



Clinical trial results:

Randomized double blind placebo-controlled phase II trial of Vargatef® in addition to first line chemotherapy with interval debulking surgery in patients with adenocarcinoma of the ovary, the fallopian tube or serous adenocarcinoma of the peritoneum

Summary

EudraCT number	2011-006288-23
Trial protocol	FR
Global end of trial date	16 November 2017

Results information

Result version number	v1 (current)
This version publication date	23 April 2023
First version publication date	23 April 2023

Trial information

Trial identification

Sponsor protocol code	GINECO-OV-119
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01583322
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ARCAGY-GINECO
Sponsor organisation address	8 rue Lamennais, Paris, France, 75008
Public contact	Sébastien ARMANET, ARCAGY, 33 184852020, sarmanet@arcagy.org
Scientific contact	Sébastien ARMANET, ARCAGY, 33 184852020, sarmanet@arcagy.org

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	27 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 November 2017
Global end of trial reached?	Yes
Global end of trial date	16 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the median Progression-free Survival (PFS) in each study arm (neoadjuvant/adjuvant treatment with or without Nintedanib(Vargatef®)).

Protection of trial subjects:

The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and with the French laws and regulations:

- Huriet law (n°88-1138) of December 20th 1988, concerning protection of participants undergoing biomedical research, modified by the Public health law (n°2004-806) of August 9th 2004. - Data Protection Act n°78-17, modified by the law n°2004-801 of August 6th 2004 ensuring the confidentiality of personal information.

The study fully adhered to the principles outlined in "Guideline for Good Clinical Practice" (November 2006) ICH Tripartite Guideline (January 1997). The investigator ensured compliance with the EU Clinical Trial Directive (2001/20/EC).

The study protocol and all the amendments were reviewed by an Independent Ethics Committee (EC):

Comité de Protection des Personnes (CPP) Ile de France n° 1

Docteur Catherine Grillot-Courvalin,

Présidente du CPP Ile de France n° 1

Hôpital Hôtel-Dieu

1, place du Parvis Notre-Dame – Place Jean-Paul II

75004 PARIS

The EC provided an initial approval on the 29th of March 2012

Background therapy:

Maximal primary cyto-reductive surgery followed by carboplatin-paclitaxel 3-weeks cycles of chemotherapy remains the standard of care as first treatment in advanced ovarian cancer. Neoadjuvant chemotherapy represents an alternative strategy for patients with stage IIIC or IV who are not considered to be completely resectable. Chemotherapy followed by interval debulking result in fewer and simpler operations and lesser morbidity for the patients involving less inconvenience and toxicity for the patient with equivalent survival outcomes.

The background therapy treatments for this trial are :

Carboplatine: AUC 5 or 6, IV, q 3 weeks

Paclitaxel: 175 mg/m², IV, q 3 weeks

Patients will receive a total number of 6 courses. Two additional cycles are allowed if required (maximum 8 cycles).

Evidence for comparator:

Vargatef® (Nintedanib) is an orally available potent small molecule triple kinase inhibitor inhibiting VEGFR 1-3, FGFR 1-3 as well as PDGF receptor α and β in the low nanomolar range. Considering its antiangiogenic mechanism of action demonstrated in vivo, it is anticipated that treatment with Vargatef® (Nintedanib) will slow tumor growth in human cancers. Moreover, tumor regression may also be achieved by induction of apoptosis of immature tumor vessels. In addition, a therapeutic effect may also result from inhibition of tumor autocrine and paracrine growth factor loops involving VEGF, PDGF and bFGF. It is likely that long-term treatment may be needed to ensure maximal clinical benefit.

Based on results of previous phase I and II clinical trials, it was decided to set up a large randomized phase III study (GCIG/ENGOT/AGO-OVAR 12 trial). The objective of this study was to investigate the efficacy and safety of Vargatef® (Nintedanib) plus chemotherapy as compared with placebo plus chemotherapy in patients with advanced ovarian cancer. Vargatef® (Nintedanib)/placebo monotherapy was continued for a maximum of 120 weeks after randomization or until AEs or disease progression,

whichever occurs first. The results showed that adding nintedanib to carboplatin–paclitaxel after upfront surgery improved PFS (but not OS), although adverse events (AEs) were increased.

Actual start date of recruitment	11 January 2013
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	France: 188
Worldwide total number of subjects	188
EEA total number of subjects	188

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)	97
From 65 to 84 years	91
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited in 31 centres in France during January 11th, 2013 to May 13th, 2015.

Pre-assignment

Screening details:

Of 191 screened patients 3 were excluded for not meeting the eligibility criteria. Subsequently, 124 were allocated to the study treatment nintedanib, 64 were allocated to the placebo.

Period 1

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

Blinding implementation details:

The trial was performed according to a parallel group, double-blind, placebo-controlled design. Patients, investigators and the sponsor's trial team involved in analyzing of this double-blind trial remained blinded with regard to the randomized treatment assignments up to database lock, with the exception of particular instances which required immediate unblinding (DSMB).

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: standard arm (placebo arm)

Arm description:

1. Neoadjuvant therapy (3 cycles)

Vargatef® placebo 200mg bid will be administered twice daily during the first 2 cycles except on day 1 of each cycle (day of chemotherapy). Placebo will not be administered during cycle before surgery (third cycle).

Patients with insufficient tumor response to allow interval debulking surgery after 3 cycles of neoadjuvant therapy will receive 4 cycles of neo-adjuvant therapy. In those patients, placebo will be skipped during cycle preceding surgery (Cycle 4).

Interval Debulking Surgery: will be performed 3 to 4 weeks after the last chemotherapy administration.

3. Adjuvant therapy: will start 4 weeks after surgery and after complete surgical wound healing

4. Maintenance therapy: Placebo 200mg bid will be administered during 2 years or until disease progression which ever occur first.

Arm type	Placebo
Investigational medicinal product name	Vargatef® (Nintedanib) 200mg bid
Investigational medicinal product code	BIBF1120
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Neo-adjuvant therapy (3 to 4 cycles): 400 mg per day (200mg twice daily) during the first 2 to 3 cycles except on day 1 of each cycle (day of chemotherapy). Vargatef® (Nintedanib) will not be administered during cycle before surgery (i.e. cycle 3 or 4).

Maintenance therapy: Vargatef® (Nintedanib): 200 mg bid will be administered during 2 years or until disease progression which ever occur first.

Arm title	Arm B: experimental arm (Vargatef® arm)
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Arm description:

1. Neo-adjuvant therapy (3 cycles):

Vargatef® (Nintedanib) 200mg bid will be administered twice daily during the first 2 cycles except on day 1 of each cycle (day of chemotherapy). Vargatef® (Nintedanib) will not be administered during cycle before surgery (cycle 3).

Patients with insufficient tumor response to allow interval debulking surgery after 3 cycles of neoadjuvant therapy will receive 4 cycles of neo-adjuvant therapy. In those patients, Vargatef®

(Nintedanib) will be skipped during cycle preceding surgery (Cycle 4).

2. Interval Debulking Surgery: will be performed 3 to 4 weeks after the last chemotherapy administration.

3. Adjuvant therapy: will start 4 weeks after surgery and after complete surgical wound healing

4. Maintenance therapy: Vargatef® (Nintedanib) 200 mg bid will be administered during 2 years or until disease progression which ever occur first.

Arm type	Experimental
Investigational medicinal product name	Vargatef® (Nintedanib) 200mg bid
Investigational medicinal product code	BIBF1120
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Neo-adjuvant therapy (3 to 4 cycles): 400 mg per day (200mg twice daily) during the first 2 to 3 cycles except on day 1 of each cycle (day of chemotherapy). Vargatef® (Nintedanib) will not be administered during cycle before surgery (i.e. cycle 3 or 4).

Maintenance therapy: Vargatef® (Nintedanib): 200 mg bid will be administered during 2 years or until disease progression which ever occur first.

Number of subjects in period 1	Arm A: standard arm (placebo arm)	Arm B: experimental arm (Vargatef® arm)
Started	64	124
Completed	64	120
Not completed	0	4
poor treatment compliance	-	2
Protocol deviation	-	2

Baseline characteristics

Reporting groups

Reporting group title	Arm A: standard arm (placebo arm)
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Reporting group description:

1. Neoadjuvant therapy (3 cycles)

Vargatef® placebo 200mg bid will be administered twice daily during the first 2 cycles except on day 1 of each cycle (day of chemotherapy). Placebo will not be administered during cycle before surgery (third cycle).

Patients with insufficient tumor response to allow interval debulking surgery after 3 cycles of neoadjuvant therapy will receive 4 cycles of neo-adjuvant therapy. In those patients, placebo will be skipped during cycle preceding surgery (Cycle 4).

Interval Debulking Surgery: will be performed 3 to 4 weeks after the last chemotherapy administration.

3. Adjuvant therapy: will start 4 weeks after surgery and after complete surgical wound healing

4. Maintenance therapy: Placebo 200mg bid will be administered during 2 years or until disease progression which ever occur first.

Reporting group title	Arm B: experimental arm (Vargatef® arm)
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Reporting group description:

1. Neo-adjuvant therapy (3 cycles):

Vargatef® (Nintedanib) 200mg bid will be administered twice daily during the first 2 cycles except on day 1 of each cycle (day of chemotherapy). Vargatef® (Nintedanib) will not be administered during cycle before surgery (cycle 3).

Patients with insufficient tumor response to allow interval debulking surgery after 3 cycles of neoadjuvant therapy will receive 4 cycles of neo-adjuvant therapy. In those patients, Vargatef® (Nintedanib) will be skipped during cycle preceding surgery (Cycle 4).

2. Interval Debulking Surgery: will be performed 3 to 4 weeks after the last chemotherapy administration.

3. Adjuvant therapy: will start 4 weeks after surgery and after complete surgical wound healing

4. Maintenance therapy: Vargatef® (Nintedanib) 200 mg bid will be administered during 2 years or until disease progression which ever occur first.

Reporting group values	Arm A: standard arm (placebo arm)	Arm B: experimental arm (Vargatef® arm)	Total
Number of subjects	64	124	188
Age categorical 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)	34	63	97
From 65-84 years	30	61	91
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	63.1	63.7	
standard deviation	± 8	± 10	-
Gender categorical Units: Subjects			
Female	64	124	188
Male	0	0	0

ECOG performance			
Units: Subjects			
zero	21	49	70
one	32	63	95
two	10	10	20
missing	1	2	3
Tumor histological type			
Units: Subjects			
Serous/papillary	56	108	164
Endometrioid	0	3	3
Mucinous	0	1	1
Clear cells	0	3	3
Undifferentiated	1	4	5
Other	6	5	11
Not available	1	0	1
Tumor histological grade			
Units: Subjects			
01	3	2	5
02	3	10	13
03	50	85	135
Unknown	7	27	34
Not available	1	0	1
FIGO stage			
Units: Subjects			
IIIC	47	98	145
IV	16	26	42
Not available	1	0	1
Uterus			
Units: Subjects			
No	16	24	40
Yes	0	1	1
Not available	0	1	1
Not recorded	48	98	146
Vagina			
Units: Subjects			
No	16	25	41
Not available	0	1	1
Not recorded	48	98	146
Bladder			
Units: Subjects			
No	16	25	41
Not available	0	1	1
Not recorded	48	98	146
Rectum			
Units: Subjects			
No	15	24	39
Yes	1	1	2
Not available	0	1	1
Not recorded	48	98	146
Abdominal peritoneum			
Units: Subjects			

No	9	15	24
Yes	7	11	18
Not available	0	0	0
Not recorded	48	98	146
Pelvic lymph nodes Units: Subjects			
No	12	22	34
Yes	4	3	7
Not available	0	1	1
Not recorded	48	98	146
Para-aortic lymph nodes Units: Subjects			
No	13	22	35
Yes	3	3	6
Not available	0	1	1
Not recorded	48	98	146
Liver Units: Subjects			
No	13	19	32
Yes	3	7	10
Not available	0	0	0
Not recorded	48	98	146
Lung Units: Subjects			
No	13	21	34
Yes	3	4	7
Not available	0	1	1
Not recorded	48	98	146
Mediastinal lymph nodes Units: Subjects			
No	13	18	31
Yes	10	7	17
Not available	1	1	2
Not recorded	40	98	138
Other tumor site Units: Subjects			
No	1	13	14
Yes	15	12	27
Not available	0	1	1
Not recorded	48	98	146
Diagnostic surgery : Coelioscopy Units: Subjects			
No	1	9	10
Yes	62	115	177
Not available	1	0	1
Diagnostic surgery : Subumbilical median Units: Subjects			
No	55	104	159
Yes	8	20	28
Not available	1	0	1

Diagnostic surgery : Supra and subumbilical median Units: Subjects			
No	57	114	171
Yes	6	10	16
Not available	1	0	1
Diagnostic surgery : Other Units: Subjects			
No	47	76	123
Yes	16	48	64
Not available	1	0	1
Resection Units: Subjects			
Resection	6	17	23
No resection	57	107	164
Not available	1	0	1
Medical history : Arterial hypertension Units: Subjects			
No	41	66	107
Former	0	1	1
Ongoing	19	41	60
Not available	0	2	2
Not recorded	4	14	18
Medical history : Other heart disease Units: Subjects			
No	55	103	158
Former	2	1	3
Ongoing	3	4	7
Not available	0	2	2
Not recorded	4	14	18
Medical history : Hypercholesterolemia Units: Subjects			
No	45	82	127
Former	1	5	6
Ongoing	14	21	35
Not available	0	2	2
Not recorded	4	14	18
Medical history : Mood disorders Units: Subjects			
No	53	96	149
Former	2	1	3
Ongoing	5	11	16
Not available	0	2	2
Not recorded	4	14	18
Medical history : Pain Units: Subjects			
No	44	92	136
Ongoing	16	16	32
Not available	2	0	2
Not recorded	2	16	18
Medical history : Other disease or surgery			

Units: Subjects			
No	7	15	22
Former	23	44	67
Ongoing	30	50	80
Not available	0	1	1
Not recorded	4	14	18
Relevant treatments : Antihypertensive			
Units: Subjects			
No	31	52	83
Ongoing	18	38	56
Not available	0	0	0
Not recorded	15	34	49
Relevant treatments : Other heart disease			
Units: Subjects			
No	46	84	130
Ongoing	3	6	9
Not available	0	0	0
Not recorded	15	34	49
Relevant treatments : Cholesterol lowering treatment			
Units: Subjects			
No	37	69	106
Former	0	1	1
Ongoing	12	20	32
Not available	0	0	0
Not recorded	15	34	49
Relevant treatments : Antidepressant			
Units: Subjects			
No	44	76	120
Ongoing	5	13	18
Not available	0	1	1
Not recorded	15	34	49
Relevant treatments : Anxiolytic			
Units: Subjects			
No	42	75	117
Ongoing	7	15	22
Not available	0	0	0
Not recorded	15	34	49
Relevant treatments : Analgesic			
Units: Subjects			
No	30	67	97
Former	1	0	1
Ongoing	18	23	41
Not available	0	0	0
Not recorded	15	34	49
Relevant treatments : Other			
Units: Subjects			
No	11	17	28
Former	6	10	16
Ongoing	32	62	94
Not available	0	1	1

Not recorded	15	34	49
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Weight Units: kilogram(s) arithmetic mean standard deviation	65.5 ± 14.3	64.2 ± 12.7	-
Height Units: centimetre arithmetic mean standard deviation	161.6 ± 7	161.2 ± 6	-
BMI Units: kilogram(s)/square metre arithmetic mean standard deviation	24.6 ± 4.8	25.2 ± 5.5	-
Sugar-Baker Index Units: score arithmetic mean standard deviation	20.1 ± 8	22.1 ± 8	-

Subject analysis sets

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients included in the study and randomized whatever the actual product intake.

Reporting group values	ITT		
Number of subjects	188		
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)	97		
From 65-84 years	91		
85 years and over	0		
Age continuous Units: years arithmetic mean standard deviation	63.5 ± 9		
Gender categorical Units: Subjects			
Female	188		
Male	0		

ECOG performance			
Units: Subjects			
zero	70		
one	95		
two	20		
missing	3		
Tumor histological type			
Units: Subjects			
Serous/papillary	164		
Endometrioid	3		
Mucinous	1		
Clear cells	3		
Undifferentiated	5		
Other	11		
Not available	1		
Tumor histological grade			
Units: Subjects			
01	5		
02	13		
03	135		
Unknown	34		
Not available	1		
FIGO stage			
Units: Subjects			
IIIC	145		
IV	42		
Not available	1		
Uterus			
Units: Subjects			
No	40		
Yes	1		
Not available	1		
Not recorded	146		
Vagina			
Units: Subjects			
No	41		
Not available	1		
Not recorded	146		
Bladder			
Units: Subjects			
No	41		
Not available	1		
Not recorded	146		
Rectum			
Units: Subjects			
No	39		
Yes	2		
Not available	1		
Not recorded	48		
Abdominal peritoneum			
Units: Subjects			

No	24		
Yes	18		
Not available	0		
Not recorded	146		
Pelvic lymph nodes			
Units: Subjects			
No	34		
Yes	7		
Not available	1		
Not recorded	146		
Para-aortic lymph nodes			
Units: Subjects			
No	35		
Yes	6		
Not available	1		
Not recorded	146		
Liver			
Units: Subjects			
No	32		
Yes	10		
Not available	0		
Not recorded	146		
Lung			
Units: Subjects			
No	34		
Yes	7		
Not available	1		
Not recorded	146		
Mediastinal lymph nodes			
Units: Subjects			
No	31		
Yes	10		
Not available	1		
Not recorded	138		
Other tumor site			
Units: Subjects			
No	14		
Yes	27		
Not available	1		
Not recorded	146		
Diagnostic surgery : Coelioscopy			
Units: Subjects			
No	10		
Yes	177		
Not available	1		
Diagnostic surgery : Subumbilical median			
Units: Subjects			
No	159		
Yes	28		
Not available	1		

Diagnostic surgery : Supra and subumbilical median Units: Subjects			
No	171		
Yes	16		
Not available	1		
Diagnostic surgery : Other Units: Subjects			
No	123		
Yes	64		
Not available	1		
Resection Units: Subjects			
Resection	23		
No resection	164		
Not available	1		
Medical history : Arterial hypertension Units: Subjects			
No	107		
Former	1		
Ongoing	60		
Not available	2		
Not recorded	18		
Medical history : Other heart disease Units: Subjects			
No	158		
Former	3		
Ongoing	7		
Not available	2		
Not recorded	18		
Medical history : Hypercholesterolemia Units: Subjects			
No	127		
Former	6		
Ongoing	35		
Not available	2		
Not recorded	18		
Medical history : Mood disorders Units: Subjects			
No	149		
Former	3		
Ongoing	16		
Not available	2		
Not recorded	18		
Medical history : Pain Units: Subjects			
No	136		
Ongoing	32		
Not available	2		
Not recorded	18		
Medical history : Other disease or surgery			

Units: Subjects			
No	22		
Former	67		
Ongoing	80		
Not available	1		
Not recorded	18		
Relevant treatments : Antihypertensive			
Units: Subjects			
No	83		
Ongoing	56		
Not available	0		
Not recorded	49		
Relevant treatments : Other heart disease			
Units: Subjects			
No	130		
Ongoing	9		
Not available	0		
Not recorded	49		
Relevant treatments : Cholesterol lowering treatment			
Units: Subjects			
No	106		
Former	1		
Ongoing	32		
Not available	0		
Not recorded	49		
Relevant treatments : Antidepressant			
Units: Subjects			
No	120		
Ongoing	18		
Not available	1		
Not recorded	49		
Relevant treatments : Anxiolytic			
Units: Subjects			
No	117		
Ongoing	22		
Not available	0		
Not recorded	49		
Relevant treatments : Analgesic			
Units: Subjects			
No	97		
Former	1		
Ongoing	41		
Not available	0		
Not recorded	49		
Relevant treatments : Other			
Units: Subjects			
No	28		
Former	16		
Ongoing	94		
Not available	1		

Not recorded	49		
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Weight			
Units: kilogram(s)			
arithmetic mean	65.05		
standard deviation	± 13.8		
Height			
Units: centimetre			
arithmetic mean	161.3		
standard deviation	± 6		
BMI			
Units: kilogram(s)/square metre			
arithmetic mean	25		
standard deviation	± 5.3		
Sugar-Baker Index			
Units: score			
arithmetic mean	21.4		
standard deviation	± 8		

End points

End points reporting groups

Reporting group title	Arm A: standard arm (placebo arm)
Reporting group description:	
1. Neoadjuvant therapy (3 cycles) Vargatef® placebo 200mg bid will be administered twice daily during the first 2 cycles except on day 1 of each cycle (day of chemotherapy). Placebo will not be administered during cycle before surgery (third cycle). Patients with insufficient tumor response to allow interval debulking surgery after 3 cycles of neoadjuvant therapy will receive 4 cycles of neo-adjuvant therapy. In those patients, placebo will be skipped during cycle preceding surgery (Cycle 4). Interval Debulking Surgery: will be performed 3 to 4 weeks after the last chemotherapy administration. 3. Adjuvant therapy: will start 4 weeks after surgery and after complete surgical wound healing 4. Maintenance therapy: Placebo 200mg bid will be administered during 2 years or until disease progression which ever occur first.	
Reporting group title	Arm B: experimental arm (Vargatef® arm)
Reporting group description:	
1. Neo-adjuvant therapy (3 cycles): Vargatef® (Nintedanib) 200mg bid will be administered twice daily during the first 2 cycles except on day 1 of each cycle (day of chemotherapy). Vargatef® (Nintedanib) will not be administered during cycle before surgery (cycle 3). Patients with insufficient tumor response to allow interval debulking surgery after 3 cycles of neoadjuvant therapy will receive 4 cycles of neo-adjuvant therapy. In those patients, Vargatef® (Nintedanib) will be skipped during cycle preceding surgery (Cycle 4). 2. Interval Debulking Surgery: will be performed 3 to 4 weeks after the last chemotherapy administration. 3. Adjuvant therapy: will start 4 weeks after surgery and after complete surgical wound healing 4. Maintenance therapy: Vargatef® (Nintedanib) 200 mg bid will be administered during 2 years or until disease progression which ever occur first.	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients included in the study and randomized whatever the actual product intake.	

Primary: Progression Free Survival

End point title	Progression Free Survival
End point description:	
PFS was assessed by tumour measurements according to the RECIST version 1.1 and defined for all patients that entered the trial and measured from the date of randomization until the date of disease progression or death, from any cause, whichever occurs first.	
End point type	Primary
End point timeframe:	
24 months	

End point values	Arm A: standard arm (placebo arm)	Arm B: experimental arm (Vargatef® arm)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	120		
Units: month				
median (full range (min-max))	16.8 (13.0 to 21.4)	14.2 (12.2 to 15.4)		

Statistical analyses

Statistical analysis title	log-rank test
Comparison groups	Arm A: standard arm (placebo arm) v Arm B: experimental arm (Vargatef® arm)
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Logrank

Secondary: Overall Survival

End point title	Overall Survival
End point description: Upper CI95% not reached for Arm 1	
End point type	Secondary
End point timeframe: Cut off 30 SEP 2017	

End point values	Arm A: standard arm (placebo arm)	Arm B: experimental arm (Vargatef® arm)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64 ^[1]	124		
Units: month				
median (confidence interval 95%)	44.1 (32.7 to 44.1)	37.7 (29.8 to 40.1)		

Notes:

[1] - Some information are not available for analysis

Statistical analyses

Statistical analysis title	log-rank test
Comparison groups	Arm A: standard arm (placebo arm) v Arm B: experimental arm (Vargatef® arm)

Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Logrank

Secondary: Response Rate

End point title	Response Rate
End point description:	
End point type	Secondary
End point timeframe:	
After 2 cycles of NACT	
24 months ?	

End point values	Arm A: standard arm (placebo arm)	Arm B: experimental arm (Vargatef® arm)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	120		
Units: percent				
number (not applicable)	57.1	34.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Best Response

End point title	Best Response
End point description:	
End point type	Secondary
End point timeframe:	
48 months	

End point values	Arm A: standard arm (placebo arm)	Arm B: experimental arm (Vargatef® arm)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	120		
Units: Subjects				
complete response	28	53		
partial response	19	29		
stable	10	28		
progression	0	4		
not evaluable	0	1		
not available	1	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of complete debulking

End point title	Rate of complete debulking
End point description: Complete debulking at IDS (%)	
End point type	Secondary
End point timeframe: 3 to 4 weeks after the last chemotherapy administration.	

End point values	Arm A: standard arm (placebo arm)	Arm B: experimental arm (Vargatef® arm)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	120		
Units: percent				
number (not applicable)				
Complete resection (CCI=0)	78.7	74.3		
No complete resection (CCI=1, 2 or 3)	21.3	25.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Biological progression-free interval (PFibio)

End point title	Biological progression-free interval (PFibio)
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End point description:	
Patients' status at the last contact (%)	
End point type	Secondary
End point timeframe:	
24 months	

End point values	Arm A: standard arm (placebo arm)	Arm B: experimental arm (Vargatef® arm)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	124		
Units: percent				
number (not applicable)				
Alive without progression	55.2	60.0		
CA-125 Progression	44.8	40.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life (FOSI score)

End point title	Quality of Life (FOSI score)
End point description:	
End point type	
Secondary	
End point timeframe:	
24 months	

End point values	Arm A: standard arm (placebo arm)	Arm B: experimental arm (Vargatef® arm)	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	64	124	188	
Units: subjects				
Baseline	62	121	183	
End of neo-adjuvant visit	48	81	129	
End of adjuvant visit	47	74	121	
3 month	39	65	104	
6 month	27	41	68	
9 month	18	32	50	
12 month	17	21	38	
15 month	11	16	27	

18 month	9	12	21	
21 month	8	10	18	
24 month	6	10	16	
End of maintenance visit	28	54	82	

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life (mean FOSI score)

End point title	Quality of Life (mean FOSI score)
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End point description:

End point type	Secondary
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End point timeframe:

24 months

End point values	Arm A: standard arm (placebo arm)	Arm B: experimental arm (Vargatef® arm)	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	64	124	188	
Units: FOSI score				
arithmetic mean (standard deviation)				
Baseline	23.5 (± 4.6)	23 (± 4.7)	23.2 (± 4.6)	
End of neo-adjuvant visit	25 (± 3.6)	24.2 (± 4.4)	24.5 (± 4.1)	
End of adjuvant visit	25 (± 3.5)	23.3 (± 4.8)	24 (± 4.4)	
3 month	25.9 (± 3.5)	23.5 (± 4.9)	24.4 (± 4.5)	
6 month	23.8 (± 5.5)	25.4 (± 3.3)	24.8 (± 4.4)	
9 month	24.7 (± 4.4)	24.1 (± 4.0)	24.3 (± 4.1)	
12 month	24.5 (± 4.0)	23.5 (± 4.1)	23.9 (± 4.0)	
15 month	25.2 (± 2.7)	23.8 (± 4.0)	24.3 (± 3.6)	
18 month	24.7 (± 2.7)	24.1 (± 4.2)	24.3 (± 3.6)	
21 month	24.1 (± 3.6)	23 (± 3.8)	23.5 (± 3.6)	
24 month	24.1 (± 5.2)	23.2 (± 5.2)	23.5 (± 5.0)	
End of maintenance visit	22.8 (± 4.5)	22.6 (± 5.1)	22.6 (± 4.9)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall trial

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21
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Reporting groups

Reporting group title	Arm A: standard arm (placebo arm)
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Reporting group description:

1. Neoadjuvant therapy (3 cycles)

Vargatef® placebo 200mg bid will be administered twice daily during the first 2 cycles except on day 1 of each cycle (day of chemotherapy). Placebo will not be administered during cycle before surgery (third cycle).

Patients with insufficient tumor response to allow interval debulking surgery after 3 cycles of neoadjuvant therapy will receive 4 cycles of neo-adjuvant therapy. In those patients, placebo will be skipped during cycle preceding surgery (Cycle 4).

Interval Debulking Surgery: will be performed 3 to 4 weeks after the last chemotherapy administration.

3. Adjuvant therapy: will start 4 weeks after surgery and after complete surgical wound healing

4. Maintenance therapy: Placebo 200mg bid will be administered during 2 years or until disease progression which ever occur first.

Reporting group title	Arm B: experimental arm (Vargatef® arm)
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Reporting group description:

1. Neo-adjuvant therapy (3 cycles):

Vargatef® (Nintedanib) 200mg bid will be administered twice daily during the first 2 cycles except on day 1 of each cycle (day of chemotherapy). Vargatef® (Nintedanib) will not be administered during cycle before surgery (cycle 3).

Patients with insufficient tumor response to allow interval debulking surgery after 3 cycles of neoadjuvant therapy will receive 4 cycles of neo-adjuvant therapy. In those patients, Vargatef® (Nintedanib) will be skipped during cycle preceding surgery (Cycle 4).

2. Interval Debulking Surgery: will be performed 3 to 4 weeks after the last chemotherapy administration.

3. Adjuvant therapy: will start 4 weeks after surgery and after complete surgical wound healing

4. Maintenance therapy: Vargatef® (Nintedanib) 200 mg bid will be administered during 2 years or until disease progression which ever occur first.

Serious adverse events	Arm A: standard arm (placebo arm)	Arm B: experimental arm (Vargatef® arm)	
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 64 (51.56%)	70 / 124 (56.45%)	
number of deaths (all causes)	1	5	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Left breast cancer			
subjects affected / exposed	1 / 64 (1.56%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Second malignancy			
subjects affected / exposed	1 / 64 (1.56%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep veinous thrombosis			
subjects affected / exposed	0 / 64 (0.00%)	2 / 124 (1.61%)	
occurrences causally related to treatment / all	0 / 0	3 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 64 (0.00%)	2 / 124 (1.61%)	
occurrences causally related to treatment / all	0 / 0	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammatory compressif lymphocele			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative compressive lymphocele			
subjects affected / exposed	1 / 64 (1.56%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected lymphocele			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right jugular vein thrombosis extending to right lateral sinus			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	3 / 9	
deaths causally related to treatment / all	0 / 0	0 / 9	
Right sural thrombo phlebitis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Upper venous thrombosis subjects affected / exposed	2 / 64 (3.13%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Ureteral stent removal subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenectomy subjects affected / exposed	1 / 64 (1.56%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary compression subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma closure subjects affected / exposed	0 / 64 (0.00%)	2 / 124 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileostomy closure subjects affected / exposed	1 / 64 (1.56%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small bowel anastomosis subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Alteration of general health subjects affected / exposed	0 / 64 (0.00%)	3 / 124 (2.42%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Deterioration of the general status subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease evolution subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extravasation subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever subjects affected / exposed	1 / 64 (1.56%)	3 / 124 (2.42%)	
occurrences causally related to treatment / all	2 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAC infection subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders Erythroderma subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Allergic reaction to taxol subjects affected / exposed	1 / 64 (1.56%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders Dyspnea subjects affected / exposed	1 / 64 (1.56%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary embolism			
subjects affected / exposed	3 / 64 (4.69%)	10 / 124 (8.06%)	
occurrences causally related to treatment / all	6 / 9	12 / 27	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	5 / 7	
deaths causally related to treatment / all	0 / 0	3 / 3	
Pneumonitis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 64 (1.56%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax post pleural puncture			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right pleural effusion			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic pain			
subjects affected / exposed	1 / 64 (1.56%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Manic episode			

subjects affected / exposed	1 / 64 (1.56%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Gamma GT increased			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic toxicity			
subjects affected / exposed	0 / 64 (0.00%)	2 / 124 (1.61%)	
occurrences causally related to treatment / all	0 / 0	7 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Increase transaminitis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver enzyme elevation			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
PAC infection			
subjects affected / exposed	0 / 64 (0.00%)	3 / 124 (2.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Intraperitoneal effusion			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipomatous hypertrophy of the interatrial septum			

subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Bilateral peripheral motor and sensitive deficit of upper limb			
subjects affected / exposed	1 / 64 (1.56%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional syndroma			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain metastasis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right vulnar nerve surgery			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suspicion of limbic encephalitis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Abdominal lymphocel			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anemia			
subjects affected / exposed	1 / 64 (1.56%)	4 / 124 (3.23%)	
occurrences causally related to treatment / all	1 / 3	9 / 14	
deaths causally related to treatment / all	0 / 1	0 / 0	

Aplasia : Neutropenia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile aplasia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 64 (0.00%)	4 / 124 (3.23%)	
occurrences causally related to treatment / all	0 / 0	9 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hematologic toxicity			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocele			
subjects affected / exposed	2 / 64 (3.13%)	3 / 124 (2.42%)	
occurrences causally related to treatment / all	0 / 6	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocele chyleux			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 64 (0.00%)	3 / 124 (2.42%)	
occurrences causally related to treatment / all	0 / 0	13 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet decreased			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	11 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			

subjects affected / exposed	2 / 64 (3.13%)	4 / 124 (3.23%)	
occurrences causally related to treatment / all	3 / 6	13 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 64 (3.13%)	2 / 124 (1.61%)	
occurrences causally related to treatment / all	3 / 6	1 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pancreatitis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascitis			
subjects affected / exposed	1 / 64 (1.56%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowel obstruction			
subjects affected / exposed	1 / 64 (1.56%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bridged ileus			
subjects affected / exposed	1 / 64 (1.56%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal fistula after surgery			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 64 (3.13%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	2 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhea			

subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Digestive bleeding			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Digestive occlusion (clamp) after interval debulking surgery			
subjects affected / exposed	1 / 64 (1.56%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disembowelment			
subjects affected / exposed	1 / 64 (1.56%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecal stasis in the transverse colon			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colocutaneous fistula			
subjects affected / exposed	0 / 64 (0.00%)	2 / 124 (1.61%)	
occurrences causally related to treatment / all	0 / 0	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal toxicity			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hematemesis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incomplete bowel obstruction			

subjects affected / exposed	1 / 64 (1.56%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal occlusion			
subjects affected / exposed	1 / 64 (1.56%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra peritoneal effusion			
subjects affected / exposed	1 / 64 (1.56%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left strangulated diaphragmatic hernia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Occlusive syndrome/ Occlusion			
subjects affected / exposed	3 / 64 (4.69%)	10 / 124 (8.06%)	
occurrences causally related to treatment / all	0 / 3	2 / 10	
deaths causally related to treatment / all	0 / 0	0 / 1	
Colonic perforation			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Recurrent digestive occlusion (clamp) after interval debulking surgery			
subjects affected / exposed	1 / 64 (1.56%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Recto vaginal fistula			

subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Severe digestive toxicity status			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sub-occlusion on eventration			
subjects affected / exposed	1 / 64 (1.56%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain syndrome			
subjects affected / exposed	0 / 64 (0.00%)	2 / 124 (1.61%)	
occurrences causally related to treatment / all	0 / 0	4 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumoral abdominal pain			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 64 (0.00%)	3 / 124 (2.42%)	
occurrences causally related to treatment / all	0 / 0	4 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting due to chemotherapy			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic cyolysis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute intrinsic renal failure subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteral dilation subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute renal failure subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ureteral fistula subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Disc herniation subjects affected / exposed	1 / 64 (1.56%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture of the right neck femur subjects affected / exposed	1 / 64 (1.56%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

<p>Infections and infestations</p> <p> Abscess on ileostomy cicatrix</p> <p> subjects affected / exposed</p> <p> occurrences causally related to treatment / all</p> <p> deaths causally related to treatment / all</p>	<p>0 / 64 (0.00%)</p> <p>0 / 0</p> <p>0 / 0</p>	<p>1 / 124 (0.81%)</p> <p>0 / 3</p> <p>0 / 0</p>	
<p>Abscess</p> <p> subjects affected / exposed</p> <p> occurrences causally related to treatment / all</p> <p> deaths causally related to treatment / all</p>	<p>0 / 64 (0.00%)</p> <p>0 / 0</p> <p>0 / 0</p>	<p>1 / 124 (0.81%)</p> <p>0 / 6</p> <p>0 / 0</p>	
<p>Bronchial infection</p> <p> subjects affected / exposed</p> <p> occurrences causally related to treatment / all</p> <p> deaths causally related to treatment / all</p>	<p>1 / 64 (1.56%)</p> <p>3 / 3</p> <p>0 / 0</p>	<p>0 / 124 (0.00%)</p> <p>0 / 0</p> <p>0 / 0</p>	
<p>Pelvic abscess</p> <p> subjects affected / exposed</p> <p> occurrences causally related to treatment / all</p> <p> deaths causally related to treatment / all</p>	<p>0 / 64 (0.00%)</p> <p>0 / 0</p> <p>0 / 0</p>	<p>1 / 124 (0.81%)</p> <p>1 / 3</p> <p>0 / 0</p>	
<p>Pneumonia</p> <p> subjects affected / exposed</p> <p> occurrences causally related to treatment / all</p> <p> deaths causally related to treatment / all</p>	<p>0 / 64 (0.00%)</p> <p>0 / 0</p> <p>0 / 0</p>	<p>1 / 124 (0.81%)</p> <p>5 / 7</p> <p>3 / 3</p>	
<p>Pyelonephritis</p> <p> subjects affected / exposed</p> <p> occurrences causally related to treatment / all</p> <p> deaths causally related to treatment / all</p>	<p>0 / 64 (0.00%)</p> <p>0 / 0</p> <p>0 / 0</p>	<p>1 / 124 (0.81%)</p> <p>0 / 3</p> <p>0 / 0</p>	
<p>Right lung infection</p> <p> subjects affected / exposed</p> <p> occurrences causally related to treatment / all</p> <p> deaths causally related to treatment / all</p>	<p>0 / 64 (0.00%)</p> <p>0 / 0</p> <p>0 / 0</p>	<p>1 / 124 (0.81%)</p> <p>0 / 3</p> <p>0 / 0</p>	
<p>Sepsis</p> <p> subjects affected / exposed</p> <p> occurrences causally related to treatment / all</p> <p> deaths causally related to treatment / all</p>	<p>1 / 64 (1.56%)</p> <p>2 / 3</p> <p>0 / 0</p>	<p>0 / 124 (0.00%)</p> <p>0 / 0</p> <p>0 / 0</p>	
<p>Sepsis of unknown origin</p>			

subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock associated with pneumonitis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Severe sepsis related to Staphylococcus aurea in febrile neutropenia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcus infection			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Denutrition			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deshydration			
subjects affected / exposed	0 / 64 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deshydration due to ileostomy			
subjects affected / exposed	1 / 64 (1.56%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalemia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hyponatremia			
subjects affected / exposed	0 / 64 (0.00%)	2 / 124 (1.61%)	
occurrences causally related to treatment / all	0 / 0	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A: standard arm (placebo arm)	Arm B: experimental arm (Vargatef® arm)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	62 / 64 (96.88%)	124 / 124 (100.00%)	
Injury, poisoning and procedural complications			
Alopecia			
subjects affected / exposed	44 / 64 (68.75%)	72 / 124 (58.06%)	
occurrences (all)	44	72	
Ungual toxicity			
subjects affected / exposed	1 / 64 (1.56%)	2 / 124 (1.61%)	
occurrences (all)	1	2	
Vascular disorders			
Thrombo-embolism			
subjects affected / exposed	3 / 64 (4.69%)	10 / 124 (8.06%)	
occurrences (all)	3	10	
Cardiac disorders			
Arterial hypertention			
subjects affected / exposed	18 / 64 (28.13%)	40 / 124 (32.26%)	
occurrences (all)	18	40	
Nervous system disorders			
Motor neuropathy			
subjects affected / exposed	7 / 64 (10.94%)	14 / 124 (11.29%)	
occurrences (all)	7	14	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	28 / 64 (43.75%)	50 / 124 (40.32%)	
occurrences (all)	28	50	
Neutropenia			

subjects affected / exposed	29 / 64 (45.31%)	68 / 124 (54.84%)	
occurrences (all)	29	68	
Lymphopenia			
subjects affected / exposed	20 / 64 (31.25%)	28 / 124 (22.58%)	
occurrences (all)	20	28	
Anaemia			
subjects affected / exposed	40 / 64 (62.50%)	94 / 124 (75.81%)	
occurrences (all)	40	94	
Thrombopenia			
subjects affected / exposed	16 / 64 (25.00%)	65 / 124 (52.42%)	
occurrences (all)	16	65	
Febrile neutropenia			
subjects affected / exposed	1 / 64 (1.56%)	6 / 124 (4.84%)	
occurrences (all)	1	6	
Haemorrhage			
subjects affected / exposed	3 / 64 (4.69%)	13 / 124 (10.48%)	
occurrences (all)	3	13	
Oedema			
subjects affected / exposed	5 / 64 (7.81%)	13 / 124 (10.48%)	
occurrences (all)	5	13	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	45 / 64 (70.31%)	91 / 124 (73.39%)	
occurrences (all)	45	91	
Nausea			
subjects affected / exposed	30 / 64 (46.88%)	75 / 124 (60.48%)	
occurrences (all)	30	75	
Fever			
subjects affected / exposed	6 / 64 (9.38%)	12 / 124 (9.68%)	
occurrences (all)	6	12	
Paraesthesia - Dysesthesia			
subjects affected / exposed	27 / 64 (42.19%)	26 / 124 (20.97%)	
occurrences (all)	27	26	
Fistula			

subjects affected / exposed occurrences (all)	1 / 64 (1.56%) 1	1 / 124 (0.81%) 1	
Pain subjects affected / exposed occurrences (all)	38 / 64 (59.38%) 38	70 / 124 (56.45%) 70	
Gastrointestinal disorders			
Vomiting subjects affected / exposed occurrences (all)	13 / 64 (20.31%) 13	36 / 124 (29.03%) 36	
Constipation subjects affected / exposed occurrences (all)	24 / 64 (37.50%) 24	21 / 124 (16.94%) 21	
Diarrhoea subjects affected / exposed occurrences (all)	15 / 64 (23.44%) 15	78 / 124 (62.90%) 78	
Digestive perforation subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0	2 / 124 (1.61%) 2	
Digestive Fistula subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0	1 / 124 (0.81%) 1	
Skin and subcutaneous tissue disorders			
Hand-foot syndrome subjects affected / exposed occurrences (all)	3 / 64 (4.69%) 3	3 / 124 (2.42%) 3	
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	11 / 64 (17.19%) 11	21 / 124 (16.94%) 21	
Myalgia subjects affected / exposed occurrences (all)	9 / 64 (14.06%) 9	6 / 124 (4.84%) 6	
Infections and infestations			
Oral Mucositis subjects affected / exposed occurrences (all)	7 / 64 (10.94%) 7	11 / 124 (8.87%) 11	

Mucositis			
subjects affected / exposed	0 / 64 (0.00%)	2 / 124 (1.61%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 August 2012	substantial modifications
04 September 2012	substantial modifications
11 December 2012	substantial modifications
16 April 2013	substantial modifications
11 June 2013	substantial modifications
03 October 2013	substantial modifications
18 July 2014	substantial modifications
05 November 2014	substantial modifications
08 December 2014	substantial modifications
16 July 2015	substantial modifications
30 September 2015	substantial modifications
10 November 2015	substantial modifications
19 January 2016	substantial modifications
11 January 2017	substantial modifications

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported