Clinical trial results:
A randomized phase II trial assessing Sorafenib (Nexavar®) in combination with irinotecan in metastatic colorectal cancer patients with KRAS mutated tumours after failure of all active drugs known to be effective.

Summary

EudraCT number	2012-000644-94
Trial protocol	FR
Global end of trial date	28 July 2019

Results information

Result version number	v1 (current)
This version publication date	21 April 2023
First version publication date	21 April 2023

Trial information

Trial identification

Sponsor protocol code	VA_2012/01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01715441
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	INSTITUT REGIONAL DU CANCER DE MONTPELLIER Cancer de Montpellier
Sponsor organisation address	208 Rue des Apothicaires, Montpellier, France, 34298
Public contact	Madame Aurore MOUSSION, Institut régional du Cancer de Montpellier (ICM), 33 04 67 61 31 02, aurore.moussion@icm.unicancer.fr
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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	09 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 December 2016
Global end of trial reached?	Yes
Global end of trial date	28 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the median progression free survival defined as the time from randomization to disease progression according to RECIST criteria (Version 1.1) or death from any cause

Protection of trial subjects:

In order to ensure the protection of the rights, safety and well-being of trial subjects, this clinical trial was performed in compliance with the principles laid down in the declaration of Helsinki, good Clinical Practice and European regulation.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 September 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 173
Worldwide total number of subjects	173
EEA total number of subjects	173

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)	109

From 65 to 84 years	64
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Baseline evaluations were performed for all patients prior to randomization to determine study eligibility.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	NEXIRI

Arm description:

Nexavar + Irinotecan

Arm type	Experimental
Investigational medicinal product name	NEXAVAR
Investigational medicinal product code	SORAFENIB
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

400 mg twice daily (total dose 800 mg/day).

Investigational medicinal product name	IRINOTECAN
Investigational medicinal product code	IRINOTECAN
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Intravenous infusion irinotecan 120 mg/m2 over 90 minutes (D1=D15) at Cycle 1, 150 mg/m² at C2 if no diarrhea > grade 1 and no other
toxicity > grade 2, and 180 mg/m² at C3 in the same conditions.
1 course = 15 days and 1 cycle = 4 weeks.

Arm title	IRINOTECAN

Arm description:

Irinotecan alone

Arm type	Active comparator
Investigational medicinal product name	IRINOTECAN
Investigational medicinal product code	IRINOTECAN
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Intravenous infusion irinotecan 180 mg/m2 over 90 minutes (D1=D15) with cross over to irinotecan and sorafenib combination at progression.

Arm title	SORAFENIB

Arm description:	
Sorafenib alone	
Arm type	Active comparator
Investigational medicinal product name	NEXAVAR
Investigational medicinal product code	SORAFENIB
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Oral sorafenib 400 mg twice daily (total dose 800 mg/day) with cross over to irinotecan and sorafenib combination at progression.

Number of subjects in period 1	NEXIRI	IRINOTECAN	SORAFENIB
Started	59	57	57
Completed	59	57	57

Baseline characteristics

Reporting groups	
Reporting group title	NEXIRI
Reporting group description: Nexavar + Irinotecan	
Reporting group title	IRINOTECAN
Reporting group description: Irinotecan alone	
Reporting group title	SORAFENIB
Reporting group description: Sorafenib alone	

Reporting group values	NEXIRI	IRINOTECAN	SORAFENIB
Number of subjects	59	57	57
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	63	62	60
full range (min-max)	35 to 81	35 to 77	31 to 82
Gender categorical Units: Subjects			
Female	24	26	23
Male	35	31	34
Clinical exam Units: Subjects			
Normal	44	41	43
Abnormal	15	14	14
Missing	0	2	0
pT Classification Units: Subjects			
Tx	15	8	11
T1	2	0	0
T2	4	1	4
T3	22	33	27
T4a-T4b	16	15	15
pN Classification			

Units: Subjects			
Nx	14	8	11
N0	12	6	11
N1a-1b	19	20	15
N2a-2b	14	23	20
pM Classification Units: Subjects			
M0	0	1	0
M1	59	56	57
Synchronous metastasis Units: Subjects			
NO	19	21	19
YES	40	36	38
Histologic type Units: Subjects			
Well or moderately differenciated adenocarcinoma	49	48	49
Poorly or undifferenciated adenocarcinoma	3	2	3
adenocarcinoma with unspecified differentiation	5	3	1
colloidal mucosal adenocarcinoma	2	3	3
Missing	0	1	1
WHO Units: Subjects			
OMS 0	26	18	21
OMS 1	32	37	36
OMS 2	0	1	0
Missing	1	1	0
Clinic exam Units: Subjects			
Normal	44	41	43
Abnormal	15	14	14
Missing	0	2	0
Body Mass Index Units: Subjects			
Underweight range	7	3	3
Healthy weight range	24	29	26
Overweight range	26	24	24
Obese range	1	1	2
Missing	1	0	2
History Units: Subjects			
No	18	20	25
Yes	41	37	32
Initial symptoms Units: Subjects			
No	24	15	16
Yes	35	42	41
Maximal grade symptom Units: Subjects			
Grade 0	24	15	16

Grade 1	20	14	17
Grade 2	11	23	19
Grade 3	4	5	5
Concomitant treatment for symptom Units: Subjects			
No	18	16	24
Yes	17	26	17
Not applicable	24	15	16
Primary tumor location Units: Subjects			
Left colon	34	23	26
Right colon	25	23	19
Other	0	11	12
Metastasis Units: Subjects			
Synchronous	40	36	40
Metachronous	19	21	17
Previous adjuvant chemotherapy Units: Subjects			
Adjuvant chemotherapy	29	29	27
No adjuvant chemotherapy	30	28	30
Previous palliative chemotherapy Units: Subjects			
Palliative line	52	51	52
No palliative line	7	6	5
Ras mutation location Units: Subjects			
Kras	50	51	51
Nras	2	1	0
Location not done	7	5	6
Ras mutation location by exon Units: Subjects			
KRAS : exon 2	49	50	49
KRAS : exon 3	0	1	2
RAS : exon 4	1	0	0
NRAS : exon 2	1	1	0
NRAS : exon 3	1	0	0
Location not done	7	5	6
Weight Units: kilogram(s)			
median	70.5	68.5	70.5
full range (min-max)	42 to 110	43.8 to 107	45 to 112
Height Units: centimetre			
median	169	170	170.5
full range (min-max)	153 to 183	145 to 195	152 to 186
Body surface area Units: square metre			
median	1.79	1.79	1.85
full range (min-max)	1.39 to 2.21	1.32 to 2.19	1.41 to 2.29

Reporting group values	Total		
Number of subjects	173		
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			
full range (min-max)	-		
Gender categorical Units: Subjects			
Female	73		
Male	100		
Clinical exam Units: Subjects			
Normal	128		
Abnormal	43		
Missing	2		
pT Classification Units: Subjects			
Tx	34		
T1	2		
T2	9		
T3	82		
T4a-T4b	46		
pN Classification Units: Subjects			
Nx	33		
N0	29		
N1a-1b	54		
N2a-2b	57		
pM Classification Units: Subjects			
M0	1		
M1	172		
Synchronous metastasis Units: Subjects			
NO	59		
YES	114		
Histologic type Units: Subjects			

Well or moderately differenciated adenocarcinoma	146		
Poorly or undifferenciated adenocarcinoma	8		
adenocarcinoma with unspecified differentiation	9		
colloidal mucosal adenocarcinoma	8		
Missing	2		
WHO Units: Subjects			
OMS 0	65		
OMS 1	105		
OMS 2	1		
Missing	2		
Clinic exam Units: Subjects			
Normal	128		
Abnormal	43		
Missing	2		
Body Mass Index Units: Subjects			
Underweight range	13		
Healthy weight range	79		
Overweight range	74		
Obese range	4		
Missing	3		
History Units: Subjects			
No	63		
Yes	110		
Initial symptoms Units: Subjects			
No	55		
Yes	118		
Maximal grade symptom Units: Subjects			
Grade 0	55		
Grade 1	51		
Grade 2	53		
Grade 3	14		
Concomitant treatment for symptom Units: Subjects			
No	58		
Yes	60		
Not applicable	55		
Primary tumor location Units: Subjects			
Left colon	83		
Right colon	67		
Other	23		
Metastasis Units: Subjects			

Synchronous	116		
Metachronous	57		
Previous adjuvant chemotherapy Units: Subjects			
Adjuvant chemotherapy	85		
No adjuvant chemotherapy	88		
Previous palliative chemotherapy Units: Subjects			
Palliative line	155		
No palliative line	18		
Ras mutation location Units: Subjects			
Kras	152		
Nras	3		
Location not done	18		
Ras mutation location by exon Units: Subjects			
KRAS : exon 2	148		
KRAS : exon 3	3		
RAS : exon 4	1		
NRAS : exon 2	2		
NRAS : exon 3	1		
Location not done	18		
Weight Units: kilogram(s) median full range (min-max)	- -		
Height Units: centimetre median full range (min-max)	- -		
Body surface area Units: square metre median full range (min-max)	- -		

End points

End points reporting groups

Reporting group title	NEXIRI
Reporting group description: Nexavar + Irinotecan	
Reporting group title	IRINOTECAN
Reporting group description: Irinotecan alone	
Reporting group title	SORAFENIB
Reporting group description: Sorafenib alone	
Subject analysis set title	Efficacy ARM A
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: All randomized patients who started chemotherapy treatment, assigned to the arm where they were actually treated.	
Subject analysis set title	Global survival ARM A
Subject analysis set type	Intention-to-treat
Subject analysis set description: All patients randomized and counted in the treatment arm in which they were randomized.	
Subject analysis set title	Tolerance
Subject analysis set type	Intention-to-treat
Subject analysis set description: All patients randomized and counted in the treatment arm in which they were randomized.	
Subject analysis set title	Efficacy ARM B
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: All randomized patients who started chemotherapy treatment, assigned to the arm where they were actually treated.	
Subject analysis set title	Efficacy ARM C
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: All patients randomized and counted in the treatment arm in which they were randomized.	
Subject analysis set title	Efficacy after crossover (ARM B + ARM C)
Subject analysis set type	Intention-to-treat
Subject analysis set description: All patients randomized and counted in the treatment arm in which they were randomized.	
Subject analysis set title	Global survival ARM B
Subject analysis set type	Intention-to-treat
Subject analysis set description: All patients randomized and counted in the treatment arm in which they were randomized.	
Subject analysis set title	Global survival ARM C
Subject analysis set type	Intention-to-treat
Subject analysis set description: All patients randomized and counted in the treatment arm in which they were randomized.	
Subject analysis set title	Progression-free survival ARM A
Subject analysis set type	Intention-to-treat
Subject analysis set description: All patients randomized and counted in the treatment arm in which they were randomized.	
Subject analysis set title	Progression-free survival ARM B

Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients randomized and counted in the treatment arm in which they were randomized.

Subject analysis set title	Progression-free survival ARM C
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients randomized and counted in the treatment arm in which they were randomized.

Primary: Non-progression rate

End point title	Non-progression rate[1]

End point description:

End point type	Primary

End point timeframe:

2 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was performed for endpoints.

End point values	Efficacy ARM A	Efficacy ARM B	Efficacy ARM C	Efficacy after crossover (ARM B + ARM C)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	57	56	57	69
Units: percent				
number (not applicable)	52.6	21.4	19.3	42

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate

End point title	Disease control rate

End point description:

End point type	Secondary

End point timeframe:

Overall treatment

End point values	Efficacy ARM A	Efficacy ARM B	Efficacy ARM C	Efficacy after crossover (ARM B + ARM C)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	57	56	57	69
Units: percent				
number (not applicable)	50.9	23.2	19.3	42

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

End point type	Secondary

End point timeframe:

Overall study

End point values	Progression-free survival ARM A	Progression-free survival ARM B	Progression-free survival ARM C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	59	57	57	
Units: month				
median (confidence interval 95%)	3.6 (2 to 4.2)	1.7 (1.7 to 1.8)	2 (1.8 to 2.3)	

Attachments (see zip file)	Progression-free survival curve/SURVIE SANS PROGRESSION. Kaplan-Meier curve/KAPLAN-MEIER.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Global survival

End point title	Global survival

End point description:

End point type	Secondary

End point timeframe:

Overall study

End point values	Global survival ARM A	Global survival ARM B	Global survival ARM C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	59	57	57	
Units: Months				
median (confidence interval 95%)	7.2 (6 to 9)	6.3 (5 to 8)	5.6 (4 to 8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Median irinotecan relative dose-intensity

End point title	Median irinotecan relative dose-intensity[2]

End point description:

End point type	Secondary

End point timeframe:

During chemotherapy

Notes:

[2] - 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: No statistical analysis was performed for endpoints.

End point values	NEXIRI	IRINOTECAN		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	57		
Units: percent				
median (confidence interval 95%)	76.3 (48 to 103)	101.8 (51 to 108)		

Statistical analyses

No statistical analyses for this end point

Secondary: Median Sorafenib relative dose-intensity

End point title	Median Sorafenib relative dose-intensity[3]

End point description:

End point type	Secondary

End point timeframe:

During Chemotherapy

Notes:

[3] - 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: No statistical analysis was performed for endpoints.

End point values	NEXIRI	SORAFENIB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	57		
Units: percent				
median (confidence interval 95%)	74.6 (21 to 118)	77.7 (26 to 101)		

Statistical analyses

No statistical analyses for this end point

Secondary: Grade 3-4 adverse events of any kind

End point title	Grade 3-4 adverse events of any kind

End point description:

End point type	Secondary

End point timeframe:

During chemotherapy

End point values	NEXIRI	IRINOTECAN	SORAFENIB	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	56	57	
Units: Subjects				
Grade 3-4 adverse events of any kind	48	33	48	
No grade 3-4 adverse events of any kind	9	23	9	

Statistical analyses

No statistical analyses for this end point

Secondary: Grade 3-4 gastrointestinal adverse events

End point title	Grade 3-4 gastrointestinal adverse events

End point description:

End point type	Secondary

End point timeframe:

During chemotherapy

End point values	NEXIRI	IRINOTECAN	SORAFENIB	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	56	57	
Units: Subjects				
Grade 3-4 gastrointestinal adverse events	20	7	13	
No Grade 3-4 gastrointestinal adverse events	37	49	44	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Progression-free survival according to genotype of cycline D1

End point title	Progression-free survival according to genotype of cycline D1

End point description:

End point type	Other pre-specified

End point timeframe:

Overall study

End point values	Progression-free survival ARM A	Progression-free survival ARM B	Progression-free survival ARM C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	45	45	40	
Units: months				
median (confidence interval 95%)				
Cycline D1 polymorphism A/A	5.3 (1.6 to 5.7)	1.7 (0.8 to 2.0)	1.9 (1.6 to 3.9)	
Cycline D1 polymorphism other than A/A	3.1 (1.9 to 4.9)	1.7 (1.6 to 1.8)	1.9 (1.7 to 2.1)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Global survival according to genotype of Cycline D1

End point title	Global survival according to genotype of Cycline D1

End point description:

End point type	Other pre-specified

End point timeframe:

Overall study

End point values	Global survival ARM A	Global survival ARM B	Global survival ARM C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	45	45	40	
Units: Months				
median (confidence interval 95%)				
Cycline D1 polymorphism A/A	19.6 (4.8 to 19.6)	9 (1.4 to 11.7)	8.1 (3.0 to 13.9)	
Cycline D1 polymorphism other than A/A	7 (5.0 to 9.4)	6.2 (3.8 to 7.7)	4.4 (3.6 to 7.5)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During treatment then until 6 months after the end of treatment.

Adverse event reporting additional description:

Analyses are performed on randomized patients who started chemotherapy treatment. Therefore, three patients who did not receive any treatment (chemotherapy) are excluded.
Each patient is assigned to the treatment arm actually received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	4

Reporting groups

Reporting group title	ARM A : NEXIRI

Reporting group description:

Patients who were randomized in the ARM A and having received experimental treatment by NEXIRI (Nexavar + Irinotécan).

Reporting group title	ARM B : IRINOTECAN

Reporting group description:

Patients randomized in the ARM B, Sorafenib alone.

Reporting group title	ARM C: SORAFENIB

Reporting group description:

Patients randomized in the ARM C, Sorafenib alone.

Reporting group title	CROSSOVER from ARM B, C to NEXIRI

Reporting group description:

The trial provides for crossover at tumor progression (documented on a TAP scan) for patients randomized to the two "monotherapy" arms.
They will then receive the combination of Sorafenib and Irinotecan (NEXIRI).

Serious adverse events	ARM A : NEXIRI	ARM B : IRINOTECAN	ARM C: SORAFENIB
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 57 (40.35%)	17 / 56 (30.36%)	26 / 57 (45.61%)
number of deaths (all causes)	8	7	13
number of deaths resulting from adverse events	4	5	11
Vascular disorders			
Vena cava thrombosis			
subjects affected / exposed	0 / 57 (0.00%)	0 / 56 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ruptured aneurysm			

subjects affected / exposed	0 / 57 (0.00%)	0 / 56 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Surgical and medical procedures			
Vertebra dorsal fracture			
subjects affected / exposed	0 / 57 (0.00%)	0 / 56 (0.00%)	1 / 57 (1.75%)
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			
Fever			
subjects affected / exposed	2 / 57 (3.51%)	1 / 56 (1.79%)	3 / 57 (5.26%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumoral fever			
subjects affected / exposed	0 / 57 (0.00%)	0 / 56 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious fever			
subjects affected / exposed	0 / 57 (0.00%)	0 / 56 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	3 / 57 (5.26%)	0 / 56 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Hyperthermia with urinary pain			
subjects affected / exposed	0 / 57 (0.00%)	0 / 56 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Severe pain			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

General disorder			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General Health status deterioration			
subjects affected / exposed	1 / 57 (1.75%)	2 / 56 (3.57%)	2 / 57 (3.51%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 2
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 57 (0.00%)	0 / 56 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	2 / 57 (3.51%)	0 / 56 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Lung Embolism			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Pleural effusion			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	0 / 57 (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
Dyspnoea			
subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Psychiatric disorders			
Depression			

subjects affected / exposed	0 / 57 (0.00%)	0 / 56 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Febrile neutropenia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac ischemia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 56 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardic infarction			
subjects affected / exposed	0 / 57 (0.00%)	0 / 56 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiovascular ischemia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiopulmonary arrest			
subjects affected / exposed	0 / 57 (0.00%)	0 / 56 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Neurological disorder			
subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	0 / 57 (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
Sciatica			
subjects affected / exposed	0 / 57 (0.00%)	0 / 56 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	2 / 57 (3.51%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	0 / 57 (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
Nausea and vomiting			
subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Vomiting			
subjects affected / exposed	0 / 57 (0.00%)	0 / 56 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation and vomiting			
subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	0 / 57 (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
Diarrhoea			
subjects affected / exposed	2 / 57 (3.51%)	0 / 56 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon perforation			
subjects affected / exposed	0 / 57 (0.00%)	0 / 56 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 11	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			

subjects affected / exposed	0 / 57 (0.00%)	0 / 56 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
icterus			
subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	0 / 57 (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
Subocclusion			
subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	0 / 57 (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
Cholecystitis			
subjects affected / exposed	0 / 57 (0.00%)	0 / 56 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholestatic icterus			
subjects affected / exposed	0 / 57 (0.00%)	0 / 56 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic encephalopathy			
subjects affected / exposed	0 / 57 (0.00%)	0 / 56 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Epigastric pain			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	0 / 57 (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
Rectal haemorrhage			
subjects affected / exposed	0 / 57 (0.00%)	0 / 56 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bilirubinuria			

subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholinergic syndrome			
subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	0 / 57 (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
Transaminases increased			
subjects affected / exposed	0 / 57 (0.00%)	0 / 56 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Anal fissure			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	0 / 57 (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
Recto bladder fistula			
subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	0 / 57 (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
Occlusive syndrome			
subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	0 / 57 (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
Skin and subcutaneous tissue disorders			
Toxic epidermal necrolysis			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Degradation of scar ileostomy			
subjects affected / exposed	0 / 57 (0.00%)	0 / 56 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Urinary infection with fever			
subjects affected / exposed	0 / 57 (0.00%)	0 / 56 (0.00%)	11 / 57 (19.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dilatation of the renal calyx			
subjects affected / exposed	0 / 57 (0.00%)	0 / 56 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrostomy tube disconnection			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	0 / 57 (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
Uretero hydronephrosis			
subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	0 / 57 (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			
Bone pain			
subjects affected / exposed	0 / 57 (0.00%)	0 / 56 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint pain			
subjects affected / exposed	0 / 57 (0.00%)	0 / 56 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 57 (1.75%)	2 / 56 (3.57%)	2 / 57 (3.51%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 2
Metabolism and nutrition disorders			
Hyperglycaemia			

subjects affected / exposed	0 / 57 (0.00%)	0 / 56 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	0 / 57 (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
Anaemia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 56 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 57 (0.00%)	0 / 56 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	CROSSOVER from ARM B, C to NEXIRI		
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 69 (24.64%)		
number of deaths (all causes)	11		
number of deaths resulting from adverse events	7		
Vascular disorders			
Vena cava thrombosis			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ruptured aneurysm			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Vertebra dorsal fracture			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

General disorders and administration site conditions			
Fever			
subjects affected / exposed	3 / 69 (4.35%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Tumoral fever			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infectious fever			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Asthenia			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperthermia with urinary pain			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Severe pain			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorder			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General Health status deterioration			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		

Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lung Embolism			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Febrile neutropenia			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac ischemia			

subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardic infarction			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiovascular ischemia			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiopulmonary arrest			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Neurological disorder			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sciatica			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nausea and vomiting			

subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Constipation and vomiting				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colon perforation				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic failure				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
icterus				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subocclusion				

subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholestatic icterus				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic encephalopathy				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Epigastric pain				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bilirubinuria				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholinergic syndrome				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Transaminases increased				

subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 1			
Anal fissure				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Recto bladder fistula				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Occlusive syndrome				
subjects affected / exposed	2 / 69 (2.90%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Skin and subcutaneous tissue disorders				
Toxic epidermal necrolysis				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Degradation of scar ileostomy				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Urinary infection with fever				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dilatation of the renal calyx				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nephrostomy tube disconnection				

subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Uretero hydronephrosis				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Bone pain				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Joint pain				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Sepsis				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Hyperglycaemia				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypercalcaemia				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anaemia				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			

Dehydration			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	ARM A : NEXIRI	ARM B : IRINOTECAN	ARM C: SORAFENIB
Total subjects affected by non-serious adverse events			
subjects affected / exposed	57 / 57 (100.00%)	56 / 56 (100.00%)	57 / 57 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	9 / 57 (15.79%)	2 / 56 (3.57%)	11 / 57 (19.30%)
occurrences (all)	19	2	17
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	52 / 57 (91.23%)	43 / 56 (76.79%)	43 / 57 (75.44%)
occurrences (all)	204	90	73
Fever			
subjects affected / exposed	8 / 57 (14.04%)	12 / 56 (21.43%)	13 / 57 (22.81%)
occurrences (all)	9	18	15
Limbs oedema			
subjects affected / exposed	2 / 57 (3.51%)	2 / 56 (3.57%)	5 / 57 (8.77%)
occurrences (all)	2	3	6
Weight decreased			
subjects affected / exposed	22 / 57 (38.60%)	10 / 56 (17.86%)	16 / 57 (28.07%)
occurrences (all)	51	16	22
Pain			
subjects affected / exposed	38 / 57 (66.67%)	30 / 56 (53.57%)	35 / 57 (61.40%)
occurrences (all)	18	53	62
Immune system disorders			
Allergic reaction			
subjects affected / exposed	2 / 57 (3.51%)	0 / 56 (0.00%)	1 / 57 (1.75%)
occurrences (all)	2	0	1
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	12 / 57 (21.05%)	5 / 56 (8.93%)	11 / 57 (19.30%)
occurrences (all)	28	11	13
Post nasal discharge			
subjects affected / exposed	6 / 57 (10.53%)	7 / 56 (12.50%)	4 / 57 (7.02%)
occurrences (all)	19	18	7
Epistaxis			
subjects affected / exposed	10 / 57 (17.54%)	4 / 56 (7.14%)	5 / 57 (8.77%)
occurrences (all)	26	7	7
Lung oedema			
subjects affected / exposed	0 / 57 (0.00%)	0 / 56 (0.00%)	0 / 57 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	14 / 57 (24.56%)	15 / 56 (26.79%)	6 / 57 (10.53%)
occurrences (all)	29	24	9
Psychiatric disorders			
Insomnia			
subjects affected / exposed	7 / 57 (12.28%)	7 / 56 (12.50%)	4 / 57 (7.02%)
occurrences (all)	14	13	5
Investigations			
Amylase increased			
subjects affected / exposed	11 / 57 (19.30%)	10 / 56 (17.86%)	8 / 57 (14.04%)
occurrences (all)	19	11	8
Lipase increased			
subjects affected / exposed	14 / 57 (24.56%)	8 / 56 (14.29%)	10 / 57 (17.54%)
occurrences (all)	30	13	12
White blood cell count decreased			
subjects affected / exposed	23 / 57 (40.35%)	12 / 56 (21.43%)	6 / 57 (10.53%)
occurrences (all)	53	17	7
Neutrophil count decreased			
subjects affected / exposed	25 / 57 (43.86%)	14 / 56 (25.00%)	5 / 57 (8.77%)
occurrences (all)	50	18	6
Platelet count decreased			
subjects affected / exposed	21 / 57 (36.84%)	14 / 56 (25.00%)	14 / 57 (24.56%)
occurrences (all)	45	30	20
Cardiac disorders			

Prolonged QTc			
subjects affected / exposed	1 / 57 (1.75%)	1 / 56 (1.79%)	0 / 57 (0.00%)
occurrences (all)	1	1	0
Thromboembolic event			
subjects affected / exposed	0 / 57 (0.00%)	0 / 56 (0.00%)	2 / 57 (3.51%)
occurrences (all)	0	0	2
Infarction			
subjects affected / exposed	0 / 57 (0.00%)	0 / 56 (0.00%)	1 / 57 (1.75%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 57 (19.30%)	5 / 56 (8.93%)	4 / 57 (7.02%)
occurrences (all)	26	8	4
Dysgeusia			
subjects affected / exposed	5 / 57 (8.77%)	7 / 56 (12.50%)	3 / 57 (5.26%)
occurrences (all)	8	17	5
Neuropathy peripheral			
subjects affected / exposed	14 / 57 (24.56%)	14 / 56 (25.00%)	12 / 57 (21.05%)
occurrences (all)	33	24	22
Paraesthesia			
subjects affected / exposed	10 / 57 (17.54%)	8 / 56 (14.29%)	6 / 57 (10.53%)
occurrences (all)	17	11	7
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	40 / 57 (70.18%)	37 / 56 (66.07%)	29 / 57 (50.88%)
occurrences (all)	91	65	54
Febrile neutropenia			
subjects affected / exposed	3 / 57 (5.26%)	0 / 56 (0.00%)	0 / 57 (0.00%)
occurrences (all)	3	0	0
Eye disorders			
Vision blurred			
subjects affected / exposed	5 / 57 (8.77%)	2 / 56 (3.57%)	1 / 57 (1.75%)
occurrences (all)	11	3	1
Gastrointestinal disorders			
Anorexia			
subjects affected / exposed	30 / 57 (52.63%)	20 / 56 (35.71%)	27 / 57 (47.37%)
occurrences (all)	69	37	41

Ascites			
subjects affected / exposed	4 / 57 (7.02%)	1 / 56 (1.79%)	1 / 57 (1.75%)
occurrences (all)	6	1	1
Constipation			
subjects affected / exposed	16 / 57 (28.07%)	14 / 56 (25.00%)	17 / 57 (29.82%)
occurrences (all)	18	21	20
Diarrhoea			
subjects affected / exposed	53 / 57 (92.98%)	35 / 56 (62.50%)	31 / 57 (54.39%)
occurrences (all)	152	63	47
Dysphagia			
subjects affected / exposed	3 / 57 (5.26%)	4 / 56 (7.14%)	4 / 57 (7.02%)
occurrences (all)	8	17	5
Haemorrhoids			
subjects affected / exposed	8 / 57 (14.04%)	5 / 56 (8.93%)	5 / 57 (8.77%)
occurrences (all)	14	7	8
Mucositis/Stomatitis			
subjects affected / exposed	19 / 57 (33.33%)	12 / 56 (21.43%)	14 / 57 (24.56%)
occurrences (all)	30	20	23
Rectorrhagia			
subjects affected / exposed	4 / 57 (7.02%)	1 / 56 (1.79%)	5 / 57 (8.77%)
occurrences (all)	4	1	7
Gastrooesophageal reflux disease			
subjects affected / exposed	7 / 57 (12.28%)	2 / 56 (3.57%)	6 / 57 (10.53%)
occurrences (all)	13	8	6
Vomiting			
subjects affected / exposed	26 / 57 (45.61%)	16 / 56 (28.57%)	11 / 57 (19.30%)
occurrences (all)	43	21	16
Hepatobiliary disorders			
Hepaltagia			
subjects affected / exposed	3 / 57 (5.26%)	2 / 56 (3.57%)	10 / 57 (17.54%)
occurrences (all)	4	2	13
Skin and subcutaneous tissue disorders			
Hand and foot syndrome			
subjects affected / exposed	24 / 57 (42.11%)	2 / 56 (3.57%)	35 / 57 (61.40%)
occurrences (all)	74	2	65
Erythrodermia			

subjects affected / exposed	7 / 57 (12.28%)	1 / 56 (1.79%)	4 / 57 (7.02%)
occurrences (all)	9	1	4
Paronychia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	0 / 57 (0.00%)
occurrences (all)	2	0	0
Pruritus			
subjects affected / exposed	9 / 57 (15.79%)	2 / 56 (3.57%)	14 / 57 (24.56%)
occurrences (all)	22	3	15
Rash maculo-papular			
subjects affected / exposed	17 / 57 (29.82%)	1 / 56 (1.79%)	13 / 57 (22.81%)
occurrences (all)	28	1	15
Dry skin			
subjects affected / exposed	15 / 57 (26.32%)	4 / 56 (7.14%)	16 / 57 (28.07%)
occurrences (all)	29	6	21
Alopecia			
subjects affected / exposed	35 / 57 (61.40%)	16 / 56 (28.57%)	4 / 57 (7.02%)
occurrences (all)	102	32	11
Renal and urinary disorders			
Fistula			
subjects affected / exposed	0 / 57 (0.00%)	1 / 56 (1.79%)	0 / 57 (0.00%)
occurrences (all)	0	1	0
Renal failure			
subjects affected / exposed	1 / 57 (1.75%)	1 / 56 (1.79%)	0 / 57 (0.00%)
occurrences (all)	1	1	0
Urinary retention			
subjects affected / exposed	1 / 57 (1.75%)	0 / 56 (0.00%)	1 / 57 (1.75%)
occurrences (all)	1	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 57 (5.26%)	3 / 56 (5.36%)	4 / 57 (7.02%)
occurrences (all)	8	7	6
Myalgia			
subjects affected / exposed	4 / 57 (7.02%)	4 / 56 (7.14%)	5 / 57 (8.77%)
occurrences (all)	11	6	5
Metabolism and nutrition disorders			

Hypocalcaemia			
subjects affected / exposed	25 / 57 (43.86%)	3 / 56 (5.36%)	14 / 57 (24.56%)
occurrences (all)	49	6	21
Hypokaliemia			
subjects affected / exposed	13 / 57 (22.81%)	4 / 56 (7.14%)	7 / 57 (12.28%)
occurrences (all)	19	4	9
Hypomagnesaemia			
subjects affected / exposed	7 / 57 (12.28%)	2 / 56 (3.57%)	5 / 57 (8.77%)
occurrences (all)	19	2	8
Hyponatraemia			
subjects affected / exposed	15 / 57 (26.32%)	10 / 56 (17.86%)	17 / 57 (29.82%)
occurrences (all)	20	10	20

Non-serious adverse events	CROSSOVER from ARM B, C to NEXIRI		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	69 / 69 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 69 (15.94%)		
occurrences (all)	20		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	64 / 69 (92.75%)		
occurrences (all)	148		
Fever			
subjects affected / exposed	19 / 69 (27.54%)		
occurrences (all)	24		
Limbs oedema			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	6		
Weight decreased			
subjects affected / exposed	29 / 69 (42.03%)		
occurrences (all)	43		
Pain			
subjects affected / exposed	46 / 69 (66.67%)		
occurrences (all)	77		

Immune system disorders			
Allergic reaction			
subjects affected / exposed	3 / 69 (4.35%)		
occurrences (all)	4		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	7 / 69 (10.14%)		
occurrences (all)	19		
Post nasal discharge			
subjects affected / exposed	7 / 69 (10.14%)		
occurrences (all)	10		
Epistaxis			
subjects affected / exposed	8 / 69 (11.59%)		
occurrences (all)	13		
Lung oedema			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	15 / 69 (21.74%)		
occurrences (all)	21		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	8 / 69 (11.59%)		
occurrences (all)	13		
Investigations			
Amylase increased			
subjects affected / exposed	12 / 69 (17.39%)		
occurrences (all)	21		
Lipase increased			
subjects affected / exposed	15 / 69 (21.74%)		
occurrences (all)	24		
White blood cell count decreased			
subjects affected / exposed	14 / 69 (20.29%)		
occurrences (all)	24		
Neutrophil count decreased			

subjects affected / exposed	15 / 69 (21.74%)		
occurrences (all)	25		
Platelet count decreased			
subjects affected / exposed	12 / 69 (17.39%)		
occurrences (all)	20		
Cardiac disorders			
Prolonged QTc			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Thromboembolic event			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	4		
Infarction			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 69 (10.14%)		
occurrences (all)	16		
Dysgeusia			
subjects affected / exposed	8 / 69 (11.59%)		
occurrences (all)	13		
Neuropathy peripheral			
subjects affected / exposed	15 / 69 (21.74%)		
occurrences (all)	25		
Paraesthesia			
subjects affected / exposed	10 / 69 (14.49%)		
occurrences (all)	16		
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	50 / 69 (72.46%)		
occurrences (all)	116		
Febrile neutropenia			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Eye disorders			

Vision blurred			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences (all)	5		
Gastrointestinal disorders			
Anorexia			
subjects affected / exposed	31 / 69 (44.93%)		
occurrences (all)	57		
Ascites			
subjects affected / exposed	5 / 69 (7.25%)		
occurrences (all)	5		
Constipation			
subjects affected / exposed	12 / 69 (17.39%)		
occurrences (all)	16		
Diarrhoea			
subjects affected / exposed	56 / 69 (81.16%)		
occurrences (all)	126		
Dysphagia			
subjects affected / exposed	6 / 69 (8.70%)		
occurrences (all)	13		
Haemorrhoids			
subjects affected / exposed	8 / 69 (11.59%)		
occurrences (all)	11		
Mucositis/Stomatitis			
subjects affected / exposed	18 / 69 (26.09%)		
occurrences (all)	29		
Rectorrhagia			
subjects affected / exposed	10 / 69 (14.49%)		
occurrences (all)	10		
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	5		
Vomiting			
subjects affected / exposed	20 / 69 (28.99%)		
occurrences (all)	37		
Hepatobiliary disorders			

Hepaltagia subjects affected / exposed occurrences (all)	5 / 69 (7.25%) 8		
Skin and subcutaneous tissue disorders Hand and foot syndrome subjects affected / exposed occurrences (all)	24 / 69 (34.78%) 73		
Erythrodermia subjects affected / exposed occurrences (all)	4 / 69 (5.80%) 6		
Paronychia subjects affected / exposed occurrences (all)	0 / 69 (0.00%) 0		
Pruritus subjects affected / exposed occurrences (all)	3 / 69 (4.35%) 6		
Rash maculo-papular subjects affected / exposed occurrences (all)	9 / 69 (13.04%) 14		
Dry skin subjects affected / exposed occurrences (all)	12 / 69 (17.39%) 26		
Alopecia subjects affected / exposed occurrences (all)	25 / 69 (36.23%) 55		
Renal and urinary disorders Fistula subjects affected / exposed occurrences (all)	0 / 69 (0.00%) 0		
Renal failure subjects affected / exposed occurrences (all)	1 / 69 (1.45%) 1		
Urinary retention subjects affected / exposed occurrences (all)	0 / 69 (0.00%) 0		
Musculoskeletal and connective tissue disorders			

Arthralgia subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all)	 3 / 69 (4.35%) 5 4 / 69 (5.80%) 7		
Metabolism and nutrition disorders Hypocalcaemia subjects affected / exposed occurrences (all) Hypokaliemia subjects affected / exposed occurrences (all) Hypomagnesaemia subjects affected / exposed occurrences (all) Hyponatraemia subjects affected / exposed occurrences (all)	 27 / 69 (39.13%) 44 17 / 69 (24.64%) 25 8 / 69 (11.59%) 10 9 / 69 (13.04%) 11		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 January 2013	-Addition of tomudex to provide a comprehensive list of molecules that can be given for the treatment of metastatic colorectal cancer. Tomudex can replace 5FU in cases of 5FU intolerance. -Acceptance of all KRAS mutated sequences so that the patient population with rare mutations is not missed for analysis. In the B and C monotherapy arms, by the time of cross-over, the patient's general condition may have deteriorated. A change from WHO = 2 at inclusion to WHO = 3 at the time of crossover will not allow these patients to be treated, which means that patients with a good general status of WHO ≤ 1 should be included in the trial. -The crossover must be performed at the time of a documented progression on the CT scan, otherwise clinicians could switch patients to arm A at the time of a rise, even small, of the markers or at the time of a small clinical evolution. -Addition of magnesium assay.
11 March 2013	-regorafenib has been granted a temporary approval in metastatic colorectal cancer. Addition of this molecule as a treatment that can be received by the patient before inclusion in the NEXIRI 2 trial.
16 September 2013	-Modification of the investigator list with the addition of various co-investigators in different centers already declared + change of the principal investigator of a center and addition of a new center.
27 January 2014	-Deletion of the circulating tumor cell (CTC) study -Addition and deletion of co-investigators -Deletion of an Investigator Centre

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The high value of 95 % interval of cycline D1 is not reported for NEXIRI arm but the database does not allow to leave an empty value so we put 20 to post results.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32737004