CLINICAL STUDY REPORT SUMMARY

TITLE

Efficacy and Safety of Mistletoe Extract in the Palliative Therapy of Patients Suffering from Pancreatic Cancer (PALM-Pan)

Author of report:	[redacted]
Release date of report:	**31-Oct-2024**
Document status:	**Version 1.0**
Phase of development:	**III**
Study no.:	**33-04**
EudraCT no.:	**2014-002386-30**
Early termination:	**Yes:** ☒ **No:** ☐

SPONSOR

Verein für Krebsforschung
(Society for Cancer Research)
Kirschweg 9, CH-4144 Arlesheim, Switzerland

EU SPONSOR REPRESENTATIVE

Gesellschaft für klinische Forschung e.V. (GKF e.V.)
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CONTRACT RESEARCH ORGANIZATION

CCDRD AG
Cooperative Clinical Drug Research
and Development AG
Lindenallee 70, 15366 Hoppegarten, Germany

This trial was conducted in compliance with Good Clinical Practice (GCP).

NAME OF COMPANY **Verein für Krebsforschung** **NAME OF FINISHED PRODUCT:** **Iscador Qu** **NAME OF ACTIVE INGREDIENT(S):** **Fermented extract of *Viscum album* [L.] grown on oak trees**	**INDIVIDUAL STUDY TABLE REFERRING TO CLINICAL DOCUMENTATION OF THE DOSSIER:** **Volume:** **Page:**	*(FOR NATIONAL AUTHORITY USE ONLY)*

Title of the trial:
Efficacy and Safety of Mistletoe Extract in the Palliative Therapy of Patients Suffering from Pancreatic Cancer (PALM-Pan)

Trial center(s)/ Investigator(s): 19 active clinical sites located in 3 countries: Bulgaria, Poland, and Serbia.

Coordinating Investigator:	[redacted] Szpital św. Elżbiety Mokotowskie Centrum Medyczne ul. Goszczyńskiego 1 62-616 Warsaw, Poland
Publication (reference):	The results are not yet published
Studied period (years): 2015 to 2020 First patient enrolled: 11-May-2015 Last patient completed: 25-Mar-2020	**Phase of development:** III

Primary Objective:

To show the efficacy of additive palliative therapy of fermented mistletoe extract (ME) on the overall survival (OS) of patients and cancer related fatigue symptoms in patients with advanced pancreatic cancer.

Secondary Objectives:

To determine the quality of life and the extent of pain, body weight, neutropenia and other disease- and therapy-related symptoms as well as the compatibility of chemotherapy with additive palliative mistletoe therapy.

Methodology:

Multinational, multicenter, prospective, parallel, randomized open label study in patients suffering from pancreatic cancer with stratified randomization of patients into treatment arms according to tumor spreading (locally advanced vs. metastatic), separately for every center.

Number of patients (planned and analyzed):	Planned for randomization	290
	Screened	223
	Randomized	201
	Patients included in ***Safety Population Set (SAF)***	200
	Patients included in ***Full Analysis Set (FAS)***	185
	Originally, the recruitment period was scheduled to take approximately one year. After exceeding this time by 300%, a re-evaluation of recruitment and overall death rates estimated a recruitment time of >10 years necessary to reach the required number of events. Therefore, the sponsor decided to discontinue recruitment after the inclusion of 201 patients. The respective amendment was approved by the responsible authorities in Bulgaria, Poland and Serbia on 22-Jun-2020, 20-Mar-2020, and 11-Jan-2021, respectively.	

Diagnosis and main criteria for inclusion:	[1] Patients with diagnosis of locally advanced or metastatic adenocarcinoma of the pancreas (UICC stage III or IV), histologically confirmed if easily accessible [2] Age 18-90 years at study enrolment, legal competence [3] Voluntarily given written informed consent in advance of any study-related procedure [4] No pre-treatment with mistletoe extracts [5] No option for surgical resection or radiation in curative intent at the time of inclusion [6] Adequate negative pregnancy test and adequate contraception for women of child-bearing age [7] Scheduled Gemcitabine mono- or Gemcitabine-based combination chemotherapy starting within the next 4 weeks but only after baseline visit [8] Adequate bone marrow function assessed by laboratory values (existing results not older than 7 days may be used): [8.1] Leucocyte count ≥ 3000 / mm^3 [8.2] Neutrophil count ≥ 1500 / mm^3 [8.3] Platelet count ≥ 100.000 / mm^3	
TEST product (Investigational product), dose and mode of administration, batch numbers:	**Name:**	**Iscador Qu**
	Formulation:	solution for injection
	Active substances:	fermented aqueous extract of *Viscum album ssp album* [L.] (mistletoe) from oak tree; fresh plant material (leaves, twigs, berries); ratio of plant to extract = 1:5
	Non-active substances:	sterile pyrogen-free water, sodium chloride
	Strength:	1 ml injection solution (1 ampoule) containing fermented extract of 0.01, 0.1, 1, 10 or 20 mg of fresh mistletoe, respectively
	Dosing schedule:	individual cyclic dose escalation with 'Series' of ME up to a maximum of 20 mg: - Series 0 (2 x 0.01 mg, 2 x 0.1 mg, 3 x 1 mg); - Series I (2 x 0.1 mg, 2 x 1 mg, 3 x 10 mg); - Series II (2 x 1 mg, 2 x 10 mg, 3 x 20 mg); - Series 20 mg (7 x 20 mg). In case of no apparent clinical reaction (clinical reaction being defined as a body temperature increase ≥ 37.5°C or any local reaction at the injection site following injection) until the end of the Series II cycle, a therapy maintenance dose of 20 mg was applied for their remaining treatment period. Progress in and change between Series depended on the extent of clinical reaction within the subsequent 24 hours after application.
	Route of administration:	subcutaneous injection, thrice weekly on day 2, 4 and 6 after chemotherapy between 7:00 and 9:00 a.m.
	Manufacturer:	Verein für Krebsforschung, Switzerland
REFERENCE product, dose and mode of administration, batch number:	Not applicable	

Standard therapy:

1) First-line chemotherapy (CTx)
   a) Gemcitabine as monotherapy or
   b) one of the following combinations of Gemcitabine-based chemotherapy:
      - Gemcitabine / Capecitabine
      - Gemcitabine / nab-Paclitaxel
      - Gemcitabine / Cisplatin
      - Gemcitabine / Oxaliplatin

   Dose: Gemcitabine: 1000 mg / m^2 per cycle over 30 minutes
   other: according to the respective SmPC of the given drug

   Mode of administration: intravenous injection

   Duration of CTx treatment: 1st cycle (8 weeks): 1 / week over 7 weeks; afterwards 1 week rest period
   2nd and following cycles (4 weeks each): 1 / week over 3 weeks; afterwards 1 week rest period; until end of life or intolerability

2) Best supportive care (BSC) over entire study period at the discretion of the investigator, e.g.:
   - nonsteroidal anti-inflammatory drugs (NSAID) or opioids to address pain;
   - metoclopramide in case of nausea and / or gastroparesis / gastric outlet obstruction;
   - megestrol acetate, prednisone to address appetite loss;
   - serotonin antagonists, steroids, neurokinin-12-antagonists, benzodiazepine, phenothiazine for nausea / vomiting;
   - stimulant laxatives (prophylactically) or glycerin suppositories to address constipation;
   - additional fluids and dietary fibers for nutritional support;
   - physical activity.

Standard chemotherapy and best supportive care were not part of the study interventions and were not financially compensated by the sponsor.

Study treatment:

Mistletoe (ME) group:

In addition to chemotherapy and best supportive care (BSC), patient applied ME s.c. three times weekly on day 2, 4 and 6 after chemotherapy between 7:00 and 9:00 a.m.

Control group:

No further therapy in addition to chemotherapy and best supportive care (BSC).

Duration of treatment:

Patients were stratified according to tumor spreading (locally advanced vs. metastatic) and randomized at the baseline visit before start of treatment. Randomization was performed by permuted blocks of size 8 using the web-based software RANDOMIZER® (Medical University of Graz, Austria, 2012).

The study was initiated with a screening period between 2 days and 2 weeks, and subsequently commenced in the ME treatment group with an individual dose titration phase (maximum dose based on the extent of local injection-site skin reaction), followed by a respective dose (series) treatment phase. Control patients did not receive any additional treatment beyond regular chemotherapy and best supportive care (BSC).

Patients attended a screening visit (Visit 0) between 2 days and 2 weeks prior to starting chemotherapy. Patients of the ME group were started on a dose of 0.01 mg ME (specifications given below), followed by individual dose titration as described above. All patients were contacted by their investigators by phone [phone visit, PV (Visit 2)] 14 days after the baseline visit to discuss patient's experiences with adverse events (all patients) or with administration and adverse reactions to ME in order to decide on the further course of dosing (ME patients). All patients returned to the investigator's site 1, 2, 3, 5, 7 and 9 months following the commencement of study procedures [Therapy Visits, TV (Visits 3-7), Final Visit 8 after 9 months] for efficacy and safety assessments.

After conclusion of the 9-month study period patients could choose to continue treatment with the corresponding commercially available ME free of charge.

Assessments:

During the 9-month study period, cancer-related fatigue was assessed by the patients themselves by completing the FACIT-FATIGUE questionnaire every four weeks. Questions on pancreatic cancer-specific pain symptoms and body weight were recorded at weekly intervals. Simultaneously, patients completed the *Physical Function* scale of the European Organisation for Research and Treatment of Cancer questionnaire (EORTC QLQ-C30) to estimate the time until definitive deterioration (TUDD), e.g. a permanent decrease in this domain by at least 10 units. All other functioning and symptom scales of this questionnaire were recorded at each Therapy Visit to assess the patients' health-related quality of life (HRQoL). Also, at these times the investigator completed a checklist on occurrence and severity of specific disease- and chemotherapy-related symptoms.

For each patient deceased during the study period, the date and specific cause of death were documented. At the time of the last patient's last visit (LPLV), investigators attempted to contact all patients that had been alive at the end of their study period or their relatives to record patients' current vital status.

For evaluating the clinical response to the study treatments, computer tomography according to the RECIST criteria were performed in addition to assessment of tumour markers C19-9 and CEA which were done at Visits 1 and 8 (Baseline and Final Visit).

Safety was evaluated on the basis of adverse drug reactions (ADR) and other events (AEs), serious adverse events (SAEs) as well as safety laboratory parameters and vital signs, recorded at screening, baseline and each therapy visit as well as up to four weeks following the end of study participation.

Data sets analyzed:

Safety Population Set (SAF):	all patients enrolled into the study, i.e., fulfilling the inclusion/exclusion criteria and having given informed consent.
Full-Analysis Set (FAS):	all patients enrolled into the study and randomized into one of the two study groups, with (at least) recorded screening/baseline outcomes and having at least taken one dose of study medication (where applicable). The primary analysis is based on the FAS.
Per-Protocol Set (PPS):	all patients completing the trial without major protocol violations, and in the mistletoe extract group applying mistletoe injections at a minimum of 80% of all scheduled times.

Only the SAF and FAS sets are referenced in this report.

Criteria for evaluation:

Primary Endpoints	– Overall Survival (OS): time from randomization to death for any reason; – Fatigue according to FACIT-FATIGUE, assessed every four weeks. The FAS population was used for the primary endpoint analysis.
Secondary Endpoints	– Time to definitive deterioration (TUDD) on the EORTC QLQ-C30 Physical Functioning Scale by 10 units as assessed by a weekly questionnaire or up to death for any reason, whichever occurred first; – QoL dimensions of the EORTC QLQ-C30 Global Health, Role Functioning, Emotional Functioning, Social Functioning, Cognitive Functioning, Physical Functioning, Nausea / Vomiting, Pain, Insomnia and Appetite Loss Scales, assessed at every study visit with exception of the phone visit; – Pancreatic cancer-specific pain symptoms, assessed by a weekly questionnaire; – Body weight, recorded weekly; – Frequency of neutropenia; – Frequency of other chemotherapy-induced adverse events; – Disease related symptoms, assessed at every study visit except the phone visit; – Compliance with planned chemotherapy regime; – Use of analgesics; – Neutrophiles to lymphocytes ratio; – Computer tomography results according to RECIST criteria. The FAS population was used for the analysis of secondary endpoints.

Safety Endpoints	– Safety laboratory; – Vital signs; – Tolerability of the ME: body temperature, local reactions at site of injection; – Adverse reactions (AR), serious adverse reactions (SAR). The SAF population was used for the analysis of safety endpoints.

Statistical methods:

The primary endpoint OS and the main secondary efficacy endpoints were analyzed as time-to-event data by a Cox regression model assuming proportional hazards including the fixed factors treatment (binary), presence of metastases (binary), type of chemotherapy (binary), and country (nominal). The ECOG score was included as independent binary variable in addition to the originally planned factors due to its high explanatory power on OS independent from metastasis status. Since this is a post-hoc modification of the originally planned analysis, its result is compared to the statistical outcome of the basic model.

OS was defined as the period of time from randomization till date of death either during the patient's study participation or until the date of the patient's leaving the study alive, as an event or censored date, respectively. At the time of the last patient's last visit (LPLV), investigators attempted to contact all patients that had been alive at the end of their study period to record their current vital status. Yet, due to the documentation of death events after the extended follow-up period not uniformly meeting the study's documentation standards, these data had to be declared unreliable and were included only in sensitivity analyses.

Primary endpoint fatigue and QoL dimensions are analyzed as mean change from baseline by a mixed linear model including the same independent factors as the model for overall survival, and additionally baseline value and study visit as continuous covariates and patients as random factor.

Multiple testing inflation of the alpha error of the primary endpoints was prevented by an *a priori* ordering of hypothesis tests.

Safety assessment consisted of analysis of the incidences of disease related symptoms, adverse drug reactions, (serious) adverse events and relevant findings in laboratory parameters and physical examinations, and analysis of ECOG and vital signs.

STUDY PATIENTS

A total of 223 patients were screened, of which 22 were considered screening failures. Two hundred one (201) patients were randomized. One patient signed the consent but not the data processing form and could therefore not be evaluated. All remaining 200 patients were included in the SAF. Further validity checks revealed previously undetected violations of study inclusion criteria in 4 control- and 11 ME-patients. The FAS, on which efficacy analyses were based, therefore included 96 control and 89 ME patients.

EFFICACY RESULTS

The first primary endpoint in this study was the assessment of overall survival (OS), i.e. the time from date of randomization until death from any reason or until the end of study participation in patients receiving ME compared to a control group of patients not receiving any additional therapy beyond standard chemotherapy and best supportive care. The confirmatory analysis was based on the full analysis set (FAS). Median survival times of patients in ME and control group estimated by a product-limit survival estimate were nearly identical at 8.4 months. The Cox proportional hazard regression model revealed a corresponding hazard ratio [and 95% confidence interval] of HR = 0.905 [0.576; 1.4520], indicating a small, non-significant survival advantage of patients receiving ME. The basic model without ECOC did not change any statistical conclusion regarding treatment effects; only the marginal difference between treatment arms vanished completely. The differences in -2 Log-Likelihoods for the model with and without ECOG status was 11.21, indicating a major variance reduction and highly significant better model fit by including this parameter (p = 0.00081). ECOG status and metastatic stage of disease both had a strong, independent influence on the hazard rate (3.414 and 2.841, respectively). The analysis of dates of death having occurred until the date of last patient's last visit (LPLV) did not change the results of the confirmatory analysis in a qualitative manner. Also, further sensitivity analyses regarding a possible interaction of ME treatment with the other independent parameters did not reveal significant interaction effects, not even at an exploratory alpha error level of 10 %.

The second primary endpoint evaluated the total score of the FACIT-FATIGUE questionnaire assessed at baseline and every four weeks until the end of the study period. The confirmatory analysis of patients receiving ME compared to a control group of patients, based on the FAS did not substitute missing values since the statistical model was capable of handling missing values, assuming missingness as non-informative drop-out. In analogy to the primary analysis of overall survival, the extended model included ECOG in addition to treatment, chemotherapy and country as fixed factors, and month and baseline FACIT-FATIGUE score as continuous covariates. Mean [95%-CI] changes from baseline in fatigue of patients in ME and control group estimated by the general linear mixed model were -1.00 [-5.14, 3.13] and -1.67 [-5.46, 2.14], respectively, indicating a less strong increase in fatigue in the ME group. The difference between the treatment arms in these estimates of 0.66 [-2.30, 3.61], however, was not statistically significant. Statistically significant regression coefficients were estimated for baseline fatigue and for study months, indicating that fatigue generally increased over the study period, and that patients with relatively high fatigue at baseline tended to get disproportionally worse. The basic model without ECOG score did only differ marginally in its estimates and did not estimate other significant relationships than the extended model. Again, the difference in the-2 Log-Likelihoods between basic and extended model of 5.7 indicated a significant improvement of general model estimate by including the ECOG score. According to the pre-planned testing procedure for the multiple-testing adjustment an *a priori* ordering of hypothesis tests was applied: the FACIT-FATIGUE scale is considered first, in confirmatory intention on the full statistical error level of $\alpha = 5\%$. If and only if this test does reveal a statistically significant difference, the subsequent test for differences in overall survival between the treatment arms is also performed on the full α error level and be interpreted in a confirmatory manner. Since the difference between FACIT-FATIGUE estimates was not statistically significant on the 5% level, no superiority of ME over control in terms of fatigue could in a confirmatory manner be confirmed, rendering the second step of the testing procedure moot.

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SAFETY RESULTS

A total number of 963 treatment emergent adverse events (TEAEs) were reported in 184 patients (control group: 420 AEs in 92 patients; ME group: 543 AEs in 92 patients).

Apart from the events regarding the patients' underlying cancer disease, AEs seen in more than 10% of all patients included the blood and lymphatic system, general and administration sites, gastrointestinal system, infections and infestations, metabolic and nutrition disorders, investigations, and vascular disorders. Most frequent individual AEs occurring in more than 5% of all patients, except from progression of cancer disease were anemia (number of control / ME subjects: 22 / 35), thrombocytopenia (22 / 26), neutropenia (20 / 26), asthenia (11 / 9), peripheral edema (8 / 9), diarrhea (7 / 9), abdominal pain (5 / 13), pyrexia (6 / 10), fatigue (9 / 6), ascites (5 / 7), and local swellings (6 / 5). None of these events showed any clinically or statistically relevant imbalance between the treatment arms. Most of all AEs (n = 670; 70%) were mild or moderate and recovered or resolved without sequelae (n = 533, 55%).

Serious adverse events (n = 173) were registered in 114 patients (control group: 74 SAEs in 52 patients; ME group: 99 SAEs in 62 patients). Most of all SAEs in both treatment arms belonged to the System Organ Class (SOC) “Neoplasms benign, malignant and unspecified (incl. cysts and polyps)”, “Blood and lymphatic system disorders” and “General disorders and administration site conditions”.

Eighty patients died in the course of the trial due to tumor progression (41 cases in the control group and 39 in the ME group).

A huge number of laboratory values outside normal range were register in the course of the trial (3455 out of range values in 85 patients in the control group and 3799 out of range values in 88 patients in the ME group). This was expected having in mind the severity of the underlying patients' disease.

There were no clinically conspicuous findings regarding vital signs or physical examinations.

The tolerability of the mistletoe extract, assessed by recording local skin reactions at injection site and body temperature, was good.

CONCLUSIONS

This study was terminated prematurely due to slow recruitment and a lower than expected mortality rate, so that only half the foreseen number of deaths were recorded during the study period, even after the recruitment period was extended by 300%. Therefore, and since 15 patients had to be excluded from the Full Analysis Set due to violations of inclusion criteria, the statistical analysis suffered from insufficient power to detect the expected treatment effect.

The overall efficacy conclusions are:

1. Cancer patients receiving mistletoe extract (ME) showed a minor but statistically non-significant advantage in overall survival (OS), i.e. the time from date of randomization until death from any reason during the study period.
2. Cancer patients showed a marginal but insignificantly better course over time with regard to fatigue symptoms as assessed by FACIT-FATIGUE.

The overall safety conclusions are:

1. Most of the observed AEs are consistent with the expected events with regard to the underlying disease and the labelled undesirable effects and do not give hints towards safety concerns.
2. The number and nature of reported adverse events and the distribution among the treatment groups and system organ class do not indicate safety problems in the groups.
3. The overall review of laboratory data and clinical examinations did not give any indication on clinically important changes or safety concerns.
4. The tolerability of the mistletoe extract was good.

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