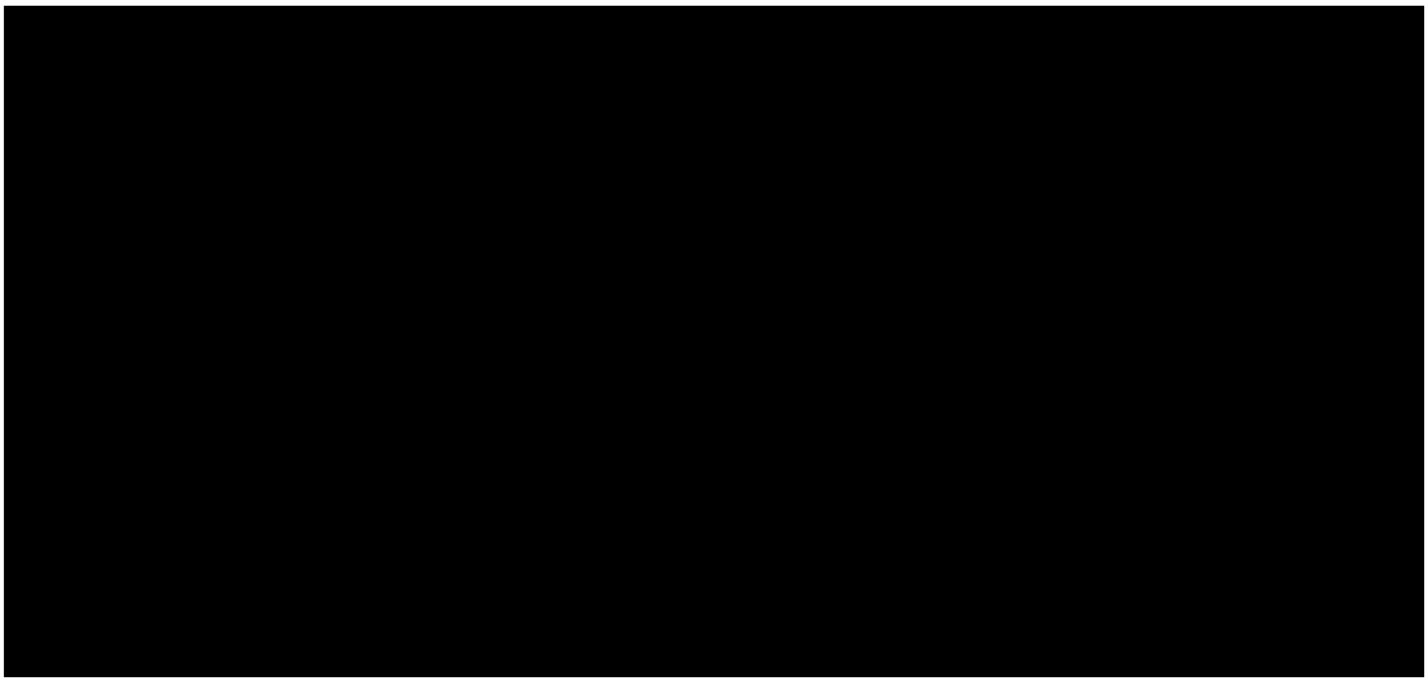

Study PANC003 v4.0

IDDI
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Statistical Analysis Plan

Sponsor:	Rafael Pharmaceuticals, Inc.
Protocol Title:	A Phase III Multicenter Open-Label Randomized Trial to Evaluate Efficacy and Safety of FOLFIRINOX (FFX) versus Combination of CPI-613 with modified FOLFIRINOX (mFFX) in Patients with Metastatic Adenocarcinoma of the Pancreas (ECOG 0-1)
Study Code:	PANC003

Approved in Vault: 7/14/2021

Confidential

[redacted]

Sponsor Representative: Sanjeev Luther, President and CEO, Rafael Pharmaceuticals, Inc.
Signature and date

Confidential

Revision History

Date	Description
11/15/2019	Initial version 1.0
10/1/2020	Version 2.0
10/15/2020	Version 3.0
07/08/2021	Version 4.0

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Table of Contents

1. List of Abbreviations and Definition of Terms

Abbreviation	Description
AE	Adverse Events
ALT (=SGPT)	Alanine Aminotransferase
ALP	Alkaline Phosphatase
AST (=SGOT)	Aspartate Aminotransferase
CA19-9	Carbohydrate Antigen 19-9
CBC	Complete Blood Count
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CR	Complete Response
CT	Computed Tomographic
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria For Adverse Events
CTEP	Cancer Therapy Evaluation Program
DOR	Duration Of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
eCRF	Electronic Case Report Forms
FFX	FOLFIRINOX
HR	Hazard Ratio
ICH	International Council For Harmonization Of Technical Requirements For Pharmaceuticals For Human Use
IDDI	International Drug Development Institute
ITT	Intent-To-Treat
IxRS	Interactive Voice/Web Response Systems
MedDRA	Medical Dictionary For Regulatory Activities
mFFX	Modified FOLFIRINOX
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
OR	Odds Ratio
ORR	Objective Response Rate
OS	Overall Survival
PD	Pharmacodynamics
PD	Progressive Disease
PFS	Progression-Free Survival
PK	Pharmacokinetics
PP	Per Protocol
PR	Partial Response
PRO	Patient-Reported Outcomes
PT	Preferred Term
QTc	Corrected QT Interval
RECIST	The Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SAF	Safety Population
SAP	Statistical Analysis Plan
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase

SOC	System Organ Class
WHO	World Health Organization

2. Introduction

This Statistical Analysis Plan was written for the clinical trial Rafael PANC003. The ICH guidelines As [illegible] used as a guide to the writing of the plan.

2.1 Study Rationale

Pancreatic cancer is an extremely deadly disease, with more than 95% of patients affected dying of their disease. The cancer is locally invasive and highly prone to metastasis. Although its prevalence in the USA is quite low (53,070 individuals per year), pancreatic cancer became the third leading cause of cancer-related deaths in 2016, surpassing breast cancer, and is expected to be the second cause of death by 2030 (Surveillance Epidemiology and End Results Program: Pancreas Cancer, 2016). Even though the exact etiology is unknown, 5-10% of pancreatic cancers have an inherited component, with an increased risk of developing pancreatic cancer if a first-degree relative is diagnosed with the disease. Other important risk factors associated with pancreatic cancer are smoking, long-standing diabetes mellitus, nonhereditary and chronic pancreatitis, obesity or inactivity or both, and the non-O blood group. Various genetic syndromes also pose an increased risk for developing pancreatic cancer (Kamisawa, 2016).

There are a number of types of pancreatic cancer with the predominant one being adenocarcinoma, which accounts for approximately 95% of cases. 60-70% of adenocarcinomas occur in the head of the pancreas, and 20-25% are located in the body and tail of the pancreas. The presenting signs and symptoms may be related to the location. Patients with pancreatic cancer most commonly present with abdominal pain, weight loss, asthenia, and anorexia. Obstructive jaundice is a common manifestation of tumors in the head of the pancreas (Ryan, 2014). Because the disease typically does not present with recognizable/distinctive symptoms in its early stages, when it is diagnosed, the disease is usually quite advanced with limited treatment options (Cascinu, 2010; Vaccaro, 2015). The lack of effective treatments for pancreatic cancer is evidenced by the low 5-year survival rate, which is estimated to be between 6% and 8%. Approximately half of pancreatic cancer patients present with metastatic disease for whom there are no curative therapies. These patients have a median life expectancy of less than one year, even with current treatment modalities.

Chemotherapy is the only treatment option for metastatic pancreatic cancer. National comprehensive cancer network (NCCN) treatment guidelines recommend FFX (oxaliplatin, folinic acid [leucovorin], irinotecan, bolus fluorouracil, infusional fluorouracil) or gemcitabine plus nab-paclitaxel for first line treatments for patients who are healthy enough to tolerate them and have a support system for a relatively aggressive medical therapy. In Phase III trials in patients with metastatic disease FFX was superior to gemcitabine in terms of objective tumor response, progression-free and overall survival. However, FFX is regarded as too toxic for use in elderly (Conroy, 2011; Stein, 2016) and poor performance status patients. Of note, the median age of diagnosis of pancreatic cancer is 71 years (Ryan, 2014). For patients who wish to pursue cancer-directed therapy but cannot manage such aggressive treatments, gemcitabine alone or alternate choices are recommended. In general, clinical trials are highly recommended for patients with metastatic disease. Another option for patients who cannot tolerate the toxic effects of FFX is to be treated with a modified dosing regimen of FFX, which significantly decreases the adverse side effects (neuropathy, diarrhea, neutropenia) associated with FFX.

There is a great medical need for better and more effective first-line systemic therapies that not only have less toxicity but also the potential for greater efficacy. Given the

favorable safety and efficacy profiles of CPI-613 when administered in combination with mFFX along with the promising efficacy results achieved in trial CCCWFU57112, the further evaluation of CPI-613 in pancreatic cancer was warranted. Based on the experience in phase I study, Rafael Pharmaceuticals initiated this phase III randomized trial of standard dose FFX versus CPI-613 + mFFX in patients with metastatic adenocarcinoma of the pancreas. The goal of the trial is to provide compelling evidence of the safety and efficacy of this approach leading to a regulatory approval for CPI-613 in combination with mFFX for use in patients with metastatic adenocarcinoma of pancreas and has the potential to address serious medical unmet needs for this indication.

3. Study Design and Objectives

3.1 Study Objectives

3.1.1 z□□□□□□□/ □□□□□□□□□

The primary objective is:

- To evaluate Overall Survival (OS) of CPI-613® (devimistat) plus mFFX versus FFX.

3.1.2 □□□□□□□□□□/ □□□□□□□□□□

The main secondary objectives are:

- To evaluate Progression-Free Survival (PFS) of CPI-613® (devimistat) plus mFFX versus FFX
- To evaluate Objective Response Rate (ORR) defined as Complete Response (CR) plus Partial Response (PR) of CPI-613 plus mFFX versus FFX
- To evaluate Duration of Response (DOR) of CPI-613 plus mFFX versus FFX
- To evaluate safety of CPI-613 plus mFFX versus FFX
- To assess Pharmacokinetics (PK) of CPI-613
- To evaluate Patient-Reported Outcomes (PROs) by FACT Hepatobiliary Symptom Index (FHSI-18) for CPI-613 plus mFFX versus FFX.

3.1.3 A□□□□□□□□□□□/ □□□□□□□□□□

Exploratory objectives are:

- To explore biomarkers using diagnostic biopsies and blood/plasma samples
- To assess PK/PD of dose/exposure-response for CPI-613 on efficacy (e.g. PFS), safety (e.g. QTc) and exploratory biomarkers.

3.2 Study Design

This is a prospective, multicenter, open label, randomized Phase III study of CPI-613 + mFFX compared to FFX in patients with metastatic (Stage IV) adenocarcinoma of the pancreas with age range of 18 to 75 years.

There will be two study arms:

- Arm 1: CPI-613 + mFFX
- Arm 2: FFX.

Subjects will be randomized in 1:1 ratio to the experimental treatment or control, using a dynamic minimization procedure based on the methodology described by Buyse (Buyse, 2000). The minimization algorithm will use the variance method to minimize overall imbalances between the treatment arms with respect to site, performance status (0 vs. 1), and primary tumor location (head vs. body vs. tail of the pancreas).

Dosing of patients randomized in the study will continue for at least six months in responding patients with acceptable tolerance to therapy (with dose modification per protocol as needed) unless a criterion for removal from study occurs. Responding patients upon completion of at least ten cycles and after having two sequential CT scans showing stable disease (no continued decrease in lesion size) will complete two additional cycles (to complete a minimum of 12 cycles) of their assigned treatment. Following 12 cycles and all the subsequent cycles, oxaliplatin can be dropped at the discretion of the treating physician if not already omitted. Cycles will continue until one of the criteria for removal from study are reached.

z[redacted]) [redacted] additional information.

3.3 Sample Size Justification

A total of 500 patients will be enrolled in this trial across approximately 100 sites in North America, Europe, Asia, and Oceania. This number accounts for ineligible and unevaluable patients, as well as for dropouts.

Dropouts refer to any subject who has been randomized but withdrew for various reasons, including misdiagnosed or exclusion criteria violations.

The sample size calculation is based on the following expected benefits of the experimental treatment (CPI-613 + mFFX) over the control treatment (FFX):

- A 30% reduction in the risk of death from any cause; specifically, median OS is assumed equal to 12 months in the control arm vs. 17.14 months in the experimental arm, i.e., an OS hazard ratio equal to 0.7. For a power of 90% and a one-sided type-I error level of 0.025, 335 deaths need to be observed.
- A 30% reduction in the risk of tumor progression or death from any cause; specifically, median PFS is assumed equal to 6.4 months in the control arm vs. 9.14 months in the experimental arm, i.e., a PFS hazard ratio equal to 0.7. For a power of 90% and a one-sided type-I error level of 0.025, 330 PFS events need to be observed.

4. Data Sources

4.1 Randomization

Subjects will be randomized in a 1:1 ratio to the experimental treatment or control via an interactive web response system (IxRS), using a minimization procedure. The minimization algorithm will use the variance method to minimize overall imbalances between the treatment arms with respect to site, and the stratification factors: performance status (0 vs. 1); and, primary tumor location (head vs. body vs. tail of the pancreas). Note that region is subsumed by site, hence minimization will also tend to balance between the treatment arms with respect to geographical region.

4.2 Study Data

Study data will be collected by sites and entered into a central EDC. The EDC is maintained by IDDI. Central laboratory data will be provided by Covance.

4.2.1 z-□□□□/ ββ

Progression-Free Survival (PFS) and Objective Response Rate (ORR) will be assessed by an independent, blinded, central review by RECIST guideline version 1.1. These data will be incorporated separately into their respective SDTM domains for further analysis.

4.3 PK

Sampling of patients for the PK analysis will occur only for the study Arm 1: CPI-613 + mFFX because the dosing level of Oxaliplatin (Eloxatin) and Irinotecan between mFFX (in Arm 1) and FFX (in Arm 2) are different. As such, PK comparison of components between mFFX and FFX is not appropriate and therefore no PK sampling for the study Arm 2: FFX.

Upon randomization through the IxRS, a patient will be designated with a code assignment for blood sampling for PK analysis of CPI-613 and its metabolites CPI-2850 and CPI-1810. Assignment will be to blood sampling for either (A) Full PK Analysis; or (B) Sparse PK Analysis. The first 10 patients will be assigned to group B. Following these 10 patients, assignment will be 24 patients to group A and the remaining 216 patients to group B. Assignment to group A will be dependent on hospital site, ability, experience, and facility to collect a more detailed blood profile over a 48-hour window.

For more details concerning the PK analysis, please refer to Section 7 of the study protocol or the separate PK Analysis Plan written and maintained by the PK vendor. As of this time, there are no planned analyses or outputs involving PK data that fall under the IDDI scope of work.

4.4 ECG

The 24 patients receiving CPI-613 plus modified FFX (i.e., Arm 1) assigned to the full PK analysis sub-study will also undergo a full ECG analysis. 12-lead ECGs will be recorded at defined intervals from 30 minutes prior to dosing of CPI-613 on cycle 1, day 1 to 6 hours after dosing on day 1. Subjects will be placed in a supine position for at least 10 minutes prior to timepoints for ECG and PK sampling. ECG recordings will be taken immediately prior to PK sample draw at each time point. ECG intervals for this full ECG analysis will be measured at a central ECG laboratory, who will be fully blinded to timepoints and subject identification.

5. General Analysis Definitions

Data will be analyzed using SAS (version 9.4 or higher).

Descriptive statistics will be tabulated as follows:

- Categorical data will be summarized in contingency tables presenting frequencies and percentages.
- Continuous data will be summarized using number of non-missing values (n), mean, standard deviation, median (25^{th}, 75^{th}), minimum, and maximum values.

The baseline tables will be created by treatment arm and overall. Tables containing post-randomization information will be displayed by treatment arm, unless otherwise specified.

Listings with individual values will be provided for all data presented in the tables, where noted. The listings will be presented by identifiers, such as treatment group, center, and patient number.

One-sided tests will be used at a significance level equal to 0.025. Two-sided confidence intervals will be computed for a coverage of 0.95.

Time-to-[illegible] Kaplan-Meier method. Subjects who have not had the event of interest at the time of the analysis will be censored at the time of the last follow up. Summary statistics will be provided by treatment arm in terms of the number of events, number of censored observations, median, and 95% confidence interval, and survival probabilities at specific time points (such as 1 year, 2 years, etc.). Survival curves will be plotted by treatment arm and compared with a log-rank test stratified by performance status and tumor location. A stratified Cox regression model will be used to estimate the hazard ratio and its 95% CI, as well as to adjust the comparison for baseline covariates.

Binary outcomes will be described by proportions by treatment arm and compared with a Cochran-Mantel-Haenszel (CMH) test stratified by performance status (0 vs. 1) and tumor location (head vs. body vs. tail of the pancreas). A logistic regression model will be used to adjust the comparison for baseline covariates.

5.1 Milestones and Planned Analyses

5.1.1 [illegible]

The final analysis will be done with 528 patients randomized about 33 months after starting accrual, when at least 335 OS events are available. If the trial reaches statistical significance for the primary endpoint, PFS and other secondary endpoints will be tested sequentially using a type-I error level of 0.025.

5.2 Study Populations

5.2.1 [illegible]

The intent-to-treat (ITT) population consists of all randomized subjects, analyzed according to the treatment arm to which they were allocated to. The ITT population will be used for all analyses of efficacy and baseline characteristics.

5.2.2 [illegible]

The per-protocol (PP) population consists of all randomized subjects who do not have any major protocol violation and received at least one dose of study treatment, analyzed according to the treatment arm to which they were randomized. The major protocol violations include inclusion or exclusion criteria deviations. The PP population will be used as a sensitivity analysis for efficacy endpoints.

5.2.3 [illegible]

The safety population consists of all randomized subjects who received at least one dose of study treatment, analyzed according to the treatment received. The safety population will be used for safety analyses.

5.3 Subgroup Definitions

Subgroup analyses will be carried out with a descriptive intent based on the subgroups described in the table at the end of this section. These analyses will repeat the OS analysis following the conventions described in section 0 using the full set of ITT patients (i.e., the subgroup analysis will take place at the same time as the final analysis). Note:

when the particular subgroup analysis is for either of the stratification factors, only one stratification factor will be included in the `strata` statement.

A forest plot will be constructed to display the treatment effects and 95% confidence limits, number (percentage) of events, and the interaction p-value testing whether the subgroup modifies the treatment effect (e.g., the right-hand side of the `model` statement in `PROC PHREG` might look like `trt01p subgroup trt01p*subgroup` or `trt01p|subgroup`). The horizontal axis labels should clearly interpret the graphical result (e.g., `<-- CPI 613 + mFFX better FFX better -->`); a vertical anchor line should be drawn at 1.

Variable	Subgroups
Performance Status	Grade 0 | Grade 1
Primary Tumor Location	Head of the pancreas | Tail or body of the pancreas
Age	>70 | 55 to 70 | <55
Sex	Female | Male
Region	North America | Europe | Asia or Pacific
Race	White | Black or African American | Asian | Native Hawaiian or Other Pacific Islander or American Indian or Alaska Native | Other
Ethnicity	Hispanic or Latino | Not Hispanic or Latino

5.4 Control Of Type I Error

This study has one primary endpoint of OS. The key secondary efficacy endpoint is PFS.

Testing of these two endpoints will proceed as follows in order to control the overall one-sided type I error of 0.025:

- OS will be tested at a significance level of 0.025. OS will be tested only once at the final analysis.
- PFS will be tested conditionally on the primary endpoint of OS reaching statistical significance, using the significance level of 0.025.
- If OS reaches statistical significance and PFS also reaches statistical significance, then the hierarchical testing procedure will continue to test the rest of the other secondary endpoints in the following order: ORR first, and then DOR, each at a significance level of 0.025.

5.5 Treatment Exposure

The first date of treatment will be defined as the earliest date in which a patient has a record of taking treatment with a nonzero dose; similarly, the latest date of treatment is defined to be the latest date in which a patient has a record of taking treatment with a nonzero dose.

A table will be provided summarizing treatment exposure by treatment arm in the safety population.

5.6 Calculated Variables

- OS = 1 + date of death of any cause or censoring □date of randomization (calculated in days then converted to months)
- PFS = 1 + date of PFS event or censoring □date of randomization (calculated in days then converted to months)
- DOR = 1 + date of first documented PFS event or censoring □date of initial documented response (CR or PR) (calculated in days then converted to months)
- For patients with no death date at the time of analysis, the Last alive date is defined as later of last non-missing eCRF dates
- Baseline is defined as the last non-missing assessment done before start of treatment
- Body Surface Area (m^2) = ([height (cm) x weight (kg)] / 3600)$^{0.5}$
- Months = Days / 30.4375.

5.7 Missing Data

For the primary and key secondary efficacy analyses, imputation will be performed. Imputation rules for partial PFS dates are as follows:

1) If year is missing, no imputation should be done;
2) If only day is missing, then impute the day as the 15th of the month;
3) If both day and month are missing, then impute the day and month as 1st of July;
4) All imputed dates have to be prior to the dates of withdrawal of consent, lost to follow-up, and death.

Imputation rules for partial death dates are as follows:

1) When only date portion is missing and month and year are available, the death date will be imputed to the last day of that month.
2) When date and month portion is missing and year is available, the death date will be imputed to maximum of (30th June of year of death / last known alive date / last follow up date / maximum date from selected SDTM datasets / end of study date).

For determination of treatment emergent adverse events the following rules will be applied for all treated subjects in case of missing start date:

- If end date is before the date of first treatment administration, the start date will remain missing
- If start date is missing and end date is after or on the date of first treatment administration or the end date is missing, the start date will be imputed by the date of first treatment administration
- If start date is incomplete and end date is after or on the date of first treatment administration or the end date is missing, the start date will be imputed as follows: if the day is missing then the start date will be imputed with the first day of the month; if the day and month are missing then the start date will be imputed with minimum of (1 December of the year and the AE end date).

6. Techniques for the Analyses

6.1 Re-Randomization Tests

Patients will be allocated to either the control arm or the experimental arm using stochastic minimization, a dynamic treatment allocation procedure that produces good balance with respect to several prognostic factors between the randomized arms (Buyse, 2000). When such a procedure is used, the preferred test is a re-randomization test (Simon, 1979) based on a large number of simulated trials in which patients are re-allocated randomly to the control arm or the experimental arm using the same stochastic minimization, so as to produce an empirical distribution of the test statistic under the null hypothesis. This empirical distribution is used to assign a statistical significance, via an empirically estimated re-randomization p-value, to the observed asymptotic test statistic calculated using the original randomization allocation. Arbitrary precision on the re-randomization p-value can be obtained by increasing the number of simulated trials.

On this study, re-randomization tests will be used as the primary method of analysis, with additional asymptotic tests used as sensitivity analyses. For each analysis where re-randomization tests are used, a total of 10000 simulations will be conducted, in which the seed passed to the stochastic minimization algorithm is randomly generated. Patients will be re-randomized in the same order they were originally randomized. As the stochastic minimization proceeds within each site, the next patient to be randomized is compared□on the basis of performance grade and tumor location (i.e., the stratification factors)□to the patients previously randomized in that site, and the preferred treatment arm is the one that minimizes the imbalance in strata. The stochastic minimization algorithm is designed so that a patient has an 80% chance of being allocated to the preferred treatment arm, therefore subsequent re-randomizations will introduce new allocations.

This process will generate a total of 10000 treatment allocations, i.e., 10000 variations of `trt01p`. For each of these treatment allocation variants, the pre-specified statistical analysis (e.g., Cochran-Mantel-Haenszel) will be carried out, and the subsequent test statistic estimates will be recorded. The empirical p-value is the frequency, calculated as total number of times out of 10000, that a simulated test statistic is strictly larger (i.e., more extreme) than the asymptotically estimated test statistic on the observed data using the original randomization allocation. For a given analysis, the summary table will display the asymptotic parameter estimate and confidence interval, plus the empirically estimated p-value.

6.2 Primary Objectives

6.2.1 / □

The OS endpoint is the time from the date of randomization until death due to any cause (i.e. date of death or censoring □date of randomization + 1). Any subject 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. All durations will be converted from days to months for reporting purposes. The ITT population will be used.

To assess for OS differences between treatment arms, the Cox PH model will be used, specifying the Efron method for ties. This will be done using `PROC PHREG` in SAS, in which performance status and tumor location will be added in a separate `strata` statement.

The significance of the asymptotically estimated statistics will be determined using a re-randomization procedure. The hazard ratio, p-value and confidence limits from the asymptotic test, plus the re-randomization p-value, will be reported.

The Kaplan-Meier estimator, and their respective confidence limits and p-values, will all be displayed in a table. To confirm proportionality of the hazards, the log-log survival plot should be inspected, using `PROC LIFETEST` and, at a minimum, specifying treatment arm in the `strata` statement (the stratification variables may also be included); these plots will not be included in the set of outputs.

Supplementing this test will be a Kaplan-Meier plot showing time to death from randomization, in months, by treatment arm. Underneath the plot should be a table displaying the number at risk by treatment arm at 0.5-month intervals. The plot should contain an inset with the hazard ratio, the corresponding confidence limits and p-values (both asymptotic and re-randomization test p-values).

Refer to the table below for a description of the primary and sensitivity analyses that will be performed.

No.	Stratified	Re-Randomized	Endpoint Review	Population
1. Primary	Yes	Yes	Not applicable	ITT
1. Sensitivity	Yes	No	Not applicable	ITT
2. Sensitivity	Yes	Yes	Not applicable	PP
3. Sensitivity	Yes	No	Not applicable	PP
4. Sensitivity	No	Yes	Not applicable	ITT
5. Sensitivity	No	No	Not applicable	ITT

The estimand corresponding to this primary endpoint is defined by the following 5 attributes:

TREATMENT

Combination CPI-613 + mFFX compared to standard of care FFX

POPULATION

Population of patients with metastatic adenocarcinoma of the pancreas, defined through inclusion/exclusion criteria to reflect the target population. Analysis will include all randomized patients (ITT population).

PRIMARY VARIABLE

Overall survival, calculated as time from date of randomization to the date of death.

INTERCURRENT EVENTS (ICE) AND STRATEGIES

Treatment discontinuation, treatment changes, use of rescue treatment: treatment policy

Any changes in the treatment or any early discontinuation of treatment will be ignored (ITT principle).

POPULATION-LEVEL SUMMARY
OS hazard ratio (CPI-613 + mFFX versus FFX)

6.3 Secondary Objectives

6.3.1 PFS

Progression-free survival (PFS) is the duration from the date of randomization to the date of progressive disease (assessed by an independent, blinded, central review) or death from any cause (date of PFS event or censoring – date of randomization + 1).

If the patient has no evaluable scans or does not have baseline data they will be censored at Day 1. Patients who are lost to follow- up, withdraw from follow-up or alive and progression free will be censored at the date of last disease assessment.

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 assessment. However, if the patient progresses or dies after two or more missed scans (defined as a gap of 126 days which is (8 weeks + 1 week) * 2), the patient will be censored at the time of the latest evaluable assessment (the scan with documented non-progression). In addition, subjects who had PFS events after initiation of new anti-cancer therapy will be censored at the last radiological assessment with documented non-progression. All durations will be converted from days to months for reporting purposes. The ITT population will be used. A sensitivity analysis will be performed without censoring for the missed visits and starting new therapy.

To assess for PFS differences between treatment arms, the Cox Proportional Hazards (PH) model will be used, specifying the Efron method for ties. This will be done using `PROC PHREG` in SAS, in which performance status and tumor location will be added in a separate `strata` statement.

The significance of the asymptotically estimated statistics will be determined using a re-randomization procedure. The hazard ratio, p-value and confidence limits from the asymptotic test, plus the re-randomization p-value, will be reported.

In addition, the Kaplan-Meier estimator, and their respective confidence limits and p-values, will all be displayed in a table. To confirm proportionality of the hazards, the log-log survival plot should be inspected, using `PROC LIFETEST` and, at a minimum, specifying treatment arm in the `strata` statement (the stratification variables may also be included); these plots will not be included in the set of outputs.

Supplementing this test will be a Kaplan-Meier plot showing time to progression or death from randomization, in months, by treatment arm. Underneath the plot should be a table displaying the number at risk by treatment arm at 0.5-month intervals. The plot should contain an inset with the hazard ratio, the corresponding confidence limits and p-values (both asymptotic and re-randomization test p-values).

Refer to the table below for a description of the primary and sensitivity analyses that will be performed.

No.	Stratified	Re-Randomized	Endpoint Review	Population	Additional Censoring
1. Primary	Yes	Yes	Central	ITT	2 missed visits: Y; New therapy: Y
1. Sensitivity	Yes	No	Central	ITT	2 missed visits: Y; New therapy: Y

2. Sensitivity	Yes	No	Central	ITT	2 missed visits: N; New therapy: Y
3. Sensitivity	Yes	No	Central	PP	2 missed visits: Y; New therapy: Y
4. Sensitivity	Yes	No	Investigator	ITT	2 missed visits: Y; New therapy: Y
5. Sensitivity	Yes	No	Investigator	PP	2 missed visits: Y; New therapy: Y

The estimand corresponding to this secondary endpoint is defined by the following 5 attributes:

TREATMENT

Combination CPI-613 + mFFX compared to standard of care FFX

POPULATION

Population of patients with metastatic adenocarcinoma of the pancreas, defined through inclusion/exclusion criteria to reflect the target population. Analysis will include all randomized patients (ITT population).

VARIABLE

Progression-free survival, calculated as time from date of randomization to the date of progressive disease (assessed by an independent, blinded, central review) or death from any cause.

INTERCURRENT EVENTS (ICE) AND STRATEGIES

Death occurring before progression is observed/documented: composite strategy

Death will be considered as an event as per PFS definition.

Events leading to 2 or more consecutive missed radiographic scans before progression or death is observed: while-on-treatment strategy

[illegible] radiological assessments before observed progression will be censored on the last radiological scan with documented non-progression.

Covid-19 pandemic related intercurrent events (other than those falling in the above categories): treatment policy

Treatment effect will be evaluated regardless of impact of the pandemic situation.

Treatment discontinuation: treatment policy

Any early discontinuation of treatment will be ignored (ITT principle).

Initiation of new anti-cancer therapy: hypothetical strategy

Subjects who had PFS events after initiation of new anti-cancer therapy will be censored at the last radiological assessment with documented non-progression.

POPULATION-LEVEL SUMMARY

PFS hazard ratio (CPI-613 + mFFX versus FFX)

6.3.1 ORR

ORR is defined as the complete response (CR) rate + partial response (PR) rate. A patient's best response after the start of study treatment will be used for this determination, as assessed by independent, blinded, central review as per RECIST guideline version 1.1 (Eisenhauer, 2009).

In order to define the best overall response, the following rules will be applied:

- CR and PR need to be confirmed no less than 4 weeks apart
- If SD or NON-CR/NON-PD is before 6 weeks after start of study treatment the SD, NON-CR/NON-PD is not taken into account and put to NE in the determination of best overall response.
- Best overall response is defined as the best response after start of study treatment in the following order of assessments: CR, PR (both need to be confirmed), SD or NON-CR/NON-PD (if not too early), PD, NE. For PD there is no confirmation needed.

Among patients in the ITT population, the overall frequency of responders, i.e., patients whose best response after the start of study treatment is CR or PR, will be compared between treatment arms using the Cochran-Mantel-Haenszel (CMH) test, stratified by performance status grade and tumor location.

Subjects who did not receive any study treatment, or who do not have a valid post-treatment efficacy assessment will be classified as not evaluable (NE) or non-responders for response classifications. These subjects will be included in the denominator of the ITT analysis for calculation of response rates.

In SAS, this will be performed with `PROC FREQ` specifying the `cmh` option in the `table` statement. Performance status grade and tumor location, both assessed at baseline, will be included as stratification factors (i.e., controlling for these variables in the `table` statement); if necessary, a single four-level categorical variable will be derived whose values represent the four distinct patterns of performance status and tumor location.

The significance of the asymptotically estimated CMH statistic will be determined using a re-randomization procedure. The Odds Ratio (OR and confidence limits from the asymptotic test, will be reported.

The Breslow-Day test should be inspected to confirm that there is no evidence of interaction between the stratification factors and treatment. Evidence of heterogeneity in one or both of the strata does not invalidate a significant treatment effect; in such a case, the finding should be reported in a separate table in which the OR and confidence limits of the treatment effect in each level of the strata should be presented.

Refer to the table below for a description of the primary and sensitivity analyses that will be performed. These will be reported only during the final analysis. Breslow-Day statistics do not need to be reported.

No.	Stratified	Re-Randomized	Endpoint Review	Population
1. Primary	Yes	Yes	Central	ITT
1. Sensitivity	Yes	No	Central	ITT
2. Sensitivity	Yes	Yes	Central	PP
3. Sensitivity	No	No	Central	PP

6.3.2 DOR

Duration of response is defined as the time from the date of first documented response until date of documented progression or death in the absence of disease progression (i.e. date of PFS event or censoring – date of first response + 1). The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the first date of the dates contributing towards the first visit response of PR or CR. If a patient does not progress following a response, then their DoR will use the PFS censoring time. DoR will not be defined for those patients who do not have documented response.

To assess for DOR differences between treatment arms, the Cox PH model will be used, specifying the Efron method for ties. This will be done using `PROC PHREG` in SAS, in which performance status and tumor location will be added in a separate `strata` statement.

The significance of the asymptotically estimated statistics will be determined using a re-randomization procedure. The hazard ratio, and confidence limits from the asymptotic test, will be reported.

The Kaplan-Meier estimator, and their respective confidence limits, will all be displayed in a table. To confirm proportionality of the hazards, the log-log survival plot should be inspected, using `PROC LIFETEST` and, at a minimum, specifying treatment arm in the `strata` statement (the stratification variables may also be included); these plots will not be included in the set of outputs.

Supplementing this test will be a Kaplan-Meier plot showing DOR duration, in months, by treatment arm. Underneath the plot should be a table displaying the number at risk by treatment arm at 0.5-month intervals. The plot should contain an inset with the hazard ratio, the corresponding confidence limits.

A log rank test will be performed as a sensitivity analysis.

6.3.3 Safety Analyses

The assessment of safety will be based mainly on the frequency of adverse events based on the Cancer Therapy Evaluation Program (CTEP) Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE 4.0) grade. The CTEP Active Version of the CTCAE is identified and located on the CTEP website. If the severity or intensity is not specifically graded by the guidance document from CTEP, the site investigators have been instructed in the protocol to revert to the general definitions of grade 1 through grade 5 shown in the table below. Additional information about adverse event or unanticipated problem reporting can be found in the protocol, section 8.

Severity	Description
Grade 1	Mild; events require minimal or no treatment and do not interfere with the participant's daily activities.
Grade 2	Moderate; events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
Grade 3	Severe; events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment.
Grade 4	Life threatening or disabling; patient at risk of death at the time of the event.

Grade 5	Death related to AE.

The following tabular summaries of adverse events will be provided using the safety population:

- All AEs by SOC and CTCAE term, by treatment arm and overall
- Patients with at least one AE by SOC and CTCAE term, by treatment arm and overall
- Patients with at least one AE by relatedness, by treatment arm and overall
- Patients with at least one AE by severity, by treatment arm and overall
- All serious AEs (SAEs) by SOC and CTCAE term, by treatment arm and overall
- Patients with at least one SAE by SOC and CTCAE term, by treatment arm and overall
- Patients with at least one AE that led to a change in study medication (e.g., dose modification, interruption, or permanent discontinuation), by treatment arm and overall
- Patients with at least one AE requiring a change in concomitant therapy (e.g., addition, interruption, discontinuation, or change in a concomitant medication, therapy, or treatment), by treatment arm and overall.

Adverse events that are still ongoing at the time of data cut-off should not be included in any of the tables described above. Instead, a separate table should be presented containing all on-going AEs by SOC and CTCAE term, by treatment arm and overall.

All SAEs which are possibly related or unexpected are required to be reported to sponsor or sponsor designated vendor using a serious adverse event report form. The SAE [illegible] β- data, or other important documents.

The number of death cases and cause of death will be summarized separately using the ITT population, by treatment arm and overall. A listing will be provided containing patient ID, site ID, age, sex, treatment arm (if applicable), relatedness to study drug (if applicable), randomization date, treatment start date (if applicable), date of death, and site-reported narrative for all patients who die during the study.

6.3.4 z,

These analyses fall outside of the scope of this SAP, please refer to the separate PK Analysis Plan managed by the PK analysis vendor.

6.3.5 zβ/

These analyses fall outside of the scope of this SAP, please refer to the separate PRO Analysis Plan managed by the PRO analysis vendor.

6.4 Exploratory Objectives

6.4.1 A[illegible]F [illegible]

These analyses fall outside of the scope of this SAP.

6.4.2 z, iz)

These analyses fall outside of the scope of this SAP.

6.5 Additional Analyses

For a given cycle, a table will be provided displaying ECG data summarized by treatment arm, day, and timepoint using the safety population, if substantial data exists for Full or Sparse ECG. There will be a table for each cycle.

7. Study Patients

7.1 Patient Disposition

Enrollment by country and center will be summarized for all randomized patients and also by treatment arm using the ITT population. The number of patients in each population will be tabulated by treatment arm and overall. Number screened and screen failed will be tabulated. Reason for screen failure will also be tabulated and listed.

The frequency of patients treated, of patients who discontinued the study treatment, and of patients who terminated the study will be displayed using the ITT population. The primary reason for discontinuation of the study treatment and terminating the study will [redacted] frequency of patients on treatment, who completed treatment, and their reason for discontinuation of treatment will be summarized by cycle.

7.2 Protocol Deviations

Protocol deviations classified as important vs non-important will be determined before database lock. The protocol deviations will be categorized by type and summarized by treatment arm, using the ITT population, for important and non-important protocol deviations separately. A listing of all protocol deviations will be provided by treatment arm.

7.3 Inclusion and Exclusion Criteria

Randomized patients who violate inclusion or exclusion entry criteria (see section 5 of the study protocol) and the specific criterion violated will be tabulated by treatment arm. Patients who are enrolled but not randomized due to a violation of the inclusion or exclusion criteria will be listed.

8. Demographic and Baseline Characteristics

All demographic and baseline disease characteristics will be summarized and listed by treatment arm using the ITT population. Categorical data will be summarized by frequency counts and percentages; the number and percentage of patients with missing data will be provided. Continuous data will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum, and maximum). BMI will be calculated as weight (in kg)/height^2 (in m); both variables will use the baseline measurements.

9. Prior and Concomitant Medications and Medical History

All prior and concomitant prescription and non-prescription medications taken during study participation will be recorded and classified using the WHO Drug Dictionary version 2018. All tables will display medications by class and specific name by treatment arm and, when applicable, by cycle. Separate tables will be provided for prior medications, defined as any medication that was discontinued on or before the date of randomization; and, for concomitant medications. Tables or listings of specific classes of medications, either prior or concomitant, are available upon request by the study investigators; in such cases, we encourage the study investigators to provide us with a specific list of drugs.

Prohibited medications that were discontinued prior to enrollment in the study will be tabulated.

Medical history and concomitant medications will be classified according to the terminology of CTCAE version 4.0 and coded using MedDRA version 21.0 or later. Medical history, defined as any condition that was resolved on or before the date of randomization, will be tabulated by system organ class (SOC) and CTCAE term and by treatment arm. Concomitant medications will be tabulated by system organ class and CTCAE term and by treatment arm and cycle. All tables will use the safety population.

10. Laboratory Data

The following laboratory parameters will be tabulated by treatment arm and cycle in the safety population:

- Glucose
- Creatinine
- Total protein
- Albumin
- Blood urea nitrogen
- AST/serum glutamic-oxaloacetic transaminase (SGOT)
- ALT/serum glutamic-pyruvic transaminase (SGPT)
- Alkaline phosphatase (ALP)
- Total bilirubin
- Na^+
- K^+
- Cl^-
- Mg
- Ca^{+2}
- PO_4
- CO_2
- Hemoglobin A1c (HbA1c) (baseline measurement only)
- CBC
- Prothrombin time
- Activated partial thromboplastin time
- CA19-9
- □HCG (pregnancy test)
- Cardiac marker (Troponin 1).

11. Questionnaires

11.1 Eastern Cooperative Oncology Group (ECOG) Performance Status Grade

11.1.1 [illegible]

ECOG Performance Status Grade of 0 or 1 is an inclusion criterion for this study and is also a stratification factor during randomization. Performance Status will be assessed during the pre-study screening visit, on day 1 of cycle 1 and any subsequent cycles, and end of treatment visit.

11.1.2 g[illegible]([illegible]

The performance status is a numeric scale, from 0 to 5, assigned b[illegible]

living abilities of the patient. The scale and criteria are provided in the table below (Oken, 1982).

ECOG Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	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.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

11.1.3 Reporting Plan

Performance status will be tabulated as a categorical variable along with the other stratification factor and the demographic and baseline characteristics.

11.2 Patient-Reported Outcomes (PRO)

11.2.1 Schedule

Patient-Reported Outcomes (PRO) using the NCCN-FACT Hepatobiliary Symptom Index (FHSI-18) will be administered on the baseline (screening or pre-dose cycle 1 day 1) visit, cycle 1 day 1, and on day 1 of every even numbered cycle, and the end of treatment visit.

11.2.2 Assessment Components

The NCCN-FACT FHSI-18 PRO questionnaire is available from the following website: https://www.facit.org/FACITOrg/Questionnaires. Each question is assessed on an ordinal scale from 0 to 4, using the following correspondence: 0 = "Not at all" | 1 = "A little bit" | 2 = "Somewhat" | 3 = "Quite a bit" | 4 = "Very much". The following prompt precedes administration of the questionnaire: "Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days**."

The components of the questionnaire are shown in the table below along with the response and specific objective that will be measured.

Item	Responses	Objective
I have a lack of energy	0, 1, 2, 3, 4	Secondary
I have pain	0, 1, 2, 3, 4	Secondary
I am losing weight	0, 1, 2, 3, 4	Secondary
I feel fatigued	0, 1, 2, 3, 4	Secondary

I have pain in my back	0, 1, 2, 3, 4	Secondary
I am bothered by jaundice or yellow color to my skin	0, 1, 2, 3, 4	Secondary
I feel ill	0, 1, 2, 3, 4	Secondary
I have discomfort or pain in my stomach area	0, 1, 2, 3, 4	Secondary
I have nausea	0, 1, 2, 3, 4	Secondary
Because of my physical condition, I have trouble meeting the needs of my family	0, 1, 2, 3, 4	Secondary
I have a good appetite	0, 1, 2, 3, 4	Secondary
I am sleeping well	0, 1, 2, 3, 4	Secondary
I worry that my condition will get worse	0, 1, 2, 3, 4	Secondary
I feel sad	0, 1, 2, 3, 4	Secondary
I am bothered by side effects of treatment	0, 1, 2, 3, 4	Secondary
I am able to do my usual activities	0, 1, 2, 3, 4	Secondary
I am able to enjoy life	0, 1, 2, 3, 4	Secondary
I am content with the quality of my life right now	0, 1, 2, 3, 4	Secondary

11.2.3 β□□□□□□□z□□□

Summary statistics of the scores and changes from baseline for each item plus the sum of all items, and change of sum of all items from pre-screen visit score, will be displayed by cycle and by treatment arm using the ITT population. The inferential comparison between treatment arms will be done using a repeated measures mixed model (see section 6.3.5).

Efforts to avoid missing data will include data collection to be done during follow-up clinic visits only or by telephone if the patient is not available for a clinical visit. No additional visits will be required to complete the questionnaire. Additionally, only the validated, user-friendly version of the questionnaire will be used for data collection. Patients will also be allowed to complete the questionnaire at home should they need additional time and results mailed.

12. Changes from the Protocol

The current version of the protocol is 9.0, which has an effective date of June 10, 2021. There are no changes to the protocol in this analysis plan to report.

13. References

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Appendix I. Schedule of Events

	Experimental Arm 1: CPI-613 + mFFX							
		Cycle 1 and Subsequent Cycles					Follow up 30 days after last dose	Follow-Up Every 2 Months Until Death
Assessments	Pre-Study Screen	Day 1	Day 2	Day 3	Day 4	Days 5-14		
Informed consent	x							
Medical history	x							
Pregnancy test for women of child-bearing potential[7]	x	x					x	
Hemoglobin A1c (HbA1c)	x							
CPI-613 administration (dosing)		x		x				
mFOLFIRINOX (mFFX)		x	x	x				
AE and con med assessment			AEs and con meds will be assessed at each patient visit					
Myeloid growth factor (±24 hours)*					x			
Evaluation of symptoms and vital signs[7]	x	x						
ECOG performance status and survival[6]	x	x						
Clinical chemistry, hematology and coagulation	x	x				x (day 7 or 8)		
Triphase contrast CT of the chest, abdomen and pelvis (or MRI if needed)	x							
Blood sampling for biomarker[1]	x							
CA19-9	x	X[7]						
Blood sampling for Full PK Analysis[2]		x	x	x	x	X		

	Experimental Arm 1: CPI-613 + mFFX							
Assessments	Pre-Study Screen	Cycle 1 and Subsequent Cycles					Follow up 30 days after last dose	Follow-Up Every 2 Months Until Death
		Day 1	Day 2	Day 3	Day 4	Days 5-14		
Blood sampling for Sparse PK Analysis[3]		x		x				
Cardiac Marker (Troponin I)[8]		x		x				
Full ECG[4]	x	x		x				
Sparse ECG[5]	x	x		x				
Phone contact								x
NCCN-FACT FHSI-18 Questionnaire[6]	x	x						

1 Prior to treatment initiation (within 4 weeks prior to 1st dose) and prior to each restaging scan.
2 see Full PK sampling schedule in Protocol Section 7.1.1, Table 12
3 see Sparse PK sampling schedule in Protocol Section 7.1.1, Table 13
4 see Full ECG measurement schedule in Protocol Section 7.1.1, Table 14
5 see Sparse ECG measurement schedule in Protocol Section 7.1.1, Table 15
6 at baseline and day 1 of every even numbered cycle
7 Vital signs include heart rate
8 see Cardiac Marker (Troponin I) schedule under Protocol Section 7

**Myeloid growth factor can be given at Day 4 or any day at the discretion of the treating physician per ASCO and institutional guidelines*

Control Arm 2: FFX								
Assessments	Pre-Study Screen	Cycle 1 and Subsequent Cycles					Follow up 30 days after last dose	Follow-Up Every 2 Months Until Death
		Day 1	Day 2	Day 3	Day 4	Days 5-14		
Informed consent	x							
Medical history	x							
Pregnancy test for women of child-bearing potential[4]	x	x					x	
Hemoglobin A1c (HbA1c)	x							
FOLFIRINOX (FFX)		x	x	x				
AE and con med assessment			AEs and con meds will be assessed at each patient visit					
Myeloid growth factor (±24 hours)*					x			
Evaluation of symptoms and vital signs[6]	x	x						
ECOG performance status and survival[5]	x	x						
Clinical chemistry, hematology and coagulation	x	x				x (day 7 or 8)		
Triphase contrast CT of the chest, abdomen and pelvis (or MRI if needed)[1]	x							
Blood sampling for biomarker[2]	x							
Cardiac Marker (Troponin I)[4]		x		x				
CA19-9	x	x						
Sparse ECG[3]	x	x		x				
Phone contact								x
NCCN-FACT FHSI-18 Questionnaire[5]	x	x						

[1]*Restaging scans will be performed every 8 weeks ±7 days*
[2]*Prior to treatment initiation (within 4 weeks prior to 1st dose) and prior to each restaging scan*
[3]*See Sparse ECG measurement schedule in Protocol Section 7.1.1*
[4] *see Cardiac Marker (Troponin I) schedule under Protocol Section 7*
[5] *At baseline (screening or pre-dose Cycle 1 Day 1) and day 1 of every even numbered cycle*
[6] *Vital signs include heart rate*

**Myeloid growth factor can be given at Day 4 or any day at the discretion of the treating physician per ASCO guidelines*

Appendix II. NCCN-FACT FHSI-18 (Version 2)

Below is a list of statements that other people with your illness have said are important.
Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

			Not at all	A little bit	Some-what	Quite a bit	Very much
DRSP	GP1	I have a lack of energy	0	1	2	3	4
	GP4	I have pain	0	1	2	3	4
	C2	I am losing weight	0	1	2	3	4
	HI7	I feel fatigued	0	1	2	3	4
	CNS7	I have pain in my back	0	1	2	3	4
	Hep2	I am bothered by jaundice or yellow color to my skin	0	1	2	3	4
	GP6	I feel ill	0	1	2	3	4
	Hep8	I have discomfort or pain in my stomach area	0	1	2	3	4
	GP2	I have nausea	0	1	2	3	4
	GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
	C6	I have a good appetite	0	1	2	3	4
	GF5	I am sleeping well	0	1	2	3	4
DRSE	GE6	I worry that my condition will get worse	0	1	2	3	4
	GE1	I feel sad	0	1	2	3	4
TSE	GP5	I am bothered by side effects of treatment	0	1	2	3	4
	An7	I am able to do my usual activities	0	1	2	3	4
FWB	GF3	I am able to enjoy life	0	1	2	3	4
	GF7	I am content with the quality of my life right now	0	1	2	3	4