



Clinical trial results:

Prospective phase II study of Gemcitabine plus platinum salt in combination with bevacizumab (Avastin®) for metastatic collecting duct carcinoma.

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2013-001179-19 |
| Trial protocol | FR |
| Global end of trial date | 07 April 2020 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 06 July 2023 |
| First version publication date | 06 July 2023 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | UC-0160/1210 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02363751 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | UNICANCER |
| Sponsor organisation address | 101 rue de Tolbiac, Paris, France, 75013 |
| Public contact | Nourredine AIT-RAHMOUNE, UNICANCER, +33 1 71 93 67 04, n.ait-rahmoune@unicancer.fr |
| Scientific contact | Nourredine AIT-RAHMOUNE, UNICANCER, +33 1 71 93 67 04, n.ait-rahmoune@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 | 24 April 2020 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 07 April 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of gemcitabine plus platinum salt in combination with bevacizumab using a co-primary endpoint composed of Objective Response Rate (CR or PR according to RECIST criteria) and Progression-Free Survival rate at 6 months.

Protection of trial subjects:

In order to ensure the protection of the rights, safety and well-being of trial subjects, this clinical trial was conducted in accordance with the Declaration of Helsinki (1964) and subsequent amendments, ICH Good Clinical Practice Guidelines (CPMP/ICH/135/95), the European Directive (2001/20/CE) and the applicable local regulatory requirements and laws.

Furthermore, an independent Ethics Committees reviewed and gave a favorable opinion to the study documents, including the initial protocol and all subsequent amendments, and all information and documents provided to subjects/patients.

Written informed consent was obtained from all patients prior to enrollment.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 09 February 2015 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 2 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | France: 34 |
| Worldwide total number of subjects | 34 |
| EEA total number of subjects | 34 |

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) | 23 |
| From 65 to 84 years | 11 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

36 patients were included from 19-FEB-2015 to 14-JAN-2019. A screen failure (diagnosis ambiguity) led to the non-inclusion of 1 patient. The data of 1 patient was not integrated in the analysis due to non-conformity (CRF tracking). The final statistical analysis was completed on 24-APR-2020 based on the data collected from 34 patients.

Pre-assignment

Screening details:

Twenty seven (27) patients will be included in stage 1. Trial will be stopped for futility after step 1 if there are 10 or less patients with an objective response (OR) and at least 10 patients who progressed within 6 months. Otherwise, 14 additional patients will be enrolled in Stage 2 for a total of 41 patients.

Period 1

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

Arms

| | |
|-----------|-------------|
| Arm title | Bevacizumab |
|-----------|-------------|

Arm description:

For this study, the investigational drug (bevacizumab), The non-investigational products (gemcitabine and platinum salts) will be administered i.v. at doses of: bevacizumab 15 mg/kg, D1; gemcitabine 1250 mg/m² (D1-D8); platinum salt (cisplatin, 70 mg/m² D1 or carboplatin AUC 5 mg/mL.min, D1), administered every 3 weeks for a period of 6 cycles. Then, bevacizumab monotherapy will be administered i.v. at the same dose every 3 weeks, until disease progression or for 24 months.

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Bevacizumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Concentrate for solution for infusion |

Dosage and administration details:

Bevacizumab (15 mg/kg, final volume 100 ml injected over 90 min), was administered for 6 cycles separated by 21 days before the non-investigational products constitutive of the standard chemotherapy. At the end of those 6 cycles, bevacizumab was to be continued as a monotherapy according to the same dosing schedule (once every 21 days) until disease progression or for 24 months. In case of toxic events, bevacizumab treatment could be discontinued for up to 4 weeks until toxicity recovery (\leq grade 1). For discontinuation shorter than 4 weeks, bevacizumab treatment was resumed. However, over 4 weeks of discontinuation, bevacizumab was permanently discontinued, and only the chemotherapy part of the treatment was administered to the patient.

| | |
|---------------------------------------|-------------|
| Number of subjects in period 1 | Bevacizumab |
| Started | 34 |
| Completed | 34 |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|---------------|
| Reporting group title | Overall Trial |
| Reporting group description: - | |

| Reporting group values | Overall Trial | Total | |
|--|---------------|-------|--|
| Number of subjects | 34 | 34 | |
| Age categorical | | | |
| Units: Subjects | | | |
| [18-50[| 8 | 8 | |
| >50 | 23 | 23 | |
| Missing | 3 | 3 | |
| Age continuous | | | |
| Out of the 34 patients included gender and age-related data were missing for 3 of them | | | |
| Units: years | | | |
| median | 61 | | |
| full range (min-max) | 23 to 78 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 26 | 26 | |
| Male | 5 | 5 | |
| Missing | 3 | 3 | |
| ECOG | | | |
| Units: Subjects | | | |
| ECOG 0 | 12 | 12 | |
| ECOG 1 | 15 | 15 | |
| ECOG 2 | 7 | 7 | |
| Weight range (kg) | | | |
| Units: Subjects | | | |
| < 50 | 1 | 1 | |
| [50-100[| 32 | 32 | |
| >100 | 1 | 1 | |

End points

End points reporting groups

| | |
|--|-------------|
| Reporting group title | Bevacizumab |
| Reporting group description: | |
| For this study, the investigational drug (bevacizumab), The non-investigational products (gemcitabine and platinum salts) will be administered i.v. at doses of: bevacizumab 15 mg/kg, D1; gemcitabine 1250 mg/m ² (D1-D8); platinum salt (cisplatin, 70 mg/m ² D1 or carboplatin AUC 5 mg/mL.min, D1), administered every 3 weeks for a period of 6 cycles. Then, bevacizumab monotherapy will be administered i.v. at the same dose every 3 weeks, until disease progression or for 24 months. | |

Primary: Objective Response Rate (ORR) at 6 months

| | |
|---|--|
| End point title | Objective Response Rate (ORR) at 6 months ^[1] |
| End point description: | |
| Complete or partial responses (CR or PR) were calculated as the number of patients with a response upon RECIST1.1 criterion out of the number of patients treated. Tumor assessment was made by thoracic-abdominal-pelvic CT scan (or abdominal-pelvic MRI and chest CT scan) and scintigraphy. | |
| Note: | |
| 10 (30.3%) out of 33 patients had a complete or partial response. | |
| 23 (69.7%) out of 34 patients displayed no response | |
| End point type | Primary |
| End point timeframe: | |
| the Objective Response Rate (complete or partial responses) according to RECIST v1.1 criteria was evaluated during the last visit taking place at or before 197 days from treatment initiation on the basis of the measurable lesions identified at baseline. | |

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: For this study, no formal statistical analysis between arms was planned. The OR rate thresholds were set at 0.25 and 0.50 to distinguish unfavorable from favorable therapy, respectively. To the same end, PFS rate thresholds were set at 0.50 and 0.70. The therapy was to be rejected if both ORR and PFSR at 6 months were as low as or lower than their null values (lower threshold).

| | | | | |
|----------------------------------|---------------------|--|--|--|
| End point values | Bevacizumab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 34 | | | |
| Units: percent | | | | |
| number (confidence interval 95%) | | | | |
| ORR | 30.3 (15.6 to 48.7) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Progression-free survival (PFS) rate at 6 months

| | |
|---|---|
| End point title | Progression-free survival (PFS) rate at 6 months ^[2] |
| End point description: | |
| PFS at 6 months (PFS6) was calculated as the number of patients with an objective progression | |

(radiological or death) out of the number of patients already treated. PFS was estimated by the Kaplan-Meier method.

| | |
|---|---------|
| End point type | Primary |
| End point timeframe: | |
| The Progression-Free Survival rate at 6 months, PFS being defined as an absence of disease progression or death evaluated during the last visit taking place at or before 197 days from treatment initiation. | |

Notes:

[2] - 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: For this study, no formal statistical analysis between arms was planned. The OR rate thresholds were set at 0.25 and 0.50 to distinguish unfavorable from favorable therapy, respectively. To the same end, PFS rate thresholds were set at 0.50 and 0.70. The therapy was to be rejected if both ORR and PFSR at 6 months were as low as or lower than their null values (lower threshold).

| | | | | |
|----------------------------------|---------------------|--|--|--|
| End point values | Bevacizumab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 34 | | | |
| Units: percent | | | | |
| number (confidence interval 95%) | | | | |
| number (confidence interval 95%) | 41.2 (24.6 to 59.3) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Progression-Free Survival (PFS)

| | |
|--|---|
| End point title | Overall Progression-Free Survival (PFS) |
| End point description: | |
| Progression-free survival (PFS) was calculated from the date of the first dose of treatment to the date of progression or death (whichever comes first), or last date with no progression; PFS was estimated by the Kaplan-Meier method. | |
| End point type | Secondary |
| End point timeframe: | |
| Progression-Free Survival (PFS) was calculated from the date of first treatment administration to the date of progression or death (whichever came first), or last date with no progression. | |

| | | | | |
|----------------------------------|------------------|--|--|--|
| End point values | Bevacizumab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 34 | | | |
| Units: month | | | | |
| median (confidence interval 95%) | | | | |
| median (confidence interval 95%) | 6.1 (5.3 to 7.6) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

| | |
|-----------------|-----------------------|
| End point title | Overall Survival (OS) |
|-----------------|-----------------------|

End point description:

Overall Survival (OS) was to be estimated by the Kaplan-Meier method.

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

End point timeframe:

The Overall Survival (OS) will be calculated from the date of the first dose of treatment to the date of death (whatever the cause) or the date of last follow-up;

| End point values | Bevacizumab | | | |
|----------------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 34 | | | |
| Units: month | | | | |
| median (confidence interval 95%) | | | | |
| median (confidence interval 95%) | 11.1 (7.6 to 15.9) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall period of the study (up to 2 years)

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|----|
| Dictionary version | 18 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Bevacizumab |
|-----------------------|-------------|

Reporting group description: -

| Serious adverse events | Bevacizumab | | |
|---|------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 21 / 34 (61.76%) | | |
| number of deaths (all causes) | 23 | | |
| number of deaths resulting from adverse events | 2 | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Clot | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Pain relief | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bladder neck resection | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|--|----------------|--|--|
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fever | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary disorder | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Confusional state | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Transfusion related Allergy | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Congenital, familial and genetic disorders | | | |
| Aplasia | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Cephalalgia | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Encephalitis | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Myoclonic jerks | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Thrombopenia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 3 / 34 (8.82%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anemia | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bicytopenia | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal perforation | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney failure | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Esophageal candidiasis | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Infection urinary tract | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Septicemia | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 3 %

| Non-serious adverse events | Bevacizumab | | |
|---|-------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 34 / 34 (100.00%) | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 12 / 34 (35.29%) | | |
| occurrences (all) | 63 | | |
| Arterial embolism | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences (all) | 2 | | |
| Hot flush | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Bruise | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 2 | | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Surgical and medical procedures | | | |

| | | | |
|--|------------------|--|--|
| Pain relief | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Bladder neck resection | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 26 / 34 (76.47%) | | |
| occurrences (all) | 114 | | |
| Fatigue | | | |
| subjects affected / exposed | 8 / 34 (23.53%) | | |
| occurrences (all) | 40 | | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 8 / 34 (23.53%) | | |
| occurrences (all) | 18 | | |
| Thoracic pain | | | |
| subjects affected / exposed | 4 / 34 (11.76%) | | |
| occurrences (all) | 7 | | |
| Fever | | | |
| subjects affected / exposed | 4 / 34 (11.76%) | | |
| occurrences (all) | 10 | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences (all) | 2 | | |
| Inflammation | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences (all) | 2 | | |
| Peripheral oedema | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences (all) | 2 | | |
| Influenza like syndrome | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences (all) | 2 | | |
| Xerosis | | | |

| | | | |
|--|--|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hyperthermia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Syncope</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Inflammatory syndrome</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>2 / 34 (5.88%)</p> <p>3</p> <p>1 / 34 (2.94%)</p> <p>1</p> <p>26 / 34 (76.47%)</p> <p>125</p> <p>1 / 34 (2.94%)</p> <p>1</p> | | |
| <p>Immune system disorders</p> <p>Hypersensitivity</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 34 (2.94%)</p> <p>1</p> | | |
| <p>Reproductive system and breast disorders</p> <p>Pelvic pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 34 (2.94%)</p> <p>1</p> | | |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Epistaxis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dyspnea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dysphonia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dyspnea on effort</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dyspnea at rest</p> | <p>14 / 34 (41.18%)</p> <p>50</p> <p>12 / 34 (35.29%)</p> <p>32</p> <p>7 / 34 (20.59%)</p> <p>15</p> <p>2 / 34 (5.88%)</p> <p>4</p> <p>1 / 34 (2.94%)</p> <p>3</p> | | |

| | | | |
|--------------------------------------|------------------|--|--|
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Cough productive | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Pulmonary disorder | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Sleep disorder | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Investigations | | | |
| Creatine increased | | | |
| subjects affected / exposed | 11 / 34 (32.35%) | | |
| occurrences (all) | 51 | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 7 / 34 (20.59%) | | |
| occurrences (all) | 23 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 7 / 34 (20.59%) | | |
| occurrences (all) | 17 | | |
| Gamma-glutamyltransferase increased | | | |

| | | | |
|--|--|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Weight loss</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Creatinine increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Serum lactic dehydrogenase increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Serum urea increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>8 / 34 (23.53%)</p> <p>37</p> <p>6 / 34 (17.65%)</p> <p>10</p> <p>1 / 34 (2.94%)</p> <p>1</p> <p>1 / 34 (2.94%)</p> <p>5</p> <p>1 / 34 (2.94%)</p> <p>3</p> | | |
| <p>Injury, poisoning and procedural complications</p> <p>Pneumonitis chemical</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Transfusion-related allergy</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pain surgical site</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 34 (2.94%)</p> <p>1</p> <p>1 / 34 (2.94%)</p> <p>1</p> <p>1 / 34 (2.94%)</p> <p>1</p> | | |
| <p>Congenital, familial and genetic disorders</p> <p>Aplasia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 34 (2.94%)</p> <p>1</p> | | |
| <p>Cardiac disorders</p> <p>Cardiac failure</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Palpitations</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>2 / 34 (5.88%)</p> <p>7</p> <p>1 / 34 (2.94%)</p> <p>1</p> | | |

| | | | |
|---------------------------------|-----------------|--|--|
| Nervous system disorders | | | |
| Peripheral Neuropathy | | | |
| subjects affected / exposed | 7 / 34 (20.59%) | | |
| occurrences (all) | 37 | | |
| Cephalalgia | | | |
| subjects affected / exposed | 5 / 34 (14.71%) | | |
| occurrences (all) | 15 | | |
| Dysgeusia | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences (all) | 2 | | |
| Paresthesia | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences (all) | 3 | | |
| Memory impairment | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Dysesthesia | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Encephalitis | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Cerebral hemorrhage | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Myoclonic jerks | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Neuralgia | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Peripheral neuropathy sensitive | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences (all) | 2 | | |
| Pre-syncope | | | |

| | | | |
|--------------------------------------|------------------|--|--|
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 3 | | |
| Sleepiness | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Balance disorder | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 7 | | |
| Blood and lymphatic system disorders | | | |
| Anemia | | | |
| subjects affected / exposed | 30 / 34 (88.24%) | | |
| occurrences (all) | 168 | | |
| Thrombopenia | | | |
| subjects affected / exposed | 22 / 34 (64.71%) | | |
| occurrences (all) | 60 | | |
| Neutropenia | | | |
| subjects affected / exposed | 21 / 34 (61.76%) | | |
| occurrences (all) | 55 | | |
| Leucopenia | | | |
| subjects affected / exposed | 6 / 34 (17.65%) | | |
| occurrences (all) | 11 | | |
| Lymphopenia | | | |
| subjects affected / exposed | 5 / 34 (14.71%) | | |
| occurrences (all) | 17 | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 3 / 34 (8.82%) | | |
| occurrences (all) | 4 | | |
| Thrombocytosis | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences (all) | 5 | | |
| Eye disorders | | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Eye pain | | | |

| | | | |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Edema palpebral | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 26 / 34 (76.47%) | | |
| occurrences (all) | 125 | | |
| Vomiting | | | |
| subjects affected / exposed | 15 / 34 (44.12%) | | |
| occurrences (all) | 35 | | |
| Constipation | | | |
| subjects affected / exposed | 11 / 34 (32.35%) | | |
| occurrences (all) | 37 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 9 / 34 (26.47%) | | |
| occurrences (all) | 10 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 5 / 34 (14.71%) | | |
| occurrences (all) | 11 | | |
| Upper abdominal pain | | | |
| subjects affected / exposed | 5 / 34 (14.71%) | | |
| occurrences (all) | 14 | | |
| Dental pain | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences (all) | 2 | | |
| Gastroesophageal reflux | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences (all) | 3 | | |
| Gingival bleeding | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences (all) | 5 | | |
| Abdominal swelling | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |

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|------------------------------|----------------|--|--|
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 2 | | |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Gingival erosion | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Glossodynia | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Gingival inflammation | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Oral mucositis | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Odynophagia | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Esophagitis | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal perforation | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Stomatitis Aphtous | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |

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|--|------------------|--|--|
| Hepatobiliary disorders | | | |
| Cholestasis | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 7 | | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 4 / 34 (11.76%) | | |
| occurrences (all) | 12 | | |
| Skin rash | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences (all) | 2 | | |
| Scar pain | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Erythema | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Pruritus | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 2 | | |
| Acral erythema | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Ungual disorder | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Renal and urinary disorders | | | |
| Proteinuria | | | |
| subjects affected / exposed | 10 / 34 (29.41%) | | |
| occurrences (all) | 58 | | |
| Dysuria | | | |
| subjects affected / exposed | 3 / 34 (8.82%) | | |
| occurrences (all) | 12 | | |
| Kidney failure | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences (all) | 13 | | |
| Acute kidney failure | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Chronic kidney failure | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 3 | | |
| Hematuria | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Pollakiuria | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 3 | | |
| Polyuria | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Lower urinary tract symptoms | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 2 | | |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 3 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 11 / 34 (32.35%) | | |
| occurrences (all) | 48 | | |
| Myalgia | | | |
| subjects affected / exposed | 4 / 34 (11.76%) | | |
| occurrences (all) | 6 | | |
| Arthralgia | | | |
| subjects affected / exposed | 3 / 34 (8.82%) | | |
| occurrences (all) | 6 | | |
| Bone pain | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences (all) | 3 | | |
| Muscular contraction | | | |

| | | | |
|-------------------------------------|----------------|--|--|
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 4 | | |
| Flank pain | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences (all) | 3 | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal pain (Thoracic) | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Pain in extremities | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 2 | | |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Radiotherapie induced low back pain | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Hip pain increased | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 3 | | |
| Infections and infestations | | | |
| Abscess periodontal | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences (all) | 5 | | |
| Bronchitis | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences (all) | 2 | | |
| Angina | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Esophageal candidiasis | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |

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|-----------------------------------|----------------|--|--|
| Erysipelas | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Influenza | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Infection | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Helicobacter infection | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Infection respiratory tract | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 2 | | |
| Infection upper respiratory tract | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Infection urinary tract | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 6 | | |
| Device related infection | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 2 | | |
| Laryngitis | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 5 | | |
| Mycosis Mouth | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Rhinolaryngitis | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Rhinopharyngitis | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |

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|------------------------------------|------------------|--|--|
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Bacterial prostatitis | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Pulpitis dental | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Rhinitis | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Septicemia | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 21 / 34 (61.76%) | | |
| occurrences (all) | 63 | | |
| Hyperkalemia | | | |
| subjects affected / exposed | 8 / 34 (23.53%) | | |
| occurrences (all) | 35 | | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 3 / 34 (8.82%) | | |
| occurrences (all) | 5 | | |
| Hyponatremia | | | |
| subjects affected / exposed | 3 / 34 (8.82%) | | |
| occurrences (all) | 5 | | |
| Dehydration | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences (all) | 2 | | |
| Hypercalcemia | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences (all) | 2 | | |
| Iron deficiency anaemia | | | |

| | | | |
|--------------------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Dyslipidemia | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 2 | | |
| Hypercreatininaemia | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 4 | | |
| Hyperlipasemia | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Hyperurecemia | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 1 | | |
| Hypokalemia | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | | |
| occurrences (all) | 2 | | |
| Serum alkaline phosphatase increased | | | |
| subjects affected / exposed | 4 / 34 (11.76%) | | |
| occurrences (all) | 18 | | |
| Hypocalcemia | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | | |
| occurrences (all) | 3 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 13 January 2015 | <ul style="list-style-type: none">• The Institut Paillo-Calmettes (Marseille) was approved as a new inclusion center. |
| 17 February 2015 | <ul style="list-style-type: none">• Protocol update: modification of the Inclusion criteria # 2: medullary collecting duct carcinomas were added.• Protocol update: modification of the Inclusion criteria # 12: creatinine clearance was extended to ≥ 40 mL/min when using carboplatin .• Protocol update: modification of the Inclusion criteria # 13: proteinuria measuring unit was corrected, proteinuria is now expressed in g/L.• Protocol update: modification of the Inclusion criteria # 15: ECG sinus rhythm was extended from "normal" to "normal or clinically insignificant as per investigator's judgement"• Protocol update: modification of the Non-Inclusion criteria # 12: "active ulcer" was replaced by "active gastro-duodenal ulcer"• Protocol update: modification of the Non-Inclusion criteria # 14: peripheral neuropathy grade "≥ 2" was replaced by "> 2".• Protocol update: modification of biological tests: proteinuria measuring unit was corrected to be expressed in g/L.• Protocol update: baseline assessment: cross-reference to 6.3 was removed.• Protocol update: dose of bevacizumab expressed in mg/m² was modified to mg/kg.• Protocol update: Introduction was substantiated with additional text and references.• Protocol update: Treatment initiation timing was modified from "7 days after" to "within 7 days" after baseline evaluation.• Protocol update: Contact information for centralized enrollment were updated.• Protocol update: Address of the Unicancer bio Bank : Centre Léon Bérard was updated.• Updates within the Information Note and Consent.• Investigator list updated for centers 5, 15 and 16. |
| 25 March 2015 | <ul style="list-style-type: none">• Investigator list updated for centers 5 and 13. |
| 12 May 2015 | <ul style="list-style-type: none">• Protocol update: modification of the Non-Inclusion criteria # 3: Brain MRI or CT scan was made mandatory at inclusion for every patient.• Protocol update: modification of the Inclusion criteria # 6: Prior adjuvant chemotherapy of localized disease was authorized as long as it did not occur within 12 months of the inclusion date.• Protocol update: modification of the Inclusion criteria # 11: AST and ALT levels were increased from $\leq 4 \times$ ULN to $\leq 5 \times$ ULN in case of liver metastases, total bilirubin level was increased from $\leq 1.5 \times$ ULN to $\leq 3 \times$ ULN in case of liver metastases or Gilbert's syndrome.• Protocol update regarding Safety (# 9.6): Adverse Events of Specific Interest (AESI) were further defined by specifying the grade from which each of them should be accounted for.• Study title modification: "kidney" was added in front of "metastatic collecting duct carcinoma". |
| 07 July 2015 | <ul style="list-style-type: none">• Investigator list updated for centers 5 and 17. |
| 30 September 2015 | <ul style="list-style-type: none">• Investigator list updated for centers 3, 12 and 18. |

| | |
|-------------------|--|
| 14 June 2016 | <ul style="list-style-type: none"> Investigator list updated for centers 2, 3, 4, 5, 7, 12, 17 and 19. |
| 11 October 2016 | <ul style="list-style-type: none"> Protocol update: modification of the Inclusion criteria # 12: the glomerular filtration rate limit was modified from from >40 to >30 mL/min for carboplatin prescription. Protocol update: modification of the Non-Inclusion criteria # 3: Patients with asymptomatic brain metastases can be included. Patients with leptomeningeal disease cannot be included. Protocol update regarding the study duration: Inclusion period extended from 2 to 4 years Duration till primary endpoint evaluation increased from 4.5 to 6.5 years Overall trial duration increased from 4.5 to 6.5 years Study flow chart modification: LVEF exam period extended from within 7 to 28 days before treatment initiation. Study flow chart modification: bone scintigraphy exams every 6 weeks were suppressed except for patients presenting bone lesions at baseline which remained scheduled for exams every 9 weeks. Update of the Information Note and Consent to conform with the General Data Protection Regulation (RGPD). |
| 16 May 2017 | <ul style="list-style-type: none"> Modification of the Coordinating investigator. Dr. Nicolas PECUCHET was replaced by Dr. Constance THIBAUT. Investigator list updated for centers 4, 5, 6, 9, 10, 11, 17, 18 and 19. |
| 16 January 2018 | <ul style="list-style-type: none"> Protocol update of the Inclusion criteria # 7: To the sentence "No irradiation within 4 weeks before inclusion" this amendement added "However, the interval can be reduced to 2 weeks after consultation with the PI". Protocol update of Prohibited Concomitant Treatments: To the sentence "Irradiation within 4 weeks before inclusion" this amendement added "However, the interval can be reduced to 2 weeks after consultation with the PI". Unicancer Clinical Project Manager was updated to Mrs. Sandra PELISSIER. Contact details of the Coordinating investigator was updated. Statistical plan correction: the cut off number of patients who progress within 6 months to stop the trial for futility was updated to 10. The end of the study definition was updated to the last patient of the last visit (LPLV). The center in charge of the centralized review for diagnosis confirmation was updated to Institut Curie. Investigator list updated for centers 3, 4, 7, 9 and 17. |
| 10 September 2019 | <ul style="list-style-type: none"> Update of the Information Note and Consent to conform with the General Data Protection Regulation (RGPD). |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported