Clinical trial results:
ENGOT-EN1/FANDANGO: A randomized phase II trial of first-line combination chemotherapy with nintedanib / placebo for patients with advanced or recurrent endometrial cancer.

Summary

EudraCT number	2016-000193-38
Trial protocol	SE DK DE FI BE FR
Global end of trial date	01 March 2022

Results information

Result version number	v1 (current)
This version publication date	20 October 2023
First version publication date	20 October 2023

Trial information

Trial identification

Sponsor protocol code	ENGOT-EN1/FANDANGO

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02730416
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Nordic Society of Gynaecological Oncology - Clinical Trial Unit (NSGO-CTU)
Sponsor organisation address	Blegdamsvej 9, Copenhagen, København, Denmark, 2100
Public contact	Medical Director, Mansoor Raza Mirza, Nordic Society of Gynaecological Oncology - Clinical Trial Unit (NSGO-CTU), +45 35453311, Mansoor.Raza.Mirza@regionh.dk
Scientific contact	Medical Director, Mansoor Raza Mirza, Nordic Society of Gynaecological Oncology - Clinical Trial Unit (NSGO-CTU), +45 35453311, Mansoor.Raza.Mirza@regionh.dk

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	26 May 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 October 2021
Global end of trial reached?	Yes
Global end of trial date	01 March 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Primary objective:
To compare Progression free survival (PFS) between arms. Progression Free Survival (PFS) is defined as the time from randomization until disease progression or death by any cause. The progression events are defined by RECIST 1.1 criteria

Protection of trial subjects:

All study subjects were required to read and sign the informed consent form.

The IDMC was established to provide independent review and assessment of the efficacy and safety data in a systematic manner and to safeguard the interest and safety of the participating patients in the study.
The IDMC consisted of 3 independent individuals, and made recommendations to the sponsor, based on their review, to continue or stop the trial based on their assessment of safety information.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the ICH-GCP guidelines. The local principal investigators were responsible for ensuring that the study was conducted in accordance with the protocol, the ethical principles of the Declaration of Helsinki, current ICH guidelines on Good Clinical practice (GCP) and applicable local regulatory requirements.

Background therapy:

Carboplatin AUC 5 Q3W and paclitaxel 175 mg/m2 Q3W for up to 6 cycles.

Evidence for comparator: -

Actual start date of recruitment	09 December 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	30 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 8
Country: Number of subjects enrolled	Sweden: 13
Country: Number of subjects enrolled	Belgium: 18
Country: Number of subjects enrolled	Denmark: 15
Country: Number of subjects enrolled	Finland: 9
Country: Number of subjects enrolled	France: 52
Country: Number of subjects enrolled	Germany: 31

Worldwide total number of subjects	146
EEA total number of subjects	146

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 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	63
From 65 to 84 years	83
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Potential candidates for the trial was identified by a member of the treatment team, by referrals from other departments/hospitals/GP. Investigator screened patients' medical records for suitability to enroll in the trial. Enrollment occured only after the patient gav written informed consent. Recruitment from Q4 2016 to Q1 2019

Pre-assignment

Screening details:

All patients had to commence treatment within 28 days of start of screening. Patients who failed screening, could be be rescreened at a later date, at the Investigators discretion, upon discussion with and approval by sponsor.

Period 1

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

Blinding implementation details:

Nintedanib and placebo treatment was blinded. The study medication was labeled using a unique Kit ID number, which was linked to the randomization scheme. The active and placebo tablets were identical and presented in the same packaging to ensure blinding of the study medication. The treatment assignment was kept separate from the trial team up to database lock.

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Treatment with 1L chemotherapy for endometrial cancer with Paclitaxel/Carboplatin, incl. IMP Nintedanib

Arm type	Experimental
Investigational medicinal product name	Nintedanib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

200 mg orally twice daily, on day 2-21 of each 21 day cycle

Arm title	Arm B

Arm description:

Treatment with 1L chemotherapy for endometrial cancer with Paclitaxel/Carboplatin, incl. Placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

200 mg orally twice daily, on day 2-21 of each 21 day cycle

Number of subjects in period 1	Arm A	Arm B
Started	72	74
End of treatment with nintedanib/placebo	72	74
Completed	0	0
Not completed	72	74
Adverse event, serious fatal	-	1
Consent withdrawn by subject	1	4
Physician decision	10	16
Adverse event, non-fatal	15	7
Intercurrent disease	-	1
Pt. requested to stop	6	2
Lack of efficacy	40	43

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description:	
Treatment with 1L chemotherapy for endometrial cancer with Paclitaxel/Carboplatin, incl. IMP Nintedanib	

Reporting group title	Arm B
Reporting group description:	
Treatment with 1L chemotherapy for endometrial cancer with Paclitaxel/Carboplatin, incl. Placebo	

Reporting group values	Arm A	Arm B	Total
Number of subjects	72	74	146
Age categorical			
Age of participating subjects			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	30	33	63
From 65-84 years	42	41	83
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	72	74	146
Male	0	0	0
Race			
Race of participating subjects			
Units: Subjects			
other	2	0	2
white	52	56	108
unknown	0	1	1
not reporting	18	17	35
Previous cancer			
Number of subjects with previous cancer			
Units: Subjects			
No	63	65	128
Yes	9	9	18
Diabetes			
Subjects with diabetes			
Units: Subjects			
No	68	60	128
Yes	4	14	18
Hypertension			
Subjects with hypertension			

Units: Subjects			
No	44	46	90
Yes	28	28	56
Previous surgery Units: Subjects			
No	42	48	90
Yes	30	26	56
Any ongoing condition			
Subjects with ongoing conditions			
Units: Subjects			
No	32	25	57
Yes	40	49	89
IHD			
Subjects with IHD			
Units: Subjects			
No	72	70	142
Yes	0	4	4
Any comorbidity			
Subjects with any comorbidities			
Units: Subjects			
No	70	68	138
Yes	2	6	8
Stage of disease			
Stage of disease			
Units: Subjects			
Stage 3C2	11	15	26
Stage 4	31	30	61
Recurrent disease	30	29	59
Prior adjuvant chemotherapy			
Subjects who have received any prior adjuvant chemotherapy			
Units: Subjects			
No	57	58	115
Yes	15	16	31
Disease status RECIST			
Disease status according to RECIST			
Units: Subjects			
Non-measurable	13	10	23
Measurable	59	64	123

End points

End points reporting groups

Reporting group title	Arm A

Reporting group description:

Treatment with 1L chemotherapy for endometrial cancer with Paclitaxel/Carboplatin, incl. IMP Nintedanib

Reporting group title	Arm B

Reporting group description:

Treatment with 1L chemotherapy for endometrial cancer with Paclitaxel/Carboplatin, incl. Placebo

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (FAS) or modified intention-to-treat population comprises all patients receiving at least one dose of study medication irrespective of their further compliance to the planned course of treatment. The FAS is the primary analysis population and will be used for evaluation of all endpoints.

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

Progression Free Survival (PFS) of patients treated with chemotherapy plus Nintedanib against chemotherapy plus placebo. The progression events are defined by RECIST 1.1 criteria. PFS was censored if the patient was lost to follow-up or refused to continue in the study (i.e. withdraws consent). For patients alive and without progression at the time of analysis, PFS was censored. In any case of censoring, the date of censoring will be the last time point documenting survival status.

End point type	Primary

End point timeframe:

Progression Free Survival (PFS) is defined as the time from randomization until disease progression or death by any cause.

End point values	Arm A	Arm B	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	72	74	146	
Units: month				
number (confidence interval 95%)	8.23 (5.77 to 10.27)	7.07 (5.40 to 9.10)	7.93 (6.0 to 8.6)	

Statistical analyses

Statistical analysis title	Survival endpoints analyses (PFS)

Statistical analysis description:

Survival end-points incl. PFS was tested using a Cox proportional hazard model adjusted for the stratification factors. Visual inspection of the Kaplan-Meier plots were used to ensure that no major deviation from the proportional hazard’s assumption was present. If, however, such a deviation was observed the analysis was adapted accordingly.

Comparison groups	Arm A v Arm B

Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	cox-proportional hazard
Parameter estimate	Cox proportional hazard
Point estimate	0.9981
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6952
upper limit	1.433
Variability estimate	Standard deviation

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall Survival (OS) is defined as the time from start of treatment until date of death by any cause or until the trial was stopped prematurely. Overall survival was censored if the patient was lost to follow-up or refused to continue in the study (i.e. withdraws consent). For patients alive at the time of analysis, overall survival was censored. In any case of censoring, the date of censoring was the last time point documenting survival status.

End point type	Secondary

End point timeframe:

Overall Survival (OS) is defined as the time from start of treatment until date of death by any cause or until the trial was stopped prematurely.

End point values	Arm A	Arm B	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	72	74	146	
Units: month				
number (confidence interval 95%)	26 (19.10 to 47.83)	25.27 (18.6 to 30.7)	25.27 (20.03 to 30.7)	

Statistical analyses

Statistical analysis title	Survival endpoints analyses (OS)

Statistical analysis description:

Survival end-points incl. OS was tested using a Cox proportional hazard model adjusted for the stratification factors. Visual inspection of the Kaplan-Meier plots was used to ensure that no major deviation from the proportional hazard’s assumption is present. If, however, such a deviation was observed the analysis was adapted accordingly.

Comparison groups	Arm A v Arm B

Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	COX-proportional hazard
Parameter estimate	Cox proportional hazard
Point estimate	0.8239
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5417
upper limit	1.2531
Variability estimate	Standard deviation

Secondary: Progression-free survival after consecutive treatment (PFS2)

End point title	Progression-free survival after consecutive treatment (PFS2)

End point description:

PFS2 is defined along the same timelines as PFS but accounts for the time from randomization to progression or death by any cause on any subsequent line of anticancer therapy.

End point type	Secondary

End point timeframe:

PFS2 is defined along the same timelines as PFS but accounts for the time from randomization to progression or death by any cause on any subsequent line of anticancer therapy.

End point values	Arm A	Arm B	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	40	36	76	
Units: day				
median (inter-quartile range (Q1-Q3))	504.5 (353.5 to 770.5)	416 (345 to 570)	459.5 (349.5 to 646.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Specific Survival (DSS)

End point title	Disease Specific Survival (DSS)

End point description:

DSS was censored if the patient was lost to follow-up or refuses to continue in the study (i.e. withdraws consent). For patients alive at the time of analysis, DSS was censored. In any case of censoring, the date of censoring was the last time point documenting survival status.

End point type	Secondary

End point timeframe:

Disease Specific Survival (DSS) is defined as the time from start of treatment until date of death from endometrial cancer.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	146[1]			
Units: days				
median (inter-quartile range (Q1-Q3))	0 (0 to 0)			

Notes:

[1] - DSS is not reported due to incomplete data collection

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first subsequent therapy (TFST)

End point title	Time to first subsequent therapy (TFST)

End point description:

TFST was censored if the patient was lost to follow-up or refused to continue in the study (i.e. withdraws consent). For patients alive and without initiation of second-line treatment at the time of analysis, TFST was censored. In any case of censoring, the date of censoring will be the last time point documenting survival status.

End point type	Secondary

End point timeframe:

Time to first subsequent therapy (TFST) is defined as the time from enrolment/randomization until initiation of second-line anti-cancer treatment following study treatment discontinuation or death.

End point values	Arm A	Arm B	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	42	37	79	
Units: day				
median (inter-quartile range (Q1-Q3))	308.5 (252 to 468)	296 (231 to 355)	304 (232 to 420)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to second subsequent therapy (TSST)

End point title	Time to second subsequent therapy (TSST)

End point description:

TSST was censored if the patient was lost to follow-up or refuses to continue in the study (i.e. withdraws consent). For patients alive and without initiation of third-line treatment at the time of analysis, TSST was censored. In any case of censoring, the date of censoring was the last time point documenting survival status.

End point type	Secondary

End point timeframe:

Time to second subsequent therapy (TSST) is defined as the time from enrolment/randomization until initiation of third-line anti-cancer treatment or death.

End point values	Arm A	Arm B	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	42	37	79	
Units: days				
median (inter-quartile range (Q1-Q3))	587.5 (441 to 1163)	608 (347 to 801)	602 (377 to 903)	

Statistical analyses

No statistical analyses for this end point

Secondary: Response Rate (RR)

End point title	Response Rate (RR)

End point description:

End point type	Secondary

End point timeframe:

The analysis of the Response Rate (RR) was performed for each treatment by calculating the point estimate of the percentage of patients in who have achieved complete response or partial response, assessed according to RECIST 1.1 criteria.

End point values	Arm A	Arm B	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	72	74	146	
Units: percent				
number (not applicable)	65.27	55.4	60.27	

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)

End point description:

The analysis of disease control rate was performed for each treatment arm by calculating the point estimate of the percentage of patients who have achieved complete response or partial response or stable disease for at least 12 weeks, assessed according to RECIST 1.1 criteria.

End point type	Secondary

End point timeframe:

Disease Control Rate (DCR = Complete Response, Partial Respons or Stable Disease for at least 12 weeks).

End point values	Arm A	Arm B	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	72	74	146	
Units: percent				
number (not applicable)	88.88	79.72	84.24	

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life (QoL)

End point title	Quality of life (QoL)

End point description:

Quality of Life (QoL) scores, assessed by EORTC's general EORTC-QLQ-C30 questionnaire and disease specific questionnaire EORTC-QLQ-EN-24, will be calculated using EORTC's Scoring Manual.

End point type	Secondary

End point timeframe:

Quality of Life (QoL) scores will be calculated for each individual patient at selected visits.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72[2]	74[3]		
Units: patients				
median (standard deviation)	0 (± 0)	0 (± 0)		

Notes:

[2] - No significant main effects on the general health score could be shown, see attachment.

[3] - No significant main effects on the general health score could be shown, see attachment.

Attachments (see zip file)	QoL scores and graphs/FANDANGO QoL scores and graphs.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs were collected from inf. consent until 30 days after last dose/study discont. AEs were recorded from 1. dose until treatment discont. AEs were followed for 30 days after last dose of investigational drug.

Adverse event reporting additional description:

AEs could be informed upon spontaneously by the patient or discovered by study staff during physical investigation or when wording opn & non-leading questions. Nature of AE, date of onset/resolution, actions taken, severity and causality to study drugs/procedures as assessed by investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Arm A (Nintedanib group)

Reporting group description:

Carboplatin + paclitaxel + nintedanib

Reporting group title	Arm B (control group)

Reporting group description:

Carboplatin + paclitaxel + placebo

Serious adverse events	Arm A (Nintedanib group)	Arm B (control group)	
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 72 (43.06%)	21 / 74 (28.38%)	
number of deaths (all causes)	42	46	
number of deaths resulting from adverse events	0		
Cardiac disorders			
Hypertension			
subjects affected / exposed	0 / 72 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Peripheral motor neuropathy			
subjects affected / exposed	0 / 72 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			

subjects affected / exposed	0 / 72 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 72 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	1 / 72 (1.39%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	2 / 72 (2.78%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 72 (2.78%)	3 / 74 (4.05%)	
occurrences causally related to treatment / all	1 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 72 (2.78%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Thrombocytopenia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			

subjects affected / exposed	0 / 72 (0.00%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Catheter related infection			
subjects affected / exposed	1 / 72 (1.39%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 72 (1.39%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 72 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	9 / 72 (12.50%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	8 / 9	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 72 (1.39%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 72 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 72 (2.78%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatobiliary disorders			
Blood alanine aminotransferase increased			
subjects affected / exposed	11 / 72 (15.28%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	10 / 11	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 72 (8.33%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	5 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bilirubin conjugated increased			
subjects affected / exposed	1 / 72 (1.39%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 72 (1.39%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 72 (1.39%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Febrile neutropenia			
subjects affected / exposed	2 / 72 (2.78%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever			
subjects affected / exposed	2 / 72 (2.78%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	0 / 72 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 72 (1.39%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	1 / 72 (1.39%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GGT increased			
subjects affected / exposed	1 / 72 (1.39%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 72 (1.39%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Arm A (Nintedanib group)	Arm B (control group)	
Total subjects affected by non-serious adverse events subjects affected / exposed	72 / 72 (100.00%)	70 / 74 (94.59%)	
Vascular disorders Edema limbs subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 2	9 / 74 (12.16%) 9	
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	17 / 72 (23.61%) 22	13 / 74 (17.57%) 23	
Fatigue subjects affected / exposed occurrences (all)	27 / 72 (37.50%) 41	22 / 74 (29.73%) 32	
Pain subjects affected / exposed occurrences (all)	9 / 72 (12.50%) 20	13 / 74 (17.57%) 18	
Immune system disorders Allergic reaction subjects affected / exposed occurrences (all)	6 / 72 (8.33%) 7	8 / 74 (10.81%) 10	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	5 / 72 (6.94%) 5	3 / 74 (4.05%) 4	
Dyspnoea subjects affected / exposed occurrences (all)	13 / 72 (18.06%) 16	12 / 74 (16.22%) 15	
Epistaxis subjects affected / exposed occurrences (all)	4 / 72 (5.56%) 4	2 / 74 (2.70%) 5	
Cardiac disorders Hypertension subjects affected / exposed occurrences (all)	3 / 72 (4.17%) 3	4 / 74 (5.41%) 5	
Nervous system disorders			

Headache			
subjects affected / exposed	7 / 72 (9.72%)	4 / 74 (5.41%)	
occurrences (all)	7	5	
Insomnia			
subjects affected / exposed	4 / 72 (5.56%)	5 / 74 (6.76%)	
occurrences (all)	6	5	
Peripheral motor neuropathy			
subjects affected / exposed	5 / 72 (6.94%)	2 / 74 (2.70%)	
occurrences (all)	6	3	
Peripheral sensory neuropathy			
subjects affected / exposed	42 / 72 (58.33%)	37 / 74 (50.00%)	
occurrences (all)	63	47	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	29 / 72 (40.28%)	27 / 74 (36.49%)	
occurrences (all)	48	59	
Leukopenia			
subjects affected / exposed	10 / 72 (13.89%)	10 / 74 (13.51%)	
occurrences (all)	19	18	
Neutropenia			
subjects affected / exposed	32 / 72 (44.44%)	26 / 74 (35.14%)	
occurrences (all)	58	52	
Thrombocytopenia			
subjects affected / exposed	25 / 72 (34.72%)	19 / 74 (25.68%)	
occurrences (all)	51	21	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	12 / 72 (16.67%)	17 / 74 (22.97%)	
occurrences (all)	13	26	
Anorexia			
subjects affected / exposed	10 / 72 (13.89%)	6 / 74 (8.11%)	
occurrences (all)	14	7	
Constipation			
subjects affected / exposed	13 / 72 (18.06%)	13 / 74 (17.57%)	
occurrences (all)	20	16	
Diarrhoea			

subjects affected / exposed	47 / 72 (65.28%)	22 / 74 (29.73%)	
occurrences (all)	110	44	
Taste disorder	Additional description: Dysguesia		
subjects affected / exposed	6 / 72 (8.33%)	6 / 74 (8.11%)	
occurrences (all)	6	6	
Dyspepsia			
subjects affected / exposed	6 / 72 (8.33%)	4 / 74 (5.41%)	
occurrences (all)	7	4	
Mucositis oral			
subjects affected / exposed	0 / 72 (0.00%)	6 / 74 (8.11%)	
occurrences (all)	0	7	
Nausea			
subjects affected / exposed	35 / 72 (48.61%)	22 / 74 (29.73%)	
occurrences (all)	55	34	
Vomiting			
subjects affected / exposed	22 / 72 (30.56%)	9 / 74 (12.16%)	
occurrences (all)	39	16	
Hepatobiliary disorders			
Alanine aminotransferase increased			
subjects affected / exposed	30 / 72 (41.67%)	6 / 74 (8.11%)	
occurrences (all)	47	9	
Aspartate aminotransferase increased			
subjects affected / exposed	22 / 72 (30.56%)	5 / 74 (6.76%)	
occurrences (all)	32	8	
ggt			
subjects affected / exposed	13 / 72 (18.06%)	2 / 74 (2.70%)	
occurrences (all)	19	2	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	34 / 72 (47.22%)	26 / 74 (35.14%)	
occurrences (all)	37	28	
Rash			
subjects affected / exposed	7 / 72 (9.72%)	6 / 74 (8.11%)	
occurrences (all)	7	7	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	9 / 72 (12.50%)	6 / 74 (8.11%)	
occurrences (all)	10	9	
Myalgia			
subjects affected / exposed	10 / 72 (13.89%)	11 / 74 (14.86%)	
occurrences (all)	15	16	
Pain in extremity			
subjects affected / exposed	2 / 72 (2.78%)	8 / 74 (10.81%)	
occurrences (all)	4	12	
Infections and infestations			
Fever			
subjects affected / exposed	4 / 72 (5.56%)	5 / 74 (6.76%)	
occurrences (all)	5	6	
Urinary tract infection			
subjects affected / exposed	8 / 72 (11.11%)	11 / 74 (14.86%)	
occurrences (all)	13	15	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	12 / 72 (16.67%)	8 / 74 (10.81%)	
occurrences (all)	17	17	
Hypomagnesaemia			
subjects affected / exposed	15 / 72 (20.83%)	9 / 74 (12.16%)	
occurrences (all)	24	15	
GGT increased			
subjects affected / exposed	13 / 72 (18.06%)	2 / 74 (2.70%)	
occurrences (all)	19	2	
Blood alkaline phosphatase increased			
subjects affected / exposed	13 / 72 (18.06%)	2 / 74 (2.70%)	
occurrences (all)	20	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 April 2019	Substantial changes to the protocol incl. changes in inclusion and exclusion criteriae, clarification that treatment with radiotherapy will result in EOS, clarification on testing in relation to the trial incl. blood/urin tests, CT-scans. Added GDPR section and specification on when to start the TR-section, will be made, when the primary endpoint is mature. The tissue samples for translational research shall be kept at sites until it is decided to conduct a TR project. Specifikation of TFST, SUSARs.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported