Clinical trial results:
A Randomised Phase II Study of Nintedanib (BIBF1120) Compared to Chemotherapy in Patients with Recurrent Clear Cell Carcinoma of the Ovary or Endometrium

Summary

EudraCT number	2013-002109-73
Trial protocol	GB FR NL DK FI NO
Global end of trial date	23 July 2020

Results information

Result version number	v1 (current)
This version publication date	16 September 2021
First version publication date	16 September 2021

Trial information

Trial identification

Sponsor protocol code	0NiCCC2013

Additional study identifiers

ISRCTN number	ISRCTN50772895
ClinicalTrials.gov id (NCT number)	NCT02866370
WHO universal trial number (UTN)	-
Other trial identifiers	European Network Gynaecological Oncological Trials: ENGOT-ov36, Sponsor Reference: GN12ON259

Notes:

Sponsors

Sponsor organisation name	NHS Greater Glasgow and Clyde
Sponsor organisation address	Dykebar Hospital, Grahamston Road, Paisley, Glasgow, United Kingdom, PA2 7DE
Public contact	Joanne McGarry, NHS Greater Glasgow and Clyde, 0044 141 3144001, joanne.mcgarry@ggc.scot.nhs.uk
Scientific contact	Joanne McGarry, NHS Greater Glasgow and Clyde, 0044 141 314 4001, oanne.mcgarry@ggc.scot.nhs.uk
Sponsor organisation name	European Organisation for Research and Treatment of Cancer
Sponsor organisation address	Avenue E. Mounierlaan 83/11, Brussels, Belgium, B-1200
Public contact	Kin Jip Cheung, European Organisation for Research and Treatment of Cancer (EORTC), 32 27741607, kin-jip.cheung@eortc.org
Scientific contact	Kin Jip Cheung, European Organisation for Research and Treatment of Cancer (EORTC), 32 27741607, kin-jip.cheung@eortc.org

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No	No

1901/2006 apply to this trial?	
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	20 August 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 July 2020
Global end of trial reached?	Yes
Global end of trial date	23 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy, safety and effect on quality of life of Nintedanib compared to chemotherapy in women with relapsed clear cell carcinoma of the ovary or endometrium

Protection of trial subjects:

Further chemotherapy is routinely given to patients who have recurrent Clear Cell Carcinoma (CCC) of the ovary or endometrium. This chemotherapy has only modest benefit as the progression free survival for these patients is only about 24 months and reported response rates are less than 10%. Although Nintedanib appears promising and well tolerated, we cannot be sure of its benefit to patients. Women randomised to Nintendanib did not receive standard chemotherapy. However all participants were assessed every 8 weeks for tumour progression with a CT scan, so if participants progressed on Nintendanib, there was an opportunity for them to change quickly to chemotherapy. There was also an early stopping rule, to limit the number of women exposed to Nintedanib alone if it appeared to be ineffective.

Additional clinic visits and tests were performed to ensure participants safety. Patient's were monitored for Drug Induced Liver Injury (DILI) (Hy's Law case), although rare. A clearly defined concept was detailed in the protocol to guard participant's safety and explained the necessary steps to take to identify and manage DILI. This included monitoring of ALT/AST result, stopping Nintedanib treatment, repeating blood tests, abdominal ultrasound and reporting such cases to study Sponsor and pharmaceutical company.

The IDMC monitored study data annually for toxicity and efficacy.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 April 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	United Kingdom: 66
Country: Number of subjects enrolled	France: 30

Worldwide total number of subjects	102
EEA total number of subjects	36

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)	80
From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Prior to commencing any study related procedures, all participants will be fully informed about the risks, benefits and procedures involved in study participation, and will sign a consent form confirming this process. Central pathology review will be performed to confirm that all basic pathology criteria are met.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	OVARIAN: Experimental arm (nintedanib)

Arm description:

Nintedanib (BIBF1120) capsules 200mg orally twice a day, continuously until disease progression. The first 6 cycles are 28 days long and from cycle 7 onwards, the cycles are 56 days long.

Arm type	Experimental
Investigational medicinal product name	Nintedanib
Investigational medicinal product code	BIBF1120
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Nintedanib (BIBF1120) capsules 200mg orally twice a day, continuously until disease progression. The first 6 cycles are 28 days long and from cycle 7 onwards, the cycles are 56 days long.

Arm title	OVARIAN: Control arm (chemotherapy)

Arm description:

Physicians' choice of chemotherapy from list below:
Paclitaxel 80mg/m2 intravenously on days 1, 8 and 15 of a 28 day cycle OR
Pegylated Liposomal Doxorubicin (PLD) 40mg/m2 intravenously on day 1 of a 28 day cycle OR
Topotecan 4mg/m2 intravenously on days 1, 8 and 15 of a 28 day cycle
Patients receive up to 6 cycles of chemotherapy but it is acceptable to continue beyond this until progression or unacceptable toxicity if the Investigator deemed this to be beneficial to the patient.

Arm type	Active comparator
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel 80mg/m2 intravenously on Days 1, 8 and 15 of a 28 day cycle. Patients receive up to 6 cycles of chemotherapy but it is acceptable to continue beyond this until progression or unacceptable toxicity if the Investigator deemed this to be beneficial to the patient.

Investigational medicinal product name	Pegylated Liposomal Doxorubicin
Investigational medicinal product code	
Other name	PLD, Caelyx

Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pegylated Liposomal Doxorubicin 40mg/m2 intravenously on Day 1 of a 28 day cycle. Patients receive up to 6 cycles of chemotherapy but it is acceptable to continue beyond this until progression or unacceptable toxicity if the Investigator deemed this to be beneficial to the patient. The maximum lifetime cumulative dose is 450mg/m2.

Investigational medicinal product name	Topotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Topotecan 4mg/m2 intravenously on Days 1, 8 and 15 of a 28 day cycle. Patients receive up to 6 cycles of chemotherapy but it is acceptable to continue beyond this until progression or unacceptable toxicity if the Investigator deemed this to be beneficial to the patient.

Arm title	ENDOMETRIAL: Experimental arm (nintedanib)

Arm description:

Nintedanib (BIBF1120) capsules 200mg orally twice a day, continuously until disease progression. The first 6 cycles are 28 days long and from cycle 7 onwards, the cycles are 56 days long.

Arm type	Experimental
Investigational medicinal product name	Nintedanib
Investigational medicinal product code	BIBF1120
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Nintedanib (BIBF1120) capsules 200mg orally twice a day, continuously until disease progression. The first 6 cycles are 28 days long and from cycle 7 onwards, the cycles are 56 days long.

Arm title	ENDOMETRIAL: Control arm (chemotherapy)

Arm description:

Physicians' choice of chemotherapy from list below:
Carboplatin AUC 5 and Paclitaxel 175mg/m2 intravenously on day 1 of a 21 day cycle OR
Doxorubicin 60mg/m2 intravenously on day 1 of a 21 day cycle.
Patients receive up to 6 cycles of chemotherapy but it is acceptable to continue beyond this until progression or unacceptable toxicity if the Investigator deemed this to be beneficial to the patient.

Arm type	Active comparator
Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Carboplatin AUC 5 (given along with Paclitaxel 175mg/m2) intravenously on day 1 of a 21 day cycle
Patients receive up to 6 cycles of chemotherapy but it is acceptable to continue beyond this until progression or unacceptable toxicity if the Investigator deemed this to be beneficial to the patient.

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel 175mg/m2 (given along with Carboplatin AUC 5) intravenously on day 1 of a 21 day cycle
Patients receive up to 6 cycles of chemotherapy but it is acceptable to continue beyond this until progression or unacceptable toxicity if the Investigator deemed this to be beneficial to the patient.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Doxorubicin 60mg/m2 intravenously on day 1 of a 21 day cycle.
Patients receive up to 6 cycles of chemotherapy but it is acceptable to continue beyond this until progression or unacceptable toxicity if the Investigator deemed this to be beneficial to the patient. The maximum lifetime cumulative dose is 450mg/m2.

Number of subjects in period 1[1]	OVARIAN: Experimental arm (nintedanib)	OVARIAN: Control arm (chemotherapy)	ENDOMETRIAL: Experimental arm (nintedanib)
Started	47	44	4
Completed	47	44	4

Number of subjects in period 1[1]	ENDOMETRIAL: Control arm (chemotherapy)
Started	5
Completed	5

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of patients in the baseline period are those in the ITT population.

Baseline characteristics

Reporting groups	
Reporting group title	OVARIAN: Experimental arm (nintedanib)
Reporting group description:	
Nintedanib (BIBF1120) capsules 200mg orally twice a day, continuously until disease progression. The first 6 cycles are 28 days long and from cycle 7 onwards, the cycles are 56 days long.	
Reporting group title	OVARIAN: Control arm (chemotherapy)
Reporting group description:	
Physicians' choice of chemotherapy from list below: Paclitaxel 80mg/m2 intravenously on days 1, 8 and 15 of a 28 day cycle OR Pegylated Liposomal Doxorubicin (PLD) 40mg/m2 intravenously on day 1 of a 28 day cycle OR Topotecan 4mg/m2 intravenously on days 1, 8 and 15 of a 28 day cycle Patients receive up to 6 cycles of chemotherapy but it is acceptable to continue beyond this until progression or unacceptable toxicity if the Investigator deemed this to be beneficial to the patient.	
Reporting group title	ENDOMETRIAL: Experimental arm (nintedanib)
Reporting group description:	
Nintedanib (BIBF1120) capsules 200mg orally twice a day, continuously until disease progression. The first 6 cycles are 28 days long and from cycle 7 onwards, the cycles are 56 days long.	
Reporting group title	ENDOMETRIAL: Control arm (chemotherapy)
Reporting group description:	
Physicians' choice of chemotherapy from list below: Carboplatin AUC 5 and Paclitaxel 175mg/m2 intravenously on day 1 of a 21 day cycle OR Doxorubicin 60mg/m2 intravenously on day 1 of a 21 day cycle. Patients receive up to 6 cycles of chemotherapy but it is acceptable to continue beyond this until progression or unacceptable toxicity if the Investigator deemed this to be beneficial to the patient.	

Reporting group values	OVARIAN: Experimental arm (nintedanib)	OVARIAN: Control arm (chemotherapy)	ENDOMETRIAL: Experimental arm (nintedanib)
Number of subjects	47	44	4
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
median	53	55.5	71
standard deviation	± 9.8	± 7.8	± 2.2
Gender categorical Units: Subjects			
Female	47	44	4
Male	0	0	0

Country			
Country of recruitment			
Units: Subjects			
France	13	10	2
Holland	2	4	0
United Kingdom	32	30	2
Previous lines of therapy Units: Subjects			
One	20	21	3
Two	17	13	1
Three	6	6	0
Four	4	3	0
Five	0	0	0
Six	0	1	0
Previous treatment with bevacizumab Units: Subjects			
Yes	14	10	0
No	33	34	4
Chemotherapy assigned at randomisation Units: Subjects			
Paclitaxel	17	17	0
PLD	21	20	0
Topotecan	9	7	0
Carboplatin & Paclitaxel	0	0	0
Doxorubicin	0	0	4

Reporting group values	ENDOMETRIAL: Control arm (chemotherapy)	Total	
Number of subjects	5	100	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
median	68		
standard deviation	± 5.4	-	
Gender categorical Units: Subjects			
Female	5	100	
Male	0	0	

Country			
Country of recruitment			
Units: Subjects			
France	5	30	
Holland	0	6	
United Kingdom	0	64	
Previous lines of therapy Units: Subjects			
One	3	47	
Two	2	33	
Three	0	12	
Four	0	7	
Five	0	0	
Six	0	1	
Previous treatment with bevacizumab Units: Subjects			
Yes	0	24	
No	5	76	
Chemotherapy assigned at randomisation Units: Subjects			
Paclitaxel	0	34	
PLD	0	41	
Topotecan	0	16	
Carboplatin & Paclitaxel	2	2	
Doxorubicin	3	7	

End points

End points reporting groups

Reporting group title	OVARIAN: Experimental arm (nintedanib)
Reporting group description:	
Nintedanib (BIBF1120) capsules 200mg orally twice a day, continuously until disease progression. The first 6 cycles are 28 days long and from cycle 7 onwards, the cycles are 56 days long.	

Reporting group title	OVARIAN: Control arm (chemotherapy)
Reporting group description:	
Physicians' choice of chemotherapy from list below: Paclitaxel 80mg/m2 intravenously on days 1, 8 and 15 of a 28 day cycle OR Pegylated Liposomal Doxorubicin (PLD) 40mg/m2 intravenously on day 1 of a 28 day cycle OR Topotecan 4mg/m2 intravenously on days 1, 8 and 15 of a 28 day cycle Patients receive up to 6 cycles of chemotherapy but it is acceptable to continue beyond this until progression or unacceptable toxicity if the Investigator deemed this to be beneficial to the patient.	

Reporting group title	ENDOMETRIAL: Experimental arm (nintedanib)
Reporting group description:	
Nintedanib (BIBF1120) capsules 200mg orally twice a day, continuously until disease progression. The first 6 cycles are 28 days long and from cycle 7 onwards, the cycles are 56 days long.	

Reporting group title	ENDOMETRIAL: Control arm (chemotherapy)
Reporting group description:	
Physicians' choice of chemotherapy from list below: Carboplatin AUC 5 and Paclitaxel 175mg/m2 intravenously on day 1 of a 21 day cycle OR Doxorubicin 60mg/m2 intravenously on day 1 of a 21 day cycle. Patients receive up to 6 cycles of chemotherapy but it is acceptable to continue beyond this until progression or unacceptable toxicity if the Investigator deemed this to be beneficial to the patient.	

Primary: Progression-free survival

End point title	Progression-free survival
End point description:	

End point type	Primary
End point timeframe:	
Baseline: within 28 days of randomisation From randomisation until week 48 (or progressive disease): 8 weekly Week 72 Then as clinically indicated	

End point values	OVARIAN: Experimental arm (nintedanib)	OVARIAN: Control arm (chemotherapy)	ENDOMETRIAL: Experimental arm (nintedanib)	ENDOMETRIAL: Control arm (chemotherapy)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	47[1]	44[2]	4[3]	5[4]
Units: PFS				
median (confidence interval 80%)	2.07 (1.94 to 3.68)	1.84 (1.84 to 1.91)	1.95 (1.71 to 3.65)	2.04 (2.00 to 6.04)

Notes:

[1] - ITT

[2] - ITT

[3] - ITT
[4] - ITT

Statistical analyses

Statistical analysis title	PFS: Grouped

Statistical analysis description:

Progression-free survival is compared between the study arms in the context of a Cox model incorporating the baseline stratification factors. To prevent any ascertainment bias as a result of earlier detection of progression on study arms with a weekly schedule, all progressions will be allocated to the next fixed CT scanning date - a grouped survival method.

Comparison groups	OVARIAN: Experimental arm (nintedanib) v OVARIAN: Control arm (chemotherapy)
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0419 [5]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.67
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.5
upper limit	0.9
Variability estimate	Standard error of the mean
Dispersion value	0.23

Notes:
[5] - One sided

Secondary: Overall survival

End point title	Overall survival

End point description:

End point type	Secondary

End point timeframe:

From baseline until end of study

End point values	OVARIAN: Experimental arm (nintedanib)	OVARIAN: Control arm (chemotherapy)	ENDOMETRIAL: Experimental arm (nintedanib)	ENDOMETRIAL: Control arm (chemotherapy)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	47[6]	44[7]	4[8]	5[9]
Units: Survival				
median (confidence interval 80%)	9.69 (7.62 to 10.41)	4.99 (3.98 to 5.85)	5.63 (1.71 to 8.02)	6.04 (4.34 to 14.13)

Notes:

[6] - ITT

[7] - ITT

[8] - ITT

[9] - ITT

Statistical analyses

Statistical analysis title	OS

Statistical analysis description:

Overall survival will be compared between the study arms in the context of a Cox model incorporating the baseline stratification factors.

Comparison groups	OVARIAN: Experimental arm (nintedanib) v OVARIAN: Control arm (chemotherapy)
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0496 [10]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.45
upper limit	0.91
Variability estimate	Standard error of the mean
Dispersion value	0.27

Notes:

[10] - One sided

Secondary: Response rate

End point title	Response rate

End point description:

Best response rate will be determined according to combined GCIG criteria (http://www.gcig.igcs.org/CA125/respdef_nov2005.pdf) for ovarian cancer patients and RECIST criteria Version 1.1 (http://www.eortc.be/recist/documents/RECISTGuidelines.pdf) for endometrial cancer

End point type	Secondary

End point timeframe:

Baseline: within 28 days of randomisation
From randomisation until week 48 (or progressive disease): 8 weekly
Week 72
Then as clinically indicated

End point values	OVARIAN: Experimental arm (nintedanib)	OVARIAN: Control arm (chemotherapy)	ENDOMETRIAL: Experimental arm (nintedanib)	ENDOMETRIAL: Control arm (chemotherapy)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	47[11]	44[12]	4[13]	5[14]
Units: Best response				
Partial response	2	2	0	1
Stable disease	16	8	1	1
Progressive disease	27	28	3	3
Unevaluable, no baseline target lesions	1	1	0	0
Unevaluable, no assessments made	1	1	0	0
Unevaluable, other reason	0	0	0	0
Died prior to response evaluation timepoint	0	3	0	0
Withdrawn consent prior to response evaluation	0	1	0	0

Notes:

[11] - ITT

[12] - ITT

[13] - ITT

[14] - ITT

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate

End point title	Disease control rate

End point description:

Disease status will be determined prior to starting treatment and the observed response [categorised as complete (CR), partial (PR), stable disease (SD), progressive disease (PD), unevaluable] at 16 weeks will be determined using GCIG criteria for ovarian cancer patients and RECIST 1.1 for endometrial cancer patients.

End point type	Secondary

End point timeframe:

At 16 weeks

End point values	OVARIAN: Experimental arm (nintedanib)	OVARIAN: Control arm (chemotherapy)	ENDOMETRIAL: Experimental arm (nintedanib)	ENDOMETRIAL: Control arm (chemotherapy)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	47[15]	44[16]	4[17]	5[18]
Units: Response				
CR/PR/SD	11	5	0	1
PD/Unevaluable	36	39	4	4

Notes:

[15] - ITT

[16] - ITT

[17] - ITT

[18] - ITT

Statistical analyses

Statistical analysis title	Logistic regression of disease control rate
Comparison groups	OVARIAN: Experimental arm (nintedanib) v OVARIAN: Control arm (chemotherapy)
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1078 [19]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.19
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	1.14
upper limit	8.92
Variability estimate	Standard error of the mean
Dispersion value	0.4

Notes:

[19] - One sided

Secondary: QTWiST

End point title	QTWiST[20]

End point description:

The Q-TWiST analysis partitions overall survival into three health states: toxicity (TOX); time without symptoms of disease of progression or toxicity (TWiST); and time from progression until death (REL), and the duration of each state is calculated for every patient.

All grade 2 and above toxicities are included in this analysis, apart from those that are experienced after progression. Due to the lack of data available regarding the duration of each toxicity, the TOX state is calculated on the assumption that any grade 1 or above toxicity listed on the CRF is experienced for the duration of the cycle. Patients experiencing no toxicity are assumed to have a TOX duration of 0 days.

The restricted mean estimates, standard error and 95% confidence intervals are calculated by the bootstrap method.

End point type	Secondary

End point timeframe:

Restricted mean health state duration, up to 26 weeks = 182 days

The TOX state captures the total number of days spent with toxicity between randomisation and stopping chemotherapy.

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Analysis not undertaken for Endometrial patients

End point values	OVARIAN: Experimental arm (nintedanib)	OVARIAN: Control arm (chemotherapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	44		
Units: Days				
arithmetic mean (standard error)	44.20 (± 0.22)	32.58 (± 0.22)		

Statistical analyses

Statistical analysis title	Restricted mean health state duration comparison
Statistical analysis description: 2-sided p-value calculated using a t-test under the normal distribution	
Comparison groups	OVARIAN: Experimental arm (nintedanib) v OVARIAN: Control arm (chemotherapy)
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	11.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	11
upper limit	12.23
Variability estimate	Standard error of the mean
Dispersion value	0.31

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs are collected from randomisation until progression or withdrawal from the trial. Number of occurences of non-serious AEs = number of patients experiencing the event due to the way that this data is collected.

Adverse event reporting additional description:

For some AEs, grade 0 & 1 cannot be distringuished from one another due to unknown limits of normal. These are reported as grade 0: hypo/hyper-glycaemia, anaemia, WBC decrease, leukocytosis, platelets/neutrophils decreased, lymphocytes increase/decreased.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	ENDOMETRIAL: Control arm (chemotherapy)
Reporting group description: -	
Reporting group title	OVARIAN: Control arm (chemotherapy)
Reporting group description: -	
Reporting group title	OVARIAN: Experimental arm (nintedanib)
Reporting group description: -	
Reporting group title	ENDOMETRIAL: Experimental arm (nintedanib)
Reporting group description: -	

Serious adverse events	ENDOMETRIAL: Control arm (chemotherapy)	OVARIAN: Control arm (chemotherapy)	OVARIAN: Experimental arm (nintedanib)
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 5 (40.00%)	22 / 40 (55.00%)	16 / 47 (34.04%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify	Additional description: Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	11 / 40 (27.50%)	7 / 47 (14.89%)
occurrences causally related to treatment / all	0 / 0	0 / 14	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 5	0 / 3
Vascular disorders			
Thromboembolic event	Additional description: Thromboembolic event		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 5 (0.00%)	2 / 40 (5.00%)	4 / 47 (8.51%)
occurrences causally related to treatment / all	0 / 0	0 / 2	4 / 5
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Surgical and medical procedures			
Surgical and medical procedures - Other, specify	Additional description: Surgical and medical procedures - Other, specify		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 40 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue	Additional description: Fatigue		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 5 (20.00%)	1 / 40 (2.50%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fever	Additional description: Fever		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 40 (2.50%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Allergic reaction	Additional description: Allergic reaction		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 40 (2.50%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylaxis	Additional description: Anaphylaxis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 40 (2.50%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			

Dyspnea	Additional description: Dyspnea		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 40 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion	Additional description: Pleural effusion		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 40 (2.50%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure	Additional description: Respiratory failure		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 40 (2.50%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Psychiatric disorders			
Confusion	Additional description: Confusion		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 40 (2.50%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased	Additional description: Alanine aminotransferase increased		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 40 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alkaline phosphatase increased	Additional description: Alkaline phosphatase increased		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 40 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased	Additional description: Aspartate aminotransferase increased		

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 40 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INR increased	Additional description: INR increased		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 40 (2.50%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations - Other, specify	Additional description: Investigations - Other, specify		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 40 (2.50%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased	Additional description: Platelet count decreased		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 40 (2.50%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Lethargy	Additional description: Lethargy		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 40 (2.50%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stroke	Additional description: Stroke		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 40 (2.50%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anemia	Additional description: Anemia		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 5 (0.00%)	3 / 40 (7.50%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia	Additional description: Febrile neutropenia		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 40 (2.50%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain	Additional description: Abdominal pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	3 / 40 (7.50%)	2 / 47 (4.26%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites	Additional description: Ascites		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 40 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic obstruction	Additional description: Colonic obstruction		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 5 (20.00%)	1 / 40 (2.50%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation	Additional description: Constipation		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	2 / 40 (5.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhea	Additional description: Diarrhea		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 5 (0.00%)	0 / 40 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea	Additional description: Nausea		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	2 / 40 (5.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction	Additional description: Small intestinal obstruction		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 40 (2.50%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting	Additional description: Vomiting		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 40 (2.50%)	3 / 47 (6.38%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Hematuria	Additional description: Hematuria		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 40 (2.50%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hyperparathyroidism	Additional description: Hyperparathyroidism		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 40 (2.50%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain	Additional description: Back pain		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 5 (0.00%)	0 / 40 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain	Additional description: Bone pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 40 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorder - Other, specify	Additional description: Musculoskeletal and connective tissue disorder - Other, specify		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	2 / 40 (5.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal infection	Additional description: Abdominal infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 5 (20.00%)	0 / 40 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations - Other, specify	Additional description: Infections and infestations - Other, specify		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 5 (20.00%)	1 / 40 (2.50%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection	Additional description: Urinary tract infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 40 (0.00%)	4 / 47 (8.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Anorexia	Additional description: Anorexia		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 5 (0.00%)	1 / 40 (2.50%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration	Additional description: Dehydration		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 5 (20.00%)	0 / 40 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcemia	Additional description: Hypercalcemia		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	2 / 40 (5.00%)	2 / 47 (4.26%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomagnesemia	Additional description: Hypomagnesemia		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 40 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	ENDOMETRIAL: Experimental arm (nintedanib)		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 4 (50.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify	Additional description: Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Vascular disorders			
Thromboembolic event	Additional description: Thromboembolic event		
alternative assessment type: Non-			

systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Surgical and medical procedures - Other, specify	Additional description: Surgical and medical procedures - Other, specify		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue	Additional description: Fatigue		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fever	Additional description: Fever		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Allergic reaction	Additional description: Allergic reaction		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anaphylaxis	Additional description: Anaphylaxis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			

Dyspnea	Additional description: Dyspnea		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleural effusion	Additional description: Pleural effusion		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory failure	Additional description: Respiratory failure		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusion	Additional description: Confusion		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased	Additional description: Alanine aminotransferase increased		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Alkaline phosphatase increased	Additional description: Alkaline phosphatase increased		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased	Additional description: Aspartate aminotransferase increased		

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
INR increased	Additional description: INR increased		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations - Other, specify	Additional description: Investigations - Other, specify		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Platelet count decreased	Additional description: Platelet count decreased		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Lethargy	Additional description: Lethargy		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Stroke	Additional description: Stroke		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anemia	Additional description: Anemia		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia	Additional description: Febrile neutropenia		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain	Additional description: Abdominal pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ascites	Additional description: Ascites		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colonic obstruction	Additional description: Colonic obstruction		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Constipation	Additional description: Constipation		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhea	Additional description: Diarrhea		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nausea	Additional description: Nausea		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction	Additional description: Small intestinal obstruction		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting	Additional description: Vomiting		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Hematuria	Additional description: Hematuria		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hyperparathyroidism	Additional description: Hyperparathyroidism		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain	Additional description: Back pain		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bone pain	Additional description: Bone pain			
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorder - Other, specify	Additional description: Musculoskeletal and connective tissue disorder - Other, specify			
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Abdominal infection	Additional description: Abdominal infection			
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations - Other, specify	Additional description: Infections and infestations - Other, specify			
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection	Additional description: Urinary tract infection			
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Anorexia	Additional description: Anorexia			
alternative assessment type: Non-systematic				

subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dehydration	Additional description: Dehydration		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypercalcemia	Additional description: Hypercalcemia		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypomagnesemia	Additional description: Hypomagnesemia		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	ENDOMETRIAL: Control arm (chemotherapy)	OVARIAN: Control arm (chemotherapy)	OVARIAN: Experimental arm (nintedanib)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	39 / 40 (97.50%)	46 / 47 (97.87%)
Vascular disorders			
HOT FLASHES	Additional description: HOT FLASHES		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 40 (2.50%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
HYPERTENSION	Additional description: HYPERTENSION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 40 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1

THROMBOEMBOLIC EVENT	Additional description: THROMBOEMBOLIC EVENT		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 40 (0.00%)	4 / 47 (8.51%)
occurrences (all)	0	0	4
General disorders and administration site conditions			
FATIGUE	Additional description: FATIGUE		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 5 (60.00%)	25 / 40 (62.50%)	19 / 47 (40.43%)
occurrences (all)	3	25	19
FEVER	Additional description: FEVER		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 40 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - OTHER, SPECIFY	Additional description: GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	2 / 40 (5.00%)	0 / 47 (0.00%)
occurrences (all)	0	2	0
MALAISE	Additional description: MALAISE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 40 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
PAIN	Additional description: PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 40 (2.50%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
ALLERGIC REACTION	Additional description: ALLERGIC REACTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	3 / 40 (7.50%)	0 / 47 (0.00%)
occurrences (all)	0	3	0
ANAPHYLAXIS	Additional description: ANAPHYLAXIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 40 (2.50%)	0 / 47 (0.00%)
occurrences (all)	0	1	0

Reproductive system and breast disorders			
PELVIC PAIN	Additional description: PELVIC PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 40 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
COUGH	Additional description: COUGH		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 5 (20.00%)	1 / 40 (2.50%)	0 / 47 (0.00%)
occurrences (all)	1	1	0
DYSPNEA	Additional description: DYSPNEA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 5 (20.00%)	1 / 40 (2.50%)	1 / 47 (2.13%)
occurrences (all)	1	1	1
EPISTAXIS	Additional description: EPISTAXIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	2 / 40 (5.00%)	0 / 47 (0.00%)
occurrences (all)	0	2	0
Psychiatric disorders			
INSOMNIA	Additional description: INSOMNIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 40 (0.00%)	2 / 47 (4.26%)
occurrences (all)	0	0	2
Investigations			
ALANINE AMINOTRANSFERASE INCREASED	Additional description: ALANINE AMINOTRANSFERASE INCREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 5 (20.00%)	7 / 40 (17.50%)	26 / 47 (55.32%)
occurrences (all)	1	7	32
ALKALINE PHOSPHATASE INCREASED	Additional description: ALKALINE PHOSPHATASE INCREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 5 (80.00%)	23 / 40 (57.50%)	30 / 47 (63.83%)
occurrences (all)	4	23	33
ASPARTATE AMINOTRANSFERASE INCREASED	Additional description: ASPARTATE AMINOTRANSFERASE INCREASED		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 5 (20.00%)	9 / 40 (22.50%)	18 / 47 (38.30%)
occurrences (all)	1	10	22
BLOOD BILIRUBIN INCREASED	Additional description: BLOOD BILIRUBIN INCREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 5 (20.00%)	6 / 40 (15.00%)	6 / 47 (12.77%)
occurrences (all)	1	6	6
CREATININE INCREASED	Additional description: CREATININE INCREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 5 (40.00%)	4 / 40 (10.00%)	11 / 47 (23.40%)
occurrences (all)	2	4	12
GGT INCREASED	Additional description: GGT INCREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 40 (0.00%)	2 / 47 (4.26%)
occurrences (all)	0	0	2
LYMPHOCYTE COUNT DECREASED	Additional description: LYMPHOCYTE COUNT DECREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 5 (80.00%)	15 / 40 (37.50%)	4 / 47 (8.51%)
occurrences (all)	4	15	4
LYMPHOCYTE COUNT INCREASED	Additional description: LYMPHOCYTE COUNT INCREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 5 (20.00%)	3 / 40 (7.50%)	2 / 47 (4.26%)
occurrences (all)	1	3	2
NEUTROPHIL COUNT DECREASED	Additional description: NEUTROPHIL COUNT DECREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	5 / 40 (12.50%)	0 / 47 (0.00%)
occurrences (all)	0	6	0
PLATELET COUNT DECREASED	Additional description: PLATELET COUNT DECREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	6 / 40 (15.00%)	3 / 47 (6.38%)
occurrences (all)	0	7	3
WEIGHT LOSS	Additional description: WEIGHT LOSS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 40 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1

WHITE BLOOD CELL DECREASED	Additional description: WHITE BLOOD CELL DECREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 5 (20.00%)	5 / 40 (12.50%)	0 / 47 (0.00%)
occurrences (all)	1	6	0
Cardiac disorders			
HEART FAILURE	Additional description: HEART FAILURE		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 5 (20.00%)	0 / 40 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
DIZZINESS	Additional description: DIZZINESS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	2 / 40 (5.00%)	0 / 47 (0.00%)
occurrences (all)	0	2	0
DYSGEUSIA	Additional description: DYSGEUSIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 40 (2.50%)	2 / 47 (4.26%)
occurrences (all)	0	1	2
HEADACHE	Additional description: HEADACHE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 40 (2.50%)	1 / 47 (2.13%)
occurrences (all)	0	1	1
ISCHEMIA CEREBROVASCULAR	Additional description: ISCHEMIA CEREBROVASCULAR		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 40 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
LETHARGY	Additional description: LETHARGY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 40 (2.50%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
NERVOUS SYSTEM DISORDERS - OTHER, SPECIFY	Additional description: NERVOUS SYSTEM DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 40 (2.50%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
PARESTHESIA	Additional description: PARESTHESIA		

alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 5 (20.00%)	0 / 40 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
PERIPHERAL MOTOR NEUROPATHY	Additional description: PERIPHERAL MOTOR NEUROPATHY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 40 (2.50%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
PERIPHERAL SENSORY NEUROPATHY	Additional description: PERIPHERAL SENSORY NEUROPATHY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	7 / 40 (17.50%)	3 / 47 (6.38%)
occurrences (all)	0	7	3
Blood and lymphatic system disorders			
ANEMIA	Additional description: ANEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 5 (80.00%)	26 / 40 (65.00%)	21 / 47 (44.68%)
occurrences (all)	6	35	25
FEBRILE NEUTROPENIA	Additional description: FEBRILE NEUTROPENIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 40 (2.50%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
LEUKOCYTOSIS	Additional description: LEUKOCYTOSIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 40 (0.00%)	3 / 47 (6.38%)
occurrences (all)	0	0	3
Ear and labyrinth disorders			
VERTIGO	Additional description: VERTIGO		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 5 (20.00%)	0 / 40 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
ABDOMINAL PAIN	Additional description: ABDOMINAL PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	4 / 40 (10.00%)	8 / 47 (17.02%)
occurrences (all)	0	4	8
ASCITES	Additional description: ASCITES		

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 40 (2.50%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
BLOATING	Additional description: BLOATING		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 40 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
CONSTIPATION	Additional description: CONSTIPATION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	4 / 40 (10.00%)	5 / 47 (10.64%)
occurrences (all)	0	4	5
DIARRHEA	Additional description: DIARRHEA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	3 / 40 (7.50%)	21 / 47 (44.68%)
occurrences (all)	0	3	21
DRY MOUTH	Additional description: DRY MOUTH		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 40 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
DYSPEPSIA	Additional description: DYSPEPSIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 40 (2.50%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
GASTROESOPHAGEAL REFLUX DISEASE	Additional description: GASTROESOPHAGEAL REFLUX DISEASE		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 40 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
GASTROINTESTINAL DISORDERS - OTHER, SPECIFY	Additional description: GASTROINTESTINAL DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 5 (20.00%)	0 / 40 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
MUCOSITIS ORAL	Additional description: MUCOSITIS ORAL		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 5 (20.00%)	9 / 40 (22.50%)	3 / 47 (6.38%)
occurrences (all)	1	9	3
NAUSEA	Additional description: NAUSEA		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 5 (40.00%)	15 / 40 (37.50%)	25 / 47 (53.19%)
occurrences (all)	2	15	25
VOMITING	Additional description: VOMITING		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	5 / 40 (12.50%)	12 / 47 (25.53%)
occurrences (all)	0	5	12
Skin and subcutaneous tissue disorders			
ALOPECIA	Additional description: ALOPECIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	3 / 40 (7.50%)	0 / 47 (0.00%)
occurrences (all)	0	3	0
DRY SKIN	Additional description: DRY SKIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 5 (20.00%)	0 / 40 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
ERYTHEMA MULTIFORME	Additional description: ERYTHEMA MULTIFORME		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 40 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
NAIL RIDGING	Additional description: NAIL RIDGING		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 40 (2.50%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME	Additional description: PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	3 / 40 (7.50%)	1 / 47 (2.13%)
occurrences (all)	0	3	1
PRURITUS	Additional description: PRURITUS		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 5 (0.00%)	1 / 40 (2.50%)	1 / 47 (2.13%)
occurrences (all)	0	1	1
RASH MACULO-PAPULAR	Additional description: RASH MACULO-PAPULAR		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	3 / 40 (7.50%)	1 / 47 (2.13%)
occurrences (all)	0	3	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - OTHER, SPECIFY	Additional description: SKIN AND SUBCUTANEOUS TISSUE DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 40 (0.00%)	2 / 47 (4.26%)
occurrences (all)	0	0	2
SKIN HYPERPIGMENTATION	Additional description: SKIN HYPERPIGMENTATION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 40 (2.50%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
HEMATURIA	Additional description: HEMATURIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 40 (2.50%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA	Additional description: ARTHRALGIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 40 (2.50%)	2 / 47 (4.26%)
occurrences (all)	0	1	2
MUSCLE WEAKNESS LOWER LIMB	Additional description: MUSCLE WEAKNESS LOWER LIMB		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 40 (2.50%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
MYALGIA	Additional description: MYALGIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 40 (2.50%)	1 / 47 (2.13%)
occurrences (all)	0	1	1
Infections and infestations			

INFECTIONS AND INFESTATIONS - OTHER, SPECIFY	Additional description: INFECTIONS AND INFESTATIONS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 5 (20.00%)	1 / 40 (2.50%)	0 / 47 (0.00%)
occurrences (all)	1	1	0
Metabolism and nutrition disorders			
ANOREXIA	Additional description: ANOREXIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 5 (60.00%)	7 / 40 (17.50%)	9 / 47 (19.15%)
occurrences (all)	3	7	9
DEHYDRATION	Additional description: DEHYDRATION		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 5 (20.00%)	0 / 40 (0.00%)	1 / 47 (2.13%)
occurrences (all)	1	0	1
HYPERCALCEMIA	Additional description: HYPERCALCEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	10 / 40 (25.00%)	11 / 47 (23.40%)
occurrences (all)	0	11	11
HYPERGLYCEMIA	Additional description: HYPERGLYCEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	6 / 40 (15.00%)	6 / 47 (12.77%)
occurrences (all)	0	6	6
HYPERKALEMIA	Additional description: HYPERKALEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 5 (20.00%)	3 / 40 (7.50%)	9 / 47 (19.15%)
occurrences (all)	1	3	9
HYPERMAGNESEMIA	Additional description: HYPERMAGNESEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 5 (20.00%)	1 / 40 (2.50%)	1 / 47 (2.13%)
occurrences (all)	1	1	1
HYPERNATREMIA	Additional description: HYPERNATREMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 5 (20.00%)	1 / 40 (2.50%)	0 / 47 (0.00%)
occurrences (all)	1	1	0
HYPOALBUMINEMIA	Additional description: HYPOALBUMINEMIA		
alternative assessment type: Non-			

systematic			
subjects affected / exposed	3 / 5 (60.00%)	21 / 40 (52.50%)	22 / 47 (46.81%)
occurrences (all)	3	21	22
HYPOCALCEMIA	Additional description: HYPOCALCEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 5 (40.00%)	9 / 40 (22.50%)	8 / 47 (17.02%)
occurrences (all)	2	10	8
HYPOGLYCEMIA	Additional description: HYPOGLYCEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 40 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
HYPOKALEMIA	Additional description: HYPOKALEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 5 (40.00%)	4 / 40 (10.00%)	12 / 47 (25.53%)
occurrences (all)	2	4	12
HYPONATREMIA	Additional description: HYPONATREMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 5 (80.00%)	36 / 40 (90.00%)	46 / 47 (97.87%)
occurrences (all)	4	36	46
HYPOMAGNESEMIA	Additional description: HYPOMAGNESEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 5 (40.00%)	10 / 40 (25.00%)	18 / 47 (38.30%)
occurrences (all)	2	10	18
HYPOPHOSPHATEMIA	Additional description: HYPOPHOSPHATEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 40 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1

Non-serious adverse events	ENDOMETRIAL: Experimental arm (nintedanib)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)		
Vascular disorders			
HOT FLASHES	Additional description: HOT FLASHES		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
HYPERTENSION	Additional description: HYPERTENSION			
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
THROMBOEMBOLIC EVENT	Additional description: THROMBOEMBOLIC EVENT			
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
General disorders and administration site conditions				
FATIGUE	Additional description: FATIGUE			
alternative assessment type: Non-systematic				
subjects affected / exposed	3 / 4 (75.00%)			
occurrences (all)	3			
FEVER	Additional description: FEVER			
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - OTHER, SPECIFY	Additional description: GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - OTHER, SPECIFY			
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
MALAISE	Additional description: MALAISE			
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
PAIN	Additional description: PAIN			
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Immune system disorders				

ALLERGIC REACTION	Additional description: ALLERGIC REACTION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
ANAPHYLAXIS	Additional description: ANAPHYLAXIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
PELVIC PAIN	Additional description: PELVIC PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
COUGH	Additional description: COUGH		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
DYSPNEA	Additional description: DYSPNEA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
EPISTAXIS	Additional description: EPISTAXIS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
INSOMNIA	Additional description: INSOMNIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Investigations			
ALANINE AMINOTRANSFERASE INCREASED	Additional description: ALANINE AMINOTRANSFERASE INCREASED		
alternative assessment type: Non-systematic			

subjects affected / exposed	3 / 4 (75.00%)		
occurrences (all)	5		
ALKALINE PHOSPHATASE INCREASED	Additional description: ALKALINE PHOSPHATASE INCREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 4 (100.00%)		
occurrences (all)	5		
ASPARTATE AMINOTRANSFERASE INCREASED	Additional description: ASPARTATE AMINOTRANSFERASE INCREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 4 (75.00%)		
occurrences (all)	4		
BLOOD BILIRUBIN INCREASED	Additional description: BLOOD BILIRUBIN INCREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
CREATININE INCREASED	Additional description: CREATININE INCREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
GGT INCREASED	Additional description: GGT INCREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
LYMPHOCYTE COUNT DECREASED	Additional description: LYMPHOCYTE COUNT DECREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 4 (75.00%)		
occurrences (all)	3		
LYMPHOCYTE COUNT INCREASED	Additional description: LYMPHOCYTE COUNT INCREASED		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
NEUTROPHIL COUNT DECREASED	Additional description: NEUTROPHIL COUNT DECREASED		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
PLATELET COUNT DECREASED	Additional description: PLATELET COUNT DECREASED			
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
WEIGHT LOSS	Additional description: WEIGHT LOSS			
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
WHITE BLOOD CELL DECREASED	Additional description: WHITE BLOOD CELL DECREASED			
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Cardiac disorders				
HEART FAILURE	Additional description: HEART FAILURE			
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Nervous system disorders				
DIZZINESS	Additional description: DIZZINESS			
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
DYSGEUSIA	Additional description: DYSGEUSIA			
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
HEADACHE	Additional description: HEADACHE			
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
ISCHEMIA CEREBROVASCULAR	Additional description: ISCHEMIA CEREBROVASCULAR			
alternative assessment type: Non-systematic				

subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
LETHARGY	Additional description: LETHARGY			
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
NERVOUS SYSTEM DISORDERS - OTHER, SPECIFY	Additional description: NERVOUS SYSTEM DISORDERS - OTHER, SPECIFY			
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
PARESTHESIA	Additional description: PARESTHESIA			
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
PERIPHERAL MOTOR NEUROPATHY	Additional description: PERIPHERAL MOTOR NEUROPATHY			
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
PERIPHERAL SENSORY NEUROPATHY	Additional description: PERIPHERAL SENSORY NEUROPATHY			
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Blood and lymphatic system disorders				
ANEMIA	Additional description: ANEMIA			
alternative assessment type: Non-systematic				
subjects affected / exposed	2 / 4 (50.00%)			
occurrences (all)	2			
FEBRILE NEUTROPENIA	Additional description: FEBRILE NEUTROPENIA			
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
LEUKOCYTOSIS	Additional description: LEUKOCYTOSIS			
alternative assessment type: Non-systematic				

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
VERTIGO	Additional description: VERTIGO		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
ABDOMINAL PAIN	Additional description: ABDOMINAL PAIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
ASCITES	Additional description: ASCITES		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
BLOATING	Additional description: BLOATING		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
CONSTIPATION	Additional description: CONSTIPATION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
DIARRHEA	Additional description: DIARRHEA		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
DRY MOUTH	Additional description: DRY MOUTH		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
DYSPEPSIA	Additional description: DYSPEPSIA		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
GASTROESOPHAGEAL REFLUX DISEASE	Additional description: GASTROESOPHAGEAL REFLUX DISEASE		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
GASTROINTESTINAL DISORDERS - OTHER, SPECIFY	Additional description: GASTROINTESTINAL DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
MUCOSITIS ORAL	Additional description: MUCOSITIS ORAL		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
NAUSEA	Additional description: NAUSEA		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 4 (75.00%)		
occurrences (all)	3		
VOMITING	Additional description: VOMITING		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
ALOPECIA	Additional description: ALOPECIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
DRY SKIN	Additional description: DRY SKIN		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
ERYTHEMA MULTIFORME	Additional description: ERYTHEMA MULTIFORME		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
NAIL RIDGING	Additional description: NAIL RIDGING		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME	Additional description: PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
PRURITUS	Additional description: PRURITUS		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
RASH MACULO-PAPULAR	Additional description: RASH MACULO-PAPULAR		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - OTHER, SPECIFY	Additional description: SKIN AND SUBCUTANEOUS TISSUE DISORDERS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
SKIN HYPERPIGMENTATION	Additional description: SKIN HYPERPIGMENTATION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
HEMATURIA	Additional description: HEMATURIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			

ARTHRALGIA	Additional description: ARTHRALGIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
MUSCLE WEAKNESS LOWER LIMB	Additional description: MUSCLE WEAKNESS LOWER LIMB		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
MYALGIA	Additional description: MYALGIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Infections and infestations			
INFECTIONS AND INFESTATIONS - OTHER, SPECIFY	Additional description: INFECTIONS AND INFESTATIONS - OTHER, SPECIFY		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
ANOREXIA	Additional description: ANOREXIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
DEHYDRATION	Additional description: DEHYDRATION		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
HYPERCALCEMIA	Additional description: HYPERCALCEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
HYPERGLYCEMIA	Additional description: HYPERGLYCEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
HYPERKALEMIA	Additional description: HYPERKALEMIA		

alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
HYPERMAGNESEMIA	Additional description: HYPERMAGNESEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
HYPERNATREMIA	Additional description: HYPERNATREMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
HYPOALBUMINEMIA	Additional description: HYPOALBUMINEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
HYPOCALCEMIA	Additional description: HYPOCALCEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
HYPOGLYCEMIA	Additional description: HYPOGLYCEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
HYPOKALEMIA	Additional description: HYPOKALEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
HYPONATREMIA	Additional description: HYPONATREMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 4 (100.00%)		
occurrences (all)	4		
HYPOMAGNESEMIA	Additional description: HYPOMAGNESEMIA		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
HYPOPHOSPHATEMIA	Additional description: HYPOPHOSPHATEMIA		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 January 2015	(UK only - Amendment No 02): In order to meet the reporting requirements of all the participating countries, SUSARS were reported on Eudravigilance. It was discovered that only the Marketing Authorisation Holder can report SUSARS on unlicensed drugs on Eudravigilance. As a result this responsibility had to be delegated by study Sponsor to Boehringer Ingelheim. This required a Vendor Assessment by Sponsor, a Variation to BI/Sponsor Contract to be put in place and the protocol to be updated and submitted as a substantial amendment.
29 March 2016	(UK Ref - Amendment No 4) : Protocol update following feedback received from the French Health Authority. The majority of changes were in accordance with the addition of information contained in the Summary of Product Characteristics for the chemotherapy agents and the updated Investigator's Brochure for Nintedanib. Eligibility criteria were updated and in addition, the treatment duration on the standard chemotherapy arm was extended (if, in the opinion of the investigator, the patient would benefit from continuing chemotherapy beyond 6 cycles).
25 September 2019	(UK Ref - Amendment 09): In preparation of BREXIT, the EORTC became the EU Sponsor for trial. NHS Greater Glasgow & Clyde remain as UK Sponsor and Lead Co-ordinator of trial. Protocol upated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported