Academic and Community Cancer Research United (ACCRU)

Phase I Study of Irinotecan Liposome (nal-IRI), Fluorouracil and Rucaparib in the Treatment of Select Gastrointestinal Metastatic Malignancies Followed by a Phase Ib of First and Second Line Treatment of both Unselected and Selected (for BRCA 1/2 and PALB2 Mutations) Patients with Metastatic Adenocarcinoma of the Pancreas then Followed by a Phase II Study of First Line Treatment of Selected Patients with Metastatic Adenocarcinoma of the Pancreas with Genomic Markers (Signature) of Homologous Recombination Deficiency (HRD)

For any communications regarding this protocol, please contact the person listed on the Protocol Resource page.
This is a stand-alone document found on the ACCRU web site ([redacted]).

Study Chairs

ACCRU: [redacted]

Statistician: [redacted]

√ Study contributor(s) not responsible for patient care.

Drug Availability
Commercial Agents: Fluorouracil (5-FU), Leucovorin
Drug Company Supplied: Rucaparib and nal-IRI (IND Exempt)

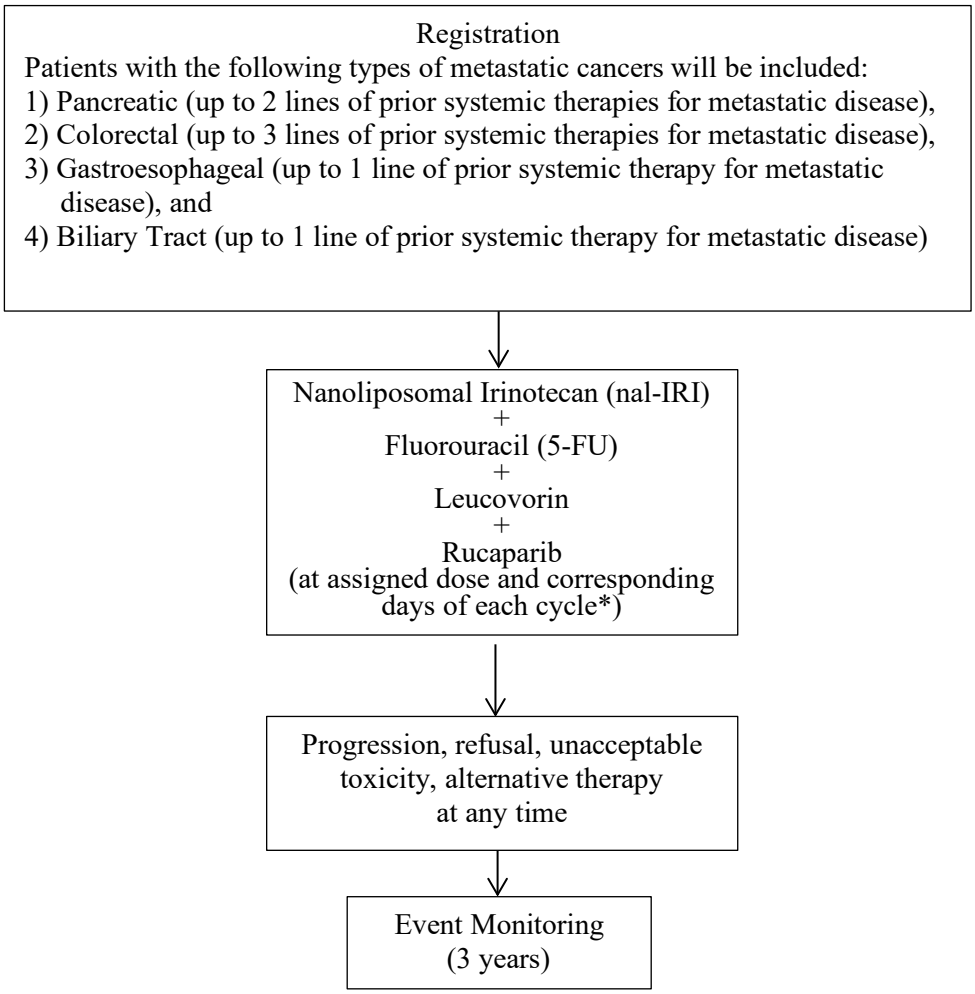
Research Coordinating Center
Academic and Community Cancer Research United
200 First Street Southwest
Rochester, MN 55905

Document History	Effective Date
Pre-activation ACCRU	September 8, 2017
Activation ACCRU	June 22, 2018
Amendment 2	August 28, 2019
Amendment 3	February 17, 2020
Amendment 4	November 19, 2021

Index

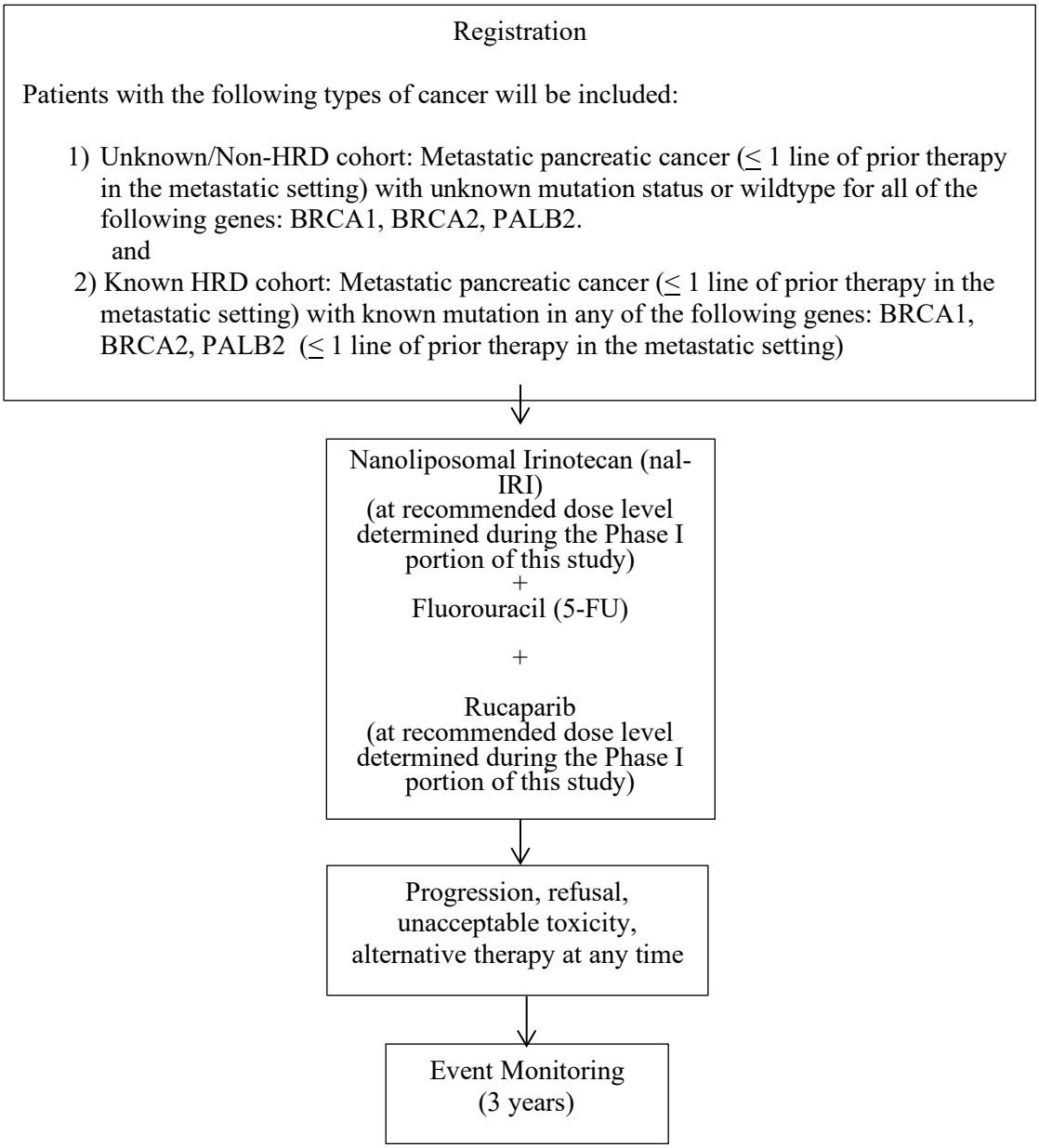
Schema - Phase I (Limited Sites)

Prior to discussing protocol entry with the patient, call the ACCRU Registration Office ([redacted]) for dose level and to ensure that a place on the protocol is open for the patient.



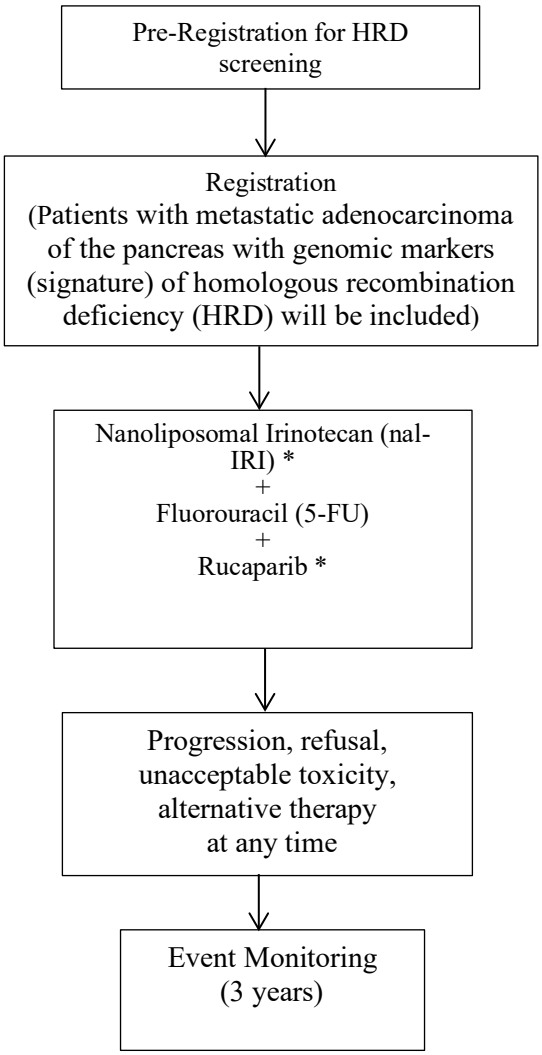
*Cycle = 28 days

Schema – Phase Ib (Limited Sites)



Cycle = 28 days

Schema - Phase II



* Dose of nal-IRI and rucaparib will be the recommended dose determined in the Phase I portion of this study.

Cycle = 28 days

Generic name: Nanoliposomal Irinotecan (nal-IRI) Brand name(s): Onivyde Availability: Clinical Research Services, A division of Rx Crossroads by McKesson	Generic name: Rucaparib Brand name(s): Rubraca® Availability: Clinical Research Services, A division of Rx Crossroads by McKesson
Generic name: 5 Fluorouracil (5-FU) Brand name(s): Aldrucil®, Efudex® Availability: Commercial Supply	Generic name: Leucovorin Availability: Commercial Supply

1.0 Background

1.1 Pancreatic Cancer:

Pancreatic cancer remains the most lethal cancer with less than 6% five-year overall survival across all stages and despite recent advances with the advent of gemcitabine and nab-paclitaxel or FOLFIRINOX.[1-3] It is the 4th most deadly cancer in the Western world and is poised to become the second most deadly by 2030.[4] There is an urgent need to improve selection of patients for current and emerging therapeutic strategies.

1.2 Genomic Instability in Pancreatic Cancer:

Pancreatic cancer is characterized by genomic instability, and several genetic mutations have been described causing DNA repair defects, such as those involving the DNA mismatch repair gene MLH1 (3-15% incidence), the tumor suppressor genes p53 (50% incidence), BRCA1/2 and PALB2 (7% incidence in sporadic and up to 17% in familial cases), and the Fanconi anemia genes FANCC and FANCG (5-10%).[5] Other key factors in DNA repair including ATM/Chk2, ATR/ Chk1, Rad51, ERCC1, and PTEN, can be mutated or inactivated in pancreatic cancer.[6] Impaired DNA damage response pathways in pancreatic cancer may create vulnerabilities in cancer cells that can be exploited therapeutically.

Recent genomic analysis of pancreatic cancer has revealed a complex mutational landscape, with whole genomic analysis redefining the mutational landscape of pancreatic cancer. A recent study defined genomic markers of defective DNA maintenance as well as defective DNA repair genes without BRCA pathway mutation.[7] Taking into account mutations of the BRCA pathway components, both somatic and germline, as well as putative surrogate measures of deficiencies in DNA maintenance (unstable genome and the BRCA mutational signature), germline mutations in BRCA (1 and2) count for only 4% of all patients. Overall, mutations in the BRCA pathway component genes and surrogate measures of defect in DNA maintenance have potential implications in selection for pancreatic cancer. As such it is likely these genomic biomarkers of defective DNA maintenance (BRCAness) will also benefit from therapies targeting DNA damage response.[8]

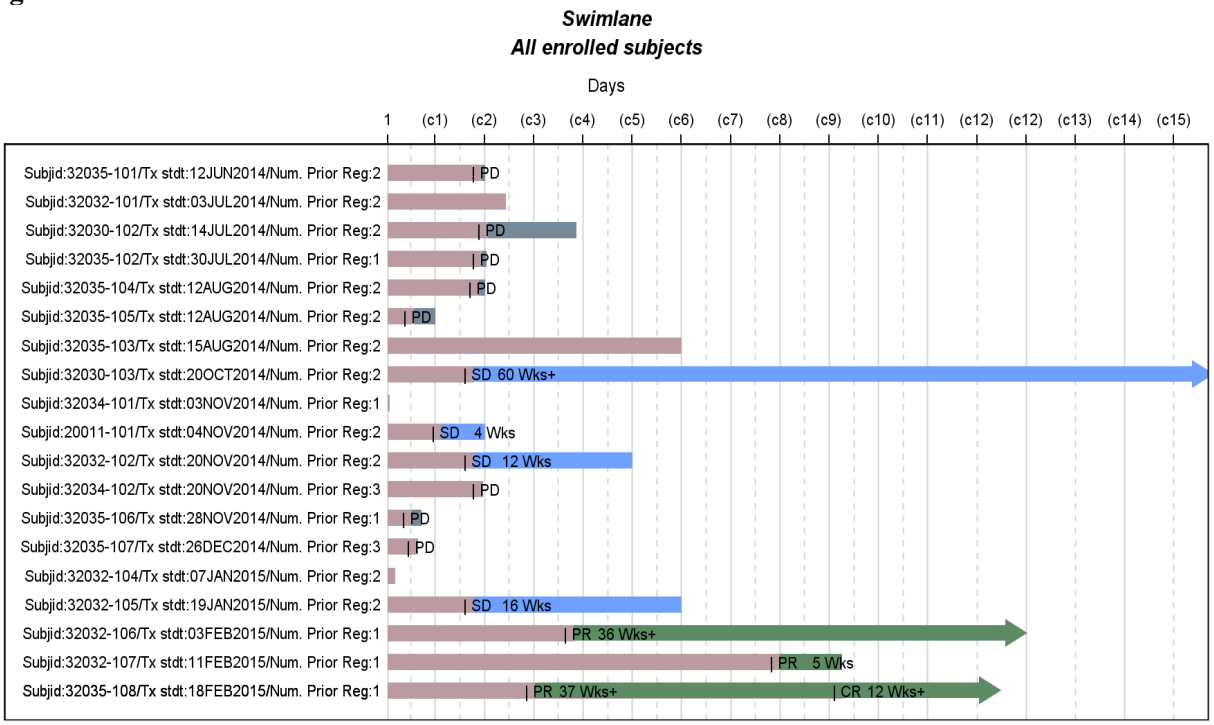
1.3 PARP inhibitors:

Poly-(ADP-ribose) polymerase 1 and 2 (PARP1 and 2) are nuclear enzymes activated by DNA single-strand breaks resulting from exposure to DNA damaging agents, which facilitate DNA repair via BER. PARP is essential in recognition and repair of DNA damage.[9] Interim results from an ongoing phase II trial with single agent olaparib in germline BRCAm-associated advanced solid tumors yielded close to 60% CBR (22% ORR).[10] Veliparib was tested in a phase 2 study in patients with advanced ovarian cancer with germline BRCA mutations. The response rate was 26%. The median PFS was 8 months.[11]

RUCAPANC is a study of rucaparib using 600 mg PO bid in refractory pancreatic cancer with BRCA mutations (somatic or germline).[12] In the first 19 patients on study (median = 2 prior lines of therapy), rucaparib as a single agent has shown evidence of

significant and sustainable impressive single agent activity (**Figure 1).** Interestingly, objective responses were only observed after cycle 2 (**Figure 1**)

Figure 1:



Date of data cutoff is 02 Feb 2016.

In the TOPARP-A study, 50 patients with advanced prostate cancer refractory to standard of care were treated with olaparib. 16 (33%) had genetic aberrations in the DNA repair pathway. 14 out of 16 (88%) had a partial response to olaparib.[28]

1.4 Nanoliposomal Irinotecan in Pancreatic Cancer:

Nanoliposomal irinotecan (nal-IRI) comprises irinotecan free-base encapsulated in liposome nanoparticles.[13] The liposome is designed to keep irinotecan in the circulation sheltered from SN-38 conversion longer than free (unencapsulated) irinotecan. This will increase and prolong intratumoral levels of both irinotecan and SN-38 compared with free irinotecan. This amounts to ~ 6 fold higher level of SN-38 found in tumors compared to plasma at 72 hours which suggests local metabolic activation of irinotecan.

Clinically, the combination of nal-IRI plus fluorouracil (5-FU)/leucovorin (LV) conferred a significant improvement in outcome over 5-FU/LV response rate of 16% (vs. 1%) and overall survival rate of 6.1 months (vs. 4.2 mos) in patients with metastatic PDAC who have progressed to first line that included gemcitabine.[14] It is now considered a standard and approved second line regimen in metastatic pancreatic adenocarcinoma. Studies to establish a role for the combination in first line are underway.

1.5 Synergistic Cytotoxicity with Irinotecan, NKTR-102, nal-IRI and SN-38:

Irinotecan and rucaparib have been demonstrated to display synergistic anti-tumor effects *in vitro* and *in vivo*. DNA damaging agents are the cornerstone treatment for pancreatic

cancer and blocking DNA repair may prevent chemo-resistance.

Topoisomerase inhibitors have been shown to induce PARP cleavage. Moreover, PARPi have been shown to enhance cytotoxicity of topoisomerase inhibitors such as nal-IRI and irinotecan.[15] For example, the DNA damage induced by irinotecan requires PARP-1 for efficient repair, and co-treatment with PARPi results in persistent and increased DNA damage breaks and apoptosis compared to irinotecan alone. These mechanisms explain the synergistic cytotoxicity observed between topoisomerase and PARP inhibitors in preclinical models.

Table 1: Combination of rucaparib and SN-38 is synergistic in multiple pancreatic cell line models *in vitro

Combination Index (CalcuSyn)								
	Naive	siNT4	siBRCA1	siBRCA2	siATM	siATR	siPALB2	siRAD51C
PANC-1	0.46	0.65	0.11	0.16	0.67	0.46	0.42	0.25
Panc 10.05	0.48			0.38			0.68	0.33
SW1990	0.44			0.11			0.46	0.53
AsPC-1	0.61			0.12			0.25	0.47
MIA PaCa-2	0.68			0.24			0.34	0.51
Average								

***Synergistic combination in naïve cell lines typically insensitive to rucaparib alone**
***Stronger synergy observed in models where HR deficiency is induced (siBRCA1/2, siPALB2, siRAD51C)**

The combination of rucaparib and SN-38 was found to be synergistic in multiple pancreatic cell line models in vitro with increased sensitivity to rucaparib or SN-38 when BRCA< ATR, RAD51C or PALB2 is knocked down (Table 1). Rucaparib and irinotecan have been demonstrated to exhibit synergistic antitumor effects. Additionally, rucaparib combined with etirinotecan pegol (NKTR-102) with a range of low- to high-doses for both agents showed similar evidence of synergism in MX-1 breast cancer model with complete responses and no re-growth at all levels.

1.6 Optimizing Dosing Strategies

BLISS analyses of rucaparib + SN-38 in PANC-1 (WT BRCA) or in BRCA1 deficient PANC1 (siRNA) suggest that maximal impact is observed when half of the efficacious does for each agent is combined. Adding a low dose of rucaparib to half maximal dose of SN-38 has a large effect whereas adding SN-38 to half maximal rucaparib dose has a gradual effect on cell viability. Combining the long-acting topoisomerase 1-inhibitor etirinotecan pegol with the PARP inhibitor rucaparib resulted in synergy and durable complete responses in a BRCA1-deficient MX-1 breast cancer model.[16]

One strategy aiming to optimize dose schedule is sequential dosing to maximize therapeutic index for the nal-IRI/PARPi combination. Delaying dosing of PARPi is predicted to allow maximizing exposure in tumor, while minimizing systemic toxicity. Delaying exposure of PARPi by 48-72 hours following nal-IRI administration may allow minimizing toxicity while achieving a higher MTD for the PARPi. Preclinical proof of

concept studies suggest that, at lower doses of nal-IRIa 48-hour delay may be optimal, while at higher doses, a 72-hour delay may be necessary.

1.7 Experience with other PARPi

Talazoparib (BMN 673), another highly potent and specific PARPi, has demonstrated synergy with irinotecan including synergy in BRCA1 mutant MX-1 model.[17] Etirinotecan pegol (NKTR-102, pegylated irinotecan) is designed to provide extended drug exposure to the tumor and in preclinical models showed improved efficacy and tolerability over irinotecan. Recently, preclinical data indicate that the combination of NKTR-102 and talazoparib is better tolerated than that of irinotecan and talazoparib, and results in stronger combination anti-tumor activity.

Clinically, FOLFIRI in combination with veliparib in a Phase I trial included 13 patients with refractory pancreatic cancer irrespective of BRCA1/2 status. Response and stable disease rates were 15% and 46% respectively with 6-month time-to-progression was 27%. Both responses were long lasting and occurred in non-BRCA mutated patients. Additionally, talazoparib and olaparib were both found to be safe to combine with irinotecan with preliminary meaningful activity noted with the respective combinations.

1.8 Homologous Recombination Deficiency (HRD) Signature

Current HRD biomarker for pancreatic includes BRCA1/2 and PALB2 (Germline and Somatic). The FoundationOne test utilizes next-generation sequencing to identify alterations in all somatic genes in human solid tumor cancers. FoundationOne interrogates the entire coding sequence of 315 cancer-related genes plus select introns from 28 genes often rearranged or altered in solid tumor cancers. These genes are known to be somatically altered in solid cancers based on recent scientific and clinical literature and are sequenced at great depth to identify the relevant, actionable somatic alterations, including single base pair change, insertions, deletions, copy number alterations, and selected fusions."

Foundation Medicine is also developing a plasma-based test that measures circulating free DNA (cfDNA), which will include the HRD signature for pancreatic and other target solid tumors. This will be available very soon and will be a key component of this study (and likely the future of genomic testing. cfDNA offers multiple advantages over tissue based testing. First, the difficulty of getting adequate tumor biopsies from most GI cancers makes this type of test more attractive for screening patients. It also represents a "real-time" snapshot of the genomic heterogeneity of the residing cancer. Additionally, analysis of a single-lesion biopsy is inadequate to guide selection of subsequent targeted therapies. cfDNA profiles allow the detection of concomitant resistance mechanisms residing in separate metastases and assessment of the effect of therapies designed to overcome resistance. Recent work has shown that patients with HRD are more likely to respond to PARP inhibitors. Indeed, a phase 2 trial (ARIEL trial) in patients with advanced ovarian cancer with HRD or genome-wide loss of heterozygosity (LOH) showed increased response rate compared to wild-type patients (RR 66%, 32% and 11% for patients with HRD vs. LOH vs. wild-type).[18]

Information on the FoundationOne test can be found at the following website [redacted]

1.9 Rationale

Pancreatic cancer remains the most lethal cancer despite recent advances. It is the 4th most deadly cancer in the Western world and is poised to become the second most deadly by 2030.[4] There is an urgent need to improve selection of patients for current and emerging therapeutic strategies.

Impaired DNA damage response pathways known as homologous recombination deficiency (HRD), in pancreatic cancer, may create vulnerabilities in cancer cells that can be exploited therapeutically.[19] Surrogate measures of defects in DNA maintenance along with mutations in the *BRCA* pathway account for about 25% of all pancreatic cancer patients. These tumors are expected to exhibit sensitivity to DNA-damaging agents.

PARP is essential in recognition and repair of DNA damage. Preliminary data suggests significant promise for inhibitors of PARP with rucaparib showing single agent durable responses in refractory pancreatic cancer patients with BRCA mutations (somatic or germline). Nanoliposomal irinotecan (nal-IRI) comprises irinotecan free-base encapsulated in liposome nanoparticles. The combination of nal-IRI plus 5-FU/LV is now considered a standard and approved post-gemcitabine exposure regimen in pancreatic adenocarcinoma with studies underway to establish a role for the combination as a first-line regimen is underway. There is significant evidence of the synergistic cytotoxicity observed between topoisomerase and PARP inhibitors in preclinical models. Rucaparib and irinotecan have been demonstrated to exhibit synergistic antitumor effects and there may be preliminary evidence of a larger synergism with novel delivery formulations of irinotecan.

Strategies aiming to optimize dose schedule include sequential dosing to maximize therapeutic index for the nal-IRI/PARPi combination. Delaying dosing of PARPi is predicted to allow maximizing exposure in tumor, while minimizing systemic toxicity with preclinical proof of concept studies suggest that at lower doses of nal-IRI, a 48-hour delay may be optimal while at higher doses a 72-hour delay may be necessary. As such our initial dosing strategy includes staggered approach schedule with nal-IRI administered on day 1, with rucaparib administered on days 4-13 of every 14-day half cycle. G iven all of the above, we hypothesize that the combination of nal-IRI (nal-IRI) and 5-FU combined with rucaparib will improve outcome in patients with untreated metastatic pancreatic cancer with genomic markers (signature) of homologous recombination deficiency (HRD). The phase I portion of this study is designed to determine the maximum tolerated dose of nal-IRI/5-FU/LV +rucaparib in patients with select GI malignancies that have known sensitivities to irinotecan and would likely benefit from the addition of the PARP inhibitor (pancreatic, colorectal, gastroesophageal, and biliary tract cancer).[20-22] This is followed by an exploratory expansion cohort (Phase Ib study) of patients with metastatic pancreatic both unselected and selected for BRCA 1/2 and PALB2 mutations . The phase II pancreatic cancer study will select for an HRD signature (based on cfDNA) that encompasses BRCA 1/2, PALB2 mutations, BRCA-like alterations and defects independent of BRCA mutations under development by Clovis and Foundation Medicine. This HRD signature will likely identify patients most likely to respond to rucaparib.

The phase I portion of this study is designed to determine the maximum tolerated dose

(MTD) and administrative schedule of nal-IRI + rucaparib combination in patients with select GI malignancies (pancreas, colorectal, gastroesophageal, and biliary tract cancer).

The expansion cohort (Phase Ib) of patients with metastatic disease from pancreatic cancer will be accrued for exploratory analysis.

The MTD and administrative schedule determined in the phase I portion of the trial will be used as the starting dose for Phase II. The phase II portion will use a 2-stage Simon design to assess the proportion of evaluable patients who reach CR/PR ≤32 weeks, and an interim analysis with relaxed probability of stopping for futility to assess the efficacy of nal-IRI+ rucaparib in patients with untreated pancreatic cancer with BRCA1/2 and PALB2. Patients with untreated pancreatic cancer with HRD other than BRCA1/2 and PALB2 will be accrued for exploratory analysis.

2.0 Goals

2.1 Phase I Portion

2.11 Primary Aim: To establish the recommended dose level for the Phase Ib and Phase II trial of nal-IRI and 5-FU with rucaparib (MFR) in patients with metastatic disease from pancreatic cancer (up to 2 lines of prior therapy), colorectal cancer (up to 3 lines of prior therapy), gastroesophageal cancer (up to 1 line of prior therapy) and biliary tract cancer (with 1 line of prior therapy allowed).

2.2 Phase Ib Portion

2.21 Primary Aim: To assess, in a preliminary fashion, antitumor efficacy, in terms of Disease Control Rate and further tolerability of the recommended dose level of combination of nal-IRI and 5-FU with rucaparib in patients with metastatic disease from pancreatic cancer (≤ 1 line of prior therapy in the metastatic setting).

2.3 Phase II Portion

2.31 Primary Aim: To estimate the proportion of evaluable patients who reach CR/PR ≤32 weeks after registration among patients with metastatic adenocarcinoma of the pancreas with genomic markers (signature) of homologous recombination deficiency (HRD), specifically BRCA1, BRCA2, and PALB2 mutation, treated with the combination of nal-IRI and 5FU with rucaparib (MFR).

2.32 Secondary Aims:

1) To estimate the progression-free survival (PFS) and overall survival (OS) for patients with metastatic adenocarcinoma of the pancreas with genomic markers (signature) of homologous recombination deficiency (HRD), specifically BRCA1, BRCA2, and PALB2 mutation, treated with the combination of nal-IRI and 5-FU with rucaparib (MFR).

2) To assess the toxicity of the combination of nal-IRI and 5-FU with rucaparib in patients with metastatic adenocarcinoma of the pancreas with genomic markers (signature) of homologous recombination deficiency (HRD), specifically BRCA1/2 and PALB2 mutations.

2.4 Exploratory Objectives

2.41 To evaluate the role of genomic markers (signature) of HRD, mutation other than BRCA1, BRCA2, and PALB2 as predictive biomarkers of response to MFR.

2.42 To evaluate BRCA1, BRCA2, and PALB2 mutations as predictive biomarker of response to MFR.

3.0 Patient Eligibility

Phase I: Prior to discussing protocol entry with the patient, call the ACCRU Registration Office [redacted] for dose level and to ensure that a place on the protocol is open to the patient.

*No waivers on eligibility per ACCRU

3.1 Inclusion Criteria

3.11 Age ≥18 years.

3.12 **Phase I** only: Histologic confirmation of pancreatic, colorectal, gastroesophageal or biliary adenocarcinoma, as follows:

- Patients with metastatic disease from pancreatic cancer who received no more than 2 lines of prior therapy in the metastatic setting.
- Patients with metastatic disease from colorectal cancer who received no more than 3 lines of prior therapy in the metastatic setting.
- Patients with metastatic disease from gastroesophageal cancer who received no more than 1 line of prior therapy in the metastatic setting.
- Patients with metastatic disease from biliary tract cancer who received no more than 1 line of prior therapy in the metastatic setting.

NOTE: No prior exposure to irinotecan in the metastatic setting will be allowed except in the phase I dose escalation portion and in colon cancer patients only. In pancreas cancer, exposure to irinotecan is only allowed in the neoadjuvant setting and no progressive disease <3 months from last dose of irinotecan.

3.13 **Phase Ib only**: Patients with metastatic adenocarcinoma of the pancreas who have received no more than 1 line of prior therapy in the metastatic setting.

NOTE: Exposure to irinotecan is only allowed in the neoadjuvant setting and no progressive disease <3 months from last dose of irinotecan.

3.14 **Phase II only:** Patients with metastatic adenocarcinoma of the pancreas with genomic markers (signature) of homologous recombination deficiency (HRD) or BRCA1 or BRCA2 or PALB2 mutation, or HRD (non-BRCA, non-PALB) who have not received any systemic therapy in the metastatic setting.

NOTE: Exposure to irinotecan is only allowed in the neoadjuvant setting and no progressive disease <3 months from last dose of irinotecan.

3.15 Measurable disease as defined in Section 11.0.

3.16 ECOG Performance Status (PS) 0 or 1 (form is available on the ACCRU web site).

3.17 The following laboratory values obtained *≤21* days prior to registration.
- Absolute neutrophil count (ANC) ≥1500/mm^3
- Platelet count ≥100,000/mm^3
- Hemoglobin >9.0 g/dL
- Total bilirubin ≤ institutional upper limit of normal (ULN)
- Aspartate transaminase (AST) ≤3 x ULN, ≤ 5.0 x ULN for patients with metastatic disease to the liver
- Aminotransferase (ALT) ≤3.0 x ULN, ≤ 5.0 x ULN for patients with metastatic disease to the liver
- Creatinine ≤1.0 mg/dL or creatinine clearance ≥45 ml/min using the Cockcroft-Gault formula below:

Cockcroft-Gault Equation:

Creatinine clearance for males = $\frac{\textbf{(140 - age)(weight in kg)}}{\textbf{(72)(serum creatinine in mg/dL)}}$

Creatinine clearance for females = $\frac{\textbf{(140 - age)(weight in kg)(0.85)}}{\textbf{(72)(serum creatinine in mg/dL)}}$

3.18 Negative serum or urine pregnancy test done ≤7 days prior to registration and repeated prior to dosing on day 1 of each cycle, for individuals of childbearing potential only.

NOTE: Individuals are considered to be of childbearing potential unless one of the following applies:

- Is postmenopausal, defined as no menses for at least 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level consistently in the postmenopausal range (30 mIU/mL or higher) may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy; however, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to confirm a postmenopausal state: or

- Considered to be permanently sterile. Permanent sterilization includes hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy.

3.19a Provide informed written consent.

3.19b Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

*Note: During the **Active Monitoring** Phase of a study (i.e., active treatment and observation), participants must be willing to return to the consenting institution for follow-up.*

3.19c Willing to provide tissue and blood samples for mandatory correlative research purposes (see Sections 6.0, 14.0 and 17.0).

3.19d Individuals of reproductive potential and their partners willing to practice total abstinence or use a highly effective method of contraception (failure rate < 1% per year) during treatment and for 6 months following the last dose of rucaparib.

The following are allowable only:

- Ongoing use of progesterone-only injectable or implantable contraceptives (eg, Depo Provera, Implanon, Nexplanon)
- Placement of an intrauterine device or intrauterine system
- Bilateral tubal occlusion
- Sterilization, with appropriate post-vasectomy documentation of absence of sperm in ejaculate
- True, complete (as opposed to periodic) abstinence.

3.19e Patients must discontinue prior chemotherapy ≥ 28 days before registration.

3.2 Exclusion Criteria

3.21 Any of the following because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:

- Pregnant individuals
- Nursing individuals
- Persons of childbearing potential who are unwilling to employ adequate contraception

3.22 Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.23 Immunocompromised patients and patients known to be HIV positive and currently receiving antiretroviral therapy.

3.24 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.25 Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm.

3.26 Previous or concurrent cancer that is distinct in primary site or histology from cancer of primary site ≤3 years prior to registration EXCEPT for curatively treated cervical cancer in situ, melanoma in situ, non-melanoma skin cancer and superficial bladder tumors [Ta (Non-invasive tumor), Tis (Carcinoma in situ) and T1 (Tumor invades lamina propria)]. Note: All cancer treatments for those distinct in a primary site other than cancer of origin must be completed ≥3 years prior to registration.

3.27 Received any prior PARPi treatment. Patients who received prior PARPi treatment in the adjuvant setting with the last dose received more than 12 months prior to registration are allowed to enroll.

3.28 QTc prolongation > 480 msec, as calculated by either the Bazett or Fridericia formula, as per institutional standard.

3.29 Inability to swallow.

4.0 Test Schedule

NOTE: Variation of ≤4 days of scheduled visit is permitted.

Tests and procedures	≤21days prior to registration	≤7days prior to registration	Active Monitoring				
			Prior to dosing on Day 1 of each cycle,* Beginning with Cycle 1 (until PD)	Day 15 of each cycle, Beginning with Cycle 1 (until PD)	Prior to 3rd and subsequent odd cycles (until PD)	End of Treatment (PD, withdrawal, or removal)	Observation[8]: 30 days of End of Treatment
History and exam, wt, ECOG PS	X		X	X		X	X
Height	X						
Adverse event assessment	X		X	X		X	X[7]
Hematology: CBC/ differential **Chemistry:** SGOT (AST), SGBT (ALT), alk phos, T. bili, creatinine, calcium, phos, glucose, Na, K	X		X	X		X	X
Tumor measurement[1]	X				X	X	
Pregnancy test[2]		X	X				
Mandatory archival tissue collection [5, R] (See Section 17)	X						
cfDNA[4, R]			X		X	X	
ECG[6]	X		X				
Cancer markers: CEA (colorectal cancer) and CA19-9 (cholangiocarcinoma) [4 R]	X				X	X	
Patient Medication Diary[3]			X			X	

* Cycle = 28 days.

(Footnotes on next page)

1. Imaging should be done using CT scan (MRI if CT is not feasible). Use same imaging throughout the study. If patient is on study for more than 2 years, allow scans 3-4 months apart.

2. For individuals of childbearing potential only. Negative urine or serum pregnancy test must be done ≤7 days prior to registration and repeated prior to dosing on day 1 of each cycle. If a patient becomes pregnant during the study the investigator is to stop dosing with study drug(s) immediately. (See Section 10.314 for additional information.)

3. The diary must begin the day the patient starts taking the medication and must be completed per protocol and returned to the treating institution OR compliance must be documented in the medical record by any member of the care team.

4. Mandatory blood draws (STRECK, EDTA and No Additive tubes) for research should not be collected and submitted until after the patient is registered onto the study, and should be done prior to dosing on Cycle 1, Day 1, then Day 1 of subsequent odd cycles, and end of treatment. Kits are required for this collection (See Section 14.0).

5. Receipt of archival tumor tissue is not required for study registration and initiation of therapy. However, it is mandatory to receive the required tissue within 60 days from registration.

6. Dose-escalation phase I, ECG should be done on baseline and Cycle 2, Day 1, measured twice at least 5 minutes apart. For Phase Ib and II – ECG should be done prior to cycle 1 only, then as indicated.

7. Any Adverse event assessment within 30 days of end of treatment will be recorded on the adverse event assessment form in the last cycle of treatment.

8. Treatment decision/patient care for patients who are off protocol treatment is at the discretion of the treating physician. The observation period is recommended by the study protocol but no data collection is required other than adverse event assessment (See Footnote 7)

R Research funded (see Section 19.0)

Event Monitoring: Patients will be followed for survival every 6 months for 3 years from registration. This can be done via a phone call to the patient and does not require the patient to return to the consenting site.

5.0 Grouping Factors:

- Phase I (Dose Escalation)- pancreatic vs.
- Phase I (Dose Escalation)- colorectal vs.
- Phase I (Dose Escalation)- gastroesophageal vs.
- Phase I (Dose Escalation)- biliary tract vs.
- Phase Ib (Dose Expansion)-pancreatic, Unknown/non-HRD patients vs.
- Phase Ib (Dose Expansion)-pancreatic, HRD patients vs.
- Phase II.

6.0 Registration/Randomization Procedures

6.1 Phase I

Prior to discussing protocol entry with the patient, call the ACCRU Registration Office (507-284-4130) for dose level and to ensure that a place on the protocol is open to the patient.

6.11 Registration Procedures

6.111 To register a patient, fax [redacted] a completed eligibility checklist to the Academic and Community Cancer Research United (ACCRU) Registration Office between 8 a.m. and 4:30 p.m. central time Monday through Friday.

6.112 Documentation of IRB approval must be on file with ACCRU before an investigator may register any patients. Approvals should be uploaded through the online ACCRU Regulatory Management System (ARMS).

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file with ACCRU no less than annually. Approvals should be uploaded through the online ACCRU Regulatory Management System (ARMS). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

Submission of annual IRB approvals to ACCRU is required until the study is closed through your IRB.

6.113 Prior to accepting the registration, registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.2 Phase Ib

6.21 Registration Procedures

To register a patient, access the ACCRU web page at [redacted] go to the Application section and click on "Registration" and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the Academic and Community Cancer Research United (ACCRU) Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

Instructions for the registration/randomization application are available on the above web page under the Study Resources section, "Application Training."

Prior to initiation of protocol study intervention, this process must be completed in its entirety and a ACCRU subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

· Contact the ACCRU Registration Office [redacted] If the patient was fully registered, the Registration Office staff can access the information from the centralized database and confirm the registration.

· Refer to "Application Training" at [redacted] click on "Registration, Installation & Entry Instructions".

6.3 Phase II

6.31 Pre-Registration (Step 0)

6.311 To pre-register a patient, access the ACCRU web page at [redacted] go to the Application section, click on "Registration" and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the Academic and Community Cancer Research United (ACCRU) Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

Users should refer to the section titled "Pre-Registration Components" for details on how to pre-register a patient to a study. At the time of pre-registration the patient will receive an ACCRU patient identification number. This number is to be used when submitting tissue or blood samples, as applicable for the study (see Section 17.0). Patient pre-registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the ACCRU Registration Office [redacted] If the patient was pre-registered, the ACCRU Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Application Training" at [redacted] "Registration, Installation & Entry Instructions".

6.312 Documentation of IRB approval must be on file with ACCRU before an investigator may pre-register any patients. Approvals should be uploaded through the online ACCRU Regulatory Management System (ARMS).

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file with ACCRU no less than annually. Approvals should be uploaded online through ARMS. If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

Submission of annual IRB approvals to ACCRU is required until the study has been permanently closed through your IRB.

6.313 Prior to accepting the pre-registration, the registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient pre-registration eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.32 Registration (Step 1)

Upon completion of the patient's submitted blood or tissue evaluation status (see Sections 14.0 and/or 17.0), the person provided on the samples submission form will be contacted by fax with the results of the sample evaluations. If based upon the sample evaluations the subject is approved for registration, the pre-registering institution must register the subject to the protocol.

6.321 To register a patient, access the ACCRU web page at [redacted] go to the Application section, click on "Registration" and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the Academic and Community Cancer Research United (ACCRU) Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

Users should refer to the section titled "Pre-Registration Component" for details on how to register a patient on step 2 of a study that has a pre-registration and registration step. The instructions for the

registration/randomization application are available using the Help button. Prior to initiation of protocol treatment, this process must be completed in its entirety and an ACCRU subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the ACCRU Registration Office [redacted] the patient was pre-registered, the ACCRU Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Application Training" at [redacted] click on "Registration, Installation & Entry Instructions".

6.322 Documentation of IRB approval must be on file with ACCRU before an investigator may register any patients. Approvals should be uploaded through the online ACCRU Regulatory Management System (ARMS).

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file with ACCRU no less than annually. Approvals should be uploaded through the online ACCRU Regulatory Management System (ARMS). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

Submission of annual IRB approvals to ACCRU is required until the study is closed through your IRB.

6.323 Prior to accepting the registration, registration/randomization application will verify the following:
- IRB approval at the registering institution
- Patient eligibility

6.4 Phase I/Ib and II

6.41 Correlative Research

A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.0, 14.0 and 17.0).

6.42 At the time of registration, the following will be recorded:
- Patient has/has not given permission to store and use his/her blood sample(s) for future research to learn about, prevent, or treat cancer.
- Patient has/has not given permission to store and use his/her blood sample(s) for future research to learn, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

- Patient has/has not given permission to store and use his/her tissue sample(s) for future research to learn about, prevent, or treat cancer.
- Patient has/has not given permission to store and use his/her tissue sample(s) for future research to learn, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
- Patient has/has not given permission for ACCRU to give his/her sample(s) to outside researchers.

6.43 Treatment on this protocol must commence at an ACCRU institution under the supervision of a cancer specialist.

6.44 Treatment cannot begin prior to registration and must begin ≤21 days after registration.

6.45 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.46 All required baseline symptoms (see Section 10.52) must be documented and graded.

6.47 Study drug is available on site.

6.48 Blood draw kit is available on site.

7.0 Protocol Treatment

7.1 Treatment Schedule – Use actual weight with dose adjustments if weight changes more than 10% from baseline.

Cycle = 28 days

Agent	Route	Day
Nanoliposomal Irinotecan (nal-IRI)	IV	Days 1 and 15
Leucovorin (LV)*	IV	Days 1 and 15, prior to 5-FU
Fluorouracil (5-FU)	IV	Days 1 and 15
Rucaparib	PO	Twice each day on Days 4-13 and Days 18-27 of a 28 day cycle.

*If there is a shortage of leucovorin (LV) in the U.S., and you are unable to obtain access, LV may be held until supply is available. LV will not be administered in the phase Ib/II portion of the study

7.11 Planned Phase I Dose Escalation Levels:

Dose Level	Agent	Dose	Route	Day
DL-2	Nanoliposomal irinotecan (nal-IRI)	43 mg/m2	Intravenous over 90 minutes	Days 1 and 15
	Leucovorin (LV)	400 mg/m2	Intravenous	Days 1 and 15, prior to 5-FU
	Fluorouracil (5-FU)	2000 mg/m2	Intravenous over 46 hours	Days 1 and 15
	Rucaparib	200 mg	Oral	Twice daily on Days 4-13 and 18-27
DL-1	nal-IRI	50 mg/m2	Intravenous over 90 minutes	Days 1 and 15
	LV	400 mg/m2	Intravenous	Days 1 and 15, prior to 5-FU
	5-FU	2400 mg/m2	Intravenous over 46 hours	Days 1 and 15
	Rucaparib	200 mg	Oral	Twice daily on Days 4-13 and days 18-27
DL1*	nal-IRI	50 mg/m2	Intravenous over 90 minutes	Days 1 and 15
	LV	400 mg/m2	Intravenous	Days 1 and 15, prior to 5-FU
	5-FU	2400 mg/m2	Intravenous over 46 hours	Days 1 and 15
	Rucaparib	400 mg	Oral	Twice daily on Days 4-13 and days 18-27
DL2-A	Nanoliposomal irinotecan (nal-IRI)	50 mg/m2	Intravenous over 90 minutes	Days 1 and 15
	Fluorouracil (5-FU)	2400 mg/m2	Intravenous over 46 hours	Days 1 and 15
	Rucaparib	600 mg	Oral	Twice daily on Days 4-13 and days 18-27
DL 2-B	nal-IRI	70 mg/m2	Intravenous over 90 minutes	Days 1 and 15
	LV	400 mg/m2	Intravenous	Days 1 and 15, prior to 5-FU
	5-FU	2400 mg/m2	Intravenous over 46 hours	Days 1 and 15
	Rucaparib	400 mg	Oral	Twice daily on Days 4-13 and days 18-27
DL 3	nal-IRI	70 mg/m2	Intravenous over 90 minutes	Days 1 and 15
	Leucovorin	400 mg/m2	Intravenous	Days 1 and 15, prior to 5-FU
	5-FU	2400 mg/m2	Intravenous over 46 hours	Days 1and 15
	Rucaparib	600 mg	Oral	Twice each day on

				Days 4-13 and days 18-27

* Starting dose level
Only patients with pancreatic, colorectal, gastroesophageal and biliary tract cancers will be included

7.12 Phase Ib Dose Expansion (Phase Ib Study at recommended dose level determined by the Phase I portion):

The recommended dose determined by phase I dose escalation is dose level 2-A (DL2-A in section 7.11)

Agent	**Dose**	**Route**	**Day**
nal-IRI	50 mg/m^2 (Recommended Dose Determined by Phase I Dose Escalation)	Intravenous over 90 minutes	Days 1 and 15
5-FU	2400 mg/m^2	Intravenous over 46 hours	Day 1 and 15
Rucaparib	600 mg (Recommended Dose Determined by Phase I Dose Escalation)	Oral	Twice daily on Days 4-13 and days 18-27 (Recommended schedule determined by phase I dose escalation)

7.13 Phase II (Phase II study at recommended dose level determined by the Phase I portion)

Agent	**Dose**	**Route**	**Day**
nal-IRI	Recommended Dose Determined by Phase I Dose Escalation	Intravenous over 90 minutes	Days 1 and 15
5-FU	2400 mg/m2	Intravenous over 46 hours	Days 1 and 15
Rucaparib	Recommended Dose Determined by Phase I Dose Escalation	Oral	Twice daily on days as determined by Phase I administration schedule

7.14 Pretreatment medication

Agent*	Dose	Route	Day
Dexamethasone	10 mg	IV	Per institutional guidelines
Ondansetron	8mg	IV	Per institutional guidelines

*Other pretreatment meds can be used per institutional guidelines.

7.2 For this protocol, the patient must return to the consenting ACCRU institution for evaluation at least every 14 days during treatment.

7.3 Treatment by a local medical doctor (LMD):

Patients must receive study treatment per protocol at the consenting ACCRU institution. However, patients are allowed to receive supportive care for any adverse events, as needed, at a non-ACCRU institution.

7.4 Phase I/Ib – determination of recommended dose level and dose expansion

7.41 Dose Escalation

7.411 This portion of the study will include patients with metastatic disease from pancreatic cancer (up to 2 lines of prior therapy), colorectal cancer (up to 3 lines of prior therapy), gastroesophageal cancer (up to 1 lines of prior therapy) and biliary tract cancer (BTC; up to 1 line of prior therapy allowed).

7.412 There will be 4 dose levels with two de-escalations to dose level -2 if dose level 1 is deemed intolerable (See Table 1).

7.413 Three patients will be evaluated at each dose level and assessed for dose limiting toxicity (DLT) during cycle 1 (4 weeks). Standard 3+3 dose escalation scheme is utilized (See Section 16.22 for MTD determination). Maximum tolerated dose (MTD) is the highest dose at which no more than 1 of 6 patients will develop a DLT.

7.414 The recommended dose level for Phase 1b and Phase 2 study will be determined based on MTD and discussion between the study team and the sponsor.

7.415 Dose expansion: Following determination of the recommended dose level from the phase I study, the study will proceed to a phase 1b study of patients with metastatic adenocarcinoma of the pancreas who have received no more than 1 line of prior therapy in the metastatic setting. See Schema for further details.

7.416 We will collect plasma samples (for cfDNA) from patients prior to initiation of therapy, prior to 3rd and subsequent odd cycles, and at progression. Paraffin embedded tissue (PET) will be collected as well.

HRD analysis will be performed as a translational component to help correlate with response (prior to therapy) and development of resistance (during and at end of therapy). PET will be used for validation. The test requires ~ 5x 10uM FFPE sections.

7.417 Similar to other follow up studies to NAPOLI, UGT1A1 will not be routinely required or tested. Testing will be performed on individual patients who may experience significant and unexpected toxicities are encountered.

7.418 Investigators are to contact the ACCRU Operations Office via email at [redacted] as soon as any dose-limiting toxicity (DLT) occurs.

7.42 Definitions of DLT

Toxicity will be assessed using the NCI CTCAE, version 4.03 unless otherwise specified. A DLT is defined as an AE or abnormal laboratory value (assessed as possibly, probably or definitely related to the study medication) which occurs ≤ 28 days following the first dose of MFR (or 1 cycles of therapy, each cycle = 28 days), and meets any of the criteria listed in Table 7.421.

If a patient experiences toxicity that fulfills the criteria for a DLT during the DLT observation window (cycle 1 day 1 through cycle 1 day 28, treatment with the study drug will be interrupted and the toxicity will be followed up. Patients will be allowed to remain on study if the DLT is resolved within 4 weeks at the discretion of the investigator. Patients will continue on study at the next lowest dose level. If treatment is reduced during the DLT observation window or is held for >28 days for any reason, this will be considered a DLT.

7.421 Dose Limiting Toxicities (DLT)

TOXICITY	DLT CRITERIA
Hematology	CTCAE grade 4 neutropenia with fever of any duration, or grade 4 neutropenia lasting more than 5 consecutive days
	CTCAE grade 4 thrombocytopenia lasting more than 5 days, or grade 3 with bleeding
	CTCAE Grade 3 or 4 neutropenia with fever (temperature ≥ 38.5°C)
Skin and subcutaneous tissue disorders	Rash, hand-foot skin reaction or photosensitivity CTCAE Grade 3 lasting more than 7 consecutive days despite skin toxicity treatment (as per local practice)
Gastro-intestinal	CTCAE grade≥ 3 nausea or vomiting lasting more than or equal to 48 hrs despite optimal anti-emetic therapy
	CTCAE grade ≥ 3 diarrhea lasting more than or equal to 48 hrs despite optimal anti-diarrhea treatment
Hepatobiliary	CTCAE grade≥ 3 total bilirubin (excluding any elevations caused by mechanical obstruction of the biliary tree by tumor or stent blockage)
	CTCAE grade ≥4 ALT (isolated increases in AST without concomitant increases in ALT will not be considered dose-limiting, because of the non-specific nature of AST)
	Serum alkaline phosphatase CTCAE Grade 4 lasting more than 7 consecutive days
ECG QTc Interval	QTc interval ≥ 501 ms on at least two separate consecutive ECGs taken 5 min apart
Renal	Serum creatinine > 6x ULN
Non-hematologic events	Any non-hematological CTCAE grade ≥ 3, except for the exclusions noted below
Other	Any related toxicity that delays treatment by > 28 days
Exceptions to DLT criteria	CTCAE grade 3 fatigue lasting fewer than 5 days
	CTCAE grade 3 edema lasting fewer than 5 days
	Grade 3 laboratory abnormalities that are responsive to oral supplementation or deemed by the investigator to be not clinically significant
CTCAE version 4.03 will be used for all grading. Optimal therapy for vomiting or diarrhea will be based in institutional guidelines, with consideration of the prohibited medications listed in this protocol.	

7.5 Phase II - The phase II study in pancreatic cancer will depend on the successful completion of the phase I trial, determination of the recommended dose level and discussion between PI and co-sponsors of the study.

7.51 Following the accrual of the first 6 patients into the phase II portion, we will assess for any unexpected serious toxicities (without halting accrual). If >1 of the first 6 patients experience grade 5 toxicity at least possibly (possible, probable, definite) related to treatment, we will halt accrual and discuss with the sponsors alternative dose levels including the possibility to de-escalate to one dose level. After reinitiating accrual, the patients who were included in the prior dose level cannot be considered for the final analysis and will have to be replaced.

7.52 In the Phase II portion of this study, all patients' tissue samples will be screened for HRD and BRCA-like signature, and only those patients with defects will be selected for the treatment study.

8.0 Dosage Modification Based on Adverse Events

Strictly follow the modifications in this table for the first **two** cycles, until individual treatment tolerance can be ascertained. Thereafter, these modifications should be regarded as guidelines to produce mild-to-moderate, but not debilitating, side effects. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

ALERT: *ADR reporting may be required for some adverse events (See Section 10)*

8.1 Dose Modifications for Rucaparib (Based on Adverse Events in Tables 8.*2* and 8.3)

Starting Dose Level	**1st Dose Modification**	**2nd Dose Modification**
600 mg BID	500 mg BID	400 mg BID
400 mg BID	300 mg BID	200 mg BID
300 mg BID	200 mg BID	300 mg QD
200 mg BID	300 mg QD	200 mg QD

NOTE: No more than two dose reductions are allowed.

8.2 Dose Modifications for Hematologic Toxicities

Worst Toxicity by CTCAE Grade[b, c]	**nal- IRI or 5-FU[e]**
Grade 2 neutropenia (ANC < 1500 – 1000 cells/mm^3)	100% of previous dose
Grade 3 or 4 neutropenia (ANC ≤ 1000 cells/mm^3) or febrile neutropenia[a]	1st occurrence: Delay treatment[d] until resolved to ≤ Grade 2, then reduce dose to by 25% 2nd occurrence: Delay treatment[d] until resolved to ≤ Grade 2, then reduce dose another 25% (50% of original dose)
≤Grade 2 thrombocytopenia (Grade 2: platelets ≤75,000/mm^3 -50,000/mm^3	If Grade 2: 100% of previous dose
Grade 3-4 thrombocytopenia: platelets <50,000/mm^3)	If Grade ≥3: 1st occurrence: Delay treatment[d] until resolved to ≤ Grade 2, then reduce dose by 25% 2nd occurrence: Delay treatment[d] until resolved to ≤ Grade 2, then reduce dose another 25% (50% of original dose)

[a]Consider the use of G-CSF for patients who experience ≥ Grade 3 neutropenia or febrile neutropenia.
[b]Anemia: no changes; transfuse as needed.
[c]Lymphocytopenia: no changes.
[d]For Grade 3 and worse neutropenia and/or platelets, delay all agents (5FU, leucovorin, nal-IRI and rucaparib) until resolve to ≤ Grade 2.
[e]The dose of the agent (5FU or nal-IRI) that is most likely the cause of the hematologic toxicity, as per investigator's assessment, will be reduced when resuming treatment.

8.21 Recommended dose modification for toxicities *except* ALT/AST/ bilirubin

NCI-CTCAE v4.03[a]	Dose Interruption	Dose Modification [b]	Dose for Subsequent Cycles
Grade 0 - < 2 Non-hematologic	Treat on time	No change	
Grade 2 Non-hematologic*	May be held and/or reduced for toxicities not adequately controlled by concomitant medication and/or supportive care at the discretion of the treating investigator.		If toxicity remains ≤ Grade 1, dose re-escalation can be considered at the discretion of the treating investigator.
Non-hematologic Grade ≥3 (with the exception of electrolyte abnormalities not considered clinically significant by the treating physician)	Delay until ≤ Grade 2	Reduce by 1 dose level Permanent discontinuation can be considered at treating investigator's discretion.	If toxicities return to baseline or ≤ Grade 1 or ≤ Grade 2 severity if not considered a safety risk for the patient, dose re-escalation can be considered at the discretion of the treating investigator.

a. NCI-CTCAE = National Cancer Institute - Common Terminology Criteria for Adverse Events, version 4.03 [redacted]
b. Excludes alopecia, non-refractory nausea/vomiting, or diarrhea adequately controlled with systemic antiemetic/antidiarrheal medication administered in standard doses according to institutional guidelines.

*Grade 2 creatinine elevations are likely to be seen due to potent inhibition of MATE1 and MATE2-K by rucaparib. Dose modifications of rucaparib for grade 2 creatinine are not needed unless the treating physician has concerns that other factors may be contributing to creatinine elevations.

8.22 Recommended dose modifications/interruptions for elevations in ALT and/or AST related to rucaparib

NCI-CTCAE v4.03[a]	Dose Interruption[b]	Dose Modification	Dose for Subsequent Cycles
Grade ≤2	Treat on time	No change	
Grade ≥3	• Treat on time • Monitor liver function tests weekly until resolution to ≤ Grade 2	No change, provided bilirubin is < ULN and alkaline phosphatase is < 3 x ULN.	If toxicity remains and levels do not decline within 2 weeks or they continue to rise, treatment interruption and resolution to ≤ Grade 2 is required before rucaparib can be resumed, either at the current dose or a reduced dose.
Grade ≥4	• Hold rucaparib • Monitor liver function tests weekly until resolution to ≤ Grade 2		Resume with a dose reduction and monitor liver function tests weekly for 3 weeks after restarting.

a. NCI-CTCAE = National Cancer Institute - Common Terminology Criteria for Adverse Events, version 4.03

[redacted]

b. Treatment with rucaparib should be held until the toxicity resolves to ≤ CTCAE Grade 2. Twice daily dosing may then be resumed at either the same dose or a lower dose, per investigator discretion. If treatment is resumed at the same dose, and the patient experiences the same toxicity, the dose should be reduced following resolution of the event to ≤ CTCAE Grade 2. If the patient continues to experience toxicity, additional dose reduction steps are permitted; however, the investigator should contact ACCRU (see Protocol Resource page) before reducing to 300 mg BID. If a patient continues to experience toxicity despite dose reduction steps to 300 mg BID, or if dosing with rucaparib is interrupted for > 14 consecutive days due to toxicity, treatment should be discontinued, unless otherwise agreed between the investigator and ACCRU.

8.3 Dose Modifications for Non-Hematologic Toxicities Other than grade 3 ALT/AST (follow recommendation by Table 8.22), Fatigue and Grade 3 Anorexia[a, d]

Worst Toxicity by CTCAE Grade*	na1-IRI	5-FU
Grade 1 diarrhea[b]	Continue same dose	Continue same dose
Grade 1 or 2 including diarrhea (except alopecia, nausea and vomiting)	Withhold nal-IRI then resume once resolved to grade 1 at 100% of previous dose	Withhold 5-FU, then resume once resolved to grade 1 at 100% of previous dose, except for Grade 2 hand foot syndrome, Grade 2 cardiac toxicity, or any grade neurocerebellar toxicity
Grade 3 or 4, including diarrhea[c] (except alopecia, nausea and vomiting)	Withhold nal-IRI then resume once resolved to grade 1 per below: 1st occurrence: Reduce dose to by 25% 2nd occurrence: Reduce dose another 25% (50% of original dose)	Withhold 5-FU then resume once resolved to grade 1 per below: 1st occurrence: Reduce dose by 25% 2nd occurrence: Reduce dose another 25% (50% of original dose)[d] *except for Grade 3 or 4 hand foot syndrome
Grade 3 or 4 nausea and/or vomiting, despite anti-emetic therapy	Optimize anti-emetic therapy AND reduce dose to 50 mg/m^2, if starting dose is 70 mg/m^2.. If the patient is already receiving 50 mg/m^2, reduce dose to 43 mg/m^2, [c]	Optimize anti-emetic therapy AND reduce dose by 25%; if the patient is already receiving a reduced dose, reduce dose an additional 25%[e]
Grade 2 hand foot syndrome	100% of previous dose	1st occurrence: Reduce dose by 25% 2nd occurrence: Reduce dose another 25% (50% of original dose)[d]
Grade 3 or 4 hand foot syndrome	1st occurrence: Reduce dose to 50 mg/m^2, if starting dose is 70 mg/m^2. 2nd occurrence: Reduce dose to 43 mg/m^2	Discontinue therapy
Any grade neurocerebellar or ≥ Grade 2 cardiac toxicity	No dose modifications required[d]	Discontinue therapy
Sensory neuropathy	No dose modifications required[d]	No dose modifications required[d]

* Located at [redacted]

[a] Fatigue and Grade 3 anorexia do not require dose modification.

[b] Grade 1 diarrhea: 2-3 stools/day > pretreatment.

[c] Grade 2 diarrhea: 4-6 stools/day > pretreatment; Grade 3 diarrhea: 7-9 stools/day > pretreatment; Grade 4 diarrhea: > 10 stools/day > pretreatment.

[d] Any toxicity ≥ Grade 2, except anemia and alopecia, can justify a dose reduction if medically indicated.

[e] Patients who require more than 2 dose reductions must be withdrawn from the study.

9.0 Ancillary Treatment/Supportive Care

9.1 Antiemetics may be used at the discretion of the attending physician. NOTE: 5-HT3 antagonists is specifically recommended as an antiemetic for rucaparib, however, patients can be treated per the treating site's institutional guidelines.

9.2 Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology (ASCO), Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2015;33:3199-3212.

9.3 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.4 Diarrhea: This could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day). Treating physicians can consider administering intravenous or subcutaneous atropine 0.25-1 mg (unless clinically contraindicated) for early onset diarrhea or any severity.

In the event of grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

10.0 Adverse Event (AE) Reporting and Monitoring

Definitions

Adverse Event
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction
Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting
Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting
Events reported to sponsor via case report forms
Events of Interest
Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site:
[redacted]

a. Adverse event monitoring and reporting is a routine part of every clinical trial.

b. Identify the grade and severity of the event using the CTCAE version 4.0

c. Determine whether the event is expected or unexpected (see Section 10.2).

d. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).

e. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).

f. Determine if other reporting is required (see Section 10.5).

g. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT).
NOTE: A severe AE, as defined by the above grading scale, is NOT the same as serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse events are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with

the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.

10.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s)/treatment.
Probable - The adverse event *is likely related* to the agent(s)/treatment.
Possible - The adverse event *may be related* to the agent(s)/treatment.
Unlikely - The adverse event *is doubtfully related* to the agent(s)/treatment.
Unrelated - The adverse event *is clearly NOT related* to the agent(s) treatment.

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug/device and the adverse event.

10.31 Special Situations for Expedited Reporting

10.311EXPECTED Serious Adverse Events: Protocol Specific Exceptions to Expedited Reporting

For Phases I and Ib of this study, **all** Serious Adverse Events will be subject to Expedited Reporting (as defined in Section 10.41). The list of Expected Serious Adverse Events and associated grades will be reviewed and determined by the study team after the completion of the Phase 1b portion of the study.

10.312 Death

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

- Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

- **Reportable categories of Death**
    - Death attributable to a CTCAE term.

- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (including cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.313 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
- All secondary malignancies that occur following treatment with an agent under an IND/IDE to be reported. Three options are available to describe the event:
    - Leukemia secondary to oncology chemotherapy (e.g., acute myeloid leukemia [AML])
    - Myelodysplastic syndrome (MDS)
    - Treatment related secondary malignancy
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.314 Second Malignancy

- A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting.

10.315 Pregnancy

If a patient becomes pregnant during the study the investigator is to stop dosing with study drug(s) immediately.

A pregnancy is not considered to be an AE or SAE; however, any pregnancy occurring in a study patient or partner of a study patient during study participation or within 6 months of last dosing must be reported within the same timelines as an SAE.

A pregnancy should be followed through to outcome, whenever possible.

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected.

In cases of fetal death, miscarriage or abortion the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

NOTE: When submitting the MedWatch 3500A Form for "pregnancy," "pregnancy loss," or "neonatal loss," the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation.

10.4 Expedited Reporting Requirements for Studies using Commercial Agent(s) ONLY:

Expedited Reporting Requirements for Adverse Events that Occur in a Non-IND/IDE trial within 30 Days of the Last Administration of a Commercial Agent [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the sponsor within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">7 Calendar Days</td><td rowspan="2">24-Hour 3 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>7 Calendar Days</td></tr>
</table>

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported via MedWatch within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Special Instructions:

- An increased incidence of an expected adverse event (AE) is based on the patients treated for this study at their site. A list of known/expected AE's are reported in the package insert or the literature, including AE's resulting from a drug overdose.

- Follow site-specific reporting guidelines.

    - Submit MedWatch form 3500A [redacted] or found on the ACCRU web site) along with the MedWatch Fax Cover Sheet (found on the ACCRU web site) to ACCRU Safety via email at: [redacted] ACCRU Safety will forward to Ipsen and Clovis, as follows:

  ☐ **Clovis**: email [redacted] or FAX: [redacted]
  NOTE: SAE's must be sent to Clovis within 24 hours of receipt by ACCRU. Pregnancies must be reported within 48 hours of receipt by ACCRU.

  ☐ **Ipsen**: email [redacted]

- ACCRU Safety will forward to ACCRU IND Coordinator [redacted] as appropriate. The ACCRU IND Coordinator will assist the sponsor-investigator in notifying the FDA if required.

- **Clovis AEs of Special Interest (AESI) for Rucaparib**
  AESI (serious or non-serious) are defined as AEs of scientific and medical concern specific to rucaparib, for which ongoing monitoring and rapid communication by the Sponsor-investigator to Clovis can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the Sponsor-Investigator to other parties (e.g., regulators) might also be warranted. AESI's should be reported within 24 hours of awareness to the ACCRU SAE Coordinator using the MedWatch form 3500A. Within 24 hours, the ACCRU SAE Coordinator will report to Clovis [redacted]

  Clovis AEs of Special Interest for this trial include:
  1. Leukemia secondary to oncology chemotherapy (e.g. Acute Myeloid Leukemia [AML]
  2. Myelodysplastic syndrome (MDS)
  3. Pneumonitis

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include 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 subject population being studied;

2. Related or possibly related to participation in the research (in this guidance document, 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 subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

If the event meets the criteria for an UPIRTSO, submit to your IRB as required by your institutional policies.

10.52 Baseline and Adverse Events Evaluations

"Investigators should complete all routine and standard of care assessments to evaluate for toxicity and symptoms of drug-induced adverse events. This may include, but is not limited to, verbal reports from the patient and/or caregiver, physical examination and laboratory findings. Adverse events should be reported throughout the course of the study, until the study termination visit, and followed through to resolution".

10.521 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per the CTCAE v4.0 grading:

System Organ Class	Adverse Event Symptom(s)	Baseline	Each Evaluation
Blood and lymphatic system disorders	Febrile neutropenia		X
Gastrointestinal	# stools per day	X	
	Diarrhea		X
	Nausea	X	X
	Vomiting	X	X
General disorders and administration site conditions	Edema limb	X	X
	Periorbital edema	X	X
	Fatigue	X	X
Investigations	Aspartate aminotransferase (AST) increase	X	X
	Alanine aminotransferase (ALT) increase	X	X
	Alkaline phosphatase, serum (ALK) increase	X	X
	Blood Bilirubin increase	X	X
	Neutrophil count decrease	X	X
	Platelet count decrease	X	X
Metabolism and nutrition disorders	Hypokalemia	X	X
Renal and urinary disorders	Serum creatinine increase	X	X

10.53 Submit via appropriate Academic and Community Cancer Research United (ACCRU) Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.5:

10.531 Phase I/Ib:

All AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure, regardless of Grade

10.532 Phase II:

Grade 1-2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.54 Grade 5 AEs (Deaths)

10.541 Any death ≤30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.542 Any death >30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.55 Refer to the instructions in the CRF Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

10.56 Reconciliation: Clovis will send Research Coordinating Center a monthly listing of SAEs received by Clovis from Research Coordinating Center in connection with the Trial and any SUSARs sent to Research Coordinating Center from Clovis. Research Coordinating Center will review the listing and notify Clovis of any omissions.

10.57 Quarterly Report: Research Coordinating Center will provide Ipsen with accrual and a toxicity report on a quarterly basis.

11.0 Treatment Evaluation Using RECIST Guideline

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1 (Eisenhauer EA, Therasse P, Bogaert J, *et al.,* 2009)). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline.

11.1 Schedule of Evaluations: For the purposes of this study, patients should be reevaluated every 8 weeks.

11.2 Definitions of Measurable and Non-Measurable Disease

11.21 Measurable Disease

11.211 A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan, CT component of a PET/CT, or MRI.

11.212 A superficial non-nodal lesion is measurable if its longest diameter is ≥ 1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging.

11.213 A malignant lymph node is considered measurable if its short axis is ≥1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

NOTE: Tumor lesions in a previously irradiated area are considered measurable disease under the following conditions:

- Tumor lesions in a previously irradiated area are considered target lesions only if they have progressed after XRT and prior to start this investigational protocol.

11.22 Non-Measurable Disease

11.221 All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥1.0 to <1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

Note: 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis <1.0 cm are considered non-pathological (i.e., normal) and should not be recorded or followed.

11.3 Guidelines for Evaluation of Measurable Disease

11.31 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-

up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.32 Acceptable Modalities for Measurable Disease:

- Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

- As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

- FDG-PET: FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible 'new' disease. A ‘positive’ FDG-PET scanned lesion is defined as one which is FDG avid with an update greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET scanned lesion is considered ‘negative.’ New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

  a. Negative FDG-PET at baseline with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

  b. No FDG-PET at baseline and a positive FDG-PET at follow-up:

     i. If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

     ii. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT at the same evaluation, additional follow-up CT scans (i.e., additional follow-up scans 8 weeks after the prior CT) are needed to determine if there is truly progression occurring at that site. In this situation, the date of PD will be the date of the initial abnormal PDG-PET scan.

     iii If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, it is not classified as PD.

11.33 Measurement at Follow-up Evaluation:

- A subsequent scan must be obtained 8 weeks following initial documentation of an objective status of either complete response (CR) or partial response (PR).

- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks (see Section 11.44).

- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

11.4 Measurement of Effect

11.41 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 11.21) up to a maximum of 5 lesions, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. <u>These lesions can be non-nodal or nodal (as defined in 11.21)</u>, where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

  Note: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.

- Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.

- Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions

(PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.

- The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

11.42 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.22) are classified as non- target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with 11.433.

11.43 Response Criteria

11.431 All target lesions and target lymph nodes followed by CT/MRI/PET-CT/Chest X-ray/physical examination must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

11.432 Evaluation of Target Lesions

- Complete Response (CR): All of the following must be true:

  a. Disappearance of all target lesions.

  b. Each target lymph node must have reduction in short axis to <1.0 cm.

- Partial Response (PR): At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (*see* Section 11.41).

- Progression (PD): At least one of the following must be true:

  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.

  b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.41). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.

  c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

11.433 Evaluation of Non-Target Lesions & Non-target Lymph Nodes

- Complete Response (CR): All of the following must be true:

  a. Disappearance of all non-target lesions.

  b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.

- Non-CR/Non-PD: Persistence of one or more non-target lesions or non-target lymph nodes.

- Progression (PD): At least one of the following must be true:

  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.

b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)

c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

11.44 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following tables:

For Patients with Measurable Disease

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR**
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

*See Section 11.431

** NOTE: This study uses the protocol RECIST v1.1 template dated 2/16/2011. For data collection and analysis purposes the objective status changed from SD to PR in the ACCRU protocol RECIST v1.1 template as of 2/16/2011 and to match RECIST v1.1 requirements.

11.45 Symptomatic Deterioration: Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

12.0 Descriptive Factors

- Phase I/Ib/II, ECOG PS: 0 vs. 1
- Phase I only, dose level: -2 vs. -1 vs. 1 vs.2-A vs. 2-B vs. 3

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Patients who are CR, PR, or SD will continue treatment per protocol.
Patients who are CR, PR, or SD at time of their reassessment and **have not** experienced intolerable toxicity will be allowed to continue protocol treatment at the same dose level until PD or maximum of 3 years whichever is earlier.

Those patients who are CR, PR, or SD but **have** experienced unacceptable toxicity may be eligible for retreatment at a lower dose until PD or maximum of 3 years whichever is earlier, at discretion of treating physician (see Section 8.0).

13.2 Patients who develop PD while receiving therapy will go to the event-monitoring phase. Treatment decision during event-monitoring phase is at the discretion of the treating physician.

13.3 Patients who go off protocol treatment for reasons other than PD will go to the event-monitoring phase per Section 18.0. Treatment decision during event-monitoring phase is at the discretion of the treating physician.

13.4 If a patient enrolled to Phase I dose escalation part of the study fails to complete the initial course of therapy (defined as drug administration ≤ 75% of expected cycle 1 total dose) for reasons other than dose-limiting toxicity defined adverse events, the patient will be regarded as uninformative in regard to the primary study goal and an additional patient will be enrolled at the current dose level

13.5 A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the event-monitoring phase of the study (or off study, if applicable).

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.
- If the patient never received treatment, on-study material must be submitted. Event monitoring will be required per Section 18.0 of the protocol.

13.6 A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Event monitoring will be required per Section 18.0 of the protocol.

13.7 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. The patient will go directly to the event-monitoring phase of the study, and event monitoring will be required per Section 18.0 of the protocol.

14.0 Body Fluid Biospecimens

14.21 Summary Table of Research Blood/Blood Products to Be Collected for This Protocol

Indicate if specimen is mandatory or optional	Collection tube description and/or additive (color of tube top)	Volume to collect per tube (number of tubes to be collected)	Blood product being processed and submitted by participating site	Baseline	Restaging [2]	End of treatment (PD, removal or withdrawal)	Additional processing required at site after blood draw?	Storage /shipping conditions[1]
Mandatory	None (red top)	10 ml (1)	Whole blood	X	X	X	No	Refrigerate (cold packs)
Mandatory	EDTA (purple top)	10mL (1)	Whole blood	X	X	X	No	Refrigerate (cold packs)
Mandatory	STRECK (tan and black marble top)	10mL (1)	Whole blood	X	X	X	No	Ambient

[1]After all samples have been processed according to kit instructions, ship all specimens according to shipping instructions (see Section 14.25 for detailed shipping instructions.)

[2] All Restaging collections of No Additive red top, EDTA purple top and STRECK tan and black top tubes will be noted as "Restaging" on kit requisition form.

14.21 **Kits are required for this study.**

14.211 The kit contains supplies and instructions for collecting, processing, and shipping specimens.

14.212 Participating institutions may obtain kits from the BAP Lab via the Mayo Clinic Research Client Request Portal (MCRCRP). Detailed instructions for using MCRCRP are available on the ACCRU website located under the study specific 'Manuals and Forms'. Because we are now being charged for all outgoing kits, a small, but

sufficient, supply of the specimen collection kits should be ordered prior to patient entry. Unused/expired kits should be disposed per institution policy. Do not send unused kits back to BAP. Kit requests must be filled in completely and accurately for quick processing. For questions regarding your kit order contact [redacted]

NOTE: Expired kit tubes may be exchanged with site stock if available.

14.213 Kits will be sent via FedEx® Ground at no additional cost to the participating institutions. **Allow at least two weeks to receive the kits.**

14.214 Kits will not be sent via rush delivery service unless the participating institution provides their own FedEx® account number or alternate billing number for express service.

NOTE: ACCRU will <u>not</u> cover the cost for rush delivery of kits.

14.22 All samples must be collected **Monday-Friday.**

14.23 Label specimen tube(s) with protocol number, ACCRU patient ID number, and time and date blood is drawn.

14.24 Collect and process all blood/blood products according to specific kit instructions and table below.

14.25 Shipping

14.251 Verify ALL sections of the Specimen Submission: Blood form (see CRF packet), BAP Requisition Form (provided in kit), and specimen collection labels are completed and filled in correctly.

14.252 Specimens must be shipped the same day they are drawn.

14.253 Specimens will be shipped in a dual-temperature shipping container. Place the refrigerated EDTA, No Additive tubes with a properly prepared cold pack in one compartment. See kit instructions for specific details for cold pack preparation (i.e., frozen or refrigerated) and proper packing of blood and cold pack to avoid freezing of specimen. Place the STRECK tube in the ambient compartment of the dual-temperature shipping container.

14.254 Ship specimens via Priority Overnight service, **Monday – Friday,** to BAP Receiving according to kit instructions. **Do not send samples on weekends or just prior to federal holidays.**

14.255 The BAP kits will include a smart shipper label (3x5 white barcoded label) affixed to the shipping boxes. The smart shipper label is a pre-addressed return label, which replaces the need for an air bill. Shipping costs will be covered by ACCRU if the shipping box provided with the BAP kit is used for shipping specimens to BAP Receiving.

Ship samples to:

14.256 BAP Freezer will receive the samples.

14.3 Study Methodology and Storage Information

14.31 Blood/blood product samples will be collected for the following research

14.311 DNA extraction and storage of DNA and buffy coats for future pharmacogenetic assays that may correlate with efficacy and tolerability. using standard laboratory protocols. DNA/serum/plasma will be sent to a Clovis 3rd party diagnostic collaborator for genomic analysis. Remaining DNA and buffy coats will be stored frozen at -70ºC by BAP, according to patient consent information until specific analyses are identified. As protocols are developed, they will be presented for ACCRU and IRB review and approval. (This collection is part of a general strategy of investigation for the majority of ACCRU studies.)

14.312 As part of ongoing ACCRU research, we will collect serum/plasma for future research studies, according to patient consent information, on molecular determinants of efficacy and tolerability. Samples will be stored frozen at -70ºC by BAP until specific analyses are identified. As protocols are developed, they will be presented for ACCRU and IRB review and approval.

14.4 Return of Genetic Testing Research Results

Because the results generated by the genetic testing included in this section are not currently anticipated to have clinical relevance to the patient or their family members, the genetic results will not be disclosed to the patients or their physicians.

If at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

15.0 Drug Information

IND exempt

15.1 Rucaparib PO

- Investigator brochure available on the ACCRU web site.

15.11 **Background**: Rucaparib camsylate is available for oral administration. Rucaparib is a potent small molecule inhibitor of poly-adenosine diphosphate (ADP) ribose polymerase (PARP) enzymes, including PARP-1, PARP-2, and PARP-3. These proteins play an important role in the repair of DNA in cells. Some cancer cells, including those with a mutation in the BRCA gene, are particularly dependent on PARPs to repair damaged DNA because they lack other proteins for repairing DNA that normal cells have.

By blocking the activity of PARPs in cancer cells, rucaparib is expected to stop the cancer cells from being able to repair damaged DNA. This eventually leads to the death of the cancer cells, thereby slowing down the growth of the cancer.

15.12 **Formulation**: The oral formulation of rucaparib contains the camphorsulfonic acid salt of the active agent rucaparib. All dosage strengths are expressed as the weight of free base rucaparib. Three strengths of oral rucaparib 200 mg, 250 mg, and 300 mg are available as immediate release film-coated tablets. The 200 mg, 250 mg, and 300 mg tablets all contain the same ratios of active agent and excipients, with different strengths achieved by increasing the total amount of material. The physical appearances of the tablets are unique in order to ensure proper identification. The 200 mg tablets are blue, round (11 mm) tablets de-bossed with 'C2'. The cosmetic blue film coating is Opadry II containing polyvinyl alcohol, titanium dioxide, polyethylene glycol/macrogol, talc, FD&C Blue #1 colorant, brilliant blue FCF aluminum lake, and FD&C blue indigo carmine aluminum lake. The 250 mg tablets are white, diamond shaped (15 mm x 11 mm) tablets de-bossed with 'C25'. The cosmetic white film coating is Opadry II containing polyvinyl alcohol, titanium dioxide, polyethylene glycol/macrogol, and talc. The 300 mg tablets are yellow, oval tablets (16 mm x 8 mm) de-bossed with 'C3'. The cosmetic yellow film coating is Opadry II containing polyvinyl alcohol, titanium dioxide, polyethylene glycol/macrogol, talc, and irradiated yellow iron oxide.

15.13 **Preparation and storage**: Tablets are provided in high-density polyethylene (HDPE) bottles with child-resistant caps and should be stored in the provided containers. Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [*see USP Controlled Room Temperature*].

15.14 **Administration:** The effect of food is not clinically significant, therefore, rucaparib may be taken with or without food.

15.15 **Pharmacokinetic information**:
AUC: 4120 (ng*h/mL)
Bioavailability: 36%
Plasma protein binding: 55%-75%
Distribution: 113-262L, indicating distribution into tissues.
Half-life elimination: 9.23-33.6hours
Cmax: 274 ng/mL
Tmax: 1.5-64 hours
Excretion: Urine samples collected for 24 hours after a single test dose resulted in 10.5% of the dose being recovered. This result indicates renal elimination is not the major elimination pathway.

15.16 **Potential Drug Interactions**:

Enzymes responsible for rucaparib metabolism have not been identified. Based on in vitro data, CYP2D6, and to a lesser extent CYP1A2 and CYP3A4, were able to metabolize rucaparib. In population PK analysis,

patients with different CYP2D6 or CYP1A2 genotypes showed comparable rucaparib PK. Although in vitro rucaparib metabolism mediated by CYP3A4 was slow, a significant contribution of CYP3A4 in vivo cannot be excluded. **Caution should be used for concomitant use of strong CYP3A4 inhibitors or inducers.**

Clinical results indicated that rucaparib, at 600 mg BID, moderately inhibited CYP1A2, weakly inhibited CYP2C9, CYP2C19, CYP3A, and BCRP, and showed no clinically significant effect on P-gp. **Caution should be exercised in the concomitant use of drugs that are substrates of the above CYP enzymes with narrow therapeutic windows.** Rucaparib also caused mild increases in plasma exposure to oral contraceptives (ie, ethinylestradiol and levonorgestrel).

CYP1A2 Substrates
When co-administering medicinal products metabolized by CYP1A2, particularly medicines which have a narrow therapeutic index (eg, tizanidine, theophylline), dose adjustments may be considered based on appropriate clinical monitoring.

CYP2C9 Substrates
When co-administering medicinal products that are CYP2C9 substrates with a narrow therapeutic index (eg, warfarin, phenytoin), dose adjustments may be considered, if clinically indicated. Exercise caution and consider additional INR monitoring with co-administration of warfarin and therapeutic drug level monitoring of phenytoin, if used concomitantly with rucaparib.

CYP2C19 Substrates
No dose adjustment is considered necessary for co-administered medicinal products that are CYP2C19 substrates.

CYP3A Substrates
Caution is advised when co-administering medicinal products that are CYP3A substrates with a narrow therapeutic index (eg, alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine). Dose adjustments may be considered, if clinically indicated based on observed AEs.

P-gp Substrates
No dose adjustment is recommended for co-administered medicinal products that are P-gp substrates.
BCRP Substrates
No dose adjustment is recommended for co-administered medicinal products that are BCRP substrates.

Oral Contraceptives
Co-administered rucaparib could increase plasma exposures of oral contraceptives. The effect is mild and no dose adjustment is recommended for oral contraceptives.

Other Enzymes and Transporters
Interaction of rucaparib with other enzymes and transporters was evaluated in vitro. Rucaparib is a weak inhibitor of CYP2C8, CYP2D6, and UGT1A1. Rucaparib down regulated CYP2B6 in human hepatocytes at clinically relevant exposures. In vitro, rucaparib is a potent inhibitor of MATE1 and MATE2-K, a moderate inhibitor of OCT1, and a weak inhibitor of OCT2. As inhibition of these transporters could decrease renal elimination and liver uptake of metformin, caution is advised when metformin is co-administered with rucaparib.

15.17 **Known potential adverse events:**

Common known potential toxicities (> 10%):

Asthenia, fatigue, anemia, increased ALT/AST, thrombocytopenia, nausea, vomiting, diarrhea, increased serum creatinine, decreased appetite, constipation, abdominal pain, dyspepsia, dysgeusia, dizziness, dyspnea, pyrexia, insomnia, photosensitivity reaction

Less common known potential toxicities (1% - 10%):
Leukopenia, lymphopenia, decreased WBC, increased serum cholesterol, hypercholesterolemia, increased transaminases, decreased lymphocyte count, decreased neutrophil count, hypophosphatemia, febrile neutropenia, upper respiratory tract infection, Myelodysplastic Syndrome, Acute Myeloid Leukemia

Rare known potential toxicities, <1% (Limited to important or life-threatening):
Pneumonitis

15.18 **Drug procurement**

Clovis will provide the commercial formula of rucaparib free of charge to Clinical Research Services, a division of Rx Crossroads by McKesson for investigational use in this study. The product will be labeled, "For Investigational Use." Each participating ACCRU treating location will order the drug from Clinical Research Services, a division of Rx Crossroads by McKesson. It will take 1-2 business days to receive the rucaparib.
Fax the Drug Order Request Form (found on the ACCRU web site) to:

Each participating ACCRU treating location will be responsible for monitoring the supply of rucaparib and will use the appropriate Drug Order Request Form to order additional supplies as needed.

Outdated or remaining drug is to be destroyed on-site as per procedures in place

at each institution after approval is received by Clovis. The Clovis IP Destruction Authorization Form should be completed by each site and submitted to Clinical Research Services, a division of Rx Crossroads by McKesson [redacted] *Clinical Research Services, a division of Rx Crossroads by McKesson will submit form to Clovis for drug destruction approval on-site. The Clovis IP Destruction Authorization Form should also be used to report drug that is to be destroyed due to damage or out of temperature specifications (temperature excursions) to Clinical Research Services, a division of Rx Crossroads by McKesson , who will then send to Clovis.*

15.19 **Nursing Guidelines:**

15.191 Common GI side effects include abdominal pain, constipation, nausea, vomiting, diarrhea, and decreased appetite. Manage symptomatically and monitor for effectiveness of intervention.

15.192 Monitor CBC w/differential. Cytopenias are common, especially when given with other chemotherapy. Instruct patients to report any signs or symptoms of infection or bleeding to the study team.

15.193 Fatigue can be seen. Instruct patient in energy conserving lifestyle.

15.194 Dizziness and headache can be seen. Treat symptomatically.

15.195 Monitor LFT's.

15.196 (For PO formulation) Rucaparib may be given with or without food. Patients should be instructed to take agent with at least 8 oz of room temperature water.

15.197 There are several drug to drug interactions, patients who are on other concomitant medications that are CYP substrates. Extra monitoring may be required for patients who are on agents with narrow therapeutic ranges (i.e warfarin). Assess patient's medication lists carefully including OTC and herbal products.

15.198 Rarely palmar-plantar erythrodysesthesia (hand-foot syndrome) may be seen. Instruct patients to use moisturizers, and to protect hands and feet.

15.199 May cause photosensitivity. Instruct patients to use good photo protection, including limiting sun exposure and using sunscreen.

15.199a Rarely patients can develop myelodysplastic syndrome or AML.

15.199b Pneumonitis has been seen. Instruct patients to report any shortness of breath, new cough, dyspnea on exertion, or chest pain to the study team.

15.2 MM-398 (nal-IRI, Onivyde®, Irinotecan Liposome Injection, PEP02)

- **Investigator brochure available on the ACCRU web site.**

15.21 **Background**: The formulation of irinotecan liposome injection was invented by Hermes Biosciences, Inc. (South San Francisco, CA), developed by PharmaEngine, Inc., and subsequently acquired by Merrimack Pharmaceuticals, Inc. In April 2017 Ipsen acquired this asset from Merrimack. Currently, Ipsen and Servier (previously Shire) are co-developing irinotecan liposome injection. Ipsen is solely responsible for commercializing irinotecan liposome injection in the United States.

Drug carrier technologies represent a rational strategy to improve the pharmacokinetics and biodistribution of irinotecan while protecting it from premature metabolism. Irinotecan liposome injection employs a novel intraliposomal drug stabilization technology for encapsulation of irinotecan into long-circulating liposomes with high drug load and high in vivo stability. The stable liposome formulation of irinotecan has several attributes that may provide an improved therapeutic index. The controlled and sustained release should improve activity of this schedule-dependent drug by increasing duration of exposure of tumor tissue to drug, an attribute that allows it to be present in a higher proportion of cells during the more sensitive S-phase of the cell cycle.

The improved pharmacokinetics, high drug retention in the liposomes, and enhanced permeability and retention (EPR) effect may result in site-specific drug delivery to solid tumors. Stromal targeting may result from the subsequent depot effect, where liposomes accumulate in tumor associated macrophages (TAMs) which release the active drug, irinotecan, and contribute to local conversion to be substantially more cytoxic SN-38, the active metabolite of irinotecan. The preferentially local biotransformation should result in reduced exposure to potential sites of toxicity and increased exposure to neighboring cancer cells within the tissue.

15.22 **Formulation**: Irinotecan liposome is supplied as a sterile solution containing 4.33 mg/ml of irinotecan on the free base basis (equivalent to 5 mg/ml of irinotecan hydrochloride trihydrate) encapsulated in liposomes. The drug product is a sterile, white to slightly yellow opaque isotonic liposomal dispersion for intravenous infusion. Each vial has a nominal fill volume of 10 mL with an overfill of approximately 0.5 mL. Each vial is intended for single use IV administration only.

15.23 **Preparation, storage, and stability**: Irinotecan liposome must be refrigerated at 2°C-8°C (36°F-46°F). Do not freeze. Protect from light. Irinotecan liposome injection is a cytotoxic drug. Follow applicable special handling and disposal procedures (including for shelf life). Prior to administration, irinotecan liposome injection must be diluted in 5% Dextrose injection or 0.9% Sodium Chloride, or per protocol-specific directions. The solution for infusion should be used immediately, but may be stored at room temperature (15º to 25ºC) for up to 4 hours . If necessary, the solution for infusion may be refrigerated (2º to 8ºC) for no more than 24 hours prior to use. The solution for infusion must not be frozen as the liposome structure will be disrupted, resulting in the

premature release of irinotecan. Irinotecan liposome has been tested for compatibility with limited materials, and no compatibility issues have been identified.

15.24 **Administration:** Irinotecan liposome is administered over 90 minutes or as directed per protocol. Do not use in-line filters. Infusion sets without in-line filters are recommended for use. However, an infusion set with an in-line filter that has a pore size of at least 0.2 microns is compatible for use.

15.25 **Pharmacokinetic information**:
Distribution: The volume of distribution (V_d) estimates in patients administered irinotecan liposome were 2.2 L/m^2.
Protein Binding: <1% **Metabolism:** Information about the metabolism and excretion of irinotecan relies on information from the physician's package insert for Camptosar®
Half-life elimination: total irinotecan: ~ 26 hours; SN-38: ~68 hours**Race:** Following the administration of irinotecan liposome injection, race was strongly associated with total irinotecan exposure. In the last updated PopPK analysis (excluding the study in Japanese patients), irinotecan clearance was 80% higher in patients of Asian ethnicity than other populations. In the PopPK model including the Japanese, exposure of total and converted SN-38 were approximately 30% and 25% higher respectively than those observed in non-Japanese subjects. This finding suggests that the higher clearance of total irinotecan in Asians resulted in higher converted amount to SN-38. Despite the observed differences by race for SN-38 exposure, myelosuppression and diarrhea, the degree of difference is not clinically substantial to suggest that dose modification by race would be needed.

15.26 **Potential Drug Interactions**:
Information about the drug interactions of irinotecan liposome relies on information from the physician's package insert for Camptosar®, which states that irinotecan and its active metabolite, SN-38, are metabolized via CYP3A4 and UGT1A1, respectively. Data from the phase 2 clinical safety study PEP0206 supported the similarity in the metabolic fate of irinotecan released from nal-IRI and from direct administration with Camptosar®.
The concentrations of 5-FU measured in the study NAPOLI-1 were consistent with the difference in the two 5-FU dose regimens. Therefore, no effects are expected of irinotecan liposome injection administration on 5-FU pharmacokinetics.
Based on population pharmacokinetic analysis, no significant association was observed between the pharmacokinetic parameters of total irinotecan and SN-38 following irinotecan liposome injection monotherapy and when co-administered with 5-FU/LV. This result is consistent with the lack of drug interaction noted between irinotecan and 5-FU.

15.27 **Known potential toxicities:** The safety of irinotecan liposome, a liposomal formulation of irinotecan, may be indirectly compared with the safety of

irinotecan, primarily based on a qualitative comparison of adverse reactions, as reported in the Camptosar US Product label for irinotecan, and as summarized in this document and reflected in the US Product Label for irinotecan liposome injection. The comparison is qualitative, since both irinotecan and irinotecan liposome injection have been used in different doses and schedules as monotherapy and combination therapy with other chemotherapeutic agents; making quantitative comparisons are difficult. The most common adverse reactions of irinotecan and irinotecan liposome injection are similar and are mainly gastrointestinal events and myelosuppression.

In single agent irinotecan therapy clinical studies, the most common adverse reactions (≥30%) observed are: nausea, vomiting, abdominal pain, diarrhea, constipation, anorexia, neutropenia, leukopenia (including lymphocytopenia), anemia, asthenia, fever, body weight decreasing, and alopecia.

Comparatively, irinotecan liposome injection, when used in combination with 5-fluorouracil and leucovorin, the most common adverse reactions (≥20 %) observed in clinical trials considered were: diarrhea, fatigue/asthenia, nausea, vomiting, decreased appetite, stomatitis, and pyrexia The most common laboratory abnormalities (≥10 % Grade 3 or 4) were lymphopenia and neutropenia (ONIVYDE USPI).

Certain known adverse reactions of irinotecan have not been observed with irinotecan liposome injection to date. This could be due to the limited cumulative patient exposure to date of irinotecan liposome injection, or the use of appropriate premedication and early recognition and treatment of expected adverse events. The adverse reactions observed with irinotecan and not yet observed with irinotecan liposome injection include anaphylaxis or anaphylactoid reaction, interstitial lung disease-like pulmonary toxicity and acute pancreatitis. There is insufficient evidence to know whether these known adverse reactions of irinotecan will also be associated with irinotecan liposome injection.

15.28 **Drug procurement:**

Ipsen will provide the commercial formula of irinotecan liposome free of charge to Clinical Research Services, a division of Rx Crossroads by McKesson for investigational use in this study. The product will be labeled, “For Investigational Use.” Each participating ACCRU treating location will order the drug from Clinical Research Services, a division of Rx Crossroads by McKesson. It will take 1-2 business days to receive the nal-IRI.

Fax or email the Drug Order Request Form (found on the ACCRU web site) to:

Each participating ACCRU treating location will be responsible for monitoring the supply of nal-IRI and will use the appropriate Drug Order Request Form to order additional supplies as needed.

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

15.29 **Nursing Guidelines:**

15.291 If possible, check for any history of hypersensitivity reaction to any previous drug formulated with polysorbate 80.

15.292 Cholinergic symptoms of lacrimation, nasal congestion, diaphoresis, flushing, ABD cramping, and diarrhea can occur at the beginning, during, or immediately after the irinotecan liposome infusion. It is suggested that the patient remain in the treatment area for a minimum of one hour following the completion of the **very first** irinotecan liposome infusion. If diarrhea occurs within one hour of infusion, refer to Section 9.2 or 15.16 for management.

15.293 Patient education is extremely important. Impress on the patient the importance of compliance with treatment of diarrhea management (see Section 9.4). Stress the need for prompt recognition and early intervention. Motivate the patient to report any complications immediately. The cholera-like syndrome can be unresponsive to conventional antidiarrheals and can result in severe dehydration.

15.294 Ondanestron and diphenhydramine should provide good relief from the nausea/vomiting/cramping. Avoid prochlorperazine on the day of treatment due to its association with akathisia (motor restlessness). Prochlorperazine may be taken between treatments.

15.295 Advise avoidance of excess caffeine, a GI stimulant. Avoid magnesium-based antacids such as Mylanta, Maalox, Rolaids, MOM, Mag-Ox 400, and Tylenol with antacid.

15.296 The pulmonary toxicity seen is usually manifested by dyspnea beginning 42-175 days after treatment and occurs at a cumulative dose ranging from 400-1000 mg/m (median 750). Instruct patient to report any cough or SOB.

15.297 Patients are at risk for developing eosinophilia and will improve on steroid therapy.

15.298 Hepatic enzyme elevations have been transient and did not require intervention.

15.299a Monitor CBC closely. Leukopenia occurs primarily as neutropenia but can be severe and dose limiting. The simultaneous occurrence of grade 4 diarrhea and grade 4 neutropenia is rare but may render the patient more susceptible to polymicrobial sepsis and potentially death.

15.299b Advise patients of probable hair loss.

15.3 Fluorouracil (Adrucil, Efudex, [5-FU])

- Refer to package insert for complete, up-to-date information.

15.31 **Background**: Antineoplastic Agent, Antimetabolite (Pyrimidine Analog). Fluorouracil is a fluorinated Pyrimidine Antimetabolite that inhibits thymidylate synthetase, blocking the methylation of deoxyuridylic acid to thymidylic acid, interfering with DNA, and to a lesser degree, RNA synthesis. Fluorouracil appears to be phase specific for the G_1 and S phases of the cell cycle.

15.32 **Formulation**: Commercially available for injection 50 mg/mL (10 mL, 20 mL, 50 mL, and 100 mL).

15.33 **Preparation, storage, and stability**: Store intact vials at room temperature and protect from light. A slight discoloration may occur with storage but usually does not denote decomposition. Dilute in 50 – 1000 mL of 0.9% NaCl or D5W. If exposed to cold, a precipitate may form; gentle heating to 60ºC will dissolve the precipitate without impairing the potency. Solutions in 50 – 1000 mL 0.9% NaCl or D5W or undiluted solutions in syringes are stable for 72 hours at room temperature. Fluorouracil should not be coadministered with either diazepam, doxorubicin, daunorubicin, idarubicin, cisplatin, or cytarabine. However, fluorouracil and leucovorin are compatible for 14 days at room temperature. Fluorouracil is compatible with vincristine, methotrexate, and cyclophosphamide.

15.34 **Administration:** Fluorouracil will be given by continuous IV infusion over 46 hours.
Refer to section 7.0 (treatment) administration instructions specific to the protocol.

15.35 **Pharmacokinetic information**:
Distribution: V_d ~ 22% of total body water; penetrates extracellular fluid, CSF, and third space fluids (e.g., pleural effusions and ascitic fluid)
Metabolism: Hepatic (90%); via a dehydrogenase enzyme; Fluorouracil must be metabolized to be active.
Half-life elimination: Biphasic: Initial: 6-20 minutes; two metabolites, FdUMP and FUTP, have prolonged half-lives depending on the type of tissue.
Excretion: Lung (large amounts as CO_2); urine (5% as unchanged drug) in 6 hours.

15.36 **Potential Drug Interactions**: Fluorouracil may increase effects of warfarin. Avoid ethanol (due to GI irritation). Avoid black cohosh.

15.37 **Known potential adverse events:** Consult the package insert for the most current and complete information.

Common known potential toxicities, > 10%:

Dermatologic: Dermatitis, pruritic maculopapular rash, alopecia.
Gastrointestinal (route and schedule dependent): Heartburn, nausea, vomiting, anorexia, stomatitis, esophagitis, anorexia, diarrhea. GI toxicity (anorexia, nausea, and vomiting) is generally more severe with continuous-infusion schedules.
Emetic potential: <1000 mg: Moderately low (10% to 30%) ≥ 1000 mg: Moderate (30% to 60%)
Hematologic: Leukopenia; Myelosuppressive (tends to be more pronounced in patients receiving bolus dosing of FU). Decreased white blood cell count with increased risk of infection; decreased platelet count with increased risk of bleeding.
Local: Irritant chemotherapy.

Less common known potential toxicities, 1% - 10%:
Dermatologic: Dry skin
Gastrointestinal: GI ulceration

Rare known potential toxicities, <1% (Limited to important or life-threatening):
Cardiac enzyme abnormalities, chest pain, coagulopathy, dyspnea, ECG changes similar to ischemic changes, hepatotoxicity; hyperpigmentation of nail beds, face, hands, and veins used in infusion; hypotension, palmar-plantar syndrome (hand-foot syndrome), photosensitization. Cerebellar ataxia, headache, somnolence, ataxia are seen primarily in intracarotid arterial infusions for head and neck tumors.

15.38 **Drug procurement:** Commercial supplies. Each participating ACCRU treating location shall obtain supplies from normal commercial supply chain or wholesaler.

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

15.39 **Nursing Guidelines:**

15.391 Monitor complete blood count and platelet count. Instruct patient to report signs and symptoms of infection, unusual bruising or bleeding to the physician.

15.392 Administer antiemetics as indicated.

15.393 Diarrhea may be dose-limiting; encourage fluids and treat symptomatically.

15.394 Assess for stomatitis; oral care measures as indicated. May try Vitamin E oil dabbed on sore, six times daily. Cryotherapy recommended with IV push administration.

15.395 Monitor for neurologic symptoms (headache, ataxia).

15.396 Inform patient of potential alopecia.

15.397 Those patients on continuous infusion may need instruction regarding central intravenous catheters and portable intravenous or intra-arterial infusion devices.

15.398 Fluorouracil–induced conjunctivitis is a common problem. Advise patient to report any eye soreness or redness to the healthcare team.

15.399 Photosensitivity may occur. Instruct patients to wear sun block when outdoors.

15.4 Leucovorin Calcium (CF)

- Refer to package insert for complete, up-to-date information.

15.41 **Background**: A reduced form of folic acid, leucovorin supplies the necessary cofactor blocked by methotrexate, enters the cells via the same active transport system as methotrexate. Stabilizes the binding of 5-dUMP and thymidylate synthetase, enhancing the activity of fluorouracil.

15.42 **Formulation**: Commercially available as:
Injection, powder for reconstitution: 50 mg, 100 mg, 200 mg, 350 mg
Injection, solution: 10 mg/mL (10mL, 30 mL)

15.43 **Preparation, storage, and stability**:
Powder for injection: Store at room temperature, protect from light. Reconstitute with sterile water for injection or bacteriostatic water for injection; dilute in 100-1000 mL 0.9% NaCl or D_5W. When doses > 10 mg/m^2 are required, reconstitute using sterile water for injection, not a solution containing benzyl alcohol. Solutions reconstituted with bacteriostatic water for injection must be used within 7 days. Solutions reconstituted with sterile water for injection must be used immediately. Parenteral admixture is stable for 24 hours stored at room temperature and for 4 days when stored under refrigeration.
Solution for injection: Prior to dilution, store vials under refrigeration, protect from light.

15.44 **Administration:** Due to calcium content, do not administer I.V. solutions at a rate > 160 mg/minute. Refer to individual protocols for specific administration instructions.
In combination with irinotecan: Leucovorin is compatible with irinotecan via Y-site injection.[3]
Leucovorin should be administered I.V. push or I.V. infusion over 30 minutes following irinotecan liposome
In combination with fluorouracil: The fluorouracil is usually given after the leucovorin infusion. Leucovorin is usually administered by I.V. bolus injection or short (10-120 minutes) I.V. infusion, however, in this trial will be given over 30 minutes. Other administration schedules have been used; refer to the treatment section of the protocol for specific directions.

15.45 **Pharmacokinetic information**:
Metabolism: Intestinal mucosa and hepatically to 5-methyl-tetrahydrofolate (5MTHF; active)
Half-life elimination: ~4-8 hours
Time to peak: I.V.: Total folates: 10 minutes; 5MTHF: ~1 hour
Excretion: Urine (primarily); feces

15.46 **Potential Drug Interactions**:
Decreased Effect: May decrease efficacy of trimethoprim/sulfamethoxazole against *Pneumocystis carinii* pneumonia.

15.47 **Known potential adverse events:** Consult the package insert for the most current and complete information.

Frequency not defined:
Dermatologic: Erythema, pruritis, skin rash, urticarial
Hematologic & oncologic: Thrombocytopenia
Hypersensitivity: Anaphylactoid reaction, hypersensitivity reaction
Respiratory: Wheezing

15.48 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

15.49 **Nursing Guidelines**

15.491 Headache may occur. Advise patient that analgesics such as Tylenol may help. Instruct patient to report any headache that is unrelieved.

15.492 Observe for sensitization reaction (rash, hives, pruritis, facial flushing, and wheezing).

15.493 May potentiate the toxic effects of fluropyrimidine (5-FU) therapy, resulting in increased hematologic and gastrointestinal (diarrhea, stomatitis) adverse effects. Monitor closely.

15.494 May cause mild nausea or upset stomach. Administer antiemetics if necessary and evaluate for their effectiveness.

15.495 If Leucovorin is being used as rescue for high dose methotrexate, does must be given on time. Impress this to the patient. If patient is taking oral Leucovorin at home and is unable to take secondary to nausea, instruct patient to notify the health care team immediately to arrange for other methods of administration.

16.0 Statistical Considerations and Methodology

16.1 Overview

This is a phase I/Ib/II study of the nal-IRI/5FU with rucaparib (MRF) combination.

The phase I portion of this study is a 3+3 trial designed to establish the recommended dose level of the nal-IRI/5FU with rucaparib combination in patients with pancreatic and gastroesophageal cancers (up to 2 lines of prior therapy), colorectal cancer (up to 3 lines of prior therapy), and biliary tract cancer (up to 1 line of prior therapy).

The phase Ib portion of this study is designed to assess, in a preliminary fashion, antitumor efficacy of the recommended dose level of MFR in patients with metastatic disease from pancreatic adenocarcinoma who have received no more than 1 line of prior therapy in the metastatic setting. The recommended dose level determined in the phase I portion of the trial will be used for the Phase Ib portion.

The phase II portion of this study will use a 2-stage Simon design with interim analysis to assess the efficacy of MFR in patients with (untreated) metastatic pancreatic cancer and BRCA1, BRCA2, or PALB2 mutation. The recommended dose level determined in the phase I portion of the trial will be used for the Phase II portion.

16.11 Primary Objective and Endpoint

Phase I: the primary objective is to determine the recommended dose level of the combination MFT nal-IRI/5FU with rucaparib. The end point to this objective is to evaluate the incidence of dose-limiting toxicities (DLT) of nal-IRI/5FU with rucaparib.

Phase Ib: the primary objective is to evaluate, in a preliminary fashion, antitumor efficacy and tolerability of the recommended dose level of MFR in patients with metastatic disease from pancreatic adenocarcinoma who have received no more than 1 line of prior therapy in the metastatic setting. The endpoint to this objective is Disease control (DC) rate which is defined to be RECIST (v 1.1) complete response, partial response, or stable disease, for at least 24 weeks from initiation of study therapy. The purpose of this Phase Ib expansion is to better understand the DC rate and appropriate patient population in order to plan a Phase II trial.

Specimens will be collected at baseline in all patients, and at 16 weeks in patients with disease control at that time.

A portion of the patients will be selected to have known homologous recombination (HR) defects, and approximately 25% of the remaining patients are expected to have HR defects.

Phase II: the primary objective is to estimate the proportion of evaluable patients who reach CR/PR, per RECIST 1.1, ≤32 weeks after registration. Evaluable is defined as patients with HRD encompassing BRCA1, BRCA2, and PALB2 deleterious mutations (germline and somatic), consented, eligible, and received any protocol treatment. The end point to this objective is to evaluate changes in size of target lesions according to RECIST 1.1

16.12 Sample Size

The phase I portion of this study is expected to require a minimum of 49 patients and a maximum of 58 patients including 40 patients who will be accrued into the expanded phase Ib cohort (see below).

The phase Ib portion of this trial consists of 2 expansion cohorts of patients adenocarcinoma who have received no more than 1 line of prior therapy in the metastatic setting. The objective of the phase Ib study is exploratory and hypothesis generating in nature. The phase 1b analysis is not powered; thus, no sample sizes were derived. We plan to enroll 40 patients to the Phase Ib, including 28 patients with either unknown mutation status or non-HRD (known wildtype for BRCA1, BRCA2, and PALB2 genes) and 12 patients with known HR deficiency (known mutation in either BRCA1, BRCA2, or PALB2 genes) with the intent of establishing the efficacy of rucaparib in combination with nal-IRI. In addition to 12 patients with known HR deficiency due to mutations in BRCA1, BRCA2, or PALB2, we expect that 7 of 28 Unknown/Non-HRD cohort patients will have HR deficiency since 25% of PDAC patients have defects in DNA repair.

The phase II portion of this study is expected to require a minimum of 11 and a maximum of 21 untreated pancreatic patients with HRD encompassing BRCA1, BRCA2, or PALB2 deleterious mutations (germline and somatic). An additional 3 patients with untreated pancreatic cancer and with BRCA1, BRCA2 or PALB2 deleterious mutation will be accrued to account for ineligibility, cancellation, major treatment violation, or other reasons. We anticipate accruing patients with

other HRD (other than BRCA1, BRCA2, or PALB2) during the phase II portion of the trial for exploratory analysis. Therefore, the phase II portion is expected to screen 200 patients and accrue 24 patients with HRD encompassing BRCA1, BRCA2 and PALB2 patients and another 28 patients with other HRD with an overall sample size will be a maximum of 52 patients.

16.13 Accrual Rate and Study Duration

The anticipated accrual rate for Phase I is 1 patient per month. At this rate, it will likely take about 4 months to enroll, treat, and evaluate each set of 3 patients in the phase I portion of this study. The phase I portion is expected to take between 12 and 24 months.

The anticipated accrual rate for Phase Ib is 3-4 pancreatic cancer patients per month. The phase Ib portion is expected to take up to 20 months.

The anticipated screening rate for Phase II portion is approximately 8-10 patients per month. The anticipated accrual rate for Phase II is approximately 1-2 patients per month for patients with untreated pancreatic cancer with HRD encompassing BRCA1, BRCA2 and PALB2 patients. Therefore, the accrual period is expected to be between 12 and 24 months, depending upon whether the trial will continue accruing patients beyond the interim analysis.

The total study duration is expected to be approximately 24 to 48 months until the last patient accrued in the Phase II portion has been observed for at least 4 months.

16.2 Phase I portion:

The phase I portion of this trial is a single arm phase I study utilizing cohort-of-3 design to determine the recommended dose level of the combination of nal-IRI and 5FU with rucaparib (MFR) in patients with metastatic disease from pancreatic cancer (up to 2 lines of prior therapy), colorectal cancer (up to 3 lines of prior therapy), gastroesophageal cancer (up to 1 line of prior therapy) and biliary tract cancer (BTC; up to 1 line of prior therapy allowed).

Decisions regarding the reopening of the cohort to new patients, the expansion of any other cohort, and the need to dose reduce patients already receiving treatment at the dose level in question will be made by the Study Chair(s).

All patients meeting the eligibility criteria who have signed a consent form and have received one dose of MFR will be included in the analysis. Patients removed from the study during cycle 1 for reasons other than toxicity maybe replaced.

16.21 MTD Definition: Maximum Tolerated Dose (MTD) is defined as the dose level below the lowest dose that induces dose-limiting toxicity (DLT) in at least one-third of patients (at least 2 of a maximum of 6 new patients). A total of 6 patients treated at the MTD will be sufficient to identify common toxicities at the MTD. For instance, those toxicities with an incidence of at least 25% will be observed with a probability of at least 82% (1-(1-0.25)6). section 7.42 for DLT definitions.

16.22 MTD Determination

16.221 The first cohort of three patients will be treated at the starting dose level (DL1).

16.222 Three patients will be treated at a given dose level and observed for at least 4weeks (Cycle 1) from start of treatment to assess toxicity.

16.223 If DLT is not seen in any of the 3 patients, 3 new patients will be accrued and treated at the next higher dose level. If DLT is seen in 2 or 3 of 3 patients treated at a given dose level, then the next 3 patients will be treated at the next lower dose level, if only 3 patients were enrolled and treated at this lower dose level.

16.224 If DLT is seen in 1 of 3 patients treated at a given dose level, up to 3 additional patients will be enrolled and treated at the same dose level. If DLT is seen in at least one of these additional three patients (≥2 of 6), the MTD will have been exceeded, and further accrual will cease to this cohort (see 16.223 for further details). If dose-limiting toxicity (DLT) is not seen in any of the three additional patients, 3 new patients will be accrued and treated at the next higher dose level.

16.225 After enrolling 6 patients on a specific dose level, if DLT is observed in at least 2 of 6 patients, then the MTD will have been exceeded and defined as the previous dose unless only 3 patients were treated at the lower dose level. In that case, 3 additional patients will be treated at this lower dose level such that a total of 6 patients are treated at the MTD to more fully assess the toxicities associated with the MTD.

16.226 Dose de-escalation: If dose-limiting toxicity meets the stopping boundaries set by the above dose escalation algorithm at dose level 1 (for example, more than 1 out of 3 patients or more than 1 out of 6 patients), the next cohort of three patients will be entered at a dose level of -1. Further dose re-escalation will depend on the toxicity profile observed at dose level -1, and re-evaluation of the regimen by the study team may be done.

16.227 If a patient fails to complete the initial course of therapy (See Section 13.4) and did not have a DLT while on study, the patient will be regarded as uninformative in regard to the primary study goal and an additional patient will be treated at the current dose level; however, all toxicity information will be utilized in the analysis.

16.228 DL2-A (formerly known as DL1-A) was added as an intermediate dose level between DL 1 and DL2-B (formerly known as DL2) (Amendment 3). Following the approval of Amendment 3, enrollment will re-open to DL2-A. If DLTs are seen in less than 2 out of 6 patients treated at DL2-A then DL2-A will be considered the MTD. If DLTs are observed in at

least 2 patients treated at DL2-A then enrollment will resume at the next lowest DL until MTD is met.

16.23 Analysis plans: All the relevant results pertaining to toxicity, MTD, laboratory correlates will be examined in an exploratory and hypothesis-generating fashion.

16.231 Adverse events profile: The number and severity of all adverse events (overall, by dose-level, and by tumor group) will be tabulated and summarized in this patient population. The grade 3+ adverse events will also be described and summarized in a similar fashion. This will provide an indication of the level of tolerance for this treatment combination in this patient group

16.232 Toxicity Profile: The term toxicity is defined as adverse events that are classified as either possibly, probably, or definitely related to study treatment. Non-hematologic toxicities will be evaluated via the ordinal CTC standard toxicity grading. Hematologic toxicity measures of thrombocytopenia, neutropenia, and leukopenia will be assessed using continuous variables as the outcome measures (primarily nadir) as well as categorization via CTC standard toxicity grading. Overall toxicity incidence as well as toxicity profiles by dose level, patient and tumor site will be explored and summarized.

16.233 Response: Objective responses, as defined per RECIST 1.1, will be summarized by simple descriptive summary statistics delineating complete and partial responses as well as stable and progressive disease.

16.3 Phase Ib portion

The phase Ib portion of this trial consists of an expansion cohort of patients with metastatic disease from pancreatic adenocarcinoma who have received no more than 1 line of prior therapy in the metastatic setting. Patients will be separated into two cohorts based on their HRD status (section 5).

16.31 Analysis plans: All the relevant results pertaining to toxicity, MTD, laboratory correlates will be examined in an exploratory and hypothesis-generating fashion.

16.32 Disease control (DC) is defined as achieving CR, PR, or maintaining SD (per RECIST v1.1) as the tumor assessment result for at least 24 weeks. Disease Control Rate will be estimated by the number of evaluable patients achieving disease control divided by the total number of evaluable patients. Evaluable patients for the primary endpoint are defined as who have signed the consent form, are eligible, received any protocol treatment. Point estimates will be generated for disease control rates within each cohort along with 95% binomial confidence intervals. (Clopper, C.J and E.S. Pearson, *The Use of Confidence or Fiducial Limits Illustrated in the Case of Binomial.* Biometricka, 1934.**26**(4).: p. 404-413).

16.4 Phase II portion

The phase II portion will include a safety run-in to assess whether there is unacceptable toxicity in the first 6 patients accrued (BRCA1/2 and PALB2, and other HRD together) without halting the trial. The phase II portion will use a 2-stage Simon design and an interim analysis with relaxed probability of stopping for futility to assess the efficacy of MFR in patients with untreated pancreatic cancer with BRCA1/2 and PALB2. Patients with untreated pancreatic cancer with HRD other than BRCA1/2 and PALB2 will be accrued for exploratory analysis. The recommended dose level determined in the phase I portion of the trial will be used as the starting dose for Phase II.

16.41 Primary Endpoint

The primary endpoint for the phase II portion of the trial will be the best response rate at 32 weeks, which is defined as the number of patients who had response ≤32 weeks of registration divided by the number of evaluable patients. Response is defined as either complete response (CR) or partial response (PR), per RECIST 1.1.

16.42 Decision Rule

The largest success proportion (proportion of evaluable patients with CR/PR) where the proposed treatment regimen would be considered ineffective in this population is 23% (Von Hoff et. al., 2013[29] and Conroy et. al., 2011[30]), and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 45%.

Evaluable patients for the primary endpoint are defined as patients with HRD encompassing BRCA1, BRCA2, and PALB2 deleterious mutations (germline and somatic), consented, eligible, and received any protocol treatment. The following two-stage Simon's design and an interim analysis with relaxed probability of stopping for futility uses a minimum of 11 and a maximum of 21 patients to test the null hypothesis that the true success proportion in a given patient population is at most 23%. The current design assumes a one-sided alpha level 0.1 and 80% power. The above power calculation was done using Simon's like design with relaxed futility stopping (Ivanova A.) and assumes a one-sided alpha level 0.1, 80% power, and lower and upper bound for the probability of stable disease (SD) to be 0.1 and 0.2, respectively.

16.421 STAGE 1

Among first 11 patients enrolled into study, if 2 or fewer patients with CR/PR/SD are observed ≤16 weeks after registration, we will consider this regimen ineffective in this patient population and terminate the study. Otherwise, if at least 3 patients with CR/PR/SD are observed ≤32 weeks after registration, we will proceed to Stage 2 and continue accrual.

16.422 STAGE 2

The regimen will be considered ineffective if either enrollment is

discontinued after stage 1 or if 7 or fewer patients with CR/PR are observed in the first 21 evaluable patients. This regimen will be considered promising if 8 or more patients with CR/PR are observed in the first 21 evaluable patients.

16.423 Over Accrual

If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision-making process. Analyses involving over accrued patients are discussed in Section 16.5.

16.424 Operating characteristics

The probability of declaring that this regimen warrants further studies (i.e. statistical power) under various success proportions and the probability of stopping accrual after the first stage can be tabulated as a function of the true success proportion as shown in the following table (based on simulation study with 10,000 replicates).

If the true success proportion is …	**0.23**	**0.30**	**0.35**	**0.40**	**0.45**
Then the probability of declaring that the regimen warrants further study is…	8.34%	27.60%	45.43%	65.77%	79.69%
And the probability of stopping at stage 1 is	12.12%	9.67%	5.44%	1.20%	0.58%

16.43 Phase II Analysis Plan

16.431 Primary Endpoint Analysis - Estimation: The proportion of best response ≤32 weeks will be estimated by the number of evaluable patients who reach CR/PR, per RECIST 1.1, ≤32 weeks since registration divided by the total number of evaluable patients. Confidence intervals for the proportion will be calculated according to the approach of Duffy and Santner (1987).

16.432 Secondary Endpoint Analyses

16.432a Overall survival: Survival time is defined as the time from registration to death due to any cause. Patients who fail to return for evaluation after beginning therapy will be censored for survival on the last day of therapy or date last known to be alive, whichever is later The distribution of survival time will be estimated using the method of Kaplan-Meier (1958).

16.432b Progression-free survival: Progression-free survival is defined as the time from registration to the earliest date documentation of disease progression or death due to any cause. Patients who fail to return for evaluation after beginning therapy will be censored for progression on the last day of therapy or date last known to be alive, whichever is later. The distribution of progression-free

survival will be estimated using the method of Kaplan-Meier (1958).

16.432c Toxicity: As per NCI CTCAE version 4.03, the term toxicity is defined as adverse events that are classified as either “possibly,” “probably,” or “definitely related” to study treatment. The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns within patient groups. In addition, we will review all adverse event data that is graded as 3, 4, or 5 and classified as either “unrelated” or “unlikely to be related” to study treatment in the event of an actual relationship developing. Adverse events and toxicities will be evaluated using all patients who have received any study treatment as well as summarizing those who have been included in the efficacy analyses. The overall adverse event rates for grade 3 or higher adverse events will be compared using Chi-Square or Fisher’s Exact tests between the two treatment groups.

16.5 Data & Safety Monitoring

16.51 This study will be monitored by the Mayo Data Safety Monitoring Board (DSMB) every 6 months. Toxicity, efficacy and administrative information for this trial will be reviewed by the study team routinely.

16.52 Adverse Event Stopping Rules

The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study reopening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

16.521 Phase I/Ib Adverse Event Stopping Rule

During the first 2 cycles, 4 of the initial 10 treated patients or 40% or more of all patients (i.e., when accrual is greater than 10 patients) have experienced a Grade 4+ adverse event at least possibly related to study treatment, per NCI Common Terminology Criteria for Adverse Events v.5.0, excluding the following:

- Grade 4 neutrophil count decreased lasting ≤7 days
- Grade 4 white blood cell decreased lasting ≤7 days
- Grade 4 platelet count decreased lasting ≤7 days
- Grade 4 diarrhea responding to optimal support

16.522 Phase II Adverse Event Stopping Rules

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as “possible”, “probable”, or “definite”) that satisfy either of the following:

- If 1 or more patients out of the first 6 patients (either HRD encompassing BRCA1, BRCA2, PALB2 or other HRD) experience grade 5 events (death) deemed at least possible (possible, probably, or definite) related to MFR, the accrual to the study will be suspended to allow for investigation. After consideration by the study team (study chair, statistician) and consultation with the sponsor, a decision will be made as to whether accrual can be resumed.

- If 6 or more patients among the first 20 patients (either HRD encompassing BRCA1, BRCA2, PALB2 or other HRD) enrolled

or 30% of the patients thereafter develop a grade4+ non-hematologic toxicities at least possible (possibly, probably or definitely) related to treatment, enrollment will be suspended so that the adverse event data can be examined and a trial recommendation will be formulated an d presented to Mayo DSMB.

- We note that we will review grade 4 and 5 adverse events deemed “unrelated” or “unlikely to be related”, to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

17.0 Pathology Considerations/Tissue Biospecimens

17.1 Tissue Biospecimen Submission

17.11 Summary Table of Tissue Biospecimens for This Protocol

Type of tissue biospecimen to submit	Mandatory or optional	When to submit	Reason for submission (background/ methodology section)	Where to find specific details for biospecimen submission
Formalin-fixed paraffin-embedded (FFPE) tissue blocks with corresponding H&E (OR total of 10 unstained (5) micron slides with corresponding H&E)	Mandatory	≤**60** days after registration	Correlative studies (Section 17.3)	Section 17.2

If an institution is not able to provide the tissue, it does not cause the patient to be ineligible; however the collection of these tissues is **strongly recommended.*

17.2 Paraffin Embedded Tissue Blocks/Slides (mandatory for research tissue)

17.21 Submit one formalin fixed paraffin-embedded (FFPE) tumor tissue block from the original and/or recurrent surgery with largest amount of invasive tumor (at least 1 cm of tumor for cases of surgical resection).

17.22 The FFPE tissue block is preferred; however, if an institution is unable to provide a tissue block, cut 10 five-micron unstained slides with corresponding H&E and mount on charged glass slides. Label the slides with the ACCRU patient ID number, accession number, and order of sections (i.e., 1-10). H&E stain the first cut slide (i.e., slide labeled 1). For samples containing less than 7 square millimeters of tumor tissue, multiple sections should be mounted onto each slide to ensure that the appropriate amount of tumor tissue is available. Ideally, each slide must have a minimum of 75% tumor tissue on the slide to be deemed adequate for study. Do not bake or place cover slips on the slides. Please do NOT use sticky labels on slides.

17.23 The following materials below are mandatory (unless indicated otherwise) and required for shipment:

- Paraffin embedded tissue blocks with corresponding H&E slide (OR 10 unstained slides with corresponding H&E(s), per instructions in Section 17.22).
- Specimen Submission: Tissue Baseline form
- Surgical Pathology Report
- Operative Report *(optional)*

Note: Please make sure each slide is labeled with the specimen surgical pathology number, block number and order of sections cut either via your institution's standard method for labeling or using a permanent marker. **Labeling with sticky labels is not acceptable.**

17.24 The block/slides must be appropriately packed to prevent damage (e.g., slides should be placed in appropriate slide container) and placed in an individual plastic bag. Label the bag with the protocol number, ACCRU patient ID number, and patient initials. During warm weather months, paraffin blocks should be shipped using a refrigerant pack to avoid heat that may melt paraffin and damage blocks.

17.25 Tissue specimens must be shipped ≤**60** days after registration.

17.26 Verify that the appropriate sections of the Specimen Submission: Tissue Baseline form are completed and filled in correctly. Enter information from the Specimen Submission: Tissue Baseline form into the remote data entry system on the same day the specimen is submitted (see CRF Packet).

17.27 Ship all block/slide tissue specimens and accompanying materials to the ACCRU Research Base:

17.28 When an appropriate request is submitted, the ACCRU Operations Office will forward the block/slides to the ACCRU Research Base Pathology Research Core, Mayo Clinic Rochester for processing.

17.29 Frozen Tumor tissue: (None)

17.3 Study Methodology and Storage Information

17.31 Submitted tissue samples will be analyzed as follows:

Tissue from biopsies will be processed at a Clovis 3rd party diagnostic collaborator to obtain comprehensive genomic profiling (CGP) using hybridization capture of all coding exons of >300 cancer-related genes and 31 genes commonly rearranged in cancer. To this end ≥50ng of DNA will be extracted from FFPE specimens. All tumors will be sequenced to high (average

>570X), uniform coverage. Genomic alterations (base substitutions, small indels, rearrangements and copy number alterations) will be determined in tissue from tumor biopsies.

We will test whether HRD in tumor samples is associated with clinical outcome including the following (among others): response to therapy, progression-free survival, and overall survival.

17.32 At the completion of the study, any unused/remaining material will be stored in the ACCRU Central Operations Office (Attn.: Pathology Coordinator) for future research according to the patient consent permission (see Section 6.15). Potential future research may include immunohistochemistry (IHC) analyses to analyze predictive biomarkers, changes in expression pattern with therapy, and correlation with response and/or adverse events. When a protocol is developed, it will be presented for IRB review and approval.

17.33 Banking of tumor tissue, according to the patient consent permission (see Section 6.32), is for future research. As protocols are developed, they will be presented for ACCRU and IRB review and approval. (This collection is part of a general strategy of investigation for ACCRU studies).

17.34 The institutional pathologist will be notified by the Pathology Coordinator if the block may be depleted.

17.35 Blocks requested to accommodate individual patient management will be returned promptly upon request.

17.4 Return of Genetic Testing Research Results

Because the results generated by the genetic testing included in this section are not currently anticipated to have clinical relevance to the patient or their family members, the genetic results will not be disclosed to the patients or their physicians.

If, at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

18.0 Records and Data Collection Procedures

The RAVE system will be used to collect data. Access the RAVE system through the iMedidata portal at [redacted] All data must be entered by Remote Date Entry (RDE) and completed by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document. Please refer to the ACCRU website for instructions [redacted]

18.1 Submission Timetables

Pre-Registration Material(s) – Phase II Only

Case Report Form (CRF)	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)
Screening (Phase II only)	Complete only if patient is NOT registered after he/she is pre-registered

Initial Material(s)

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)
Institutional Contacts	≤2 weeks after registration
Phase of Study	
On-Study	
On-Study: Pancreatic Cancer[2]	
On-Study: Gastroesophageal Cancer[2]	
On-Study: Colorectal Cancer[2]	
On-Study: Biliary Tract Cancer[2]	
On-Study: Prior Surgery[2]	
On-Study: Prior Radiation[2]	
On-Study: Prior Neoadjuvant, Adjuvant or Metastatic Therapies[2]	
Laboratory Tests & Results: Baseline	
Adverse Events: Baseline	
RECIST Measurements: Baseline	
Supporting Documentation: Baseline[1]	
Specimen Submission: Blood Baseline (see Section 14.0)	
Specimen Submission: Tissue Baseline (see Section 17.0)	
Patient Status: Baseline	
OP and Path Reports (see Section 17.0)[1]	
Off Treatment[2]	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy
ACCRU Deviation Form[2]	Submit only if applicable during ***all*** **phases** of the study (initial, active and observation)

1. Upload Op, Path Reports, and tumor molecular profiling report (if available) via the Supporting Documentation: Baseline form. This is in addition to the pathology material requirements for tissue submission (Section 17.0).
2. Submit only if applicable.

Test Schedule Material(s)

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)		
	At each evaluation during treatment	**At end of treatment**	**Observation**
Treatment (Intervention)	X	X	
Treatment (Intervention): Dose Modifications, Omissions and Delays[2]	X		
Adverse Events: Solicited	X	X	
Adverse Events: Other[2]	X	X	
Dose Limiting Toxicities (Phase I only)[2]	X		
RECIST Measurements[1]	X	X	X
Supporting Documentation[1]	X	X	X
Day 1 Laboratory Tests and Results[3]	X		
Day 15 Laboratory Tests and Results[4]	X		
Specimen Submission: Blood	X (see Section 14.0)		
Patient Status: Treatment (Intervention)	X	X	
Notice of New Primary[2]	X	X	X
Consent Withdrawal (choose appropriate form)[3] • Consent Withdrawal: Specimen Only • Consent Withdrawal: Clinical Follow-Up Only • Consent Withdrawal: All Follow-Up	X	X	X
Off Treatment		X	
Lost to Follow-up[2]	X	X	X
ACCRU Deviation Form[2]	X	X	X

1. Prior to 3rd and subsequent odd cycles (until PD). Upload a copy of documentation of progression in RAVE on the Supporting Documentation Form.
2. Submit only if applicable.
3. Day 1 of each cycle, beginning with Cycle 1 (until PD).
4. Day 15 of each cycle, beginning with Cycle 1 (until PD).

Follow-up Material(s)

CRF	Event Monitoring Phase[1]				
	q. 6 months until PD[2]	At PD[2]	After PD q. 6 mos.	Death	At Each Event Occurrence
Patient Status: Survival and Disease Status Follow-Up/Event Monitoring	X[2]	X[2]	X	X	
Adverse Events: Late[3]					X
Notice of New Primary[3]					X
Consent Withdrawal (choose appropriate form)[3] • Consent Withdrawal: Specimen Only • Consent Withdrawal: Clinical Follow-Up Only • Consent Withdrawal: All Follow-Up					X
Lost to Follow-Up[3]					X
ACCRU Deviation Form[3]	X[3]	X[3]	X[3]	X[3]	

1. If a patient is still alive 3 years after registration, no further follow-up is required.
2. Upload a copy of documentation of progression in RAVE on the Supporting Documentation Form.
3. Submit only if applicable.

19.0 Budget

19.1 Each site should review the test schedule (Section 4.0), taking into account local and regional coverage policies, to determine which items are standard of care and which are research at their site. Refer to the payment synopsis for funding provided per accrual for covering study costs, as well as any additional invoiceables that may be allowed.

19.2 Tests to be research funded:

19.21 Mandatory archival tissue collection

19.22 cfDNA

19.3 Other budget concerns:

19.31 Clovis will provide rucaparib free of charge to patients while they are participating in this study.

19.32 Ipsen will provide irinotecan liposome free of charge to patients while they are participating in this study.

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ACCRU Informed Consent Template for Cancer Treatment Trials (English Language)

***NOTES FOR LOCAL INVESTIGATORS:** **[NOTE: Retain this section and asterisk item below for ACCRU model consents]**

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant.
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: The NCI web site has information explaining clinical trials. The web page is entitled: "Taking Part in Cancer Treatment Research Studies." A free PDF may be downloaded from the NCI web site: [redacted]
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*These notes for {authors and} investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

ACCRU-GI-1603, Phase I Study of Irinotecan Liposome (nal-IRI), Fluorouracil, Leucovorin and Rucaparib in the Treatment of Select Gastrointestinal Metastatic Malignancies Followed by a Phase Ib of First and Second Line Treatment of both Unselected and Selected (for BRCA ½ and PALB2 Mutations) Patients with Metastatic Adenocarcinoma of the Pancreas then Followed by a Phase II Study of First Line Treatment of Selected Patients with Metastatic Adenocarcinoma of the Pancreas with Genomic Markers (Signature) of Homologous Recombination Deficiency (HRD)

This is an important form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you need to sign this form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this research study because you have cancer of the pancreas, colorectal, gastroesophageal, or biliary tract.

NOTE: If you have advanced colorectal cancer and have not received standard treatment with FOLFOX or FOLFIRI prior to entering the study, please note that FOLFOX and FOLFIRI have proved to provide more benefit than receiving 5FU alone.

Why is this research study being done?

This study is being done in three parts: Phase I, Phase 1b and Phase II. You are being asked to take part in the Phase I portion of the study because you have pancreatic, colorectal, gastroesophageal or biliary tract cancer. The purpose of this Phase I research study is to find the highest dose of nal-IRI and rucaparib that can safely be given in combination with 5-FU and leucovorin to patients who have colorectal, pancreatic, gastroesophageal or biliary tract cancer without causing bad side effects.

How many people will take part in the research study?

About 9 people will take part in the Phase I study.

At the beginning of the study, 3 patients will be treated with a low dose of the drugs. If this dose does not cause bad side effects, it will slowly be made higher as new patients take part in the study. A total of 9 patients are the most that will be able to enter the Phase I part of this study.

What will happen if I take part in this research study?

Before you begin the study …

Within 1 to 3 weeks before study registration – You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Medical history and physical exam; your doctor will also ask how well you perform activities in your daily life.
- A check to see if any of the side effects that may be caused by the study drugs are already present.
- Routine blood tests – equal to about the amount in 2 tablespoons will be taken from a vein in your arm.
- Research blood tests – when you have the routine blood test done, we will also take between 2 teaspoons and 4 tablespoons of additional blood for research and banking for future research. Giving this extra blood is required if you participate in this study.
- CT scan or MRI to measure your tumor
- Electrocardiogram (ECG) to look at your heart and heart valves to see how well they are working.
- A pregnancy test done by taking a blood sample from a vein in your arm within 21 days of being registered on the study, and again within 7 days of being registered – if you are a woman of childbearing potential. The pregnancy test results must be negative in order for you to continue on the study.
- Collection of a tumor sample from your previous surgery or biopsy for research purposes; *no additional tumor tissue will be taken from you during this study*.
- This sample will be used to look for genes in your tumor that will predict the effectiveness of the study drugs in future patients with pancreatic, colorectal, gastroesophageal or biliary tract cancer.

During the study …

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

- Medical history and physical exam; your doctor will also ask how well you perform activities in your daily life and review your Patient Medication Diary..
- A check to see if any of the side effects that may be caused by the study drugs are already present.
- Routine blood tests – equal to about the amount in 2 tablespoons will be taken from a vein in your arm.
- CT scan or MRI to measure your tumor
- A pregnancy test done by taking a blood sample from a vein in your arm every 28 days before each treatment (if you are a woman of childbearing potential). The pregnancy test results must be negative in order for you to continue on the study.

You will need the following tests and procedures that are part of regular cancer care. They are being done more often because you are in this study.

- A pregnancy test done by taking a blood sample from a vein in your arm every 28 days before each treatment (if you are a woman of childbearing potential). The pregnancy test results must be negative in order for you to continue on the study.

You will need these tests and procedures that are either being tested in this study or being done to see how the study is affecting your body.

- Research blood tests – when you have the routine blood test done, we will also take between 2 teaspoons and 4 tablespoons of additional blood for research and banking for future research. Giving this extra blood is required if you participate in this study.

This research will explore possible genetic or inherited reasons for how patients respond to medications. Your blood and tissue samples contain genes, which are made up of DNA and proteins that serve as the "instruction book" for the cells that make up our bodies. Your samples will help us study how genes interact with other factors to influence the development and treatment of diseases. Because the genetic tests in this study are not used for regular medical care, you will not be told the results of the test(s), and the test results will not be put in your medical record.

There is more information about these research tests at the end of this form.

Once it is determined that you are eligible for the study and agree to take part, you will begin treatment. Treatment takes place over several 28-day periods; each 28-day period is called a cycle.

For the first 28-day cycle, treatment includes the following…

On days 1 and 15 of every 28-day cycle, about 30-60 minutes before receiving the study drugs noted below, you will be given medications (dexamethasone (or similar) and ondansetron (or similar)) through a needle placed in your arm (also referred to as an IV (intravenous)) to make side effects less serious and less uncomfortable. These medications are sometimes known as pretreatment medications.

On days 1 and 15, after receiving the pretreatment medications, you will receive nal-IRI (50mg), 5-FU (2400mg) and leucovorin (400mg). These drugs will be given to you through the IV.

In addition to the IV study drugs, you will also take the study drug, rucaparib (400mg), in pill form, by mouth, two times every day beginning on day 4 of the first week, and continue through day 13. You will **not** take this drug on days 14-17. On day 18 you will start taking rucaparib again, and continue taking through day 27, then ***stop*** taking this drug again on day 28 (see study calendar below).

For the second 28-day cycle, the dose of nal-IRI will be increased to 70 mg, and treatment includes the following…

On days 1 and 15 of every 28-day cycle, you will receive nal-IRI (70mg), 5-FU (2400mg) and leucovorin (400mg). These drugs will be given to you through a needle placed in your arm (also

referred to as an IV (intravenous)). You will be given some medications 30-60 minutes before you receive the IV study drugs to lessen the side effects of the chemotherapy.

Before receiving the above-mentioned study drugs, you will be given medications (dexamethasone (or similar) and ondansetron (or similar)) through the IV to make side effects less serious and less uncomfortable.

In addition to the IV study drugs, you will also take the study drug, rucaparib (400mg), in pill form, by mouth, two times every day beginning on day 4 of the first week, and continue through day 13. You will **not** take this drug on days 14-17. On day 18 you will start taking rucaparib again, and continue taking through day 27, then ***stop*** taking this drug again on day 28 (see study calendar below).

For the third 28-day cycle, the dose of rucaparib will be increased to 600 mg, and treatment includes the following…

On days 1 and 15 of every 28-day cycle, you will receive nal-IRI (70mg), 5-FU (2400mg) and leucovorin (400mg). These drugs will be given to you through a needle placed in your arm (also referred to as an IV (intravenous)). You will be given some medications 30-60 minutes before you receive the IV study drugs to lessen the side effects of the chemotherapy.

Before receiving the above-mentioned study drugs, you will be given medications (dexamethasone (or similar) and ondansetron (or similar)) through the IV to make side effects less serious and less uncomfortable.

In addition to the IV study drugs, you will also take the study drug, rucaparib (600mg), in pill form, by mouth, two times every day beginning on day 4 of the first week, and continue through day 13. You will **not** take this drug on days 14-17. On day 18 you will start taking rucaparib again, and continue taking through day 27, then ***stop*** taking this drug again on day 28 (see study calendar below).

If, you have side effects that get too bad at any time during these cycles, the doses listed above will be decreased until the side effects get better. Treatment may discontinue completely if side effects are too bad or your cancer gets worse.

Medication Diary

You will be asked to keep a daily record (Patient Medication Diary) of when you take the study medication, rucabarib, and every day write down the day and time you take the medication. If you notice any side effects, you can include this information in the Comments section of the diary.

Study Calendar

You will receive nanoliposomal irinotecan (nal-IRI) + leucovorin + fluorouracil (5-FU) + rucaparib as outlined in the calendar below over a 28-day period. This 28-day period of time is called a cycle. The cycle will be repeated 3 times. Each cycle is numbered in order. The chart below shows what will happen to you during Cycle 1 and future treatment cycles as explained previously. The left-hand column shows the day in the cycle and the right-hand column tells you what to do on that day.

Day	What you do
Up to 21 days before starting treatment	• Medical history and physical exam; your doctor will also ask how well you perform activities in your daily life. • A check to see if any of the side effects that may be caused by the study drugs are already present. • Routine blood tests • CT scan or MRI • Electrocardiogram (ECG) • Mandatory submission of a tumor sample from your previous surgery or biopsy
Up to 7 days before starting treatment	• Pregnancy test (only if you are a woman of childbearing potential) • Mandatory research blood tests
Day 1 of each cycle	• **Prior to dosing -** Pregnancy test (only if you are a woman of childbearing potential) • Medical history and physical exam; your doctor will also ask how well you perform activities in your daily life. • A check to see if you are having any side effects from study drugs. • Review Patient Medication Diary • Routine blood tests • ECG • Receive pretreatment medications through an IV. • Receive nal-IRI, 5-FU and leucovorin through an IV.
Days 4-13	• Take rucaparib, in pill form, by mouth, two times every day beginning on day 4 of the first week, and continue through day 13.
Days 14-17	• **Stop taking rucaparib.**
Day 15	• Medical history and physical exam; your doctor will also ask how well you perform activities in your daily life. • A check to see if you are having any side effects from study drugs. • Routine blood tests • Receive pretreatment medications through an IV. Receive nal-IRI (50mg), 5-FU (2400mg) and leucovorin (200mg) through an IV.
Days 18-27	• Take rucaparib, in pill form, by mouth, two times every day beginning on day 18 and continue through day 27.
Days 22 – 28	• On **one** of these days (Day 22 – 28) before every odd-numbered cycle (i.e., before cycle 3 or cycle 5, etc.), do the following: ☐ CT scan or MRI to measure your tumor ☐ Routine blood tests

Study Calendar – Continued

Day	What you do
Day 28	• **Stop taking rucaparib.**
Cycle 2	• Repeat Days 1-28 as above
Cycle 3	• Repeat Days 1-28 as above
End of Treatment (after you complete the full treatment, or if your disease progresses or you stop the treatment for any reason)	• Medical history and physical exam; your doctor will also ask how well you perform activities in your daily life. • A check to see if you are having any side effects from study drugs. • Review Patient Medication Diary • Routine blood tests • Mandatory research blood tests • CT scan or MRI

When you are finished taking the study drugs…

Within about 30 days after your last treatment, the following tests and procedures will be done:

- Medical history and physical exam; your doctor will also ask how well you perform activities in your daily life and review your Patient Medication Diary.
- A check to see if you are having any side effects from study drugs.
- Routine blood tests – equal to about the amount in 2 tablespoons will be taken from a vein in your arm.
- Research blood tests – when you have the routine blood test done, we will also take between 2 teaspoons and 4 tablespoons of additional blood for research and banking for future research.

How long will you be in the research study?

For the Phase I part of this study, you will be asked to take nal-IRI, 5-FU, leucovorin and rucaparib for about 3 months or until your disease gets worse, or you have side effects that you are unable to tolerate.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

After you are finished taking the study drugs, the study doctor will ask you to visit the office for periodic follow-up exams for about 3 years.

Can I stop being in the research study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the nal-IRI, 5-FU, leucovorin and rucaparib can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

What side effects or risks can I expect from being in the research study?

If you have not previously received standard treatments for your cancer and decide to take part in this research study, you are declining standard treatment and the potential benefits of these standard treatments.

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the combination of nal-IRI + 5-FU + leucovorin + rucaparib. In some cases, side effects can be serious, long lasting, or may never go away. **There also is a risk of death.**

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to <u>rucaparib</u>:

Oral rucaparib is an experimental drug that may have side effects that cannot be predicted at this time.

Rare or unknown side effects could possibly occur, **including life-threatening reactions**.

Common Side Effects of Rucaparib

The following is a list of the most commonly-reported side effects reported by patients who have received rucaparib, whether taking rucaparib alone or at the same time they were receiving chemotherapy:

- Low blood counts (especially of the white blood cells, but sometimes of red blood cells and platelets). Sometimes fever occurs with the low blood counts
    - A low white blood cell count puts you at higher risk for infection. If you have a temperature higher than 100.4°F (38.0°C) at any time during the study, you must tell the study doctor immediately.
    - A low red blood cell count may make you feel tired or dizzy. If you feel dizzy while taking rucaparib, you should avoid potentially hazardous tasks such as driving or operating machinery.
    - A low platelet count affects the ability of your blood to clot and could lead to bleeding events
- Stomach-related effects such as nausea, vomiting, diarrhea, loss of appetite, heartburn, and constipation
- Feeling tired (Fatigue)
- Headache
- Abdominal pain
- Elevated liver enzymes
- Dizziness
- Bad taste in mouth (or altered sense of taste)

- Increased sensitivity to sunlight- please use appropriate sun protection
- Increased serum creatinine
- Increase in cholesterol
- Rash
- Pruritis (itchy skin)
- Dyspnea (difficult or labored breathing)
- Due to the risk of permanent damage or death to a developing embryo/fetus, both women of childbearing potential and men and their opposite sex partners of reproductive potential should use contraception during dosing and for 6 months after completing treatment with rucaparib.

Rare Side Effects (less than 1% of patients)

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) have been reported in a very small number of patients treated with rucaparib. MDS is a pre-cancerous condition where the bone marrow is not as good at producing blood cells (red and/or white blood cells and/or platelets) as it was before. People with MDS need transfusions (red blood cells and/or platelets) and/or other treatments. In some cases MDS will progress to AML, which is a cancer of the bone marrow where more abnormal and immature white blood cells (also called blasts) are made than normal white blood cells. People with AML need treatment with chemotherapy and/or a transplant. Patients may develop AML without first being diagnosed with MDS. MDS/AML can be fatal and led to death in 2 patients on rucaparib (0.5%).

Events of MDS and AML have also been reported with PARP inhibitors similar to rucaparib. At this time it is not known whether PARP inhibitors cause MDS or AML or if these developed as a result of previous chemotherapy these patients received. Your Study Doctor will closely monitor your blood cell levels during treatment. If he/she has any concerns about your blood counts you may be asked to have a biopsy of your bone marrow.

If you develop low blood counts, or if you have any other significant side effects, you may need to stop taking rucaparib until you recover from these side effects. The study doctor may also decide to lower your dose of rucaparib if you experience certain side effects.

Allergic Reactions

As with any drug, it is possible that you could have allergic reactions to rucaparib, such as itching, skin rash, facial swelling, and/or a severe or sudden drop in blood pressure. A sudden drop in blood pressure could lead to shock with loss of consciousness and/or possible seizures, including the possibility of death. If you have any of the above symptoms, seek medical attention right away.

Risks and side effects related to <u>nal-IRI + 5-FU + leucovorin</u> include those which are:

<u>Likely</u> (more than 10%)

In a clinical trial evaluating the effectiveness of nal-IRI in the treatment of metastatic pancreatic cancer, 117 patients received nal-IRI in combination with 5-FU and leucovorin. In this group of patients, the most

common side effects that happened in at least 12 of the 117 patients (more than 10% of those patients) included the following:

- Diarrhea
- Vomiting
- Nausea
- Decreased appetite
- Fatigue (tiredness)
- Anemia (decreased red blood cells or hemoglobin, which may cause tiredness and lack of energy)
- Fever
- Neutropenia (decrease in a type of white blood cells called neutrophils, may increase the risks of infections)
- Abdominal pain
- Constipation
- Asthenia (lack of energy)
- Weight loss
- Leukopenia (decrease in white blood cells)
- Hair loss (alopecia)
- Stomatitis (inflammation of the lining of the mouth)
- Back pain
- Dizziness
- Hypokalemia (decrease in blood potassium levels)
- Peripheral edema (collection of fluid in the tissues of the body)
- Mucosal inflammation (lining of mouth, esophagus, stomach and intestines)
- Thrombocytopenia (a decrease in platelets (particles that help the blood to clot, may cause bruising or bleeding)

Less Likely (between 5% and 10% of patients)

The less commonly seen side effects that occurred in at least 6 of the 117 patients (more than 5% of those patients) were:

- Upper abdominal pain
- Dehydration
- Hypomagnesemia (decrease in blood magnesium levels)
- Hypoalbuminemia (decrease in a type of blood protein called albumin)

Rare (less than 5% of patients):

- Sepsis

The most common serious side effects of nal-IRI + 5FU + Leucovorin

- Diarrhea (occurring in 5.1% of patients)
- Vomiting (occurring in 7.7% of patients)
- Nausea (occurring in 3.4% of patients)

As with any medication, allergic reactions are a possibility.

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your

healthcare provider about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

Risks of CT scans and MRIs: This research study involves exposure to radiation from up to 6 CT scans per year. The CT scans that are to be performed as part of this study are considered standard of care and would be done regardless of your participation in this research study. This radiation may involve low risk of a later cancer; however, we believe that this risk is not clinically relevant. If you have any questions regarding the use of radiation or the risk involved, please consult the physician conducting this study.

Risks of Blood draws and intravenous (IV) infusions: Drawing of blood or insertion of an intravenous catheter to infuse a drug may cause local pain, swelling, bruising, bleeding, or (rarely) infection at the place where your blood is drawn. The decision to use a catheter (a thin tube) for blood collecting is made by the study staff. The study staff will explain the catheter to you if its use is necessary.

While you are taking part in this study, you are at risk for the above-mentioned side effects. You should talk to the researcher and/or your medical doctor about these side effects. There also may be other side effects that are not known. Side effects may range from mild to life-threatening.. Many side effects go away shortly after the drugs are stopped, but in some cases side effects can be serious, long lasting, or may never go away.

For more information about risks and side effects, ask your study doctor.

Electrocardiograms (ECG): This procedure requires you to lie still for a few minutes. The ECG records the rhythm and electrical activity of your heart. Small sticky patches called electrodes are placed on your arms, legs, and chest and connected by wires to an ECG recording machine to record the rhythm and electrical activity of your heart. The information is recorded and printed onto paper. The whole test takes about five minutes and is completely painless.

Are there benefits to taking part in the research study?

Taking part in this study may or may not make your health better. While doctors hope the combination of nal-IRI + 5-FU + leucovorin + rucaparib will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about using this drug combination as a treatment for cancer. This information could help future cancer patients.

What other choices do you have if you do not take part in this research study?

You do not have to be in this study to receive treatment for your cancer.

Your other choices may include:

- Getting treatment or care for your cancer without being in a study

- Taking part in another study
- Getting no treatment
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Academic and Community Cancer Research United (ACCRU)
- Government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- Institutional Review Boards
- Clovis Oncology and their 3rd party collaborator
- Ipsen Group

A description of this clinical trial will be available on [redacted] as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of study results. You can search this Web site at any time.

[Note to Informed Consent Authors: the above paragraph complies with the new FDA regulation found at 21 CFR 50.25(c) and must be included verbatim in all informed consent documents. The text in this paragraph cannot be revised.]

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

What are the costs of taking part in this research study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

You won't need to pay for tests and procedures which are done just for this research study. These tests and procedures are:

- Research blood tests
- Submission of mandatory tumor tissue samples for research purposes

The study agents, rucaparib and nal-IRI, will be provided free of charge while you are taking part in this study. However, if you should need to take the study agent much longer than usual, the stock of free study agent could run out. If the free supply runs out, your study doctor will discuss with you how to get more drug from the manufacturer. You may be asked to pay for it.

The study agents, 5-FU and leucovorin, can be bought with a prescription. You and/or your health plan will need to pay for all costs associated with this treatment. You and/or your health plan will also have to pay for other drugs or treatment that are given to help control side effects as well as the cost of tests or exams to evaluate possible side effects.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at [redacted] You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this research study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this research study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer questions about the research study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number]*.

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study.

About Using Biological Samples for Research

We would like to keep some of the blood and tissue that is left over for future research. If you agree, this blood and tissue will be kept and may be used in research to learn more about cancer and other diseases. Please read the online booklet called "Providing Your Tissue for Research: What You Need To Know," to learn more about tissue research: [redacted]

Your blood and tissue may be helpful for research whether you do or do not have cancer. The research that may be done with your blood and tissue is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your blood and tissue will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the blood and tissue for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your blood and tissue can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue. Then any blood and tissue that remains will no longer be used for research.

In the future, people who do research may need to know more about your health. While ACCRU may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes blood and tissue is used for genetic research (about diseases that are passed on in families). Even if your blood and tissue is used for this kind of research, the results will not be put in your health records.

Your blood and tissue will be used only for research and will not be sold. The research done with your blood and tissue may help to develop new products in the future.

Benefits

The benefits of research using blood and tissue include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at the IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. My blood sample(s) may be kept for use in future research to learn about, prevent, or treat cancer.

☐ Yes ☐ No Please initial here: _____ Date: _____

2. My blood sample(s) may be kept for use in future research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

☐ Yes ☐ No Please initial here: _____ Date: _____

3. My tissue sample(s) may be kept for use in future research to learn about, prevent, or treat cancer.

☐ Yes ☐ No Please initial here: _____ Date: _____

4. My tissue sample(s) may be kept for use in future research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

☐ Yes ☐ No Please initial here: _____ Date: _____

If you want your sample(s) destroyed at any time, write to the Secretary of the _____ Institutional Review Board _____.
ACCRU has the right to end storage of the sample(s) without telling you.

The sample(s) will be the property of ACCRU. Outside researchers may one day ask for a part of your sample(s) for studies now or future studies.

How do outside researchers get the sample?

Researchers from universities, hospitals, and other health organizations do research using blood and tissue. They may call ACCRU and ask for samples for their studies. ACCRU looks at the way that these studies will be done, and decides if any of the samples can be used. ACCRU sends the samples and some information about you to the researcher. ACCRU will not send your name, address, phone number, social security number, or any other identifying information to the researcher. If you allow your sample(s) to be given to outside researchers, it will be given to them with a code number. If researchers outside ACCRU use the sample(s) for future research, they will

decide if you will be contacted and, if so, they would have to contact the researchers at ACCRU. Then ACCRU will contact the clinic where you registered for this study, who will contact you.

Please read the following statements and mark your choice:

I permit ACCRU to give my sample(s) to outside researchers:

☐ Yes ☐ No Please initial here:_____ Date:_____

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

[redacted]

You may also visit the NCI Web site at [redacted]

- For NCI's clinical trials information, go to: [redacted]
- For NCI's general information about cancer, go to [redacted]

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all __ pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Printed Participant Name: _____

Participant Signature: _____

Date: _____

Printed name of person obtaining informed consent:

_____

Signature of person obtaining informed consent:

_____

Date _____

This model informed consent form has been reviewed by the ACCRU and is the official consent document for this study. Local IRB changes to this document are allowed. Sections "What are the risks of the research study" or "What other choices do I have if I don't take part in this research study?" should always be used in their entirety if possible. Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to these sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language and justification must be forwarded to the Academic and Community Cancer Research United (ACCRU) Operations Office for approval before a patient may be registered to this study.

Consent forms will have to be modified for each institution as it relates to where information may be obtained on the conduct of the study or research subject. This information should be specific for each institution.

ACCRU Informed Consent Template for Cancer Treatment Trials

(English Language)

***NOTES FOR LOCAL INVESTIGATORS:** **[NOTE: Retain this section and asterisk item below for ACCRU model consents]**

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant.
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: The NCI web site has information explaining clinical trials. The web page is entitled: "Taking Part in Cancer Treatment Research Studies." A free PDF may be downloaded from the NCI web site: [redacted]
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*These notes for {authors and} investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

ACCRU-GI-1603, Phase I/Ib Study of Irinotecan Liposome (nal-IRI), Fluorouracil and Rucaparib in the Treatment of Select Gastrointestinal Metastatic Malignancies Followed by a Phase Ib of First and Second Line Treatment of both Unselected and Selected Patients with Metastatic Adenocarcinoma of the Pancreas then Followed by a Phase II Study of First Line Treatment of Selected Patients with Metastatic Adenocarcinoma of the Pancreas with Genomic Markers (Signature) of Homologous Recombination Deficiency (HRD)

This is an important form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you need to sign this form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this research study because you have cancer of the pancreas or gastroesophageal cancer that has spread to other parts of your body (metastasized), and you have not received more than two other types of treatment before taking part in this study.

Why is this research study being done?

This study is being done in three parts: Phase I, Phase 1b and Phase II. You are being asked to take part in the Phase Ib portion of the study. The purpose of this Phase Ib research study is to learn more about the safety and side effects of the combination of nal-IRI + rucaparib + 5-FU in patients who have pancreatic cancer that has spread to other parts of the body (metastasized) , and who have received no more than one treatment before taking part in this study.

How many people will take part in the research study?

About 40 people will take part in this Phase Ib study: 28 patients with cancer of the pancreas with either unknown mutation (a change in the usual DNA sequence of a gene that prevents the gene from working normally) status or non-HRD and 12 patients with cancer of the pancreas with known HR deficiency.

What will happen if I take part in this research study?

Before you begin the study …

Within 1 to 3 weeks before study registration – You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Medical history and physical exam; your doctor will also ask how well you perform activities in your daily life.
- A check to see if any of the side effects that may be caused by the study drugs are already present.
- Routine blood tests – equal to about the amount in 2 tablespoons will be taken from a vein in your arm.
- Research blood tests – when you have the routine blood test done, we will also take between 2 teaspoons and 4 tablespoons of additional blood for research and banking for future research. Giving this extra blood is required if you participate in this study.
- CT scan or MRI to measure your tumor
- Electrocardiogram (ECG) to look at your heart and heart valves to see how well they are working.
- A pregnancy test done by taking a blood sample from a vein in your arm within 21 days of being registered on the study, and again within 7 days of being registered – if you are a woman of childbearing potential. The pregnancy test results must be negative in order for you to continue on the study.
- Collection of a tumor sample from your previous surgery or biopsy for research purposes; *no additional tumor tissue will be taken from you during this study*.
- This sample will be used to look for genes in your tumor that will predict the effectiveness of the study drugs in future patients with pancreatic or gastroesophageal cancer treated with the combination of nal-IRI + rucaparib + 5-FU.

During the study …

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

- Medical history and physical exam; your doctor will also ask how well you perform activities in your daily life and review your Patient Medication Diary.
- A check to see if any of the side effects that may be caused by the study drugs are already present.
- Routine blood tests – equal to about the amount in 2 tablespoons will be taken from a vein in your arm.
- CT scan or MRI to measure your tumor

- A pregnancy test done by taking a blood sample from a vein in your arm every 28 days before each treatment (if you are a woman of childbearing potential). The pregnancy test results must be negative in order for you to continue on the study.

You will need the following tests and procedures that are part of regular cancer care. They are being done more often because you are in this study.

- A pregnancy test done by taking a blood sample from a vein in your arm every 28 days before each treatment (if you are a woman of childbearing potential). The pregnancy test results must be negative in order for you to continue on the study.

You will need these tests and procedures that are either being tested in this study or being done to see how the study is affecting your body.

- Research blood tests – when you have the routine blood test done, we will also take between 2 teaspoons and 4 tablespoons of additional blood for research and banking for future research. Giving this extra blood is required if you participate in this study.

This research will explore possible genetic or inherited reasons for how patients respond to medications. Your blood and tissue samples contain genes, which are made up of DNA and proteins that serve as the "instruction book" for the cells that make up our bodies. Your samples will help us study how genes interact with other factors to influence the development and treatment of diseases. Because the genetic tests in this study are not used for regular medical care, you will not be told the results of the test(s), and the test results will not be put in your medical record.

There is more information about these research tests at the end of this form.

Once it is determined that you are eligible for the study and agree to take part, you will begin treatment. Treatment takes place over three 28-day periods; each 28-day period is called a cycle.

Treatment during each cycle includes the following:

On days 1 and 15 of every 28-day cycle, about 30-60 minutes before receiving the study drugs noted below, you will be given medications (dexamethasone (or similar) and ondansetron (or similar)) through a needle placed in your arm (also referred to as an IV (intravenous)) to make side effects less serious and less uncomfortable. These medications are sometimes known as pretreatment medications.

On days 1 and 15, after receiving the pretreatment medications, you will receive nal-IRI + 5-FU. These drugs will be given to you through the IV.

In addition to the IV study drugs, you will also take the study drug, rucaparib, in pill form, by mouth, two times every day beginning on day 4 of the first week and continue through day 13. You will **not** take this drug on days 14-17. On day 18 you will start taking rucaparib

again, and continue taking through 27, then stop taking this drug again on day 28 (see study calendar below).

If you have side effects that get too bad at any time during these cycles, the doses listed above will be decreased until the side effects get better. Treatment may discontinue completely if side effects are too bad or your cancer gets worse.

Medication Diary

You will be asked to keep a daily record (Patient Medication Diary) of when you take the study medication, rucaparib, and every day write down the day and time you take the medication. If you notice any side effects, you can include this information in the Comments section of the diary.

Study Calendar

You will receive nal-IRI + 5-FU + rucaparib in this study every one to two weeks over a 28-day period. This 28-day period of time is called a cycle. The cycle will be repeated 3 times. The chart below shows what will happen to you during each Cycle, as explained previously. The left-hand column shows the day in the cycle and the right-hand column tells you what to do on that day.

Day	What you do
Up to 21 days before starting treatment	• Medical history and physical exam; your doctor will also ask how well you perform activities in your daily life. • A check to see if any of the side effects that may be caused by the study drugs are already present. • Routine blood tests • CT scan or MRI • Electrocardiogram (ECG) • Mandatory submission of a tumor sample from your previous surgery or biopsy
Up to 7 days before starting treatment	• Pregnancy test (only if you are a woman of childbearing potential) • Mandatory research blood tests
Day 1 of each cycle	• **Prior to dosing -** Pregnancy test (only if you are a woman of childbearing potential) • Medical history and physical exam; your doctor will also ask how well you perform activities in your daily life. • A check to see if you are having any side effects from study drugs. • Review Patient Medication Diary • Routine blood tests • ECG • Receive pretreatment medications through an IV. • Receive nal-IRI, 5-FU through an IV.
Days 4-13	• Take rucaparib, in pill form, by mouth, two times every day beginning on day 4 of the first week and continue through day 10.

Days 14-17	• **Stop taking rucaparib.**

Study Calendar – Continued

Day	What you do
Day 15	• Medical history and physical exam; your doctor will also ask how well you perform activities in your daily life. • A check to see if you are having any side effects from study drugs. • Routine blood tests • Receive pretreatment medications through an IV. • Receive nal-IRI, 5-FU through an IV.
Days 18-27	• Take rucaparib, in pill form, by mouth, two times every day beginning on day 15 and continue through day 21.
Day 28	• **Stop taking rucaparib.** • On **one** of these days (Day 22 – 28) before every odd-numbered cycle (before cycle 3, cycle 5, etc.), do the following: ☐ CT scan or MRI to measure your tumor ☐ Routine blood tests
Cycle 2	• Repeat Days 1-28 as above
Cycle 3	• Repeat Days 1-28 as above
End of Treatment (after you complete the full treatment, or if your disease progresses or you stop the treatment for any reason)	• Medical history and physical exam; your doctor will also ask how well you perform activities in your daily life. • A check to see if you are having any side effects from study drugs. • Review Patient Medication Diary • Routine blood tests • Mandatory research blood tests • CT scan or MRI

When you are finished taking the study drugs…

Within about 30 days after your last treatment, the following tests and procedures will be done:

- Medical history and physical exam; your doctor will also ask how well you perform activities in your daily life and review your Patient Medication Diary.
- A check to see if you are having any side effects from study drugs.
- Routine blood tests – equal to about the amount in 2 tablespoons will be taken from a vein in your arm.
- Research blood tests – when you have the routine blood test done, we will also take between 2 teaspoons and 4 tablespoons of additional blood for research and banking for future research.

How long will you be in the research study?

You will continue to receive the combination of nal-IRI + 5-FU and rucaparib for about 3 months, or until your disease gets worse, or you have side effects that you are unable to tolerate.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

After you are finished taking the study drugs, the study doctor will ask you to visit the office for follow-up exams for about 3 years.

Can I stop being in the research study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the nal-IRI, 5-FUand rucaparib can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

What side effects or risks can I expect from being in the research study?

If you have not previously received standard treatments for your cancer and decide to take part in this research study, you are declining standard treatment and the potential benefits of these standard treatments.

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the combination of nal-IRI + 5-FU + rucaparib. In some cases, side effects can be serious, long lasting, or may never go away. **There also is a risk of death.**

You should talk to your study doctor about any side effects that you have while taking part in the study.

Oral rucaparib is an experimental drug that may have side effects that cannot be predicted at this time.

Rare or unknown side effects could possibly occur, including life-threatening reactions.

Common Side Effects

The following is a list of the most commonly reported side effects reported by patients who have received rucaparib, whether taking rucaparib alone or at the same time they were receiving chemotherapy:

- Low blood counts (especially of the white blood cells, but sometimes of red blood cells and platelets). Sometimes fever occurs with the low blood counts
    - A low white blood cell count puts you at higher risk for infection. If you have a temperature higher than 100.4°F (38.0°C) at any time during the study, you must tell the study doctor immediately.
    - A low red blood cell count may make you feel tired or dizzy. If you feel dizzy while taking rucaparib, you should avoid potentially hazardous tasks such as driving or operating machinery.
    - A low platelet count affects the ability of your blood to clot and could lead to bleeding events
- Stomach-related effects such as nausea, vomiting, diarrhea, loss of appetite, heartburn, and constipation
- Feeling tired (Fatigue)
- Headache
- Abdominal pain
- Elevated liver enzymes
- Dizziness
- Bad taste in mouth (or altered sense of taste)
- Increased sensitivity to sunlight- please use appropriate sun protection
- Increased serum creatinine
- Increase in cholesterol
- Rash
- Pruritis (itchy skin)
- Dyspnea (difficult or labored breathing)
- Due to the risk of permanent damage or death to a developing embryo/fetus, both women of childbearing potential and men and their opposite sex partners of reproductive potential should use contraception during dosing and for 6 months after completing treatment with rucaparib.

Less Common Side Effects (>1% - <5% of patients)

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) have been reported in a very small number of patients treated with rucaparib. MDS is a pre-cancerous condition where the bone marrow is not as good at producing blood cells (red and/or white blood cells and/or platelets) as it was before. People with MDS need transfusions (red blood cells and/or platelets) and/or other treatments. In some cases, MDS will progress to AML, which is a cancer of the bone marrow where more abnormal and immature white blood cells (also called blasts) are made than normal white blood cells. People with AML need treatment with chemotherapy and/or a transplant. Patients may develop AML without first being diagnosed with MDS. MDS/AML can be fatal and led to death in 2 patients on rucaparib (0.5%).

Events of MDS and AML have also been reported with PARP inhibitors similar to rucaparib. At this time it is not known whether PARP inhibitors cause MDS or AML or if these developed as a result of previous chemotherapy these patients received. Your Study Doctor will closely monitor your blood cell levels during treatment. If he/she has any concerns about your blood counts you

may be asked to have a biopsy of your bone marrow.

If you develop low blood counts, or if you have any other significant side effects, you may need to stop taking rucaparib until you recover from these side effects. The study doctor may also decide to lower your dose of rucaparib if you experience certain side effects.

Pneumonitis (inflammation of the lung tissue) has been designated by Clovis as an adverse event of special interest. Pneumonitis has been reported with PARP inhibitor treatment, including in clinical studies evaluating rucaparib. To date, pneumonitis cases were reported in approximately 0.6% patients. In clinical studies evaluating rucaparib as monotherapy, cases of pneumonitis were reported in approximately 0.1% patients. Currently, however, there is a lack of understanding of a mechanistic link between pneumonitis and PARP inhibitor treatment. Cases of pneumonitis lack a consistent clinical pattern, and are often confounded with risk factors, such as cancer and/or metastases in lungs, underlying pulmonary disease, smoking history, and/or previous chemotherapy and radiotherapy.

Allergic Reactions

As with any drug, it is possible that you could have allergic reactions to rucaparib, such as itching, skin rash, facial swelling, and/or a severe or sudden drop in blood pressure. A sudden drop in blood pressure could lead to shock with loss of consciousness and/or possible seizures, **including the possibility of death**. If you have any of the above symptoms, seek medical attention right away.

Risks and side effects related to <u>nal-IRI + 5-FU</u> include those which are:

<u>Likely</u> (more than 10%)

In a clinical trial evaluating the effectiveness of nal-IRI in the treatment of metastatic pancreatic cancer, 117 patients received nal-IRI in combination with 5-FU . In this group of patients, the most common side effects that happened in at least 12 of the 117 patients (more than 10% of those patients) included the following:

- Diarrhea
- Vomiting
- Nausea
- Decreased appetite
- Fatigue (tiredness)
- Anemia (decreased red blood cells or hemoglobin, which may cause tiredness and lack of energy)
- Fever
- Neutropenia (decrease in a type of white blood cells called neutrophils, may increase the risks of infections)
- Abdominal pain

- Constipation
- Asthenia (lack of energy)
- Weight loss
- Leukopenia (decrease in white blood cells)
- Hair loss (alopecia)
- Stomatitis (inflammation of the lining of the mouth)
- Back pain
- Dizziness
- Hypokalemia (decrease in blood potassium levels)
- Peripheral edema (collection of fluid in the tissues of the body)
- Mucosal inflammation (lining of mouth, esophagus, stomach and intestines)
- Thrombocytopenia (a decrease in platelets (particles that help the blood to clot, may cause bruising or bleeding)

Less Likely (more than 5% of those patients)

The less commonly seen side effects that occurred in at least 6 of the 117 patients (more than 5% of those patients) were:

- Upper abdominal pain
- Dehydration
- Hypomagnesemia (decrease in blood magnesium levels)
- Hypoalbuminemia (decrease in a type of blood protein called albumin)

Rare (less than 5% of those patients):

- Sepsis

The most common serious side effects of nal-IRI + 5FU

- Diarrhea (occurring in 5.1% of patients)
- Vomiting (occurring in 7.7% of patients)
- Nausea (occurring in 3.4% of patients)

As with any medication, allergic reactions are a possibility.

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your health care provider about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

Risks of CT scans and MRIs: CT scans or MRIs may be done to check your tumor. When these are done you will be exposed to low doses of radiation. These doses of radiation that you will receive have a low risk of harmful effects. These types of scans are also commonly used to

monitor cancer.

Risks of Blood draws and intravenous (IV) infusions: Drawing of blood or insertion of an intravenous catheter to infuse a drug may cause local pain, swelling, bruising, bleeding, or (rarely) infection at the place where your blood is drawn. The decision to use a catheter (a thin tube) for blood collecting is made by the study staff. The study staff will explain the catheter to you if its use is necessary.

While you are taking part in this study, you are at risk for the above-mentioned side effects. You should talk to the researcher and/or your medical doctor about these side effects. There also may be other side effects that are not known. Side effects may range from mild to life-threatening..

Many side effects go away shortly after the drugs are stopped, but in some cases side effects can be serious, long lasting, or may never go away.

For more information about risks and side effects, ask your study doctor.

Electrocardiograms (ECG): This procedure requires you to lie still for a few minutes. The ECG records the rhythm and electrical activity of your heart. Small sticky patches called electrodes are placed on your arms, legs, and chest and connected by wires to an ECG recording machine to record the rhythm and electrical activity of your heart. The information is recorded and printed onto paper. The whole test takes about five minutes and is completely painless.

Are there benefits to taking part in the research study?

Taking part in this study may or may not make your health better. While doctors hope the combination of nal-IRI + 5-FU + rucaparib will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about using this drug combination as a treatment for cancer. This information could help future cancer patients.

What other choices do you have if you do not take part in this research study?

You do not have to be in this study to receive treatment for your cancer.

Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Academic and Community Cancer Research United (ACCRU)
- Government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- Institutional Review Boards
- Clovis Oncology and their 3rd party collaborator
- Ipsen Group

A description of this clinical trial will be available on [redacted] as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of study results. You can search this Web site at any time.

[Note to Informed Consent Authors: the above paragraph complies with the new FDA regulation found at 21 CFR 50.25(c) and must be included verbatim in all informed consent documents. The text in this paragraph cannot be revised.]

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

What are the costs of taking part in this research study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

You won't need to pay for tests and procedures which are done just for this research study. These tests and procedures are:

- Research blood tests
- Submission of mandatory tumor tissue samples for research purposes

The study agents, rucaparib and nal-IRI, will be provided free of charge while you are taking part in this study. However, if you should need to take the study agent much longer than usual, the

stock of free study agent could run out. If the free supply runs out, your study doctor will discuss with you how to get more drug from the manufacturer. You may be asked to pay for it.

The study agent 5-FU can be bought with a prescription. You and/or your health plan will need to pay for all costs associated with this treatment. You and/or your health plan will also have to pay for other drugs or treatment that are given to help control side effects as well as the cost of tests or exams to evaluate possible side effects.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at [redacted] You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this research study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this research study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer questions about the research study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number).* *[Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study.

About Using Biological Samples for Research

We would like to keep some of the blood and tissue that is left over for future research. If you agree, this blood and tissue will be kept and may be used in research to learn more about cancer and other diseases. Please read the online booklet called "Providing Your Tissue for Research: What You Need To Know," to learn more about tissue research:

[redacted]

Your blood and tissue may be helpful for research whether you do or do not have cancer. The research that may be done with your blood and tissue is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your blood and tissue will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the blood and tissue for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your blood and tissue can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your blood and tissue. Then any blood and tissue that remains will no longer be used for research.

In the future, people who do research may need to know more about your health. While ACCRU may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes blood and tissue is used for genetic research (about diseases that are passed on in families). Even if your blood and tissue is used for this kind of research, the results will not be put in your health records.

Your blood and tissue will be used only for research and will not be sold. The research done with your blood and tissue may help to develop new products in the future.

Benefits

The benefits of research using blood and tissue include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at the IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. My blood sample(s) may be kept for use in future research to learn about, prevent, or treat cancer.

☐ Yes ☐ No Please initial here: _____ Date: _____

2. My blood sample(s) may be kept for use in future research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

☐ Yes ☐ No Please initial here: _____ Date: _____

3. My tissue sample(s) may be kept for use in future research to learn about, prevent, or treat cancer.

☐ Yes ☐ No Please initial here: _____ Date: _____

4. My tissue sample(s) may be kept for use in future research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

☐ Yes ☐ No Please initial here: _____ Date: _____

If you want your sample(s) destroyed at any time, write to the Secretary of the _____ Institutional Review Board _____.

ACCRU has the right to end storage of the sample(s) without telling you.

The sample(s) will be the property of ACCRU. Outside researchers may one day ask for a part of your sample(s) for studies now or future studies.

How do outside researchers get the sample?

Researchers from universities, hospitals, and other health organizations do research using blood and tissue. They may call ACCRU and ask for samples for their studies. ACCRU looks at the

way that these studies will be done, and decides if any of the samples can be used. ACCRU sends the samples and some information about you to the researcher. ACCRU will not send your name, address, phone number, social security number, or any other identifying information to the researcher. If you allow your sample(s) to be given to outside researchers, it will be given to them with a code number. If researchers outside ACCRU use the sample(s) for future research, they will decide if you will be contacted and, if so, they would have to contact the researchers at ACCRU. Then ACCRU will contact the clinic where you registered for this study, who will contact you.

Please read the following statements and mark your choice:

I permit ACCRU to give my sample(s) to outside researchers:

☐ Yes ☐ No Please initial here:_____ Date:_____

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI Web site at [redacted]

- For NCI's clinical trials information, go to: [redacted]
- For NCI's general information about cancer, go to [redacted]

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Printed Participant Name: _____

Participant Signature: _____

Date: _____

Printed name of person obtaining informed consent:

_____

Signature of person obtaining informed consent:

_____

Date _____

This model informed consent form has been reviewed by the ACCRU and is the official consent document for this study. Local IRB changes to this document are allowed. Sections "What are the risks of the research study" or "What other choices do I have if I don't take part in this research study?" should always be used in their entirety if possible. Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to these sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language and justification must be forwarded to the Academic and Community Cancer Research United (ACCRU) Operations Office for approval before a patient may be registered to this study.

Consent forms will have to be modified for each institution as it relates to where information may be obtained on the conduct of the study or research subject. This information should be specific for each institution.

Patient Medication Diary - Rucaparib

Patient Name_____ Study Number: ACCRU-GI-1603

Instructions

1. Please bring your Medication Diary and any empty or unused medication container(s) with you to every appointment.
2. Use an ink pen when completing the Medication Diary as these will be retained in our research record.
3. Contact your physician and study coordinator any time you go into the hospital. Your physician can advise if you should stop taking your medication or continue it.
4. *Every day,* in the table below, record each dose as soon as you take it. Write the date and time you took the Rucaparib, and the amount (e.g., 200 mg).
5. Indicate on the calendar below every day that you take your study medication by placing the time dose was taken on the line under the date.
6. If you miss a dose, place a "**0**" under the date (morning and/or evening), but, remember to take your prescribed dose at the next regularly scheduled time. NOTE: If you vomit after taking the daily dose of Rucaparib, DO NOT repeat dosing. Resume taking rucaparib at the next scheduled time. Remember to write a comment on your diary if this happens.
7. To correct an error or mistake, please make a single line through that entry and write your initials and date next to the error or mistake.
8. If you have any comments or notice any side effects, please record them in the Comments section (attach an additional page of comments, if needed).
9. Store your study drug at normal room temperature and keep out of the reach of children and pets.

Study Medications	**MG**
Rucaparib	*MG*

	Day 1	***Day 2***	***Day 3***	***Day 4***	***Day 5***	***Day 6***	***Day 7***
Date:							
Dose:							
Time of Morning Dose	*AM*	*AM*	*AM*	*AM*	*AM*	*AM*	*AM*
Time of Evening Dose	*PM*	*PM*	*PM*	*PM*	*PM*	*PM*	*PM*
Comments							

	Day 8	***Day 9***	***Day 10***	***Day 11***	***Day 12***	***Day 13***	***Day 14***
Date:							
Dose:							
Time of Morning Dose	*AM*	*AM*	*AM*	*AM*	*AM*	*AM*	*AM*
Time of Evening Dose	*PM*	*PM*	*PM*	*PM*	*PM*	*PM*	*PM*
Comments							

	Day 15	***Day 16***	***Day 17***	***Day 18***	***Day 19***	***Day 20***	***Day 21***
Date:							
Dose:							
Time of Morning Dose	*AM*	*AM*	*AM*	*AM*	*AM*	*AM*	*AM*
Time of Evening Dose	*PM*	*PM*	*PM*	*PM*	*PM*	*PM*	*PM*
Comments							

	Day 22	***Day 23***	***Day 24***	***Day 25***	***Day 26***	***Day 27***	***Day 28***
Date:							
Dose:							
Time of Morning Dose	*AM*	*AM*	*AM*	*AM*	*AM*	*AM*	*AM*
Time of Evening Dose	*PM*	*PM*	*PM*	*PM*	*PM*	*PM*	*PM*
Comments							

*Participant Signature*_____ *Date:* _____

Area Below To Be Completed By Study Staff Only

Number of Pills returned: _____ Study Coordinator Initials: _____

MAYO CLINIC

PATIENT EDUCATION

How to Manage Diarrhea During Chemotherapy

Signs that you have diarrhea	Be sure to call Mayo Clinic Cancer Center right away if you have any of these signs
• More stools per day than you had before starting chemotherapy • Softer, looser, or more watery stool • Stomach pain or feeling weak • More cramping and/or gas	• Fever (a temperature of 100.5 degrees Fahrenheit or higher) • Flu-like symptoms • Chills, Sweating, Feeling Hot • Severe stomach pain or cramps

What to Drink	What to Eat
• Drink at least 8 to 10 large glasses of fluid a day (water, Gatorade, Pedialyte, clear broth) • Drink a little at a time, continuously throughout the day • Limit fluids at mealtimes to 4 to 6 ounces • Avoid milk or dairy products, alcohol, coffee and very hot or very cold fluids	• Eat small meals frequently • Follow the BRAT diet (Bananas, Rice, Applesauce, Toast) • Avoid fatty or fried foods, spicy foods, high-fiber foods, raw fruits and vegetables, beans, chocolate

Taking Medicine for your diarrhea
Imodium A-D® (Loperamide)

First Episode of Diarrhea	Continued Diarrhea
Take 2 caplets (4mg) with first bowel movement of diarrhea	Take 1 caplet (2mg) every 2 hours
Then take 1 caplet (2mg) every 4 hours or with each unformed stool	
Stop taking loperamide if you do not have a bowel movement for 12 hours. If diarrhea continues (more than 4 bowel movements in a 24 hour time frame), see directions for continued diarrhea	Stop taking loperamide if you do not have a bowel movement for 12 hours. If diarrhea continues (more than 4 bowel movements in a 24 hour time frame), please call the Mayo Clinic cancer center.

Mayo Clinic Cancer Center: **480-342-4800** or **480-301-8000** (after hours)