UNICANCER Tumour Group: UCGI

PRODIGE 65 – UCGI 36

Protocol n°: UC-0110/1809 _ EudraCT n°: 2018-002886-21

A Phase III randomized study evaluating gemcitabine and paclitaxel versus gemcitabine alone after FOLFIRINOX failure or intolerance in Metastatic Pancreatic Ductal Adenocarcinoma.

Abbreviated title: **GEMPAX**

Version n°6 – 13 july 2023

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LIST of ABBREVIATIONS

AE	Adverse event
ANSM	Agence nationale de sécurité du médicament et des produits de santé
ALAT, ALT (SGPT)	Alanine aminotransferase
ANC	Absolute neutrophil count
ASAT, AST (SGOT)	Aspartate aminotransferase
CBC	Complete blood count
CDA	Cytidine deaminase
CEA	Carcinoembryonic antigen
CPP	Comité de protection des personnes
CR	Complete response
CRF	Case report form
CRA	Clinical research associate
CSR	Comité stratégique recherche
CTCAE	Common terminology criteria for adverse events
DCF	Data correction form
DCR	Disease control rate
DNA	Deoxyribonucleic acid
EC	Ethic committee
ECG	Electrocardiogram
ECOG	Eastern cooperative oncology group
Ecrf	Electronic case report form
EDTA	Ethylene diamine tetra acetic
EMA	European medicines agency
EORTC	European organisation for research and treatment of cancer
ESDO	European Society of digestive Oncology
ESMO	European Society for Medical Oncology
G	Gram
GCP	Good clinical practice
G-CSF	Granulocyte-Colony Stimulating Factor
GGT	Gamma-glutamyl transferase
HIV	Human Immunodeficiency virus
HR	Hazard ratio
Hb	Haemoglobin
ICH	International conference on harmonisation
IDMC	Independent data monitoring committee
IEC	Independent Ethic Committee
IMF	Investigator master file
IMF-P	Investigator master file-pharmacy

IMP	Investigational medicinal products
INN	International non-proprietary name
INR	International normalised ratio
IRB	Institutional review board
ITT	Intent-to-treat
IV	Intravenous
L	Litre
LDH	lactate dehydrogenase
MCID	Minimal clinically important difference
Mg	milligram(s)
Min	minute(s)
Ml	millilitre(s)
NCI	National cancer institute
NLR	Neutrophil to Lymphocyte rate
OS	Overall survival
ORR	Objective response rate
PD	Progression disease
PDAC	Pancreatic ductal adenocarcinoma
PR	Partial response
PS	Performance status
PFS	Progression-free survival
PTT	Partial thromboplastin time
QLQ	Quality of life questionnaire
QoL	Quality of life
RBC	Red blood cell count
RECIST	Response evaluation criteria in solid tumours
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAR	Serious adverse reaction
SD	Stable disease
SUSAR	Suspected unexpected serious adverse reaction
SmPC	Summary of product characteristics
TMF	Trial Master File
ULN	Upper limit of normal
WBC	White blood cell
WHO	World health organisation

STATEMENT OF COMPLIANCE

UNICANCER, the trial sponsor, certifies that the trial GEMPAX will be conducted in compliance with the protocol described in this document, and in accordance with the French national regulatory requirements:

- Declaration of Helsinki, as modified in 2008,
- Loi n°2012-300 du 5 mars 2012 relative aux recherches impliquant la personne humaine, as modified in 2016
- Regulation (EU) 2016/679 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation)
- Loi Informatique et Libertés n°78-17 du 6 janvier 1978 modifiée, relative à la protection des personnes physiques à l'égard des traitements de données à caractère personnel,
- Loi n° 2004-800 du 6 août 2004 modifiée, relative à la bioéthique,
- Décision du 24 novembre 2006 fixant les règles de Bonnes Pratiques Cliniques pour les recherches biomédicales portant sur des médicaments à usage humain
- Arrêté du 24 mai 2006 relatif au contenu et aux modalités de présentation d'un protocole de recherche biomédicale portant sur un médicament à usage humain
- Good Manufacturing Practices, in particular, Annex 13 on investigational medicinal products.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the ethics committee (EC) for review and approval. Approval of both the protocol and the consent form will be obtained before any participant is included. Any amendment to the protocol will require review and approval by the EC before the changes are implemented in the study. In addition, all changes to the consent form will be EC-approved. Depending on the consent form modifications a decision will be made whether a new consent is required for patients who have already given consent.

PROTOCOL SUMMARY

Synopsis

A) TRIAL IDENTIFICATION	
Sponsor – protocol code number: PRODIGE 65 – UCGI 36	
Version (Number & date): V6 13 JULY 2023	
Trial title: A Phase III randomized study evaluating gemcitabine and paclitaxel versus gemcitabine alone after FOLFIRINOX failure or intolerance in metastatic pancreatic ductal adenocarcinoma.	
Abbreviated title: GEMPAX	
Coordinating investigator: Dr. Christelle de La Fouchardière	
Number of centres: 35	Number of patients: 210

B) SPONSOR IDENTIFICATION	
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C) TRIAL GENERAL INFORMATION
Indication: Metastatic Pancreatic Ductal Adenocarcinoma
Trial description/design: A phase III, Randomized open label, comparative multicentric phase III trial comparing gemcitabine + paclitaxel vs gemcitabine alone after FOLFIRINOX failure or intolerance
Primary objective: The main objective of this study is to evaluate the superiority in terms Overall Survival (OS) of gemcitabine + solvent-based (sb)-paclitaxel over gemcitabine alone in metastatic pancreatic ductal adenocarcinoma after FOLFIRINOX failure or intolerance.
Secondary objectives: The secondary objectives are the evaluation of: ✓ The efficacy of the treatments in terms of:

- Objective Response rate (according to RECIST 1.1) (ORR)
- Progression-Free Survival (PFS)
- Disease Control Rate at 4 months (4m-DCR)

✓ Prognostic and predictive values of several biomarkers (Ca 19-9, CEA, neutrophil to lymphocyte ratio, albumin, modified Glasgow prognostic score)
✓ Dose intensity of chemotherapy
✓ Safety and tolerability of treatment (NCI-CTCAE version 5.0)
✓ The effect of treatments on Quality of Life
✓ The rate of subsequent chemotherapy (after progression)
✓ Potential new biomarkers that may provide relevant information for clinicians as to whether the patients benefit from chemotherapy and to study the biomarkers dynamics across time and their association with primary and secondary endpoints of the trial.

DIAGNOSIS AND INCLUSION CRITERIA:

1. Histologically or cytologically confirmed metastatic pancreatic ductal adenocarcinoma (PDAC).
2. Age ≥18 years old.
3. At least one evaluable lesion according to RECIST 1.1 (Response Evaluation Criteria in Solid Tumors) outside any previously irradiated area.
4. Failure of first line FOLFIRINOX therapy due to progressive disease during or within 3 months (+/- 15 days) after the end of therapy (including mFOLFIRINOX in adjuvant setting) or patient with FOLFIRINOX intolerance
5. Performance Status (PS) ECOG 0 to 2.
6. Life expectancy ≥12 weeks.
7. Negative serology (HIV, hepatitis B and C)
8. Adequate organs function:
   ✓ Absolute neutrophils count ≥1.5x10^9/L
   ✓ Platelets count ≥100x10^9/L
   ✓ Haemoglobin ≥9 g/dl
   ✓ Serum bilirubin levels <2 times upper limit of normal (ULN), up to 2.5 times ULN in case of hepatic metastasis (biliary drainage allowed)
   ✓ Transaminases <5 times ULN.
9. Evidence of post-menopausal status, or negative urinary or serum pregnancy test for female pre-menopausal patients.
10. Woman of childbearing potential and male patients must agree to use adequate contraception for the duration of trial participation and up to 6 months after completing treatment/therapy
11. Patients affiliated to the social security system
12. Patient must have signed a written informed consent form prior to any trial specific procedures

NON-INCLUSION CRITERIA:

1. Any other primary tumor or secondary malignancy except basal cell carcinoma of the skin or in situ carcinoma of the cervix uteri (patients adequately treated for other malignancies and without tumor during the last 5 years are eligible).
2. Known cerebral metastasis.
3. Uncontrolled severe infections.
4. Patients with Kaposi's sarcoma
5. Peripheral neuropathy exceeding CTCAE (Common Terminology Criteria for Adverse Events) v5.0 grade 2.
6. Previous treatment with taxane and/or gemcitabine. Patients treated with taxane and/or gemcitabine for another cancer are eligible.
7. Patients with known allergy or severe hypersensitivity to any of the trial drugs or any of the trial drug excipients
8. Patients with any other disease or illness which requires hospitalisation or is incompatible with the trial treatment.
9. Patients unable to comply with trial obligations for geographic, social, or physical reasons, or who are unable to understand the purpose and procedures of the trial.
10. Participation in another clinical trial within 14 days prior to randomization.
11. Patients deprived of liberty or under legal protection measure(s) or patients whose willingness to participate in this clinical trial may be unduly influenced

PRIMARY ENDPOINT: Overall survival (OS), defined as the time from date of randomization to the date of death from any cause. If a patient is alive at the database cut-off date, then the patient will be censored at the last date of follow-up

SECONDARY ENDPOINT(S):

- ✓ Efficacy objective:
  - ORR (according to RECIST 1.1 criteria) defined as the percentage of patients with Complete Response (CR) or Partial Response (PR). Patients who discontinue treatment without a tumour assessment will be considered non-responders for the analysis
  - PFS defined as the time from the date of randomisation to date of disease progression (radiological or clinical) or death from any cause, whichever occurs first. Patients without tumour progression or death at the time of analysis will be censored at the date of their last tumour assessment.
  - 4m-DCR is defined as proportion of patients with CR, PR, or a stable disease (SD), 4 months after treatment initiation.
- ✓ Value of biomarkers (Ca 19-9, CEA, Lymphocyte to Neutrophil ratio, albumin, modified Glasgow prognostic score) will be described by absolute or relative variation from baseline. To assess their prognostic or predictive values, baseline values of these biomarkers will be tested using Cox or logistic regression models.
- ✓ Dose intensity of chemotherapy will be calculated from doses actually given instead of from targeted doses. Ratio between dose received compared to theoretical ones will be calculated by patient and presented as a percentage.
- ✓ Safety and tolerability of treatment (NCI-CTCAE version 5.0) determined through the incidence of adverse events, treatment related adverse events, serious adverse Events (SAE), and death.

- ✓ Quality of life (EORTC QLQ-C30) during treatment. A deterioration of scores for five-targeted dimensions: pain, physical and emotional functioning, fatigue, and appetite will be compared between the two treatment arms, while other dimensions will be regarded as exploratory. 5-point deterioration in HRQoL scores will be considered as the minimal clinically important difference (MCID).
- ✓ Rate of subsequent chemotherapy (after progression). The type and the date of beginning of first-cycle of each line will be collected.
- ✓ Translational research to identify biomarkers predictive of response in this clinical context

D) INVESTIGATIONAL MEDICINAL PRODUCTS

PRODUCT NAMES AND ADMINISTRATION:

Drug name (INN)	Registered name(1)	Pharmaceutical form	Administration route	Posology
Gemcitabine		Powder for solution for IV injection	intravenous (IV)	1000 mg/m²

Drug name (INN)	Registered name(1)	Pharmaceutical form	Administration	Posology
Paclitaxel		Solution for injection	intravenous (IV)	80 mg/m2

(1) When any generic drug can be/is used indicate only the INN name. The choice of the registered name or brand name used in the trial is at the investigation centre discretion.

THERAPEUTIC REGIMENS:

Arm A : **Experimental group**
GEMPAX (D1=D29) :
Paclitaxel 80 mg/m² in IV infusion over 60 minutes at D1, D8 and D15 followed by 1 week of rest, every 28 days.
Gemcitabine 1000 mg/m² in IV infusion over 30-40 minutes at D1, D8, D15 followed by 1 week of rest, every 28 days.

At each infusion day, paclitaxel will be administered before gemcitabine.

Arm B : Control group
GEM (D1=D29) :
Gemcitabine 1000 mg/m² in IV infusion over 30-40 minutes at D1, D8, D15 followed by 1 week of rest, every 28 days.

TREATMENT DURATION:
The patient will be randomized in one of the two treatments arms and will receive their treatment every 28 days until disease progression, toxicity or patient's decision.

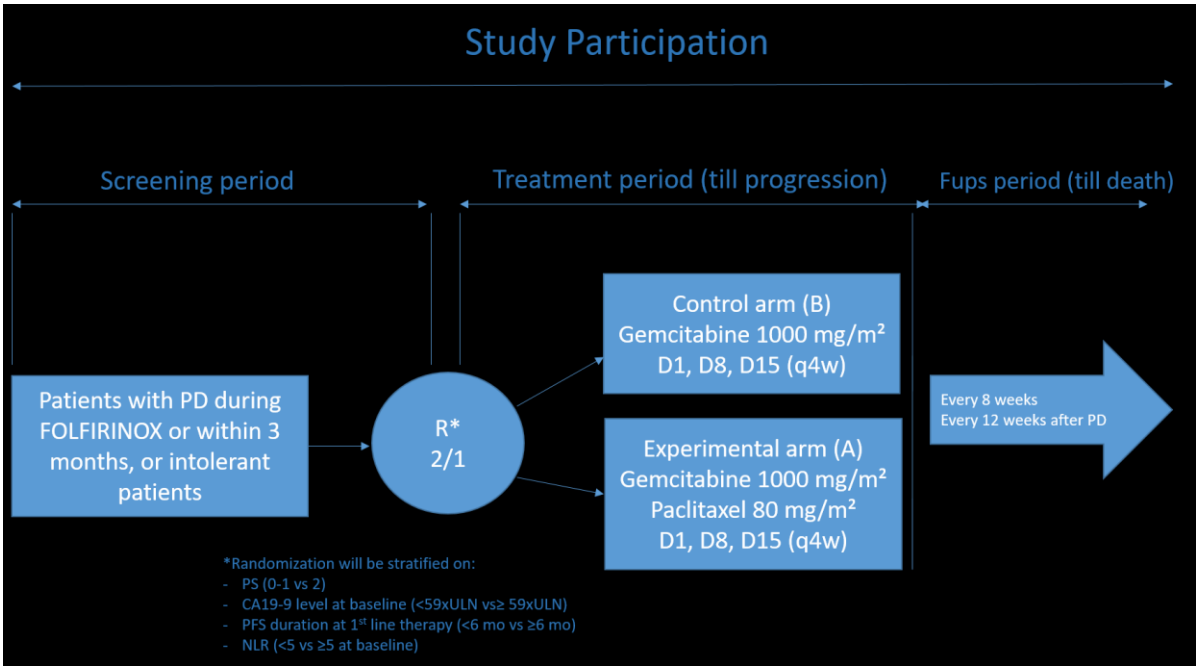
E) STATISTICAL ANALYSIS PLAN

REQUIRED NUMBER OF PATIENTS TO BE SCREENED/INCLUDED: 210

STATISTICAL ANALYSIS:

The GEMPAX study was calibrated to detect a treatment effect hazard ratio (HR) of 0.625, translating in an improvement in median OS from 5 months (control arm: GEM) to 8 months (experimental arm: GEMPAX), with a 2:1 randomization.

A total of 184 events in the study (deaths) would have 85% power to show statistically significant OS at a 2-sided 5% alpha (including one interim analysis of superiority according to OS spending function). Considering a recruitment duration of 24 months and a 12-months follow-up for the last included patient (total duration for the study: 36 months), 210 patients will be randomized in the study (70 patients in the control arm and 140 patients in the experimental arm). One interim analysis of efficacy after half of the planned events have occurred will be done. An independent data monitoring committee (IDMC) will review this analysis. In order to strongly control the type I error the Lan and DeMets approach that approximates the O'Brien and Fleming spending function will be used (Lan and DeMets 1983). The 2-sided significance level at the interim analysis will be calculated based on the number of events occurred at the interim analysis.



F) SAMPLES COLLECTED FOR TRANSLATIONAL RESEARCH

SAMPLE TYPES: Blood Sample and archived tumour tissues

SAMPLE QUANTITIES: 30 mL of blood (5 EDTA tubes of 6 mL) collected at day 1 and day 15 of cycle 1 and at disease progression (total: 90 mL of blood collected per patient)

ARCHIVED TUMOUR TISSUES: Archived tumor tissues available will be collected for analysis (frozen and/or FFPE tissues).

G) TRIAL DURATIONS

INCLUSION PERIOD: 24 MONTHS

TRIAL TREATMENT PERIOD: 6 MONTHS (ESTIMATE)

FOLLOW-UP: 6 MONTHS (ESTIMATE)

DURATION UNTIL PRIMARY ENDPOINT EVALUATION: 20 MONTHS

OVERALL TRIAL DURATION (INCLUDING FOLLOW-UP): 36 MONTHS

Section H: Trial flow chart

	Baseline	Visits during study treatment						End of Treatment (EOT) visit	Follow-up
	Within 14 days prior to first study treatment. Imagery can be done within 28 days prior to first study treatment	Cycle 1			Cycles 2, 3, 4, etc.			35 days (±5 days) after last study treatment injection	Every 8 weeks after EOT. Every 12 weeks after progressive disease
		D1	D8	D15	D1	D8	D15		
Consent signature	X								
Eligibility criteria	X								
Randomization	X								
Diagnosis & prior anticancer therapies	X								
Demographics, Medical history & signs and symptoms	X								
Prior medication & concomitant medication	X	X	X	X	X	X	X	X	
Clinical exam (physical exam, PS) + vital signs[1]	X	X			X			X	X[6]
Neurological exam (peripheral neuropathy evaluation)[8] – only for Arm A		X			X			X	
Modified Glasgow Prognostic Score evaluation[7]	X								
Adverse events		X	X	X	X	X	X	X	X
ECG	X								
Serology (HIV, hepatitis B/C)	X								
Pregnancy test (as applicable)	X								
Complete Blood Count[2]	X	X	X	X	X	X	X	X	
Coagulation factors[3]	X	X			X			X	
Serum chemistries[4]	X[9]	X	X[5]	X[5]	X	X[5]	X[5]	X	
Tumor biomarkers CEA & CA19-9 (every 8 weeks from D1C3, till disease progression)	X				X			X	X
CT-Scan (Thorax, Abdomen, Pelvis) (every 8 weeks from D1C3, till disease progression)	X				X			X	X
QoL questionnaire (EORTC QLQ-C30) (every 8 weeks from D1C3 till disease progression)	X				X			X	X
Optional procedures if patient consented to translational research									
Blood sample (5 EDTA tubes of 6 mL)		X		X	X (at disease progression)				
Archived tumor material preparation and shipment	X								

1) Vital signs : height, weight, blood pressure, pulse, body temperature. Height only at baseline.

2) CBC: hemoglobin, RBC counts, WBC and differential (neutrophils, eosinophils, basophils, monocytes, lymphocytes), platelets
3) Coagulation factors: partial thromboplastin time (PTT), fibrin, prothrombin ratio, sedimentation rate
4) Serum chemistries: Na, Ca, P, Mg, K, Cl, HCO3-, creatinine, urea, creatinine clearance, total protein, albumin, glucose, alkaline phosphatase, total bilirubin, conjugated bilirubin (as appropriate), AST, ALT, LDH, γGT
5) Serum chemistries at days 8 and 15 of each cycle: only urea and creatinine
6) During FUP visits: only physical examination and evaluation of PS (vital signs are not to be done)
7) Modified Glasgow Prognostic Score calculation method: see Appendix 7
8) Neurological exam for the evaluation of peripheral neuropathy related to paclitaxel is to be done only in Arm A (gemcitabine + paclitaxel)
9) Serum chemistries at baseline, in addition to the parameters reported at item 4), must also include the C-reactive protein to allow modified Glasgow prognostic score calculation. Regarding inclusion criteria n°8, total bilirubin only can be done to confirm eligibility. Nevertheless, if total bilirubin at baseline is abnormal but remains < x 2 ULN (or < x 2.5 ULN in case of liver metastases), conjugated bilirubin must be done and be < x 2 ULN (or < x 2.5 ULN in case of liver metastases) to confirm eligibility.

1. INTRODUCTION

1.1 Background information

1.1.1 Pathology epidemiology

A recent study estimating cancer epidemiology in 2014 (within Europe) showed that pancreatic cancer was the fourth most common cause of cancer-related death in men after lung, colorectal, and prostate cancers, and in women after breast, colorectal and lung cancers. With a life expectancy of ~5% at 5 years, the prognosis of this cancer has not improved over the past 20 years, and incidence and mortality rates are very similar. Death due to pancreatic carcinoma is increasing in Europe with the number rising from 75 439 in 2009 to a projected 82 300 deaths in 2014 (+19%). Pancreatic adenocarcinoma is expected to be the second leading cause of cancer-related mortality in 2020.

We designed this clinical trial in order to evaluate prospectively the efficacy and the tolerance of sb-paclitaxel in association with gemcitabine in metastatic pancreatic ductal adenocarcinoma (PDAC). Indeed, few prospective data exist concerning the role of taxanes in PDAC. Nab-paclitaxel monotherapy has been prospectively and successfully evaluated in the first-line metastatic setting but it is not reimbursed in France. A recent small phase II study reported prolonged overall survival for the combination of oxaliplatin and docetaxel after gemcitabine failure. The use of taxanes was also suggested by the results of previous retrospective trials. With the hypothesis that paclitaxel is as efficient as nab-paclitaxel, our goal is to establish a standard treatment after FOLFIRINOX failure or intolerance, and to work around the reimbursement gap for nab-paclitaxel.

1.1.2 Prognosis

Prognosis of PDAC is dismal with a life expectancy below 5% after 5 years [22].

1.1.3 Investigational medicinal products (IMP)

Gemcitabine (Gemzar®) (difluorodeoxycytidine) is a pyrimidine antimetabolite, which is an analogue of deoxycytidine. It was initially synthesized as a potential antiviral drug but selected for anticancer development because of its activity in *in-vivo* and *in-vitro* tumors. Gemcitabine is approved for the treatment of patients with pancreatic cancer and will be obtained commercially and relabeled as clinical supplies. Gemcitabine should be stored, reconstituted and administered according to the manufacturer's recommendation. Gemzar is for intravenous use only. In pancreatic Cancer it is used at 1000 mg/m2 over 30 minutes once weekly for the first 7 weeks, then one week rest, then once weekly for 3 weeks of each 28-day cycle. For further details, see the most recent version of the summary of product characteristics (SmPC) for gemcitabine.

Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis. TAXOL (paclitaxel) Injection is a clear, colourless to slightly yellow viscous solution. It is supplied as a non-aqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. TAXOL is available in 30 mg (5 mL), 100 mg (16.7 mL), and 300 mg (50 mL) multidose vials. Each mL of sterile nonpyrogenic solution contains 6 mg paclitaxel, 527 mg of purified

Cremophor® EL* (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP. For further details, see the most recent version of the SmPC for Paclitaxel.

1.2 Trial rationale

Chemotherapy is the mainstay of treatment for advanced PDAC. While gemcitabine remained the standard first-line agent for 15 years, Folfirinox has become, since 2011, the standard of care in the first-line metastatic setting for patients with normal bilirubin levels and a good performance status (ECOG-PS of 0 or 1). In the phase III PRODIGE4/ACCORD11 trial, patients receiving Folfirinox achieved a median overall survival of 11.1 months vs 6.8 months in patients who received gemcitabine (hazard ratio (HR)=0.57; 95%CI [0.45–0.73]; P<0.001) [1]. Two years later, comparable results have been achieved (over gemcitabine monotherapy) by the combination of gemcitabine plus nab-paclitaxel (nanoparticle albumin-bound paclitaxel), with a median OS of 8.5 months in the gemcitabine-nab-paclitaxel group compared with 6.7 months in the gemcitabine group (HR=0.72; 95%CI [0.62-0.83]; p<0.001) [2]. In a comparative cost-analysis study, Goldstein et al showed that the most-costly regimen was the gemcitabine plus nab-paclitaxel combination when compared with Folfirinox or gemcitabine alone [3]. In France, Folfirinox is the preferred first-line regimen in metastatic, good general status PDAC patients. After its failure, about half of the patients receive a second-line chemotherapy, mainly gemcitabine-based, as recommended by the ESMO-ESDO current clinical practice guidelines [4].
No prospective studies have evaluated second-line therapy for metastatic pancreatic cancer at progression after Folfirinox or gemcitabine plus nab-paclitaxel chemotherapy. The benefit of second-line treatment derives from a meta-analysis of clinical trials comparing second-line chemotherapy with best supportive care alone favoring chemotherapy, leading to a 6 months-median OS compared with 2.8 months with best supportive care [5]. The extrapolation of 3 randomized clinical trials in patients with metastatic pancreatic cancer that progressed on first-line gemcitabine represent also a basis from current recommendations [6]. Two of these studies used 5-fluorouracile (5FU) plus oxaliplatin and showed conflicting results about the benefits of adding oxaliplatin to 5FU in the second-line setting (CONKO-003 and PANCREOX) [7,8]. The NAPOLI-1 study recently demonstrated the interest of nanoliposomal irinotecan, in combination with fluorouracil plus folinic acid with a significant improvement of median OS (6.1 versus 4.2 months), PFS and ORR in the intent-to-treat population over fluorouracil/folinic acid alone [9]. Interestingly, nab-paclitaxel has been used in the second-line setting in small retrospective and prospective cohort studies, showing that gemcitabine-nab-paclitaxel was effective and well tolerated [10,11]. In the prospective cohort, median overall and progression free survivals were 8.8 (95%CI [6.2–9.7]) and 5.1 months (95%CI [3.2–6.2]) respectively and only few patients (7/57 = 12.5%) had to stop nab-paclitaxel permanently because of peripheral neurotoxicity despite previous treatment with oxaliplatin. However, these results do not provide enough information regarding the management of tumor progression after first-line Folfirinox and prospective data are strongly needed [12].
Nab-paclitaxel is a solvent-free albumin-stabilized nanoparticle formulation of paclitaxel (solvent-based paclitaxel, sb-paclitaxel), developed to improve the solubility of paclitaxel and avoid infusion-related reactions associated with sb-paclitaxel. It shares the same mechanism of action of other taxanes family's members, mainly sb-paclitaxel and docetaxel, by targeting tubulin. Its superiority over sb-paclitaxel has never been demonstrated whether in breast or gastric cancers [11, 12]. Furthermore, no significant differences of grade 3 to 4 hematological and non-hematological toxicities was showed in a meta-analysis in metastatic breast cancer recently published by Liu et al, except a more prominent sensory neuropathy for nab-paclitaxel-based chemotherapy (16.9% vs. 10.0%, OR = 1.89, 95% CI =1.36–2.61, P < 0.001; I2 = 42.5%) [13]. Identically, in the randomized, non-inferiority phase 3 trial in gastric cancer, weekly nab-paclitaxel was non-inferior to weekly sb-paclitaxel (hazard ratio 0.97, 97.5% CI 0.76–1.23; non-inferiority one-sided p=0.0085). However, as in breast cancer, the toxicity profile favored sb-paclitaxel with less grade 3 neutropenia and febrile neutropenia (g3 neutropenia: 29% vs 65%; febrile neutropenia: 1% vs 12%) and less neuropathy (2% vs 20%). As

expected, only the hypersensitivity reactions rate was superior in sb-paclitaxel arm, (5% vs 1%). A pharmacokinetic rationale exists to combine paclitaxel and gemcitabine as paclitaxel inhibits cytidine deaminase (CDA), the enzyme responsible for the liver inactivation of gemcitabine. Administration of paclitaxel combined with gemcitabine results in an increased intratumoral accumulation of gemcitabine [15–17]. In 2013, following the MPACT study's results, nab-paclitaxel became a new treatment option for patients with metastatic pancreatic cancer in the first-line setting. It also brought up to date the potential utility of taxanes in the treatment of PDAC. However, only few studies examined prospectively the efficacy of paclitaxel or docetaxel in metastatic PDAC and mainly after first-line gemcitabine's failure [18,19]. However, in contrast to breast and gastric cancer, no comparative data with sb-paclitaxel are available in PDAC. France and United Kingdom authorities consider that nab-paclitaxel provides a minor improvement of medical benefit in metastatic PDAC compared to the high cost supported by the society. Thereby, this drug has been registered but is not reimbursed by Social Security in France and has to be paid by the hospitals on their own resources. This decision has led to disparities in the management of patients, the vast majority of hospitals being unable to finance the treatment.

Based on the lack of prospective second-line studies in metastatic PDAC, the similar mechanism of action between nab- and sb- paclitaxel (stabilization of microtubules), and a lower cost of sb-paclitaxel, we propose to set up a phase III trial, comparing gemcitabine versus gemcitabine + sb-paclitaxel in metastatic PDAC patients after Folfirinox failure or intolerance.

1.3 Justification for the therapeutic regimens and treatment durations

Previous studies have shown the efficacy and the tolerance of weekly paclitaxel and gemcitabine in particular in non-small cell lung and bladder cancers administrated 3 weeks/4 at 80 mg/m² for paclitaxel and 1,000 mg/m² for gemcitabine.

During this trial, the drug will be administrated as indicated below:

Experimental group
GEMPAX (D1=D29):
Gemcitabine 1000 mg/m² in IV infusion over 30-40 minutes at D1, D8, D15 followed by 1 week of rest, every 28 days.

Paclitaxel 80 mg/m² in IV infusion over 60 minutes at D1, D8 and D15 followed by 1 week of rest, every 28 days. A premedication to prevent hypersensitivity reactions (e.g., dexamethasone, diphenhydramine, H2 blockers) will be applied according to the Summary of Products Characteristics. Initial antiemetic prophylaxis is also recommended.

Secondary prophylaxis of neutropenia (G-CSF) for weekly chemotherapy is not planned in EORTC recommendations. Center's practices will be applied. Of note, the coordinator of the study is used to prescribe successfully pegylated G-CSF (pegfilgastrim=Neulasta®) on D1 and D15 of each cycle according to other published experience for weekly chemotherapy schedules [20].

At each infusion day, paclitaxel will be administered before gemcitabine.

Control group

GEM (D1=D29):
Gemcitabine 1000 mg/m2 in IV infusion over 30-40 minutes at D1, D8, D15 followed by 1 week of rest, every 28 days.

1.4 Potential risks and benefits

1.4.1 Known potential risks

- **Know potential risks with gemcitabine**

The following adverse drug reactions are observed in patients treated with gemcitabine:

- ✓ Very common (incidence ≥1/10 patients): leucopenia, thrombocytopenia, anaemia, dyspnea, nausea, vomiting, increases in transaminases (ASAT, ALAT, phosphatase alkaline), cutaneous eruption, alopecia, haematuria, proteinuria, flu-like syndrome, peripheral oedema
- ✓ Common (≥1/100 but <1/10): febrile neutropenia, anorexia, headaches, insomnia, somnolence, cough, rhinitis, diarrhoea, stomatitis and mouth ulcers, constipation, bilirubin increase, sweating, pruritis, myalgia, dorsal pain, fever, asthenia, shivers
- ✓ Uncommon (≥1/1000 but <1/100): interstitial pneumonia, bronchospasm.
- ✓ Rare (≥1/10 000 but <1/1000): myocardial infarction, hypotension, GGT increase, ulceration, shedding, injection site reaction
- ✓ Very rare (<1/10 000): thrombocytosis, anaphylactic reaction, severe cutaneous reaction

The main dose-limiting toxicity is the haematological toxicity with leucopenia, thrombocytopenia and anaemia. The patients treated with gemcitabine must have complete blood counts before each injection. Dose adaptation must be considered when such toxicities occur.

For further details, see the most recent version of the summary of product characteristics (SmPC) for gemcitabine.

- **Know potential risks with paclitaxel**

The following adverse drug reactions are observed in patients treated with paclitaxel:

- ✓ Very common (incidence ≥1/10 patients): infection, myelosuppression, bleeding, hypersensitivity reaction, neurotoxicity, hypotension, bradycardia, diarrhoea, nausea, vomiting, mucosal inflammation, alopecia, arthralgia, myalgia
- ✓ Common (≥1/100 but <1/10): injection site reaction, slight and temporary changes of skin and nails, severe ASAT and phosphatase alkaline increase
- ✓ Uncommon (≥1/1000 but <1/100): severe bilirubin increase, thrombosis, hypertension, tachycardia, cardiomyopathy, syncope with atrio ventricular block, myocardial infarction, heart failure, hypersensitivity reactions requiring treatment, septic shock
- ✓ Rare (≥1/10 000 but <1/1000): pneumonia, peritonitis, sepsis, febrile neutropenia, anaphylactic reaction, motor neuropathy, pulmonary embolism, interstitial pneumonia, pleural effusion, dyspnea, respiratory failure, pulmonary fibrosis, pancreatitis, ischemic colitis, intestinal occlusion, intestinal

perforation, rash, pruritus, erythema, increased creatinaemia, pyrexia, dehydration, asthenia, oedema, fainting

- ✓ Very rare (<1/10 000): acute myeloid leukaemia, myelodysplastic syndrome, anaphylactic shock, anorexia, mental confusion, autonomous neuropathy, tonic-clonic seizure, encephalopathy, ataxia, headaches, seizure, dizziness, visual troubles, ototoxicity, vertigo, tinnitus, hearing loss, supraventricular tachycardia, auricular fibrillation, vascular shock, cough, mesenteric thrombosis, ascites, constipation, oesophagitis, colitis, hepatic necrosis, hepatic encephalopathy, Stevens-Johnson syndrome, onycholysis, urticarial, multiform erythema, epidermic necrolysis

The main dose-limiting toxicity is the haematological toxicity (mainly neutropenia). The patients treated with paclitaxel must have complete blood counts before each injection. Dose adaptation must be considered when such toxicities occur. Neurotoxicity will also be carefully monitored.

For further details, see the most recent version of the summary of product characteristics (SmPC) for paclitaxel.

- **Know potential risks with gemcitabine combined with paclitaxel**

The gemcitabine is already combined with paclitaxel in inoperable, locally advanced or metastatic breast cancer after relapse to neoadjuvant/adjuvant chemotherapy. In this indication, the frequency of grade 3 and 4 hematological toxicity (notably neutropenia) is significantly increased in the combination therapy. Nevertheless, this increased frequency is not associated to increased incidence of infections or haemorrhages. Fatigue and febrile neutropenia occur more frequently in the combination therapy. The fatigue usually recovered after the first cycle [21].
The combination of gemcitabine and nab-paclitaxel is already approved in PDAC. The toxicity of nab-paclitaxel-based chemotherapy was also compared to sb-paclitaxel-based chemotherapy or docetaxel-based chemotherapy in a meta-analysis in metastatic breast cancer. No significant differences of grade 3 to 4 hematological and non-hematological toxicities was showed [13].
Identically, in the randomized, non-inferiority phase 3 trial in gastric cancer, weekly nab-paclitaxel was non-inferior to weekly sb-paclitaxel. However, as in breast cancer, the toxicity profile favored sb-paclitaxel with less grade 3 and febrile neutropenia (g3 neutropenia: 29% vs 65%; febrile neutropenia: 1% vs 12%) and less neuropathy (2% vs 20%). The hypersensitivity reactions rate only, was superior in sb-paclitaxel arm, as expected (5% vs 1%).

Thus, the combination of paclitaxel and gemcitabine is not expected to be more toxic than the nab-paclitaxel and gemcitabine combination, which is already approved in PDAC. In our trial, in patients receiving gemcitabine and paclitaxel we could expect a similar toxicity profile to that described above.

1.4.2 Known potential benefits

The combination of gemcitabine and nab-paclitaxel is already approved in metastatic PDAC in first line, with a median OS of 8.5 months in the gemcitabine-nab-paclitaxel group compared with 6.7 months in the gemcitabine group (HR=0.72; 95%CI [0.62-0.83]; p<0.001) [2]. Due to the same mechanism of action of sb-paclitaxel and the appropriate safety profile, we can expect similar potentials benefits. For patients treated in the gemcitabine arm, we could expect similar benefits as those observed in the routine clinical practice where around 50% of patients receive gemcitabine alone after failure to FOLFIRINOX [4].

We can also expect that the combined treatment will have acceptable tolerance as was seen in others indications.

1.5 Trial population

The trial population is composed of men and women, aged ≥18 years old with confirmed metastatic pancreatic ductal adenocarcinoma.

2. TRIAL OBJECTIVES

2.1 Primary objective

The primary objective of the trial is to evaluate the superiority in terms Overall Survival (OS) of gemcitabine + sb-paclitaxel over gemcitabine alone in metastatic pancreatic ductal adenocarcinoma after FOLFIRINOX failure or intolerance.

2.2 Secondary objective(s)

The secondary objectives are the evaluation of:

- ✓ Objective Response rate (according to RECIST 1.1 criteria) (ORR)
- ✓ Progression-Free Survival (PFS)
- ✓ Disease Control Rate (4m-DCR) at 4 months
- ✓ Evolution of several biomarkers (Ca 19-9, CEA, neutrophil to lymphocyte ratio, albumin, modified Glasgow prognostic score) to assess their prognostic value at baseline and their predictive value under treatment
- ✓ Dose intensity of chemotherapy
- ✓ Safety and tolerability of treatment (NCI-CTCAE version 5.0)
- ✓ To evaluate the effect of treatments on Quality of Life
- ✓ To evaluate the rate of subsequent chemotherapy (after progression)
- ✓ To study and identify biomarkers that may provide relevant information for clinicians as to whether the patients benefit from chemotherapy and to study the biomarkers dynamics across time and their association with primary and secondary endpoints of the trial.

3. TRIAL DESIGN AND ENDPOINTS

3.1 Description of the trial Design

This is a phase III, comparative, randomized open-label, multicentric trial comparing gemcitabine + paclitaxel over gemcitabine alone in metastatic pancreatic ductal adenocarcinoma after FOLFIRINOX failure or intolerance.

3.2 Trial Endpoints

3.2.1 Primary endpoint

The primary end point is to evaluate the overall survival (OS), defined as the time from date of randomization to the date of death due to any cause. If a patient is alive at the database cut-off date, then the patient will be censored at the last date of follow-up.

3.2.2 Secondary endpoint(s)

The secondary objectives are the evaluation of:

- ✓ Efficacy endpoints:
  - ORR (according to RECIST 1.1 criteria) defined as the percentage of patients with Complete Response (CR) or Partial Response (PR). Patients who discontinue treatment without a tumour assessment will be considered non-responders for the analysis
  - PFS defined as the time from the date of randomisation to date of disease progression (radiological or clinical) or death from any cause, whichever occurs first. Patients without tumour progression or death at the time of analysis will be censored at the date of their last tumour assessment.
  - 4m-DCR is defined as proportion of patients with CR, PR, or a stable disease (SD), 4 months after treatment initiation.
- ✓ Value of biomarkers (Ca 19-9, CEA, Lymphocyte to Neutrophil ratio, albumin, modified Glasgow prognostic score) will be described by absolute or relative variation from baseline. To assess their prognostic or predictive values, baseline values of these biomarkers will be tested using Cox or logistic regression models.
- ✓ Dose intensity of chemotherapy will be calculated from doses actually given instead of from targeted doses. Ratio between dose received compared to theoretical ones will be calculated by patient and presented as a percentage.
- ✓ Safety and tolerability of treatment (NCI-CTCAE version 5.0) determined through the incidence of adverse events, treatment related adverse events, serious adverse Events (SAE), and death.
- ✓ Quality of life (QoL) (EORTC QLQ-C30) during treatment. A deterioration of scores for five-targeted dimensions: pain, physical and emotional functioning, fatigue, and appetite will be compared between the two treatment arms, while other dimensions will be regarded as exploratory. 5-point deterioration in Health-Related QoL (HRQoL) scores will be considered as the minimal clinically important difference (MCID).
- ✓ Rate of subsequent chemotherapy (after progression). The type and the date of beginning of first-cycle of each line will be collected.
- ✓ Translational research to identify biomarkers predictive of response in this clinical context

3.3 Progression of the trial

Patients participating in the trial will comply with the protocol for a total number of 12 months after randomization, including an estimate of 6 months of treatment and 6 months of follow-up.

The investigation/examination schedule is defined by the trial schedule of activities in Section H of the protocol synopsis.

3.4 Randomisation procedure

After the eligibility criteria have been fulfilled and the patient consent has been obtained, the patient will be randomised in the trial.

According to randomization, patients will be assigned in a 2:1 ratio to receive Gemcitabine + Paclitaxel or Gemcitabine alone.

Stratification factors at randomization which will be centralized and use minimization method will include:

- ✓ ECOG-PS at baseline 0-1 or 2.
- ✓ PFS duration at first-line therapy <6 months or ≥ 6 months
- ✓ Ca 19-9 level at baseline <59× ULN or ≥59× ULN
- ✓ Neutrophil Lymphocyte Ratio (NLR) at baseline ≤5 or >5

The randomization will be performed using the module of the eCRF / Ennov Clinical® software.

After the consent form has been signed and all inclusion/non-inclusion criteria checked, the investigator will proceed with the randomization through the Unicancer online e-CRF: https://ecrf.icm.unicancer.fr/CSOnline/

An automatic reply will be sent by e-mail to confirm the success of the randomization procedure to the:

- Sponsor
- Investigator
- Data manager
- Statistician

The procedure of use of eCRF for randomization will be given to all investigators during the study opening of each of the centers.

3.5 Premature Trial Terminations and Suspension

The trial can be suspended or stopped by the sponsor after meeting with the coordinating investigator or following a request by the respective regulatory authority and/or the responsible Ethics Committee for the following reasons:

- ✓ high frequency and/or unexpected severity of toxicity,
- ✓ insufficient patient enrolment,
- ✓ lack of efficacy (established at the planned interim analysis),
- ✓ Insufficient quality of data collection.

3.6 Patient's trial withdrawal and discontinuation

Patient withdrawal concerns patients who stop treatment and all other protocol-defined procedures. This can occur under the following circumstances:

- Patient withdraws consent and stipulates that no further data be collected (this should be noted in the patient's medical file).

- The principle investigator may terminate a patient's participants from the study, if this is in the interest of the patient.

Study patients may withdraw their consent at any time without justification, irrespective of the reason(s). In the case of study withdrawal the investigator should attempt to obtain as much information as possible. This information should be noted in the patient's medical file. The patient's withdrawal of consent does not impact the patient's right to receive medical treatment.

4. PATIENT SELECTION

4.1 Diagnosis and inclusion criteria

The following criteria must be verified during the baseline phase and before randomisation.

In order to participate in the trial all patients must meet all of the following inclusion criteria:

1. Histologically or cytologically confirmed metastatic pancreatic ductal adenocarcinoma (PDAC).
2. Age ≥18 years old.
3. At least one evaluable lesion according to RECIST 1.1 (Response Evaluation Criteria in Solid Tumors) outside any previously irradiated area.
4. Failure of first line FOLFIRINOX therapy due to progressive disease during or within 3 months (+/- 15 days) after end of therapy (including mFOLFIRINOX in adjuvant setting) or patient with FOLFIRINOX intolerance.
5. Performance Status (PS) ECOG 0 to 2.
6. Life expectancy ≥12 weeks.
7. Negative serology (HIV, hepatitis B and C).
8. Adequate organs function:
   - ✓ Absolute neutrophils count ≥1.5x10^9/L
   - ✓ Platelets count ≥100x10^9/L
   - ✓ Haemoglobin ≥9 g/dl
   - ✓ Serum bilirubin levels <2 times upper limit of normal (ULN), up to 2.5 times ULN in case of hepatic metastasis (biliary drainage allowed)
   - ✓ Transaminases <5 times ULN.
9. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients.
10. Woman of childbearing potential and male patients must agree to use adequate contraception for the duration of trial participation and up to 6 months after completing treatment/therapy
11. Patients affiliated to the social security system
12. Patient must have signed a written informed consent form prior to any trial specific procedures

4.2 Non-inclusion criteria

Patients are not eligible to participate in the trial if they comply with any of the following criteria:

1. Any other primary tumor or secondary malignancy except basal cell carcinoma of the skin or in situ carcinoma of the cervix uteri (patients adequately treated for other malignancies and without tumor during the last 5 years are eligible)
2. Known cerebral metastasis.
3. Uncontrolled severe infections
4. Patients with Kaposi's sarcoma
5. Peripheral neuropathy exceeding CTCAE (Common Terminology Criteria for Adverse Events) v5.0 grade 2
6. Previous treatment with taxane and/or gemcitabine. Patients treated with taxane and/or gemcitabine for another cancer are eligible.
7. Patients with known allergy or severe hypersensitivity to any of the trial drugs or any of the trial drug excipients
8. Patients with any other disease or illness which requires hospitalisation or is incompatible with the trial treatment.
9. Patients unable to comply with trial obligations for geographic, social, or physical reasons, or who are unable to understand the purpose and procedures of the trial
10. Participation in another clinical trial within 14 days prior to randomization
11. Patients deprived of liberty or under legal protection measure(s) or patients whose willingness to participate in this clinical trial may be unduly influenced

5. TRIAL TREATMENTS/INTERVENTIONS

5.1 Description of trial treatments/interventions

Patients who have signed the informed consent form and who met all inclusion and non-inclusion criteria will be randomized and a treatment will be allocated.

The investigational products will be prepared according to the chemotherapy safety standards.

Treatment products will be supplied from the pharmacy stocks of each research hospital.

For experimental group:
Arm A : GEMPAX (D1=D29) :
Paclitaxel 80 mg/m² in IV infusion over 60 minutes at D1, D8 and D15 followed by 1 week of rest, every 28 days.
Gemcitabine 1000 mg/m² in IV infusion over 30-40 minutes at D1, D8, D15 followed by 1 week of rest, every 28 days.
A premedication to prevent hypersensitivity reactions (e.g., dexamethasone, diphenhydramine, H2 blockers) will be applied according to the Summary of Products Characteristics. Initial antiemetic prophylaxis is also recommended.

Secondary prophylaxis of neutropenia (G-CSF) for weekly chemotherapy is not planned in EORTC recommendations. Center's practices will be applied. Of note, the coordinator of the study is used to prescribe

successfully pegylated G-CSF (pegfilgastrim=Neulasta®) on D1 and D15 of each cycle according to other published experience for weekly chemotherapy schedules [20].

At each infusion day, paclitaxel will be administered before gemcitabine.

For control group:
Arm B : GEM (D1=D29) :
Gemcitabine 1000 mg/m² in IV infusion over 30-40 minutes at D1, D8, D15 followed by 1 week of rest, every 28 days.

5.2 Acquisition, reception, and storage

Gemcitabine and paclitaxel will be taken from the pharmacy stock at the investigator's site.

The pharmacist is responsible for a safe and proper handling and storage of the investigational medicinal products at the investigational centre. The investigational products must be stored in a locked facility with restricted access to the pharmacist and authorised personnel, and under environmental conditions consistent with the drug manufacturer recommendations (gemcitabine and paclitaxel SmPC).

- Gemcitabine must be stored at room temperature
- Paclitaxel must be stored at room temperature without exceeding +25°C, protected from light

Up to date temperature logs must be maintained by the pharmacist/investigator to document adequate storage during the trial. These logs must be available at the site during monitoring visits, and in the event of an audits or inspection.

If the storage conditions as indicated above are exceeded (e.g. temperature excursion) the pharmacist/investigator must place the corresponding treatments in quarantine and immediate notify the sponsor who will indicate the procedure to follow. Under no circumstances should these treatments be delivered to trial patients without prior authorisation by the sponsor.

5.3 Trial treatments accountability, return and destruction

The pharmacist or authorised staff must document the dispensation, and destruction of all investigational products used during this trial. Records on investigational products inventory at the centre, the delivery to each patient, and destruction by the site must be implemented and maintained by the pharmacist or another appropriately trained individual at the investigational centre. The following minimum information must be present: all relevant dates (dispensation and destruction), quantities, and expiry date and batch numbers. Accountability form will be provided by the sponsor to ensure trial treatment accountability.

The pharmacist will implement an accounting of medicinal products dispensed, used and unused. The accountability of the used products will be systematically done by the pharmacist of the site.

This process will be monitored by the UNICANCER CRA during the trial. The CRA will check that the accountability documentation has been filled in and signed by the pharmacist before the investigational products, used and unused, are destroyed.

All remaining investigational products, used and unused, shall be collected and returned for destruction. The destruction will take place at the investigator centres under the responsibility of their pharmacist in accordance with national regulatory requirements, and with prior formal agreement from the sponsor. A certificate of destruction, identifying concerned products, will be given to the sponsor.

5.4 Formulation, appearance, packaging, and labelling

Gemcitabine is formulated as powder for solution for injection. Each type I glass bottle contains gemcitabine chlorhydrate corresponding to 200 mg or 1 000 mg of gemcitabine. After reconstitution, the solution contains 38 mg/mL of gemcitabine (gemcitabine chlorhydrate). Each packaging of gemcitabine contains one or five bottles.

Paclitaxel is formulated as a solution to dilute for injection. Each type I glass bottle to dilute contains 6 mg/mL of paclitaxel:
A bottle of 5 mL contains 30 mg of paclitaxel
A bottle of 16.7 mL contains 100 mg of paclitaxel
A bottle of 25 mL contains 150 mg of paclitaxel
A bottle of 50 mL contains 300 mg of paclitaxel
A bottle of 100 mL contains 600 mg of paclitaxel
Each packaging of paclitaxel contains one or five bottles.

5.5 Preparation

Please refers to the most recent version of the summary of product characteristics (SmPC) for gemcitabine and paclitaxel.

5.6 Conditions for stopping the treatment

Toxicities will be graded according to NCI-CTCAE (version 5.0).
If a dose reduction is necessary, the reduced posology (dosage) will be maintained until the end of treatment protocol. In case of recurrent grade 4 toxicity despite dose reduction, the clinical investigator and the patient may discuss the possibility of stopping treatment protocol.

The decision to reduce the doses will be based on the maximum toxicity observed during the cycle.

The dose adjustments should be based on the most significant toxicity grades. If a patient has several types of toxicity, the dose administered will be the one with the least risk to the patient.

5.7 Patients' discontinuations of treatment

5.7.1 Delays cycles of chemotherapy- or rules for dose omissions and modified schedules

Day 1 dose missed:

If the dose held or missed was to be given at day 1, the cycle will not be considered to start until the day 1 dose is actually administered to the patient.

Day 8 dose is missed:

If day 8 is not given, the treatment cycle continues per protocol, with one dose omitted.

Day 15 dose missed:

If day 15 is not given at a given cycle, the next cycle will start as planned per protocol, i.e. 4 weeks after day 1 of previous cycle.

A delay of 4 weeks maximum is allowed in this study. In case of delay >4 weeks, decision regarding end of study treatment will be discussed on a case-by-case basis between the investigator, the coordinating investigator and the sponsor.

5.7.2 Dose adaptation

Dose reductions may or may not be concomitant. A maximum of 2 dose level reductions are allowed.
Patients experiencing study drug-related toxicities that require a delay in scheduled paclitaxel or gemcitabine dosing for more than 21 days will be discontinued from further treatment in this study (except for peripheral neuropathy).

Dose Level	Gemcitabine (mg/m2)	Paclitaxel (mg/m2)
Study dose	1000	80
-1	800	60
-2	600	40

5.7.3 Doses modifications tables for hematologic toxicity

Dose modifications due to hematologic toxicity within a treatment cycle should be adjusted.

At Day 1 :

Absolute Neutrophil Count (ANC)		Platelets	Timing
≥ 1.5 x 10^9/L	AND	≥ 100 x 10^9/L	Treat on time
< 1.5 x 10^9/L	OR	< 100 x 10^9/L	Delay by 1 week intervals until recovery

At Day 8 :

Absolute Neutrophil Count (ANC)		Platelets (Plt)	Timing
≥ 1.0x10^9/L	AND	≥75x10^9/L	Treat on time
0.5 x10^9/L≤ANC<1.0x10^9/L	OR	50x10^9/L≤Plt<75x10^9/L	Decrease dose by 1 level (treat on time)
ANC< 0.5 x109/L	OR	Plt < 50x109/L	Hold and decrease next dose by 1 level

At Day 15 :

Absolute Neutrophil Count (ANC)		Platelets (Plt)	Timing

≥ 1.0x10^9/L	AND	≥75x10^9/L	Treat on time
0.5 x10^9/L≤ANC<1.0x10^9/L	OR	50x10^9/L≤Plt<75x10^9/L	Same dose as D8 + GCSF [a]
ANC< 0.5 x109/L	OR	Plt < 50x109/L	Hold + GCSF [a]

[a] G-CSF is useless if descent only affects platelets.

In case of febrile neutropenia (grade 3 or 4), hold upon recovery. Upon resuming dosing, either use GCSF for further cycles or decrease gemcitabine and paclitaxel to next lower dose levels.
In case of recurrent febrile neutropenia (grade 3 or 4) occuring depsite G-CSF, hold upon recovery and decrease all drugs to next lower dose level.

5.7.4 Doses modifications tables for non- hematologic toxicity

Toxicity or dose held	Gemcitabine / Gemcitabine-Paclitaxel
Grade 0, 1 or 2 toxicity	Same as Day 1 of previous cycle
Grade 3 toxicity [a, c]	Decrease gemcitabine +/- paclitaxel to next lower dose level
Grade 4 toxicity [a, b, c]	Off protocol treatment
Dose held in 2 previous consecutive cycles	Decrease gemcitabine +/- paclitaxel to next lower dose level and continue throughout the rest of treatment

[a] If the toxicity only affects neuropathy, then only paclitaxel should be reduced.
[b] Pulmonary embolism (Grade 4 toxicity in the CTCAE tables) if mild or asymptomatic, will be exempt from this requirement.
[c] except for nausea/vomiting and alopecia.

Dose modifications may also be made for non-hematological toxicity within a cycle :

Toxicity or dose held	% of D1 Gemcitabine / Gemcitabine-Paclitaxel doses
Grade 0 1 or 2 toxicity (and Grade 3 nausea/vomiting and alopecia)	100%
Grade 3 toxicity [a, c]	Hold either one or both drugs until resolution to ≤Grade 1. Then resume treatment at the next lower dose level.
Grade 4 toxicity [a, b, c]	Hold

[a] If the toxicity only affects neuropathy, then only paclitaxel should be reduced.
[b] Pulmonary embolism (Grade 4 toxicity in the CTCAE tables) if mild or a symptomatic, will be exempt from this
requirement.
[c] except for nausea/vomiting and alopecia.
The decision as to which drug should be modified will depend upon the type of non-hematologic toxicity seen and which course is medically most sound in the judgment of the physician/investigator.

Patients can discontinue the trial treatment/therapy for the following reasons:
- Limiting toxicity.
- Any delay in treatment administration of more than 4 weeks
- Patients decline further treatment/therapy but accept to continue with protocol.
- Investigator's decision.

After discontinuing all trial treatment, further treatment is left to the physician's discretion.
Patients who discontinue trial treatment will continue with the trial and the protocol-defined procedures, unless they specifically withdraw their consent and indicate that they do not want to perform any further trial-related visits or assessments (for patient withdrawals see Section 3.7.).

5.8 Concomitant medications and therapies

All medications (including herbal preparations) and therapies taken by the patients or administered to the patients from the onset of trial and given in addition to the investigational products during the trial are considered as concomitant medications. Any concomitant medication(s) trial will be recorded in the case report form (CRF).

5.8.1 Authorised concomitant treatments

All symptomatic treatments/therapies required for the patients' comfort (antiemetics, antidiarrhetics, antibiotics, sunscreen, and corticosteroids cream) are authorised. The posology and duration of administration are at the investigator's discretion, as per standard of care.

5.8.2 Prohibited concomitant treatments

The metabolism of paclitaxel is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when paclitaxel is concomitantly administered with known substrates (eg, midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (eg, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (eg, rifampin and carbamazepine) of CYP3A4. No specific drug interaction studies have been conducted with gemcitabine.
The following treatments/therapies are prohibited during the trial:

- Other antitumor treatments (investigational or not), including chemotherapies, radiation therapies, hormonal therapies, biological response modifiers, and targeted therapies. Local treatment of isolated cancer lesions, excluded target lesions, for palliative intent, is acceptable (e.g., local surgery or radiotherapy)
- Systemic corticoids, except in case of an urgent indication or as antiemetics. Their use will require the highest precaution in patients with diabetes.
- It is advised not to use the association of warfarin (Coumadin®) with chemotherapy. It is preferable to use heparin and therapeutic anticoagulation with low-molecular weight heparin. If warfarin cannot be avoided, the rate of prothrombin must be checked more frequently and INR monitored.
- Pimozide (Orap®) and cisapride (Prepulsid®) are strictly contraindicated: they are associated with a major risk of ventricular rhythm disorder.
- Yellow fever vaccine.

All concomitant medication must be recorded in the patient's medical records and documented as appropriate in the CRF. The decision to withdraw a patient on the basis of concomitant medication should preferably be made jointly by the Sponsor and the Investigator.

5.8.3 Rescue medications and therapies/Treatment at disease progression

At disease progression the treatment will be at the investigator's discretion.

5.8.4 Contraception during the trial

Definitions
Females of childbearing potential are those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal (for the definition of post-menopausal see below).

Post-menopausal status is defined as:

Women will be considered post-menopausal if they have been amenorrhea for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrhea for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilisation (bilateral oophorectomy or hysterectomy).
- Women ≥50 years of age would be considered post-menopausal if they have been amenorrhea for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilisation (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

Acceptable contraception during the trial

- **Female patients of child-bearing potential**

Females of childbearing potential who are sexually active with a non-sterilised male partner must use one or more highly effective method of contraception (See Table 1 below) during the trial and for 6 months after the last trial treatment/therapy administration. Non-sterilised male partners of a female patient must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Female patients should also refrain from breastfeeding throughout this period.

Table 1 - Highly effective methods of contraception (<1% failure rate)

Barrier/Intrauterine methods	Hormonal methods
Copper T intrauterine device Levonorgestrel-releasing intrauterine system (e.g., Mirena®)[a]	Etonogestrel implants: e.g., Implanon or Norplan Intravaginal device: e.g., ethinylestradiol and etonogestrel Medroxyprogesterone injection: e.g., Depo-Provera Normal and low dose combined oral contraceptive pill Norelgestromin/ethinylestradiol transdermal system Cerazette (desogestrel)
[a]This is also considered as a hormonal method.	

- **Male patients with a female partner of childbearing potential**

Non-sterilised males who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide during the trial and for 6 months after the last trial treatment/therapy administration. Male patients should refrain from sperm donation throughout this period.

6. EVALUATION OF TREATMENT EFFICACY AND SAFETY

6.1 Efficacy evaluation

Tumor assessment will be performed at baseline and every 8 weeks from day 1 of cycle 3.
Treatment efficacy will be evaluated by measuring changes in tumour size in response to treatment; measured by Thoraco-Abdominal and Pelvic CT-Scan and assessed by RECIST v1.1 (see Appendix 3).

6.2 Safety evaluation

Treatment safety evaluation will be based on adverse event (AE) occurrence, the use of concomitant treatments, and changes occurring during treatment including those observed: during physical examinations, in vital signs (blood pressure, pulse, body temperature), in electrocardiogram (ECG), and with biological and clinical examinations (biochemistry, haematology). Safety criteria will be evaluated using the National Cancer Institute - common terminology criteria for adverse events (NCI-CTCAE) v5.0 (see Appendix 4).

In case of emergency, the patient, a patient's relative or the patient's general practitioner will have to inform by phone the investigator about the occurrence of an AE. The possible treatment interruption or dose adaptation (decrease) for the investigational product will be considered as well as adequate concomitant treatment if necessary.

6.3 Centralised review

No centralised review.

7. DESCRIPTION OF VISITS AND INVESTIGATIONS

Patients will be monitored from the date of their consent's signature until the date of death or study's end.
A summary of the visit schedule and follow-up examination is provided in Section H of protocol synopsis – Schedule of activities.

7.1 Baseline visit

Each candidate patient will be examined before starting the study to determine eligibility for participation. This must be done within 14 days prior to the first study treatment administration, except for radiologic assessment which can have been performed up to 4 weeks prior to study treatment start. The following investigations will be performed:

- Informed consent: obtain written patient informed consent prior to any study specific procedure. Consent for the translational study (optional) will also be obtained during this visit.
- Verification of eligibility criteria
- Randomization
- Diagnosis and prior anticancer therapies
- Demographics, signs and symptoms, medical history, including non-cancer medical history, and concurrent illnesses
- Prior and concomitant medications
- Physical examination (weight, height, WHO Performance Status, vital signs (pulse, blood pressure, body temperature)
- Modified Glasgow prognostic score evaluation (see Appendix 7 for calculation method)
- Electrocardiogram (ECG)
- Serology (HIV, hepatitis B/C)
- Pregnancy test (all women of child bearing potential)
- Complete Blood Count (CBC) *(refer to section H of synopsis for details)*
- Coagulation factors *(refer to section H of synopsis for details)*
- Serum biochemistries, including C-reactive protein *(refer to section H of synopsis for details)*
- Tumor biological markers (CEA and CA19-9)
- Thoraco-Abdominal and Pelvic CT-Scan
- QLQ-C30
- Archived tumour material preparation and shipment organization (shipments can be pooled with several patients): can be done anytime during the patient's study participation.

7.2 Visits and assessment during treatment period

During the treatment period, patients will come at hospital at day 1, day 8 and day 15 of each cycle (1 cycle = 28 days. Delay ≤3 days is allowed).

At day 1 of each cycle, patients will be assessed as follows prior to chemotherapy administration *(refer to section H of synopsis for details)*:

- Documentation of concomitant medication
- Physical examination
- Neurological examination for the evaluation of potential peripheral neuropathy due to paclitaxel. Only for patients randomized in Arm A (gemcitabine + paclitaxel)
- Vital signs and WHO performance status
- Recording of adverse events that occurred since last cycle
- Complete Blood Count (CBC) *(refer to section H of synopsis for details)*
- Coagulation factors *(refer to section H of synopsis for details)*
- Serum biochemistries *(refer to section H of synopsis for details)*
- Tumor biological markers (CEA and CA19-9), at day 1 cycle 3 then every 8 weeks till disease progression
- CT-Scan (Thorax Abdomen Pelvis), at day 1 cycle 3 then every 8 weeks till disease progression
- QLQ-C30, at day 1 cycle 3 then every 8 weeks till disease progression
- Blood samples for translational research (optional, if patient consented)

At day 8 and day 15 of each cycle, patients will be assessed as follows *(refer to section H of synopsis for details)*:

- Documentation of concomitant medication
- Recording of adverse events that occurred since last cycle
- Complete Blood Count (CBC) *(refer to section H of synopsis for details)*
- Limited serum biochemistries *(refer to section H of synopsis for details)*
- Blood samples for translational research → only at day 15 of cycle 1 (optional, if patient consented)

7.3 End-of-treatment visit

Patients will perform an end-of-treatment visit 35 days (±5 days) following the last study drug administration:

- Documentation of concomitant medication
- Physical examination
- Neurological examination for the evaluation of potential peripheral neuropathy due to paclitaxel. Only for patients randomized in Arm A (gemcitabine + paclitaxel)
- Vital signs and WHO performance status
- Recording of adverse events
- Complete Blood Count (CBC) *(refer to section H of synopsis for details)*
- Coagulation factors *(refer to section H of synopsis for details)*
- Serum biochemistries *(refer to section H of synopsis for details)*
- Tumor biological markers (CEA and CA19-9), every 8 weeks till disease progression
- CT-Scan (Thorax Abdomen Pelvis), every 8 weeks till disease progression
- QLQ-C30, every 8 weeks till disease progression

7.4 Follow-up

In absence of progression, patients will perform follow-up visits every 8 weeks (±2 weeks) until documented progressive's disease, start of new anticancer therapy or end of study, whatever occurs first.

The following assessments will be performed during the follow-up period *(refer to section H of synopsis for details)*:

- Physical examination
- WHO Performance status
- Information on safety data.
- Tumor markers: CEA and CA 19-9
- Thoraco-Abdominal and Pelvic CT-Scan
- QLQ-C30
- Information on further anticancer therapy

After progression or starting of a new anticancer therapy (whatever occurs first), follow-up will only be performed every 12 weeks (±2 weeks) until patient's death or end of study, whatever occurs first, and will consist in getting data about overall survival and safety data (if applicable).

7.5 Provisions in case of treatment or trial interruption

If the trial treatment is discontinued for a patient, further treatment will be at the investigator's discretion as per standard of care.

8. REPORTING OF ADVERSE EVENTS

8.1 Adverse event: general definition

An adverse event (AE) is defined as any untoward medical occurrence, in a patient or clinical trial subject treated by a medicinal product and which does not necessarily have a causal relationship with this treatment.

8.2 Serious adverse event: general definition

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is medically relevant in the context of the pathology and the clinical trial

These characteristics/consequences are to be considered at the time of the event. For example, regarding a life-threatening event, this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

The terms disability and incapacity correspond to any clinically relevant physical or psychological handicap, transient or permanent, which impacts the patient's physical condition/activity and/or the quality of life.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life-threatening or result in death or hospitalisation, but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed in the definition above (for example: overdose, second cancer, etc.).

The investigator will assess whether a reasonable causal relationship exists between the event and the treatment/therapy. If the sponsor disagrees with the investigator's causality assessment, the opinion of both the investigator and the sponsor will be reported.

The following events leading to a hospitalization or prolongation of hospitalization are not considered as Serious Adverse Events:

- Hospitalisation already scheduled before the start of the trial,
- Hospitalisation required as part of the protocol (biopsy, chemotherapy, etc.),

The following events are considered as SAEs but should not be managed according to the section 8.3. These events do not require immediate reporting and should be reported only in the case report form:

- Hospitalization occurring in the context of tumor progression of disease under trial,
- Progression of disease under trial,
- Events related to progression of disease under trial.

An Adverse reaction is a response to a medicinal product which is noxious an unintended

A Serious adverse reaction (SAR) is an adverse reaction which results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly/birth defect, or is a medically relevant.

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined as any serious adverse reaction, the nature, severity or outcome is not consistent with the applicable drug information (e.g. Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

The assessment of expected/unexpected character of the event is the responsibility of the sponsor. The reference document for assessment of expectedness in this study will be the SMPC of Gemcitabine and Paclitaxel.

- **New event**: is defined as any new event relating to the conduct of the trial or the development of the investigational medicinal product where that new event is likely to affect the safety of the subjects.
- **Severity criterion**: the severity criterion must not be confused with the seriousness criterion which is the guide for defining the reporting requirements.

The intensity (severity) of events will be estimated using the extract of CTCAE v5.0 classification (see Appendix 4). The intensity of adverse events not listed in this classification will be assessed according to the following qualifiers:

- **Grade 1** (**mild):** asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2 (moderate):** minimal local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
- **Grade 3:** s**evere** or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL.
- **Grade 4:** Life-threatening consequences; urgent intervention indicated.
- **Grade 5: Death** related to the event.

8.3 Measures to be taken in case of a serious adverse event

The investigator ensures that adequate medical care is provided to the patient. The investigator must **immediately** following knowledge of the event, notifies the UNICANCER pharmacovigilance unit of any SAE or any new event defined here above, whether or not related to the research, which occurs during the 'trial reporting period'. This reporting period:

- Starts at the date of the signature of the informed consent form,
- covers the entire period during which the patient is receiving the investigational treatment or is subject to specific procedures related to the trial,

- covers a period of 30 days after the last administration of the investigational product.

Any later SAE, i.e. occurring after a period of 30 days, which is considered to be related to the experimental treatment(s) or to the research (other treatment used, diagnostic procedures and examinations carried out during the research) must be reported without any limitation in terms of deadline.

Notification must be carried out immediately by fax to the UNICANCER pharmacovigilance unit by sending the form “notification of a SAE”, located in the Investigator Master File, completed as precisely as possible, dated and signed by the physician-investigator.

Notification must be carried out immediately by fax to the UNICANCER pharmacovigilance unit:

UNICANCER
Pharmacovigilance unit, France
Phone: +33 (0)1 44 23 04 16 – Fax: +33 (0)1 44 23 55 70
Email: pv-rd@unicancer.fr

Abnormal laboratory results should be reported as SAE if they possibly put at risk the patient or they require medical intervention to prevent an outcome corresponding to one of severity criteria.

Second cancer, whether or not related to the research, must be reported to the UNICANCER pharmacovigilance unit without any limitation in terms of deadline.

In the event of pregnancies:
Pregnancy is not considered as an SAE but must be reported with the same modalities as an SAE, using a Pregnancy Notification Form. Pregnancy will be subject to a specific follow-up until the end of pregnancy. While pregnancy is not considered as a SAE, any anomaly detected in the foetus or child, any elective termination of a pregnancy for medical reasons, or spontaneous abortion will be reported as an SAE, using the same procedure as an SAE.

Any pregnancy in a female partner of a male subject occurring during the treatment period or within 30 days after last trial treatment administration must be reported using the same procedure as an SAE.

The investigator **shall send additional information to the UNICANCER pharmacovigilance unit** using a SAE declaration form (by ticking the Follow-up X box to specify that it is a follow-up and not an initial report) as soon as he is aware of the event. The investigator must also submit the last follow-up at the resolution or stabilisation of the SAE.

The investigator is responsible for appropriate medical follow-up of patients until the resolution or stabilisation of the event or until the death of the patient. This can sometimes mean that the follow-up continues after the patient has left the trial.

The investigator must keep the documents concerning the suspected SAE in order to supplement the information previously submitted if necessary.

Requests for clarification and additional information may be sent to the investigator by the UNICANCER pharmacovigilance unit or CRA sponsor of the trial to document and treat the case.

The physician-investigator should also attach to the form «notification of a SAE», whenever possible:

- a copy of the hospital report or extended hospitalisation report
- a copy of all results of additional investigations carried out, including also relevant negative results, and enclosing the normal laboratory values
- a copy of the autopsy report if necessary
- any other document deemed to be useful and pertinent

All these documents must be anonymised.

9. ANCILLARY/TRANSLATIONAL STUDY(IES)

Ancillary studies (translational research and basic research lab) will address a clinically relevant issue in this disease, i.e. to identify biomarkers that may provide relevant information for clinicians as to whether the patients benefit from chemotherapy in this clinical context.

It will include at least the analysis of constitutional DNA and circulating tumor DNA, performed before treatment to investigate constitutional (polymorphisms) or somatic (tumor-related molecular alterations) molecular factors with prognostic or predictive value. The correlation of tumor molecular biomarkers with clinical outcomes will also be analyzed.

The following analyses will be performed for each treatment regimen:
Descriptive statistics will be used to summarize biomarkers for responders versus non-responders. To assess relationship between response and biomarkers, a logistic regression analysis will be performed with effects for biomarker and treatment regimen in the model. To assess the relationship of overall survival (and PFS) with biomarkers, a Cox regression analysis will be used with effects for biomarker and treatment regimen in the model. In addition, for biomarkers with binary measures, survival will be summarized by median survival time for each biomarker category along with the hazard ratio. For each treatment regimen, the Kaplan-Meier curve for survival will be presented graphically for each biomarker category and differences in the curves will be tested using the log-rank test.

We will study the biomarkers dynamics across time and their association with primary and secondary endpoints of the trial. These studies will be managed in the Cancer Research Centre of Lyon.

Blood samples will be collected at day 1 (before treatment), day 15 of cycle 1 (before treatment) and at disease progression. Archived tumour tissues will be also collected (frozen and/or FFPE tissues). The biomarkers will be evaluated for their clinical relevance at different levels (circulating cell-free DNA, constitutive DNA, etc.). Analysis of mutations in a panel of genes (e.g. KRAS) will be done.
All the samples will be transported and centralised at Centre des Ressources Biologiques d'UNICANCER, (CRB-CLB), under the responsibility of Ms. Séverine Tablone-Eglinger, located at the following address:

Centre Léon Berard, 28 rue Laënnec – 69373 Lyon cedex 08, Bâtiment CHENEY B Rez de Chaussée – CRB échantillons biologiques) - France

A separate laboratory manual is provided to detail the procedures for blood samples and archived tumour tissues preparation, storage and shipment.

10. DESCRIPTION OF STATISTICAL METHODS

A comprehensive Statistical analysis plan (SAP) for the trial will be prepared before any statistical analysis. It will include detailed information on the analysis of primary and secondary outcome measures and the definition of major protocol deviations. Any revision of the SAP will be validated by the Steering Committee.
The SAS software version 9.4 will be used for the analysis.

10.1 Statistical hypothesis and sample size determination

The study was calibrated to detect a treatment effect hazard ratio (HR) of 0.625, translating in an improvement in median OS from 5 months (control arm: GEM) to 8 months (experimental arm: GEMPAX), with a 2:1 randomization.

A total of 184 events in the study (deaths) would have 85% power to show statistically significant OS at a 2-sided 5% alpha (including one interim analysis of superiority according to OS spending function). Considering a recruitment duration of 24 months and a 12-months follow-up for the last included patient (total duration for the study: 36 months), 210 patients will be randomized in the study (70 patients in the control arm and 140 patients in the experimental arm). One interim analysis of efficacy after half of the planned events have occurred will be done. An independent data monitoring committee (IDMC) will review this analysis. In order to strongly control the type I error the Lan and DeMets approach that approximates the O'Brien and Fleming spending function will be used (Lan and DeMets 1983). The 2-sided significance level at the interim analysis will be calculated based on the number of events occurred at the interim analysis. As an example, if exactly 50% of the final number of deaths have occurred at the interim analysis (92 deaths), then the significance level will be 0.3% at the interim and, accounting for the expected correlation between the proportion of events at the interim and at the final analysis, the 2-sided significance level at the final analysis will be approximately 4.9%

10.2 Trial populations to be analysed

All efficacy analyses will be performed on the ITT population including all randomized patients analysed according to the randomization scheme.

A Per Protocol (PP) population defined as a subgroup of the ITT population containing all patients who do not have any major protocol violation and received study treatment at least once could be used as a sensitivity analysis for the primary endpoint. Major protocol violations will be defined in the Statistical Analysis Plan.

The safety data will be analysed on the safety analysis set including all randomized patients having received at least one dose of study treatment and one safety follow-up, whether withdrawn prematurely or not.

10.3 Planned statistical analysis

10.3.1 General considerations

All statistical methods will be based on the International Conference on Harmonisation (ICH) E9 document "Statistical Principles for Clinical Trials".

Qualitative variables will be described using frequency and percentage distributions. The number of missing data will be given, but will not be considered for the calculation of proportions.
Quantitative data will be described using the number of observations, mean, standard deviation, median, minimum and maximum values.
Patient characteristics and other baseline data (demographics, disease characteristics, clinical and biological data) will be summarized per treatment arm and in global, in order to characterize the study population and to ensure the initial comparability of the 2 study arms. For each parameter considered, baseline value will be the value before the 1st administration of study treatment. No formal statistical comparison between study arms is planned regarding baseline characteristics, except in case of obvious difference for a given item. The date of randomization will serve as a reference for calculation of durations unless otherwise indicated.

10.3.2 Primary endpoint

Definitions
OS will be defined as the time from the date of randomization to the date of death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive and censored at the date of last contact for patients alive at this time.
Analyses
OS will be estimated using the Kaplan-Meir method and described in terms of median OS in each arm and hazard ratio between arms, along with the associated 2-sided 95% CIs for the estimates. OS distributions will be compared between the 2 arms using the Log-Rank test (stratified on Centre, PFS during first-line therapy <6 months or ≥ 6 months, and randomization.Ca 19-9 level at baseline <59× ULN or ≥59× ULN).

10.3.3 Secondary endpoints

Definitions
Objective response rate (ORR) is defined as the proportion of patients with a complete or a partial response (CR or PR) as best overall response during the study.

Progression Free Survival (PFS) is defined as the time from randomization until the date of event defined as the first documented progression, according to investigator assessment of RECIST version 1.1, or death (by any cause in the absence of progression). Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment.

Disease Control Rate at 4 months (4m-DCR) is defined as proportion of patients with a complete response (CR) of a partial response (PR) or a stable disease (SD), 4 months after treatment initiation.

Dose intensity will be calculated from doses actually given instead of from targeted doses. Ratio between dose received compared to theoretical ones will be calculated by patient and presented as a percentage.

Analysis
ORR and 4m-DCR will be summarized by arm and in the whole population by a proportion together with its 95% confidence interval and compared between the 2 study arms using a chi-square test if applicable, a Fisher exact test otherwise.

PFS will be analysed using survival method similar to those described for primary endpoint.

Dose Intensity will be summarized by arm and in the whole population. Correlation between dose intensity and efficacy parameters (PFS, OS) will be assessed using multivariate analysis.

The safety will be determined through the incidence of adverse events, treatment related adverse events, serious adverse Events (SAE) and death. Tolerance will be assessed using the NCI-CTC AE v5.0 grading scale. Descriptive statistics will be provided for characterizing and assessing patients' tolerance to treatment.

The QoL will be assessed using the EORTC QLQ-C30 questionnaire. QLQ-C30 scores will be calculated at each time point according to the EORTC scoring manual. Descriptive statistics will be used to evaluate baseline scores and evolution of scores from baseline to each time point. A threshold of 5 points in score change from baseline will be considered as clinically relevant.

Evolution of biomarkers (Ca 19-9, CEA, neutrophil to lymphocyte ratio, albumin, modified Glasgow prognostic score) will be described by absolute or relative variation from baseline. To assess their prognostic or predictive values, baseline values of these biomarkers will be tested using Cox or logistic regression models.

11. OVERSIGHT COMMITTEES

11.1 Independent data monitoring committee

The Independent Data Monitoring Committee (IDMC), with expertise and experience in the pathology, and without direct involvement in the conduct of the trial, will be set up specifically to guarantee effective protection of patients, insure the ethical conduct of the trial, benefit/risk ratio of the trial, and to ensure the independent review of the scientific results during the trial and at the end of the trial.
An IDMC charter must be available upon initial submission of the trial protocol to the Competent authority.

The IDMC will be composed of at least:

- Two oncologists
- A statistician

The IDMC will meet at a first meeting 6 months after the first patient's randomization to evaluate that the Benefit/Risk ratio is always in favour of the continuation of the study. A particular attention will be paid in observed haematological toxicities. It will also review one interim analysis of efficacy after half of the planned events have occurred. The IDMC will decide during this first meeting the further frequency of IDMC meetings (at least annually).

Data presented to IDMC are strictly confidential. Interim analyses will be presented to the IDMC

The IDMC may recommend the early termination of the trial if one of the following conditions is met:

- The results of the interim analysis clearly show that the experimental treatment is superior to the reference treatment;
- An unacceptable toxicity
- Data available from the trial or any other source of information are sufficiently convincing to influence the therapeutic practice of the majority of clinicians.

The IDMC has only a consultative role; it will inform the sponsor who will decide whether the IDMC recommendation will be followed.

11.2 Steering Executive Committee

The Unicancer Project leader will coordinate the day-to-day study activities according to the planned calendar. The study progress and any relevant information or issues will be communicated to the coordinating Investigators, and discussed with the collaborative UCGI group.

A dedicated steering committee, including at least the Study Coordinators, the Project Leader, and representatives from the investigational sites will meet regularly to supervise the trial. The steering committee will be responsible for the review of clinical issues arising during the study, the quality of the trial, verification of study-related collaborations, the interpretation of results, and the development of a communication strategy for the study. SAEs and SUSARs reported, study accrual, as well as, difficulties encountered by investigators will be discussed during steering committee meetings. The committee may decide to amend the study during these meetings, if required. The Steering Committee will meet as frequently as needed to discuss potential critical points but no less than twice annually. The UCGI steering committee will also monitor the trial and ensure the good execution and progress of the trial.

The Steering executive committee will assist UNICANCER in resolving issues and/or questions encountered during the trial and will consider with UNICANCER changes to the protocol as necessary.

12. QUALITY ASSURANCE

12.1 Data collection

All data necessary for the research must be entered into the trial case report forms (CRFs) in a timely manner. CRFs will be completed by the principle investigator and other staff members duly designated. The data entered must be accurate and complete.

In order to guarantee the authenticity and credibility of the data in accordance with the Good Clinical Practices, the sponsor will set up an assurance quality program that includes:

- specific procedures for the protocol
- management of the trial according to trial specific procedures provided by UNICANCER.
- control of the quality of the data provided by the investigation site is performed by the study monitor the role of which is to match and check the consistency of the data reported in the observation handbook with respect to the source-documents,
- possible audit of investigational sites,
- conducting a centralized review covering certain aspects of the protocol (to be specified).

The trial database will be hosted by:

Institut du Cancer Montpellier (ICM) – Val d'Aurelle
Unité de Biométrie – CTD INCa

208 rue des Apothicaires - Parc Euromédecine
34298 Montpellier Cedex 5 – France

Database management will be provided by an electronic Case Report Form (eCRF) developed using the CSOnline module of Ennov Clinical® software. In case of technical problem with the eCRF, the investigator may refer to the specific operating procedure of the eCRF or directly contact:

ICM – Unité de Biométrie – CTD INCa
Data centre UNICANCER
from Monday to Friday 9 am-5 pm
email: support.ecrf@icm.unicancer.fr
Fax: +33 (0)4 67 61 37 18
Tel: +33 (0)4 67 61 45 48/24 52

The access code (login) and passwords to access the eCRF will be sent directly to each users personal email account. The logins and personal passwords to connect to the eCRF, via the website - https://ecrf.icm.unicancer.fr/ CSOnline, will automatically be generated by CSOnline.

A password non-disclosure certificate will be signed by the principal investigator of each centre engaging his/her responsibility regarding the confidentiality of the access codes for all users of the eCRF at their centre.

Trial data will be entered directly by the principle investigator or by designated staff members of each centre, via the eCRF, and will be controlled and validated according to the standard procedures (included those in the software and the sponsor's quality assurance procedures). When using the eCRF, traceability of access and changes made to the eCRF are traced by the software (audit trail). At the end of the trial and once all the eCRF data are validated, the investigator will login to the eCRF to sign all the pages to validate the data entered for each patient.
The sponsor will create and send an electronic copy (PDF file) of each patient's CRF to the corresponding investigator. This pdf file must be printed and signed by the investigator, and then archived at the investigator's site.

The CRF will be considered as the source document for the data indicated above.

12.2 Access to data

The sponsor has direct access to all investigator sites, original records, source data/document and reports to allow quality control and auditing by the sponsor or on behalf of the sponsor.

Investigators will make available to the authorised persons the documents and the patients' individual data that are essential to monitor the trial on an ongoing basis, to perform quality control and audit of this research in accordance with national regulatory requirements.

12.3 Trial monitoring

- The management and the monitoring of the trial according to UNICANCER procedures. The monitoring strategy is built according to a systematic, prioritised, risk-based approach, and is documented in the monitoring plan.
- The quality control of data at the investigational centres by the monitor(s), which involves:
  - ✓ verifying that the protocol, as well as the current guidelines ICH-GCP, the national regulatory requirements, are adhered to
  - ✓ verifying the informed consent and the eligibility of each patient participating in the trial
  - ✓ verifying that the CRF data is consistent and in agreement with the source documents
  - ✓ verifying the notification of each SAE
  - ✓ verifying the drug traceability (dispatching, storage, and accountability)
  - ✓ verifying *(if applicable)* that patients are not already participating in another clinical study making them ineligible for this protocol.
- The quality control of data by a centralised monitoring process. Centralised monitoring is a remote evaluation of data, performed in a timely manner, supported by appropriately qualified and trained persons (e.g., data managers, biostatisticians). Review, that may include statistical analyses, of accumulating data from centralised monitoring can be used to:
  - ✓ Identify missing data, inconsistent data, data outliers, unexpected lack of variability, and protocol deviations.
  - ✓ Examine data trends such as the range, consistency, and variability of data within and across sites.
  - ✓ Evaluate for systematic or significant errors in data collection and reporting at a site or across sites; or potential data manipulation or data integrity problems.
  - ✓ Analyse site characteristics and performance metrics.
  - ✓ Select sites and/or processes for targeted on-site monitoring.
- The audit of participating investigational centres when deemed necessary

The monitors/CRAs in charge of trial monitoring will be mandated by the sponsor. They must have direct access to all patient data required to perform their duty in accordance with the national regulatory requirements. The monitors/CRAs are bound by professional secrecy under the national regulatory requirements. Written reports must be issued to ensure the traceability of monitoring visits.

To ensure optimal research quality control the investigator will ensure that the monitor/CRA has direct access to all trial patient files.

12.4 Audits and inspections

As part of UNICANCER's audit program, the sponsor may audit some investigational centres. The centre and the investigator agree that audits be carried out by Sponsor or any person duly authorised during the trial and for at least 15 years after the trial.

The investigational centre and the investigator agree to devote the time necessary for the audit procedures, allow the control of the trial documentation, and provide additional information requested by the sponsor.

A Competent Authority may also request a trial inspection (during the trial or after its completion). If a Competent Authority requests an inspection, the investigator must inform the sponsor immediately of this request. The investigator must allow the inspectors direct access to the trial documents and source documents. The investigational centre and the investigator agrees to devote the time necessary for inspections procedures, allow the control of the trial documentation, and provide additional information requested by the inspectors of the concerned Competent Authority.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1 General requirements

Prior to the start of the trial, the sponsor or the investigator will submit the trial protocol, patient information sheet(s), informed consent form(s), and other trial-related documents as required by local regulations, to the respective regulatory authorities for their authorizations and the responsible Independent Ethic Committee (IEC)/Institutional Review Board (IRB) for their written approval.

The sponsor or the investigator will inform the IEC/IRB and regulatory authorities, according to local regulatory requirements, about protocol amendments including any new information that require an ethical/regulatory reconsideration of the trial protocol.
The collection of biological samples implemented within the framework of the trial was declared to ANSM in the same time that the request of Clinical Trial Authorization. After the trial, and in case of storage, the storage of the collection of biological samples will be notified to the Minister of Research (and submitted to the CPP to notice if change of purpose of Research).

The trial must be conducted in accordance with the French national regulatory requirements:

- The principles of ethics as stated in the last version of the Declaration of Helsinki.
- Loi n°2012-300 du 5 mars 2012 relative aux recherches impliquant la personne humaine as modified in 2016
- Regulation (EU) 2016/679 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation).
- Amended Loi Informatique et Libertés n° 78-17 du 6 janvier 1978, relative à la protection des personnes physiques à l'égard des traitements de données à caractère personnel,
- Amended Loi n° 2004-800 du 6 août 2004, relative à la bioéthique,
- Décision du 24 novembre 2006 fixant les règles de bonnes pratiques cliniques pour les recherches biomédicales portant sur des médicaments à usage humain
- Good Manufacturing Practices, in particular, Annex 13 on investigational medicinal products.

13.2 Patient identification

Patient will be identified by a code, the first letter of the last name/surname, the first letter of the first name, and the month and year of the date of birth.

All patients will receive a unique patient identification number when signing the informed consent form by the patient and before any trial procedure is performed. This number will be used to identify the patient throughout the trial and must be used on all trial documentation related to this patient. The patient identification number must remain constant throughout the trial.

13.3 Patient information and consent

Patient information and informed consent from the patient must be handled in accordance with the "French regulation, especially article L.1122-1 and subsequent articles.
Prior to the participation of a patient in the trial, this patient will be informed both verbally and in writing about the objectives of the trial, its methods, anticipated benefits and potential risks and the discomfort to which they may be exposed. All items must be explained by the investigator in a language and in terms that are easy to understand by the patient. The patients must be given enough time to consider their participation and decide whether they wish to participate or not in the trial. Patients will also be informed that their participation is voluntary and that they have the right to withdraw from the trial at any time without giving the reasons and without this impacting their subsequent medical care.
The patient information sheet and the informed consent form must be associated within the same document to ensure that all information regarding the trial is provided to the patient. Patients will confirm their consent in writing prior to starting the trial and before undergoing any trial-related procedure. Two original informed consent forms must be personally dated and signed by the patient and investigator. An original copy will be filed in the Trial Master File (TMF). The other original patient information sheet and the signed informed consent form will be given to the patient.
If the patient decides to withdraw from the trial, the patient is not obliged to give reason(s) for withdrawing. However, the investigator should make a reasonable effort to obtain the reason(s) while fully respecting the patient's rights.
In conformance with the data protection regulation, the patient may use their right to access to, rectify or oppose the use of their personal data in the research. In these situations, the investigator shall inform the sponsor without delay in order to take the appropriate steps.

If any changes in the written patient information or informed consent form occur during the trial, the investigator will ensures that all patients impacted by the changes and still participating in the trial receive the updated patient information in a timely manner and are asked for written consent for the changes made.

13.4 Insurance compensation

UNICANCER, the sponsor of the trial certifies that it has taken out a civil liability insurance policy covering its civil liability for this clinical trial under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the sponsor does not exempt the investigator and its team from maintaining their own liability insurance policy.

13.5 Investigator responsibilities

The principal investigator of each investigator site participating in the trial commits to conduct the trial as specified in this protocol and in accordance with the "Décision portant sur les Bonnes Pratiques Cliniques, 24 November 2006".

It is the responsibility of the principal investigator to:

- Provide to the sponsor with their curriculum vitae (CV) and those of their collaborators, and evidence that the centre will be able to conduct the trial. The CV must be current (no older than 1 year), dated and signed;
- Identify the members of their team who participate in the trial and define each team members role and responsibilities;
- Start recruiting patients only after receiving approval from the sponsor;

- Be available for monitoring visits, audits, and investigator meetings (if applicable).

It is the responsibility of each principal investigator and each investigator team member to:

- Ensure the confidentiality of all data recorded during the trial;
- Collect the informed consent, written, dated, and signed personally by each individual research participant before any specific selection procedure for the trial;
- Regularly complete the case report form (CRF) for each patients included in the trial and allow clinical research associate(s) (CRA), mandated by the sponsor, direct access to the source documents in order to validated the data collected in the CRF;
- Declare to the sponsor as soon as being aware of, any serious adverse event occurring during the trial according to provisions of this protocol;
- Accept regular visits by the CRA(s) and possibly those of auditors mandated by the sponsor or the inspectors of the respective regulatory authorities;
- Date, correct, and sign the corrections made in the CRF and the requests of the data correction forms (DCF) for each patient included in the trial.

13.6 Federation of the Patient Committees for Clinical Research in Cancerology

This committee reviews trial documents provided to patients in oncology clinical studies, and makes suggestions for improving these, in terms of the quality of information given to patients.
The French patient committees' federation is coordinated by the "Ligue Nationale Contre le Cancer" and the French NCI (INCa).

13.7 Human biological samples collection

Biological studies are necessary to increase the knowledge of diseases, which may allow the development of new and more effective treatments. These studies use human biological samples (blood samples) that are collected from patients either while they receive medical care (examination, surgery) or specifically for the research purpose.

These biological samples will be prepared, stored, shipped, and used for the purpose of research.

These biological samples are subject to written consent from the patient. This consent is revocable at any time during the trial. Similarly, at any time during the research, the patient has the possibility to request the destruction of their samples.

Furthermore, it must be noted that the results of biological studies may be published only if all data relative to the patients are made anonymous.

Concerning genetic research patients must consent to participation in these studies after being informed of the proposed research, irrespective of the type of sample collected (already existing or specifically collected).

Furthermore, it must be noted that the results of biological studies may be published only if all data relative to the patients are made anonymous.

13.7.1 Collecting additional biological samples for research purpose

The study includes a translational research aiming to study and identify relevant biomarkers that may provide relevant information for clinicians as to whether the patients benefit from chemotherapy in this clinical context.

It will include at least the analysis of constitutional DNA and circulating tumor DNA, performed before treatment to investigate constitutional (polymorphisms) or somatic (tumor-related molecular alterations) molecular factors with prognostic or predictive value. The correlation of tumor molecular biomarkers with clinical outcomes will also be analyzed.

Blood samples will be done at day 1 (before treatment), day 15 of cycle 1 and at disease progression. These biological samples will be prepared, stored and used for the purpose of the research. These additional samples are optional and subject to a specific additional written consent from the patient. This specific consent for the translational research is revocable at any time. In addition, the patient has the right to request the destruction of their samples at any moment. The patient can participate to the main study if he refuses to participate to the translational study.

14. DATA PROCESSING AND CONSERVATION OF DOCUMENTS AND DATA OF THE RESEARCH

14.1 Data processing

14.1.1 Under the responsibility of the sponsor

The statistical data will be transferred to the trial statistician for analysis. The trial data remain the property of UNICANCER, the research sponsor.

The software Clinsight® will be used for data entry, management, and archiving of data. The statistical analysis will be performed using Stata software version 13.0.

14.1.2 In the investigational centre, when computerised medical records are used

If computerised patient records are used in a participating centre to process or store trial data, the centre must:

- Verify and document that the computer system used to process the data conforms with the requirements concerning data completeness, accuracy, and reliability with respect to expected performances (quality validation)
- Define and follow the standardised procedures related to these systems
- Ensure that these systems allow modifications of collected data, that each modification is automatically authentified, and that the data cannot be removed (i.e. any change or modification of the data must be traceable)
- Set up and maintain a security control to prevent unauthorised access to the data
- Establish and regularly update the list of persons authorised to have access and modify the data
- Carry out appropriate backups of the data
- Ensure confidentiality, whenever it is applicable (e.g. during data input)
  Ensure that the individual computerised patient data are processed in accordance with the “Loi Informatique et Libertés n° 78-17, 6 January 1978 modified”

If data are transformed while being processed, it should always be possible to compare them with the original observations/records.

The computerised system used to identify trial patients must not be ambiguous must allow the identification of all data collected for each patient while maintaining confidentiality in accordance with the "Loi Informatique et Libertés n° 78-17, 6 January 1978 modified".

14.2 Retention of documents by investigator sites

The investigator must maintain source documents for each trial patient.

All information in case report forms must be traceable and consistent with source documents, which are generally maintained in the patient's file. The source documents should contain all demographic and medical information, laboratory data, radiology, electrocardiograms, etc., including the original copy of the signed patient information sheet and informed consent form.

The investigator must retain essential documents as described below. The investigator agrees to adhere to the document retention procedures by signing the protocol. Essential documents include:

- Approvals from the CPP for the trial protocol and all relevant amendments
- Authorisations from the ANSM for the trial protocol and all relevant amendments
- All source documents and laboratory records;
- CRF copies;
- Patients' informed consent forms;
- Investigator master file (IMF) and Investigator master file-pharmacy (IMF-P);
- Any other pertinent trial document.

All trial documents must be kept in a locked and secured place and be considered as confidential.

Data will be archived under the responsibility of the principal investigator of each participating centre according to the "Décision portant sur les Bonnes Pratiques Cliniques, 24 November 2006". The trial documents, including a list of patient's identifications for a minimum period of 15 years after the end of the trial. UNICANCER will inform the investigational centres when the trial-related records are no longer required.
The investigational centre may destroy the data only after written authorisation from the sponsor.

15. DATA OWNERSHIP AND CONFIDENTIALITY

By signing the protocol, the investigator agrees to keep all information provided by UNICANCER strictly confidential and to ensure similar confidentiality from their staff. This obligation does not cover information provided to the patients and information already publically available.

Trial documents provided by UNICANCER (protocols, investigators' brochures, CRFs, and other material) will be stored appropriately to ensure their confidentiality. The information provided by UNICANCER to the physician-investigator may not be disclosed to others without direct written authorisation from UNICANCER.

The physician-investigator commits to not publish, spread or use in any manner, directly or indirectly, the scientific and technical information and results related to the trial.

16. PUBLICATION RULES

All information resulting from this trial is considered to be confidential, at least until appropriate analysis and checking has been completed by the sponsor, the principal investigator and the statistician of the trial.

Any publication, abstract or oral presentations including results of the trial must be submitted to the sponsor (UNICANCER) for approval.

Additionally, all communications, manuscripts or oral presentations must include a section mentioning UNICANCER as well as any institution, physician-investigators, collaborative research group, scientific society that has contributed to the trial, including organisations that have provided financial support.

The first author and writer of the main publication will be the principal investigator. The principal investigator may however designate another person to (co-) write the publication.

As for the main publication authors are listed in the following order:

- the trial coordinator (first or last author)
- the other investigators will appear in the list of co-authors in decreasing order, according to the number of recruited patients regardless of their affiliation to a cooperative group
- a person representing each cooperating group, if a representative is not listed in the sites with the highest recruitment rates
- the statistician (The statistician's position is among the first three authors or the last author of the publication)
- a UNICANCER representative

Similarly, publication of the sub-studies (e.g. biological/ancillary studies) will include persons who have carried out the sub-studies as well as the names of all individuals who have contributed to these sub-studies and a sponsor representative.

It is desirable to include the contributors from weakly recruiting centres who have not been mentioned in the first article in the later publications.

Any conflict regarding publication authorship will initially be submitted to the trial IDMC and then to the CSR (Comité Stratégique Recherche [Strategic Research Committee]) for resolution in case of major disagreement.

UNICANCER will arbitrate and rule any dispute that may arise.

17. REFERENCES

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18. APPENDICES

1. Performance status evaluation – WHO scale
2. ICH Harmonised Tripartite Guideline for Good Clinical Practice (ICH-GCP)
3. A brief summary of tumour classification RECIST v1.1
4. Toxicity criteria (NCI-CTCAE) version 5.0
5. Patient questionnaire(s) – QLQ-C30
6. Gemcitabine and paclitaxel SmPC
7. Modified Glasgow Prognostic Score for Cancer Outcomes: calculation method

Appendix 1. Performance status evaluation – WHO scale

Performance status ECOG-ZUBROD/ OMS	value
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 self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care, 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. ICH Harmonised Tripartite Guideline for Good Clinical Practice (ICH-GCP)

The current ICH-GCP can be found on the European Medicine Agency web page via the link provided below:

http://www.ema.europa.eu/

Appendix 3. A brief summary of tumour classification RECIST v1.1

(Eur. J. Cancer, 45(2009), 228-247 [47])

Full article available at: http://ctep.cancer.gov/

"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.

Summary:

Measurability of tumour at baseline:

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

Measurable

Tumour lesions: Must be accurately measured in a 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 calliper measurement by clinical exam;
- 20 mm by chest (=X-ray);

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). 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 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.

Remark:

Bone lesions, cystic lesions, and lesions previously treated with local therapy require special considerations regarding lesion measurability (see below):

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.
- Blastic bone lesions are non-measurable.

Target lesions

When more than one measurable lesion is present at baseline all lesions up to a **maximum of five lesions total (and a maximum of two lesions per organ)** representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan.

The baseline sum diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.

Non-target lesions
All other lesions (or sites of disease) including pathological lymph nodes 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', 'absent', or in rare cases 'unequivocal progression' during 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

Warning: 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 trial. 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 CR, 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.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (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. (Note: the appearance of one or more new lesions is also considered progression).

Warning: when a progression is recorded with respect to the Nadir but there is a response with respect to baseline, progression must be considered.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on trial.

Non-target lesions

Complete Response (CR): Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.

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Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: 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	=	**Not-evaluable**
PD	No change	Yes or No	=	**PD**
No change	PD	Yes or No	=	**PD**
No change	No change	Yes	=	**PD**

Special considerations regarding baseline lesion measurability

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) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic 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. Trial protocols should detail the conditions under which such lesions would be considered measurable.

Appendix 4. Toxicity criteria (NCI-CTCAE)

In the present trial, adverse events will be recorded according to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE), *(Publish Date November 27, 2017)*

Toxicity evaluation scale provided separately in attached documents or download it from the NCI website

NATIONAL CANCER INSTITUTE
Cancer Therapy Evaluation Program

http://ctep.cancer.gov/

Appendix 5. Patient questionnaire(s)

http://groups.eortc.be/qol/sites/default/files/img/slider/specimen_qlq-c30_english.pdf

Appendix 6. Summary of product characteristics (SmPC)

Please refer to the following websites for gemcitabine and paclitaxel SmPC :

Gemcitabine SmPC: http://agence-prd.ansm.sante.fr/php/ecodex/extrait.php?specid=67728176

Paclitaxel SmPC : http://agence-prd.ansm.sante.fr/php/ecodex/extrait.php?specid=61174122

Appendix 7. Modified Glasgow Prognostic Score for Cancer Outcomes: Calculation method

C-reactive protein level (mg/L)	Albumin level (g/dL)	Modified Glasgow Prognostic Score (mGPS)	Interpretation
≤ 10	≥ 3.5	0	Good prognosis
	≤ 3.5		
> 10	≥ 3.5	1	Intermediate prognosis
> 10	≤ 3.5	2	Poor prognosis

Website link for calculation: https://www.mdcalc.com/modified-glasgow-prognostic-score-mgps-cancer-outcomes