

Tab. 2. Summary of clinical trials with mistletoe therapy - listed according to different preparations

Reference	Type of study	Diagnosis / therapeutic indication	Patients included n / analysed (n)	Treatment	Results	Statistics	AE / side-effects	Notes
Eurixor (EUR)								
<i>RCT / CT</i>								
Goebell et al. 2002(62)	prospective, randomised, ctrl Phase II (3 years)	superficial bladder ca, relapse prophylaxis after transurethral resection (pTa stage 1-2) (adjuvant mistletoe therapy)	n = 45 (44) total n = 23 (23) EUR n = 22 (21) Ctrl (after 3 mo n = 21 due to 1 death) duration: 3 mo EUR, 3 mo break EUR, then 2nd cycle	EUR: 1 ml EUR 2/wk s.c. for 3 months (= 1st cycle, 3 mo break, then 2nd cycle) Ctrl: untreated	1) relapse-free interval EUR: 6.4 mo, ctrl: 6.3 mo 2) additional: relapses after 18 mo: EUR: 31 vs Ctrl: 30 disease-free survival: EUR: 9 mo, Ctrl: 10.5 mo	no statistical comparison	EUR: none observed Ctrl: 1 death not related to disease or therapy	no data on: study location, study period, ITT/PP, target parameters, preparation name (ascertained indirectly), dropouts
Steuer-Vogt et al. 2001(72)	prospective, randomised, ctrl, multi-ctr, phase III A: 1993-1996 B: 1993-1997	head and neck ca: (T1-T4, N0-N3) (adjuvant mistletoe therapy)	n = 588 total n = 495 randomised (477) A: n = 202 Ctrl: n = 104/105 EUR: n = 97 B: n = 275 Ctrl: n = 137 EUR: n = 138 ITT: n = 477 PP: n = 364 duration: 60 wks	A: Ctrl: Op (tumour resection or unilateral or bilateral neck dissection) EUR: OP + EUR B: Ctrl: OP + RTX (50-75 Gy) EUR: OP+ RTX (see above) + EUR (1 ng ML-1/kg BW, 2/wk s.c. for 60 wks, in intervals of 12 wks EUR and 4 wks pause)	1) disease-free survival (5 y): ITT: hazard ratio 0.96 (95% CI: 0.73-1.27; 200/477 = 42% relapse after 4 y) PP: 0.88 (95% CI 0.63-1.21) 2) disease-spec. survival (5 y): PP: 0.96 (95% CI 0.66-1.38) additional Information: immune parameters (n = 230): CD3+, CD4+, CD8+, CD19+, CD16+56+3+ Quality of life (n = 443): (EORTC-QLQ-C30)*	n.s. n.s. n.s. n.s. n.s.	local or systemic side effects with start of the EUR injection: A: n = 47 (initially 48%; after 32 wk 1-4%) B: n = 54 (initially 39%; after 32 wk 4-8%) most common ADR: redness: A: n = 44 (initially 45%; after 32 wk 1-4%) B: n = 54 (of 39%; to 1-5%) pruritis: A: n = 29 (initially 30%; after 32 wk 1-3%) B: n = 41 (from 30% to 3-7%) Induration: A: n = 6 (initially 6%; after ≥22 wk 1-5%) B: n = 11 (of 8%; to 1-5%) general drug reactions: myalgia, fever, insomnia, fatigue, feeling cold/hot, sneezing 1-4% EUR injections discontinued due to ADR: A: n = 16 (16%)	dropouts: 18 (unclear: A: Ctrl (n = 104/105) protocol violations during the first treatment n = 48 ethics committee rejected blinding due to frequent local reactions under EUR

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							B: n = 27 (20%)	
Heiny et al. 1998(64)	prospective, randomised, matched-pair	advanced metastasised colorectal ca (adjuvant mistletoe therapy with CTX)	n = 107 (79) total n = 41 Ctrl (= A) n = 38 EUR (= B) duration: 8 wks therapy + 4 wks break (repeated multiple times until 42nd wks)	Ctrl: CTX (5-FU 600 mg/m ² 5/wk + folic acid 200 mg/m ² 5/wk i.v.) EUR: CTX (see above) + EUR (0.5-1 ng ML-I/kg BW 2/wk s.c.)	1) QoL (FACT scale, sum score): EUR better than Ctrl (from 12th to 42nd wk = end of study) 2) additional information: survival time: EUR: 52.8 wk vs Ctrl: 50 wk duration of remission: EUR 23.1 wk vs Ctrl 21.4 wk progression-free interval: EUR 30.8 wk vs Ctrl 31.2 wk	p = 0.0001 n.s. n.s. n.s.	total side effects in % (n = 79): nausea, vomiting: III WHO n.s., EUR 14.4, Ctrl 16.1; diarrhoea: n.s., EUR 25 Ctrl 29; hand-foot syndrome: n.s., EUR 0, Ctrl 3.2; breast pain: n.s. EUR 3.6, Ctrl 4.5; mucositis III: frequency with EUR 17.9 vs Ctrl 25.8, p = 0.03 (duration in d shorter with EUR 12.3 vs Ctrl 16.8, P = 0.03) ⁸ ; leukopenia: p = 0.01, EUR 32.1 vs Ctrl 38.7;; thrombopenia: n.s., EUR 10.7 Ctrl 12.9	dropouts: 28 (reason: did not meet analysis criteria) no data on: decision of ethics committee, informed consent, study location/time, ITT/PP unclear: target parameters except for QoL
Lenartz D et al. 2000(81)	follow-up to Lenartz 1996	malignant glioma	n = 38 total n = 20 (20) EUR n = 18 (18) Ctrl duration: 50 mo follow-up	see below	1) Survival time: total: EUR 21.7 ± 3.7 mo vs Ctrl 17.3 ± 3.9 mo stratified (grade III-IV): longer with EUR 20.05 ± 3.5 mo vs Ctrl 9.9 ± 2.1 mo 2) relapse-free: total: EUR: 14.41 ± 2.7 mo vs Ctrl 14.76 ± 3.6 mo stratified (grade III-IV): trend for EUR 17.43 ± 8.2 mo vs Ctrl 10.45 ± 3.9 mo (relapse rate after 1 y: for both groups 50%)	n.s. p = 0.035 n.s. n.s.	no data	9 dropouts: see below no data on: 3 more patients, change in tumour grade, stratification, decision of ethics committee, informed consent, study location/time, ITT/PP, Kaplan-Meier survival curve in a pilot study
Lenartz D et al. 1996(65)	prospective, randomised (Pilot study 1994-95)	malignant glioma grade III/IV (immunomodulating mistletoe therapy for neo-adjuvant CTX)	n = 35 (26) total n = 18 (13) EUR n = 17 (13) Ctrl duration: 3 mo therapy + 3 mo follow-up	Ctrl: OP + perioperative DX (24 mg/d) + RTX (total 60 Gy) EUR: OP + DX + RTX (see above) + EUR (from 1st d post-OP 1 ng ML-I/kg BW 2/wk s.c.)	1) Immune parameters: increase in CD-3 ⁺ , CD-4 ⁺ , CD-8 ⁺ , CD-25 ⁺ T-lymphocytes after 3 mo with EUR compared to pre-OP 2) QoL (Spitzer index): trend: improvement with EUR	p < 0.05 n.s.	no data	9 dropouts: (reason: insufficient therapy and diagnosis schedule) no data on: decision of ethics committee, informed consent, study location/time, ITT/PP
Heiny	prospective,	advanced breast	n = 46 (40) total	Ctrl:	1) Blood count:		EUR:	dropouts:

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1991(82)	randomised, pl-ctrl	ca (additive mistletoe therapy with palliative CTX)	n = 21 (19) Ctrl n = 25 (21) EUR duration: 6 intervals interrupted by 28-d pause	CTX (VEC - 3, 40, 750 mg/m ² ; 6 cycles with 28-day break each) + pl (NaCl per infusion) + ondansetron (3 x 8 mg/d for 5 d) EUR: CTX + EUR i.v., (1st, 2nd, 4th, 5th d each 1 ng ML-1/kg BW per infusion in NaCl; then 1-2/Wo s.c.) + ondansetron (see above)	recovery leukocytes from 2nd CTX cycle to approx. 2,800 with EUR; thrombocytes: 2) Mental state index, anxiety index (each sum score): improved mental state index with EUR (after 6th cycle); decreased anxiety with EUR (after 3rd cycle)	p ≤ 0.001 n.s. p ≤ 0.01 p ≤ 0.01	granulocytosis (up to 24 h after EUR) and elevated CRP (80% of the patients) moderate fever and flu-like symptoms (e.g. joint pain, chills, abnormal fatigue 13/21 patients) (for skin reaction over 5 cm dose reduced to 1/wk)	6 after the 1st cycle (= 4 EUR, 2 Ctrl, reason: Tumour progression = dropout criterion) additional motivation of the patients in interviews pre-testing for allergy to EUR no data on: decision of ethics committee, informed consent, study location/time, ITT/PP
<i>Cohort studies (retrolective studies)</i>								
Schumacher et al. 2003(83)	retrolective, ctrl	primary, not metastasised breast ca	n = 1248 (689) n = 470 Ctrl n = 219 EUR	Ctrl: standard (surgery, chemo-, radio-, hormone therapy) EUR: EUR (2 x 1 mL/wk) + standard (see above) duration: EUR = 270 d follow-up: EUR = 284 d (median) Ctrl = 285 d (median)	1) Change of disease/therapy related symptom score at start and end postoperative treatment: improvement except for dyspnoe at work, headache 2) KPI: Ctrl = minus 7.5% ; EUR = plus 8.2% 3) relapses: EUR = 6 (2.78%) vs Ctrl = 24 (5.22%) 4) relapse-free time: EUR vs Ctrl (HR after multivariate adjustment)	OR = 0.7133 (CI: 0.65–0.77, p = 0.0001) no data no data p = 0.0053 (HR: 0.28, CI: 0.1–0.76, p = 0.012)	EUR-related: n = 28 (12.8%)	randomisation limited to selection of centres n = 559 excluded due to protocol violations no data on: ITT/PP according to authors, the observation period relativises the statement on relapses
Helixor (HEL)								
<i>RCT</i>								
Piao et al. 2004(70)	Prospective, multi-ctr., randomised, open, comparative study 3 centres in	breast, ovarian, non-small cell lung cancer (breast cancer n = 68 ovarian cancer n = 71)	n = 233 total (224) n = 118 (115) HEL n = 115 (109) Ctrl duration:	HEL: CTX + HEL A, 3/wk s.c. starting with 1 mg to 200 mg Ctrl CTX + lentinan 4 mg/d	1) KPI (n = 223): increase HEL (n = 115) 50.4 % vs Ctrl (n = 108) (30.4 %) 2) TCM (sum score) (n = 220): decrease = improvement with HEL (n = 113) -1 point vs Ctrl (n = 107) 0 points	(stratified) p = 0.002 (stratified) p = 0.0007	AE total: HEL 52 vs Ctrl 90 (each symptom), related to CTX: HEL 28 vs Ctrl 77	dropouts: no data excluded: 9 patients (reason: no measured data, treated ≤ 4 weeks)

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	China 2000-2001	non-small cell lung cancer n = 94)	HEL 1-8 wks Ctrl 2-12 wks	i.m. (CTX: breast cancer: adriamycin, cisplatin, cyclophosphamide, 5-FU ovarian cancer: carboplatin, cisplatin, cyclophosphamide, ifosfamid non-small cell lung cancer: cisplatin, mitomycin, vindesin, vinorelbine)	3) FLIC (n = 222): improvement with HEL (n = 115) 6 points vs Ctrl (n = =107) 3 points	(stratified) p = 0.014	SAE: HEL 5 (1 HEL-related angioedema/urticaria - improvement after 2 d) vs Ctrl 10 (1 lentinan- related) related to CTX: HEL 2 vs Ctrl 4 side effects HEL: 4 x fever, 7 x redness, pruritis at the injection site (no withdrawl)	no data on: CTX dose, study location, validation of the TCM index, PP usual dosage for lentinan: 0.4– 4 mg/wk instead of 4 mg/d
Douwes et al. 1986(84)	prospective, randomised	metastasised colorectal ca (effect of biological response modifiers on duration of remission and QoL)	n = 60 total n = 20 Ctrl (= A) n = 20 HEL (= B) n = 20 Ney (= C) duration: no data	Ctrl: CTX (570 mg/m ² 5-FU + 200 mg/m ² folic acid i.v., 1st-5th d, repeat after 5 d, 5-16 cycles) HEL: CTX (see above) + HEL (increasing dose up to 200-300 mg daily, s.c.) Ney: CTX (see above) + Ney (increasing dose to 30 mg 2/wk i.v. or s.c.)	1) Remission: A: 12/20 (60%) 3 CR, 6 PR, 3 MC vs B: 13/20 (65%) 3 CR, 7 PR, 3 MC vs C: 13/20 (55%) 3 CR, 5 PR, 5 MC 2) mean survival time (CR, PR, NC = responders): A: 13.6 ±4.4 mo vs B: 26.7 ±11.9 mo vs C: 23.7 ±9.6 mo	n.s. no stat. analysis	CTX – side effects: stomatitis, diarrhoea, thrombopenia – more common in A than B and C (no more specific data), alopecia Most common side effect: nausea no withdrawal due to SAE	uncertainties: patient figures (MC/NC), % figures, dosage HEL, target parameter, results no data on: decision of ethics committee, informed consent, study location/time, randomisation ITT/PP, stratification previous CTX: 2-4 pat. in each group before ≥3 mo
Iscador (ISC)								
<i>RCT / CT</i>								
Kleeberg et al. 2004(57)	prospective, randomised, ctrl (phase III) (EORTC 18871; DKG 80-1) (1988-1996)	primary melanoma stage II (Breslow thickness >3 mm) + stage III (curative dissection of regional lymph node metastases) (adjuvant mistletoe therapy	n = 830 (793) total EORTC n = 139 rIFN-α2 n = 142 rIFN-γ n = 142 Ctrl DKG n = 101 rIFN-α2 n = 102 rIFN-γ n = 102 Ctrl	rIFN-α2b: OP (resection pr. melanoma or curative dissection) + IF (1 MU s.c. every other d for 1 y) r IFN-γ: OP (see above) + IF (0.2 mg s.c. q.o.d. for 1 y) ISC:	1) disease-free interval (DFI): IFN α and also γ vs Ctrl ISC vs Ctrl 2) survival time: each treatment group vs Ctrl	n.s. (p = 0.77) n.s. (p = 0.12) n.s.	minor side effects: rIFN approx. 1/3 of the patients (fever, chills, night sweats, fatigue, muscle pain, joint pain, headache) grade 3-4 toxicity acc. to WHO and treatment discontinuation: rIFN-α2: 11/240 patients	dropouts: no explicit info ineligible: 37/830 (4.6%) eligibility not assessable: 13/830 (1.6 %) due to insufficient documentation

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	45 centres in 13 countries	after curative OP)	n = 102 ISC duration: 1 y or until tumour progression; follow-up 8 yrs	OP + ISC-M (0, then 0.01 until 1 mg/mL q.o.d. for 2/wk, 3-d break, repeat until 14 doses 20 mg/ml, 7 d break)			(4.6%) rIFN- γ : 19/244 patients (7.8%) ISC: 5/102 patients (4.9%) (e.g. due to anorexia, general malaise, depression, fever, local skin inflammation at the injection site)	no data on: decision of ethics committee, informed consent, PP somewhat unclear: study design, patient numbers, data presentation, ITT, ISC dose randomisation for ISC discontinued after 8-year recruitment phase
Dold et al. 1991(63)	prospective, randomised, multi ctr., pl-ctrl, 3-arm (stratification acc. to clinic and TNM)	advanced inoperable non-small cell bronchial ca stage Ia-IV (T1 N0 M0 to T3 N1-2 M1) (adjuvant therapy)	n = 408 total (337) n = 114 ISC n = 110 Polyerga n = 113 pl duration: 1978-1987	ISC: Qu c. Hg or U c. Hg (1 ml 0.001-30 mg active substance - increasing dose 3/wk s.c.) Polyerga: 1 ml (with 30 μ g glucopeptides 1/wk i.m.) Ctrl: (Vit. B complex 2 ml 1/wk i.m.)	1) median survival time (312/337): ISC 9.1 mo vs Polyerga: 9.0 mo or vs Ctrl: 7.6 mo 2) tumour response 3) subjective well-being (301/337): improvement with ISC 59% vs Ctrl 45% (Polyerga 43%) 4) QoL (physical complaints)	n.s. n.s. p = 0.018 n.s.		dropouts: 71 justified study end: due to discontinuation of therapy n = 32/337; due to death 221/337
Toelg et al. 2005(85)	prospective, non-randomised, ctrl, post-marketing surveillance	gynaecological tumours after resection	n = 128 n = 107 (ITT) n = 53 lsc n = 54 Ctrl duration: 6 mo	lsc: lsc (lscador M) + CTX Ctrl: CTX	1) overall health (lsc:Ctrl in %): worsened = 23:20 stabilised = 26:43 improved = 51:37 2) mental condition: ISC = + 16.7% Ctrl = + 7.0% 3) QoL: ISC = + 17% Ctrl = + 33%	n/a	ISC: n = 7 (11%) (fever, redness at the injection site)	dropouts: n = 5 lsc n = 5 Ctrl died: n = 6 lsc n = 5 Ctrl baseline: Ctrl = ovarian ca 4 x more often ADR: ISC imprecise data; Ctrl no data
<i>Cohort studies (retrolective studies)</i>								
Augustin et al. 2005(73)	multicentre retrolective, ctrl, epidemiologic	resected primary malignant melanoma UICC/AJCC	N = 783 (686 PP) n = 329 ISC n = 357 Ctrl	ISC: OP + ISC (P, M or Q; s.c. 2-3/wk, \geq 3 mo) + chemo- (10%), radio- (7.9%),	1) tumor-related survival: ISC = 8.9% vs Ctrl = 10.7% [adjusted: HR 0.41 (0.23 - 0.71)]	p = 0.017 p = 0.002	ISC related (adjusted): systemic reactions = 11 (3.3%) local react., = 42 (12.8%)	dropouts: 5 due to local reaction; 2 due to syst. reaction

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	al cohort study	stages II-III (adjuvant therapy)	centres = 35 duration: 6 mo follow-up: ≥ 3 yrs (or death)	immuno- (9.1 %), chemo/immunotherapy 3 % Ctrl: OP + watchful waiting + chemo- (5.9 %), radio- (5.9 %), immuno- (17.6 %), chemo / immunotherapy 2.2 %)	2) overall survival (adjusted HR): overall = 0.64 (0.42 - 0.96) disease-free = 0.73 (0.55 - 0.97)	p = 0.033 p = 0.029	WHO/CTC grade: 1-2 dropouts = 6 (1.2%) no indication of tumour enhancement; decreased HR for brain metastasis (HR = 0.33; CI 0.13-0.86; p = 0.024)	no data on: dosage, ITT, PP according to authors: significance of study type limited in terms of survival
Bock et al. 2004(69)	multicentre, retrolective, ctrl, epidemiologic cohort study	resected primary non-metastasised breast carcinoma UICC/AJCC stages I-III (adjuvant therapy)	n = 1442 total n = 710 ISC n = 732 Ctrl centres = 16 evaluation = PP duration: 52 mo observation: ISC = 81 mo Ctrl = 52 mo	ISC: standard + ISC, s.c., 2-3 x / wk, ≥ 3 mo Ctrl: standard (chemo-, radio- and hormone therapy) follow-up observation period: ≥ 3 y.; median = 61 or 67 mo	1) symptom-free at aftercare: (in particular: concentration, exhaustion, depression, sleep) ISC = 78% vs Ctrl = 39% 2) survival time (overall, adjusted): ISC vs Ctrl	p = 0.0001, OR: 0.47 (CI: 0.32-0.67) p = 0.038 HR = 0.46 (CI: 0.22-0.96)	disease-related (adj.): ISC = 16.3% Ctrl = 54.1% ISC-related: syst. react. 6/710 = 0.8% local react. 123/710 = 17.3% no indications of tumour enhancement	dropouts: ISC: n = 4 not randomised, baselines differ change of treatment ISC: n = 7
Grossarth-Maticek et al. 2001(66)	prospective, matched-pair (patients from retrolective cohort study with 10,226 patients: 1668 lscador, 83 other mistletoe preparation, 8,475 no mistletoe)	different tumour entities	n = 98 total = 49 pairs (n = 78 or 39 pairs) n = 39 ISC n = 39 Ctrl ITT: not analysed PP: no data duration: 1973-1982	ISC: ISC - no data on dose or other therapies Ctrl: no lscador; no data on other therapies	1) change to the value for psychosomatic self-regulation (T 0 vs T 3 mo): ISC increase from 3.41 to 3.87 vs Ctrl decline from 3.85 to 3.62 2) mean survival time: ISC longer (3.49 a) vs Ctrl (2.45 a)	p = 0.022 p = 0.04	no data	dropouts: 1 fatality before therapy 9 due to lack of consent by the doctor or no therapy no data on: informed consent, ethics committee, study location; dosing, validation of the questionnaire on self-regulation
	see above (same publication)	breast ca UICC stage III A-III B	n = 34 total = 17 pairs (n = 34 or 17 pairs) n = 17 ISC n = 17 Ctrl	ISC: standard therapy + ISC (dose and medication n/a) Ctrl: no lscador, no data on other therapy	1) change to the value for psychosomatic self-regulation: ISC from 2.92 to 3.70 vs Ctrl from 2.87 to 2.99 2) mean survival time: ISC longer (4.79 a) vs Ctrl (2.41 a)	n.s. p = 0.02	no data	dropouts: none no data on: informed consent, ethics committee, study location; dosing, validation of the questionnaire on self-regulation

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Isorel (ISO)								
<i>RCT / CT</i>								
Cazacu et al. 2003(86)	prospective, randomised, ctrl A: Duke C: 16 + D: 5 B: Duke C: 18, D: 11 C: Duke C: 6, D: 8 (1997-2000)	advanced colon tumour (Duke C: n = 40, Duke D: n = 24) (CTX with adjuvant biotherapy)	n = 64 total n = 21 (= A) Ctrl 1 n = 29 (= B) ISO n = 14 (= C) Ctrl 2 duration: 6 cycles + 3 mo follow-up	Ctrl 1: OP + CTX (5-FU, 6 cycles) ISO: OP + CTX (see above) + ISO (5 mg/kg BW i.v.-infusion 3/wk, entire postoperative period) Ctrl 2: OP	1) MTT bioassay: concentration-dependent reduction of cell growth: 1%: moderate (10%), 10%: ED ₅₀ achieved 15/20%: complete inhibition 2) mean survival time: Duke C: ISO (757 d) vs Ctrl 1 (547 d) Duke C: ISO (757 d) vs Ctrl 2 (502 d) Duke D: Ctrl 1 (214 d) vs ISO (505 d) Duke D: Ctrl 2 (451 d) vs ISO (505 d) 3) cumulative survival time according to Kaplan-Meier: Duke C Duke D	p < 0.05 no data no data p < 0.05 p < 0.05 p < 0.05 p < 0.05 n.s. n.s.	side effects: CTX: diarrhoea, haematological toxicity Ctrl 1: n = 4/21 (19%) ISO: n = 0/29 ISO: none observed	no data on: dropouts, decision of the ethics committee, informed consent, study location, randomisation, ITT/PP, target criteria, duration, analysis stratified according to Duke
Enesel et al. 2005(87)	prospective, randomised, ctrl	gastrointestinal cancer (heterogeneous group, stage II-III)	n = 70 n = 40 Isorel n = 30 Ctrl	ISO: 2 wks before and after OP 1 to 3 vials every other day s.c. Ctrl: not mentioned	1) cellular immunity: leukozytes, lymphocytes, CD4/CD8, NK 2) Karnofsky Index 3) Analogic Scale of Anxiety	no data (significant changes in the ISO group but no comparison between groups)	not mentioned	some data missing
Lektinol (LEK)								
<i>RCT / CT</i>								
Semiglazov et al. 2006(67)	multicentre, randomised, ctrl (placebo), double blind	Inclusion crit.: resected breast cancer TNM staging pT1-T3 pN0-N+ pM0	n = 337 (352) total n = 169 Lektinol n = 168 placebo duration: 16 wk treatment LEK/Ctrl = 169/168 24 wk treatment LEK/Ctrl = 103/104 2 mo follow-up	LEK: CTX (cyclo-phosphamide, methotrexate, fluorouracil) + LEK (30 ng/mL, 2/wk s.c.) Ctrl: CTX + placebo	1) FACT-G (16 and 24 weeks) LEK vs Ctrl 2) GLQ-8, 5 and 3: LEK vs Ctrl 3) Spitzer's uniscale LEK vs Ctrl	p < 0.0001 GLQ-8 and 5: p < 0.0001; GLQ-3: p = 0.0007 p < 0.0001	ADR: total: LEK= 82 (46.6%) Ctrl = 63 (35.8%) probable related: LEK = 17.6%; Ctrl = 1.7% local: LEK = 31; Ctrl = 2	dropouts: 1 due to allergic skin reaction in the LEK group QoL after 2 mo follow-up without CTX: LEK sign. better than Ctrl

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Semiglasov et al. 2004(68)	prospective, multi-centre, randomised, pl-ctrl, db, parallel groups 9 centres in Russia, Ukraine, Bulgaria	Breast cancer stage II/III without metastases (p T1-T3, N0-N+ 0-10 pos. lymph nodes, M0) (influence of mistletoe on QoL with adjuvant CTX)	without CTX n = 272 total n = 66 LEK 1 n = 65 LEK 2 n = 64 LEK 3 n = 66 Ctrl n = 261 ITT duration: 15 wks	Ctrl: CTX (CMF, 4 cycles i.v. + 10 mg Dx + 10 mg metoclopramide per d of the CTX) + pl LEK 1: CTX (see above) + LEK (0.5 mL 10 ng ML/ml 2 x /wk s.c.) LEK 2: CTX (see above) + LEK (0.5 mL 30 ng ML/ml 2 x /wk s.c.) LEK 3: CTX (see above) + LEK (0.5 mL 70 ng ML/ml 2 x /wk s.c.)	1) GLQ-8 – sum score: total: confirmatory analysis: trend toward improvement in LEK 2 and LEK 3 vs LEK1 and Ctrl; trend toward improvement in LEK 1 and LEK 2 vs Ctrl; LEK 1 vs Ctrl; explorative comp. in pairs confirms LEK 2 vs Ctrl; LEK 1 vs Ctrl; LEK 3 vs Ctrl; 2) Spitzer's uniscale: total: LEK 2 vs Ctrl (after baseline adjustment) 3) QLQ-C-30 EORTC: 4) additional: haematology, use of antiemetic/analgesic medications and hospital days immune parameters (n = 43): dose-dependent increase in T-helper cells and CD4+ /CD8+ ratio after 4 and 15 wk NK increase after 4 wk	n.s. p = 0.0035 p = 0.0017 n.s. p = 0.007 (ITT) n.s. n.s. n.s. p = 0.0016 (p = 0.0021) n.s. n.s. p < 0.05 p = 0.05	4 AE: safety analysis: n = 272 (≥ 1 x study medication); 127 patients (46.7%) with 244 AE (mult. occurrences in 1 patient counted as 1) LEK: - SAE: LEK 3 - 1 x erythema, compl. recovery after discontinuation (but death due to necr. ulcerizing colitis, not related) - non-SAE (most common): dose-dependent local reaction (Ctrl 0%, LEK 1 9%, LEK 2 17.9%, LEK 3 32.4%; possible / probable related; no dropouts) - other AE: 4 patients (chills, muscle pain, headache, allerg. skin reaction or conjunctivitis - possible relation) CTX: white blood cell, RES disorders (Ctrl 20%, LEK 1: 22.4%, LEK 2: 16.4%, LEK 3: 20.6%) gastrointestinal (Ctrl 8.6%, LEK 1: 9%, LEK 2: 9%, LEK 3: 14.7%) resistance mechanism disorders (Ctrl 5.7%, LEK 1: 6%, LEK 2: 7.8%, LEK 3: 8.8%) red blood cell disorders (Ctrl 5.7%, LEK 1: 3.0%, LEK 2: 3%, LEK 3: 11.8%)	dropouts: 11 withdrawal: 4 AE: (2 Ctrl, 2 LEK), 4 patient request, 3 other reasons major protocol violations: n = 18 (reason: 17 no compliance with the trial plan) insufficient information: consent, withdrawal (n = 11), PP no data on: study time, locations, blinding, validation of the questionnaires after translation into Russian and Bulgarian interim analysis with n = 178, p = 0.0172

Notes:

*: Divided analysis of the QoL with lower number of questionnaires starting at week zero.

&: Lower incidence with EUR can be interpreted as relief provided by mistletoe therapy. But no overall conclusions can be drawn about side-effects with mistletoe therapy.

Melzer J, Iten F, Hostanska K, Saller R: Efficacy and safety of mistletoe preparations (*Viscum album*) for patients with cancer diseases.

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Abbreviations:

ADR = adverse drug reaction; AE = adverse event; an = analysed; BW = body weight; ca = carcinoma; CI = Confidence interval; Ctrl = control; CMF = cyclophosphamide, methotrexate, fluorouracil; CR = complete remission; CRP = C-reactive protein; CTX = chemotherapy; d = day; DKG= Deutsche Krebsgesellschaft - German Cancer Society; DX = dexamethasone; EORTC = European Organisation for Research and Treatment of Cancer; EUR = Eurixor[®] (ML-I stand. mistletoe extract); FACT = Functional Assessment of Cancer Therapy Scale; FLIC = Functional Living Index - Cancer; HEL = Helixor; HR = hazard ratio; ISC = Iscador (depending on the host tree (see M, P, Q); ISO 0 Isorel; ITT = intention to treat; i.v. = intravenous; kg = kilogram; KPI = Karnovsky Performance Index; M = malus (Latin) apple; MC = mixed cellularity; ml = milliliter; ML = mistletoe lectin; mo = month; MR = mortality rate; MTT bioassay = tetrazolium salt based colourimetric assay to assess viability of cells; n = number of patients; n/a = not available; NaCl = sodium chloride; NC = not changed; Ney = Ney-Tumorin[®] (xenogenic peptide); n/d = no data; NK = natural killer cells; n.s. = not significant; OP = operation; OR = odds ratio; P = pinus (Latin) pine; pl = Placebo; PP = per protocol; PR = partial remission; Q = quercus (Latin) oak; QoL = quality of life; . q.o.d. = every other day; RTX = radiotherapy; SAE = serious adverse event; s.c. = subcutaneous; sign. = significant; ST= survival time; VEC= vindesine, epirubicin, cyclophosphamide; TCM = Traditional Chinese Medicine Index; vs = versus; wk(s) = week(s); y(rs) = year(s)