Clinical trial results:
MISTRAL - Mistletoe therapy in primary and recurrent inoperable pancreatic cancer -
A phase III prospective, randomized, double blinded, multicenter, parallel group, placebo controlled clinical trial on overall survival and health-related quality of Life

Summary

EudraCT number	2014-004552-64
Trial protocol	SE
Global end of trial date	10 January 2023

Results information

Result version number	v1 (current)
This version publication date	28 May 2025
First version publication date	28 May 2025

Trial information

Trial identification

Sponsor protocol code	131016

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02948309
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Karolinska University Hospital
Sponsor organisation address	Hälsovägen 13, K53, Huddinge, Sweden, 14186
Public contact	Clinnical Trial Unit, Medical Unit Upper Abdomen (former Center for Digestive Diseases, Karolinska University Hospital), +46 0707374261, kathrin.wode@regionstockholm.se
Scientific contact	Clinnical Trial Unit, Medical Unit Upper Abdomen (former Center for Digestive Diseases, Karolinska University Hospital), +46 0707374261, kathrin.wode@regionstockholm.se

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 January 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 January 2023
Global end of trial reached?	Yes
Global end of trial date	10 January 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective is to compare mistletoe therapy to placebo in the endpoint overall survival (time from randomization to death of any cause) in palliative patients with inoperable pancreatic cancer.

Protection of trial subjects:

The trial was approved by the ethical board and the MPA in Sweden. All study personal was trained in GCP. The study was monitored on a regular basis. A data safety committee reviewed all SAE´s during the trial.

Background therapy:

Standard of care for pancreatic cancer.

Evidence for comparator:

Not applicable (placebo)

Actual start date of recruitment	01 June 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 290
Worldwide total number of subjects	290
EEA total number of subjects	290

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	85
From 65 to 84 years	199
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

Between 7 June 2016 and 3 December 2021, 290 patients were recruited and randomized to 2 groups. The trial was conducted at 9 studysites in Sweden.

Pre-assignment

Screening details:

n=924 patients were assessed for eligibility.
n=634 were excluded due to
- not meeting the eligibility criteria (n=257)
- declined to participate (n=346)
- reasons for ineligiblity not documented (n=31)

Period 1

Period 1 title	Baseline period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Mistletoe (ME)

Arm description:

injections with mistletoe extract (ME)

Arm type	Experimental
Investigational medicinal product name	Fermented Aqueous Extract (1:5) from Mistletoe Grown on Oak Trees
Investigational medicinal product code	
Other name	Iscador Qu
Pharmaceutical forms	Injection, Solution for injection
Routes of administration	Subcutaneous use, Injection

Dosage and administration details:

Treatment starts with low dose and is gradually increased by using 2 x 0,01 mg; 4 x 0,1 mg; 4 x 1 mg and 4 x 10 mg before reaching highest possible dose of 20 mg, which is to be continued for the rest of remaining time

Arm title	placebo

Arm description:

Isotonic solution of sodium chloride

Arm type	Placebo
Investigational medicinal product name	Isotonic solution of sodium chloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Injection , Subcutaneous use

Dosage and administration details:

Treatment starts with low dose and is gradually increased using 2 x 0,01 mg; 4 x 0,1 mg; 4 x 1 mg and 4 x 10 mg before reaching highest
possible dose of 20 mg, which is to be continued for the rest of remaining time in the trial.

Number of subjects in period 1	Mistletoe (ME)	placebo
Started	143	147
Completed	111	129
Not completed	32	18
Consent withdrawn by subject	31	18
Adverse event, non-fatal	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Mistletoe (ME)
Reporting group description: injections with mistletoe extract (ME)	
Reporting group title	placebo
Reporting group description: Isotonic solution of sodium chloride	

Reporting group values	Mistletoe (ME)	placebo	Total
Number of subjects	143	147	290
Age categorical Units: Subjects			
Adults (18-64 years)	31	54	85
From 65-84 years	110	89	199
85 and over	2	4	6
Age continuous Units: years			
median	70	68	
inter-quartile range (Q1-Q3)	65 to 74	60 to 76	-
Gender categorical			
males and females			
Units: Subjects			
Female	73	73	146
Male	70	74	144

Subject analysis sets	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description: For calculation of primary endpoint OS: no drop-outs	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: All subjects randomized in the trial	
Subject analysis set title	PPT
Subject analysis set type	Per protocol

Subject analysis set description:

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).

Reporting group values	Full analysis set	ITT	PPT
Number of subjects	290	290	219
Age categorical Units: Subjects			
Adults (18-64 years)	85	85	58
From 65-84 years	199	199	157
85 and over			
Age continuous Units: years			
median	69	69	70
inter-quartile range (Q1-Q3)	63 to 75	63 to 75	64 to 74
Gender categorical			
males and females			
Units: Subjects			
Female	144	144	110
Male	146	146	109

End points

End points reporting groups

Reporting group title	Mistletoe (ME)
Reporting group description: injections with mistletoe extract (ME)	
Reporting group title	placebo
Reporting group description: Isotonic solution of sodium chloride	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description: For calculation of primary endpoint OS: no drop-outs	
Subject analysis set title	ITT
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· 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).

Primary: overall survival

End point title	overall survival

End point description:

End point type	Primary

End point timeframe:

from inclusion to end of study

End point values	Mistletoe (ME)	placebo	Full analysis set	ITT
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	143	147	290	290
Units: survival status				
dead	135	136	271	271
alive	8	11	19	19

End point values	PPT			
Subject group type	Subject analysis set			
Number of subjects analysed	219			
Units: survival status				
dead	201			
alive	18			

Attachments (see zip file)	Publication/Wode_2024_MistralOS_eng.pdf

Statistical analyses

Statistical analysis title	Survival analyss comparing ME vs placebo

Statistical analysis description:

The primary endpoint was survival, comparing ME vs placebo based on the ITT analysis set.

Comparison groups	ITT v Full analysis set
Number of subjects included in analysis	580
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Hazard ratio (HR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.44
Variability estimate	Standard error of the mean
Dispersion value	0.123

Notes:

[1] - The primary analysis was evaluated by Cox proportional hazards regression and testing the HR for overall survival in the ME versus the placebo arm, with additional study centre as covariate and planned chemotherapy (yes/no) as strata. The primary analysis was based on all eligble follow up for the ITT comparison group.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From randomization to end of study participation	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	5.0

Reporting groups	
Reporting group title	mistletoe extract
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	mistletoe extract	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 143 (20.28%)	28 / 147 (19.05%)	
number of deaths (all causes)	143	146	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Thromboembolic event			
subjects affected / exposed	3 / 143 (2.10%)	3 / 147 (2.04%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 143 (0.70%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 143 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
occlusion biliary drainage			

subjects affected / exposed	0 / 143 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
post surgical complications			
subjects affected / exposed	0 / 143 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death NOS			
subjects affected / exposed	0 / 143 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Disease progression			
subjects affected / exposed	1 / 143 (0.70%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Allergic reaction			
subjects affected / exposed	2 / 143 (1.40%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary edema			
subjects affected / exposed	1 / 143 (0.70%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 143 (0.70%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
intoxiacation with drugs			

subjects affected / exposed	0 / 143 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arythmia			
subjects affected / exposed	1 / 143 (0.70%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 143 (0.70%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 143 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 143 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stroke	Additional description: inclusive transitoric ischemic attack		
subjects affected / exposed	3 / 143 (2.10%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 1	
dysarthria			
subjects affected / exposed	0 / 143 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Hemolysis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Jaundice			
subjects affected / exposed	0 / 143 (0.00%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ileus	Additional description: inclusive subileus		
subjects affected / exposed	1 / 143 (0.70%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
upper gastrointestinal hemorrhage			
subjects affected / exposed	1 / 143 (0.70%)	3 / 147 (2.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
diarrhea			
subjects affected / exposed	0 / 143 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ascites			
subjects affected / exposed	0 / 143 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 143 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
herniation disc			
subjects affected / exposed	0 / 143 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infections			

subjects affected / exposed	16 / 143 (11.19%)	11 / 147 (7.48%)	
occurrences causally related to treatment / all	0 / 14	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	mistletoe extract	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 143 (32.17%)	46 / 147 (31.29%)	
Vascular disorders			
Vascular disorders	Additional description: dizziness, flashes, hyptension, hypertension, stroke, thromboembolic event		
subjects affected / exposed	11 / 143 (7.69%)	14 / 147 (9.52%)	
occurrences (all)	13	15	
Surgical and medical procedures			
Surgery			
subjects affected / exposed	1 / 143 (0.70%)	0 / 147 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Allergic reaction	Additional description: inclusive pseudoallergic reaction		
subjects affected / exposed	3 / 143 (2.10%)	1 / 147 (0.68%)	
occurrences (all)	3	1	
Respiratory, thoracic and mediastinal disorders			
Respiratory disorders	Additional description: dyspnea, pulmory edema, thitis, sore throat		
subjects affected / exposed	3 / 143 (2.10%)	4 / 147 (2.72%)	
occurrences (all)	3	5	
Psychiatric disorders			
Psychiatric disorders	Additional description: anxiety, confusion, insomnia		
subjects affected / exposed	2 / 143 (1.40%)	1 / 147 (0.68%)	
occurrences (all)	2	1	
Investigations			
Elevation blood parameters	Additional description: elevation bilirubine, C-reactive protein, enzymes		
subjects affected / exposed	1 / 143 (0.70%)	2 / 147 (1.36%)	
occurrences (all)	1	3	
Injury, poisoning and procedural complications			
Injury, poisoning, complications	Additional description: fracture, access complication, poisoning		

subjects affected / exposed	2 / 143 (1.40%)	1 / 147 (0.68%)	
occurrences (all)	2	1	
Cardiac disorders			
cardiac symtoms	Additional description: fibrillation, failure, infarction, murmur, myocarditis, tachycardia		
subjects affected / exposed	5 / 143 (3.50%)	3 / 147 (2.04%)	
occurrences (all)	5	3	
Nervous system disorders			
Nervous system disorders	Additional description: dizziness, heachache, neuropathya, stroke, syncope, TIA		
subjects affected / exposed	5 / 143 (3.50%)	8 / 147 (5.44%)	
occurrences (all)	8	11	
Blood and lymphatic system disorders			
blood disorders	Additional description: anemia, hemolytic uremic thrombocytopenia, hemolysius, syndrome		
subjects affected / exposed	4 / 143 (2.80%)	3 / 147 (2.04%)	
occurrences (all)	5	3	
Eye disorders			
Eye disorders	Additional description: diplopia, retinopathy, watery secretion		
subjects affected / exposed	1 / 143 (0.70%)	1 / 147 (0.68%)	
occurrences (all)	1	2	
Gastrointestinal disorders			
Gastrointestinal symtoms	Additional description: oral mucositis, dry mouth, dyspepsia, nausea, vomiting, constipation, diarrhea, anorexia, gastropath		
subjects affected / exposed	11 / 143 (7.69%)	15 / 147 (10.20%)	
occurrences (all)	14	21	
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	0 / 143 (0.00%)	2 / 147 (1.36%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Skin disorders	Additional description: eczema, local reaction, erythodysesthesia, pruritus, prupura, rash, skin induration, urticaria		
subjects affected / exposed	12 / 143 (8.39%)	7 / 147 (4.76%)	
occurrences (all)	12	8	
Renal and urinary disorders			
Urinary disorders	Additional description: urinary retention		
subjects affected / exposed	1 / 143 (0.70%)	0 / 147 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Infections	Additional description: viarl, bacterial, fungus		

subjects affected / exposed	24 / 143 (16.78%)	21 / 147 (14.29%)	
occurrences (all)	37	29	
Metabolism and nutrition disorders			
Metobolism disorders	Additional description: Hyperglycemia, hypokalemia, hyponatremia, acidosis		
subjects affected / exposed	3 / 143 (2.10%)	2 / 147 (1.36%)	
occurrences (all)	3	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 November 2016	Amendment to the ethical authority and MDA Sweden (26 june 2017). Addition of 2 new study sites incl PIs Addition of ancillary substudy with bloodsamples for biomarkers
28 June 2017	Amendment to the ethical authority: increase of accasions for bloodsampling from 4 to 5 and change of occasion when the bloodsamples are taken. Less blood/sample. New separate patients´ information and consent form for blood samples
22 March 2018	Amendment to the ethical authority Addition of 1 new study site incl PI
06 December 2019	Amendment ot ethical authority addition of 1 study site incl PI Possibility to check cause of death in the national "register for cause of death" (dödsorsaksregister)
19 February 2020	Amendment to the ethical authority Addition of 1 study site incl PI Increase of economical compenstation for study sites per included participant

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/38915151