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

RAFAEL
Pharmaceuticals, Inc.

"To Save A Life Is To Save A Universe"

Protocol Number: PANC003

Investigational Product: CPI-613® (devimistat)

IND number: 074530

EudraCT Number: 2018-001587-32

Principal Investigator: Philip A. Philip (MD, PhD, FRCP)

Version Number: 9.00

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Sponsor: Rafael Pharmaceuticals Inc.

1 Duncan Drive

Cranbury - 08512

New Jersey

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AE	Adverse Events
ALT (SGPT)	Alanine Aminotransferase
ALCOA-C	Attributable, Legible, Contemporaneous, Original, Accurate, Complete
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
AST (=SGOT)	Aspartate Aminotransferase
ATP	Adenosine Triphosphate
AUC	Area Under the plasma concentration versus time Curve
AUC_{0-t}	Area Under the plasma concentration versus time Curve from time 0 to final time measured
AUC_{inf}	Area Under the plasma concentration versus time Curve from Time 0 to Infinity
BSA	Body Surface Area
CA19-9	Carbohydrate Antigen 19-9
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CKBB	Creatine Kinase, Brain Type
CKMB	Creatine Kinase, Muscle and Brain
CKMM	Creatine Kinase, Muscle
CL	Clearance
C_{min}	The Trough Plasma Concentration of a Drug Before Administration
C_{max}	The Peak Plasma Concentration of a Drug After Administration
CMH	Cochran-Mantel-Haenszel
CMP	Clinical Monitoring Plan
CNS	Central Nervous System
CPK	Creatine Phosphokinase
CR	Complete Response
CT	Computed Tomographic

CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
D5W	Dextrose 5% in Water
DCC	Data Coordinating Center
DDI	Drug-Drug Interaction
DEHP	Diethylhexyl Phthalate
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DOR	Duration of Response
DPD	Dihydropyrimidine Dehydrogenase
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Forms
ESMO	European Society for Medical Oncology
FA	Folinic Acid
FBS	Fetal Bovine Serum
FDA	Food and Drug Administration
FFX	FOLFIRINOX
5-FU	5-Fluorouracil
GCP	Good Clinical Practice
GDP	Good Documentation Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practices
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
IC50	The Half Maximal Inhibitory Concentration
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	The International Committee of Medical Journal Editors

IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-To-Treat
IUD	Intrauterine Device
IV	Intravenous
IxRS	Interactive Voice/Web Response Systems
K2EDTA	k2- Ethylenediaminetetraacetic Acid
KGDH	Alpha-Ketoglutarate Dehydrogenase
LPLV	Last patient last visit
MedDRA	Medical Dictionary for Regulatory Activities
mFFX	Modified FOLFIRINOX
MOA	Mechanism of Action
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerable Dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NYHA	New York Heart Association
OHRP	Office for Human Research Protections
ORIS	Office of Regulatory Information Systems
ORR	Objective Response Rate
OS	Overall Survival
PD	Pharmacodynamics
PD	Progressive Disease
PDH	Pyruvate Dehydrogenase
PFS	Progression-Free Survival
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per Protocol
PR	Partial Response
PVC	Polyvinyl Chloride
QC	Quality Control

QTc	Corrected QT Interval
RECIST	The Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOP	Standard Operating Procedures
STRC	Safety and Toxicity Review Committee
$T_{1/2}$	Elimination Half-Life
TCA	Tricarboxylic Acid
TEA	Triethanolamine
T_{max}	Time to Reach the Maximum Plasma Concentration
ULN	Upper Limit of Normal
UP	Unanticipated Problems
US	United States
USA	United States of America
USP	United States Pharmacopeia
V_d	Volume of Distribution
WBC	White Blood Cells

Sponsor Signatories

I have read the protocol in its entirety and agree to conduct the study accordingly in compliance with Good Clinical Practice (GCP) as required by:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)
- ICH E6

I confirm that I have read this protocol. I will comply with the protocol and the principles of Good Clinical Practice (GCP), as described in the United States Code of Federal Regulation (CFR) 21 Parts 11, 50, 54, 56, and 312 and the appropriate International Conference on Harmonization guidance documents.

Protocol: PANC003

Version: 9.0

June 10, 2021

Protocol Title: A Phase III Multi-Center 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

_____. _____

Investigator Signature Date

_____

Print Name and Title

Site# _____

Site Name _____

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
Summary:	**Phase:** III **Study Design:** prospective, open label, multicenter, randomized trial **Sample Size: Approximately 500** **Study Groups:** ▪ **Arm 1:** CPI-613® (devimistat) + modified FOLFIRINOX (mFFX) * ▪ **Arm 2:** FOLFIRINOX (FFX) ** **Schedule of Interventions:** Patients will be dosed with 500 mg/m^2 of CPI-613® (devimistat) on day 1 and 3 of a 14-day cycle- (+/- 24 hours). **Schedule for Key Specimen or Data Collection:** ▪ **Radiology (cross-sectional):** every 8 weeks (+/-7days) ▪ **Survival:** every 2 months until death (after completion of therapy) ▪ **Safety:** every 2 weeks (on treatment) ▪ **ECG:** Full ECG and Sparse ECG (see schedules in Section 7.1.1) ▪ **PK:** Full PK and Sparse PK (see schedules in Section 7.1.1) ▪ **Patient-Reported Outcomes (PROs):** every 4 weeks (i.e. even number of cycles)

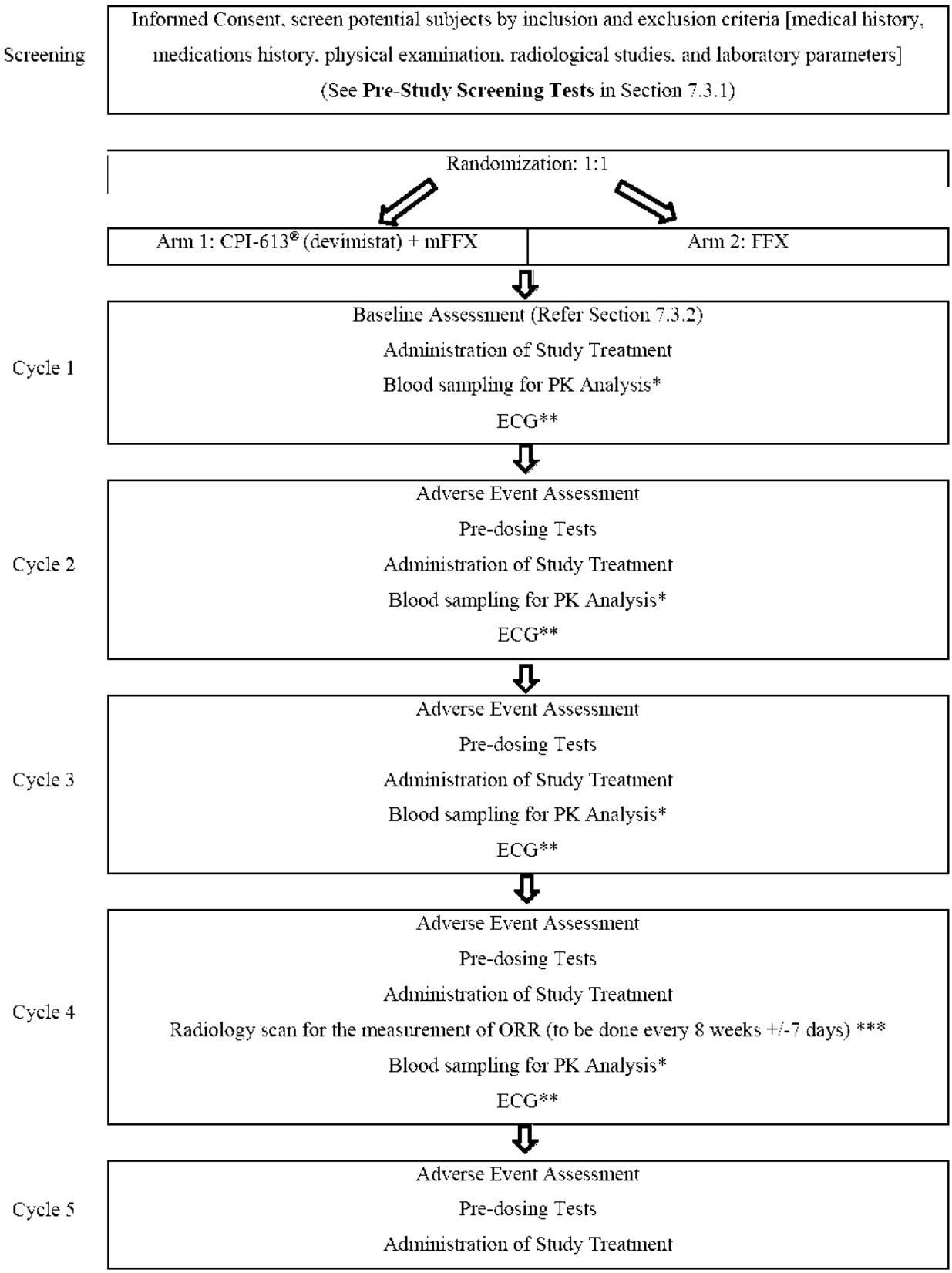
	Analyses to be Performed: ▪ Measurement of tumor response as per RECIST guideline version 1.1 ▪ Measurement of ECG ▪ PK of the parent drug (CPI-613® (devimistat)) and metabolites (CPI-2850 and CPI-1810) ▪ Change in PROs from baseline and comparison between the two study arms

Objectives:	**Primary Objective:** ▪ To evaluate Overall Survival (OS) of CPI-613® (devimistat) plus mFFX versus FFX. **Secondary Objectives:** ▪ To evaluate Progression-Free Survival (PFS) of CPI-613® (devimistat) plus mFFX versus FFX ▪ To evaluate Objective Response Rate (ORR) [Complete Response (CR) + Partial Response (PR)] of CPI-613® (devimistat) plus mFFX versus FFX (control arm) by independent, blinded, central review by RECIST guideline version 1.1 ▪ To evaluate Duration of Response (DOR) of CPI-613® (devimistat) plus mFFX versus FFX ▪ To evaluate safety of CPI-613® (devimistat) plus mFFX versus FFX ▪ To assess Pharmacokinetics (PK) of CPI-613® (devimistat) ▪ To evaluate Patient-Reported Outcomes (PROs) by FACT Hepatobiliary Symptom Index (FHSI-18) for CPI-613® (devimistat) plus mFFX versus FFX **Exploratory Objectives:** ▪ To explore biomarkers using diagnostic biopsies and blood/plasma samples ▪ To assess PK/PD of dose/exposure-response for CPI-613® (devimistat) on efficacy (e.g. PFS), safety (e.g. QTc) and exploratory biomarkers
Endpoints:	▪ **Primary Endpoints:** OS ▪ **Secondary Endpoints:** PFS, ORR (CR+PR), DOR, Safety, PK, PROs ▪ **Exploratory Endpoints:** Biomarkers, PK/PD

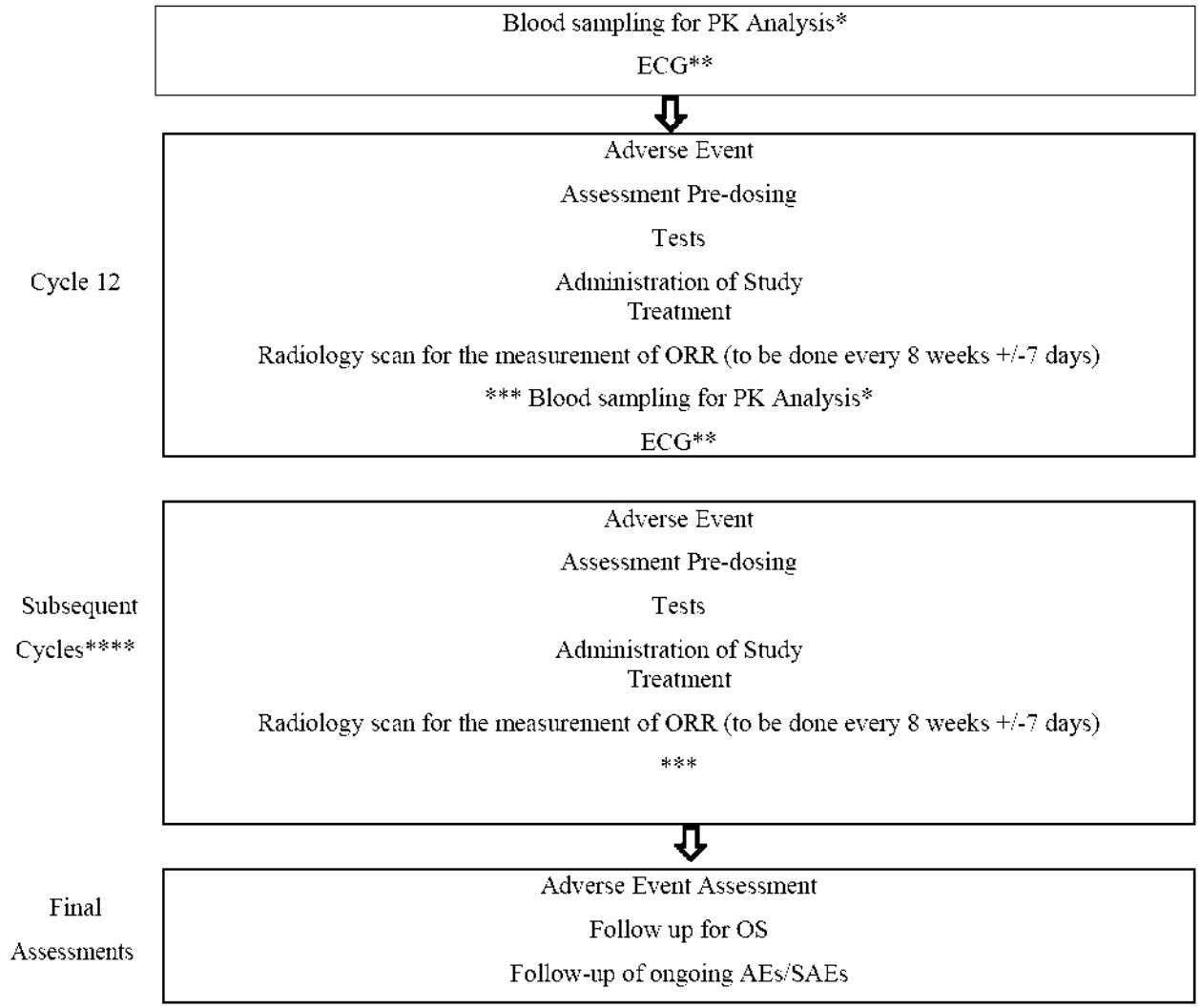
Population:	▪ **Sample Size:** Approximately 500 patients ▪ **Gender:** Both male and female ▪ **Age:** 18 – 75-year-old ▪ **Demographic Group:** All ▪ **General Health Status:** ECOG performance status 0 – 1 ▪ **Geographic Location:** North America, Europe and Asia
Phase:	III
Number of Sites enrolling	~ 78 sites
Description of Study Agent:	▪ **Study Agent:** CPI-613® (devimistat) ▪ **Mechanism of Action:** Selectively targets altered energy metabolism in cancer cells by inhibiting the enzymes pyruvate dehydrogenase (PDH) and alpha-ketoglutarate dehydrogenase (KGDH) ▪ **Dose:** 500 mg/m^2 ▪ **Route of Administration:** Intravenous (IV) infusion at the rate of 4 mL/min on Day 1 and Day 3 of each 2-week (14-day) cycle (+/- 24 hours)
Study Duration (estimated):	**Final Analysis (all endpoints):** 33 months

**mFFX: oxaliplatin (reduced dose), folinic acid, irinotecan (reduced dose), bolus fluorouracil, infusional fluorouracil*

***FFX: oxaliplatin, folinic acid, irinotecan, bolus fluorouracil, infusional fluorouracil*



	Blood sampling for PK Analysis* ECG**
Cycle 6	Adverse Event Assessment Pre-dosing Tests Administration of Study Treatment Blood sampling for PK Analysis* ECG**
Cycle 7	Adverse Event Assessment Pre-dosing Tests Administration of Study Treatment Blood sampling for PK Analysis* ECG**
Cycle 8	Adverse Event Assessment Pre-dosing Tests Administration of Study Treatment Radiology scan for the measurement of ORR (to be done every 8 weeks +/-7 days) *** Blood sampling for PK Analysis* ECG**
Cycle 9	Adverse Event Assessment Pre-dosing Tests Administration of Study Treatment Blood sampling for PK Analysis* ECG**
Cycle 10	Adverse Event Assessment Pre-dosing Tests Administration of Study Treatment Blood sampling for PK Analysis* ECG**
Cycle 11	Adverse Event Assessment Pre-dosing Tests Administration of Study Treatment



**In 250 patients treated with CPI-613® (devimistat) (15 patients for full PK analysis and 235 patients for sparse PK blood sampling in Arm 1: CPI-613® (devimistat) + mFFX)*

***In 250 patients treated with CPI-613® (devimistat) (Up to 24 patients for full ECG analysis and 225 patients for sparse ECG sampling in Arm 1: CPI-613® (devimistat) + mFFX). All 250 patients treated in Arm 2, with control FFX patients, will have sparse ECG sampling to monitor the risk of Cardiotoxicity.*

****Please note that the imaging studies must be performed every 8 weeks +/- 7 days irrespective of the timing in relation of a treatment cycle to ensure consistency across the two study arms*

***** Cycles will continue until one of the criteria for removal from study are reached (see Section 5.3.1)*

Amendment 1

There were no major changes in this version (version 4) of the protocol from version 3. The purpose of the small changes was to: modify the FDA approved protocol to make it operational for the study sites to use. Sections previously identified as "to be determined" have been updated with study specific information.

	Changes to note	Protocol page
1	Updated the protocol to include Covance Inc. were the sponsor has delegated their study authority to Covance Inc.	19, 96, 99, 101, 102, 116, 119
2	Section 1 was updated with a Medical Monitor name and a drug safety contact phone number	19
3	Section 3: Interim Analysis will also capture investigator response	49
4	Section 5.2: Entry criteria 5.2.10 was removed as redundant exclusion criteria for pregnant or women of childbearing potential. The entry criteria information is identified in the study's inclusion criteria 5.1.7	54
5	Section 6: STUDY DRUGS, DRUG ADMINISTRATION, DOSE MODIFICATIONS: Study wording was modified and updated throughout section	57-69
6	Section 7.1.1: Clarified Arm 1's Sparse PK analysis will be limited to one sample collection per patient	71
7	Section 7.3.5: Schedule of Events Tables was updated to make it consistent with scheduled events in the protocol's text	92 & 93
8	Section 8.4.2: SAE reporting was modified to identify Covance Inc.'s contact information	101
9	Section 9: Monitor Plan section was removed. Supporting study document will be made available in the study's TMF for this sponsor lead study	103
10	Section 12.1: CRFs will be in EDC format and training will be provided by the sponsor or a designee	117
11	Section 13.1: steering committee will include a sponsor representative	119
12	Appendix's were removed. These supporting source documents will be made available to study sites	123+

Detailed changes can be seen in the Clinical Trial Change Document (compares PANC003 version #3 to version#4).

Global Amendment 2

Changes in this version 5 were prompted from correspondences with study sites and regulatory agencies. The purpose of the Global Amendment 2 (Version 5) is to add further clarification to the protocol. In addition, the statistical sections were clarified.

Changes to note		Protocol page
1	Schematic of study design: added additional cycles to schematic to clearly illustrate the study's treatment schedule.	*19*
2	Section 2.1.4.1 – Addition of tox language	*31-41*
3	Sections 3 and 4.2.1 – the study's primary objective and endpoints PFS and ORR will be assessed by independent, blinded, central review	*66 & 68*
4	Section 3: Updated Interim Futility Analysis (ORR); Interim Analysis (PFS); Final Analysis (ORR & PFS)	*66*
5	Biopsy tissue slides will be collected from pre-study diagnostic biopsies	*93*
6	Section 5.1.10 - Bilirubin ≤1.5x UNL; bilirubin ≤ 2.5x ULN for subjects with Gilbert's syndrome	*72*
7	Section 5.2.6 – add exclusion criteria for patients with hypersensitivity to CPI-613® (devimistat), FFX treatment or any of their excipients.	*72*
8	Section 5.2.10 – NAP which stood for not applicable, was removed to reduce confusion	*73*
9	Section 5.2.14 and 8.1.4 - Addition of pregnant partner language	*73 & 121*
10	New section (Section 5.4) was added to define End of Trial	*77*
11	Section 6.1.1 – Added "The study drug is accepted by QA"	*78*
12	Section 7.1.1. - Full PK Analysis Sampling and Full ECG Analysis changes. The Day 1 and Day 3 8-hr timepoints post infusion time has been changed to 6-hr post infusion for easier patient assessments and better compliance.	*94 & 99*
13	Table 16 and Table 17 – added monthly pregnancy testing & pregnancy test for follow up 30 days after last dose	*116 & 118*
14	Removed names of study chair and added Medical Director	*91*
15	Table 15 - Sparse ECG measurement schedule has been updated for Arm 2 (control arm)	*101*
16	Section 7.3.2 and Section 7.3.5 - FHSI-18 Questionnaire should be completed for baseline assessment (screening or at pre-dose cycle 1 day 1) and day 1 of every even numbered cycle	*107, 117, & 119*
17	Change from 46hr to 42-48 hr FFX infusion	*105, 105, 107, 109, 106, 107, 108, & 109*
18	Addition of +/- 24 hours window to the cycles	*14, 16, 82, 87, 106, 107,*

		110, 116, & 118
19	Section 7.3.5 Pregnancy testing was added to every treatment cycle	*116 & 118*
20	Section 8.2.1 Name added – "AE Severity Grading"	*112*
21	Change from Neulasta to Myeloid Growth Factor	*49, 108, & 109*
22	Statistical Analysis: Changed first interim analysis for futility only	*130 & 136*
23	Statistical Analysis: Splitting of alpha into 0.005 for ORR and 0.2 for PFS (instead of 0.1 for ORR and 0.15 for PFS)	*131 & 132*
24	Section 9.4.2 – Testing Procedure and Control of Type 1 Error for ORR has been revised	*132*
25	Section 9.4.6 – Interim analysis of PFS at 50% information fraction	*136*
26	Section 9.4.6 – Name changed to – Planned Futility, Interim, Final Analyses and Follow up	*136*
27	Table 19: Updated Timelines	*137*
28	Table 20: Statistical Decision Rules updated	*137*
29	Section 10 – Added "Data should meet the standard for ALCOA+002E."	*141*
30	Section 12.1 Data Handling & Record Keeping section revised	*146*
31	Heart rate added with Vital signs	*105, 105, 107, & 109*
32	Addition of Cardiac Marker (Troponin I)	*97, 107, 108, 109, 109, 117, 117, 118, & 118*
33	5.1.10 – Changed AST UNL to correlate with ALT	*124*
34	5.2.5 – Addition of "if < 6 months to disease progression	*72*
35	6.1.5 – Addition of language – There is no maximum dose and patients' actual weight to be used for dose calculation	*81*
36	7.3.2 – Asterisks deleted next to CA19-9	*104, 107*
37	Appendix I – Log of Protocol Amendments	*154*
38	Appendix II – RECIST 1.1	*155-157*
39	8.2.2 Severity of Adverse Events updated	*122-125*
40	5.1.8 – Definition for double barrier method added	*71*
41	5.2.30 – Contraindications for 5FU updated	*74*

Detailed changes can be seen in the Change Document (compares PANC003 version #4 to version#5).

Global Amendment 3

Changes in this version 6 were prompted from correspondences with study sites and regulatory agencies. The purpose of the Global Amendment 3 (Version 6) is to add further clarification to the protocol.

Changes to note		Protocol page
1	Synopsis, Sections 4.4, 9.2, and 9.4 – co-primary endpoints changed to primary endpoints.	*16, 121, 122*
2	Section 3 – CTCAE changed back from version 5 to version 4	*61*
3	Section 5.3 – Section updated with new language for clarification	*70*
4	Section 5.3.1 Update to section on Discontinuation of Treatment	*70*
5	Section 7.1.1 Addition of clarification language to Cardiac marker (Troponin I)	*90*
6	Section 7.1.1 – Table 14, Addition of baseline timepoint for Cycle 1, Day 3	*92*
7	Section 7.3.2 - Cycle 1, Day 1 – inclusion of language to emphasize implementation of PRO and to clarify timing of blood sampling for Troponin I	*98*
8	Section 7.3.3 – Coagulation was added next to Clinical hematology for the purpose of clarity	*103*
9	Section 7.3.4 – Section on Long-Term Follow-up added for clarity and for direction on those patients who will continue beyond Cycle 12	*107*

Detailed changes can be seen in the Change Document (compares PANC003 version #5 to version#6).

Global Amendment 4

Changes in this version 7 were prompted from correspondences with study sites and regulatory agencies. The purpose of the Global Amendment 4 (Version 7) is to add changes and further clarification to the protocol.

Changes to note		Protocol page
1	Section 7.1.1. – Blood Sampling for Pharmacokinetic (PK) Analysis: Removed "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."	*89*
2	Section 7.1.1., 7.3.2. and 7.3.6. – Full PK blood sampling schedule. – Removed Time point "24 hr ± 15 min" and comment "Day 2" from Cycle 1, Day 1	*90, 100, 108*
3	Section 7.1.1., 7.3.2. and 7.3.6. – Full PK blood sampling schedule. – Removed Time points "24 hr ± 15 min" & "48 hr ± 15 min" and comments "Day 4" & "Day 5" from Cycle 1, Day 3	*90, 100, 108*
4	Section 7.1.1., 7.3.3. and 7.3.6. – Full PK blood sampling schedule. – Removed all cycles from Cycle 2, Day 1 to Cycle 12, Day 3	*90, 104-106, 108*
5	Section 7.1.1. – Full ECG Analysis - Updated phrase "30 minutes prior to dosing of devimistat on Cycle 1, Day 1 to 6 hours after dosing on Day 1."	*93*
6	Section 7.1.1. – Full ECG Analysis - Updated phrase "For Cycle 1, Day 1 (9 time points) and Cycle 1, Day 3 (9 time points), continuous 12-lead digital ECG data will be recorded and stored onto SD memory cards. ECGs will be uploaded onto a central ERT server.	*93*
7	Section 7.1.1., 7.3.2. and 7.3.6. – Full ECG Measurement Schedule – Removed Time point "24 hr ± 15 min" from Cycle 1, Day 1	*93, 100, 108*
8	Section 7.1.1., 7.3.2. and 7.3.6. – Full ECG Measurement Schedule – Removed Time points "24 hr ± 15 min" & "48 hr ± 15 min" and comments "Day 4" & "Day 5" from Cycle 1, Day 3	*93, 100, 108*
9	Section 7.1.1., 7.3.3. and 7.3.6. – Full ECG Measurement Schedule – Removed all cycles from Cycle 2, Day 1 to Cycle 12, Day 3	*93, 104-106, 108*
10	Section 7.1.1. – Change in Table 14 Full ECG Measurement Schedule – Removed note "*Cycle 1, Day 1 and Cycle 1, Day 3's 24 hour assessments will be recovered from the SD memory card used during continuous monitor."	*93*
11	Section 7.3.4. – Updated Sentence – "After the End of Treatment Visit (subsequent cycles after Cycle 12), subjects will enter long-term follow-up during which information on the subject's survival status and subsequent anticancer therapy will be obtained by the site every 2 months according to the protocol **with a time window of +/- 7 days."**	*108*
12	Section 1 - Medical Monitor name updated	*28*

Detailed changes can be seen in the Change Document (compares PANC003 version #6 to version#7).

Global Amendment 5

Changes in this version 8.0 were prompted from correspondences with study sites and regulatory agencies. Global Amendment 5 (Version 8.0) incorporated the following updates:

Changes to note		Protocol page
1	Protocol Summary: Objectives: Primary and secondary objectives were revised Endpoints: Primary and secondary endpoints revised Number of site enrolling: updated to 78 sites approx.… Study duration: Removed interim and updated timelines for final and follow-up analysis	*14, 15*
2	Schematic of study design: Removed ECG and blood sampling for PK from additional cycles	*18*
3	Section 3: Objectives Primary objective: Futility and interim analyses removed and final analysis was updated by removing ORR. Secondary objectives: ORR was added	*63*
4	Section 4: Study design and endpoints 4.2 Study endpoints: Primary and Secondary updated to reflect changes to primary and secondary objectives 4.2.3 Exploratory endpoint: PK/PD – removed ORR and replaced with PFS	*64, 65*
5	Section 5.2 Exclusion criteria: 5.2.29 slightly revised	*69*
6	Section 5.3.1 Discontinuation of treatment: Parts of the sections were slightly revised for better clarity	*71-73*
7	5.4 End of Trial: Definition revised	*73*
8	Section 6.1.2 Formulation. Appearance. Packaging and Labeling: Molecular weight and melting point numbers revised	*74-75*
9	Section 6.1.4 Preparation and handling: Removed retest date	*76*
10	7.1.1 Study specific procedures: Slightly revised Tumor assessment section for PFS and OS	*86, 87*
11	Section 7.3.5 Long term follow-up: Clarified End of treatment by removing subsequent cycles after cycle 12 in parenthesis	*106*
12	Section 7.3.4 End of treatment visit: Removed "the end of treatment is Cycle 12."	*105*

13	Section 7.3.6. Schedule of Events table: Table 16 and table 17 – added end of treatment column	*108*
14	Section 7.4 Concomitant medications. treatments and procedures: Added clarification on use of drugs that could prolong QTc Also. added list of drugs that can be used during trial.	*110*
15	Section 9 Statistical Considerations: 9.2 Trial Design and Statistical Hypotheses – Section revised by removing interim analysis and ORR with PFS 9.4 Treatment procedure and control of type 1 error – endpoint revised from 2 to 1 and removed ORR. P value revised 9.4.3.2 PFS – slightly revised the paragraph "…..last radiographic visit that the patient was known to be alive and progression-free." 9.4.3.3. OS – This section was revised to reflect changes to primary objective. 9.4.3.4. ORR – Objective changed from primary to secondary 9.4.6 Final analysis and follow-up – revised heading by removing futility and interim. Revised projections and decision rules 9.5 Sample size – Type 1 error revised from 0.020 to 0.025. Number of events for PFS revised from 350 to 330. Accrual rate removed	*122, 124, 126, 127*

Detailed changes can be seen in the Change Document (compares PANC003 version #7 to version#8).

Global Amendment 6

Changes in this version 9.0 were prompted by correspondence from regulatory agency, and reflect the fact that there will be a single analysis of the trial with Overall Survival (OS) as primary efficacy endpoint. Global Amendment 6 (Version 9.0) incorporated the following updates:

Changes to note		Protocol page
1	Protocol Summary: Objectives: Primary and secondary objectives were revised Endpoints: Primary and secondary endpoints revised Study duration: Updated timelines for single final analysis	*14, 15*
2	Section 1. Key roles Updated Covance medical Monitor	*28*
3	Section 3. Objectives Primary Objective: Revised to OS from PFS Secondary Objective: Revised to PFS from OS	*65*
4	Section 4.2. Study Endpoints 4.2.1. Primary endpoint revised to OS 4.2.2. Secondary endpoint revised to PFS	*66*
5	Section 5.3.1 Discontinuation of treatment Updated patient follow-up text	*74*
6	Section 5.4. End of Trial Definition for end of trial updated	*75*
7	Section 7. Study Procedures and Schedule 7.1.1 Study specific procedures: Tumor assessment section revised for OS and PFS	*89*
8	Section 7.3.2 Enrollment/baseline and treatment cycles details Updated text for Observations after the intervention	*103*
9	Section 7.3.5 Long-term Follow-Up Updated text for collection of PD status	*108*
10	Section 9. Statistical Considerations 9.2 Trial Design and Statistical Hypotheses – Section revised to specify a single final analysis with OS as primary endpoint and PFS as secondary endpoint 9.4.2 Testing Procedure and Control of Type I Error – Section revised to specify use of hierarchical testing with one-sided significance level of 0.025 9.4.3 Efficacy Analysis – Subsection numbers changed to reflect the fact that OS is now the primary endpoint and PFS is now a secondary endpoint	*123 to 129*

	9.4.3.3 PFS – Detailed rules for censoring modified for consistency with FDA recommendations 9.4.6 Final Analysis – Section revised to remove follow-up analysis, and number of OS events required for the final analysis 9.5 Sample size – Section revised to show power of the trial for OS and PFS	

Detailed changes can be seen in the Change Document (compares PANC003 version #8 to version #9).

[redacted]

[redacted]

[redacted]

2.1. Background Information

2.1.1. Clinical, Epidemiological and Public Health Background:

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.[1] 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.[2]

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.[3] 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.[4-5] 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.

2.1.2. FOLFIRINOX

Chemotherapy is the only treatment option for metastatic pancreatic cancer. National comprehensive cancer network (NCCN) treatment guidelines recommend FFX (oxaliplatin, folinic acid, 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[6,7] and poor performance status patients. Of note, the median age of diagnosis of pancreatic cancer is 71 years.[3] 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. Based on the compelling safety and efficacy signals from the Phase I CCCWFU57112 trial, we will proceed with the Phase III PANC003 trial for devimistat in patients with metastatic adenocarcinoma of pancreas.

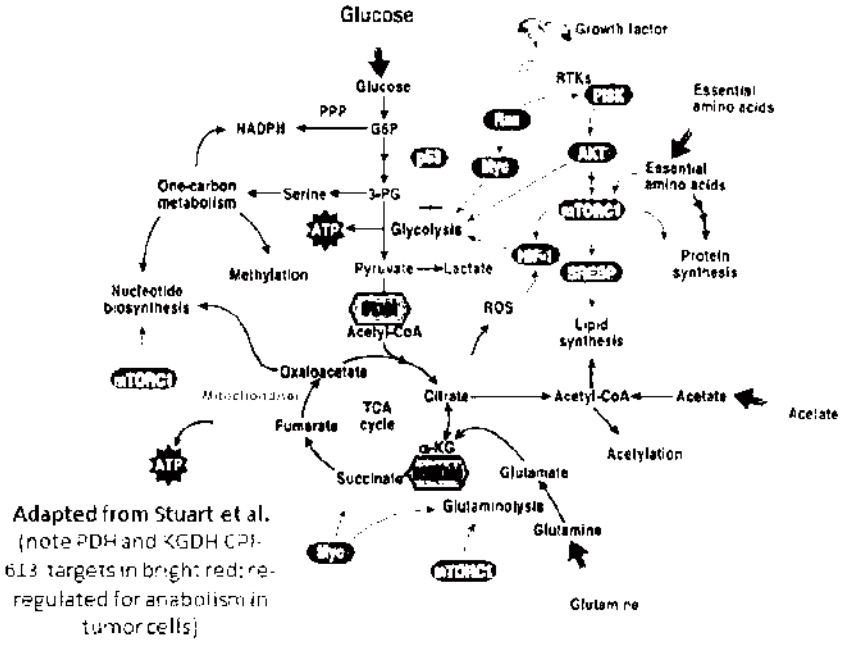
2.1.3. CPI-613® (devimistat): Mechanism of Action

The profoundly altered metabolism of tumor cells is the emerging as one of the most promising new areas for therapeutic targeting of cancer (reviewed in Vander Heiden[8]). In most cancer cells, uptake of glucose and/or glutamine is substantially increased, and the metabolic activity of the TCA cycle is re-regulated for more anabolic purposes. Some key features of cancer metabolism are summarized in Figure 1. Glucose is metabolized to pyruvate which then is either (a) reduced to lactate by lactate dehydrogenase (LDH) or (b) transported to the mitochondria, where PDH converts pyruvate to acetyl coenzyme A (AcCoA). The AcCoA acetyl group can then be used for either energy generation or biosynthetic intermediate production. Glutamine is an additional carbon source important for sustaining the TCA cycle in tumor cells. Glutamine transport is upregulated in many tumor types. Glutamine is converted to glutamate and further to α-ketoglutarate (α-KG). α-KG is then converted to succinyl-CoA by α-ketoglutarate

dehydrogenase (KGDH) for subsequent processing through the TCA cycle (Figure 1, Figure 2A).

Devimistat is the first of a novel class of such anti-cancer agents. This drug is a tumor-specific anti-mitochondrial metabolism agent and a stable analog of lipoic acid (lipoate) catalytic intermediates that are normally assessed by specific components of the regulatory machinery for two enzyme complexes, pyruvate dehydrogenase (PDH) and α-ketoglutarate dehydrogenase (KGDH), (Figure 1, bottom and Figure 2A). Thus, devimistat targets forms of these mitochondrial enzymes based on their dysregulation in tumor cells. Treatment of tumor cells with devimistat substantially inhibits these two enzymes, central to the tricarboxylic acid (TCA) cycle or Kreb's cycle, thereby collapsing mitochondrial metabolism. This collapse of mitochondrial metabolism leads, in turn, to redundant activation of apoptotic and necrotic cell death pathways.

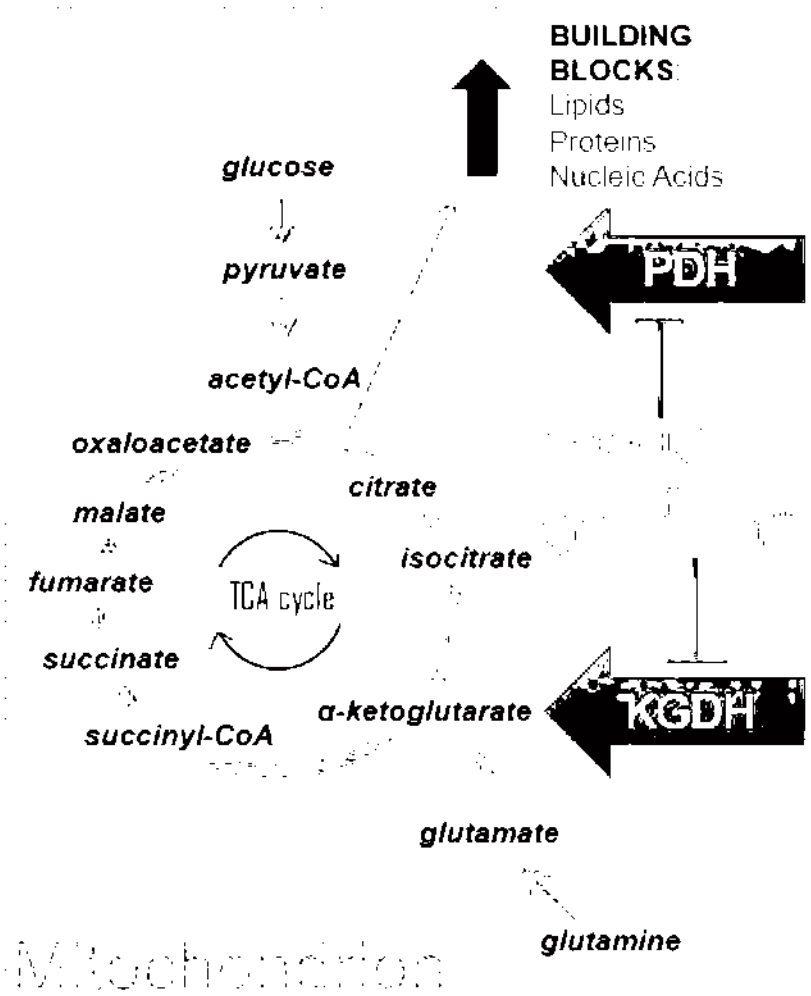
Figure 1 Altered Metabolism in Cancers



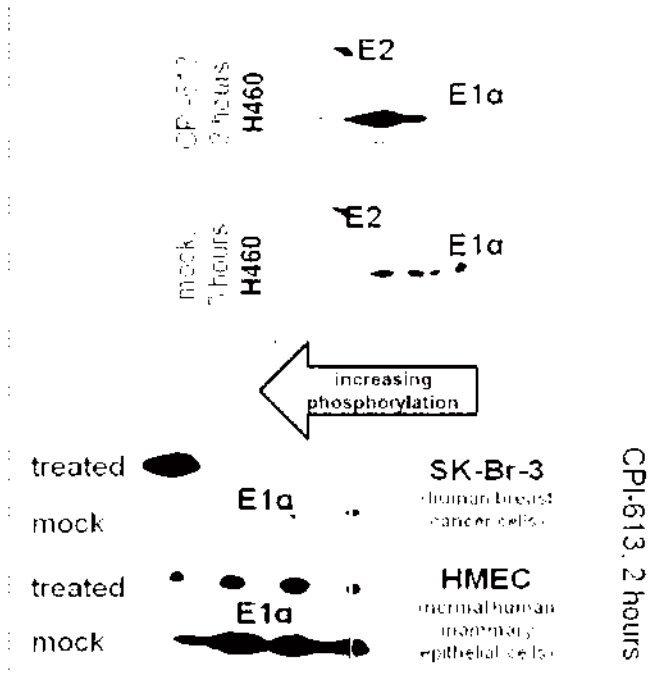
Devimistat is a stable analog of normally transient, acylated catalytic intermediates of lipoate, an essential co-factor for both the PDH and KGDH enzyme complexes (Figure 1, Figure 2A). These lipoate intermediates are monitored by regulatory systems to control flux through these two enzymes. Regulatory systems controlling this flux are significantly modified during anabolic reprogramming in cancer (Figure 1) such that they are more responsive to devimistat. These regulatory modifications include isozyme replacement for members of the PDH regulatory kinase (PDK) family, for example. As well, tumor cells take up devimistat preferentially, apparently through up-regulated vitamin and fatty acid transporters (unpublished). Thus, devimistat acts with substantial selectivity on tumor cells (Figure 2B for exemplary data), apparently accounting for the low side-effect toxicity of this drug. As summarized in "Pyruvate attenuates the anti-neoplastic effect of Carnosine independently from oxidative phosphorylation" (Oppermann et al, 2016)[9], devimistat selectively inactivates PDH in tumor cells by hyper-activating the corresponding regulatory pyruvate dehydrogenase kinases (PDKs). PDKs phosphorylate and inactivate PDH (Figure 2B top, for exemplary data). Devimistat simultaneously inactivates KGDH by hyper- activating a redox feedback loop normally controlling the enzyme's activity (Figure 2B bottom, for exemplary data). The simultaneous inhibition of these two TCA cycle enzymes dramatically compromises mitochondrial metabolic flows, triggering multiple, redundant cell death pathways, selectively in tumor cells.

Figure 2 Mechanism of Action of CPI-613® (devimistat)

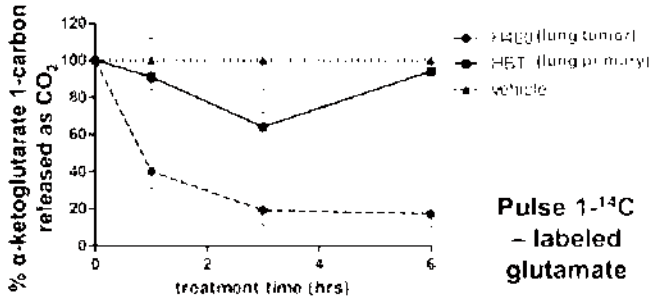
A.



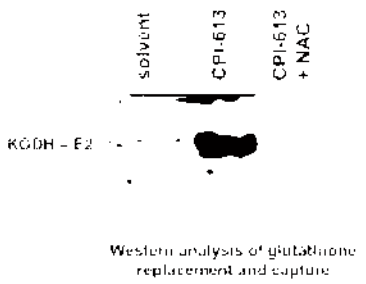
B.



2-dimensional Western gel analysis (and additional data in Zachar, et al., 2011; 17) demonstrates that CPI-613 hyper-activates specific PDK regulatory kinases, inducing extensive, **inactivating** PDH E1α phosphorylation **selectively** in tumor cells. (*White line indicates unphosphorylated, active PDH.*)



Flux metabolomic analysis shows **tumor-specific** inhibition of KGDH by CPI-613 (see Stuart, et al., 2014; 18)



CPI-613 induces oxidative modification of tumor cell KGDH, including lipoate sulfhydryls and glutathionylation (also see Stuart, et al., 2014; 18)

2.1.4. CPI-613® (devimistat) Pre-Clinical Studies:

Several non-clinical pharmacology and toxicology studies were conducted to investigate pharmacokinetics (PK), drug metabolites, anticancer activity and safety of devimistat in non-tumor bearing and tumor bearing animals. In *in vitro* cell testing against a variety of tumor cell lines and patient derived circulating tumor cells demonstrated anticancer activity with an IC_{50} value of approximately 100 to 200 µM. These values varied somewhat with the cell type being examined and were dependent on the concentration of fetal bovine serum (FBS) in cell culture media due to the extensive plasma protein binding characteristics of devimistat. In *in vitro* cell culture assay conditions binding to plasma proteins acts as a "sink" for devimistat making less free drug available for uptake into cells. In vivo binding to plasma proteins improves accumulation of drug within a tumor mass through the enhanced permeation and retention phenomena characteristic of solid tumors and the potential for overexpression of albumin receptors for the mediation of drug uptake depending on cell type and micro-environmental conditions. Anticancer activity has been shown for both cells derived from solid tumors and for cancer cells derived from various leukemias. Differences in sensitivity to devimistat among the various cell types has been suggested to be due to differences in the cellular uptake, intracellular metabolism, and accumulation of drug in cancer cell mitochondria. Those cells less responsive or not responsive to devimistat even at the highest drug concentrations, take up lower levels of drug into cells with drug metabolized to an inactive form (CPI-810), a by-product of the oxidation of one or more of the sulfur groups present in devimistat. The principal metabolite of devimistat produced in the mitochondria of cancer cells is CPI-2850, a by-product of mitochondrial beta oxidation of the drug. Chemically synthesized CPI-2850 demonstrated comparable anticancer activity to devimistat but in some cell types was found to be substantially more potent. Devimistat was found to not be taken up into or to be without effect in a variety of murine and human healthy cells tested in culture, suggesting the potential for safe use as a cancer therapeutics. In vitro and in vivo anticancer activity studies against a variety of human cancer cell lines that were resistant to the most commonly used chemotherapeutic drugs was also performed. Despite high levels of chemotherapy resistance, sensitivity to devimistat was shown at concentrations above 100-500 µM capable of inhibiting 100% of cell growth in soft agar or in adhesion cell culture conditions. These data suggest the possibility of anticancer activity in vivo with a target plasma concentration of drug and active metabolites of at least 100-200 µM. In

vivo efficacy models using immuno-deficient mice bearing diverse tumor types[10,11,12], including pancreatic, were used to evaluate dose response, pharmacokinetics, accumulation of drug within tumors and drug metabolism. The primary metabolites observed in the plasma of these animals in addition to the administered devimistat were CPI-2850 and CPI-1810. Both metabolites can be formed within cancer cells and in the liver. Anticancer activity was demonstrated in both growth inhibition (NCL-034) and tumor shrinkage models (Studies NCL-023 and NCL-024). A relationship between the rates of drug metabolism and the nature of the specific metabolites detected in plasma and overall response is being investigated.

An understanding of devimistat mechanisms of action in diverse cancer cell populations allows for the intelligent selection of other chemotherapeutic drugs to be used in combination. Given the heterogeneity of disease and cell populations it is believed that the use of chemotherapy in combination with devimistat is more likely to maximize patient benefit than the use of single agent. Prolonged survival was observed when compared to non-treated controls and more commonly used chemotherapeutic agents in pancreatic cancer mouse models (NCL-023 and NCL- 082). Devimistat was well-tolerated in all animal models tested. As a result of selective uptake into cancer cells and accumulation into cancer mitochondria remarkably low minimal effective dosages were also observed with a maximal therapeutic effect well below the maximally tolerated dose.

Several nonclinical studies evaluating the pharmacokinetic profile of devimistat were conducted. A nonclinical safety pharmacology study showed that devimistat does not inhibit hERG cannels and hence is unlikely to cause QTc interval prolongation (NCL-043). Devimistat and its metabolites are eliminated from the body through hepatic and renal clearance. Please see detail in IB, section 4.3.

In vitro inhibition of devimistat on 10 CYP450 enzymes has been evaluated in study NCL-130, and IC50 values are listed in the table below. The phenotyping (devimistat as a substrate), of 8 CYP450 enzymes was also evaluated in study NCL-128 and are also summarized in the table below. In addition, the literature information of the co-administered components of FOLFIRINOX are also listed. Based on comprehensive data analysis (NCL-128, NCL-130) and

literature below (based on PubMed and Google search as of June 2019), the potential of DDI (drug-drug interactions) between devimistat and co-medications (substrates, inhibitors and inducers of CYP450 enzymes) is expected to be low.

Summary of CPI-613® (devimistat) and FOLFORINIX (FFX; including Irinotecan, 5-FU, Oxaliplatin and Folinic acid) regarding CYP450 enzymes; SN-38 as major metabolite of irinotecan

CYP450	Inhibition CPI-613® (devimistat) (IC_{50})	CPI-613® (devimistat) as Substrate	R>1.02[c] cut-off for non-competitive inhibitors	R>1.02[c] cut-off for competitive inhibitors	Irinotecan as Inhibitor	SN38 as Inhibitor	5-FU as Inhibitor	Oxaliplatin as Inhibitor	Folinic acid as Inhibitor	Irinotecan as Substrate	SN38 as Substrate	5-FU as Substrate	Oxaliplatin as Substrate	Folinic acid as Substrate
enzymes		(Yes or No)	(Yes or No)	(Yes or No)	(Yes or No)	(Yes or No)	(Yes or No)	(Yes or No)	(Yes or No)	(Yes or No)	(Yes or No)	(Yes or No)	(Yes or No)	(Yes or No)
CYP1A2	32.2 uM	Yes	No	No	No	NR	No	NR	No	No	NR	No	NR	No
CYP2A6	39 uM	NT[e]	No	No	NR	Yes	No	NR	No	NR	NR	No	NR	No
CYP2B6	19.8 uM	No	No	No	No	NR	No	Yes (weak)	No	NR	NR	No	NR	No
CYP2C8	0.93 uM	Yes	Yes	Yes	No	NR	No	NR	No	No	NR	No	NR	No
CYP2C9	27.9 uM	Yes	No	No	NR	Yes	Yes	Yes (weak)	No	No	NR	No	NR	No
CYP2C19	10.1 uM	Yes	No	Yes	NR	NR	No	NR	No	NR	NR	No	NR	No
CYP2D6	84 uM	Yes	No	No	NR	NR	No	NR	No	NR	NR	No	NR	No
CYP2E1	92.8 uM	NT	No	No	NR	NR	No	NR	No	NR	NR	No	NR	No
CYP3A4/5	26.7 (Ta) & 17.4 (Mb)	Yes	No[a] & No[b]	No[a] & No[b]	Yes (moderate)	Yes	No	NR	No	Yes	Yes	No	NR	No

[a] testosterone 6-hydroxylase (T-6-H): [b] midazolam 1'-hydroxylase (M-1`-H): [c] R>1.02 as cut-off based on FDA DDI draft guidance Oct. 24. 2017: [d] NR = not reported by literature or product inserts: [e] NT = not tested; [f] SN38 is major metabolite of Irinotecan

Estimation of DDI potential with estimated R values, discussed below, were calculated based on the latest version of FDA draft guideline on DDI dated on Oct. 24, 2017. *In vitro*, devimistat shows a R value of > 1.02 for CYP2C8, 2C19 and 2B6 inhibition, which is the cut-off value for potential DDI. However, all components of FOLFIRINOX (Irinotecan, its major metabolite, SN38, 5-FU, Oxaliplatin, and Folinic acid), have not been reported as substrates for the above 3 CYP enzymes. Therefore, there is no potential for DDI between devimistat and FOLFIRINOX regarding CYP2C8 and 2C19.

In addition, even though devimistat has shown in vitro R values > 1.02 for CYP2C8 and 2C19 (as mentioned above), devimistat's R value is 1.13-1.27 (just a little bit above the cut-off value of 1.02) for CYP2C8 inhibition and per FDA draft guideline on DDI there is only 1 drug (repaglinide) as CYP2C8 index substrate. Literature searching (via PubMed as of June 2019) could not find a report for repaglinide's use in PANC patients, suggesting the likelihood of DDI is low between devimistat and co-medications which are substrate of CYP2C8. Devimistat's R value is 1.02-1.03 (just on the board line of cut-off value of 1.02) for CYP2C19 inhibition, suggesting the likelihood of DDI is low or none between devimistat and co-medications (which are substrate of CYP2C19).

When considering devimistat as a CYP450 substrate, multiple CYP450 enzymes (CYP2C8, 2C19, 3A4, 2D6, 3A5, 2C9 and 1A2, in rank order of turnover rate) have been identified to be involved its biotransformation. It should be emphasized that this allows for multiple alternative metabolism pathways for the metabolism of devimistat by CYP450, and therefore even if one or more of these isozymes are inhibited by co-administered drugs, there exists the potential for the other isozmes to compensate toward the metabolism of devmistat. Thus, DDI potential will be low even if one or more of these CYP450 enzymes involved in the metabolism of devmistat are inhibited by co- administered drugs. In this regard, Irinotecan has been reported as an inhibitor of CYP3A4, SN38 as an inhibitor of CYP3A4 and 2C9, 5-Fu as an inhibitor of 2C9, Oxaliplatin as a weak inhibitor of CYP2B6 and 2C9. Folinic acid has not been reported as an inhibitor of any CYP450 enzyme.

Thus, the likelihood of DDI between devimistat (as victim) and FOLFIRINOX components Irinotecan (and SN38 as major metabolite), 5-FU, Oxaliplatin and Folinic acid (as predators) is expected to be low.

In addition, as discussed above, since 7 CYP isozymes are involved in the metabolism of devimistat, the potential for any co-meds (which are either inhibitors or inducers of the CYP isozymes) that are involved in the metabolism of devimistat, is also expected to be low.

Key GLP toxicology (Tox) studies for devimistat were conducted in rats and minipigs. In addition to preliminary Tox studies were conducted in mice, rats and minipigs. Key summaries of these Tox studies are described below. Devimistat has shown very good safety margins based on much higher TK exposures (C_{max} and AUC) from pre-clinical GLP Tox (toxicology) studies in rats and minipigs at MTD (maximum tolerated doses) to cover PK exposures (C_{max} and AUC) from PANC (pancreatic cancer) and AML (acute myeloid leukemia) patients.

2.1.4.4.1. GLP Tox 4-Week Study in Rats (NCL-122)

Devimistat was dosed to Sprague-Dawley rats at 0 (vehicle control), 50, 100, 200, 350, 400, 450 and 500 mg/kg/day in this 4-week dose range finding (DRF) study (NCL-122). Administration was performed over 2 hours via intravenous infusion through a jugular vein. A dosing cycle consisted of infusion once daily for 5 days, followed by 9 days without dosing. Two dosing cycles were performed in this study.

This GLP Tox 4-week rat study resulted in mortality of animals that were administered ≥ 450/350 mg/kg/day. Dose-dependent, but recoverable, post-dose effects were observed in animals that were administered ≥ 200 mg/kg/day, with increasing severity/frequency and incidence. Reduced body weight gain or food consumption were seen in animals that were dosed ≥ 50 mg/kg/day. Microscopically, dose-dependent kidney effects, including pigment and/or tubular nephropathy, in animals administered ≥ 100 mg/kg/day and focal necrosis in the liver of animals administered 400/350 mg/kg/day were noted. Kidney changes were considered adverse in animals administered ≥ 400/350 mg/kg/day because of associated clinical pathology changes (in vivo hemolysis) and the increased severity/incidence of morphological changes in these animals. Other changes, including hepatocyte hypertrophy, adrenal cortical hypertrophy, and extramedullary hematopoiesis, were considered to be an adaptive and/or regenerative response and, therefore, not adverse. With the exception of minor clinical observations or body weight effects in animals administered 50, 100, or 200 mg/kg/day and changes in the kidneys of animals administered 100 or 200 mg/kg/day, no devimistat-related organ weight or macroscopic or

microscopic findings were present in animals that were administered ≤ 200 mg/kg/day. Since there was no additional animal group in this study to fine tune the dose level between 200 and 350 mg/kg/day and based on toxicity findings from 200 and 350 mg/kg/day groups, 300 mg/kg/day was reasonably proposed as the MTD for this study. The plasma concentration corresponding to this dose was estimated to have a mean devimistat highest concentration (C_{max}) and area under the concentration-time curve (AUC_{0-24hr}) values of 258,000 ng/mL (=664 uM) and 522,000 hr x ng/mL (1,343 uM x hr), which are much higher than the highest observed mean C_{max} and AUC_{0-24} values at MTD from PANC and AML patients (see Section 2.1.4.4.5).

2.1.4.4.2. GLP Tox 13-week Study in Rats (NCL-124)

Study NCL-124 evaluated the toxicity (Tox) of the test article, devimistat, following intravenous (IV) infusion to rats with seven (7) cycles that lasted 13 weeks. Devimistat was dosed at 0 (control article), 100, 200, or 300/250 mg/kg/day. The control article was 1 M triethanolamine (TEA) in water for injection. The control article (vehicle diluent) was 5% dextrose in water (5% Glucose BP). Each cycle consisted of 2 hours/day IV infusion for 5 consecutive days, followed by 9 days without dosing. The final cycle consisted of a 2 hours/day IV infusion for 5 days followed by 2 days without dosing.

This GLP Tox 13-week rat study resulted in cannulation or dosing procedure-related mortality for males across all groups, (including controls), and for females that were administered 200 or 300/250 mg/kg/day. These unscheduled deaths were not devimistat related. Other effects were considered to be test article-related, and in general, were limited to animals that were administered ≥ 200 mg/kg/day. A few test article-related findings were also observed in animals that were administered 100 mg/kg/day but were not determined to be adverse. Administration of devimistat caused dose-related tubular nephropathy and pigment accumulation in the kidney of animals that were administered ≥ 100 mg/kg/day, symptoms that were still present at the end of the recovery phase. The increased severity of haemopoiesis in the spleen of animals that were administered ≥ 100 mg/kg/day was considered to be an adaptive response secondary to the kidney changes. Thus, it was concluded that MTD for devimistat formulation was 100 mg/kg/day for rats. This dose level corresponded to the highest observed mean C_{max} of 88,500 ng/mL (227 uM) and AUC_{0-24h} of 177,000 ng x hr/mL (455 uM x hr), suggesting safety margins of 2.5 – 10.2 folds at MTD from this GLP Tox 13-week rat study divided by the highest observed C_{max} and AUC at MTD from PANC and AML patients (see safety margins tables in

Section 2.1.4.4.5, Table 1 and Table 2).

2.1.4.4.3. GLP Tox 4-week Study in Minipigs (NCL-123)

Male and female Gottingen minipigs were administered doses of devimistat at 0 (vehicle control), 50, 100, 200 and 400 mg/kg/day. Animals were dosed by intravenous (IV) infusion for 2 hours into the vena cava via the femoral vein. Animals were dosed for two cycles, with each cycle consisting of dosing for 5 days, followed by 9 days without dosing. The vehicle control was 1 M Triethanolamine (TEA) that was diluted with 5% Dextrose in water (D5W) to the appropriate dosing concentrations.

Dose levels up to 100 mg/kg/day were generally well tolerated, with only transient and mild clinical observations. Animals that were administered 150 mg/kg/day had more pervasive clinical observations and required veterinary intervention to complete the dosing cycle. Clinical pathology changes in these animals were primarily indicative of adverse inflammation. Dose levels of 200 or 400 mg/kg/day were not tolerated, and animals in those dose groups were sacrificed on Day 1.

Devimistat-related thrombus occurred at the infusion site in animals from all dose groups. Thus, the MTD for this GLP Tox 4-week minipig study was determined to be 100 mg/kg/day. This dose level corresponded to the highest observed mean C_{max} of 143,000 ng/mL (368 uM) and AUC_{0-24} of 303,000 hr x ng/mL (780 uM x hr), which are much higher than the highest observed mean C_{max} and AUC_{0-24} values at MTD from PANC and AML patients (Section 2.1.4.4.5).

2.1.4.4.4. GLP Tox 13-week Study in Minipigs (NCL-125)

This GLP Tox 13-week study evaluated the toxicity (Tox) of the test article, devimistat, following intravenous (IV) infusion to minipigs with seven (7) dosing cycles for 13 weeks. Administration consisted of six cycles of 2 hours/day IV infusion for 5 consecutive days, with each cycle followed by 9 days without dosing, and with one final cycle of 2 hours/day IV infusion for 5 days followed by 2 days without dosing. Minipigs were dosed devimistat at 0 (vehicle control), 25, 50, 100/75 mg/kg/day (animals dosed for two cycles at 100 mg/kg/day, and then at 75 mg/kg/day for the remaining cycles).

Although no unique-devimistat-related toxicity findings were identified, administration of

100/75 mg/kg/day was not tolerated due to increased mortality, and as the intended dosing regimen was unable to be completed. Devimistat-related toxicology observations were generally limited to sporadic emesis, vomitus, and excessive salivation during dose administration, predominantly in animals administered 100 mg/kg/day and were frequently associated with low or no food consumption. The dose level was reduced from 100 to 75 mg/kg/day after the first two dosing cycles, although observations generally persisted when animals were administered 75 mg/kg/day, albeit generally at a lower severity. Although unscheduled sacrifices eventually occurred in all groups due to moribund condition, including 1 control female, 2 males administered 25 mg/kg/day, 1 female administered 50 mg/kg/day, and 3 males and 3 females administered 100 or 100/75 mg/kg/day, administration of 100/75 mg/kg/day was ultimately not tolerated, as the manifestation of the clinical observations required more veterinary intervention and they were such that dosing had to be discontinued early and animals were unable to complete the intended dosing regimen due to six unscheduled sacrifices in this group. Animals administered ≤50 mg/kg/day were able to complete the full dose regimen while microscopic findings were similar to the vehicle control unscheduled sacrifices and all pathology findings were determined to be related to inflammation at the catheter/infusion sites and were not considered to be related to devimistat.

Thus, in this GLP Tox 13-week study, the MTD for devimistat formulation was 50 mg/kg/day for minipigs, in the absence of any test article related mortality but minimal to moderate tubular nephropathy. This dose level corresponded to the highest observed mean C_{max} of 88,800 ng/mL (228.5 uM) and $AUC_{0\text{-}24h}$ of 177,000 ng x hr/mL (455.5 uM x hr), suggesting safety margins of 2.5 – 10.2 folds at MTD from this GLP Tox 13-week rat study divided by the highest observed C_{max} and AUC at MTD from PANC and AML patients (see safety margins tables in Section 2.1.4.4.5, Table 1 and Table 2).

2.1.4.4.5. Toxicokinetic Safety Margins Based on GLP Tox 13-week Studies

The MTD was determined as 100 mg/kg in GLP Tox 13-week rats and 50 mg/kg in GLP Tox 13- week minipigs, respectively. The toxicokinetic (TK) exposures of C_{max} and AUC in 13-week rat and 13-week minipig studies have demonstrated very good safety margins (SM) (2.5 – 3.5 folds) to cover pharmacokinetic (PK) exposures of C_{max} and AUC at the highest therapeutic doses (2,000 and 2,500 mg/m^2) of devimistat in combination with Cytarabine and Mitoxantrone from Phase I clinical trial CCCWFU 22112 in AML patients (Table 1 below).

Table 1 Summary of TK safety margins (SM) of Devimistat from GLP Tox 13-week rats and minipigs to cover AML patients:

					13-week Rat MTD Devimistat @ 100 mg/kg				13-week Minipig MTD Devimistat @ 50 mg/kg			
Indication	Clinical Trial #	Dose (mg/m^2)	Devimistat C_{max} (ng/mL)	Devimistat AUC (h*ng/mL)	C_{max} (ng/mL)	C_{max} SM (folds)	AUC (h*ng/mL)	AUC SM (folds)	C_{max} (ng/mL) (mean)	C_{max} SM (folds)	AUC (h*ng/mL)	AUC SM (folds)
AML	22112	2,000	23.668	50.440	88.500	**3.7**	177.000	**3.5**	88.800	**3.8**	177.000	**3.5**
AML	22112	2,500	35.308	52.380	88.500	**2.5**	177.000	**3.4**	88.800	**2.5**	177.000	**3.4**

In addition, the completed and ongoing clinical Phase I and II trials where more than 350 cancer patients (including 114 AML patients) were dosed with devimistat have demonstrated favorable clinical safety profiles.

The TK exposures of C_{max} and AUC in 13-week rat and 13-week minipig studies have demonstrated very good safety margins (SM) (4.6 – 11.6 folds) to cover PK exposures of C_{max} and AUC at the highest therapeutic doses (500 mg/m^2) of devimistat in combination with modified FOLFIRINOX (mFFX) in PANC patients from Phase I clinical trial CCCWFU 57112 (Table 2 below).

Table 2 Summary of TK safety margins (SM) of Devimistat from GLP Tox 13-week rats and minipigs to cover pancreatic cancer patients:

					13-week Rat MTD Devimistat @ 100 mg/kg				13-week Minipig MTD Devimistat @ 50 mg/kg			
Indication	Clinical Trial #	Dose (mg/m^2)	Devimistat C_{max} (ng/mL)	Devimistat AUC (h*ng/mL)	C_{max} (ng/mL)	C_{max} SM (folds)	AUC (h*ng/mL)	AUC SM (folds)	C_{max} (ng/mL) (mean)	C_{max} SM (folds)	AUC (h*ng/mL)	AUC SM (folds)
PANC	57112	500	19.261	15.256	88.500	**4.6**	177.000	**11.6**	88.800	**4.6**	177.000	**11.6**

Also, completed and ongoing clinical Phase I and II trials for relapsed pancreatic cancer patients have demonstrated favorable clinical safety profiles.

In summary, both pre-clinical and clinical studies mentioned above strongly support the safety profile of devimistat in clinical development programs.

2.1.4.4.6. Historic (Preliminary) Tox studies

In addition to the above mentioned GLP Tox studies, numerous other studies have been conducted historically. Single dose or repeat dose studies were conducted to evaluate the toxicity of devimistat. In single-dose or repeat dose toxicity studies, devimistat exhibited local reactions at the injection site and increase in spleen weight (NCL-025, NCL-030, NCL-027, NCL-048, CPL-044, CPL-045). Devimistat did not induce any severe irreversible toxicity in another repeat dose toxicity study in mini-pigs (NCL-027). Transient adverse events like: local inflammatory reactions (reactions around the injection site, visible inflammations in ear, neck and nose), bilateral pupil dilation, reduced activity, head tilt, increased salivation, excessive lacrimation of both eyes were observed in animals. A study on the lethal dose of devimistat was also conducted to identify the doses to be used in subsequent toxicology studies (NCL-048). In another toxicokinetic study in rat, no biological or toxicological effects of the test article was observed on the measured pathology or hematology parameters (CPL-044). Adverse events like: morbidity, distended abdomen, hunched posture, thin, impaired limb function, decreased activity, abnormal stool, decreased defecation, material in pan/bedding, necrosis, extended penis, abnormal testes, and material around the nose, skin discoloration was observed. In another toxicology study in mini-pigs, there was no difference in creatine phosphokinase (CPK), creatine kinase, muscle (CKMM), creatine kinase, muscle and brain (CKMB) and serum creatine kinase BB (CKBB) between devimistat treated and vehicle treated male animals (CPL-045). In a combination therapy toxicology study of devimistat with gemcitabine, no additive toxicity of devimistat was observed (Study NCL-038). Reproductive and developmental nonclinical toxicology studies have not been conducted to date.

2.1.5. Clinical Experience with CPI-613® (devimistat):

To date, 20 studies have been conducted with devimistat including 14 completed trials and 6 ongoing trials. Over 500 subjects have received one or more doses of devimistat in these clinical studies.

Four clinical studies have evaluated the plasma PK of devimistat.

2.1.5.1.1. Study CL-CPI-613-002

This was a Phase I open label, 2-stage dose-escalation trial in cancer patients:

- Single-Patient Dose-Escalation Stage: The starting dose was 21 mg/m^2 IV infusion over 2 hrs. given twice weekly for three consecutive weeks. Dose level was escalated (by doubling the previous dose) if there was no toxicity or if the toxicity was ≤ Grade 1.

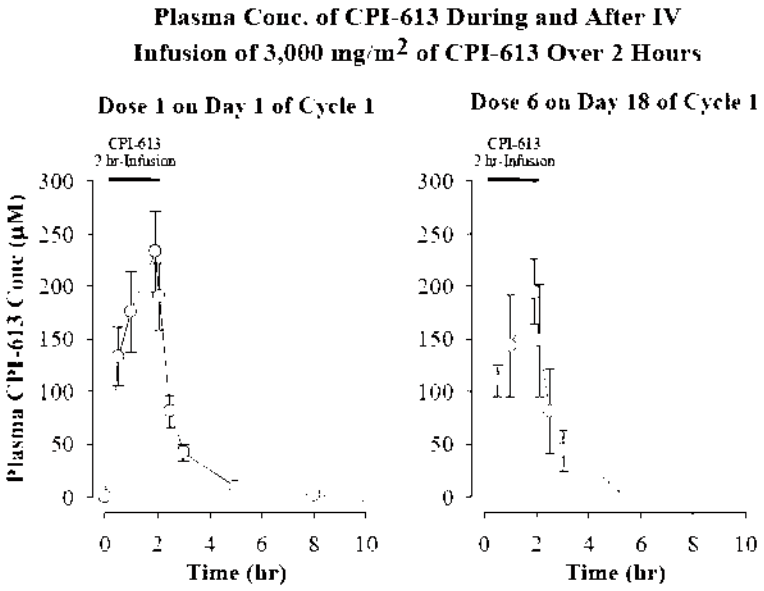
- Traditional Dose Escalation: The planned escalating dose levels were the multiples (1.0, 2.0, 3.3, 5.0, 7.0, 9.0, 12.0, and 16.0) of the dose level which was the last dose level for the Single-Patient Dose-Escalation Stage.

A treatment cycle was 3 consecutive weeks of 2x weekly dosing of devimistat, followed by 1 week of rest. The starting dose of 21 mg/m^2 represented a one-tenth of significant toxicity dose (210 mg/m^2) in rats.

Plasma samples for measurement of devimistat concentrations associated with the 1st and 6th administrations of devimistat in Treatment Cycle 1 were obtained pre-dose (~5 min before dosing), and at 30 min, 60 min and 115 min during infusion, as well as at 5 min, and 0.5, 1, 3, 6, 8, 24, 48 and 72 hr. after completion of the 2-hr infusion. The 8-hr samples were collected after completion of the 1st and 6th doses are optional, and the 72-hr sample were collected after completion of the 1st dose can be pre-dose sample for Day 4 dosing. Additionally, plasma samples for measurement of devimistat concentrations were obtained pre-dose (~5 min before dosing) for all other administrations of devimistat (i.e., 2nd, 3rd, 4th and 5th administrations of devimistat) of Treatment Cycle 1.

The plasma devimistat concentrations in patients treated with devimistat at 3,000 mg/m^2 (the highest dose tested) are shown in Figure 3. PK profiles of plasma devimistat from patients treated with 21 to 3,000 mg/m^2 of devimistat are shown in Figure 3. The results indicated that the Cmax and AUC values were directly related to the dose of devimistat (Figure 4). The elimination $T_{1/2}$ from 0-8 hours post-administration of devimistat was ~1 hr., Vd was ~5 L/kg, and CL was ~5 L/hr/kg. The results from 1st and 6th (last) dose of devimistat were similar, indicating that repeated dosing does not result in a change in the $T_{1/2}$ and CL and Vd values and there was no evidence of accumulation on multiple dosing during the dosing interval (Figure 5).

Figure 3 Results of plasma concentrations of CPI-613® (devimistat) in patients treated with 3,000 mg/m^2 (the highest dose tested) from Clinical Study CL-CPI-613- 002



Results are shown as mean ± Standard Error of the Mean (SEM).

Figure 4 Maximum plasma concentration (Cmax) of CPI-613® (devimistat) (left), and area under the concentration-time curve (AUC) (right), for the tested dose range from 21 to 3,000mg/m^2 of CPI-613® (devimistat) in Study CL-CPI-613-002

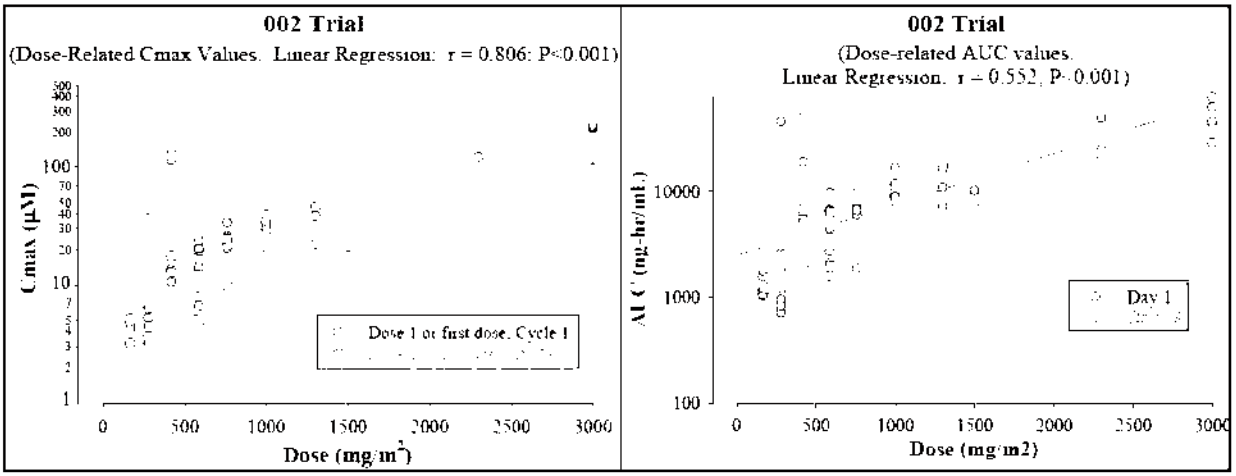
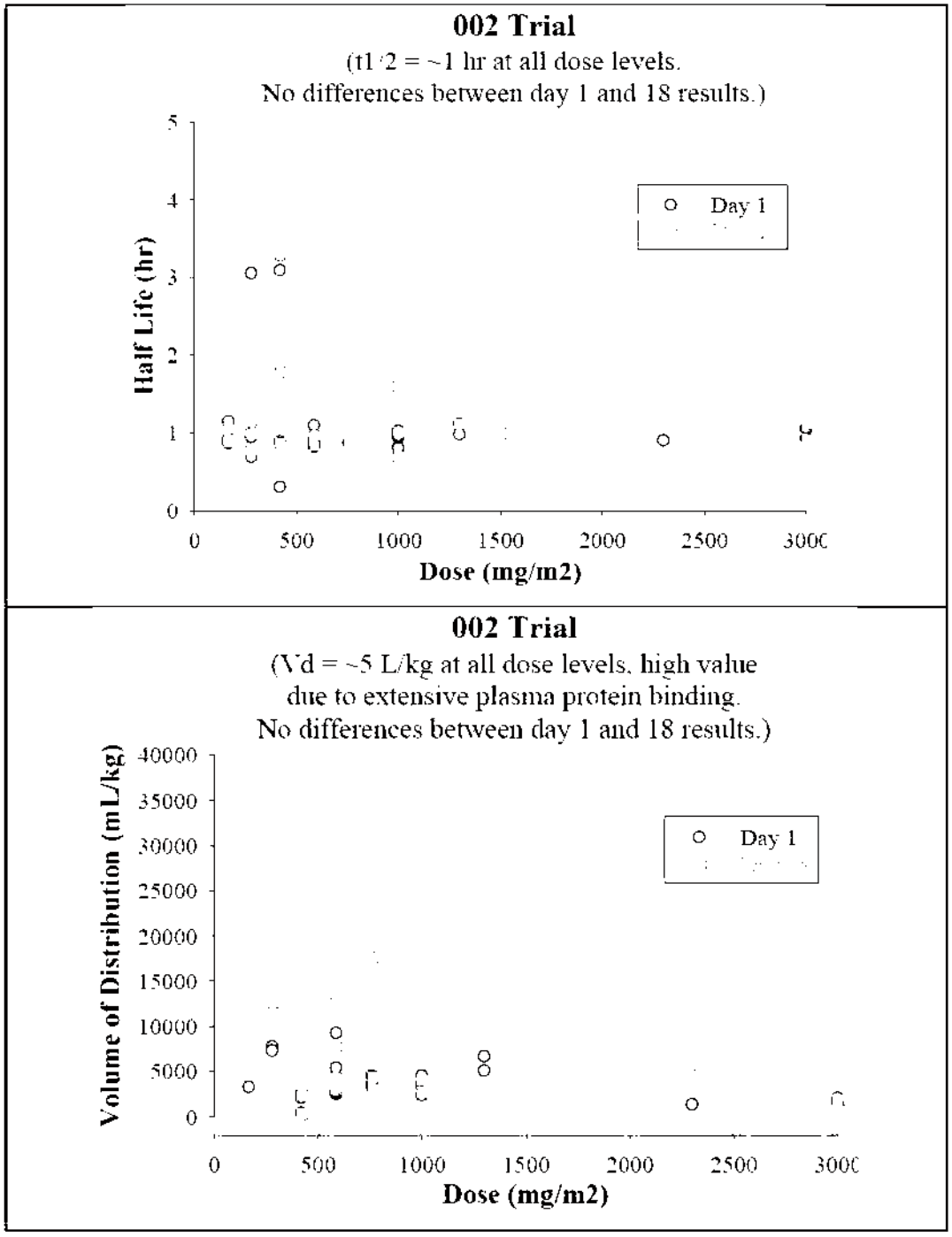
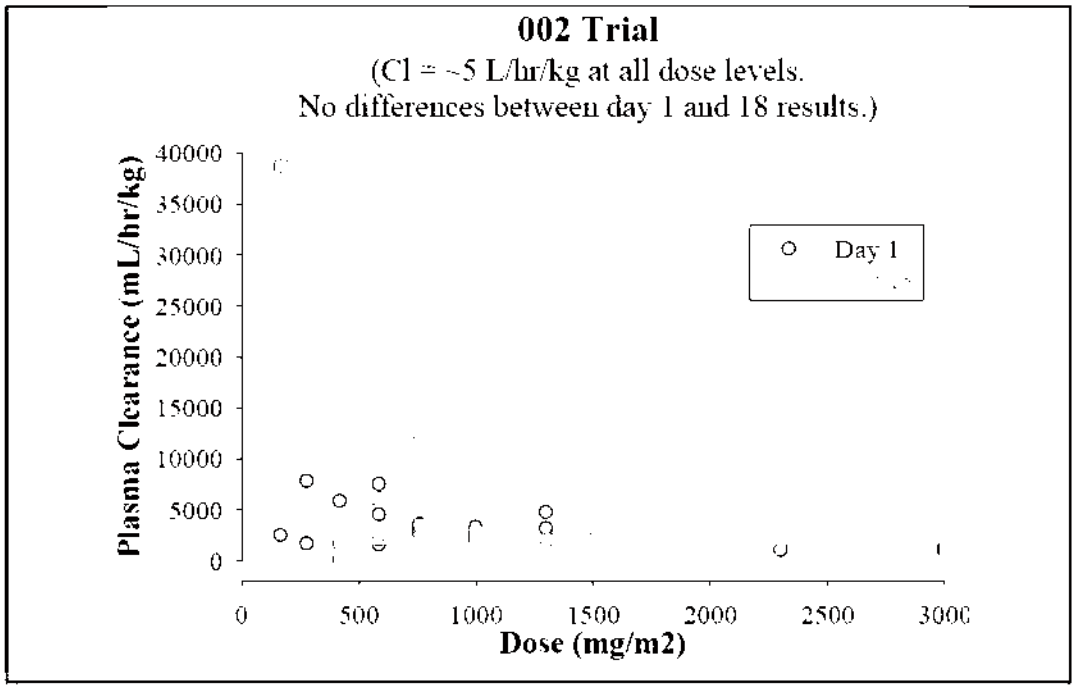


Figure 5 Half-life, Vd and CL associated with 21 to 3,000 mg/m^2 of CPI-613® (devimistat) in Study CL-CPI-613-002





2.1.5.1.2. Study CCCWFU 29109

This was a Phase I open label, dose-escalation trial in 26 patients with advance hematologic malignancies involving 2 steps – the Dose Escalation step and the Infusion Rate/Time Escalation step.

- **Step 1 or the Dose Escalation step used a 2-stage dose-escalation scheme (single-patient & traditional stages):** In the single-patient stage, the starting dose was 420 mg/m^2 IV infusion over 2 hours given twice weekly for three consecutive weeks. A single patient was accrued per dose level. The second patient was dosed at 840 mg/m^2 and a Grade 2 toxicity was attributed as possible and the standard (traditional) dose escalation phase was triggered. In the traditional dose-escalation stage, the planned escalating dose levels are the multiples (1.0, 2.0, 3.3, 5.0, 7.0, 9.0, 12.0, and 16.0) of the dose level which was the last dose level for the Single-Patient Dose-Escalation Stage. After the dose had been escalated to 2,940 mg/m^2 without identification of a DLT, the trial was amended to shorten the infusion time to 1 hour.

- **Step 2 or the Infusion Rate/Time Escalation step** began once 2,940 mg/m^2 (rounded up to 3,000 mg/m^2) of devimistat has been found to be safe according to Step 1. When infused over 1 hour, 2 patients developed Grade 3 renal failure. Infusion time was returned to 2 hours and dose escalation resume. The dose was escalated in using a 1-3-6 scheme in 6 cohorts to a final dose of 3,780 mg/m^2. At a dose of 3,780 mg/m^2, one

patient experienced prolonged Grade 3 nausea and one patient Grade 3 renal failure, defining this dose as above the MTD. A total of 6 patients were treated at a dose of 2,940 mg/m^2 over 2 hours with no dose-limiting toxicities observed, establishing this as the MTD.

Plasma samples for measurement of devimistat concentrations associated with the 1st and 6th administrations of devimistat in Treatment Cycle 1 were obtained pre-dose (~5 min before dosing), and at 0.5, 1, 1.5, 2, 4, 6, 8, 24, 48 and 72 hr. post dose. The 8-hr samples should be done if time and personnel permit, and the 72-hr sample for Day 1 dosing can be the pre-dose sample for Day 4 dosing. Additionally, pre-dose samples associated with all other doses (i.e., 2nd - 5th doses) were also obtained.

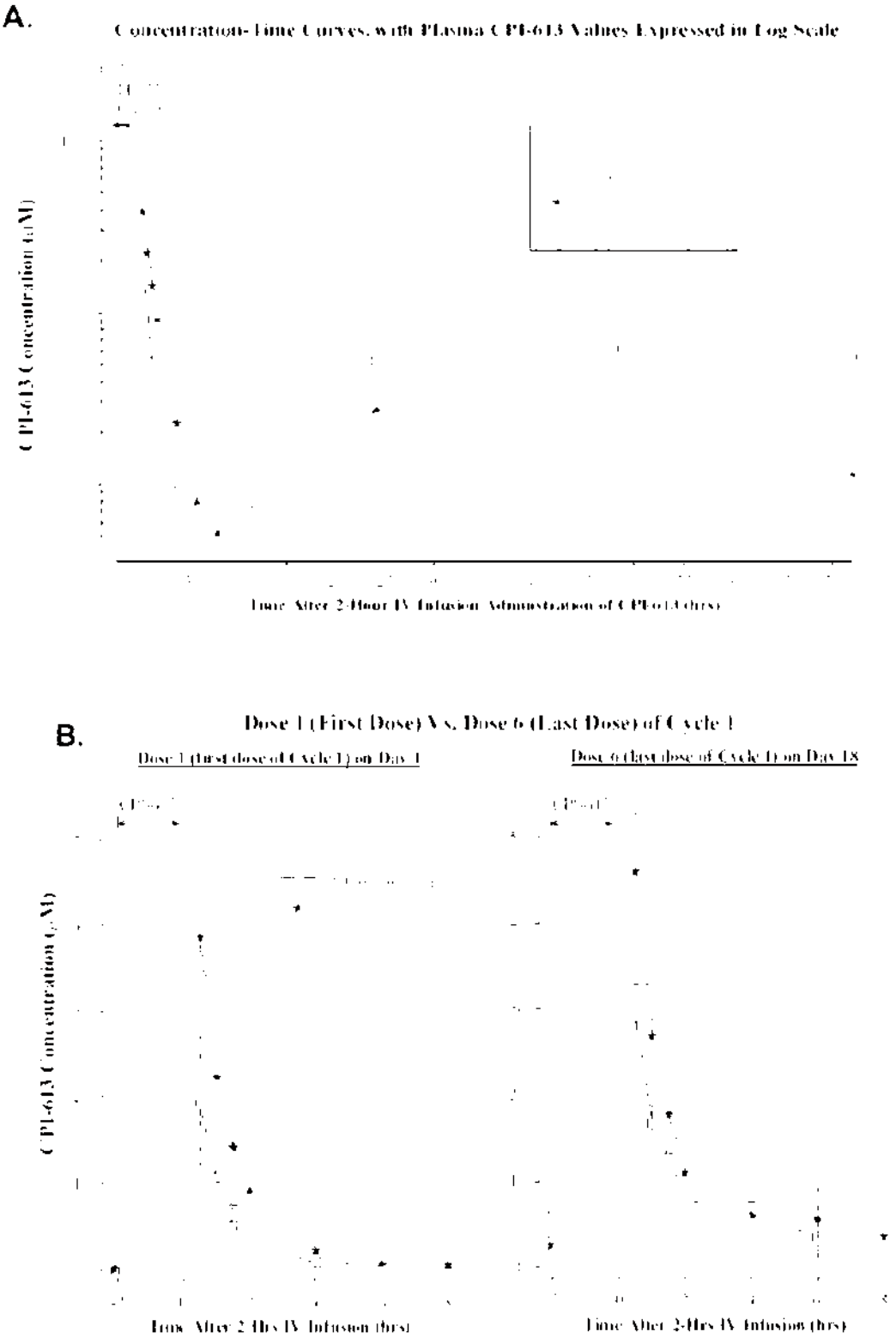
The results from all 26 patients, except 3, follow a similar pattern associated with the timing of dosing in that there was a relatively rapid decline in plasma levels during the first 8-10 hours post- administration followed by low plasma devimistat values that persist for several days. The 3 patients that had plasma levels not following this pattern were Patient #2, 3, and 5. The plasma devimistat levels of these 3 patients were erratic. The erratic results from these 3 patients were not observed in other patients treated with similar dose levels of devimistat in other clinical trials. Due to the erratic results from these patients, the 420 and 840 mg/m^2 dose groups, which contained these 3 patients, were not included in subsequent analysis.

The concentration-time curves associated with all dose levels of devimistat were triphasic. The α- phase occurred during the first 6-8 hours post-administration and was associated with a relatively rapid decline in the mean plasma devimistat concentrations with a half-life of ~1.3 hrs. and mean residence time of ~1.8 hours. The β-phase occurred from 6-8 hours to 24 hours post-administration and was associated with a modest increase in the mean plasma devimistat values, from ~0.5 to 4μM when averaged across all dose levels. The γ or final phase started from 24 hours until 72 hours post-administration and was associated with a very slow decline in mean plasma devimistat values, consistent with the high plasma protein binding properties of devimistat (Figure 6).

Devimistat could not be detected in the plasma prior to administering the 1st dose, but the baseline plasma devimistat values associated with Dose 6 had an overall average value of ~3 μM. The amount of devimistat present in the plasma prior to the 6th dose was only ~10% of the C_{max} value of ~45 μM induced by the MTD (2,940 mg/m^2 given over 2 hours) of devimistat. The

small residual devimistat in the plasma did not have any significant drug accumulation effects, as reflected by the concentration-time curves associated with Dose 1 being comparable to that of the 6th (last) dose of Cycle 1 (Figure 6).

Figure 6 Plasma CPI-613® (devimistat) concentration-time profiles (Study CCCWFU 29109)



Source: [Pardee et al., 2014][14]

2.1.5.1.3. Study CCCWFU 57112

This is a Phase I open-label dose-escalation trial of devimistat in combination with modified FOLFIRINOX in patients with metastatic pancreatic cancer using a two-stage dose-escalation scheme (Single-Patient Dose-Escalation and Traditional Dose-Escalation design):
In the Single-Patient Dose-Escalation stage, a single patient was accrued per dose level. The starting dose of devimistat was 500 mg/m^2/day given over 2-hour infusion. Single-Patient Dose-Escalation was used to escalate the dose of devimistat in no more than 3 dose levels.
In the Traditional Dose-Escalation stage, the escalating dose levels of devimistat were the multiples (1.0, 2.0, 3.3, 5.0, and 6.0) of the dose level which was the last dose level for the Single- Patient Dose-Escalation Stage. The maximum allowable dose was set at 3,000 mg/m^2/day.

Treatment was given in two-week cycles, with devimistat administered prior to other therapy on Day 1 and after completion of therapy on day 3, and FOLFIRINOX administered on Days 1-3. Plasma samples for determination of devimistat concentrations and its major metabolite, CPI-2850, and possibly other analyses associated with Cycle 1 were obtained pre-dose (~5 min before dosing), and at 0.08, 0.5, 1, 1.5, 2, 4, 6, 8 (optional) and 24 hours after the first dose of devimistat on Day 1, as well as immediately prior to the administration of devimistat on Day 3 and immediately prior to the administration of Myeloid Growth Factor on Day 4, if feasible.

Devimistat is rapidly and extensively converted to its principal metabolite CPI-2850 which is produced predominantly in tumors by beta oxidation of the parent drug. This conversion has been observed in patients dosed with devimistat as a single agent and when dosed in combination with FOLFIRINOX. Both devimistat and CPI-2850 exhibit extensive and high affinity binding to serum albumin (greater than 99.7%).

Pancreatic cancer patients in the 57112 study were dosed over an approximate 20-30 minutes in combination with FOLFIRINOX as described. Blood samples from patients were taken at the time points indicated in over a 72-hour period beginning 5 minutes post IV infusion. Cellular components were removed by centrifugation and plasma prepared for each time point. Devimistat as well as CPI-2850 and other potential metabolites were extracted from plasma using an acetonitrile solvent mix. HPLC analysis with UV detection was performed and calibration curves generated for retention time characterization, spike and recovery measurement

and quantification using chemically synthesized devimistat, CPI-2850 and each of the additional metabolites described earlier as standards.

Figure 7 below show the averaged results for 15 evaluable patients with the bars showing the range of levels observed for both devimistat and CPI-2850 over 24 and 72 hours.

Figure 7 Plasma concentration-time profiles of CPI-613® (devimistat) and CPI-2850 (Study CCCWFU 57112)

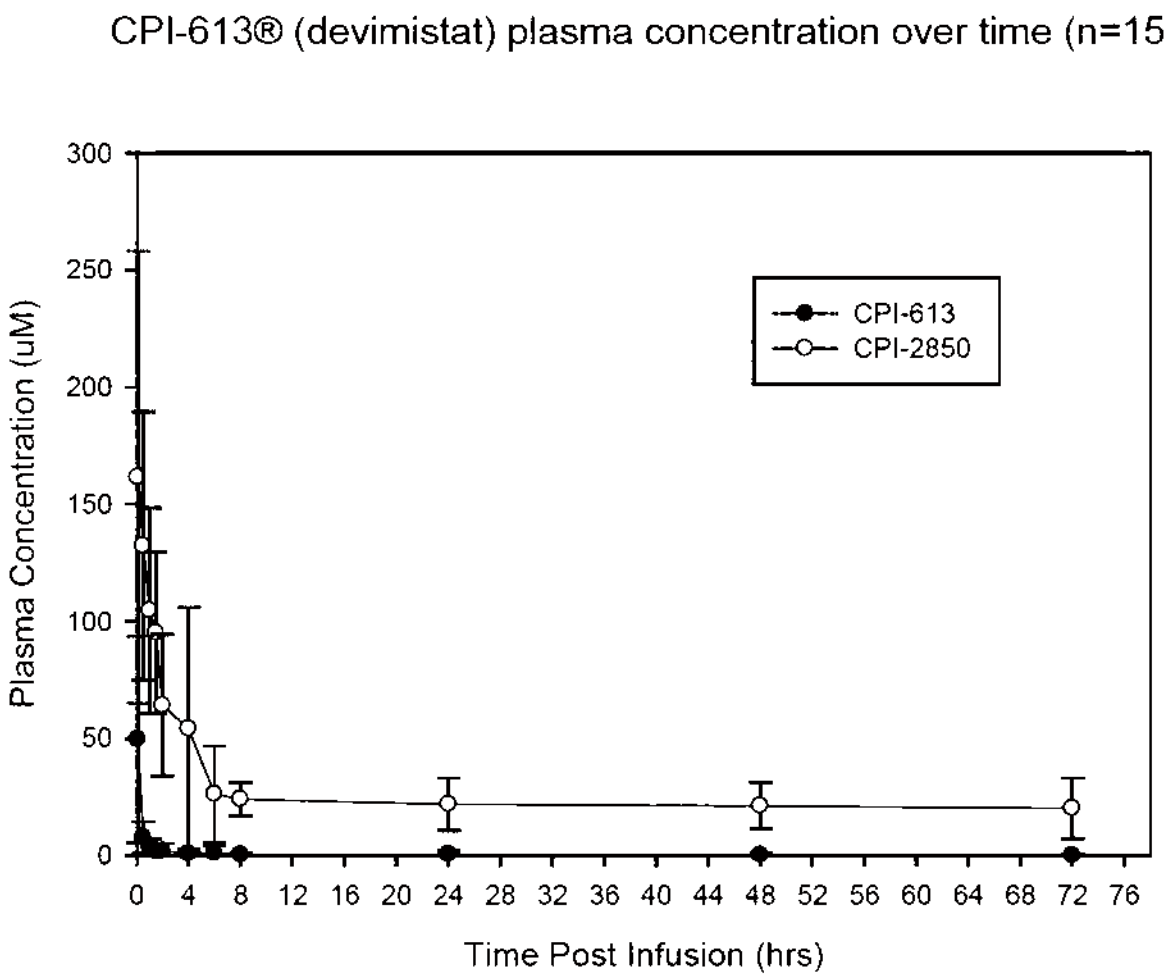
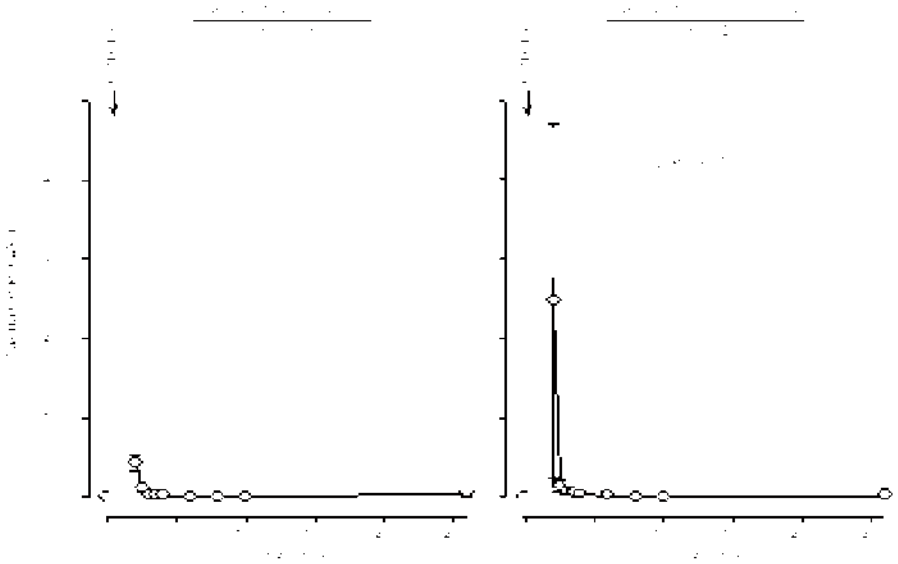


Figure 8 (Below). Metabolism and elimination pharmacokinetics from patient plasma when devimistat was dose escalated in combination with FOLFIRINOX and measured as described above. Devimistat was rapidly and extensively converted to CPI-2850 independent of the dose given with a substantially higher C_{max} for both devimistat and CPI-2850 at 1.000 mg/m^2 when compared to the 500 mg/m^2 dosing.

Figure 8 Plasma concentration-time profiles of CPI-613® (devimistat) and CPI-2850 after administration of CPI-613® (devimistat) in combination with FOLFIRINOX (Study CCCWFU 57112)



2.1.5.1.4. Study CCCWFU 22112

This is a Phase I open label, dose-escalation trial devimistat given with high dose cytarabine and mitoxantrone (HAM) in patients with relapsed or refractory AML using a 3-stage dose-escalation scheme (Single-Patient Dose-Escalation, Traditional Dose-Escalation, and Extended Cohort Escalation).

In the Single-Patient Dose-Escalation stage, a single patient was accrued per dose level. The starting dose of devimistat was 500 mg/m^2/day IV infusion given over 2 hours on days 1-5. Cytarabine was given at 3gm/m^2 for age <60 or 1.5 gm/m^2 IV infusion for age ≥60 over 3 hours every 12 hours for 5 doses starting on day 3. Mitoxantrone was given at 6 mg/m^2 IV infusion daily for 3 doses given over 15 minutes after 1st, 3rd and 5th doses of Cytarabine. Devimistat dose level was escalated by increasing the dose by 500 mg/m^2 and the final devimistat dose in this stage was 1,000 mg/m^2.

In the Traditional Dose-Escalation stage, the devimistat dose started at 1,000 mg/m^2 and the dose escalation step was 250 mg/m^2. The dose was escalated to 2,250 mg/m^2. In the Extended Cohort Escalation stage, the devimistat doses were started at 1,750 mg/m^2 and escalated to 2,750 mg/m^2.

After the dose limiting toxicity (DLT) was observed in 2,750 mg/m^2 dose level, protocol was

amended to expand 1,500 and 2,000 mg/m^2 dosing levels. Plasma samples for measurement of devimistat concentrations associated with the 1st and 5th administrations of devimistat in Treatment Cycle 1 were obtained pre-dose (~5 min before dosing) and at the following times after the completion of infusion: 0.08, 0.5, 1, 1.5, 2, 4, 6, and 8 hours (if time and personnel permit). Additionally, plasma samples for measurement of devimistat concentrations were obtained pre- dose (~5 min before dosing) for all other administrations of devimistat (i.e., 2nd, 3rd, 4th and 5th) administrations of devimistat of Treatment Cycle 1.

A total of 40 patients with advanced pancreatic cancer have been dosed with devimistat, both in single agent and combination trials. Of these 40 patients, 14 received devimistat as a single agent in trials CPI-613-002, CL-CPI-613-023, and CCCWFU 57113; 6 received devimistat in combination with gemcitabine in trial CL-CPI-613-004; and 20 received devimistat in combination with mFFX in trial CCCWFU 57112.

In a phase I open-label, single arm clinical trial of devimistat in patients with metastatic and locally advanced pancreatic adenocarcinoma and poor performance status (CCCWFU57113), 9 patients were dosed with devimistat alone. The safety of devimistat was evaluated in 6 patients. A total of 124 toxicities were reported of which 18 were considered Grade 3 or above (15%). Devimistat monotherapy in pancreatic cancer exhibited 100% disease progression. In a Phase I/II open-label, single arm, dose-escalation clinical trial of devimistat in combination with gemcitabine in cancer patients (CL-CPI-613-004), 6 pancreatic cancer patients were dosed with devimistat in combination with gemcitabine. Out of these 6 patients 2 exhibited stable disease. In a phase I open label, dose-escalation study of devimistat monotherapy in cancer patients (CL-CPI-613-002); 4 patients with pancreatic cancer were dosed with devimistat and all patients exhibited stable disease. In a phase II open label study of devimistat monotherapy in cancer patients (CL-CPI-613- 023), only one pancreatic cancer patient was dosed with devimistat and the patient exhibited disease progression.

2.1.5.2.1. CCCWFU 57112:

Phase I Study of CPI-613® (devimistat) + modified FOLFIRINOX in Patients with Metastatic Pancreatic Cancer

The interim result of this trial was presented in European Society for Medical Oncology

(ESMO) annual meeting in 2016, in Gastrointestinal Cancers Symposium 2016 and a manuscript is now published in Lancet Oncology (Lancet Oncol. 2017 Jun;18(6):770-778).

This trial, which was an investigator-initiated trial conducted under IND 117500, was a Phase I open-label, dose-escalation trial of devimistat in combination with mFFX in patients with metastatic pancreatic cancer and good performance status. All patients had to have an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1. The objectives of the trial included determining the MTD of devimistat when used in combination with mFFX, overall survival, and progression-free survival (PFS) along with obtaining safety data and preliminary efficacy data. The mFFX regimen was identical to the standard FOLFIRONOX regimen with the exceptions of a dose reduction of oxaliplatin at 65 mg/m^2 and irinotecan at 140 mg/m^2. These dose reductions were incorporated to reduce the potential for overlapping hematologic and gastrointestinal toxicities with devimistat. Treatment was given in 2-week cycles with devimistat administered prior to other therapy on Day 1 and after completion of therapy on Day 3; mFFX was administered on Days 1-3.

This trial followed a two-stage dose-escalation scheme (single patient and traditional 3+3 design). In the single patient stage, a single patient was to be accrued per dose level. The starting dose of devimistat was 500 mg/m^2/day given over 2-hour infusion via a central catheter. This starting dose was chosen as it was significantly less than the Phase I single-agent trials dosing of 3,000 mg/m^2. The devimistat dose level was escalated by doubling the previous dose if there was no toxicity greater than Grade 1 within 4 weeks attributed as probably or definitely related to devimistat. The traditional 3+3 dose-escalation stage was triggered if toxicity attributed as probably or definitely related to devimistat was greater than or equal to Grade 2. The maximum allowable dose was set at 3,000 mg/m^2 (the single agent MTD).

The initial patient received devimistat 500 mg/m^2/day plus mFFX. No toxicity ≥ Grade 2 was attributed to devimistat; therefore, the devimistat dose was increased to 1,000 mg/m^2 for the second patient enrolled into the study. A DLT was observed, so the cohort was expanded with the third enrolled patient receiving 1,000 mg/m^2. This patient also experienced a DLT. The DLTs experienced by the two patients who received 1,000 mg/m^2 included anemia, pulmonary embolus, electrolyte deficiencies, and dehydration. Because the second and third patients who received 1,000 mg/m^2 experienced DLTs, the dose was decreased back to 500 mg/m^2. Three patients were enrolled at this lower dose and none experienced a DLT. An additional three

patients were enrolled, and none experienced a DLT. At this point, the dose of 500 mg/m^2/day given over 2 hours on day 1 and day 3 of each cycle was considered to be the MTD. An additional 11 patients (for a total of 18) were then enrolled at this dose to further evaluate toxicity and preliminary efficacy. None of these additional 11 patients experienced a DLT.

Tumor response was assessed after every 4 cycles (approximately 2 months) of treatment with devimistat plus mFFX using magnetic resonance imaging (MRI) of the abdomen and contrast computed tomographic (CT) of the chest. If the investigator determined that tumor progression had occurred, the patient was removed from the study. If the investigator determined that the patient had stable disease or other favorable response, the patient continued treatment for an additional 4 cycles (approximately 2 months) at which time the patient underwent re-imaging with MRI of the abdomen and contrast CT of the chest. Again, only patients who were determined by the investigator to have stable disease or other favorable response continued with subsequent re- imaging after every 4 cycles of treatment until unacceptable toxicity, evidence of disease progression, or patient request to withdrawal.

Efficacy:

A total of 20 patients, ages 48-72, were dosed with devimistat plus mFFX of which 18 were evaluable. The 2 patients who experienced DLTs were not evaluable as they did not have follow-up radiology assessments per RECIST guidelines version 1.1. Patients must have completed one treatment cycle to be considered evaluable. Overall, 17% of patients achieved a complete response (CR), 44% achieved a partial response (PR), 17% achieved stable disease (SD), and 22% had progressive disease (PD). The overall response rate (ORR=CR+PR) was 61%. Median Overall Survival (OS) is 19.9 months, median Progression Free Survival (PFS) is 9.9 months, and Duration of Response (DOR) is 9.2 months. These Median OS, PFS and DOR have been estimated as per the latest available data (March 2018). Given that the Phase III clinical trial evaluating the FFX regimen reported an ORR of 31.6%, CR of <1%, median OS of 11.1 months, median PFS of months, and DOR of 5.9 months reported in literature, the further evaluation of devimistat in pancreatic cancer is warranted and the present Phase III trial has been proposed.

Table 3 Efficacy results of trial CCCWFU57112 (data cut-off as of August 2018):

N	Median Age	Median OS (months)	Median PFS (months)	Response (RECIST v1.1) N (%)				
				CR	PR	SD	PD	ORR (CR + PR) *
18	64	19.9	9.9	3 (17%)	8 (44%)	3 (17%)	4 (22%)	11 (61%)

Abbreviations: CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease.

**Investigator assessment of radiology*

Table 4 CPI-613[§] (devimistat) in Combination with Modified FOLFIRINOX in Metastatic Pancreatic Cancer: Exhibited Substantially Higher Efficacy Compared to Current Standard of Care

	Gemcitabine	Gemcitabine + nab-Paclitaxel	FOLFIRINOX	FOLFIRINOX (Historical)	mFOLFIRINOX + devimistat
N	171	431	171	14	18
OS	6.8	8.5	11.1	-	19.9
PFS	3.3	5.5	6.4	-	9.9
CR	0%	<1%	<1%	0%	17%
PR	9.4%	23%	31%	14%	44%
SD	41.5%	27%	38.6%	29%	17%
PD	34.5%	20%	15.2%	57%	22%
NE	14.6%	30%	14.6%	-[§]	-[§]
ORR	9.4%	24%	31.6%	14%	61%
DOR[†]	3.9	-	5.9	-	9.2**
Median Age	61	62	61	60	64
	N Engl J Med 2011;364:1817-25.	*N Engl J Med 2013;369:1691-703*	*N Engl J Med 2011;364:1817-25.*	*Wake Forest University Historical Cohort*	*Lancet Oncol. 2017 Jun;18(6):790-797*

§ Analysis in evaluable patients

†Duration of Response

***Duration of response - removing SD/PD (N = 11)*

≠ Median (Months)

Safety:

The median relative dose intensities were 92% (IQR 77–98) for fluorouracil, 85% (72–85) for irinotecan, and 77% (59–77) for oxaliplatin. 13 (72%) patients underwent oxaliplatin reduction, two (11%) underwent irinotecan reduction, and seven (38%) underwent fluorouracil reduction based on haematological and non-haematological toxicity per protocol. Nine (50%) patients had more than 12 cycles of treatment and seven (38%) patients had more than 24 cycles.

A dose-limiting toxicity was not recorded in the first patient enrolled during the single-patient dose-escalation stage at a dose of 500 mg/m^2, and the dose was increased. Two patients were enrolled at this higher dose (1,000 mg/m^2) and both had a dose-limiting toxicity. The dose-limiting toxicities for patient 2 were anaemia, lymphopenia, pulmonary embolus, hyponatraemia, and dehydration. This patient refused further treatment and opted for hospice care. The dose-limiting toxicities for patient 3 were hyponatraemia, hypotension, and lymphopenia. This patient came off the study because of drug-related toxicity. Thus, the dose was lowered to the original dose (500 mg/m^2). Three patients were enrolled at this lower dose and none reported a dose-limiting toxicity. An additional three patients were enrolled, none of whom experienced a dose-limiting toxicity. At this point, 500 mg/m^2 per day given at a rate of 4 mL/min on day 1 and day 3 of each cycle was deemed the maximum tolerated dose. An additional 11 patients (for a total of 18) were then enrolled at this dose to further assess toxic effects and preliminary activity. None of these additional 11 patients had a dose-limiting toxicity.

We recorded two unexpected serious adverse events, both for the first patient enrolled at the 500 mg/m^2 dose: possible leaching due to infusion of devimistat via non-poly(vinyl chloride) tubing, and the patient re-accessed her port at home after accidental de-access. Neither incident resulted in a negative clinical outcome.

Expected serious adverse events were: thrombocytopenia, anaemia, and lymphopenia (all for patient number 2, with anaemia and lymphopenia being a dose-limiting toxicity); hyperglycaemia (patient number 7); hypokalaemia, hypoalbuminaemia, and sepsis (patient number 11); and neutropenia (patient number 20). No deaths due to adverse events occurred.

As anticipated, electrolyte imbalance was most frequent and managed with supportive care. No patients died while on active treatment; 11 study participants died, with cause of death as terminal pancreatic cancer.

A total of 20 patients were dosed with devimistat in combination with mFFX and all are included in the safety evaluation. A total of 690 toxicities were reported by the 20 patients, of which 118 were considered Grade 3 or above (17%).

Table 5 Summary of Toxicities in Study CCCWFU57112

CCCWFU57112 (N = 20) - As of April 23, 2019	**%***
Grade 3 and Above Toxicities (Treatment Related + Not Related):	**17% (118 out of 690 reported toxicities)**
Most Frequent Treatment Related Toxicities (All Grades) Occurring ≥10% of Patients:**	
Blood and lymphatic system disorders / Anemia	80%
General disorders and administration sit / Fatigue	75%
Investigations / Platelet count decreased	75%
Gastrointestinal disorders / Diarrhea	70%
Gastrointestinal disorders / Nausea	70%
Metabolism and nutrition disorders / Hyponatremia	70%
Nervous system disorders / Peripheral sensory neuropathy	65%
Investigations / Alkaline phosphatase increased	60%
Investigations / Lymphocyte count decreased	60%
Metabolism and nutrition disorders / Hypokalemia	60%
Investigations / Aspartate aminotransferase increased	55%
Metabolism and nutrition disorders / Anorexia	55%
Investigations / Alanine aminotransferase increased	50%
Metabolism and nutrition disorders / Hypomagnesemia	50%
Nervous system disorders / Dysgeusia	50%
Metabolism and nutrition disorders / Hyperglycemia	45%
Investigations / White blood cell decreased	40%
Metabolism and nutrition disorders / Hypoalbuminemia	40%
Investigations / Neutrophil count decreased	35%
Investigations / Weight loss	35%
Metabolism and nutrition disorders / Dehydration	35%
Metabolism and nutrition disorders / Hypocalcemia	30%
Gastrointestinal disorders / Vomiting	25%
Renal and urinary disorders / Chronic kidney disease	25%
General disorders and administration sit / Pain	20%
Blood and lymphatic system disorders / Leukocytosis	15%

Investigations / Blood bilirubin increased	15%
Metabolism and nutrition disorders / Hypophosphatemia	15%
Gastrointestinal disorders / Mucositis oral	10%
General disorders and administration sit / Edema limbs	10%
General disorders and administration sit / General disorders and administration site conditions – Other	10%
Metabolism and nutrition disorders / Hypernatremia	10%
Metabolism and nutrition disorders / Hypoglycemia	10%
Nervous system disorders / Dizziness	10%
Psychiatric disorders / Insomnia	10%
Vascular disorders / Thromboembolic event	10%
Grade 5 Toxicities (Treatment Related + Not Related):	**0%**
Grade 4 Toxicities (Treatment Related + Not Related):	
Blood and lymphatic system disorders / Anemia	5%
Investigations / Platelet count decreased	5%
Investigations / Lymphocyte count decreased	5%
Metabolism and nutrition disorders / Hypokalemia	5%
Metabolism and nutrition disorders / Hyperglycemia	5%
Metabolism and nutrition disorders / Hypoalbuminemia	5%
Investigations / Neutrophil count decreased	5%
Infections and infestations / Sepsis	5%
Grade 3 Toxicities (Treatment Related + Not Related) Occurring ≥10% Patients:	
Metabolism and nutrition disorders / Hyperglycemia	45%
Investigations / Lymphocyte count decreased	30%
Metabolism and nutrition disorders / Hypokalemia	30%
Gastrointestinal disorders / Diarrhea	25%
Metabolism and nutrition disorders / Hyponatremia	25%
Nervous system disorders / Peripheral sensory neuropathy	25%
Vascular disorders / Thromboembolic event	25%
Blood and lymphatic system disorders / Anemia	20%
Investigations / Neutrophil count decreased	20%
Vascular disorders / Hypertension	20%
Gastrointestinal disorders / Abdominal pain	20%
Investigations / Platelet count decreased	15%
General disorders and administration sit / Fatigue	15%
Metabolism and nutrition disorders / Dehydration	15%
Gastrointestinal disorders / Vomiting	15%
Blood and lymphatic system disorders / Leukocytosis	15%
Metabolism and nutrition disorders / Hypophosphatemia	15%

Gastrointestinal disorders / Nausea	10%
Cardiac disorders / Cardiac disorders - Other	10%
Respiratory, thoracic and mediastinal di / Dyspnea	10%
Infections and infestations / Enterocolitis infectious	10%
Infections and infestations / Lung infection	10%
Respiratory, thoracic and mediastinal di / Hypoxia	10%

**% of patients unless otherwise specified; **Adverse events considered by the investigator to be related (probably or possibly related) to study drug treatment in combination [related here refers to combination of both devimistat and mFFX (not devimistat alone)]*

Table 6 Clinical Experience of CPI-613® (devimistat) in Solid Tumors and Hematological Malignancies

No.	Trial ID, NCT ID, US FDA IND No.	Phase	Indication	Treatment Detail	#Dosed	#Evaluated for Efficacy	#Evaluated for Safety	Efficacy Summary	Recruitment Status	Result (Interim/Final)	
										Efficacy	Safety
1	*CCCWFU 22215; NCT02484391;* 107800*	II	Relapsed or Refractory Acute Myeloid Leukemia (AML); Granulocytic Sarcoma	CPI-613® (devimistat) + Cytarabine + Mitoxantrone hydrochloride	48	47	48	CR: 32% CRi: 13%	*Closed (Active not recruiting)*	Final *(October 11, 2018)*	(April 23, 2019)
2	*CCCWFU 22112; NCT01766805;* 107800*	I	Relapsed or Refractory Acute Myeloid Leukemia (AML)	CPI-613® (devimistat) + Cytarabine + Mitoxantrone hydrochloride	67	62	66	CR: 42% CRi: 8%	*Closed (Completed)*	Final *(March 07, 2017)*	Final *(September 29, 2016)*
3	*CCCWFU 57112; NCT01835041;* 117500**	I	Metastatic Pancreatic Cancer	CPI-613® (devimistat) + mFOLFIRINOX	20	18	20	Median OS: 19.9 months Median PFS: 9.9 months ORR: 61% Median	*Closed (Active not recruiting)*	Final *(March 07, 2017)*	Final *(September 29, 2016*

No.	Trial ID, NCT ID, US FDA IND No.	Phase	Indication	Treatment Detail	#Dosed	#Evaluated for Efficacy	#Evaluated for Safety	Efficacy Summary	Recruitment Status	Result (Interim/Final)	
										Efficacy	Safety
								DOR #: 9.2 months			
4	*GA CPI-613; NCT0343 5289;* 136461**	I	Locally Advanced or Metastatic Pancreatic Cancer	CPI-613® (devimistat) + Gemcitabine – Nab-paclitaxel	16	8	16	ORR: 63.0%		*(May 13, 2019)*	*(May 15, 2019)*
5	*CCCWF U57113; NCT018 3 9981;* 117500**	I	Locally Advanced or Metastatic Pancreatic cancer	CPI-613® (devimistat)	9	5	9	PD: 100%	*Closed (Completed)*	Final *(December 2016)*	Final *(January 26, 2018)*
6	*CCCWF U28314; NCT021 68140;* 123218*	I	Relapsed or Refractory T- Cell Lymphoma or Hodgkin Lymphoma	CPI-613® (devimistat) + Bendamustine hydrochloride	14	8	14	Median OS: 9.2 months Median PFS: 6.4 months ORR: 75%	*Closed (Now not recruiting)*	*(January 23, 2019)*	*(April 23, 2019)*
7	*CCCWF U29113; NCT019 0 2381;* 107800*	II	Relapsed or Refractory Myelodysplastic Syndrome (MDS)	CPI-613® (devimistat)	12	12	12	CRi: 8% Marrow CR: 8%	*Closed (Suspended – lack of accrual)*	Final *(November 21, 2018)*	Final *(April 23,2019)*
8	*CCCWF U29109; NCT010 3 4475;* 107800*	I	Advanced Hematological Malignancies	CPI-613® (devimistat)	26	20	26	CR:5% MLFS: 5% PR: 10%	*Closed (Completed)*	Final *(April 21, 2015*	Final *(March 01, 2015)*
9	*CCCWF U59212; NCT017 6 0219;* 117500**	I/II	Cholangiocarcinoma: Liver Cancer; Bile Duct Cancer	CPI-613® (devimistat)	17	13	17	SD: 15%	*Closed (Completed)*	Final *(December 27, 2017)*	Final *(September 14, 2018)*
10	*CCCWF U59314; NCT022 3 2152;* 117500**	I	Metastatic Colorectal Cancer	CPI-613® (devimistat) + Fluorouracil	18	6	18	MR: 17%		*(December 2017*	*(April 23, 2019*

No.	Trial ID, NCT ID, US FDA IND No.	Phase	Indication	Treatment Detail	#Dosed	#Evaluated for Efficacy	#Evaluated for Safety	Efficacy Summary	Recruitment Status	Result (Interim/Final)	
										Efficacy	Safety
11	*CCCWFU 62113; NCT01983787;* 119491**	I	Relapsed or Refractory Small Cell Lung Cancer	CPI-613® (devimistat)	14	13	8	PD: 100%	*Closed (Completed)*	Final *(December 2016*	Final *(March 01, 2015)*
12	*CCCWFU 28114; NCT02168907;* 123218*	I	Relapsed or Refractory B- Cell Non-Hodgkin Lymphoma	CPI-613® (devimistat) + Bendamustine hydrochloride + Rituximab	1	1	1	PD: 100%	*Closed (Terminated)*	Final *(December 2016)*	Final *(July 2016)*
13	*CL-CPI-613-002; NCT00744403;* 74530	I	Advanced Cancer	CPI-613® (devimistat)	41	41	39	SD: 61%	*Closed (Completed)*	Final *(April 21, 2015)*	Final
14	*CL-CPI-613-004; NCT00907166;* 74530	I/II	Cancer; Pancreatic Cancer	CPI-613® (devimistat) + Gemcitabine	38	31	33	SD: 68%	*Closed (Terminated)*	Final *(April 21, 2015)*	Final
15	*CL-CPI-613-023; NCT01832857;* 74530	II	Cancer	CPI-613® (devimistat)	7	5	7	SD: 40%	*Closed (Terminated)*	Final *(June 02, 2015)*	Final

 # Duration of Response
**Cross referred to Rafael IND 114372*
***Cross referred to Rafael IND 74530*

2.2. Rationale

Current Limitations of Knowledge or Therapy in Pancreatic Cancer:

Pancreatic cancer is the third leading cause of cancer death, and its prognosis is grim: 5-year survival rate being 6-8%[3]. Due to a lack of treatment options, gemcitabine became the reference regimen for advanced pancreatic cancer for many years, even though gemzar alone offers only marginal improvement in overall survival (5.6 vs. 4.4 months, gemzar vs. fluorouracil)[16]. The combination of gemzar with a variety of cytotoxic and targeted agents has generally shown no significant survival advantage as compared with gemzar alone[13]. Some clinical studies have suggested a benefit with gemzar -based cytotoxic combinations in patients with good performance status[16]. However, gemzar -based cytotoxic combinations are very toxic and patients experience poor quality of life during treatment. The most promising results reported to date is FFX (a 4-drug combination of 5-FU, folinic acid, irinotecan and oxaliplatin)[12], and the

nab-paclitaxel + gemzar combination[13], which provide a median overall survival of 11.1 months and 8.5 months, respectively, in metastatic pancreatic cancer patients. However, these drugs have high toxicity and only patients with favorable performance status are eligible to receive these regimens. Although these drugs significantly improve patient survival, the median overall survival of approximately 11 months in patients with good performance status is still unsatisfactory. A safer and more effective therapy for advanced pancreatic cancer is currently an active area of research and development.

Importance of the study:

Given the favorable safety and efficacy profiles of devimistat when administered in combination with mFFX along with the promising efficacy results achieved in trial CCCWFU57112, the further evaluation of devimistat in pancreatic cancer was warranted. Based on the experience in phase I study, Rafael Pharmaceuticals will initiate a phase III randomized trial of standard dose FFX versus devimistat + mFFX[17] in patients with metastatic adenocarcinoma of the pancreas. The goal of this trial is to provide compelling evidence of the safety and efficacy of this approach leading to a regulatory approval for devimistat 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.

2.3. Risk/Benefit Assessment

Please refer to the appendix III for study-specific assessment for details.

Primary Objective:

- To determine efficacy of devimistat plus mFFX compared to standard care FFX in terms of **Overall Survival (OS)**

Secondary Objectives:

- To determine efficacy of devimistat plus mFFX compared to standard care FFX in terms of **Progression-Free Survival (PFS)**.
- To determine efficacy of devimistat plus modified FOLFIRINOX (mFFX) compared to standard care FOLFIRINOX (FFX) in terms of **Objective Response Rate (ORR)**. ORR is defined as Complete Response (CR) plus Partial Response (PR).
- To evaluate **Duration of Response (DOR)**
- **Safety Analysis:** The assessment of safety will be based mainly on the frequency of adverse events based on the Common Terminology Criteria for Adverse Events (CTCAE version 4) grade. Adverse events will be coded according to MedDRA. The safety outcomes will include the occurrence of at least one serious adverse event, of at least one grade 3/4 adverse event, and of at least one adverse event requiring the discontinuation of study treatment. **QTc** intervals will be also evaluated as part of safety analysis.
- To assess **PK** of devimistat.
- To evaluate **Patient-Reported Outcomes (PRO)** for devimistat plus mFFX compared to standard care FFX.

Exploratory Objectives:

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

4.1. Description of the Study Design

This is a prospective, **multicenter**, **open label**, **randomized Phase III** study of **CPI-613® (devimistat) + 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:**

1. **Arm 1:** devimistat + mFFX
2. **Arm 2:** FFX

Subjects will be randomized in 1:1 ratio to the experimental treatment or control, using a minimization procedure (Buyse, 2000)[20]. 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).

4.2. Study Endpoints

4.2.1. Primary Endpoints

This study has one primary endpoint:

Overall Survival (OS), defined as the duration from the date of randomization to the date of death from any cause.

4.2.2. Secondary Endpoints

This study has six secondary endpoints:

- **Progression-Free Survival (PFS),** defined as 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. PFS will be confirmed by investigator's assessment with the intent to perform sensitivity analyses.
- **Objective Response Rate (ORR)**, defined as the rate of Complete Response (CR) plus Partial Response (PR). A patient's best response within the first 12 cycles will be used for this determination, as assessed by independent, blinded, central review as per RECIST guideline version 1.1.[18] ORR will be confirmed by investigator's assessment with the intent to perform sensitivity analyses.

- **Duration of Response (DOR)**
- **Safety: AEs, SAEs, QTc**.
- **Pharmacokinetics:** Full PK – C_{max}, T_{max}, AUC_{0-t}, AUC_{inf}, CL, V, $T_{1/2}$; Sparse PK – concentrations from Sparse PK sampling plus concentrations from Full PK sampling time points to be used for Population PK analysis
- **Patient-Reported Outcomes (PRO)**: At baseline and day 1 of every even numbered cycle, patient will be required to complete one self-administered quality of life instrument.
  NCCN-FACT FHSI-18 is a widely used PRO questionnaire for patients with hepatobiliary cancer (liver, bile duct and pancreas) developed by FACIT.org available at: *http://www.facit.org/FACITOrg/Questionnaires*. Summary statistics of the scores will be shown by cycle (pre and post treatment). Scores will be compared between standard and study arms. Efforts to avoid missing data will include data collection to be done during follow up clinic visits only and 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.

4.2.3. Exploratory Endpoints

- **Exploratory biomarkers:** 10 unstained slides from baseline and time of progression biopsies will be collected when available. These slides will be used for IHC staining for PDKs, PDH, KGDH, SOD2 and CD79a. They will also be used as a source of material for RNA and whole exome sequencing. Additionally, blood samples will be used as a source of circulating tumor cells and germline DNA for SNP analysis for predictors of response, resistance or toxicity. Serum samples will be utilized to analyze the concentrations of systemic metabolites.
- **PK/PD:** dose/exposure-response of devimistat on efficacy (e.g. PFS), safety (e.g. QT) and exploratory biomarkers.

5.1. Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet **all** of the following criteria:

5.1.1 Histologically or cytologically confirmed metastatic Stage IV adenocarcinoma of the pancreas

5.1.2 No prior treatments for stage IV pancreatic adenocarcinoma (prior adjuvant or neoadjuvant treatment is allowed provided completed ≥ 6 months prior to disease recurrence)

5.1.3 Eastern Cooperative Oncology Group (ECOG) performance status 0 – 1[17]

5.1.4 Male and female patients 18 – 75 years of age

5.1.5 Measurable disease determined using guidelines of Response Evaluation Criteria In Solid Tumors (RECIST version 1.1)

5.1.6 Expected survival >3 months

5.1.7 Women of child-bearing potential (i.e., women who are pre-menopausal or not surgically sterile) must use accepted highly effective contraceptive methods (abstinence, intrauterine device [IUD], oral contraceptive(s), intrauterine hormone releasing system (IUS), bilateral tubal occlusion or vasectomized partner) during and for 6 months after last study dose and must have a negative serum or urine pregnancy test within 1 week prior to treatment initiation, at monthly interval (*day 1 of every even numbered cycle)*, at the end of systemic exposure, and at 30 days after the systemic exposure

5.1.8 Males with female partners (of childbearing potential) and female partners (of child bearing potential) with male partners must agree to use double barrier contraceptive measure (a combination of male condom with either cap, diaphragm or sponge with spermicide) in addition to oral contraception or avoidance of intercourse during the study and for 6 months after last study dose is received

5.1.9 At least 2 weeks must have elapsed from any prior surgery with resolution of any sequela for randomization

5.1.10 Laboratory values ≤2 weeks prior to randomization must be:

- Adequate hematologic values
    - Platelet count ≥100,000 cells/mm^3 or ≥100 bil/L:
    - Absolute neutrophil count [ANC] ≥1,500 cells/mm^3 or ≥1.5 bil/L:

- Hemoglobin ≥9 g/dL or ≥90 g/L)

- Adequate hepatic function
  - Aspartate aminotransferase [AST/SGOT] ≤3x upper normal limit [UNL] (≤5x UNL if liver metastases present)
  - Alanine aminotransferase [ALT/SGPT] ≤3x UNL (≤5x UNL if liver metastases present)
  - Bilirubin (≤1.5x UNL); bilirubin ≤ 2.5 x ULN for subjects with Gilbert's syndrome
  - Serum albumin ≥ 3.0 g/dL
- Adequate renal function

  serum creatinine clearance CL_{cr} > 30 mL/min). (Cocroft-Gault Formula should be used for CrCl calculation)
- Adequate coagulation function

  International Normalized Ratio or INR must be <1.5 unless on therapeutic blood thinners).

5.1.11 No evidence of active infection and no serious infection within the past 30 days.

5.1.12 Mentally competent, ability to understand and willingness to sign the informed consent form

5.2. Exclusion Criteria

An individual who meets **any** of the following criteria will be excluded from participation in this study:

5.2.1 Endocrine or acinar pancreatic carcinoma

5.2.2 Known cerebral metastases, central nervous system (CNS), or epidural tumor

5.2.3 Prior treatment with any chemotherapy for metastatic adenocarcinoma of the pancreas

5.2.4 Completion of a gemcitabine-based adjuvant chemotherapy regimen within less than 6 months at the time of screening.

5.2.5 Receipt of neoadjuvant or adjuvant FOLFIRINOX therapy if <6 months prior to disease recurrence

5.2.6 Patients with hypersensitivity to devimistat, FFX treatment or any of their excipients

5.2.7 Presence of clinically significant abdominal ascites

5.2.8 Patients receiving any other standard or investigational treatment for their cancer, or any other investigational agent for any indication within the past 2 weeks prior to initiation of

devimistat treatment

5.2.9 Serious medical illness that would potentially increase patients` risk for toxicity

5.2.10 Any active uncontrolled bleeding, and any patients with a bleeding diathesis (e.g., active peptic ulcer disease)

5.2.11 Female patients who are pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment and for an additional 6 months after the last dose of study treatment

5.2.12 Female patients of childbearing potential with a positive pregnancy test assessed by a serum pregnancy test at screening

5.2.13 Female patients of childbearing potential unwilling to use 1 highly effective method of contraception during treatment and for 6 months after the last dose of study treatment

5.2.14 Male patients with a pregnant partner who are unwilling to practice abstinence or use a condom during treatment and for 6 months after completion of study treatment

5.2.15 Male patients unwilling to abstain from donating sperm during treatment and for 6 months after completion of study treatment

5.2.16 Life expectancy less than 3 months

5.2.17 Any condition or abnormality which may, in the opinion of the investigator, compromise the safety of patients

5.2.18 Unwilling or unable to follow protocol requirements

5.2.19 Active heart disease including but not limited to symptomatic congestive heart failure (NYHA class 3 or 4), symptomatic coronary artery disease, symptomatic angina pectoris, or symptomatic myocardial infarction

5.2.20 Patients with a history of myocardial infarction that is <3 months prior to registration

5.2.21 Evidence of active infection, or serious infection within the past 30 days.

5.2.22 Patients with known HIV infection

5.2.23 Patients who have received cancer immunotherapy of any type within the past 2 weeks prior to initiation of devimistat treatment (steroids given for supportive care or in response to allergic reactions are allowed at any time)

5.2.24 Requirement for immediate palliative surgery, radiation or chemotherapy of any kind. Stenting for bile duct obstruction and need for pain medications are allowed provided all other inclusion criteria are met

5.2.25 Prior malignancy except for the following: adequately treated basal or squamous cell skin cancer, *in situ* cervical cancer, adequately treated cancer from which the patient has been disease-free for at least 3 years prior to screening

5.2.26 Unwilling or unable to avoid the concomitant use of strong CYP3A4 inducers or inhibitors during treatment with irinotecan

5.2.27 A marked baseline prolongation of QT/QTc interval (e.g., repeated demonstration of a QTc interval > 480 milliseconds (ms) (CTCAE grade 1) using Fredericia's QT correction formula (i.e. QTcF)

5.2.28 A history of additional risk factors for TdP (e.g., heart failure, hypokalemia, family history of long QT syndrome)

5.2.29 The use of concomitant medications that prolong the QT/QTc intervals are excluded at screening and C1D1

5.2.30 Contraindications to any of the FFX treatment as follows:

Folinic Acid

- Calcium Folinate is contraindicated in patients who have previously shown hypersensitivity to folinate or any of the excipients.
- Calcium Folinate Injection is contraindicated in the treatment of pernicious anemia or other megaloblastic anemias where vitamin B12 is deficient. Its use can lead to an apparent response of the hematopoietic system, but neurological damage may occur or progress if already present.
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take calcium folinate tablets.

5FU/ Fluorouracil

- Fluorouracil is contraindicated in patients who have any known hypersensitivity to fluorouracil, are seriously debilitated or are suffering from bone marrow depression after radiotherapy or treatment with other antineoplastic agents, or who are suffering from a potentially serious infection.
- Fluorouracil is strictly contraindicated in pregnant or breast-feeding women.
- Flourouracil should not be used in the management of non-malignant disease.
- Fluorouracil must not be taken or used concomitantly with brivudin, sorivudine and analogues. Brivudin, sorivudine and

analogues are potent inhibitors of the enzyme dihydropyrimidine dehydrogenase (DPD) which degrades fluorouracil

- In patients with known complete absence of dihydropyrimidine dehydrogenase (DPD) activity

Oxaliplatin

- Oxaliplatin is contraindicated in patients who have a known history of hypersensitivity to oxaliplatin or to any of the excipients
- are breast-feeding.
- have myelosuppression prior to starting first course, as evidenced by baseline neutrophils <2x109/l and/or platelet count of <100x109l.
- have a peripheral sensitive neuropathy with functional impairment prior to first course.
- have a severely impaired renal function (creatinine clearance less than 30 ml /min)

Irinotecan

- Chronic inflammatory bowel disease and/or bowel obstruction
- History of severe hypersensitivity reactions to Irinotecan hydrochloride trihydrate or to any of the excipients
- Bilirubin > 3 times the ULN
- Severe bone marrow failure.
- WHO performance status > 2.
- Concomitant use with St John's wort

5.3. End of Treatment

Subjects should return to the study site for an End of Treatment Visit within approximately 7 days after treatment discontinuation of all study medication (CPI 613® + mFFX or FFX) and prior to initiation of subsequent anticancer therapy. Adverse events and concomitant medications will be reviewed at this visit, and the following assessments should be completed:

- Physical Examinations
- Vital Signs
- ECOG Performance Status
- Weight/BSA
- Obtain CT scan (or MRI) if radiologic disease progression was not documented in the previous CT scan (or MRI) unless the latter one was performed within the last 14 days
- Blood sample collection for the following tests: Hematology, Blood Chemistry, and CA 19-9
- Collect AE and SAE
- Pregnancy test
- NCCN-FACT FHSI-18 Questionnaire

5.3.1. Discontinuation of Treatment

The Investigator must protect the subject's welfare and may discontinue any study treatment at any time when this action appears to be in the subject's best interest. The reason for the subject's discontinuation must be recorded in the subject's electronic case report. Possible reasons for the discontinuation may include, but are not limited to, the following:

- Disease Progression defined as follow: disease progression documented by CT scan (or MRI) based on RECIST version 1.1 criteria, as determined in the protocol;
- Adverse Event;
- Any significant Protocol Violation as per protocol;
- Withdrawal of consent by an enrolled subject.

5.3.1.1 Patients requiring delay for more than 3 weeks because of toxicity.

5.3.1.2 Unacceptable toxicity from FFX or mFFX + devimistat (Grade 3 or more severity of toxicity).

5.3.1.3 The subject becomes pregnant (treatment should be discontinued immediately) Intercurrent illness with a condition, injury, or disease unrelated to the intended disease for which the study is investigating, that renders continuing the treatment unsafe or regular follow-up impossible.

5.3.1.4 General or specific changes in the patient's condition that in the opinion of the treating physician renders the patient ineligible for further investigational treatment.

5.3.1.5 Recurrent grade 4 adverse events despite all appropriate dose reductions.

5.3.1.6 Non-compliance with investigational treatment, protocol-required evaluations or follow-up visits.

5.3.1.7 Other reasons as determined by the Investigator or Sponsor: A subject may have study treatment discontinued if, in the opinion of the Investigator or Sponsor, it is not in the subject's best interest to continue; Unambiguous clinical progression documented by the Investigator in the absence of radiological confirmation.

Subjects who discontinue all study medication for any reason should remain in the study for long-term follow up assessments unless they withdraw informed consent, die, or become lost to follow up. Long-term follow up evaluations will be performed accordingly as described in the protocol. In the event of study treatment discontinuation, the subject should be instructed to report to the site as early as possible after the decision to discontinue study treatment has been made. All End of Treatment procedures should be performed according to the protocol.

When discontinuing study treatment during this trial, the investigator should make every effort to contact the patient and to perform an End of Treatment (EOT) evaluation. Also, the reason(s) for withdrawal from the study must be recorded. Survival and post-study treatment will be documented bi-monthly after patient completes treatment on this trial. All patients will be followed until the number of events met for the primary endpoint and database is locked.

5.3.2. Reasons for Withdrawal from the Trial

Patients are free to discontinue from the trial at any time without giving any reasons:

5.3.2.1 Patient withdrawal of consent

5.3.2.2 Participation in any other trial during the subject's participation in this trial

In case of withdrawal, patient(s) will be asked to continue safety and survival follow-up every 2 months.

5.3.3. Premature Discontinuation of the Trial

The whole trial may be discontinued prematurely in the event of any of following:

5.3.3.1 New information leading to unfavorable risk benefit judgement of the investigational drug

5.3.3.2 Termination of the clinical trial by the sponsor

5.3.3.3 Evidence of inefficacy

5.3.4. Handling of Participant Withdrawals or Termination

Every effort will be made to keep all randomized patients in the study regardless of their adherence to treatment. Patients who stop their therapy for any reason will be followed until death.

5.4. End of Trial

The definition of end of trial is when the number of events are met for the primary outcome (OS), all available data have been entered into the study database and the study database has been locked. Remaining patients post end of trial, if any, can request Rafael via. compassionate use program.

6.1. Description of Study Drugs

6.1.1. Accountability

- The Sponsor (or designee) will ship the study drug product to drug depot. The study drug is accepted by QA and from there it will be supplied to investigational sites. The initial study shipment will be shipped after all the required regulatory documentation has been received and CTA fully executed. Subsequent study drug shipments will be made according to an automated resupply algorithm managed by IxRS.

- The study drug will only be dispensed to patients that meet eligibility criteria and are randomized to a treatment arm in the trials. The number of study drug product vials dispensed will be recorded on an Investigational Product Accountability log. In addition, all doses dispensed should be accounted for by recording the date, study number, patient identification, and balance forward. These records must be maintained and kept at the study site, and will be reviewed by CRO, or its designee, during periodic monitoring visits.

- At the end of the study, any unused drug can be destroyed in compliance with applicable environmental regulations and institution guidelines. Drug destruction must be adequately documented.

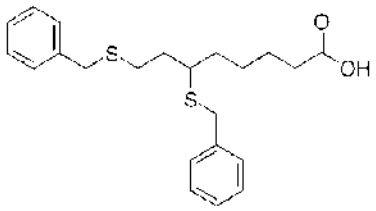
Procurement of Investigational drugs:

- FOLFIRINOX or modified FOLFIRINOX will not be supplied. They will be obtained from commercially available sources and reimbursed by insurance companies or Rafael Pharmaceutical if it is not offered as a standard of care.

6.1.2. Formulation, Appearance, Packaging, and Labeling

CPI-613® (devimistat):

CPI-613® (devimistat) is also known as 6,8-bis(benzylthio)-octanoic acid. The chemical name of devimistat is 6,8-bis(benzylsulfanyl) octanoic acid. It is a white to off white crystalline powder with slight sulphurous odor. Its empirical molecular formula is $C_{22}H_{28}S_2O_2$ and the molecular weight is 388.6 Da. Devimistat has the following chemical structural formula:



Devimistat is freely soluble (~ 140-174 mg/mL) in acetone, chloroform, ethyl acetate, tetrahydrofuran and toluene and insoluble in water (~ 2 mg/mL). The melting point of devimistat is in the range of 65-67°C and predicted pKa value is between 4.9 and 5.4.

Devimistat injection is a sterile, nonpyrogenic, clear, colorless to light yellow solution suitable for intravenous (IV) administration. Devimistat injection is supplied in 10-mL USP type-I amber glass vial with 20 mm grey butyl stopper and royal blue flip off seal. Each mL contains: 50 mg of devimistat and 150 mg of Triethanolamine (TEA). Devimistat injection is a concentrate and must be diluted with 5% dextrose (D5W) injection before use. Devimistat injection is not compatible with saline solution.

FOLFIRINOX:

See locally approved prescribing information for 5-Fluorouracil, folinic acid, oxaliplatin and irinotecan.

6.1.3. Product Storage and Stability

CPI-613® (devimistat):

Devimistat injection must be stored in a refrigerator, 2°- 8°C (36° to 46°F) and protected from light. After dilution, the devimistat injection is chemically and physically stable for upto 24 hours at room temperature with normal light exposure. If devimistat injection is to be transferred from one storage area to another, or is to be prepared for dosing, care must be taken to maintain appropriate product temperature. Devimistat injection is slightly photosensitive when exposed to intense light. Therefore, after removal of devimistat drug product from the amber vials, devimistat injection should be administered to patients without unnecessary delay to minimize excessive exposure to light.

FOLFIRINOX (FFX):

All components of FFX including 5-FU, Folinic Acid, oxaliplatin and irinotecan should be handled and stored as per manufactures instructions on the locally approved prescribing information.

6.1.4. Preparation and Handling

CPI-613® (devimistat):

The contents of devimistat injection must be visually inspected prior to dilution to confirm that the contents are clear and colorless to light yellow. If not, it should not be used.

Devimistat is supplied in a 10 mL vial with 500 mg of drug in each vial. Devimistat injection must be diluted from 50 mg/mL to 12.5 mg/mL with 5% dextrose (D5W) prior to administration. The diluted drug product should be visually inspected for clarity. If haziness or precipitate is observed, do not use the diluted drug product for dosing. After dilution with sterile D5W[18], the solution is clear and has a pH of 8.4 - 8.8. The diluted devimistat injection has been found to be stable for 24 hrs. with normal light exposure (please refer to the Pharmacy Manual for study drug dilution and administration guidelines).

D5W will not be supplied.

Handling of CPI-613® (devimistat):

Devimistat is an investigational drug and the toxicity in humans is not fully understood. All necessary precautions in handling potentially toxic chemicals must be strictly adhered to. Gloves and protective clothing must be worn when handling devimistat. Avoid contact by all modes of exposure. If the solution contacts the skin, it must be washed immediately and thoroughly with soap and water. If the solution comes in contact with mucous membranes, the membranes must be flushed thoroughly with water. Spills should be picked up with chemo spill kit. Devimistat drug product is slightly photosensitive. Therefore, after removal of devimistat drug product from the amber vials, devimistat drug product should be protected from excessive light before administration to patients.

Each study site must ensure that the study drug is not used beyond expiry date.

6.1.5. Dosing and Administration

CPI-613® (devimistat) and modified FOLFIRINOX (Experimental Arm1: CPI-613® (devimistat) + mFFX):

Calculation of the Dose of CPI-613® (devimistat) and modified FOLFIRINOX for Each Patient:

The amount of devimistat and each of the drug constituents of modified FFX is based on the body surface area (BSA) of each patient. The BSA values will be calculated based on the height and body weight taken during screening and this BSA value is used throughout the study using a standard formula, such as Mosteller formula. If the subject's body weight changes by >10% from one visit to the next, the BSA should be recalculated and the dose adjusted. There is no maximum dose and patients' actual weight should be used for dose calculation.

The Timing of Dosing (CPI-613® (devimistat)):

In a 14-day's cycle (+/- 24 hours), devimistat is to be given on Day 1, prior to administration of mFFX. It is also given on Day 3, after completion of mFFX administration. On day 3, in the event that time will not permit devimistat administration following 5-FU infusion, devimistat may be administered concurrently with 5-FU via a double lumen port.

Administration (CPI-613® (devimistat)):

Devimistat must be administered intravenously, via a central venous catheter that is free flowing and free of air in the dead space of the IV catheter, to minimize vascular irritation, inflammation and acute toxicity of devimistat. Accidental co-administration of extra air in the dead space of IV catheters during administration of devimistat has demonstrated the potential to induce acute toxicity of devimistat according to animal studies. Also, accidental leakage of devimistat into the perivascular space during IV administration, which prolongs exposure of perivascular tissue to devimistat, can induce significant local inflammation according to animal studies. To avoid local reactions at and around the site of administration, devimistat must be administered via a central venous catheter.

Diluted devimistat MUST be administered as by **IV infusion** and not as bolus via a central venous catheter **at the rate of 4 mL/min** on Day 1 and Day 3 of each cycle via an infusion pump. This is to minimize potential acute toxicity of devimistat, according to animal studies. Devimistat infusion must be administered concurrently with D5W at the rate of 125mL/hour (2.08mL/min) via a central venous catheter.

The following precautions must be taken when administering devimistat:

1. Confirmation of the placement of the IV line to ensure a lack of leakage of devimistat into the perivascular space
2. Confirmation that the IV line is free flowing
3. Confirmation that the IV line is free of dead air space
4. Dilute devimistat drug product with D5W, as instructed in the study protocol
5. Administer devimistat by infusion, not as a bolus
6. After administration of devimistat, flush the IV line with ~10 mL of D5W to remove residual devimistat and to avoid local reactions at and around the site of administration

Intravenous Infusion Sets, Syringes and IV Bags to be Used for Administration of CPI-613® (devimistat):

Devimistat must be administered **IV by infusion at the rate of 4 mL/min**, via central venous catheter with D5W running on Day 1 and Day 3 of each cycle. Devimistat infusion must be administered concurrently with D5W at the rate of 125mL/hour (2.08mL/min) via a central venous catheter. To avoid local reactions at and around the site of administration, devimistat should be administered via a central venous catheter. Subsequent sections describe the appropriate types of IV catheters, IV bags, syringes and clinical solutions that can be used in mixing and administering devimistat to patients.

Leaching of Diethylhexyl Phthalate (DEHP) by CPI-613® (devimistat):

Devimistat can cause leaching of DEHP from IV infusion sets and IV bags. Therefore, DEHP-containing IV infusion sets, IV bags or syringes SHOULD NOT be used in mixing or administration of devimistat.

Devimistat drug product is slightly photosensitive. Therefore, after removal of devimistat drug product from the amber vials, devimistat drug product should be protected from excessive light before administration to patients.

Disposal of CPI-613® (devimistat):

Please refer to the study-specific pharmacy Manual for specific details on the investigational product disposal process. The following procedures are to be taken in disposal of devimistat:

- During the study, store the used devimistat vials (which must be separate from the unused

devimistat vials) at controlled room temperature (20°C-25°C) in an access-limited area. Alternatively, destroy the used devimistat vials according to institutional guidelines and in compliance with applicable environmental guidelines or return the used and empty vials to the depot. Drug destruction must be adequately documented.

- At the end of the study, deface the label (both used and unused vials) with a permanent marking pen. Destroy used devimistat vials according to institutional guidelines and in compliance with applicable environmental guidelines or return the used and empty vials to depot. Drug destruction must be adequately documented.

- All unused devimistat vials must be returned to the depot

The Timing of Dosing (modified FOLFIRINOX; mFFX):

mFFX is a combination of following 4 drugs:

1. oxaliplatin: day 1
2. folinic acid (calcium folinate or FA): day 1 immediately after oxaliplatin
3. irinotecan: day 1 concurrently with folinic acid
4. flurouracil (5-FU): day 1 bolus followed by a 42-48-hr infusion, starting immediately after completion of folinic acid and irinotecan

Administration (modified FOLFIRINOX; mFFX) (see Table 7 below in detail):

1. oxaliplatin: IV infusion
2. folinic acid (calcium folinate or FA): IV infusion
3. irinotecan: IV infusion
4. flurouracil (5-FU): IV bolus, followed by IV infusion

Maximum Hold Time of modified FOLFIRINOX (mFFX) once Reconstituted before Administration:

As per the manufacturer's instructions found on locally approved packaging information.

Handling of modified FOLFIRINOX (mFFX):

As per the manufacturer's instructions found on locally approved packaging information.

Disposal of modified FOLFIRINOX (mFFX)

Destroy used vials according to institutional guidelines and in compliance with applicable environmental guidelines. Drug destruction must be adequately documented.

The Table 7 below summarizes the administration of devimistat and mFFX.

Table 7 Administration of CPI-613® (devimistat) and modified FOLFIRINOX (mFFX) in study Arm 1 for Patients with Metastatic Pancreatic Cancer

Treatment Cycle		Administration of CPI-613® (devimistat) and modified FOLFIRINOX (mFFX) in Study Arm 1
Cycle	**Day**	
Cycle 1	Day 1	**Devimistat: IV infusion at the rate of 4 mL/min** at the dose of **500 mg/m² concurrently with D5W at the rate of 125mL/hour (2.08mL/min) via a central venous catheter** mFFX (given immediately after devimistat administration): - Oxaliplatin at 65 mg/m² given as a 2-hr IV infusion - Folinic acid at 400 mg/m² given as a 90-min (1.5 hr) infusion immediately after oxaliplatin, and concurrently with Irinotecan at 140 mg/m² given as a 90-min IV infusion via a Y-connector. - Flurouracil (5-FU) at 400 mg/m² as bolus followed by a 42-48-hr infusion at2,400 mg/m², starting immediately after completion of folinic acid and irinotecan
	Day 2	mFFX: - Completing the remaining of the 5-FU 42-48-hr infusion starting on Day 1
	Day 3	mFFX: - Completing the remaining of the 5-FU 42-48-hr infusion starting on Day 1, 2 and disconnect the 5-FU pump. devimistat: - **Devimistat (500 mg/m²), IV infusion at the rate of 4 mL/min** via a central venous catheter after completion of 5-FU infusion. Devimistat infusion must be administered concurrently with D5W at the rate of 125mL/hour (2.08mL/min) via a central venous catheter. In the event that time will not permit devimistat administration following 5-FU infusion, devimistat may be administered concurrently with 5-FU via a double lumen port.
	Day 4 (+/- 24 hours)	Myeloid Growth factor per institutional guidelines
	Days 5 -14	No treatment
Cycle 2 and subsequent Cycles (every 2 weeks)	Same as Cycle 1	

Dosing as above will continue for at least 6 months in responding patients with acceptable tolerance to therapy (with dose modifications per protocol as needed) unless a criterion for removal from study occurs. Responding patients upon completion of at least 10 cycles and after having two sequential CT scans showing stable disease (no continued decrease in lesion size) will complete 2 additional cycles (to complete a minimum of 12 cycles) of their assigned treatment.

Following 12 cycle 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 (Section 5.3.1).

FOLFIRINOX (Control Arm 2; FFX):

Calculation of the Amount of FOLFIRINOX for Each Patient:

The amount of each of the drug constituents of FFX is based on the BSA of each patient. The BSA values will be calculated based on the height and body weight taken during screening and this BSA value is used throughout the study. The BSA values will be calculated based on a standard formula, such as Mosteller formula. **If the subject's body weight changes by >10% from the dose to the next dose, BSA should be recalculated and the dose adjusted.**

The Timing of Dosing (FFX):

FFX is a combination of following 4 drugs:

1. oxaliplatin: day 1
2. folinic acid (calcium folinate or FA): day 1 immediately after oxaliplatin
3. irinotecan: day 1 concurrently with folinic acid
4. flurouracil (5-FU): day 1 bolus followed by a 42-48-hr infusion, starting immediately after completion of folinic acid and irinotecan

Administration of FOLFIRINOX (FFX) (see Table 8 below in detail):

1. oxaliplatin: IV infusion
2. folinic acid (calcium folinate or FA): IV infusion
3. irinotecan: IV infusion
4. flurouracil (5-FU): IV bolus, followed by IV infusion

Maximum Hold Time of FOLFIRINOX (FFX) once Reconstituted before Administration:

As per the manufacturer's instructions found on locally approved prescribing information.

Handling of FOLFIRINOX (FFX):

As per the manufacturer's instructions found on locally approved prescribing information.

Disposal of FOLFIRINOX (FFX)

Destroy used vials according to institutional guidelines and in compliance with applicable environmental guidelines. Drug destruction must be adequately documented.

The Table 8 below summarizes the administration of FFX.

Table 8 Administration of FOLFIRINOX (FFX) in study Arm 2 for Patients with Metastatic Pancreatic Cancer

Treatment Cycle		Administration of FOLFIRINOX (FFX) in study Arm 2
Cycle	**Day**	
Cycle 1	Day 1	FOLFIRNOX (FFX): - Oxaliplatin at 85 mg/m^2 given as a 2-hr IV infusion - Folinic acid at 400 mg/m^2 given as a 90-min (1.5 hr) infusion immediately after oxaliplatin, and concurrently with irinotecan (Irinotecan at 180 mg/m^2 given as a 90-min IV infusion) via a Y-connector. - Flurouracil (5-FU) at 400 mg/m^2 as bolus followed by a 42-48-hr infusion at2.400 mg/m^2, starting immediately after completion of folinic acid and irinotecan
	Day 2	FOLFIRNOX (FFX): - Completing the remaining of the 5-FU 42-48-hr infusion starting on Day 1
	Day 3	FOLFIRNOX (FFX): - Completing the remaining of the 5-FU 42-48-hr infusion starting on Day 1,2 and disconnect the 5-FU pump.
	Day 4 (+/- 24 hours)	Myeloid Growth factor per institutional guidelines
	Days 5 – 14	No treatment
Cycle 2 and subsequent cycles (every 2 weeks)	Same as Cycle 1	

Dosing as above will continue for at least 6 months in responding patients with acceptable tolerance to therapy (with dose modifications per protocol as needed) unless a criterion for

removal from study occurs. Responding patients upon completion of at least 10 cycles and after having two sequential CT scans showing stable disease (no continued decrease in lesion size) will complete 2 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 (see Section 5.3.1).

6.1.6. Dose Adjustments/Modifications/Delays

No dose modifications are allowed for devimistat in this study.

The dose of Folinic Acid is not modified for any toxicity but is omitted if fluorouracil is omitted. Once a dose of any of the drugs comprising FFX is decreased, re-escalation of the dose is not permitted. Patients are taken off the study if they develop the same Grade 4 toxicity despite dose reduction. The dose adjustment scheme for FFX is dependent on the type of toxicities, as described below.

Hematologic Toxicity

Once hematologic toxicity is observed in a patient, do not retreat the patient with mFFX or FFX until the absolute neutrophil count is $\geq 1.5 \times 10^9$/L and the platelet count is $\geq 75 \times 10^9$/L. The dose modification schemes for FFX related to hematologic toxicity are shown in Table 9.

Primary prophylaxis with myeloid growth factor will be at the discretion of the treating physician and as per the ASCO guidelines. If the patient is not being treated with myeloid growth factor the initial modification for neutropenia should be the addition of a myeloid growth factor. If the patient is already on a myeloid growth factor, then dose adjustments are as outlined in Table 9.

Table 9 Dose Modifications for Hematological Toxicities on Day 1 of a Cycle. Cycles are Every Two Weeks.

Day 1	Delay the Start of a Treatment Cycle*	Doses Reduction		
		Irinotecan	Oxaliplatin	Fluorouracil (5-FU)
ANC <1.5x10^9/L	Withhold treatment until granulocytes ≥1.5x10^9/L.	1st occurrence: Continue same dose	1st occurrence: Continue same dose	1st occurrence: Delete bolus 5-FU
		2nd occurrence: Reduce to 80% of starting dose	2nd occurrence: Continue same dose	
		3rd occurrence: Reduce to 50% of starting dose	3rd occurrence: Reduce to 80% of starting dose	
		4th occurrence: Discontinue irinotecan	4th occurrence: Continue on 80% of starting dose	
Platelets <75x10^9/L	Withhold treatment until platelets ≥75x10^9/L.	1st occurrence: No dose reduction	1st occurrence: No dose reduction	1st occurrence: Delete bolus 5-FU
		2nd occurrence: Reduce to 80% of starting dose	2nd occurrence: Reduce to 80% of starting dose	
		3rd occurrence: Reduce to 50% of starting dose	3rd occurrence: Discontinue oxaliplatin	
		4th occurrence: Discontinue irinotecan	4th occurrence: Discontinue oxaliplatin	

Table 10 Dose Adjustments According to Non-Hematological Toxicities (Excluding Alopecia, Nausea and Vomiting).

Adverse Events	Dose Reduction for Subsequent Treatment Cycles
Diarrhea Grade 3-4, or diarrhea + fever and/or neutropenia Grade 3-4 Patients must be instructed in the use of loperamide as treatment for diarrhea and must have a supply of this drug upon starting treatment. Patients should not be retreated with irinotecan until diarrhea is ≤Grade 1 (without loperamide for at least 24 hrs.). If acute cholinergic syndrome appears (defined as early diarrhea and certain other signs and symptoms such as sweating, abdominal cramps, miosis and salivation), atropine sulphate (0.25 mg subcutaneously) should be administered unless clinically contraindicated. In patients who experienced an acute and severe cholinergic syndrome, the use of prophylactic atropine sulphate is recommended with subsequent doses of Irinotecan hydrochloride.	1st occurrence: Reduce the irinotecan dose to 80% of the original dose and delete the bolus 5-FU dose 2nd occurrence: Reduce also the oxaliplatin dose to 80% of the original dose AND reduce the dose of continuous 5-FU to 75 % of the original dose 3rd occurrence: Discontinue treatment
Mucositis or "Hand-Foot" Syndrome	Grade 1-2 toxicity - continue on same doses of drugs Grade 3-4 toxicity - delete bolus 5-FU and a reduction of 25% in continuous 5-FU doses in subsequent treatment cycles. If mucositis is related to oxaliplatin, delay oxaliplatin or modify the dose until the toxicity grade ≤ 1.
Myocardial Ischemia – Monitored by Cardiac Enzymes (CK/CKMB, TP)	5-FU must be permanently discontinued.
Hyperbilirubinemia	Obstruction of the biliary system or progressive disease must be established, and the treatment cycle delayed if the cause is biliary obstruction that can be addressed to reduce the hyperbilirubinemia. If bilirubin is persistently >1.5x of Upper Limit of Normal (ULN), irinotecan must be omitted. If there is no potentially reversible obstruction, then irinotecan must be discontinued.
Other Toxicities	To be discussed with Medical Director.

7.1. Study Procedures/Evaluations

7.1.1. Study Specific Procedures

Medical History:
Will be obtained by direct interview with the patient during the course of standard clinic visits or hospital admission.

Physical Examination:
Will be obtained during the course of standard clinic visits or hospital admission.

ECOG Performance Status scales[19] will be used to assess how a patient's disease is progressing and assess how the disease affects the daily living abilities of the patient. The scale is listed in Table 11 below.

Table 11 Scales Used in ECOG Performance Status Grade

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 housework, 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

Radiographic or Other Imaging Assessments:

Tumor Assessment:
Objective response assessment will be determined by triphasic contrast CT of the chest abdomen and pelvis as per RECIST guideline version 1.1 every 8 weeks +/-7 days while patients are on treatment. MRI assessments of tumor status may replace CT scans if needed for tumor response evaluation. However, the same imaging modality must be followed serially. Target lesions will be identified and documented prospectively from the baseline scan prior to assessments of any follow up scans. Each tumor lesion will be assigned a unique identifier consisting of the patient

study ID number followed by a letter. Should a lesion completely resolve during treatment that lesion will be scored as a 0 (zero) and not left blank to ensure lesion resolution is accurate and not a reflection of missing data. The timing and location of any new lesions will be recorded upon evaluation of the first scan to demonstrate this lesion. Patients will continue on assigned treatment until one of the stopping criteria are met (see Section 5.3.1). Patients who are allergic to contrast should get an MRI and those allergic to both, they can get a non-contrasted study.

The patient's best response within the first 12 cycles of treatment as determined by the independent assessment will be used in the recording of the ORR for each patient. OS will be monitored every 2 months via telephone contact after treatment termination. (Note: During post-study treatment telephone contact, information related to cancer treatment received after the study will also be collected). OS will be calculated from the day of randomization. The duration of OS will be measured until the date of death or censored at follow-up. Patients who are lost to follow- up, withdraw from follow-up or alive and progression free will be censored at the date of last follow-up for OS.

Progression free survival (PFS) is calculated from the date of randomization to the date of progressive disease or death from any cause. Patients who have neither progressed nor died will be censored at the day of their last radiographic tumor assessment, if available, or date of randomization if no post initiation radiographic assessment is available. If death or PD occurs after 2 or more missing radiographic visits, censoring will occur at the date of the last radiographic visit that the patient was known to be alive and progression-free.

Duration of response is calculated from the date of randomization to the date of confirmed clinical/radiological progression or death from any cause.

Biological Specimen Collection and Laboratory Evaluations:

Up to 10 unstained slides will be submitted when available from the pre-study diagnostic biopsy and the study's progression of disease biopsy (if available).

Blood Sampling for Pharmacokinetic (PK) Analysis:

PK sampling will occur only for the study Arm 1: devimistat + mFFX because the dosing level of Oxaliplatin 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 interactive web response system (IxRS) system, a patient will be designated with a code assignment for blood sampling for PK analysis of devimistat 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. 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. A patient is considered evaluable post one time point after infusion for PK analysis.

A. Full PK Analysis Sampling

Upon enrollment through the IxRS system, a patient may be assigned a code for blood sampling for full PK Analysis. One goal of Full PK sampling on Cycle 1, Day 1 will be able to detail the peak plasma concentration (C_{max}), area under the plasma concentration versus time curve from time 0 to t (AUC_{0-t}), area under the plasma concentration versus time curve from time 0 to infinity (AUC_{inf}), elimination half-life ($T_{1/2}$), time to reach the maximum plasma concentration (T_{max}), clearance (CL), and volume of distribution (V_d) after the first dose and multiple doses of devimistat to fully characterize PK profiles of both the parent drug (devimistat) and its major metabolites (CPI-2850 and CPI-1810). The other goal of Full PK sampling on Cycle 1, Day 3 will be to evaluate devimistat and metabolite accumulation following multiple dosing during the course of multiple rounds of treatment through the assessment of Day 3 / Day 1 accumulation ratios (R) for C_{max} and AUC_{0-t}. A Table 12 of time points to sample is following.

Table 12 Full PK blood sampling schedule. Time points are counted from the start of CPI-613® (devimistat) IV infusion.

Cycle # Day #	Time point	N	Comment
Cycle 1, Day 1	0 hr. ±15 min (pre-dose) 0.25 hr. ±15 min 0.5 hr. ±15 min 1 hr. ±15 min 2 hr. ±15 min 2.5 hr. ±15 min 3 hr. ±15 min 4 hr. ±15 min 6 hr. ±15 min	15 patients in Arm 1 (devimistat + mFFX)	Pre-infusion

Cycle 1, Day 3	0 hr. ±15 min (pre-dose) 0.25 hr. ±15 min 0.5 hr. ±15 min 1 hr. ±15 min 2 hr. ±15 min 2.5 hr. ±15 min 3 hr. ±15 min 4 hr.±15 min 6 hr. ±15 min	15 patients above	Pre-infusion

B. Sparse PK Analysis Sampling

Upon enrollment through the IxRS system, in the pool of remaining patients in Arm 1: devimistat + mFFX, a patient may be assigned a code for blood sampling for "sparse" Population PK analysis. Patients will be randomly assigned to one of the following 12 groups for sparse PK sampling where each group will be sampled at a single time point within 0-24 hours counted as starting from IV infusion on the day selected by IxRS. Each group will be composed of approximately 18-20 patients.

Table 13 Sparse PK blood sampling schedule. Time points are counted from the start of CPI-613® (devimistat) IV infusion.

Group #	Cycle #	Time point Window
1	Cycle 1	Day 1: 0-24 hr.*
2	Cycle 2	Day 1: 0-24 hr.*
3	Cycle 3	Day 1: 0-24 hr.*
4	Cycle 4	Day 1: 0-24 hr.*
5	Cycle 5	Day 1: 0-24 hr. *
6	Cycle 6	Day 1: 0-24 hr.*
7	Cycle 7	Day 1: 0-24 hr.*
8	Cycle 8	Day 1: 0-24 hr.*
9	Cycle 9	Day 1: 0-24 hr. *
10	Cycle 10	Day 1: 0-24 hr.*
11	Cycle 11	Day 1: 0-24 hr.*
12	Cycle 12	Day 1: 0-24 hr.*

*One blood sampling at the patient/sites choosing during the time point window

In addition to measurement of the study agent and metabolites, plasma concentrations of the components of the mFFX and FFX standard of care regimen will also be evaluated.

All PK samples should be shipped to the Central Lab. Mailing address, contact name and phone number will be provided in laboratory manual.

The bioanalytical assays using validated LC/MS/MS methods for the parent drug devimistat and metabolites CPI-2850 and CPI-1810, as well as components of mFFX, will be provided in laboratory manual.

Cardiac marker (Troponin I)

As PANC003 is a Phase III trial for CPI-613® (devimistat) in pancreatic cancer, every effort should be made to ensure sites, investigators and patients comply with the study protocol for evaluation of elevated Troponin I. 24 patients in each arm (Arm 1 and Arm 2) will be evaluated for elevated Troponin I.

Troponin I testing should occur within 24 hours prior to the first dose (Cycle 1, Day 1) of study treatment dosing, but no sooner that 30 minutes prior to dosing. This does not require an extra sample collection, as other labs are collected at the same time point.

Troponin I testing should occur after the completion of all study medications. This will require an additional blood sample.

The schedule is detailed below.

ARM 1: CPI-613® (devimistat) + mFFX

Phase, Cycle, Day	Time Points	N	Comment
Cycle 1, Day 1	0 hr (up to 30 min pre-dose)	24 patients	Pre- CPI-613® (devimistat) infusion
Cycle 1, Day 3	After completion of last dose of all study drugs (+ 30 min)*	24 patients	Post- CPI-613® (devimistat) infusion

*This test for Troponin I will require an additional blood sample.

ARM 2: FFX

Phase, Cycle, Day	Time Points	N	Comment

Cycle 1, Day 1	0 hr (up to 30 min pre-dose)	24 patients	Pre-FFX infusion
Cycle 1, Day 3	After completion of last dose of all study drugs (+ 30 min)	24 patients	Post-FFX infusion

ECG Analysis

A. Full ECG Analysis in:

Up to 24 **patients receiving devimistat 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 (see Table 14 below) from 30 minutes prior to dosing of devimistat 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 fully blinded to timepoints and subject identification.** 12-lead ECGs in these patients will be recorded using a Global Instrumentation (Manlius, NY, USA) M12R ECG continuous 12-lead digital recorder. For Cycle 1, Day 1 (9 time points) and Cycle 1, Day 3 (9 time points), continuous 12-lead digital ECG data will be recorded and stored onto SD memory cards. ECGs will be uploaded onto a central ERT server. Safety ECGs can be printed on-site with the same device. At each protocol-specified timepoint, QT and RR intervals will be measured from up to 10 replicate ECGs. The QTc interval will be derived using Fridericia's formula from the preceding RR interval and the QT interval in each beat and the median QTcF in each replicate will be calculated. The mean across medians from all replicates will be used as the subject's reportable value at that timepoint. All medications administered to subjects from 4 hours prior to the first EKG reading through all time points will be recorded (including doses and time of administration). Measurement of PR and QRS intervals will be performed semi-automatically on three sequential beats from each of the three replicates. The mean value will be calculated for each replicate and then the mean of these used as the subject's reportable value at the timepoint (adapted from Darpo et. al.).[19]

Time points for ECG recordings are listed in Table 14.

Table 14 Full ECG Measurement Schedule. Time points are counted from the start of CPI-613® (devimistat) IV infusion.

Cycle #, Day #	Timepoints	N	Comment
Cycle 1, Day 1	0 hr. ±15 (pre-dose) 0.25 hr. ±15 min 0.5 hr. ±15 min 1 hr. ±15 min 2 hr. ±15 min 2.5 hr. ±15 min 3 hr. ±15 min 4 hr. ±15 min 6 hr. ±15 min	Up to 24 patients (i.e. same patients on Arm 1 for Full PK analysis)	Pre-devimistat infusion
Cycle 1, Day 3	0 hr. ±15 (pre-dose) 0.25 hr. ±15 min 0.5 hr. ±15 min 1 hr. ±15 min 2 hr. ±15 min 2.5 hr. ±15 min 3 hr. ±15 min 4 hr. ±15 min 6 hr. ±15 min	Up to 24 patients above	Pre-infusion

B. Sparse ECG Measurement Schedule:

The remaining patients randomized to CPI-613® (devimistat) plus modified FFX (i.e. Arm 1) and all patients on FFX (i.e. Arm 2) will undergo a Sparse ECG analysis. 12-lead ECGs will be recorded at defined intervals. Subjects will be placed in a supine position for at least 10 minutes prior to timepoints for ECG recording. **This Sparse ECG measurement will be measured at a local ECG laboratory and confirmed by central read**. At each protocol-specified timepoint, QT and RR intervals will be measured from each of the three independent 12-lead ECG recordings (i.e., 3 replicates). The QTc interval will be derived using Fridericia's formula from the preceding RR interval and the QT interval in each beat and the median QTcF in each replicate will be calculated. The mean across medians from all replicates will be used as the subject's reportable value at that timepoint. All medications administered to subjects from 4 hours prior to the first ECG reading through all time points will be recorded (including doses and time of administration). Measurement of PR and QRS intervals will be performed semi-automatically on three sequential beats from each of the three replicates. The mean value will be

calculated for each replicate and then the mean of these used as the subject's reportable value at the timepoint (adapted from Darpo et. al.[19]). Time points for sparse ECG recordings are listed in Table 15 below.

Table 15 Sparse ECG measurement schedule.

Cycle #, Day #	**Timepoints** a = 5 min window between the ECG's	**N**	**Comment on Assessment Timepoint**
Cycle 1, Day 1	0 hr. (pre-dose) 0.25 hr. 0.5 hr.	Approx. 476 patients = Remaining 225 patients on Arm 1 + All 250 patients on Arm 2	Arm 1: Pre-devimistat infusion Arm 2: Pre-Oxaliplatin infusion
Cycle 1, Day 3	0 hr. (pre-dose) 0.25 hr. 0.5 hr.	Approx. 476 patients above	Arm 1: Pre-devimistat infusion Arm 2: Just prior to completion of 5-FU infusion
Cycle 2, Day 3	0 hr. (pre-dose) 0.25 hr. 0.5 hr.	Approx. 476 patients above	Arm 1: Pre-devimistat infusion Arm 2: Just prior to completion of 5-FU infusion
Cycle 3, Day 3	0 hr. (pre-dose) 0.25 hr. 0.5 hr.	Approx.476 patients above	Arm 1: Pre-devimistat infusion Arm 2: Just prior to completion of 5-FU infusion
Cycle 6, Day 3	0 hr. (pre-dose) 0.25 hr. 0.5 hr.	Approx. 476 patients above	Arm 1: Pre-devimistat infusion Arm 2: Just prior to completion of 5-FU infusion

Cycle 9, Day 3	0 hr. (pre-dose) 0.25 hr. 0.5 hr.	Approx. 476 patients above	Arm 1: Pre-devimistat infusion Arm 2: Just prior to completion of 5-FU infusion
Cycle 12, Day 3	0 hr. (pre-dose) 0.25 hr. 0.5 hr.	Approx. 476 patients above	Arm 1: Pre-devimistat infusion Arm 2: Just prior to completion of 5-FU infusion

Blood Sampling for Biomarker Analysis:

The following is for Optional Sampling and "Banking" of Blood and Serum Samples for Biomarker analysis. A separate informed consent will be provided to patients with optional sampling.

Blood samples will be obtained prior to treatment initiation (within 4 weeks prior to 1st dose), as well as prior to each restaging scan.

All samples for biomarkers will be retained for up to 10 years after the end of the study and then destroyed or an extension will be requested from appropriate regulatory authorities and IRB/IECs.

All optional samples and specimens should be shipped to the Central Lab. Mailing address, contact name and phone number will be provided in lab manual.

Administration of Questionnaires / Other Instruments for Patient-Reported Outcomes:

Patient-Reported Outcomes (**PRO**) using the NCCN-FACT Hepatobiliary Symptom Index (FHSI- 18). Summary statistics of the scores will be shown by cycle (pre and post treatment). Scores will be compared between standard and study arms.

7.2. Laboratory Procedures/Evaluations

7.2.1. Clinical Laboratory Evaluations

Clinical Chemistry, Hematology, Coagulation and Other assessments: Clinical chemistry assessed includes:

- 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

Hematology:

- Hemoglobin A1c (HbA1c; baseline measurement only)
- CBC

Coagulation:

- PT
- aPTT

Others:

- CA19-9
- β-HCG pregnancy test

Note: Renal function will be assessed utilizing the Cockcroft-Gault formula. CBC (complete blood count) and CMP (comprehensive metabolic panel) will be monitored weekly, on Day 1 and Day 7 or 8 (may be done ±1-2 days if falls on a weekend or holiday), for toxicity assessment of study drugs.

7.3. Study Schedule

7.3.1. Screening

7.3.1.1 **Screening Visit**: day: -28

7.3.1.2 **Informed Consent:** Obtain informed consent of potential participant verified by signature on written informed consent for screening form

7.3.1.3 **Medical History:** Review medical history to determine eligibility based on inclusion/exclusion criteria

7.3.1.4 **Medical Examinations:** Perform medical examinations needed to determine eligibility based on inclusion/exclusion criteria

Pre-Study Screening Tests & Pre-Study Safety Assessment:

Pre-Study Screening Tests:

Pre-study screening tests, which are also enrollment evaluations, must be performed according the following time frames:

- Within 4 weeks of randomization: tumor assessments (triphasic contrast CT of the chest, abdomen and pelvis or MRI), and optional blood and serum samples.
- Within 2 weeks of randomization: medical history, physical exam, vital signs (including heart rate), height, weight, ECG, ECOG, Hemoglobin A1c, evaluation of symptoms and medications, clinical chemistry, hematology, CA19-9 and coagulation.
- Within 1 week of randomization: Serum pregnancy test for women of child- bearing potential.

Pre-Study Safety Assessment:

All safety assessment tests are performed during screening (performed within 2 weeks prior to treatment with devimistat) with results available from local labs for review within 24 hrs. before administration of the anti-tumor agents. These safety assessments include:

- Evaluation of symptoms
- Vital signs including heart rate
- ECOG performance status and survival
- Clinical chemistry
- NCCN-FACT FSHI-18 questionnaire (PRO)
- Renal function
- Hematology
- Coagulation (PT and aPTT)
- CA19-9

7.3.2. Enrollment/Baseline & Treatment Cycle Details

7.3.2.1 Enrollment/Baseline Visit: Cycle 1, Day 1

7.3.2.2 Administration of Study Treatment: Eligible subjects will be randomized to treatment following screening. The study site will obtain subject's identification and randomization to treatment arm from the IxRS.

CPI-613® (devimistat): 500 mg/m^2 of devimistat will be administered on days 1 and 3 of every 14 days (2 weeks) cycle (+/- 24 hours) at the rate of 4mL/min via a central venous catheter. Devimistat infusion must be administered concurrently with D5W at the rate of 125mL/hour (2.08mL/min) via a central venous catheter.

mFFX: mFFX will be administered on days 1, 2 and 3 of every 14 days (2 weeks cycle) using the regimen below via IV line.

- Oxaliplatin at 65 mg/m^2 given as a 2-hr IV infusion
- Folinic acid at 400 mg/m^2 given as a 90-min (1.5 hr) infusion immediately after oxaliplatin, and concurrently with irinotecan (Irinotecan at 140 mg/m^2 given as a 90-min IV infusion) via a Y-connector
- Flurouracil (5-FU) at 400 mg/m^2 as bolus followed by a 42-48-hr infusion at 2,400 mg/m^2, starting immediately after completion of folinic acid and irinotecan

FFX: FFX will be administered on days 1, 2 and 3 of every 14 days (2 weeks cycle +/- 24 hours) using the regimen below via IV line.

- Oxaliplatin at 85 mg/m^2 given as a 2-hr IV infusion

- Folinic acid at 400 mg/m^2 given as a 90-min (1.5 hr) infusion immediately after oxaliplatin, and concurrently with irinotecan (Irinotecan at 180 mg/m^2 given as a 90-min IV infusion) via a Y-connector

- Flurouracil (5-FU) at 400 mg/m^2 as bolus followed by a 42-48-hr infusion at 2,400 mg/m^2, starting immediately after completion of folinic acid and irinotecan

CYCLE: 1 (Day 1 – Day 14 +/- 24 hours:):

Devimistat Arm1 (devimistat+mFFX)

Day 1:

I. Pre-dosing Tests:

- Evaluation of vital signs (including heart rate)*,
- ECOG performance status*,
- Survival*,
- Clinical chemistry*,
- Hematology*,
- Coagulation*,
- Triphase contrast CT of the chest, abdomen and pelvis **,
- CA19-9**,
- NCCN-FACT FSHI-18 questionnaire (if not collected during Screening) (also referred to as PRO is this protocol),
- Blood sampling for PK (see Full PK or Sparse PK sampling schedule in Section 7.1.1, Table 12 or Table 13),
- Blood sampling for Cardiac marker (Troponin I) (Please make certain that this test occurs no sooner than 30 minutes prior to dosing.),
- ECG measurement (see Full ECG or Sparse ECG measurement schedule in Section 7.1.1, Table 14 or Table 15)

II. Devimistat 500 mg/m^2 infused at the rate of 4 mL/min concurrently with D5W at the rate of 125mL/hour (2.08mL/min) via a central venous catheter on days 1 and day 3 of each 14-day cycle of mFFX (given immediately after devimistat administration on Day 1) #:

a. Oxaliplatin at 65 mg/m^2 given as a 2-hr IV infusion

b. Folinic acid at 400 mg/m^2 given as a 90-min (1.5 hr) IV infusion immediately after oxaliplatin

c. Irinotecan at 140 mg/m^2 given as a 90-min (1.5 hr) IV infusion via a Y- connector concurrently with Folinic acid

d. Flurouracil (5-FU) at 400 mg/m^2 as IV bolus followed by a 42-48-hr continuous IV infusion at 2,400 mg/m^2, starting immediately after completion of folinic acid and irinotecan

Note:

**These tests are performed in local labs with results available for review within 24 hrs. before administration of the anti-tumor agents.*

*** Performed at the end of every 4th cycle.*

#Dosing of agents in the mFFX regimen with devimistat are based on clinical practice and literature (e.g., Stein S, et.al, BJC (2016) 114:737-743).

Day 2:

I. Completing the remaining of the 5-FU 42-48-hr infusion starting on Day 1

II. Blood sampling for PK (see Sparse PK sampling schedule in Section 7.1.1, Table 13)

Day 3:

I. Completing the remaining of the 5-FU 42-48-hr infusion starting on Day 1 and disconnect the 5-FU pump

II. Devimistat (may be administered concurrently with 5-FU via a double lumen port)

III. Myeloid Growth Factor will be given as per institutional guidelines

IV. Blood sampling for PK (see Full PK or Sparse PK sampling schedule in Section 7.1.1, Table 12 or Table 13)

V. Blood sampling for Cardiac marker (Troponin I [>30 minutes post dosing])

VI. ECG measurement (see Full ECG or Sparse ECG measurement schedule in Section

7.1.1, Table 14 or Table 15).

Note:

Dosing of agents in the mFFX regimen with devimistat are based on clinical practice and literature (e.g., Stein S, et.al, BJC (2016) 114:737-743).

In the event that time will not permit devimistat administration following 5-FU infusion, devimistat may be administered concurrently with 5-FU via a double lumen port.

FOLFIRINOX Arm 2: FFX

I. Pre-dosing Tests:

- Evaluation of vital signs (including heart rate)*,
- ECOG performance status*,
- Survival*,
- Clinical chemistry*,
- Hematology*,
- Coagulation*,
- NCCN-FACT FSHI-18 questionnaire (if not collected during screening)
- Triphase contrast CT of the chest, abdomen and pelvis **,
- CA19-9**
- ECG (see Sparse ECG measurement schedule in Section 7.1.1, Table 15).
- Blood sampling for Cardiac marker (Troponin I)

II. Oxaliplatin at a dose of 85 mg/m^2, given as a 2-hr IV infusion

III. Folinic acid at 400 mg/m^2, given as a 2-hour IV infusion immediately after oxaliplatin

IV. Irinotecan at 180 mg/m^2, given as a 90-minute IV infusion via a Y-connector

V. concurrently with folinic acid infusion

VI. Fluorouracil (5-FU) at 400 mg/m^2 as IV bolus, followed by a 42-48-hr continuous IV infusion at 2,400 mg/m^2, starting immediately after completion of folinic acid and irinotecan

VII. Myeloid Growth Factor will be given as per institutional guidelines.

VIII. Blood sampling for Cardiac marker (Troponin I) post 30 minutes of completion of FFX dose

Note:

**These tests are performed in local labs with results available for review within 24 hrs. before administration of the anti-tumor agents.*

***Performed at the end of every 4th cycle.*

1. **Duration of Treatment:** Treatment will continue for at least 6 months (i.e. a minimum of 12 cycles) in responding patients with acceptable tolerance to therapy (with dose modifications per protocol as needed) unless a criterion for removal from study occurs. Responding patients upon completion of at least 10 cycles and after having two sequential CT scans showing stable disease (no continued decrease in lesion size) will complete 2 additional cycles (to complete a minimum of 12 cycles) of their assigned treatment. Following 12 cycle, 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 (see Section 5.3.1).

2. **Observations after the Intervention:** OS will be monitored every 2 months via telephone contact after treatment termination. (Note: During every 2 months post- study treatment telephone contact, information related to cancer treatment received will also be collected).

7.3.3. Treatment Phase

Treatment dosing continues for at least 6 months (i.e. a minimum of 12 cycles) until disease progression (radiological) or a criterion for removal from study are reached. Every cycle will be allowed window of +/- 24 hours.

All patients, on both arms, will complete radiology scans for RECIST evaluation every 8 weeks (+/- 7 days). Radiology will be assessed using triphase contrast CT of the chest, abdomen and pelvis. MRI assessments of tumor status may replace CT scans if needed. Serum levels of tumor marker CA19-9 and performance status also will be assessed every 8 weeks.

Chemotherapy breaks, of 3 weeks or less only, for patient emergencies are allowed and must be

documented.

CYCLE: 2 (Day 15 – Day 29):

1. **Adverse Event Assessment:** record adverse events as reported by participant or observed by investigator
2. **Pre-dosing Tests:** Clinical hematology (including coagulation) and chemistry tests as well as PRO has to be done at this cycle
3. **Administration of Study Treatment:** same as Cycle 1
4. **Sparse PK sampling** (see Sparse PK sampling schedule in Section 7.1.1, Table 13)
5. **Sparse ECG** (see Sparse ECG measurement schedule in Section 7.1.1, Table 15)

CYCLE: 3 (Day 30 – Day 44):

1. **Adverse Event Assessment:** record adverse events as reported by participant or observed by investigator
2. **Pre-dosing Tests:** Clinical hematology (including coagulation) and chemistry tests
3. **Administration of Study Treatment:** same as Cycle 1
4. **Sparse PK sampling** (see Sparse PK sampling schedule in Section 7.1.1, Table 13)
5. **Sparse ECG** (see Sparse ECG measurement schedule in Section 7.1.1, Table 15)

CYCLE: 4 (Day 45 – Day 59):

1. **Adverse Event Assessment:** record adverse events as reported by participant or observed by investigator
2. **Pre-dosing Tests:** Clinical hematology (including coagulation) and chemistry tests as well as PRO has to be done at this cycle
3. **Administration of Study Treatment:** same as Cycle 1
4. **Observations after the Intervention:** radiology scan for the measurement of ORR (approximate, all scans will be done every 8 weeks, +/-7 days), CA19-9, and optional blood draw
5. **Sparse PK sampling** (see Sparse PK sampling schedule in Section 7.1.1, Table 13)

CYCLE: 5 (Day 60 – Day 74):

1. **Adverse Event Assessment:** record adverse events as reported by participant or observed by investigator

2. **Pre-dosing Tests:** Clinical hematology (including coagulation) and chemistry tests
3. **Administration of Study Treatment:** same as Cycle 1
4. **Sparse PK sampling** (see Sparse PK sampling schedule in Section 7.1.1, Table 13)

CYCLE: 6 (Day 75 – Day 89):

1. **Adverse Event Assessment:** record adverse events as reported by participant or observed by investigator
2. **Pre-dosing Tests:** Clinical hematology (including coagulation) and chemistry tests as well as PRO has to be done at this cycle
3. **Administration of Study Treatment:** same as Cycle 1
4. **Sparse PK sampling** (see Sparse PK sampling schedule in Section 7.1.1, Table 13)
5. **Sparse ECG** (see Sparse ECG measurement schedule in Section 7.1.1, Table 15)

CYCLE: 7 (Day 90 – Day 104):

1. **Adverse Event Assessment:** record adverse events as reported by participant or observed by investigator
2. **Pre-dosing Tests:** Clinical hematology (including coagulation) and chemistry tests
3. **Administration of Study Treatment:** same as Cycle 1
4. **Sparse PK sampling** (see Sparse PK sampling schedule in Section 7.1.1, Table 13)

CYCLE: 8 (Day 105 – Day 119):

1. **Adverse Event Assessment:** record adverse events as reported by participant or observed by investigator
2. **Pre-dosing Tests:** Clinical hematology (including coagulation) and chemistry tests as well as PRO has to be done at this cycle
3. **Administration of Study Treatment:** same as Cycle 1
4. **Observations after the Intervention:** radiology scan for the measurement of ORR (approximate, all scans will be done every 8 weeks, +/-7 days), CA19-9 and optional blood draw
5. **Sparse PK sampling** (see Sparse PK sampling schedule in Section 7.1.1, Table 13)

CYCLE: 9 (Day 120 – Day 134):

1. **Adverse Event Assessment:** record adverse events as reported by participant or observed by investigator
2. **Pre-dosing Tests:** Clinical hematology (including coagulation) and chemistry tests
3. **Administration of Study Treatment:** same as Cycle 1
4. **Sparse PK sampling** (see Sparse PK sampling schedule in Section 7.1.1, Table 13)
5. **Sparse ECG** (see Sparse ECG measurement schedule in Section 7.1.1, Table 15)

CYCLE: 10 (Day 135 – Day 149):

1. **Adverse Event Assessment:** record adverse events as reported by participant or observed by investigator
2. **Pre-dosing Tests:** Clinical hematology (including coagulation) and chemistry tests as well as PRO has to be done at this cycle
3. **Administration of Study Treatment:** same as Cycle 1
4. **Sparse PK sampling** (see Sparse PK sampling schedule in Section 7.1.1, Table 13)

CYCLE: 11 (Day 150 – Day 164):

1. **Adverse Event Assessment:** record adverse events as reported by participant or observed by investigator
2. **Pre-dosing Tests:** Clinical hematology (including coagulation) and chemistry tests
3. **Administration of Study Treatment:** same as Cycle 1
4. **Sparse PK sampling** (see Sparse PK sampling schedule in Section 7.1.1, Table 13)

CYCLE: 12 (Day 165 – Day 179):

1. **Adverse Event Assessment:** record adverse events as reported by participant or observed by investigator
2. **Pre-dosing Tests:** Clinical hematology (including coagulation) and chemistry tests as well as PRO has to be done at this cycle
3. **Administration of Study Treatment:** same as cycle 1.
4. **Observations after the Intervention:** radiology scan for the measurement of ORR (approximate, all scans will be done every 8 weeks, +/-7 days), CA19-9 and optional blood draw
5. **Sparse PK sampling on Cycle 12** (see Sparse PK sampling schedule in Section 7.1.1,

Table 13)

6. **Sparse ECG** (see Sparse ECG measurement schedule in Section 7.1.1, Table 15)

**After the first cycle (Cycle 1)*

All subsequent cycles (beyond Cycle 12), the following assessments should be completed:

- Physical Examinations
- Vital Signs
- Obtain CT scan (or MRI) every 8 weeks
- Blood sample collection for the following tests: Hematology, Blood Chemistry, Coagulation, and CA 19-9 every 4 weeks (or even cycle (eg, Cycle 14, Cycle 16, etc).
- Collect AE and SAE
- Pregnancy test
- Dosing of drug (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 treatment are reached. (see Section 5.3.1)
- NCCN-FACT FHSI-18 Questionnaire (PRO)

7.3.4. End of Treatment Visit

Subjects should return to the study site for an End of Treatment Visit within approximately 7 days after treatment discontinuation of all study medication (CPI 613® + mFFX or FFX) and prior to initiation of subsequent anticancer therapy. Adverse events and concomitant medications will be reviewed at this visit, and the following assessments should be completed:

- Physical Examinations
- Vital Signs
- ECOG Performance Status
- Obtain CT scan (or MRI) if radiologic disease progression was not documented in the previous CT scan (or MRI) unless the latter one was performed within the last 14 days
- Blood sample collection for the following tests: Hematology, Blood Chemistry, and CA 19-9

- Collect AE and SAE
- Pregnancy test
- NCCN-FACT FHSI-18 Questionnaire

7.3.5. Long-Term Follow-up

After the End of Treatment visit, subjects will enter long-term follow-up during which information on the subject's survival status, disease progression and subsequent anticancer therapy will be obtained by the site every 2 months according to the protocol with a time window of +/- 7 days. Information may be collected by chart review, phone calls, clinic visits, or other means as appropriate. Long-term follow-up will continue until the subject dies, is lost to follow up, or withdraws consent.

Follow up for OS:

OS will be monitored every 2 months via telephone contact, review of hospital records, death records, social media, etc. as allowed by local laws after treatment termination (Note: During every post-study treatment telephone contact, information related to cancer treatment received will also be collected). OS and PFS will be calculated from the day of randomization.

7.3.6. Schedule of Events Table

Table 16 Schedule of Events: Experimental Arm

Experimental Arm: devimistat + mFFX								
Assessments	Pre-Study Screen	**Cycle 1 (+/- 24 hr.) and Subsequent Cycles (+/- 24 hr.)**					End of treatment	Follow-Up Every 2 Months Until Death
		Day 1	Day 2	Day 3	Day 4	Days 5-14		
Informed consent	√							
Medical history	√							
Pregnancy test for women of childbearing Potential (monthly- day 1 of even numbered cycle)	√	√					√	
Hemoglobin A1c (HbA1c)	√							
devimistat administration (dosing)		√		√				

mFOLFIRINOX (mFFX)		√	√	√				
AE and Con. Med. Assessment		AEs and con meds will be assessed at each patient visit						
Myeloid growth factor (as per institutional guidelines)*					√			
Evaluation of symptoms and vital signs[7]	√	√					√	
ECOG performance status[6] and survival	√	√					√	
Clinical chemistry, hematology and coagulation	√	√				√ (day 7 or 8)	√	
Triphase contrast CT of the chest, abdomen and pelvis (or MRI if needed) (every 8 weeks)	√						√ (unless one was performed within the last 14 days	
Blood sampling for biomarker[1]	√							
CA19-9 (every 8 weeks up to 12 cycles and every 4 weeks beyond 12 cycles)	√	√					√	
Blood sampling for Full PK Analysis[2]		√		√				
Blood sampling for Sparse PK Analysis[3]		√		√				
Cardiac Marker (Troponin I)[8]		√		√				
Full ECG[4]		√		√				
Sparse ECG[5]		√		√				
Phone contact								√
NCCN-FACT FHSI-18 Questionnaire[6]	√	√					√	

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

[1] *Prior to treatment initiation (within 4 weeks prior to 1st dose) and prior to each restaging scan.*

[2] *Full PK analysis will be carried out only for cycle 1. For Full PK sampling schedule see Section 7.1.1, Table 12*

[3] *see Sparse PK sampling schedule in Section 7.1.1, Table 13*

[4] *Full ECG measurement will be carried out only for cycle 1. For Full ECG measurement schedule see Section 7.1.1, Table 14*

[5] *see Sparse ECG measurement schedule in 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 Section 7*

Table 17 Schedule of Events: Control Arm

Control Arm 2: FFX								
Assessments	**Pre- Study Screen**	**Cycle 1 (+/- 24 hr.) and Subsequent Cycles (+/- 24 hr.)**					**End of Treatment**	**Follow-Up Every 2 Months Until Death**
		Day 1	**Day 2**	**Day 3**	**Day 4**	**Days 5-14**		
Informed consent	√							
Medical history	√							
Pregnancy test for women of childbearing potential (monthly- day 1 of even numbered cycle)	√	√					√	
Hemoglobin A1c (HbA1c)	√							
FOLFIRINOX (FFX)		√	√	√				
AE and Con. Med. Assessment		AEs and con. meds will be assessed at each patient visit						
Myeloid growth factor (as per institutional guidelines)*					√			
Evaluation of symptoms and vital signs[6]	√	√					√	
ECOG performance status[5] and survival	√	√					√	
Clinical chemistry, hematology and coagulation	√	√				√ (day 7 or 8)	√	
Triphase contrast CT of the chest, abdomen and pelvis (or MRI if needed)[1]	√						√ (unless one was performed within the last 14 days	
Blood sampling for biomarker[2]	√							
Cardiac Marker (Troponin I)[4]		√		√				
CA19-9 every 8 weeks up to 12 cycles and every 4 weeks beyond 12 cycles)	√	√					√	
Sparse ECG[3]		√		√				
Phone contact								√
NCCN-FACT FHSI-18 Questionnaire[5]	√	√					√	

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

[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 Section 7.1.1, Table 15*

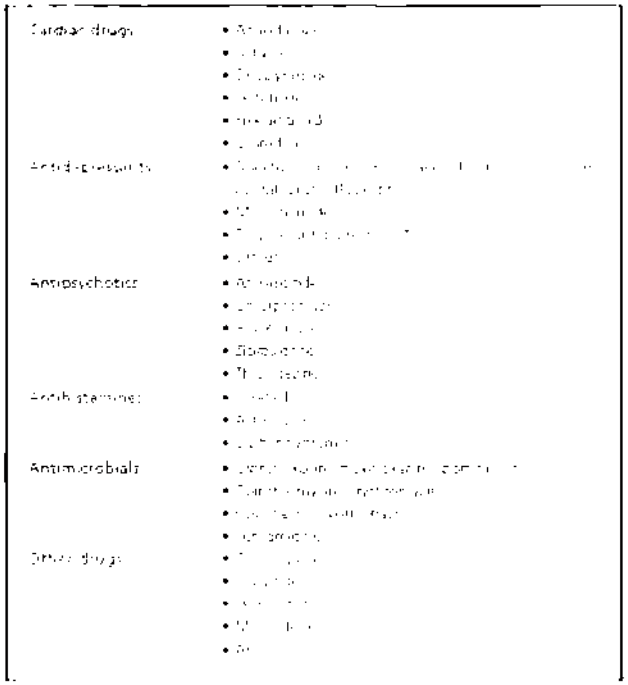
[4] *see Cardiac Marker (Troponin I) schedule under Section 7*

[5] *at baseline and day 1 of every even numbered cycle*

[6] *Vital signs include heart rate*

7.4. Concomitant Medications, Treatments, and Procedures

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs) such as prescription medications, over the counter medication, non- prescription medications. Concomitant use of anti-emetics is permitted for patients with disease- related nausea. Concomitant medicines that prolong QTc such as those listed in the table below can be taken after patient enrollment/baseline visit (C1D1) at the discretion of treating physician to manage an emergent condition. If the treating physician determines there is a need for other medications that are not listed below, it should be discussed with trial medical monitor.



7.5. Prophylactic Medications, Treatments, and Procedures

All supportive measures are at the discretion of the treating physician. Supportive treatment as co- medications may include anti-emetic, anti-diarrhea, anti-pyretic, anti-allergic, anti-hypertensive medications, analgesics, antibiotics, allopurinol, and others such as blood products and bone marrow growth factors. Patients may use erythropoietin for chronic anemia. The treating physician may utilize erythropoietic factors, or blood or platelet transfusions at their discretion in addition to protocol mandated dose adjustments (see Section 6.1.6.2). The use of co-medications will be documented through treatment for individual patients.

7.6. Participant Access to Study Agent at Study Closure

Rafael Pharmaceuticals will make every attempt to ensure patients randomized to the study arm who are deriving clinical benefit will continue to have access to devimistat following study closure.

8.1. Specification of Safety Parameters

8.1.1. Definition of Adverse Events (AE)

An adverse event (AE) is defined as any undesired medical occurrence in a patient receiving a study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the study treatment, whether or not related to the study drug.

8.1.2. Definition of Serious Adverse Events (SAE)

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Results in death
- Is life-threatening
- Requires hospitalization (initial or prolonged)
- Results in persistent or significant disability/ incapacity
- Is a congenital anomaly/birth defect
- Is otherwise considered as medically important

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events not to be considered as AEs/SAEs

Medical conditions present at the initial trial visit that do not worsen in severity or frequency

during the trial are defined as baseline medical conditions and NOT to be considered AEs.

8.1.3. Definition of Unanticipated Problems (UP)

OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

1. Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
2. Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This study will use the OHRP definition of UP.

8.1.4. Pregnancy

Female subjects and male subjects with pregnant partners who becomes pregnant during the study must stop IMP and the Principal Investigator should report the pregnancy to Covance Safety (CRO/Rafael) on the applicable pregnancy report form. The subject must be discontinued from the trial medication immediately and the subject or the pregnant partner will be followed until the conclusion of the pregnancy with the outcome being reported as an update to the pregnancy form.

8.2. Classification of an Adverse Event

8.2.1. AE Severity Grade

Table 18 Adverse Event Severity Grading

Severity (Toxicity Grade)	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

8.2.2. Severity of Adverse Events

The Cancer Therapy Evaluation Program (CTEP) Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE 4.0) will be utilized for Adverse Event (AE) reporting. The CTEP Active Version of the CTCAE is identified and located on the CTEP website at: *http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm*
All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE. If a particular AE's severity/intensity is not specifically graded by the guidance document, the investigator will revert to general definitions of grade 1 through grade 5 and use his or her best medical judgement.

Evaluation of an Adverse Event (AE):

- **Definitely Related –** A clinical event follows a reasonable temporal sequence from the time of Investigational Product (devimistat) administration, cannot be reasonably explained by other factors such as the subjects medical condition, or concurrent medical condition, or concurrent medication(s) AND either occurs following active Investigational Product (devimistat) administration, improves on stopping the Investigational Product (devimistat), or reappears on re-exposure

- **Probably Related –** A clinical event follows a reasonable temporal sequence from the time

of Investigational Product (devimistat) administration. The toxicity cannot be reasonably explained by other factors such as the subjects clinical state or concurrent medical condition, or concurrent medication(s)

- **Possibly Related –** A clinical event follows a reasonable temporal sequence from the time of active Investigational Product (devimistat) administration but could also have been produced by other factors such as the subjects clinical state, or concurrent medical condition, or concurrent medication(s)

- **Unlikely Related –** A clinical event is doubtfully related to active Investigational Product (devimistat). The event was most likely related to other factors such as the subject's clinical state, or concurrent medical condition, or concurrent medication(s) or the temporal relationship to the administration and/or exposure suggests that a causal relationship is unlikely

- **Not Related** - The event is clearly due to causes other than the Investigational Product (devimistat)

<u>List of adverse events (AEs) for devimistat:</u>

Definitely Related to devimistat:

- Hyponatremia
- Hyperglycemia
- Lymphocyte Count Decrease

Probably related to devimistat:

- *Increased Creatinine
- *Vomiting
- *Nausea
- *Diarrhea

Asterisk (*) denotes expected Adverse Events.

Possibly related to devimistat:

- Increased Alkaline phosphatase

- Anorexia
- ALT (SGPT)
- AST (SGOT)
- Bilirubin (hyperbilirubinemia)
- Calcium (hypercalcemia, hypocalcemia)
- Flushing
- Hemoglobin (anemia)
- Leukocytes
- Lymphopenia
- Neutrophils (neutropenia)
- Platelets (thrombocytopenia)
- Potassium

List of adverse events for FFX

Definitely related to FFX:

- Neutropenia
- Febrile neutropenia
- Thrombocytopenia
- Anemia
- Fatigue
- Vomiting
- Diarrhea
- Sensory neuropathy

Possibly related to FFX:

- Elevated level of alanine aminotransferase
- Thromboembolism

Tumor flare leading to biliary obstruction is also a possible side effect of treatment but will not disqualify patients from study participation. In the event that tumor flare occurs, patients may be treated with a stent.

8.2.3. Expectedness

AEs can be 'Unexpected' or 'Expected' for expedited reporting purposes only.
Covance will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information present in the Investigator's brochure.

8.3. Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured in the CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship, action taken with study drug (drug withdrawn, dose reduced), other treatment for AE (drug therapy, other procedure) and outcome of AE. All AEs will be followed to adequate resolution (return to baseline).

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode. Disease progression will not be considered as an AE/SAE.

The PI will record all reportable events with start dates occurring any time after informed

consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last dose of the study drug. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.4. Reporting Procedures

8.4.1. Adverse Event Reporting

At each visit the subject will be queried on changes in his/her condition. During the reporting period of the trial any untoward changes in the subject's condition will be recorded as AE, whether reported by the subject or observed by investigator.

Any treatment-emergent abnormal laboratory result which is clinically significant (defined as meeting one or more of the below must be documented on the CRF.

1. Accompanied by clinical symptoms
2. Leading to a change in study medication (e.g., dose modification, interruption or permanent discontinuation)
3. Requiring a change in concomitant therapy (e.g., addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment)

It is the responsibility of the investigator to document all AEs that occur during the study. AEs should be reported on the appropriate page of the CRF. AEs should be reported for their actual grade and duration. The severity of the AE will be graded according to the NCI CTCAE Grading Scale (Current version).

8.4.2. Serious Adverse Event Reporting

Timeframes:

The study clinician will complete a SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the Covance safety/study sponsor within 24 hours of site awareness.
- Other SAEs regardless of relationship, will be submitted to the Covance safety/study sponsor within 24 hours of site awareness.

Description:

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the DCC/study sponsor and should be provided as soon as possible.

Study staff are responsible for completing and signing off on the SAE reports & Receiver of Notification of SAEs:

All SAEs which are serious, possibly related and unexpected are required to be reported to Covance using a serious adverse event report form. The SAE should be accompanied by relevant subject's medical records, the eCRF and other important documents.

SAE reports must be submitted to Covance PV by phone, fax or email to the following address:

Covance, Inc.

Covance PV and DSS

Email: SAEintake@covance.com

USA fax number 1-888-887-8097

EU: +44 1628 540 028

When events are reported to various oversight and regulatory groups:

The investigator will also assure that all AEs meeting IRB/IEC and regulatory authorities' criteria are documented and communicated appropriately. All documentation and communications to the IRB/IEC and applicable regulatory authorities will be provided to the Sponsor and maintained within the Trial Master File.

8.4.3. Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the DCC/study sponsor. The UP report will include the following information:

1. Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
2. A detailed description of the event, incident, experience, or outcome;
3. An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
4. A description of any changes to the protocol or other corrective actions that have been

taken or are proposed in response to the UP

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

1. UPs and SUSARs will be reported to regulatory authority/sites/central IRBs by day 7 for initial reports for fatal and life- threatening events and day 15 for all other events
2. Sites should send UPs to their local IRBs and institutions as appropriate per SOPs

8.5. Safety Oversight

Safety oversight will be under the direction of a DMC composed of individuals with the appropriate expertise, including medical oncology with experience treating metastatic pancreatic cancer patients, statistical analysis. The DMC will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMC will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DMC. At this time, each data element that the DMC needs to assess will be clearly defined. The DMC will provide its input to Rafael Pharmaceuticals.

9.1. Statistical Analysis Plan

The full statistical methods will be detailed in a Statistical Analysis Plan (SAP), which will be finalized prior to the first database lock.

9.2. Trial Design and Statistical Hypotheses

The primary endpoint is overall survival (OS). The primary hypothesis will be tested in the trial, aiming at claiming superior efficacy of the experimental Arm 1 (devimistat + mFFX) over the control Arm 2 (FFX) at the final analysis when the pre-specified number of deaths is reached. The trial is powered to detect an OS hazard ratio equal to 0.7 (a 30% reduction in the risk of death from any cause), assuming a median OS equal to 12 months in the control arm vs. 17.14 months in the experimental arm. Progression-free survival (PFS) will be tested if the primary endpoint reaches significance. Specifically, the hypotheses of interest is that PFS is equal to 6.4 months in the control arm vs. 9.14 months in the experimental arm, i.e. a PFS hazard ratio (HR) equal to 0.7 (a 30% reduction in the risk of tumor progression or death from any cause).

9.3. Analysis Populations

The following populations will be defined for the statistical analysis:

- The intent-to-treat (ITT) population includes all randomized subjects in the treatment arm they were allocated to
- The Per Protocol (PP) population consists of randomized subjects who do not have any major protocol violation and received at least one dose of study treatment
- The safety population consists of all subjects who received at least one dose of study treatment and have at least one post-baseline safety assessment

The ITT population will be used for all analyses of efficacy and baseline characteristics. The PP population will be used as a sensitivity analysis for efficacy endpoints. The safety population will be used for safety analyses.

Every effort will be made to keep all randomized patients in the study regardless of their adherence to treatment. Patients who stop their therapy for any reason will be followed until confirmed disease progression and/or death.

9.4. Description of Statistical Methods

9.4.1. General Analytical Considerations

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 event outcomes ("survival times") will be described by treatment arm using the 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, 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 and tumor location. A logistic regression model will be used to adjust the comparison for baseline covariates.

9.4.2. Testing Procedure and Control of Type I Error

This study has one primary efficacy endpoint of OS. The key secondary efficacy endpoint is PFS. Only one efficacy analysis is planned for all endpoints.

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 other secondary endpoints in the following order: ORR first, and then DOR, each at a significance level of 0.025.

9.4.3. Efficacy Analysis

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)[20]. When such a procedure is used, the preferred test is a re-randomization test (Simon, 1979)[21] 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 (a re-randomization *P*-value) to the observed test statistic. Arbitrary precision on the re-randomization *P*-value can be obtained by increasing the number of simulated trials. Full details on the re-randomization tests will be provided in the Statistical Analysis Plan. Re-randomization tests will be used as the primary method of analysis, with asymptotic tests used as sensitivity analyses.

The primary analysis will compare the OS observed under the combination therapy devimistat plus mFFX compared to standard care FFX in the ITT population. The comparison will use a re-randomization test based on the log-rank test-statistic, stratified by performance status (0 vs 1) and primary tumor location (head vs. body vs. tail of the pancreas). A stratified log-rank test will be performed as sensitivity analysis. Additional analyses with an unstratified log-rank test and re-randomization test with an unstratified log-rank test-statistic will also be performed. In addition, other sensitivity analyses will be performed, including the censoring of patients who changed treatment at the day the patient received the new treatment and performing all analyses described above on the PP population. The estimation of the survival curves for the 2 treatment groups will be generated using the Kaplan-Meier methodology. More details will be contained in the Statistical Analysis Plan (SAP).

PFS is defined as the duration from the date of randomization to the date of progressive disease or death from any cause. Patients who have neither progressed nor died will be censored at the day of their last radiographic tumor assessment, if available or date of randomization if no post initiation radiographic assessment is available. If death or PD occurs after 2 or more missing

radiographic visits, censoring will occur at the date of the last radiographic visit that the patient was known to be alive and progression-free. Patients who switch to another treatment prior to PD will be censored at the time of the treatment switch.

The primary analysis will compare the PFS observed under the combination therapy devimistat plus mFFX compared to standard care FFX based on the central assessment in the ITT population. The comparison will use a re-randomization test based on the log-rank test-statistic, stratified by performance status (0 vs 1) and primary tumor location (head vs. body vs. tail of the pancreas). A stratified log-rank test will be performed as sensitivity analysis. Additional analyses with an unstratified log-rank test and re-randomization test with an unstratified log-rank test-statistic will also be performed. The estimation of the survival curves for the 2 treatment groups will be generated using the Kaplan-Meier methodology. More details will be contained in the Statistical Analysis Plan (SAP).

The final analysis of PFS will include sensitivity analyses under the following conditions:

- Using central review PFS from the Per Protocol population
- Using the investigator provided PFS but censoring patients who changed treatment at the day the patient received the new treatment
- Using the Investigator provided PFS from the Per Protocol population

The SAP will further elaborate on other sensitivity analyses considering different censoring rules to control for missing data and/or lost to follow-up.

The secondary endpoint ORR will be estimated as the proportion of responders in each treatment arm of the ITT, defined as a patient whose best overall response is PR or better during the treatment period. All responses must be confirmed at least 4 weeks after the initial response is seen. The ORR analysis will compare the ORR per central assessment observed under the combination therapy devimistat plus mFFX compared to standard care FFX in the ITT population, considering patients without response assessment as non-responders. The comparison will use a re- randomization test based on the CMH test-statistic. The odds ratio and 95 % confidence interval of the odds ratio will be presented.

As a sensitivity analysis, a CMH test will be performed. In addition, both analyses (re-

randomization and CMH test) will be performed on the PP population.

The duration of response is the interval from date of initial documented response (CR or PR) to the first documented date of disease progression or death. Patients who do not relapse or die are censored at the day of their last tumor assessment. The DOR analysis will be a re- randomization test on the ITT population, based on the log-rank test-statistic. As a sensitivity analysis, a log-rank test will be performed. These analyses will only include responders.

9.4.4. Safety Analyses

The assessment of safety will be based mainly on the frequency of adverse events based on the Common Terminology Criteria for Adverse Events (CTCAE version 4) grade. Adverse events will be coded according to MedDRA, current version. The safety outcomes will include the occurrence of at least one serious adverse event, of at least one grade 3/4 adverse event, and of at least one adverse event requiring the discontinuation of study treatment.

9.4.5. Analysis of Patient-Reported Outcome (PRO)

Patient-Reported Outcomes (PRO) using the NCCN-FACT Hepatobiliary Symptom Index (FHSI-18). NCCN-FACT FHSI-18 is a widely used PRO questionnaire for patients with hepatobiliary cancer (liver, bile duct and pancreas) developed by FACIT.org available at: *http://www.facit.org/FACITOrg/Questionnaires*. Summary statistics of the scores will be shown by cycle (pre and post treatment). Scores will be compared between standard and study arms. Efforts to avoid missing data will include data collection 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. Summary statistics of the scores will be shown by cycle (pre and post treatment). The inferential comparison between 2 arms will be done using repeated measure mixed model, and the details of the analysis will be described in the SAP.

9.4.6. Final Analysis

The modified trial design foresees accrual of 500 patients over a period of 33 months, and a single final analysis.

The final analysis of OS will be done when approximately 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.

A Data Monitoring Committee (DMC) will be appointed to review, on a periodic basis, accumulating safety data. The DMC will review unblinded data that will not be shared with anyone else (Sponsor or investigators). At each of their meetings, the DMC will recommend a course of action: stop the trial, amend the trial protocol, or continue the trial unchanged. The DMC recommendation will be based on safety considerations. None of these considerations will be considered binding, as DMC recommendation will be based on the totality of the evidence presented to them regarding general trial conduct as well as patient safety.

9.4.7. Additional Sub-Group Analyses

Sub-group analyses will be carried out with a descriptive intent. Treatment effects will be estimated and tested for important baseline factors, including the factors used in the treatment allocation procedure (performance status and primary tumor location), and displayed as forest plots. Interaction tests will be carried between treatment and each of these prognostic factors.

9.4.8. Blinding Plan for Statistical Analysis

Biostatistician Team: At least 3 biostatisticians will be involved in the statistical analysis of PANC003. Project Statisticians will be blinded or masked. There will be at least one senior project biostatistician who will perform SAP analysis, reporting, programming, QC and final analysis.

Another blinded or masked biostatistician or programmer will perform programming and QC. In addition to project biostatistician, there will be one independent senior biostatistician in the DMC (Data Monitoring Committee). This DMC biostatistician will be unblinded. This DMC biostatistician will be involved in the DMC charter development, data monitoring and analysis

for the DMC meetings. Blinded and unblinded statistical teams will be separated by a firewall and preferably be located in 2 different geographical locations.

9.5. Sample Size

Approximately 500 patients will be entered in the trial. This number accounts for ineligible and unevaluable patients, as well as for dropouts.

The sample size calculation is based on the following expected benefits of the experimental treatment (devimistat + 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 type-1 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 type-I error level of 0.025, 330 PFS events need to be observed.

9.6. Measures to minimize Bias

9.6.1. Enrollment/ Randomization/ Masking Procedures

Subjects will be randomized in 1:1 ratio to the experimental treatment or control, using a minimization procedure. Such a procedure is commonly used in open label cancer trials carried out in a large number of sites, because it produces good balance with respect to several prognostic factors while keeping the treatment allocations unpredictable.

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). A stochastic minimization will be used so that no treatment allocation is deterministic. Note that region is subsumed by site, hence minimization will also tend to balance between the treatment arms with respect to geographical region.

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practice (GLP), Good Manufacturing Practice (GMP)). Data should meet the standard for ALCOA-C

The investigational site will provide direct access without undue restriction to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor or designee, and inspection by local and regulatory authorities.

11.1. Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6 (R2).

11.2. Institutional Review Board/ Independent Ethics Committee

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

11.3. Informed Consent Process

11.3.1. Consent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting any study procedures.

11.3.2. Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved, and the participant will be asked to read and review the document. The investigator (or their designee) will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to

participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

11.4. Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations. Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Covance This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Covance research staff will be secured, and password protected. At the end of the study, all study databases will be de-identified and archived at the Rafael Pharmaceuticals.

11.4.1. Research Use of Stored Human Samples, Specimens or Data

Intended Use: Samples and data collected under this protocol may be used to study pancreatic cancer.

Storage: Access to stored samples will be limited. Samples and data will be stored using codes assigned by the IxRS. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.

Tracking: Data will be tracked using study patient identifiers. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

11.5. Future Use of Stored Specimens

Data collected for this study will be analyzed and stored at Rafael Pharmaceuticals. After the study is completed, the de-identified, archived data will be transmitted to and stored at the Sponsor (Rafael Pharmaceuticals).

With the participant's approval and as approved by local IRs, de-identified biological samples will be stored at Rafael Pharmaceuticals (or it's designee) These samples could be used for research into the causes of pancreatic cancer, its complications and other conditions for which individuals with pancreatic cancer are at increased risk, and to improve treatment. Rafael Pharmaceuticals (or it's designee) will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the masking of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to bio-sample storage will not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided through Rafael Pharmaceuticals (or its designee).

12.1. Data Collection and Management Responsibilities

Data should be in compliance with ALCOA-C, Attributable, Legible, Contemporaneous, Original, Accurate, Complete accessible. This is required for paper and electronic sources. Sites shall ensure procedures and training are in place to assure data integrity.

If paper source documents are used, they should be completed in a neat, legible manner to ensure accurate interpretation of data. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into the EDC that is compliant with 21 CFR Part 11-compliant. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

Clinical data will be entered directly from the source documents. Training on the EDC will be provided by the sponsor or a designee. Training will include data integrity compliance.

12.2. Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

12.3. Protocol Deviations

A protocol deviation is an unplanned lack of adherence to the protocol. Each investigator is responsible for ensuring the study is conducted in accordance with this protocol and must protect the rights, safety and welfare of the enrolled subjects. The investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to trial subjects. A protocol waiver is a documented prospective approval of a request from an investigator to deviate from the protocol. Protocol waivers are not allowed.

When a deviation from the protocol is identified, the investigator or designee must notify the Sponsor/designee. The Sponsor/designee will follow-up with the investigator, as applicable, to assess the deviation and the possible impact to the safety and/or efficacy of the subject to determine subject continuation in the study. If a deviation impacts the safety of a subject, the investigator must contact the Sponsor/designee immediately. All deviations will be reviewed by Covance and Rafael pharma team.

The investigator will also assure that deviations meeting IRB/IEC and regulatory authorities' criteria are documented and communicated appropriately. All documentation and communications to the IRB/IEC and applicable regulatory authorities will collected by CRAs and filed with in electronic Trial Master File.

Deviations will be totaled for each arm and for each treating institution at the completion of the study. Sites with excessive deviations (as determined by the Sponsor) will be audited and if not corrected may be subject to halting accrual until such time as the underlying issues have been identified and resolved.

NOTE: Other deviations outside of the categories defined above that are required to be reported by the IRB/IEC in accordance with local requirements will be reported, as applicable.

12.4. Publication and Data Sharing Policy

Any publications and presentations of the results either in whole or in part, by investigators or their representatives will require pre-submission review by the Sponsor.

13.1. Study Leadership

The Steering Committee will govern the conduct of the study. The Steering Committee will be composed of representatives from Rafael Pharmaceuticals, four oncologists, and one statistician. The Steering Committee will meet in person every quarter.

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

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16.1. APPENDIX I: Log of Protocol Amendments

Protocol Version	Date	Local	Global	Countries Applicable
V4.0	September 1, 2018		√	USA, S. Korea and Israel EU –Belgium, Italy, France, Germany, Spain
V4.1	June 26, 2019	√		EU –Belgium, Italy, France, Germany, Spain
V5.0	August 29, 2019		√	USA, S. Korea and Israel EU –Belgium, Italy, France, Germany, Spain
V6.0	March 23, 2020		√	USA, S. Korea and Israel EU –Belgium, Italy, France, Germany, Spain
V7.0	May 19, 2020		√	USA, S. Korea and Israel EU –Belgium, Italy, France, Germany, Spain
V8.0	October 10, 2020		√	USA, S. Korea and Israel EU –Belgium, Italy, France, Germany, Spain
V9.0	June 10, 2021		√	USA, S. Korea and Israel EU –Belgium, Italy, France, Germany, Spain

16.2. APPENDIX II: Response Evaluation Criteria in Solid Tumors (RECIST) 1.1

New Response evaluation criteria in Solid tumors: Revised RECIST criteria [EJC 4 (2): 228-247, 2009] are summarized below.

Measurable (Target)/Non-Measurable (Non-Target) Lesions. Each tumor lesion or site of disease identified at baseline is categorized as either a measurable lesion or a non-measurable lesion according to the following definitions.

Measurable Lesions:

Non-nodal tumor lesions ≥ 10 mm in longest diameter (LD)

- On axial image on CT or MRI (slice thickness ≤ 5 mm). If slice thickness ≤ 5 mm, the LD should be at least 2 times the slice thickness
- By caliper measurement by clinical exam (when superficial)
- If chest X- Ray and if tumor clearly defined and surrounded by aerated lung - LD ≥ 20 mm

Malignant lymph nodes > 15 mm in short axis (SA)

- 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 Lesions:

- 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

Special considerations:

- Bone lesions: Lytic or mixed lytic-blastic bone lesions with soft tissue component that

meets the definition of measurability (on CT or MRI) can be considered measurable. Blastic bone lesions are non-measurable

- Cystic lesions: Simple cysts: presumed benign. Complex cysts may be measurable: but prefer to use solid lesions as target
- Lesions with prior local treatment: Tumor lesions situated in an area subjected to locoregional therapy (ex RT) are usually not considered measurable unless there has been demonstrated progression in that lesion

Evaluation of baseline tumor burden

Target lesions

- Select the largest and reproducibly (by imaging) measurable lesions – a maximum 5 in total up to 2 per organ, representative of all involved organs
- Measure and add up longest diameters (LD) of non-nodal lesions
- Measure and add up short axis (SA) of lymph nodes - Lymph nodes are considered to be one organ
- The result is "sum of diameters" (SD)

Non-Target lesions

- All other lesions (non-measurable + measurable but not selected as target lesions)
- No measurement required - to be followed qualitatively only

Evaluation of response: Target Lesions

Response	Definition
Complete Response (CR)	Disappearance of all extranodal target lesion Any pathological lymph-node, if defined as target lesion, must have 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 SD
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD

Progressive Disease (PD)	Sum of diameters increased by at least 20% taking as reference the smallest value on study (including baseline, if that is the smallest) and The SD must also demonstrate an absolute increase of at least 5mm.

Evaluation of Response: Non-target lesions

Response	Definition
Complete Response (CR)	Disappearance of all extranodal non-target lesion All pathological lymph-node must have short axis < 10 mm Normalisation of tumor marker level
Non-CR/NonPD	Persistence of one or more NTL and/or maintenance of tumor marker level above normal limits
Progressive Disease (PD)	*Unequivocal progression* of existing *NTLs* *(Note: the appearance of one or more new lesions is also considered progression)*

RECIST 1.1: Overall response for patients with Target (+/- Non-Target) Lesions

Target lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

16.3. APPENDIX III: Benefit Risk Assessment for CPI-613® (devimistat) for Pancreatic Cancer

Frequency of Expected Serious Adverse Events (SAE) of devimistat in a Trial where devimistat was Investigated in Combination with Modified FOLFIRINOX in First Line Metastatic Pancreatic Cancer Patients (CCCWFU 57112):

Frequency of expected SAEs of devimistat in a trial where devimistat was investigated in combination with modified FOLFIRINOX in first line Metastatic Pancreatic Cancer is described in below table.

Table: Frequency of Expected Serious Adverse Events of CPI-613 in a Trial where CPI-613 was Investigated in Combination with Modified FOLFIRINOX in First Line Metastatic Pancreatic Cancer (Trial ID: CCCWFU 57112)

Number of Subjects Exposed (N) = 20	
Expected Serious Adverse Events	**N (%)**
Thrombocytopenia	1 (5%)
Anemia	1 (5%)
Lymphopenia	1 (5%)
Hyperglycemia	1 (5%)
Hypokalemia	1 (5%)
Hypoalbuminemia	1 (5%)
Sepsis	1 (5%)
Neutropenia	1 (5%)

Table Risk-Benefit Analysis for CPI-613®(devimistat) in Combination with Modified FOLFIRINOX in the Treatment of Patients with Metastatic Adenocarcinoma of Pancreas:

Parameter	Summary
Disease	Patients with metastatic adenocarcinoma of pancreas, who have not been previously treated with chemotherapy for metastatic disease, have a serious and life-threatening condition with a median Overall Survival (OS) of approximately 11 months when treated with current chemotherapy regimens. Treatment with standard chemotherapies are associated with limited benefit and results in a wide range of serious toxicities.

Unmet Medical Need	Metastatic adenocarcinoma of pancreas is a life-threatening disease. First-line treatment for these patients primarily depends on the performance status of the patient. Patients with good performance status (i.e. healthy enough to tolerate relatively aggressive therapy) are usually treated with FOLFIRINOX (which is a combination of 4 drugs: Folinic Acid, 5-Fluorouracil, Irinotecan and Oxaliplatin) or gemcitabine as a monotherapy or in combination with other drugs like albumin bound paclitaxel or erlotinib. In Phase III trials in patients with metastatic disease, FOLFIRINOX was superior to gemcitabine in terms of Objective Response Rate (ORR), Progression Free Survival (PFS) and OS. However, FOLFIRINOX is regarded as too toxic for use in elderly and poor performance status patients. Of note, the median age of diagnosis of pancreatic cancer is 71 years. For patients who wish to pursue cancer-directed therapy but cannot manage such aggressive treatments (i.e. patients with poor performance status), gemcitabine alone or alternate choices are recommended. So, 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.
Clinical Benefit	In a single arm phase I study in patients with metastatic adenocarcinoma of pancreas with good performance status (CCCWFU 57112), devimistat in combination with modified FOLFIRINOX exhibited ORR of 61%, median OS of 19.9 months and median PFS of 9.9 months. This efficacy of devimistat in combination with modified FOLFIRINOX is substantially higher than standard therapy [FOLFIRINOX: ORR: 31.6%, median OS: 11.1 months (N Engl J Med 2011;364:1817-25), Gemcitabine in combination with nab-Paclitaxel: ORR: 24% and median OS: 8.5 months (N Engl J Med 2013;369:1691-703) and Gemcitabine: ORR: 9.4% and median OS: 6.8 months (N Engl J Med 2011;364:1817-25.)]
Risk	Overall, the safety of devimistat in combination with modified FOLFIRINOX appears to be acceptable relative to the benefit. Total 18 patients were treated with 500 mg/m^2 devimistat and none of

	them experienced any dose-limiting toxicity. So, 500 mg/m^2 per day given at a rate of 4 mL/min on day 1 and day 3 of each cycle was deemed the maximum tolerated dose and in planned phase III study, this dose was selected. No deaths due to adverse events occurred. Two unexpected serious adverse events were recorded, both for the first patient enrolled at the 500 mg/m^2 dose: possible leaching due to infusion of devimistat via non-poly (vinyl chloride) tubing, and the patient re-accessed her port at home after accidental de-access. Neither incident resulted in a negative clinical outcome. Expected serious adverse events were thrombocytopenia*, anemia*, lymphopenia*; hyperglycemia; hypokalemia, hypoalbuminemia, sepsis and neutropenia. For the 18 patients given the maximum tolerated dose, the most common non-hematological grade 3–4 adverse events were hypokalemia reported in 6 (33%), diarrhea in 5 (28%), abdominal pain in 4 (22%) and hyperglycemia in 10 (55%) patients. Grade 3 peripheral sensory neuropathy was observed in 5 (28%) patients. The most common grade 3–4 hematological adverse events were neutropenia in 5 (28%), lymphopenia 5 (28%), anemia 4 (22%) and thrombocytopenia 3 (17%). Sensory neuropathy in 17 (94%) patients developed late and was mainly grade 1–2. Electrolyte imbalance was most frequent and managed with supportive care. **In patient with 1,000 mg/m^2, this dose is above the MTD and higher than the planned dosed for phase III study*
Conclusions	Devimistat in combination with modified FOLFIRINOX demonstrated substantially better efficacy over currently available therapies (historical cohort) with a risk profile acceptable compared with the clinical benefit offered (favorable benefit-risk profile).

Source of Data: *Lancet Oncol. 2017 Jun;18(6):770-778, and the toxicity summary of CCCWFU 57112 as of August 14, 2017. This document was last updated on September 6, 2019.*