Supportive Care in Cancer (2026) 34:952
https://doi.org/10.1007/s00520-026-11154-3

RESEARCH

Improved quality of life and prolonged survival with add-on homeopathic treatment in patients with non-small cell lung cancer: a prospective, randomized, placebo-controlled, double-blind, three-arm, multicenter study

Michael Frass[1,8,9] · Peter Lechleitner[2] · Christa Gründling[3] · Katharina Gaertner[4] · Cornelia Duscheck[1,8,9] · Ilse Muchitsch[5] · Raj K. Manchanda[6] · Otto C. Burghuber[7]

Received: 12 February 2026 / Accepted: 22 August 2026

Abstract

Background Alongside conventional anticancer treatment, add-on homeopathy might help to alleviate adverse effects of conventional therapy.

Aim The aim of this study was to replicate previous studies on the effect of adjunctive homeopathy on quality of life (QoL) and survival in non-small cell lung cancer (NSCLC) patients.

Method In this prospective, randomized, placebo-controlled, double-blind, three-arm multicenter phase III study with quadruple-checked data analysis, we investigated the potential effects of an add-on homeopathic treatment compared to placebo in patients with stage IV NSCLC in terms of QoL. Ninety-eight received either individualized homeopathic medicinal products (HMPs; $n=51$) or placebo ($n=47$) in a double-blinded fashion. Fifty-two control patients without homeopathic treatment were only observed in terms of their survival rate. The ingredients of the various HMPs were mainly prepared of plant, mineral, or animal origin. The data entry and statistical analysis were subject to an exceptional quadruple-checked data analysis process. The analysis presented in this article was inspired by our earlier report of this trial published in The Oncologist in 2020, which was retracted by that journal in November 2025 after two corrections; a majority of the co-authors disagreed with this decision. The present article is based on the same trial dataset but was deliberately designed to highlight the unique research methodology: design and preparation by a lead statistician, data entry, data clearing and independent statistical evaluation were performed in four mutually independent steps, reporting follows the CONSORT statement, and the interpretation of the findings has been reframed conservatively.

Results Global health status (QoL) was higher in the homeopathy group than in the placebo group after 9 weeks and after 18 weeks ($p<0.001$). With the exception of cognitive functioning at 9 weeks and of pain, diarrhea and financial difficulties at 9 weeks, all functional and symptom scales of the EORTC QLQ-C30 favored the homeopathy group ($p<0.001$ for the multivariate comparisons), with between-group differences exceeding the threshold of 10 points that is generally regarded as clinically meaningful. Median survival time over the 730-day observation period was 435 days in the homeopathy group, 257 days in the placebo group ($p=0.010$), and 228 days in the non-randomized control group ($p<0.001$); the corresponding

Highlights Implications for practice: Add-on homeopathic care could be delivered alongside conventional oncological treatment without observed interference or adverse effects. In this trial, based on a quadruple-checked data analysis, patients allocated to add-on homeopathy reported a better quality of life and showed longer survival than patients allocated to placebo. These observations require independent replication.

(Affiliations are given at the time of the study; MF, PL, IM, and OB retired)

Extended author information available on the last page of the article

Published online: 10 September 2026

2-year survival rates were 45.1%, 23.4%, and 13.5% (homeopathy vs. placebo $p = 0.020$; homeopathy vs. control $p < 0.001$). The difference between the placebo group and the non-randomized control group was not statistically significant ($p = 0.154$).
Conclusion In this trial, add-on homeopathy was associated with better quality of life across most functional and symptom domains, with clinically meaningful effect sizes congruently to a previous open study. Survival time was significantly longer in the homeopathy group compared to both the placebo and control groups. Independent replication, ideally within contemporary immuno-oncological treatment regimens is required.
Trials registration ClinicalTrials.gov; No.: NCT01509612; January 7, 2012

Keywords Add-on homeopathy · Adult oncology · Complementary and alternative medicine (CAM) · Global health status · Lung cancer · Survival · Whole systems research

Abbreviations

ALK	Anaplastic Lymphoma Kinase
CAM	Complementary and alternative medicine
CRF	Case report form
EGFR	Epidermal Growth Factor Receptor
EORTC	European Organisation for Research and Treatment of Cancer
Ph.Eur.	European Pharmacopoeia
GHP	German Homoeopathic Pharmacopoeia
HMP	Homeopathic medicinal product
ITSC	Information Technology Solution Center
NSCLC	Non-small cell lung cancer
QLQ-C30	Quality of Life Questionnaire Core-30
QoL	Quality of Life
RDA	Research, Documentation and Analysis
SF-36	36-Item Short-Form Health Survey
VAS	Visual Analogue Scale
WSR	Whole systems research

Introduction

Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer death worldwide, with almost 2.5 million cases (1 in 8 cancers) and 1.8 million deaths (1 in 5 deaths) [1]. Particularly in lung cancer, differences have been observed by Global Cancer Incidence, Mortality And Prevalence (GLOBOCAN) estimations for 2020 revealing there are sex differences according to continents [2]. North America and Oceania have higher proportion of female lung cancer incidence as compared with males (35.7 versus 30.1 and 27.4 versus 21, respectively, age-standardized rate by world standard population) than in other continents wherein the proportion of women is less than half than that of the men incidence [2]. In general, about 13% of all lung cancers are small cell lung cancer (SCLC), and about 77% are non-small cell lung cancer (NSCLC) [3]. The management of NSCLC has improved considerably, especially in the past 10 years [4]. The systematic screening of populations at risk with low-dose computed tomography (CT), the implementation of novel surgical and radiotherapeutic techniques and a deeper biological understanding of NSCLC that has led to innovative systemic treatment options have improved the prognosis of patients with NSCLC [4]. In non-metastatic NSCLC, the combination of various perioperative strategies and adjuvant immunotherapy in locally advanced disease seems to enhance cure rates. In metastatic NSCLC, the implementation of novel drugs might prolong disease control together with preserving quality of life. The further development of predictive clinical and genetic markers will be essential for the next steps in individualized treatment concepts [4].

Approximately 90% of patients with advanced NSCLC suffer from two or more disease-related symptoms, including pulmonary complaints such as cough and dyspnea, as well as general fatigue, pain, and anorexia [5]. One study examined a total of 2205 newly diagnosed lung cancer patients who completed questionnaires on emotional problems, quality of life, and symptom burden [6]. Emotional problems at diagnosis were associated with younger age, female gender, current cigarette smoking, current employment, advanced lung cancer disease, and surgical or chemotherapy treatment. Additionally, strong associations were found between greater severity of emotional problems, lower quality of life, and greater symptom burden [6].

One survey found that 68% of patients preferred treatment that eased disease-related symptoms without prolonging their life [7]. Moreover, shorter overall survival has been associated with poor health-related quality of life at diagnosis, and higher symptom burden at the outset of treatment [8, 9]. There is growing understanding of the extent to which mind and body are connected, and awareness that psychosocial characteristics and variables can contribute to both the symptom experiences and to patient outcomes, including survival [10].

A large number of patients with cancer experience reduced life expectancy and have metastatic disease at time of death. However, the more precise causes of mortality and

patient deterioration prior to death remain poorly understood. This scarcity of information, in particular the lack of mechanistic insights, presents a challenge for the development of novel treatment strategies to improve the quality of, and potentially extend life, for patients with late-stage cancer. In addition, earlier deployment of existing strategies to prolong quality of life is highly desirable [11].

Homeopathy is one form of complementary and alternative medicine (CAM). For the purposes of this manuscript, we define CAM as any medical practice or product that is used alongside or in place of conventional treatment but is not considered part of standard medical care; "conventional treatment" refers to standard oncological care including chemotherapy, radiotherapy, immunotherapy, and targeted therapy as indicated by current guidelines. It is based on two theories: firstly, the law of similars, i.e. diseases can be cured by substances that cause similar symptoms in healthy people ("like cures like"), and secondly, the law of minimum dosage—the lower the dosage, the more effective the medicine [12, 13]. A detailed clinical history is recorded by the homeopath, relying on the totality of symptoms described by the patient. The symptoms are then listed and repertorized, which means that the homeopath matches the complete symptom profile of the patient to the symptom profile of the most suitable remedy by help of a repertory such as a book or a computerized program. In repertorizing, the practitioners mainly focus on individual physical symptoms and compare them to the signs and symptoms found in homeopathic research, so-called provings. Then, the homeopath determines the least amount of medicine needed to achieve the desired effect [12, 13]. The homeopathic medicinal products (HMPs) are not only diluted but also shaken (potentized) which, according to homeopathic theory, enhances their effect on the patient.

Homeopathy is a system in which HMPs are customized to individuals, based on broad themes characteristics elicited from the totality of the presenting physical, mental and emotional symptoms [12, 13]. Because homeopathy sees disease as unique to each patient and thus treats it with a unique, specifically tailored medication, it is difficult to perform randomized, controlled trials—a method suited to research on groups rather than individuals.

Previously, we published the results of a pragmatic, randomized, controlled trial of 410 cancer patients in which homeopathic treatment was an add-on therapy to conventional oncological treatment [14]. In this trial, the global health status and subjective wellbeing of these patients improved significantly with individualized homeopathic treatment. - An oncologist at the Medical University of Vienna (MUV), Austria, noticed that brain cancer patients treated with adjunct homeopathy seemed to have an improved survival rate. A retrospective evaluation found that homeopathic therapy administered to patients with several types of advanced cancer provided a statistically significant advantage ($p < 0.001$) for survival, as compared to control [15].

We therefore investigated complementary individualized homeopathy as a possible means of reproducing an earlier open-label study on improving quality of life (QoL) and subjective well-being in patients with advanced NSCLC [14] and a retrospective study on prolonging the survival time of cancer patients [15].

The analysis presented in this article was inspired by our earlier report of the same trial, which was published in The Oncologist in 2020 [16]. That article was corrected in 2021, received an Expression of Concern in 2022 following a request by the Commission for Research Integrity of the Austrian Agency for Scientific Integrity, was corrected a second time in 2024 and was finally retracted by the journal in November 2025 [17]. The retraction notice states that, in the light of continued uncertainty, the journal no longer had confidence in the results and conclusions; nine co-authors disagreed with the decision to retract, one agreed and the remaining authors did not comment [17]. We report this history explicitly so that readers can judge the provenance of the data presented here. The present article is based on the same trial dataset, but it is not a reprint of the earlier report. It was written with the declared goal of enhancing the description of the methodology of the analysis and the transparency of the reporting. It is emphasized that the study preparation and evaluation occurred in four mutually independent steps (quadruple-checked data analysis, described below): the study was designed by a lead statistician, data were entered in a university data management system, then transferred to another independent statistician through the formal data clearing process of the Medical University of Vienna, followed by evaluation by this statistician. The reporting follows the CONSORT statement, the interpretation of effect sizes is anchored in published thresholds for clinically meaningful change, and the conclusions have been reframed conservatively. In this sense, the present article adds an independently verified and methodologically strengthened analysis to the literature rather than duplicating an earlier claim.

To avoid any suggestive effect from homeopaths or placebo effects from HMPs, we designed a double-blind, prospective, randomized, placebo-controlled, three-arm, multicenter phase III trial with data analysis verified in four independent steps (quadruple-checked data analysis) in patients with advanced stages of NSCLC. Since it is often claimed that the beneficial effects of homeopathy are due to placebo, we added a third group of non-randomized patients, who declined before consenting to participate and therefore did not receive any additional homeopathic treatment as a non-interventional control group. Those patients could not be randomized since open treatment would have

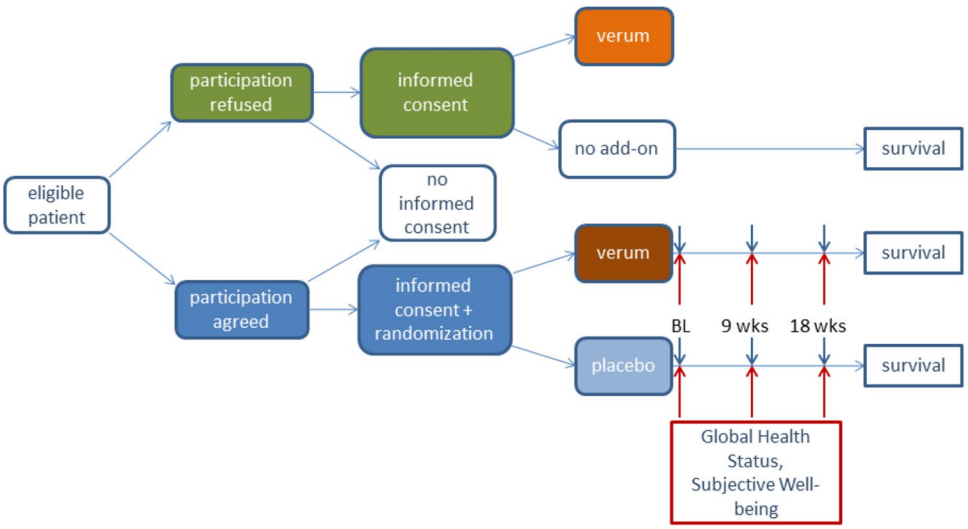

Fig. 1 Study protocol. BL, baseline; verum, homeopathy; wks, weeks

flawed results.—Our hypothesis was that there would be no significant difference between homeopathy and placebo in terms of QoL and survival rate in the double-blind study.

Materials and methods

Trial design

This phase III study, which investigated homeopathic treatment as an adjunct to conventional treatment, was prospective, three-armed, randomized, double-blind, placebo-controlled, stratified, and multicenter with quadruple-checked data analysis; until the end of the statistical evaluation, neither the patients nor the treating physicians knew whether they were receiving verum or placebos. The three arms evaluated were add-on homeopathy, placebo, and control. Two parallel groups randomized to homeopathy or placebos were compared in a double-blind fashion. Controls (third group) were patients who refused participation in the randomized trial but agreed to observation of their course of disease without any homeopathic intervention (Fig. 1). The study was conducted in four outpatients' centers: the Medical University of Vienna (MUV; General Hospital of Vienna), Department of Medicine I, Division of Oncology; the then Otto Wagner Hospital, Department of Pulmonology I, Vienna; the Hospital of Lienz, Department of Medicine, Tyrol; and the Elisabethinenspital, Department of Medicine, Linz, Austria.

The study protocol was approved by the ethics committees of the participating institutions (Ethical Committee of the Medical University of Vienna No. 709/2010). The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice Guidelines, and applicable local regulations, and registered at Clinical Trials.gov (ClinicalTrials.gov Identifier: NCT01509612; January 07, 2012). All participating patients gave their written informed consent prior to study entry.

During first registration, we planned to include 600 patients suffering from three tumor entities: non-small cell lung cancer (NSCLC), glioblastoma, and metastasized sarcoma. Recruitment for glioblastoma and metastatic sarcoma was stopped when it became clear that recruitment of these cohorts was not feasible. Not a single patient was included into those cohorts. Following elimination of these two tumor entities the protocol was amended, and the sample size calculation revised by the statistician resulting in a sample size of 300 NSCLC patients with the option of an interim analysis after 140 patients. This change was approved by the MUV Ethics Committee.

Eligibility

Patients with histologically or cytologically confirmed stage IIIB, IIIC, or IV NSCLC diagnosed within the last 8 weeks were invited to participate in the study. The date of the printed histology/cytology finding was determined as date of diagnosis. Patients were randomly assigned at a ratio of 1:1 to either classical individualized homeopathic treatment or placebo as add-ons to conventional treatment. Patients who chose not to participate in the study served as a no-add-on control group after signing informed consent [18]. This control group was formed to exclude a possible placebo effect of the homeopaths. The control group did not receive any homeopathic consultation and received no treatment in addition to conventional therapy. Patients who refused to be randomized and opted to undergo homeopathic treatment were excluded from the study.

Inclusion criteria were (a) histologically or cytologically confirmed stage IIIB/IIIC or IV NSCLC within the preceding 8 weeks and (b) age above 18 years.

There were numerous exclusion criteria, which were essentially the same as those for chemotherapy: (a) sensitizing mutation of the EGFR gene or translocation of the ALK gene; (b) refusal to sign informed consent; (c) pregnancy; (d) hematological, hepatic or renal pathology; (e) coronary heart disease; (f) history of secondary tumor; (g) major surgery within 4 weeks prior to study entry; (h) active infection, and symptomatic peripheral neuropathy (National Cancer Institute's common toxicity criteria, version 2, grade ≥ 2); (i) central nervous system metastases unless the metastases were treated and stable; (j) active autoimmune disease; (k) use of systemic immunosuppressive treatment; (l) use of systemic treatment during the previous 2 years; (m) active interstitial lung disease, or a history of pneumonitis for which glucocorticoids were prescribed; (n) previous systemic therapy for metastatic disease or previous irradiation; and (o) use of any CAM, including homeopathy other than the research treatment, during the trial. The exclusion criteria are standard in oncological treatment and were followed from the beginning by independent cancer pulmonologists. Eligibility screening and recruitment was carried out before randomization and performed entirely by conventional oncologists, not by homeopathic physicians.

Patient-reported outcome measures

The primary endpoint was global health status, measured by the patient-reported Quality of Life Questionnaire Core-30 (QLQ-C30) of the European Organisation for Research and Treatment of Cancer (EORTC) [19].

Furthermore, we assessed QoL by the 36-item Short-Form Health Survey (SF-36) [20]. A valid and reliable tool, broadly used in cancer populations, the SF-36 comprises eight subscales which assess physical function and limitations secondary to emotional and physical problems, body pain, general health, vitality, and emotional and social well-being with higher scores defining a more favorable health status and better QoL. A subjective well-being questionnaire comprising a visual analogue scale (VAS) was used for definition of subjective well-being.

All three questionnaires were completed at the start of the study (visit 1) and 9 weeks (visit 2) and 18 weeks (visit 3) after randomization to adhere to the schedule of our previous open-label pragmatic study [14]. Except for the baseline questionnaires, the forms were filled in 1 or 2 days before appointments at home. The date of the respective follow-up was noted by hand on the questionnaires given to the patients. If the appointment had to be postponed by a few days (for reasons ranging from simple reasons such as unavailability, altered plans, transport issues or neutropenia preventing showing up for follow-up), the questionnaires were returned later and the date was changed by hand, accordingly. The completed questionnaires were then given to the study nurses.

The secondary endpoints were:

1. Overall survival, defined as the time from randomization until death or until 2 years later. Date of death was provided by the independent Information Technology Solution Center (ITSC), Austria, and recorded by an individual with no involvement in the study (EE).
2. A questionnaire to gauge the attitude of patients toward homeopathy ("attitude questionnaire") and to CAM in general was completed only at study entry. The second part of this questionnaire aimed at gauging in which of the two randomized groups patients thought they were and whether they believed that the treatment had an influence on the psychological or physical sphere. The second part was completed only at the second visit. This questionnaire focusing on subjective well-being was developed by one of the authors (MF) without any validating procedures (Subjective Well-Being Questionnaire).

All questionnaires were given and explained to patients and collected from them after completion by individuals uninvolved in the study. Safety was assessed by evaluating the incidence of adverse clinical events and laboratory variables, graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0. Patients in the third non-randomized, untreated group were compared with the two treatment groups solely with respect to overall survival.

Chemotherapy

Cisplatin plus gemcitabine or cisplatin plus pemetrexed was the standard regimen for first-line treatment of advanced squamous or non-squamous NSCLC at the start of our study [21]. Chemotherapy consisted of cisplatin 80 mg/m^2 or carboplatin [Dose (mg) = target AUC x (GFR + 25)] given intravenously on day 1 combined with either gemcitabine 1000 mg/m^2 given intravenously on day 1 and day 8 or with pemetrexed 500 mg/m^2 given intravenously on day 1 every 3-week cycle for up to six cycles.

Study medications (S1, Preparation of the Q-potencies and Instructions for use)

Homeopathy uses a wide variety of source materials, which means that various methods of preparation are necessary depending on the substance being processed. Homeopathic

medicinal products (HMPs) are derived from plants, herbs, minerals or animal products [22].

All study medications (D, CH, LM and Q-Potencies) were prepared (Maria Treu Pharmacy, Vienna, Austria) in accordance with the current version of the European Pharmacopoeia (Ph.Eur.), the German Homoeopathic Pharmacopoeia (GHP) and the Q-potencies according to Hahnemann's 6th edition of the Organon of Medicine [13]. The HMPs are manufactured by stepwise dilution and succussion, thereby preparing stable GMP grade formulations.

HMPs were produced through sequential agitated dilutions in alcohol/water or by trituration in powdered lactose in decimal (1:10), centesimal (1:100) or quinquaginta millesimal (1:50,000) potencies (Q-potencies) [22]/LM-potencies (Table S1, Preparation of the Q-potencies and Instructions for use) [22].

All liquid HMPs started with Q1 potencies of the selected HMPs for 3 weeks, and continued in ascending order with Q2, Q3, of either the same remedy or a selected alternative (three weeks each) towards Q30. If the substance being examined was changed for any reason based on the homeopath's assessment and decision, the new cycle started again from the beginning with Q1. A primary reason for changing the study substance was disease deterioration.

The Q-potencies were applied as liquids, after being shaken and diluted daily by the patient (Table S1). The package leaflet also mentions the number of succussions to be carried out by the patient every day and the number of drops or spoonful to be taken [22]. They were used in the trial as constitutional medication based on the mental, emotional and physical symptoms displayed by any patient. The D-, C- and LM-potencies were applied as sugar granules. Five pellets comprised one dose, which was taken orally by sucking.

Treatment protocol

Within a period of eight weeks, NSCLC patients who had been diagnosed by lung cancer oncologists not involved in the study were invited to participate in the study. At study entry, all eligible patients (those who met all the inclusion and none of the exclusion criteria, and had signed informed consent) were required to complete a series of questionnaires—the EORTC QLQ-C30, the SF-36, the Subjective Well-Being Questionnaire, and one which gauged their attitudes toward homeopathy and CAM. Demographic information was collected, after which a thorough and detailed homeopathic medical history was taken for all patients [12, 13]. Based on these homeopathic interviews, homeopathic physicians determined the most appropriate constitutional and symptomatic HMPs for each individual following the classical principles of homeopathy of individualization. In addition to conventional medicine, the homeopathic individualization process requires intensive postdoctoral study and appropriate training. At the beginning of the study, one female homeopath was 45 years old with 8 years of experience with homeopathy and 19 years with conventional medicine while a male homeopath was 53, with 8 years of experience with homeopathy and 30 years with conventional medicine. The last homeopath was 56 years with 22, and 32 years of experience accordingly.

Nature of the intervention

The intervention is conceptualized as a pragmatic, whole-system clinical approach. Researchers in CAM are proposing whole systems research (WSR) as an additional research approach for modern systems of care, whether they include CAM or not [23]. The current status of WSR methodology development is mainly theoretical. Necessary components of the methodology include focus on interventions, context, process, outcomes, and philosophy. Further development should be based on observational studies using both qualitative and quantitative approaches, often combined. Only when modern health-seeking systems of treatment behaviors are thoroughly understood should fine-tuning of hypothesis-testing research methods be continued [23]. Similar to other individualized healthcare interventions—such as psychotherapy or acupuncture [24]—it relies on professional judgment exercised within an established therapeutic framework rather than a fixed, uniform treatment protocol. Accordingly, the intervention is best understood and evaluated using methodological perspectives defined as complex and individualized clinical systems, rather than those designed exclusively for standardized pharmaceutical interventions.

This whole-systems perspective is also supported by foundational methodological work emphasizing qualitative methods, treatment individualization, patient-practitioner interaction, therapeutic context, and the potential synergy of multiple components within complex complementary-care systems [25–27]. Constitutional HMPs were largely tailored for mental, emotional and general symptoms, regardless of reactions to the anti-cancer treatment. Symptomatic HMPs were given to combat the adverse effects of this treatment. The homeopathic physician explained the patient how to prepare and how to take the prescribed homeopathic Q-potencies after vigorous succussion, dilution and stirring on a daily basis.

The name and all other details of prescribed medications were faxed to the pharmacy (Maria Treu Pharmacy), where both HMPs and placebo for the study were prepared.

Method used to generate the random allocation sequence

Subjects were randomized for permuted blocks randomization in a 1:1 ratio by a web-based randomization service (Randomizer©, Medical University of Graz, Austria),

stratified by age, gender, Karnofsky performance status and treatment center. An outstanding feature of this randomization program is the automatic creation of a log ("audit trail") permanently recording all patient inclusions and exclusions thereby guaranteeing integrity of the study and excluding any manipulation.

Randomization for homeopathy and placebo medication was carried out at the pharmacy by a person not involved in the preparation of the HMPs on receipt of the medication name determined and faxed by the physician for each individual patient. Investigators and patients were blinded to treatment allocation until study completion and finish of data analyses.

Following randomization, a pharmacist prepared the prescribed study substances (placebo/HMPs) for the respective patient. HMPs and placebo showed identical appearance. To avoid contact between pharmacist and patients and, thus, any information bias, medications were sent to patients by regular mail together with plastic cups and spoons in neutral wrapping. The study substances were labeled with a code held at the pharmacy not visible to the homeopathic physicians. This design was set up to maintain the double-blind design of the study; neither the treating physician nor the patient knew which treatment he/she received.

The pharmacy was responsible for both preparing the study medications and dispatching them to patients via regular mail in neutral wrapping. Names of HMPs were kept from patients to maintain double-blind design and to obviate any attempt to avoid the placebo.

From the recruitment of the first patient (February 21, 2012), all patients in the homeopathy group and the placebo group were treated double-blind, randomized, and placebo-controlled. Patients were followed up every 9 weeks until death. At each visit, the homeopathic physician evaluated whether to continue with the same HMPs or change them, based on patient reporting and routine cancer assessment. Patients were asked to complete again the questionnaires they answered on study entry [14]. The physician completed a case report form (CRF) at every visit. The duration of the first visit at the homeopath's office was about 60 min; the follow-up visits which took place every 9 weeks lasted for about 30 min.

All authors guarantee the accuracy and completeness of the data and analyses which was controlled and certified by physicians not involved in the study.

Statistical analysis and sample size calculation

Sample size calculation was based on a significance level of 5% and a median survival of 10.1 months [28]. Furthermore, a 60-month recruitment period with a 24-month observational period in each patient was planned. Under these assumptions, 300 patients (corresponding to an average accrual rate of 5 patients per month) gave 85% power to detect a difference of 10.1 vs. 14.5 months. Because the trial duration was quite long, a two-stage design (O'Brien-Fleming type with equal information rates; [29]) with an interim analysis was planned using the above assumptions (Addplan, Version 6.0.8): An interim analysis with non-binding stopping for futility option was projected after the observation of 140 events. Early rejection of the null hypothesis at interim was planned to be tested at a two-sided significance level of 0.0052; the null hypotheses were accepted at interim (stopping for futility) if the p-value exceeded 0.5. The two-sided significance level for the second stage was 0.048. Maximum sample size was estimated to be 302 (corresponding to 279 events), expected (average) number of events was 209 under the null hypothesis and 242 under the alternative.

Efficacy was assessed in the intention-to-treat sample, which included all randomized patients. Safety was assessed in the as-treated sample, which included all randomized patients who had received at least one dose of the assigned therapy. Randomized patients were prescribed at least three Q-potencies of the assigned homeopathic therapy.

IBM SPSS statistics 26.0 was used for all analyses, $\alpha = 5\%$ (two-sided). Frequencies (n) and valid percentage were used for reporting dichotomous and categorical data; minimum and maximum (range), mean and standard deviation for continuous variables. Group comparisons for 2×2 crosstabs were calculated via Fisher's exact test, those for larger crosstabs via X^2-test. Univariate comparisons of two group means were done with t-test for homogenous respectively heterogenous variances (homogeneity tested by Levene's test), comparisons of two group medians with Mann–Whitney-U-tests, univariate comparisons of three group means by analyses of variances (ANOVA) and prior testing of homogeneity of variances and co-variances (Levene test; [30]) and pairwise post hoc Scheffé tests [31]. Multivariate comparison of means for multiple assessment scales of psychological tests was done via General Linear Model (multivariate analyses of variances with preceding test for homogeneity of variances and covariances via Box-M-Test) respectively via General logistic model for repeated measurements (with preceding test for homogeneity of variances and covariances via Box-M-Test test estimation: Wilk's λ). Kaplan–Meier curves were used to graphically display the survival comparison between the groups, Log-Rank-test (Mantel-Cox; two-sided) was used to assess group differences in survival, estimates of mean survival time in days (hazard ratios) and 95% CIs are given overall and as well for each study group. Survival rates for study groups are given in %, Wilcoxon (Gehan) Statistic is used for overall and pairwise comparison of rates.

The obtained and recorded raw data from this 3-arm trial was sent blinded to the statistician and was used to

compare between the two randomized groups with regard to the following outcomes:

Primary outcome: QoL as evaluated as global health status and subjective well-being at 9 and 18 weeks (third visit after second prescription) versus base line (EORTC-QLQ-C30 remaining dimensions; SF-36; subjective well-being) in the two treatment groups using the EORTC QLQ-C30-scoring manual.
Secondary outcome: overall survival time. Each patient was observed for 24 months regarding survival from the date of his/her study inclusion.

All three groups were compared overall and pairwise to each other with respect to overall survival.
After statistical analysis, data was unblinded.

We used the CONSORT checklist by Schulz KF et al. for the CONSORT Group 2010 Statement: updated guidelines for reporting parallel group randomized trials.

Quadruple checked data analysis:

In order to conduct the study according to the best objective criteria, we introduced a unique fourfold control:

1) The planning statistician used the computer-assisted randomization program Randomizer®, which was developed by the Medical University of Graz, Austria. This program automatically creates a protocol ("audit trail") when a patient is included or excluded. None of the authors of the study had any influence on the randomization program. The audit trail proves that no "post-hoc exclusions" were made beyond those listed above (mutations, glioblastomas, and metastatic sarcomas). The automatically generated log tracks all entries and deletions, thereby ensuring error-free and tamper-proof data management.
2) All patient data, including questionnaires, were forwarded in anonymized form to two individuals who were not involved in the study. The data was recorded using a double entry method on the MUV's "Research, Documentation and Analysis" (RDA) platform [32]. This scientific platform enables data to be stored in various formats: form-oriented documentation, project-oriented data collections for registries and studies (monocentric and multicentric), patient-related or pseudonymized documentation; pseudonymized web documentation for multicenter registries; automatic transfer of data from various sources (laboratory systems, etc.); and a strong authorization concept. It was adapted to the requirements of the study by members of the Center for Medical Statistics, Informatics, and Intelligent Systems at MUV [33].
3) In order to separate the two statisticians responsible for planning the study and analyzing the data, the data was processed in a complex clearing process in compliance with data protection guidelines by Ernst Eigenbauer (Chief Analyst, Information Technology Solution Center, Research, Documentation and Analysis (RDA), Scientific Platform, Center for Medical Statistics, Informatics and Intelligent Systems, Medical University of Vienna) [34]. As part of this clearing process, the data was transferred from the MUV to the evaluating statistician.
4) An independent statistician evaluated the data. This complex quadruple-checked data analysis is unusual especially for a study not sponsored by any company.

Results

Accrual

After 5 years, enrollment of patients was terminated, since the proposed time frame for recruitment and the proposed number for an interim analysis was reached. From February 2012 to July 2017, 158 patients of European ancestry with NSCLC IV were enrolled in the study, 52 of whom did not consent to participate in the randomized experiment but agreed to observation of their course of disease as untreated controls with no participation in any homeopathic intervention (Fig. 2). The remaining 106 were randomized. Eight of the randomized patients had to be excluded because of sensitizing EGFR mutations or ALK translocations reported immediately after randomization (four in the homeopathy group, four in the control group). This left 98 patients in total in the two double-blind groups (Fig. 2).

Treatment course (Tables 1, S2, S3)

A total of 98 patients received allocated treatment (51 in the homeopathy group, and 47 in the control group). Fifty-two patients were observed regarding the course of disease without any homeopathic intervention. Altogether, 150 patients were investigated. Seventy-nine patients (46 patients in the homeopathy group and 33 patients in the placebo group) attended the third visit. All patients were treated as intended (Fig. 2). Attendance at the third visit therefore differed between the randomized groups (90.2% in the homeopathy group vs. 70.2% in the placebo group) due to different mortality times, which has to be taken into account when interpreting the QoL comparison at 18 weeks.

There were no statistically significant differences between the groups with respect to gender distribution,

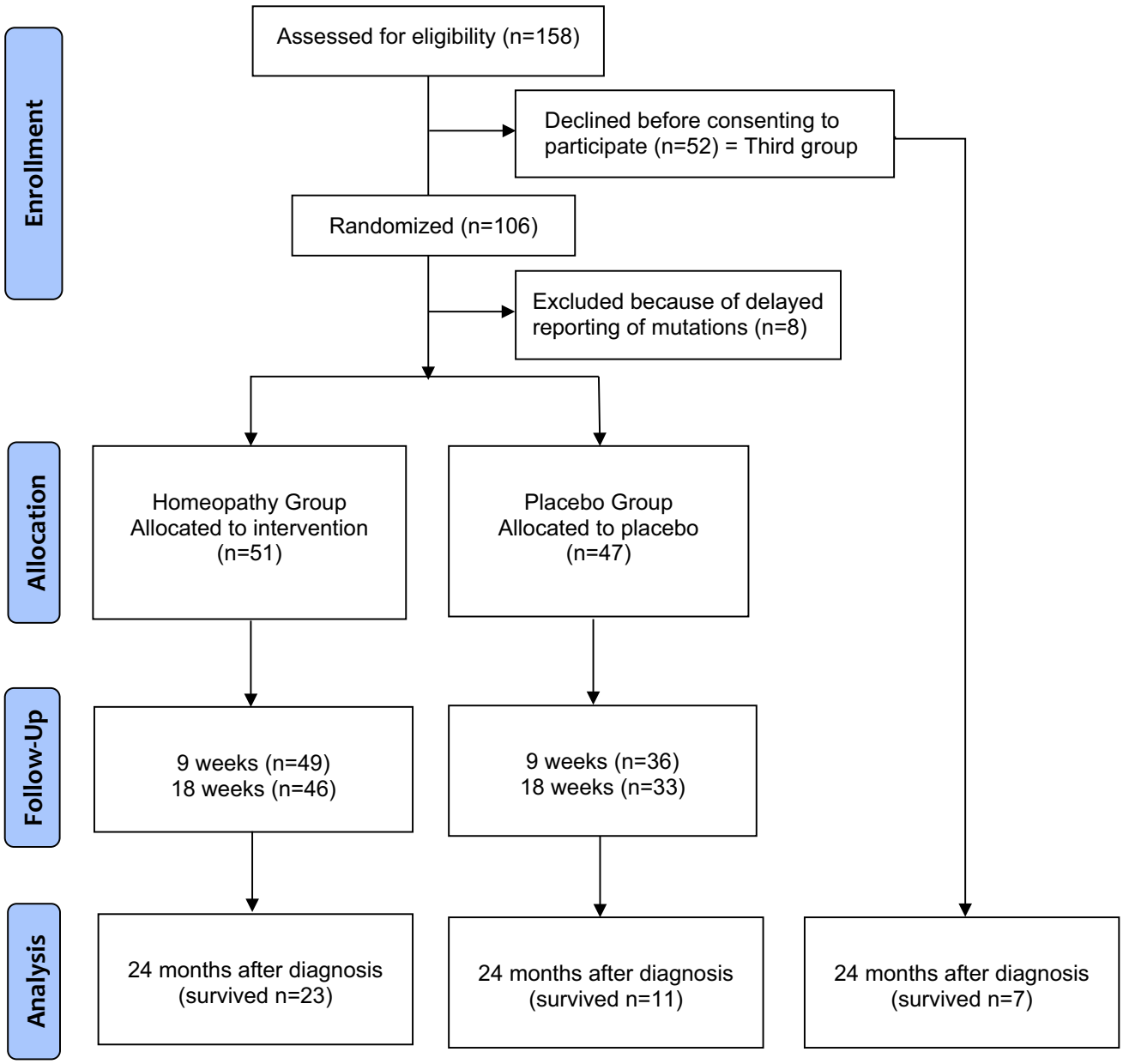

Fig. 2 CONSORT diagram

age, age groups, Karnofsky index, smoking status, T-staging, M-staging, stage groups (IIIB, IIIC, IV), chemotherapy, radiotherapy, brain or liver metastases, whole brain radiation therapy, surgery, pneumonectomy, chemotherapy cycles, change to carboplatin, and immuno-oncological therapy (Table 1). There was a statistically significant difference between treatment groups and the control group with regard to N stage with a higher number of N staging 0 and 1 in the control group and more N stage 3 in the treatment groups ($p = 0.010$); however, no difference between the two treatment groups was found.

Histology revealed adenocarcinoma in 39 patients in the homeopathy group and 40 patients in the placebo group; squamous cell carcinoma in 10 patients in the homeopathy group and four patients in the placebo group; lung carcinoma-not otherwise specified (NSCLC-NOS) in one patient in the homeopathy group and three patients in the placebo group; and large-cell bronchial carcinoma in one patient in the homeopathy group and none in the placebo group ($p = 0.219$; Table 1). There was also no significant difference from the control group ($p = 0.421$).

Lists of prescribed HMPs Q-, LM-, C- and D-potencies are shown in Table S2 (Homeopathic HMPs: Q-potencies

Table 1 Baseline characteristics and treatment

	Total sample	Homeopathy	Placebo	Control	Homeopathy vs. Placebo		Treatment[#] vs. Control	
n	150	51	47	52	RR	*p*	RR	*p*
% of total sample		34.0	31.3	34.7				
Male, *n* (% [95% CI])	81 (54.0 [46.0;62.0])	26 (51.0 [37.3;64.7])	27 (57.4 [43.3;71.6])	28 (53.8 [40.3;67.4])	0.89	0.331[a]	1.01	0.557[a]
Age (yrs), mean (SD) [95% CI] {Min;Max}	63.2 (8.9) [61.8;64.6] {33;87}	63.2 (8.8) [60.8;65.7] {33;83}	62.5 (8.9) [59.7;65.0] {43;81}	63.9 (9.1) [61.4;66.4] {35;87}		0.686[b]		0.892[b]
Age group, *n* (% [95% CI])								
<45	3 (2.0 [0.0;4.2])	1 (2.0 [0.0;5.8])	1 (2.1 [0.0;6.3])	1 (1.9 [0.0;5.7])	0.95	0.995[a]	1.07	0.148[a]
45–65	88 (58.7 [50.8;66.5])	33 (64.7 [51.6;77.8])	30 (63.8 [50.1;77.6])	25 (48.1 [34.5;61.7])	1.01		1.34	
>65	59 (39.3)	17 (33.3 [20.4;46.3])	16 (34.0 [20.5;47.6])	26 (50.0 [36.4;63.6)	0.98		0.67	
Histology, *n* (% [95% CI])								
adenocarcinoma	117 (78.0 [71.4;84.6])	39 (76.5 [64.8;88.1])	40 (85.1 [74.9;95.3])	38 (73.1 [61.0;85.1])	0.90	0.219[a]	2.17	0.421[a]
squamous cell carcinoma	27 (18.0 [11.9;24.1])	10 (19.6 [8.4;30.5])	4 (8.5 [0.5;16.5])	13 (25.0 [13.2;36.8])	2.3		0.57	
lung carcinoma-NOS*	5 (3.3 [0.5;6.2])	1 (2.0 [0.0;5.8])	3 (6.4 [0.0;13.4])	1 (1.9 [0.0;5.7])	0.3		2.15	
large-cell carcinoma	1 (0.7 [0.0;2.0])	1 (2.0 [0.0;5.8])	0 (0.0)	0 (0.0)	-		-	
Karnofsky-Index, mean (SD) [95% CI] {Min;Max}	85.6 (15.7) [83.1;88.1] {50–100}	82.8 (15.9) [78.3;87.2] {50–100}	86.8 (17.5) [81.7;91.9] {50–100}	87.3 (13.4) [83.6;91.1] {50–100}		0.231[b]		0.301[c]
Smoking status, *n* (% [95% CI])	142	49	45	48				
Non- or Ex-smoker	55 (38.7 [30.7;46.7])	22 (44.9 [31.0;58.8])	18 (40.0 [25.7;54.3])	15 (31.3 [18.1;44.4])	1.12	0.393[a]	1.36	0.130[a]
Smoker	87 (61.3 [53.3;69.3])	27 (55.1 [41.2;69.0])	27 (60.0 [45.7;74.3])	33 (68.8 [55.6;81.9])	0.92		0.83	
T-staging, *n* (% [95% CI])	150	51	47	52				
1	4 (2.7 [0.1;5.2])	0 (0.0)	2 (4.3 [0.0;10.0])	2 (3.8 [0.0;9.1])	-	0.549[a]	0.54	0.502[a]
1a	7 (4.7 [1.3;8.0])	2 (3.9 [0.0;9.2])	3 (6.4 [0.0;13.4])	2 (3.8 [0.0;9.1])	0.61		1.34	
1b	9 (6.0 [2.2;9.8])	3 (5.9 [0.0;12.3])	0 (0.0)	6 (11.5 [2.9;20.2])	-		0.27	
1c	1 (0.7 [0.0;2.0])	1 (2.0 [0.0;5.8])	0 (0.0)	0 (0.0)	-		-	

Table 1 (continued)

	Total sample	Homeopathy	Placebo	Control	Homeopathy vs. Placebo		Treatment[#] vs. Control	
n	150	51	47	52	RR	*p*	RR	*p*
2	14 (9.3 [4.7;14.0])	4 (7.8 [0.5;15.2])	5 (10.6 [1.8;19.5])	5 (9.6 [1.6;17.6])	0.74		0.96	
2a	25 (16.7 [10.7;22.6])	9 (17.6 [7.2;28.1])	10 (21.3 [9.6;33.0])	6 (11.5 [2.9;20.2])	0.83		1.69	
2b	10 (6.7 [2.7;10.7])	2 (3.9 [0.0;9.2])	3 (6.4 [0.0;13.4])	5 (9.6 [1.6;17.6])	0.61		0.53	
3	35 (23.3 [16.6;30.1])	14 (27.5 [15.2;39.7])	9 (19.1 [7.9;30.4])	12 (23.1 [11.6;34.5])	1.44		1.02	
4	39 (26.0 [19.0;33.0])	14 (27.5 [15.2;39.7])	12 (25.5 [13.1;38.0])	13 (25.0 [13.2;36.8])	1.08		1.06	
X	6 (4.0 [0.9;7.1])	2 (3.9 [0.0;9.2])	3 (6.3 [0.0;13.4])	1 (1.9 [0.0;5.7])	0.62		2.69	
N-staging, n (% [95% CI])	150	51	47	52				
0	14 (9.3 [4.7;14.0])	2 (3.9 [0.0;9.2])	2 (4.3 [0.0;10.0])	10 (19.2 [8.5;29.9])	0.91	0.519[a]	0.21	***0.010***[a]
1	20 (13.3 [7.9;18.8])	5 (9.8 [1.6;18.0])	4 (8.5 [0.5;16.5])	11 (21.2 [10.1;32.3])	1.15		0.43	
1a	1 (0.7 [0.0;2.0])	1 (2.0 [0.0;5.8])	0 (0.0)	0 (0.0)	-		-	
2	54 (36.0 [28.3;43.7])	19 (37.3 [24.0;50.5])	18 (38.3 [24.4;52.2])	17 (32.7 [19.9;45.4])	0.97		1.15	
2c	1 (0.7 [0.0;2.0])	1 (2.0 [0.0;5.8])	0 (0.0)	0 (0.0)	-		-	
3	56 (37.3 [29.6;45.1])	20 (39.2 [25.8;52.6])	23 (48.9 [34.6;63.2])	13 (25.0 [13.2;36.8])	0.80		1.76	
X	4 (2.7 [0.1;5.2])	3 (5.9 [0.0;12.3])	0 (0.0)	1 (1.9 [0.0;5.7])	-		1.61	

Table 1 (continued)

	Total sample	Homeopathy	Placebo	Control	Homeopathy vs. Placebo		Treatment[#] vs. Control	
n	150	51	47	52	RR	*p*	RR	*p*
M-staging, *n* (% [95% CI])	150	51	47	52				
0	17 (11.3 [6.3;16.4])	3 (5.9 [0.0;12.3])	8 (17.0 [6.3;27.8])	6 (11.5 [2.9;20.2])	0.35	0.238[a]	0.98	0.688[a]
1	2 (1.3 [0.0;3.2]	1 (2.0 [0.0;5.8])	0 (0.0)	1 (1.9 [0.0;5.7])	-		0.54	
1a	42 (28.0 [20.8;35.2]	16 (31.4 [18.6;44.1])	10 (21.3 [9.6;33.0])	16 (30.8 [18.2;43.3])	1.47		0.86	
1b	87 (58.8 [50.1;65.9])	30 (58.8 [45.3;72.3])	29 (61.7 [47.8;75.6])	28 (53.8 [40.3;67.4])	0.95		1.12	
3	1 (0.7 [0.0;20.0]	1 (2.0 [0.0;5.8])	0 (0.0)	0 (0.0)	-		-	
X	1 (0.7 [0.0;20.0]	0 (0.0)	0 (0.0	1 (1.9 [0.0;5.7])	-		-	
Stage groups, *n* (% [95% CI])	150	51	47	52				
IIIB	11 (7.3 [3.2;11.5])	3 (5.9 [0.0;12.3])	3 (6.4 [0.0;13.4])	5 (9.6 [1.6;71.6])	0.92	0.102[a]	0.64	0.081[a]
IIIC	4 (2.7 [0.1;5.2])	0 (0.0)	4 (8.5 [0.5;16.5])	0 (0.0)	-		-	
IV	135 (90.0 [85.2;94.8])	48 (94.1 [87.7;100.0])	40 (85.1 [74.9;95.3])	47 (90.4 [82.4;98.4])	1.11		0.99	
Radiotherapy, *n* (% [95% CI])	13 (8.7 [4.2;13.2])	4 (7.8 [0.5;15.2])	4 (8.5 [0.5;16.5])	5 (9.6 [1.6;17.6])	0.92	0.772[a]	0.85	0.631[a]
Whole brain radiation, *n* (% [95% CI])	28 (18.7 [12.4;24.9])	9 (17.6 [7.2;28.1])	10 (21.3 [9.6;33.0])	9 (17.3 [7.0;27.6])	0.83		1.12	
Operation, *n* (% [95% CI])	1 (0.7 [0.0;20.0]	0 (0.0)	0 (0.0	1 (1.9 [0.0;5.7])	-		-	
Pneumonectomy, *n* (% [95% CI])	1 (0.7 [0.0;20.0]	1 (2.0 [0.0;5.8])	0 (0.0)	0 (0.0)	-		-	
Chemotherapy, cycles mean (median)	4.5 (4)	4.7 (4)	4.3 (4)	4.5 (4)		0.800[d]		
Brain metastases, *n* (% [95% CI])	35 (23.3 [16.6;30.1])	12 (23.5 [11.9;35.2])	10 (21.3 [9.6;33.0])	13 (25.0 [13.2;36.8])	1.10	0.846[a]	0.90	0.908[a]

Table 1 (continued)

	Total sample	Homeopathy	Placebo	Control	Homeopathy vs. Placebo		Treatment[#] vs. Control	
n	150	51	47	52	RR	*p*	RR	*p*
Liver metastases, *n* (% [95% CI])	23 (15.3 [9.6;21.1])	7 (13.7 [4.3;23.2])	7 (14.9 [4.7;25.1])	9 (17.3 [7.0;27.6])	0.92	0.921[a]	0.83	0.876[a]
Change to carboplatin, *n* (% [95% CI])	20 (13.3 [7.9;18.8])	7 (13.7 [4.3;23.2])	6 (12.8 [3.2;22.3])	7 (13.5 [4.2;22.7])	1.07	0.948[a]	0.98	0.990[a]
Immunotherapy, *n* (% [95% CI])	30 (20.0 [13.6;26.4])	11 (21.6 [10.3;32.9])	9 (19.1 [7.9;30.4])	10 (19.2 [8.5;29.9])	1.13	0.762[a]	1.06	0.942[a]

[a]X^2-test/Fisher's exact test
[b]*t*-test for independent sample and homogenous variances
[c]Mann–Whitney-*U*-Test
[d]ANOVA: analysis of variance (all over group comparison)
[#]Treatment = Homeopathy or Placebo Treatment
[*]lung carcinoma-NOS: lung carcinoma-not otherwise specified
Numbers in parentheses are percentages
italicized *p* values mean significant
Abbreviation: *p*: *p* values

(prescribed in series) and Table S3 (Homeopathic HMPs, LM-, C- and D-potencies). There was no difference between homeopathy and placebo groups with respect to selection of HMPs or change of Q-potencies between the two treatment groups (change of Q-potencies: 11 times (21.6%) in homeopathy patients, 14 times (29.8%) in placebo patients, $p = 0.242$).

Questionnaire EORTC QLQ-C30 data (Table 2)

The changes in global health status, functional scales, and symptom scales at baseline, 9 and 18 weeks (visits 1, 2 and 3) for patients in the treatment groups are summarized in Table 2. A total of 26,390 data points were collected. In 96 cases, or 3.6‰, patients corrected their own outcome measures by hand. Only one patient was missing a point. Based on our experience from a previous large-scale study [14], we explicitly instructed patients to answer all questions on the questionnaires in full. This request was obviously fully understood by the patients. Therefore, imputation was not necessary.

At baseline, there were no significant differences between the treatment groups found apart from constipation ($p = 0.048$), which was more common in the homeopathy group. At 9 and 18 weeks, the global health status of the verum group was significantly higher than that of the placebo group ($p < 0.001$). According to all the functional scales, apart from cognitive functioning (no difference between groups after 9 weeks), patients in the homeopathy group at both follow-up visits had significantly higher functional scales than patients in the placebo group, both by univariate analysis of the individual functional scales and by multivariate consideration of all functional scales. Multivariate analysis (general logistic model for repeated measurements, test size: Wilk's λ) revealed a significant time effect ($p < 0.001$) for the functional scales, i.e. the mean scale values change between the survey times, with a significant difference both between baseline and 9 weeks and between baseline and 18 weeks ($p < 0.001$ and $p < 0.001$ respectively), and a significant group effect (<0.001), but additionally a significant interaction between time and group (<0.001), caused by an improvement in homeopathy group and worsening in the placebo group.

After 9 weeks, all symptom scales except pain, diarrhea, and financial difficulties, scores were significantly lower (i.e., less symptom burden) in the homeopathy group than in the placebo group by both univariate analysis of the individual symptom scales and by multivariate analysis of all symptom scales. After 18 weeks, scores were significantly lower for all symptom scales in the homeopathy group than in the placebo group by both univariate and multivariate

Table 2 Questionnaire EORTC QLQ-C30

	Total treatment sample			Homeopathy			Placebo			Homeopathy vs. Placebo *p* values	Homeopathy vs. Placebo *p* values
	n	Mean [95% CI]	SD	*n*	Mean [CI]	SD	*n*	Mean [CI]	SD	Univariate[a/b]	Multivariate[c]
Visit 1 (Baseline)											
Global health status (QoL)	98	48.8 [43.5;54.4]	26.8	51	46.6 [39.5;54.2]	25.8	47	51.2 [43.0;59.4]	28.0	0.397[a]	
Functional **scales**											
Physical functioning	98	66.4 [61.3;71.4]	25.0	51	65.0 [58.0;71.8]	24.0	47	67.9 [60.2;75.6]	26.1	0.561[a]	0.815
Role functioning	98	51.7 [44.9;58.2]	32.8	51	52.7 [42.8;61.9]	33.3	47	50.7 [41.1;60.2]	32.6	0.768[a]	
Emotional functioning	98	63.0 [57.1;68.1	27.3	51	62.5 [53,8;69.7]	28.2	47	63.5 [55.7;71.3]	26.5	0.864[a]	
Cognitive functioning	98	80.8 [76.0;85.2]	22.8	51	79.1 [72.1;85.3]	23.2	47	82.6 [76.0;89.2]	22.5	0.451[a]	
Social functioning	97	66.4 [60.8;67.0]	27.6	50	66.7 [58.6;74.8]	28.6	47	66.0 [58.1;73.9]	26.9	0.910[a]	
Symptom scales											
Fatigue	98	51.3 [45.6;57.7]	29.8	51	50.8 [42.4;60.3]	31.5	47	51.9 [43.6;60.2]	28.3	0.850[a]	0.200
Nausea vomiting	98	13.7 [9.3;18.3]	22.4	51	14.7 [8.1;21.9]	24.2	47	12.5 [6.5;18.5]	20.5	0.627[a]	
Pain	97	32.1 [25.3;39.0]	34.2	50	29.4 [20.1;38.7]	32.7	47	35.1 [24.6;45.6]	35.8	0.411[a]	
Dyspnea	97	39.5 [32.2;46.8]	36.2	50	39.3 [29.0;49.6]	36.1	47	39.7 [28.9;50.4]	36.6	0.959[a]	
Insomnia	97	39.2 [31.6;46.7]	37.3	50	37.3 [26.5;48.1]	37.9	47	41.1 [30.3;52.0]	37.0	0.616[a]	
Appetite loss	97	26.4 [19.4;33.5]	35.0	50	30.6 [19.7;41.6]	38.6	47	22.0 [13.0;31.0]	30.6	0.227[a]	
Constipation	98	24.5 [18.1;31.4]	33.0	51	30.7 [20.9;41.7]	36.5	47	17.7 [10.0;14.4]	27.7	***0.048***[b]	
Diarrhea	98	12.6 [7.1;18.3]	27.7	51	16.3 [7.2;26.0]	32.9	47	8.5 [2.6;14.5]	20.3	0.159[b]	
Financial difficulties	97	13.4 [8.4;18.4]	24.8	50	12.6 [5.3;20.0]	26.0	47	14.1 [7.1;21.1]	23.8	0.770[a]	
Visit 2 (9 weeks)											
Global health status (QoL)	85	54.9 [48.7;61.2]	28.9	49	64.2 [56.6;71.7]	26.3	36	42.4 [33.0;51.8]	27.7	***<0.001***[a]	

Table 2 (continued)

	Total treatment sample			Homeopathy			Placebo			Homeopathy vs. Placebo *p* values	Homeopathy vs. Placebo *p* values
	n	Mean [95% CI]	SD	*n*	Mean [CI]	SD	*n*	Mean [CI]	SD	Univariate[a/b]	Multivariate[c]
Functional scales											
Physical functioning	85	66.2 [60.1;73.4]	28.5	49	77.0 [70.2;83.8	23.6	36	51.5 [42.0;61.1]	28.2	***<0.001***[a]	***<0.001***
Role functioning	85	54.7 [47.2;62.2]	34.8	49	68.7 [60.0;77.4]	30.4	36	35.7 [25.0;46.4]	31.7	***<0.001***[a]	
Emotional functioning	85	66.3 [60.2;72.5]	28.4	49	77.0 [69.6;84.3]	25.5	36	51.5 [43.2;60.6]	28.2	***<0.001***[a]	
Cognitive functioning	85	81.3 [76.5;86.2]	22.3	49	84.6 [78.6;90.6]	20.9	36	76.9 [68.9;84.9]	23.6	0.113[a]	
Social functioning	85	64.8 [57.3;72.2]	33.6	49	76.0 [66.6;85.4]	32.8	36	49.5 [38.9;60.1]	31.3	***<0.001***[a]	
Symptom scales											
Fatigue	85	47.3 [40.0;54.5]	33.9	49	33.2 [24.8;41.7]	29.4	36	66.4 [56.5;76.4]	29.5	***<0.001***[a]	***<0.001***
Nausea vomiting	85	18.9 [13.6;24.1]	24.4	49	11.2 [6.0;16.5]	18.5	36	29.2 [19.9;38.5]	27.4	***0.001***[b]	
Pain	85	25.1 [18.5;31.8]	30.8	49	19.8 [11.2;28.4]	30.0	36	32.4 [22.0;42.9]	30.9	0.061[a]	
Dyspnea	85	33.7 [26.3;41.0]	34.0	49	23.1 [14.3;31.9]	30.6	36	48.1 [36.8;59.4]	33.4	***0.001***[a]	
Insomnia	85	37.2 [29.2;45.3]	37.3	49	22.4 [13.4;31.5]	31.5	36	57.4 [45.4;69.4]	35.4	***<0.001***[a]	
Appetite loss	85	30.2 [22.9;37.5]	33.7	49	20.4 [11.7;29.1]	29.6	36	43.6 [32.4;55.0]	33.7	***0.001***[a]	
Constipation	85	29.4 [21.7;37.0]	35.5	49	20.4 [11.9;28.9]	29.7	36	41.6 [28.3;55.0]	39.4	***0.008***[b]	
Diarrhea	85	11.4 [6.3;16.4]	23.4	49	10.2 [3.6;16.7]	22.8	36	13.0 [4.7;21.2]	24.3	0.590[a]	
Financial difficulties	85	15.0 [9.0;21.0]	27.8	49	11.1 [4.1;18.2]	24.7	36	20.3 [9.8;30.8]	31.1	0.134[a]	
Visit 3 (18 weeks)											
Global health status (QoL)	79	67.7 [60.6;74.8]	31.7	46	86.4 [81.0;91.8]	18.1	33	41.6 [31.6;51.5]	28.1	***<0.001***[b]	
Functional scales											

Table 2 (continued)

	Total treatment sample			Homeopathy			Placebo			Homeopathy vs. Placebo *p* values	Homeopathy vs. Placebo *p* values
	n	Mean [95% CI]	SD	*n*	Mean [CI]	SD	*n*	Mean [CI]	SD	Univariate[a/b]	Multivariate[c]
Physical functioning	79	72.6 [65.5;79.6]	31.5	46	90.0 [85.3;94.7]	15.9	33	48.2 [37.0;59.5]	31.8	***<0.001***[b]	***<0.001***
Role functioning	79	61.6 [53.6;69.6]	35.8	46	83.3 [76.8;89.8]	22.0	33	31.3 [21.2;41.5]	28.6	***<0.001***[a]	
Emotional functioning	79	73.4 [66.9;80.0]	29.3	46	89.8 [85.7;93.9]	13.7	33	50.6 [39.9;61.2]	30.0	***<0.001***[b]	
Cognitive functioning	79	81.0 [75.4;86.5]	24.7	46	89.1 [84.1;94.1]	16.9	33	69.7 [59.3;80.1]	29.3	***0.001***[b]	
Social functioning	79	70.5 [62.4;78.6]	36.3	46	86.6 [79.0;94.3]	25.7	33	48.0 [34.8;61.2]	37.2	***<0.001***[b]	
Symptom scales											
Fatigue	79	37.1 [29.2;45.0]	35.3	46	16.3 [9.9;22.8]	21.7	33	66.0 [55.4;76.7]	30.0	***<0.001***[b]	***<0.001***
Nausea vomiting	79	16.9 [10.7;23.1]	27.5	46	6.9 [2.5;11.3]	14.8	33	30.8 [18.6;43.1]	34.6	***0.001***[b]	
Pain	79	21.5 [14.9;28.3]	30.2	46	8.7 [3.1;14.4]	18.9	33	39.4 [27.3;51.4]	34.0	***<0.001***[b]	
Dyspnea	79	28.3 [20.9;35.7]	33.0	46	10.1 [3.9;16.4]	21.0	33	53.5 [42.8;64.2]	30.1	***<0.001***[b]	
Insomnia	79	26.5 [19.0;34.0]	33.5	46	10.1 [4.6;15.5]	18.4	33	49.5 [36.5;62.4;]	36.5	***<0.001***[b]	
Appetite loss	79	24.9 [17.4;32.4]	33.6	46	12.3 [6.2;18.3]	20.3	33	42.5 [28.2;56.7]	40.3	***<0.001***[b]	
Constipation	79	19.0 [12.2;25.7]	30.1	46	10.1 [4.3;16.0]	19.7	33	31.3 [18.1;44.6]	37.3	***0.005***[b]	
Diarrhea	79	11.0 [5.1;16.8]	26.0	46	4.3 [0.0:8.8]	15.1	33	20.2 [8.0;32.4]	34.3	***0.017***[b]	
Financial difficulties	79	10.5 [5.5;15.5]	22.3	46	5.0 [0.9;9.2]	14.0	33	18.1 [7.9;28.4]	29.0	***0.021***[b]	

[a] *t*-test for independent sample and homogenous variances

[b] *t*-test for independent sample and heterogenous variances

[c] General Linear Model

All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. Thus a high score for a functional scale represents a high/healthy level of functioning, a high score for the global health status/Quality of Life (QoL) represents a high QoL, but a high score for a symptom scale/item represents a high level of symptomatology/problems

italicized *p* values mean significant Abbreviation: EORTC: European Organisation for Research and Treatment of Cancer

analysis. There was also an improvement between visit 1 and visit 2 and between visit 2 and 3 within the homeopathy group, but not in the placebo group. Multivariate analysis revealed a significant time effect both between baseline and 9 weeks ($p < 0.001$) and baseline and 18 weeks ($p < 0.001$) and a significant group effect (<0.001), and also a significant interaction between time and group (<0.001).

The same effects could be seen for Global Health status, with a significant time effect ($p < 0.001$), group effect ($p < 0.001$) and interaction between time and group ($p = 0.002$).

Questionnaire SF-36 (Table 3)

The changes in the indices of the SF-36 questionnaire at baseline, 9 and 18 weeks for the treatment groups are summarized in Table 6 demonstrating significantly better values for the patients of the homeopathy group vs. placebo group.

Self-assessment of subjective well-being (Table 4)

Self-assessment of subjective well-being, which was evaluated using a visual analog scale, yielded similar results to those obtained with EORTC-QLQC30 and SF-36 (Table 7) demonstrating significantly better values for the patients of the homeopathy group vs. placebo group.

Survival (Table 5, Fig. 3)

The median survival time over the observation period of 730 days for the homeopathy group (435 days) was significantly longer than the placebo group (257 days; $p = 0.010$). Median survival of the control group (228 days) was significantly shorter than that of the homeopathy group ($p < 0.001$), but not than that of the placebo group ($p = 0.258$).

When comparing treatment groups (homeopathy plus placebo group) to control group, there was a significant difference with regard to the pairwise comparison of homeopathy vs placebo (treatment groups vs control: $p = 0.002$).

Regarding patients who died within the 730-day period, there was no significant difference in the median survival time between the homeopathy and the placebo groups ($p = 0.172$); however, the homeopathy group had a significantly longer survival time than the control group ($p = 0.020$). There was no significant difference between placebo and control groups ($p = 0.747$) or between the two treatment groups and the control group ($p = 0.142$).

Estimated survival time (hazard ratio for mean) was 477 (95% CI 410–545) days in homeopathy group, 352 (95% CI 278–427) days in placebo group and 274 (95% CI 215–333) days in control group ($p < 0.001$ comparing all 3 groups; $p = 0.014$ homeopathy vs. placebo group; $p < 0.001$ homeopathy vs. control; $p = 0.145$ placebo vs. control group). Survival rate in homeopathy group was 45.1%, 23.4% in placebo group and 13.5% in control group. While survival rate in homeopathy group differed significantly from placebo ($p = 0.020$) and from control group ($p < 0.001$), the difference between placebo and control ($p = 0.154$) was not significant (overall difference was significant at $p < 0.001$).

An independent doctor evaluated the cause of death and assured that all patients who died did so as a direct consequence of their underlying cancer; none died because of other reasons such as myocardial infarction, pulmonary embolism, or other major diseases. No adverse effects were reported.

Attitude towards homeopathy (Table 6)

No differences regarding attitude towards homeopathy were detected between the two treatment groups except for referral to previous homeopathic treatment and expectation regarding prognosis: while the majority of homeopathy patients (57.1%) had been referred by practitioners (only 17.6% of placebo patients), placebo patients significantly more often opted for homeopathic treatment themselves (47.1%, only 7.1% in homeopathy patients; $p = 0.039$). In the homeopathy group, the expectation of the effect of homeopathy on the prognosis was significantly more negative ($p = 0.010$). In the placebo group, patients perceived significantly more minor adverse effects such as nausea and diarrhea ($p = 0.023$).

Patients' use of CAM treatments (Table 7)

Regarding previous CAM use, no statistically significant difference could be found between the two treatment groups. Psychotherapy was the most used CAM modality in all groups.

Discussion

Summary of principal findings

In this prospective, randomized, placebo-controlled, double-blind, three-arm, multicenter phase III study with quadruple-checked data analysis, patients allocated to add-on homeopathy reported a better QoL than patients allocated to placebo.

Table 3 Questionnaire SF-36: 36-Item Short Form Health Survey

	Total treatment sample			Homeopathy			Placebo			Homeopathy vs. Placebo *p* values	Homeopathy vs. Placebo *p* values
	n	Mean [95% CI]	SD	*n*	Mean [CI]	SD	*n*	Mean [CI]	SD	Univariate[a/b]	Multivariate[c]
Visit 1 (Baseline)											
Functioning Index	93	57.7 [52.4;64.3]	28.8	47	56.6 [49.3;65.1]	26.5	46	58.9 [50.2;68.7]	31.7	0.705	0.257
Role-Physical Index	93	36.7 [27.9;44.7]	40.3	47	40.4 [28.7;52.5]	39.5	46	32.8 [19.9;44.3]	41.2	0.366	
Role-Emotional Index	92	48.0 [37.7;56.0]	44.0	46	45.6 [31.4;57.4]	43.6	46	50.4 [36.0;62.6]	44.8	0.609	
Social Functioning Index	92	60.9 [53.8;66.9]	31.7	46	61.3 [50.5;70.3]	33.1	46	60.5 [51.3;69.3]	30.6	0.906	
Mental Health Index	92	58.1 [52.6;62.5]	23.6	46	55.4 [47.2;62.7]	25.7	46	61.0 [53.7;66.5]	21.1	0.259	
Bodily Pain Index	92	64.7 [57.5;70.8]	32.0	46	69.9 [60.5;77.9]	28.9	46	59.4 [49.1;69.3]	34.3	0.118	
Vitality Index	92	45.9 [40.7;51.2]	25.4	46	44.7 [36.4;52.3]	26.2	46	47.2 [40.2;54.8]	24.7	0.634	
General Health Perceptions Index	91	50.3 [46.1;55.0]	21.2	45	46.7 [39.5;53.9]	20.1	46	53.8 [49.1;59.6]	17.5	0.110	
Visit 2 (9 weeks)											
Functioning Index	83	63.0 [56.4;69.5]	29.9	45	74.3 [66.6;82.1]	25.7	38	49.5 [39.9;59.1]	29.2	***< 0.001***	***< 0.001***
Role-Physical Index	83	43.0 [34.3;52.2]	41.1	45	60.0 [47.5;76.2]	41.8	38	22.3 [13.6;33.2]	29.3	***< 0.001***	
Role-Emotional Index	83	58.1 [48.4;67.2]	43.2	45	69.7 [57.6;81.7]	40.1	38	44.1 [29.8;57.8]	43.1	***0.007***	
Social Functioning Index	83	65.0 [58.5;71.7]	30.3	45	77.4 [70.4;84.5]	23.5	38	49.8 [40.4;60.6]	31.0	***< 0.001***	
Mental Health Index	83	63.2 [58.1;68.2]	23.1	45	74.0 [68.8;79.2]	17.3	38	50.1 [43.0;57.7]	22.7	***< 0.001***	
Bodily Pain Index	83	72.5 [65.4;78.5]	29.9	45	81.0 [73.0;88.9]	26.4	38	62.1 [51.1;71.4]	30.9	***0.004***	
Vitality Index	83	54.1 [48.2;60.5]	28.4	45	68.4 [61.1;75.8]	24.6	38	36.6 [30.0;45.2]	22.6	***< 0.001***	
General Health Perceptions Index	83	54.4 [48.5;59.8]	26.0	45	65.4 [58.5;72.4]	23.3	38	40.9 [33.3;48.2]	22.9	***< 0.001***	
Visit 3 (18 weeks)											
Functioning Index	78	67.9 [60.5;75.5]	33.3	44	88.6 [83.6;93.7]	16.6	34	41.2 [30.6;51.7]	30.3	***< 0.001***	***< 0.001***
Role-Physical Index	78	54.8 [44.5;65.1]	45.6	44	79.0 [68.4;89.6]	34.9	34	23.5 [10.1;36.9]	38.4	***< 0.001***	
Role-Emotional Index	78	68.8 [59.0;78.6]	43.4	44	87.1 [77.5;96.7]	31.5	34	45.1 [29.2;61.0]	45.6	***< 0.001***	
Social Functioning Index	78	69.5 [61.3;77.8]	36.6	44	88.7 [81.5;95.9]	25.6	34	44.7 [32.2;44.1]	35.7	***< 0.001***	
Mental Health Index	78	68.2 [62.1;74.3]	27.1	44	83.6 [78.9;88.2]	15.4	34	48.4 [39.2;57.5]	26.2	***< 0.001***	
Bodily Pain Index	78	78.7 [72.1;85.3]	29.3	44	92.4 [87.0;97.8]	17.8	34	60.9 [49.8;72.0]	31.9	***< 0.001***	
Vitality Index	78	59.2 [51.7;66.7]	33.2	44	81.1 [75.1;87.2]	19.9	34	30.9 [22.4;39.3]	24.2	***< 0.001***	
General Health Perceptions Index	78	59.6 [52.4;66.8]	32.0	44	81.2 [75.4;87.1]	19.2	34	31.7 [24.0;39.3]	21.9	***< 0.001***	

[a] *t*-test for independent sample and homogenous variances

[b] *t*-test for independent sample and heterogenous variances

[c] General Linear Model; italicized p values mean significant

Table 4 Self-assessment of subjective well-being (VAS[a])

	Total treatment sample			Homeopathy		Placebo		Homeopathy vs. Placebo *p* value	Time effect vs. baseline *p* value	Time x group effect *p* value
	n	Mean [95% CI]	SD	Mean [95% CI]	SD	Mean [95% CI]	SD	Univariate	GLM for time effects[d]	
Visit 1 (Baseline)	97	3.99 [3.67;4.31]	1.59	3.84 [3.43;4.26]	1.48	4.15 [3.64;4.66]	1.71	0.342[b]		
Visit 2 (9 weeks)	87	4.37 [4.00;4.41]	1.75	5.08 [4.65;5.52]	1.51	3.45 [2.92;3.98]	1.61	***<0.001***[b]	0.155	***<0.001***
Visit 3 (18 weeks)	80	4.95 [4.51;5.39]	1.99	6.21 [5.88;6.54]	1.12	3.15 [2.60;3.70]	1.54	***<0.001***[c]	***0.010***	***<0.001***

[a]VAS: Visual Analogue Scale

[b]*t*-test for independent sample and homogenous variances

[c]*t*-test for independent sample and heterogeneous variances

[d]General Linear Model

Italicized *p* values mean significant

Global health status differed statistically significant at 9 weeks and at 18 weeks on the EORTC QLQ-C30 scale ($p < 0.001$). According to established interpretation guidelines, differences exceeding 10 points on the EORTC QLQ-C30 are considered clinically meaningful [35, 36]. All functional scales favored the homeopathy group at 18 weeks, while cognitive functioning did not differ between the groups at 9 weeks; among the symptom scales, pain, diarrhea and financial difficulties did not differ significantly at 9 weeks, whereas all symptom scales favored the homeopathy group at 18 weeks. These findings were corroborated by the SF-36 questionnaire and by the visual analog scale assessment of subjective well-being. Multivariate analysis revealed significant time and group effects as well as a significant interaction between time and group ($p < 0.001$), indicating that scores improved over time in the homeopathy group while they deteriorated in the placebo group.

A difference in survival was also observed. Median survival time was 435 days in the homeopathy group compared with 257 days in the placebo group ($p = 0.010$) and 228 days in the non-randomized control group ($p < 0.001$). The 2-year survival rate was 45.1% in the homeopathy group, 23.4% in the placebo group and 13.5% in the control group. The direction of the effect corresponds to that of our previous retrospective analysis of survival in cancer patients receiving additive homeopathy [15]; because that analysis shares investigators and setting with the present work, it does not constitute independent confirmation. There were slightly more patients with squamous cell carcinoma in the homeopathy group. Since the prognosis of squamous cell carcinoma is generally less favorable than that of adenocarcinoma [38], this imbalance is unlikely to have produced a spurious advantage for the homeopathy group; the difference was not statistically significant and the sample is too small for this consideration to carry substantial weight.

Comparison with prior literature

Our QoL findings point in the same direction as our earlier pragmatic randomized controlled trial of 410 cancer patients, in which individualized homeopathic treatment as an add-on to conventional oncological care improved global health status and subjective wellbeing [14]. The present study extends those observations to a double-blind, placebo-controlled setting. Because both randomized groups received an identical homeopathic consultation and an identical treatment ritual, the double-blind comparison annihilates the likelihood that the difference between the two randomized groups is explained by expectation regarding the act of taking a preparation. It does not, however, exclude non-specific effects of the homeopathic consultation itself, which were present in both groups and are discussed in a separate section below.

The survival difference between the placebo and control groups in our study is consistent with the landmark findings of Temel et al. [37], who demonstrated that palliative care integrated with standard oncological care prolonged median survival in metastatic NSCLC patients (11.6 vs. 8.9 months, $p = 0.02$) despite less aggressive end-of-life care. This parallel suggests that interventions addressing symptom burden and overall wellbeing may independently contribute to survival, possibly through improved treatment tolerance, reduced psychological distress, or enhanced immune function.

Recently, the IMPROVE trial reported that a digitally delivered integrative medicine intervention (combining exercise and mind–body therapies) improved overall survival in patients with solid tumors receiving systemic therapy (estimated 24-month OS: 69.1% vs. 52.6%, $p = 0.037$) [38]. While the interventions differ fundamentally from homeopathy, these findings support the broader hypothesis that

Table 5 24-months (730-days) mortality

	Total sample	Homeopathy	Placebo	Control	Homeopathy vs. Placebo *p* values	Homeopathy vs. Control *p* values	Placebo vs. Control *p* values	Treatment vs. Control *p* values
n	150	51	47	52				
Mortality rate, *n* (% [95% CI])	109 (72.7 [65.5;79.8])	28 (54.9 [41,2;68.6])	36 (76.6 [64.5;88.7])	45 (86.5 [77.3;95.8])	***0.020***[a]	***<0.001***[a]	0.154[a]	***0.004***[a]
Observation time (=days of survival) in total group								
Missing values	0	0	0	0				
Minimum	11	54	24	11				
Maximum	730	730	730	730				
Mean (SD) [95% CI]	367 (255) [324;406]	477 (247) [405;542]	352 (264) [275;429]	272 (216) [212;330]	***0.017***[b]	***<0.001***[d]	0.105[d]	***<0.001***[d]
25th percentile	141	235	110	108				
median	274	435	257	228	***0.010***[c]	***<0.001***[c]	0.258[c]	***0.002***[c]
75th percentile	730	703	619	382				
Observation time in mortality group								
n	109	28	36	45				
Missing values	0	0	0	0				
Minimum	11	54	24	11				
Maximum	619	497	619	578				
Mean (SD) [95% CI]	231 (148) [203;259]	270 (220) [224;316]	237 (181) [175;298]	203 (131) [163;242]	0.377[d]	***0.030***[b]	0.349[d]	0.092[b]
25th percentile	110	186	66	104				
median	204	257	192	160	0.172[c]	***0.020***[c]	0.747[c]	0.142[c]
75th percentile	336	378	377	272				

[a]X^2-test/Fisher's exact test

[b]*t*-test for independent sample and homogenous variances

[c]Mann–Whitney-*U*-Test

[d]*t*-test for independent sample and heterogeneous variances

Italicized *p* values mean significant

supportive care interventions addressing patient-reported outcomes may positively influence survival.

A systematic review of homeopathy by Hamre et al. [39] reported that homeopathy was significantly more effective than placebo across multiple meta-analyses. However, the biological plausibility of highly diluted homeopathic preparations remains a subject of scientific debate, and the mechanisms by which such preparations could influence tumor biology or host defense are not established.

Specific and non-specific components of homeopathic care: a whole systems perspective

Insights from WSR suggest that the homeopathic medicinal product should not be equated with homeopathic treatment as a whole [26]. WSR conceptualizes traditional and complementary systems of care as complex, multi-component interventions in which the therapeutic agent, the practitioner, the diagnostic and prescribing process, the therapeutic relationship and the context of care form an interdependent package that cannot be meaningfully reduced to any single component [26, 27]. In our trial, this package comprised a homeopathic case history of approximately 60 min at study entry and follow-up consultations of approximately 30 min every 9 weeks, in which patients were invited to describe their physical, emotional and mental state in detail, an individualized repertorization and prescription process, and a daily self-administered treatment ritual that required the patient to succuss and dilute the HMP. Each of these elements may contribute to the observed outcomes independently of the

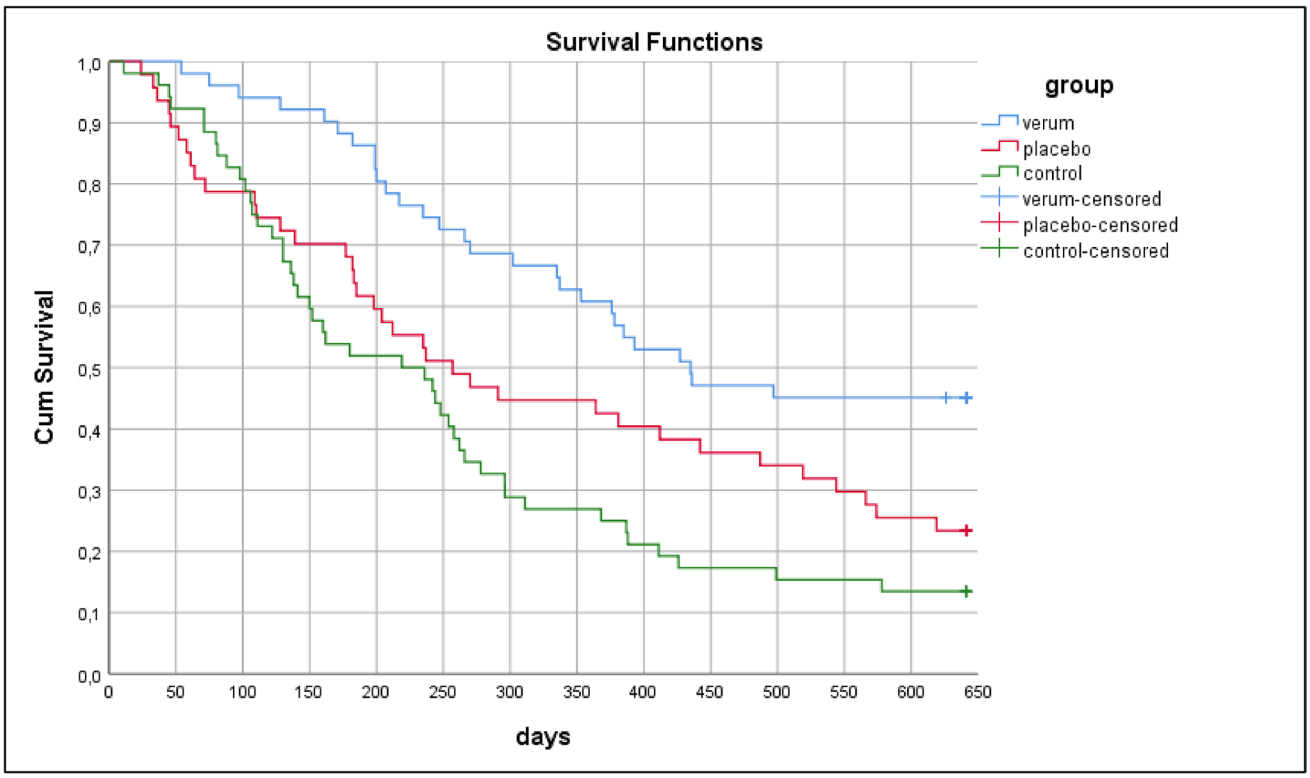

Fig. 3 Kaplan–Meier estimates of overall survival time in the three groups. Crosses indicate time points of censoring (i.e., no patients died after this time point in this study group). Bold italicized values are statistically significant

pharmacological or physicochemical properties of the highly diluted preparation itself.

The literature indicates that these non-specific or contextual components can be substantial. In a double-blind randomized trial in rheumatoid arthritis, Brien et al. dissociated the consultation from the remedy and reported clinically relevant benefits attributable to the homeopathic consultation but not to the homeopathic remedy [18]. Comparable conclusions have been drawn from qualitative and mixed-methods work describing the extended homeopathic encounter as an intervention in its own right, characterized by prolonged attentive listening, narrative elaboration of the illness experience, validation of symptoms that are often not addressed in routine oncological consultations, and strengthening of the patient's sense of agency and of doctor-patient rapport [40, 41]. These mechanisms overlap conceptually with the wider literature on the therapeutic encounter, in which assessment and observation, the therapeutic ritual and a warm, confident patient-practitioner relationship have been shown to contribute incrementally to clinical improvement [42].

It is essential to state clearly what our design can and cannot separate. Both randomized groups received an identical package of homeopathic care: the same homeopathic physicians, consultations of the same length and frequency, the same individualized prescribing process and the same daily preparation ritual. The two groups differed exclusively in whether the dispensed preparation was the individually selected homeopathic medicinal product or an indistinguishable placebo. The comparison of homeopathy versus placebo therefore isolates the contribution of the HMP within the context of homeopathic care, but it cannot quantify the contribution of the consultation itself. Conversely, the comparison with the non-randomized control group, which received no homeopathic consultation at all, reflects the effect of the entire package of care together with any selection effects arising from the non-randomized allocation, and must not be read as an effect of the HMP.

The observation that survival time was numerically longer in the placebo group than in the control group, though it did not reach statistical significance (median 257 versus 228 days; $p = 0.258$ for the medians and $p = 0.154$ for the survival rates), is conceivable as a result of the consultation itself, but by no means constitutes proof of this, and the non-randomized nature of the control group precludes any causal interpretation of this comparison. We consider the impossibility of completely separating the specific effect of the remedy from the non-specific effects of the homeopathic consultation within the framework of the present three-arm design to be a potential limitation of this study. Future studies should be designed accordingly, for example

Table 6 Attitude towards homeopathy

	Total treatment sample	Homeopathy	Placebo	Homeopathy vs. Placebo	
n	98	51	47	**RR**	***p* values**
Basic attitude towards homeopathy, *n* (% [95% CI])					
Valid cases, *n*	95	50	45		
Rejecting	1 (1.1 [0.0;3.1])	1 (2.0 [0.0;5.9])	0 (0.0)	-	0.590[c]
Very sceptic	12 (12.6 [6.0;19.3])	8 (16.0 [5.8;26.2])	4 (8.9 [0.6;17.2])	1.80	
Sceptic	26 (27.4 [18.4;36.3])	12 (24.0 [12.2;35.8])	14 (31.1 [17.6;44.6])	0.77	
Positive	56 (58.9 [49.1;68.8])	29 (58.0 [44.3;71.7])	27 (60.0 [45.7;74.3])	0.97	
Use of homeopathy in the past, *n* [valid cases] (% [95% CI])	32 [96] (33.3 [23.9;42.8])	15 [20] (30.0 [17.3;42.7])	17 [50] (37.0 [23.0;50.9])	0.81	0.306[a]
If yes, who suggested homeopathic therapy?, *n* (% [95% CI])					
Valid cases	31	14	17		
Practitioner	11 (35.5 [18.6;52.3])	8 (57.1 [31.2;83.1])	3 (17.6 [0.0;35.8])	3.24	***0.039[a]***
Patient himself/herself	9 (29.0 [13.1;45.0])	1 (7.1 [0.0;20.6])	8 (47.1 [23.3;70.8])	0.15	
Alternative practitioner	5 (16.1 [3.2;29.1])	3 (21.4 [0.0;42.9])	2 (11.8 [0.0;27.1])	1.81	
Someone else	6 (19.4 [5.4;33.3])	2 (14.3 [0.0;332.6])	4 (23.5 [3.4;43.7])	0.61	
Guess about treatment group, *n* (% [95% CI])					
Valid cases	98	51	47		
Homeopathy	14 (14.3 [7.4;21.2])	9 (17.6 [7.2;28.1])	5 (10.6 [1.8;19.5])	1.66	0.222[a]
Placebo	15 (15.3 [8.2;22.4])	10 (19.6 [8.7;30.5])	5 (10.6 [1.8;19.5])	1.85	
Don't know	69 (70.4 [61.4;79.4])	32 (62.7 [49.5;76.0])	37 (78.7 [67.0;90.4])	0.80	
Expectation regarding quality of life, *n* (% [95% CI])					
Valid cases	98	51	47		
No improvement	12 (12.2 [5.8;18.7])	8 (15.7 [5.7;25.7])	4 (8.5 [0.5;16.5])	1.85	0.383[a]
Improvement	40 (40.8 [31.1;50.5])	22 (43.1 [29.5;56.7])	18 (38.3 [24.4;52.2])	1.13	
Don't know	46 (46.9 [37.1;56.8])	21 (41.2 [27.7;54.7])	25 (53.2 [38.9;67.5])	0.77	
Expectation regarding prognosis, *n* (% [95% CI])					
Valid cases	98	51	47		

Table 6 (continued)

	Total treatment sample	Homeopathy	Placebo	Homeopathy vs. Placebo	
No improvement	22 (22.4 [14.2;30.7])	17 (33.3 [20.4;46.3])	5 (10.6 [1.8;19.5])	3.14	***0.010***[a]
Improvement	25 (25.5 [16.9;34.1])	14 (27.5 [15.2;39.7])	11 (23.4 [11.3;35.5])	1.18	
Don't know	51 (52.0 [42.1;61.9])	20 (39.2 [25.8;52.6])	31 (66.0 [52.4;79.5])	0.59	
Assessment of convenience of homeopathic treatment, *n* (% [95% CI])					
Valid cases	98	51	47		
Moderate	11 (11.2 [5.0;17.5])	6 (11.8 [2.9;20.6])	5 (10.6 [1.8;19.5])	1.11	0.643[a]
Good	64 (65.3 [55.9;74.7])	35 (68.6 [55.9;81.4])	29 (61.7 [47.8;75.6])	1.11	
Don't know	23 (23.5 [15.1;31.9])	10 (19.6 [8.7;30.5])	13 (27.7 [14.9;40.4])	0.71	
Willingness to further homeopathic treatment, *n* (% [95% CI])					
Valid cases	98	51	47		
Yes	72 (73.5 [64.7;82.2])	40 (78.4 [67.1;89.7])	32 (68.1 [54.8;81.4])	1.15	0.498[a]
Perception of adverse effects, *n* (% [95% CI])					
Valid cases	98	51	47		
Yes	3 (3.1 [0.0;6.5])	0 (0.0)	3 (6.4 [0.0;13.4])	-	***0.023***[a]

[a]X^2-test/Fisher's exact test

[b]*t*-test for independent sample and homogenous variances

[c]Mann–Whitney-*U*-Test

Italicized *p* values mean significant

using a four-arm design in which consultation and remedy are factorially varied, as proposed by WSR and implemented by Brien et al. [18, 26], or by complementing quantitative endpoints with qualitative process evaluation. The reason for the lack of randomization in the control group is simply that these patients would have had to consent to homeopathic treatment if they had been randomly assigned to that group, which would have been unlikely given their refusal to participate in the study. Therefore, a four-arm design is not feasible in clinical practice.

Ethical considerations regarding prolonged survival

The observation of prolonged survival in the homeopathy group warrants careful ethical consideration. A central question is whether the extended survival was accompanied by preserved or improved QoL, or whether it risked prolonging a period of suffering [43]. In our study, the data suggest that the survival benefit was accompanied by sustained QoL improvements: patients in the homeopathy group reported significantly better global health status, functional capacity, and lower symptom burden throughout the observation period. Five patients in the homeopathy group consistently reported the highest possible QoL scores across all 66 questionnaire items, independent of their survival time, suggesting excellent subjective wellbeing even in advanced disease stages. All patients who died did so as a direct consequence of their underlying cancer, and no adverse effects were reported in any group.

From the patient perspective, these findings suggest that the survival extension was not associated with increased suffering but rather with maintained or improved quality of life. This is consistent with the observation by experienced palliative care clinicians that patients with advanced cancer often adapt remarkably well to their condition and may describe their QoL as good even in the terminal phase [44]. Nevertheless, the possibility that prolonged survival in some patients may extend a period of declining function cannot be entirely excluded, particularly beyond the 18-week QoL assessment window. Future studies should incorporate longitudinal QoL assessments extending to the end-of-life period to more fully characterize the benefit-burden balance.

Table 7 Previous CAM treatments

	Total treatment sample	Homeopathy	Placebo	Homeopathy vs. placebo	
N	98	51	47	**rr**	***p* values**
Psychotherapy, *n* (% [95% CI])	13 (13.3 [6.5;20.0])	5 (9.8 [1.6;18.0])	8 (17.0 [6.3;27.8])	0.58	0.226[a]
Spiritual practices, *n* (% [95% CI])	2 (2.0 [0.0;4.8])	2 (3.9 [0.0;9.2])	0 (0.0)	-	0.268[a]
Religious practices, *n* (% [95% CI])	5 (5.1 [0.7;9.5])	4 (7.8 [0.5;15.2])	1 (2.1 [0.0;6.3])	3.71	0.208[a]
Vitamins, *n* (% [95% CI])	6 (6.1 [1.4;10.9])	2 (3.9 [0.0;9.2])	4 (8.5 [0.5;16.5])	0.46	0.301[a]
Mistletoe treatment, *n* (% [95% CI])	6 (6.1 [1.4;10.9])	2 (3.9 [0.0;9.2])	4 (8.5 [0.5;16.5])	0.46	0.301[a]
Acupuncture, *n* (% [95% CI])	5 (5.1 [0.7;9.5])	1 (2.0 [0.0;5.8])	4 (8.5 [0.5;16.5])	0.24	0.157[a]
Bach flowers, *n* (% [95% CI])	2 (2.0 [0.0;.4.8])	1 (2.0 [0.0;5.8])	1 (2.1 [0.0;6.3])	0.95	0.732[a]
Herbal medicine, *n* (% [95% CI])	1 (1.0 [0.0;3.0])	1 (2.0 [0.0;5.8])	0 (0.0)	-	0.520[a]
Schuessler salts, *n* (% [95% CI])	1 (1.0 [0.0;3.0])	0 (0.0)	1 (2.1 [0.0;6.3])	-	0.480[a]
Selenium, *n* (% [95% CI])	1 (1.0 [0.0;3.0])	0 (0.0)	1 (2.1 [0.0;6.3])	-	0.480[a]
Myco therapy, *n* (% [95% CI])	1 (1.0 [0.0;3.0])	0 (0.0)	1 (2.1 [0.0;6.3])	-	0.480[a]
Barley grass juice, *n* (% [95% CI])	2 (2.0 [0.0;4.8])	1 (2.0 [0.0;5.8])	1 (2.1 [0.0;6.3])	0.95	0.732[a]
Vital mushroom, *n* (% [95% CI])	1 (1.0 [0.0;3.0])	1 (2.0 [0.0;5.8])	0 (0.0)	-	0.520[a]
Green tea, *n* (% [95% CI])	1 (1.0 [0.0;3.0])	1 (2.0 [0.0;5.8])	0 (0.0)	-	0.520[a]
Jiaogulan tea, *n* (% [95% CI])	1 (1.0 [0.0;3.0])	1 (2.0 [0.0;5.8])	0 (0.0)	-	0.520[a]
Coffee enema, *n* (% [95% CI])	1 (1.0 [0.0;3.0])	1 (2.0 [0.0;5.8])	0 (0.0)	-	0.520[a]
Linseed oil, *n* (% [95% CI])	1 (1.0 [0.0;3.0])	1 (2.0 [0.0;5.8])	0 (0.0)	-	0.520[a]
Dr. Coy diet, *n* (% [95% CI])	1 (1.0 [0.0;3.0])	1 (2.0 [0.0;5.8])	0 (0.0)	-	0.520[a]

[a]X^2-test/Fisher's exact test

Bias and validity considerations

Attribution of adverse effects

All patients in both randomized groups received standard conventional oncological treatment (chemotherapy, radiotherapy, or both) concurrently with the study intervention. Adverse effects reported during the study period were attributed to conventional cancer treatment rather than to the homeopathic or placebo intervention, based on the known toxicity profiles of the administered chemotherapy regimens and the established safety profile of highly diluted homeopathic preparations. No adverse effects attributable to the study intervention were reported in either the homeopathy or placebo group. The observation that patients in the placebo group perceived significantly more minor adverse effects such as nausea and diarrhea ($p = 0.023$) may suggest either a protective effect of homeopathy against treatment-related toxicity or differences in symptom perception between groups. This finding warrants further investigation in future studies with systematic adverse event monitoring and formal causality assessment.

CAM use during the study period

Use of any CAM modality, including homeopathy other than the research treatment, was an explicit exclusion criterion in this study. Participants were screened for CAM use at enrollment, and compliance was monitored throughout the study period. Previous CAM use was systematically assessed (Table 7) and showed no statistically significant differences between the treatment groups. Psychotherapy was the most commonly reported prior CAM modality across all groups. While we cannot entirely exclude unreported concurrent CAM use during the study, the strict exclusion criterion and monitoring procedures minimize this potential source of bias. The absence of significant between-group differences in prior CAM use supports the internal validity of the comparison between homeopathy and placebo groups.

An additional source of potential bias is participants' pre-existing preference for complementary and alternative medicine. CAM research may preferentially attract patients with favorable prior attitudes or expectations, which can influence study experience and the reporting of patient-reported outcomes [45]. In the present randomized comparison, baseline attitudes toward homeopathy and previous CIMCAM use were broadly similar between the homeopathy and placebo groups, and blinding reduced differential expectation regarding receipt of the active preparation. Nevertheless, because both randomized groups elected to participate in a homeopathy trial, a general preference or openness toward CAM may have affected subjective QoL reporting in both groups and may limit generalizability to patients without such preferences. This possibility should be considered particularly when interpreting patient-reported outcomes, even though it is less likely to explain the between-group survival difference.

"Antidote" considerations

Classical homeopathic doctrine posits that certain substances—including coffee, camphor, menthol, and strong aromatic compounds—as well as some conventional medications may "antidote" (i.e., suppress or interfere with) the action of homeopathic remedies [46]. In the context of standard oncological care, patients routinely receive multiple conventional drugs including corticosteroids (e.g. dexamethasone as antiemetic premedication), opioid analgesics, antiemetics, and cytotoxic chemotherapy agents, any of which could theoretically antidote homeopathic remedies according to this doctrine.

If antidoting were a clinically significant phenomenon in this context, one would expect the concurrent administration of conventional oncological drugs to diminish or abolish the effects of the homeopathic intervention. However, our results demonstrate significant and clinically meaningful differences between the homeopathy and placebo groups despite both groups receiving identical conventional treatment regimens. This observation has two possible interpretations: either (a) the antidoting effect of conventional drugs on homeopathic remedies is not clinically relevant in this setting, or (b) the homeopathic effect, if present, is robust enough to manifest despite potential antidoting influences. A recent review by de Carvalho [46] has reinterpreted the concept of antidoting as "early empirical descriptions of system-level modulation rather than substance antagonism", suggesting that the classical notion of antidoting may require revision in light of contemporary systems medicine.

A broader interpretation is provided by whole-systems research. From this perspective, homeopathy is conceptualized as a complex medical system in which the medicinal product is only one component of an interconnected therapeutic package: practitioner approach, individualized assessment and prescribing, the consultation process, the therapeutic relationship, and the context and ritual of care may interact and potentially act synergistically [25–27]. Accordingly, the whole may not be reducible to the effect of the remedy considered in isolation. This perspective does not establish which component produced the observed findings, but it cautions against interpreting the antidote question solely as a pharmacological interaction between a homeopathic preparation and conventional medication. It also reinforces the need to interpret the present findings as arising within the overall package of add-on homeopathic care and to investigate specific and contextual components separately in future whole-systems research.

Additional methodological strengths and limitations

A methodological strength of the study is the quadruple-checked data analysis, which was implemented to maximize the traceability and reproducibility of data entry and statistical evaluation. It addresses the integrity of the data-handling process while it cannot validate the clinical interpretation of the findings. This quadruple-check is unusual for a non-commercial study. In particular, the use of a state-of-the-art computerized randomization program, which could only be controlled by the planning statistician, proved that retrospective exclusion of patients was impossible. All inclusion and exclusion events are logged and trackable in the Audit Trail of the randomization program. In addition, the strict deadline for enrolling patients within eight weeks of diagnosis prevents any "immortal time bias" [15]. The precisely defined date of diagnosis and death ensures the validity of the survival data.

A limitation of the study is the relatively long study period. However, during the whole study period basic conventional therapy remained essentially unchanged.

The only change to exclusion criteria after the trial started was the decision to exclude mutated cases. These were included in the original protocol but later publications showed that mutated cases had a significantly better prognosis due to new target therapies. This finding was not known at the time the protocol was drafted. The discrepancy in expected survival times would have significantly falsified the result. However, this change was reported to and accepted by the Ethics Committee of the Medical University of Vienna.

A further limitation is that conventional therapy in this study was performed in almost all patients without the nowadays usual immuno-oncologic therapy [47], because the study had started before 2015. While EGFR/ALK tyrosine kinase inhibitors (TKIs) have become standard first-line strategy in patients with advanced, EGFR-mutation-positive or ALK fusion oncogene-positive NSCLC with improved outcome, standard therapy for untreated patients suffering from NSCLC without mutations comprised conventional chemotherapy only during the study. The approvals of immune checkpoint inhibitors such as nivolumab, pembrolizumab, and atezolizumab for the second-line therapy of NSCLC after platinum failure based on the Checkmate 017, Checkmate 057, KEYNOTE 010, and OAK trials, might have had an influence on OS analysis of this trial. However, this potential bias is likely not relevant, since the number of patients treated with subsequent immuno-oncological therapy was comparable ($p = 0.942$) between the groups (Table 1).

Today, immuno-oncologic and chemotherapy are established as first-line therapy. Therefore, further studies with immuno-oncologic therapy are necessary to investigate the effect of homeopathic therapy with modern forms of therapy.

The number of corrections (96 crossed-out and overwritten entries) made by the patients themselves is in the lower per mille range of the total number of data elements recorded (3.6‰ of 26,390 outcome measures) and therefore had no significant impact on the final results. This small number of data changes made by patients is statistically irrelevant, but it does demonstrate the accuracy and reliability of the forms completed by the patients surveyed, who may make mistakes and change their minds during filling out the questionnaires.

Several limitations must be emphasized: first, we acknowledge a potential limitation concerning patients who report an excellent quality of life. Such patients may have pre-existing favorable attitudes toward homeopathy and may also be inclined to provide responses they perceive as desirable to the researchers, potentially introducing response or expectancy bias into their QoL assessments. However, the double-blind study design mitigates this concern, as patients were unaware of their treatment allocation. Second, as set out above, the design cannot separate the specific effect of the HMP from the non-specific effects of the homeopathic consultation and of the daily treatment ritual regarding comparison of randomized double blind groups versus control group. Third, due to clinical obstacles explained above, the control group was not randomized but consisted of patients who declined randomization; the comparison with this group is therefore subject to selection bias and cannot support causal statements, even though the baseline characteristics presented in Table 1 were largely comparable and the observed difference in N stage was not in a direction that would favor the homeopathy group. Fourth, QoL was assessed only up to 18 weeks, so that no conclusions can be drawn about QoL trajectories beyond this window, and in particular about the terminal phase. Fifth, attrition was substantial and differed between the groups: 46 of 51 patients in the homeopathy group but only 33 of 47 patients in the placebo group attended the third visit due to higher mortality in the placebo group. Because patients who died or experienced clinical deterioration were unable to complete the questionnaires, and because deterioration occurred more frequently in the placebo group, the QoL comparison at 18 weeks may have been affected by informative dropout. This differential attrition could have introduced attrition bias and potentially contributed to an overestimation of the observed between-group difference. Sixth, adverse events were recorded, but no formal causality assessment was performed. Seventh, the questionnaire used to assess subjective well-being was developed by one of the authors without a formal validation procedure.

Homeopathy remains a controversially discussed intervention. Its use as an add-on can be framed within the three pillars of evidence-based medicine as defined by David Sackett, which combine clinical expertise, external evidence and patient preference [48]; this framing describes how such a treatment may be discussed with an individual patient. Furthermore, a relatively recent systematic review of six homeopathic meta-analyses of randomized placebo-controlled homoeopathy trials for any indication found that homeopathy is significantly more effective than placebo [39].

Costs for add-on HMPs are very low compared with immuno-oncological approaches. Thereby, add-on expenses of homeopathic drugs are negligible in the context of anticancer treatment costs. From a methodological point of view, add-on homeopathy provides a tool compatible with all other conventional interventions. The advantages are that there are no interactions with other therapeutic interventions, no burden to metabolism of the patients and that the cost is low.

Clinical implications

The observed QoL improvements and survival differences carry potential implications for clinical practice, though several caveats apply. First, the significant and clinically

meaningful improvements in global health status, functional scales, and symptom burden suggest that add-on homeopathy may serve as a low-risk, low-cost supportive care option for patients with advanced NSCLC receiving conventional treatment. The absence of reported adverse effects and the theoretical lack of pharmacological interactions with conventional drugs support its safety profile as an adjunctive intervention [49, 50].

Second, the survival benefit, while statistically significant, should be interpreted with caution given the relatively small sample size of this endpoint. Before translation into routine clinical practice, the following safeguards and evidence requirements should be met: (a) independent replication of these findings by research groups without prior involvement in homeopathy research; (b) confirmation of results in the context of current standard-of-care regimens including immune checkpoint inhibitors; (c) larger sample sizes with adequate power for survival as a primary endpoint; (d) extended QoL follow-up through the end-of-life period; and (e) health economic evaluation of the cost-effectiveness of add-on homeopathy in the oncological setting.

Third, the findings align with a growing body of evidence suggesting that supportive care interventions addressing patient-reported outcomes may positively influence not only QoL but also survival in patients with advanced cancer [37, 38, 49]. Regardless of the specific mechanism, the consistent observation across multiple study designs that improved symptom control and wellbeing are associated with better survival outcomes underscores the importance of integrating patient-centered supportive care into standard oncological practice.

Finally, clinicians considering the integration of homeopathy into oncological care should ensure that: (a) it is offered strictly as an adjunct to, not a replacement for, evidence-based conventional treatment; (b) patients are fully informed about the current state of evidence, including the need for independent replication; (c) treatment is provided by qualified practitioners working in coordination with the oncology team; and (d) patient outcomes including QoL and treatment adherence are systematically monitored [50, 51].

Conclusion

In this three-arm trial, patients with advanced NSCLC who received add-on homeopathic care in addition to conventional oncological treatment reported a better quality of life and showed longer survival than patients who received placebo in addition to the same homeopathic care, and non-randomized patients who received conventional treatment alone (Fig. 3). These are associations observed in a single trial, in which survival was a secondary endpoint and in which the non-randomized control group is subject to selection bias. Independent replication conducted within contemporary immuno-oncological standards of care is required.

Acknowledgements We thank Prof. Dr. Wolfgang Schütz, then Dean of the MUV, Austria, Prof. DDr. Christoph Zielinski, then Head of the Division of Oncology, Department Medicine I, MUV, and Prof. Dr. Reinhard Krepler, then Director of the General Hospital of Vienna, for establishing the Outpatient´s Unit "Homeopathy in malignant disease" in March 2004, and for encouraging us to perform this study. We also want to thank Dr. Thorsten Füreder, MUV, Department of Medicine I, Clinical Division of Oncology, Vienna, Austria, for carefully revising the manuscript. Furthermore, we thank Dr. Menachem Oberbaum, Center for Integrative Complementary Medicine at the Shaare-Zedek Medical Center, Jerusalem, Israel, for providing the impetus to perform this study.

Abbreviations of authors, study contributors, and study assistants in alphabetical order of family names (The affiliations are as of the time of the study; some have since changed positions, while others have retired.)

OB: Otto C Burghuber, MD, Department of Respiratory and Critical Care Medicine and Ludwig Boltzmann Institute for Lung Health, Otto Wagner Hospital and Sigmund Freud University, Medical School, Vienna, Austria; CD: Cornelia Duscheck MD, Hospital Lilienfeld, Lilienfeld, Austria; EE: Ernst Eigenbauer, degreed engineer, chief analyst, Informations Technology Solution Center (ITSC), Research, Documentation and Analysis (RDA), scientific platform, Center for Medical Statistics, Informatics, and Intelligent Systems, Medical University of Vienna; MF: Michael Frass, MD, Medical University of Vienna, Department of Medicine I, Clinical Division of Oncology, Vienna; Scientific Society for Homeopathy, Koethen, Germany; Institute for Homeopathic Research, Vienna, Austria; MeF: Melanie Fraunschiel, degreed engineer, Research, Documentation and Analysis (RDA), scientific platform, Center for Medical Statistics, Informatics, and Intelligent Systems, Medical University of Vienna; TF: Thorsten Füreder, MD, Medical University of Vienna, Department of Medicine I, Division of Oncology, Vienna, Austria; KG: Katharina Gaertner, MD, University of Witten/Herdecke, Faculty of Health Sciences, Germany; AG: Andreas Gleiß, PhD, Center for Medical Statistics, Informatics, and Intelligent Systems, Medical University of Vienna; CG: Christa Gründling, MD, General Practitioner, Enns; PL: Peter Lechleitner, MD, Hospital of Lienz, Department of Medicine, Lienz, Austria; RKM: Raj K. Manchanda, MD, Director General, Central Council for Research in Homoeopathy, Ministry of AYUSH, Govt. of India; Secretary Research, LMHI; West Delhi, Delhi, India; IM: Ilse Muchitsch, Mag. pharm., Austrian Chamber of Pharmacists, Department Vienna, HomResearch, Interdisciplinary Homeopathic Research Group, Vienna, Austria; BNB: Birgit Negedly-Blauensteiner, MD, Traiskirchen, Austria; MO: Menachem Oberbaum, MD, Head of the Department of Complementary Medicine at the Shaare-Zedek University, Jerusalem, Israel; RP: Robert Pirker, MD, Medical University of Vienna, Department of Medicine I, Division of Oncology, Vienna, Austria; WR: Wilhelm Raneburger, MD, Hospital of Lienz, Department of Medicine, Lienz, Austria; AS: Andrea Schrott, MSc, Dr, StatistikAmbulanz, Formal analysis, Software, Private Business, Vienna, Austria; MS: Michael Schumacher, MD, Elisabethinenspital, Department of Medicine, Linz, Austria; JS: Judith Stellnberger, Cand. med., Mag. phil., Medical University of Vienna, Department of Medicine I, Division of Oncology; KT: Karin Thieves, Research Fellow, Sola Salus, Geilenkirchen, Germany; PW: Petra Weiermayer, PhD, Scientific Society for Homeopathy (WissHom), Koethen, Germany; TW: Thomas Wrba, PhD, Research, Documentation and Analysis (RDA), scientific platform, Center for Medical Statistics, Informatics, and Intelligent Systems, Medical University of Vienna.

Author contributions Michael Frass is the guarantor of the manuscript and takes responsibility for the integrity of the data and the accuracy of the data analysis. Michael Frass: Conceptualization, Funding acquisition, Investigation, Visualization, Roles/Writing—original draft Peter Lechleitner: Investigation, Writing—review & editing Christa Gründling: Investigation, Writing—review & editing Katharina Gaertner: Conceptualization, Methodology Cornelia Duscheck: Validation Ilse Muchitsch: Resources, Writing—review & editing Raj K Manchanda: Conceptualization, Supervision Otto C Burghuber: Conceptualization, Supervision

Funding This work was supported by the Institute for Homeopathic Research, Vienna, Austria [grant number 0112].

Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Competing interests We provide a full and explicit disclosure of all professional activities of the investigators related to the HMPs used in this study. No financial incentives, commercial interests, reimbursements, marketing activities or performance-related benefits were associated with patient recruitment, participation, or study outcomes. The conduct of the study and the reporting of results were independent of any financial considerations linked to the HMPs. There was no connection between the conduct of the study and private practice.

Declaration of generative AI and AI-assisted technologies in the writing process We did not use AI or AI-assisted technologies in the writing process.

Key messages/lessons learned Add-on homeopathic care could be delivered alongside conventional oncological treatment without observed interference or adverse effects.

In this trial, quality of life was better in NSCLC patients allocated to add-on homeopathy than in those allocated to placebo.
Survival was longer in the homeopathy group; this observation requires independent replication.

References

1. American Cancer Society: Facts and Figures. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/global-cancer-facts-and-figures/global-cancer-facts-and-figures-2024.pdf accessed August 9, 2025, 08.49 pm
2. Poleri C (2022) Sex-based differences in lung cancer: does it matter? J Thorac Oncol 17(5):599–601. https://doi.org/10.1016/j.jtho.2022.03.002
3. American Cancer Society: Lung cancer. https://www.cancer.org/cancer/types/lung-cancer/about/key-statistics.html accessed August 9, 2025, 08.52 am
4. Hendriks LEL, Remon J, Faivre-Finn C, Garassino MC, Heymach JV, Kerr KM, Tan DSW, Veronesi G, Reck M (2024) Non-small-cell lung cancer. Nat Rev Dis Primers 10(1):71. https://doi.org/10.1038/s41572-024-00551-9
5. Tanaka K, Akechi T, Okuyama T, Nishiwaki Y, Uchitomi Y (2002) Impact of dyspnea, pain, and fatigue on daily life activities in ambulatory patients with advanced lung cancer. J Pain Symptom Manage 23(5):417–423. https://doi.org/10.1016/s0885-3924(02)00376-7
6. Morrison EJ, Novotny PJ, Sloan JA, Yang P, Patten CA, Ruddy KJ, Clark MM (2017) Emotional problems, quality of life, and symptom burden in patients with lung cancer. Clin Lung Cancer 18(5):497–503. https://doi.org/10.1016/j.cllc.2017.02.008
7. Cella D, Peterman A, Hudgens S, Webster K, Socinski MA (2003) Measuring the side effects of taxane therapy in oncology: the functional assesment of cancer therapy-taxane (FACT-taxane). Cancer 98(4):822–831. https://doi.org/10.1002/cncr.11578
8. Wang XS, Shi Q, Lu C, Basch EM, Johnson VE, Mendoza TR, Mobley GM, Cleeland CS (2010) Prognostic value of symptom burden for overall survival in patients receiving chemotherapy for advanced nonsmall cell lung cancer. Cancer 116(1):137–145. https://doi.org/10.1002/cncr.24703
9. Sloan JA, Zhao X, Novotny PJ, Wampfler J, Garces Y, Clark MM, Yang P (2012) Relationship between deficits in overall quality of life and non-small-cell lung cancer survival. J Clin Oncol 30(13):1498–1504. https://doi.org/10.1200/jco.2010.33.4631
10. Daly BJ, Douglas SL, Foley H, Lipson A, Liou CF, Bowman K, Kwilosz D, Koroukian S, O'Toole E, Smyth K, Townsend A, Von-Gruenigen V, Rose J (2007) Psychosocial registry for persons with cancer: a method of facilitating quality of life and symptom research. Psychooncology 16(4):358–364. https://doi.org/10.1002/pon.1091
11. Boire A, Burke K, Cox TR, Guise T, Jamal-Hanjani M, Janowitz T, Kaplan R, Lee R, Swanton C, Vander Heiden MG, Sahai E (2024) Why do patients with cancer die? Nat Rev Cancer 24(8):578–589. https://doi.org/10.1038/s41568-024-00708-4
12. Kent J (1993) Lectures on Homoeopathic Philosophy. B. Jain Publishers Ltd, New Delhi, India, pp 92–3
13. Hahnemann S (2002) Organon of Medicine, 5th & 6th Edition. B Jain Publishers Pvt Ltd, Noida, Uttar Pradesh
14. Frass M, Friehs H, Thallinger C, Sohal NK, Marosi C, Muchitsch I, Gaertner K, Gleiss A, Schuster E, Oberbaum M (2015) Influence of adjunctive classical homeopathy on global health status and subjective wellbeing in cancer patients - a pragmatic randomized controlled trial. Complement Ther Med 23(3):309–317. https://doi.org/10.1016/j.ctim.2015.03.004
15. Gleiss A, Frass M, Gaertner K (2016) Re-analysis of survival data of cancer patients utilizing additive homeopathy. Complement Ther Med 27:65–67. https://doi.org/10.1016/j.ctim.2016.06.001
16. Frass M, Lechleitner P, Gründling C, Pirker C, Grasmuk-Siegl E, Domayer J, Hochmair M, Gaertner K, Duscheck C, Muchitsch I, Marosi C, Schumacher M, Zöchbauer-Müller S, Manchanda RK, Schrott A, Burghuber O (2020) Homeopathic treatment as an add-on therapy may improve quality of life and prolong survival in patients with non-small cell lung cancer: a prospective, randomized, placebo-controlled, double-blind, three-arm, multicenter study. Oncologist 25(12):e1930–e1955. https://doi.org/10.1002/onco.13548(retracted;seereference17)
17. Retraction of: Homeopathic treatment as an add-on therapy may improve quality of life and prolong survival in patients with non-small cell lung cancer: a prospective, randomized, placebo-controlled, double-blind, three-arm, multicenter study (2025)

Oncologist 30(11):oyaf364. https://doi.org/10.1093/oncolo/oyaf364
18. Brien S, Lachance L, Prescott P, McDermott C, Lewith G (2011) Homeopathy has clinical benefits in rheumatoid arthritis patients that are attributable to the consultation process but not the homeopathic remedy: a randomized controlled clinical trial. Rheumatology (Oxford) 50(6):1070–1082. https://doi.org/10.1093/rheumatology/keq234
19. Fayers P, Bottomley A (2002) Quality of life research within the EORTC-the EORTC QLQ-C30. European Organisation for Research and Treatment of Cancer. Eur J Cancer 38(Suppl 4):S125–S133. https://doi.org/10.1016/s0959-8049(01)00448-8
20. Hays RD, Sherbourne CD, Mazel RM (1993) The RAND 36-item health survey 1.0. Health Econ 2(3):217–27. https://doi.org/10.1002/hec.4730020305
21. Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, Serwatowski P, Gatzemeier U, Digumarti R, Zukin M, Lee JS, Mellemgaard A, Park K, Patil S, Rolski J, Goksel T, de Marinis F, Simms L, Sugarman KP, Gandara D (2023) Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 41(14):2458–2466. https://doi.org/10.1200/JCO.22.02544
22. Muchitsch I (2015) Remedy production and quality, potentisation. In: Frass MMB (ed) Homeopathy in intensive and emergency medicine. Narayana Publishers, Kandern, Germany, pp 37–55
23. Verhoef MJ, Vanderheyden LC, Fønnebø V (2006) A whole systems research approach to cancer care: why do we need it and how do we get started? Integr Cancer Ther 5(4):287–292. https://doi.org/10.1177/1534735406295041
24. Kligler B, Khung M, Schult T, Whitehead A (2023) What we have learned about the implementation of whole health in the Veterans Administration. J Integr Complement Med 29(12):774–780. https://doi.org/10.1089/jicm.2022.0753
25. Verhoef MJ, Casebeer AL, Hilsden RJ (2002) Assessing efficacy of complementary medicine: adding qualitative research methods to the "gold standard." J Altern Complement Med 8(3):275–281. https://doi.org/10.1089/10755530260127961
26. Ritenbaugh C, Verhoef M, Fleishman S, Boon H, Leis A (2003) Whole systems research: a discipline for studying complementary and alternative medicine. Altern Ther Health Med 9(4):32–36
27. Verhoef MJ, Lewith G, Ritenbaugh C, Boon H, Fleishman S, Leis A (2005) Complementary and alternative medicine whole systems research: beyond identification of inadequacies of the RCT. Complement Ther Med 13(3):206–212. https://doi.org/10.1016/j.ctim.2005.05.001
28. Pirker R, Pereira JR, Szczesna A, von Pawel J, Krzakowski M, Ramlau R, Vynnychenko I, Park K, Yu CT, Ganul V, Roh JK, Bajetta E, O'Byrne K, de Marinis F, Eberhardt W, Goddemeier T, Emig M, Gatzemeier U, FLEX Study Team (2009) Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. Lancet 373(9674):1525–1531. https://doi.org/10.1016/S0140-6736(09)60569-9
29. O'Brien PC, Fleming TR (1979) A multiple testing procedure for clinical trials. Biometrics 35(3):549–556. https://doi.org/10.2307/2530245
30. Derrick B, Ruck A, Toher D, White P (2018) "Tests for equality of variances between two samples which contain both paired observations and independent observations" (PDF). J Appl Quantitative Methods 13(2):36–47
31. Maxwell, Scott E.; Delaney, Harold D. (2004). Designing experiments and analyzing data: a model comparison. Lawrence Erlbaum Associates. pp. 217–218. ISBN 0–8058–3718–3.
32. https://www.meduniwien.ac.at/web/mitarbeiterinnen/it-hilfe-support/it4science/plattformen/rda/ accessed July 5, 2026, 9.44 pm
33. https://data-science.meduniwien.ac.at/en/institutes/medical-statistics/ accessed July 5, 2026, 9.48 pm
34. https://www.meduniwien.ac.at/web/en/about-us/organisation/committees/data-clearing-house/ accessed July 5, 2026, 9.52 pm
35. Osoba D, Rodrigues G, Myles J, Zee B, Pater J (1998) Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 16(1):139–144. https://doi.org/10.1200/JCO.1998.16.1.139
36. Cocks K, King MT, Velikova G, de Castro G Jr, Martyn St-James M, Fayers PM, Brown JM (2012) Evidence-based guidelines for interpreting change scores for the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. Eur J Cancer 48(11):1713–21. https://doi.org/10.1016/j.ejca.2012.02.059
37. Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, Dahlin CM, Blinderman CD, Jacobsen J, Pirl WF, Billings JA, Lynch TJ (2010) Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 363(8):733–742. https://doi.org/10.1056/NEJMoa1000678
38. Daly B, Bryl KL, Santos Teles M, Baser RE, Mao JJ (2026) Survival results from the Integrative Medicine for Patient-Reported Outcomes, Values, and Experience (IMPROVE) trial. JCO Oncol Adv 3:e2500154. https://doi.org/10.1200/OA-25-00154
39. Hamre HJ, Glockmann A, von Ammon K, Riley DS, Kiene H (2023) Efficacy of homoeopathic treatment: systematic review of meta-analyses of randomised placebo-controlled homoeopathy trials for any indication. Syst Rev 12(1):191. https://doi.org/10.1186/s13643-023-02313-2
40. Eyles C, Leydon GM, Lewith GT, Brien S (2011) A grounded theory study of homeopathic practitioners' perceptions and experiences of the homeopathic consultation. Evid Based Complement Alternat Med. https://doi.org/10.1155/2011/957506
41. Thompson TD, Weiss M (2006) Homeopathy - what are the active ingredients? An exploratory study using the UK Medical Research Council's framework for the evaluation of complex interventions. BMC Complement Altern Med 6:37. https://doi.org/10.1186/1472-6882-6-37
42. Kaptchuk TJ, Kelley JM, Conboy LA, Davis RB, Kerr CE, Jacobson EE, Kirsch I, Schyner RN, Nam BH, Nguyen LT, Park M, Rivers AL, McManus C, Kokkotou E, Drossman DA, Goldman P, Lembo AJ (2008) Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. BMJ 336(7651):999–1003. https://doi.org/10.1136/bmj.39524.439618.25
43. Akdeniz M, Yardımcı B, Kavukcu E (2021) Ethical considerations at the end-of-life care. SAGE Open Med 9:20503121211000920. https://doi.org/10.1177/20503121211000918
44. Crawford GB, Dzierżanowski T, Hauser K, Larkin P, Luque-Blanco AI, Murphy I, Puchalski CM, Ripamonti CI (2021) Care of the adult cancer patient at the end of life: ESMO Clinical Practice Guidelines. ESMO Open 6(4):100225. https://doi.org/10.1016/j.esmoop.2021.100225
45. Lüdtke R, Musial F (2008) Wie kann man komplementärmedizinische Verfahren in ihrer Wirksamkeit erforschen? Komplementärmedizinische Methoden 2:76–81
46. de Carvalho JF (2026) Antidotes in homeopathy: classical doctrine, clinical relevance and scientific re-interpretation. Homeopathy. https://doi.org/10.1055/a-2797-3848
47. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, Domine M, Clingan P, Hochmair MJ, Powell SF, Cheng SY, Bischoff HG, Peled N, Grossi F, Jennens RR, Reck M, Hui R, Garon EB, Boyer M, Rubio-Viqueira B, Novello S, Kurata T, Gray JE, Vida J, Wei Z, Yang J, Raftopoulos H, Pietanza MC, Garassino MC (2018) Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 378(22):2078–92. https://doi.org/10.1056/NEJMoa1801005
48. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS (1996) Evidence based medicine: what it is and what it isn't. BMJ 312(7023):71–72. https://doi.org/10.1136/bmj.312.7023.71

49. Latte-Naor S, Mao JJ (2019) Putting integrative oncology into practice: concepts and approaches. J Oncol Pract 15(1):7–14. https://doi.org/10.1200/JOP.18.00554
50. Witt CM, Balneaves LG, Cardoso MJ, Greenlee H, Johnstone P, Kücük Ö, Mailman J, Mao JJ (2017) A comprehensive definition for integrative oncology. J Natl Cancer Inst Monogr. https://doi.org/10.1093/jncimonographs/lgx012
51. Frenkel M, Cohen L (2014) Effective communication about the use of complementary and integrative medicine in cancer care. J Altern Complement Med 20(1):12–18. https://doi.org/10.1089/acm.2012.0533

Authors and Affiliations

Michael Frass[1,8,9] · Peter Lechleitner[2] · Christa Gründling[3] · Katharina Gaertner[4] · Cornelia Duscheck[1,8,9] · Ilse Muchitsch[5] · Raj K. Manchanda[6] · Otto C. Burghuber[7]

✉ Michael Frass
office@ordination-frass.at

1 Department of Medicine I, Clinical Division of Oncology, Medical University of Vienna, Vienna, Austria
2 Department of Medicine, Hospital of Lienz, Lienz, Austria
3 Enns, Austria
4 Faculty of Health Sciences, Witten/Herdecke University, Witten, Germany
5 Austrian Chamber of Pharmacists, Department Vienna, HomResearch, Interdisciplinary Homeopathic Research Group, Vienna, Austria
6 Ministry of AYUSH, Government of India and LMHI, Central Council for Research in Homoeopathy, West Delhi, Delhi, India
7 Department of Respiratory and Critical Care Medicine and Ludwig, Boltzmann Institute for Lung Health, Otto Wagner Hospital and Sigmund Freud University, Medical School, Vienna, Austria
8 Scientific Society for Homeopathy (WissHom), Koethen, Germany
9 Institute for Homeopathic Research, Columbusgasse 20/18, 1100 Vienna, Austria