



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			

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

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		

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		

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		

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		

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