	Total	67	0	10.8	1.7	5.0	10.0	11.0	12.0	13.0
Pain	Helixor	35	0	10.1	2.2	6.0	8.0	11.0	12.0	13.5
	Lentinan	32	0	8.6	2.2	5.0	7.0	8.0	10.5	13.0
	Total	67	0	9.4	2.3	5.0	7.0	9.0	11.0	13.5

Figure 16 Breast cancer – FLIC subscales at screening

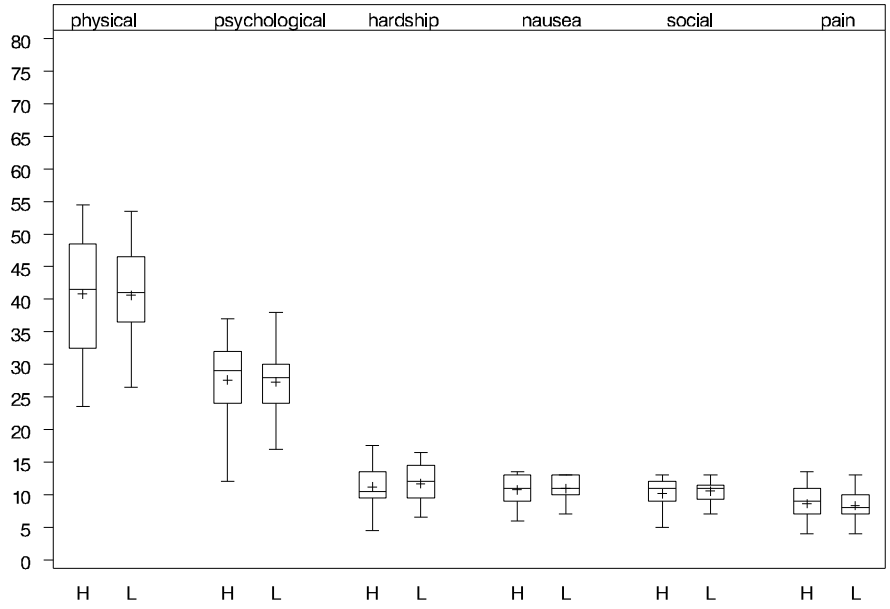
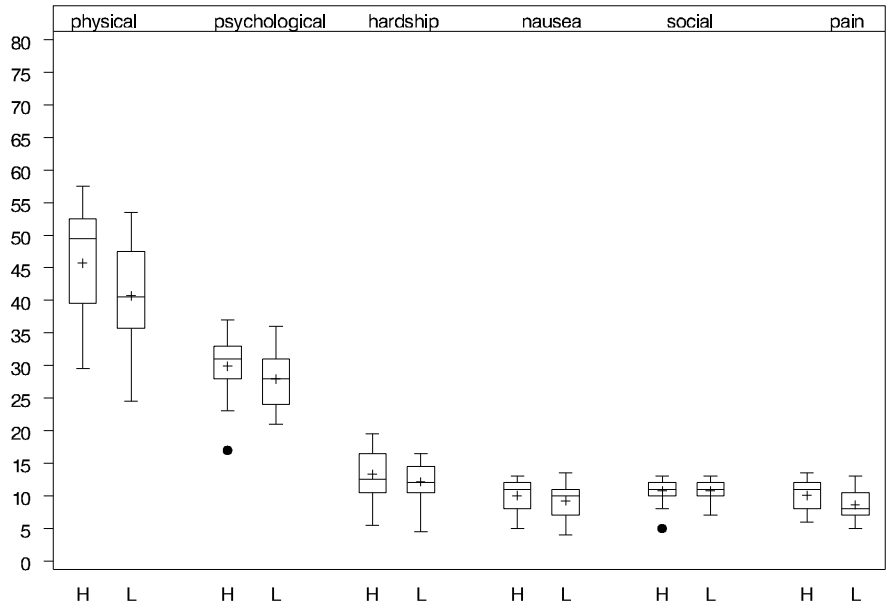


Figure 17 Breast cancer – FLIC subscales at final investigation



The difference of the global FLIC score as well as the differences of all subscales between screening and final investigation are shown in **Table 75**. The difference of the global FLIC score is highly significant between verum and control treatment group (p=0.003), even after Bonferroni-Holm adjustment for multiple testing.

Table 75 Breast cancer – difference of FLIC between screening and final investigation

BREAST	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value	95%-CI
FLIC score	Helixor	35	0	9.1	13.1	-20.0	-1.0	9.5	19.0	33.0	0.003	4;16
	Lentinan	32	0	-0.3	11.9	-19.0	-7.5	-1.5	6.0	38.0		
	Total	67	0	4.6	13.3	-20.0	-5.0	4.0	14.0	38.0		
Physical well-being	Helixor	35	0	4.9	6.0	-7.0	1.0	4.0	9.0	20.0	0.003	2;7.5
	Lentinan	32	0	0.1	5.7	-12.0	-4.0	-0.5	4.0	17.0		
	Total	67	0	2.6	6.3	-12.0	-1.0	2.0	6.0	20.0		
Psycho-logical well-being	Helixor	35	0	2.3	3.6	-5.0	-1.0	2.0	5.0	9.0	0.055	0;3
	Lentinan	32	0	0.7	3.1	-4.0	-1.0	0.0	2.0	10.0		
	Total	67	0	1.5	3.4	-5.0	-1.0	1.0	4.0	10.0		
Hardship due to cancer	Helixor	35	0	2.1	2.8	-4.0	0.0	2.0	4.0	9.0	0.010	0.5;3
	Lentinan	32	0	0.5	2.7	-4.0	-1.0	0.0	2.3	8.0		
	Total	67	0	1.3	2.9	-4.0	-1.0	1.0	3.0	9.0		
Nausea/ vomiting	Helixor	35	0	-0.7	2.8	-8.0	-2.0	-0.5	1.0	4.0	0.164	0;2
	Lentinan	32	0	-1.7	2.9	-9.0	-3.0	-2.0	0.0	3.0		
	Total	67	0	-1.2	2.9	-9.0	-3.0	-1.0	1.0	4.0		
Social well-being	Helixor	35	0	0.6	2.2	-3.0	-1.0	0.0	2.0	6.0	0.666	-1;1
	Lentinan	32	0	0.2	1.3	-3.0	0.0	0.0	1.0	3.0		
	Total	67	0	0.4	1.8	-3.0	-0.5	0.0	1.0	6.0		
Pain	Helixor	35	0	1.4	2.1	-3.0	0.0	1.0	3.0	7.0	0.043	0;2
	Lentinan	32	0	0.3	1.9	-4.0	-1.0	0.0	1.8	4.0		
	Total	67	0	0.9	2.1	-4.0	0.0	1.0	2.0	7.0		

Difference: (value of final investigation minus value of screening).
* Because of discrete data, be careful in interpreting the limits of the confidence intervals.

3.1.3.4 Ovarian cancer

For the entity ovarian cancer the global FLIC score and the subgroups of physical well-being, psychological well-being, hardship due to cancer, nausea/vomiting, social well-being and pain at time of screening are shown in **Table 76**, at time of final investigation in **Table 77**.

Table 76 Ovarian cancer – FLIC total score and FLIC subscales at screening

OVARIAN	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
FLIC score	Helixor	33	0	106.6	18.7	70.0	90.0	111.0	121.0	144.0	0.724
	Lentinan	32	1	104.8	19.4	73.0	89.0	106.5	121.5	138.0	
	Total	65	1	105.7	18.9	70.0	89.0	107.0	121.0	144.0	
Physical well-being	Helixor	33	0	43.2	9.9	16.5	38.5	44.5	50.5	62.5	0.561
	Lentinan	32	1	42.3	10.2	26.5	34.0	42.0	49.5	58.5	
	Total	65	1	42.7	10.0	16.5	36.5	43.5	49.5	62.5	
Psychological well-being	Helixor	33	0	29.9	5.1	20.0	26.0	30.5	33.0	41.5	0.543
	Lentinan	32	1	28.8	5.6	19.0	24.5	30.3	33.0	39.0	
	Total	65	1	29.4	5.4	19.0	26.0	30.5	33.0	41.5	
Hardship due to cancer	Helixor	33	0	12.0	3.9	4.5	9.5	12.0	15.5	17.5	0.609
	Lentinan	32	1	11.8	3.5	6.5	9.5	10.5	14.5	19.5	
	Total	65	1	11.9	3.7	4.5	9.5	11.5	14.5	19.5	
Nausea/ vomiting	Helixor	33	0	10.3	2.4	4.0	9.0	11.0	12.0	14.0	0.272
	Lentinan	32	1	10.8	2.6	5.0	9.0	11.8	13.0	14.0	
	Total	65	1	10.6	2.5	4.0	9.0	11.0	13.0	14.0	
Social well-being	Helixor	33	0	11.2	1.8	7.0	9.5	11.0	13.0	14.0	0.861
	Lentinan	32	1	11.0	2.1	3.0	10.0	11.0	13.0	13.0	
	Total	65	1	11.1	2.0	3.0	10.0	11.0	13.0	14.0	
Pain	Helixor	33	0	8.8	3.0	3.0	6.5	9.0	11.0	14.0	0.849
	Lentinan	32	1	9.0	3.1	3.0	6.5	9.0	11.5	14.0	
	Total	65	1	8.9	3.0	3.0	6.5	9.0	11.0	14.0	

Table 77 Ovarian cancer – FLIC total score and FLIC subscales at final investigation

OVARIAN	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX
FLIC score	Helixor	33	0	112.8	15.9	80.0	101.0	115.0	124.0	137.0
	Lentinan	31	2	106.8	19.0	72.0	87.0	108.0	122.5	137.0
	Total	64	2	109.9	17.6	72.0	97.0	113.0	123.5	137.0
Physical well-being	Helixor	33	0	46.4	7.6	29.5	42.5	48.5	51.5	57.0
	Lentinan	31	2	43.4	9.8	25.0	34.5	45.5	51.5	57.5
	Total	64	2	44.9	8.8	25.0	40.5	46.5	51.5	57.5
Psychological well-being	Helixor	33	0	30.9	4.7	22.0	28.0	32.0	35.0	38.5
	Lentinan	31	2	29.6	6.1	18.0	24.0	30.0	35.0	39.0
	Total	64	2	30.3	5.4	18.0	26.5	31.5	35.0	39.0
Hardship due to cancer	Helixor	33	0	14.2	3.1	7.5	12.5	14.5	16.5	18.5
	Lentinan	31	2	12.6	3.2	7.5	9.5	12.5	15.5	19.5
	Total	64	2	13.4	3.2	7.5	11.0	13.5	16.5	19.5
Nausea/ vomiting	Helixor	33	0	10.1	2.1	3.0	8.5	10.5	11.5	14.0
	Lentinan	31	2	9.7	2.3	5.0	8.0	11.0	11.0	13.0
	Total	64	2	9.9	2.2	3.0	8.0	10.8	11.3	14.0
Social well-being	Helixor	33	0	11.2	1.6	7.0	11.0	11.0	13.0	13.0
	Lentinan	31	2	11.5	1.3	9.0	11.0	11.0	13.0	13.0
	Total	64	2	11.4	1.5	7.0	11.0	11.0	13.0	13.0
Pain	Helixor	33	0	9.9	2.7	4.0	8.0	11.0	12.0	14.0
	Lentinan	31	2	9.4	3.0	3.0	6.5	9.0	12.0	14.0
	Total	64	2	9.7	2.8	3.0	7.8	10.0	12.0	14.0

Figure 18 Ovarian cancer – FLIC subscales at screening

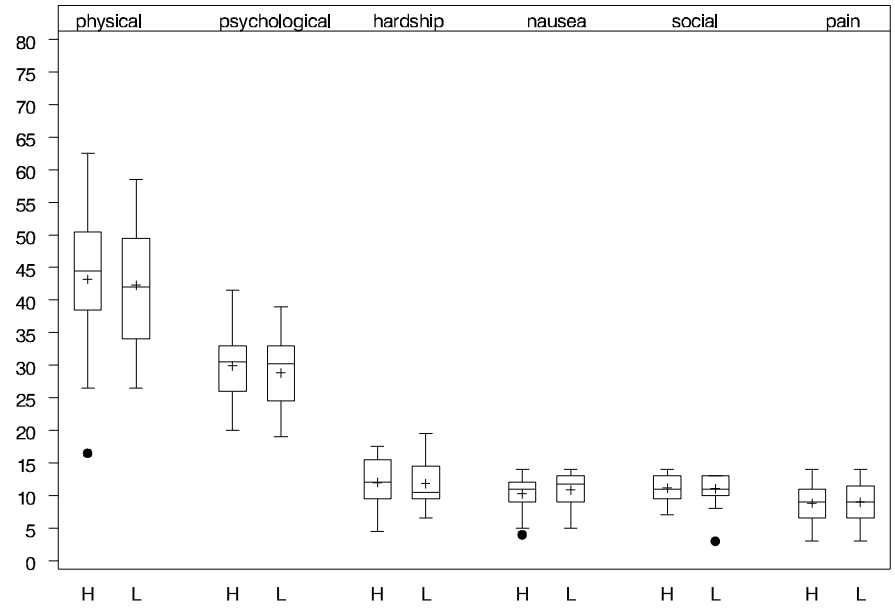
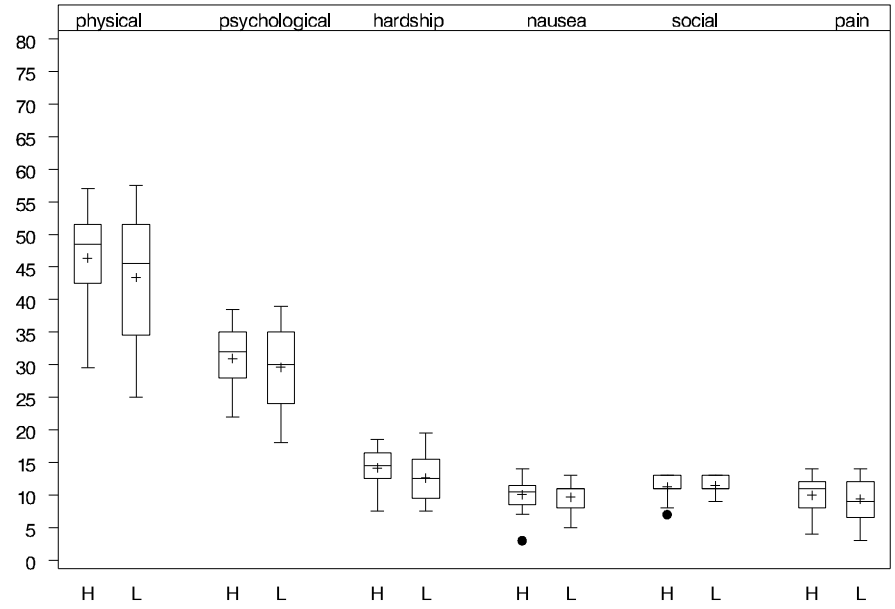


Figure 19 Ovarian cancer – FLIC subscales at final investigation



The difference of the global FLIC score as well as the differences of all subscales between screening and final investigation are shown in **Table 78**. Looking at the global FLIC score there is no statistically significant difference between verum and control group.

Table 78 Ovarian cancer – difference of FLIC between screening and final investigation

OVARIAN	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value	95%-CI
FLIC score	Helixor	33	0	6.2	15.3	-32.0	-1.0	4.5	19.0	35.5	0.556	-4.5;11
	Lentinan	31	2	2.9	14.2	-32.0	-5.0	5.0	11.0	29.0		
	Total	64	2	4.6	14.7	-32.0	-3.0	4.8	11.5	35.5		
Physical well-being	Helixor	33	0	3.2	8.9	-22.0	0.0	2.0	7.5	24.0	0.534	-2.5;5.5
	Lentinan	31	2	1.6	7.9	-14.5	-3.0	2.0	7.5	17.0		
	Total	64	2	2.4	8.4	-22.0	-1.5	2.0	7.5	24.0		
Psycho-logical well-being	Helixor	33	0	1.0	4.0	-12.5	-1.0	1.0	3.0	8.0	0.794	-2;2
	Lentinan	31	2	0.9	4.3	-9.0	-2.0	1.0	5.0	8.0		
	Total	64	2	0.9	4.1	-12.5	-1.8	1.0	4.3	8.0		
Hardship due to cancer	Helixor	33	0	2.2	3.4	-4.0	0.0	1.0	4.0	11.0	0.249	-0.5;2.5
	Lentinan	31	2	1.0	3.6	-7.0	-1.0	0.5	3.5	10.0		
	Total	64	2	1.6	3.5	-7.0	0.0	1.0	3.8	11.0		
Nausea/ vomiting	Helixor	33	0	-0.2	2.5	-5.0	-2.0	0.0	1.0	8.0	0.164	0;2
	Lentinan	31	2	-1.1	2.5	-7.0	-2.0	-1.0	0.0	4.0		
	Total	64	2	-0.6	2.5	-7.0	-2.0	0.0	0.3	8.0		
Social well-being	Helixor	33	0	0.1	1.4	-3.0	0.0	0.0	0.0	3.5	0.606	-1;0.5
	Lentinan	31	2	0.5	2.2	-3.0	-1.0	0.0	1.0	8.0		
	Total	64	2	0.3	1.8	-3.0	-1.0	0.0	1.0	8.0		
Pain	Helixor	33	0	1.1	3.1	-7.0	0.0	1.0	3.0	9.0	0.196	0;2
	Lentinan	31	2	0.5	3.0	-6.0	-1.0	0.0	2.0	8.0		
	Total	64	2	0.8	3.0	-7.0	0.0	0.0	2.5	9.0		

Difference: (value of final investigation minus value of screening).
* Because of discrete data, be careful in interpreting the limits of the confidence intervals.

3.2 Body Weight and Body Mass Index

Body weight data of the study population in different treatment groups are listed in **Table 79**. The weight parameter is ordered in the categories reduced, stable and increased. Reduced or increased weight is defined as loss or gain of at least 1 kg, respectively. The majority of patients have stable weight during the trial

period. There is no statistically significant difference between the HELIXOR® A and Lentinan groups in the overall population as well as for tumor entities.

Table 79 Weight of study population during trial period

ALL		**Helixor N=113**		**Lentinan N=109**		**Total N=222**		**strat. p-value**
		N	%	N	%	N	%	
Weight	Reduced	16	14.2	24	22.0	40	18.0	0.110
	Stable	84	74.3	76	69.7	160	72.1	
	Increased	13	11.5	9	8.3	22	9.9	

NSCLC		**Helixor N=45**		**Lentinan N=45**		**Total N=90**		**p-value**
		N	%	N	%	N	%	
Weight	Reduced	4	8.9	9	20	13	14.4	0.440
	Stable	37	82.2	30	66.7	67	74.4	
	Increased	4	8.9	6	13.3	10	11.1	

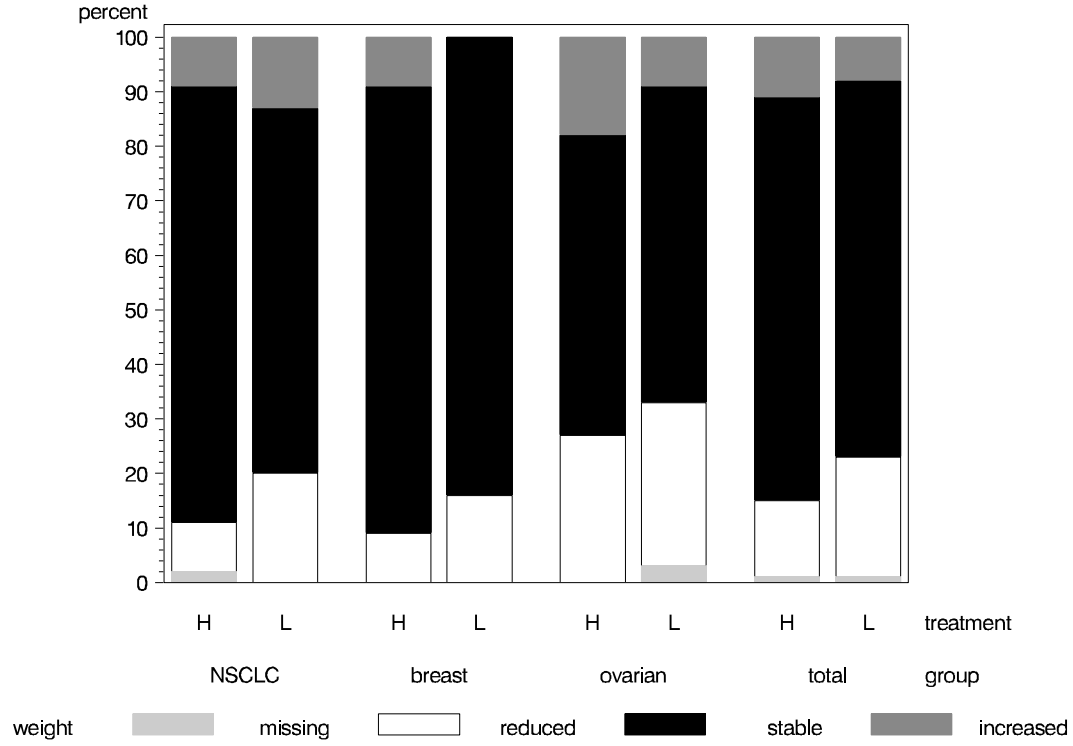
BREAST		**Helixor N=35**		**Lentinan N=32**		**Total N=67**		**p-value**
		N	%	N	%	N	%	
Weight	Reduced	3	8.6	5	15.6	8	11.9	0.135
	Stable	29	82.9	27	84.4	56	83.6	
	Increased	3	8.6	0	0	3	4.5	

OVARIAN		**Helixor N=33**		**Lentinan N=32**		**Total N=65**		**p-value**
		N	%	N	%	N	%	
Weight	Reduced	9	27.3	10	31.3	19	29.2	0.507
	Stable	18	54.5	19	59.4	37	56.9	
	Increased	6	18.2	3	9.4	9	13.8	

Reduced: weight loss of at least 1 kg over trial period; Increased: weight gain of at least 1 kg over trial period;

Graphically these data are presented in **Figure 20** subdivided by treatment group and tumor entity.

Figure 20 Total study population, NSCLC, breast cancer, ovarian cancer – weight evaluated as reduced, stable and increased



The Body Mass Index of the study population, which is measured as body weight divided by the square of body height, is recorded in **Table 80** and **Table 81**. BMI, weight and height have already been evaluated for the comparability of the study population at screening (item 2.1). Here, the Body Mass Index is given at time of final investigation and as difference between time of final investigation and screening. Although in the total study population the difference of the Body Mass Index between screening and final investigation has a significant p-value of 0.027 between verum and control treatment group, the different changes of the Body Mass Index during trial period seem negligible (s. Table 81: 95% confidence interval for the difference between verum and control treatment group is 0 to 0.3).

Table 80 Body Mass Index at time of final investigation

ALL	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX
Body Mass	Helixor	113	1	23.5	3.2	15.8	21.0	23.5	26.1	30.1
Index	Lentinan	109	1	23.2	3.1	16.6	20.8	23.0	25.2	32.0
	Total	222	2	23.3	3.2	15.8	20.8	23.4	25.6	32.0

NSCLC	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX
Body Mass	Helixor	45	1	23.4	3.6	15.8	20.3	23.4	26.1	30.1
Index	Lentinan	45	0	23.2	3.3	16.8	21.0	23.7	25.2	29.1
	Total	90	1	23.3	3.4	15.8	20.6	23.7	25.8	30.1

BREAST	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX
Body Mass	Helixor	35	0	24.2	2.8	17.4	22.1	24.2	26.3	29.7
Index	Lentinan	32	0	23.7	3.1	17.7	21.2	23.2	25.6	32.0
	Total	67	0	24.0	2.9	17.4	21.7	23.8	26.1	32.0

OVARIAN	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX
Body Mass	Helixor	33	0	23.0	3.1	18.0	20.2	23.1	25.6	29.1
Index	Lentinan	32	1	22.5	2.9	16.6	20.1	22.4	24.6	28.7
	Total	65	1	22.8	3.0	16.6	20.1	22.5	25.1	29.1

Table 81 Body Mass Index – Difference between screening and final investigation

ALL	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	strat. p-value	95%-CI
Body Mass	Helixor	113	1	-0.1	1.2	-5.4	0.0	0.0	0.3	5.0	0.027	0;0.3
Index	Lentinan	109	1	-0.1	0.8	-4.8	-0.4	0.0	0.0	2.4		
	Total	222	2	-0.1	1.0	-5.4	-0.4	0.0	0.2	5.0		

NSCLC	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value	95%-CI
Body Mass	Helixor	45	1	-0.1	0.9	-5.4	0.0	0.0	0.0	1.8	0.209	0;0.3
Index	Lentinan	45	0	-0.0	0.7	-1.1	-0.4	0.0	0.3	2.0		
	Total	90	1	-0.0	0.8	-5.4	-0.2	0.0	0.0	2.0		

BREAST	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value	95%-CI
Body Mass	Helixor	35	0	0.1	1.0	-2.3	0.0	0.0	0.4	3.6	0.007	0;0.4
Index	Lentinan	32	0	-0.2	0.5	-1.5	-0.4	0.0	0.0	0.8		
	Total	67	0	-0.0	0.8	-2.3	-0.1	0.0	0.0	3.6		

OVARIAN	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value	95%-CI
Body Mass	Helixor	33	0	-0.2	1.6	-3.9	-0.7	0.0	0.3	5.0	0.762	-0.4;0.4
Index	Lentinan	32	1	-0.2	1.1	-4.8	-0.8	0.0	0.4	2.4		
	Total	65	1	-0.2	1.4	-4.8	-0.8	0.0	0.4	5.0		

Difference: (value of final investigation minus value of screening).

3.3 Heart Function

The parameters systolic and diastolic blood pressure and pulse at time of the final investigation are listed in **Table 82** for the total study population and in **Table 83, Table 84** and **Table 85** for single tumor entities.

Table 82 Total study population – final investigation

ALL	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX
RR syst	Helixor	113	1	122.3	12.7	95.0	110.0	120.0	130.0	170.0
[mmHg]	Lentinan	109	1	122.8	13.0	90.0	115.0	120.0	130.0	160.0
	Total	222	2	122.5	12.9	90.0	112.0	120.0	130.0	170.0
RR diast	Helixor	113	1	80.0	7.7	60.0	75.0	80.0	85.0	105.0
[mmHg]	Lentinan	109	1	79.1	7.3	60.0	75.0	80.0	85.0	95.0
	Total	222	2	79.6	7.5	60.0	75.0	80.0	85.0	105.0
Pulse	Helixor	114	0	82.6	5.9	68.0	80.0	82.0	85.0	112.0
[beats/min.]	Lentinan	109	1	82.3	8.7	28.0	80.0	82.0	85.0	110.0
	Total	223	1	82.5	7.4	28.0	80.0	82.0	85.0	112.0

Table 83 Non small cell lung cancer – final investigation

NSCLC	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX
RR syst	Helixor	46	0	125.4	14.1	100.0	120.0	120.0	130.0	170.0
[mmHg]	Lentinan	45	0	124.2	13.6	90.0	120.0	120.0	130.0	160.0
	total	91	0	124.8	13.8	90.0	120.0	120.0	130.0	170.0
RR diast	Helixor	46	0	81.7	6.6	70.0	80.0	80.0	90.0	95.0
[mmHg]	Lentinan	45	0	80.0	7.1	60.0	75.0	80.0	85.0	90.0
	Total	91	0	80.9	6.8	60.0	80.0	80.0	85.0	95.0
Pulse	Helixor	46	0	82.8	4.5	70.0	80.0	82.0	85.0	95.0
[beats/min.]	Lentinan	45	0	83.0	6.4	65.0	80.0	84.0	88.0	96.0
	Total	91	0	82.9	5.5	65.0	80.0	84.0	85.0	96.0

Table 84 Breast cancer - final investigation

BREAST	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX
RR syst	Helixor	34	1	119.0	9.3	100.0	110.0	120.0	126.0	140.0
[mmHg]	Lentinan	32	0	122.6	11.1	105.0	117.5	120.0	127.5	150.0
	Total	66	1	120.7	10.3	100.0	110.0	120.0	126.0	150.0
RR diast	Helixor	34	1	78.1	7.0	60.0	75.0	80.0	80.0	90.0
[mmHg]	Lentinan	32	0	79.3	6.8	68.0	75.0	80.0	82.5	95.0
	Total	66	1	78.6	6.9	60.0	75.0	80.0	80.0	95.0
Pulse	Helixor	35	0	82.5	7.2	70.0	78.0	82.0	84.0	112.0
[beats/min.]	Lentinan	32	0	82.3	6.7	70.0	78.0	83.0	84.5	110.0
	Total	67	0	82.4	6.9	70.0	78.0	82.0	84.0	112.0

Table 85 Ovarian cancer – final investigation

OVARIAN	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX
RR syst	Helixor	33	0	121.2	13.2	95.0	115.0	120.0	125.0	165.0
[mmHg]	Lentinan	32	1	121.0	14.2	90.0	110.0	120.0	132.5	150.0
	Total	65	1	121.1	13.6	90.0	110.0	120.0	130.0	165.0
RR diast	Helixor	33	0	79.8	9.2	60.0	75.0	80.0	85.0	105.0
[mmHg]	Lentinan	32	1	77.7	8.0	60.0	70.0	80.0	85.0	90.0
	Total	65	1	78.7	8.6	60.0	70.0	80.0	85.0	105.0
Pulse	Helixor	33	0	82.5	6.2	68.0	80.0	84.0	88.0	98.0
[beats/min.]	Lentinan	32	1	81.3	12.7	28.0	80.0	82.0	85.5	108.0
	Total	65	1	81.9	9.9	28.0	80.0	82.0	86.0	108.0

Changes in blood pressure or pulse during period of trial are presented in **Table 86, Table 87, Table 88** and **Table 89** for the overall population and tumor entities. Treatment groups of Helixor® A and Lentinan are comparable for heart function parameters that show only minor changes during study period.

Table 86 Total study population – difference between final investigation and screening

ALL	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value	95%-CI
RR syst	Helixor	113	1	-1.3	10.8	-50.0	0.0	0.0	0.0	30.0	0.645	0;0
[mmHg]	Lentinan	109	1	-2.0	11.7	-50.0	-5.0	0.0	0.0	40.0		
	Total	222	2	-1.6	11.2	-50.0	-3.0	0.0	0.0	40.0		
RR diast	Helixor	113	1	0.6	7.5	-30.0	0.0	0.0	5.0	20.0	0.594	0;0
[mmHg]	Lentinan	109	1	1.0	7.4	-15.0	0.0	0.0	5.0	30.0		
	Total	222	2	0.8	7.5	-30.0	0.0	0.0	5.0	30.0		
Pulse	Helixor	113	1	0.1	5.4	-28.0	-2.0	0.0	2.0	14.0	0.761	0;1
[beats/min]	Lentinan	109	1	-0.4	7.5	-52.0	-2.0	0.0	2.0	22.0		
	Total	222	2	-0.2	6.5	-52.0	-2.0	0.0	2.0	22.0		

Table 87 Non small cell lung cancer – difference between final investigation and screening

NSCLC	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value	95%-CI
RR syst	Helixor	46	0	0.6	7.6	-30.0	0.0	0.0	0.0	20.0	0.416	0;0
[mmHg]	Lentinan	45	0	-1.7	12.5	-50.0	0.0	0.0	0.0	20.0		
	Total	91	0	-0.5	10.3	-50.0	0.0	0.0	0.0	20.0		
RR diast	Helixor	46	0	2.0	5.4	-10.0	0.0	0.0	5.0	15.0	0.225	0;5
[mmHg]	Lentinan	45	0	1.1	6.6	-10.0	0.0	0.0	0.0	20.0		
	Total	91	0	1.6	6.0	-10.0	0.0	0.0	5.0	20.0		
Pulse	Helixor	46	0	0.1	3.3	-12.0	-2.0	0.0	2.0	7.0	0.626	0;2
[beats/min]	Lentinan	45	0	-0.4	5.6	-20.0	-3.0	0.0	2.0	14.0		
	Total	91	0	-0.2	4.5	-20.0	-2.0	0.0	2.0	14.0		

Table 88 Breast cancer - difference between final investigation and screening

BREAST	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value	95%-CI
RR syst	Helixor	34	1	-0.4	10.4	-30.0	-4.0	0.0	4.0	30.0	0.625	0;2
[mmHg]	Lentinan	32	0	-2.1	9.2	-35.0	0.0	0.0	0.0	10.0		
	Total	66	1	-1.2	9.8	-35.0	0.0	0.0	0.0	30.0		
RR diast	Helixor	34	1	-0.4	7.8	-20.0	0.0	0.0	5.0	15.0	0.809	0;4
[mmHg]	Lentinan	32	0	0.5	7.5	-15.0	0.0	0.0	0.0	30.0		
	Total	66	1	0.0	7.6	-20.0	0.0	0.0	5.0	30.0		
Pulse	Helixor	34	1	0.9	6.5	-20.0	-2.0	0.0	4.0	14.0	0.687	-2;2
[beats/min]	Lentinan	32	0	0.6	5.6	-12.0	-1.0	0.0	2.5	22.0		
	Total	66	1	0.8	6.0	-20.0	-2.0	0.0	3.0	22.0		

Table 89 Ovarian cancer – difference between final investigation and screening

OVARIAN	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value	95%-CI
RR syst	Helixor	33	0	-4.9	13.9	-50.0	-5.0	0.0	0.0	15.0	0.680	-5;3
[mmHg]	Lentinan	32	1	-2.3	13.2	-35.0	-5.0	0.0	2.5	40.0		
	Total	65	1	-3.6	13.5	-50.0	-5.0	0.0	0.0	40.0		
RR diast	Helixor	33	0	-0.3	9.5	-30.0	-5.0	0.0	5.0	20.0	0.646	-5;3
[mmHg]	Lentinan	32	1	1.5	8.5	-15.0	-5.0	0.0	6.5	20.0		
	Total	65	1	0.6	9.0	-30.0	-5.0	0.0	5.0	20.0		
Pulse	Helixor	33	0	-0.8	6.5	-28.0	-2.0	0.0	2.0	8.0	0.619	-2;2
[beats/min]	Lentinan	32	1	-1.4	11.0	-52.0	-3.0	0.0	2.0	18.0		
	Total	65	1	-1.1	8.9	-52.0	-2.0	0.0	2.0	18.0		

3.4 Laboratory, including basic blood count -, immunological - and liver/kidney parameters

Laboratory parameters including basic blood count, immunological and liver/kidney parameters are listed for time at screening, final investigation and as difference between final examination and screening to evaluate changes during the clinical trial.

3.4.1 Basic Blood Count Parameters

3.4.1.1 Total study population

Basic blood counts including Hemoglobin (Hb), Platelets, total leucocytes, neutrophils, segmented forms, band forms, basophils, monocytes and lymphocytes are presented in **Table 90** at time of screening, in **Table 91** at final investigation and in **Table 92** to show changes in blood counts during trial period. These tables indicate, that all blood parameters under observation are comparable in the verum and the control group.

Table 90 Total study population – Basic blood count parameters at screening

ALL	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
Hb	Helixor	114	0	11.9	1.6	6.9	10.7	12.0	13.1	15.3	0.674
[g/dl]	Lentinan	110	0	11.8	1.7	7.1	10.8	12.0	12.9	17.0	
	Total	224	0	11.9	1.7	6.9	10.8	12.0	13.0	17.0	
Platelets	Helixor	113	1	247.7	85.3	93.0	186.0	232.0	295.0	559.0	0.103
[$x10^9$/l]	Lentinan	110	0	269.8	93.6	82.0	196.0	246.5	347.0	482.0	
	Total	223	1	258.6	90.0	82.0	189.0	238.0	318.0	559.0	
Total	Helixor	114	0	6.4	2.1	2.6	5.0	6.0	7.4	14.6	0.469
leucocytes	Lentinan	110	0	6.5	1.9	3.3	5.1	6.2	7.3	12.4	
[($x10^6$/l]	Total	224	0	6.5	2.0	2.6	5.1	6.1	7.3	14.6	
Neutrophils	Helixor	114	0	69.5	11.2	0.7	63.9	70.7	75.6	92.7	0.884
[%]	Lentinan	110	0	69.5	12.1	0.7	65.0	70.7	76.7	94.0	
	Total	224	0	69.5	11.6	0.7	64.3	70.7	76.0	94.0	
Segmented	Helixor	42	72	52.5	30.2	0.0	45.0	66.6	73.2	84.9	0.729
Forms	Lentinan	41	69	55.6	25.9	0.0	52.0	64.0	72.0	86.3	
[%]	Total	83	141	54.0	28.1	0.0	48.0	65.0	73.0	86.3	
Band forms	Helixor	41	73	1.3	3.5	0.0	0.0	0.0	0.0	20.0	0.709
[%]	Lentinan	41	69	0.7	1.3	0.0	0.0	0.0	1.0	5.0	
	Total	82	142	1.0	2.6	0.0	0.0	0.0	1.0	20.0	
Eosinophils	Helixor	85	29	0.9	1.4	0.0	0.0	0.4	1.0	7.0	0.210
[%]	Lentinan	84	26	0.6	0.9	0.0	0.0	0.0	1.0	4.0	
	Total	169	55	0.8	1.2	0.0	0.0	0.0	1.0	7.0	
Basophils	Helixor	79	35	0.2	0.5	0.0	0.0	0.0	0.0	2.0	0.435
[%]	Lentinan	81	29	0.1	0.4	0.0	0.0	0.0	0.0	2.0	
	Total	160	64	0.2	0.5	0.0	0.0	0.0	0.0	2.0	
Monocytes	Helixor	100	14	2.9	3.6	0.0	0.0	1.2	4.3	15.8	0.975
[%]	Lentinan	102	8	3.2	4.3	0.0	0.0	1.6	6.0	17.7	
	Total	202	22	3.1	3.9	0.0	0.0	1.3	5.0	17.7	
Lymphocytes	Helixor	113	1	26.0	10.1	0.2	18.0	26.3	31.4	59.7	0.472
[%]	Lentinan	110	0	25.0	10.0	0.2	18.5	24.0	30.6	48.0	
	Total	223	1	25.5	10.0	0.2	18.4	25.3	31.0	59.7	

Table 91 Total study population – Basic blood count parameters at final investigation

ALL	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX
Hb	Helixor	114	0	11.0	1.4	7.0	10.0	11.0	12.1	13.8
[g/dl]	Lentinan	109	1	10.9	1.7	5.9	9.9	11.1	12.0	15.0
	Total	223	1	11.0	1.5	5.9	10.0	11.1	12.1	15.0
Platelets	Helixor	114	0	244.4	95.5	67.0	174.0	229.0	308.0	519.0
[$x10^9$/l]	Lentinan	108	2	246.1	107.1	73.0	168.0	217.5	302.5	649.0
	Total	222	2	245.2	101.1	67.0	170.0	224.0	305.0	649.0
Total	Helixor	114	0	5.1	2.2	1.4	3.8	4.6	6.0	14.9
Leucocytes	Lentinan	108	2	5.4	2.8	1.4	3.9	5.1	6.2	22.3
[($x10^6$/l]	Total	222	2	5.3	2.5	1.4	3.9	4.9	6.0	22.3
Neutrophils	Helixor	114	0	63.0	13.4	0.8	56.5	64.5	71.2	90.2
[%]	Lentinan	109	1	65.5	13.6	0.6	59.1	66.0	75.0	90.5
	Total	223	1	64.2	13.5	0.6	58.0	65.0	72.0	90.5
Segmented	Helixor	42	72	49.4	26.8	0.0	35.9	60.0	68.9	85.0
Forms	Lentinan	41	69	54.5	24.9	0.0	54.0	61.0	69.2	85.9
[%]	Total	83	141	51.9	25.9	0.0	48.0	60.7	69.0	85.9
Band forms	Helixor	41	73	2.2	6.0	0.0	0.0	0.0	1.0	30.0
[%]	Lentinan	40	70	0.7	1.1	0.0	0.0	0.0	1.5	3.0
	Total	81	143	1.4	4.4	0.0	0.0	0.0	1.0	30.0
Eosinophils	Helixor	87	27	1.5	2.9	0.0	0.0	0.7	2.0	20.0
[%]	Lentinan	80	30	0.7	1.3	0.0	0.0	0.0	1.0	8.0
	Total	167	57	1.1	2.3	0.0	0.0	0.0	1.0	20.0
Basophils	Helixor	80	34	0.2	0.5	0.0	0.0	0.0	0.0	2.0
[%]	Lentinan	80	30	0.1	0.4	0.0	0.0	0.0	0.0	2.0
	Total	160	64	0.2	0.5	0.0	0.0	0.0	0.0	2.0
Monocytes	Helixor	100	14	3.5	4.6	0.0	0.0	2.0	4.9	18.8
[%]	Lentinan	100	10	3.2	4.5	0.0	0.0	2.0	3.9	21.0
	Total	200	24	3.4	4.6	0.0	0.0	2.0	4.7	21.0
Lymphocytes	Helixor	113	1	30.5	11.7	4.2	23.0	30.6	38.0	67.2
[%]	Lentinan	108	2	28.8	11.9	0.2	21.3	30.3	37.7	62.1
	Total	221	3	29.6	11.8	0.2	22.0	30.5	38.0	67.2

Table 92 Total study population – Difference of basic blood count parameters between final investigation and screening

ALL	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value	95%-CI
Hb	Helixor	114	0	-0.9	1.5	-4.2	-2.0	-0.7	0.4	2.4	0.822	-0.4;0.5
[g/dl]	Lentinan	109	1	-0.9	1.7	-7.2	-1.9	-0.8	0.1	2.4		
	Total	223	1	-0.9	1.6	-7.2	-2.0	-0.8	0.2	2.4		
Platelets	Helixor	113	1	-4.3	105.2	-319.0	-72.0	-1.0	52.0	332.0	0.127	-6;45
[$x10^9$/l]	Lentinan	108	2	-23.7	102.4	-305.0	-87.0	-35.0	34.0	225.0		
	Total	221	3	-13.8	104.1	-319.0	-75.0	-17.0	41.0	332.0		
Total	Helixor	114	0	-1.3	2.6	-8.0	-2.6	-1.2	0.0	8.7	0.651	-0.8;0.4
leucozytes	Lentinan	108	2	-1.1	3.1	-9.2	-2.5	-1.1	0.3	16.0		
[($x10^6$/l]	Total	222	2	-1.2	2.8	-9.2	-2.6	-1.1	0.2	16.0		
Neutrophils	Helixor	114	0	-6.5	13.3	-42.7	-14.4	-6.4	2.6	40.9	0.136	-6;0.8
[%]	Lentinan	109	1	-3.8	12.5	-43.5	-12.2	-1.8	3.5	34.5		
	Total	223	1	-5.2	12.9	-43.5	-13.8	-4.0	3.2	40.9		
Segmented	Helixor	39	75	-3.9	14.5	-52.0	-12.3	0.0	2.0	22.0	0.706	-6.8;2
Forms	Lentinan	40	70	-0.5	12.9	-27.0	-6.4	-0.1	1.5	49.0		
[%]	Total	79	145	-2.2	13.7	-52.0	-9.1	0.0	2.0	49.0		
Band forms	Helixor	40	74	0.9	3.6	-2.0	0.0	0.0	0.0	19.0	0.875	0;0
[%]	Lentinan	40	70	-0.0	1.2	-4.0	0.0	0.0	0.0	3.0		
	Total	80	144	0.4	2.7	-4.0	0.0	0.0	0.0	19.0		
Eosinophils	Helixor	85	29	0.5	3.0	-5.0	0.0	0.0	1.0	20.0	0.397	0;0
[%]	Lentinan	80	30	0.1	1.2	-3.0	0.0	0.0	0.0	5.0		
	Total	165	59	0.3	2.3	-5.0	0.0	0.0	0.7	20.0		
Basophils	Helixor	78	36	-0.0	0.7	-2.0	0.0	0.0	0.0	2.0	0.980	0;0
[%]	Lentinan	79	31	0.0	0.6	-2.0	0.0	0.0	0.0	2.0		
	Total	157	67	0.0	0.6	-2.0	0.0	0.0	0.0	2.0		
Mono-	Helixor	98	16	0.7	3.3	-9.9	-0.9	0.0	2.0	11.3	0.211	0;1
cytes	Lentinan	100	10	0.0	3.3	-9.4	-1.0	0.0	1.0	11.0		
[%]	Total	198	26	0.3	3.3	-9.9	-1.0	0.0	1.3	11.3		
Lympho-	Helixor	113	1	4.5	12.6	-40.9	-4.6	3.6	13.7	43.8	0.583	-2.4;4
cytes	Lentinan	108	2	3.6	12.1	-37.3	-2.9	2.3	11.0	33.0		
[%]	Total	221	3	4.1	12.4	-40.9	-3.8	3.0	12.0	43.8		

Difference: (value of final investigation minus value of screening).

3.4.1.2 Non small cell lung cancer

Basic blood count parameters are listed for time at screening, final investigation and as difference between final examination and screening to evaluate changes during medication trial in **Table 93, Table 94** and **Table 95.** All parameters are comparable for verum and control treatment groups at time of screening and different changes during the period of trial are observed only for neutrophils. Patients under Helixor treatment show a significant reduction of neutrophils in comparison to patients treated with Lentinan (p = 0.046). However, under consideration of multiple testing this p-value is only descriptive.

Table 93 Non small cell lung cancer –Basic blood count parameters at screening

NSCLC	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
Hb	Helixor	46	0	12.6	1.5	8.5	11.7	12.8	13.6	15.3	0.339
[g/dl]	Lentinan	45	0	12.3	2.0	7.1	11.6	12.2	13.2	17.0	
	Total	91	0	12.4	1.8	7.1	11.7	12.4	13.6	17.0	
Platelets	Helixor	46	0	246.8	81.4	93.0	186.0	229.0	291.0	474.0	0.353
[$x10^9$/l]	Lentinan	45	0	266.6	95.7	119.0	193.0	244.0	335.0	452.0	
	Total	91	0	256.6	88.8	93.0	192.0	234.0	315.0	474.0	
Total	Helixor	46	0	6.9	2.1	3.9	5.4	6.5	7.9	14.6	0.542
leucocytes	Lentinan	45	0	6.6	1.8	4.0	5.3	6.3	7.3	12.4	
[($x10^6$/l]	Total	91	0	6.8	2.0	3.9	5.4	6.4	7.8	14.6	
Neutrophils	Helixor	46	0	71.7	9.6	40.3	67.0	73.0	78.3	86.3	0.250
[%]	Lentinan	45	0	68.4	14.6	0.7	65.2	72.0	75.3	94.0	
	Total	91	0	70.1	12.4	0.7	66.3	72.3	77.0	94.0	
Segmented	Helixor	12	34	46.5	35.4	0.0	0.0	62.9	73.5	84.9	0.287
Forms	Lentinan	10	35	28.2	33.3	0.0	0.0	12.5	69.9	74.5	
[%]	Total	22	69	38.2	34.9	0.0	0.0	46.5	72.0	84.9	
Band forms	Helixor	13	33	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.346
[%]	Lentinan	12	33	0.3	0.9	0.0	0.0	0.0	0.0	3.0	
	Total	25	66	0.1	0.6	0.0	0.0	0.0	0.0	3.0	
Eosinophils	Helixor	28	18	0.4	0.8	0.0	0.0	0.0	0.7	3.0	0.280
[%]	Lentinan	26	19	0.4	0.4	0.0	0.0	0.4	0.7	1.0	
	Total	54	37	0.4	0.6	0.0	0.0	0.0	0.7	3.0	
Basophils	Helixor	24	22	0.1	0.2	0.0	0.0	0.0	0.1	1.0	0.613
[%]	Lentinan	24	21	0.1	0.1	0.0	0.0	0.0	0.2	0.2	
	Total	48	43	0.1	0.2	0.0	0.0	0.0	0.2	1.0	
Monocytes	Helixor	39	7	4.0	4.3	0.0	0.0	2.3	8.2	13.7	0.511
[%]	Lentinan	40	5	5.0	5.0	0.0	0.0	4.9	7.9	16.0	
	Total	79	12	4.5	4.7	0.0	0.0	3.0	8.0	16.0	
Lymphocytes	Helixor	45	1	23.5	10.8	3.7	15.3	21.5	29.0	59.7	0.342
[%]	Lentinan	45	0	24.6	9.8	0.2	18.4	23.3	30.1	48.0	
	Total	90	1	24.1	10.3	0.2	16.1	23.2	29.6	59.7	

Table 94 Non small cell lung cancer – Basic blood count parameters at final investigation

NSCLC	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX
Hb	Helixor	46	0	10.9	1.6	7.0	9.8	11.0	12.0	13.8
[g/dl]	Lentinan	45	0	10.7	1.7	7.1	9.3	10.7	11.9	15.0
	Total	91	0	10.8	1.7	7.0	9.8	10.9	12.0	15.0
Platelets	Helixor	46	0	226.0	92.6	87.0	163.0	198.0	270.0	483.0
[$x10^9$/l]	Lentinan	44	1	238.2	118.7	105.0	151.5	189.0	294.5	649.0
	Total	90	1	232.0	105.7	87.0	159.0	193.5	275.0	649.0
Total	Helixor	46	0	5.6	2.7	1.4	4.2	4.9	6.2	14.9
leucocytes	Lentinan	44	1	6.1	3.8	1.4	4.0	5.5	6.9	22.3
[($x10^6$/l]	Total	90	1	5.8	3.3	1.4	4.1	5.0	6.8	22.3
Neutrophils	Helixor	46	0	63.4	13.9	26.1	54.6	65.6	72.1	90.2
[%]	Lentinan	45	0	65.1	17.1	0.6	59.6	66.2	75.8	90.5
	Total	91	0	64.2	15.5	0.6	57.1	66.2	74.0	90.5
Segmented	Helixor	12	34	44.3	34.0	0.0	0.0	57.0	69.4	85.0
Forms	Lentinan	10	35	34.7	36.9	0.0	0.0	27.5	73.0	74.0
[%]	Total	22	69	39.9	34.8	0.0	0.0	54.5	71.0	85.0
Band forms	Helixor	13	33	0.0	0.0	0.0	0.0	0.0	0.0	0.0
[%]	Lentinan	12	33	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Total	25	66	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Eosinophils	Helixor	28	18	1.1	3.9	0.0	0.0	0.0	0.4	20.0
[%]	Lentinan	24	21	0.4	0.9	0.0	0.0	0.0	0.7	4.0
	Total	52	39	0.8	2.9	0.0	0.0	0.0	0.7	20.0
Basophils	Helixor	23	23	0.0	0.1	0.0	0.0	0.0	0.0	0.2
[%]	Lentinan	25	20	0.0	0.1	0.0	0.0	0.0	0.0	0.2
	Total	48	43	0.0	0.1	0.0	0.0	0.0	0.0	0.2
Monocytes	Helixor	38	8	4.5	5.9	0.0	0.0	1.5	7.8	18.8
[%]	Lentinan	39	6	4.1	5.5	0.0	0.0	2.0	6.5	21.0
	Total	77	14	4.3	5.7	0.0	0.0	2.0	6.7	21.0
Lymphocytes	Helixor	45	1	29.4	13.7	4.2	18.7	29.1	38.1	67.2
[%]	Lentinan	44	1	27.4	13.0	0.2	20.0	28.0	35.0	62.1
	Total	89	2	28.4	13.3	0.2	19.3	29.0	36.0	67.2

Table 95 Non small cell lung cancer – Difference of basic blood count parameters between final investigation and screening

NSCLC	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value	95%-CI
Hb	Helixor	46	0	-1.7	1.3	-4.2	-2.9	-1.7	-0.6	1.3	0.806	-0.7;0.6
[g/dl]	Lentinan	45	0	-1.6	1.8	-7.2	-2.3	-1.6	-0.8	2.4		
	Total	91	0	-1.7	1.5	-7.2	-2.9	-1.6	-0.7	2.4		
Platelets	Helixor	46	0	-20.7	99.9	-226.0	-82.0	-12.0	32.0	268.0	0.612	-31;50
[$x10^9$/l]	Lentinan	44	1	-31.2	110.0	-281.0	-93.5	-38.5	13.0	200.0		
	Total	90	1	-25.9	104.5	-281.0	-92.0	-27.5	24.0	268.0		
Total	Helixor	46	0	-1.3	3.2	-7.8	-3.6	-1.3	-0.2	8.7	0.256	-1.8;0.4
leucocytes	Lentinan	44	1	-0.5	3.6	-7.2	-2.4	-1.0	0.6	16.0		
[($x10^6$/l]	Total	90	1	-0.9	3.4	-7.8	-2.8	-1.2	0.3	16.0		
Neutrophils	Helixor	46	0	-8.3	14.6	-40.9	-17.0	-9.3	0.1	40.9	0.046	-11;-0.2
[%]	Lentinan	45	0	-3.4	13.7	-43.5	-11.6	-2.4	5.2	34.5		
	Total	91	0	-5.8	14.3	-43.5	-14.6	-4.7	3.8	40.9		
Segmented	Helixor	11	35	-7.9	17.1	-52.0	-15.1	0.0	0.2	10.3	0.260	-20.4;0.1
Forms	Lentinan	10	35	6.4	15.6	-0.8	0.0	0.0	1.1	49.0		
[%]	Total	21	70	-1.1	17.6	-52.0	0.0	0.0	1.0	49.0		
Band forms	Helixor	13	33	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.346	0;0
[%]	Lentinan	12	33	-0.3	0.9	-3.0	0.0	0.0	0.0	0.0		
	Total	25	66	-0.1	0.6	-3.0	0.0	0.0	0.0	0.0		
Eosinophils	Helixor	28	18	0.7	3.9	-2.0	0.0	0.0	0.0	20.0	0.340	0;0.4
[%]	Lentinan	24	21	0.0	1.0	-1.0	-0.7	0.0	0.0	4.0		
	Total	52	39	0.4	2.9	-2.0	0.0	0.0	0.0	20.0		
Basophils	Helixor	23	23	-0.1	0.2	-1.0	0.0	0.0	0.0	0.2	0.897	0;0
[%]	Lentinan	24	21	-0.0	0.1	-0.2	0.0	0.0	0.0	0.0		
	Total	47	44	-0.0	0.2	-1.0	0.0	0.0	0.0	0.2		
Mono-	Helixor	38	8	0.5	3.8	-9.9	-1.0	0.0	2.0	11.3	0.247	-0.01;2.23
cytes	Lentinan	39	6	-0.9	3.5	-9.4	-2.2	0.0	0.1	7.0		
[%]	Total	77	14	-0.2	3.7	-9.9	-1.2	0.0	0.8	11.3		
Lympho-	Helixor	45	1	5.9	13.1	-40.9	-1.2	4.0	15.0	34.2	0.193	-1.5;7.6
cytes	Lentinan	44	1	2.8	11.6	-37.3	-3.3	1.9	10.7	33.0		
[%]	Total	89	2	4.4	12.4	-40.9	-2.6	3.0	12.5	34.2		

Difference: (value of final investigation minus value of screening).

3.4.1.3 Breast cancer

Basic blood count are shown for time at screening, final investigation and difference between final examination and screening to evaluate changes during medication trial in **Table 96, Table 97** and **Table 98**, respectively. Except for eosinophils all parameters seem to be comparable for verum and control treatment groups at time of screening. However, the p-value of 0.042 for eosinophils has to be interpreted descriptive because of multiple testing.Different changes in verum and control treatment groups during time of study are not found for any of the listed parameters.

Table 96 Breast cancer –Basic blood count parameters at screening

BREAST	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
Hb	Helixor	35	0	11.8	1.4	6.9	11.0	12.0	12.7	14.9	0.836
[g/dl]	Lentinan	32	0	11.9	1.3	9.7	10.8	12.2	13.0	14.0	
	Total	67	0	11.9	1.3	6.9	10.9	12.0	12.9	14.9	
Platelets	Helixor	34	1	233.7	75.0	125.0	175.0	227.0	274.0	460.0	0.346
[$x10^9$/l]	Lentinan	32	0	255.1	88.5	82.0	196.5	229.0	314.5	469.0	
	Total	66	1	244.1	81.9	82.0	186.0	228.0	281.0	469.0	
Total	Helixor	35	0	5.9	1.5	2.6	5.0	5.7	6.5	10.2	0.117
leucocytes	Lentinan	32	0	6.8	2.0	4.2	5.2	6.2	8.1	12.3	
[($x10^6$/l]	Total	67	0	6.3	1.8	2.6	5.1	5.8	7.0	12.3	
Neutrophils	Helixor	35	0	69.4	8.1	53.0	64.9	70.0	74.0	86.4	0.307
[%]	Lentinan	32	0	71.0	7.4	52.0	64.4	71.4	77.6	82.1	
	Total	67	0	70.1	7.8	52.0	64.9	70.3	75.0	86.4	
Segmented	Helixor	17	18	61.6	23.5	0.0	63.0	70.4	74.5	81.0	0.982
Forms	Lentinan	12	20	67.7	10.6	46.0	61.2	67.6	77.2	82.1	
[%]	Total	29	38	64.1	19.2	0.0	62.0	70.2	75.0	82.1	
Band forms	Helixor	15	20	2.5	5.4	0.0	0.0	0.0	5.1	20.0	0.088
[%]	Lentinan	11	21	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
	Total	26	41	1.4	4.2	0.0	0.0	0.0	0.0	20.0	
Eosinophils	Helixor	29	6	1.2	1.7	0.0	0.0	1.0	1.0	7.0	0.042
[%]	Lentinan	26	6	0.5	1.1	0.0	0.0	0.0	1.0	4.0	
	Total	55	12	0.9	1.5	0.0	0.0	0.0	1.0	7.0	
Basophils	Helixor	28	7	0.2	0.5	0.0	0.0	0.0	0.0	2.0	0.193
[%]	Lentinan	26	6	0.1	0.4	0.0	0.0	0.0	0.0	2.0	
	Total	54	13	0.2	0.5	0.0	0.0	0.0	0.0	2.0	
Monocytes	Helixor	33	2	2.2	3.5	0.0	0.0	1.0	2.0	15.8	0.390
[%]	Lentinan	29	3	1.3	2.2	0.0	0.0	0.0	2.0	8.0	
	Total	62	5	1.8	3.0	0.0	0.0	0.4	2.0	15.8	
Lymphocytes	Helixor	35	0	26.8	9.4	0.2	21.6	27.4	31.4	44.2	0.421
[%]	Lentinan	32	0	25.8	9.2	0.3	20.3	24.3	31.5	48.0	
	Total	67	0	26.3	9.3	0.2	21.1	26.7	31.4	48.0	

Table 97 Breast cancer – Basic blood count parameters at final investigation

BREAST	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX
Hb	Helixor	35	0	11.2	1.3	7.4	10.6	11.5	12.1	13.2
[g/dl]	Lentinan	32	0	11.4	1.4	8.0	10.5	11.5	12.3	14.3
	Total	67	0	11.3	1.3	7.4	10.6	11.5	12.1	14.3
Platelets	Helixor	35	0	269.1	100.9	106.0	198.0	240.0	340.0	519.0
[$x10^9$/l]	Lentinan	32	0	256.2	105.1	110.0	164.0	244.0	320.0	442.0
	Total	67	0	263.0	102.3	106.0	172.0	242.0	338.0	519.0
Total	Helixor	35	0	4.9	1.9	2.0	3.3	4.7	6.0	12.0
leucocytes	Lentinan	32	0	5.3	1.7	3.1	4.0	5.0	6.2	10.8
[($x10^6$/l]	Total	67	0	5.1	1.8	2.0	3.8	4.9	6.0	12.0
Neutrophils	Helixor	35	0	65.6	9.2	37.5	60.2	65.9	71.3	83.4
[%]	Lentinan	32	0	68.1	10.0	51.1	60.4	67.7	76.8	85.9
	Total	67	0	66.8	9.6	37.5	60.2	66.7	74.0	85.9
Segmented	Helixor	17	18	54.2	20.9	0.0	50.0	63.3	66.0	71.3
forms	Lentinan	12	20	68.2	11.0	49.0	60.9	67.6	74.8	85.9
[%]	Total	29	38	60.0	18.6	0.0	57.1	64.5	69.0	85.9
Band forms	Helixor	15	20	3.2	7.9	0.0	0.0	0.0	4.3	30.0
[%]	Lentinan	11	21	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Total	26	41	1.9	6.1	0.0	0.0	0.0	0.0	30.0
Eosinophils	Helixor	29	6	1.9	2.9	0.0	0.0	1.0	2.0	14.0
[%]	Lentinan	26	6	0.9	1.7	0.0	0.0	0.2	1.0	8.0
	Total	55	12	1.4	2.4	0.0	0.0	1.0	2.0	14.0
Basophils	Helixor	28	7	0.3	0.6	0.0	0.0	0.0	0.2	2.0
[%]	Lentinan	26	6	0.2	0.5	0.0	0.0	0.0	0.0	2.0
	Total	54	13	0.2	0.5	0.0	0.0	0.0	0.2	2.0
Monocytes	Helixor	33	2	3.8	4.3	0.0	0.0	2.0	5.0	14.1
[%]	Lentinan	29	3	2.6	3.8	0.0	0.0	2.0	3.0	16.2
	Total	62	5	3.2	4.1	0.0	0.0	2.0	4.7	16.2
Lymphocytes	Helixor	35	0	29.0	10.5	9.4	21.0	30.2	35.3	57.8
[%]	Lentinan	32	0	27.7	11.5	0.2	19.5	27.6	37.9	47.6
	Total	67	0	28.3	10.9	0.2	20.3	30.0	36.0	57.8

Table 98 Breast cancer – Difference of basic blood count parameters between final investigation and screening

BREAST	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value	95%-CI
Hb	Helixor	35	0	-0.6	1.3	-3.0	-1.3	-0.5	0.5	1.6	0.817	-0.8;0.7
[g/dl]	Lentinan	32	0	-0.5	1.5	-3.6	-1.6	-0.6	1.0	2.1		
	Total	67	0	-0.6	1.4	-3.6	-1.6	-0.6	0.6	2.1		
Platelets	Helixor	34	1	32.7	104.2	-171.0	-30.0	18.0	76.0	332.0	0.124	-10;78
[$x10^9$/l]	Lentinan	32	0	1.2	101.4	-196.0	-63.5	-22.0	41.5	225.0		
	Total	66	1	17.4	103.3	-196.0	-48.0	5.5	59.0	332.0		
Total	Helixor	35	0	-1.0	2.1	-4.3	-2.6	-1.2	0.6	5.6	0.722	-0.8;1.4
leucocytes	Lentinan	32	0	-1.4	2.5	-6.9	-2.9	-1.5	0.3	3.2		
[($x10^6$/l]	Total	67	0	-1.2	2.3	-6.9	-2.6	-1.4	0.3	5.6		
Neutrophils	Helixor	35	0	-3.8	12.1	-34.1	-12.0	-1.6	5.6	15.5	0.866	-5.7;5.7
[%]	Lentinan	32	0	-2.8	11.1	-26.7	-9.0	-1.2	1.5	24.5		
	Total	67	0	-3.3	11.5	-34.1	-9.9	-1.3	3.5	24.5		
Segmented	Helixor	16	19	-6.3	12.0	-33.0	-11.1	-5.4	1.4	15.5	0.398	-14.3;3.1
Forms	Lentinan	12	20	0.5	11.8	-15.5	-6.4	-0.6	2.0	24.5		
[%]	Total	28	39	-3.4	12.2	-33.0	-9.3	-2.5	1.5	24.5		
Band forms	Helixor	15	20	0.7	2.7	-1.5	0.0	0.0	0.0	10.0	1.000	0;0
[%]	Lentinan	11	21	0.0	0.0	0.0	0.0	0.0	0.0	0.0		
	Total	26	41	0.4	2.0	-1.5	0.0	0.0	0.0	10.0		
Eosinophils	Helixor	29	6	0.7	2.7	-4.1	0.0	0.0	1.0	12.0	0.706	-0.2;1
[%]	Lentinan	26	6	0.4	1.3	-2.0	0.0	0.0	1.0	5.0		
	Total	55	12	0.6	2.2	-4.1	0.0	0.0	1.0	12.0		
Basophils	Helixor	28	7	0.1	0.6	-2.0	0.0	0.0	0.0	2.0	0.981	0;0
[%]	Lentinan	26	6	0.1	0.7	-2.0	0.0	0.0	0.0	2.0		
	Total	54	13	0.1	0.6	-2.0	0.0	0.0	0.0	2.0		
Mono-	Helixor	33	2	1.6	2.9	-4.7	0.0	1.0	2.7	10.0	0.404	-0.9;1.3
Cytes	Lentinan	29	3	1.2	2.6	-2.0	-0.3	0.0	2.0	9.2		
[%]	Total	62	5	1.4	2.8	-4.7	0.0	1.0	2.7	10.0		
Lympho-	Helixor	35	0	2.2	13.2	-19.8	-8.9	0.0	12.0	43.8	0.769	-7.1;4.8
Cytes	Lentinan	32	0	1.9	11.7	-26.5	-2.7	0.8	9.4	28.9		
[%]	Total	67	0	2.1	12.4	-26.5	-5.6	0.5	9.8	43.8		

Difference: (value of final investigation minus value of screening).

3.4.1.4 Ovarian cancer

Basic blood count parameters are listed for time at screening, final investigation and difference between final examination and screening to evaluate changes during medication trial in **Table 99, Table 100** and **Table 101,** respectively. All parameters are comparable for verum and control treatment groups at time of screening, different changes over period of trial are not observed.

Table 99 Ovarian cancer –Basic blood count parameters at screening

OVARIAN	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
Hb	Helixor	33	0	11.0	1.6	7.9	9.8	10.7	12.3	13.4	0.601
[g/dl]	Lentinan	33	0	11.2	1.5	8.2	10.1	11.2	12.1	14.3	
	Total	66	0	11.1	1.5	7.9	10.1	11.1	12.2	14.3	
Platelets	Helixor	33	0	263.4	99.5	100.0	200.0	259.0	324.0	559.0	0.242
[$x10^9$/l]	Lentinan	33	0	288.5	95.3	153.0	198.0	287.0	363.0	482.0	
	Total	66	0	276.0	97.4	100.0	198.0	266.5	345.0	559.0	
Total	Helixor	33	0	6.2	2.3	3.1	4.6	5.6	7.4	12.5	0.655
leucocytes	Lentinan	33	0	6.3	2.0	3.3	5.0	6.0	6.9	12.0	
[($x10^6$/l]	Total	66	0	6.3	2.1	3.1	4.7	6.0	7.3	12.5	
Neutrophils	Helixor	33	0	66.6	15.0	0.7	62.0	69.6	75.0	92.7	0.641
[%]	Lentinan	33	0	69.5	12.0	43.6	65.0	69.0	80.0	90.0	
	Total	66	0	68.1	13.6	0.7	62.0	69.3	75.9	92.7	
Segmented	Helixor	13	20	46.3	32.2	0.0	7.0	58.0	72.6	80.0	0.394
Forms	Lentinan	19	14	62.3	17.7	0.0	58.0	65.0	71.0	86.3	
[%]	Total	32	34	55.8	25.4	0.0	53.5	64.0	72.1	86.3	
Band forms	Helixor	13	20	1.2	2.0	0.0	0.0	0.0	2.0	7.0	0.433
[%]	Lentinan	18	15	1.4	1.5	0.0	0.0	1.0	2.0	5.0	
	Total	31	35	1.3	1.7	0.0	0.0	1.0	2.0	7.0	
Eosinophils	Helixor	28	5	1.2	1.4	0.0	0.0	1.0	2.0	6.0	0.360
[%]	Lentinan	32	1	0.9	1.0	0.0	0.0	0.9	1.5	3.0	
	Total	60	6	1.0	1.2	0.0	0.0	1.0	2.0	6.0	
Basophils	Helixor	27	6	0.3	0.7	0.0	0.0	0.0	0.0	2.0	0.482
[%]	Lentinan	31	2	0.2	0.5	0.0	0.0	0.0	0.0	2.0	
	Total	58	8	0.2	0.6	0.0	0.0	0.0	0.0	2.0	
Monocytes	Helixor	28	5	2.2	2.0	0.0	1.0	2.0	3.0	9.0	0.796
[%]	Lentinan	33	0	2.8	4.0	0.0	1.0	2.0	3.0	17.7	
	Total	61	5	2.5	3.2	0.0	1.0	2.0	3.0	17.7	
Lymphocytes	Helixor	33	0	28.6	9.3	7.3	23.2	27.9	34.0	49.0	0.161
[%]	Lentinan	33	0	24.9	11.2	4.2	15.0	26.0	32.0	48.0	
	Total	66	0	26.7	10.4	4.2	19.6	27.4	33.0	49.0	

Table 100 Ovarian cancer – Basic blood count parameters at final investigation

OVARIAN	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX
Hb	Helixor	33	0	11.0	1.3	7.9	10.0	11.0	12.0	13.3
[g/dl]	Lentinan	32	1	10.9	1.8	5.9	9.9	11.2	12.0	13.2
	Total	65	1	10.9	1.5	5.9	10.0	11.0	12.0	13.3
Platelets	Helixor	33	0	243.9	90.5	67.0	193.0	234.0	332.0	420.0
[$x10^9$/l]	Lentinan	32	1	246.7	94.0	73.0	185.0	231.5	301.0	450.0
	Total	65	1	245.3	91.5	67.0	188.0	234.0	308.0	450.0
Total	Helixor	33	0	4.7	1.3	3.1	3.8	4.5	5.0	8.8
leucocytes	Lentinan	32	1	4.6	1.7	1.6	3.6	5.0	5.6	9.3
[($x10^6$/l]	Total	65	1	4.7	1.5	1.6	3.8	4.6	5.4	9.3
Neutrophils	Helixor	33	0	59.5	15.8	0.8	53.0	60.0	70.0	87.1
[%]	Lentinan	32	1	63.5	11.0	46.0	56.0	62.5	70.0	90.0
	Total	65	1	61.5	13.7	0.8	55.6	61.0	70.0	90.0
Segmented	Helixor	13	20	47.8	27.5	0.0	22.0	58.0	72.0	80.0
Forms	Lentinan	19	14	56.4	16.7	0.0	54.0	60.0	62.0	79.0
[%]	Total	32	34	52.9	21.8	0.0	50.0	59.5	64.0	80.0
Band forms	Helixor	13	20	3.2	6.2	0.0	0.0	1.0	2.0	19.0
[%]	Lentinan	17	16	1.5	1.3	0.0	0.0	2.0	3.0	3.0
	Total	30	36	2.3	4.2	0.0	0.0	1.5	2.0	19.0
Eosinophils	Helixor	30	3	1.4	1.7	0.0	0.0	1.0	2.0	7.0
[%]	Lentinan	30	3	0.8	1.1	0.0	0.0	0.0	1.0	4.0
	Total	60	6	1.1	1.5	0.0	0.0	0.9	2.0	7.0
Basophils	Helixor	29	4	0.2	0.6	0.0	0.0	0.0	0.0	2.0
[%]	Lentinan	29	4	0.2	0.5	0.0	0.0	0.0	0.0	2.0
	Total	58	8	0.2	0.5	0.0	0.0	0.0	0.0	2.0
Monocytes	Helixor	29	4	1.7	1.9	0.0	0.0	1.0	2.0	7.0
[%]	Lentinan	32	1	2.9	3.6	0.0	1.0	2.0	3.0	13.0
	Total	61	5	2.3	3.0	0.0	1.0	1.0	2.0	13.0
Lymphocytes	Helixor	33	0	33.6	9.6	12.9	26.0	33.0	41.0	54.5
[%]	Lentinan	32	1	31.7	10.5	2.6	28.0	32.0	40.0	51.0
	Total	65	1	32.7	10.0	2.6	27.0	32.0	40.0	54.5

Table 101 Ovarian cancer – Difference of basic blood count parameters between final investigation and screening

OVARIAN	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value	95%-CI
Hb	Helixor	33	0	-0.0	1.5	-4.1	-0.6	0.1	0.7	2.4	0.167	-0.2;0.9
[g/dl]	Lentinan	32	1	-0.3	1.2	-3.2	-0.9	-0.1	0.5	1.5		
	Total	65	1	-0.2	1.4	-4.1	-0.7	0.1	0.7	2.4		
Platelets	Helixor	33	0	-19.5	106.8	-319.0	-76.0	-23.0	23.0	258.0	0.540	-30;62
[$x10^9$/l]	Lentinan	32	1	-38.2	90.6	-305.0	-84.5	-36.5	26.0	131.0		
	Total	65	1	-28.7	98.8	-319.0	-76.0	-26.0	23.0	258.0		
Total	Helixor	33	0	-1.5	2.0	-8.0	-2.6	-1.0	-0.1	0.8	0.922	-1;0.9
leucocytes	Lentinan	32	1	-1.5	2.7	-9.2	-2.7	-1.0	-0.3	3.5		
[($x10^6$/l]	Total	65	1	-1.5	2.4	-9.2	-2.6	-1.0	-0.2	3.5		
Neutrophils	Helixor	33	0	-7.1	12.4	-42.7	-13.9	-7.0	1.0	19.8	0.779	-8;5
[%]	Lentinan	32	1	-5.5	12.4	-30.0	-15.0	-4.5	4.0	16.0		
	Total	65	1	-6.3	12.3	-42.7	-15.0	-6.0	2.0	19.8		
Segmented	Helixor	12	21	2.9	13.5	-17.6	-5.6	0.0	16.0	22.0	0.185	-2;17
forms	Lentinan	18	15	-5.0	10.7	-27.0	-15.0	-2.0	2.0	12.0		
[%]	Total	30	36	-1.8	12.4	-27.0	-13.0	-1.5	2.0	22.0		
Band forms	Helixor	12	21	2.2	5.8	-2.0	0.0	0.0	0.5	19.0	0.944	-1;1.4
[%]	Lentinan	17	16	0.1	1.7	-4.0	0.0	0.0	1.0	3.0		
	Total	29	37	1.0	4.0	-4.0	0.0	0.0	1.0	19.0		
Eosinophils	Helixor	28	5	0.2	2.2	-5.0	-0.5	0.0	1.5	7.0	0.653	0;1
[%]	Lentinan	30	3	-0.0	1.1	-3.0	-0.7	0.0	0.0	3.0		
	Total	58	8	0.1	1.7	-5.0	-0.7	0.0	1.0	7.0		
Basophils	Helixor	27	6	-0.1	1.0	-2.0	0.0	0.0	0.0	2.0	0.937	0;0
[%]	Lentinan	29	4	0.0	0.7	-2.0	0.0	0.0	0.0	2.0		
	Total	56	10	-0.0	0.8	-2.0	0.0	0.0	0.0	2.0		
Mono-	Helixor	27	6	-0.2	2.7	-5.0	-2.0	0.0	0.0	5.9	0.636	-1;1
cytes	Lentinan	32	1	0.0	3.5	-8.8	-1.0	0.0	1.0	11.0		
[%]	Total	59	7	-0.1	3.1	-8.8	-1.0	0.0	1.0	11.0		
Lympho-	Helixor	33	0	5.0	11.2	-20.0	-4.9	6.0	13.0	24.1	0.855	-7.5;5.6
cytes	Lentinan	32	1	6.5	13.2	-16.0	-2.5	6.0	14.3	32.8		
[%]	Total	65	1	5.7	12.2	-20.0	-3.2	6.0	13.7	32.8		

Difference: (value of final investigation minus value of screening).

3.4.2 Immunological Parameters

3.4.2.1 Total study population

At time of screening all parameters are comparable for verum and control treatment groups except the NK cells activity. Changes of immunological parameters during the period of trial are observed between treatment groups only for the percentage of CD3 cells (descriptive p-value = 0.034). In contrast, the total amount of CD3 cells in counts $x10^3/mm^3$ are comparable between the two treatment groups.

Table 102 Total study population – Immunological parameters at screening

ALL	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
CD3 cells	Helixor	62	52	1183.2	475.2	463.0	780.0	1125.5	1484.0	2616.0	0.195
[x10³/mm³]	Lentinan	59	51	1059.7	473.3	118.0	750.0	973.0	1470.0	2642.0	
	Total	121	103	1123.0	476.3	118.0	779.0	1060.0	1476.0	2642.0	
CD3 cells	Helixor	113	1	67.9	12.2	1.8	62.0	69.0	75.1	90.0	0.337
[%]	Lentinan	106	4	68.5	13.8	6.0	64.0	71.0	77.0	89.0	
	Total	219	5	68.2	13.0	1.8	63.0	70.0	76.6	90.0	
CD4 cells	Helixor	62	52	640.9	269.3	234.0	408.0	630.5	818.0	1497.0	0.435
[x10³/mm³]	Lentinan	59	51	610.0	285.1	144.0	390.0	555.0	736.0	1730.0	
	Total	121	103	625.8	276.4	144.0	408.0	612.0	757.0	1730.0	
CD4 cells	Helixor	113	1	37.9	9.4	11.2	32.7	38.0	44.0	63.5	0.523
[%]	Lentinan	106	4	38.8	9.0	12.0	33.3	39.3	44.0	59.0	
	Total	219	5	38.4	9.2	11.2	33.0	39.0	44.0	63.5	
CD8 cells	Helixor	62	52	471.1	263.0	25.0	299.0	409.5	567.0	1329.0	0.792
[x10³/mm³]	Lentinan	59	51	468.2	231.9	136.0	315.0	405.0	623.0	1225.0	
	Total	121	103	469.7	247.3	25.0	312.0	405.0	587.0	1329.0	
CD8 cells	Helixor	113	1	27.6	9.7	0.0	22.8	25.5	32.0	62.7	0.081
[%]	Lentinan	106	4	29.7	9.2	15.5	23.2	27.9	34.0	62.0	
	Total	219	5	28.6	9.5	0.0	22.9	27.0	34.0	62.7	
CD4/CD8	Helixor	113	1	1.5	0.7	0.0	1.1	1.4	1.8	5.0	0.572
	Lentinan	105	5	1.5	0.6	0.2	1.0	1.4	1.7	3.4	
	Total	218	6	1.5	0.7	0.0	1.0	1.4	1.8	5.0	
NK cells	Helixor	111	3	18.7	10.0	1.2	11.0	17.8	24.0	73.0	0.048
activity	Lentinan	106	4	15.9	7.7	0.2	10.1	15.4	21.0	42.5	
	Total	217	7	17.3	9.0	0.2	11.0	16.3	22.0	73.0	

Table 103 Total study population – Immunological parameters at final investigation

ALL	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX
CD3 cells	Helixor	62	52	1105.0	383.9	485.0	798.0	1028.5	1381.0	2007.0
[x10³/mm³]	Lentinan	58	52	995.2	402.3	259.0	734.0	977.5	1263.0	2225.0
	Total	120	104	1052.0	395.1	259.0	755.5	1021.5	1315.0	2225.0
CD3 cells	Helixor	113	1	72.8	11.7	0.7	67.2	73.0	80.0	93.8
[%]	Lentinan	104	6	70.7	15.2	4.0	67.2	74.0	79.3	91.2
	Total	217	7	71.8	13.5	0.7	67.2	73.2	79.5	93.8
CD4 cells	Helixor	62	52	584.0	208.7	216.0	413.0	568.5	671.0	1350.0
[x10³/mm³]	Lentinan	58	52	553.6	252.4	52.0	353.0	526.5	739.0	1059.0
	Total	120	104	569.4	230.4	52.0	388.5	553.0	699.5	1350.0
CD4 cells	Helixor	113	1	40.8	9.2	20.6	35.0	40.0	46.0	67.0
[%]	Lentinan	104	6	40.9	10.3	8.0	36.0	40.7	47.5	75.0
	Total	217	7	40.8	9.7	8.0	36.0	40.0	46.0	75.0
CD8 cells	Helixor	62	52	444.0	241.0	36.0	265.0	401.5	561.0	1175.0
[x10³/mm³]	Lentinan	58	52	418.4	192.2	50.0	299.0	404.0	475.0	1075.0
	Total	120	104	431.6	218.3	36.0	272.5	403.0	498.0	1175.0
CD8 cells	Helixor	113	1	29.5	9.6	12.9	23.0	27.5	35.0	64.0
[%]	Lentinan	104	6	30.6	9.3	15.1	24.0	29.0	35.8	72.8
	Total	217	7	30.1	9.4	12.9	24.0	28.0	35.1	72.8
CD4/CD8	Helixor	113	1	1.6	0.7	0.3	1.2	1.4	1.8	4.8
	Lentinan	104	6	1.7	2.1	0.4	1.0	1.4	1.8	22.1
	Total	217	7	1.6	1.5	0.3	1.1	1.4	1.8	22.1
NK cells	Helixor	113	1	18.0	9.2	3.4	11.0	15.0	24.0	49.0
activity	Lentinan	104	6	16.6	8.5	3.0	10.0	14.8	21.8	46.0
	Total	217	7	17.3	8.9	3.0	10.4	15.0	23.0	49.0

Table 104 Total study population – Difference of immunological parameters between final investigation and screening

ALL	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value	95%-CI
CD3 cells	Helixor	62	52	-78.1	405.7	-887.0	-323.0	-60.5	141.0	1048.0	0.457	-173;84
[x10³/mm³]	Lentinan	58	52	-66.0	385.0	-1249.0	-296.0	17.0	159.0	824.0		
	Total	120	104	-72.3	394.2	-1249.0	-312.5	-24.0	153.5	1048.0		
CD3 cells	Helixor	113	1	4.9	12.6	-70.3	0.0	4.4	8.6	61.4	0.034	0;4
[%]	Lentinan	104	6	2.4	7.1	-29.0	-2.0	2.6	6.7	22.0		
	Total	217	7	3.7	10.4	-70.3	-1.3	3.9	8.0	61.4		
CD4 cells	Helixor	62	52	-56.8	246.2	-548.0	-210.0	-56.0	54.0	1034.0	0.514	-102;54
[x10³/mm³]	Lentinan	58	52	-59.7	257.8	-865.0	-215.0	-2.0	91.0	660.0		
	Total	120	104	-58.2	250.8	-865.0	-213.5	-37.5	77.0	1034.0		
CD4 cells	Helixor	113	1	2.9	9.4	-24.0	-1.3	2.4	8.0	34.0	0.355	-1;3
[%]	Lentinan	104	6	2.0	8.6	-24.0	-2.0	1.5	7.3	36.2		
	Total	217	7	2.4	9.0	-24.0	-2.0	2.0	7.4	36.2		
CD8 cells	Helixor	62	52	-27.1	228.4	-512.0	-161.0	-34.0	60.0	743.0	0.731	-70;57
[x10³/mm³]	Lentinan	58	52	-47.8	215.9	-754.0	-143.0	-0.5	59.0	633.0		
	Total	120	104	-37.1	221.8	-754.0	-160.0	-10.0	59.0	743.0		
CD8 cells	Helixor	113	1	1.9	8.4	-27.1	-2.0	1.0	5.0	32.0	0.457	-1;1.94
[%]	Lentinan	104	6	1.1	7.5	-24.0	-1.1	0.0	4.0	47.5		
	Total	217	7	1.6	8.0	-27.1	-1.5	0.2	4.1	47.5		
CD4/CD8	Helixor	113	1	0.0	0.6	-2.0	-0.2	0.0	0.3	1.7	0.390	-0.06;0.15
	Lentinan	103	7	-0.0	0.5	-1.5	-0.2	0.0	0.2	1.5		
	Total	216	8	0.0	0.5	-2.0	-0.2	0.0	0.3	1.7		
NK cells	Helixor	111	3	-0.5	8.6	-50.0	-4.0	0.0	3.0	28.6	0.341	-2.1;0.9
activity	Lentinan	104	6	0.6	6.0	-18.0	-2.0	0.0	3.1	21.0		
	Total	215	9	0.0	7.5	-50.0	-3.0	0.0	3.0	28.6		

Difference: (value of final investigation minus value of screening).

3.4.2.2 Non small cell lung cancer

Table 105 Non small cell lung cancer – Immunological parameters at screening

NSCLC	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
CD3 cells	Helixor	20	26	1022.6	564.1	465.0	624.0	802.5	1289.5	2616.0	0.592
[x10³/mm³]	Lentinan	18	27	1002.4	474.7	118.0	721.0	1002.5	1542.0	1771.0	
	Total	38	53	1013.0	516.7	118.0	650.0	909.5	1388.0	2616.0	
CD3 cells	Helixor	46	0	65.6	13.8	1.8	63.2	69.0	74.0	83.3	0.552
[%]	Lentinan	44	1	65.7	17.0	6.0	61.4	69.5	76.2	87.0	
	Total	90	1	65.7	15.4	1.8	62.3	69.0	75.0	87.0	
CD4 cells	Helixor	20	26	538.9	287.4	272.0	335.0	414.0	768.0	1399.0	0.562
[x10³/mm³]	Lentinan	18	27	590.2	272.3	156.0	312.0	642.0	745.0	1064.0	
	Total	38	53	563.2	277.8	156.0	334.0	454.0	750.0	1399.0	
CD4 cells	Helixor	46	0	36.0	10.2	11.2	29.0	36.6	43.0	63.5	0.726
[%]	Lentinan	44	1	36.6	9.8	12.0	30.5	36.7	42.8	56.0	
	Total	90	1	36.3	10.0	11.2	29.8	36.7	43.0	63.5	
CD8 cells	Helixor	20	26	432.4	326.9	25.0	252.5	322.5	462.5	1329.0	0.049
[x10³/mm³]	Lentinan	18	27	527.8	240.9	224.0	391.0	438.0	625.0	1225.0	
	Total	38	53	477.6	289.6	25.0	320.0	403.5	575.0	1329.0	
CD8 cells	Helixor	46	0	27.5	10.0	0.0	21.4	25.7	34.0	51.0	0.203
[%]	Lentinan	44	1	31.5	10.9	15.5	23.6	28.5	36.9	62.0	.
	Total	90	1	29.5	10.6	0.0	22.8	27.9	35.0	62.0	
CD4/CD8	Helixor	46	0	1.5	0.8	0.0	1.0	1.3	1.8	5.0	0.624
	Lentinan	44	1	1.3	0.7	0.2	0.8	1.3	1.7	3.4	
	Total	90	1	1.4	0.7	0.0	0.9	1.3	1.7	5.0	
NK cells	Helixor	44	2	20.1	8.1	5.0	14.0	20.0	24.0	44.9	0.106
activity	Lentinan	44	1	17.3	8.2	3.0	11.2	16.5	22.3	42.5	
	Total	88	3	18.7	8.2	3.0	12.9	18.6	24.0	44.9	

Table 106 Non small cell lung cancer – Immunological parameters at final investigation

NSCLC	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX
CD3 cells	Helixor	20	26	1054.2	424.4	485.0	679.5	946.0	1450.0	1861.0
[x10³/mm³]	Lentinan	18	27	871.6	447.9	259.0	471.0	805.5	1280.0	1609.0
	Total	38	53	967.7	439.5	259.0	648.0	867.0	1324.0	1861.0
CD3 cells	Helixor	46	0	70.6	8.2	48.8	65.0	71.1	75.2	86.2
[%]	Lentinan	44	1	67.4	18.3	4.0	66.7	72.9	77.8	87.1
	Total	90	1	69.0	14.1	4.0	66.0	72.0	76.8	87.1
CD4 cells	Helixor	20	26	537.4	187.9	216.0	389.5	531.0	641.5	988.0
[x10³/mm³]	Lentinan	18	27	533.4	301.5	100.0	291.0	496.0	739.0	1059.0
	Total	38	53	535.5	244.8	100.0	350.0	516.0	659.0	1059.0
CD4 cells	Helixor	46	0	39.3	9.6	20.6	34.0	38.5	45.0	67.0
[%]	Lentinan	44	1	40.0	11.7	12.0	30.3	40.3	48.9	75.0
	Total	90	1	39.6	10.6	12.0	34.0	39.4	46.0	75.0
CD8 cells	Helixor	20	26	415.6	225.7	50.0	251.0	333.5	642.0	942.0
[x10³/mm³]	Lentinan	18	27	395.8	160.5	151.0	295.0	426.0	456.0	811.0
	Total	38	53	406.2	195.2	50.0	252.0	390.5	471.0	942.0
CD8 cells	Helixor	46	0	29.0	8.3	12.9	22.8	27.9	35.0	50.0
[%]	Lentinan	44	1	30.9	11.6	15.1	22.4	27.7	36.4	72.8
	Total	90	1	29.9	10.0	12.9	22.8	27.9	35.4	72.8
CD4/CD8	Helixor	46	0	1.6	0.8	0.5	1.1	1.3	1.7	4.8
	Lentinan	44	1	1.5	0.7	0.4	1.0	1.4	1.9	3.7
	Total	90	1	1.5	0.8	0.4	1.0	1.3	1.8	4.8
NK cells	Helixor	46	0	18.9	8.4	5.1	11.2	18.5	25.0	42.5
activity	Lentinan	44	1	18.3	9.6	6.6	10.4	18.6	23.2	46.0
	Total	90	1	18.6	9.0	5.1	11.0	18.6	24.1	46.0

Table 107 Non small cell lung cancer – Difference of immunological parameters between final investigation and screening

NSCLC	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value	95%-CI
CD3 cells	Helixor	20	26	31.6	487.4	-887.0	-212.5	29.5	190.0	1048.0	0.478	-139;413
[x10³/mm³]	Lentinan	18	27	-130.8	415.6	-1107.0	-284.0	33.5	121.0	529.0		
	Total	38	53	-45.3	456.2	-1107.0	-284.0	30.5	149.0	1048.0		
CD3 cells	Helixor	46	0	5.0	11.4	-15.0	-1.0	4.0	8.0	61.4	0.258	-1;4.46
[%]	Lentinan	44	1	1.7	7.7	-29.0	-1.6	1.6	6.0	15.0		
	Total	90	1	3.4	9.8	-29.0	-1.2	3.1	7.0	61.4		
CD4 cells	Helixor	20	26	-1.5	246.2	-411.0	-184.5	-4.0	167.5	515.0	0.553	-129;215
[x10³/mm³]	Lentinan	18	27	-56.8	281.8	-618.0	-212.0	-0.5	82.0	660.0		
	Total	38	53	-27.7	261.5	-618.0	-190.0	-0.5	126.0	660.0		
CD4 cells	Helixor	46	0	3.3	10.2	-24.0	-1.0	3.3	8.9	29.7	0.784	-3.16;4
[%]	Lentinan	44	1	3.5	9.9	-21.0	-2.5	2.7	8.2	36.2		
	Total	90	1	3.4	10.0	-24.0	-1.3	3.0	8.9	36.2		
CD8 cells	Helixor	20	26	-16.9	268.6	-512.0	-113.0	-3.0	97.5	535.0	0.233	-31;210
[x10³/mm³]	Lentinan	18	27	-131.9	229.3	-754.0	-169.0	-30.5	12.0	51.0		
	Total	38	53	-71.4	254.2	-754.0	-146.0	-6.0	32.0	535.0		
CD8 cells	Helixor	46	0	1.5	7.6	-22.2	-2.0	0.0	3.6	24.6	0.084	-0.12;3.74
[%]	Lentinan	44	1	-0.6	9.3	-24.0	-3.0	-0.5	0.7	47.5		
	Total	90	1	0.5	8.5	-24.0	-2.0	-0.1	2.1	47.5		
CD4/CD8	Helixor	46	0	0.1	0.6	-2.0	-0.1	0.1	0.3	1.7	1.000	-0.16;0.14
	Lentinan	44	1	0.1	0.5	-1.2	-0.0	0.1	0.3	1.5		
	Total	90	1	0.1	0.5	-2.0	-0.1	0.1	0.3	1.7		
NK cells	Helixor	44	2	-0.9	7.6	-20.9	-6.0	0.9	3.0	28.6	0.511	-4.1;1.3
activity	Lentinan	44	1	1.0	5.6	-9.0	-1.8	0.0	3.1	21.0		
	Total	88	3	0.1	6.7	-20.9	-4.0	0.2	3.0	28.6		

Difference: (value of final investigation minus value of screening).

3.4.2.3 Breast cancer

Table 108 Breast cancer – Immunological parameters at screening

BREAST	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
CD3 cells	Helixor	18	17	1284.2	352.7	685.0	1045.0	1297.0	1476.0	2130.0	0.443
[x10³/mm³]	Lentinan	19	13	1151.7	449.8	420.0	858.0	1060.0	1540.0	1813.0	
	Total	37	30	1216.2	405.5	420.0	979.0	1238.0	1498.0	2130.0	
CD3 cells	Helixor	34	1	68.9	10.3	34.0	62.0	70.0	77.0	84.6	0.512
[%]	Lentinan	30	2	70.0	11.0	28.0	65.0	71.9	77.0	82.4	
	Total	64	3	69.4	10.5	28.0	62.9	71.0	77.0	84.6	
CD4 cells	Helixor	18	17	709.5	223.4	234.0	627.0	720.5	829.0	1081.0	0.360
[x10³/mm³]	Lentinan	19	13	656.7	271.6	304.0	390.0	555.0	967.0	1151.0	
	Total	37	30	682.4	247.3	234.0	527.0	672.0	829.0	1151.0	
CD4 cells	Helixor	34	1	39.3	9.4	18.0	34.8	40.1	44.0	57.8	0.830
[%]	Lentinan	30	2	39.6	8.4	16.0	35.8	39.8	44.0	56.0	
	Total	64	3	39.5	8.9	16.0	35.3	39.8	44.0	57.8	
CD8 cells	Helixor	18	17	493.5	212.8	228.0	325.0	432.0	598.0	1091.0	0.729
[x10³/mm³]	Lentinan	19	13	466.2	238.1	136.0	270.0	420.0	675.0	965.0	
	Total	37	30	479.5	223.4	136.0	325.0	420.0	623.0	1091.0	
CD8 cells	Helixor	34	1	28.0	8.7	12.0	24.0	26.0	28.7	62.7	0.663
[%]	Lentinan	30	2	28.1	7.6	17.0	21.0	27.5	34.0	46.0	
	Total	64	3	28.0	8.2	12.0	23.2	26.5	30.5	62.7	
CD4/CD8	Helixor	34	1	1.5	0.6	0.3	1.3	1.5	1.8	3.3	0.721
	Lentinan	29	3	1.6	0.6	0.7	1.2	1.4	1.9	3.0	
	Total	63	4	1.5	0.6	0.3	1.2	1.5	1.8	3.3	
NK cells	Helixor	34	1	18.1	11.7	7.6	11.0	16.5	22.0	73.0	0.574
activity	Lentinan	30	2	15.5	6.1	4.0	11.0	15.5	21.0	28.0	
	Total	64	3	16.9	9.5	4.0	11.0	16.0	21.5	73.0	

Table 109 Breast cancer – Immunological parameters at final investigation

BREAST	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX
CD3 cells	Helixor	18	17	1172.6	415.4	492.0	944.0	1117.5	1381.0	2007.0
[x10³/mm³]	Lentinan	19	13	1049.2	362.9	432.0	750.0	1095.0	1280.0	1739.0
	Total	37	30	1109.2	388.9	432.0	794.0	1096.0	1335.0	2007.0
CD3 cells	Helixor	34	1	74.8	9.0	57.0	68.0	75.0	80.0	93.0
[%]	Lentinan	30	2	73.4	14.0	24.0	66.0	78.5	83.7	91.2
	Total	64	3	74.1	11.5	24.0	67.2	76.0	82.0	93.0
CD4 cells	Helixor	18	17	666.3	252.3	320.0	519.0	664.0	800.0	1350.0
[x10³/mm³]	Lentinan	19	13	568.2	215.9	144.0	450.0	510.0	755.0	924.0
	Total	37	30	615.9	236.3	144.0	476.0	625.0	755.0	1350.0
CD4 cells	Helixor	34	1	43.5	8.1	31.0	39.0	41.5	48.0	58.7
[%]	Lentinan	30	2	40.8	9.7	8.0	37.0	40.4	48.0	58.0
	Total	64	3	42.3	8.9	8.0	38.0	40.9	48.0	58.7
CD8 cells	Helixor	18	17	445.2	228.0	176.0	273.0	418.5	476.0	1051.0
[x10³/mm³]	Lentinan	19	13	461.4	191.5	202.0	272.0	459.0	631.0	836.0
	Total	37	30	453.5	207.3	176.0	273.0	429.0	529.0	1051.0
CD8 cells	Helixor	34	1	28.2	7.6	17.0	22.1	26.3	33.0	48.0
[%]	Lentinan	30	2	31.9	7.6	20.0	27.0	30.7	38.0	48.0
	Total	64	3	29.9	7.8	17.0	24.0	28.0	35.3	48.0
CD4/CD8	Helixor	34	1	1.6	0.6	0.7	1.3	1.5	1.9	3.3
	Lentinan	30	2	2.1	3.8	0.6	1.1	1.4	1.7	22.1
	Total	64	3	1.9	2.6	0.6	1.2	1.5	1.8	22.1
NK cells	Helixor	34	1	17.0	8.1	3.4	11.0	15.0	23.0	43.0
activity	Lentinan	30	2	14.7	7.1	3.0	10.0	14.0	20.0	31.0
	Total	64	3	15.9	7.7	3.0	10.3	14.3	21.2	43.0

Table 110 Breast cancer – Difference of immunological parameters between final investigation and screening

BREAST	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value	95%-CI
CD3 cells	Helixor	18	17	-111.6	285.8	-637.0	-266.0	-120.0	21.0	495.0	0.774	-225;238
[x10³/mm³]	Lentinan	19	13	-102.5	354.8	-531.0	-402.0	-195.0	217.0	824.0		
	Total	37	30	-106.9	318.6	-637.0	-328.0	-151.0	85.0	824.0		
CD3 cells	Helixor	34	1	5.9	9.9	-15.0	1.1	5.0	9.1	41.0	0.291	-1.68;5
[%]	Lentinan	30	2	3.4	5.6	-7.0	-2.0	4.5	6.8	14.8		
	Total	64	3	4.7	8.2	-15.0	0.5	5.0	8.4	41.0		
CD4 cells	Helixor	18	17	-43.2	310.0	-333.0	-253.0	-88.0	48.0	1034.0	0.916	-104;159
[x10³/mm³]	Lentinan	19	13	-88.6	211.3	-374.0	-231.0	-191.0	126.0	397.0		
	Total	37	30	-66.5	261.2	-374.0	-231.0	-135.0	48.0	1034.0		
CD4 cells	Helixor	34	1	4.2	10.2	-17.8	-1.6	3.9	8.0	34.0	0.136	-1;6.7
[%]	Lentinan	30	2	1.2	5.5	-8.0	-2.0	-0.3	4.8	16.0		
	Total	64	3	2.8	8.4	-17.8	-2.0	2.0	7.0	34.0		
CD8 cells	Helixor	18	17	-48.3	157.7	-287.0	-159.0	-83.0	-14.0	325.0	0.518	-145;72
[x10³/mm³]	Lentinan	19	13	-4.7	207.4	-249.0	-163.0	-8.0	74.0	633.0		
	Total	37	30	-25.9	183.7	-287.0	-159.0	-52.0	45.0	633.0		
CD8 cells	Helixor	34	1	0.2	7.9	-27.1	-3.0	0.1	3.5	13.2	0.026	-5.4;-0.56
[%]	Lentinan	30	2	3.8	4.9	-2.0	0.0	3.5	6.0	21.0		
	Total	64	3	1.9	6.8	-27.1	-1.0	1.2	5.0	21.0		
CD4/CD8	Helixor	34	1	0.1	0.6	-1.6	-0.1	0.1	0.4	1.6	0.020	0.05;0.47
	Lentinan	29	3	-0.2	0.4	-1.5	-0.4	-0.1	0.1	0.6		
	Total	63	4	-0.0	0.5	-1.6	-0.2	0.0	0.3	1.6		
NK cells	Helixor	34	1	-1.1	11.1	-50.0	-3.0	-1.0	2.4	22.0	0.931	-2;3
activity	Lentinan	30	2	-0.8	5.0	-10.0	-3.0	-1.0	2.9	9.0		
	Total	64	3	-1.0	8.7	-50.0	-3.0	-1.0	2.7	22.0		

Difference: (value of final investigation minus value of screening).

3.4.2.4 Ovarian cancer

Table 111 Ovarian cancer – Immunological parameters at screening

OVARIAN	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
CD3 cells	Helixor	24	9	1241.2	458.5	463.0	884.5	1166.5	1543.5	2355.0	0.082
[x10³/mm³]	Lentinan	22	11	1027.2	501.2	328.0	779.0	912.0	1185.0	2642.0	
	Total	46	20	1138.8	486.2	328.0	798.0	1017.5	1466.0	2642.0	
CD3 cells	Helixor	33	0	70.1	11.5	44.0	61.8	69.0	79.0	90.0	0.624
[%]	Lentinan	32	1	70.8	10.5	45.0	65.1	71.0	79.5	89.0	
	Total	65	1	70.4	11.0	44.0	63.6	69.0	79.0	90.0	
CD4 cells	Helixor	24	9	674.3	270.8	313.0	525.5	637.0	816.0	1497.0	0.120
[x10³/mm³]	Lentinan	22	11	585.9	313.5	144.0	420.0	519.0	693.0	1730.0	
	Total	46	20	632.0	292.1	144.0	456.0	570.5	736.0	1730.0	
CD4 cells	Helixor	33	0	39.2	8.0	23.0	34.0	39.0	45.0	56.8	0.404
[%]	Lentinan	32	1	41.2	7.9	24.0	35.9	42.0	44.0	59.0	
	Total	65	1	40.2	8.0	23.0	35.0	40.7	45.0	59.0	
CD8 cells	Helixor	24	9	486.6	244.3	128.0	311.0	432.0	569.5	1175.0	0.361
[x10³/mm³]	Lentinan	22	11	421.3	218.3	150.0	262.0	336.0	587.0	819.0	
	Total	46	20	455.4	232.0	128.0	299.0	366.5	578.0	1175.0	
CD8 cells	Helixor	33	0	27.3	10.3	14.0	19.0	24.0	32.0	56.0	0.155
[%]	Lentinan	32	1	28.9	8.0	16.0	25.0	27.0	32.0	49.0	
	Total	65	1	28.1	9.2	14.0	22.8	25.5	32.0	56.0	
CD4/CD8	Helixor	33	0	1.6	0.6	0.6	1.2	1.5	1.8	2.9	0.774
	Lentinan	32	1	1.5	0.6	0.7	1.2	1.4	1.8	3.1	
	Total	65	1	1.6	0.6	0.6	1.2	1.5	1.8	3.1	
NK cells	Helixor	33	0	17.4	10.3	1.2	10.1	13.0	26.0	45.0	0.274
activity	Lentinan	32	1	14.4	8.3	0.2	8.9	12.5	19.0	35.0	
	Total	65	1	15.9	9.4	0.2	9.8	13.0	22.0	45.0	

Table 112 Ovarian cancer – Immunological parameters at final investigation –

OVARIAN	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX
CD3 cells	Helixor	24	9	1096.8	329.6	594.0	834.5	1028.5	1327.0	1767.0
[x10³/mm³]	Lentinan	21	12	1052.5	390.2	463.0	828.0	962.0	1212.0	2225.0
	Total	45	21	1076.1	355.7	463.0	828.0	1012.0	1215.0	2225.0
CD3 cells	Helixor	33	0	73.9	17.0	0.7	69.0	78.0	84.5	93.8
[%]	Lentinan	30	3	72.7	10.0	44.0	69.0	74.2	78.0	90.0
	Total	63	3	73.3	14.0	0.7	69.0	75.0	81.0	93.8
CD4 cells	Helixor	24	9	561.2	177.6	293.0	457.5	548.0	643.5	1031.0
[x10³/mm³]	Lentinan	21	12	557.8	248.6	52.0	409.0	538.0	711.0	975.0
	Total	45	21	559.6	211.1	52.0	421.0	545.0	670.0	1031.0
CD4 cells	Helixor	33	0	40.1	9.4	21.0	33.0	40.0	43.0	59.5
[%]	Lentinan	30	3	42.1	8.8	20.0	37.0	42.0	45.1	63.0
	Total	63	3	41.1	9.1	20.0	36.0	40.3	45.1	63.0
CD8 cells	Helixor	24	9	466.9	269.0	36.0	272.5	393.0	620.0	1175.0
[x10³/mm³]	Lentinan	21	12	398.8	218.6	50.0	312.0	384.0	452.0	1075.0
	Total	45	21	435.1	246.4	36.0	299.0	384.0	481.0	1175.0
CD8 cells	Helixor	33	0	31.7	12.5	13.0	24.0	28.6	36.0	64.0
[%]	Lentinan	30	3	29.0	6.8	17.0	25.0	28.6	31.8	44.0
	Total	63	3	30.4	10.2	13.0	24.0	28.6	35.0	64.0
CD4/CD8	Helixor	33	0	1.5	0.6	0.3	1.1	1.5	1.8	2.9
	Lentinan	30	3	1.5	0.7	0.5	1.2	1.4	1.6	3.6
	Total	63	3	1.5	0.7	0.3	1.1	1.4	1.8	3.6
NK cells	Helixor	33	0	17.9	11.1	6.0	9.9	12.1	26.0	49.0
activity	Lentinan	30	3	15.9	7.9	3.0	8.9	17.2	21.0	30.0
	Total	63	3	17.0	9.7	3.0	9.4	14.0	25.0	49.0

Table 113 Ovarian cancer – Difference of immunological parameters between final investigation and screening

OVARIAN	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value	95%-CI
CD3 cells	Helixor	24	9	-144.4	404.9	-835.0	-422.5	-101.5	135.5	629.0	0.102	-440;25
[x10³/mm³]	Lentinan	21	12	22.6	386.1	-1249.0	-77.0	106.0	201.0	441.0		
	Total	45	21	-66.5	400.7	-1249.0	-310.0	8.0	177.0	629.0		
CD3 cells	Helixor	33	0	3.9	16.4	-70.3	-1.0	4.9	9.0	35.0	0.159	-1;7
[%]	Lentinan	30	3	2.3	7.8	-13.0	-4.0	1.0	6.9	22.0		
	Total	63	3	3.1	13.0	-70.3	-2.0	3.4	8.4	35.0		
CD4 cells	Helixor	24	9	-113.1	183.3	-548.0	-232.5	-69.5	-4.0	168.0	0.029	-207;-14
[x10³/mm³]	Lentinan	21	12	-36.0	283.4	-865.0	-69.0	40.0	98.0	376.0		
	Total	45	21	-77.1	235.8	-865.0	-151.0	-26.0	51.0	376.0		
CD4 cells	Helixor	33	0	0.9	7.0	-16.8	-2.0	1.3	6.0	13.9	0.810	-4;3.9
[%]	Lentinan	30	3	0.6	9.1	-24.0	-3.0	1.5	8.1	16.0		
	Total	63	3	0.8	8.0	-24.0	-3.0	1.3	7.0	16.0		
CD8 cells	Helixor	24	9	-19.8	244.8	-338.0	-211.5	-22.0	67.5	743.0	0.557	-183;76
[x10³/mm³]	Lentinan	21	12	-14.6	200.5	-461.0	-66.0	18.0	67.0	277.0		
	Total	45	21	-17.3	222.7	-461.0	-176.0	0.0	67.0	743.0		
CD8 cells	Helixor	33	0	4.4	9.6	-16.8	0.0	2.0	6.1	32.0	0.104	-0.14;4.7
[%]	Lentinan	30	3	1.0	5.9	-11.0	-1.0	0.0	3.1	19.0		
	Total	63	3	2.8	8.2	-16.8	-0.7	2.0	5.0	32.0		
CD4/CD8	Helixor	33	0	-0.1	0.4	-1.0	-0.3	-0.0	0.1	0.9	0.542	-0.29;0.14
	Lentinan	30	3	-0.0	0.5	-1.3	-0.3	-0.0	0.3	1.2		
	Total	63	3	-0.1	0.5	-1.3	-0.3	-0.0	0.2	1.2		
NK cells	Helixor	33	0	0.6	7.0	-15.0	-2.3	0.0	3.0	24.0	0.302	-5;1.26
activity	Lentinan	30	3	1.6	7.4	-18.0	-1.0	1.0	6.0	17.0		
	Total	63	3	1.0	7.1	-18.0	-2.0	1.0	4.0	24.0		

Difference: (value of final investigation minus value of screening).

3.4.3 Liver and Kidney Parameters

3.4.3.1 Total study population

Liver and kidney parameters including ALT – Alanin aminotransferase, AST – Aspartat aminotransferase, BUN - blood urea nitrogen, are depicted in **Table 114** for time at screening, in **Table 115** for time at final

investigation and in **Table 116** for changes during trial period. Major differences between treatment groups cannot be observed.

Table 114 Total study population – Liver and kidney parameters at screening

ALL	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
ALT	Helixor	110	4	18.9	14.0	3.0	11.0	15.5	21.0	97.0	0.478
[IU/l]	Lentinan	106	4	22.8	27.7	4.0	10.0	16.0	26.0	243.0	
	Total	216	8	20.8	21.9	3.0	11.0	16.0	23.0	243.0	
AST	Helixor	112	2	23.3	11.0	7.0	17.0	21.0	26.0	98.0	0.716
[IU/l]	Lentinan	106	4	23.0	14.2	7.0	17.0	20.0	26.0	149.0	
	Total	218	6	23.1	12.7	7.0	17.0	21.0	26.0	149.0	
BUN	Helixor	113	1	5.2	1.8	2.5	3.9	5.0	6.0	16.0	0.638
[IU/l]	Lentinan	107	3	5.4	2.5	1.4	4.0	5.2	5.9	25.0	
	Total	220	4	5.3	2.2	1.4	4.0	5.1	6.0	25.0	

Table 115 Total study population – Liver and kidney parameters at final investigation

ALL	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX
ALT	Helixor	110	4	21.1	16.1	6.0	13.0	17.0	22.0	127.0
[IU/l]	Lentinan	104	6	23.1	17.6	4.0	12.0	18.5	27.5	85.0
	Total	214	10	22.1	16.9	4.0	12.0	17.4	25.0	127.0
AST	Helixor	112	2	22.5	9.2	7.0	17.0	21.0	24.5	79.0
[IU/l]	Lentinan	104	6	24.5	12.7	7.0	17.5	21.0	28.0	79.0
	Total	216	8	23.5	11.0	7.0	17.0	21.0	26.0	79.0
BUN	Helixor	112	2	5.2	2.6	1.7	4.0	4.8	6.0	22.0
[IU/l]	Lentinan	104	6	5.3	2.5	2.3	4.1	4.8	6.0	25.0
	Total	216	8	5.2	2.6	1.7	4.1	4.8	6.0	25.0

Table 116 Total study population – Difference of liver and kidney parameters between final investigation and screening

ALL	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value	95%-CI
ALT	Helixor	108	6	2.1	17.5	-51.0	-3.0	1.0	6.0	114.0	0.767	-2.2;3
[IU/l]	Lentinan	103	7	0.1	30.6	-227.0	-5.0	0.0	9.0	55.0		
	Total	211	13	1.1	24.7	-227.0	-4.0	1.0	7.0	114.0		
AST	Helixor	111	3	-0.8	12.9	-83.0	-5.0	-1.0	4.0	63.0	0.185	-3;1
[IU/l]	Lentinan	103	7	1.6	17.6	-130.0	-4.0	0.0	5.0	53.0		
	Total	214	10	0.4	15.3	-130.0	-4.0	0.0	4.0	63.0		
BUN	Helixor	112	2	0.0	2.3	-4.7	-1.2	-0.0	0.7	17.1	0.977	-0.43;0.4
[IU/l]	Lentinan	104	6	-0.0	1.7	-4.1	-1.1	-0.2	0.9	5.9		
	Total	216	8	-0.0	2.0	-4.7	-1.1	-0.1	0.8	17.1		

Difference: (value of final investigation minus value of screening).

3.4.3.2 Non small cell lung cancer

Table 117 Non small cell lung cancer – Liver and kidney parameters at screening

NSCLC	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
ALT	Helixor	46	0	20.4	13.7	3.0	11.0	18.5	23.0	64.0	0.454
[IU/l]	Lentinan	44	1	19.9	20.7	6.0	9.5	14.5	22.5	137.0	
	Total	90	1	20.2	17.4	3.0	10.0	16.0	23.0	137.0	
AST	Helixor	46	0	22.5	8.1	7.0	17.0	22.0	27.0	46.0	0.183
[IU/l]	Lentinan	44	1	20.8	7.6	7.0	15.5	20.0	23.5	48.0	
	Total	90	1	21.7	7.9	7.0	17.0	20.0	26.0	48.0	
BUN	Helixor	46	0	5.2	1.5	2.7	3.9	5.2	6.2	9.5	0.856
[IU/l]	Lentinan	45	0	5.6	3.4	1.4	3.9	5.2	5.8	25.0	
	Total	91	0	5.4	2.6	1.4	3.9	5.2	6.0	25.0	

Table 118 Non small cell lung cancer – Liver and kidney parameters at final investigation

NSCLC	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX
ALT	Helixor	46	0	19.0	11.6	6.0	12.0	16.0	21.0	73.0
[IU/l]	Lentinan	44	1	20.1	12.4	4.0	12.0	19.0	25.0	57.1
	Total	90	1	19.5	11.9	4.0	12.0	17.0	23.0	73.0
AST	Helixor	46	0	21.0	6.4	12.0	16.0	19.5	24.0	37.0
[IU/l]	Lentinan	44	1	22.5	10.7	7.0	17.0	20.0	25.5	72.0
	Total	90	1	21.7	8.8	7.0	17.0	20.0	25.0	72.0
BUN	Helixor	46	0	5.3	3.1	1.7	4.0	4.8	6.3	22.0
[IU/l]	Lentinan	44	1	5.7	3.4	2.4	4.1	4.9	6.4	25.0
	Total	90	1	5.5	3.2	1.7	4.1	4.8	6.3	25.0

Table 119 Non small cell lung cancer– Difference of liver and kidney parameters between final investigation and screening

NSCLC	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value	95%-CI
ALT	Helixor	46	0	-1.4	14.6	-51.0	-7.0	-0.5	5.0	42.0	0.462	-6;3
[IU/l]	Lentinan	43	2	0.0	21.0	-108.0	-5.0	-1.0	8.0	49.1		
	Total	89	2	-0.7	17.9	-108.0	-6.0	-1.0	6.0	49.1		
AST	Helixor	46	0	-1.6	6.9	-21.0	-6.0	-1.5	3.0	18.0	0.178	-5;1
[IU/l]	Lentinan	43	2	1.8	10.0	-12.0	-4.0	0.0	5.0	49.0		
	Total	89	2	0.0	8.7	-21.0	-4.0	-1.0	4.0	49.0		
BUN	Helixor	46	0	0.1	3.2	-4.7	-1.2	-0.1	0.7	17.1	0.408	-1;0.39
[IU/l]	Lentinan	44	1	0.1	1.6	-2.8	-1.0	-0.0	1.1	4.9		
	Total	90	1	0.1	2.5	-4.7	-1.1	-0.1	1.0	17.1		

Difference: (value of final investigation minus value of screening).

3.4.3.3 Breast cancer

Table 120 Breast cancer – Liver and kidney parameters at screening

BREAST	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
ALT	Helixor	34	1	17.9	17.9	3.0	11.0	14.0	18.0	97.0	0.081
[IU/l]	Lentinan	30	2	31.3	43.8	6.0	10.0	20.0	36.0	243.0	
	Total	64	3	24.2	33.1	3.0	10.5	15.0	24.0	243.0	
AST	Helixor	34	1	23.1	15.7	7.0	15.0	19.0	26.0	98.0	0.232
[IU/l]	Lentinan	30	2	26.6	24.3	7.0	18.0	21.0	26.0	149.0	
	Total	64	3	24.7	20.1	7.0	16.0	20.0	26.0	149.0	
BUN	Helixor	34	1	5.3	2.3	2.5	3.9	5.2	6.1	16.0	0.159
[IU/l]	Lentinan	30	2	5.5	1.0	3.6	5.0	5.6	6.1	8.0	
	Total	64	3	5.4	1.8	2.5	4.4	5.4	6.1	16.0	

Table 121 Breast cancer – Liver and kidney parameters at final investigation

BREAST	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX
ALT	Helixor	33	2	25.8	24.3	9.0	14.0	18.0	22.0	127.0
[IU/l]	Lentinan	30	2	32.6	25.0	8.0	14.0	21.0	47.0	85.0
	Total	63	4	29.0	24.6	8.0	14.0	19.0	33.0	127.0
AST	Helixor	34	1	23.8	12.2	7.0	18.0	22.0	24.0	79.0
[IU/l]	Lentinan	30	2	30.3	17.8	7.0	19.0	23.5	38.0	79.0
	Total	64	3	26.8	15.3	7.0	18.0	22.0	29.5	79.0
BUN	Helixor	34	1	5.4	2.8	2.5	4.2	5.0	6.0	20.0
[IU/l]	Lentinan	30	2	5.1	1.5	2.3	4.1	5.1	5.9	9.0
	Total	64	3	5.3	2.3	2.3	4.1	5.0	5.9	20.0

Table 122 Breast cancer– Difference of liver and kidney parameters between final investigation and screening

BREAST	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value	95%-CI
ALT	Helixor	33	2	7.7	23.7	-38.0	-1.0	4.0	8.0	114.0	0.671	-9;6
[IU/l]	Lentinan	30	2	1.2	50.5	-227.0	-4.0	5.0	20.0	55.0		
	Total	63	4	4.6	38.7	-227.0	-2.0	5.0	14.0	114.0		
AST	Helixor	34	1	0.7	20.2	-83.0	-3.0	1.5	6.0	63.0	0.265	-9;2
[IU/l]	Lentinan	30	2	3.7	30.0	-130.0	-3.0	3.5	12.0	53.0		
	Total	64	3	2.1	25.1	-130.0	-3.0	2.0	7.5	63.0		
BUN	Helixor	34	1	0.1	1.5	-2.4	-1.0	0.1	0.8	4.6	0.078	-0.08;1.2
[IU/l]	Lentinan	30	2	-0.5	1.4	-3.0	-1.6	-0.6	0.2	3.7		
	Total	64	3	-0.1	1.5	-3.0	-1.2	-0.0	0.6	4.6		

Difference: (value of final investigation minus value of screening).

3.4.3.4 Ovarian cancer

Table 123 Ovarian cancer – Liver and kidney parameters at screening

OVARIAN	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value
ALT	Helixor	30	3	17.8	8.8	8.0	12.0	15.5	21.0	43.0	0.773
[IU/l]	Lentinan	32	1	18.8	10.4	4.0	10.5	17.0	26.0	44.0	
	Total	62	4	18.3	9.6	4.0	11.0	16.0	23.0	44.0	
AST	Helixor	32	1	24.4	8.7	12.0	19.5	22.0	27.5	48.0	0.794
[IU/l]	Lentinan	32	1	22.7	5.9	13.0	19.0	21.5	27.0	38.3	
	Total	64	2	23.6	7.4	12.0	19.5	22.0	27.0	48.0	
BUN	Helixor	33	0	5.0	1.6	2.5	4.0	4.6	5.8	9.3	0.774
[IU/l]	Lentinan	32	1	4.8	1.7	2.0	3.6	4.8	5.5	9.4	
	Total	65	1	4.9	1.6	2.0	3.8	4.8	5.5	9.4	

Table 124 Ovarian cancer – Liver and kidney parameters at final investigation

OVARIAN	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX
ALT	Helixor	31	2	19.4	9.2	7.0	13.0	16.0	23.0	45.0
[IU/l]	Lentinan	30	3	18.2	10.8	5.0	10.0	14.0	26.0	41.0
	Total	61	5	18.8	10.0	5.0	12.0	15.0	23.0	45.0
AST	Helixor	32	1	23.4	8.8	14.0	17.5	21.0	28.5	52.0
[IU/l]	Lentinan	30	3	21.6	6.2	9.0	18.0	20.5	26.0	38.0
	Total	62	4	22.6	7.6	9.0	18.0	21.0	27.0	52.0
BUN	Helixor	32	1	4.8	1.5	2.3	3.9	4.4	5.3	9.3
[IU/l]	Lentinan	30	3	4.9	1.7	2.7	3.9	4.6	5.4	10.4
	Total	62	4	4.8	1.6	2.3	3.9	4.5	5.4	10.4

Table 125 Ovarian cancer– Difference of liver and kidney parameters between final investigation and screening

OVARIAN	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	p-value	95%-CI
ALT	Helixor	29	4	1.3	11.0	-30.0	-2.0	1.0	5.0	29.0	0.158	-1;6
[IU/l]	Lentinan	30	3	-1.1	9.7	-25.0	-6.0	-2.0	3.0	30.0		
	Total	59	7	0.1	10.4	-30.0	-4.0	0.0	3.0	30.0		
AST	Helixor	31	2	-1.2	9.1	-26.0	-6.0	-2.0	4.0	16.0	0.852	-4;3
[IU/l]	Lentinan	30	3	-0.8	5.3	-11.0	-4.0	-1.0	2.0	11.0		
	Total	61	5	-1.0	7.4	-26.0	-5.0	-2.0	3.0	16.0		
BUN	Helixor	32	1	-0.3	1.5	-3.8	-1.1	-0.2	0.5	3.9	0.405	-0.99;0.48
[IU/l]	Lentinan	30	3	0.1	1.9	-4.1	-0.6	-0.3	0.9	5.9		
	Total	62	4	-0.1	1.7	-4.1	-0.9	-0.2	0.8	5.9		

Difference: (value of final investigation minus value of screening).

3.5 Urine and Stool Examination

Urine and stool examination are given at time of screening and final investigation as 'normal' (N) and 'abnormal' (A). Parameters of urine are not changing in the group of Helixor-treated patients during period of

clinical trial. In the control group of Lentinan-treated patients, however, a significant number of patients shows improvement of urine parameters during the trial period ($p < 0.001$).

Table 126 Urine and stool examination – before / after treatment

	Helixor					Lentinan				
	N/N	**N/A**	**A/N**	**A/A**	**p-value**	**N/N**	**N/A**	**A/N**	**A/A**	**p-value**
Urine examination	95	5	6	7	1.000	94	0	11	2	<.001
Stool examination	111	1				106	1			

N=normal, A=abnormal; McNemar test

Using Fisher's exact test to assess a difference between both treatment groups with respect to the Urine examination pattern (before/after) shows a significant difference ($p = 0.022$).

4 Evaluation of Efficacy

The evaluation criteria for chemotherapy (remission rate) documented in the „Diagnostic Guideline about widespread malignant tumors in China“ published by the Chinese Health Ministry contains five categories CR (complete remission), PR (partial remission), MR (minor remission), SD (stable disease) and PD (progressive disease). The evaluation of the tumor change at final investigation is listed in **Table 127**.

Table 127 Remission rate at final investigation

ALL		**Helixor N=114**		**Lentinan N=110**		**total N=224**	
		N	%	N	%	N	%
Tumor size evaluation	Missing	6	2.7	8	3.6	14	6.3
	CR	28	12.5	26	11.6	54	24.1
	PR	20	8.9	20	8.9	40	17.9
	MR	10	4.5	14	6.3	24	10.7
	SD	45	20.1	31	13.8	76	33.9
	PD	5	2.2	11	4.9	16	7.1

Chi²-Test for ordinal data, p = 0.974

A crude comparison (without adjustment for center, previous treatment, and tumour entity) of the two treatment groups based on Table 127 shows no significant difference between both treatment groups with respect to tumor response (p=0.974).

In the study protocol the efficacy rate after two cycles was defined as the proportion of CR and PR. Therefore in the present analysis a responder is defined as a patient with CR or PR as tumor change at final investigation, a non-responder is defined as a patient with MR, SD or PD at final investigation.

A multivariate logistic regression model was used to estimate the treatment effect with respect to the tumor change. The nuisance parameters *patient had a previous operation* / *patient had no previous operation* and *patient had a measurable tumor and/or metastases finding before treatment* / *patient had no measurable tumor and/or metastases finding before treatment* were included in order to get an adjustment for the different initial conditions of the patients at screening. Furthermore the tumor entity and the center were added as nuisance parameters to adjust the treatment effect for possible confounders. Interaction terms of a nuisance parameter with the treatment have been seen as relevant if the corresponding p-value in the full logistic model is less than 0.15; then the interaction term was included to estimate the adjusted treatment effect.

The tumor entity does not appear as relevant nuisance parameter to estimate the treatment effect in the model just described.

There is a clear center by treatment interaction: The effect of the treatment is singnificantly different in center Shenyang compared to the centers Beijing and Tianjin. The adjusted treatment effect in the center Shenyang and the adjusted treatment effect in the centers Beijing and Tianjin are contrary as depicted in **Table 128**.

Table 128 Logistic regression for remission rate – Odds ratio for adjusted treatment effect in the centers Beijing, Tianjin, Shenyang

	odds ratio estimate for adjusted treatment effect	95% confidence limits for the odds ratio estimate
BEIJING, TIANJIN	1.739	0.721 to 4.195
SHENYANG	0.612	0.284 to 1.321

Nuisance parameters: previous operation yes/no, measurable tumor and/or metastases yes/no, tumor entity.

The odds ratio for Helixor versus Lentinan is the ratio of the predicted odds of being responder for Helixor versus Lentinan, which has been shown to be 1.739 (95% confidence limits: 0.721 to 4.195) for the pooled centers Beijing and Tianjin and to be 0.612 (95% confidence limits: 0.284 to 1.321) in the center Shenyang. Therefore, looking at the pooled centers Beijing and Tianjin patients treated by Helixor have a better chance to be responder than the patients treated by Lentinan, whereas in the center Shenyang the patients treated by Helixor have a lower chance to be responder than the patients treated by Lentinan.

5 Evaluation of Safety

5.1 Toxicitiy Criteria according to WHO

5.1.1.1 Total study population

Toxicity of chemotherapeutic agents according to WHO is graphically presented for time at screening and final examination for the Helixor (H) and Lentinan (L) group in **Figure 21** and **Figure 22.**

Figure 21 Total study population at screening – toxicity of chemotherapeutic agents according to WHO

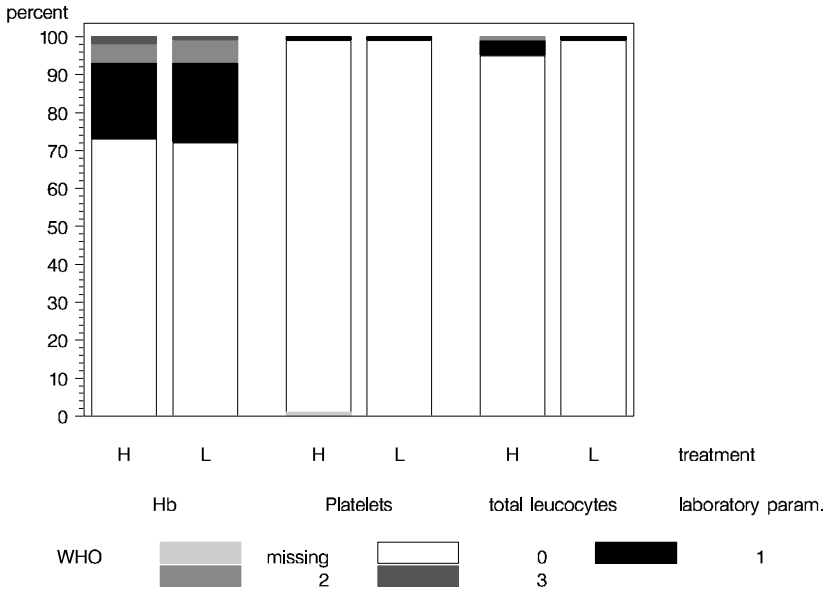
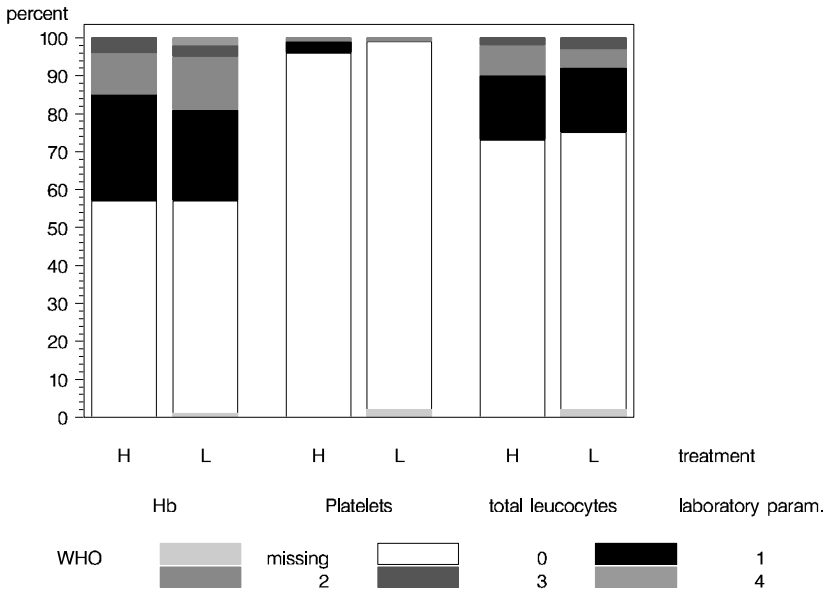


Figure 22 Total study population at final investigation – toxicity of chemotherapeutic agents according to WHO



5.2 Adverse Events (AE) and Serious Adverse Events (SAE)

A serious adverse event (SAE) is per definition any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. On contrary, any adverse finding associated with drug use is defined as adverse event (AE) including, signs, symptoms, abnormal assessment or clusters of these.

Adverse and serious adverse events are presented by categorical parameters intensity and severity for the overall population and separately for tumor entities in **Table 129**. This table contains all 233 randomised patients. An AE analysis for the per protocol population was not performed. The total number of adverse events and serious adverse events in patients treated with HELIXOR® A is 52 (NSCLC: 30, breast: 10, ovarian: 12), in Lentinan 90 (NSCLC: 18, breast: 22, ovarian: 50) out of the total study population.

Treatment groups of HELIXOR® A and Lentinan obviously vary in the intensity of adverse events, while 50% of all adverse events in the Lentinan treatment group appear moderate and 41.1% light, in the HELIXOR® A treated patients show 32.7% and 46.2% in the respective groups. However, severe adverse events in the HELIXOR® A group (17.3%) prevail severe events in the control group (7.8%). In the overall comparison of serious adverse events (SAE yes/no) the two treatment groups appear comparable in the total study population as well as in the groups of non small lung cancer and breast cancer. Surprisingly, the population of ovarian cancer patients vary widely from the other groups. First, a disproportionate amount of adverse and serious adverse events of Lentinan-treated patients occurs in the group of ovarian cancer (50 out of 90 events), with a majority of adverse events only. Secondly, almost half of the adverse events occurring in the Helixor-treated population of ovarian cancer are classifed as 'serious adverse events'. Despite the small number of adverse events occurring in ovarian cancer patients under HELIXOR® A therapy, the difference in intensity, severity and incidence of serious adverse events is very different from Lentinan treated patients.

Table 129 Adverse and serious adverse events

ALL		**Helixor N=52**		**Lentinan N=90**		**Total N=142**	
		N	%	N	%	N	%
Intensity	Missing	2	3.8	0	0.0	2	1.4
	Light	24	46.2	37	41.1	61	43.0
	Moderate	17	32.7	45	50.0	62	43.7
	Severe	9	17.3	7	7.8	16	11.3
	Not evaluable	0	0.0	1	1.1	1	0.7
Severity	Missing	2	3.8	0	0.0	2	1.4
	Not serious	44	84.6	80	88.9	124	87.3
	Death	1	1.9	4	4.4	5	3.5
	Life-threatening	4	7.7	2	2.2	6	4.2
	Hospitalization	1	1.9	4	4.4	5	3.5
SAE	No	46	88.5	80	88.9	126	88.7
	Yes	6	11.5	10	11.1	16	11.3

NSCLC		Helixor N=30		Lentinan N=18		Total N=48	
		N	%	N	%	N	%
Intensity	Light	16	53.3	5	27.8	21	43.8
	Moderate	10	33.3	11	61.1	21	43.8
	Severe	4	13.3	2	11.1	6	12.5
Severity	Not serious	29	96.7	16	88.9	45	93.8
	Death	1	3.3	2	11.1	3	6.3
SAE	No	29	96.7	16	88.9	45	93.8
	Yes	1	3.3	2	11.1	3	6.3

Breast cancer		Helixor N=10		Lentinan N=22		Total N=32	
		N	%	N	%	N	%
Intensity	Light	6	60.0	15	68.2	21	65.6
	Moderate	4	40.0	7	31.8	11	34.4
Severity	Not serious	10	100.0	21	95.5	31	96.9
	Hospitalization	0	0.0	1	4.5	1	3.1
SAE	No	10	100.0	21	95.5	31	96.9
	Yes	0	0.0	1	4.5	1	3.1

Ovarian cancer		Helixor N=12		Lentinan N=50		Total N=62	
		N	%	N	%	N	%
Intensity	Missing	2	16.7	0	0.0	2	3.2
	Light	2	16.7	17	34.0	19	30.6
	Moderate	3	25.0	27	54.0	30	48.4
	Severe	5	41.7	5	10.0	10	16.1
	Not evaluable	0	0.0	1	2.0	1	1.6
Severity	Missing	2	16.7	0	0.0	2	3.2
	Not serious	5	41.7	43	86.0	48	77.4
	Death	0	0.0	2	4.0	2	3.2
	Life-threatening	4	33.3	2	4.0	6	9.7
	Hospitalization	1	8.3	3	6.0	4	6.5
SAE	No	7	58.3	43	86.0	50	80.6
	Yes	5	41.7	7	14.0	12	19.4

The frequency of the adverse events of Helixor and Lentinan group is listed in **Table 130 and Table 131**. Five of the 'moderate' and three of the 'severe' adverse events are caused explicitely by HELIXOR® A. However, only two moderate adverse events are caused by therapy with Lentinan. For further details see tables.

Table 130 Adverse events (AE) in HELIXOR® A group

Relation to treatment	Light AE					Moderate AE					Severe AE				
	none	poss	prob	sure	ne	none	poss	prob	sure	ne	none	poss	prob	sure	ne
Gastro-intestinal system disorders	**4 (7.7%)**				**2 (3.8%)**	**3 (5.8%)**				**2 (3.8%)**	**1 (1.9%)**				
DIARRHOE	1										1				
VOMITTING	1				1	1				1					
NAUSEA	2				1	2				1					
Cardiovascular disorder, general											**1 (1.9%)**				
HEART FAILURE											1				
Respiratory system disorders*/ °															
RESPIRATORY TRACT OBSTRUCTION ***/ °**															
Red blood cell disorders	**3 (5.8%)**														
HB LOW	3														
White cell and RES disorders	**6 (11.5%)**					**2 (3.8%)**									
LEUKOCYTES LOW	6					2									
Neoplasms											**1 (1.9%)**				
NO SYMPTOMS											1				
Body as a whole-general disorders	**3 (5.8%)**		**1 (1.9%)**		**1 (1.9%)**	**3 (5.8%)**			**3 (5.8%)**		**1 (1.9%)**			**1 (1.9%)**	**2 (3.8%)**
ALOPEZIA AREATA						1									
POOR APPETITE															1 °
FEVER	1		1		1	1			3		1				
FACIAL EDEMA														1 °	
COUGH	1														
SHORT BREATH						1 °									
FATIGUE															1 °
PAIN OF CHEST	1														
Application site disorders*/ °		**3 (5.8%)**	**1 (1.9%)**				**2 (3.8%)**		**2 (3.8%)**					**2 (3.8%)**	
INFLAMMATORY SWELLING		1					1		1						
RASH ***/ °**															
ITCHING		2					1								
INFILTRATION AT SITE OF INJ.			1												
INFLAMMATION AT SITE OF INJ.									1					1	
REACTION AT SITE OF APPLICATION														1 °	

* intensity of reaction is not documented, causal relation to trial medication is documented as 'sure'.

° patients who received therapy for less than 4 weeks and therefore are not included in the remaining analysis.

relation to treatment: none (no relationship), poss (possible), pro (probable), sure, ne (not evaluable)

Table 131 Adverse events (AE) in Lentinan group

Relation to treatment	Light AE					Moderate AE					Severe AE				
	none	poss	prob	sure	ne	none	poss	prob	sure	ne	none	poss	prob	sure	ne
Skin and appendages disorders	**1 (1.1%)**					**1 (1.1%)**									
SKIN REACTION	1														
HERPES SIMPLEX						1 °									
Gastro-intestinal system disorders*/ °	**11 (12.2%)**					**20 (22.2%)**					**3 (3.3%)**				
DIARRHOE						1					1 °				
VOMITTING	5					9(1°)					1				
GI-TRACT BLEEDING NNB */ °															
NAUSEA	6(1°)					9(1°)					1				
VOELLEGEFUEHL						1									
Respiratory system disorders									**1 (1.1%)**						
OBSTRUCTION OF NOSE									1						
Red blood cell disorders	**6 (6.7%)**					**1 (1.1%)**									
HB LOW	6					1									
White cell and RES disorders	**15 (16.7%)**					**14 (15.6%)**					**1 (1.1%)**				
GRANULOZYTOPENIE	5					6									
LEUKOCYTE S LOW	10					8					1				
Platelet, bleeding & clotting disorders	**2 (2.2%)**														
THROMBOCYTES LOW	1														
THROMBOCYTOPENIE	1														
Urinary system disorders									**1 (1.1%)**						
URINE PRECIPITATE PATH.									1 °						
Neoplasms											**2 (2.2%)**				
ASCITES											1				
TUMOR RELAPSE											1				
Body as a whole-general disorders	**2 (2.2%)**					**5 (5.6%)**				**1 (1.1%)**	**1 (1.1%)**				
ABDOMI NAL PAIN						1					1				
FEVER						3				1					
COUGH						1									
FATIGUE	2														
Application site disorders									**1 (1.1%)**						
PAINFUL SITE OF INJECTION									1						

* intensity of reaction is documented as not evaluable, causal relation to trial medication is documented as 'none'.
° patients who received therapy for less than 4 weeks and therefore are not included in the remaining analysis.
relation to treatment: none (no relationship), poss (possible), pro (probable), sure, ne (not evaluable)

For both treatment groups the serious adverse events are listed in **Table 132**. Causal relationship to trial medication for the HELIXOR® A treatment group is documented for one patient who had a reaction on application site and a facial edema. One patient in the control group has shown urine precipitate pathological as consequence of trial medication. Other serious adverse events are causally related to chemotherapy treatment or independent of medication.

Table 132 Serious adverse events (SAE) in HELIXOR® A and Lentinan group

	Pat.	Start date	Last chemo-therapy	Last trial medi-cation	Intensity	Degree of seriousness	Date of death	Relation-ship to chemo-therapy	Relation-ship to trial medi-cation
Helixor									
Cardiovascular disorder, general / HEART FAILURE									
Died from heart disease	17	26/10/00	08/09/00	18/09/00	severe	death	26/10/00	none	none
Application site disorders / REACTION AT SITE OF APPLICATION									
Red nodules > 5 cm	117	17/02/01	03/02/01	16/02/01	severe	life-threatening		none	sure
Body as a whole-general disorders / FACIAL EDEMA									
Heavy edema face and neck	117	17/02/01	03/02/01	16/02/01	severe	life-threatening		none	sure
Neoplasms / kein Syntom angegeben									
Tumor mass in abdomen	120	18/08/00	14/08/00	18/08/00	severe	hospitali-zation		none	none
Gastro-intestinal system disorders / DIARRHOE									
Diarrhea	125	24/02/01	16/02/01	23/02/01	severe	life-threatening		probable	none
Body as a whole-general disorders / FEVER									
High fever (up to 40°C)	125	24/02/01	16/02/01	23/02/01	severe	life-threatening		probable	none
Lentinan									
Gastro-intestinal system disorders / DIARRHOE									
Diarrhea	61	03/10/00	27/09/00	02/10/00	severe	death	25/10/00	sure	none
Skin and appendages disorders / HERPES SIMPLEX									
Herpes	61	09/10/00	27/09/00	08/10/00	moderate	death	25/10/00	probable	none
Gastro-intestinal system disorders / VOMITTING									
Vomitting	164	06/12/00	06/12/00	06/12/00	moderate	hospitali-zation		sure	none
Gastro-intestinal system disorders / NAUSEA									
Nausea	164	06/12/00	06/12/00	06/12/00	moderate	hospitali-zation		sure	none
Body as a whole-general disorders / FEVER									
Fever	164	07/12/00	07/12/00	07/12/00	moderate	hospitali-zation		none	none
Body as a whole-general disorders / ABDOMINAL PAIN									
Pain in the abdomen	170	24/01/01	22/12/00	07/01/01	severe	death	01/04/01	None	none
Neoplasms / ASCITES									
Ascites getting more	170	24/01/01	22/12/00	07/01/01	severe	death	01/04/01	none	none
Neoplasms / TUMOR RELAPSE									
Tumor getting bigger	170	24/01/01	22/12/00	07/01/01	severe	life-threatening	01/04/01	none	none
Gastro-intestinal system disorders / GI-TRACT BLEEDING NNB									
Digestive tract bleeding	184	01/11/00	20/10/00	01/11/00	not evaluable	life-threatening		none	none
Urinary system disorders / URINE PRECIPITATE PATHOLOGICAL									
White precipitate in the urine	280	28/11/00	19/11/00	28/11/00	moderate	hospitali-zation		none	sure

Table 133 Patients who died some time after the clinical trial

Pat.ID	Trial medication	Date of death	Comment from the CRF
Pat.17 Helixor	NSCLC – NVB+PDD cycle 1: 03/08/00, cycle 2: 01/09/00 Helixor from 03/08/00 to 18/09/00	26/10/00	Died from heart disease. After finishing the clinical trial, the patient discharged from hospital. One month later a follow up call revealed, that the patient died from heart disease at home. Causal relationship to chemotherapy: none, causal relationship to trial medication: none.
Pat.61 Lentinan	NSCLC – NVB+PDD cycle 1: 20/09/00 Lentinan from 20/09/00 to 16/10/00	25/10/00	Diarrhea since 03/10/00 causal relationship to chemotherapy: sure, causal relationship to trial medication: none. Herpes since 09/10/00 causal relationship to chemotherapy: probable, causal relationship to trial medication: none. Cause of death: Multiple organs failure, In the first cycle of chemotherapy, WBC low, then infection of the lung, hypoalbuminemia, herpes, gastrointestinal dysfunction, vomitting and diarrhea, in the end multi-organs failure to die.
Pat.170 Lentinan	Ovarian – CP cycle 1: 27/11/00, cycle 2 21/12/00 Lentinan from 27/11/00 to 07/01/01	01/04/01	Ascites getting more since 24/01/01, causal relationship to chemotherapy: none, causal relationship to trial medication: none. Tumor getting bigger since 24/01/01 causal relationship to chemotherapy: none, causal relationship to trial medication: none.
Pat.184 Lentinan	Ovarian – IFO+CBP or PDD cycle 1: 17/10/00 Lentinan from 17/10/00 to 05/10/00.	29/01/01	Cause of death: Recurrence of cancer, intestinal obstruction and general organ function exhaustion to death. During chemotherapy the patient had hemorrhoids of the digestive tract. After treatment no any effect. So drop out.

6 Characteristics of HELIXOR® A Treatment

6.1 Dosage of HELIXOR® A

The number of injections given per patient and maximum dosage of HELIXOR® A are listed in **Table 134**. HELIXOR® A was applied in ascending dosage from 1 to 200 mg during 6-8 weeks as listed in **Table 1**. For patients reaching a tolerance limit, therapy was continued at a dosage according to discretion of the physician.

Table 134 Number of injections and maximum dosage of HELIXOR® A [mg] per patient

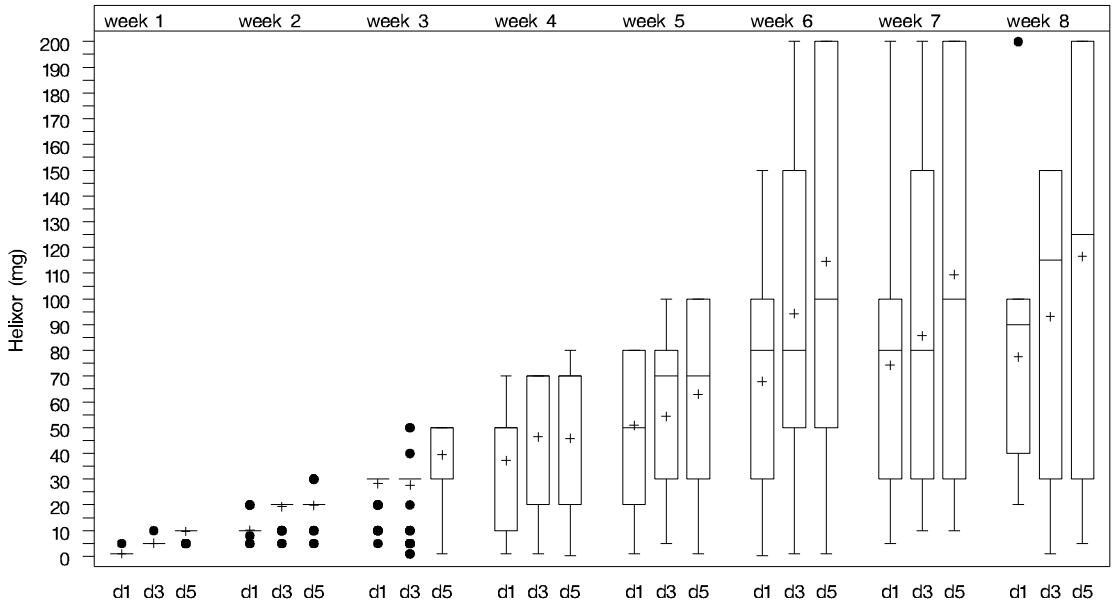
	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX
Number of injections	NSCLC	46	0	17.4	2.0	13.0	17.0	18.0	18.0	23.0
	Breast cancer	35	0	17.1	2.4	13.0	15.0	18.0	18.0	24.0
	Ovarian cancer	33	0	19.5	3.4	13.0	18.0	18.0	24.0	24.0
	Total	114	0	17.9	2.7	13.0	17.0	18.0	18.0	24.0
Maximum dosage/ injection	NSCLC	46	0	125.9	73.4	20.0	50.0	125.0	200.0	200.0
	Breast cancer	35	0	111.7	78.5	20.0	30.0	70.0	200.0	200.0
	Ovarian cancer	33	0	119.4	74.7	10.0	50.0	100.0	200.0	200.0
	Total	114	0	119.6	75.0	10.0	50.0	100.0	200.0	200.0

The course of HELIXOR® A treatment is shown graphically in **Figure 23** for the overall population and in **The second** line of the legend contains for the 8 treatment weeks for each treatment day the number of patients treated. For example, the legend for Figure 23 states that in week 1, 114 patients were treated at day

1, 114 patients were treated at day 3, and 113 patients were treated at day 5. Similar information is given for weeks 2 to 8.

Figure 24**, Figure 25** and **Figure 26** for the single tumor entities. The trial plan determined HELIXOR® A medication in ascending manner from 1 to 200 mg, given 3 times a week on weekdays 1, 3 and 5 (d1, d3, d5) for 6 weeks concerning NSCLC and breast cancer as well as ovarian cancer and 8 weeks in the case of certain ovarian cancer patients under (IFO+CBP or PDD)-chemotherapy treatment plan. Patients reaching a tolerance limit of HELIXOR® A during treatment period obtained dosage according to the discretion of the physician. The graphical presentation shows that patients tolerate very different dosages of mistletoe medication as seen from the wide distribution of dosage especially at the end of therapy.

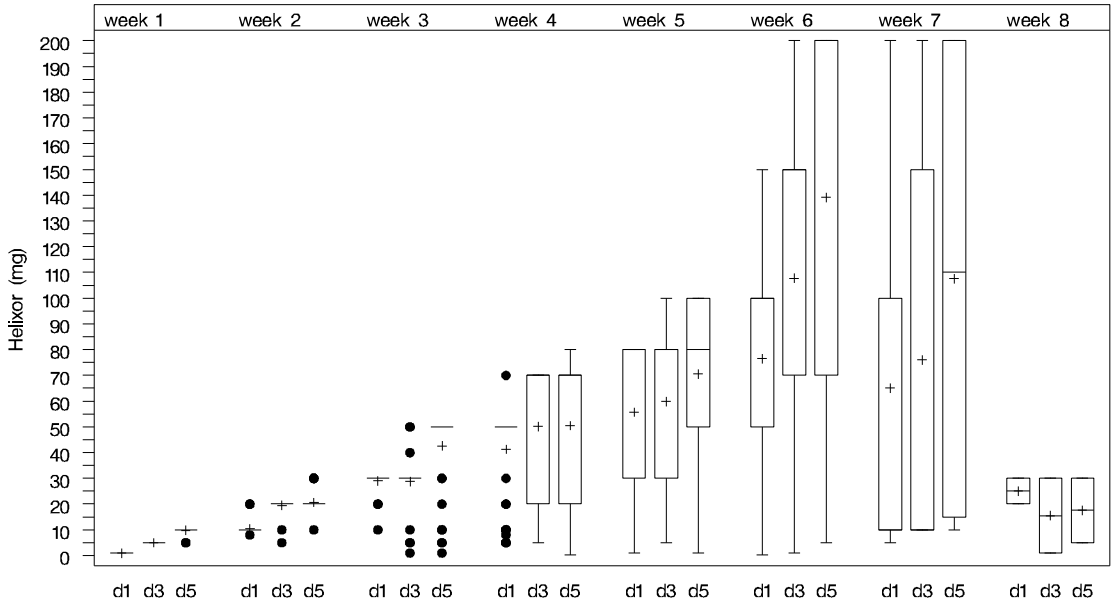
Figure 23 Total study population - Dosage of HELIXOR® A medication during trial period



Number of patients under treatment at days 1, 3, 5 of week k (k: d1/d3/d5):
1: 114/114/113, 2: 114/113/113, 3: 106/97/98, 4: 102/104/110, 5: 109/104/111, 6: 107/102/100, 7: 22/21/19, 8: 16/16/16

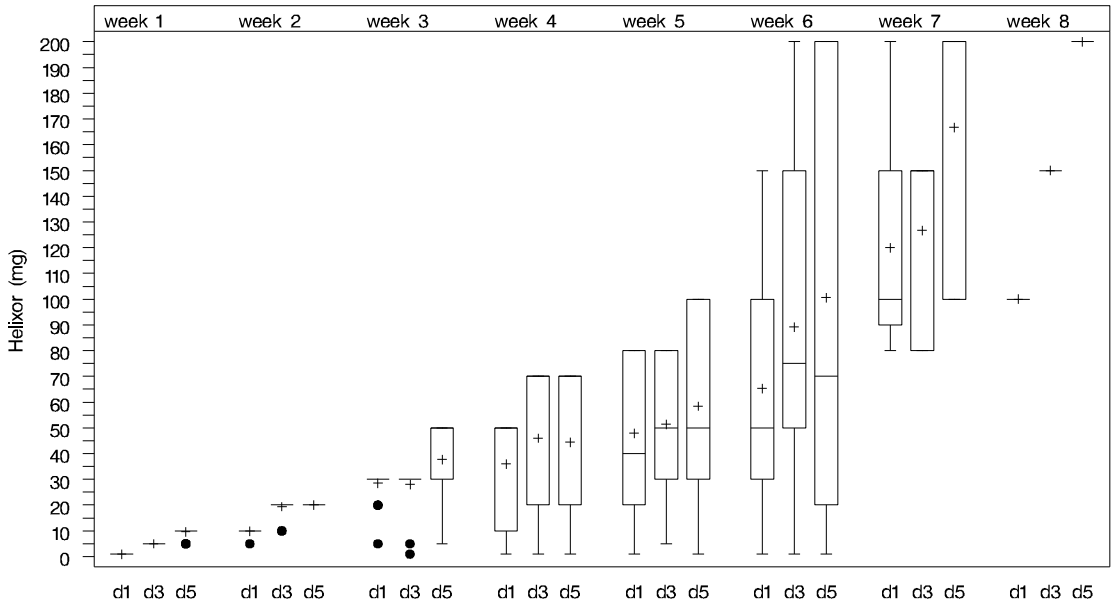
The second line of the legend contains for the 8 treatment weeks for each treatment day the number of patients treated. For example, the legend for Figure 23 states that in week 1, 114 patients were treated at day 1, 114 patients were treated at day 3, and 113 patients were treated at day 5. Similar information is given for weeks 2 to 8.

Figure 24 NSCLC population - Dosage of HELIXOR® A medication during trial period



Number of patients under treatment at days 1, 3, 5 of week k (k: d1/d3/d5):
1: 46/46/45, 2: 46/46/46, 3: 44/40/39, 4: 41/42/43, 5: 45/44/45, 6: 43/41/39, 7: 5/5/4, 8: 2/2/2

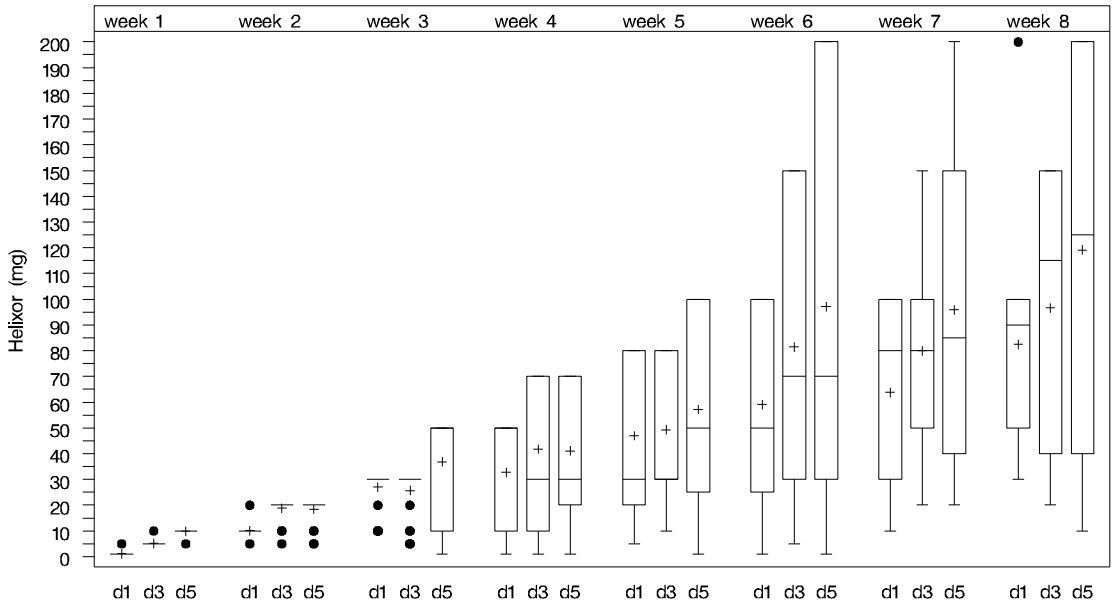
Figure 25 Breast cancer population - Dosage of HELIXOR® A medication during trial period



Number of patients under treatment at days 1, 3, 5 of week k (k: d1/d3/d5):
1: 35/35/35, 2: 35/35/35, 3: 31/28/29, 4: 31/31/34, 5: 32/31/34, 6: 32/30/29, 7: 4/3/3, 8: 2/2/2

The second line of the legend contains for the 8 treatment weeks for each treatment day the number of patients treated. For example, the legend for Figure 25 states that in week 1, 35 patients were treated at day 1, 35 patients were treated at day 3, and 35 patients were treated at day 5. Similar information is given for weeks 2 to 8.

Figure 26 Ovarian cancer population - Dosage of HELIXOR® A medication during trial period



Number of patients under treatment at days 1, 3, 5 of week k (k: d1/d3/d5):
1: 33/33/33, 2: 33/32/32, 3: 31/29/30, 4: 30/31/33, 5: 32/29/32, 6: 32/31/32, 7: 13/13/12, 8: 12/12/12

6.2 Local Skin Reaction to HELIXOR® A

The skin reaction to HELIXOR® A for the whole population as well as for the different tumor entities by dosage and maximum size of local reaction is shown in **Table 135**. Time and dosage of the first skin reaction in combination are represented in **Table 136**.

Table 135 Local skin reaction

ALL	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX
Dosage with first local skin reaction	NSCLC	40	6	22.2	24.9	1.0	10.0	10.0	30.0	100.0
	Breast cancer	33	2	17.8	15.9	1.0	10.0	10.0	20.0	80.0
	Ovarian cancer	28	5	27.7	21.1	5.0	10.0	20.0	40.0	80.0
	Total	101	13	22.3	21.4	1.0	10.0	20.0	30.0	100.0
Maximum of size of local skin reaction [mm]	NSCLC	46	0	43.7	26.6	0.0	30.0	49.0	60.0	120.0
	Breast cancer	35	0	50.5	25.3	0.0	30.0	51.0	70.0	110.0
	Ovarian cancer	32	1	41.4	34.4	0.0	20.0	40.0	55.0	150.0
	Total	113	1	45.1	28.6	0.0	20.0	50.0	60.0	150.0

Table 136 First skin reaction – time and dosage of first skin reaction to HELIXOR® A

Tumor entity	First skin reaction	Dosage of Helixor	Number of reactions	%
ALL	week1 day1	1	11	10.9
	week1 day3	5	5	5.0
	week1 day5	5	2	2.0
	week1 day5	10	9	8.9
	week2 day1	5	1	1.0
	week2 day1	10	19	18.8
	week2 day3	10	1	1.0
	week2 day3	20	10	9.9
	week2 day5	20	11	10.9
	week2 day5	30	2	2.0
	week3 day1	30	9	8.9
	week3 day3	30	6	5.9
	week3 day5	50	4	4.0
	week4 day1	50	4	4.0
	week4 day5	70	1	1.0
	week5 day3	80	3	3.0
	week5 day5	100	1	1.0
	week6 day1	100	1	1.0
	week6 day3	70	1	1.0
NSCLC	week1 day1	1	7	17.5
	week1 day3	5	1	2.5
	week1 day5	5	1	2.5
	week1 day5	10	6	15.0
	week2 day1	10	8	20.0
	week2 day3	20	2	5.0
	week2 day5	20	1	2.5
	week2 day5	30	2	5.0
	week3 day1	30	3	7.5
	week3 day3	30	3	7.5
	week3 day5	50	2	5.0
	week4 day1	50	1	2.5
	week5 day3	80	1	2.5
	week5 day5	100	1	2.5
	week6 day1	100	1	2.5
Breast cancer	week1 day1	1	4	12.1
	week1 day3	5	1	3.0
	week1 day5	5	1	3.0
	week1 day5	10	2	6.1
	week2 day1	5	1	3.0
	week2 day1	10	8	24.2
	week2 day3	20	2	6.1
	week2 day5	20	6	18.2
	week3 day1	30	4	12.1
	week3 day3	30	2	6.1
	week4 day1	50	1	3.0
	week5 day3	80	1	3.0
Ovarian cancer	week1 day3	5	3	10.7
	week1 day5	10	1	3.6
	week2 day1	10	3	10.7
	week2 day3	10	1	3.6
	week2 day3	20	6	21.4
	week2 day5	20	4	14.3
	week3 day1	30	2	7.1
	week3 day3	30	1	3.6
	week3 day5	50	2	7.1
	week4 day1	50	2	7.1
	week4 day5	70	1	3.6
	week5 day3	80	1	3.6
	week6 day3	70	1	3.6

Size of skin reaction allocated in ≤ 5 cm and > 5 cm is listed in **Table 137**.

Table 137 Size of skin reaction

		NSCLC		Breast cancer		Ovarian cancer		Total	
		Number of reactions	%	Number of reactions	%	Number of reactions	%	Number of reactions	%
Size of skin reaction	≤ 5 cm	696	91.3	496	87.5	571	93.8	1763	91.0
	> 5 cm	66	8.7	71	12.5	38	6.2	175	9.0

Graphically the data of local skin reaction/dosage and maximum local skin reaction/age are presented in **Figure 27** and **Figure 28.** Special patterns can not be seen in the presented figures. The figures contain a smoothing spline to give a description of a possible trend in the data.

Figure 27 HELIXOR® A population – local skin reaction in relation to dosage

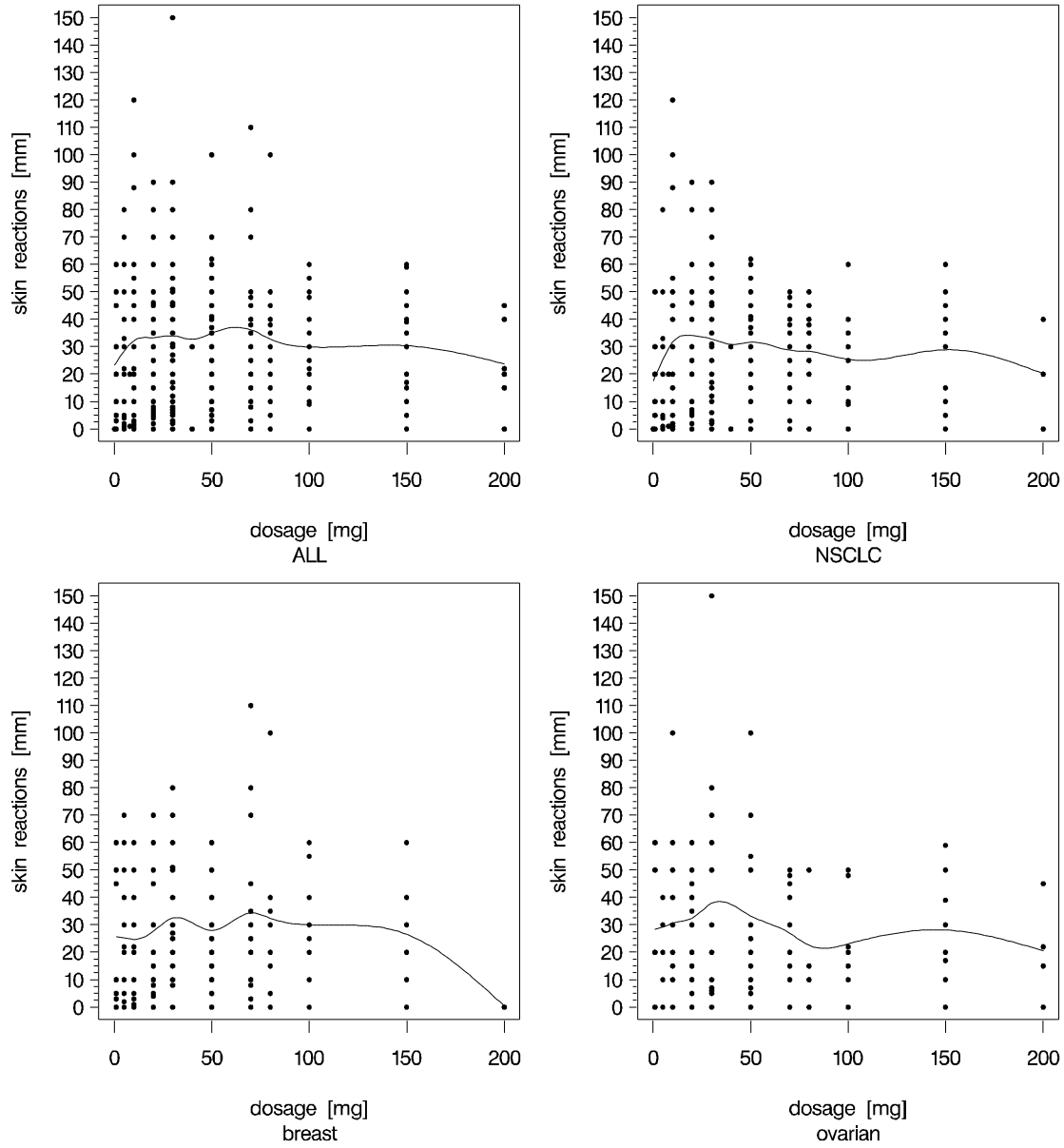
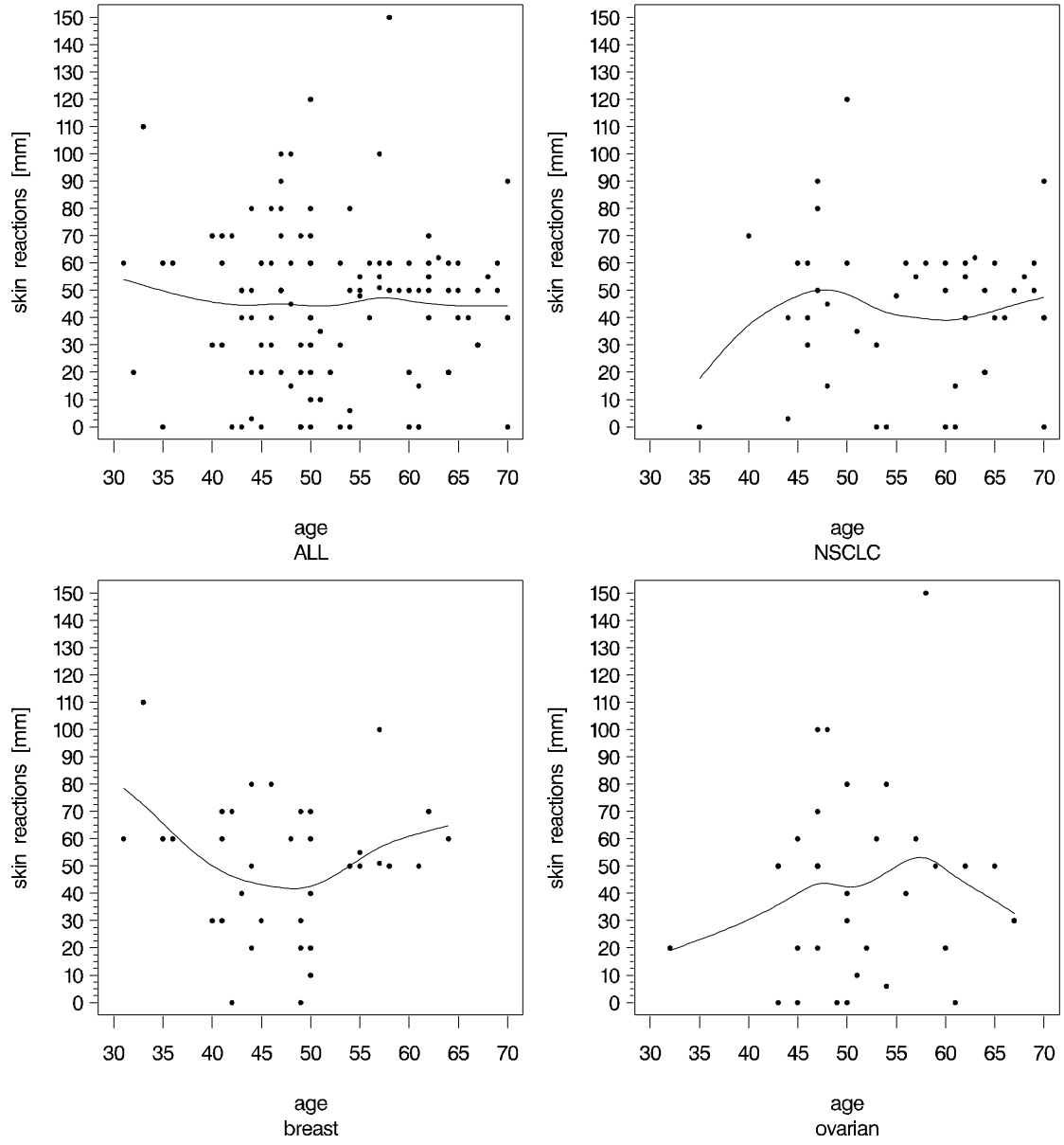


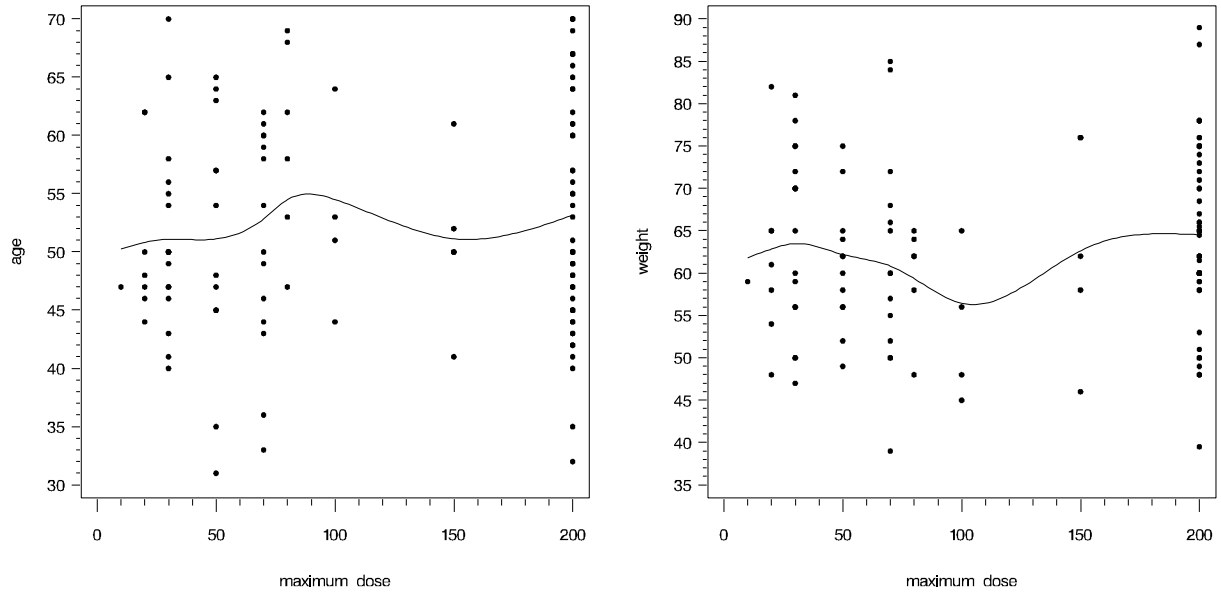
Figure 28 HELIXOR® A population - maximum of local skin reaction/age



6.3 Correlation of maximum Dosage of HELIXOR® A to Age or Weight of Patients

A possible correlation of the maximum application rate of HELIXOR® A to age or weight of patient cannot be seen from the graph illustrated in **Figure 29**. Neither the age nor the weight of patients seem to influence the maximum dose which a patient can tolerate.

Figure 29 Dependence of the maximum dose of HELIXOR® A on age and weight of patients



6.4 Immunological parameters under HELIXOR® A therapy

The immunological parameters like total lymphocytes and NK cell activity are determined at screening. This is graphically presented in correlation to the maximum dose of HELIXOR® A in **Figure 30**. The immune status of patients entering the trial does obviously not affect the tolerance towards mistletoe medication. Whether changes of immunological parameters during trial period correlate with the maximum dose of HELIXOR® A is further indicated in **Figure 31**. The graphical illustration does not support the assumption of a correlation between lymphocyte count/ NK cell count and maximum application rate of HELIXOR® A.

Figure 30 Dependence of the maximum dose of HELIXOR® A on total lymphocytes and NK cell at screening

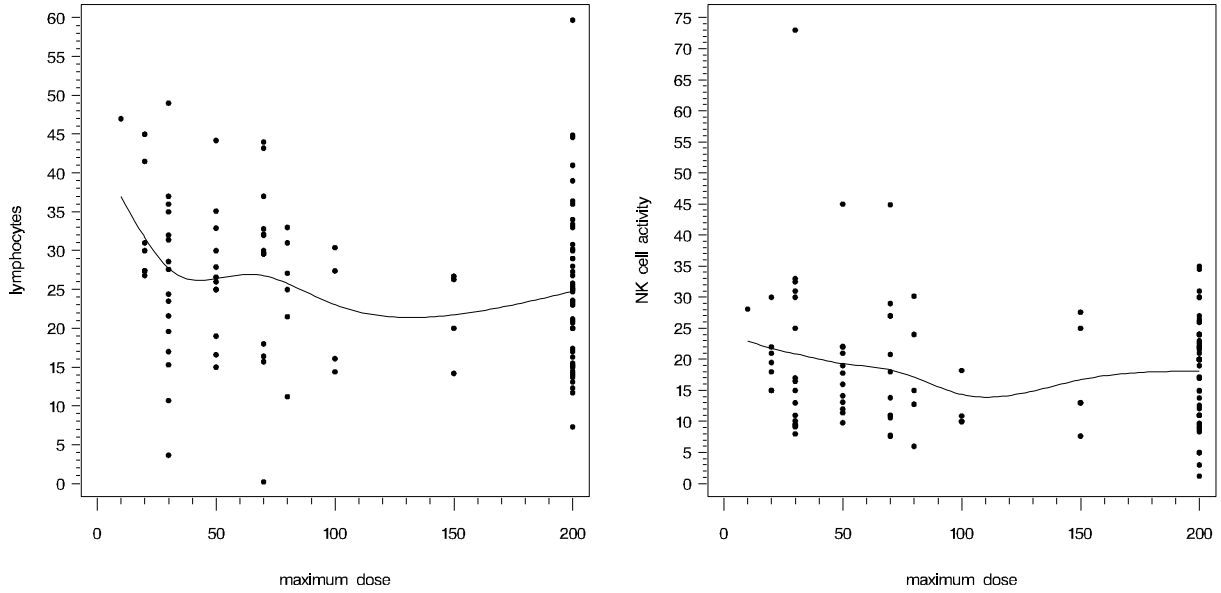
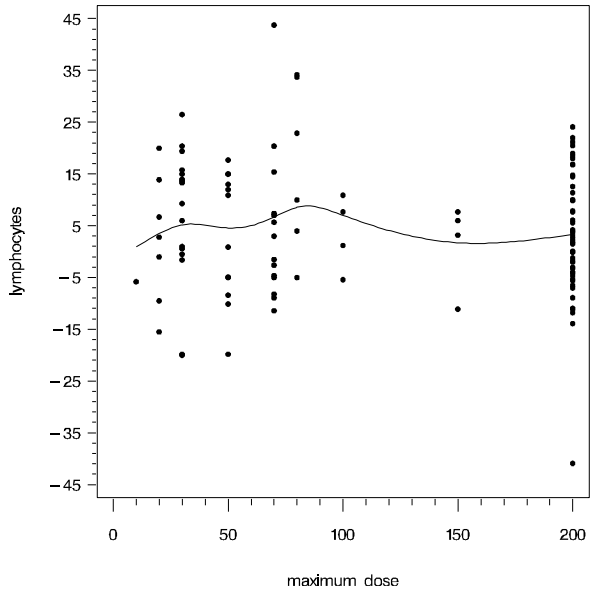
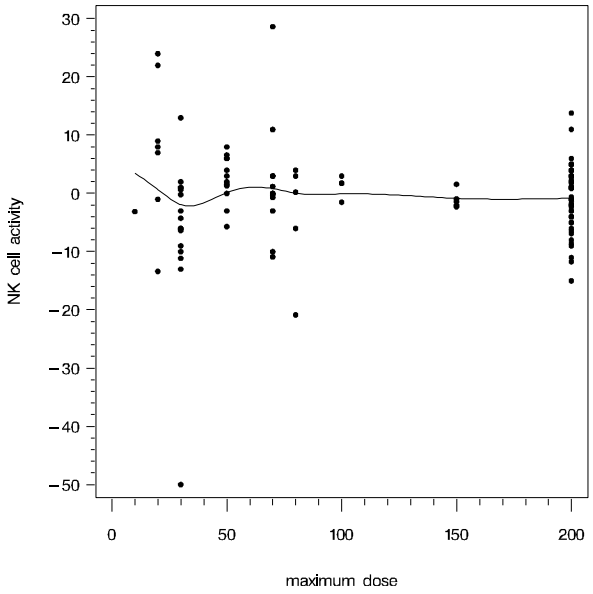


Figure 31 Dependence of the maximum dose of HELIXOR® A on changes of total lymphocytes and NK cell activity between final investigation and screening





7 Relation between Quality of Life Parameters

Before assessing agreement of the different quality of life parameters surveyed in this study one has to keep in mind the specific objective of each of the parameters. First, the Karnofsky Perfomance Index merely evaluates the physical condition of the patient and is judged by the physician. Similarly, the Traditional Chinese medicine-score or TCM-index includes the evaluation of the following physical symptoms, general fatigue, insomnia, anorexia, nausea/vomiting and pain and is assessed by a physician. In contrast, the third quality of life parameter, the Functional Living Index or FLIC-score is a questionnaire for the patients covering not only the physical state of health but also psychological and social concerns (questions developed on a western cultural background). Whether any of these parameters can be exchanged with reliability will be answered in the following agreement analysis.

Agreement is evaluated by the weighted Kappa statistics. Kappa (κ) takes values between 0 and 1 and can be interpreted as degree of agreement with the following guidelines from Altman (1991, adapted from Landis and Koch (1977), *Biometrics*, **33**, p158-74):

Value of κ	Strength of agreement
< 0.20	Poor
0.21 – 0.40	Fair
0.41 – 0.60	Moderate
0.61 – 0.80	Good
0.81 – 1.00	Very good

7.1 Relation between KPI and TCM score (excluding the item 'picture of tongue')

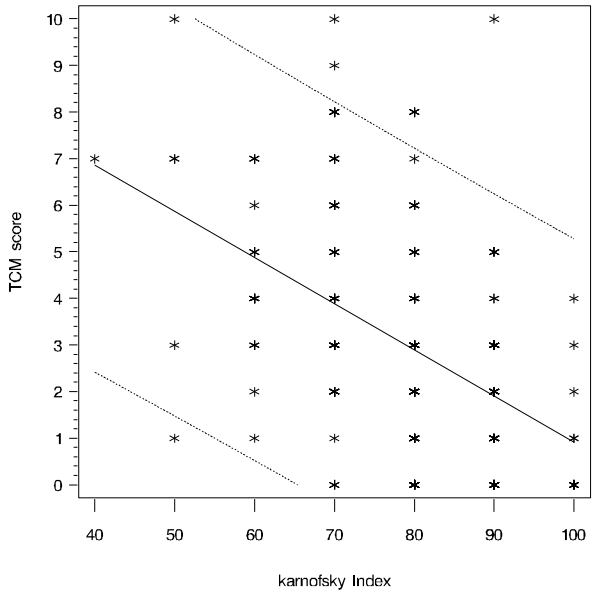
The relation between the quality of life parameter KPI and TCM is presented in **Figure 32** with regression line, confidence limits and values of linear regression parameters.

The KPI takes values from 0 to 100, while the range of the TCM is from 0 to 15. If both scales do agree in the assessment of a patient, an increase in KPI of 10 would correspond to a decrease in TCM of 15/10 = 1.5. Therefore, a perfect agreement would imply a transformation of TCM = 15 – 0.15·KPI. The regression line calculated from the data is given by TCM = 10.82 – 0.1·KPI and the 95% CI (confidence interval) of the coefficients show that the intercept as well as the regression coefficient are not in agreement with the theoretical line of reason. The 95% CI of the intercept does not contain 15 and the 95% CI of the regression coefficient is above –0.15. This implies that a change in KPI corresponds only slightly in a change in the TCM. This means it was expected a more perfect match of both scales. Furthermore a linear transformation of KPI to TCM does only include 21% of the observed variation (R^2=0.21).

Similar observations can be made in the three cancer subgroups.

Figure 32 Relation between KPI and global TCM, with regression line and confidence limits

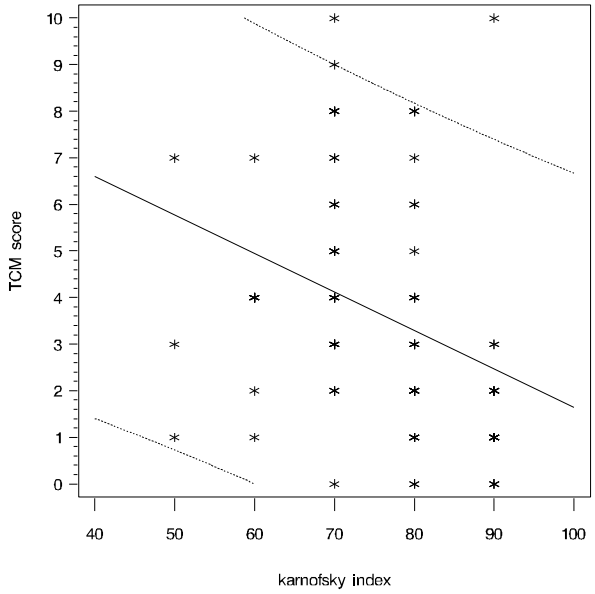
ALL:



		95%-CI
a=	10.82	8.77 ; 12.88
b=	-0.10	-0.13 ; -0.07
R^2=	0.21	

a: intercept of regression line; b: slope of regression line; R^2: square of the correlation coefficient; CI: confidence interval

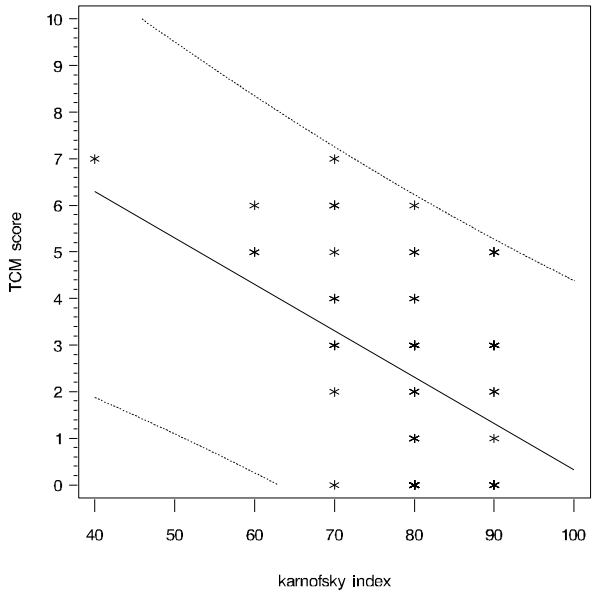
NSCLC:



		95%-CI
a=	9.90	6.08 ; 13.72
b=	-0.08	-0.13 ; -0.03
R^2=	0.11	

a: intercept of regression line; b: slope of regression line; R^2: square of the correlation coefficient; CI: confidence interval

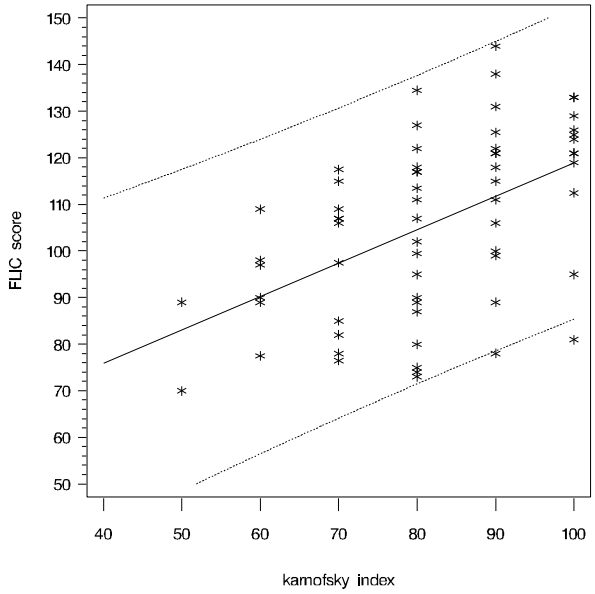
Breast cancer:



		95%-CI
a=	10.28	6.12 ; 14.44
b=	-0.10	-0.15 ; -0.05
R^2=	0.18	

a: intercept of regression line; b: slope of regression line; R^2: square of the correlation coefficient; CI: confidence interval

Ovarian cancer:



		95%-CI
a=	11.43	8.35 ; 14.52
b=	-0.10	-0.14 ; -0.07
R^2=	0.33	

a: intercept of regression line; b: slope of regression line; R^2: square of the correlation coefficient; CI: confidence interval

Agreement between the quality of life parameters Karnofsky Performance Index and global TCM is listed in **Table 139**. The degree of agreement indicates fair agreement regarding the total study population. In regard to tumor entities κ indicates moderate, poor and fair agreement for non small cell lung cancer, breast cancer and ovarian cancer, respectively. The Karnofsky Performance Index as well as the observed TCM values were each subdivided into three categories using the 33.3% and 66.6% quantile. In this case, the Kappa value indicates the agreement between KPI and TCM for patients belonging to the lower, middle or upper third of KPI and TCM.

Table 138 Agreement of Karnofsky and global TCM

		Karnofsky Performance Index							
		40-70%		80%		90-100%			
	Total TCM score	N	%	N	%	N	%	Kappa	95%-CI
ALL	**4-10**	47	21.2	25	11.3	8	3.6	0.32	0.23 ; 0.42
N=222	**2-3**	23	10.4	27	12.2	23	10.4		
	0-1	6	2.7	32	14.4	31	14.0		
NSCLC	**4-10**	29	32.6	11	12.4	1	1.1	0.42	0.27 ; 0.57
N=89	**2-3**	10	11.2	11	12.4	7	7.9		
	0-1	3	3.4	7	7.9	10	11.2		
Breast cancer	**4-10**	10	14.9	5	7.5	3	4.5	0.19	0.00 ; 0.37
N=67	**2-3**	4	6.0	10	14.9	8	11.9		
	0-1	1	1.5	20	29.9	6	9.0		
Ovarian cancer	**4-10**	8	12.1	9	13.6	4	6.1	0.27	0.09 ; 0.45
N=66	**2-3**	9	13.6	6	9.1	8	12.1		
	0-1	2	3.0	5	7.6	15	22.7		

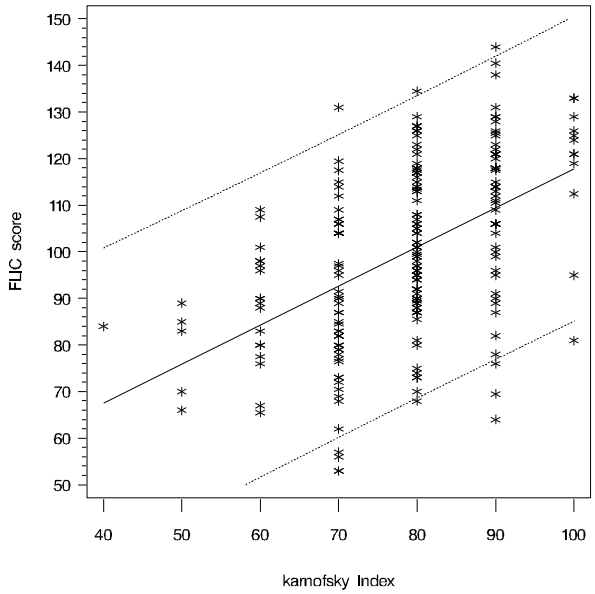
7.2 Relation between KPI and FLIC score

Relation between the life parameter KPI and global FLIC is presented in **Figure 33** with regression line, confidence limits and values of linear regression parameters.

The KPI takes values from 0 to 100, while the range of the FLIC is from 22 to 154. If both scales do agree in the assessment of a patient, an increase in KPI of 10 would correspond to an increase in FLIC score of (154-22)/10 = 13.2. Therefore, a perfect agreement would imply a transformation of FLIC = 22 + 1.32·KPI. The regression line calculated from the data is given by FLIC = 44 + 0.84·KPI. The 95% CI of the coefficients show that the intercept could be in agreement with the theoretical line of reason, however, in this way the regression coefficient is estimated as too low. The 95% CI of the intercept does contain 22 and the 95% CI of the regression coefficient is below 1.32. This implies that a change in KPI corresponds to a change in the FLIC which is less as expected from a perfect match of both scales. Furthermore a linear transformation of KPI to FLIC does only capture 25% of the variation observed (R^2=0.25).

Figure 33 Relation between KPI and global FLIC, with regression line and confidence limits

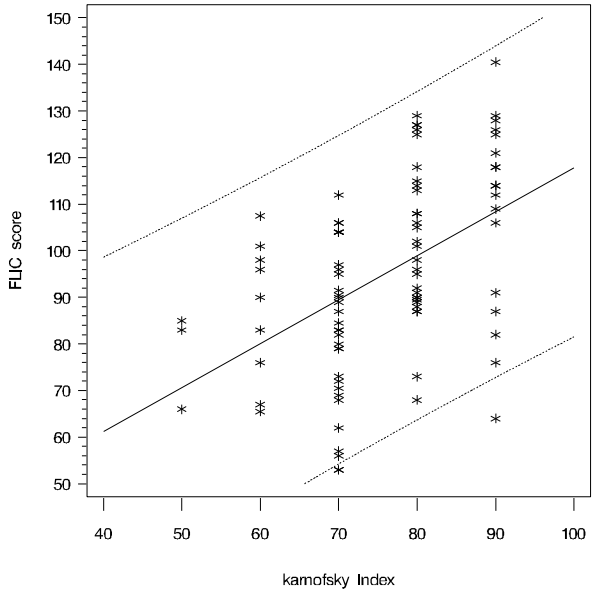
ALL:



		95%-CI
a=	33.96	18.61 ; 49.30
b=	0.84	0.64 ; 1.03
R^2=	0.25	

a: intercept of regression line; b: slope of regression line; R^2: square of the correlation coefficient; CI: confidence interval

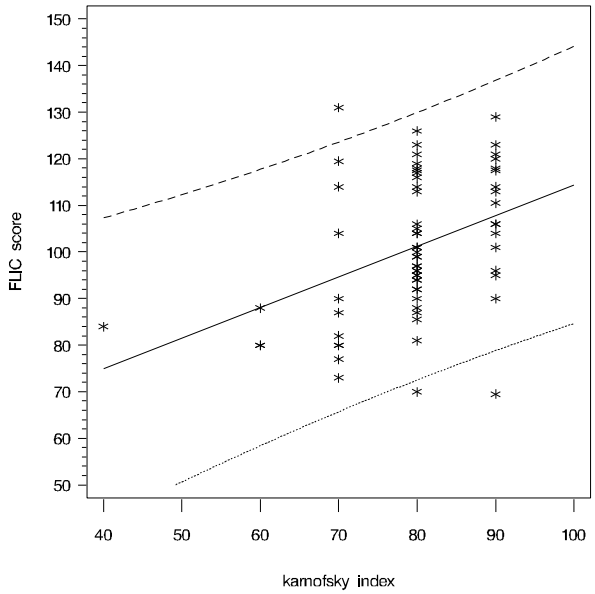
NSCLC:



		95%-CI
a=	23.41	-4.03 ; 50.84
b=	0.94	0.58 ; 1.30
R^2=	0.23	

a: intercept of regression line; b: slope of regression line; R^2: square of the correlation coefficient; CI: confidence interval

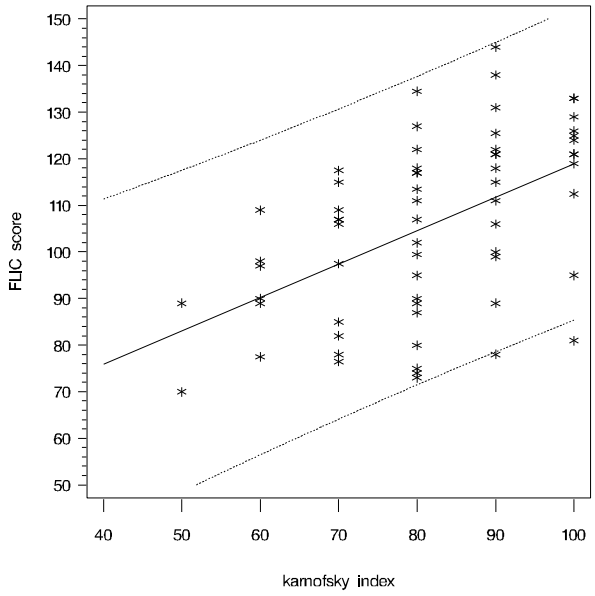
Breast cancer:



		95%-CI
a=	48.53	18.02 ; 79.04
b=	0.66	0.28 ; 1.04
R^2=	0.15	

a: intercept of regression line; b: slope of regression line; R^2: square of the correlation coefficient; CI: confidence interval

Ovarian cancer:



		95%-CI
a=	47.12	21.75 ; 72.49
b=	0.72	0.41 ; 1.03
R^2=	0.26	

a: intercept of regression line; b: slope of regression line; R^2: square of the correlation coefficient; CI: confidence interval

Agreement between the life quality parameters Karnofsky and global FLIC is evaluated in **Table 138**. Kappa κ can be interpreted using the guidelines mentioned above. The strength of agreement between Karnofsky and global FLIC is border line between fair and moderate and does not support the assumption that life quality parameters are inter-exchangeable. One should keep in mind that the FLIC score reflects physical, psychological and social items in contrast to Karnofsky's Performance Index which exclusively contains the physical state of health.

Table 139 Agreement of KPI and FLIC score for the total study population and single tumor entities

		Karnofsky Performance Index							
		40-70%		80%		90-100%			
	total FLIC score	N	%	N	%	N	%	Kappa	95%-CI
ALL	**< 90**	44	19.7	18	8.1	8	3.6	0.40	0.31 ; 0.50
N=222	**90 – 108.5**	26	11.7	38	17.0	13	5.8		
	≥ 109	8	3.6	27	12.1	41	18.4		
NSCLC	**< 90**	26	28.6	7	7.7	4	4.4	0.41	0.26 ; 0.57
N=89	**90 – 108.5**	17	18.7	13	14.3	2	2.2		
	≥ 109	1	1.1	9	9.9	12	13.2		
Breast cancer	**< 90**	10	14.9	5	7.5	1	1.5	0.38	0.19 ; 0.57
N=67	**90 – 108.5**	2	3.0	20	29.9	7	10.4		
	≥ 109	3	4.5	10	14.9	9	13.4		
Ovarian cancer	**< 90**	8	12.3	6	9.2	3	4.6	0.33	0.15 ; 0.51
N=66	**90 – 108.5**	7	10.8	5	7.7	4	6.2		
	≥ 109	4	6.2	8	12.3	20	30.8		

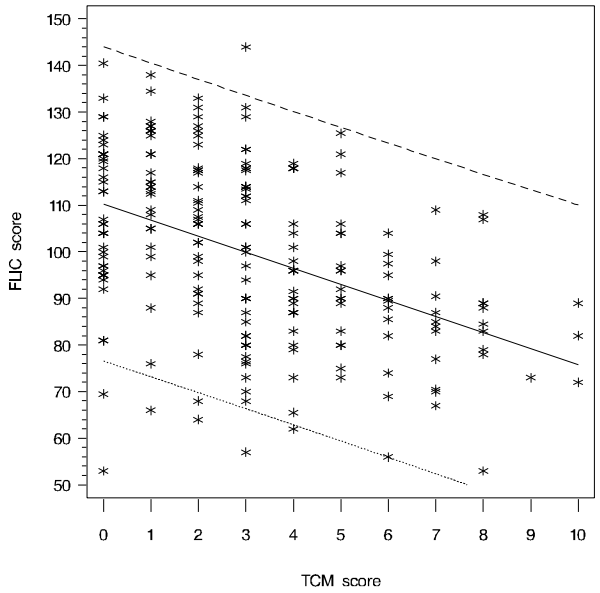
Karnofsky Index as well as the FLIC score values observed were divided using the 33.3% and 66.6% quantile. Therefore, the Kappa value studies the agreement between the judgment if a patient belongs to the lower, middle or upper third of the population observed.

7.3 Relation between TCM and FLIC score (excluding the item 'picture of tongue')

Relation between the life parameter global TCM and global FLIC score is presented in **Figure 34** with regression line, confidence limits and values of linear regression parameters. The TCM takes values from 0 to 15, while the range of the FLIC is from 22 to 154. If both scales agree in the assessment of a patient, an increase of 1 point in TCM would correspond to a decrease of the FLIC score of (154-22)/15 = 8.87. Therefore, a perfect agreement would imply a transformation of FLIC = 154 - 8.87·TCM. The regression line calculated from the data is given by FLIC = 110.3 – 3.45·KPI. The 95% CI of the coefficients show that the estimate of the intercept does not agree with the theoretical reasoning, and that the regression coefficient is estimated as too low. The 95% CI of the intercept is below 154 and the 95% CI of the regression coefficient is far above –8.87. This implies that in the given data a change in TCM corresponds to a change in the FLIC which is less as expected from a perfect match of both scales. Furthermore a linear transformation of TCM to FLIC does only capture 20% of the variation observed (R^2=0.20).

Figure 34 Relation between global TCM and global FLIC, with regression line and confidence limits

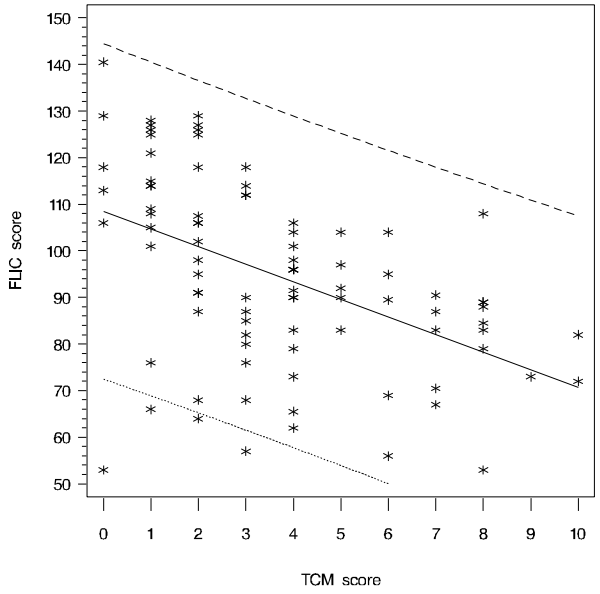
ALL:



		95%-CI
a=	110.29	106.69 ; 113.89
b=	-3.45	-4.37 ; -2.53
R^2=	0.20	

a: intercept of regression line; b: slope of regression line; R^2: square of the correlation coefficient; CI: confidence interval

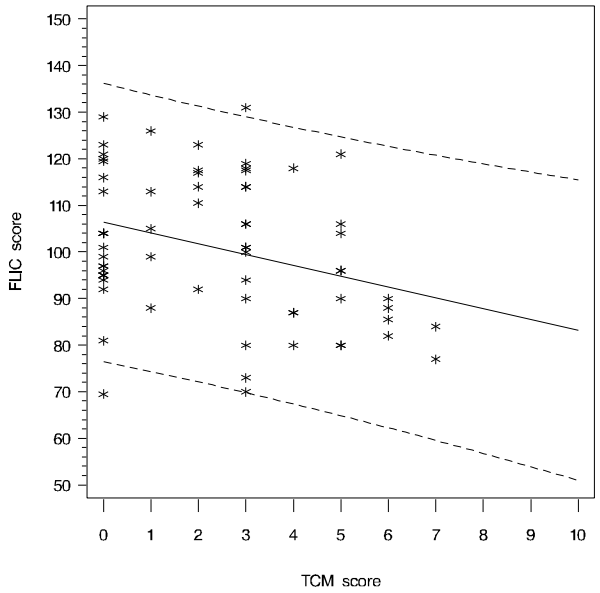
NSCLC:



		95%-CI
a=	108.46	101.92 ; 115.01
b=	-3.78	-5.25 ; -2.31
R^2=	0.23	

a: intercept of regression line; b: slope of regression line; R^2: square of the correlation coefficient; CI: confidence interval

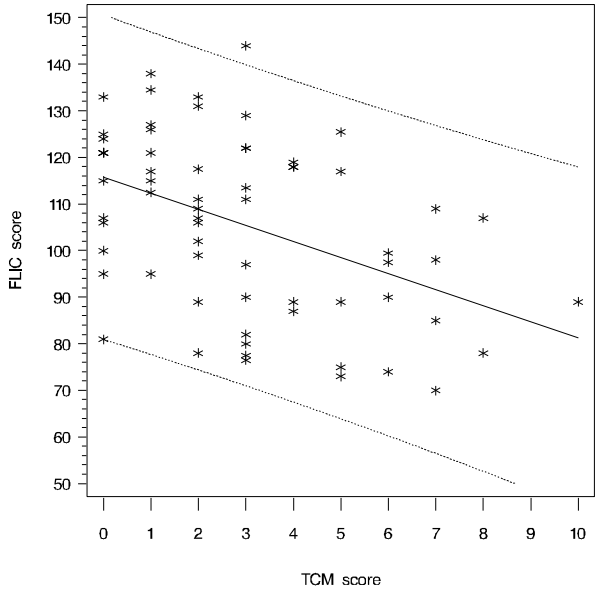
Breast cancer:



		95%-CI
a=	106.32	100.94 ; 111.70
b=	-2.31	-4.00 ; -0.62
R^2=	0.10	

a: intercept of regression line; b: slope of regression line; R^2: square of the correlation coefficient; CI: confidence interval

Ovarian cancer:



		95%-CI
a=	115.75	109.09 ; 122.41
b=	-3.44	-5.20 ; -1.69
R^2=	0.20	

a: intercept of regression line; b: slope of regression line; R^2: square of the correlation coefficient; CI: confidence interval

Agreement between the global TCM and total FLIC score is shown in **Table 140**. Kappa κ, the measure of agreement points at fair agreement for the total study population as well as for the separate tumor entities.

Table 140 Agreement of global TCM and global FLIC for the total study population and single tumor entities

		Total TCM score							
		4-10		2-3		0-1			
	total FLIC score	N	%	N	%	N	%	Kappa	95%-CI
ALL	**< 90**	43	19.5	19	8.6	7	3.2	0.32	0.23 ; 0.42
N=221	**90 – 108.5**	29	13.1	23	10.4	24	10.9		
	≥ 109	8	3.6	31	14.0	37	16.7		
NSCLC	**< 90**	23	25.8	10	11.2	3	3.4	0.38	0.23 ; 0.53
N=89	**90 – 108.5**	18	20.2	9	10.1	4	4.5		
	≥ 109	0	0.0	9	10.1	13	14.6		
Breast cancer	**< 90**	10	14.9	3	4.5	3	4.5	0.21	0.02 ; 0.40
N=67	**90 – 108.5**	6	9.0	8	11.9	15	22.4		
	≥ 109	2	3.0	11	16.4	9	13.4		
Ovarian cancer	**< 90**	10	15.4	6	9.2	1	1.5	0.31	0.13 ; 0.49
N=65	**90 – 108.5**	5	7.7	6	9.2	5	7.7		
	≥ 109	6	9.2	11	16.9	15	23.1		

TCM score as well as the FLIC score values observed were divided using the 33.3% and 66.6% quantile. Therefore, the Kappa value studies the agreement between the judgment if a patient belongs to the lower, middle or upper third of the population observed.

This is to summarize the result of the analysis regarding the agreement of different quality of life parameters. This analysis does not support the notion that the quality of life parameters do match with each other. Furthermore mentioned, the total FLIC score seems to be less suitable for this kind of testing as it reports on the overall patient's condition. The other two quality of life parameters, TCM and Karnofsky Performance Index, describe merely the physical performance and were expected to be in better accordance. However, the Kappa for total TCM score and Karnofsky Performance Index indicates only fair agreement.

8 Summary

A total of 233 patients was randomized in this study on two treatment groups: HELIXOR® A and Lentinan. Only 224 out of the 233 patients were considered in the final analysis (114 treated with HELIXOR® A, 110 treated with Lentinan), excluding patients treated with verum or control medication for less than 4 weeks. Violations against inclusion and exclusion criteria as well as violations against the trial protocol are summarized at the beginning of section 2.

The final analysis of the present report follows the *as treated* principle, that means all participants are included in the HELIXOR® A or Lentinan treatment group according to their real treatment. The statistical methods used in the final analysis are described in detail in section 1.4.

The assignment of patients according to the randomization plan resulted in comparable treatment groups. Parameters taken into consideration include sex, age, tumor characteristics and chemotherapy plan. However, the subgroup of non small cell lung cancer patients has to be considered carefully concerning the primary tumor status since patients treated with HELIXOR® A incline to have less invasive primary tumors.

Quality of life

The Karnofsky Performance Index (KPI) is analysed in the categories *reduced*, *stable* or *increased* as change over the period of treatment time. *Reduced* or *increased* signifies a change of at least 10% and is calculated as difference of the KPI at the final investigation minus KPI at screening.

The total study population shows a significant difference (p=0.003) between the HELIXOR® A and Lentinan group concerning KPI. Half of the patients in the HELIXOR® A group show an increase in the KPI in comparison to only 33% of patients under Lentinan. All three tumor entities show a higher percentage of increase in the KPI in the HELIXOR® A group. But only for the patients with non small cell lung cancer adjustment after Bonferroni-Holm provides a significant result in favour of HELIXOR® A. The results for the remaining two tumor entities show a trend in favour of HELIXOR® A.

The TCM (Traditional Chinese Medicine) index evaluates various symptoms including fatigue, insomnia, anorexia, nausea/vomiting and pain. All these symptoms are added up to a single overall TCM score.

Looking at the various symptoms of the TCM score at screening and at final investigation it is noticeable that the frequency of occurrence of the assessment *middle* and *serious* is significantly reduced in favour of *none* and *slight* in the HELIXOR® A group during the trial period. For the total study population this results in a significant difference between the HELIXOR® A and Lentinan group concerning TCM. In the HELIXOR® A treatment group there is a reduction of the overall TCM score of 1 point in median and therefore an improvement of the condition of the patients whereas in the Lentinan treatment group there was no change in median during the trial. The three tumor entities itself do not show uniform results: Patients with non small cell lung cancer have a reduction of the overall TCM score of 1 point in median in both treatment groups. Patients with breast cancer show no change in median in the HELIXOR® A group but a deterioration of 1 point in median in the Lentinan group. Patients with ovarian cancer treated by HELIXOR® A have a reduction of the overall TCM score of 1 point in median whereas patients with ovarian cancer treated by Lentinan shows no change in median. Looking at the three tumour entities separateley and adjusting for multiple testing, the difference observed in breast cancer patients is still significant, while the other two entites show a trend in favour for Helixor A.

The Functional Living Index (FLIC) consists of 22 questions grouped into physical well-being and ability (9 items), psychological well-being (6 items), hardship due to cancer (3 items), social well-being (2 items), nausea/vomiting (2 items) and pain (2 items). All these items are added up to a single overall FLIC score with a possible range from 22 to 154.

First, it should be mentioned that at time of screening the psychological well-being in patients treated with HELIXOR® A is significantly better than in the control group. The possibility of a bias introduced by this fact into the analysis is reduced by considering the difference between status at baseline and status at end of study.

In the total study population the median difference concerning FLIC final minus screening is 5.8 in the HELIXOR® A group whereas 3.5 in the Lentinan group. Therefore, in the median, patients under

HELIXOR® A have a greater increase in life quality according to the overall FLIC score. The corresponding statistical test gives a significant result (p=0.015). The difference between the two treatment groups is mainly based on differences for the subscales *physical well-being, hardship due to cancer, nausea/vomiting* and *pain*. The three tumor entities have median differences (final minus screening) as follows: Patients with non small cell lung cancer have an improvement of the overall FLIC score of 4.8 points in median in the HELIXOR® A group and of 4 points in median in the Letinan group. Patients with breast cancer show an improvement of 9.5 points in median in the HELIXOR® A group but a deterioration of 1.5 points in the Lentinan group. Patients with ovarian cancer treated by HELIXOR® A have an improvement of 4.5 points in median, treated by Lentinan an improvement of 5 points in median. After adjusting for multiple testing there was a significant result for the breast cancer patients while the results for patients with lung and ovarian cancer shows a trend.

Summarizing the results of the quality of life parameters it holds that in the total study population as well as for every tumor entity there is a higher percentage of increase of the Karnofsky Performance Index in the HELIXOR® A treatment group than in the Lentinan treatment group. The results for the overall TCM score are more complex: In the total study population and for the patients with ovarian cancer there is a reduction of the TCM score of 1 point in median in the HELIXOR® A group but no change in median in the Lentinan group. Patients with non small cell lung cancer have a reduction of 1 point in median in both treatment groups. Patients with breast cancer show no change in median in the HELIXOR® A group but a deterioration of 1 point in median in the Lentinan group. On the whole, patients under HELIXOR® A have a greater increase in the overall FLIC score than patients under Lentinan.

Body weight and body mass index

With respect to the body height and the body weight the two treatment groups seem not to be comparable. In the total study population the patients in the HELIXOR® A group are a significantly taller (p=0.039) and heavier (p=0.035).

Weight changes were assessed by an ordinal variable: reduced, stable, increased. There are no significant differences between both treatment groups with respect to the categorised weight change. However, the majority of HELIXOR® A patients (85.5%) have stable or increased weight during the trial period compared to 78% in the Lentinan group. Inspite of no clear trend (p=0.11) with respect to differences in weight change categories between both treatment groups, there is a significant difference (p=0.027) in the change of body mass index during the study with a stronger BMI increase in patients treated with HELIXOR® A. This effect was very clear for breast cancer patients (p=0.007).

Heart function, laboratory, urine and stool examination

Treatment groups of HELIXOR® A and Lentinan are comparable for heart function parameters that show only minor changes during study period .

Laboratory parameters evaluated include basic blood count, immunological and liver/kidney parameters.
For the total study population all basic blood count parameters under observation are comparable in the verum and the control group. The subgroup analysis within the three tumor entites als shows no significant differences in blood count and immunological parameters when adjusted for multiple testing. For the total study population major differences in liver and kidney parameters between the two treatment groups cannot be observed.

Efficacy

The evaluation criteria for chemotherapy (remission rate) contains five categories CR (complete remission), PR (partial remission), MR (minor remission), SD (stable disease) and PD (progressive disease). There is no significant difference between both treatment groups with respect to tumour response (p=0.974).

In a second step tumor response was dichotomised: A responder was defined as a patient with CR or PR as tumor response at final investigation, a non-responder with MR, SD or PD at final investigation.
A multivariate logistic regression was used to estimate the treatment effect (by adjusting for center and tumor entity). The analysis showed a center effect: Beijing, Shenyang being different to Tianjin with respect to the treatment effect. The adjusted treatment effect in the center Shenyang (odds ratio for being responder under HELIXOR® A versus Lentinan 0.612 with 95% confidence limits 0.284 to 1.321) and the adjusted treatment effect in the centers Beijing and Tianjin are different (odds ratio of being responder under HELIXOR® A versus Lentinan 1.739 with 95% confidence limits 0.721 to 4.195).

Safety

The total number of adverse events and serious adverse events in patients treated with HELIXOR® A is 52 (non small cell lung cancer: 30, breast cancer: 10, ovarian cancer: 12), in Lentinan 90 (non small cell lung cancer: 18, breast cancer: 22, ovarian cancer: 50) out of the total study population.

9 ITT Analysis

The *ITT population* differs from the *as treated* population by one patient. The following chapter contains the results of the ITT analysis as well as a short discussion.

9.1 Results

The Karnofsky Performance Index (KPI) evaluates physical conditions of patients and classifies them as reduced, stable or increased. In total 223 patients could be evaluated (sME group n = 115; control group n = 108) (Tables I and IV). As shown in Table IV, patients complementarily treated with sME presented an increased KPI in 50.4 % (32.4 % in the control group) and a reduced KPI in 3.5 % (11.1 % in the control group; Table IV). The KPI improvement of the study group was statistically significant as compared to the control group (p=0.002).

According to TCM, various symptoms were evaluated by scoring. As shown in Table I and VI a total of 220 patients could be evaluated (sME group n = 113; control group n = 107). Concerning nausea, fatigue, insomnia, anorexia (Table V) more patients improved and fewer patients deteriorated in the study group as compared to the control group (Table V). However, the difference in the overall TCM score between the beginning and termination of the tumor-destructive chemotherapy demonstrates a statistically significant improvement of the quality of life in the sME study group (p=0.0007) as compared to the control group (Table VI). The TCM score consists of the sum of five symptoms; each symptom is quantified with four levels reaching from 0 to 3 and a higher level expresses higher severity in the symptom. Therefore, an improvement in TCM comparing baseline and final examination results in a negative number. A change of –1 describes an improvement by one level in the total TCM score and may be interpreted as the improvement in one single symptom of one level while no change in severity happens in the three remaining symptoms.

As shown in Table I and VII, a total of 222 patients could be evaluated (sME group n = 115; control group n = 107) for the global FLIC score. The global FLIC score demonstrated a significant improvement (p=0.0141) of QoL for patients of the sME study group as compared to those of the control group (TableVII).

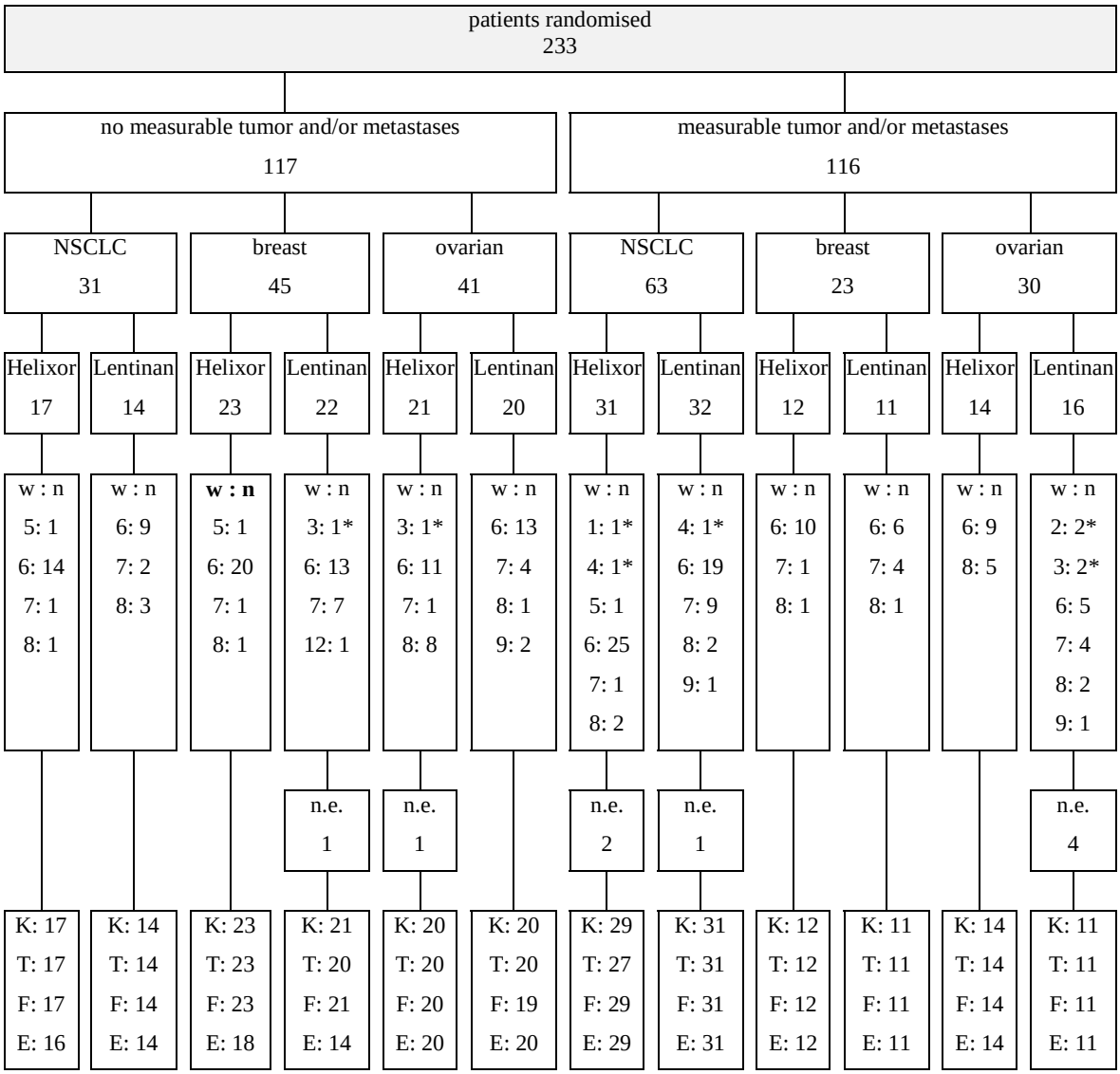
The total number of adverse events (AEs) was 52 in the sME study group and 90 in the Lentinan control group (serious AEs: 6 versus 10). Chemotherapy related AEs were 28 for the sME and 77 for the Lentinan group. Each symptom of an adverse event was classified as one AE, for example nausea and vomiting following standard chemotherapy were registrated as two AEs, despite being pathogenetically closely related. If all simultaneously occurring and closely related symptoms were registrated as one patient-related AE, the total number of AEs and SAEs would drop down from 52 to 32 for the study group and from 90 to 59 for the control group, respectively. However, the relationship of AEs and SAEs between study and control group would be unchanged.

In the verum as well as in the control group only one serious AE was allocated to complementary treatment on account of hospitalization. In the study group one patient responded to the sME application with angioedema and urticaria. After discontinuation of the sME administration and anti-allergic treatment the patient recovered from angioedema within 2 days, however, skin reactions remained for about 7 days. All other side-effects of sME (fever in 4 patients, rubor/pruritus at the injection site in 7 patients) were harmless, self-limiting and did not warrant therapeutical intervention. Also in the control group one serious AE occurred which was allocated

to the phytopharmacon Lentinan. All other cases of serious AEs were allocated to chemotherapy or to the basic disease.

9.2 Tables

Table I: Patient flow chart: Number of patients with corresponding treatment and evaluation scheme



- Treatment scheme described in weeks (w:n): w = duration of medication in weeks : n = number of patients treated
- * patients with ≤ 4 weeks of treatment n.e.: number of not evaluated patients
- Number of patients, evaluated by: K: Karnofsky Index; T: TCM; F: FLIC; E: tumor evaluation

Table II: Total study population - Comparison of sex and tumor characteristics in treatment groups

ALL		Helixor N=118		Lentinan N=115		total N=233		p-value
		N	%	N	%	N	%	
center	Beijing	22	18.6	24	20.9	46	19.7	0.709
	Shenyang	64	54.2	65	56.5	129	55.4	
	Tianjin	32	27.1	26	22.6	58	24.9	
sex	male	27	22.9	24	20.9	51	21.9	0.753
	female	91	77.1	91	79.1	182	78.1	
pT	1	10	8.5	16	13.9	26	11.2	0.121
	2	46	39.0	31	27.0	77	33.0	
	3	36	30.5	31	27.0	67	28.8	
	4	19	16.1	23	20.0	42	18.0	
	X	7	5.9	14	12.2	21	9.0	
pN	0	51	43.2	43	37.4	94	40.3	0.325
	1	19	16.1	18	15.7	37	15.9	
	2	33	28.0	27	23.5	60	25.8	
	3	9	7.6	16	13.9	25	10.7	
	X	6	5.1	11	9.6	17	7.3	
M	0	73	61.9	75	65.2	148	63.5	0.683
	1	45	38.1	40	34.8	85	36.5	

Table III: Total study population – demographic characteristics and general anamnesis

ALL	GROUP	N	NMISS	MEAN	SDEV	MIN	Q1	MEDIAN	Q3	MAX	P-VALUE
age	Helixor	118	0	52.6	9.4	31.0	46.0	50.0	61.0	70.0	0.618
	Lentinan	115	0	51.7	10.1	25.0	45.0	51.0	59.0	70.0	
	total	233	0	52.2	9.7	25.0	45.0	51.0	60.0	70.0	
weight	Helixor	118	0	63.0	10.6	39.0	56.0	62.0	70.0	92.0	0.030
	Lentinan	115	0	60.8	10.3	42.0	54.0	59.0	65.0	100.0	
	total	233	0	61.9	10.5	39.0	55.0	60.0	67.0	100.0	
body mass index	Helixor	118	0	23.7	3.4	15.8	21.0	23.4	26.4	33.0	0.457
	Lentinan	115	0	23.3	3.3	16.5	20.8	22.9	25.5	32.0	
	total	233	0	23.5	3.4	15.8	20.8	23.4	25.8	33.0	

Table IV: Total study population – Karnofsky Performance Index evaluated as reduced, stable and increased

ALL		**Helixor N=115**		**Lentinan N=108**		**Total N=223**		**strat. p-value**
		N	%	N	%	N	%	
KPI	Reduced	4	3.5	12	11.1	16	7.2	0.002
	Stable	53	46.1	61	56.5	114	51.1	
	Increased	58	50.4	35	32.4	93	41.7	

Table V: Total study population – comparison of scores for each TCM symptom

TCM Criteria	Missing value		Remarkable improvement		Improvement		Deterioration		Stable	
	HELIXOR N	Lentinan N	HELIXOR N / %	Lentinan N / %	HELIXOR N / %	Lentinan N / %	HELIXOR N / %	Lentinan N / %	HELIXOR N / %	Lentinan N / %
General	0	1	7 (6,1 %)	2 (1,8 %)	37 (32,5 %)	30 (27,5 %)	6 (5,3 %)	17 (15,6 %)	65 (56,1 %)	61 (55,0 %)
Insomnia	0	2	11 (9,6 %)	2 (1,9 %)	21 (18,4 %)	18 (16,7 %)	4 (2,6 %)	9 (9,3 %)	79 (69,3 %)	78 (72,2 %)
Anorexia	1	1	10 (8,8 %)	4 (3,7 %)	31 (27,4 %)	19 (17,4 %)	12 (10,6 %)	27 (24,8 %)	61 (53,1 %)	58 (54,1 %)
Nausea	0	1	2 (1,8 %)	0 (0 %)	18 (15,8 %)	6 (5,5 %)	14 (11,4 %)	28 (26,6 %)	81 (71,1 %)	74 (67,9 %)
Pain	1	1	5 (4,4 %)	19 (17,4 %)	18 15,9 %)	5 (4,6 %)	3 (2,7 %)	8 (7,3 %)	88 (77,0 %)	76 (70,6 %)

Remarkable improvement means improvement in at least two steps: from „middle“ to „none“, from „serious“ to „slight“ or „none“.
Improvement means improvement in one step: from „slight“ to none, from „middle“ to „slight“, from „serious“ to „middle“.

Table VI: Total study population – difference of TCM total score between screening and final investigation

ALL	GROUP	N	NMISS	MEAN	SDEV	MIN	MEDIAN	MAX	strat. p-value
TCM score	Helixor	113	2	-1.3	2.4	-8.0	-1.0	5.0	0.0007
	Lentinan	107	2	-0.2	2.3	-6.0	0.0	6.0	
	total	220	4	-0.8	2.5	-8.0	0.0	6.0	

Table VII: Total study population – difference of FLIC between screening and final investigation

ALL	GROUP	N	NMISS	MEAN	SDEV	MIN	MEDIAN	MAX	strat.p-value
FLIC score	Helixor	115	0	9.0	16.6	-32.0	6.0	56.0	0.0141
	Lentinan	107	2	4.7	17.5	-32.0	3.0	89.0	
	Total	222	2	6.9	17.1	-32.0	4.5	89.0	

10 References

Conover W.J. (1980). Practical non-parametric statistics. Wiley&Sons, New York.

Altman D.G. (1991). Practical statistics for medical research. Chapman&Hall, London.

11 Listings

Listings of individual patient data are stored on attached CD-ROM.