GETUG Tumour Group

GETUG-AFU 19/0903 PROTOCOL

EudraCT No.: 2009-011882-10

INTENSIFIED METHOTREXATE, VINBLASTINE, DOXORUBICIN AND CISPLATIN (I-MVAC) WITH OR WITHOUT PANITUMUMAB AS FIRST-LINE TREATMENT OF ADVANCED UROTHELIAL CARCINOMA IN PATIENTS WITHOUT H-Ras NOR K-Ras MUTATIONS. RANDOMISED PHASE II STUDY

Version 2.1 of November 05, 2010
Amendment 3 included

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APPROVAL AND SIGNATURES OF THE GETUG-AFU 19/0903 PROTOCOL

Intensified methotrexate, vinblastine, doxorubicin and cisplatin (I-MVAC) with or without panitumumab as first-line treatment of advanced urothelial carcinoma in patients without H-Ras nor K-Ras mutations. Randomised phase II study

COMPETENT AUTHORITY	***Agence Française de Sécurité Sanitaire des Produits de Santé* (Afssaps)**	**Authorisation date:** FEBRUARY 24, 2010 **Afssaps Ref. :** A91517- 41
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SYNOPSIS – GETUG-AFU 19/0903

A) IDENTIFICATION OF THE CLINICAL TRIAL

SPONSOR PROTOCOL CODE: **GETUG-AFU 19/0903**
VERSION AND DATE: V2.1 – NOVEMBER 2010

TITLE OF THE TRIAL: Intensified methotrexate, vinblastine, doxorubicin and cisplatin (I-MVAC) with or without panitumumab as first-line treatment of advanced urothelial carcinoma in patients without H-Ras nor K-Ras mutations. Randomised phase II study

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ESTIMATED NUMBER OF SITES: 10	**ESTIMATED NUMBER OF REGISTERED PATIENTS: 107** **NUMBER OF RANDOMISED PATIENTS: 93**

B) IDENTIFICATION OF THE SPONSOR

NAME OF THE ORGANISATION: *Fédération Nationale des Centres de Lutte Contre le Cancer* (FNCLCC)-*Bureau d'Etudes Cliniques et Thérapeutiques* (BECT)

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C) GENERAL INFORMATION ON THE TRIAL

INDICATION: Advanced urothelial carcinoma. First-line treatment.

METHODOLOGY:
Multicentre, randomised phase II study evaluating the efficacy of intensified methotrexate, vinblastine, doxorubicin and cisplatin (I-MVAC) with or without panitumumab as first-line treatment of advanced urothelial carcinoma in patients without H-Ras nor K-Ras mutations.

PRIMARY OBJECTIVE:
Evaluation of efficacy in terms of progression-free survival at 9 months of the combination of intensified methotrexate, vinblastine, doxorubicin and cisplatin (I-MVAC) with or without panitumumab as first-line treatment of advanced urothelial carcinoma in patients without H-Ras nor K-Ras mutations.

SECONDARY OBJECTIVE(S):
- To assess toxicity (CTC AE v4.0)
- To assess response rate (RR)
- To assess overall survival (OS)
- To assess time to progression (TTP)
- To study the correlation between response rate, time to progression, overall survival and biological parameters.

C) GENERAL INFORMATION ON THE TRIAL (cont.)

INCLUSION CRITERIA:

1. Primary tumour of the bladder or upper urinary tract
2. Histologically confirmed infiltrating urothelial carcinoma (epidermoid and/or glandular forms are accepted)
3. Patients without H-Ras nor K-Ras mutations
4. Advanced disease defined by a locally advanced stage (T4 and/or N+) ineligible for surgical resection, or a metastatic stage (M1)
5. Patients with at least 1 evaluable lesion as per RECIST criteria (version 1.1)
6. 18 ≤ age ≤ 75 years
7. General condition 0 or 1 as per the WHO scale
8. Absence of previous chemotherapy for advanced disease (chemotherapy with gemcitabine and platinum salt delivered as an adjuvant is accepted if this ended more than a year ago)
9. Haematological function: Haemoglobin > 11 g/dl, neutrophils ≥ 1500/mm^3, platelets ≥ 100,000/mm^3
10. Liver function: Grade* 0 ASAT and ALAT (< grade* 3 for liver metastases), grade* 0 alkaline phosphatases, normal bilirubin
11. Renal function: calculated (or measured) creatinine clearance > 60 ml/min
12. Patients covered by a social security scheme
13. Patient having read the information sheet and signed the informed consent form.

EXCLUSION CRITERIA:

1. Pure adenocarcinoma or pure epidermoid carcinoma or mixed or pure small-cell neuroendocrine carcinoma
2. Previous treatment with one of the following molecules: methotrexate, vinblastine, doxorubicin or EGF-R inhibitor
3. History of interstitial pneumonitis or pulmonary fibrosis
4. History of cardiovascular disease (including myocardial infarction, unstable angina, symptomatic congestive heart failure, uncontrolled serious cardiac arrhythmia) in the year prior to randomisation (≤ 1 year)
5. Ventricular ejection fraction < 50%
6. Blood calcium and/or magnesium ≥ grade* 1
7. History of cancer in the 5 years prior to entry in the trial other than basal cell skin cancer or *in situ* epithelioma of the cervix,
8. Treatment with radiotherapy for analgesic purposes (unless treatment was discontinued at least 15 days prior to inclusion in the trial)
9. Potential allergy to panitumumab
10. Male or female patients not agreeing to use an effective method of contraception throughout the duration of treatment **and** for 6 months after treatment discontinuation
11. Pregnant women, or female subjects liable to become pregnant or currently breast-feeding,
12. Patient already included in another therapeutic trial on an investigational medicinal product,
13. Persons deprived of their freedom or under judicial protection (including guardianship),
14. Unable to receive medical follow-up during the trial owing to geographical, social or psychological reasons.

* CTC AE v4.0

PRIMARY ENDPOINT:

The primary endpoint is the evaluation of efficacy, in terms of progression-free survival at 9 months of the combination I-MVAC with or without panitumumab.

The criterion for progression will be evaluated as per RECIST criteria (version 1.1 in Appendix 6) for measurable lesions or by the development of at least 1 new lesions evidenced during bone scintigraphy.

SECONDARY ENDPOINTS:

Evaluation of toxicity (CTC AE v4.0): safety will be evaluated according to NCI-CTC.
Evaluation of response (RECIST v1.1): response will be evaluated according to RECIST criteria.
Evaluation of overall survival (OS): survival rates will be estimated according to Kaplan-Meier.
Evaluation of time to progression (TTP): survival rates will be estimated according to Kaplan-Meier.
Correlation between response, TTP OS and biological variables (optional study).

D) DESCRIPTION OF THE INVESTIGATIONAL MEDICINAL PRODUCTS

MEDICINAL PRODUCTS:

Name of the medicinal product (INN)	Name of proprietary medicinal product(1)	Pharmaceutical form	Route of administration	Dose administered
Methotrexate	Generic	Lyophilisate for infusion 1-g vials	IV	30 mg/m^2 on day 1 of each cycle
Name of the medicinal product (INN)	Name of proprietary medicinal product(1)	Pharmaceutical form	Route of administration	Dose administered
Vinblastine	Generic	Powder for solution for injection 10-mg vials	IV	3 mg/m^2 on day 2 of each cycle
Name of the medicinal product (INN)	Name of proprietary medicinal product(1)	Pharmaceutical form	Route of administration	Dose administered
Doxorubicin	According to standard institutional practice	- Lyophilisate for infusion, 10-mg and 50-mg vials - Solution for injection for infusion, vials containing 10mg/5ml and 50mg/25ml	IV	30 mg/m^2 on day 2 of each cycle
Name of the medicinal product (INN)	Name of proprietary medicinal product(1)	Pharmaceutical form	Route of administration	Dose administered
Cisplatin	According to standard institutional practice	Lyophilisate for infusion 10-mg vials	IV	70 mg/m^2 on day 2 of each cycle

Name of the medicinal product (INN)	Name of proprietary medicinal product[(1)]	Pharmaceutical form	Route of administration	Dose administered
Panitumumab	Vectibix®	20 mg/ml concentrate for solution for infusion 5, 10, or 20 ml vials	IV	6 mg/kg on day 2 of each cycle

E) TREATMENT REGIMEN

TREATMENT REGIMEN:
Patients having signed the consent form will be randomised to receive their allocated study treatments :

Arm A: I-MVAC protocol as per the following regimen:

- METHOTREXATE 30 mg/m^2 on day 1
- VINBLASTINE 3 mg/m^2 on day 2
- DOXORUBICIN 30 mg/m^2 on day 2
- CISPLATIN 70 mg/m^2 on day 2
- G-CSF as Filgrastim (as Neupogen®) 5µg/Kg /d via subcutaneous injection from day 3 to day 9 of each cycle.

Each cycle is administered every 2 weeks (D1=D14). Six cycles in total are scheduled.

Arm B: I-MVAC plus panitumumab protocol as per the following regimen:

- METHOTREXATE 30 mg/m^2 on day 1
- VINBLASTINE 3 mg/m^2 on day 2
- DOXORUBICIN 30 mg/m^2 on day 2
- CISPLATIN 70 mg/m^2 on day 2
- PANITUMUMAB 6 mg/kg on day 2
- G-CSF as Filgrastim (as Neupogen®) 5µg/Kg /d via subcutaneous injection from day 3 to day 9 of each cycle.

Each cycle is administered every 2 weeks (D1=D14). Six cycles in total are scheduled.

After stopping treatment with I-MVAC, if panitumumab is well tolerated and in the absence of disease progression, panitumumab will be continued alone as per the same regimen up to disease progression or the end of follow-up at 24 months.

TREATMENT DURATION: Up to disease progression
1 cycle = 2 weeks (D1=D14)

F) STATISTICAL ANALYSIS

NUMBER OF SUBJECTS REQUIRED:

The total number of patients is **93**, with a 1:2 randomisation ratio (31 patients in the I-MVAC arm and 62 in the I-MVAC + panitumumab arm). The number of patients was determined from the estimated 9-month median progression-free survival rate reported in the I-MVAC arm in the randomised trial in comparison with standard MVAC [16]. Using a one stage Fleming design, in the I-MVAC + panitumumab arm, treatment will be considered to be active and potentially evaluable in other studies if at least 37 patients among 62 do not show tumour progression at 9 months. This decision will take into account the observed PFS rate in the control arm. Treatment will be considered insufficiently active if 26 patients or more experience progression in the 9 months following treatment initiation (p0=0.50, p1=0.70, alpha=0.08 and beta=0.03). No formal statistical comparisons are planned between the two treatment arms due to the small sample size of this trial. The I-MVAC control arm is used only for the purpose of validating the initial hypothesis in assuring appropriate patient selection.

A safety analysis will be performed after the inclusion of 10 patients in the I-MVAC+ panitumumab arm in order to determine the feasibility of this protocol in terms of toxicity.

STATISTICAL ANALYSIS ENDPOINTS:

Categorical data will be summarized as a percentage and when necessary will be compared between groups with a chi-squared test. Continuous data will be summarized by the median and the range and when necessary will be compared between groups with the non parametric Kruskal Wallis test.
All descriptive analyses will be made by treatment arm (Standard vs Experimental) according to the intent to treat principal. Confidence interval for median survival will be calculated according to Brookmeyer-Crowley method.
Survival times will be calculated from the date of randomisation to the date of progression or death for PFS and to the date of death (whatever the cause) for OS. For PFS, patients without progression nor death will be censored at the date of last tumour assessment (CT or bone) or at the date of second treatment initiation.
The objective response rate will be presented with a 90% confidence interval. Safety will be evaluated according to NCI-CTC. In order to be considered evaluable for toxicity, patients should have received at least one dose of treatment. Toxicity will be presented by cycle and by patient for each treatment arm.

G) TRIAL DURATION

INCLUSION PERIOD: 2 YEARS

TREATMENT PERIOD: UP TO PROGRESSION

FOLLOW-UP PERIOD: UP TO DEATH OR 24 MONTHS AFTER TREATMENT COMPLETION.

SUMMARY TABLE OF INVESTIGATIONS

Visits	Screening	Baseline[5]	Treatment period (C1 to C6)	Follow-up until progression: every 6 weeks	Follow-up after progression: every 3 months
Consent(s) for: 1. Biomedical study 2. Optional ancillary study	x				
Registration	x				
Test for H-Ras and K-Ras mutations	x				
Inclusion/exclusion criteria	x	X[1]			
Randomisation		X[4]			
CLINICAL EXAMINATION					
Height/Weight/Body surface area	X	X[1]	x	x	
ECOG	X	X[1]	x	x	
Vital signs (pulse, BP; T°)	X	X[1]	x	x	
Toxicity assessment		x	x	x	
Medical history		x			
Concomitant reatments		x	x	x	
Vital status					x
LABORATORY TESTS					
Haematology: CBC/platelets + INR (for patients receiving anticoagulants)	X	X[1]	x	x	
Electrolytes with blood calcium and agnesium	X	X[1]	x	x	
Liver function tests (ASAT, ALAT, ALP)	X	X[1]	x	x	
Renal assessment (Creat, urea, uric ac.)	X	X[1]	x	x	
Pregnancy test	X				
PARACLINICAL EXAMINATIONS/TUMOUR EVALUATION					
Chest-abdominal-pelvic CT scan	X[2]	X[1]	X[3]	x	
Bone scintigraphy	X[2]	X[1]	X[6]	X[6]	
LVEF (scintigraphy or ultrasonography)	X[2]	X[1]	X[7]	X[8]	
TREATMENT					
I-MVAC			x		
Panitumumab (Arm B)			x	x	
BIOLOGICAL ANCILLARY STUDY (Optional)					
Blood samples collection at D1C1			X[9]		

(1) Tests will not be repeated if they were carried out during screening within 7 calendar days (28 for paraclinicals examinations) prior to starting treatment (2) Tests to be carried out within 28 days prior to starting treatment
(3) Every 6 weeks from the 1st day of chemotherapy, i.e. at C3 and C6
(4) Depending on the screening results, randomisation will be done as soon as possible from the patient's mutation status is received by the investigator. Screening results will be available within 10 calendar days at maximum after the tumour block is received in the Department of Pathology (5) Baseline may correspond to the day of treatment initiation or not more than 7 calendar days before starting treatment. (6) Test to be carried out every 3 months (7) Test to be carried out at cycle 6 (8) Test to be carried out at the panitumumab treatment stop
(9) For the ancillary study: 2 blood samples will be collected (using 7ml-EDTA -tubes) during the laboratory test performed for the first cycle (D1C1) and sent to the plateform of Creteil for analysis.

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1 INTRODUCTION AND STUDY RATIONALE

1.1 Introduction

A very large majority of tumours of the bladder and upper urinary tract correspond, in terms of anatomical pathology, to urothelial carcinoma. The so-called advanced stages include locally advanced disease (T4b, N2 or N3) and metastatic disease, which cannot be cured by surgical resection of the bladder. Chemotherapy is therefore the reference treatment [1].

1.2 Study rationale

1.2.1 The MVAC era (1985-2000)

The MVAC era began in 1985, when preliminary results of combined treatment with methotrexate, vinblastine, doxorubicin and cisplatin in patients with advanced urothelial carcinoma (AUC) [2] were published. The two main characteristics of this combined regimen corresponded to combination of four agents yielding the best response rates as single-agent therapy, and administration on intermediate days for methotrexate and vinblastine on D15 and D22. Fifteen years of clinical research conducted with the MVAC protocol have led to the following main conclusions:

1. AUC is chemo-sensitive: several phase II studies first made it possible to show significant response rates; according to French experience, the objective response rates were 57%, including 19% complete responses among 67 patients [3]; phase III studies then highlighted the statistically significant superiority of the MVAC protocol compared with cisplatin used alone [4] or in combination with cyclophosphamide and doxorubicin [5], in terms of objective response rate and overall survival; at the end of the 20th century, the MVAC protocol thus became the reference in the treatment of AUC.
2. AUC is not, however, cured by chemotherapy: analysis of the long-term results of the phase III study having compared cisplatin with MVAC made it possible to assess the limits of chemotherapy [6]; after a minimum follow-up period of 6 years, 11 of the 246 patients included in the trial had survived, 2 treated with cisplatin alone, and 9 treated with MVAC; furthermore, only 6 of the 9 survivors treated with M-VAC were free from tumour progression since 3 patients had bladder-infiltrating recurrence; metastatic urothelial tumours are therefore chemo-sensitive, but rarely cured by chemotherapy; median survival is approximately 12 months.
3. the MVAC protocol is associated with appreciable toxicity: all of the phase II and III studies conducted with the MVAC protocol emphasised the noteworthy toxicity of this combination [4,5,7]; the main side effects concerned the gastrointestinal system (10-20% grade 3 or 4 vomiting), haematological system (25-50% episodes of grade 3 or 4 neutropenia, including 40-60% with fever) and mucous membranes (10-20% grade 3 or 4 mucositis); in addition, most studies have reported a mortality rate of 3 to 5% related to septic complications of neutropenia.

4. the two main negative prognostic factors affecting the survival of patients treated with the MVAC protocol correspond to deterioration in general condition (Karnofsky index below 80%) and the presence of organ metastases (liver, bone, lungs) [8,9]; median survival of patients with 0, 1 or 2 of these factors was 33, 13 and 9 months, respectively, in a population of 203 patients [8].
5. surgery involving the resection of residual low-volume lesions after chemotherapy is of interest: the outcome of patients undergoing surgery after the MVAC protocol appears to be identical to that of patients having obtained a complete response after chemotherapy alone, with median survival of approximately 42 months [10].
6. several alternatives, which were designed to improve the safety of the MVAC protocol, have not been validated: removal of doxorubicin (CMV protocol), replacing doxorubicin with epirubicin, or substituting cisplatin with carboplatin. The efficacy of the CMV protocol was reported as early as 1985, with a complete response rate of 28% and median survival of 8 months in a population of 60 patients [11]; a British publication reported very similar results, with a complete response rate of 24% and median survival of 7 months among 33 patients [12]. Since the CMV and MVAC protocols were not studied in a randomised study, the efficacy and toxicity of the two treatment regimens cannot be accurately compared. Several phase II studies substituted doxorubicin with an anthracycline analogue; however, the benefit of this approach compared with conventional MVAC could not be demonstrated. Lastly, although the results of the phase II studies point in favour of equivalent efficacy and lower gastrointestinal, renal and neurological toxicity, for combined carboplatin-based protocols, three randomised phase II studies have suggested a lower response rate in patients treated with carboplatin [13-15].
7. the legacy of the MVAC era is the intensified MVAC (I-MVAC) protocol: combination of a haematopoietic growth factor (G-CSF) with the standard MVAC protocol enhances delivery of the theoretical doses owing to lesser toxicity, but patient survival is not increased; another method of administering G-CSF was to include it as part of a modified, i.e. intensified regimen of the MVAC protocol, with D1 combining the 4 conventional agents repeated every 14 days, and the intermediate days being withdrawn; the consequences of this are a twofold increase in the dose-intensity of adriamycin and cisplatin, and a simultaneous 30% reduction in the dose-intensity of methotrexate and vinblastine; the results of a prospective trial comparing conventional MVAC with I-MVAC evidenced superior complete response rates in the I-MVAC arm (21% *versus* 9%, p=0.009), an increased progression-free survival at 2 years (25% *versus* 12%), and an increased median progression–free survival (9.1 *versus* 8.2 months, p=0.037) but no impact on overall survival (15.5 months *versus* 14.1 months). The rates of febrile neutropenia and mucosal toxicity were lower in the I-MVAC arm; however, the number of toxicity-retaled deaths was similar (3% in the intensified arm, 4% in the standard arm) [16].

1.2.2 The gemcitabine era (2000-…)

Evidence of the activity of gemcitabine in AUC made it possible for a new reference protocol to be defined, in the early part of the decade, combining gemcitabine and cisplatin (GC). Objective response rates of between 23% and 29% were observed, including 4% to 13% complete responses in the phase II studies conducted with gemcitabine as single-agent therapy [17]. The main results of a phase III trial, which included 405 patients treated with the GC protocol (gemcitabine 1000 mg/m^2/day D1, D8, D15, and cisplatin 70 mg/m^2 D2 every 28 days) or the standard MVAC protocol, were as follows [18,19]:

1. the objective response rates after independent review were 45.7% and 49.4%, respectively, for patients treated with MVAC and GC, including 11.9% and 12.2% complete responses.

2. treatment administration was characterised by a median number of 4 and 6 chemotherapy cycles, respectively, per patient in the MVAC and GC arms; dose adjustment was necessary in 63% of MVAC cycles and 37% of GC cycles; the dose-intensity of the cytotoxic agents was 65% for methotrexate, 76% for vinblastine, 95% for doxorubicin and cisplatin in the M-VAC arm, and 80% for gemcitabine and 102% for cisplatin in the GC arm.
3. in terms of toxicity, the MVAC protocol resulted in a significantly higher incidence of febrile neutropenia, serious mucositis, alopecia and deaths due to toxicity; a higher incidence of anaemia and grade 3 or 4 thrombocytopenia was observed in patients treated with the GC combination, but did not give rise to any differences in transfusion requirements between the 2 arms; this toxicity led to an approximately twofold increase in the use of haematopoietic growth factors, parenteral antibiotics, antiviral and antifungal agents in the MVAC arm, and a greater number of hospital admissions.
4. median survival, the primary endpoint, was not different between the 2 arms; the sample size was defined so as to evidence a 4-month increase in overall survival (12 to 16 months) in favour of the GC arm, with 80% power; the difference in the time to treatment failure, defined by time to disease progression or treatment discontinuation due to toxicity, was only significant with Wilcoxon's test, in favour of the GC arm (p=0.04); in an analysis performed more than 5 years after inclusion of the last patient, progression-free survival (8.3 months in the MVAC arm and 7.7 months in the GC arm), overall survival (15.2 months in the MVAC arm and 14.0 months in the GC arm) and overall survival was not significantly different.

Alongside the development of gemcitabine, a potential benefit of three cytotoxic agents was shown in phase II studies in AUC: docetaxel [20], paclitaxel [21] and vinflunine [22]. However, the combination of docetaxel and cisplatin was shown to be inferior, in terms of efficacy, to the MVAC protocol [23], and comparison of a combination of paclitaxel and carboplatin with MVAC was unsuccessful [24]. In a phase III study conducted under second-line conditions *versus* best supportive care [25], a moderate increase in survival was observed with vinflunine. The targeted treatments evaluated to date have not demonstrated noteworthy efficacy [26].

1.2.3 Chemotherapy procedures in 2009

In patients whose renal function permits the use of cisplatin, two chemotherapy protocols are currently available, the efficacy of which does not differ statistically, for the first-line management of patients with AUC: the I-MVAC and GC protocols. The I-MVAC protocol is more effective than the standard MVAC protocol (and in principle than GC) in terms of response rate, without any repercussions on median survival. The GC protocol is often used in practice owing to its lesser toxicity. **Nevertheless, the I-MVAC protocol still has an important role, particularly among patients with a good prognosis, in whom the search for optimum disease reduction is the best guarantee for prolonged survival**. However, no standard protocols have been defined for patients with impaired renal function, even though cisplatin is readily replaced by carboplatin in such instances. Likewise, no standard protocols have been defined for patients having failed on the MVAC or GC protocols.

1.2.4 Role of the EGF/EGF- R pathway in urothelial carcinoma

Numerous studies conducted in the 1990s suggested the role of the EGF/EGF-R (ErbB-1) pathway in AUC. Increased expression of EGF-R was particularly associated with stage, grade, metastatic phenotype and survival without nonetheless having any independent prognostic value [27,28].

More recent data have emphasised the excessively "simplistic" nature of this approach. At least 5 other ligands of EGF-R exist (transforming growth factor-α, amphiregulin, β-cellulin, epiregulin and heparin-binding EGF-like growth factor). Out of these, epiregulin could be of major prognostic value [29]. Furthermore, the level of expression of other members of the ErbB receptor group could also be involved [30]. In vivo preclinical studies evidenced the antitumour activity of gefitinib, an EGF-R tyrosine kinase inhibitor, partly related to an anti-angiogenic effect [31,32]. The antiproliferative effect of gefitinib could be explained by the degradation of cyclin D1 after activation of glycogen-synthase kinase-3β [33]. In humans, gefitinib has not demonstrated any noteworthy efficacy in patients having experienced failure of a platinum salt [34]. However, encouraging preliminary results have been reported in the same population with lapatinib, a tyrosine kinase inhibitor of the receptors EGF-R and ErbB-2 in a small cohort of 19 patients, with 1 partial response and 8 instances of stable disease [35].

1.2.5 Panitumumab

Panitumumab is a fully human recombinant IgG2 monoclonal antibody with a high binding affinity and specificity to human EGF-R, a transmembrane glycoprotein, belonging to a subgroup of type I tyrosine kinase receptors including EGF-R (HER1/c- ErbB-1), HER2, HER3, and HER4.

EGFR promotes cell growth in normal epithelial tissue and is expressed on a variety of tumour cells.

Panitumumab binds to the binding domain of the EGF-R ligand and inhibits receptor autophosphorylation induced by all known EGF-R ligands. Binding of panitumumab to EGFR results in internalisation of the receptor, inhibition of cell growth, induction of apoptosis, and decreased interleukin 8 and vascular endothelial growth factor production.

More than 1 700 cancer patients were included in phase I, II, and III clinical studies, and received panitumumab doses ranging from 0.01 mg/kg to 5 mg/kg administered once a week, 6 mg/kg every 2 weeks, and 9 mg/kg every 3 weeks. Panitumumab has been studied as single-agent therapy in numerous studies conducted in patients with metastatic colorectal cancer (mCRC) and solid tumours (kidney, prostate, pancreas, non-small-cell lung, oesophagus, head and neck). Panitumumab has also been studied in combination with chemotherapy in non-small-cell lung cancer, and in combination with chemotherapy and bevacizumab in the treatment of mCRC.

Single-agent therapy with panitumumab has generally been well tolerated. As is the case with other EGFr inhibitors, the adverse reactions most frequently reported for panitumumab were skin reactions. In most cases, skin toxicity signs and symptoms were of mild to moderate severity. Such toxicity signs and symptoms led to panitumumab discontinuation only in 2% of patients. Other common treatment-related reactions were fatigue and diarrhoea.

Infusion reactions, including anaphylactic reactions, bronchospasm, and hypotension, have been reported in the clinical trials and post-marketing experience (including fatal outcomes). However, most symptoms related to potential infusion have been of mild to moderate intensity and, in certain cases, have resolved without treatment. Administration of panitumumab did not need to be modified or suspended in isolated cases. Infusion-related reactions should be mild and uncommon; panitumumab infusions may therefore be carried out without specific premedication.
Fatal reactions have also been observed in patients with a history of prior hypersensitivity reaction to panitumumab including a case of fatal angioedema occurring more than 24 hours following the administration of panitumumab

A potential risk associated with panitumumab administration is the emergence of antibodies directed against the product. The immunogenicity of panitumumab has been very low to date, using a highly

sensitive methodology for detection of these antibodies. The development of anti-panitumumab antibodies has not been associated with any pharmacokinetic or clinical consequences.

Cardiac monitoring was performed during clinical studies owing to the initial findings of toxicology studies. No signs of cardiotoxicity arising from panitumumab were detected further to analysis of intermediate data collected among more than 300 patients. Therefore, cardiac monitoring is no longer part of the routine safety monitoring procedure among patients included in studies conducted on panitumumab.

Signs of vascular toxicity related to administration of panitumumab were reported in 17 patients. These symptoms included: peripheral oedema, oedema, pulmonary embolism, hypertension, stroke, deep vein thrombosis and superficial thrombophlebitis. The majority of vascular adverse reactions attributed to treatment were of mild to moderate severity.

The respiratory adverse reactions most frequently reported during clinical trials on panitumumab as single-agent therapy were as follows: dyspnoea, cough, pleural effusion, productive cough and exertional dyspnoea. The majority of respiratory treatment-related adverse reactions were considered to be of mild to moderate severity, and most patients had lung metastases at study entry. No cases of interstitial pneumonia were reported as adverse reactions.

Hypomagnesaemia (all grades) was observed in 41% of patients in clinical studies in which magnesium levels were measured at specific intervals during treatment with panitumumab. These reductions were mild in 25% of patients and moderate in 10% of patients. Grade 3 or 4 hypomagnesaemia was observed in 7% of patients, the majority of whom received replacement therapy with IV electrolytes. All serious adverse reactions were considered attributable to treatment and occurred 1.5 months or more (up to 6.5 months) after the first dose of panitumumab. In 1% of patients, the hypomagnesaemia-type adverse reactions were combined with hypocalcaemia-type adverse reactions.

Clinical data indicate that hypomagnesaemia and hypocalcaemia related to treatment with panitumumab are similar to those observed with other EGFr inhibitors. Hence, routine monitoring of blood electrolytes is recommended in patients receiving panitumumab.

Panitumumab was evaluated in combination with chemotherapy in patients with CRC and NSCLC.

Amgen study 20040249 (PACCE) was an open-label controlled study on bevacizumab and chemotherapy administered with or without panitumumab as first-line treatment of patients with metastatic colorectal cancer. The chemotherapy protocols consisted of oxaliplatin or irinotecan. An intermediate analysis based on 257 events (death or disease progression) in the oxaliplatin stratum evidenced a reduction in progression-free survival and increased mortality in patients having received panitumumab combined with bevacizumab plus chemotherapy. Furthermore, an increased incidence of severe adverse reactions corresponding to diarrhoea, dehydration, infection and pulmonary embolism was observed in patients having received panitumumab relative to those not having received the product. Based on this analysis, panitumumab was discontinued during the trial.

Severe diarrhoea was more common, compared with single-agent therapy studies, during studies on panitumumab combined with irinotecan, bolus 5-fluorouracil and leucovorin (IFL protocol) for the treatment of mCRC. Other adverse reactions frequently reported during combined administration of panitumumab and the IFL protocol corresponded to cases of skin toxicity, asthenia and nausea. Since the IFL protocol induced medically significant cases of diarrhoea, the study was amended in order to

modify the chemotherapy regimen and change to the FOLFIRI protocol (irinotecan, 5-fluorouracil infusion and leucovorin). Adverse reactions corresponding to diarrhoea, asthenia and nausea were less common with this protocol.

No additional significant adverse reactions were observed in the treatment of NSCLC with the combination of panitumumab and carboplatin/paclitaxel. A case of pulmonary fibrosis was described in one patient treated with this combination. Patients with signs of interstitial pneumonia or pulmonary fibrosis were no longer included in the clinical trials from 2004 onwards; however, this patient, who had a history of idiopathic pulmonary fibrosis, was enrolled before the new exclusion criteria had been implemented.

Enrolment has currently been suspended in a two-part open-label dose-finding study of AMG 706 administered in combination with panitumumab and gemcitabine- and cisplatin-based chemotherapy in patients with advanced cancer. Suspension of enrolment was decided due to three cases of dose-limiting toxicity: sudden death, grade 3 diarrhoea and grade 4 asthenia. An analysis of these toxicity signs and other serious adverse reactions (thromboembolic events) is currently in progress.

Another two-part open-label study is currently underway in order to determine the dose of AMG 706 in combination with panitumumab and/or carboplatin/paclitaxel in patients with advanced NSCLC. Forty of the 85 patients anticipated were included and 21 received panitumumab. Serious adverse reactions were reported in 8 patients in total, 3 of whom had received panitumumab (pneumonia, NSCLC, hypoxia and pulmonary embolism). The pulmonary embolism-type effects were considered to be attributable to AMG 706. One patient died from disease progression during the 30 days following administration of the last dose of the investigational medicinal product.

1.2.6 Combination of I-MVAC and panitumumab in AUC

In 2009, median survival of patients with AUC is still moderate, around of 12 to 14 months. In order to improve the efficacy of medical treatment, combination of chemotherapy yielding the best response rates (I-MVAC) and targeted treatment inhibiting a relevant molecular effector therefore seems logical. Before considering setting up a phase III study evaluating the impact of overall patient survival, it seemed essential initially to set up a randomised phase II study with the following objective:

A. to assess the feasibility of the combination I-MVAC + panitumumab: although the feasibility of combining chemotherapy with panitumumab has already been demonstrated, no studies with the I-MVAC protocol have been reported to date; early safety assessment observed in the first 10 patients in the combination arm will therefore need to be carried out before validating continuation of the study.
B. to confirm a tendency towards an increase in progression-free survival in the combination arm: if this is not the case, the probability of reaching a positive conclusion during a phase III study would be too low in order for the study to be relevant.

1.2.7 H-Ras and K-Ras genotyping in Patients with stage III-IV Bladder Cancer treated with Panitumumab

In mammals, the Ras Superfamily is composed of 3 proteins:

- Hras (Harvey Ras), was the first one to be identified in 1964, then found in a bladder cancer cell line, in 1982 [36]
- Kras (Kirsten Ras), well known in colorectal cancer and

- Nras (Neuroblastoma Ras).

The 3 proteins are different but their sequences are closely homologous (85%), with important structural similarities. They differ mainly by 40 n terminal amino-acids [37].
The ras proteins have a binding site for GDP/GTP, a GTPase activity and are regulated in probably the same manner. They are involved in signal transuction and regulate cell growth.
For these 3 proteins, genes mutations are frequent in human tumors and can impact the sequence amino acids 12,13 and less frequently 61 and 59, therefore leading to a constitutively activated protein that promotes the transforming potential not only in cell cultures but also in tumors [38]:
–H-RAS: primarily in skin and skeletal muscle
–K-RAS: primarily in colon and thymus
–N-RAS: primarily in thymus and in male germ cells
For instance, patients with Costello syndrome have a mutated H-ras codon 12 and have an increased risk of « transitional cell carcinoma of the bladder » before 20 years.

Ras proteins activity and regulation:

Ras proteins have different interaction with downstream effector molecules:
Mutated *KRAS* preferentially activates Raf/ERK1/2
Mutated *HRAS* preferentially activates PI3K/AKT [39].

The activation of Ras proteins depends on their binding to GTP or GDP.
If the protein is bound to GDP, it is inactive but, if bound to GTP, it is activated and thus it stimulates the downstream signals of proliferation, metastasis and resistance to apoptosis.
Their expression is controlled in a tissue-specific manner.
Based on tissue and onogenesis specificities, tumors are often associated with specific Ras isoforms which can interact with different proteins downstream.
EGFR is often overexpressed in urothelial bladder cancer and represents a good target for anti HER1 drugs. However, it is considered that there is a majority of non mutated H-Ras genotypes in bladder cancer, about 12% (7 to 17%)of the patients have a mutation in tumor cells (1151 ladder cancers, 142 are H-Ras mutated that is to say 12% , cosmic sanger) [39, 42, 43]. Mutations of H-Ras lead consequently to a constitutively activated protein and have been correlated to tumor progression and recurrence after treatment. Hot Spots are Codons 12 and 13 (90% of the mutations) and 59, 61 but the most frequent mutation is a substitution that replaces Gly12 in Val.

Concerning the other members of Ras super family; we have to keep in mind that between 5 and 7% of patients with bladder cancer have K-Ras mutated tumor cells, better known in colon cancer.
It seems obvious that an antiHER1 drug used in the treatment of a patient with bladder cancer with either H-Ras or K-Ras relevant mutation would be inefficient [41]
Therefore, H-Ras and K-Ras pretherapeutic genotyping appear highly necessary to target patients who will benefit from Panitumumab
We can assume that about 15 to 25% of patients have one of these mutations and will not be able to enter the study. This number of patients should be taken in account in the calculation of the number of patients in the trial.

2 OBJECTIVES OF THE TRIAL

2.1 Primary objective

Evaluation of efficacy in terms of progression-free survival at 9 months of the combination of intensified methotrexate, vinblastine, doxorubicin and cisplatin (I-MVAC) with or without panitumumab as first-line treatment of advanced urothelial carcinoma in patients without H-Ras nor K-Ras mutations.

2.2 Secondary objectives

- To assess toxicity (CTC AE v4.0)
- To assess response rate (RR)
- To assess overall survival (OS)
- To assess time to progression (TTP)
- To study the correlation between response rate, time to progression, overall survival and biological parameters.

3 METHODOLOGY

Multicentre, randomised phase II trial, evaluating the I-MVAC protocol combined with panitumumab (arm B) using the I-MVAC protocol as a concurrent control.

4 PATIENT SELECTION

4.1 Inclusion criteria

- Primary tumour of the bladder or upper urinary tract
- Histologically confirmed infiltrating urothelial carcinoma (epidermoid and/or glandular forms are accepted)
- Patients without H-Ras nor K-Ras mutations
- Advanced disease defined by a locally advanced stage (T4 and/or N+) ineligible for surgical resection, or a metastatic stage (M1)
- Patients with at least 1 evaluable lesion as per RECIST criteria (version 1.1)
- 18 ≤ age ≤ 75 years
- General condition 0 or 1 as per the WHO scale
- Absence of previous chemotherapy for advanced disease (chemotherapy with gemcitabine and platinum salt delivered as an adjuvant is accepted if this ended more than a year ago)
- Haematological function: Haemoglobin > 11 g/dl, neutrophils ≥ 1500/mm^3, platelets ≥ 100,000/mm^3
- Liver function: Grade* 0 ASAT and ALAT (< grade* 3 for liver metastases), grade* 0 alkaline phosphatases, normal bilirubin
- Renal function: calculated (or measured) creatinine clearance > 60 ml/min
- Patients covered by a social security scheme
- Patient having read the information sheet and signed the informed consent form.

* CTC AE v4.0

4.2 Exclusion criteria

- Pure adenocarcinoma or pure epidermoid carcinoma or mixed or pure small-cell neuroendocrine carcinoma
- Previous treatment with one of the following molecules: methotrexate, vinblastine, doxorubicin or EGF-R inhibitor
- History of interstitial pneumonitis or pulmonary fibrosis
- History of cardiovascular disease (including myocardial infarction, unstable angina, symptomatic congestive heart failure, uncontrolled serious cardiac arrhythmia) in the year prior to randomisation (≤ 1 year)
- Ventricular ejection fraction < 50%
- Blood calcium and/or magnesium ≥ grade* 1
- History of cancer in the 5 years prior to entry in the trial other than basal cell skin cancer or *in situ* epithelioma of the cervix,
- Treatment with radiotherapy for analgesic purposes (unless treatment was discontinued at least 15 days prior to inclusion in the trial)
- Potential allergy to panitumumab
- Male or female patients not agreeing to use an effective method of contraception throughout the duration of treatment **and** for 6 months after treatment discontinuation
- Pregnant women, or female subjects liable to become pregnant or currently breast-feeding,
- Patient already included in another therapeutic trial on an investigational medicinal product,
- Persons deprived of their freedom or under judicial protection (including guardianship),
- Unable to receive medical follow-up during the trial owing to geographical, social or psychological reasons.

* CTC AE v4.0

5 PATIENT REGISTRATION

After initialling the patient information sheet, signing the consent form (Appendix 5) and validation of the screening results, the eligible patients may be registered.

Then, depending on the screening results, **randomisation will be done as soon as possible from the patient's mutation status is received by the investigator**, in compliance with the procedure below.

The randomisation will be performed directly by the investigator, via an internet connexion to the **TenAlea** software at the following addresse:
https://fr.tenalea.net/valdaurelle/ALEAStudyDef/default.aspx.
Once the randomisation is performed by the investigator, he/she will receive automatic confirmation by mail in PDF format. This confirmation will also be sent automatically to the Biostatistics Unit at CRLC Val d'Aurelle (Montpellier) as well as to the project team at the Clinical Trials Office at the F.N.C.L.C.C.
In case of problems during the randomisation procedure, or impossibility to connect to the internet site, the investigator should contact the CRLC Val d'Aurelle by telephone or by fax (at the address below), which can then proceed with the randomisation.

S. THEZENAS

Biostatistics Unit at the Val d'Aurelle-Paul Lamarque Regional Cancer Center

Montpellier, France

Monday to Friday 9:00 pm to 1700 pm.

Phone : 33 (0)4 67 61 30 35 Fax : 33 (0)4 67 61 37 18 Secretary : 33 (0)4.67.61.25.40

6 SCREENING

After having signed the informed consent form, for each registered patient fulfilling criteria for inclusion, the pathologist in charge with initial diagnosis will be asked to select a FFPE (Formalin Fixed and Paraffin Embedded) tissue block, and fill a pathological form (appendix 8), including protocol identification code (protocol number), investigational site number and name, investigator's mail address (or fax number), patient anonymised ID (patient's initials patient's birth date and patient's sex).The Tumour block, with a control HES stained section and accompanying form (appendix 8) will be immediately sent to the Department of Pathology at the following address:

Département de Pathologie
A l'attention du Docteur Yves ALLORY
Hôpital Henri Mondor
51, Av du Maréchal De Lattre de Tassigny
94 000 Créteil, France

Tumour blocks will be registered anonymously in the laboratory management software (DIAMIC CS).

Tumour blocks will be give back at the end of the inclusions.

Extraction of DNA will be performed from 5 to 10 µm sections of pre-selected areas (using QIAGEN EZ1 IVD labelled system).
K-Ras 2 codon 12 and 13 mutations will be determined with Taqman assays which have been validated for the screening of these mutations in colo-rectal cancer (STIC program). H-Ras mutations on codons 12, 13 and 61 will be determined by capillary sequencing of PCR products.

The results of K-Ras and H-Ras mutations will be made available and transmitted by fax or e-mail to the investigator within 10 calendar days at maximum after the tumour block is received in the Department of Pathology as well as to the project manager. Patients without mutations will be randomised in the trial.

7 TREATMENT

7.1 Description of the treatments

Patients having signed the consent form and fulfilling all the eligibility criteria will then be randomised to receive their allocated study treatments.

Arm A: I-MVAC protocol as per the following regimen:

METHOTREXATE	30 mg/m^2 on day 1
VINBLASTINE	3 mg/m^2 on day 2
DOXORUBICIN	30 mg/m^2 on day 2
CISPLATIN	70 mg/m^2 on day 2

G-CSF as filgrastim (as Neupogen®) 5µg/Kg /d via subcutaneous injection from day 3 to day 9 of each cycle.

Each cycle is administered every 2 weeks (D1=D14). Six cycles in total are scheduled.

Arm B: I-MVAC plus panitumumab protocol as per the following regimen:

METHOTREXATE	30 mg/m^2 on day 1
VINBLASTINE	3 mg/m^2 on day 2
DOXORUBICIN	30 mg/m^2 on day 2
CISPLATIN	70 mg/m^2 on day 2
PANITUMUMAB	6 mg/kg on day 2

G-CSF as filgrastim (as Neupogen®) 5µg/Kg /d via subcutaneous injection from day 3 to day 9 of each cycle.

Each cycle is administered every 2 weeks (D1=D14). Six cycles in total are scheduled.

After stopping treatment with I-MVAC, if panitumumab is well tolerated and in the absence of disease progression, panitumumab will be continued alone as per the same regimen up to disease progression or the end of follow-up at 24 months.

7.2 Packaging and labelling

Panitumumab is a human IgG2 monoclonal antibody, produced from a mammalian cell line (CHO) by means of the recombinant DNA method. It will be prepared in compliance with Good Manufacturing Practice (GMP) guidelines, and supplied directly to the clinical investigation sites by AMGEN.

Panitumumab will be supplied at a concentration of 20 mg/ml in 5, 10 or 20 ml vials.

The boxes and vials will be labelled in compliance with the Community Guide to Good Manufacturing Practice as per the special instalment of official bulletin no. 2007/1 bis (revised on December 11, 2006, published in the Official Journal on December 29, 2006).

7.3 Storage conditions

The investigational medicinal products should be stored in locked premises with limited access, and in accordance with the manufacturer's recommendations.

Panitumumab should be stored between 2℃ and 8℃ (3 6° and 46°F) in secure premises upon receipt. The vials should be stored in the original outer packaging in refrigerated premises between 2℃ and 8℃ (36 ° and 46°F) up to use. The product should be protected from direct exposure to sunlight, and should not be frozen or excessively shaken.

In-use physicochemical stability has been established for 24 hours at + 25℃. Panitumumab does not contain any antimicrobial preservatives or bacteriostatic agents. From a microbiological perspective, the product should be used immediately after dilution. If it is not used immediately, the storage duration and conditions prior to use are the responsibility of the user and should not usually exceed 24 hours between + 2℃ and + 8℃, unless dilution was perfor med under controlled and validated aseptic conditions.

Records of real storage conditions during the study period should be maintained.

7.4 Distribution and accounts

Only panitumumab will be distributed to the different pharmacies within the healthcare centres by AMGEN in compliance with Good Distribution Practice guidelines.
The other treatments, which represent standard treatment for this disease, will be taken from the pharmacies at the investigating sites.

The healthcare centre pharmacist should acknowledge receipt of all panitumumab shipments by returning a duly completed acknowledgement of receipt to the distributor.

The healthcare centre pharmacist will draw up accounts for medicinal products which are dispensed, used, unused and/or returned by the patient.

The clinical research associate appointed by the sponsor will check the accounts relating to the medicinal products supplied and will ensure that an accounts form has been validated and signed by the healthcare centre pharmacist before any requests for destruction are sent to the sponsor.

7.5 Implementation of treatment

The chemotherapy cycles are administered over approximately 48 hours under standard hospitalisation conditions, via a central access. **Treatment dosage will be calculated on the basis of the patient's real weight at the start of each cycle.**

The recommended procedures should follow the sequence below. However, apart from the administration procedures for panitumumab, these may be adapted according to standard institutional practice.

DAY 1:

SETRON**:** 8 mg administered intravenously over 15 min
METHOTREXATE: intravenous administration at a dose of 30mg/m² over 30 min in 100 ml of G5
HYPERHYDRATION: 3 litres of 0.9% sodium chloride/24 hours

DAY 2:

APREPITANT**:** 120 mg p.o. 1 hour before the start of chemotherapy
SETRON: 8 mg administered intravenously over 15 min
METHYLPREDNISOLONE: 120 mg administered intravenously over 15 min

VINBLASTINE: intravenous administration at a dose of 3 mg/m^2 over 15 min in 50 ml of 0.9% sodium chloride (normal saline solution, supplied by the site).

DOXORUBICIN: intravenous administration at a dose of 30 mg/m^2 over 30 min in 100 ml of 5% glucose solution (G5, supplied by the site).

CISPLATIN: intravenous administration at a dose of 70 mg/m^2 over 2 hours in 250 ml of 0.9% sodium chloride (normal saline solution, supplied by the site), in between hyperhydration with 3 litres of 0.9% sodium chloride/24 hours, having started 24 hours before the cisplatin infusion and to be continued up to 24 hours after the end of the cisplatin infusion. Administration of magnesium to prevent magnesium loss may be performed.

PANITUMUMAB (**for arm B only**)**:** IV administration at a dose of 6 mg/kg, 1 hour after cisplatin, for 1 hour using an infusion pump and an in-line filter with low protein-binding potential and a pore size of 0.2 or 0.22 microns, via a peripheral access or tunnelled catheter.

Strict compliance with aseptic techniques is required during preparation and administration of panitumumab. The bag should be labelled in compliance with the standard operating procedures of the site pharmacy, then rapidly transferred to the nursing team for administration.

Panitumumab will be diluted in a volume of 100 ml of 0.9% sodium chloride solution (normal saline solution, supplied by the site).
The maximum concentration of the diluted solution for infusion should not exceed 10 mg/mL; if necessary, the volume of saline solution should be increased.

! The administration procedures for panitumumab described above should be strictly followed.

DAY 3:

APREPITANT: 80 mg p.o.
FILGRASTIM will be daily administered at a dose of 5µg/Kg per day as a subcutaneous injection until day 9 of each cycle. Filgrastim (as Neupogen®) is specifically recommended since its pharmacokinetic profile makes it possible to avoid overlap with subsequent chemotherapy.

DAY 4:

APREPITANT: 80 mg p.o.

7.6 Toxicity and dose adjustment

Toxicities will be recorded as adverse events on the Adverse Event case report form and must be graded using The National Cancer Institute's Common Terminology Criteria (CTC) version 4.0 (Appendix 3), with the exception of skin- or nail-related toxicities, which must be graded using CTC version 3.0 with modifications (see Appendix 7).

7.6.1 Toxicity related to the I-MVAC cycles

I-MVAC cycles will be administered at the full dose every 14 days if the following conditions are met:
- Neutrophils > 1,000/mm^3
- Platelets > 100,000/mm^3
- Calculated (or measured) creatinine clearance > 60 ml/min
- Recovery from any non-haematological toxicity up to grade 1, apart from alopecia.

In the absence of haematological recovery, a complete blood count will be performed twice a week so as to start treatment as soon as haematological parameters permit. As regards non-haematological toxicity, the situation will be re-assessed once a week so as to start treatment upon improvement to grade 1 toxicity.

If treatment is to be temporarily discontinued (postponement of a course), all treatments (including panitumumab) must be postponed.

In the absence of haematological or non-haematological recovery after treatment has been postponed for more than 14 days, chemotherapy with I-MVAC shall be permanently discontinued. **On the other hand, except in case of toxicity related to panitumumab, panitumumab can be continued until progressive disease or the end of follow-up at 24 months.**

Excluding non-febrile neutropenia and alopecia (which do not required adjustment), and renal insufficiency (which requires cisplatin dose adjustment as a function of creatinine clearance, cf. below), **the onset of grade 4 toxicity during a cycle requires a 15% dose reduction for the 4 agents of the protocol during subsequent cycles**.

↳ **The onset of further grade 4 toxicity despite dose reduction shall lead to permanent discontinuation of chemotherapy**.

Cisplatin dose adjustments are performed on the basis of creatinine clearance:

* > 60 ml/min: 70 mg/m^2
* Between 40 and 60 ml/min: 35 mg/m^2
* < 40 ml/min: no cisplatin

NB: Severe reactions related to extravasation of vinblastine or doxorubicin have been reported. The general recommendations in the event of extravasation are as follows for all of the treatments administered:

- stop the infusion immediately,
- do not remove the needle or catheter,
- using the same needle draw up as much of the injected product as possible,
- apply ice to the injected area for 15 to 20 minutes every 4 to 6 hours over 72 hours,
- topical corticosteroids,
- check the injection site over the following days, to determine whether treatment is necessary. Do not hesitate to seek surgical opinion if there is the slightest doubt.

7.6.2 Toxicity related to panitumumab

7.6.2.1 Skin reactions

Skin reactions, particularly acneiform rash, are the most frequently adverse events related to panitumumab.
Approximately 90% of patients treated with panitumumab have experienced product-related skin reactions, a pharmacological effect observed with epidermal growth factor receptor (EGF-R) inhibitors.
The majority of these reactions are of mild to moderate intensity. In the event of **grade 3 or higher** skin reactions (as per NCI-CTC/CTC AE criteria v4, Appendix 3), or if they are considered intolerable, **panitumumab must be discontinued temporarily up to 6 weeks until the reactions improve (≤ grade 2) then reintroduced halving the initial dose.**

If the reactions do not recur, the panitumumab dose should be increased in 25% increments, up to the recommended dose.

If the reactions do not improve (≤ grade 2) after discontinuing one or two doses of panitumumab (or after 6 weeks of stopping panitumumab) or if the reactions recur or become intolerable with 50% of the initial dose, **panitumumab should be permanently discontinued.**

Infectious complications (including septicaemia), which has proved fatal in rare cases, together with local abscesses requiring incisions and drainage, were reported in clinical trials, further to the onset of severe skin reactions (including stomatitis). The onset of infectious or inflammatory complications should be monitored in patients with signs of severe dermatological reactions or presenting exacerbation of these reactions during treatment with panitumumab, and appropriate treatment should be rapidly implemented. Patients are advised to use sun cream, wear a hat and limit exposure to sun throughout the duration of treatment with panitumumab and if rash/skin toxicity develops since sunlight may exacerbate any potential skin reactions.

7.6.2.2 Guidelines for Diarrhoea Management

Symptoms of diarrhoea and/or abdominal cramping may occur at any time and should be managed according to standard institutional practice.
Subjects should also be instructed to notify the investigator or nurse for the occurrence of bloody or black stools, symptoms of dehydration, fever, inability to take liquids by mouth, inability to control diarrhoea (return to baseline) within 24 hours. Subjects with diarrhoea should be evaluated frequently by a nurse or physician until resolution of diarrhoea.

Changes in electrolytes, even without BUN/urea and/or creatinine elevation, may reflect early physiologic consequences of treatment-induced gastrointestinal toxicity. Subjects with clinically significant electrolyte changes should be evaluated for dehydration and receive aggressive fluid and electrolyte replacement, if indicated.
It should be notice that acute renal failure has been observed in patients who develop severe diarrhea and dehydration.

7.6.2.3 Electrolyte Management

Patients should be evaluated as outlined in Section 7 and managed as per local medical practice. If hypomagnesaemia is present, replacement should be managed with either oral or parenteral replacement, or both, according to institutional practice and to the degree of hypomagnesaemia present. It is recommended that subject's serum magnesium level should be maintained within the normal range during study treatment.

It is important to assess and manage serum potassium and calcium (adjusted for albumin) in subjects who have concomitant hypomagnesaemia. Subject's serum potassium and calcium parameters are recommended to be maintained, as per local medical practice, within the normal ranges during study treatment.

7.6.2.4 Reaction of Panitumumab Infusion

Hypersensitivity reactions have been reported, including a fatal case of angioedema that occurred more than 24 hours after the infusion.
Subjects who experience any serious infusion reaction during panitumumab administration will have the infusion stopped. Continuation of dosing will be based on the severity and resolution of the event and will be at the discretion of the investigator.
Suspected infusion reactions should be reported as an adverse event. All subjects who experience such an event will be followed for safety.

7.6.2.5 Panitumumab Dosage Adjustments

For subjects who experience toxicities while on study, one or more doses of panitumumab may need to be withheld, reduced, or delayed (administered at > 14 day intervals). On resolution of toxicity, a limited number of attempts to re-escalate reduced panitumumab doses will be allowed (outlined in Figure 1).

Dose escalations above 6 mg/kg starting dose are not allowed. Panitumumab dose reductions are listed in Table 1.

Table 1. Panitumumab Dose Reductions

	Starting Dose	1st Dose Reduction	2nd Dose Reduction
Percentage (%)	100	80	60
mg/kg	6	4.8	3.6

7.6.2.6 Criteria for Withholding a Dose of Panitumumab

Skin- or nail-related toxicities:

- Symptomatic skin- or nail-related toxicity requiring narcotics, systemic steroids, or felt to be intolerable by the subject
- Skin or nail infection requiring IV antibiotic or IV antifungal treatment
- Need for surgical debridement
- Any skin- or nail-related serious adverse event

Non-skin- or nail-related toxicities:

- Any grade 3 or 4 toxicity with the following exceptions:
- Panitumumab will only be withheld for symptomatic hypomagnesaemia and/or hypocalcaemia that persists despite aggressive magnesium and/or calcium replacement
- Panitumumab will only be withheld for grade 3 or 4 nausea, diarrhoea, or vomiting that persists despite maximum supportive care (see Section 6.5.2.2 for diarrhoea management guidelines)
- Panitumumab will only be withheld for grade ≥ 3 anaemia or grade 4 thrombocytopenia that cannot be managed by transfusion(s) or cytokine therapy

7.6.2.7 Criteria for Re-treatment with Panitumumab

Skin- or nail-related toxicities:

Panitumumab administration may recommence once:

- The adverse event has improved to ≤ Grade 2 or returned to baseline, or;
- The subject has recovered to the point where symptomatic skin- or nail-related toxicity is felt to be tolerable; or,
- Systemic steroids are no longer required, or
- IV antibiotic or IV antifungal treatment is no longer required

Non-skin- or nail-related toxicities:
Panitumumab administration may recommence once the adverse event has improved to ≤ Grade 1 or returned to baseline.

7.6.2.8 Dose Modification Schedule

Subjects should be assessed for toxicity before each dose. Dose modification should be performed according to the schedule described below and outlined in Figure 1.

Subjects who develop a toxicity that does not meet the criteria for withholding a dose of panitumumab (Section 7.6.2.6) should continue to receive panitumumab and their symptoms should be treated.

Panitumumab-related toxicity will be considered resolved if it improves to a degree that allows for re-treatment with panitumumab (Section 7.6.2.7).

For subjects who experience a toxicity that meets the criteria for withholding a dose of panitumumab:

- Subjects receiving either 100% or 80% of the starting dose of panitumumab are allowed to have up to 2 subsequent doses withheld for toxicity. However a second dose should only be withheld if the toxicity has not resolved by the time that the subsequent dose is due.
- Subjects treated at the 100% dose level whose toxicity resolves after 1 dose of panitumumab is withheld should be re-started at the 100% dose level (recommended but not required, reduction to the 80% dose is allowed as an alternative to re-challenge with the 100% dose).
- If toxicity recurs, subjects treated at the 100% dose or 80% dose should be re-started at the 80% dose or 60% dose, respectively, when the toxicity resolves after withholding 1 or 2 doses of panitumumab.
- Subjects treated at the 100% dose level whose toxicity resolves only after 2 subsequent doses of panitumumab are withheld should be re-started at the 80% dose level.
- Subjects treated at the 80% dose level whose toxicity resolves after withholding 1 or 2 doses of panitumumab should be re-started at the 60% dose level.
- Subjects who experience toxicity at the 60% dose level will not be re-treated with panitumumab.

It is recommended that panitumumab doses will be escalated in subjects whose toxicity resolves to the degree that meets the criteria for re-starting a dose of panitumumab (Section 7.6.2.7). Dose escalations are recommended but not required. Dose escalations should occur in the following manner:

- Subjects treated at the 80% dose level whose toxicity does not recur should receive the 100% dose level at the next dose unless a previous attempt to re-escalate to the 100% dose level was not tolerated (re-initiation of the 80% dose is allowed as an alternative to dose escalation).
- Subjects treated at the 60% dose level whose toxicity does not recur should receive the 80% dose at the next dose unless a previous attempt to re-escalate to the 80% dose level was not tolerated (re-initiation of the 60% dose is allowed as an alternative to dose escalation).

Subjects who miss more than 2 consecutive scheduled doses due to toxicity or are unable to receive a dose of panitumumab within 6 weeks of having received their previous dose of panitumumab due to toxicity will be considered unable to tolerate panitumumab and will not be retreated with panitumumab.

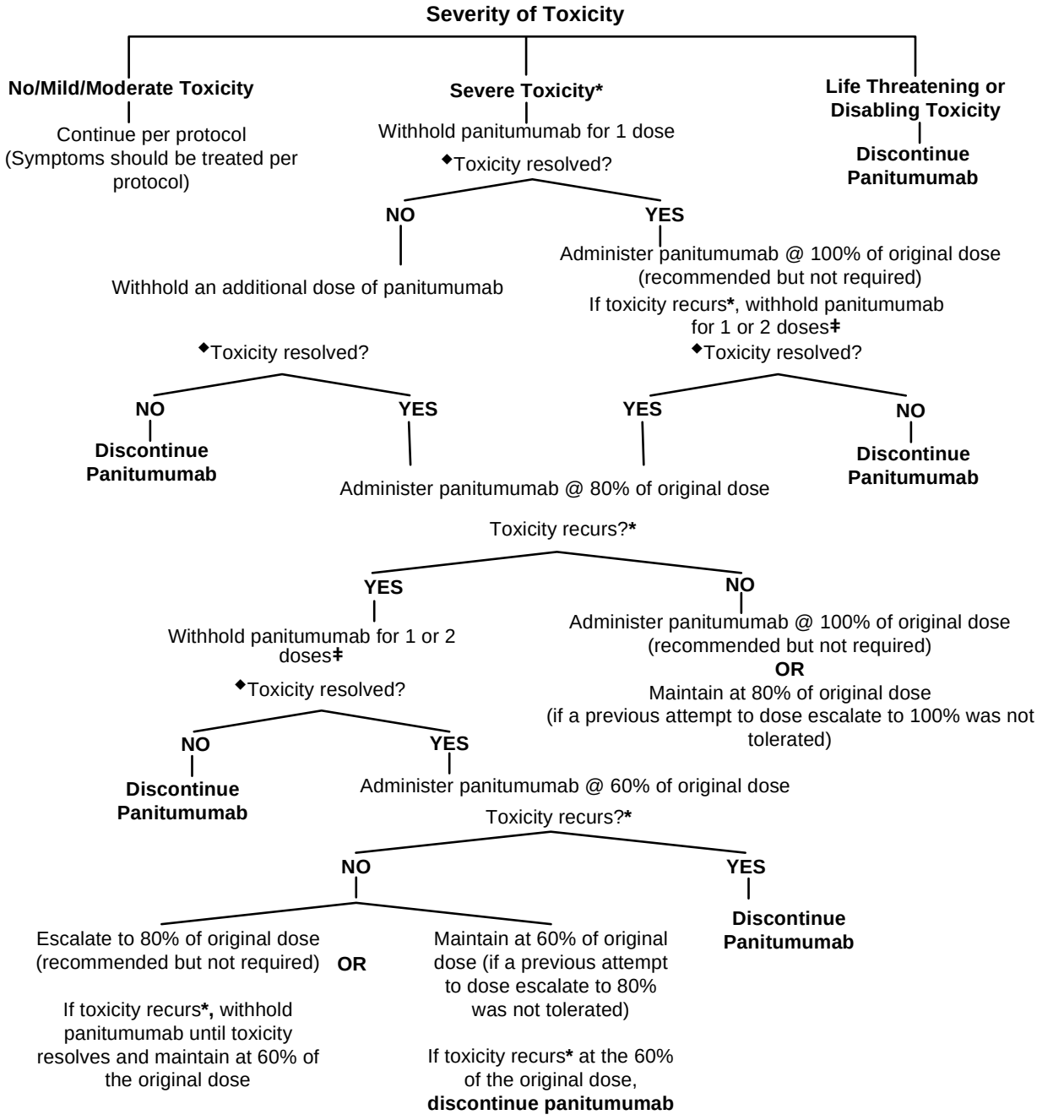
7.6.2.9 Panitumumab Delayed- or Missed-Doses

(For combination studies, include instructions on how the administration of chemotherapy and panitumumab should be managed due to toxicity)

Panitumumab should be given on the first day of each treatment period. Delays of panitumumab administration beyond 6 weeks from the previous dose of panitumumab are not allowed.

Reasons to withhold a dose of panitumumab are described in Section 7.5.2.6. More than 2 consecutively missed doses (i.e. 6 weeks without panitumumab) are not allowed. Missed panitumumab doses will not be made up.

Figure 1. Panitumumab Dose Modification Algorithm for Toxicity



***** Assess toxicity before each cycle. Toxicity recurs = meets the criteria for withholding a dose of panitumumab at any time during the study (See Section 6.3.1).

◆ Assess toxicity before each cycle. Toxicity resolved = meets the criteria for restarting panitumumab (see section 6.3.2). Subjects from whom > 2 subsequent cycles of panitumumab are required to be withheld should not be re-treated with panitumumab.

‡ Up to 2 subsequent doses of panitumumab may be withheld but panitumumab may not be withheld longer than 6 weeks from the previous dose. The second dose should only be withheld if the toxicity has not resolved by the time that the subsequent cycle of chemotherapy is due.

7.7 Concomitant medication

No **antitumour treatments** (chemotherapy, agents modifying biological response) other than the study treatments will be used.

Radiotherapy (even for analgesic purposes) is not authorised throughout the duration of treatment and up to progression. If radiotherapy is required for analgesic purposes, the date of the first radiotherapy session will be the censor date.

Treatments associated with renal or auditory toxicity (such as aminosides) are to be used under surveillance owing to the possible additive effects with cisplatin.

A risk of seizures has been described when using phenytoin with cisplatin and vinblastine, due to reduced gastrointestinal absorption of phenytoin by cytotoxic agents. Temporary combination with an anticonvulsant benzodiazepine is recommended.

Attenuated live vaccines are inadvisable owing to the risk of generalised vaccine reactions. Use of an inactivated vaccine is recommended if available. It should be noted that use of the yellow fever vaccine is contraindicated.

A possible interaction is observed between oral anticoagulants and anticancer chemotherapy in addition to an increased risk of thrombosis during certain tumour disorders.

8 STUDY IMPLEMENTATION

Inclusion clinical examinations and laboratory tests should be performed in patients having signed the consent form to take part in the study within 7 days prior to treatment start, and inclusion paraclinical examinations within 28 days prior to treatment start, either during screening or at baseline if screening takes place more than 7 days prior to treatment start.

Each patient is expected to take part in the trial for at least 3 months and up to disease progression. The patient monitoring period from the randomisation date up to progression and the patient assessment schedule are described in the synopsis.

8.1 Screening

After initialling the patient information sheet, signing the consent form (Appendix 5) and validation of the screening results, eligible patients may be registered.

- **Clinical examination (within 7 days prior to treatment start)**
  Physical examination with determination of weight, height and body surface area,
  ECOG performance status (Appendix 1),
  Vital signs (pulse, blood pressure, temperature),

- **Laboratory tests (within 7 days prior to treatment start)**
  Haematology: CBC/platelets + INR (for patients receiving anticoagulants)

Blood electrolytes with blood calcium and magnesium
Liver function tests (bilirubin, ASAT, ALAT, and ALP)
Renal assessment (creatinine, urea, uric acid),
Pregnancy test, if applicable,

- **Paraclinical examination (within 28 days prior to treatment start)**
  Chest-abdominal-pelvic CT scan,
  Bone scintigraphy,
  Determination of left ventricular ejection fraction (LVEF) by ultrasonography or scintigraphy,

8.2 Baseline

Depending on the patient's mutation status, i.e. if the patient does not present H-Ras or K-Ras mutations, **randomisation will be done as soon as possible from the patient's mutation status is received by the investigator**. Screening results will be available within 10 calendar days at maximum after the tumour block is received in the Department of Pathology

Baseline should take place within a maximum period of 7 days prior to the start of treatment and on the day on which treatment is started at the very least.

- **Randomisation**

- **Concomitant medication and previous treatments taken during the 12 months prior to inclusion report**,

- **Medical history report,**

- **Toxicity** assessment (from signing the consent form),

The following tests will not be repeated if carried out at screening within the required time-limits (7 days prior to treatment start for clinical examinations and laboratory tests, and 28 days for the paraclinical examinations).

- **Clinical examination (within 7 days prior to treatment start)**
  Physical examination with determination of weight, height and body surface area,
  ECOG performance status (Appendix 1),
  Vital signs (pulse, blood pressure, temperature),

- **Laboratory tests (within 7 days prior to treatment start)**
  Haematology: CBC/platelets + INR (for patients receiving anticoagulants)
  Blood electrolytes with blood calcium and magnesium
  Liver function tests (bilirubin, ASAT, ALAT, ALP)
  Renal assessment (creatinine, urea, uric acid),
  Pregnancy test, if applicable

- **Paraclinical examination (within 28 days prior to treatment start)**
  Chest-abdominal-pelvic CT scan,

Bone scintigraphy,
Determination of left ventricular ejection fraction (LVEF) by ultrasonography or scintigraphy,

8.3 Assessments during treatment (6 x 2 week cycles where D1 = D14).

- **Clinical examination every 14 days**
  Physical examination with determination of weight, height and body surface area,
  ECOG performance status (Appendix 1),
  Vital signs (pulse, blood pressure, temperature),
  Toxicity assessment during the period between courses,
  Concomitant medication report,

- **Laboratory tests every 14 days (before the treatment course)**
  Haematology: CBC/platelets once a week + INR (for patients receiving anticoagulants)
  Blood electrolytes with blood calcium and magnesium
  Liver function tests (bilirubin, ASAT, ALAT, ALP)
  Renal assessment (creatinine, urea, uric acid),

- **Paraclinical examinations**
  Chest-abdominal-pelvic CT scan (every 6 weeks),
  Bone scintigraphy (every 3 months),
  LVEF (ultrasonography or scintigraphy (at C6 only)

All examinations showing a treatment-related toxicity must be repeated periodically until toxicity resolves or is thought to be irreversible.

8.4 Tumour evaluations during the treatment period

During treatment, tumour evaluations by means of a chest-abdominal-pelvic CT scan will be repeated **every 6 weeks i.e. at C3 and C6 using the same device and the same sections from the first day of chemotherapy, then up to progression.**
Bone scintigraphy will be carried out at C6.

8.5 Assessments after treatment and up to progression: every 6 weeks.

A tumour evaluation based on the measurable lesions defined during screening or at baseline by means of a chest-abdominal-pelvic CT scan will be carried out **every 6 weeks from the last day of chemotherapy up to progression.**
Bone scintigraphy will be carried out every 3 months.

- **Clinical examination**
  Physical examination with determination of weight and body surface area,
  ECOG performance status (Appendix 1),
  Vital signs (pulse, blood pressure, temperature),
  Toxicity assessment
  Concomitant medication report

- **Laboratory tests**

  Haematology: CBC/platelets + INR (for patients receiving anticoagulants)
  Blood electrolytes with blood calcium and magnesium
  Liver function tests (bilirubin, ASAT, ALAT, ALP)
  Renal assessment (creatinine, urea, uric acid),

- **Paraclinical examinations**

  Chest-abdominal-pelvic CT scan (every 6 weeks),
  Bone scintigraphy (every 3 months),
  Determination of left ventricular ejection fraction (LVEF) by ultrasonography or scintigraphy (at the panitumumab treatment stop only.)

All examinations showing a treatment-related toxicity must be repeated periodically until toxicity resolves or is thought to be irreversible.

8.6 Monitoring assessments after progression

After progression, patient management will be at the discretion of the investigator. All treatments, including radiotherapy, are authorised.

Patients will be followed up **every 3 months** for vital status and toxicity assessment.

All examinations showing a treatment-related toxicity must be repeated periodically until toxicity resolves or is thought to be irreversible.

9 PREMATURE DISCONTINUATION OF TREATMENT

Treatment may be discontinued prematurely for the following reasons:

- toxicity,
- disease progression,
- refusal to continue the trial,
- withdrawal of consent,
- patient lost to follow-up,
- major deviation from the protocol,

Insofar as possible, patients having prematurely discontinued treatment will be followed up according to the same procedures as the other patients.

10 STUDY DISCONTINUATION CRITERIA

The trial may be suspended or discontinued by the sponsor after discussion with the coordinator at the request of the competent authorities and/or ethics committee (EC) for the following reasons:

- decision by the sponsor further to the expert report from the independent committee having convened for the review of safety data (cf. section 12.3)
- unexpected frequency and/or severity of toxicity,
- insufficient patient enrolment,
- insufficient data collection quality.

11 ENDPOINTS

11.1 Primary endpoint

The primary endpoint is the evaluation of efficacy, in terms of progression-free survival at 9 months of the combination I-MVAC with or without panitumumab.
The criterion for progression will be evaluated as per RECIST criteria (version 1.1 in Appendix 6) for measurable lesions or by the development of at least 1 new lesions evidenced during bone scintigraphy.
Survival rates will be estimated according to Kaplan-Meier. The event times for the analysis of PFS will be calculated from the date of randomisation to the date of progression or death. Patients who do not progress nor die will be censored at the date of last tumour assessment (CT or bone).

11.2 Secondary endpoints

Evaluation of toxicity (CTC AE v4.0)
Safety will be evaluated according to NCI-CTC. In order to be considered evaluable for toxicity, patients should have received at least one dose of treatment. Toxicity will be presented by cycle and by patient.

Evaluation of response (RECIST)
Response will be evaluated according to RECIST criteria v1.1. The objective response rate will be presented with a 90% confidence interval.

Evaluation of overall survival (OS)
Survival rates will be estimated according to Kaplan-Meier. The event times for the analyse of OS will be calculated from the date of randomisation to the date of death whatever the cause. Patients alive at last follow-up news will be censored at the last visit date.

Evaluation of time to progression (TTP)
Survival rates will be estimated according to Kaplan-Meier. The event times for the analysis of TTP will be calculated from the date of randomisation to the date of progression. Patients alive at last follow-up news will be censored at the date of last tumour assessment (CT or bone). Patients who die from causes other than progression will be censored at the date of death. Patients who do not progress nor

die will be censored at the date of last tumour assessment (CT or bone), or at the date of a secondary treatment initiation in the case of absence of progression.
The predictive impact of biological variables on objective response will be evaluated with logistic regression. Concerning survival criteria, the prognostic impact will be evaluated with Cox models.

12 DETERMINATION OF THE NUMBER OF PATIENTS AND STATISTICAL ANALYSIS

12.1 Number of subjects required

The total number of patients is 93 randomised in the ratio 1:2 (31 patients in the I-MVAC arm and 62 in the I-MVAC + panitumumab arm).
The number of patients was determined from the estimated 9-month median progression-free survival reported in the I-MVAC arm in the randomised trial in comparison with standard MVAC [16]. Using a oe stage Fleming design in the I-MVAC + panitumumab arm, treatment will be considered to be active and potentially evaluable in other studies if at least 37 patients among 62 do not show tumour progression at 9 months. This decision will take into account the observed PFS rate in the control arm. Treatment will be considered insufficiently active if 26 patients or more experience progression in the 9 months following initiation (p0=0.50, p1=0.70, alpha=0.08 and beta=0.03) (Fleming. Biometrics 1982) No formal statistical comparisons are planned between the two treatment arms due to the small sample size of this trial. The I-MVAC control arm is used only for the purpose of validating the initial hypothesis in assuring appropriate patient selection [van Glabbeke M, European Journal of Cancer 2002, 38:635-638].
A safety analysis will be performed after the inclusion of 10 patients in the I-MVAC + panitumumab arm in order to determine the feasibility of this protocol in terms of toxicity.

12.2 Statistical analysis

Categorical data will be summarized as a percentage and when necessary will be compared between groups with a chi-squared test. Continuous data will be summarized by the median and the range and when necessary will be compared between groups with the non parametric Kruskal Wallis test.
All descriptive analyses will be made by treatment arm (Control and Experimental) according to the intent to treat principal. Confidence interval for median survival will be calculated according to Brookmeyer-Crowley method.
Survival times will be calculated from the date of randomisation to the date of progression or death for PFS and to the date of death (whatever the cause) for OS. For PFS, patients without progression nor death will be censored at the date of last tumour assessment (CT or bone) .The objective response rate will be presented with a 90% confidence interval. Safety will be evaluated according to NCI-CTC. In order to be considered evaluable for toxicity, patients should have received at least one dose of treatment. Toxicity will be presented by cycle and by patient for each treatment arm.

A detailed statistical analysis plan (PAS) will be elaborated before the first data base lock.

12.3 Trial monitoring: analysis of safety data by an independent committee

The feasibility of combining chemotherapy with panitumumab has already been demonstrated; however, no studies with the I-MVAC protocol have been reported to date. An early safety assessment will therefore need to be carried out.
In order to decide whether the study should continue, an independent committee will review the safety data observed for the first 10 patients included in the combination arm (arm B) during the first 3 courses.
Furthermore, in order to allow all the participating sites to communicate with each other about clinical cases during this first period of the trial (the 3 first courses for the 10 first patients included in the arm B), a list of all participating sites with the principal investigator phone number and e-mail will be given to all sites during the initiation visit.
During this first period of the trial, if necessary, the participating sites could ask the sponsor to organise call conference to discuss specific clinical cases.

13 ANCILLARY STUDIES

These studies will concerned only patients randomised in the arm B (MVAC-I + panitumumab).

The first objective is to set-up a collection of tissue for patients randomised in arm B of the trial to allow for subsequent analysis of biomarkers that could impact response to treatment and a collection of blood samples for subsequent analysis of genetic polymorphism that could impact the response to treatment.

The second objective is to analyze in depth EGFR signalling pathways in the tumours of the patients randomised in the arm B of the trial to search for biomarkers which could predict response or resistance to this drug. Activating mutations of *RAS* and *PIK3CA,* and loss of PTEN expression have been associated with anti-EGFR based therapy resistance in other cancer types. Candidate biomarkers will include expression levels of EGFR family members (EGFR, ERBB2, ERBB3, ERBB4) and their ligands (EGF, HBEGF, EREG, TGFα and AREG), activation / inactivation of key EGFR downstream signalling mediators (RAS, PTEN, PIK3CA), genomic gains and activation (phosphorylation) status of EGFR or ERBB2.

Biomarkers predictive of response will be investigated using formalin fixed and paraffin embedded (FFPE) tumour specimen (obtained from primary tumours).

13.1 Ethical issues

At the inclusion step, patients will get precise information and will give informed consent for the scheduled biological studies.
The project will have to be submitted to an IRB for approval

13.2 Collection

After patient registration, blood collected in tubes with EDTA (2 x 7 ml) will be collected (during the laboratory test performed for the first cycle) and sent with the form appendix 8 to the Platform of Biological Resources of Hospital Henri Mondor (certification NF S96-900) at the following address:
Biothèque CIC

Plateforme de Ressources Biologiques
Hôpital Henri Mondor
51, Av du Maréchal De Lattre de Tassigny
94 000 Créteil, France

For each case, an attestation of the investigator that the patient has signed an informed consent form will be required.

The Platform will register protocol, hospital, and patient anonymised IDs according to the form in appendix 8, store blood samples and extracted genomic DNA with NucleonBac kits, according to standardised procedures.

The tumour blocks received in the Pathology Department will be punched and gathered into Tissue Microarray (TMA) Blocks, which will be stored for further studies.
Tumour blocks will be give back at the en of the inclusions.

13.3 Ancillary Biological Studies

Immunohistochemistry:
EGFR, ERBB2, PTEN, expression will be assessed using immuno-histochemistry. Phospho-EGFR and phospho-ERBB2 expression, related to activation status of the receptors, will also be assessed with specific antibodies. These techniques will be performed on TMA, with automatic acquisition / analysis of the slides.

mRNA expression:
After optimization of FFPE based assays, expression of EGFR family (EGFR, ERBB2, ERBB3, ERBB4) and ligands (EGF, EREG, HBEGF, TGFα and AREG) will be assessed using RT-QPCR.

Mutations:
N-RAS and PIK3CA mutational status in tumoural tissue will be detected capillary sequencing of PCR products.

Amplifications:
EGFR and ERBB2 amplifications will be searched using FISH assays on TMA sections.

13.4 Statistical analysis

The association between markers and response will be estimated using chi square tests and logistic regression. The association between markers and time to progression, progression-free survival and overall survival will be estimated using Kaplan Meier analysis, log rank tests and Cox regression models.

14 SERIOUS ADVERSE EVENTS

14.1 General definition

A serious adverse event (SAE) is any event that:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly, birth defect or miscarriage,

The terms *disability* and *incapacity* correspond to any clinically significant, temporary or persistent physical or psychological handicap having an impact on the patient's physical activity and/or quality of life.

The following are not considered to be serious adverse events (SAE):

- Hospitalisation < 24 hours,
- Hospitalisation scheduled prior to the start of the trial and/or stipulated by the protocol (biopsy, chemotherapy, etc.).
- Progressions
- Any grade 3 or 4 biologicals abnormalities that not correspond to SAE definition

14.2 Definition of an expected serious adverse reaction (E-SAR)

An E-SAR is an event already mentioned in the most recent version of the investigator's brochure or in the Summary of Product Characteristics (SPC) for medicinal products which have already been granted marketing authorisation (MA). This definition also applies to the study medication when administered for a given population outside the MA indication.

14.3 Definition of an unexpected serious adverse reaction (U-SAR)

A U-SAR (or SUSAR) is an event which has not been mentioned or which differs in terms of nature, severity, and outcome from the information in the investigator's brochure or the Summary of Product Characteristics (SPC) for medicinal products which have already been granted marketing authorisation (MA).

14.4 Severity criterion

The severity (or intensity) criterion should not be confused with the seriousness criterion which serves as a guide to define the reporting requirements.

The severity of the events shall be estimated according to the extract from the CTC-AE classification version 4.0 (cf. Appendix 3). The severity of adverse events not listed in the classification shall be assessed according to the following terms:
Mild (grade 1): does not affect the patient's normal everyday activity
Moderate (grade 2): interferes with the patient's normal everyday activity
Severe (grade 3): prevents the patient's normal everyday activity
Very severe (grade 4): requires intensive care measures/is life-threatening
Death (grade 5)

14.5 Procedure to be followed for a serious adverse event

The investigator informs the Pharmacovigilance Unit of the *Bureau d'Etudes Cliniques et Thérapeutiques* (PV-BECT) of all **expected (E-SAE) and unexpected (U-SAE) serious adverse events,** whether related to the research or not, which occur during the study from the day of the consent form signature or within 30 days following the last dose.

All delayed serious adverse events considered to be reasonably related to the protocol treatment(s) or to the research must be reported without any limitation in terms of deadline.

SAE are notified sending by fax the "SAE report form" (cf. Appendix 2), from the date of the consent form signature, immediately as soon as they have been brought to the investigator's attention, to PV-BECT.

***Bureau d'Etudes Cliniques et Thérapeutiques* (BECT)**
Pharmacovigilance
Tel.: 01 44 23 04 16 – Fax: 01 44 23 55 70
Email: pv-bect@fnclcc.fr

The investigator shall record details including the following for each event:

- Its description as clearly as possible according to the medical terminology,
- The severity,
- The date of the start and end of the event,
- The measures taken and whether corrective treatment was necessary or not,
- If the study treatment was discontinued,
- Its outcome. If the event was not fatal, the outcome should be monitored up to recovery, return to the previous state, or stabilisation of any sequelae,
- The causal relationship between the event and the study treatment or any of the requirements related to the study (treatment-free period, additional examinations requested as part of the study, etc.),
- The causal relationship with the disease treated another disease or another treatment.
- The investigator should also enclose the following with the serious adverse event report, whenever possible:
  - A copy of the hospital report or extended hospitalisation report,
  - A copy of the post-mortem report,
  - A copy of all results of any additional examinations conducted, including relevant negative results together with normal laboratory ranges,
  - Any other document considered to be useful and relevant.

All of the above documents must be anonymised.

Additional information may be requested (by fax, telephone or during a visit) by the monitor and/or Pharmacovigilance Unit of the BECT using the DCF.

Nevertheless, any reactions which are expected but differ in terms of severity, outcome or frequency will be considered as unexpected by the Pharmacovigilance Unit.

14.6 SAE monitoring

The investigator is in charge of conducting appropriate medical monitoring of patients until the reaction has resolved or stabilised, or up to the death of the patient. **Monitoring may therefore sometimes need to be extended after the patient has been withdrawn from the trial.**

The investigator shall send additional information to PV-BECT using a SAE report form (ticking the box "Follow-up report no." to specify that this is a follow-up report and not an initial report) as soon as it is brought to the investigator's attention. Another report is also sent following resolution or stabilisation of the SAE.

He/she files the documents relating to the suspected serious adverse event so that the information previously submitted may be supplemented as required.
He/she responds to requests for additional information by PV-BECT to document the initial case.

14.7 Pregnancy exposures

Pregnancy exposures should be reported within 7 working days from the day the pregnancy have been brought to the investigator knowledge by faxing the "Pregnancy exposure Form" (cf. Appendix 9) to the BECT Pharmacovigilance Department at the following number: 01 44 23 55 70.

15 QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Monitoring committees

A trial steering committee consisting of the principal investigator, the sponsor's project manager and the trial statistician (STCOM = study steering committee) shall be set up in order to guarantee patient protection, to ensure that the trial is conducted in an ethical manner, to assess the benefit/risk ratio of the trial, and to review the scientific results during or at the end of the trial.

A review committee will also be created in order to examine all CT scan or MRI slides which will make it possible to confirm the primary study endpoint.

15.2 Quality assurance

15.2.1 Data collection

All of the data required for the study shall be recorded, as soon as possible, in the study case report forms, in a legible manner using a black ballpoint pen. Pencils and correction fluid must not be used.
If corrections prove necessary, these shall be made by the investigator or an authorised member of his/her team, as follows: erroneous data must be crossed out, while remaining legible, and the correct data written alongside. Corrections must be certified with the date and initials. As regards corrections concerning adverse events or the primary efficacy variable, the reason for correction must be provided.
The original copy of each information sheet and informed consent form shall be kept in the investigator's file.

Data are collected in a case report form filled in by the investigating physician or authorised person:

- physical examination, weight, height, vital signs,
- blood and biochemistry tests,
- tumour evaluation report as per RECIST criteria,

- serious and non-serious adverse events that occurred during each cycle,
- etc.

15.2.2 Study monitoring

So as to ensure the authenticity and credibility of data in compliance with GCP of November 24, 2006, the sponsor has set up a quality assurance system which consists of:

- management and monitoring of the trial in compliance with the procedures of the *Fédération Nationale des centres de Lutte contre le cancer*,
- quality control of data at the investigating site by the monitor whose role it is to:
  - verify compliance with the protocol, GCP guidelines and current laws and regulations,
  - verify the consent and eligibility of each patient taking part in the study,
  - verify the similarity and consistency of data in the case report form against the source documents,
  - verify the notification of each serious adverse event,
  - monitor the traceability of study medication (supply, storage and accountability),
  - ensure, where appropriate, that individuals liable to take part in the study are not already taking part in a study which would prevent them from being included in the proposed study. The monitor shall also ensure that patients have not taken part in a study for which an exclusion period is currently required.
- possible audit of investigating sites,
- centralised review of objective responses.

The monitors responsible for quality control of the biomedical study shall be duly appointed for this purpose by the sponsor and must have access, subject to the agreement of the individuals involved, to the individual data of study participants, which are strictly necessary for these checks. Monitors are bound by professional secrecy as defined in articles 226-13 and 226-14 of the French Penal Code. The traceability of monitoring visits is made possible by a written monitoring report.

To help monitors carry out study quality control as effectively as possible, investigators undertake to allow them direct access to each patient's medical records. This also applies to representatives from the health authorities.

16 OWNERSHIP OF DATA AND CONFIDENTIALITY

The investigator undertakes, both personally and on behalf of all individuals involved in monitoring the performance of the trial, to ensure the confidentiality of all information provided by the *Fédération Nationale de Lutte Contre le Cancer* (FNCLCC) until the trial results are published. This confidentiality obligation shall not apply to information which the investigator will need to provide to patients as part of their participation in the trial nor to individuals which have already been published.
The investigator undertakes not to publish, disclose or use, in any manner whatsoever, trial-related scientific or technical data, whether directly or indirectly.

Nevertheless, in compliance with Article R 5121-13 of the French Public Health Code, the site and investigator may provide the following with trial-related information:
- the Minister of Health,
- public health inspecting physicians,

- public health inspecting pharmacists,
- the Director General and inspectors from the Afssaps.

The trial may not be the subject of any written or verbal comments without the agreement of the sponsor; all of the information provided or obtained during the implementation of the trial are the rightful property of the *Fédération Nationale de Lutte Contre le Cancer* which may use this information as it so pleases.

17 PUBLICATION GUIDELINES

All information resulting from this trial is considered confidential at least until the appropriate analysis and verification by the sponsor, coordinating investigator and trial statistician are complete.

All publications, abstracts or presentations comprising the results of the trial must be submitted to the sponsor (FNCLCC) for approval.

In addition, all papers, manuscripts or presentations must include a section imperatively mentioning the FNCLCC, the *Ligue nationale Contre le Cancer*, all institutions, investigators, collaborating groups, and learned societies having contributed to the implementation of the trial, together with any organisations which provided financial support for the research.

The coordinating investigator of the trial will be the main signatory of the paper and the author of the document; the latter may assign this task to another person if appropriate.

The subsequent investigators will be cited in proportion to the number of patients enrolled irrespective of collaborating group, followed by a representative from each collaborating group from among the investigating sites with the highest enrolment rate.

The trial statistician together with the sponsor's representative will also be cited.

Likewise, publications of ancillary results (biological study) will include the name of the person having carried out the ancillary research together with the names of all other persons concerned by the ancillary research.

18 ETHICAL AND REGULATORY ASPECTS

Patients included in this study may not simultaneously take part in another study; there is a 6-month exclusion period at the end of the study.
The clinical trial must be conducted in compliance with:

- the ethical principles of the most recent version of the Declaration of Helsinki currently in force,
- Good Clinical Practice guidelines dated November 24, 2006,
- European Directive (2001/20/EC) on the conduct of clinical trials,
- the French Huriet Act *("Loi Huriet")* (no. 88-1138) of December 20, 1988, relative to the protection of individuals taking part in biomedical research, as amended by the French Public Health framework act (no. 2004-806) of August 9, 2004,

- the French data protection law "*Informatique et Libertés*" no. 78-17 of January 6, 1978, as amended by law no. 2004-801 of August 6, 2004, relating to the protection of individuals with regard to the processing of personal data,
- the French bioethics act no. 2004-800 of August 6, 2004.

18.1 Clinical trial authorisation

The protocol was submitted to the ethics committee which issued a favourable opinion.

The protocol was submitted to the AFSSAPS which granted authorisation.

18.2 Information and consent of participants

Prior to conducting biomedical research on an individual, their freely given, written, informed consent must be obtained after they have received thorough information from the investigator.

The information sheet and informed consent form (Appendix 5) must constitute a single document in order to ensure that the individual taking part in the study has been provided with full information.

The consent form must be personally signed and dated by the individual taking part in the study and the investigator. The participant must also initial each page of the information sheet. The original copy shall be kept in the investigator's file, and the duplicate given to the individual taking part in the study.

As regards trials aiming to carry out genomic or proteomic analyses, the information sheet should specify the type of research to be conducted and patients should have the opportunity to agree or object to their biological samples being stored for the purpose of scientific research.

As part of this biomedical study, personal data shall be processed so as to make it possible to analyse clinical study results in view of the study objective.
Medical data concerning the patients and data relating to their lifestyle shall be provided to the sponsor for this purpose. These data shall be identified by means of a code number and the first three letters of the patient's surname. These data may also be provided to the health authorities in France or abroad, under conditions ensuring the confidentiality thereof. In compliance with the provisions of the French data protection law, the patient has a right of access and rectification. They also have a right to object to the transfer of data protected by professional secrecy, liable to be used and processed as part of this study.
They may also have access to all of their medical data in pursuance of the provisions of Article L 1111-7 of the French Public Health Code, either directly or via a physician of their choice.
They may exercise these rights with the physician following them up as part of the study and who is aware of their identity.

18.3 Responsibilities of the sponsor

The sponsor of the clinical trial, i.e. the *Fédération Nationale des Centres de Lutte Contre le Cancer*, has initiated this biomedical study; it is responsible for managing the study and ensuring that funding is obtained.
The main responsibilities of the sponsor are as follows:

- taking out civil liability insurance policy,

- obtaining the EudraCT no. and registering the trial in the European database (European Drug Regulatory Authorities Clinical Trials) and PDQ,
- obtaining clinical trial authorisation for the initial project and any amendments from the ethics committee and the AFSSAPS; ethics committee opinion and AFSSAPS decision,
- notifying any suspected unexpected serious adverse events to the relevant authorities, and forwarding this information to the ethics committee and trial investigators,
- sending the annual safety report to the as part of authorities and the ethics committee,
- informing the institution directors, pharmacists and investigators of the trial,
- notifying the start and end of the trial to the relevant authorities,
- drafting the final study report and sending the summary to the AFSSAPS,
- informing the relevant authorities, the ethics committee and individuals taking part in the research of the study results,
- archiving the essential study documents in the sponsor's file for at least 15 years after the end of the study.

18.4 Responsibilities of the investigators

The principal investigator at each institution involved undertakes to conduct the clinical trial in compliance with the protocol authorised by the ethics committee and the relevant authorities (AFSSAPS).
The investigator should not make any amendments to the protocol without written authorisation from the sponsor and if the ethics committee and relevant authorities have not authorised the suggested amendments.

The principal investigator is responsible for:

- providing the sponsor with his/her curriculum vitae together with those of the co-investigators,
- identifying the members of his/her team taking part in the trial and defining their responsibilities,
- starting patient enrolment after authorisation from the sponsor,
- ensuring that he/she is available for monitoring visits and investigator meetings.

Each investigator is responsible for:

- complying with the requirements for trial confidentiality,
- collecting the informed consent forms, personally signed and dated by each individual taking part in the study prior to any trial-specific screening procedures,
- regularly filling in the case report forms (CRF) for each patient included in the trial and allowing the monitor (CRA) appointed by the sponsor direct access to source documents in order to validate the CRF data,
- notifying any serious adverse events occurring during the study to the sponsor as soon as possible,
- agreeing to regular visits by the monitor and, if need be, by auditors appointed by the sponsor or inspectors from the regulatory authorities,
- dating, correcting and signing the corrections in the case report forms (CRF) and data correction forms (DCF).

18.5 Regulations relating to the collection of human biological samples

As part of the translational research in this study tumour samples are required both for anatomical pathology analyses and genetic analyses; these are subject to specific written consent by the patient. This consent, which is different to the consent to take part in a clinical trial, may be withdrawn at any time. Likewise, the patient is able to request that their samples be disposed of, at any time during the study.

At the end of the study, if the patient does not object and the samples have not been used in their entirety, they may be the subject of subsequent scientific investigation(s) exclusively authorised by the sponsor. If subsequent genetic research is carried out, in compliance with the bioethics law, further consent shall be requested from patients.

As part of the translational research, personal data processing shall also be carried out to make it possible to analyse results of the biological investigations.
Biological data, including genetic data shall be combined with certain medical data from the clinical research and provided to the sponsor for this purpose. These data shall be identified by means of a code number and/or the initials or first three letters of the surname [specify as appropriate]. These data may also be provided to the health authorities in France or abroad, to other entities [Sponsor's name], under conditions ensuring the confidentiality thereof. In compliance with the provisions of the French data protection law, the patient has a right of access and rectification. They also have a right to object to the transfer of data protected by professional secrecy, liable to be used and processed as part of this study.
They may also have access to all of their biological and medical data in pursuance of the provisions of Article L 1111-7 of the French Public Health Code, either directly or via a physician of their choice.
They may exercise these rights with the physician following them up as part of the study and who is aware of their identity.

18.6 Fédération des Comités de Patients pour la Recherche Clinique en Cancérologie

The *Fédération des Comités de Patients pour la Recherche Clinique en Cancérologie* (FCPRCC) was created on the initiative of the *Fédération des Centres de Lutte Contre le Cancer* (FNCLCC) and the *Ligue Nationale Contre le Cancer* to review clinical trial protocols in the field of oncology. The FCPRCC, coordinated by the *Bureau d'Etudes Cliniques et Thérapeutiques* (BECT) and FNCLCC, brings together patient committees from the *Ligue Nationale Contre le Cancer* together with other healthcare institutions. It undertakes to review protocols and propose improvements namely concerning the quality of the information sheet, the availability of a treatment and monitoring plan, and suggested measures aiming to improve patient comfort.

19 DATA PROCESSING, AND ARCHIVING OF DOCUMENTS AND STUDY DATA

19.1 Data processing

The FNCLCC has entrusted the Biostatistics Department of EURAXI PHARMA with the processing of the study data (data entry + data management). This shall be carried out using the XXXX software program. The Biostatistics Department has notified the corresponding database to the CNIL, and the data shall remain the property of FNCLCC, the study sponsor.
Data processing shall be carried out in compliance with the ancillary guidelines relating to IT systems stipulated by the European Community Good Clinical Practice Guidelines.

The FNCLCC complies with reference methodology MR001 of the *Commission Nationale de l'Informatique et des Libertés* in compliance with the revised French data protection law "*informatique et liberté*" of August 6, 2004, and its implementing decree.

19.2 Archiving of documents

All trial-related documentation (protocol, consent forms, case report forms, investigator's file, etc.), together with the original documents (laboratory results, X-rays, visit reports, clinical examination reports, etc.) are considered confidential and must be stored in secure premises.

For each site and in accordance with the French decree of November 8, 2006, the principal investigator is required to file the data together with a list enabling patient identification for at least 15 years after the end of the study. After this period, the site may only destroy this documentation after obtaining written agreement from the sponsor.

20 REFERENCES

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21 APPENDIX

APPENDIX 1 – EVALUATION OF GENERAL CONDITION - ECOG

EVALUATION OF GENERAL CONDITION AS PER THE ECOG CLASSIFICATION

GENERAL CONDITION ECOG-ZUBROD/WHO	GRADE
Fully active, able to carry on all pre-disease performance without restriction.	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.	1
Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	4

APPENDIX 2 – NOTIFICATION OF A SERIOUS ADVERSE EVENT FORM

Notification Of A Serious Adverse Event Form For IMP

TO BE FAXED TO PHARMACOVIGILANCE – PARIS OFFICE N° + 33 (0)1 44 23 55 70

PROTOCOL N°:	EUDRACT N°:	COUNTRY:
SPONSOR IDENTIFICATION N°:	INVESTIGATOR SITE :	N°:
DATE OF THIS REPORT : |__|__|/|__|__|/|__|__|__|__|	INITIAL REPORT ☐	FOLLOW-UP REPORT N°|__|__| FINAL REPORT ☐

1. PATIENT IDENTIFICATION

INCLUSION N°: |_____| SURNAME (3 LETTERS): |__\|__\|__\| 1ST NAME (2 LETTERS): |__\|__\| DATE OF BIRTH : |__\|__\|/|__\|__\|/|__\|__\|__\|__\|

SEX : F ☐ M ☐ WEIGHT (KG) : |_____| HEIGHT (CM) : |_____| TREATMENT ARM : |____|

2. INFORMATION ON EVENT

DATE OF ONSET : |__\|__\|/|__\|__\|/|__\|__\| TOXICITY (GRADE NCI – CTC) : 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

DIAGNOSIS *OR MAIN SYMPTOM* : **only one diagnosis or one symptom (except for linked symptoms)**.....

.....

.....

DESCRIBE EVENT AND TREATMENT GIVEN *(INCLUDING RELEVANT TEST/LAB DATA)* :

.....

.....

.....

.....

3. SERIOUSNESS CRITERIA

☐ DEATH.....DATE |__\|__\|/|__\|__\|/|__\|__\|__\|__\|

☐ LIFE-THREATENING

☐ REQUIRING/PROLONGING HOSPITALIZATION (> 24H) : DATE OF ADMISSION |__\|__\|/|__\|__\|/|__\|__\|__\|__\|

☐ MEDICALLY RELEVANT

☐ PERSISTENT/SIGNIFICANT DISABILITY/INCAPACITY

☐ OTHER CANCER : .....

☐ CONGENITAL DISORDER/BIRTH DEFECT

4. OUTCOME

☐ ONGOING EVENT

☐ RECOVERED WITHOUT SEQUELA, DATE |__\|__\|/|__\|__\|/|__\|__\|__\|__\|

IF APPLICABLE DATE OF END OF HOSPITALIZATION : |__\|__\|/|__\|__\|/|__\|__\|__\|__\|

☐ RECOVERED WITH SEQUELA, DATE |__\|__\|/|__\|__\|/|__\|__\|__\|__\|

SPECIFY SEQUELA : .....

IF APPLICABLE DATE OF END OF HOSPITALIZATION: |__\|__\|/|__\|__\|/|__\|__\|__\|__\|

☐ DEATH RELATED TO THIS EVENT, DATE : |__\|__\|/|__\|__\|/|__\|__\|__\|__\|

☐ DEATH UNRELATED TO THIS EVENT, DATE : |__\|__\|/|__\|__\|/|__\|__\|__\|__\|

☐ UNKNOWN

☐ AUTOPSY YES ☐ NO ☐

5. INVESTIGATIONAL MEDICINAL PRODUCT (S) / RADIOTHERAPY

INVESTIGATIONAL MEDICINAL PRODUCT(S) INDICATE THE INTERNATIONAL COMMON DENOMINATION OF THE IMP / RADIOTHERAPY	ROUTE	SAE CYCLE NUMBER	DATES: DATE OF FIRST ADMINISTRATION (1ST DAY OF 1ST CYCLE)	DATES: DATE OF LAST ADMINISTRATION BEFORE SAE	DOSE & UNIT: LAST DOSE ADMINISTRATED BEFORE SAE – DOSE	LAST DOSE ADMINISTRATED BEFORE SAE – UNIT	CUMULATIVE DOSE SINCE THE 1ST ADMINISTRATION – DOSE	CUMULATIVE DOSE SINCE THE 1ST ADMINISTRATION – UNIT
1.			|__|__|/|__|__|/|__|__|__|__|	|__|__|/|__|__|/|__|__|__|__|				
2.			|__|__|/|__|__|/|__|__|__|__|	|__|__|/|__|__|/|__|__|__|__|				
3.			|__|__|/|__|__|/|__|__|__|__|	|__|__|/|__|__|/|__|__|__|__|				
4.			|__|__|/|__|__|/|__|__|__|__|	|__|__|/|__|__|/|__|__|__|__|				
5.			|__|__|/|__|__|/|__|__|__|__|	|__|__|/|__|__|/|__|__|__|__|				
6			|__|__|/|__|__|/|__|__|__|__|	|__|__|/|__|__|/|__|__|__|__|				
7.			|__|__|/|__|__|/|__|__|__|__|	|__|__|/|__|__|/|__|__|__|__|				

UNBLINDING : YES ☐ NO ☐ NA ☐

HAS ONE (OR SEVERAL) TREATMENT(S) BEEN STOPPED?

☐ YES N° |__\| N° |__\| N° |__\| N° |__\| N°|__\| N°|__\| ☐ NO ☐ NA

DID THE EVENT DISAPPEAR AFTER TREATMENT(S) STOPPED?

☐ YES ☐ NO ☐ NA

HAS ONE (OR SEVERAL) TREATMENT(S) BEEN REINTRODUCED?

☐ YES N° |__\| N° |__\| N° |__\| N° |__\| N°|__\| N°|__\| ☐ NO ☐ NA

DID THE EVENT REAPPEAR AFTER TREATMENT REINTRODUCTION?

☐ YES ☐ NO ☐ NA

Notification Of A Serious Adverse Event Form For IMP

To be faxed to Pharmacovigilance – Paris office n° + 33 (0)1 44 23 55 70

Protocol N°:	EudraCT N°:	Country:
Sponsor identification N°:	Investigator site :	N°:
Inclusion N°: |_____|	Surname (3 letters): |__|__|__|	1st name (2 letters): |__|__| Date of birth : |__|__|/|__|__|/|__|__|__|__|

6. CONCOMITANT DRUG(S)– *(exclude those used to treat reaction)*

Concomitant drug	Route	Date started	Date stopped	Ongoing	Indication
1.		From |__|__|__|__|__|__|	To |__|__|__|__|__|__|	☐	
2.		From |__|__|__|__|__|__|	To |__|__|__|__|__|__|	☐	
3.		From |__|__|__|__|__|__|	To |__|__|__|__|__|__|	☐	
4.		From |__|__|__|__|__|__|	To |__|__|__|__|__|__|	☐	

7. OTHER RELEVANT HISTORY *(e.g. diagnostics, allergies, pregnancy with last month of period, etc…)*

.....
.....
.....

8. ASSESSMENT, In your opinion, this event is related to:

☐ Investigational medicinal product (s), specify the number *(one or more)*: N° |__| N° |__| N° |__| N° |__| N°|__| N°|__| N°|__|
☐ Radiotherapy

IF NOT RELATED TO EITHER IMP OR RADIOTHERAPY :

Please Tick only one box

☐ Protocol
☐ Concomitant treatment(s) .....
☐ Concomitant disease(s), specify .....
☐ Other, specify .....

9. NOTIFICATOR

Name :

Function :

Address :

Phone : Fax :

E-mail :

INVESTIGATOR

Date |__\|__\|/|__\|__\|/|__\|__\|__\|__\|

Name :

Signature :

For the Sponsor only: Do Not Fulfil this part

Sponsor Identification Number:

Date of receipt by the sponsor :|__\|__\|/|__\|__\|/|__\|__\|__\|__\| *Date of this report :*|__\|__\|/|__\|__\|/|__\|__\|__\|__\|

ASSESSMENT:

☐ *Investigational medicinal product (s), specify the number°* N° |__| N° |__| N° |__| N° |__| N°|__| N°|__| N°|__|
↳ *Is it a Suspected Unexpected Serious Adverse Reaction (SUSAR)* YES ☐ NO ☐

☐ *Radiotherapy*
☐ *Protocol*
☐ *Concomitant treatment(s)*
☐ *Concomitant disease(s), specify* .....
☐ *Other, specify* .....

SPONSOR

Date |__\|__\|/|__\|__\|/|__\|__\|__\|__\|

Name and Signature :

APPENDIX 3 – TOXICITY CRITERIA (CTCAE V4.0))

Refer to the CTCAE toxicity evaluation scale which is enclosed separately and may be downloaded from the NCI site

Cancer Therapy Evaluation Program

http://ctep.cancer.gov/

Common Terminology Criteria for Adverse Events v4.0 (CTCAE)
(Publish Date May 28, 2009)

CTCAE v4.0, a new version of the CTEP, NCI CTC v3.0, includes Adverse Events applicable to all oncology clinical trials regardless of chronicity or modality.

APPENDIX 4 – SUMMARY OF PRODUCT CHARACTERISTICS

The most recent versions in force may be accessed via the websites of the regulatory agencies, Afssaps, EMEA, or on the VIDAL site:

http://agmed.sante.gouv.fr/
http://www.emea.eu.int/
http://www.vidalpro.net/

APPENDIX 5A - PATIENT INFORMATION SHEET AND CONSENT FORM

Notes d'information(1) et formulaire de recueil de consentement destinés aux patients participant à la recherche biomédicale GETUG-AFU 19/0903- N°EudraCT : 2009-011882-10

(1) ***Toutes les pages de ce document doivent être paraphées par le patient et l'investigateur et un exemplaire, dont le formulaire de recueil de consentement cosigné, doit lui être remis.***

Titre du protocole :

Méthotrexate, vinblastine, doxorubicine et cisplatine intensifié (MVAC-I) avec ou sans panitumumab dans le traitement de première ligne des carcinomes urothéliaux avancés chez des patients qui ne portent pas de mutations H-Ras ni K-Ras. Etude de phase II randomisée.

Note d'information destinée aux patients.

Madame, Monsieur,

Votre médecin vous a expliqué que vous êtes atteint d'un cancer de la vessie dont le traitement nécessite une chimiothérapie (médicament anticancéreux). Il vous propose de participer à l'étude de recherche biomédicale GETUG-AFU 19/0903 pour le traitement de votre maladie.
La chimiothérapie habituellement donnée dans votre cas est composée d'une association de 4 médicaments : le méthotrexate, la vinblastine, la doxorubicine et le cisplatine administrés tous les 14 jours. Ce protocole de traitement est appelé « MVAC-I».

1- Quel est l'objectif de cette étude?

L'étude à laquelle nous vous proposons ici de participer a pour objectif d'évaluer l'efficacité du traitement « MVAC-I » associé ou non au panitumumab chez les patients dont la tumeur ne présente pas de mutation sur les gènes H-Ras et K-Ras.

Le panitumumab est une molécule qui va se lier spécifiquement à la surface de certaines cellules cancéreuses et a ainsi pour but de les empêcher de se multiplier. Nous pensons que le panitumumab n'est pas efficace sur les cellules tumorales qui présentent la mutation H-Ras ou K-Ras, c'est pourquoi seuls les patients dont la tumeur ne porte pas ces mutations pourront participer à cette étude.

2- Combien de personnes vont participer à cette étude ?

Cette étude se déroulera en France pendant 4 ans et demi. Il est prévu d'inclure 93 patients.

3- Comment va se dérouler cette étude ?

Si vous acceptez de participer à cette étude nous allons tout d'abord regarder si les gènes H-Ras et K-Ras de votre tumeur présentent ou non une mutation en analysant le prélèvement déjà réalisé pour le diagnostic de votre maladie.

- Si votre tumeur présente une mutation sur l'un ou l'autre de ces 2 gènes, vous ne pourrez pas participer à cette étude. Ceci ne vous empêchera pas de recevoir les soins nécessaires et le traitement le plus adapté à votre cas.

- Si votre tumeur ne présente pas ces mutations, vous pourrez participer à cette étude. Le traitement que vous allez recevoir vous sera attribué par tirage au sort :
  - Soit vous recevrez le protocole MVAC-I (6 cycles de 14 jours)
  - Soit vous recevrez le protocole MVAC-I associé au panitumumab (6 cycles de 14 jours). Si vous tolérez bien ce traitement et qu'il s'avère efficace, le panitumumab vous sera donné seul après les 6 cycles de MVAC-I, selon la même procédure que pendant les cycles de chimiothérapie et ce jusqu'à progression de votre maladie ou pendant au maximum 2 ans après la fin des cycles de MVAC-I.

Quel que soit le traitement qui vous a été attribué, vous serez hospitalisé pendant une période de 48 heures tous les 14 jours.
Afin de vous administrer votre traitement, votre médecin mettra en place une voie veineuse centrale. Il s'agit d'un dispositif (appelé chambre) implantable sous la peau, qui est posé sous anesthésie dans une grosse veine située à proximité de la clavicule. Ce cathéter est laissé en place

pendant toute la durée du traitement, ce qui permet de l'utiliser à chaque fois qu'une perfusion est nécessaire.

Avant chaque cycle de chimiothérapie, votre médecin vous examinera et une prise de sang vous sera faite régulièrement.
Afin de suivre l'évolution de votre maladie, un scanner abdomino-pelvien, une scintigraphie osseuse ainsi qu'une échographie ou une scintigraphie cardiaque seront réalisés régulièrement, selon le calendrier des examens que vous trouverez ci-après.

Si votre maladie progresse, c'est-à-dire si elle évolue défavorablement, au cours du traitement ou après les cycles de chimiothérapie, votre médecin vous proposera une prise en charge qui sera la plus adapté à votre cas.

Le cas échéant, une contraception efficace est nécessaire pendant toute la durée du traitement et 6 mois après l'arrêt du traitement afin d'éviter une grossesse. En effet, les médicaments que vous allez prendre peuvent présenter un risque potentiel pour le fœtus. Il convient donc d'éviter toute conception si l'un des deux partenaires est traité. Si vous apprenez que vous êtes enceinte ou si votre partenaire apprend qu'elle est enceinte, vous devez immédiatement en informer votre médecin.

Enfin, il est recommandé aux patients traités par le panitumumab de mettre de la crème solaire, de porter un chapeau et de limiter l'exposition au soleil pendant toute la durée du traitement par le panitumumab et lors de l'apparition de problèmes dermatologiques, la lumière du soleil pouvant accentuer les réactions cutanées possibles.

4- Quelle est la durée de votre participation à cette étude ?

Le traitement comprend 6 cycles de 14 jours, soit une durée de traitement d'environ 3 mois. Ensuite, votre médecin vous verra toutes les 6 semaines après la fin de la chimiothérapie et ceci pendant, au maximum, 2 ans. Si votre maladie progresse, vous reverrez votre médecin tous les 3 mois pour le suivi de votre maladie.

5- Quels sont les risques possibles ?

La chimiothérapie par MVAC-I peut entrainer les effets indésirables suivants :

- des nausées et vomissements lors des perfusions et dans les jours qui suivent. Des médicaments anti-vomitifs vous seront donnés pour prévenir et limiter ces effets.
- Une perte de cheveux qui repousseront quelques semaines après la fin de la chimiothérapie.
- Une diminution du nombre de globules blancs, de globules rouges et de plaquettes. La surveillance de cette possible diminution nécessitera des prises de sang régulières. Pour limiter la baisse des globules blancs, un médicament vous sera donné du 3ème au 9ème jour de chaque cycle par injections sous-cutanées.
  En cas de fièvre nous vous demandons de contacter ou de consulter immédiatement votre médecin afin que celui-ci puisse prendre les mesures qui s'imposent. Vous serez éventuellement hospitalisé pour vous administrer un traitement antibiotique ou des transfusions de sang.
- Une altération du fonctionnement de votre cœur qui sera surveillée par les examens (une échographie ou scintigraphie) prévus au cours de cette étude.

Le panitumumab peut entrainer les effets secondaires suivants :

- des réactions cutanées comme un rash (éruption transitoire, c'est-à-dire passagère), des rougeurs de la peau, des démangeaisons, une sécheresse de la peau, des fissures de la peau, une exfoliation et une inflammation autour des ongles, sont les effets secondaires les plus souvent observés.

- des réactions comme des frissons, de la fièvre ou une respiration difficile liées à la perfusion peuvent survenir au cours de l'administration du panitumumab et dans les 24h00 après l'administration du médicament
- des diarrhées ou des douleurs abdominales. Vous devez contacter votre médecin ou une infirmière si vous observez la présence de sang dans vos selles, si vos selles sont noires, si vous avez de la fièvre, si vous ne parvenez pas à absorber une boisson ou encore si la diarrhée ne cesse pas dans les 24 heures après sa prise en charge par votre médecin
- une fatigue
- une modification de la quantité de calcium, de magnésium et/ou de potassium dans votre sang. Dans ce cas, votre médecin vous traitera selon les pratiques habituelles.

6- Quels sont les bénéfices attendus de cette étude

Actuellement, le traitement de référence de votre maladie est la chimiothérapie par MVAC-I. Nous pensons que l''ajout du panitumumab dont l'action sur les tumeurs est ciblée permettra d'augmenter l'efficacité de la chimiothérapie.

7- Aspects réglementaires

Pour participer à cette étude, vous devez être bénéficiaire d'un régime de sécurité sociale en tant qu'assuré ou ayant-droit. Vous ne serez inclus dans l'étude que si vous signez et paraphez ce consentement qui vous sera remis. Vous ne pourrez pas participer en même temps à une autre recherche biomédicale. Après votre participation à l'étude GETUG-AFU 19, vous pourrez participer à une autre étude que dans un délai de 30 jours.

Si vous acceptez de participer à cette étude, vous pourrez vous retirer à tout moment sans justification, sans conséquence sur la suite de votre traitement ni sur la qualité des soins qui vous seront fournis et sans conséquence sur la relation avec votre médecin. Vous serez suivi par la même équipe médicale. Si vous en faites la demande écrite, les données recueillies jusqu'à votre retrait de participation ne seront pas utilisées.

Le promoteur de cet essai qui en assure la gestion et la responsabilité est la Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) située au 101, rue de Tolbiac, 75654 Paris Cedex 13 – France. Elle en assure également la prise en charge globale.

La FNCLCC a pris toutes les dispositions prévues par la loi sur les Recherches Biomédicales (anciennement Loi Huriet- décret d'application 2006-477 du 26 avril 2006 modifiant le titre II du livre 1 du Code de la Santé Publique) relative à la protection des personnes se prêtant à des recherches biomédicales.

La FNCLCC devant assumer l'indemnisation des éventuelles conséquences dommageables de la recherche biomédicale pour la personne qui s'y prête, a souscrit une assurance de recherches biomédicales, conformément à la législation en vigueur (n° de contrat 906812009004 Protocole GETUG-AFU 19/0903), auprès de la Société Gerling France (111-113 rue de Longchamp, 75016 Paris – Tél. 01 44 05 56 00)

Lorsque la responsabilité du promoteur n'est pas engagée, les participants peuvent être indemnisés auprès de l'ONIAM, (Office National d'Indemnisation des Accidents Médicaux, 36, Avenue du Général de Gaulle, 93175 BAGNOLET Cedex, N° Vert : 0800 779 887).

Ce protocole a été autorisé par 2 instances ayant pour mission de vérifier la pertinence scientifique et éthique de l'essai, les conditions requises pour votre protection et le respect de vos droits.

Ces instances sont les suivantes :
1) L'Autorité Compétente (l'Agence Française se Sécurité Sanitaire des Produits de Santé, l'AFSSAPS) qui a autorisé cet essai le 24 février 2010 sous le n° A91517-41.
2) Le Comité de Protection des Personnes CPP Ile de France 8, qui a rendu un avis délibératif favorable le 26 février 2010.

Votre dossier médical reste confidentiel et ne peut être consulté que sous la responsabilité du médecin s'occupant de votre traitement ainsi que par les autorités de santé et par des personnes dûment mandatées par le promoteur de l'essai et soumises au secret professionnel.

Dans le cadre de la recherche biomédicale à laquelle il vous est proposé de participer, un traitement automatisé et anonyme de vos données personnelles sera fait.

Vos données médicales sont transmises au Promoteur de la recherche. Ces données sont identifiées par un numéro de code et/ou vos initiales. Ces données peuvent également, dans des conditions assurant leur confidentialité, être transmises aux autorités de santé françaises.

Conformément à la loi relative à l'informatique et aux libertés (loi n° 78-17 du 6 janvier 1978 modifiée par la loi n° 2004-801 du 6 août 2004) vous disposez d'un droit d'accès, de rectification et d'opposition relative au traitement de vos données personnelles. Ces droits s'exercent auprès du médecin en charge de la recherche qui seul connaît votre identité. Vous pouvez également accéder directement ou par l'intermédiaire d'un médecin de votre choix à l'ensemble de vos données médicales en application des dispositions de l'article L 1111-7 du Code de la Santé Publique. Les informations concernant votre identité seront tenues confidentielles par votre médecin.

Par ailleurs, toutes informations nouvelles survenant au cours de l'étude et susceptibles de modifier le consentement vous seront transmises. De même, vous serez informé, à votre demande auprès du médecin qui vous a pris en charge dans le cadre de cette étude, des résultats globaux de l'essai.

Enfin, vous pouvez avoir accès à des informations sur l'essai en consultant le site Internet de la Fédération (http://www.fnclcc.fr/)

8- <u>A qui devez-vous vous adresser en cas de question ou de problème?</u>

En cas de problèmes, d'événements indésirables en cours d'essai ou de questions, vous pouvez-vous adresser aux personnes suivantes :

Vos contacts dans l'étude ***(titre, nom, prénom, adresse et téléphone)*** **:**
…… ……
Coordonnées du médecin référent du patient
…… ……

9- Quel est le calendrier des examens et du traitement ?

Visites	Screening	Baseline[5]	Période de traitement : cycles C1 à C6	Suivi jusqu'à progression : toutes les 6 semaines	Suivi après progression : tous les 3 mois
Consentement(s) (1. Etude biomédicale ; 2. Etude ancillaire si accord du patient)	x				
Enregistrement	x				
Recherche des mutations H-Ras & K-Ras	x				
Vérification des critères d'inclusion/non inclusion	x	X [1]			
Randomisation		X [4]			
EXAMENS CLINIQUES					
Taille/Poids/Surface corporelle	X	X [1]	x	x	
ECOG (OMS)	X	X [1]	x	x	
Signes vitaux (pouls, TA ; T°)	X	X [1]	x	x	
Recueil des Toxicités		x	x	x	
Antécédents médicaux		x			
Traitements concomitants		x	x	x	
Statut vital					x
EXAMENS BIOLOGIQUES					
Hématologie : NFP + INR (pour les patients sous anticoagulant)	X	X [1]	x	x	
Ionogramme avec calcémie et magnésémie	X	X [1]	x	x	
Bilan hépatique (Bilirubine totale, ASAT, ALAT, PAL)	X	X [1]	x	x	
Bilan rénal (Créat, urée, ac.urique)	X	X [1]	x	x	
Test de grossesse *(si applicable)*	X				
EXAMENS PARACLINIQUES / EVALUATION TUMORALE					
Scanner thoraco-abdomino-pelvien	X [2]	X [1]	X [3]	x	
Scintigraphie osseuse	X [2]	X [1]	X [6]	X [6]	
FEVG (scintigraphie ou échographie)	X [2]	X [1]	X [7]	X [8]	
TRAITEMENT					
MVAC-I (Bras A et B)			x		
Panitumumab (Bras B)			x	x	
ETUDE BIOLOGIQUE ANCILLAIRE (optionnelle)					
Prélèvement d'échantillon sanguin à J1C1 (2 x 7ml) (Bras B seulement)			X [9]		

(1) Les examens ne seront pas refaits s'ils ont été réalisés en screening dans les 7 jours calendaires (28 jours pour les examens paramédicaux) avant le début du traitement. (2) Examens à réaliser dans les 28 jours avant le début du traitement. (3) Toutes les 6 semaines à partir du 1er jour de chimiothérapie soit aux cycles C3 et C5. (4) En fonction du statut mutationnel du patient, la randomisation se fera, au maximum, dans les 10 jours calendaires suivant la signature du consentement. (5) La baseline peut être faite le jour du début du traitement ou au maximum dans un délai de 7 jours calendaires avant le début du traitement. (6) Examen à réaliser tous les 3 mois. (7) Examen à réaliser au cycle 6. (8) Examen à réaliser à l'arrêt du panitumumab. (9) Pour les patients du bras B qui ont donné leur accord de participation à l'étude ancillaire, prélever 2 tubes sanguins (Tubes EDTA de 7ml) au cours du bilan du 1er jour du 1er cycle de chimiothérapie MVAC-I (J1C1).

LEXIQUE

Echographie : technique d'examen qui montre des images d'une partie du corps ou de certains organes à l'aide d'ultrasons. Il s'agit d'un examen d'imagerie. Une échographie du sein s'appelle une échographie mammaire, du foie, une échographie hépatique, de la partie basse de l'abdomen, une échographie pelvienne, du cœur, une échographie cardiaque.

Scanner : examen qui permet des images d'une partie du corps à l'aide de rayons X. Les images sont reconstituées par un ordinateur, ce qui permet une analyse précise.

Scintigraphie : technique d'imagerie utilisant des substances radioactives que l'on injecte à l'intérieur d'un organisme en quantité infime, et qui ont la propriété de se fixer temporairement sur les organes ou les tissus. Grace à une caméra spécifique, on enregistre le rayonnement qui est émis par l'organe ou le tissu. On obtient de cette manière plusieurs images des organes intéressés, afin de voir les éventuelles anomalies ou altérations qui peuvent être la cause de la maladie. La scintigraphie peut être utilisée au niveau du cœur, des os mais aussi des poumons et de la thyroïde.

Echographie : technique d'imagerie médicale qui permet d'explorer un organe ou une région du corps. Cette technique utilise les ultrasons de haute fréquence.

Exfoliation : destruction puis élimination des cellules de la couche superficielle de la peau (épiderme).

Statut vital : données relatives à la survie ou au décès du patient.

FORMULAIRE DU RECUEIL DE CONSENTEMENT DE PARTICIPATION DU PATIENT A L'ETUDE GETUG-AFU 19/0903, N°EudraCT : 2009-011882-10

Titre de l'essai : Méthotrexate, vinblastine, doxorubicine et cisplatine intensifié (MVAC-I) avec ou sans panitumumab dans le traitement de première ligne des carcinomes urothéliaux avancés chez des patients qui ne portent pas les mutations H-Ras et K-Ras. Etude de phase II randomisée.

Promoteur de l'étude : Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC), 101 rue de Tolbiac, 75654 PARIS cedex 13

Investigateur coordonnateur : Pr. Stéphane Culine, Service d'Oncologie Médicale, Hôpital Henri Mondor, 51 Avenue du Maréchal de Lattre de Tassigny, 94000 Créteil

Je soussigné(e) : Nom :.....Prénom :.....

Adresse :.....

Ai pris connaissance de la note d'information m'expliquant le protocole de recherche mentionné ci-dessus.

- J'ai reçu et j'ai bien compris les informations qui m'ont été remises par le Dr ..... qui m'a expliqué l'objectif et le déroulement de cette recherche biomédicale.
- J'ai pu poser toutes les questions que je voulais, j'ai reçu des réponses adaptées et j'ai pu disposer d'un temps de réflexion suffisant entre l'information et ma décision de participer à cet essai.
- J'ai bien noté que je serai libre à tout moment d'arrêter ma participation, j'en informerai par écrit le Dr .....
- J'ai bien noté le droit d'accès prévu par la loi "Informatique et Libertés" du 6 janvier 1978, modifiée par les lois n°94-548 du 1er juillet 1994, n°2002-303 du 4 mars 2002 et n°2004-801 du 6 août 2004. Le droit d'accès est prévu article 39 et le droit de rectification article 40 et s'exerce à tout moment auprès du médecin en charge de la recherche, qui seul connaît mon identité.
- J'ai été informé(e) et j'accepte que certaines données nominatives me concernant et issues de la recherche feront, pour cette étude, l'objet d'un traitement informatisé par le promoteur ou pour son compte conformément à la loi n° 2004-801 du 6 août 2004 relative à la protection des personnes physiques à l'égard des traitements de données à caractère personnel et modifiant la loi n° 78-17 du 6 janvier 1978 relative à l'informatique, aux fichiers et aux libertés.
- J'ai été informé de mon droit de m'opposer au traitement automatisé des données nominatives me concernant.
- J'ai bien noté que le promoteur a pris toutes les dispositions prévues par la loi sur les Recherches Biomédicales (anciennement Loi Huriet- décret d'application 2006-477 du 26 avril 2006 modifiant le titre II du livre 1 du Code de la Santé Publique) relative à la protection des personnes se prêtant à des recherches biomédicales.
- J'ai bien noté que le droit d'accès et de rectification, que m'ouvrent les textes susvisés, pourra s'exercer à tout moment auprès du Dr..... et

que les données me concernant pourront m'être communiquées par l'intermédiaire d'un médecin de mon choix.

- Je certifie sur l'honneur être affilié à un régime de Sécurité Sociale ou bénéficiaire d'un tel régime.
- Je m'engage à ne participer à aucun autre protocole pendant cette étude
- J'ai bien noté que cette étude a reçu l'autorisation de l'AFSSAPS et du CPP Ile de France VIII.
- J'ai compris que les données de cette étude resteront strictement confidentielles. Je n'autorise leur consultation que par les personnes qui collaborent à la recherche, désignées par le promoteur.
- J'ai bien noté que j'ai le droit, à ma demande, d'être informé des résultats globaux de cette recherche selon les modalités qui ont été précisées dans la note d'information.
- J'ai lu et reçu un exemplaire signé de ce document et j'accepte de participer au présent protocole.

Compte-tenu des informations qui m'ont été transmises : ***cocher les cases appropriées en fonction de votre volonté (OUI/NON)***	**OUI**	**NON**
J'accepte librement et volontairement de participer à la recherche biomédicale [a] [b] de l'essai GETUG-AFU 19/0903 N° EudraCT: 2009-011882-10	☐	☐

[a]. loi sur les Recherches Biomédicales (anciennement Loi Huriet- décret d'application 2006-477 du 26 avril 2006 modifiant le titre II du livre 1 du Code de la Santé Publique) ».
[b] loi n° 2004-801 du 6/08/2004 relative à la protection des personnes physiques à l'égard des traitements de données à caractère personnel et modifiant la loi n°78-17 du 6/01/1978 relative à l'informatique, aux fichiers et aux libertés.

Mon consentement ne décharge pas les organisateurs de la recherche de leurs responsabilités. Je conserve tous mes droits garantis par la loi.

Partie à remplir par le participant à la recherche	***Partie à remplir par le médecin investigateur***
Nom et prénom	Nom et prénom
Signature :	Signature :
Date :	Date :

[1] un exemplaire cosigné doit être remis à la personne qui participe à la recherche

APPENDIX 5B - PATIENT INFORMATION SHEET AND CONSENT FORM FOR THE BIOLOGICAL STUDIES

NOTE D'INFORMATION(1) DESTINEE A L'UTILISATION DES PRELEVEMENTS TISSULAIRES ET SANGUINS DANS LE CADRE DU PROTOCOLE GETUG-AFU 19/0903
N°EudraCT: 2009-011882-10

plateforme de ressources biologiques en vue d'analyses ultérieures pertinentes complémentaires compte tenu de l'avancée des connaissances scientifiques, sous réserve d'un nouvel accord du comité d'éthique.

3- Vos droits en tant que participant aux études biologiques et génétiques

Si vous acceptez de nous donner votre accord pour réaliser ces recherches nous vous demandons de bien vouloir exprimer votre consentement, en complétant, datant et signant le formulaire de consentement ci-après. Vous pouvez exprimer votre refus de la même manière, ce qui n'aura aucune conséquence sur la suite de votre traitement dans le cadre du protocole.

Même si vous avez donné votre accord, vous aurez toujours la possibilité de revenir sur votre décision, sans avoir à en expliquer les raisons ; il vous suffira de nous le faire savoir.

Dans le cadre des études citées ci-dessus, un traitement des données personnelles sera également mis en œuvre pour permettre d'analyser les résultats des recherches.
A cette fin, vos données biologiques seront associées à certaines de vos données médicales de la recherche clinique afin de pouvoir corréler les données cliniques aux données biologiques et seront transmises au Promoteur. Ces données, seront identifiées par un numéro de code et/ou par les initiales. Ces données, qui resteront en France, pourront également, dans des conditions assurant leur confidentialité, être transmises aux autorités de santé françaises. Conformément aux dispositions de loi relative à l'informatique aux fichiers et aux libertés, vous disposez d'un droit d'accès et de rectification. Vous disposez également d'un droit d'opposition à la transmission des données couvertes par le secret professionnel susceptibles d'être utilisées dans le cadre de cette recherche et d'être traitées.
Vous pouvez, enfin, accéder directement ou par l'intermédiaire d'un médecin de votre choix, à l'ensemble de vos données biologiques et médicales en application des dispositions de l'article L 1111-7 du Code de la Santé Publique.
Ces droits s'exercent auprès du médecin qui vous suit dans le cadre de la recherche et qui connaît son identité.

Dans le cas où vous n'aurez pas exprimé de refus, et si vos données médicales sont utilisées dans le cadre d'une recherche, elles seront rendues anonymes avant leur utilisation.
Les résultats de cette étude vous seront donnés si vous en faites la demande auprès du médecin qui vous propose l'étude.

Par ailleurs, les résultats de ces recherches peuvent faire l'objet de publications scientifiques mais ils ne seront pas disponibles immédiatement dans la mesure où il faut suffisamment de temps pour collecter tous les prélèvements biologiques et les données des patients.

Lexique

Marqueur : substances spécifique produites par les cellules cancéreuses et qui contribuent à les identifier.

Anatomopathologie : examen au microscope des tissus prélevés par biopsie.

Biopsie : prélèvement qui permet d'obtenir un fragment de tissu vivant. Ce terme désigne aussi bien l'acte (faire une biopsie) que son produit (examiner une biopsie).

Polymorphisme : variations normales entre les individus dans la constitution des gênes. Ces variations peuvent notamment expliquer pourquoi les individus vont réagir différemment à un même traitement.

FORMULAIRE DE RECUEIL DU CONSENTEMENT[1] DESTINE A L'UTILISATION DES PRELEVEMENTS TISSULAIRES ET SANGUINS DANS LE CADRE DU PROTOCOLE GETUG-AFU 19/0903

N°EudraCT: 2009-011882-10

[1] Toutes les pages de ce formulaire doivent être paraphées par patient et l'investigateur.

Titre de l'étude : Méthotrexate, vinblastine, doxorubicine et cisplatine intensifié (MVAC-I) avec ou sans panitumumab dans le traitement de première ligne des carcinomes urothéliaux avancés chez des patients qui ne portent pas les mutations H-Ras et K-Ras. Etude de phase II randomisée.

Promoteur : Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC), 101 rue de Tolbiac, 75654 PARIS cedex 13
Investigateur coordonnateur : Pr. Stéphane Culine, Service d'Oncologie Médicale, Hôpital Henri Mondor, 51 Avenue du Maréchal de Lattre de Tassigny, 94000 Créteil
Investigateur co-coordonnateur : Dr. Hervé Wallerand, Service d'urologie, CHU de Bordeaux, Hôpital Pellegrin, Place Amélie Raba-Léon, 33000 BORDEAUX

Je soussigné(e) :
Nom : ..... Prénom :.....

Adresse : .....

- J'ai reçu et j'ai bien compris les informations qui m'ont été remises par le Dr ..... qui m'a expliqué l'objectif et le déroulement de cette recherche biologique. J'ai pris connaissance de la note d'information m'expliquant l'utilisation des échantillons de tumeur et de sang dans le cadre du protocole de recherche biomédicale GETUG-AFU 19/0903, N°EudraCT = 2009-011882-10.

- J'ai bien été informé(e) qu'il était possible de participer à l'étude clinique principale GETUG-AFU 19/0903 sans participer à l'étude annexe.

- J'ai pu poser toutes les questions que je voulais, j'ai reçu des réponses adaptées et j'ai pu disposer d'un temps de réflexion suffisant entre l'information et ma décision de participer à cet essai.

- J'ai été informé(e) que certaines données nominatives me concernant et issues de la recherche biologique feront, pour cette étude, l'objet d'un traitement informatisé par le promoteur ou pour son compte conformément à la loi n° 2004-801 du 6 août 2004 relative à la protection des personnes physiques à l'égard des traitements de données à caractère personnel et modifiant la loi n° 78-17 du 6 janvier 1978 relative à l'informatique, aux fichiers et aux libertés.

- J'ai bien noté le droit d'accès prévu par la loi "Informatique et Libertés" du 6 janvier 1978, modifiée par les lois n°94-548 du 1er juillet 1994, n°2002-303 du 4 mars 2002 et n°2004-801 du 6 août 2004. Le droit d'accès est prévu article 39 et le droit de rectification article 40 et s'exerce à tout moment auprès de mon médecin en charge de la recherche, qui seul connaît mon identité.

- J'ai bien noté que le promoteur a pris toutes les dispositions prévues par la loi n°2004-806 du 09 août 2004 relative à la politique de santé publique et le décret d'application n°2006-477 du 26 avril 2006.

- Si initialement j'ai donné mon accord de participation, j'ai bien noté que je serai libre à tout moment d'arrêter ma participation, j'en informerai par écrit le Dr.....

- Si initialement je n'ai PAS donné mon accord de participation, j'ai bien noté que je serai libre à tout moment de proposer ma participation, j'en informerai par écrit le Dr.....

◆ J'ai été informé(e) et j'accepte que certaines données me concernant et issues de la recherche biologique fasse l'objet d'éventuelles publications scientifiques. Seules les informations ne faisant mention, ni de mon nom, ni de mon adresse, peuvent être utilisées. Les données qui me concernent resteront strictement confidentielles.

◆ J'ai été informé(e) et je n'autorise leur consultation que par des personnes mandatées par l'organisateur de la recherche ou par un représentant des Autorités de Santé.

◆ J'ai bien noté que je pouvais accéder aux données médicales me concernant, conformément à l'article L1111-7 du Code de la Santé Publique, directement ou par l'intermédiaire d'un médecin de mon choix.

◆ J'ai été informé(e) de mon droit de m'opposer au traitement automatisé des données nominatives me concernant.

◆ J'accepte que ma tumeur soit analysée à des fins de recherches biologiques.

◆ J'accepte qu'un prélèvement sanguin soit analysé à des fins de recherches génétiques.

◆ J'ai bien noté que je serai libre à tout moment d'arrêter ma participation, j'en informerai par écrit le Dr.....

◆ Je certifie sur l'honneur être affilié(e) à un régime de Sécurité Sociale ou bénéficiaire d'un tel régime.

◆ Je m'engage à ne participer à aucun autre protocole pendant cette étude

◆ J'ai bien noté que cette étude biologique a reçu l'autorisation de l'Afssaps et du CPP IIe de France XIII de Boulogne-Billancourt.

◆ J'ai compris que les données de cette étude resteront strictement confidentielles. Je n'autorise leur consultation que par les personnes qui collaborent à la recherche, désignées par le promoteur ou par les représentants des Autorités de Santé.

◆ J'ai bien noté que j'ai le droit d'être informé(e) des résultats globaux de cette recherche selon les modalités qui ont été précisées dans la note d'information.

◆ J'ai lu et reçu un exemplaire signé de ce document et j'accepte de participer au présent protocole.

Compte-tenu des informations qui m'ont été transmises : *cocher les cases appropriées en fonction de votre volonté (OUI/NON)*:	OUI	NON
[(a), (b)(c)] J'accepte librement et volontairement que ma tumeur soit utilisée ultérieurement à des fins de recherches biologiques dans le cadre de l'étude GETUG-AFU 19/0903, N°EudraCT = 2009-011882-10	☐	☐
[(a), (b)(c)] J'accepte librement et volontairement qu'un prélèvement sanguin soit utilisé ultérieurement à des fins de recherches génétiques dans le cadre de l'étude GETUG-AFU 19/0903, N°EudraCT = 2009-011882-10	☐	☐

[a] loi n° 88-1138 du 20/12/1988 dite Huriet-Sérusclat relative à la protection des personnes qui se prêtent à des recherches biomédicales, modifiée par la loi de santé publique n° 2004-806 du 9/08/2004.
[b] loi n° 2004-801 du 6/08/2004 relative à la protection des personnes physiques à l'égard des traitements de données à caractère personnel et modifiant la loi n° 78-17 du 6/01/1978 relative à l'informatique aux fichiers et aux libertés.
[c] loi n° 2004-800 du 6/08/2004 relative à la bioéthique.

GETUG-AFU 19/0903
Version 1.1 du 15Fev10

Paraphe patient et investigateur :

4 / 5

Mon consentement ne décharge pas les organisateurs de la recherche de leurs responsabilités. Je conserve tous mes droits garantis par la loi.

Partie à remplir par le patient	***Partie à remplir par le médecin investigateur***
Nom et prénom	Nom et prénom
Signature :	Signature :
Date :	Date :

Un exemplaire cosigné de ce formulaire de recueil de consentement doit être remis au patient

APPENDIX 6- RECIST CRITERIA V1.1

Evaluation of tumour response (RECIST criteria v1.1)

"New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)" E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij;
Eur J Cancer , 4 5 (2 0 0 9) 2 2 8 –2 4 7.

Lesions at baseline:

At baseline, tumour lesions/lymph nodes will be categorised measurable or non-measurable as follows:

Measurable:

Tumour lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- ≥ 10 mm by CT scan (CT scan slice thickness no greater than 5 mm),
- ≥ 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable),
- 20 mm by chest X-ray,
- to be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis (the short axis being the perpendicular axis to the largest dimension of the lymph node). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable:

All other lesions, including small lesions (longest diameter < 10 mm by CT scan or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques, and cystic lesions.
NB: Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment (cf. comments below).

Target lesions:

Target lesions should be selected among measurable lesions present at baseline. **A maximum of 5 target lesions total are selected and a maximum of 2 target lesions per organ.** Target lesions should be selected such that these are representative of all involved organs, choosing the largest lesions (with the longest diameter) which, in addition, lend themselves to reproducible repeated measurements throughout the trial with the method used at baseline. Lymph nodes may be identified as target lesions if their short axis (by CT scan) is ≥ 15 mm.

The sum of diameters for all target lesions (longest axis for lesions, short axis for lymph nodes) will be monitored throughout the trial to assess response or progression.

Non-target lesions

All other lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present' throughout the trial.

Response criteria

Target lesions:

Complete response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in *short axis* to < 10 mm.

NB: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. In order to qualify for complete response, each node must achieve a short axis < 10 mm.

Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters (BASELINE examination).

Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (NADIR), (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
NB: the appearance of one or more new lesions is also considered progression.
Note: if progression is observed with reference to the NADIR and a response is noted relative to the BASELINE examination, progression is recorded.

Stable disease (SD): Neither PR (or CRC), nor PD.

Non-target lesions

Complete response: Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size < 10 mm.
Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.
Progressive disease: **Unequivocal** progression of existing non-target lesions. The appearance of one or more new lesions is also considered progression.

Overall response:

Target lesions	Non-target lesions	New lesions		Overall response
CR	CR	No	=	**CR**
CR	Non-CR/Non-PD	No	=	**PR**
CR	Not evaluated	No	=	**PR**
PR	Non-PD or not all evaluated	No	=	**PR**
SD	Non-PD or not all evaluated	No	=	**SD**
Not all evaluated	Non-PD	No	=	**NE**
PD	Any	Yes or no	=	**PD**
Any	PD	Yes or no	=	**PD**
Any	Any	Yes	=	**PD**

Special considerations regarding lesion measurability at baseline

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable).
- Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

APPENDIX 7- DERMATOLOGY/SKIN/NAIL ASSESSMENT (FROM CTCAE VERSION 3.0 WITH MODIFICATIONS)

Adverse Event (Short Name)	Grade 1	Grade 2	Grade 3	Grade 4
Nail changes (Nail changes)	Discolouration; ridging (koilonychias; pitting) paronychia: intervention not indicated	Partial or complete loss of nail(s); pain in nailbed(s), paronychia: intervention indicated	Interfering with activities of daily living (ADL)	___
Erythema (Erythema)	Painless erythema	Painful erythema	Erythema with desquamation*	Life-threatening; disabling
Pruritus/itching (Pruritis)	Mild or localised	Intense or widespread	Intense or widespread and interfering with ADL	___
Rash: acne/acneiform (Acne)	Intervention not indicated	Intervention indicated	Associated with pain requiring narcotic analgesics, ulceration, or desquamation*	___
Rash/desquamation* (Rash) [Use for non-acneiform rash or non-folliculitis rash]	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms; localised desquamation* or other lesions covering < 50% of body surface area (BSA)	Severe, generalised erythroderma or macular, papular or vesicular eruption; desquamation* covering ≥ 50% BSA	Generalised exfoliative, ulcerative, or bullous dermatitis
Ulceration (Ulceration)	___	Superficial ulceration < 2 cm size; local wound care; medical intervention indicated	Ulceration ≥ 2 cm size; operative debridement, primary closure or other invasive intervention indicated (eg, hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (eg complete resection, tissue reconstruction, flap, or grafting)

*Desquamation is defined as sloughing of skin and does not apply to dry flaking skin.

APPENDIX 8A- TRANSMITTAL FORM FOR BIOLOGICAL SAMPLES

GETUG-AFU 19/0903 PROTOCOL
EudraCT No.: 2009-011882-10
TRANSMITTAL FORM FOR BIOLOGICAL SAMPLES

Investigational site:

Investigational site number: I____I____I Investigator's name:_____

Investigator's e-mail:_____@_____ Investigator's fax number:_____

Patient's information:

Patient's registration number: I____I____I____I

Patient's Name: I____I____I____I Patient's First name: I____I____I

Patient's birth date: _ _/_ _/_ _ _ _ Sex: I____I (M or F)

I thereby certify that the informed consent form corresponding to:
☐ inclusion in GETUG-AFU19/0903 protocol ☐ ancillary biological studies
have been signed by the patient:
(investigator's name, date, signature) :

Samples

☐ **Screening**
☐ **1 FFPE Block** **OR** ☐ **4 unstained 6 µm paraffin sections**
Shipment address: Département de Pathologie , A l'attention du Docteur Yves ALLORY, Hôpital Henri Mondor, 51, Av du Maréchal De Lattre de Tassigny, 94 000 Créteil, France

☐ **Biological studies**		
	Blood: ☐ **2 x 7ml / EDTA** **Date of sampling :** - - / - - / - - **Time of sampling :** - - h - -	**Tissue:** ☐ **1 FFPE Block**
Shipment address:	Biothèque CIC Plateforme de Ressources Biologiques Hôpital Henri Mondor 51, Av du Maréchal De Lattre de Tassigny 94 000 Créteil, France e-mail :biothèque.prb@hmn.aphp.fr Phone : 33-1-49.81.37.86	Département de Pathologie A l'attention du Docteur Yves ALLORY Hôpital Henri Mondor 51, Av du Maréchal De Lattre de Tassigny 94 000 Créteil, France Phone : 33-1-49.81.27.39

1- This form must be filled for each shipment. No exams will be performed without this form in the shipment.
2-This form should be send to the sponsor at the following fax number: 01 44 23 55 69
3- Please note that the FFPE Block will be give back at the end of the inclusions: please specify the address: _____

Reception date and hour, name:
Comment :

GETUG-AFU 19/0903
Transmittal Form V2.0-15juin09 – Amdt 1 inclus 1/1

APPENDIX 8B- TRANSMITTAL FORM FOR SCREENING RESULTS

GETUG-AFU 19/0903 PROTOCOL
EudraCT No.: 2009-011882-10

TRANSMITTAL FORM FOR SCREENING RESULTS

Investigational site:

Investigational site number: I____I____I Investigator's name:_____

Investigator's e-mail:_____@_____ Investigator's fax number:_____

Patient's information:

Patient's registration number: I____I____I____I

Patient's Name: I____I____I____I Patient's First name: I____I____I

Patient's birth date: _ _/_ _/_ _ _ _ Sex: I____I (M or F)

Screening results:

Date : _ _/_ _/_ _ _ _

Results: H-Ras mutation Yes ☐ No ☐ K-Ras mutation Yes ☐ No ☐

If mutated, indicate which mutation was detected in the sample :

_____

This form should be send
- to the investigator (by fax or e-mail)
- to the sponsor at the following fax number: 01 44 23 55 69

APPENDIX 9- PREGNANCY EXPOSURE FORM

PREGNANCY NOTIFICATION FORM

To be faxed to BECT Safety Department – Paris – France Office nr +33 1 44 23 55 70

Pregnancy exposures should be reported within 15 working days from the day the pregnancy has been brought to the investigator knowledge

Protocol nr: EudraCT nr: **Other Id nr (eg:IND nr)** Sponsor Identification nr: BECT	
Date of this report (dd/mm/aaaa):	**Initial report: Yes ☐ No ☐** **Follow-up report nr:**
Investigator site name and nr:	
Patient Identification /Inclusion nr: **Date of birth (dd/mm/aaaa):** I_I_II_I_II_I_I_I_I_I **Last name (3 letters):** I_I_I_I **1st Name (2 letters):** I_I_I **Gender:** **The Pregnant individual is the** ☐ The patient ☐ a patient partner, specify: DOB/initials	
Treatment Arm:	
Please provide details of all treatments administered : (date, dose of investigational drugs, concomitant treatments)	
Date of last menstrual period (dd/mm/yyyy)	
Estimated date of delivery (dd/mm/yyyy)	
Was the patient using contraception?	**Yes ☐ No ☐**
Parents Relevant medical history **Mother:** **Father:**	
Information on the follow-up of the pregnancy can be obtained from	**Pr-Dr** ..... **Institution**..... **Address**..... **E-mail**..... **Phone/fax**.....

Notificator Name:.....
Function: .....
Address: .....
.....
City: ..... **Zipcode:** .....
Country:.....

Phone: **Fax:**
E-mail:

Date: (dd/mm/yyyy) **Signature**

PLEASE RETURN FORM COMPLETED TO : BECT SAFETY DEPARTMENT
FAX NR + 33 1 44 23 55 70 - E-MAIL:PV-BECT@FNCLCC.FR

G:\AFRQ\PV\Pregnancy Notification Form version 12/2009.doc PAGE 1 OF 1