

**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 (current)
This version publication date	
First version publication date	

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	Fundación CRIS de investigación para vencer el cáncer, Gestión científica, 0034, 900 813 075, cris@criscancer.org
Scientific contact	Fundación CRIS de investigación para vencer el cáncer, Gestión científica, 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 \geq 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 \geq 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 during 2 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 occurrences (all)	2 / 7 (28.57%) 3	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0
Epistaxis subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0
Productive cough subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1	0 / 9 (0.00%) 0
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 9 (11.11%) 1
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	1 / 7 (14.29%) 1	3 / 9 (33.33%) 11
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	1 / 7 (14.29%) 1	3 / 9 (33.33%) 14
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	2 / 9 (22.22%) 2
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1	1 / 9 (11.11%) 2
Blood creatinine increased subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 7 (0.00%) 0	2 / 9 (22.22%) 3
Blood glucose increased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 9 (11.11%) 1
Blood iron decreased subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0
Blood lactate dehydrogenase increased			

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

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

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

subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 2	1 / 7 (14.29%) 2	2 / 9 (22.22%) 5
Odynophagia			
subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 9 (11.11%) 1
Oral mucosal erythema			
subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 9 (11.11%) 1
Pancreatitis acute			
subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1	0 / 9 (0.00%) 0
Proctalgia			
subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 7 (14.29%) 2	1 / 9 (11.11%) 1
Rectal haemorrhage			
subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 7 (0.00%) 0	1 / 9 (11.11%) 1
Stomatitis			
subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 9 (11.11%) 2
Vomiting			
subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1	0 / 9 (0.00%) 0
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1	0 / 9 (0.00%) 0
Hepatotoxicity			
subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	3 / 9 (33.33%) 7
Hypertransaminaemia			
subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 7 (0.00%) 0	1 / 9 (11.11%) 1
Jaundice			
subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 9 (11.11%) 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 erythrodysesthesia 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 occurrences (all)	1 / 7 (14.29%) 1	0 / 7 (0.00%) 0	0 / 9 (0.00%) 0
Renal impairment subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 7 (14.29%) 2	0 / 9 (0.00%) 0
Renal pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 9 (11.11%) 1
Urinary tract obstruction subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1	0 / 9 (0.00%) 0
Endocrine disorders			
Hyperthyroidism subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1	0 / 9 (0.00%) 0
Hypothyroidism subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 2	0 / 7 (0.00%) 0	2 / 9 (22.22%) 5
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	3 / 7 (42.86%) 3	2 / 9 (22.22%) 2
Muscle spasms subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	1 / 7 (14.29%) 4	0 / 9 (0.00%) 0
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	1 / 7 (14.29%) 1	0 / 9 (0.00%) 0
Myalgia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1	0 / 9 (0.00%) 0
Pain in extremity subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 7 (14.29%) 2	1 / 9 (11.11%) 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

Period 2

Period 2 title	Phase II (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Population of trial subjects**Subjects enrolled per country**

Country: Number of subjects enrolled	Spain: 67
Worldwide total number of subjects	67
EEA total number of subjects	67

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)	24
From 65 to 84 years	43
85 years and over	0

Arms

Are arms mutually exclusive?	Yes
------------------------------	-----

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.

Number of subjects in period 1	DL1.1 (100 + 40)
Started	51
Completed	51

Baseline characteristics

Reporting groups

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 values	DL1.1 (100 + 40)
Number of subjects	51
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)	18
From 65-84 years	33
85 years and over	0
Age continuous	
Units: years	
median	67
full range (min-max)	37 to 82
Gender categorical	
Units: Subjects	
Female	1
Male	6
Primary tumor location	
Units: Subjects	
Urothelial	51
Renal	0
Number of affected locations	
Units: Subjects	
1 location	18
2 locations	25
3 locations	5
4 locations	2
5 locations	1

Previous Surgery Units: Subjects	
Yes	44
No	7
Previous radiotherapy Units: Subjects	
Yes	11
No	40
Previous chemotherapy Units: Subjects	
Yes	51
No	0
Previous immunotherapy Units: Subjects	
Yes	40
No	11
Other previous treatments Units: Subjects	
Yes	32
No	19
Site of metastases (Lymph node) Units: Subjects	
Yes	41
No	10
Site of metastases (Lung) Units: Subjects	
Yes	14
No	37
Site of metastases (Liver) Units: Subjects	
Yes	13
No	38
Site of metastases (Bone) Units: Subjects	
Yes	9
No	42
Site of metastases (Soft tissue) Units: Subjects	
Yes	9
No	42
Site of metastases (Peritoneal carcinomatosis) Units: Subjects	
Yes	1
No	50
Site of metastases (Other) Units: Subjects	
Yes	0
No	7

No. Cycles administered	
Units: Cycle	
arithmetic mean	7.6
standard deviation	± 5

End points

End points reporting groups

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.	

Primary: Dose limiting toxicity

End point title	Progression free Survival
End point description: Evaluate the efficacy of niraparib plus cabozantinib combination in patients with advanced urothelial cancer (6 months PFS).	
End point type	Primary
End point timeframe: Six months progression-free survival	

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	DL1.1 (100 + 40)
Subject group type	Reporting group
Number of subjects analysed	51
Units: months	
arithmetic mean	3.947
standar deviation	0.990

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicities

End point title	Efficacy
-----------------	----------

End point description:

Evaluate the efficacy of niraparib plus cabozantinib according to: Objective Response Rate (ORR) as evaluated by RECIST 1.1 criteria, Disease Control Rate (DCR), Duration of response, Overall Survival (OS)

End point type	Secondary
----------------	-----------

End point timeframe:

Disease assessment every 8 weeks (+/-1 week) until month 6 and every 12 weeks (+/-2 weeks) onwards, until PD.

Overall survival assessment Every 6 months for 2 years and annually thereafter.

End point values	DL1.1 (100 + 40)
Subject group type	Reporting group
Number of subjects analysed	51
Complete Response	
Units: Subjects	
Yes	1
No	50
Partial Response	
Units: Subjects	
Yes	9
No	42
Stable disease	
Units: Subjects	
Yes	20
No	31
Progression disease	
Units: Subjects	
Yes	20
No	31
Not evaluable/Not done	
Units: Subjects	
Yes	1
No	50

End point values	DL1.1 (100 + 40)
Subject group type	Reporting group
Number of subjects analysed	51
Overall Survival	
Units: months	
median	10.724
standard deviation	1.466

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	DL1.1 (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.

Non-serious adverse events	DL1.1 (100 + 40)
Total subjects affected by serious adverse events	
subjects affected / exposed	21 / 51 (70.00%)
number of deaths (all causes)	34
number of deaths resulting from adverse events	1
Vascular disorders	
Deep vein thrombosis	
subjects affected / exposed	2 / 51 (3.9%)
occurrences causally related to treatment / all	0 / 2
deaths causally related to treatment / all	0 / 0
Arterial thrombosis	
subjects affected / exposed	1 / 51 (2.0%)
occurrences causally related to treatment / all	0 / 1
deaths causally related to treatment / all	0 / 0
General disorders and administration site conditions	
Death	
subjects affected / exposed	1 / 51 (2.0%)
occurrences causally related to treatment / all	0 / 1
deaths causally related to treatment / all	0 / 0
Gait disturbance	
subjects affected / exposed	1 / 51 (2.0%)
occurrences causally related to treatment / all	0 / 1
deaths causally related to treatment / all	0 / 0
General physical health deterioration	
subjects affected / exposed	1 / 51 (2.0%)
occurrences causally related to treatment / all	0 / 1
deaths causally related to treatment / all	0 / 0
Inadequate analgesia	
subjects affected / exposed	2 / 51 (3.9%)
occurrences causally related to treatment / all	0 / 2
deaths causally related to treatment / all	0 / 0

Respiratory, thoracic and mediastinal disorders Pulmonary embolism subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 2 / 51 (3.9%) 1 / 1 0 / 0
Psychiatric disorders Panic attack subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 51 (2.0%) 0 / 1 0 / 0
Blood and lymphatic system disorders Febrile neutropenia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 51 (2.0%) 0 / 1 0 / 0
Gastrointestinal disorders Intestinal obstruction subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Intestinal perforation subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Stomatitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 51 (2.0%) 0 / 1 0 / 0 1 / 51 (2.0%) 0 / 1 0 / 0 1 / 51 (2.0%) 0 / 1 0 / 0
Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Bladder perforation subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Haematuria subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Perinephric collection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Renal failure subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 2 / 51 (3.9%) 0 / 2 0 / 0 1 / 51 (2.0%) 1 / 1 0 / 0 2 / 51 (3.9%) 0 / 2 0 / 0 1 / 51 (2.0%) 0 / 1 0 / 0 1 / 51 (2.0%) 1 / 1 0 / 0

<p>Musculoskeletal and connective tissue disorders</p> <p>Back pain subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all</p>	<p>2 / 51 (3.9%) 0 / 2 0 / 0</p>
<p>Infections and infestations</p> <p>Lower respiratory tract infection viral subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all</p> <p>Pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all</p> <p>Peritoneal abscess subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all</p> <p>Pulmonary sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all</p> <p>Pyelonephritis acute subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all</p> <p>Urinary tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all</p>	<p>1 / 51 (2.0%) 0 / 1 0 / 0</p> <p>1 / 51 (2.0%) 0 / 1 0 / 0</p> <p>1 / 51 (2.0%) 0 / 1 0 / 0</p> <p>1 / 51 (2.0%) 0 / 1 0 / 1</p> <p>1 / 51 (2.0%) 0 / 1 0 / 0</p> <p>5 / 51 (9.8%) 0 / 5 0 / 0</p>

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

Non-serious adverse events	DL1.1 (100 + 40)
Total subjects affected by non-serious adverse events subjects affected / exposed	 51 / 51 (100.00%)
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	 24 / 51 (47.1%) 8
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Chest pain subjects affected / exposed occurrences (all) Discomfort subjects affected / exposed occurrences (all) Mucosal inflammation subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	 44 / 51 (86.3%) 9 4 / 51 (7.8%) 4 3 / 51 (5.9%) 8 11 / 51 (21.6%) 4 3 / 51 (5.9%) 4 5 / 51 (9.8%) 4
Respiratory, thoracic and mediastinal disorders Dysphonia subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Haemoptysis subjects affected / exposed occurrences (all) Pulmonary embolism subjects affected / exposed occurrences (all)	 9 / 51 (17.6%) 16 3 / 51 (5.9%) 4 3 / 51 (5.9%) 14 3 / 51 (5.9%) 4
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 3 / 51 (5.9%) 8

Investigations	
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	10 / 51 (19.6%) 23
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	9 / 51 (17.6%) 26
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	5 / 51 (9.8%) 42
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	3 / 51 (5.9%) 17
Blood creatinine increased subjects affected / exposed occurrences (all)	5 / 51 (9.8%) 10
Neutrophil count decreased subjects affected / exposed occurrences (all)	3 / 51 (5.9%) 3
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	5 / 51 (9.8%) 6
Platelet count decreased subjects affected / exposed occurrences (all)	4 / 51 (7.8%) 7
Weight decreased subjects affected / exposed occurrences (all)	8 / 51 (15.7%) 7
Nervous system disorders	
Dysgeusia subjects affected / exposed occurrences (all)	9 / 51 (17.6%) 3
Paraesthesia subjects affected / exposed occurrences (all)	4 / 51 (7.8%) 3
Blood and lymphatic system disorders	
Anaemia subjects affected / exposed occurrences (all)	14 / 51 (27.5%) 16
Thrombocytopenia subjects affected / exposed occurrences (all)	6 / 51 (11.8%) 5
Gastrointestinal disorders	
Abdominal pain subjects affected / exposed occurrences (all)	9 / 51 (17.6%) 42

Abdominal pain upper subjects affected / exposed occurrences (all)	8 / 51 (15.7%) 11
Constipation subjects affected / exposed occurrences (all)	18 / 51 (35.3%) 23
Diarrhoea subjects affected / exposed occurrences (all)	18 / 51 (35.3%) 11
Dyspepsia subjects affected / exposed occurrences (all)	3 / 51 (5.9%) 10
Nausea subjects affected / exposed occurrences (all)	13 / 51 (25.5%) 3
Proctalgia subjects affected / exposed occurrences (all)	3 / 51 (5.9%) 12
Vomiting subjects affected / exposed occurrences (all)	9 / 51 (17.6%) 3
Hepatobiliary disorders Hypertransaminasaemia subjects affected / exposed occurrences (all)	9 / 51 (17.6%) 9
Skin and subcutaneous tissue disorders Palmar-plantar erythrodysesthesia syndrome subjects affected / exposed occurrences (all)	10 / 51 (19.6%) 4
Rash subjects affected / exposed occurrences (all)	3 / 51 (5.9%) 18
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	13 / 51 (25.5%) 5
Haematuria subjects affected / exposed occurrences (all)	9 / 51 (17.6%) 4
Renal impairment subjects affected / exposed occurrences (all)	3 / 51 (5.9%) 16
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	4 / 51 (7.8%) 19

<p>Musculoskeletal and connective tissue disorders</p> <p>Back pain subjects affected / exposed occurrences (all)</p> <p>Myalgia subjects affected / exposed occurrences (all)</p> <p>Pain in extremity subjects affected / exposed occurrences (all)</p>	<p>14 / 51 (27.5%) 7</p> <p>4 / 51 (7.8%) 8</p> <p>6 / 51 (11.8%) 4</p>
<p>Infections and infestations</p> <p>COVID-19 subjects affected / exposed occurrences (all)</p> <p>Upper respiratory tract infection subjects affected / exposed occurrences (all)</p> <p>Urinary tract infection subjects affected / exposed occurrences (all)</p>	<p>4 / 51 (7.8%) 12</p> <p>3 / 51 (5.9%) 10</p> <p>15 / 51 (29.4%) 86</p>
<p>Metabolism and nutrition disorders</p> <p>Decreased appetite subjects affected / exposed occurrences (all)</p> <p>Hyperkalaemia subjects affected / exposed occurrences (all)</p> <p>Hyperglycaemia subjects affected / exposed occurrences (all)</p> <p>Hyponatraemia subjects affected / exposed occurrences (all)</p> <p>Hypophosphataemia subjects affected / exposed occurrences (all)</p>	<p>22 / 51 (43.1%) 14</p> <p>5 / 51 (9.8%) 15</p> <p>3 / 51 (5.9%) 3</p> <p>4 / 51 (7.8%) 5</p> <p>8 / 51 (15.7%) 9</p>

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 January 2020	<p>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.</p> <p>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.</p> <p>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.</p> <p>Minor additional changes have been implemented in the protocol. Protocol and PIS have been updated accordingly with mentioned changes.</p>
05 November 2020	<p>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.</p> <p>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.</p> <p>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.</p> <p>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.</p>
02 August 2022	<p>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.</p>

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: