Original Article

Mistletoe Extract in Patients With Advanced Pancreatic Cancer

A Double-Blind, Randomized, Placebo-Controlled Trial (MISTRAL)

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Summary

Background: Patients with advanced pancreatic cancer have limited survival and few treatment options. We studied whether mistletoe extract (ME), in addition to comprehensive oncological treatment and palliative care, prolongs overall survival (OS) and improves health-related quality of life (HRQoL).

Methods: The double-blind, placebo-controlled MISTRAL trial was conducted in Swedish oncology centers. The main inclusion criteria were advanced exocrine pancreatic cancer and Eastern Cooperative Oncology Group (ECOG) performance status 0–2. The subjects were randomly assigned to ME (n=143) or placebo (n=147) and were stratified by study site and by eligibility (yes/no) for palliative chemotherapy (June 2016–December 2021). ME or placebo was injected subcutaneously three times a week for nine months. The primary endpoint was overall survival (OS); one of the secondary endpoints was the HRQoL dimension global health/ QoL (EORTC–QLQ–C30), as assessed at seven time points over nine months. Trial registration: EudraCT 2014–004552–64, NCT02948309

Results: No statistically significant benefit of adding ME to standard treatment was seen with respect to either OS or global health/ QoL. The adjusted hazard ratio for OS was 1.13 [0.89; 1.44], with a median survival time of 7.8 and 8.3 months for ME and placebo, respectively. The figures for the HRQoL dimension "global health/QoL" were similar in the two groups (p=0.86). The number, severity, and outcome of the reported adverse events were similar as well, except for more common local skin reactions at ME injection sites (66% vs. 1%).

Conclusion
ME is unlikely to have a clinically significant effect on OS or the HRQoL dimension global health/QoL when administered in patients with advanced pancreatic cancer in addition to comprehensive cancer care.

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Pancreatic cancer is among the most lethal tumors. When locally advanced growth or systemic spread preclude curative resection, the options for effective treatment are limited and mainly consist of multidrug chemotherapy (1). Patients' rapidly deteriorating performance status constitute significant obstacles for disease-modifying treatments. Single-drug chemotherapy or best supportive care (BSC) often remain the last resort, yielding survival times of around six and two months, respectively. Patients' increasing symptom burden and impaired health-related quality of life (HRQoL) (2) necessitate multidisciplinary management and integrated palliative care (PC) (1).

Plants have been a successful source for anticancer drugs. Mistletoe (*Viscum album L*) is a hemiparasitic shrub growing on various host trees. Mistletoe extract (ME) is frequently prescribed in integrative cancer therapy (3–5), in addition to oncological treatment or BSC. ME is well known and acknowledged among physicians in Germany (6) and patients express a strong preference for ME (7). Mistletoe constituents stimulate both innate immunity and the adaptive immune response (8, 9). Low doses are injected subcutaneously to improve HRQoL and immune functions. High doses are administered, mostly locally (off-label use), to exert direct antitumoral effects (10–12). Systematic reviews reported a medium-sized effect on HRQoL (3) and a possible effect on survival (13). However, the studies were mostly of insufficient methodological quality (7). An open-label, randomized controlled trial (RCT) (MAPAC) investigated subcutaneous ME in

220 patients with advanced pancreatic cancer and reported both a significant survival benefit and better HRQoL (*eBox 1*) (14, 15).

The MAPAC trial's promising results and ME's good safety profile, low cost, and widespread use motivated the present study, in which we investigated whether ME can make a clinically useful contribution to the multidisciplinary management of patients with advanced pancreatic cancer. Recruiting patients for RCTs is difficult in countries where ME treatment is widespread and clear patient preferences exist for or against ME (16). In Sweden, ME is approved for palliative care but it is rarely used (17). Therefore, Sweden was considered a suitable context for this trial. Multidisciplinary inpatient and outpatient PC is fully integrated in the Swedish health care system. Patients' eligibility for palliative chemotherapy was preliminarily assessed by multidisciplinary tumor boards and the final decision whether chemotherapy was given or not was adapted to the individual patient's medical condition, comorbidities, and personal preference. This decision was made within routine oncology independent of trial participation. The study's aim was to examine whether ME complementing standard treatment (palliative chemotherapy or BSC) may prolong overall survival (OS) and improve HRQoL with regard to global health/QoL in patients with advanced pancreatic cancer.

Methods

A double-blind, randomized, placebo-controlled trial was conducted at nine Swedish oncology centers (referred to in the following as study sites). The main inclusion criteria were a recent diagnosis of advanced exocrine pancreatic cancer or relapse, Eastern Cooperative Oncology Group (ECOG) performance status ≤2, life expectancy >4 weeks (*eMethods 1*). Drug treatment was provided for symptom management (analgesics, antiemetics, anxiolytics, glucocorticoids), and participants had access to palliative care (specialized multidisciplinary home or inpatient PC) if needed (17, 18).

A data safety committee ensured patient safety. Quality assurance further included:

- regular independent monitoring
- spot sample check of the collected data
- ensuring correct content and assignment of the study drug
- a final independent check of the data set
- an audit of the entire study (*eMethods 1*).

The study participants were randomly assigned at a ratio of 1:1 to either ME injection (fermented aqueous extract of *Viscum album L* grown on oak tree) or placebo, each in addition to standard treatment. We stratified by oncology center (study site) and preliminary eligibility for palliative chemotherapy. Participants, medical staff, and evaluators were blinded to treatment allocation and application. Following the manufacturer's recommendations (19) and in accordance with the MAPAC trial (14), the study drug was injected subcutaneously at an initially increasing, individually adapted dosage (0.01–20 mg) thrice weekly for nine months (*eMethods 1*). Follow-up was performed by physicians and study nurses at five to six weeks, two, three, four, six and nine months after randomization, including assessment of participants' need for palliative home care (*eMethods 1*). After completion of the nine-month study(treatment) period, ME treatment was offered to all participants without knowledge of treatment arm allocation *(eMethods 1)*. Overall survival was the primary endpoint, defined as the time from randomization to death of any cause, as documented in the medical records at the participating study sites (*eMethods 1*). Secondary endpoints included the HRQol dimension "global health/QoL", assessed at study visits, using the EORTC QLQ-C30 questionnaire (20); glucocorticoid use; and patient safety, i.e. the occurrence of (serious) adverse events (SAE). The remaining secondary outcomes—HRQoL (QLQ-C30, QLQ-PAN-26), and body weight, as well as the nested qualitative and biomarker studies—will be published later.

Stockholm's Regional Ethical Review Board approved the study (2 March 2016, 2016/122–31/2). The Declaration of Helsinki and Good Clinical Practice were implemented. Written informed consent was obtained from all participants before any trial-related procedure took place. Trial registration: EudraCT 2014–004552–64, NCT02948309. Trial protocol (17).

Statistical analysis

The study was designed to detect a HR of 0.67 between the ME and the placebo arm (17), based on the results of the MAPAC trial. Using a two-sided log-rank test, a sample size of 290 patients (145 participants per arm) was required to achieve a power of 90% at a 5% significance level.

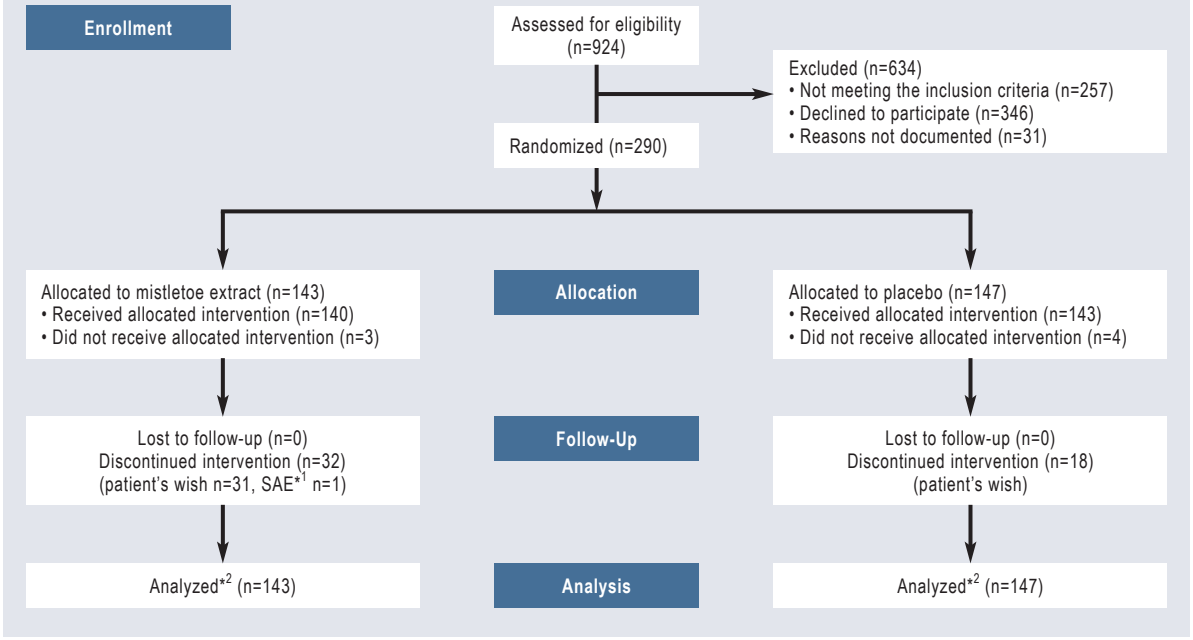
The primary analysis including all participants was evaluated by Cox proportional hazards regression with "study site" as covariate and "preliminary eligibility for chemotherapy (yes/no)" as strata, and tested the adjusted hazard ratio (AHR) for OS in the ME versus the placebo arm. This analysis was based on the full study period (*eMethods 2*).

An additonal analysis evaluated OS up to the end of the treatment period with follow-up censored at nine months (*eMethods 2*). Kaplan–Meier product-limit estimators were used to estimate OS in the respective treatment arms and p-values were calculated using the log-rank test. Point estimates with 95% confidence intervals were calculated for each treatment arm in order to determinate the median OS time. For sensitivity analysis, the Cox regression model included variables whose distribution differed between treatment arms and that were modeled as an interaction with the treatment (*eMethods 2*). Furthermore, based on these variables, Kaplan–Meier curves were generated to enable comparison of the treatment arms by subgroup. For details on Per Protocol analysis and the secondary outcome "global health/QoL" see *eMethods 2*. Patient safety data (adverse events/severe adverse events) are presented by treatment arm as counts, percentages, or by number of events per month in the study. All tests were two-sided at 5% significance level. The analyses were performed using R (21).

Results

Between 7 June 2016 and 3 December 2021, 290 patients were randomized to two groups (*Figure 1,*

Figure 1



Flow chart of patients in the trial
*1 Urticaria; *2 Patients who discontinued the intervention were still followed up regarding survival status *(eMethods 1)*

eSupplement–Table 1). In 15 cases, the tumor board's preliminary assessment of patients' eligibility for palliative chemotherapy was not changed (*eTable 1*). A total of 19 patients were censored at the time of last contact (*Figure 2, eMethods 1*). The baseline characteristics were well balanced except for differences in distributions of tumor stages (T-stages), primary diagnoses, and relapses (*Table, eBox 2*).

The primary analysis based on the total follow-up time did not find an effect of ME on overall survival compared to placebo (AHR 1.13 [0.89; 1.44], primary endpoint) nor did the corresponding analysis with follow-up limited to the nine-months' treatment period (AHR 1.05 [0.77; 1.43]). Median OS was 7.8 months [6.4; 9.4] in the ME and 8.3 months [6.9; 9.7] in the placebo arm (*Figure 2*). Per-protocol analysis yielded similar results (*eSupplement-Figures 1 and 2*).

Since many participants opted for ME treatment after study participation, nine-month follow-up is reported for all following analyses. Analyses based on total follow-up time did not change the findings. Sensitivity analyses (*eMethods 2*) adjusting for pancreatic cancer as the primary diagnosis or relapse yielded an AHR of 1.00 [0.74; 1.37] and adjusting for T-stage yielded an AHR of 0.85 [0.60; 1.22]; among the subgroup of participants receiving BSC, the AHR for OS was 1.30, [0.70; 2.41] (*eSupplement–Figures 3–6*).

The patients' study visits were performed in compliance with the study protocol (median –1 to +3 days from the projected date). The corresponding HRQoL questionnaires were returned in 99% and 76% of cases (*eSupplement–Table 2*). The HRQoL dimension "global health/QoL" was comparable in both groups (p=0.86) (*Figure 3, eSupplement–Tables 3–4*).

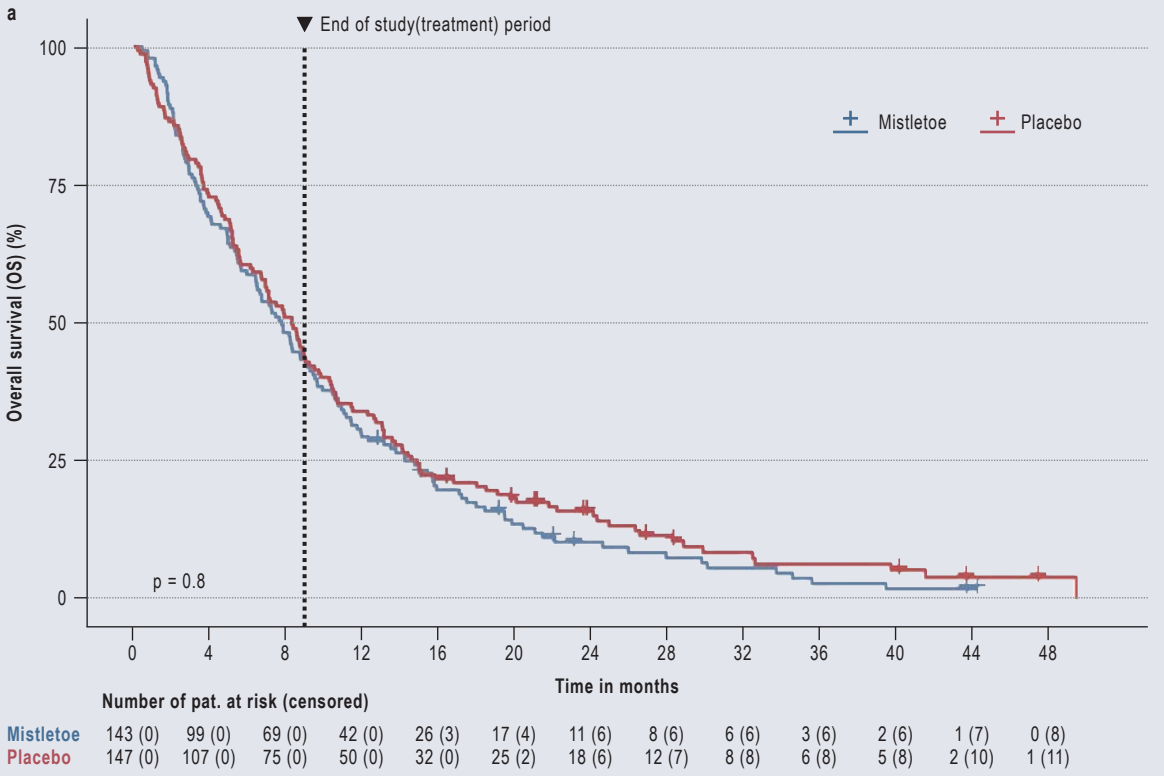
Of the 283 patients whose data constituted the safety data set (*eBox 2*), 64 (46%) in the ME and 65 (45%) in the placebo arm reported at least one adverse event (AE) or serious adverse event (SAE); the event rates by time in study and severity of AEs were comparable in both arms (*eBox 2, eTable 2*). Local skin reactions (LSR) were reported by 93/140 and 2/143 participants in the ME and placebo arm, respectively. For details on LSR, administered study drug injections, and dose adaptations, see *eBox 2*, *eTable 3*, and *eFigure*.

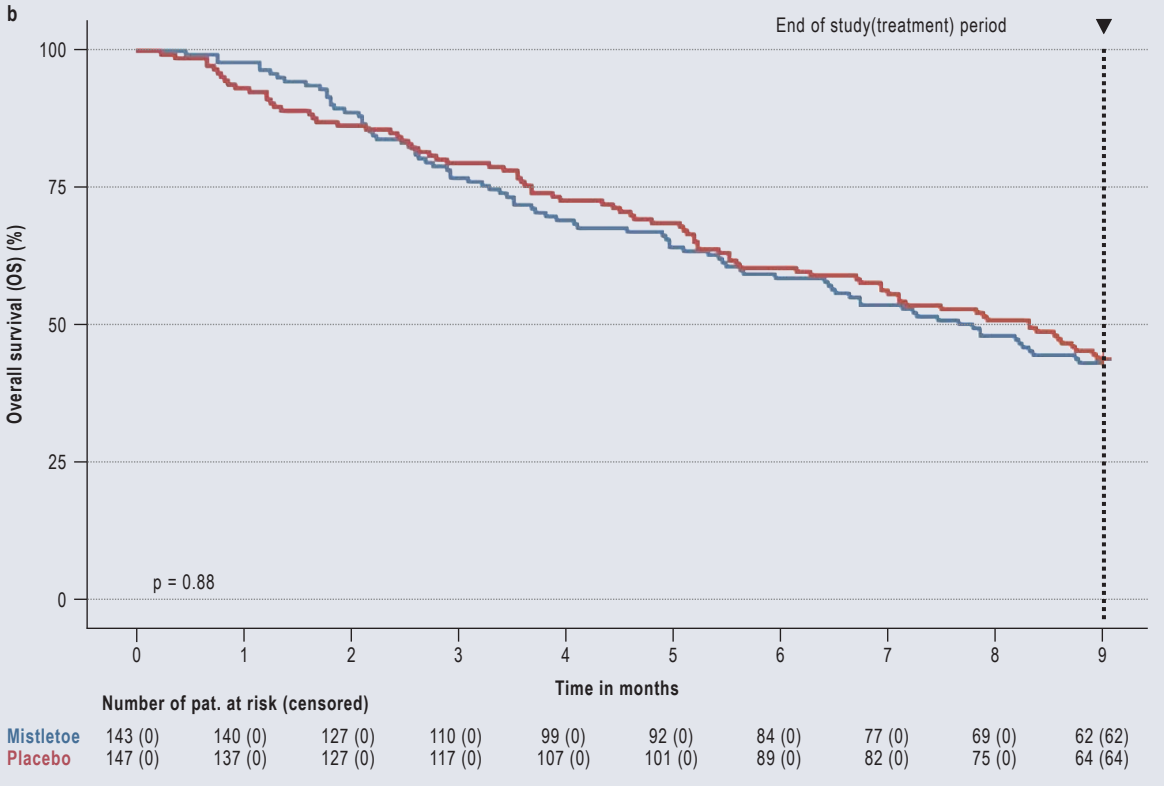
The distribution of chemotherapy regimens was balanced between the groups. The median length of chemotherapy treatment was 3.8 months in the ME and 4.5 months and placebo arm, amounting to 64% of patients' time in the study in either one of the groups (IQR 36% ME and 30% placebo arm) (*eBox 2, eSupplement–Tables 5–6, eSupplement–Figure 7*). Glucocorticoids were given to 130/143, (91%, ME arm) and 129/147 (88% placebo arm) participants, for the following indications:

- for symptom relief (e.g., cancer-related fatigue, pain, or loss of appetite)
- as an antiemetic drug in addition to chemotherapy
- to treat comorbidy (e.g., obstructive pulmonary disease).

Glucocorticoid use in relation to patients' time in the study was similar in both groups in terms of doses and length of treatment (*eSupplement–Figure 8*). The OS of participants without glucocorticoids use was similar in both treatment arms (HR 0.91, [0.35–2.36]) (*eSupplement–Figure 9*).

Figure 2





Kaplan–Meier curves of overall survival (OS)
OS based on the total eligible follow-up time (a) and on the follow-up time during the nine-month study(treatment)period (b). Median survival time with Mistletoe extract (ME), 7.8 months [6.4; 9.4]; with placebo, 8.3 months [6.9; 9.7]. To the right of the vertical line at nine months in (a), data are shown for all patients after the nine-month study(treatment) period including those who opted for post-trial treatment with ME (44 [86%] of patients in the ME arm and 52 [85%] of patients in the placebo arm).

Discussion

We did not find an effect of ME as an addition to standard treatment on OS (primary endpoint) nor on the HRQoL dimension "global health/QoL" compared to placebo. The slightly longer OS in the placebo arm could be explained by minor differences in relevant baseline characteristics. The relatively high proportion of participants treated with palliative chemotherapy (22) is due to patients' relatively good performance status at baseline (*eMethods 1*).

Our results did not confirm those of prior clinical studies on subcutaneous ME treatment for pancreatic cancer (*eBox 1*), which had reported a benefit of ME on OS (14, 23–26) and HRQoL (15, 25, 26). The trial most comparable with MISTRAL is the open-label MAPAC RCT (14, 15, 27), which was conducted in Serbia and reported a significant improvement in both OS and HRQoL with ME. Given the known immune resistance in pancreatic cancer (28) and taking into account ME's main mechanism of action via stimulation of both the innate and adaptive immune response, the present study's results would not have been surprising—without the results from MAPAC.

It was not expected that the results of MISTRAL would diverge to such an extent from those of MAPAC and other previous studies. We therefore explored whether there were differences in study populations, treatment, or immunoreactivity, and conducted a variety of sensitivity analyses that had not originally been planned. We found no indication, however, that any such discrepancies could explain the differences in outcome: Neither the MISTRAL patients' better prognosis altered the results for OS, nor did the inclusion of patients with a relapse, the details of ME treatment (duration, dose, number of injections, LSRs), or concomitant treatment (chemotherapy, glucocorticoids) (*eMethods 3*).

The blinded study design is a major difference between MISTRAL and earlier studies. All participants were informed of the possibility of nonspecific reactions occurring at the injection site. Even so, the development of LSR (in 66% of the MISTRAL population in the ME treatment arm) might have revealed ME. However, this does not seem to have affected the outcome for HRQoL or OS.

The level to which PC is integrated into Sweden's health care system is very high (advanced integration, level 4b out of 4b) whereas Serbia is reported to provide generalized PC (level 3b) (29). The palliative chemotherapy regimens delivered during the MISTRAL trial are in line with the current state of knowledge (1). Early access to PC has been shown to prolong survival and improve HRQoL in terminally ill patients (30). In MISTRAL, participants' need for palliative home care was regularly evaluated and provided if indicated. It is conceivable that optimized PC and extensive oncological treatment with modern palliative chemotherapy provided in MISTRAL might have left less room for improvement in the primary endpoint of OS and the secondary endpoint of "global health/QoL" by adding ME treatment.

No major safety concern arose during MISTRAL. The two SAEs (1.4%) related to the study drug consisted of known side effects of ME (urticaria, pseudoallergic reaction), and their frequency of occurrence was in line with earlier reports (0%–1.5%) (14, 26, 31, 32).

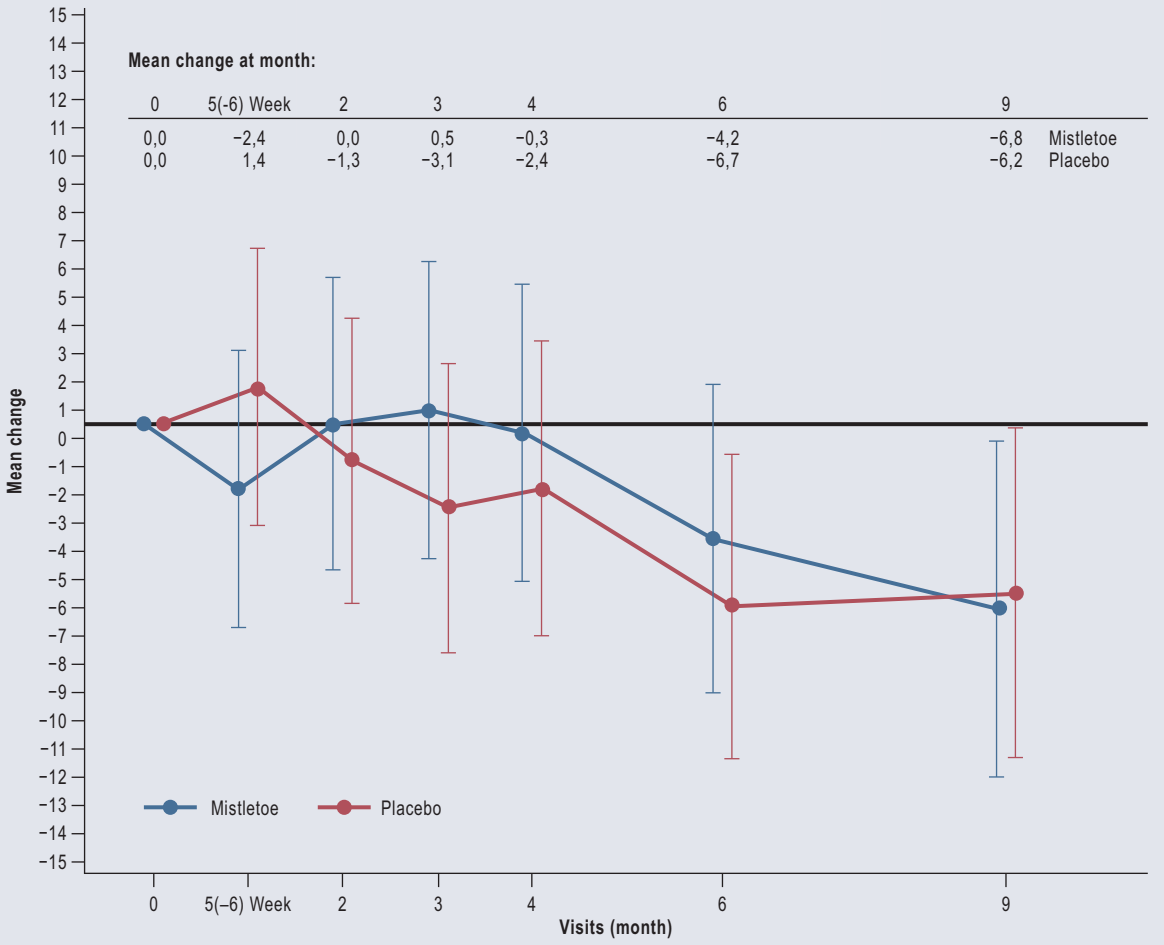
Table

Baseline characteristics of the intention-to-treat population, n=290

		Mistletoe extract (ME) n=143	Placebo n=147
Sex, female		73 (51%)	73 (50%)
Age, years		70 (65–74)	68 (60–76)
Time from diagnosis*1 to date of randomization, days		38 (27–62)	41 (27–66)
ECOG performance status	0	61 (43%)	66 (45%)
	1	61 (43%)	51 (35%)
	2	21 (14%)	30 (20%)
Recommended standard treatment			
Palliative chemotherapy		121 (85%)	120 (82%)
Best supportive care (BSC)		22 (15%)	27 (18%)
Pancreatic cancer, primary diagnosis *2		**106 (74%)**	**101 (69%)**
Clinical/pathological T stage	T0/Tis	0 (0%)	0 (0%)
	T1	3 (3%)	2 (2%)
	T2	10 (9%)	15 (15%)
	T3	29 (27%)	26 (26%)
	T4	55 (52%)	47 (46%)
	TX	9 (9%)	11 (11%)
	N0	44 (42%)	43 (42%)
	N1	30 (28%)	27 (27%)
	NX*3	32 (30%)	31 (31%)
	M1	85 (80%)	86 (85%)
	M0	20 (19%)	13 (13%)
	MX	1 (1%)	2 (2%)
Relapse of pancreatic cancer *2		**37 (26%)**	**46 (31%)**
Local recurrence	yes	16 (43%)	21 (46%)
	no	20 (54%)	24 (52%)
	unknown	1 (3%)	1 (2%)
Distant metastases	yes	34 (92%)	38 (83%)
	no	3 (8%)	7 (15%)
	unknown	0 (0%)	1 (2%)

Data presented as n (%) or median (interquartile range, IQR)
*1 Confirmed by imaging and/or histopathology
*2 i.e., a primary diagnosis of pancreatic cancer or a relapse of previous pancreatic cancer
*3 Numbers include missing information on N-status: n=4 (4%) in the ME arm and n=3 (3%) in the placebo arm

Figure 3



Mean change in quality-of-life scores
Overall health status compared to baseline scores (95% confidence interval), calculated using mixed model regression; the data were collected using the EORTC-QLQC30 questionnaire. Higher scores indicate better quality of life.

Major concerns have been voiced that botanicals may interfere negatively with chemotherapy, potentially impacting treatment efficacy and safety (33). In our trial, we did not find any indications pointing to increased or decreased survival times or toxicity when ME was added to chemotherapy. This is just a rough assessment though, as our trial was neither designed nor powered to investigate this question. However, this assessment is supported by the results of a phase I study that found no influence of ME on the metabolism of gemcitabine—the most frequently used chemotherapy in pancreatic cancer (34).

The strengths of the present study include:

- a placebo-controlled design with a study protocol conforming to SPIRIT guidelines (17)
- a multicenter design in an academic setting
- conducted in a country where comprehensive oncological PC is being provided
- public and non-profit funding
- a multidisciplinary team of experts specializing in oncology, pharmacology, nursing, integrative medicine, and PC.

In addition, the robustness of the data set was assured by implementing quality control.

The study has high internal validity as evidenced—for example—by good adherence to the scheduled dates for study visits and HRQoL assessments, and the number of returned questionnaires. This is remarkable as almost half of the study period (2.5 of 5.5 years) coincided with the COVID-19 pandemic, which resulted in more study visits having to be done by telephone and in delays in patient recruiting. All data were comprehensively analyzed and presented.

Cancer patients who wish to be treated with ME usually actively seek out treatment in a setting of integrative oncology (26, 31). Treatment settings that enable patients' active involvement in their therapy have been assumed to be beneficial beyond the specific treatment effect (35). ME treatment in this trial was stripped from such a context, and this may have caused lower external validity in terms of the HRQoL dimension "global health/QoL" not accurately reflecting the context in which most cancer patients use ME today.

Conclusion

We regard it as unlikely that we missed a potentially clinically significant effect for ME treatment. Our findings will be of importance for all those involved in the care of patients with advanced pancreatic cancer. Although we found no effect of ME in this given clinical situation, our study did not show any risks associated with its use either. Future research should investigate the impact of ME on malignancies that are more responsive to immune activating therapies.

Data sharing

Sharing data was not intended at the outset of the study. Patients were not asked for their informed consent and their data will thus not be made available.

Acknowledgments

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Conflict of interest statement

The authors declare that no conflict of interest exists.

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Editorial note

Dr G S Kienle is a colleague in the medical-scientific editorial team of *Deutsches Ärzteblatt* and also a co-author of this article. She was not at any point involved in the editorial team's reading, review, revision, and decision-making regarding this article. Furthermore, she did not have any access to information that exceeded that provided to the corresponding author, Dr Wode.

The editorial team placed the initial assessment, the selection of peer reviewers, and decisions regarding revision (including checking the revised manuscript), as well as manuscript acceptance, into the hands of an external expert from the scientific advisory board of *Deutsches Ärzteblatt*. We thank Prof Dr Martin Schuler from the West German Cancer Centre at the University Hospital of Essen.

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Supplementary material
eReferences, eMethods, eBoxes, eTables, eFigure:
www.aerzteblatt-international.de/m2024.0080

Supplementary material to:

Mistletoe Extract in Patients With Advanced Pancreatic Cancer

A Double-Blind, Randomized, Placebo-Controlled Trial (MISTRAL)

by Kathrin Wode, Gunver S. Kienle, Ove Björ, Per Fransson, Lena Sharp, Nils O. Elander, Britt-Marie Bernhardson, Birgit Johansson, Christina Edwinsdotter Ardnor, Ursula Scheibling, Johanna Hök Nordberg, and Roger Henriksson

Dtsch Arztebl Int 2024; 121: 347–54. DOI: 10.3238/arztebl.m2024.0080

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eMETHODS 1

Methods

Study design, inclusion and exclusion criteria

A detailed description of the study protocol has been published (17).

A fixed block length (= number of participants per block) of four was used. A variable block length was considered less practicable since some of the study sites were quite small and this would, in some cases, have resulted in imbalances and very small groups. The block length was not known to anyone except for the data manager.

Nine oncology centers in Sweden participated in the study [among them, three university hospitals].

Inclusion criteria

- Signed written informed consent
- Age ≥ 18 years
- Inoperable locally advanced or metastatic pancreatic cancer or relapse of pancreatic cancer
  - Primary diagnosis: If histology is not clinically achievable, the diagnosis is to be confirmed according to local practice which needed to be sufficient for diagnosis and choice of therapy (such as CA19–9 and CT)
  - Relapse: Histology (not mandatory) or diagnosis according to local practice, e.g. based on clinical signs and/or imaging and/or CA19–9
- ECOG performance status 0–2
- Negative pregnancy test and adequate contraception (where appropriate)

Exclusion criteria

- Life expectancy less than 4 weeks
- Pregnancy or breastfeeding
- Neuroendocrine tumors of the pancreas
- Current use of interferon, granulocyte-colony stimulating factor (G-CSF), or thymus preparations
- Symptomatic brain edema due to brain metastases
- Known hypersensitivity to mistletoe extract (ME)
- Current use of ME preparations in any form
- Chronic granulomatous disease or active autoimmune disease or autoimmune disease with immunosuppressive treatment
- Medical, psychiatric, cognitive or other conditions that may compromise the patient's ability to understand the patient information, give informed consent, comply with the study protocol or complete the study (e.g. needle phobia).

Quality assurance

A data safety committee consisting of two oncologists (a senior consultant oncologist and a specialist in internal medicine and palliative care with extensive experience with ME treatment) reviewed all reports of severe adverse events. Independent monitoring was performed after initial inclusion and thereafter once or twice per year, depending on the inclusion rates. To ensure the highest possible quality for the collected data, 10% of the digitalized HRQoL questionnaires and laboratory test results were spot-checked. The Iscador AG checked and ensured the content and assignment of the study product, and our data manager verified that correct batches had been provided to all participants. In addition, an audit of the entire study was performed at the end of the trial and an external data manager checked the dataset before the code was broken.

Blinding, study drug dosing and dose adjustments, local skin reactions

ME and placebo looked identical in appearance, shape, labelling—including drug information in milligram (mg)—, and packaging. The subcutaneous injections were given by the participants (or next of kin) into the abdominal wall, preferably in the morning, on chemotherapy-free days. The initial dose (two injections of 0.01 mg each) was gradually increased to four injections of 0.1 mg, then four injections of 1.0 mg, then to four injections of 10 mg, and finally to the highest (maintenance) dose of 20 mg at the end of the fifth week. The doses were adjusted if malaise, flu-like symptoms, fever ≥38°C, acute infections, or activation of chronic inflammatory processes occurred, as well as after treatment pauses, e.g. during hospital stays. Local skin reactions (LSR) with redness of a skin area <5 cm and/or lasting for <48 h led to maintenance of the current dose, whereas large LSR (>5 cm and/or lasting for >48 h) led to dose reduction. LSR were registered but not reported as adverse events.

Assessment of need for palliative care, post-trial treatment, follow-up of survival status

Participants' need for palliative home care (PC) was assessed at study visits and a referral to PC provided where required. In line with the recommendations for post-trial provisions in the declaration of Helsinki, all participants were offered ME (the study drug) after the 9 months' study (treatment) period. 86% (n=96) of the participants who had completed the 9 month study(treatment) period chose to receive post-trial ME-treatment (ME arm: 44, 86%; placebo arm: 52, 85%); the remaining patients did not receive post-trial treatment with ME.

All randomized patients' survival status was checked—whether they had fulfilled the study(treatment) period of 9 months or had discontinued the intervention—and reported according to their electronic patient records by the corresponding study sites right before the end of the trial (January 2023, final end of study). This procedure had been outlined in the study protocol (17) and is in line with the Swedish regulatory framework. Participants for whom no date of death was known were censored at the date of their last recorded vital status. Since all electronic health records in Sweden are automatically updated via a central registry within days if death occurs in Sweden, and within weeks if it occurs abroad, it is likely that all censored participants were still alive.

eMETHODS 2

Statistics

Sensitivity analysis

Details of the statistical analyses for the primary and secondary endpoints are specified in the Statistical Analysis Plan (SAP), which was approved and signed on 22 December 2022. The study was unblinded on 2 January 2023. For the primary outcome analysis we calculated a Cox analysis (Cox Proportional Hazards Regression) as predefined in the SAP: Included were the stratification variables of the randomization procedure (study center and recommendation of chemotherapy). All further (secondary) adjusted Cox analyses using other variables are only regarded as sensitivity analyses. Here, variables were selected after looking at the baseline characteristics and were not specified in advance.

T-stage and primary diagnosis versus relapse of pancreatic cancer at inclusion differed in distribution in both groups. Therefore, a sensitivity analysis was conducted, using the adjusted Cox model, and further adjusting for the inclusion of patients with a primary diagnosis versus relapse and for T-stage in patients included with a primary diagnosis of pancreas cancer. T-stage was included in the model as a dummy variable in four categories: Tx/missing, T1/T2, T3, T4. We could not find an interaction effect in the adjusted Cox model between T-stage and treatment (p=0.58) or between *primary diagnosis of pancreatic cancer* versus *relapse at inclusion* and treatment (p=0.08) by performing a likelihood ratio test; therefore the results are based on the main effect from a model without an interaction term.

Whether or not patients received chemotherapy was dependent on their health and on an eventual response to ME treatment and could thereby affect the choice of using or not using chemotherapy later on. Therefore, due to a risk of selection bias, chemotherapy (yes/no) was not included in the Cox regression model and best supportive care (BSC) was solely analyzed as a subgroup.

The results of this study differ from those of previous studies. The survival probabilities were calculated for the subgroups to enable better comparability with other studies. In the supplement we present Kaplan–Meier curves for subgroups *(eSupplement–Figures 3–6)*.

Analysis of the outcomes "overall survival" (OS) and the HRQoL dimension "global health/QoL"

As defined in the protocol, the following patients were excluded from the per-protocol (PP) analysis:

- those with at least one significant protocol deviation that was believed to have a potential impact on the efficacy outcome (OS)
- those who were only treated for <4 weeks or who received <66% of possible injections.

A total of 219 participants (106 in the ME arm, 113 in the placebo arm) were included in the PP analysis. The following were excluded:

- severe protocol violations (2 in ME and 2 in placebo arm)
- no study treatment received (3 in ME and 4 in placebo arm)
- treatment period <4 weeks (19 in ME, 20 in placebo arm) and
- <66,6% of possible injections received (13 in ME and 8 in placebo arm).

The PP analysis was performed using adjusted Cox regression with "study site" as covariate and "preliminary eligibility for chemotherapy" (yes/no) as strata; the survival probabilities are presented using Kaplan–Meier curves.

For the PP population, based on the total follow-up period, the aHR from Cox regression was 1.11 [0.84; 1.47] and 1.04 [0.70; 1.54] for the nine-month study(treatment) period (*eSupplement–Figures 1 and 2*).

For the secondary outcome, the scores for the HRQoL dimension "global health/QoL" as obtained at each visit by use of the EORTC QLQ-C30 questionnaire (21) were compared between the ME and and the placebo arm. Only patients who completed the HRQoL questionnaire at baseline and at least one follow-up visit were included in the analysis. The outcomes analyzed were changes in HRQoL scores at each follow-up visit compared to baseline. The primary analysis of HRQoL was based on linear mixed models. The fixed effects "treatment" (ME/placebo) and "study visit" were included in the model as categorical variables, the baseline HRQoL score was included as natural cubic splines with 4 degrees of freedom, and the patients were modeled as a "random intercept". Interaction effects for treatment and study visits were also estimated using mixed models.

eMETHODS 3

Discussion

Considering the variety of administered chemotherapy regimens, the inclusion and exclusion criteria, and the fact that OS was calculated from randomization (performed 27–66 days after diagnosis) to death, we consider the MISTRAL survival rates in line with the reported OS of other patients with advanced pancreatic cancer both internationally (e5, e6) and in Sweden. An observational study from Karolinska University Hospital (which was also the largest study site in MISTRAL), for example, found an OS (calculated from diagnosis) of 1.8 months for patients who received BSC and of 5.8 to 10.6 months for patients who were treated with palliative chemotherapy (22).

Comparing MISTRAL with MAPAC and other studies on ME in pancreatic cancer

The median OS of those participants in MISTRAL and MAPAC participants who were most similar in terms of treatment and prognosis were compared with each other: The subgroup that received only BSC in the placebo arm of MISTRAL (n=27) had longer OS than those in the control arm in MAPAC (4.8 vs 2.7 months). It could be speculated that the longer OS in the MISTRAL trial might have left less room for improvement through additional ME treatment. It is therefore unlikely that a generally better prognosis in MISTRAL diminished a potential ME effect. Another difference in study population was that MAPAC only included patients with a primary diagnosis of pancreatic cancer while MISTRAL also included patients with a relapse. For MISTRAL, one could hypothesize that previous adjuvant chemotherapy might have impaired the immune response to ME, thus weakening a possible effect on survival. The subanalysis of the OS of the MISTRAL population (n = 207), in which patients with a relapse were excluded, showed a lower hazard ratio (HR) and the 95% confidence intervals of the two survival rates (MAPAC and MISTRAL) overlap slightly. However, there ist still quite a difference compared to the size of the MAPAC HR and we found no survival benefit either: aHR 0.92 [0.70; 1.22] (*eSupplement–Figure 3*). Thus, the inclusion of patients with a relapse did not alter the general result for OS.

With regard to treatment, the ME dosage scheme used in MISTRAL (0.01–20 mg), corresponds to the manufacturer's recommendations (19) and most clinical ME trials (e8). In MISTRAL, the mean maintenance dose was slightly higher than in MAPAC (12.7 mg and 10 mg, respectively). In daily practice, clinicians prescribe up to 30 mg for patients with pancreatic cancer (24). Previous studies reported ME treatment durations of between >3 weeks and 15.2 months (23–26). The number of injections given during the study(treatment) periods was identical in MISTRAL and MAPAC (a median of 61 and 61.5 injections, respectively). Thus, neither the duration of treatment nor the dosage explains the different results in MISTRAL compared to previous studies.

Local skin reactions (LSR) are considered to indicate a non-specific immune response and are used to guide dose adjustment (19, 32, e9). The proportion of ME-treated patients who developed LSR is similar in MISTRAL and MAPAC (65% and 61%, respectively). In the MISTRAL trial, LSR was seen in more patients who received chemotherapy than in those who did not (72% vs. 28%). This finding contrasts with a retrospective study that reported fewer LSR during oncological therapies (32), but aligns with a prospective study in breast cancer patients that found more and larger LSR during chemotherapy (31).

Immunosuppression

Theoretically, immunosuppressive medications such as chemotherapy and glucocorticoids might interfere negatively with an immunostimulatory drug such as ME. However, a subgroup analysis of MISTRAL participants receiving no chemotherapy but only BSC (n=60) found no indication of a better OS with ME: aHR 1.30 [0.70; 2.41] *(eSupplement–Figure 6)*. Thus, treatment with chemotherapy is unlikely to explain that we found no effect of ME on OS. The administration of glucocorticoids was not reported for MAPAC but may have been administered in the context of palliative care (PC) (14, 15, 27); however, a subgroup analysis of participants in MISTRAL's ME and placebo arms who were not treated with glucocorticoids (n=13 and n=18 respectively) did not reveal any difference in OS (HR 0.91, [0.35; 2.36] *(eSupplement–Figure 9)*. Due to the small number of patients the HR is not adjusted, and the result should be interpreted with caution. Presuming that immunosuppressive effects may be more pronounced with longer glucocorticoid treatment, the survival rates of patients treated with ME were compared to those treated with placebo. This was done using Cox regression, adjusted for the duration of glucocorticoid treatment (in percent of time in the study). This calculation also showed no clear change in the OS either, suggesting that glucocorticoid treatment was unlikely to have suppressed an immunologically mediated effect of ME on OS (aHR 1.05, [0.77; 1.43]). However, this must be interpreted with caution since adjusting for glucocorticoid use in the Cox model could cause collider bias because the choice for administering glucocorticoid treatment could be influenced both by the study treatment and by changes in health.

Thus, the main difference that may explain the diverging results of MISTRAL compared to MAPAC may be the amount and quality of palliative treatment and care received as well as MISTRAL's double-blind design.

eBOX 1

Clinical evidence on mistletoe therapy in pancreatic cancer from earlier studies

Before the present study was conducted, the best evidence regarding the efficacy of mistletoe therapy came from the MAPAC study on metastatic or locally advanced pancreatic cancer (14, 15, 27): This open label, randomized, controlled phase III study compared the subcutaneous administration of mistletoe extract (ME) with best supportive care (BSC) alone in 220 patients with advanced pancreatic cancer who were not receiving chemotherapy. The median survival time was 4.8 months in the ME treatment arm and 2.7 months in the control arm (hazard ratio [HR] 0.49, [0.36; 0.65], p<0.0001). In patients with a poor prognosis, the survival time was 3.4 in the ME group vs 2.0 months in the control group; the corresponding figures for patients with a good prognosis were 6.6 and 3.2 months, respectively. ME-treated patients gained weight and scored better in all six functional scales of the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire as well as in seven out of nine symptom scales.

A retrospective study investigated survival under ME treatment as a complement to adjuvant chemotherapy after surgical removal of the tumor. Data from patient files of 396 consecutive patients in UICC stage I–IV were analyzed. The authors reported a longer survival for patients treated with ME with an adjusted HR (aHR) of 0.52 [0.40; 0.68] (26). As this was an observational study, selection bias or confounding cannot be ruled out. Collider bias or immortal time bias could also have influenced the results. A small prospective single-arm study (25) and four retrospective studies (23, 24, e1, e2) in which data from patient files and registers were analyzed reported beneficial effects of ME on survival. However, due to inadequate methodology and due to possible selection bias, immortal time bias, and confounding the validity of these results is questionable.

Case reports and case series describe tumor remission or unusually long survival times in patients with pancreatic cancer who received partly local, partly high dose ME treatment, mostly in combination with anticancer therapy (for example, e3–e5).

eBOX 2

Results:

The last patient completed participation in the study on 5 September 2022. Participant's survival status was reported by the study sites from 19 to 23 December 2022, and on 2 January 2023, the end of the trial was declared and the code for treatment assignment was broken.

- **Baseline characteristics and treatment with chemotherapy**

The baseline characteristics were well balanced except for small differences in the distribution of tumor stages (T-stages) in participants with a primary diagnosis of pancreatic cancer, to the disadvantage of the mistletoe extract (ME) arm. Furthermore, a primary diagnosis of pancreatic cancer was slightly more common in the ME arm and relapse more common in the placebo arm.

The four most frequently used chemotherapy regimens in both arms were Paclitaxel-Gemcitabine combinations, Gemcitabine monotherapy, 5-FU-Irinotecan-Oxaliplatine combinations, and 5-FU-Oxaliplatine combinations. First-line therapy was administered in n=114, 80% (ME) and n=116, 79% (placebo) of participants over a mean period (SD) of 3.1 (2.5) and 3.5 (2.5) months, respectively. Second-line therapy was administered in n=37, 26% (ME) and n=37, 25% (placebo) of participants over a mean period (SD) of 2.0 (1.6) and 2.2 (1.9) months, respectively (*eSupplement–Tables 5 and 6*).

- **Recovery from severe adverse events (SAEs)**

Complete recovery from SAEs was seen in 21/37 (57%) of cases in the ME and in 15/38 (40%) of cases in the placebo arm. Two SAEs in the ME arm were assessed as related to the study drug. These were known side-effects: one case of urticaria led to discontinuation of treatment intervention and one case of pseudoallergic reaction led to an adjustment in study drug dosage.

- **Local skin reactions (LSR), received treatment**

LSRs were reported by 2/143 participants (1%) in the placebo arm, by 93/140 participants (66%) in the ME arm, and by 82/114 (72%) of participants in the subgroup of the ME arm that was treated with chemotherapy.

Large LSR leading to dose reduction were reported by 80/140 (57%) of participants in the ME arm and by 0/143 (0%) in the placebo arm.

One or more dose adjustments (due to LSR, malaise, flu-like symptoms, fever, acute infections, hospitalization etc) were made in more patients in the ME arm (72%) compared to the placebo arm (27%).

The proportion of injections administered in relation to maximum possible injections was 81% in the ME arm and 84% in the placebo arm. The number of administered injections (standard deviation, SD) per patient was on average 61.1 (41.4) in the ME arm and 69.1 (41.5) in the placebo arm (*eTable 3*).

The mean maintenance dose (calculated from week 5) was 9.5–14.3 mg in the ME arm and 18.2–20.0 mg in the placebo arm (*eFigure*).

- **Patient safety data set**

The safety data set includes all randomized patients who received at least one injection of ME or placebo. Seven participants received no injection at all (3 in the ME arm and 4 in the placebo arm). The remaining 283 patients' data constitute the safety data set.

eTable 1

Participants treated with palliative chemotherapy or best supportive care (BSC)

Treatment arm	Palliative chemotherapy	BSC	Total
Mistletoe extract (ME)	114 (50%)	29 (48%)	143 (49%)
Placebo	116 (50%)	31 (52%)	147 (51%)
Total	230 (100%)	60 (100%)	290 (100%)

Number of patients (%)
At the time of randomization, 241 patients had been preliminary assessed eligible for palliative chemotherapy and 49 for BSC. For medical reasons and/or according to patients' preferences, the tumor board's preliminary assessment was deviated from in 15 cases: two patients received chemotherapy (1 in the ME arm, 1 in the placebo arm) and 13 BSC (8 in the ME arm, 5 in the placebo arm) counter to the initial treatment decision.

eTable 2

Adverse events and serious adverse events

	Count		Percent		Incidence of AE/SAE per month in the study		
	Mistletoe	Placebo	Mistletoe	Placebo	Mistletoe	Placebo	IRR (95% CI) *
No AE/SAE	76	78	54	55			
At least one AE or SAE	64	65	46	45	0.060	0.053	1.11 [0.77; 1.59]
– At least one AE	46	46	33	32	0.038	0.033	1.13 [0.73; 1.73]
– At least one SAE	29	28	21	20	0.084	0.075	1.17 [0.67; 2.03]
Total	**140 (76+64)**	**143 (78+65)**	100	100			

Distribution of adverse events (AE) and serious adverse events (SAE) as count, percent, and rate by time in the study. Time in the study was defined as the time from baseline visit to early study termination (discontinuation of the intervention or death) or the end of the nine-month treatment period.
* Incidence rate ratio (IRR, mistletoe/placebo) with 95% confidence interval (CI); CI for the incidence rate ratio based on Wald confidence intervals

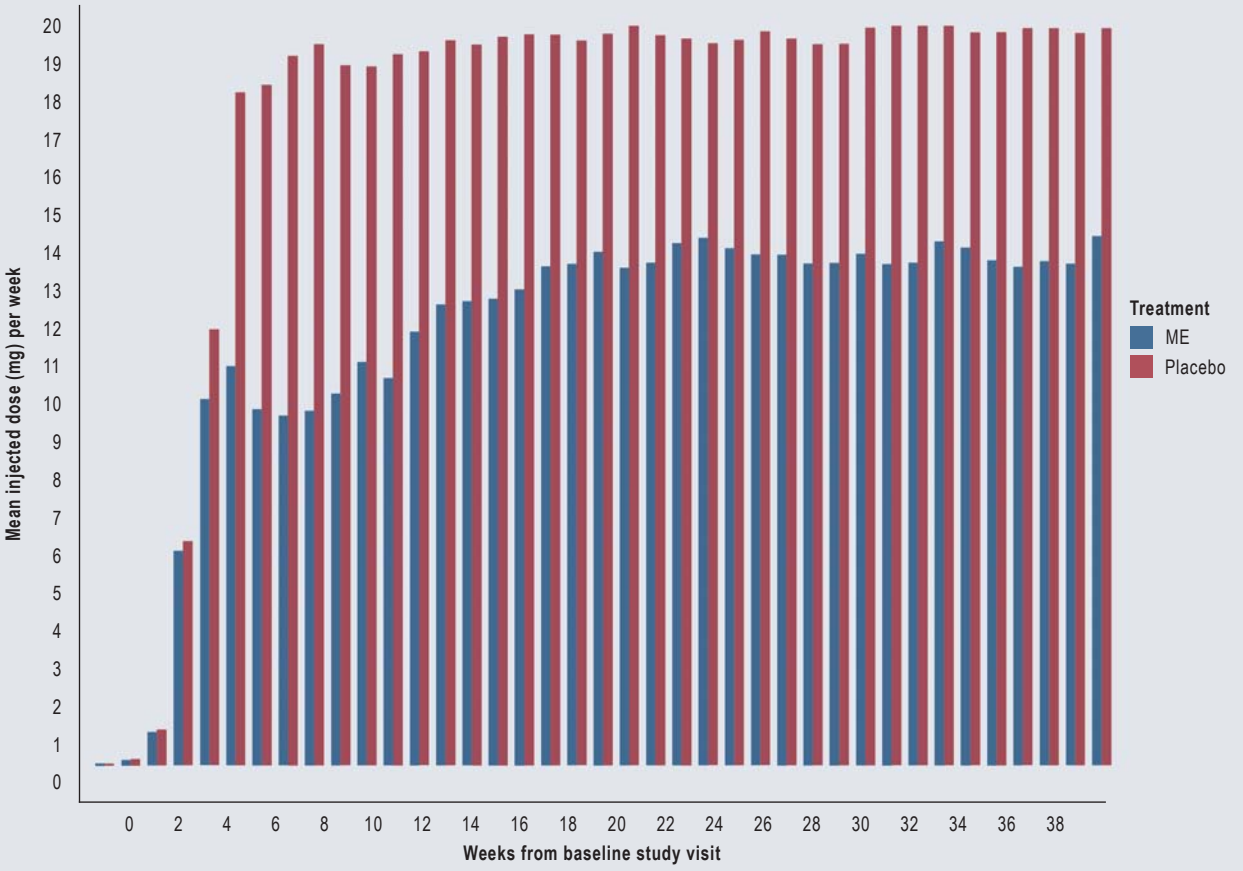
eTable 3

Number of administered study drug injections

Treatment	Number of randomized patients	Number of patients injected with the treatment substance according to diary	Average number of administered doses (SD) per patient	Proportion of administered doses in relation to the maximum possible number of doses per patient*
Mistletoe extract	143	140	61.1 (41.4)	81.0 %
Placebo	147	143	69.1 (41.5)	84.3 %

* Maximum possible number of doses from first baseline visit to patients' last visit before the occurrence of any of the following: beginning of follow-up period after completion of the nine-month study(treatment) period; early termination of treatment or death in the nine-month study(treatment) period. The maximum possible number of doses per patient was set at 3 expected doses per week.
SD, standard deviation

eFigure



Mean doses of study drug administered
Mean injected dose per week: in mg (mean) per injection according to the diary entries. Three injections were planned per week. The maintenance dose was calculated from week 5. ME, mistletoe extract

eSupplement

Mistletoe Extract in Patients With Advanced Pancreatic Cancer: a Double-Blind, Randomized, Placebo-Controlled Trial (MISTRAL)

K. Wode, G. S. Kienle, O. Björ, P. Fransson, L. Sharp, N. O. Elander, B.-M. Bernhardson, B. Johansson, C. Edwinsdotter Ardnor, U. Scheibling, J. Hök Nordberg, R. Henriksson

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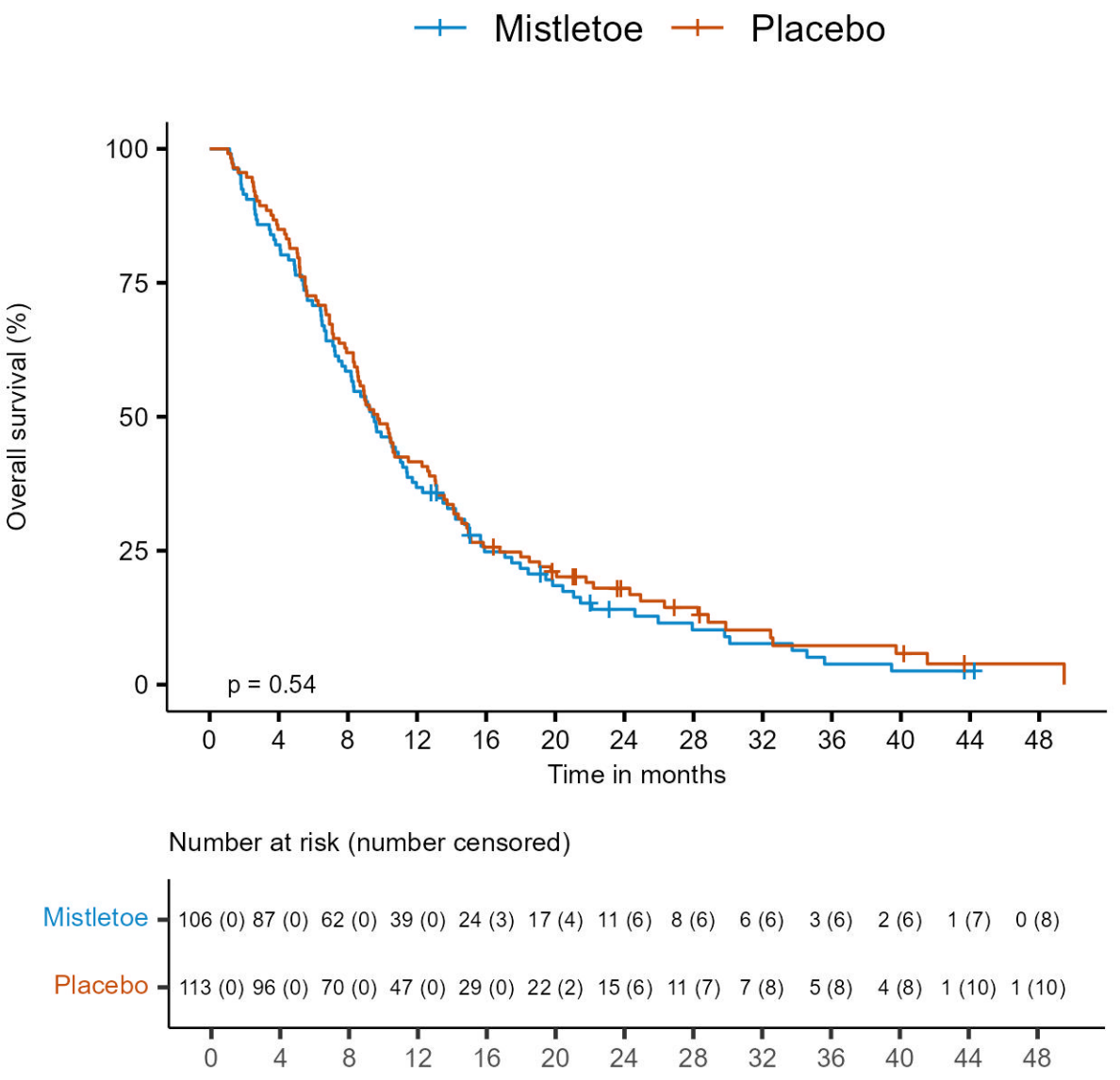
eTable 1: Screened patients´ reasons to decline participation.

According to study nurses´ notes on screening log.

Patients reasons to decline participation	**N**
No further reasons given for declining participation	142
No energy/ too burdensome	46
Difficult to interpret study nurses´ notes	40
Too long to travel to hospital	23
Study design with placebo (did not want to risk getting placebo)	22
Missed (e.g. due to Covid19 pandemic, high workload of study nurses, doctor did not ask the patient, signature too late,..)	20
Did not want to take injections (incl. fear of needles)	19
Not interested/did not show up when should have answered question on participation	19
Did not want to receive treatment (or just mistletoe?)	6
Blank (no information)	3
Changed their mind	3
Did not accept palliative state	1
Did not want to receive mistletoe	1
Other priorities in life	1
Sum	**346**

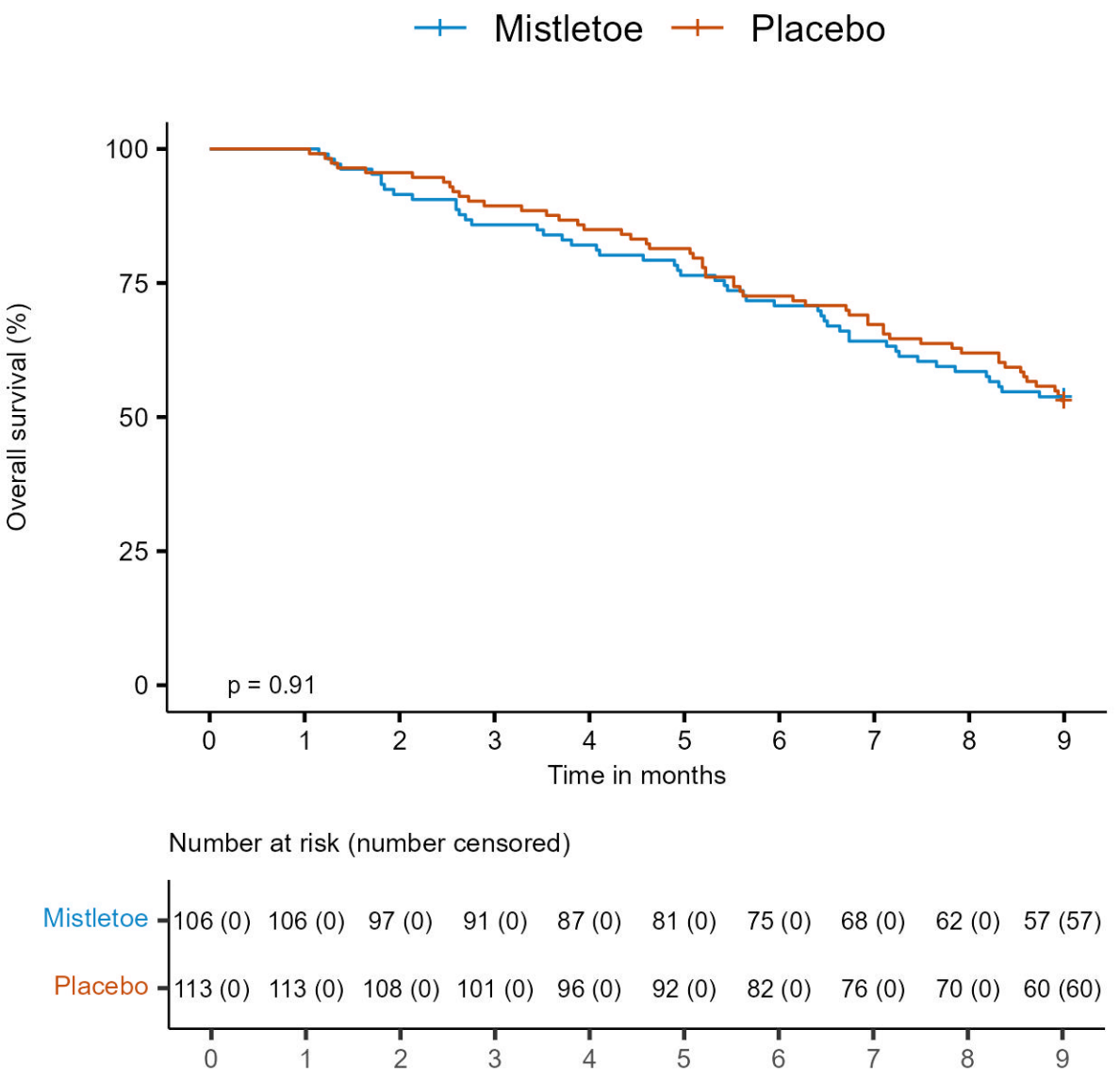
eFigure 1: Per Protocol analysis of overall survival for total follow up time.

Kaplan-Meier curves for patients included in the Per Protocol (PP) dataset of overall survival for total follow-up time. Displayed on the graph are p-values from log-rank test. Median survival time for patients treated with Mistletoe extract: 9.5 and placebo: 9.7 months.



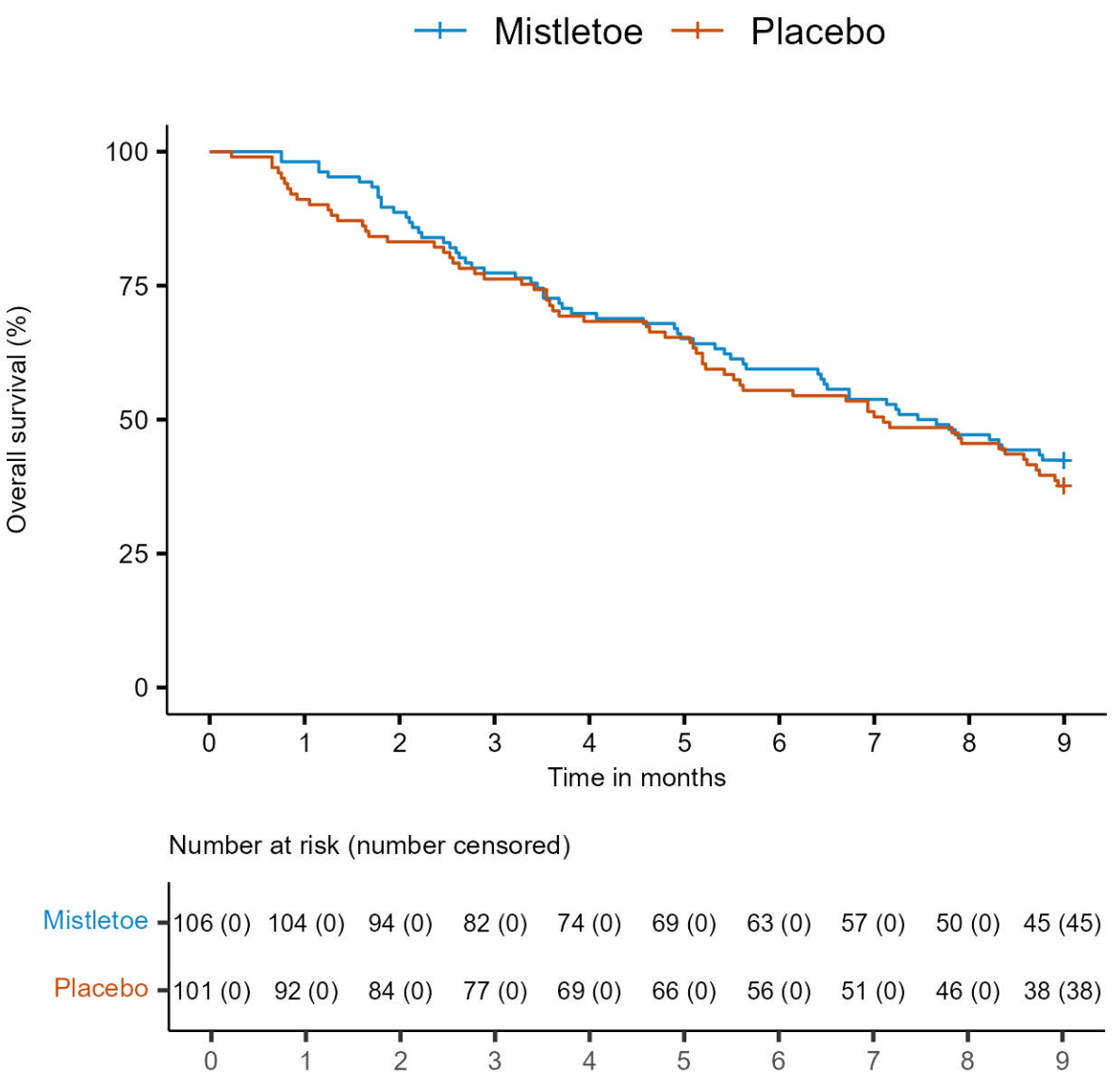
eFigure 2: Per Protocol (PP) analysis of overall survival for nine-months treatment period.

Kaplan-Meier curves for patients included in the PP dataset of overall survival delimited to the nine-month treatment period. Displayed on the graph are p-values from log-rank test.
No treatment reached median survival time.



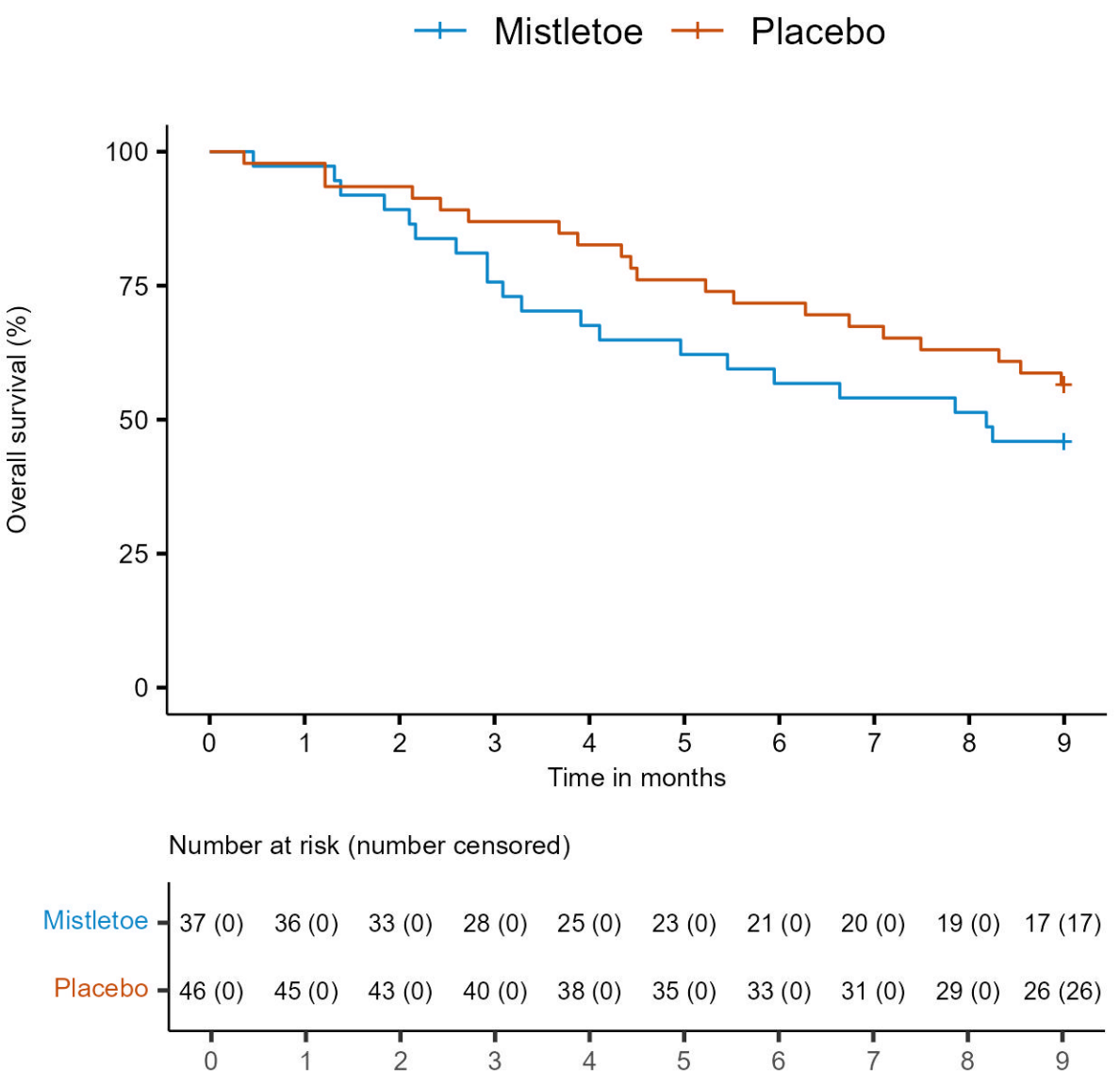
eFigure 3: Overall survival for patients with primary diagnosis pancreatic cancer.

Kaplan-Meier curves of overall survival for patients with primary diagnosis pancreatic cancer. Median survival time for patients treated with Mistletoe extract: 7.6 and placebo: 7.1 months.



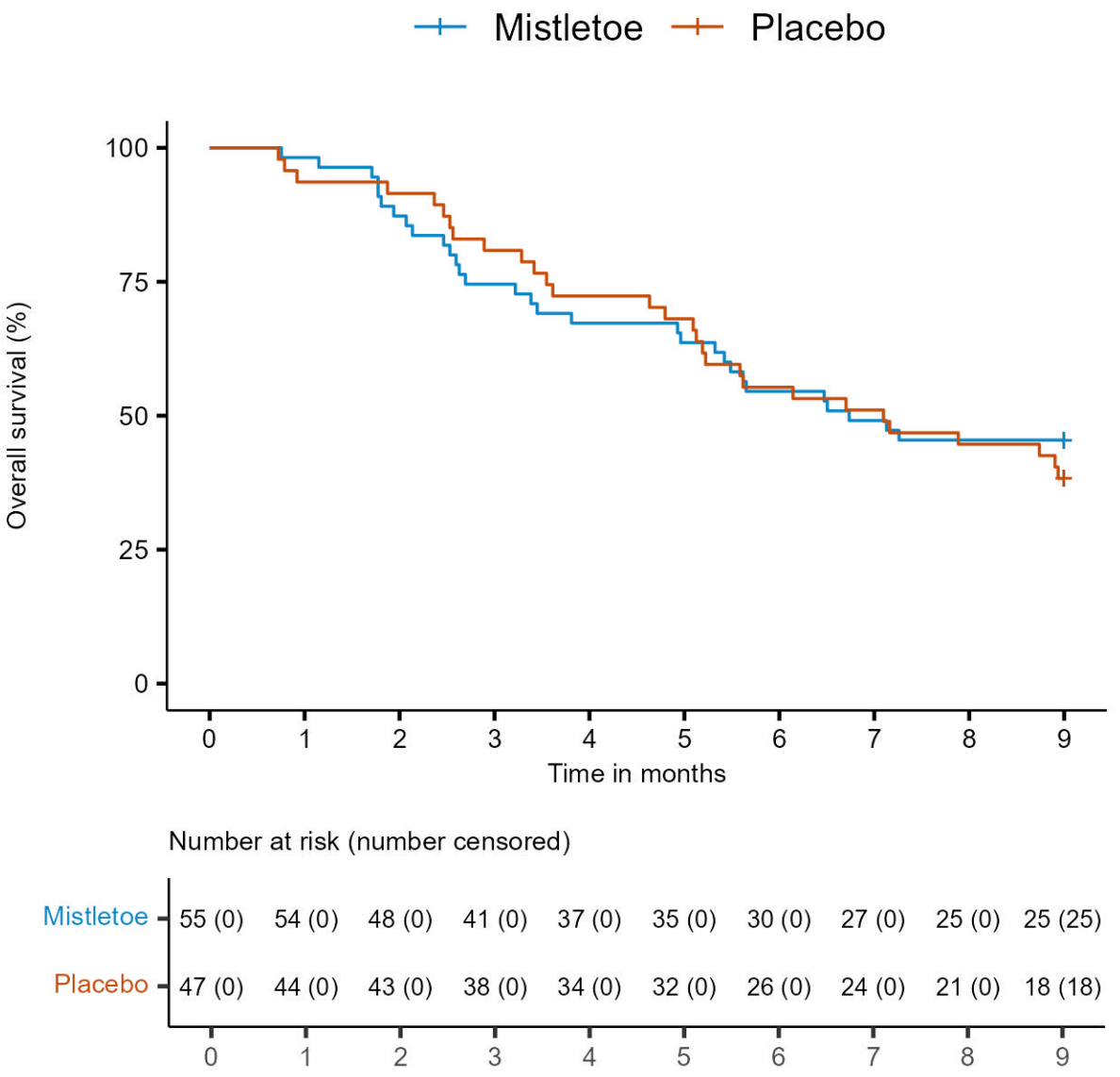
eFigure 4: Overall survival for patients with relapse of pancreatic cancer.

Kaplan-Meier curves of overall survival for patients with relapse of pancreatic cancer.
Median survival time for patients treated with Mistletoe extract: 8.2 months and placebo: NA.



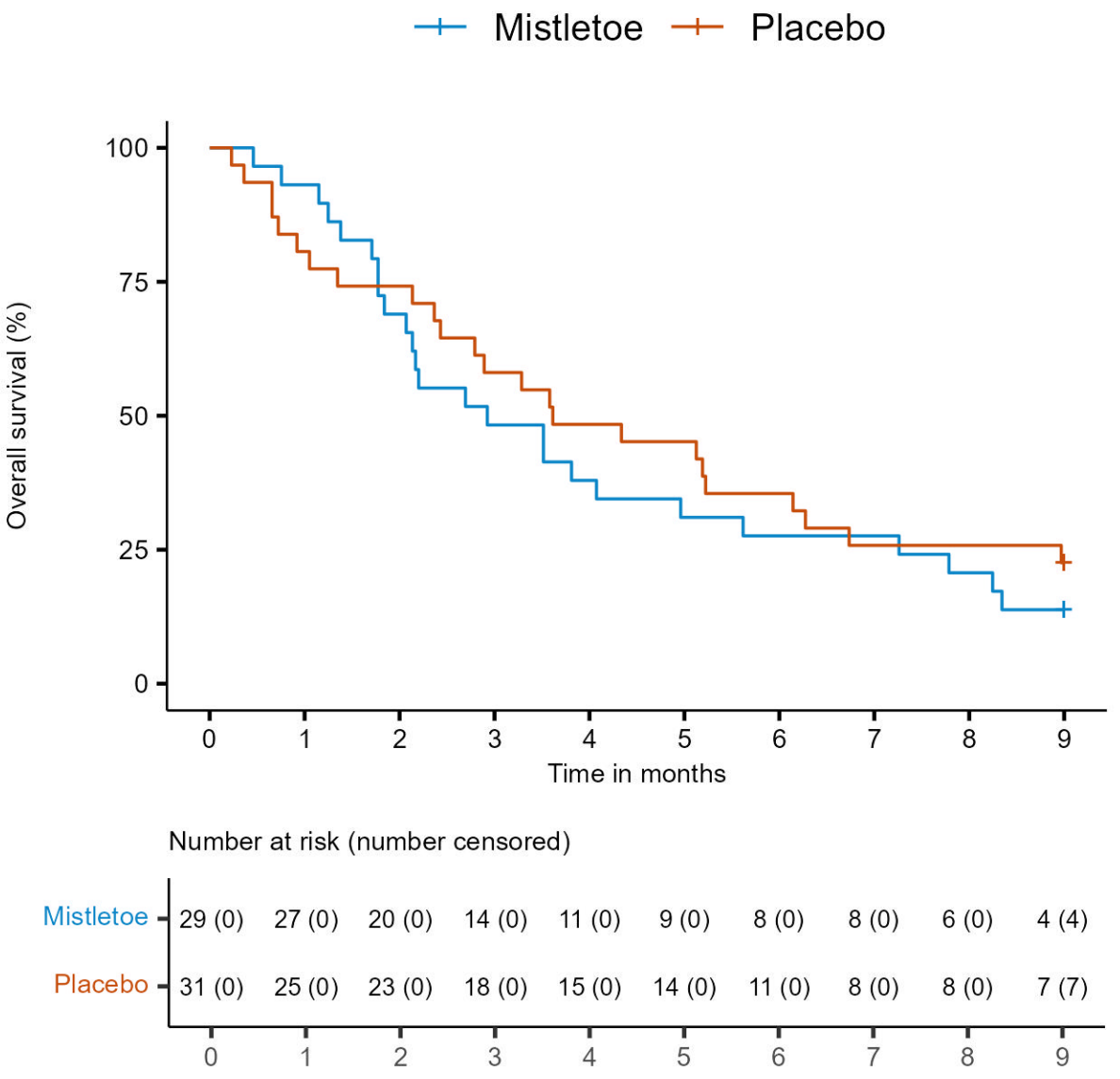
eFigure 5: Overall survival for patients with stage T4 tumours at primary diagnosis.

Kaplan-Meier curves of overall survival for patients with stage T4 tumours at primary diagnosis. Median survival time for patients treated with Mistletoe extract: 6.7 and placebo: 7.1 months.



eFigure 6: Overall survival for patients treated with best supportive care.

Kaplan-Meier curves of overall survival for patients treated with best supportive care.
Median survival time for patients treated with Mistletoe extract: 2.9 and placebo: 3.6 months.



eTable 2: Visits and assessments of health-related quality of life.

Number of visits, timepoint of visits, number of health-related quality of life (HRQoL) questionnaires, timepoint of responses and coverage of HRQoL questionnaires by visit and treatment (ME=Mistletoe extract).

Arm	Visit (expected number of days from baseline visit)	Number of visits	Median number of days from baseline visit (min–max)	Expected number of HRQoL question-naires[1]	Number of received HRQoL question-naires	Median number of days of HRQoL response (min–max)	HRQoL Coverage (%)[2]	Number of HRQoL question-naires in follow-up analysis set	Follow-up analysis set Coverage (%)
ME	Baseline visit (0)	143	0 (0–0)	142	140	0 (0–27)	98.6	120	84.5
ME	5-6 weeks (35–42)	126	35 (21–54)	134	121	35 (21–60)	90.3	119	88.8
ME	2 months (61)	101	63 (42–91)	118	90	63 (43–111)	76.3	89	75.4
ME	3 months (91)	90	91 (60–115)	104	86	93 (60–118)	82.7	85	81·7
ME	4 months (122)	82	123 (93–165)	96	83	124 (93–491)	86.5	82	85.4
ME	6 months (183)	71	181 (147–230)	80	67	182 (143–250)	83.8	66	82.5
ME	9 months (274)	51	273 (248–312)	57	50	273 (209–322)	87.7	50	87.7
Placebo	Baseline visit (0)	147	0 (0–0)	146	145	0 (-4–30)	99.3	121	82.9
Placebo	5-6 weeks (35–42)	125	35 (19–49)	131	119	35 (15–49)	90.8	118	90.1
Placebo	2 months (61)	115	63 (46–88)	123	111	63 (46–101)	90.2	110	89.4
Placebo	3 months (91)	107	92 (65–114)	116	97	92 (65–115)	83.6	97	83.6
Placebo	4 months (122)	95	125 (98–152)	106	88	125 (98–176)	83.0	88	83.0
Placebo	6 months (183)	82	185 (147–217)	87	77	186 (164–217)	88.5	77	88.5
Placebo	9 months (274)	61	275 (263–307)	62	56	276 (254–307)	90.3	56	90.3

[1] Approximated as the number of patients still alive at planned day of visit+15 days.
[2] When study visits were performed digitally (e.g., in cases of late palliative stage or during the Covid19 pandemic), HRQoL questionnaires were sent and returned by post. Coverage is displayed in % of expected responses

eTable 3: Means and effects on global health/quality of live (QoL) score differences from baseline.

Mean (SD[1]) baseline scores, overall mean [95 % CI] difference from baseline in score between mistletoe extract (ME) and placebo, p-values from mixed model regression.

Mean (SD) baseline QoL score			Mixed model regression		
ME patients	**Placebo patients**	**Overall mean difference ME-placebo[2]**	**p-value, treatment effect**	**p-value, interaction effect[3]**	**p-value, visit effect**
56.1 (23.5)	59.4 (21.7)	0.5 [-3.5; 4.5]	0.86	0.22	0.004

[1] Standard deviation
[2] Higher values are more favourable for the patient
[3] Interaction effect of treatment and visit

eTable 4: Means and effects on global health/quality of life (QoL) score differences from baseline by visit.

Means of individual global health/QoL score differences from baseline by mistletoe extract (ME), placebo and visit. Mean differences based on raw score values and by marginal means estimated from mixed model regression.

	Mean (SD[1]) QoL score difference from baseline visit score based on raw values		**Mean QoL score difference from baseline visit score based on mixed model regression**		
Month of visit	**ME**	**Placebo**	**ME**	**Placebo**	**Contrast estimate ME-placebo [95% CI][2]**
0	0 (0)	0 (0)	0	0	0
5-6 weeks	-0.3 (21.4)	1.4 (20.2)	-2.4	1.4	-3.7 [-9.0–1.5]
2	0.1 (22.4)	-1.1 (21.2)	-0.0	-1.3	1.3 [-4.3–7.0]
3	2.1 (24.6)	-3.1 (23.5)	-0.5	-3.1	3.6 [-2.2–9.4]
4	1.0 (23.2)	-2.9 (21.6)	-0.3	-2.4	2.0 [-3.9–8.0]
6	-1.6 (22.7)	-6.6 (23.8)	-4.2	-6.7	2.5 [-3.9–8.8]
9	-2.0 (19.9)	-5.8 (21.4)	-6.8	-6.2	-0.6 [-6.5–7.8]

[1] Standard deviation
[2] Higher values are more favourable for the patient.

eTable 5: Mean duration of different chemotherapy regimen.

Months and number of patients by treatment arm and type of chemotherapy treatment.

Chemotherapy treatment	**Mean duration (SD[1]) in months**		**Number of patients**	
	Mistletoe extract	Placebo	Mistletoe extract	Placebo
Fluorouracil-Irinotecan-Oxaliplatine combinations	2.9 (2.1)	3.4 (2.7)	15	14
Fluorouracil-Irinotecan combinations	2.2 (2.1)	1.4 (1.6)	13	8
Fluorouracil-Oxaliplatine combinations	1.9 (2.5)	2.6 (1.4)	16	14
Fluorouracil mono	3.1 (2.8)	1.3 (1.8)	10	5
Capecitabine	2.1 (1.1)	1.4 (1.8)	5	3
Capecitabine/Irinotecan	1.2 (..)		1	
Capecitabine/Oxaliplatin	2.6 (..)	4.5 (2.8)	1	2
Capecitabine/Temozolomide		2.4 (..)		1
Carboplatin/Etoposide		3.6 (..)		1
Gemcitabine	2.2 (2.5)	2.5 (2.0)	30	30
Gemcitabine-Fluorouracil	5.1 (0.0)	3.3 (2.0)	2	2
Gemcitabine/Capecitabine	1.5 (1.1)	3.3 (2.0)	5	7
Liposomal irinotecan	0.03 (..)		1	
Paclitaxel-Gemcitabine combinations	3.5 (2.4)	3.8 (2.8)	61	67
Panitumumab-Fluorouracil-Irinotecan		0.1 (..)		1
Tegafur/gimeracil/oteracil		5.8 (..)		1

[1] Standard deviation

eTable 6: Mean duration of chemotherapy treatment lines.

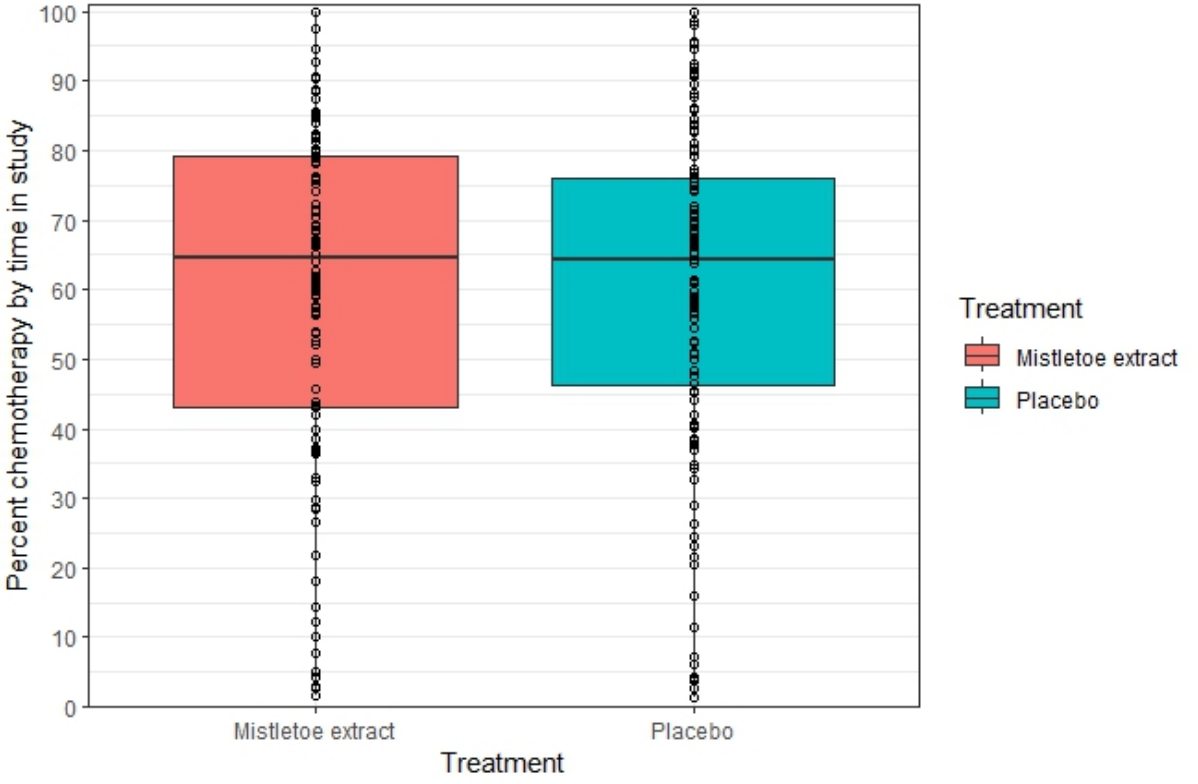
Months and number of patients by treatment arm and line.

Line	Mean (SD[1]) months		Number of patients	
	Mistletoe extract	Placebo	Mistletoe extract	Placebo
1	3.1 (2.5)	3.5 (2.5)	114	116
2	2.0 (1.6)	2.2 (1.9)	37	37
3	1.4 (1.5)	0.6 (0.4)	8	3
4	0.1 (..)		1	

[1] Standard deviation

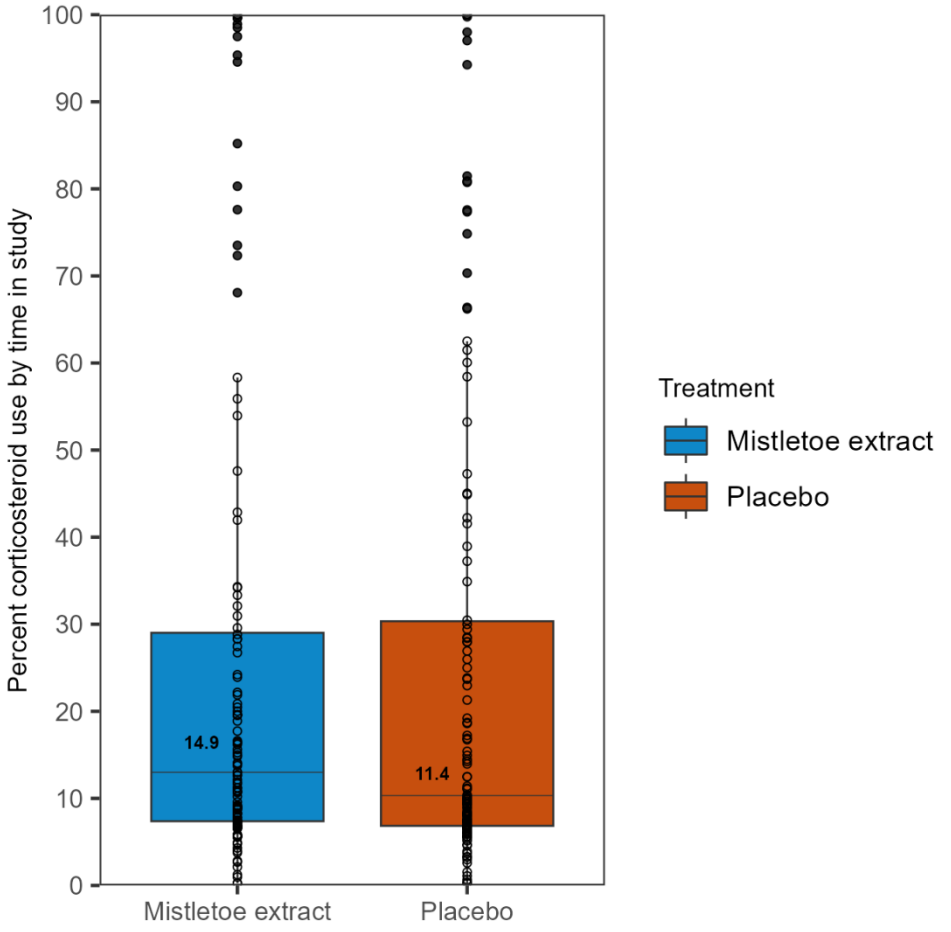
eFigure 7: Share of days with chemotherapy of days in study by treatment arm.

Boxplot of share of days with chemotherapy treatment of days in study in percent counted from baseline visit, by treatment arm. Time in study is defined as time from baseline visit to discontinued intervention or end of nine-months treatment period. 114 ME patients and 116 placebo patients.



eFigure 8: Corticosteroid use during time in study.

Boxplot of corticosteroid use by percent treatment time of total time in study. The median (IQR) percentage of glucocorticoid in days of use by time in study was 14.9% (35%) for ME and 11.4% (35%) for the placebo arm. Time in study was defined as time from baseline visit to discontinued intervention or end of nine-months treatment period.



eFigure 9: Overall survival for patients without corticosteroid treatment.

Kaplan-Meier curves of overall survival for patients not treated with corticosteroids by treatment group. Median survival time for patients treated with Mistletoe extract: 8.2 and placebo: 5.2 months.