Clinical trial results:
A Randomized Phase II Trial Evaluating an Organ-conserving Strategy With Radiotherapy + CDDP + Gemcitabine vs Radiotherapy + CDDP in Muscle-infiltrative Bladder Cancer (GETUG V04)

Summary

EudraCT number	2011-000408-17
Trial protocol	FR
Global end of trial date	25 July 2022

Results information

Result version number	v1 (current)
This version publication date	26 October 2023
First version publication date	26 October 2023
Summary attachment (see zip file)	statistical report (RapportStat_GETUGv04_20220919.pdf)

Trial information

Trial identification

Sponsor protocol code	VA 2011/01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01495676
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	Dr Jean-Pierre BLEUSE, CRLC Val d'Aurelle - Paul Lamarque, 33 4 67 61 23 44/31 02 , drci-icm105@icm.unicancer.fr
Scientific contact	Dr Jean-Pierre BLEUSE, CRLC Val d'Aurelle - Paul Lamarque, 33 4 67 61 23 44/31 02 , drci-icm105@icm.unicancer.fr

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	25 July 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 July 2022
Global end of trial reached?	Yes
Global end of trial date	25 July 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the combination of radiotherapy + cisplatin + gemcitabine in terms of disease-free survival (At 2 years) in non metastatic muscle invasive urothelial cancer patients.

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 laws down in the declaration of Helsinki, good Clinical Practice and European Regulation

Background therapy:

If radical cystectomy remains the standard of care for muscle invasive bladder cancer, consequences of this surgical procedure are often harsh. Over the past years, concurrent chemo-radiotherapy has imposed itself as an alternative treatment. Published data on concomitant radiochemotherapy (radiotherapy/cisplatin or radiotherapy/cisplatin/5-fluorouracil combinations) showed local control rates with bladder preservation at 5 years ranging from 40% to 65% according to the disease stage, and overall survival probabilities ranging from 40% to 50% at 5 years. In order to improve local and systemic prognosis, evaluation of other chemotherapy agents with higher radiosensitizing effect, such as gemcitabine, is justified. Gemcitabine possesses its own anti-cancer activities on urothelial diseases and has a synergetic activity with cisplatin. The investigators completed a monocenter phase I study combining radiotherapy, cisplatin, and twice-weekly gemcitabine, and determined a recommended dose of gemcitabine 25 mg/m². The objective of the present study is to evaluate the combination of radiotherapy + cisplatin + gemcitabine in terms of disease-free survival in non metastatic muscle invasive urothelial cancer patients.

Evidence for comparator:

Arm A (control arm) : Radiotherapy + Cisplatin
Arm B (experimental arm) : Radiotherapy + Cisplatin + Gemcitabine

Actual start date of recruitment	06 July 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
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: 69
Worldwide total number of subjects	69
EEA total number of subjects	69

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)	17
From 65 to 84 years	50
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

period of recrutement : From 06-JUL-2011 to 27-SEP-2021 (10, 2 years)

Pre-assignment

Screening details:

Patient with a Muscle invasive urothelial cancer (front line or following the progression of a superficial tumor), pT2-pT3 stage without lymphatic impairment (N0) and without detectable metastases (M0). An optimal macroscopic resection (TURB) have to be performed

Period 1

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

Blinding implementation details:

blinding was not applicable to the period.

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A : Active comparator arm

Arm description:

first step : radiotherapy + Cispaltin during 5 weeks
Evaluation by cystoscopy : if complete histological response, the treatement continue
second step : radiotherapy + Cispaltin during 2 weeks

Arm type	Active comparator
Investigational medicinal product name	Radiotherapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Not assigned
Routes of administration	External use

Dosage and administration details:

first step : RT 1.8 Gy/fraction, 25 séances (5 weeks)
Second step : RT 1.8 Gy/fraction, 10 séances (2 weeks)

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in administration system
Routes of administration	Intravenous use

Dosage and administration details:

First step : 20 mg/m² at day 2 to day 5 and day 23 to day 26 (5 weeks)
second step : 20 mg/m² at day 2 to day 5 (2 weeks)

Arm title	Arm B : Experimental arm

Arm description:

first step : radiotherapy + Cispaltin = Gemcitabine during 5 weeks
Evaluation by cystoscopy : if complete histological response, the treatement continue
second step : radiotherapy + Cispaltin + Gemcitabine during 2 weeks

Arm type	Experimental

Investigational medicinal product name	Radiotherapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Not assigned
Routes of administration	External use

Dosage and administration details:

first step : RT 1.8 Gy/fraction, 25 séances (5 weeks)
Second step : RT 1.8 Gy/fraction, 10 séances (2weeks)

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in administration system
Routes of administration	Intravenous use

Dosage and administration details:

First step : 20 mg/m² at day 2 to day 5 and day 23 to day 26 (5 weeks)
second step : 20 mg/m² at day 2 to day 5 (2 weeks)

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in administration system
Routes of administration	Intravenous use

Dosage and administration details:

First step : 25 mg/m² to day 2,5,9,12,16,19,23,26,30,33 (5 weeks)
second step : 25 mg/m² to day 2,5,9,12 (2 weeks)

Number of subjects in period 1	Arm A : Active comparator arm	Arm B : Experimental arm
Started	24	45
Completed	22	35
Not completed	2	10
suicide	-	1
Lack of efficacy	2	8
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	69	69	
Age categorical Units: Subjects			
Adults (18-64 years)	19	19	
From 65-84 years	48	48	
85 years and over	2	2	
Gender categorical			
The ratio M/F is 7,6			
Units: Subjects			
Female	8	8	
Male	61	61	
Macroscopic hematuria			
Macroscopic hematuria was performed in 16 pts (23.2%), with an abnormal result in 50. % of them (n=7).			
Units: Subjects			
Abnormal	7	7	
Normal	16	16	
Not Done (NA)	46	46	

Subject analysis sets	
Subject analysis set title	Intention to Treat Patient
Subject analysis set type	Intention-to-treat

Subject analysis set description:

all randomized patients, whether treated or not, eligible or not. Patients are analyzed in the arm assigned by randomization (if applicable).

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

all patients who have received at least one treatment administration. Patients will be analyzed in the treatment arm they actually received.

Reporting group values	Intention to Treat Patient	Safety population	
Number of subjects	69	67	
Age categorical Units: Subjects			
Adults (18-64 years)	19	19	
From 65-84 years	48	46	
85 years and over	2	2	
Gender categorical			
The ratio M/F is 7,6			
Units: Subjects			

Female	8	8	
Male	61	59	

Macroscopic hematuria			
Macroscopic hematuria was performed in 16 pts (23.2%), with an abnormal result in 50. % of them (n=7).			
Units: Subjects			
Abnormal	7	7	
Normal	16	16	
Not Done (NA)	46	44	

End points

End points reporting groups

Reporting group title	Arm A : Active comparator arm

Reporting group description:

first step : radiotherapy + Cispaltin during 5 weeks
Evaluation by cystoscopy : if complete histological response, the treatement continue
second step : radiotherapy + Cispaltin during 2 weeks

Reporting group title	Arm B : Experimental arm

Reporting group description:

first step : radiotherapy + Cispaltin = Gemcitabine during 5 weeks
Evaluation by cystoscopy : if complete histological response, the treatement continue
second step : radiotherapy + Cispaltin + Gemcitabine during 2 weeks

Subject analysis set title	Intention to Treat Patient
Subject analysis set type	Intention-to-treat

Subject analysis set description:

all randomized patients, whether treated or not, eligible or not. Patients are analyzed in the arm assigned by randomization (if applicable).

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

all patients who have received at least one treatment administration. Patients will be analyzed in the treatment arm they actually received.

Primary: Primary efficacy endpoint

End point title	Primary efficacy endpoint[1]

End point description:

to evaluate the combination of radiotherapy + cisplatin + gemcitabine in terms of disease-free survival in non metastatic muscle invasive urothelial cancer patients.

End point type	Primary

End point timeframe:

The time to relapse is defined as the time from the date of randomisation to the date of the first event. Time to relapse for patients without any event (local, regional, distance, or death) will be censored at the date of latest information (Time Frame:

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: At the end of the inclusions, if 51 patients or less among 65 patients show success, the experimental treatment may be considered insufficiently active. If at least 52 patients show success, the experimental treatment may be considered active enough to be studied in phase III provided that the control arm results are close to the results expected in this arm.
The expected number of necessary subjects not being reached it is not possible to conclude.

End point values	Arm A : Active comparator arm	Arm B : Experimental arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	43		
Units: month				
median (confidence interval 95%)				
Patients	14 (0 to 70)	41 (0 to 85)		
Percentage	58.3 (0 to 70)	60 (0 to 85)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event are reported from baseline to the end of study

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Arm A : Active comparator arm

Reporting group description:

first step : radiotherapy + Cispaltin during 5 weeks
Evaluation by cystoscopy : if complete histological response, the treatement continue
second step : radiotherapy + Cispaltin during 2 weeks

Reporting group title	Arm B : Experimental arm

Reporting group description:

first step : radiotherapy + Cispaltin = Gemcitabine during 5 weeks
Evaluation by cystoscopy : if complete histological response, the treatement continue
second step : radiotherapy + Cispaltin + Gemcitabine during 2 weeks

Serious adverse events	Arm A : Active comparator arm	Arm B : Experimental arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 24 (41.67%)	23 / 45 (51.11%)	
number of deaths (all causes)	2	2	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon	Additional description: Sigmoid colon carcinoma grade 3		
subjects affected / exposed	1 / 24 (4.17%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute myeloid leukaemia	Additional description: Acute myeloid leukemia ,(Severe sepsis on febrile aplasia) grade 5		
subjects affected / exposed	0 / 24 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Basal cell carcinoma	Additional description: Basocellular carcinoma grade 2		
subjects affected / exposed	0 / 24 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Glioblastoma	Additional description: Glioblastome grade 5		
subjects affected / exposed	1 / 24 (4.17%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lip squamous cell carcinoma	Additional description: Squamous cell of the lower left lip grade 3		
subjects affected / exposed	0 / 24 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma	Additional description: IgG Kappa monoclonal dysglobunemia -Myeloma type I grade 3		
subjects affected / exposed	0 / 24 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injury, poisoning and procedural complications			
Radiation proctitis	Additional description: radiation sigmoidis grade 3		
subjects affected / exposed	1 / 24 (4.17%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
hypertension	Additional description: high blood pressure grade 3		
subjects affected / exposed	0 / 24 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
atrial flutter	Additional description: atrial flutter grade 3 for the same patient		
subjects affected / exposed	0 / 24 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 24 (0.00%)	3 / 45 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
neutropenia	Additional description: neutropenia grade 4		

subjects affected / exposed	0 / 24 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
asthenia	Additional description: asthenia grade 3		
subjects affected / exposed	0 / 24 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal obstruction	Additional description: small bowel and colon obstructive syndrome on radiation induced lesion		
subjects affected / exposed	1 / 24 (4.17%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal stenosis	Additional description: stenosis of the rectosigmoid junction grade 4		
subjects affected / exposed	0 / 24 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction	Additional description: occlusive syndrome of the small intestine grade 3		
subjects affected / exposed	1 / 24 (4.17%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis radiation	Additional description: Radiation ileitis grade 3 Hemorrhagic radiation rectosigmoiditis grade 3		
subjects affected / exposed	2 / 24 (8.33%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure	Additional description: Acute respiratory failure grade 4		
subjects affected / exposed	1 / 24 (4.17%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Completed suicide	Additional description: suicide grade 5		

subjects affected / exposed	0 / 24 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal and urinary disorders			
Acute kidney injury	Additional description: acute renal failure grade 2 (experimental arm) acute renal failure grade 1 (experimental arm)		
subjects affected / exposed	0 / 24 (0.00%)	2 / 45 (4.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
hematuria	Additional description: hematuria grade 3 (experimental arm) hematuria grade 3 (control arm) hematuria grade 3 (experimental arm)		
subjects affected / exposed	1 / 24 (4.17%)	2 / 45 (4.44%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure	Additional description: renal failure grade 3 (experimental arm) renal failure grade 2 (experimental arm)		
subjects affected / exposed	0 / 24 (0.00%)	2 / 45 (4.44%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
urinary retention	Additional description: urinary retention grade 2		
subjects affected / exposed	0 / 24 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis	Additional description: septicemia to E.coli and enterobacteria grade 4		
subjects affected / exposed	0 / 24 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis	Additional description: sepsis at streptococus grade 3		
subjects affected / exposed	0 / 24 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Arm A : Active comparator arm	Arm B : Experimental arm	
Total subjects affected by non-serious adverse events subjects affected / exposed	24 / 24 (100.00%)	45 / 45 (100.00%)	
Cardiac disorders			
Dyspnoea	Additional description: experimental arm : grade 1 : 1		
subjects affected / exposed	0 / 24 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Nervous system disorders			
Neuropathy peripheral	Additional description: control arm : grade 1 : 1 Experimental arm : grade 1 : 2		
subjects affected / exposed	1 / 24 (4.17%)	2 / 45 (4.44%)	
occurrences (all)	1	2	
General disorders and administration site conditions			
Alopecia	Additional description: grade 2 (experimental arm)		
subjects affected / exposed	0 / 24 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Asthenia	Additional description: control arm : grade 1 : 10 grade 2 : 3 grade 3 : 2 experimental arm : grade 1 : 15 grade 2 : 9 grade 3 : 3		
subjects affected / exposed	15 / 24 (62.50%)	27 / 45 (60.00%)	
occurrences (all)	15	27	
Abdominal pain	Additional description: control arm : grade 1 : 2 grade 2 : 1 experimental arm : grade 1 : 9 grade 2 : 3		
subjects affected / exposed	3 / 24 (12.50%)	12 / 45 (26.67%)	
occurrences (all)	3	12	
Ear and labyrinth disorders			
Auditory disorder	Additional description: control arm : grade 1 : 1 Experimental arm : grade 1 : 2 grade 2 : 1		
subjects affected / exposed	1 / 24 (4.17%)	3 / 45 (6.67%)	
occurrences (all)	1	3	
Gastrointestinal disorders			
Anorexia and bulimia syndrome	Additional description: control arm : grade 2 : 1 experimental arm : grade 1 : 11		

	grade 2 : 2 grade 3 : 1		
subjects affected / exposed	1 / 24 (4.17%)	14 / 45 (31.11%)	
occurrences (all)	1	14	
Diarrhoea	Additional description: control arm : grade 1 : 8 grade 2 : 5 experimental arm : grade 1 : 10 grade 2 : 13 grade 3 : 2		
subjects affected / exposed	13 / 24 (54.17%)	25 / 45 (55.56%)	
occurrences (all)	13	25	
Dysgeusia	Additional description: control arm : grade 1 : 1 experimental arm : grade 1 : 3 grade 2 : 1		
subjects affected / exposed	1 / 24 (4.17%)	4 / 45 (8.89%)	
occurrences (all)	1	4	
Nausea	Additional description: control arm : grade 1 : 7 grade 2 : 1 Experimental arm : grade 1 : 18 grade 2 : 5		
subjects affected / exposed	8 / 24 (33.33%)	23 / 45 (51.11%)	
occurrences (all)	8	23	
Rectal haemorrhage	Additional description: control arm : grade 1 : 2 grade 2 : 1 Experimental arm : grade 1 : 2		
subjects affected / exposed	3 / 24 (12.50%)	2 / 45 (4.44%)	
occurrences (all)	3	2	
Vomiting	Additional description: control arm : grade 1 : 2 grade 2 : 1 Experimental arm : grade 1 : 2 grade 2 : 3		
subjects affected / exposed	3 / 24 (12.50%)	5 / 45 (11.11%)	
occurrences (all)	3	5	
Renal and urinary disorders			
dysuria	Additional description: control arm : grade 1 : 5 grade 2 : 1 experimental arm : grade 1 : 14 grade 2 : 2		
subjects affected / exposed	6 / 24 (25.00%)	16 / 45 (35.56%)	
occurrences (all)	6	16	
hematuria	Additional description: control arm : grade 2 : 1		

	grade 3 : 1 experimental arm : grade 2 : 1		
subjects affected / exposed	2 / 24 (8.33%)	1 / 45 (2.22%)	
occurrences (all)	2	1	
Pollakiuria	Additional description: control arm : grade 1 : 4 grade 2 : 12 grade 3 : 1 Experimental arm : grade 1 : 13 grade 2 : 13		
subjects affected / exposed	16 / 24 (66.67%)	26 / 45 (57.78%)	
occurrences (all)	16	26	
Infections and infestations			
fever	Additional description: experimental arm : grade 1 : 2 grade 4 : 1		
subjects affected / exposed	0 / 24 (0.00%)	3 / 45 (6.67%)	
occurrences (all)	0	3	
infection	Additional description: experimental arm : grade 2 : 1		
subjects affected / exposed	0 / 24 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Urinary infection	Additional description: control arm : grade 1 : 8 grade 2 : 6 experimental arm : grade 1 : 11 grade 2 : 13		
subjects affected / exposed	14 / 24 (58.33%)	24 / 45 (53.33%)	
occurrences (all)	14	24	
Metabolism and nutrition disorders			
Mucositis	Additional description: control arm : grade 1 : 3		
subjects affected / exposed	3 / 24 (12.50%)	0 / 45 (0.00%)	
occurrences (all)	3	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 January 2012	Updated investigator's list Updated Cisplatin Administration procedure
10 April 2013	Updated investigator's list
03 June 2015	Updated investigator's list Recruitment period extended by 2 years.
13 September 2017	Updated sponsor contact information Protocol modification: clarification, deletion of the CSI, update of the calendar, update of the randomization procedure, update of pharmacovigilance part. Recruitment period extended
12 September 2018	Updating contact information of romotor Protocol modification: addition of monitoring for patients in progress, update to regulatory standards in terms of pharmacovigilance, update of ICH, update concerning the application of the GDPR Deletion of Appendix: Deletion of Insurance Attestation and ISC Charter Modification of the list of investigators.
05 September 2019	Modification of the list of investigators. Deletion of the investigatory list in the appendices.
09 September 2020	Extension of the duration of inclusion in the protocol Update of the pharmacovigilance part in the protocol Updating of pharmacovigilance forms in the annexes

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
30 March 2020	Because of the major impact of the COVID19 pandemic on our personal, professional and patient management lives, we made the decision in agreement with the coordinators to temporarily stop the inclusion in the study	06 May 2020

Notes:

Limitations and caveats

None reported