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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**

Statistical Analysis Plan

V1.1 – 02/04/2020

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SAP Signatures

Version	**Version 1.1 dated 02/04/2020**
Approved by:	
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Versions of statistical analysis plan

Type of version	**Version n° - Date**	**Comments / Main Changes**
Draft	V1.0 – 23/03/2020	SAP for the 1st safety analysis (IDMC n°1)
Validated version before the 1st interim safety analysis	V1.1 – 02/04/2020	Minor modifications following comments of UNICANCER on V1.0

1 Introduction

This SAP describes the analysis sets, the derived variables and the statistical analyses to be produced for the GEMPAX study.

1.1 Study objectives

1.1.1 Primary objective

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

1.1.2 Secondary objectives

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.

1.2 Study design and treatment

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.

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.

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

1.3 Sample size calculation and design

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%.

2 General statistical methods and analysis populations definition

2.1 General statistical methods

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

The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

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.

Statistical analyses will be performed using SAS® software version 9.4 or later.

2.2 Analysis populations

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, providing that population differs from the ITT population by more than 10%. Major protocol violations will be defined during the blind review (BR) meeting and documented in the BR report.

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.
Patients will be analysed according to the treatment actually received (and not according to the arm allocated by the randomization).

For interim safety analyses, the safety population will include patients of the safety analysis set, randomized within the timeframe defined in the protocol for a given interim safety analysis.

2.3 Oversight committees

2.3.1 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.

2.3.2 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.

3 Statistical Analysis

3.1 Analysis population description

- Total number (counts, %) of screened patients

In total and per treatment arm :

- Number (counts, %) of randomized (ITT population)
- Number (counts, %) of patients included in each analysis population and reason for exclusion when applicable

3.1.1 Patients and disease baseline characteristics

The following data will be described on the ITT population, in total and per treatment arm.

- Demography (age, sex)
- ECOG at baseline
- Disease characteristics
    - Localisation
    - Differenciation
    - pT, pN, pM

3.2 Treatment exposure

The following data will be described on the safety population, in total and per treatment arm.

- Patients with at least one treatment modification (reduction or interruption) for toxicity
- In the experimental arm,
    - GEMCITABINE - patients with at least one treatment modification (reduction or interruption) for toxicity
    - PACLITAXEL - patients with at least one treatment modification (reduction or interruption) for toxicity
- Patients having definitely discontinued treatment and:
    - reason for definite discontinuation
    - Duration of treatment exposure calculated as: duration between the date of first dose of treatment and the date of last dose of treatment

3.3 Study discontinuation

Number of patients of the ITT population having terminated the study and reason for study discontinuation.

3.4 Follow-up duration

Follow up duration will be calculated as the time from randomization to the date of last news defined at the most recent date between the following : date of last tumoral evaluation (RS), date of death, date of last visit (DS).

3.5 Analysis of safety data

Safety analyses will be based on the safety population.

The assessment of safety will be based on the frequency of Adverse Events (AE) based on the common toxicity criteria (CTC-AE-V5.0) grade. Descriptive statistics will be provided for characterizing and assessing patient tolerance to treatment.

The following data will be summarized in total, and per treatment arm:

Number of patients (counts, %) with:

- at least one AE / grade>=3 AE / grade 5 AE
- at least one treatment-related AE, at least one AE related to each type of treatment (all, grade>=3, grade 5)
- at least one serious AE
- at least one treatment-related SAE

The following data will be summarized per system organ class and preferred term, in total, and per treatment arm:

- treatment-related AEs
- grade>=3 AEs
- treatment-related grade >=3 AEs

A listing of all adverse events will be provided including : patient identifier, description of the event, grade, seriousness, relation to treatment.

All listing of all SAEs will also be provided.

If applicable, a summary of deaths and causes of deaths will be presented. In particular number of deaths due to treatment-related AEs will be presented.

4 Statistical tables template

Table 1 Patients disposition

	Total patients screened N=xx	
Total patients randomised (ITT population)	xx	(%)
ARM A	xx	(%)
ARM B	xx	(%)
Total not randomised patients	xx	(%)
	xx	
INVESTIGATOR DECISION	xx	(%)
OTHER	xx	(%)

Table 2 Analysis populations

	Randomization arm		ITT population
	ARM A N=xx	ARM B N=xx	N=xx
Safety population	xx (%)	xx (%)	xx (%)

Table 3 Patients characteristics

	Randomization arm		ITT population
	ARM A N=xx	ARM B N=xx	N=xx
Age			
N	xx	xx	xx
Missing	x	x	x
Mean (Std)	xx.x (x.x)	xx.x (x.x))	xx.x (x.x)
Median (min; max)	xx (xx; xx)	xx (xx; xx)	xx (xx; xx)
Sex			
MALE	xx (%)	xx (%)	xx (%)
FEMALE	xx (%)	xx (%)	xx (%)
ECOG at baseline			
0	xx (%)	xx (%)	xx (%)
1	xx (%)	xx (%)	xx (%)
2	xx (%)	xx (%)	xx (%)

Table 4 Disease characteristics

	Randomization arm		ITT population
	ARM A N=xx	ARM B N=xx	N=xx
Localization			
HEAD (WITHOUT POSSIBLE PRECISION)	xx (%)	xx (%)	xx (%)
HEAD EXCEPT HOOK	xx (%)	xx (%)	xx (%)
….	xx (%)	xx (%)	xx (%)
…	xx (%)	xx (%)	xx (%)
…	xx (%)	xx (%)	xx (%)
OTHER	xx (%)	xx (%)	xx (%)
…	xx (%)	xx (%)	xx (%)
…	xx (%)	xx (%)	xx (%)
DIFFERENTIATION			
MODERATELY DIFFERENTIATED	xx (%)	xx (%)	xx (%)
…..	xx (%)	xx (%)	xx (%)
pT CLASSIFICATION			
1A	xx (%)	xx (%)	xx (%)
2	xx (%)	xx (%)	xx (%)
..	xx (%)	xx (%)	xx (%)
..	xx (%)	xx (%)	xx (%)
pN CLASSIFICATION			
0	xx (%)	xx (%)	xx (%)
1	xx (%)	xx (%)	xx (%)
…	xx (%)	xx (%)	xx (%)
pM CLASSIFICATION			
0	xx (%)	xx (%)	xx (%)
1	xx (%)	xx (%)	xx (%)
…	xx (%)	xx (%)	xx (%)

Table 5 Duration of follow-up - Safety population

	Randomization arm		Safety population
	ARM A N=xx	ARM B N=xx	N=xx
Duration of follow up (months)			
N	xx	xx	xx
Missing	x	x	x
Mean (Std)	xx.x (x.x)	xx.x (x.x))	xx.x (x.x)
Median (min; max)	xx (xx; xx)	xx (xx; xx)	xx (xx; xx)

Table 10 Treatment discontinuation

	Randomization arm		Safety population
	ARM A N=xx	ARM B N=xx	N=xx
Patients having definitely discontinued treatment	xx (%)	xx (%)	xx (%)
Reason for definite treatment discontinuation			
DEATH	xx (%)	xx (%)	xx (%)
OTHER	xx (%)	xx (%)	xx (%)
PHYSICIAN DECISION	xx (%)	xx (%)	xx (%)
PROGRESSIVE DISEASE	xx (%)	xx (%)	xx (%)
Duration of treatment exposure* (months)			
N	xx	xx	xx
Missing	x	x	x
Mean (Std)	xx.x (x.x)	xx.x (x.x))	xx.x (x.x)
Median (min; max)	xx (xx; xx)	xx (xx; xx)	xx (xx; xx)

*in pts having definitely discontinued treatment

Table 11 Treatment modifications for toxicity

	Randomization arm		Safety population
	ARM A N=xx	ARM B N=xx	N=xx
At least one treatment modification for toxicity			
NO	xx (%)	xx (%)	xx (%)
YES	xx (%)	xx (%)	xx (%)
GEMCITABINE - At least one treatment modification for toxicity			
NO	xx (%)	xx (%)	xx (%)
YES	xx (%)	xx (%)	xx (%)
PACLITAXEL - At least one treatment modification for toxicity			
NO	xx (%)	xx (%)	xx (%)
YES	xx (%)	xx (%)	xx (%)

Table 15 End of study

	Randomization arm		ITT population
	ARM A N=xx	ARM B N=xx	N=xx
Patients having discontinued the study	xx (%)	xx (%)	xx (%)
DEATH	xx (%)	xx (%)	xx (%)
OTHER	xx (%)	xx (%)	xx (%)
PATIENT DECISION	xx (%)	xx (%)	xx (%)

Table 30 Summary of adverse events (AEs)

	Randomization arm		Safety population
	ARM A N=xx	ARM B N=xx	N=xx
At least one AE	xx (%)	xx (%)	xx (%)
At least grade>=3 AE	xx (%)	xx (%)	xx (%)
At least grade 5 AE	xx (%)	xx (%)	xx (%)
At least one treatment-related AE	xx (%)	xx (%)	xx (%)
At least one AE related to GEMCITABINE	xx (%)	xx (%)	xx (%)
At least one AE related to PACLITAXEL	xx (%)	xx (%)	xx (%)
At least one grade>=3 treatment-related AE	xx (%)	xx (%)	xx (%)
At least one grade>=3 AE related to GEMCITABINE	xx (%)	xx (%)	xx (%)
At least one grade>=3 AE related to PACLITAXEL	xx (%)	xx (%)	xx (%)
At least one grade 5 treatment-related AE	xx (%)	xx (%)	xx (%)
At least one grade 5 AE related to GEMCITABINE	xx (%)	xx (%)	xx (%)
At least one grade 5 AE related to PACLITAXEL	xx (%)	xx (%)	xx (%)
At least one SAE	xx (%)	xx (%)	xx (%)
At least one treatment-related SAE	xx (%)	xx (%)	xx (%)

Table 31 Description of treatment-related (AEs)

	Prefer Term Name	ARM A N=xx	ARM B N=xx	Safety population N=xx
BLOOD AND LYMPHATIC SYSTEM DISORDERS	ANAEMIA	xx (%)	xx (%)	xx (%)
	HYPERLEUKOCYTOSIS	xx (%)	xx (%)	xx (%)
	NEUTROPENIA	xx (%)	xx (%)	xx (%)
	THROMBOCYTOPENIA	xx (%)	xx (%)	xx (%)
GASTROINTESTINAL DISORDERS	ABDOMINAL PAIN	xx (%)	xx (%)	xx (%)
	ASCITES	xx (%)	xx (%)	xx (%)
	DIARRHOEA	xx (%)	xx (%)	xx (%)
	FLATULENCE	xx (%)	xx (%)	xx (%)
	NAUSEA	xx (%)	xx (%)	xx (%)
…….	…	xx (%)	xx (%)	xx (%)
	…	xx (%)	xx (%)	xx (%)
	…	xx (%)	xx (%)	xx (%)
	…	xx (%)	xx (%)	xx (%)
INVESTIGATIONS	ALANINE AMINOTRANSFERASE INCREASED	xx (%)	xx (%)	xx (%)
	NEUTROPHIL COUNT DECREASED	xx (%)	xx (%)	xx (%)
	PLATELET COUNT DECREASED	xx (%)	xx (%)	xx (%)
…….	…	xx (%)	xx (%)	xx (%)
	…	xx (%)	xx (%)	xx (%)
	…	xx (%)	xx (%)	xx (%)
	…	xx (%)	xx (%)	xx (%)

The table describes the number of pts having experienced each type of event at least once

Table 32 Description of grade>=3 AEs, related or not

	Prefer Term Name	ARM A N=xx	ARM B N=xx	Safety population N=xx
BLOOD AND LYMPHATIC SYSTEM DISORDERS	ANAEMIA	xx (%)	xx (%)	xx (%)
	HYPERLEUKOCYTOSIS	xx (%)	xx (%)	xx (%)
	NEUTROPENIA	xx (%)	xx (%)	xx (%)
	THROMBOCYTOPENIA	xx (%)	xx (%)	xx (%)
GASTROINTESTINAL DISORDERS	ABDOMINAL PAIN	xx (%)	xx (%)	xx (%)
	ASCITES	xx (%)	xx (%)	xx (%)
	DIARRHOEA	xx (%)	xx (%)	xx (%)
	FLATULENCE	xx (%)	xx (%)	xx (%)
	NAUSEA	xx (%)	xx (%)	xx (%)
…….	…	xx (%)	xx (%)	xx (%)
	…	xx (%)	xx (%)	xx (%)
	…	xx (%)	xx (%)	xx (%)
	…	xx (%)	xx (%)	xx (%)

The table describes the number of pts having experienced each type of event at least once

Table 33 Description of grade>=3 treatment-related (AEs)

	Prefer Term Name	ARM A N=xx	ARM B N=xx	Safety population N=xx
BLOOD AND LYMPHATIC SYSTEM DISORDERS	ANAEMIA	xx (%)	xx (%)	xx (%)
	HYPERLEUKOCYTOSIS	xx (%)	xx (%)	xx (%)
	NEUTROPENIA	xx (%)	xx (%)	xx (%)
	THROMBOCYTOPENIA	xx (%)	xx (%)	xx (%)
GASTROINTESTINAL DISORDERS	ABDOMINAL PAIN	xx (%)	xx (%)	xx (%)
	ASCITES	xx (%)	xx (%)	xx (%)
	DIARRHOEA	xx (%)	xx (%)	xx (%)
	FLATULENCE	xx (%)	xx (%)	xx (%)
	NAUSEA	xx (%)	xx (%)	xx (%)
……	…	xx (%)	xx (%)	xx (%)
	…	xx (%)	xx (%)	xx (%)
	…	xx (%)	xx (%)	xx (%)
	…	xx (%)	xx (%)	xx (%)

The table describes the number of pts having experienced each type of event at least once

Table 36 Description of deaths

	Randomization arm		ITT population
	ARM A N=xx	ARM B N=xx	N=xx
Patients deceased	xx (%)	xx (%)	xx (%)
PROGRESSIVE DISEASE	xx (%)	xx (%)	xx (%)
……	xx (%)	xx (%)	xx (%)

Listing 34 Listing of SAEs

Subject Identifier for the Study	Randomization arm	Visit name	Toxicity name	SOC Name	Prefer Term Name	Grade	Causality
XXX	ARM X	CYCLE X	……	……	……	GRADE X	……
XXX	ARM X	CYCLE X	……	……	……	GRADE X	……
XXX	ARM X	CYCLE X	……	……	……	GRADE X	……

Listing 35 Listing of all Aes

Subject Identifier for the Study	Randomization arm	Visit name	Toxicity name	SOC Name	Prefer Term Name	Grade	Causality	SAE
XXX	ARM X	CYCLE X	……	……	……	GRADE X	……	Yes
XXX	ARM X	CYCLE X	……	……	……	GRADE X	……	No
XXX	ARM X	CYCLE X	……	……	……	GRADE X	……	……