



## 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/m<sup>2</sup>. 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 recruitment : 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 |
|------------------------------|-----|

|                  |                               |
|------------------|-------------------------------|
| <b>Arm title</b> | Arm A : Active comparator arm |
|------------------|-------------------------------|

Arm description:

first step : radiotherapy + Cisplatin during 5 weeks

Evaluation by cystoscopy : if complete histological response, the treatment continue

second step : radiotherapy + Cisplatin 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/m<sup>2</sup> at day 2 to day 5 and day 23 to day 26 (5 weeks)

second step : 20 mg/m<sup>2</sup> at day 2 to day 5 (2 weeks)

|                  |                          |
|------------------|--------------------------|
| <b>Arm title</b> | Arm B : Experimental arm |
|------------------|--------------------------|

Arm description:

first step : radiotherapy + Cisplatin + Gemcitabine during 5 weeks

Evaluation by cystoscopy : if complete histological response, the treatment continue

second step : radiotherapy + Cisplatin + 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/m<sup>2</sup> at day 2 to day 5 and day 23 to day 26 (5 weeks)

second step : 20 mg/m<sup>2</sup> 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/m<sup>2</sup> to day 2,5,9,12,16,19,23,26,30,33 (5 weeks)

second step : 25 mg/m<sup>2</sup> to day 2,5,9,12 (2 weeks)

| <b>Number of subjects in period 1</b> | 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:<br>first step : radiotherapy + Cisplatin during 5 weeks<br>Evaluation by cystoscopy : if complete histological response, the treatment continues<br>second step : radiotherapy + Cisplatin during 2 weeks                             |                               |
| Reporting group title  | Arm B : Experimental arm      |
| Reporting group description:<br>first step : radiotherapy + Cisplatin + Gemcitabine during 5 weeks<br>Evaluation by cystoscopy : if complete histological response, the treatment continues<br>second step : radiotherapy + Cisplatin + Gemcitabine during 2 weeks |                               |
| Subject analysis set title   | Intention to Treat Patient    |
| Subject analysis set type  | Intention-to-treat            |
| Subject analysis set description:<br>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:<br>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 <sup>[1]</sup> |
| End point description:<br>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:<br>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, distant, 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

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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 + Cisplatin during 5 weeks

Evaluation by cystoscopy : if complete histological response, the treatment continue

second step : radiotherapy + Cisplatin during 2 weeks

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Arm B : Experimental arm |
|-----------------------|--------------------------|

Reporting group description:

first step : radiotherapy + Cisplatin + Gemcitabine during 5 weeks

Evaluation by cystoscopy : if complete histological response, the treatment continue

second step : radiotherapy + Cisplatin + 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          |
| 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          |
| 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          |
| 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          |
| neutropenia                                    |  |   |                |
|  | deaths causally related to treatment / all   | 0 / 0   | 0 / 0          |
|  | 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<br>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)<br>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)<br>hematuria grade 3 (control arm)<br>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)<br>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 streptococcus 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 :<br>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 :<br>grade 1 : 1                                |                          |  |
|   | Experimental arm :<br>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 :<br>grade 1 : 10<br>grade 2 : 3<br>grade 3 : 2 |                          |  |
|   | experimental arm :<br>grade 1 : 15<br>grade 2 : 9<br>grade 3 : 3                    |                          |  |
| subjects affected / exposed                           | 15 / 24 (62.50%)  | 27 / 45 (60.00%)         |  |
| occurrences (all)                                     | 15  | 27                       |  |
| Abdominal pain  | Additional description: control arm :<br>grade 1 : 2<br>grade 2 : 1                 |                          |  |
|   | experimental arm :<br>grade 1 : 9<br>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 :<br>grade 1 : 1                                |                          |  |
|   | Experimental arm :<br>grade 1 : 2<br>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 :<br>grade 2 : 1                                |                          |  |
|   | experimental arm :<br>grade 1 : 11  |                          |  |

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

|  |   |                        |  |
|--|---|------------------------|--|
| subjects affected / exposed<br>occurrences (all) | grade 3 : 1<br>experimental arm :<br>grade 2 : 1  |                        |  |
|  | 2 / 24 (8.33%)<br>2   | 1 / 45 (2.22%)<br>1    |  |
|  | Additional description: control arm :<br>grade 1 : 4<br>grade 2 : 12<br>grade 3 : 1<br><br>Experimental arm :<br>grade 1 : 13<br>grade 2 : 13 |                        |  |
| Pollakiuria                                      |   |                        |  |
| subjects affected / exposed<br>occurrences (all) | 16 / 24 (66.67%)<br>16  | 26 / 45 (57.78%)<br>26 |  |
| Infections and infestations                      |   |                        |  |
| fever  |   |                        |  |
| subjects affected / exposed<br>occurrences (all) | Additional description: experimental arm :<br>grade 1 : 2<br>grade 4 : 1  |                        |  |
|  | 0 / 24 (0.00%)<br>0   | 3 / 45 (6.67%)<br>3    |  |
| infection  |   |                        |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 24 (0.00%)<br>0   | 1 / 45 (2.22%)<br>1    |  |
| Urinary infection                                |   |                        |  |
| subjects affected / exposed<br>occurrences (all) | Additional description: control arm :<br>grade 1 : 8<br>grade 2 : 6<br><br>experimental arm :<br>grade 1 : 11<br>grade 2 : 13                 |                        |  |
|  | 14 / 24 (58.33%)<br>14  | 24 / 45 (53.33%)<br>24 |  |
| Metabolism and nutrition disorders               |   |                        |  |
| Mucositis  |   |                        |  |
| subjects affected / exposed<br>occurrences (all) | 3 / 24 (12.50%)<br>3  | 0 / 45 (0.00%)<br>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<br>Updated Cisplatin Administration procedure  |
| 10 April 2013     | Updated investigator's list  |
| 03 June 2015      | Updated investigator's list<br>Recruitment period extended by 2 years.   |
| 13 September 2017 | Updated sponsor contact information<br>Protocol modification: clarification, deletion of the CSI, update of the calendar, update of the randomization procedure, update of pharmacovigilance part.<br>Recruitment period extended  |
| 12 September 2018 | Updating contact information of romotor<br>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<br>Deletion of Appendix: Deletion of Insurance Attestation and ISC Charter<br>Modification of the list of investigators. |
| 05 September 2019 | Modification of the list of investigators.<br>Deletion of the investigatory list in the appendices.  |
| 09 September 2020 | Extension of the duration of inclusion in the protocol<br>Update of the pharmacovigilance part in the protocol<br>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