Clinical trial results:
A phase I-II study to evaluate the efficacy and safety of niraparib in combination with cabozantinib (XL184) in patients with advanced urothelial cancer after failure to first-line platinum-based chemotherapy.

Summary

EudraCT number	2017-004367-12
Trial protocol	ES
Global end of trial date	14 June 2024

Results information

Result version number	v1
This version publication date	06 March 2025
First version publication date	06 March 2025
Summary attachment (see zip file)	ct_result_2017-004367-12_Periods1&2 (ct_result_2017-004367-12.pdf)

Trial information

Trial identification

Sponsor protocol code	FCR173009

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03425201
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Fundación CRIS de investigación para vencer el cáncer
Sponsor organisation address	Avda. Manoteras, 22, 3º - Office 109, Madrid, Spain, 28050
Public contact	Gestión científica, Fundación CRIS de investigación para vencer el cáncer, 0034 900 813 075, cris@criscancer.orgs
Scientific contact	Gestión científica, Fundación CRIS de investigación para vencer el cáncer, 0034 900 813 075, cris@criscancer.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	20 November 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 June 2024
Global end of trial reached?	Yes
Global end of trial date	14 June 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

PHASE I
Determine Maximum tolerated dose (MTD) of niraparib plus cabozantinib combination in patients with advanced urothelial cancer or renal cell carcinoma.
PHASE II
Evaluate the efficacy of niraparib plus cabozantinib combination in patients with advanced urothelial cancer (6 months PFS).

Protection of trial subjects:

The patient signed the informed consent before carrying out any procedure related to the study. Physical examination, vital signs, 12-lead ECG, hematology, biochemistry, urinalysis, pregnancy test if applicable and tumor evaluation were made before to start study treatment and during their participation in the study, according to the protocol.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 September 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 23
Worldwide total number of subjects	23
EEA total number of subjects	23

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)	8

From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

23 patients were recruited in phase I and 44 patients were recruited in phase II.

Pre-assignment

Screening details:

Of the 90 patients that signed the informed consent, 23 were screening failures and 67 patients started treatment in the trial.
23 patients were screening failures, most of them because they did not meet the eligibility criteria of the trial.

Period 1

Period 1 title	Phase I (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	DL1 (100+20)

Arm description:

Patients received niraparib p.o. once daily (100mg) and cabozantinib p.o. once daily (20mg) in 28-day cycles.

Arm type	Experimental
Investigational medicinal product name	Niraparib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Niraparib was administered as a flat-fixed, continuous daily dose.

Investigational medicinal product name	Cabozantinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Cabozantinib was administered in continuous daily dose.

Arm title	DL1.1 (100 + 40)

Arm description:

Patients will receive niraparib p.o. once daily (100mg) and cabozantinib p.o. once daily (40mg) in 28-day cycles.

Arm type	Experimental
Investigational medicinal product name	Niraparib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Niraparib was administered as a flat-fixed, continuous daily dose.

Investigational medicinal product name	Cabozantinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Cabozantinib was administered in continuous daily dose.

Arm title	DL2 (200 + 20)

Arm description:

Patients received niraparib p.o. once daily (200mg) and cabozantinib p.o. once daily (20mg) in 28-day cycles.

Arm type	Experimental
Investigational medicinal product name	Niraparib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Niraparib was administered as a flat-fixed, continuous daily dose.

Investigational medicinal product name	Cabozantinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Cabozantinib was administered in continuous daily dose.

Number of subjects in period 1	DL1 (100+20)	DL1.1 (100 + 40)	DL2 (200 + 20)
Started	7	7	9
Completed	7	7	9

Baseline characteristics

Reporting groups	
Reporting group title	DL1 (100+20)
Reporting group description:	
Patients received niraparib p.o. once daily (100mg) and cabozantinib p.o. once daily (20mg) in 28-day cycles.	
Reporting group title	DL1.1 (100 + 40)
Reporting group description:	
Patients will receive niraparib p.o. once daily (100mg) and cabozantinib p.o. once daily (40mg) in 28-day cycles.	
Reporting group title	DL2 (200 + 20)
Reporting group description:	
Patients received niraparib p.o. once daily (200mg) and cabozantinib p.o. once daily (20mg) in 28-day cycles.	

Reporting group values	DL1 (100+20)	DL1.1 (100 + 40)	DL2 (200 + 20)
Number of subjects	7	7	9
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)	4	2	2
From 65-84 years	3	5	7
85 years and over	0	0	0
Age continuous Units: years			
median	64	66	71
full range (min-max)	50 to 79	61 to 71	51 to 78
Gender categorical Units: Subjects			
Female	0	1	2
Male	7	6	7
Primary tumor location Units: Subjects			
Urothelial	5	7	6
Renal	2	0	3
Number of affected locations Units: Subjects			
1 location	3	1	4
2 locations	3	6	1
3 locations	1	0	4
4 locations	0	0	0
5 locations	0	0	0

Previous Surgery Units: Subjects			
Yes	7	6	6
No	0	1	3
Previous radiotherapy Units: Subjects			
Yes	1	3	1
No	6	4	8
Previous chemotherapy Units: Subjects			
Yes	5	7	6
No	2	0	3
Previous immunotherapy Units: Subjects			
Yes	6	7	9
No	1	0	0
Other previous treatments Units: Subjects			
Yes	7	7	8
No	0	0	1
Site of metastases (Lymph node) Units: Subjects			
Yes	6	5	8
No	1	2	1
Site of metastases (Lung) Units: Subjects			
Yes	2	2	4
No	5	5	5
Site of metastases (Liver) Units: Subjects			
Yes	2	1	2
No	5	6	7
Site of metastases (Bone) Units: Subjects			
Yes	2	3	1
No	5	4	8
Site of metastases (Soft tissue) Units: Subjects			
Yes	0	2	0
No	7	5	9
Site of metastases (Peritoneal carcinomatosis) Units: Subjects			
Yes	0	0	0
No	7	7	9
Site of metastases (Other) Units: Subjects			
Yes	0	0	3
No	7	7	6

No. Cycles administered			
Units: Cycle			
arithmetic mean	6	7.6	6.4
standard deviation	± 4.6	± 5	± 4.3

Reporting group values	Total		
Number of subjects	23		
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)	8		
From 65-84 years	15		
85 years and over	0		
Age continuous			
Units: years			
median			
full range (min-max)	-		
Gender categorical			
Units: Subjects			
Female	3		
Male	20		
Primary tumor location			
Units: Subjects			
Urothelial	18		
Renal	5		
Number of affected locations			
Units: Subjects			
1 location	8		
2 locations	10		
3 locations	5		
4 locations	0		
5 locations	0		
Previous Surgery			
Units: Subjects			
Yes	19		
No	4		
Previous radiotherapy			
Units: Subjects			
Yes	5		
No	18		
Previous chemotherapy			
Units: Subjects			
Yes	18		
No	5		
Previous immunotherapy			

Units: Subjects			
Yes	22		
No	1		
Other previous treatments Units: Subjects			
Yes	22		
No	1		
Site of metastases (Lymph node) Units: Subjects			
Yes	19		
No	4		
Site of metastases (Lung) Units: Subjects			
Yes	8		
No	15		
Site of metastases (Liver) Units: Subjects			
Yes	5		
No	18		
Site of metastases (Bone) Units: Subjects			
Yes	6		
No	17		
Site of metastases (Soft tissue) Units: Subjects			
Yes	2		
No	21		
Site of metastases (Peritoneal carcinomatosis) Units: Subjects			
Yes	0		
No	23		
Site of metastases (Other) Units: Subjects			
Yes	3		
No	20		
No. Cycles administered Units: Cycle arithmetic mean standard deviation	 -		

End points

End points reporting groups

Reporting group title	DL1 (100+20)
Reporting group description:	
Patients received niraparib p.o. once daily (100mg) and cabozantinib p.o. once daily (20mg) in 28-day cycles.	
Reporting group title	DL1.1 (100 + 40)
Reporting group description:	
Patients will receive niraparib p.o. once daily (100mg) and cabozantinib p.o. once daily (40mg) in 28-day cycles.	
Reporting group title	DL2 (200 + 20)
Reporting group description:	
Patients received niraparib p.o. once daily (200mg) and cabozantinib p.o. once daily (20mg) in 28-day cycles.	

Primary: Dose limiting toxicity

End point title	Dose limiting toxicity[1]
End point description:	
The following toxicities were considered DLTs: 1) Febrile neutropenia or grade 4 neutropenia without fever for >5 days. 2) Grade 4 thrombocytopenia or anemia. 3) Grade 3 non-hematologic toxicity except for nausea, vomiting, diarrhea or electrolyte abnormality corrected within 48 hours, or elevated creatinine corrected within 24 hours. 4) Any related ≥ Grade 3 AE which is unexpected in severity and/or duration compared to the known safety profiles of cabozantinib and niraparib when used as single agents, and that cannot be managed by dose modification (reduction or interruption) and adequate supportive care, and requires permanent discontinuation of cabozantinib and/or niraparib. 5) The inability to take ≥ 75% of the total planned cabozantinib or niraparib dose during DLT evaluation period.	
End point type	Primary
End point timeframe:	
Toxicity of patients included in this phase was evaluated during2 cycles (56 days).	
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: Not statistical analysis have been performed, study non-randomised.	

End point values	DL1 (100+20)	DL1.1 (100 + 40)	DL2 (200 + 20)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	7	9	
Units: Subjects				
number (not applicable)				
Yes	0	1	3	
No	5	5	5	
Not evaluable	2	1	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicities

End point title	Toxicities

End point description:

End point type	Secondary

End point timeframe:

Safety analysis were performed for the first 2 cycles (56 days)

End point values	DL1 (100+20)	DL1.1 (100 + 40)	DL2 (200 + 20)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	7	9	
Units: Subjects				
number (not applicable)				
Yes	4	6	9	
No	3	1	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Every 7 days during the first 2 cycles and every 15 days in the following cycles.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	27

Reporting groups	
Reporting group title	DL1 (100+20)
Reporting group description: Patients received niraparib p.o. once daily (100mg) and cabozantinib p.o. once daily (20mg) in 28-day cycles.	
Reporting group title	DL1.1 (100 + 40)
Reporting group description: Patients will receive niraparib p.o. once daily (100mg) and cabozantinib p.o. once daily (40mg) in 28-day cycles.	
Reporting group title	DL2 (200 + 20)
Reporting group description: Patients received niraparib p.o. once daily (200mg) and cabozantinib p.o. once daily (20mg) in 28-day cycles.	

Serious adverse events	DL1 (100+20)	DL1.1 (100 + 40)	DL2 (200 + 20)
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 7 (71.43%)	4 / 7 (57.14%)	4 / 9 (44.44%)
number of deaths (all causes)	7	6	8
number of deaths resulting from adverse events	1	0	0
Injury, poisoning and procedural complications			
Medication error			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 9 (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
Nervous system disorders			
Spinal cord compression			

subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 9 (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
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 9 (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
Gait disturbance			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 9 (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
General physical health deterioration			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 9 (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
Inadequate analgesia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 9 (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
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			

subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 9 (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	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 9 (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
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 9 (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
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 9 (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
Pneumonia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			

subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 9 (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
Urinary tract infection			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	DL1 (100+20)	DL1.1 (100 + 40)	DL2 (200 + 20)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	7 / 7 (100.00%)	9 / 9 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 7 (57.14%)	4 / 7 (57.14%)	3 / 9 (33.33%)
occurrences (all)	6	4	5
Lymphoedema			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Subclavian vein thrombosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
White coat hypertension			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	1 / 9 (11.11%)
occurrences (all)	1	1	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 7 (14.29%)	5 / 7 (71.43%)	9 / 9 (100.00%)
occurrences (all)	3	11	18
Chest pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Fatigue			

subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	5	0	0
Gait disturbance			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Mucosal dryness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Mucosal inflammation			
subjects affected / exposed	0 / 7 (0.00%)	4 / 7 (57.14%)	3 / 9 (33.33%)
occurrences (all)	0	5	4
Oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	2
Oedema peripheral			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 9 (11.11%)
occurrences (all)	0	2	1
Reproductive system and breast disorders			
Scrotal oedema			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Aphonia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Cough			
subjects affected / exposed	3 / 7 (42.86%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	5	0	0
Dysphonia			
subjects affected / exposed	0 / 7 (0.00%)	3 / 7 (42.86%)	1 / 9 (11.11%)
occurrences (all)	0	3	1
Dyspnoea			

subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	3	0	0
Epistaxis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Productive cough			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	3 / 9 (33.33%)
occurrences (all)	1	1	11
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	3 / 9 (33.33%)
occurrences (all)	1	1	14
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 9 (22.22%)
occurrences (all)	0	0	2
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 9 (11.11%)
occurrences (all)	0	1	2
Blood creatinine increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	2 / 9 (22.22%)
occurrences (all)	1	0	3
Blood glucose increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Blood iron decreased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Blood lactate dehydrogenase increased			

subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	2 / 9 (22.22%)
occurrences (all)	2	0	3
Blood potassium decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	2
Blood uric acid increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Platelet count decreased			
subjects affected / exposed	2 / 7 (28.57%)	1 / 7 (14.29%)	2 / 9 (22.22%)
occurrences (all)	7	1	3
Protein total increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Protein urine present			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	2
Transaminases increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	1 / 9 (11.11%)
occurrences (all)	0	3	1
Injury, poisoning and procedural complications			
Medication error			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Cardiac disorders			

Arrhythmia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Sinus tachycardia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Dysgeusia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 7 (28.57%)	0 / 9 (0.00%)
occurrences (all)	1	7	0
Paraesthesia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 9 (11.11%)
occurrences (all)	0	4	2
Somnolence			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 7 (14.29%)	3 / 7 (42.86%)	5 / 9 (55.56%)
occurrences (all)	1	5	11
Lymphopenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Neutropenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	3
Thrombocytopenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 9 (22.22%)
occurrences (all)	0	0	5
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Eye disorders			

Abdominal pain upper			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	2 / 9 (22.22%)
occurrences (all)	3	0	3
Abdominal pain lower			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	2
Anal fistula			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Anal inflammation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	2 / 7 (28.57%)	4 / 7 (57.14%)	5 / 9 (55.56%)
occurrences (all)	2	7	6
Diarrhoea			
subjects affected / exposed	2 / 7 (28.57%)	5 / 7 (71.43%)	1 / 9 (11.11%)
occurrences (all)	7	6	2
Dry mouth			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	2 / 9 (22.22%)
occurrences (all)	0	3	3
Dysphagia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Gastritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Nausea			

subjects affected / exposed	2 / 7 (28.57%)	1 / 7 (14.29%)	2 / 9 (22.22%)
occurrences (all)	2	2	5
Odynophagia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Oral mucosal erythema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Pancreatitis acute			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Proctalgia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 9 (11.11%)
occurrences (all)	0	2	1
Rectal haemorrhage			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
Stomatitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	2
Vomiting			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Hepatotoxicity			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	3 / 9 (33.33%)
occurrences (all)	0	0	7
Hypertransaminasaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
Jaundice			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1

Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Dry skin			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Eczema			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Erythema			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	3
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 7 (14.29%)	4 / 7 (57.14%)	1 / 9 (11.11%)
occurrences (all)	1	8	4
Rash			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 9 (11.11%)
occurrences (all)	0	2	1
Dysuria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Haematuria			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Nocturia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 9 (22.22%)
occurrences (all)	0	0	2
Polyuria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Proteinuria			

subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Renal impairment			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Renal pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Urinary tract obstruction			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Hypothyroidism			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	2 / 9 (22.22%)
occurrences (all)	2	0	5
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 7 (0.00%)	3 / 7 (42.86%)	2 / 9 (22.22%)
occurrences (all)	0	3	2
Muscle spasms			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	0 / 9 (0.00%)
occurrences (all)	1	4	0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Myalgia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 9 (11.11%)
occurrences (all)	0	2	1
Infections and infestations			

Anal abscess			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Gingivitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Oral candidiasis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)	3 / 7 (42.86%)	2 / 9 (22.22%)
occurrences (all)	0	3	3
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 7 (28.57%)	4 / 7 (57.14%)	3 / 9 (33.33%)
occurrences (all)	3	7	3
Hyperkalaemia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	1 / 9 (11.11%)
occurrences (all)	0	2	1
Hypertriglyceridaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 9 (11.11%)
occurrences (all)	0	1	4
Hyperuricaemia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Hypocalcaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 9 (22.22%)
occurrences (all)	0	0	2
Hypomagnesaemia			

subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	2 / 9 (22.22%)
occurrences (all)	1	1	2
Hyponatraemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 9 (11.11%)
occurrences (all)	0	1	2
Hypophosphataemia			
subjects affected / exposed	1 / 7 (14.29%)	3 / 7 (42.86%)	0 / 9 (0.00%)
occurrences (all)	1	6	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 January 2020	Niraparib IB has been updated to a new version, frequency of adverse events has changed and new version of SAE notification form has been added as annex in the protocol. Exclusion criteria number 4 will be applicable only to patients included in phase II in which main objective is to evaluate the effectiveness of the combination. It has been detailed that if one of the study agents need to be interrupted due to toxicity, patient can continue only with the other agent. Furthermore, frequency of stool samples collecting for molecular studies has been modified, stool sample at end of study or progression disease is replaced by day 1 from cycle 4. Minor additional changes have been implemented in the protocol. Protocol and PIS have been updated accordingly with mentioned changes.
05 November 2020	In the analysis of the second cohort of patients included in the study (DL2: niraparib 200 mg/day and cabozantinib 20 mg/day), adverse events have been documented that would correspond to dose-limiting toxicities (DLTs) as defined in the protocol. However, at the investigators' meeting on 21 September, individual cases were reviewed and it was determined that some of the reported adverse events that would be considered TLDs could be justified by reasons unrelated to the study medication. On the other hand, the remaining patients included in the study, both at dose level 1 (DL1: niraparib 100 mg/day and cabozantinib 20 mg/day) and dose level 2 (DL2) showed mostly excellent tolerability to treatment with minimal toxicities reported, so it was considered preparing this protocol amendment to include three additional patients at dose level DL2 to assess with a larger number of patients whether the dose level is safe for use in phase II. In the event that the three new patients included in DL2 do not report any DLT, this dose level would be used in phase II of the study. If a new dose-limiting toxicity grade 3-4 as specified in the study protocol is reported in the 3 additional level 2 patients, it is propose to explore a new dose level not established in the initial protocol, but due to the characteristics of each drug and toxicity/efficacy profiles we understand that it would be feasible in this scenario of patients with advanced disease progressed to previous therapeutic lines. In the new cohort called DL1.1, a dose of 100 mg/day of niraparib and 40 mg/day of cabozantinib is set to investigate a dose that is safe and optimises the potential benefit that patients could derive from this combination.
02 August 2022	The section related to the reporting of adverse events, special situations and Product Complaints to the marketing holders of investigational products has been updated, following their request.

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.

none

Notes: