



UNICANCER Tumor Group: GETUG
Protocol N°: UC-0160/1210 GETUG-AFU 24- EudraCT N°: 2013-001179-19

SYNOPSIS – PROTOCOL N° UC-0160/1210 GETUG-AFU 24

A) TRIAL IDENTIFICATION

CODE NAME ALLOCATED BY THE SPONSOR: UC-0160/1210 GETUG-AFU 24

VERSION AND DATE: V5.1-22.03.2017

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

ABBREVIATED TITLE: BEVABEL

Coordinating investigator: Dr Constance THIBAULT

Medical Oncology
Hôpital Européen Georges Pompidou
20, rue Leblanc,
75908 Paris Cedex 15
Tel : +33 (0)1 56 09 29
Fax : +33 (0)1 56 09 24 15
E-mail : constance.thibault@aphp.fr

Coordinating co-Investigator: Dr Marc-Olivier TIMSIT

Urology
Hôpital Européen Georges Pompidou
20, rue Leblanc,
75908 Paris Cedex 15, France
Phone: +33 (0) 1 56 09 56 45
Fax: +33 (0) 1 56 09 56 17
Email: marc-olivier.timsit@egp.aphp.fr

NUMBER OF PARTICIPATING CENTERS (ESTIMATE): 25

NUMBER OF PATIENTS: 41

B) SPONSOR IDENTIFICATION

NAME: UNICANCER

CONTACT PERSON: Muriel Habibian
101, rue de Tolbiac
75013 Paris, France
Tel. : +33 (0)1 76 64 78 07 – Fax : +33 (0)1 85 34 33 79
Email: m-habibian@unicancer.fr

C) TRIAL GENERAL INFORMATION

INDICATION: Metastatic collecting duct carcinoma.

METHODOLOGY: Open-label, non-randomized, multicenter, phase II, single arm non comparative trial evaluating toxicity and efficacy of gemcitabine plus platinum salt in combination with bevacizumab in first-line setting in metastatic collecting duct carcinoma.

PRIMARY OBJECTIVE: 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.

SECONDARY OBJECTIVE(S):

- Evaluation of the Progression-free survival (PFS)
- Evaluation of the Overall Survival (OS)
- Evaluation of the Safety
- To set up several biological material bank resources (plasma sample, tumor and for patients who underwent nephrectomy, non tumor tissu) for further ancillary studies (molecular, immunologic and pharmacogenomic studies)

INCLUSION CRITERIA:

- 1- Patients should be aged ≥ 18 years at the inclusion,
- 2- Patients with histologically confirmed metastatic collecting duct carcinoma (medullary accepted),
- 3- Available tumor samples for centralized reading by anatomopathologist,
- 4- Patients with or without nephrectomy,
- 5- At least one measurable lesion as per RECIST criteria (RECIST v1.1),
- 6- Patients naive for anti-angiogenic drugs ; Prior adjuvant chemotherapy of localised disease admitted if it is stopped for more than 12 months at the inclusion date.
- 7- No irradiation within 4 weeks before inclusion,
- 8- Absolute neutrophil counts (ANC) $\geq 1.5 \times 10^9/L$,
- 9- Platelets $\geq 100 \times 10^9/L$,
- 10- Hemoglobin ≥ 9 g/dL,
- 11- Hepatic function : AST and ALT $\leq 1.5 \times$ ULN ($\leq 5 \times$ ULN in case of liver metastases); total bilirubin $\leq 1.5 \times$ ULN (except in case of liver metastases and $\leq 3 \times$ ULN in case of Gilbert's syndrome); alkaline phosphatase $< 2 \times$ ULN ($\leq 4 \times$ ULN in case of bone metastases),
- 12- Renal function : creatinine clearance ≥ 60 mL/min (MDRD calculation method) when using cis-platin and > 30 mL/min when using carboplatin,
- 13- Absence of proteinuria at baseline defined by < 0.3 g/L of protein on urine sample or < 0.5 g/24h00 on urine collection,
- 14- Prothrombin time (TP) or partial thromboplastin time (PTT) strictly less than 50% deviation from normal limits, of international normalized ratio (INR) strictly below 2,

Note: The use of full-dose oral or parenteral anticoagulants as well as aspirin or clopidogrel is permitted as long as the INR or a PTT is within therapeutic limits (according to the medical standard of the institution) and the patient has been on a stable dose of anticoagulants for at least two weeks at the time of study enrolment. Prophylactic use of anticoagulants is allowed.
- 15- ECG with normal or clinically insignificant as per investigator's judgement sinus rhythm,
- 16- ECOG Performance Status: 0 – 2,
- 17- Estimated life expectancy ≥ 12 weeks,
- 18- Patients who have received the information sheet, dated and signed the informed consent form,
- 19- Patient of child-bearing potential (for female patient: study entry after a menstrual period and a negative pregnancy test) must agree to use two medically acceptable methods of contraception (one for the patient and one for the partner) during the study and for 6 months after the last study treatment intake.
- 20- Patients must be willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures,
- 21- Patients affiliated to the Social Security System,

NON-INCLUSION CRITERIA:

1. Treatment with any other investigational agent, or participation in another clinical trial within 28 days prior to enrolment,
2. Prior systemic treatment with chemotherapy or anti-angiogenic tyrosine kinase inhibitors such as axitinib, sunitinib, sorafenib, pazopanib, tivozanib, mTOR inhibitor (Temsirrolimus or everolimus) and targeted VEGF drugs such as bevacizumab and VEGF trap,
3. Evidence of current spinal cord compression or leptomeningeal disease. Please note that patients with asymptomatic brain metastases are eligible.
4. Another histological type of renal cancer
5. Other malignancy within 3 years prior to inclusion (except basal cell carcinoma of the skin and/or in situ carcinoma of the cervix, and/or pT1/a bladder cancer),
6. Uncontrolled hypertension (≥ 160 mm Hg systolic and/or ≥ 90 mm Hg diastolic) while receiving medication,
7. Cardio-vascular disorders: congestive heart failure \geq NYHA II, myocardial infarction or coronary artery bypass graft in the previous six months, ongoing severe or unstable angina,
8. LVEF value strictly less than 50%,
9. Current or recent (within 2 weeks of study enrolment) initiation of aspirin, clopidogrel), oral or parenteral anticoagulants or thrombolytic agents for therapeutic purposes.
10. History of clinically significant hemorrhagic or thromboembolic events in the past six months, or known inherited predisposition to bleeding or thrombosis or History of abdominal fistula, GI perforation, intra-abdominal abscess or active GI bleeding within 6 months prior to the first study treatment; History of haemoptysis \geq grade 2 (defined as ≥ 2.5 mL bright red blood per episode) within 1 month of study enrolment,
11. Patients who underwent, according to the investigator, a significant surgery such as but not limited to , abdominal, thoracic or neurologic surgery within 28 days before the first treatment administration or patient with a wound that is not already healed at the first treatment administration or patients who underwent a minor surgical procedure including placement of a vascular access device, within 2 days of the first study treatment,
12. Patients with active gastro-duodenal ulcer,
13. Patients with untreated bone fracture,
14. Peripheral neuropathy grade > 2 (Toxicity Criteria-(CTCAE) v4.0),
15. Patients with active infection requiring intravenous antibiotics at the time of first study treatment,
16. In the opinion of the investigator, any evidence of other severe or uncontrolled systemic disease (e.g. unstable or uncompensated respiratory, cardiac, hepatic or renal disease), or any other acute or chronic medical condition that would make the patient inappropriate with this study,
17. Immunocompromised patients, including known seropositivity for human immunodeficiency virus (HIV),
18. Known hypersensitivity to any component of the investigational drugs or excipients,
19. Pregnant or lactating women,
20. Person deprived of their liberty or under judicial protection (including guardianship),
21. Patients with significantly altered mental status prohibiting the understanding of the study or with psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule or any condition which, in the opinion of the investigator, would preclude participation in this trial. Those conditions should be discussed with the patient before registration in the trial.

PRIMARY ENDPOINT:

The primary endpoint is composed of:

- the objective response rate (CR or PR) according to RECIST criteria (V1.1) on the basis of measurable lesions defined at baseline,
- the progression-free survival (PFS) rate at 6 months , PFS is defined as the absence of disease progression or death.

SECONDARY ENDPOINTS:

- Progression-free survival (PFS) will be 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;
- 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;
- The toxicity will be evaluated according to the NCI-CTC scale version 4.0;

D) INVESTIGATIONAL PRODUCTS**DRUGS:**

Drug name (INN)	Registered name ⁽¹⁾	Pharmaceutical form	Administration	Posology/dosage
CISPLATIN	Cisplatin [®]	Solution for infusion	IV	70mg/m ²
CARBOPLATIN	Carboplatin [®]	Solution for infusion	IV	AUC 5
GEMCITABINE	Gemzar [®]	Powder for solution for injection	IV	1250mg/m ²
BEVACIZUMAB	Avastin [®]	Solution for infusion	IV	15mg/Kg

(1) In case a generic drug is used indicate only the INN name. The choice of the registered or brand name is left to the decision of the investigation center.

THERAPEUTIC REGIMENS:

D1 and D8: GEMCITABINE 1250 mg/m²

D1 CISPLATIN: 70mg/m² **or** CARBOPLATIN AUC 5

D1 BEVACIZUMAB: 15 mg/Kg.

The theoretical range inter cycle is 21 days (D1=D22), except in cases of non-recovery of hematologic or other toxicity.

TREATMENT DURATION

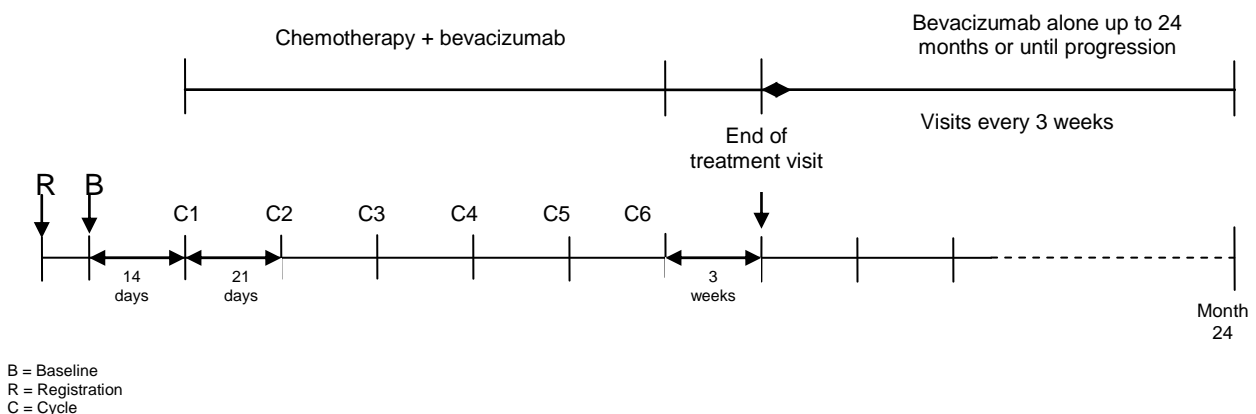
Patients will be treated for a maximum of 6 chemotherapy cycles.

Treatment duration will be adjusted according to tolerability and efficacy. Any patient receiving one chemotherapy cycle or more will be evaluable for efficacy.

In case of disease control (complete, partial or stable disease) treatment with bevacizumab 15mg/Kg monotherapy every 21 days will be continued until disease progression or until the end of the 24 months of follow-up.

In case of non-response or progression, treatment will be let at the investigator's discretion.

Treatment scheme



Follow-up after progression: visits will be planned every 3 months until 24 months from the registration date.

For patients who receive bevacizumab during 24 months, additional visits must be planned at 1 and 6 months after the last administration of bevacizumab for vital status and toxicities collection.

E) STATISTICAL ANALYSIS PLAN

END POINTS:

The main end point is made of 2 co-primary endpoints: PFS rate at 6 months (PFS6) and objective response rate (ORR). Progression free survival will be calculated from date of first dosing to progression / death (whichever comes first) or last contact using the kaplan-Meier estimates. PFS6 will be calculated as the number of patients with an objective progression (radiological or death) out of the number of patients treated.

Objective Response Rate will be calculated as the number of patients with a response (CR or PR) upon RECIST1.1 criteria out of the number of patients treated.

REQUIRED NUMBER OF PATIENTS:

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 18 patients who progressed within 6 months (or if the composite outcomes belongs to stage 1 futility region). Otherwise, 14 additional patients will be enrolled in Stage 2 for a total of 41 patients.

A two-stage ordinal design will be used. This design is a Simon like two-stage minimax design. It allows to optimize single arm phase II trials designs by use of a multinomial stopping rule based on 2 ordinal outcomes. In this study, efficacy of the therapy will be assessed based on Objective Response Rate (ORR) and Progression-Free Survival Rate (PFSR) at 6 months.

According to previous studies, the null ORR rate was set to 0.25, and the ORR rate of a promising therapy to 0.50. The null PFSR at 6 months was set to 0.50, and the PFSR rate of a promising therapy to 0.7. Therefore :

- ORR:
 - H0: response ≤ 0.25
 - Ha: response ≥ 0.5
 - one-sided alpha = 0.05
 - power $\geq 80\%$
- PFS Rate at 6-months:
 - H0: event free rate ≤ 0.5
 - Ha: event free rate ≥ 0.7
 - one-sided alpha = 0.05
 - power $\geq 80\%$

The probability of early stopping after stage 1 is 0.92.

The therapy will be considered promising if at least one of the ORR or PFSR at 6 months are higher than their corresponding null rates. The therapy will be rejected if both ORR and PFSR at 6 months are as low as or lower than their null values. Therefore, the therapy will be considered promising after stage 2 if among all patients included in the trial, there are at least 15 patients with an objective response OR at least 25 patients who did not progress within 6 months (and if, the composite outcome does not belong to the final futility region).

F) SAMPLES COLLECTED FOR TRANSLATIONAL RESEARCH

SAMPLE TYPES: Blood samples and tumor blocks (or unstained 6 μ m paraffin sections)

G) STUDY DURATIONS

INCLUSION: 4 YEARS

TREATMENTS: 4.5 MONTHS

FOLLOW-UP: 2 YEARS FROM INCLUSION DATE

DURATION UNTIL PRIMARY ENDPOINT EVALUATION:

- STEP 1 (FUTILITY ANALYSIS): 16 MONTHS
- EVALUATION STEP 2 : 6.5 YEARS

OVERALL TRIAL DURATION (INCLUDING FOLLOW-UP): 6.5 YEARS

H) STUDY FLOW-CHART

VISITS ⁹	Registration and Baseline	Follow-up during treatment (chemotherapy + bevacizumab)						End of chemotherapy visit (3 weeks after the last treatment administration)	Follow-up during bevacizumab treatment and until progression (every 3 weeks up to 24 months from the registration date or until progression)	Follow-up after progression or in case of premature discontinuation of treatment (every 3 months until 24 months from the registration date)
		V1 D1C1	V2 D1C2	V3 D1C3	V4 D1C4	V5 D1C5	V6 D1C6			
Visit n°	V0	V1 D1C1	V2 D1C2	V3 D1C3	V4 D1C4	V5 D1C5	V6 D1C6	V7	From V8	
Inclusion / non-inclusion criteria	X									
Signed informed consent form	X									
CLINICAL EXAMINATION										
Height, Weight, PS (ECOG)	X	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	
Medical history	X									
Concomitant treatments	X	X	X	X	X	X	X	X	X	
Toxicity	X	X	X	X	X	X	X	X	X	X
PARACLINICAL EXAMINATION										
CT scan (Thoracic-Abdominal-Pelvic) or MRI ⁴	X ¹			X		X		X	X ⁸	
Scintigraphy	X ¹			X		X		X	X ⁸	
Brain MRI or CT scan	X ¹									
ECG	X ⁵			X		X		X	X ⁷	
LVEF	X ⁵	X ²	X ²	X ²	X ²	X ²	X ²	X ²	X ²	
BIOLOGICAL TESTS										
Hematology (Hb, WBC, ANC, Platelets)	X	X	X	X	X	X	X	X	X	
Hemostasis (INR or PT and PTT)	X	X	X	X	X	X	X	X	X	
Hepatic and renal function (AST, ALT, PAL, total bilirubin, creatinin, creatinin clearance,)	X	X	X	X	X	X	X	X	X ⁶	
Urinalysis (dipstick) ³	X	X	X	X	X	X	X	X	X	
TSH	X									
Serum Pregnancy Test (if required)	X									
TRANSLATIONAL RESEARCH										
Blood samples collection and tumor block (or unstained paraffin sections)	X									

1. within 28 days prior to inclusion; 2. In case of symptoms of heart failure only; 3. if 2+, a 24h proteinuria is required. 4. MRI of the abdomen and pelvis and a chest TDM can be performed instead of CT scan. The same imaging modality (CT or MRI) has to be performed throughout the trial. If an unscheduled CT-scan or MRI of the abdomen and pelvis had been performed within six weeks of a scheduled image, it does not need to be repeated; 5. Within 7 days before the first treatment administration; 6. Renal function and proteinuria only; 7. Only in case of doubt; 8. Every 6 weeks. 9. For patients who receive bevacizumab during 24 months, additional visits must be planned at 1 and 6 months after the last administration of bevacizumab for vital status and toxicities collection