A Phase II Trial of Irinotecan Liposome and Bevacizumab in Women with Platinum Resistant Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Principal Investigator: Daniela Matei, MD
Northwestern University Feinberg School of Medicine
303 E. Superior St., Suite 04-107
Chicago, IL 60611
Phone: 312-472-4684
Email: daniela.matei@northwestern.edu

Biostatistician: Masha Kocherginsky, PhD
Northwestern University Feinberg School of Medicine
Email: mkocherg@northwestern.edu

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Coordinating Center: Clinical Trials Office
The Robert H. Lurie Comprehensive Cancer Center (RHLCC)
Northwestern University
676 N. St. Clair, Suite 1200
Chicago, IL 60611
https://www.cancer.northwestern.edu/research/clinical-trials-office/index.html

NU Study Number: NU 20G02
Ipsen Study Number: A-US-60010-011

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse event
ALT/SGPT	Alanine aminotransferase/serum glutamic pyruvic transaminase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST/SGOT	Aspartate aminotransferase/serum glutamic oxaloacetic transaminase
CA-125	Cancer antigen 125
CBC	Complete blood count
CBR	Clinical Benefit Rate
CMP	Comprehensive metabolic panel
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTO	Clinical Trials Office
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic Acid
DOR	Duration of response
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCIG	Gynecological Cancer Intergroup
GCP	Good clinical practice
H&PE	History & physical exam
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
INR	International normalized ratio
IRB	Institutional Review Board
IV (or iv)	Intravenously
LLN	Lower limit of normal
mAb	Monoclonal antibody
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PARP	Poly (ADP-ribose) polymerase

PD	Progressive disease
PFS	Progression-free survival
PFS-16	16 week progression-free survival
PI	Principal Investigator
PR	Partial response
PT	Prothrombin time
QAM	Quality Assurance Monitor
RECIST	Response Evaluation Criteria in Solid Tumors
RNI	Reportable new information
SAE	Serious adverse event
SD	Stable disease
TKI	Tyrosine kinase inhibitor
TTR	Time to response
ULN	Upper limit of normal
VEGF	Vascular Endothelial Growth Factor
WBC	White blood cells

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STUDY SCHEMA

Phase II Trial
Single center, Single arm, Open label

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Recurrent Ovarian, Fallopian Tube, and Primary Peritoneal Cancer
n=30 subjects (may enroll up to 33 to obtain at least 30 who are evaluable)

Platinum resistant disease
Epithelial histology
ECOG performance status 0-2
Adequate organ function
RECIST 1.1 measurable disease
Multiple prior therapies permitted; refer to full eligibility criteria (Section 3.0) for details.

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1 Cycle = 28 Days

Irinotecan Liposome	+	**Bevacizumab**
70 mg/m^2 IV		10 mg/kg
Every 2 weeks		Every 2 weeks
Reductions to 50 and 43 mg/m^2 permitted		Reductions to 5 mg/kg permitted for HPT & proteinuria

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Simon's Optimal Two Stage Design with Safety Lead-In during Stage 1

Stage 1 with Safety Lead-In (n=10, including the lead-in)*	**Stage 2** (n=20)
First 6 subjects = Safety lead-in If ≤ 1/6 subjects with DLTs, continue enrollment. First 10 evaluable subjects = Stage 1 If ≥ 2/10 responses, continue to Stage 2.	Primary endpoint: ORR Secondary & Exploratory endpoints: Best Response, CBR, DOR, Duration of SD, TTR, PFS, PFS-16, Toxicity, and CA-125 Levels

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Toxicity Assessment:
Every cycle (q4w)

Imaging Response Assessment (RECIST 1.1):
Every 2 cycles for the first 5 cycles; Every 3 cycles thereafter.

Continue treatment until disease progression or unacceptable toxicity.

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Follow Up

After discontinuing treatment, follow q3m x 1 year, then q6m x 2 years, until progression or start of subsequent anti-cancer therapy.

*The study will suspend enrollment twice for interim analysis: 1) after ≥2 of 6 subjects experience DLT or at n=6 for safety lead-in and 2) at n=10 for stage 1. HPT=hypertension, ORR=objective response rate; CBR=clinical benefit rate; DOR=duration of response; SD=Stable Disease; TTR=time to response; PFS= progression free survival; PFS-16=16 week PFS. Refer to Section 7 for definitions, endpoints and evaluability and to Section 8 for statistical plans.

STUDY SUMMARY

Title	A Phase II Trial of Irinotecan Liposome and Bevacizumab in Women with Platinum Resistant Ovarian, Fallopian Tube, or Primary Peritoneal Cancer
Version	Protocol version January 20, 2022 (Amendment 3)
Study Center(s)	Single center trial at Northwestern University
Study Design	This is a single center, single arm, open label, phase II trial with a Simon's optimal two-stage design. A safety run-lead cohort has been designed, wherein the first 6 subjects who receive at least 1 dose of combination trial therapy will be observed for at least 42 days for dose limiting toxicity, in order to ensure the safety of the experimental combination of irinotecan liposome and bevacizumab. Study endpoints are defined in Section 7.0. Criteria for stopping the study early are described in Section 8.4.
Study Population & Diagnosis	Platinum-resistant ovarian cancer, fallopian cancer, and primary peritoneal cancer
Treatment Plan	This is a single center, single arm, open label, phase II trial of bevacizumab in combination with irinotecan liposome in women with recurrent, platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer. Each cycle of combination trial therapy will be 28 days. Bevacizumab will be administered at a starting dose of 10 mg/kg IV every two weeks (i.e., on days 1 and 15 of each 28 day cycle), with dose reduction to 5 mg/kg permitted for toxicity. Irinotecan liposome will be administered at a starting dose of 70 mg/m^2 IV every two weeks (i.e., on days 1 and 15 of each 28 day cycle), with dose reductions to 50 mg/m^2 and 43 mg/m^2 permitted for toxicity. Trial therapy will continue until disease progression, unacceptable toxicity, withdrawal, or death (whichever occurs first). To exclude prohibitive toxicity, a safety lead-in cohort of the initial 6 subjects will be conducted. If unacceptable dose limiting toxicity (DLT) is observed, a protocol amendment to explore alternate dosing schemes will be considered. Refer to Section 4.0 for the full treatment plan and DLT criteria.

Key Eligibility Criteria	**Key Inclusion Criteria:**
	• Histologically or cytologically confirmed epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer
	• Recurrent, platinum resistant disease, defined as progression < 6 months after completion of a platinum-based therapy regimen or as persistent disease that remains after completion of a platinum-based therapy
	• Measurable disease as assessed by RECIST 1.1
	• Must have received at least 1 but no more than 3 prior platinum-based chemotherapy regimens
	• Age ≥ 18 years
	• ECOG performance status of 0-2
	• Adequate organ and bone marrow function
	
	Key Exclusion Criteria:
	• Exclusions for receipt of prior systemic anti-cancer therapy:
	  ○ No prior irinotecan-based therapies.
	  ○ No more than 3 prior platinum-based chemotherapy regimens.
	  ○ No more than 2 prior non-platinum, cytotoxic chemotherapy regimens.
	• Exclusions for washout from prior systemic anti-cancer therapy:
	  ○ No chemotherapy, immunotherapy, monoclonal antibody (mAb) therapy, hormonal therapy, or other targeted therapy within ≤ 14 days prior to registration.
	  ○ No investigational agents or investigational devices within ≤ 14 days prior to registration.
	  ○ No VEGF-targeting agents, including bevacizumab, within ≤ 3 months prior to registration
	
	Refer to Section 3.0 for a full list of eligibility criteria.

'Objectives	**Primary Objective** • Objective Response Rate (ORR) **Secondary Efficacy Objectives** • Best Overall Response • Clinical Benefit Rate (CBR) • Duration of Response (DOR) • Duration of Stable Disease (Duration of SD) • Time to Response (TTR) • Median Progression-Free Survival (PFS) • 16 Week Progression-Free Survival (PFS-16) **Secondary Safety Objective** • Toxicity profile of irinotecan liposome in combination with bevacizumab according to NCI-CTCAE v5.0 **Exploratory Objective** • To measure serum CA-125 levels Refer to Section 2.0 and Section 7.0 for additional information.
Sample Size	In this phase II design, we anticipate enrolling 30 subjects who are evaluable for the primary endpoint; up to 33 subjects may be enrolled to yield at least 30 evaluable subjects. Refer to Section 8.0 for additional details.

Statistical Methodology	Thirty evaluable subjects will be analyzed in this phase II study. The study is designed to achieve 80% power with 5% one-sided type 1 error rate (alpha) to test the primary hypothesis of 20% improvement in objective response rate (ORR) per RECIST 1.1 vs. the null hypothesis of 11.8% ORR in the historic controls.[1] The proportion of evaluable subjects experiencing an objective response will be estimated with a 95% exact binomial confidence interval. The confidence interval will be adjusted for the sequential nature of the two-stage procedure. As this trial uses an optimum two-stage design, an interim analysis is planned after 10 evaluable subjects have been accrued and evaluated for ORR. Additionally, the first 6 evaluable subjects who receive at least 1 dose of combination trial therapy will be observed for at least 42 days as part of an initial safety lead-in. Refer to Section 8.0 for the full statistical analysis plan and early stopping criteria.

1.0 INTRODUCTION—BACKGROUND & RATIONALE

1.1 Disease Background

Ovarian cancer causes more deaths than any other female reproductive tract cancer.[2,3] Standard management includes cytoreductive surgery and neoadjuvant/adjuvant platinum-based chemotherapy. However, the majority of women diagnosed with advanced-stage epithelial ovarian cancer experience tumor recurrence and subsequent resistance to platinum-based therapies. Platinum resistant ovarian cancer is uniformly fatal.[4] The development of novel therapies for this deadly cancer is critically needed.

Recent investigation in the platinum-resistant ovarian cancer setting demonstrates that U.S. Food and Drug Administration (FDA)-approved cytotoxic monotherapies are more efficacious when combined with the vascular endothelial growth factor (VEGF) receptor-targeted therapy bevacizumab.[1] While these combinations are tolerable, toxicity management remains challenging. As such, the development of novel drug delivery systems (such as liposomal formulations) and targeted therapies for ovarian cancer are of interest to reduce toxicity and improve efficacy. The current trial seeks to study the combination of irinotecan liposome and bevacizumab in women with recurrent, platinum resistant ovarian cancer.

1.2 Rationale for the Current Study

Platinum resistant ovarian cancer has limited therapeutic options.[5] FDA-approved single agent treatment strategies include topotecan, liposomal doxorubicin, paclitaxel, etoposide, gemcitabine, and bevacizumab.[6] Following the AURELIA trial, the FDA-approved the use of bevacizumab in combination with any one of the following cytotoxic agents: topotecan, liposomal doxorubicin, or paclitaxel. The AURELIA trial demonstrated that combining single agent FDA-approved chemotherapy (topotecan, liposomal doxorubicin or paclitaxel) with anti-angiogenic bevacizumab improved response rates and induced longer progression-free survival (PFS), when compared to single agent chemotherapy alone, in women with recurrent, platinum-resistant ovarian cancer who had received no more than 2 prior lines of systemic therapy. The RECIST objective response rate in this trial was 27% for the combination regimen, as compared to 11.8% for single agent chemotherapy. Median PFS also increased from 3.4 months to 6.7 months when the anti-angiogenic agent was added to single agent chemotherapy.[1] Based on the findings from this trial, we propose that combining bevacizumab with novel cytotoxic agents, such as irinotecan liposome, would be of significant clinical interest in women with recurrent platinum-resistant ovarian cancer for whom response rates to traditional cytotoxic agents remain low (e.g., 11.8% ORR in AURELIA).[1]

Limited evaluation of irinotecan with bevacizumab in ovarian cancer has been undertaken to date. Irinotecan is a camptothecin derivative whose active metabolite, SN-38, inhibits the action of topoisomerase I. In a prior study, irinotecan in combination with bevacizumab induced an ORR of approximately 27% in subjects with recurrent platinum sensitive and resistant ovarian cancer.[7] In another study, low dose bevacizumab and weekly irinotecan induced an ORR of approximately 40% in bevacizumab-naïve ovarian cancer subjects.[8] Additionally, no clinically meaningful effects on the pharmacokinetics of irinotecan or its active metabolite, SN-38, were observed when bevacizumab was administered in combination with irinotecan. These prior results provide a strong rationale to further study

irinotecan and bevacizumab combination treatment strategies in this setting. Liposomal irinotecan drug formulations have not yet been evaluated for the treatment of ovarian cancer. We hypothesize that the liposomal encapsulation will enhance drug delivery and bioavailability, thereby improving efficacy and reducing toxicity.

The goal of this trial is to test the combination of bevacizumab and irinotecan liposome for the first time in platinum resistant ovarian cancer, aiming to demonstrate activity in the range (or better) of that observed in the AURELIA trial,[1] which targeted a population of subjects who received either fewer or a similar number of prior lines of therapy than the present trial design.

The present trial will study bevacizumab at a standard starting dosing regimen of 10 mg/kg IV every 2 weeks (per the AURELIA trial),[1] in combination with investigational irinotecan liposome. Prior experience with irinotecan liposome in a phase I dose finding trial for solid tumors demonstrated a maximum tolerated dose (MTD) of 80 mg/m^2 when dosed IV every 2 weeks as monotherapy.[9] The subsequent NAPOLI-1 trial of irinotecan liposome used in combination with other agents for pancreatic adenocarcinoma demonstrated a reasonable safety profile for the 80 mg/m^2 dose.[10,11] The FDA-recommended dose for the same patient population as NAPOLI-1 is 70mg/m^2 with dose reductions to 50 mg/m^2 and 43 mg/m^2. In light of this prior experience, the current trial has been designed with a safety lead-in cohort to test a starting dose of irinotecan liposome of 70 mg/m^2 IV in combination with a starting dose of bevacizumab of 10 mg/kg IV, every two weeks. If unacceptable dose limiting toxicity (DLT) is observed during the safety lead-in, the protocol will be suspended, and additional dosing strategies (such as a reduced starting dose of 50 mg/m^2 for irinotecan liposome) will be explored in a protocol amendment. Dose reductions for toxicity will be permitted to 5 mg/kg IV every 2 weeks for bevacizumab, and to 50 mg/m^2 and 43 mg/m^2 IV every 2 weeks for irinotecan liposome.

1.3 Intervention Background & Overview

1.3.1 Bevacizumab

1.3.1.1 Bevacizumab—Mechanism of Action

Bevacizumab (sold under the trade name Avastin® and marketed by Genentech/Roche) is a recombinant humanized monoclonal IgG1 antibody (mAb) that specifically binds to and inhibits vascular endothelial growth factor A (VEGF-A). VEGF regulates angiogenesis, vascular permeability, and endothelial cell growth and migration. Because sustained angiogenesis is a hallmark of many cancers, including ovarian cancer, inhibiting the VEGF pathway is an attractive approach for cancer therapy. Anti-VEGF agents, such as bevacizumab, prevent tumor growth and cause tumor regression by inhibiting neovascularization and normalizing tumor vasculature. Due to its mechanism of action as a targeted therapy, there has been recent interest to combine bevacizumab with standard cytotoxic chemotherapeutic regimens that have non-overlapping toxicity profiles.

1.3.1.2 Bevacizumab—Clinical Experience and Toxicity Profile

Bevacizumab is U.S. FDA-approved for the treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan at a dose of 10 mg/kg every 2 weeks (with paclitaxel, pegylated liposomal doxorubicin, or topotecan given every week) or 15 mg/kg every 3 weeks (with topotecan given every 3 weeks).

Leading to its FDA-approval, bevacizumab was investigated in a multicenter, open-label, randomized study (AURELIA trial / MO22224 / NCT00976911)[1] of 361 patients with recurrent, platinum-resistant, epithelial ovarian, fallopian tube, or primary peritoneal cancer who recurred within < 6 months of their most recently received platinum-based therapy. This two-arm study compared chemotherapy alone to the combination of bevacizumab + chemotherapy. Chemotherapy options were at the discretion of the investigator and included paclitaxel (80 mg/m^2 on days 1, 8, 15 and 22 every 4 weeks), pegylated liposomal doxorubicin (40 mg/m^2 on day 1 every 4 weeks), and topotecan (4 mg/m^2 on days 1, 8 and 15 every 4 weeks or 1.25 mg/m^2 on days 1-5 every 3 weeks). In the bevacizumab arm, patients received bevacizumab at a dose of 10 mg/kg IV every 2 weeks or 15 mg/kg IV every 3 weeks. Patients were treated until disease progression, unacceptable toxicity, or withdrawal. The addition of bevacizumab to cytotoxic chemotherapy demonstrated a statistically significant improvement (p-value < 0.0001) in progression-free survival (PFS), where the combination regimens that included bevacizumab had a median PFS of 6.8 months, compared to 3.4 months for the single agent chemotherapy regimens [HR 0.38 (95% CI: 0.30-0.49)]. These data support the use of bevacizumab in combination with cytotoxic drugs for the treatment of platinum-resistant, recurrent epithelial ovarian, fallopian tube, and primary peritoneal cancer.[1]

The toxicity profile of bevacizumab is manageable and expected for agents of its class. Common adverse reactions may include (but are not limited to) epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain, exfoliative dermatitis, fatigue, poor appetite, diarrhea, dizziness, weight loss, arthralgia and myalgia. Serious adverse reactions include gastrointestinal perforation, fistula, surgery and wound healing complications, hemorrhage, arterial and venous thromboembolic events, hypertensive crisis, posterior reversible encephalopathy syndrome, nephrotic syndrome, proteinuria, infusion-related reactions, ovarian failure, and congestive heart failure.

Refer to the full FDA prescribing information and current U.S. Package Insert for additional details, including a full toxicity profile.

1.3.2 Irinotecan Liposome

1.3.2.1 Irinotecan Liposome—Mechanism of Action

Irinotecan liposome (sold under the trade name ONIVYDE™ and marketed by Ipsen) is a lipid-encapsulated form of the drug irinotecan. Irinotecan is a camptothecin derivative whose active metabolite, SN-38, inhibits the action of topoisomerase I. By binding to the topoisomerase I-DNA complex, SN-38 prevents re-ligation of DNA single-strand breaks, which ultimately leads to exposure time-dependent DNA double strand breaks and cell death.

Irinotecan liposome consists of a lipid bilayer vesicle that encapsulates irinotecan in an aqueous space. The liposome is designed to protect irinotecan from early conversion to SN-38. As such, the liposomal formulation has therapeutic advantages over the free form of the drug (irinotecan), including improved drug delivery in tumor tissue and sustained levels of bioavailable active drug. Ninety-five percent of irinotecan remains contained within the liposome during circulation, protecting healthy tissues from exposure. Additionally, in mice bearing human tumor xenografts, liposomal irinotecan achieved similar intratumoral exposure of SN-38 as irinotecan when administered at a 5-fold lower dose than the irinotecan-equivalent dose.[12,13]

1.3.2.1 Irinotecan Liposome—Clinical Experience and Toxicity Profile

Irinotecan liposome is U.S. FDA-approved in combination with fluorouracil and leucovorin for the treatment of patients with recurrent, metastatic pancreatic adenocarcinoma, following prior treatment with gemcitabine. The indicated dose of irinotecan liposome in this combination regimen is 70 mg/m^2 IV every 2 weeks, with recommended dose reductions to 50 and 43 mg/m^2 IV every 2 weeks for toxicity management.

Leading to its FDA-approval, irinotecan liposome was investigated in a global, multicenter, open-label, randomized phase III trial (NAPOLI-1 trial / NCT01494506)[10,11] of 417 patients with metastatic pancreatic ductal adenocarcinoma who had progressed following prior treatment with gemcitabine-based therapy. Patients were randomized to receive either irinotecan liposome monotherapy (120 mg/m^2 every 3 weeks) or fluorouracil + folinic acid. A third arm consisting of irinotecan liposome (80 mg/m^2) with fluorouracil + folinic acid every 2 weeks was added later (1:1:1), in a protocol amendment. Patients were treated until disease progression, unacceptable toxicity, or withdrawal. In this trial, the combination of irinotecan liposome + fluorouracil + folinic acid significantly prolonged median overall survival (OS) and progression-free survival (PFS) compared with fluorouracil + folinic acid control therapy. The median OS for irinotecan liposome + fluorouracil + folinic acid was 6.2 months, compared to 4.2 months for the control therapy fluorouracil + folinic acid [p-value=0.039, HR 0.75 (95% CI: 0.57-0.99)]. The median PFS for irinotecan liposome + fluorouracil + folinic acid was 3.1 months,

compared to 1.5 months for the control therapy fluorouracil + folinic acid [p-value < 0.001, HR 0.57 (95% CI: 0.43-0.76)]. Irinotecan liposome-based combination therapy had a manageable safety profile; the most common toxicities were hematologic or gastrointestinal. The grade 3 or 4 adverse events that occurred most frequently were neutropenia, diarrhea, vomiting, and fatigue.[10-13] Additional serious toxicities of the drug include interstitial lung disease, hypersensitivity reactions, and sepsis.

Refer to the full FDA prescribing information, current U.S. Package Insert, and Investigator's brochure for additional details, including a full toxicity profile.

Collectively, these data support the development of future oncology clinical trials to investigate irinotecan liposome in combination regimens. Its use in the platinum-resistant, recurrent ovarian cancer setting in combination with bevacizumab is a novel opportunity that remains to be explored.

1.4 Exploratory Studies

Evaluation of the serum biomarker CA-125 is frequently used as a standard of care assessment in the management of recurrent ovarian cancer. However, its use as a reliable endpoint for tumor response in the setting of recurrent disease has remained understudied, until recently.[14] The criteria for defining progression according to CA-125 response have been validated in the recurrent setting,[14] and the Gynecological Cancer Intergroup (GCIG) requests that data from all clinical trials using these definitions be made available, so that continual validation and improvement can be accomplished.[15] Towards this goal, the current study will perform an exploratory analysis of serum CA-125 levels as a surrogate marker of tumor response and progression.

2.0 OBJECTIVES

2.1 Primary Objective

2.1.1 To assess the antineoplastic efficacy of irinotecan liposome in combination with bevacizumab in women with recurrent, platinum resistant ovarian cancer, as measured by the Objective Response Rate (ORR).

2.2 Secondary Efficacy Objectives

2.2.1 To determine the Overall Best Response per RECIST 1.1 in women with recurrent, platinum resistant ovarian cancer who have received treatment with irinotecan liposome in combination with bevacizumab.

2.2.2 To determine the Clinical Benefit Rate (CBR) for irinotecan liposome in combination with bevacizumab in women with recurrent, platinum resistant ovarian cancer.

2.2.3 To calculate the Duration of Response (DOR) for irinotecan liposome in combination with bevacizumab in women with recurrent, platinum resistant ovarian cancer.

2.2.4 To calculate the Duration of Stable Disease (Duration of SD) for irinotecan liposome in combination with bevacizumab in women with recurrent, platinum resistant ovarian cancer.

2.2.5 To calculate the Time to Response (TTR) for irinotecan liposome in combination with bevacizumab in women with recurrent, platinum resistant ovarian cancer.

2.2.6 To measure Median Progression-Free Survival (PFS) in women with recurrent, platinum resistant ovarian cancer who have received treatment with irinotecan liposome in combination with bevacizumab.

2.2.7 To measure 16 Week Progression-Free Survival (PFS-16) in women with recurrent, platinum resistant ovarian cancer who have received treatment with irinotecan liposome in combination with bevacizumab.

2.3 Secondary Safety Objective

2.3.1 To assess the Toxicity Profile of irinotecan liposome in combination with bevacizumab in women with recurrent, platinum resistant ovarian cancer according to NCI-CTCAE v5.0.

2.4 Exploratory Objective

2.4.1 To measure Serum CA-125 Levels in women with recurrent, platinum resistant ovarian cancer who have received treatment with irinotecan liposome in combination with bevacizumab.

3.0 SUBJECT ELIGIBILITY

The target population for this study is subjects with recurrent, platinum resistant ovarian, fallopian tube, or primary peritoneal cancer. This will be a single center trial conducted at the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (RHLCCC), which will serve as the coordinating center for this study. Potential subjects may be referred to the Principal Investigator (PI).

Eligibility will be evaluated by the study team according to the following criteria. Eligibility waivers are not permitted. Subjects must meet all of the inclusion and none of the exclusion criteria to be registered to the study. Any questions regarding eligibility should be directed to the lead PI and the assigned quality assurance monitor (QAM; croqualityassurance@northwestern.edu). Study treatment may not begin until after a subject has been registered. Refer to Section 11 for complete instructions regarding registration procedures.

3.1 Inclusion Criteria

3.1.1 Subjects must have histologically or cytologically confirmed epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer.

NOTE: Subjects with carcinosarcoma histology and/or mixed epithelial histology are not eligible.

3.1.2 Subjects must have recurrent, platinum resistant or refractory disease, defined as progression < 6 months after completion of a platinum-based chemotherapy regimen or as persistent disease that remains after completion of a platinum-based therapy.

3.1.3 Subjects must have measurable disease as assessed by RECIST 1.1.[16] See Section 7.5.1 and Appendix C for the evaluation of measurable disease.

3.1.4 Subjects must have received at least 1 but no more than 3 prior platinum-based chemotherapy regimens.

3.1.5 Subjects must have adequately recovered (in the opinion of the treating investigator) from adverse events due to prior anti-cancer therapy, with the exceptions of any grade alopecia and ≤ grade 2 peripheral neuropathy per NCI-CTCAE version 5.0.

3.1.6 Subjects must be age ≥ 18 years.

3.1.7 Subjects must exhibit an ECOG performance status of 0-2.

3.1.8 Subjects must have adequate organ and bone marrow function as defined below:

System	Laboratory Value
HEMATOLOGIC	
Hemoglobin	≥ 9.0 g/dL*
White blood cell (WBC) count	≥ 3.0 x 10^9/L*
Absolute neutrophil count (ANC)	≥ 1.5 x 10^9/L*
Platelet count	≥ 75 x 10^9/L*
	*See exclusion criterion 3.2.5 for exclusions regarding receipt of growth factor support and/or blood products within ≤14 days prior to registration.
HEPATIC	
Serum total bilirubin	≤ 1.5 x ULN or direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 x ULN
AST(SGOT) and ALT(SPGT)	≤ 2.5 x ULN or ≤ 5.0 x ULN for subjects with liver metastases.
Serum albumin	≥ 3.0 g/dL
RENAL	
Creatinine clearance	≥ 60 mL/min Creatinine clearance should be calculated using the Cockcroft-Gault formula (Appendix E).
Urine protein	< 2+ (urine dipstick) or < 100 mg/dL (random protein urinalysis) or < 1 g/24h (24 hour urine collection)
COAGULATION	
International Normalized Ratio (INR)	≤ 1.5 x ULN or For subjects receiving anticoagulant therapy, INR must be within the therapeutic range of intended use of anticoagulants, as determined by the treating investigator.
Activated Partial Thromboplastin Time (aPTT)	≤ 1.5 x ULN or For subjects receiving anticoagulant therapy, aPTT must be within the therapeutic range of intended use of anticoagulants, as determined by the treating investigator.

3.1.9 For subjects with a known history of human immunodeficiency virus (HIV), the HIV viral load must be undetectable for ≥ 6 months prior to registration, and subjects must be receiving effective anti-retroviral HIV therapy, if indicated.

NOTE: HIV testing is not required for subjects without a known history of HIV, unless mandated by a local health authority.

NOTE: Use of strong CYP3A4 inhibitors/inducers is prohibited (refer to Section 4.4.3 and Exclusion Criterion 3.2.7). Subjects who are using concurrent strong CYP3A4 inhibitors/inducers (e.g., ritonavir, cobicistat) as part of their anti-retroviral therapy (ART) regimen may be switched to an alternative ART regimen (with minimal drug-drug interaction profile) before study participation; however, they are excluded from the study if their regimen cannot be altered.

3.1.10 For subjects with a known history of hepatitis B virus (HBV) infection or hepatitis C virus (HCV) infection, the HBV/HCV viral load must be undetectable, and subjects must be receiving effective suppressive HBV/HCV therapy, if indicated.

NOTE: HBV and HCV testing is not required for subjects without a known history of HBV or HCV, unless mandated by a local health authority.

3.1.11 Subjects with previously treated brain metastases are eligible if follow-up brain imaging after central nervous system (CNS)-directed therapy shows no evidence of progression for ≥ 28 days prior to registration, and any neurologic symptoms have returned to baseline.

3.1.12 Subjects with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen for this trial are eligible.

3.1.13 Subjects with a known history severe cardiac disease, current symptoms of cardiac disease (e.g., unstable angina pectoris or cardiac arrhythmia), or a history of treatment with cardiotoxic agents should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification (Appendix B). To be eligible for this trial, these subjects must be class 2B or better.

3.1.14 For subjects with hypertension, hypertension must be well controlled on medication.

NOTE: For the purposes of determining eligibility only, uncontrolled hypertension at baseline is defined as a consistent baseline bp of ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic, on initial and repeat checks. (A repeat check is only required if the initial check is ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic.)

3.1.15 Females of reproductive potential must agree to undergo a urine or serum pregnancy test, and the results must be negative in order to initiate treatment.

NOTE: A female of reproductive potential is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- *Has not undergone a hysterectomy or bilateral oophorectomy*
- *Has had menses at any time in the preceding 12 consecutive months (and therefore has not been naturally postmenopausal for > 12 months)*

3.1.16 Females of reproductive potential must agree to use adequate contraception (abstinence or two methods of birth control, such as a barrier method in combination with hormonal contraception) while receiving trial therapy and for 7 months following completion of trial therapy. Should a woman become pregnant or suspect she is pregnant while is participating in this study, she should inform her treating physician immediately.

NOTE: A female of reproductive potential is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- *Has not undergone a hysterectomy or bilateral oophorectomy*
- *Has had menses at any time in the preceding 12 consecutive months (and therefore has not been naturally postmenopausal for > 12 months)*

3.1.17 Subjects must agree to not nurse/breastfeed while receiving trial therapy and for 6 months after the last dose of trial therapy.

Note: These subjects are excluded because there is an unknown but potential risk for adverse events to the nursing infant.

3.1.18 Surgical wounds (including wounds from tooth extractions and jaw-invasive dental procedures) must be fully healed and subjects must have adequately recovered (in the opinion of the treating investigator) from adverse events due to prior surgical procedures.

NOTE: Refer to exclusion criterion 3.2.3 for additional information regarding prior surgeries.

3.1.19 Subjects (or their legally authorized representative if subject has impaired decision-making capacity) must have the ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Exclusions for receipt of prior systemic anti-cancer therapy:

- Subjects must not have received any prior irinotecan-based therapies.
- Subjects must not have received more than 3 prior platinum-based chemotherapy regimens.
- Subjects must not have received more than 2 prior non-platinum, cytotoxic chemotherapy regimens.

Note: Prior receipt of biological therapies is permitted. These may include but are not limited to hormonal therapies, immunotherapies, monoclonal antibodies (mAbs), tyrosine kinase inhibitors (TKIs), poly (ADP-ribose) polymerase (PARP) inhibitors, or other targeted agents. Refer to the below exclusion criterion for washout rules.

3.2.2 Exclusions for washout from prior systemic anti-cancer therapy:

- Subjects must not have received chemotherapy, immunotherapy, monoclonal antibody (mAb) therapy, hormonal therapy, or other targeted therapy within ≤ 14 days prior to registration.
- Subjects must not have received investigational agents or investigational devices within ≤ 14 days prior to registration.
- Subjects must not have received VEGF-targeting agents, including bevacizumab, within ≤ 3 months prior to registration.

3.2.3 Subjects must not have received prior radiotherapy to the pelvis or abdomen within ≤ 3 months prior to registration. Subjects must not have received prior radiotherapy to other areas within ≤ 14 days prior to registration.

3.2.4 Subjects must not have undergone a surgical procedure or jaw-invasive dental procedure (including tooth extraction) within ≤ 28 days prior to registration.

NOTE: Refer to inclusion criterion 3.1.18 for additional information regarding prior surgeries.

3.2.5 Subjects must not have a known history of hypersensitivity reactions attributed to compounds of similar chemical or biologic composition to bevacizumab, irinotecan liposome, or any of their excipients.

3.2.6 Subjects must not have received hematologic growth factors and/or blood products (transfusions) within ≤ 14 days prior to registration.

3.2.7 Subjects must not be taking any of the medications listed in Section 4.4.3. Subjects receiving any medications or substances that are known strong CYP3A4 inducers, known strong CYP3A4 inhibitors, and/or known strong UGT1A1 inhibitors are ineligible.

- Known strong CYP3A4 inducers must be discontinued at least 2 weeks prior to initiation of irinotecan liposome to be eligible.
  - *Strong CYP3A4 inducers include, but are not limited to, the following: phenytoin, phenobarbital, primidone, carbamazepine, rifampin, rifabutin and rifapentine.*
- Known strong CYP3A4 and UGT1A1 inhibitors must be discontinued at least 1 week prior to initiation of irinotecan liposome to be eligible.
  - *Strong CYP3A4 inhibitors include, but are not limited to, the following: ketoconazole, clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, voriconazole. (Note: fosaprepitant is permitted).*
  - *Strong UGT1A1 inhibitors include, but are not limited to, the following: atazanavir, gemfibrozil, indinavir and ketoconazole.*

NOTE: Sites should refer to a current pharmacy reference manual for a full list of strong CYP3A4 inducers/inhibitors and strong UGTA1 inhibitors.

3.2.8 Subjects must not have active peptic ulcer disease, active inflammatory bowel disease, active ulcerative colitis, or other active gastrointestinal condition with increased risk of perforation. Subjects must not have a history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within ≤ 6 months prior to registration.

3.2.9 Subjects must not have current clinical symptoms of bowel obstruction or a history of bowel obstruction within ≤ 6 months prior to registration.

3.2.10 Subjects must not have a history of a significant thromboembolic or vascular disorders within ≤ 3 months prior to registration, including but not limited to:

- Pulmonary embolism
- Deep vein thrombosis
- Other arterial or venous thromboembolic events
- Cerebrovascular accident (CVA) or transient ischemic attack (TIA)
- Peripheral arterial ischemia ≥ Grade 3 (per NCI-CTCAE v5.0)

3.2.11 Subjects must not have a history of a significant bleeding disorder within ≤ 6 months prior to registration, including but not limited to:

- Hematemesis, hematochezia, melena or other gastrointestinal bleeding ≥ Grade 2 (per NCI-CTCAE v5.0)

- Hemoptysis of ½ teaspoon (2.5 mL) or more of red blood, or other pulmonary bleeding ≥ Grade 2 (per NCI-CTCAE v5.0)
- Hematuria or other genitourinary bleeding ≥ Grade 2 (per NCI-CTCAE v5.0)

3.2.12 Subjects must not have a current non-healing wound, bone fracture, skin ulcer, or osteonecrosis of the jaw.

3.2.13 Subjects must not be pregnant or expecting to conceive from the time of informed consent through 6 months after the last dose of trial treatment.

NOTE: These subjects are excluded because there is an unknown but potential risk for adverse events to the developing fetus.

3.2.14 Subjects must not have a known UGT1A1* variant or Gilbert's syndrome.

3.2.15 Subjects must not have received a live vaccine within ≤ 30 days prior to registration.

NOTE: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines and are not allowed. If a subject receives SARS-CoV-2 vaccinations (COVID-19 vaccinations) during study participation, it is the responsibility of the investigator to determine the suitability of the vaccine being given with the information provided by the manufacturer.

3.2.16 Subjects must not have a condition or an uncontrolled intercurrent illness including, but not limited to any of the following:

- Ongoing or active infection requiring systemic treatment, except uncomplicated urinary tract infection (UTI) or uncomplicated upper respiratory tract infection (URI);
- Psychiatric illness/social situation that would limit compliance with study requirements;
- Any other illness or condition that the treating investigator feels would interfere with study compliance or would compromise the subject's safety or study endpoints.

4.0 TREATMENT PLAN

4.1 Treatment Overview

This is a single center, single arm, open label, phase II trial of bevacizumab in combination with irinotecan liposome in women with recurrent platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer. Women who meet all eligibility criteria will be candidates for participation. The trial uses a Simon's optimal two-stage design[17] with a safety lead-in cohort. Study endpoints are defined in Section 7.0. Statistical analysis plans and criteria for stopping the study early are described in Section 8.0.

Subjects must initiate trial therapy within ≤ 14 days of registration, or they will be removed from the study. Re-screening is permitted.

Each cycle of combination trial therapy will be 28 days. Bevacizumab will be administered at a starting dose of 10 mg/kg IV every two weeks (i.e., on days 1 and 15 of each 28 day cycle), with dose reduction to 5 mg/kg IV every two weeks permitted for toxicities of hypertension and proteinuria, as described in Table 4.3.1. Irinotecan liposome will be administered at a starting dose of 70 mg/m^2 IV every two weeks (i.e., on days 1 and 15 of each 28 day cycle), with dose reductions to 50 mg/m^2 and 43 mg/m^2 IV every two weeks permitted for toxicity, as described in Table 4.3.2. Trial therapy will continue until disease progression, unacceptable toxicity, withdrawal, or death (whichever occurs first), or as otherwise described in Section 4.5. The trial is designed as a combination regimen consisting of bevacizumab and irinotecan liposome; however, if one agent is discontinued due to toxicity or other reasons, subjects may continue receiving treatment with the second agent as a monotherapy (Refer to Section 4.2 for details).

To exclude prohibitive toxicity, a safety lead-in cohort of the initial 6 subjects will be conducted. All subjects in the lead-in cohort will be observed for at least 42 days after receipt of the first dose of combination trial therapy (i.e., for 2 weeks after C1D28, which is two weeks after completion of cycle 1) for dose limiting toxicity (DLT) as described in Section 4.2.3 and Section 4.2.4. If unacceptable dose limiting toxicity is observed, a protocol amendment to explore alternate dosing schemes will be considered.

4.2 Treatment Administration

Table 4.1: Treatment Administration Summary

Schedule	Premedication	Agent	Dose/Route	Schedule	Supportive Therapies
D1 and D15 of each 28-Day Cycle	Premedications are not required for bevacizumab, but they are permitted, if indicated, per treating investigator discretion and/or institutional standards.***	Bevacizumab	IV 10 mg/kg * every two weeks BEFORE irinotecan liposome	Bevacizumab infusion rate is per institutional standards.	Supportive therapies are not required for bevacizumab, but they are but permitted, if indicated, per treating investigator discretion and/or institutional standards. ***
	Administer a corticosteroid and an anti-emetic approx. 30 min prior to infusing irinotecan liposome. *** Choice of corticosteroid and anti-emetic is per treating investigator discretion and/or according to Institutional standards. Additional premedications may be used per treating investigator discretion and/or Institutional standards.	Irinotecan liposome	IV 70 mg/m2 ** AFTER Bevacizumab	Administer infusion over 90 minutes (± 10 minutes) The infusion rate will not be modified in the case of dose reduction.**	Supportive therapies are not required for irinotecan, but they are but permitted, if indicated, per treating investigation discretion and/or institutional standards. ***

* The starting dose for bevacizumab is 10 mg/kg. Refer to Table 4.3.1 for permitted dose reductions.
** The starting dose for irinotecan liposome is 70 mg/m^2. Refer to Table 4.3.2 for permitted dose reductions.
***Refer to Section 4.4 regarding prohibited medications.

Monotherapy allowances:
The trial is designed as a combination regimen consisting of bevacizumab and irinotecan liposome; however, if irinotecan liposome is withheld or discontinued, subjects may continue receiving bevacizumab as a monotherapy, as long as any toxicity warranting the interruption/discontinuation is only related to irinotecan liposome and not related to bevacizumab. The converse is also permitted. If bevacizumab is withheld or discontinued, subjects may continue receiving irinotecan liposome as a monotherapy, as long as any toxicity warranting the interruption/discontinuation is only related to bevacizumab and not related to irinotecan liposome. If a single agent is withheld while the second agent is continued as a monotherapy, missed doses of the withheld agent should not be made up when the withheld agent is later resumed.

4.2.1 Bevacizumab

- Dose/Route:

  Bevacizumab will be administered IV at a starting dose of 10 mg/kg, with dose reduction to 5 mg/kg permitted for hypertension and proteinuria according to Table 4.2.1 and Section 4.3.1.

Table 4.2.1—Bevacizumab Dose Levels	
Dose Level	**Bevacizumab Dose**
0 (Starting Dose)	10 mg/kg, IV, q2w
-1 (Dose Reduction)¥,*	5 mg/kg, IV, q2w¥,*

¥ Dose re-escalation is not permitted following a dose reduction.

* Dose reduction to 5 mg/kg bevacizumab is permitted only under certain circumstances, as described in Section 4.3.1. Dose reduction to less than 5 mg/kg is not permitted. Should a subject require a further dose reduction, the subject should discontinue bevacizumab.

- Schedule:

  Administer bevacizumab on day 1 and day 15 of each 28-day cycle (i.e., every 2 weeks). Bevacizumab infusion rate is per institutional standards.

  Administer bevacizumab prior to administering irinotecan liposome.

  DO NOT ADMINISTER OR MIX BEVACIZUMAB WITH DEXTROSE SOLUTION.

- Drug Preparation:

  Refer to Section 9.1 for bevacizumab preparation instructions.

- Premedications and Supportive Care:

  Refer to Table 4-1 and Section 4.4.

- Monotherapy Allowances:

  Refer to Section 4.2.

- Dose Interruptions and Modifications

  Refer to Section 4.3.1.

4.2.2 Irinotecan Liposome

- Dose/Route:

  Irinotecan liposome will be administered IV at a starting dose of 70 mg/m^2, with dose reductions to 50 mg/m^2 and 43 mg/m^2 permitted for toxicity according to Table 4.2.2 and Section 4.3.2.

Table 4.2.2—Irinotecan Liposome Dose Levels	
Dose Level	**Irinotecan Liposome Dose**
0 (Starting Dose)	70 mg/m^2, IV, q2w
-1 (First Dose Reduction)¥	50 mg/m^2, IV, q2w¥
-2 (Second Dose Reduction)*	43 mg/m^2, IV, q2w¥,*

¥ Dose re-escalation is not permitted following a dose reduction.

* Dose reduction to less than 43 mg/m^2 is not permitted. Should a subject require a further dose reduction, the subject should discontinue irinotecan liposome.

- Schedule:

  Irinotecan liposome will be infused over 90 minutes (± 10 minutes) on day 1 and day 15 of each 28-day cycle (i.e., every 2 weeks). The infusion rate will not be modified in the case of dose reduction.

  Administer irinotecan liposome after administering bevacizumab.

- Drug Preparation:

  Refer to Section 9.2 for irinotecan liposome preparation instructions.

- Premedications and Supportive Care:

  Refer to Table 4-1 and Section 4.4.

- Monotherapy Allowances:

  Refer to Section 4.2.

- Dose Interruptions and Modifications:

  Refer to Section 4.3.2.

4.2.3 Safety Lead-In Cohort

Drug interaction and increased toxicity is not anticipated; however, there is no clinical experience with the combination of bevacizumab and irinotecan liposome. To exclude prohibitive toxicity, the initial 6 subjects will constitute a safety lead-in cohort. All subjects in the lead-in cohort will be treated with combination therapy, as outlined in Table 4.1, and observed for dose limiting toxicity (DLT), as defined in Table 4.2.4.

Accrual will be suspended for interim safety analysis (Section 8.4) after the first 6 evaluable subjects have been enrolled. All subjects in the lead-in cohort will be observed for at least 42 days after receipt of the first dose of combination trial therapy (i.e., for two weeks after C1D28, which is two weeks after completion of cycle 1) for dose limiting toxicity (DLT) as defined in Table 4.2.4 below. Accrual will re-commence if ≤ 1 of 6 evaluable subjects in the safety lead-in cohort experiences a DLT (as defined in Section 4.2.4). If ≥ 2 of 6 evaluable subjects in the safety lead-in cohort experience a DLT, the study will remain suspended, and an amendment to explore alternate dosing schemes will be considered. If 1 of the initial 6 subjects discontinues combination therapy before completing the DLT observation period for reasons other than having experienced a DLT, then this subject will not be evaluable for the DLT analysis, and an additional subject will be added to the safety lead-in cohort.

All study teams are expected to notify the Principal Investigator and assigned QAM (croqualityassurance@northwestern.edu) when a DLT has occurred.

4.2.4 Definition of Dose Limiting Toxicity (DLT)

Table 4.2.4: Definition of DLT

Toxicity Category	Criteria Defining a DLT¥
Hematologic£	≥ Grade 4 hematologic toxicity [with the exception of uncomplicated Grade 4 leukopenia/neutropenia persisting for < 7 days]
	≥ Grade 4 leukopenia persisting for ≥ 7 days
	≥ Grade 4 non-febrile neutropenia persisting for ≥ 7 days
	≥ Grade 3 febrile neutropenia
	≥ Grade 3 thrombocytopenia associated with bleeding
	Any Grade hematologic toxicity that is treatment-related* and which results in a >14 day delay in Cycle 2 Day 1 dosing
	Any hematologic event that requires the use of growth factors for clinical management
Non-hematologic£	An elevated alanine or aspartate aminotransferase (ALT or AST) lab value that is ≥ 3X the ULN, and at the same time, an elevated serum total bilirubin lab value that is ≥ 2X the ULN, and at the same time, an alkaline phosphatase (ALP) lab value that is < 2X the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.
	≥ Grade 3 treatment-related* non-hematologic toxicity despite the use of adequate/maximal medical interventions and/or prophylaxis as dictated by local institutional clinical practices or the judgment of the treating Investigator, EXCEPT: • those that are clearly and incontrovertibly due to disease progression or extraneous causes • ≥ Grade 3 fatigue lasting < 7 days
	Any Grade non-hematologic toxicity that is treatment-related* and which results in a >14 day delay in Cycle 2 Day 1 dosing
Grade 5 Events£	Any death that is not clearly due to the underlying disease, comorbidity, or extraneous causes

¥ All toxicities are to be assessed according to NCI CTCAE version 5.0.

* Treatment-related is defined as any toxicity that is possibly, probably or definitely related to either bevacizumab or irinotecan liposome.

£ All study teams are expected to notify the Principal Investigator and assigned QAM (croqualityassurance@northwestern.edu) when a DLT has occurred.

4.3 Toxicity Management & Dose Modifications/Interruptions

Routine dosing on D1 and D15 of each cycle has a window of ±3 calendar days. Additionally, dose interruptions of ≤ 14 days to accommodate scheduling constraints (holidays, subject vacations, etc.) are permitted.

Dose interruptions of ≤ 28 days are permitted for the management of toxicity/adverse events.

Refer to Section 4.4.4 for guidelines on dose interruptions for bevacizumab for 28 days before and 28 days after surgical procedures.

4.3.1 Bevacizumab Dose Modifications/Interruptions

Table 4.3.1 describes dose modifications for bevacizumab for toxicity management. A dose reduction to dose level -1 (bevacizumab 5 mg/kg IV every two weeks) is allowed per treating Investigator discretion for the management of hypertension and proteinuria that do not meet the criteria for discontinuation, per Table 4.3.1. Dose re-escalation is not permitted following a dose reduction.

In addition to what is described in Table 4.3.1, bevacizumab dose interruptions of ≤28 days and/or dose reductions to dose level -1 (bevacizumab 5 mg/kg IV every two weeks) may be implemented at any time for any grade toxicity considered intolerable by the subject, or if thought to be in the best interest of the subject, if the event does not meet treatment discontinuation criteria as defined in Table 4.3.1.

Monotherapy allowances:
The trial is designed as a combination regimen consisting of bevacizumab and irinotecan liposome; however, if irinotecan liposome is withheld or discontinued, subjects may continue receiving bevacizumab as a monotherapy, as long as any toxicity warranting the interruption/discontinuation is only related to irinotecan liposome and not related to bevacizumab. The converse is also permitted. If bevacizumab is withheld or discontinued, subjects may continue receiving irinotecan liposome as a monotherapy, as long as any toxicity warranting the interruption/discontinuation is only related to bevacizumab and not related to irinotecan liposome. If a single agent is withheld while the second agent is continued as a monotherapy, missed doses of the withheld agent should not be made up when the withheld agent is later resumed.

Table 4.3.1 – Bevacizumab Dose Modifications for Toxicity Management		
Adverse Reaction	**Severity (NCI CTCAE v5.0)****	**Dose Modification***
Gastrointestinal Perforations and Fistulae	• Gastrointestinal perforation, any grade • Tracheoesophageal fistula, any grade • Fistula, Grade 4 • Fistula formation involving any internal organ	Discontinue bevacizumab.
Wound Healing Complications	• Wound healing complications requiring medical intervention • Necrotizing fasciitis	Discontinue bevacizumab.
Hemorrhage	• Grade 3 or 4	Discontinue bevacizumab.
	• Hemoptysis of ½ teaspoon (2.5 mL) or more	Hold bevacizumab (for a maximum of 4 weeks) until bleeding has improved to ≤Grade 1; resume bevacizumab at the same dose* once bleeding has improved to ≤Grade 1; discontinue bevacizumab if unable to resume within 4 weeks.
Thromboembolic Events	• Arterial thromboembolism, severe	Discontinue bevacizumab.
	• Venous thromboembolism, Grade 4	Discontinue bevacizumab.
Hypertension Hypertension, Continued	• Hypertensive crisis • Hypertensive encephalopathy	Discontinue bevacizumab. Continue to monitor blood pressure at regular intervals in subjects with bevacizumab-induced or -exacerbated hypertension after discontinuing bevacizumab. Table continues on the following page.

Table 4.3.1 – Bevacizumab Dose Modifications for Toxicity Management		
Adverse Reaction	**Severity (NCI CTCAE v5.0)****	**Dose Modification***
	• Hypertension, severe	Monitor blood pressure regularly and treat hypertension with appropriate anti-hypertensive therapy. Hold bevacizumab (for a maximum of 4 weeks) if blood pressure is not controlled with medical management. *(Uncontrolled is defined as a consistent bp of ≥160 mmHg systolic or ≥ 100 mmHg diastolic, on initial and repeat checks)*; resume bevacizumab at the same dose¥,* once controlled; discontinue bevacizumab if unable to control or if bevacizumab cannot be resumed within 4 weeks. Continue to monitor blood pressure at regular intervals in subjects with bevacizumab-induced or -exacerbated hypertension after discontinuing bevacizumab. ¥A dose reduction to bevacizumab 5 mg/kg IV every two weeks is allowed per treating physician discretion for the management of hypertension that does not meet the criteria for discontinuation.
Posterior Reversible Encephalopathy Syndrome (PRES)	• Any	Discontinue bevacizumab.
Renal Injury and Proteinuria Renal Injury and Proteinuria, Continued	• ≥ 2+ (urine dipstick) • ≥ 100 mg/dL (random protein urinalysis)	Undergo further assessment with a 24-hour urine collection. Table continues on the following page.

Table 4.3.1 – Bevacizumab Dose Modifications for Toxicity Management

Adverse Reaction	Severity (NCI CTCAE v5.0)**	Dose Modification*
	• Proteinuria ≥ 2 grams per 24 hours in absence of nephrotic syndrome	Monitor urine protein at regular intervals; hold bevacizumab (for a maximum of 4 weeks) until proteinuria < 2 grams per 24 hours; resume bevacizumab at the same dose[¥,*] once proteinuria improves to < 2 grams per 24 hours; discontinue bevacizumab if unable to resume within 4 weeks. [¥]A dose reduction to bevacizumab 5 mg/kg IV every two weeks is allowed per treating physician discretion for the management of proteinuria that does not meet the criteria for discontinuation.
	• Nephrotic syndrome	Discontinue bevacizumab.
Infusion-Related Reactions	• Severe	Discontinue bevacizumab and administer medical therapy (e.g., epinephrine, corticosteroids, intravenous antihistamines, bronchodilators and/or oxygen).
	• Moderate	Interrupt infusion; resume at a decreased rate of infusion after symptoms resolve.
	• Mild	Decrease infusion rate.
Congestive Heart Failure	• Any	Discontinue bevacizumab.
Other Bevacizumab-Related*** Event that is Not Described Elsewhere in this Table	• Grade 3 or Grade 4	Hold bevacizumab (for a maximum of 4 weeks); resume bevacizumab at the same dose* once event improves to ≤ Grade 2; discontinue bevacizumab if unable to resume within 4 weeks.
	• Grade 1 or Grade 2	No dose modification required.*

* Bevacizumab dose interruptions of ≤28 days and/or dose reductions to bevacizumab dose level -1 (5 mg/kg IV every two weeks) may be implemented at any time for any grade toxicity considered intolerable by the subject, or if thought to be in the best interest of the subject, if the event does not meet treatment discontinuation criteria as defined in Table 4.3.1. Refer to Table 4.2.1 for permitted dose levels. If a dose reduction to less than dose level -1 is required, the subject should discontinue bevacizumab.

** Event Grade according to NCI-CTCAE v5.0 = National Cancer Institute Common Toxicity Criteria for Adverse Events Version 5.0.

*** Bevacizumab-related event is defined as an event that is definitely, probably, or possibly related to bevacizumab.

4.3.2 Irinotecan Liposome Dose Modifications/Interruptions

Table 4.3.2 describes dose modifications for irinotecan liposome for toxicity management. A dose reduction to dose level -1 and -2 (irinotecan liposome 50 mg/m^2 and 43 mg/m^2 IV every two weeks, respectively) is allowed for the management of toxicity that does not meet the criteria for discontinuation, per Table 4.3.2. Dose re-escalation is not permitted following a dose reduction.

In addition to what is described in Table 4.3.2, irinotecan liposome dose interruptions of ≤ 28 days and/or dose reductions to dose levels -1 and -2 may be implemented at any time for any grade toxicity considered intolerable by the subject, or if thought to be in the best interest of the subject, if the event does not meet treatment discontinuation criteria as defined in Table 4.3.2.

Monotherapy allowances:
The trial is designed as a combination regimen consisting of bevacizumab and irinotecan liposome; however, if irinotecan liposome is withheld or discontinued, subjects may continue receiving bevacizumab as a monotherapy, as long as any toxicity warranting the interruption/discontinuation is only related to irinotecan liposome and not related to bevacizumab. The converse is also permitted. If bevacizumab is withheld or discontinued, subjects may continue receiving irinotecan liposome as a monotherapy, as long as any toxicity warranting the interruption/discontinuation is only related to bevacizumab and not related to irinotecan liposome. If a single agent is withheld while the second agent is continued as a monotherapy, missed doses of the withheld agent should not be made up when the withheld agent is later resumed.

Table 4.3.2 –Irinotecan Liposome Dose Modifications for Toxicity Management

Adverse Reaction	**Severity (NCI CTCAE v5.0)****	**Dose Modification***
Interstitial Lung Disease	Any Grade/Severity	Discontinue irinotecan liposome.
Anaphylactic Reaction	Any Grade/Severity	Discontinue irinotecan liposome.
Diarrhea	Grade 3 or 4 Late Onset Diarrhea	• Hold irinotecan liposome (for a maximum of 4 weeks); • Initiate loperamide; recommended loperamide regimen is 4 mg after the first loose bowel movement followed by 2 mg every 2 hours thereafter (4 mg every 4 hours at night), until 12 hours have passed without a bowel movement. • Resume irinotecan liposome at a reduced dose level[***] once event improves to ≤ Grade 1; • Discontinue irinotecan liposome if unable to resume within 4 weeks.
	Grade 2 Late Onset Diarrhea	• Hold irinotecan liposome (for a maximum of 4 weeks); • Initiate loperamide; recommended loperamide regimen is 4 mg after the first loose bowel movement followed by 2 mg every 2 hours thereafter (4 mg every 4 hours at night), until 12 hours have passed without a bowel movement. • Resume irinotecan liposome at the same dose level or a reduced dose level[***] per Treating Investigator discretion, once event improves to ≤ Grade 1; • Discontinue irinotecan liposome if unable to resume within 4 weeks. Table continues on the following page.

Diarrhea, continued	Grade 3 or 4 Early Onset Diarrhea	• Hold irinotecan liposome (for a maximum of 4 weeks); • Administer intravenous or subcutaneous atropine 0.25 to 1 mg (unless clinically contraindicated); • Resume irinotecan liposome at a reduced dose level*** once event improves to ≤ Grade 1; • Discontinue irinotecan liposome if unable to resume within 4 weeks.
	Grade 2 Early Onset Diarrhea	• Hold irinotecan liposome (for a maximum of 4 weeks); • Administer intravenous or subcutaneous atropine 0.25 to 1 mg (unless clinically contraindicated); • Resume irinotecan liposome at the same dose level or a reduced dose level*** per Treating Investigator discretion once event improves to ≤ Grade 1; • Discontinue irinotecan liposome if unable to resume within 4 weeks.
Other Irinotecan Liposome-Related**** Event that is Not Described Elsewhere in this Table	Grade 3 or Grade 4	• Hold irinotecan liposome (for a maximum of 4 weeks); • Resume irinotecan liposome at a reduced dose level*** once event improves to ≤ Grade 1; • Discontinue irinotecan liposome if unable to resume within 4 weeks. • Maximum supportive care/prophylaxis is permitted, as described in Section 4.4.
	Grade 1 or Grade 2	• No dose modification required.*

* Irinotecan liposome dose interruptions of ≤28 days and/or dose reductions to dose level -1 or -2 (refer to Table 4.2.2 for dose levels) may be implemented at any time for any grade toxicity considered intolerable by the subject, or if thought to be in the best interest of the subject, if the event does not meet treatment discontinuation criteria as defined in Table 4.3.2.

Footnotes continue on the following page.

** Event Grade according to NCI-CTCAE v5.0= National Cancer Institute Common Toxicity Criteria for Adverse Events Version 5.0.

*** Refer to Table 4.2.2 for permitted dose levels. If a dose reduction to less than dose level -2 (43 mg/m^2) is required, the subject should discontinue irinotecan liposome.

**** Irinotecan liposome-related event is defined as an event that is definitely, probably, or possibly related to bevacizumab.

4.4 Concomitant Medications/Treatments

4.4.1 Concomitant Medication Reporting

All medications taken from the time of informed consent through the time of the safety follow-up visit must be reported in the eCRF.

4.4.2 Pre-Medications

- Premedications for Irinotecan Liposome:
  Administer a corticosteroid and an anti-emetic approx. 30 min prior to infusing irinotecan liposome. Choice of corticosteroid and anti-emetic is per treating investigator discretion and/or local Institutional standards.

- Premedications for Bevacizumab:
  Bevacizumab does not require pre-medications, but they are permitted, if indicated, per treating investigator discretion and/or local institutional standards.

Refer to Section 4.2 for additional information.

Local institutional practices should be followed in case of a reaction to trial therapy.

Additional oral and IV premedications and supportive care/prophylaxis measures may be used per Treating Investigation discretion and/or local Institutional standards as clinically indicated. (Examples may include but are not limited to dexamethasone, ondansetron, atropine, loperamide, palonosetron, fosaprepitant, aprepitant, and/or corticosteroid on day 1, 2 and 3, etc.) Refer to Table 4.4.3 for prohibited Medications and Therapies.

4.4.3 Prohibited Medications and Therapies

While subjects are receiving trial therapy, all medications and medical therapy required for supportive care and/or the health of the subject are permitted (e.g., antibiotics, analgesics, and antiemetics), except for the prohibited medications listed in Table 4.4.3. Local institutional practices for supportive care should be followed in case of a reaction to trial therapy and for management of AEs.

Table 4.4.3 – Prohibited Medications & Therapies	
Concurrent anti-cancer therapies not specified in	Not permitted within ≤ 14 days prior to registration or while receiving trial therapy. These include but are not limited to:

Table 4.4.3 – Prohibited Medications & Therapies	
this protocol	• Hormonal therapy • Chemotherapy • Radiation therapy • Immunotherapy • Biologics • Anti-cancer radionuclides NOTE: Refer to Section 4.4.4 for restrictions regarding when surgery is permitted.
Concurrent investigational agents not specified in this protocol	Not permitted within ≤ 14 days prior to registration or while receiving trial therapy.
Hematologic growth factors and blood products (transfusions)	Not permitted within ≤ 14 days prior to registration for all subjects. Not permitted while receiving trial therapy for subjects participating in the safety lead-in portion of the study. Should a subject who is participating in the safety lead-in portion of the study require the use of these agents while receiving trial therapy, trial therapy must be discontinued. *(Note: These agents are permitted for subjects who are not participating in the safety lead-in.)*
Live vaccines	Not permitted within ≤ 30 days prior to registration or while receiving trial therapy. Should a subject require the use of these agents while receiving trial therapy, trial therapy must be discontinued. *NOTE: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines and are not allowed. If a subject receives SARS-CoV-2 vaccinations (COVID-19 vaccinations) during study participation, it is the responsibility of the investigator to determine the suitability of the vaccine being given with the information provided by the manufacturer.*
Select herbal supplements	The following herbal supplements are not permitted while receiving irinotecan liposome: • Curcumin supplements • Licorice supplements (all species are prohibited) • Panax/Asian ginseng supplements (American ginseng is permitted.) • St. John's wort supplements • Turmeric supplements

Table 4.4.3 – Prohibited Medications & Therapies	
Known strong CYP3A4 inducers (medications or substances)*	Not permitted within ≤ 2 weeks prior to initiation of irinotecan liposome or while receiving irinotecan liposome. These include, but are not limited to: • Phenytoin • Phenobarbital • Primidone • Carbamazepine • Rifampin • Rifabutin • Rifapentine
Known strong CYP3A4 inhibitors (medications or substances)*	Not permitted within ≤ 1 week prior to initiation of irinotecan liposome or while receiving irinotecan liposome. These include, but are not limited to: • Ketoconazole *(Note: The antiemetic fosaprepitant is permitted.)* • Clarithromycin • Indinavir • Itraconazole • Lopinavir • Nefazodone • Nelfinavir • Ritonavir • Saquinavir • Telaprevir • Voriconazole
Known strong UGT1A1 inhibitors (medications or substances)*	Not permitted within ≤ 1 week prior to initiation of irinotecan liposome or while receiving irinotecan liposome. These include, but are not limited to: • Atazanavir • Gemfibrozil • Indinavir • Ketoconazole

*Sites should refer to a current pharmacy reference manual for a full list of strong CYP3A4 inducers/inhibitors and strong UGTA1 inhibitors.

4.4.4 Surgery

Hold bevacizumab for at least 28 days prior to elective surgery, including jaw-invasive dental procedures. Do not administer bevacizumab for at least 28 days after surgery, and until the wound is fully healed. Discontinue bevacizumab in subjects who develop wound healing complications that require medical intervention or necrotizing fasciitis.

Subjects must not have undergone a surgical procedure within ≤ 28 days prior to registration. Refer to exclusion criterion 3.2.3 for additional information.

4.5 Duration of Therapy

Subjects will continue to receive trial therapy until disease progression, unacceptable toxicity, withdrawal, or death; whichever occurs first.

Subjects also can be taken off study medication treatment at any time per their own request, or per the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation of study medication must be clearly documented on the appropriate eCRF and may include (but are not limited to) the following:

- Subject completes the recommended course of study medication treatment;
- Subject experiences disease progression while receiving study medication;

  NOTE: Serological progression (i.e., a rise in CA-125 alone) in the absence of clinical or radiographical signs of progression does not meet the definition of progressive disease.

  NOTE: For equivocal findings of progression per RECIST 1.1 (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, trial therapy should be discontinued, and the date of progression should be the earlier date when progression was suspected.
- Subject experiences unacceptable toxicity related to study medication;
- Subject voluntarily withdraws from study medication treatment;
- Subject develops an inter-current illness, second malignancy, or other circumstance that prevents further administration of study medication;
- Subject requires a treatment that is not permitted while on study or would interfere with study endpoints (See Section 4.4.3);
- Subject becomes pregnant;
- Subject's study therapy is delayed/interrupted beyond the allowed period (See Section 4.3).
- Treating investigator determines that the subject should discontinue study medication treatment for any reason (i.e. changes in condition, inability to comply

with protocol requirements, treatment is no longer in the subject's best interest, etc.).

- Drug manufacturer can no longer provide study medication;
- Death.

The reason(s) for protocol therapy discontinuation and the corresponding date(s) of discontinuation must be documented in the eCRF.

Following the last dose of protocol therapy, subjects will be considered off treatment. Off-treatment subjects will proceed to follow up per Section 4.6. Subjects who are off protocol therapy are to be followed until they meet the criteria for Off Study (see Section 4.7). Follow-up data will be required unless consent was withdrawn.

4.6 Duration of Follow Up

Refer to Section 4.4 and Section 10.0 regarding the duration for reporting concomitant medications, AEs, and SAEs during the follow-up period.

NOTE: For subjects with bevacizumab-induced or -exacerbated hypertension, continue to monitor blood pressure at regular intervals after discontinuing bevacizumab, until blood pressure returns to baseline or stabilizes and is well controlled. Refer to Section 4.3 for details.

NOTE: Collection of RECIST 1.1 and CA-125 data is critical for study endpoints. Refer to Section 5.0 regarding the timing of when these assessments should be performed in subjects who discontinue protocol therapy and enter the follow up phase of the study.

4.6.1 Short Term (Safety) Follow Up Phase

End of Treatment (EOT) Visit

Refer to Section 5.0 for details on the assessments that are to be conducted at the EOT visit. Subjects who have received at least 1 dose of either irinotecan liposome or bevacizumab will have an end of treatment (EOT) visit ≤14 days after the decision to permanently discontinue trial therapy. If feasible, it is recommended that the EOT visit occur prior to the initiation of subsequent therapy.

EXCEPTION: The EOT visit is not required if it would fall within ≤ 14 days of the safety follow up visit; in these cases, the EOT visit may be skipped, and instead the patient may proceed to the safety follow up visit. See the following paragraph for details regarding the safety follow up visit.

Safety Follow Up Visit

Refer to Section 5.0 for details on the assessments that are to be conducted at the safety follow up visit. All subjects who have received at least 1 dose of either irinotecan liposome or bevacizumab will have a safety follow up visit approximately 30 days (± 7 days) after the last dose of study medication. Subjects will be followed for toxicity and concomitant medication use through this visit. In addition, subjects who are removed from treatment for unacceptable

adverse events will be followed clinically (per standard of care) until resolution or stabilization of the adverse event, or as indicated.

After completion of the Safety Follow Up Visit, patients who have discontinued trial therapy for reasons other than disease progression will proceed to the Long Term Follow Up Phase of the study (Section 4.6.2). Patients who have discontinued trial therapy due to disease progression will discontinue study participation upon completion of the Safety Follow Up Visit (i.e., Long Term Follow Up Phase is not required).

NOTE: Subjects experiencing ongoing drug-related toxicity at the time of the Safety Follow Up Visit may continue to be followed clinically (per standard of care) until resolution or stabilization of the adverse event, or as indicated.

4.6.2 Long Term Follow Up Phase

Following the last dose of trial therapy, subjects who have not yet progressed will be followed for up to 3 years, or until progression, initiation of subsequent anti-cancer therapy, withdrawal, or death; whichever occurs first. As outlined in Section 5.0, follow every 3 months (± 14 days) for 1 year post-last dose, then every 6 months (± 30 days) thereafter, for up to a total of 3 years.
Information to be collected at each long term follow up time point:

1. Survival status
2. Disease status (i.e., has the subject progressed?)
3. Subsequent anti-cancer therapies received

NOTE: Collection of RECIST 1.1 and CA-125 data is critical for study endpoints. Refer to Section 5.0 regarding the timing of when these assessments should be performed in subjects who discontinued protocol therapy for reasons other than disease progression.

Upon completion of follow-up, subjects will be considered off study, per Section 4.7.

4.7 Removal of Subjects from the Study as a Whole/Off-Study Criteria

This section describes reasons that a subject would discontinue study participation (i.e. “off study”). Refer to Section 4.7 for reasons that a subject would discontinue trial therapy (i.e., “off treatment”).

Subjects can be removed from the study at any time per their own request, or at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation must be clearly documented on the appropriate eCRF and may include (but are not limited to) the following:

- Subject completes the study follow-up period, (Refer to Section 4.6);
- Subject withdraws consent for further data submissions, (No follow-up permitted);

- Treating investigator determines that the subject should discontinue study participation for any reason, (i.e., inability to comply with study procedures, study participation is no longer in the subject's best interest, etc.);
- Termination of the study by the study Sponsor;
- Subject becomes lost to follow-up (LTF) per institutional standard;
- Death.

The reason(s) for discontinuation of study participation and the corresponding date(s) of participation/discontinuation must be documented in the eCRF.

5.0 STUDY PROCEDURES AND SCHEDULE OF ASSESSMENTS

Trial Period:	**Screening**				**Treatment[1, 19]**			**Post-Treatment**	
Cycles/Visits:	Screening/Baseline				D1 of each Cycle[1]	D15 of each Cycle	End of Treatment Visit	Safety Follow Up Visit	Long Term Follow Up
Scheduling Window (Calendar Days), **Unless Otherwise Indicated**:	≤28 days prior to registration	≤28 days prior to treatment initiation	≤14 days prior to treatment initiation	≤3 days prior to treatment initiation	≤ 3 days prior to D1	≤ 3 days prior to D15	≤14 days after the decision to discontinue trial therapy [20]	30 days (± 7) after the last dose of trial therapy	Follow q3m (± 14 days) after the last dose of trial therapy x 1 year then q6m (± 30 days) thereafter x 2 years
Administrative Procedures									
Informed Consent & Eligibility Criteria	X								
Demographics and Medical History	X								
Review Concomitant Medications [2]	X				X			X	
Cardiac Function Risk Assessment [3]	X								
Contraception and Breastfeeding Counseling [4]	X								
Survival Status and Follow Up [5,6]								X[5]	X[6]
Clinical Procedures/Assessments									
Review AEs or Baseline Symptoms [7]	X				X			X	
Physical Examination	X				X		X[20]	X	
ECOG Performance Status [8]	X				X			X	
Blood Pressure [9]	X				X	X	X[20]	X	
Other Vitals [10]	X				X	X	X[20]	X	
Laboratory Procedures/Assessments									
CBC w/ Differential and Platelets [11]	X				X	X		X	
CMP [12]	X				X	X		X	
Coagulation Tests [13]	X								
Urine Protein Analysis [14]	X				X	X	X[20]	X	
CA-125 [15]			X[15]		X[15]			X[15]	
Urine or Serum Pregnancy Test [16]				X[16]	X	X			
HIV, HBV, and HCV Testing [17]	X								
Efficacy Measurements									
Tumor imaging/assessment[18]		X			X			X	
Study Treatment									
Irinotecan Liposome[19]					D1	D15			
Bevacizumab[19]					D1	D15			

Refer to footnotes on the following pages.

1. Initiate trial treatment within ≤ 14 days after registration.
2. All medications taken from the time of informed consent through the time of the safety follow-up visit must be reported in the eCRF. Refer to Section 4.4 and Exclusion Criterion 3.2.6 for information regarding permitted and prohibited medications.
3. Subjects with a known history severe cardiac disease, current symptoms of cardiac disease (e.g., unstable angina pectoris or cardiac arrhythmia), or a history of treatment with cardiotoxic agents should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification (Appendix B) within ≤ 28 days prior to registration. To be eligible for this trial, subjects must be class 2B or better. Refer to Inclusion Criterion 3.1.13 for details.
4. Prior to registration, females of reproductive potential must agree to use adequate contraception (abstinence or two methods of birth control, such as a barrier method in combination with hormonal contraception) while receiving trial therapy and for 7 months following completion of trial therapy. Refer to Inclusion Criterion 3.1.16 for details. Prior to registration, subjects must also agree to not nurse /breastfeed while receiving trial therapy and through 6 months after the last dose of trial therapy. Refer to Inclusion Criterion 3.1.17 for details.
5. All subjects who have received at least 1 dose of trial therapy will have a safety follow up visit approximately 30 days (± 7) after the last dose. Subjects will be followed for toxicity and concomitant medication use through this visit. In addition, subjects who discontinue treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Refer to Section 4.6 for details.
6. Following the last dose of trial therapy, subjects will be followed for up to 3 years, or until disease progression, initiation of subsequent anti-cancer therapy, withdrawal, or death; whichever occurs first. Follow every 3 months (± 14 days) for 1 year post-last dose, then every 6 months (± 30 days) thereafter, for up to a total of 3 years. Collect subject survival status, disease status (i.e., has the subject progressed?), and subsequent anti-cancer therapies received. Additionally, subjects who discontinue treatment due to unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Refer to Section 4.6 for details.
7. All routine AEs, regardless of attribution or clinical significance, occurring from the time of subject registration, through 30 days after the last administration of trial therapy, must be recorded. Any event that occurs more than 30 days after the last dose of trial therapy and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported as an adverse event or expedited adverse event, as applicable. All SAEs, regardless of attribution, occurring from time of signed informed consent, through 30 days after the last administration of study drug, must be reported upon discovery or occurrence. Refer to Section 10.0 for details.
8. Refer to Appendix A for ECOG performance status criteria.
9. For subjects with hypertension at baseline, hypertension must be well controlled [uncontrolled at baseline is defined as a baseline bp of ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic on initial and repeat checks (A repeat check is only required if the initial check is ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic)] on medication within ≤ 28 days prior to registration. Refer to Inclusion Criterion 3.1.14 for details. For all subjects who are receiving bevacizumab, monitor blood pressure prior to each cycle or at regular intervals, approximately every 2-4 weeks. After discontinuing bevacizumab, continue to monitor blood pressure at regular intervals in subjects with bevacizumab-induced or -exacerbated hypertension, until blood pressure returns to baseline or stabilizes and is well controlled. Refer to Section 4.3 for details.
10. Other vitals are to include weight, and height (height is required at baseline only).
11. Complete blood cell count (CBC) is to include a full differential and platelets.
12. Serum comprehensive metabolic panel (CMP) is to include sodium, potassium, chloride, CO_2, creatinine, glucose (fasting is not required), BUN, total protein, albumin, calcium, alkaline phosphatase, ALT, AST, and total bilirubin.
13. Coagulation tests are to include PT/INR (prothrombin time/international normalized ratio) and aPTT (activated partial thromboplastin time).

Footnotes continue on the following page.

14. Conduct dipstick urinalysis (or random protein urinalysis) at the indicated times to monitor for the development or worsening of proteinuria. Subjects with a ≥ 2+ urine dipstick reading (or ≥ 100 mg/dL random protein urinalysis) should undergo further assessment with a 24-hour urine collection. Refer to Inclusion Criterion 3.1.8 and Section 4.3.1 for details.
15. Conduct the serum CA-125 test on D1 (≤14 days) of each cycle and at the time of disease progression (or as soon as is feasible after progression is documented). Subjects who discontinue trial therapy for reasons other than disease progression should continue to have their serum CA-125 drawn every 4 weeks (± 7 days) during follow-up until disease progression, initiation of subsequent anti-cancer therapy, end of study, withdrawal, or death (whichever occurs first). If the subject experiences a CA-125 response (Section 7.4), conduct a confirmatory CA-125 test ≥ 28 days later. If the subject experiences a CA-125 progression (Section 7.4), conduct a confirmatory CA-125 test ≥ 7 days later.

    NOTE: Serological progression (i.e., a rise in CA-125 alone) in the absence of clinical or radiographical signs of progression does not meet the definition of progressive disease.
16. Pregnancy test at the indicated times is only required for females of reproductive potential. During screening, females of reproductive potential must agree to undergo a urine or serum pregnancy test within ≤ 3 days prior to initiating trial therapy. The result must be negative in order to initiate trial therapy. Refer to Inclusion Criterion 3.1.15 for details.
17. HIV, HBV, and HCV testing within ≤ 28 days prior to registration is only required for subjects with a known HIV, HBV, or HCV infection, respectively. Note that for subjects with a known history of HIV, the subject's medical history must indicate that the HIV viral load has been undetectable for ≥ 6 months prior to registration. Refer to Inclusion Criteria 3.1.9 and 3.1.10 for details.
18. Imaging results will be assessed according to RECIST 1.1 criteria. Tumor imaging is to consist of CT scan of chest abdomen and pelvis. CT scan with contrast is the preferred imaging assessment; CT scan without contrast is permitted if contrast is not clinically indicated/feasible. Chest X-ray and MRI are permitted in lieu of CT scan only as described in the published RECIST 1.1 criteria.[16]

    During screening/baseline, conduct imaging:
    - Within ≤ 28 days prior to registration.

    While receiving trial therapy, conduct imaging:
    - Every 2 cycles for the first 5 cycles [i.e. prior to initiation of C3D1 and C5D1 (-7 day window).]
    - Every 3 cycles thereafter [i.e., prior to initiation of C8D1, C11D1, C14D1, etc. (-7 day window).]
    - At the time of disease progression (or as soon as is feasible).

      NOTE: Serological progression (i.e., a rise in CA-125 alone) in the absence of clinical or radiographical signs of progression does not meet the definition of progressive disease. For equivocal findings of progression per RECIST 1.1 (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, trial therapy should be discontinued, and the date of progression should be the earlier date when progression was suspected.
      A complete response (CR) or partial response (PR) per RECIST 1.1 must be confirmed via repeat imaging ≥ 28 days after the response was first observed.

    During follow up, conduct imaging:

    Subjects who discontinue trial therapy for reasons other than disease progression should continue to be imaged every 12 weeks (± 7 days) or as clinically indicated per standard of care until disease progression, initiation of subsequent anti-cancer therapy, end of study, withdrawal, or death (whichever occurs first).
19. Routine dosing on D1 and D15 of each cycle has a window of ±3 calendar days. Refer to Section 4.0 for the treatment plan. Refer to Section 4.3 for permitted dose modifications/interruptions. Refer to Section 4.5 for details on the duration of trial therapy and reasons why subjects should discontinue trial therapy.

    NOTE: Serological progression (i.e., a rise in CA-125 alone) in the absence of clinical or radiographical signs of progression does not meet the definition of progressive disease. For equivocal findings of progression per RECIST 1.1 (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, trial therapy should be discontinued, and the date of progression should be the earlier date when progression was suspected.

Footnotes continue on the following page.

20. Subjects who have received at least 1 dose of either irinotecan liposome or bevacizumab will have an end of treatment (EOT) visit ≤14 days after the decision to permanently discontinue trial therapy. If feasible, it is recommended that the EOT visit occur prior to the initiation of subsequent therapy. See Section 4.6 for additional detail.

    EXCEPTION: The EOT visit is not required if it would fall within ≤ 14 days of the safety follow up visit; in these cases, the EOT visit may be skipped, and instead the patient may proceed to the safety follow up visit. See footnote 5 and Section 4.6 for additional detail.

6.0 CORRELATIVES/SPECIAL STUDIES

This trial does not have any correlative/special studies. There is no correlative specimen collection.

7.0 ENDPOINT ASSESSMENTS AND EVALUABILITY

In this phase II design, we anticipate enrolling 30 subjects who are evaluable for the primary endpoint. In anticipation of some subjects not being evaluable, up to 33 subjects may be enrolled to yield at least 30 evaluable subjects. Refer to Section 8.2 for details.

7.1 Primary Endpoint and Evaluability

7.1.1 Objective Response Rate (ORR)

The **primary objective** is to assess the antineoplastic efficacy of irinotecan liposome in combination with bevacizumab in women with recurrent, platinum resistant ovarian cancer, as measured by the Objective Response Rate (ORR).

The **primary endpoint** of ORR is defined as the proportion of treated subjects who experience an objective response [confirmed complete response (CR) or confirmed partial response (PR) per RECIST 1.1[16]]. Confirmation of response should be conducted via imaging ≥ 28 days after the response was first documented. The date of first response for either CR or PR will be used for the calculation of ORR.

ORR data will be collected from baseline until the response has been confirmed, the subject experiences disease progression, the subject initiates subsequent anti-cancer therapy, or the subject completes study participation (whichever occurs first).

Evaluability: All eligible subjects who receive at least 1 dose of trial combination therapy will evaluable for the primary endpoint.

7.2 Secondary Efficacy Endpoints and Evaluability

7.2.1 Overall Best Response

To determine the Overall Best Response per RECIST 1.1, this endpoint will tabulate the proportion of subjects who experience each the following as their best response to trial therapy: CR, PR, SD, PD or not evaluable (NE) per RECIST 1.1.[16]

Overall Best Response data will be collected from baseline until the subject experiences disease progression, the subject initiates subsequent anti-cancer therapy, or the subject completes study participation (whichever occurs first).

Evaluability: All eligible subjects who receive at least 1 dose of trial combination therapy will evaluable for this endpoint.

7.2.2 Clinical Benefit Rate (CBR)

To determine the CBR, this endpoint will calculate the proportion of treated, evaluable subjects who experience clinical benefit from trial therapy.

Clinical benefit is defined as confirmed complete response (CR); confirmed partial response (PR); or stable disease (SD) for ≥ 4 months (calculated from the initiation of trial therapy on C1D1) per RECIST 1.1.[16]

CBR data will be collected from baseline until the subject experiences disease progression, initiates subsequent anti-cancer therapy, or completes study participation (whichever occurs first).

Evaluability: All eligible subjects who receive at least 1 dose of trial combination therapy will evaluable for this endpoint.

7.2.3 Duration of Response (DOR)

To calculate the DOR for the combination of irinotecan liposome and bevacizumab, this endpoint will be calculated as the time that elapsed between the day of first documented response to trial therapy (CR or PR, whichever is first recorded) and subsequent disease progression (taking as reference for progressive disease the smallest tumor measurements recorded on study).

For DOR analysis, response is defined as complete response (CR) or partial response (PR) per RECIST 1.1; and disease progression is defined as progressive disease (PD) per RECIST 1.1.[16]

DOR data will be collected from the time of first response to trial therapy until the subject experiences disease progression, initiates subsequent anti-cancer therapy, or completes study participation (whichever occurs first). If disease progression is not observed prior to initiating subsequent anti-cancer therapy or completing study participation, the DOR will be censored as the last available disease assessment.

Evaluability: All eligible subjects who receive at least 1 dose of trial combination therapy will evaluable for this endpoint.

7.2.4 Duration of Stable Disease (Duration of SD)

To calculate the Duration of SD (CR, PR, and SD) for the combination of irinotecan liposome and bevacizumab, this endpoint will be calculated as the time that elapsed between the day of initiation of trial therapy and subsequent disease progression (taking as reference for progressive disease the smallest measurements recorded on study).

Duration of SD analysis will capture subjects who achieve a best response of CR, PR, or SD, as defined per RECIST 1.1. For Duration of SD analysis, disease progression is defined as progressive disease (PD) per RECIST 1.1.[16]

Duration of SD data will be collected from baseline until the subject experiences disease progression, initiates subsequent anti-cancer therapy, or completes study participation. If disease progression is not observed prior to initiating subsequent anti-cancer therapy or completing study participation, the Duration of SD will be censored as the last available disease assessment.

Evaluability: All eligible subjects who receive at least 1 dose of trial combination therapy will evaluable for this endpoint.

7.2.5 Time to Response (TTR)

To calculate the Time to Response (TTR) for the combination of irinotecan liposome and bevacizumab, this endpoint will be calculated as the time that elapsed between the initiation of trial therapy (C1D1) and the day of first documented response to therapy.

For TTR analysis, a response to therapy is defined as a confirmed complete response (CR) or confirmed partial response (PR) per RECIST 1.1.[16] The first date of response will be used for the calculation.

TTR data will be collected from baseline until the subject experiences response, initiates subsequent anti-cancer therapy, or completes study participation. If response is not observed prior to initiating subsequent anti-cancer therapy or completing of study participation, the TTR will be censored as the last available disease assessment.

Evaluability: All eligible subjects who receive at least 1 dose of trial combination therapy will evaluable for this endpoint.

7.2.6 Median Progression-Free Survival (PFS)

To measure Median Progression-Free Survival (PFS) for the combination of irinotecan liposome and bevacizumab, this endpoint will calculate the progression-free survival time as the time that elapsed between the initiation of trial therapy (C1D1) and the day of first documented disease progression or death from any cause for all evaluable subjects. Median PFS will be calculated based on the Kaplan-Meier estimates of PFS. Refer to Section 8.0 for the full statistical plan.

For PFS analysis, disease progression is defined as progressive disease (PD) per RECIST 1.1,[16] other documented clinical or radiographical progression per physician judgement, or death due to disease. *NOTE: Serological progression (i.e., a rise in CA-125 alone) in the absence of clinical or radiographical signs of progression does not meet the definition of progressive disease.*

PFS data will be collected from baseline until the subject experiences disease progression, initiates subsequent anti-cancer therapy, completes study participation, or experiences death from any cause (whichever is sooner). If disease progression or death from any cause is not observed prior to initiating subsequent anti-cancer therapy or completing study participation, the PFS will be censored as the last available disease assessment.

Evaluability: All eligible subjects who receive at least 1 dose of trial combination therapy will evaluable for this endpoint.

7.2.7 16 Week Progression-Free Survival (PFS-16)

To measure 16 Week Progression-Free Survival (PFS-16) for the combination of irinotecan liposome and bevacizumab, this endpoint will be calculated based on the Kaplan-Meier estimates of PFS as the proportion of subjects who are alive and progression-free at 16 weeks after initiating trial therapy. Refer to Section 8.0 for the full statistical plan.

For PFS analysis, disease progression is defined as progressive disease (PD) per RECIST 1.1,[16] other documented clinical or radiographical progression per physician judgement, or death due to disease.

NOTE: Serological progression (i.e., a rise in CA-125 alone) in the absence of clinical or radiographical signs of progression does not meet the definition of progressive disease.

PFS data will be collected from baseline until the subject experiences disease progression, initiates subsequent anti-cancer therapy, completes 16 weeks of study participation, or experiences death from any cause (whichever is sooner). If disease progression or death from any cause is not observed prior to initiating subsequent anti-cancer therapy or completing 16 weeks of study participation, the PFS will be censored as the last available disease assessment.

Evaluability: All eligible subjects who receive at least 1 dose of trial combination therapy will evaluable for this endpoint.

7.3 Secondary Safety Endpoints and Evaluability

7.3.1 Toxicity Profile

To assess the Toxicity Profile of irinotecan liposome in combination with bevacizumab, this secondary endpoint will collect and report the frequency of adverse events by type, severity (grade), timing, and attribution to irinotecan liposome and bevacizumab according the NCI-CTCAE version 5.0 (Appendix D).

Evaluability: All subjects who receive at least 1 dose of trial therapy (combination therapy or monotherapy) will evaluable for this endpoint.

Note that this study will include a safety lead-in of the first 6 subjects in stage 1. If a subject who is enrolled in the safety lead-in cohort discontinues combination trial therapy for reasons other than DLT before completing the DLT observation period, an additional subject will be added to the safety run-in cohort. Refer to Section 8.4 and Section 4.2.3 for details.

7.4 Exploratory Endpoints and Evaluability

7.4.1 Serum CA-125 Levels

To measure serum CA-125 levels in women with recurrent, platinum resistant ovarian cancer who have received treatment with irinotecan liposome in combination with bevacizumab, this endpoint will tabulate serum CA-125 levels and determine the following, according to the Gynecological Cancer Intergroup (GCIG) criteria:[15]

- CA-125 Response Rate
- CA-125 Complete Response Rate
- CA-125 Progression Rate

The CA-125 Response Rate is defined as the proportion of evaluable subjects who experience a CA-125 Response. A CA-125 Response is defined as a ≥50% reduction in CA-125 levels from a pre-treatment sample. The response must be confirmed and maintained for at least 28 days. The date when the CA-125 level is first reduced by 50% is the date of the CA-125 response.

The CA-125 Complete Response Rate is defined as the proportion of evaluable subjects who are CA-125 Complete Responders. A CA-125 Complete Responder is defined as a subject who has a CA-125 Response and whose CA-125 level falls to within the reference range. Subjects who have a fall/decrease in CA-125 to within the reference range but whose initial CA-125 was less than twice the upper limit of the reference range have not had a CA-125 Response and cannot be classified as a CA-125 Complete Responder.

The CA-125 Progression Rate is defined as the proportion of evaluable subjects who experience a CA-125 Progression Event. A CA-125 Progression Event is defined as a subject who meets any of the following:

- Subject with elevated CA-125 pretreatment, followed by normalization of CA-125, followed by a subsequent increase in CA-125, where the increase demonstrates a CA-125 ≥ 2X ULN, with confirmation ≥ 1 week later; the date when the CA-125 first increases to ≥ 2X ULN is the date of the CA-125 Progression Event; death will also count as a Progression Event.
- Subject with elevated CA-125 pretreatment, which never normalizes, followed by subsequent increase in CA-125, where the increase demonstrates a CA-125 ≥ 2X the nadir, with confirmation ≥ 1 week later; the nadir is the lowest CA-125 value recorded while on study prior to the increase; the date when the CA-125 first increases to ≥ 2X the nadir is

the date of the CA-125 Progression Event; death will also count as a Progression Event.

- Subject with CA-125 in the reference range before treatment, followed by subsequent increase in CA-125, where the increase demonstrates a CA-125 ≥ 2X ULN, with confirmation ≥ 1 week later; the date when the CA-125 first increases to ≥ 2X ULN is the date of the CA-125 Progression event. Death will also count as a Progression Event.

Serum CA-125 data will be collected from ≤ 14 days prior to treatment initiation until the EOT visit, or until the time of confirmation, whichever is later.

Evaluability: Eligible subjects who meet all of the following will be evaluable for this endpoint:

- *Completion of a pre-treatment serum CA-125 test. (For the endpoints of CA-125 Response Rate and CA-125 Complete Response Rate, the pre-treatment CA-125 value must be ≥ 2X ULN within 2 weeks before starting treatment.)*
- *Receipt of ≥1 dose of trial combination therapy, followed by completion of an interim CA-125 test.*

7.5 Definitions

7.5.1 RECIST 1.1 Response Criteria

RECIST 1.1 response criteria[16] (Appendix C) will be used to assess tumor response for the primary endpoint. RECIST 1.1 uses the following categories of response: Complete Response (CR), Partial Response (PR), Stable Disease (SD), and Progressive Disease (PD).

At each scheduled imaging response assessment (refer to Section 5.0 for the schedule), a radiologic response will be determined, based on the RECIST 1.1 response criteria. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation should always be done rather than clinical examination, unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

For subjects who achieve a CR or PR, responses should be confirmed ≥ 28 days after the initial response was observed. The date of first response will be used in the calculation for ORR.

CT scan with contrast is the preferred imaging assessment; CT scan without contrast is permitted if contrast is not clinically indicated/feasible. Chest X-ray and MRI are permitted in lieu of CT scan only as described in the published criteria by Eisenhower et. al.[16] Refer to the published criteria for more information. Questions regarding the criteria should be directed to the lead PI.

7.5.2 NCI-CTCAE v5.0

The National Institutes of Health Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 will be used to assess adverse events for this trial and is available here. Refer to Section 10.0 for additional details on adverse events assessment and reporting.

7.5.3 Objective Response Rate (ORR)

The ORR is defined as the proportion of treated subjects who experience an objective response [confirmed complete response (CR) or confirmed partial response (PR) per RECIST 1.1 criteria]. Refer to Section 7.1 for additional details.

7.5.4 Clinical Benefit Rate (CBR)

The CBR is defined as the proportion of treated subjects who experience clinical benefit [confirmed complete response (CR); confirmed partial response (PR); or stable disease (SD) for ≥ 4 months per RECIST 1.1 criteria]. Refer to Section 7.2.2 for additional details.

7.5.5 Duration of Response (DOR)

DOR is defined as the time that elapses between the first day of documented response to trial therapy and subsequent disease progression. For DOR analysis, response is defined as complete response (CR) or partial response (PR) per RECIST 1.1 criteria; and disease progression is defined as progressive disease (PD) per RECIST 1.1 criteria. Refer to Section 7.2.3 for additional details.

7.5.6 Duration of Stable Disease (SD)

Duration of SD is defined as the time that elapses between the day of initiation of trial therapy and subsequent disease progression (taking as reference for progressive disease the smallest measurements recorded on study). Duration of SD analysis will capture subjects who achieve a best response of CR, PR, or SD, as defined per RECIST 1.1 criteria. For Duration of SD analysis, disease progression is defined as progressive disease (PD) per RECIST 1.1 criteria. Refer to Section 7.2.4 for additional details.

7.5.7 Time to Response (TTR)

TTR is defined as the time that elapses between the initiation of trial therapy (C1D1) and the day of first documented response to therapy. For TTR analysis, a response to therapy is defined as a confirmed complete response (CR) or confirmed partial response (PR) per RECIST 1.1 criteria. Refer to Section 7.2.5 for additional details.

7.5.8 Progression-Free Survival (PFS)

PFS is defined as the amount of time that elapses between the initiation of trial therapy (C1D1) and the day of first documented disease progression. Refer to Section 7.2.6 and Section 7.278 for additional details.

7.5.9 CA-125 Response

CA-125 Response is defined as a ≥50% reduction in CA-125 levels from a pre-treatment sample. The response must be confirmed and maintained for at least 28 days. The date when the CA-125 level is first reduced by 50% is the date of the CA-125 response. Refer to Section 7.4.1 for additional details.

7.5.10 CA-125 Complete Responder

A CA-125 Complete Responder is defined as a subject who has a CA-125 Response and whose CA-125 level falls to within the reference range. The date when the CA-125 first falls to within the reference range is the date of the CA-125 Complete Response. Subjects who have a fall of CA-125 to within the reference range but whose initial CA-125 was less than twice the upper limit of the reference range have not had a CA-125 Response and cannot be classified as a CA-125 Complete Responder. Refer to Section 7.4.1 for additional details.

7.5.11 CA-125 Progression

A CA-125 Progression event is defined as a subject who meets any of the following:

- Subject with elevated CA-125 pretreatment, followed by normalization of CA-125, followed by a subsequent increase in CA-125, where the increase demonstrates a CA-125 ≥ 2X ULN, with confirmation ≥ 1 week later; the date when the CA-125 first increases to ≥ 2X ULN is the date of the CA-125 Progression event.
- Subject with elevated CA-125 pretreatment, which never normalizes, followed by subsequent increase in CA-125, where the increase demonstrates a CA-125 ≥ 2X the nadir, with confirmation ≥ 1 week later; the nadir is the lowest CA-125 value recorded while on study prior to the increase; the date when the CA-125 first increases to ≥ 2X the nadir is the date of the CA-125 Progression event.
- Subject with CA-125 in the reference range before treatment, followed by subsequent increase in CA-125, where the increase demonstrates a CA-125 ≥ 2X ULN, with confirmation ≥ 1 week later; the date when the CA-

125 first increases to ≥ 2X ULN is the date of the CA-125 Progression event.

Refer to Section 7.4.1 for additional details.

8.0 STATISTICAL CONSIDERATIONS

8.1 Study Design

This is a single center, single arm, open label, phase II trial with a Simon's optimal two-stage design.[17] A safety lead-in cohort has been designed for the first 6 subjects who complete at least 1 cycle of treatment, in order to ensure the safety of the experimental combination of irinotecan liposome and bevacizumab. Study endpoints are defined in Section 7.0. Criteria for stopping the study early are described in Section 8.3.

8.2 Sample Size

In this phase II design, we anticipate enrolling 30 subjects who are evaluable for the primary endpoint. In anticipation of some subjects not being evaluable, up to 33 subjects may be enrolled to yield at least 30 evaluable subjects.

If a subject who is enrolled in the safety lead-in cohort discontinues combination trial therapy for reasons other than a DLT before completing the DLT observation period, an additional subject should be added to the safety lead-in cohort. Refer to Section 4.2.3 for details on the safety lead-in design and to Section 4.2.4 for the definition of a DLT.

8.3 Power Analysis

The primary endpoint of the study is the objective response rate (ORR), defined as the proportion of evaluable subjects experiencing a confirmed CR or PR per RECIST 1.1 Criteria. The ORR for single agent chemotherapy was 11.8% in the AURELIA trial.[1] The current study is designed to test a 20% improvement in ORR (goal ORR of ≥31.8%), as compared to the AURELIA historical control.

Specifically, the study is designed with 80% power and 5% one-sided type 1 error rate (alpha) to test the null hypothesis (H0) that the proportion of evaluable subjects responding to the drug combination (P) is ≤0.118 versus the alternate hypothesis (H1) that P is ≥0.318. With 30 evaluable subjects, if the number of objective responses is 7 or more, the null hypothesis (H0:P≤0.118) is rejected with an error rate of 0.045 (target alpha was 0.050). If the number of objective responses is less than or equal to 6, the alternate hypothesis (H1:P≥0.318) is rejected with an error rate of 0.190 (target beta was 0.200).

The statistical software program PASS was used to calculate the sample size. Refer to Section 7.0 for details on evaluability.

8.4 Criteria for Stopping the Study Early

8.4.1 Safety Criteria

The first six evaluable subjects who complete at least 1 cycle of combination trial therapy will be part of an initial safety lead-in cohort. A safety analysis will be conducted after all six subjects have been observed for at least 42 days after receipt of the first dose of combination trial therapy (i.e., for two weeks after C1D28, which is two weeks after completion of cycle 1) for dose limiting toxicity (DLT). All toxicities will be tabulated. The study will re-commence enrollment if ≤ 1 of 6 evaluable subjects in the safety lead-in cohort experience(s) a DLT (as defined in Section 4.2.4). If ≥ 2 of 6 evaluable subjects in the safety lead-in cohort experience a DLT, the study will remain suspended, and an amendment to explore alternate dosing schemes will be considered. This decision rule is based on the traditional "3+3" Phase I design decision rule for the maximum tolerated dose (MTD) cohort. Toxicity counts, toxicity rates, and the results of the analysis will be reviewed by the DSMC.

If a subject who is enrolled in the safety lead-in cohort discontinues combination trial therapy for reasons other than DLT before completing the DLT observation period, an additional subject will be added to the safety run-in cohort.

Refer to Section 4.2.3 for details on the safety lead-in design and to Section 4.2.4 for the definition of a DLT.

8.4.2 Efficacy Criteria

As this trial uses an optimum two-stage design,[17] an interim analysis is planned after 10 evaluable subjects have been accrued. Specifically, after testing the drug combination on 10 subjects in the first stage, the two stage design considerations indicate that the trial should be terminated if 1 or fewer subjects experiences an objective response (confirmed CR or PR per RECIST1.1 criteria). If two or more of the 10 subjects respond, the study will continue to the second stage. If the trial continues to the second stage following completion of the first stage analysis, a total of 30 anticipated evaluable subjects (from both stages combined) will be studied. All evaluable subjects, including those enrolled in the first stage and the safety run-in cohort, will be included in endpoint analyses.

The target is 30 evaluable subjects. In anticipation of some subjects not being evaluable, up to 33 subjects may be enrolled to yield at least 30 evaluable subjects.

8.5 Accrual and Feasibility

It is anticipated that accrual will be completed in approximately 2.5 years. Approximately 1-3 subjects will be possible candidates and will screened for participation each month, and approximately 1 subject will be enrolled each month.

8.6 Data Analysis Plans

8.6.1 Analysis Plan for the Primary Objective

The primary endpoint is the objective response rate (ORR) per RECIST 1.1. The proportion of evaluable subjects experiencing an objective response will be estimated with a 95% exact binomial confidence interval. The confidence interval will be adjusted for the sequential nature of the two-stage procedure.[18]

8.6.2 Analysis Plans for Secondary Objectives

Safety and tolerability will be summarized by providing a frequency of adverse events by severity, type, timing and attribution. Overall best response rate and Clinical benefit rate (CBR) will be estimated with a proportion and confidence interval. Duration of response (DOR) and Duration of stable disease will be estimated as median and interquartile range (IQR) or mean and a confidence interval depending on the distribution. Descriptive statistics (e.g., mean, median, SD, IQR, min and max) will be used to summarize data for continuous variables, and counts and corresponding percentages will be used to summarize data for discrete variables. Progression-free survival (PFS) and time to response (TTR) will be analyzed using the Kaplan-Meier method. Median PFS and 16-week PFS estimates will be reported along with the confidence intervals.

8.6.3 Analysis Plans for the Exploratory Objective

Serum CA-125 levels will be summarized using descriptive statistics for the time points of interest, and CA-125 response rate and CA-125 complete response rate will be summarized as counts and percentages. Time to CA-125 progression or death will be estimated using the method of Kaplan-Meier, and CA-125 progression rate at time points of interest will be estimated based on these Kaplan-Meier estimates.

9.0 DRUG INFORMATION

9.1 Bevacizumab

9.1.1 Other names

AVASTIN® (Marketed by Genentech, Inc.)
MVASI™/bevacizumab-awwb (Marketed by Amgen, Inc.)

NOTE: The preferred drug of choice is AVASTIN, whenever feasible. Biosimilars are only permitted in cases where AVASTIN is not covered by health insurance.

9.1.2 Classification - type of agent

Bevacizumab is a vascular endothelial growth factor inhibitor. Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that contains human framework regions and murine complementarity-determining regions. Bevacizumab is produced in a mammalian cell (Chinese Hamster Ovary)

expression system. Refer to the current Package Insert / FDA prescribing information for additional information.

9.1.3 Mode of action

Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors on the surface of cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in *in vitro* models of angiogenesis. Refer to the current Package Insert / FDA prescribing information for additional information.

9.1.4 Storage and stability

Refer to the current Package Insert / FDA prescribing information for storage and stability information.

9.1.5 Protocol dose specifics

Commercial supply of bevacizumab will be administered IV on day 1 and day 15 of each 28-day cycle at a starting dose of 10 mg/kg, with dose reduction to 5 mg/kg permitted according to Table 4.3.1.

Bevacizumab dosing is based on subject baseline weight on C1D1; however, doses will be adjusted for subjects who experience a ≥10% change in weight from baseline. Actual weight will be used. Rounding is permissible within 5% of the nominal dose.

Administer bevacizumab prior to administering irinotecan liposome.

9.1.6 Preparation

Refer to the current U.S. Package Insert / FDA prescribing information for preparation instructions.

9.1.7 Route of administration for this study

Administer bevacizumab as an intravenous (IV) infusion on day 1 and day 15 of each 28-day cycle. Bevacizumab infusion rates are per institutional standards.

9.1.8 Incompatibilities

DO NOT ADMINISTER OR MIX BEVACIZUMAB WITH DEXTROSE SOLUTION.

9.1.9 Side Effects

Refer to the current Package Insert / FDA prescribing information for a complete listing of all toxicities.

9.1.10 Availability & Supply

Bevacizumab is commercially available and will not be supplied by the study.

9.1.11 Return and Retention of Study Drug

All unused and/or partially used and/or expired drug may be destroyed at the site per Institutional policy for commercially supplied agents.

9.1.12 Accountability

The site Investigator, or a responsible party designated by the Investigator, is responsible for keeping accurate records of the amount administered to subjects per Institutional policy for commercially supplied agents.

9.2 Irinotecan Liposome

9.2.1 Other names

ONIVYDE™ (marketed by Ipsen)
Irinotecan liposome injection

9.2.2 Classification - type of agent

Irinotecan liposome is formulated with irinotecan hydrochloride trihydrate, a topoisomerase I inhibitor, into a liposomal dispersion for intravenous use.

9.2.3 Mode of action

Irinotecan liposome injection is a topoisomerase 1 inhibitor encapsulated in a lipid bilayer vesicle or liposome. Topoisomerase 1 relieves torsional strain in DNA by inducing single-strand breaks. Irinotecan and its active metabolite SN-38 bind reversibly to the topoisomerase 1-DNA complex and prevent re-ligation of the single-strand breaks, leading to exposure time-dependent double-strand DNA damage and cell death. In mice bearing human tumor xenografts, irinotecan liposome administered at irinotecan HCl-equivalent doses 5-fold lower than irinotecan HCl achieved similar intratumoral exposure of SN-38. [12,13]

9.2.4 Storage and stability

Store irinotecan liposome vials refrigerated at 2ºC to 8ºC (36°F to 46°F). Do not freeze. Protect from light. See Section 9.1.6 (Preparation) for storage conditions for the diluted product prior to admiration to subjects.

9.2.5 Protocol dose specifics

Irinotecan liposome will be administered at a starting dose of 70 mg/m^2, IV, q2w, with dose reductions permitted to 50 mg/m^2 and 43 mg/m^2 as described in Section 4.0. Doses are expressed as free base.

Irinotecan liposome dosing is based on subject baseline BSA on C1D1; however, doses will be adjusted for subjects who experience a ≥5% change in BSA from baseline. Actual weight will be used when calculating BSA. Rounding is permissible within 5% of the nominal dose.

[NOTE: The drug strength of irinotecan liposome injection in the United States is expressed on the basis of irinotecan free base. Should a dose need to be converted from a dose based on irinotecan hydrochloride trihydrate salt (“salt”) to

a dose based on irinotecan free base, this can be is accomplished by substituting the molecular weight of irinotecan hydrochloride trihydrate salt (677.19 g/mole) with the molecular weight of irinotecan free base (586.68 g/mole), which results in a conversion factor of 0.866. Therefore, the 80 mg/m^2 salt dose is equivalent to a 69.3 mg/m^2 irinotecan free base dose (rounded to 70 mg/m^2.)]

9.2.6 Preparation

Irinotecan liposome is a cytotoxic drug. Follow applicable Institutional special handling and disposal procedures.

Prior to administration, irinotecan liposome injection must be diluted in 5% Dextrose or Normal Saline (0.9% Sodium Chloride) to a suitable volume for infusion. The solution for infusion (irinotecan liposome injection and its admixtures) must not be frozen. Freezing will disrupt the liposome structure and result in the release of free irinotecan.

Preparation Instructions

- Withdraw the calculated volume of irinotecan liposome from the vial.
- Dilute in 500 mL 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP and mix diluted solution by gentle inversion.
- Protect diluted solution from light.
- The diluted solution for infusion should be administered immediately, but may be stored at room temperature (15º to 30ºC) for up to 4 hours prior to the start of the infusion. If necessary, the solution for infusion may be refrigerated [2ºC to 8ºC (36ºF to 46ºF)] for no more than 24 hours prior to use. Do not freeze.
- Allow diluted solution to come to room temperature prior to administration.
- Use Institutional standards on overfill.

9.2.7 Route of administration for this study

The diluted solution of irinotecan liposome should be administered as a 90-minute (± 10 minutes) intravenous infusion without the use of an in-line filter. The infusion rate will not be modified in the case of dose reduction.

9.2.8 Incompatibilities

None known. Irinotecan liposome injection has been tested for compatibility with a number of materials, and no compatibility issues have been identified. Infusion sets without inline filters are recommended for use. However, an infusion set with an in-line filter that has a pore size of at least 0.2 µm is compatible for use.

9.2.9 Side effects

Refer to the current Investigator's Brochure (IB) for a complete listing of all toxicities.

9.2.10 Availability & Supply

Irinotecan liposome will be provided by Ipsen in sterile single-dose vials, each containing 43 mg irinotecan free base at a concentration of 4.3 mg/mL (which converts to 5.0 mg/mL irinotecan hydrochloride trihydrate salt). It will be provided directly to each participating site's investigational pharmacy at no charge to subjects participating in the clinical trial. Drug ordering information is available in NOTIS as a stand-alone document.

The treating investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

9.2.11 Return and Retention of Study Drug

The site investigator or designee is responsible for taking an inventory of each shipment of irinotecan liposome received, and comparing it with the accompanying form. Accurate records will be kept in the source documentation of all irinotecan liposome administration (including dispensing and dosing), and the amount remaining at the conclusion of the trial. Upon completion or termination of the study (or at other times, as per local site institutional policy/norms), all unused and/or partially used investigational product will be destroyed at the site per local institutional policy. The manufacturer will provide memos with lot number and expiration dates, and expired drug may be destroyed per local policy. It is the site Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. Irinotecan liposome is a cytotoxic drug. Follow applicable Institutional special handling and disposal procedures.

9.2.12 Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents provided by the Study. Store and maintain a separate Drug Accountability Records (DARF) for each agent. Sites may use standard DARFs according to Institutional SOPs.

10.0 ADVERSE EVENTS

10.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. In addition, certain adverse events must be reported in an expedited manner to allow for optimal monitoring and subject safety and care.

10.2 Definitions & Descriptions

10.2.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product or undergoing an experimental intervention, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product or experimental intervention, whether or not related to the investigational product or intervention.

All routine AEs, regardless of attribution or clinical significance, occurring from time of subject registration, through 30 days after the last administration of trial therapy, must be recorded. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly as an adverse event or expedited adverse event, as applicable. See Section 10.3.1 for instructions on recording routine AEs.

Recording of AEs should be done in a concise manner using standard, acceptable medical terms, referencing CTCAE when applicable. In general, AEs are not procedures or measurements, but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement. Preexisting conditions that worsen in severity or frequency during the study should also be recorded (a preexisting condition that does not worsen is not an AE). Further, a procedure or surgery is not an AE; rather, the event leading to the procedure or surgery is considered an AE.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the AE whenever possible. However, a complete description of the signs, symptoms and investigations that led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, “hepatitis” and not “elevated liver function tests” should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an AE, using appropriate medical terminology (e.g., thrombocytopenia, peripheral edema, QT prolongation).

10.2.1.1 Adverse Event Assessment

This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly as an adverse event or expedited adverse event, as applicable.

1. Identify the type of adverse event using the NCI CTCAE v 5.0. (Appendix D)
2. Grade the adverse event using the NCI CTCAE v 5.0.
3. Determine whether the adverse event is related to the protocol therapy.
    - Attribution categories are as follows:
        - Definite: AE is *clearly related* to the study treatment.
        - Probable: AE is *likely related* to the study treatment.
        - Possible: AE *may be related* to the study treatment.
        - Unlikely: AE *not likely to be related* to the study treatment.
        - Unrelated: AE is *clearly NOT related* to the study treatment.
4. Determine the prior experience of the adverse event.

    Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

    - the current protocol
    - the drug package insert
    - the current Investigator's Brochure

10.2.1.2 Severity of Adverse Events

All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The CTCAE v5 is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

If no CTCAE grading is available, the severity of an AE is graded as follows:

- Mild (grade 1): Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- Moderate (grade 2): Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
    - *Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe (grade 3): Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
    - **Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
- Life-threatening (grade 4): Life-threatening consequences; urgent intervention indicated.
- Fatal (grade 5): Death related to AE.

10.2.2 Serious Adverse Event (SAE)

All SAEs, regardless of attribution, occurring from time of signed informed consent, through 30 days after the last administration of study drug, must be reported upon discovery or occurrence. See Section 10.3.2 for instructions on reporting SAE's.

An SAE is defined in regulatory terminology as any untoward medical occurrence that:

- Results in *death*.

  If death results from (progression of) the disease, should be reported as **Grade 5 "disease progression"** in the system class "General disorders and administration site conditions." 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.
- Is *life threatening*.

  The subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires *in-subject hospitalization* or *prolongation of existing hospitalization* for ≥ 24 hours.
- Results in *persistent or significant disability or incapacity*.
- Is a *congenital anomaly/birth defect.*
- Any *important medical event* that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the subject, may be considered for reporting as a serious adverse event. The event may require medical or

surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".

For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

10.2.3 Unanticipated Problem Involving Risks to Subject or Others (UPIRSO)

A UPIRSO is a type of SAE that includes events that meet ALL of the following criteria:

- is *unexpected* (in terms of nature, severity, or frequency) given the procedures described in the research protocol documents (e.g., the IRB-approved research protocol and informed consent document) and the characteristics of the human subject population being studied
- is *related or possibly related* to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places human subjects or others at *a greater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized, even if no harm has actually occurred.

10.3 Event Reporting

10.3.1 Routine Reporting

All routine adverse events, such as those that are expected, or are unlikely or definitely not related to study participation, are to be reported on the appropriate eCRF. Routine AEs will be reviewed by the Data and Safety Monitoring Committee (DSMC) according to the study's phase and risk level, as outlined in the DSMP.

10.3.2 Expedited Reporting

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via expedited reporting via the NU CTO SAE Form. On the "Seriousness Criteria" drop down box of the SAE Form, select "Pregnancy." Any pregnancy occurring in a subject or subject's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome.

10.3.2.1 Reporting to the Northwestern University QAM/DSMC

All SAEs must be reported to the assigned QAM within 24 hours of becoming aware of the event. Completion of the NU CTO SAE Form, provided as a separate document, is required.

The completed form should assess whether or not the event qualifies as a UPIRSO. The report should also include:

- Protocol description and number(s)
- The subject's identification number
- A description of the event, severity, treatment, and outcome (if known)
- Supportive laboratory results and diagnostics
- The hospital discharge summary (if available/applicable)
- Country of incidence

All SAEs will be reported to, and reviewed by, the DSMC, per the DSMP.

All expedited events require both expedited reporting and routine reporting.

10.3.2.2 Reporting to the Northwestern University IRB

The following information pertains to the responsibilities of the lead site (Northwestern University) and to participating sites whom have reporting responsibilities to Northwestern University. Participating sites should follow their local IRB guidelines for reporting to their local IRBs.

- Any death of an NU subject that is unanticipated in nature and at least possibly related to study participation will be promptly reported to the NU IRB within 24 hours of notification.
- Any death of a non-NU subject that is unanticipated and at least possibly related and any other UPIRSOs will be reported to Northwestern University and to the NU IRB within 5 working days of notification.
- Information pertaining to an NU subject that fits into any of the categories listed on the Reportable New Information page will be reported to the NU IRB within 5 business days of knowledge or notification.

10.3.2.3 Reporting to the FDA

The FDA will be notified within 7 calendar days of any SAE that is associated with study treatment, is unexpected, and is fatal or life threatening.

The FDA will be notified within 15 calendar days of any SAE that is associated with the study treatment, unexpected, and serious but not fatal or life threatening. This includes any previous SAEs that were not initially deemed reportable, but are later determined to meet the criteria for reporting (i.e. by the DSMC).

All other SAEs will be reported on an annual basis as part of the annual FDA report.

10.3.2.4 Reporting to Ipsen

All Serious Adverse Events (SAEs) and events of pregnancy occurring from the time of informed consent through 30 days following the last dose of trial therapy will be reported by the Coordinating Center to Ipsen using the CTO SAE form. Any SAEs occurring more than 30 days following the last dose of the study treatment that are believed to be related to study drug will also be reported to Ipsen.

The Coordinating Center will send the initial completed SAE form within 24 hours of notification via email to Ipsen (drugsafety.USA@ipsen.com). If only limited information is initially available and new information later becomes available, or if an ongoing SAE changes in its intensity or relationship to the study drug, a follow-up report will be generated and sent to Ipsen as information becomes available.

For questions regarding the reporting process, please contact Ipsen:

- Pharmacovigilance Telephone Call Center (24 hours/7 days): 855-463-5127
- Pharmacovigilance Fax: 855-631-0644
- General and Emergency email: drugsafety.USA@Ipsen.com
- Affiliate general Pharmacovigilance mailbox: pharmacovigilance.USA@ipsen.com

11.0 STUDY MANAGEMENT

11.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB approved consent form.

Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

11.1.1 Consenting Subjects with Limited Proficiency in English

For potential study patients with limited proficiency in English, a short form consent document (written in the language understood by the patient) will be used during the initial consent process. In addition, the services of an interpreter who is fluent in both English and the language understood by the potential study patient will be used to explain the contents of the long form consent document (written in English). If the patient enrolls, they will be re-consented using an IRB-approved long form consent document that has been translated to the language understood by the patient, when it is available. The process will be conducted in accordance with guidelines and policies of the IRB of record.

11.2 Amendments

Amendments to the protocol will be maintained by the assigned Medical Writer. Requests for revisions may come from multiple sources, including but not limited to the Principal Investigator, study team, drug company, or FDA. All amendments will be subject to the review and approval of the appropriate local, institutional, and governmental regulatory bodies, as well as by Ipsen. Amendments will be distributed by the lead institution (Northwestern) to all participating sites upon approval by the Northwestern University IRB.

11.3 Registration Procedures

11.3.1 Registering a Subject to the Safety Lead-In Cohort

For potential subjects for the safety lead-in portion, study teams are asked to inform the assigned QAM (croqualityassurance@northwestern.edu) of the date and time that the subject will need to be registered.

BEFORE a subject can be treated on study, the following items must be completed and submitted to confirm eligibility and receive an identification number:

- Subject's signed and dated informed consent form (upload to NOTIS and keep original hard copy in a secure location/study chart)
- Copy of the pathology report (upload to NOTIS)
- Signed and dated Eligibility Checklist (upload to NOTIS and keep original hard copy in a secure location/study chart)

The assigned QAM will review all source documentation required to confirm eligibility that is readily available in the subject's electronic medical record (EMR). Any information that is not available in the EMR must be de-identified and emailed to the QAM. Once the QAM confirms the subject is eligible, he or she will register the subject, assign a subject identification number, provide a cohort assignment (as applicable), and send a confirmation of registration to involved

personnel. Registration will then be complete and the subject may begin study treatment.

11.3.2 Registering a Subject after the Safety Lead-In Cohort has been Filled

For potential subjects for phase II/III and select pilot studies, study teams are asked to inform the assigned QAM (croqualityassurance@northwestern.edu) of the date and time that the subject will need to be registered.

BEFORE a subject can be treated on study, the following items must be completed and submitted to confirm eligibility and receive a subject identification number:

- Subject's signed and dated informed consent form (upload to NOTIS and keep original hard copy in a secure location/study chart)
- Copy of the pathology report (upload to NOTIS)
- Signed and dated Eligibility Checklist (upload to NOTIS and keep original hard copy in a secure location/study chart)

The assigned QAM will review the registration documents. Once review is complete, he or she will register the subject, assign a subject identification number, provide a cohort assignment (as applicable) and send a confirmation of registration to involved personnel. Registration will then be complete and the subject may begin study treatment.

11.4 Data Submission

Data collection for this study will be done through NOTIS. Access to the trial in NOTIS is granted to appropriate roles identified at the time of participating site activation, or upon request. Site users will not be able to access the study in NOTIS until all required and study specific trainings are completed.

Once a subject is confirmed and registered to the study, eCRFs should be submitted according to the study procedures table. Generally, all data for safety run-ins during the period subjects are evaluated for Dose Limiting Toxicities (DLTs) must be submitted on a weekly basis. Generally, for all other phase II subjects, data are due with 10 days of a visit or end of cycle. A set amount of data may also be requested for any screen failures, as is defined by the study. In most instances, this will include collection of adverse events and baseline data from the time of registration to the date of screen failure.

11.5 Instructions for External Participating Sites

Not applicable.

11.6 Data Management and Monitoring/Auditing

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (please refer to the CTO website for additional information). The level of risk attributed to this study requires high intensity monitoring, as outlined in the DSMP. The assigned QAM,

with oversight from the Data and Safety Monitoring Committee, will monitor this study in accordance with the study phase and risk level. In addition, the study will abide by all safety reporting regulations, as set forth in the Code of Federal Regulations.

11.7 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.7.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, a modification must be submitted to the NU IRB within 5 business days of making the change, and the assigned QAM must be notified within 24 hours of such change. Such modifications also need to be reported to the FDA, as applicable, within the appropriate timelines.

11.7.2 Other Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that is under the investigator's control and that has not been approved by the Institutional Review Board (IRB). Protocol deviations must be reported according to the policies and procedures of the IRB of record.

A protocol deviation may be considered an instance of Reportable New Information (RNI) if it:

- Has harmed or increased the risk of harm to one or more research participants
- Has compromised the rights and welfare of the research subject
- Has damaged the scientific integrity of the data collected for the study
- Results from willful or knowing misconduct on the part of the investigator(s)
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies

All protocol deviations will be documented by the study team on a paper or electronic deviation tracking log (see NOTIS for copy of log) as they occur. The deviation tracking log must be made available upon request for review by the assigned QAM. The deviation tracking log must be reviewed, signed, and dated by the investigator prior to each monitoring visit, or otherwise in a timely manner, whichever occurs first. The PI signed and dated deviation tracking log will be uploaded to eCRFs prior to each scheduled monitoring visit or upon request.

Deviations will be reviewed per the DSMP.

11.8 Investigator Obligations

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The PI is responsible for personally overseeing the treatment of all study subjects. The PI must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected, entered onto the appropriate eCRFs, and submitted within the study-specific timeframes. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. The study may also be subject to routine audits by the Audit Committee, as outlined in the DSMP.

11.9 Publication Policy

All potential publications and/or data for potential publications (e.g. manuscripts, abstracts, posters, clinicaltrials.gov releases) must be approved in accordance with the DSMC Data Release Policies and Processes. The assigned QAM will prepare a preliminary data set for DSMC approval no later than 3 months after the study reaches its primary completion date, as defined by ClinicalTrials.gov. This is the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated. If the investigator would like data release to be approved by the DSMC prior to when study design specifies, and/or prior to three months after a study's primary completion date, the PI must send a written request for data approval to the QAM which includes justification. Requests must be made a minimum of six to eight weeks in advance of the expected deadline. The request will be presented to the DSMC at their next available meeting. Any DSMC decisions regarding data release will be provided to the PI. If the request is approved, the QAM will present the data set to the DSMC for approval. A final, DSMC-approved dataset, as applicable, will then be released 6-8 weeks after the request was made. The investigators are expected to use only DSMC-approved data and statistical analyses any time they are disseminating trial data. The investigators must send a copy of the draft abstract/poster/manuscript to the study's biostatistician and assigned QAM to confirm that the DSMC-approved data and statistical analyses are used appropriately. Once the biostatistician and QAM gives final approval, the publication may be submitted to external publisher.

APPENDICES

Appendix A Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

ECOG (Zubrod) Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Adapted from:
Oken, M.M., et. al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Appendix B New York Heart Association (NYHA) Classification of Cardiac Failure

NYHA Functional Classification	
Class	**Symptoms** Those with cardiac disease and the following symptoms:
I	**No limitation of physical activity**. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	**Slight limitation of physical activity.** Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	**Marked limitation of physical activity.** Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
IV	**Unable to carry on any physical activity without discomfort.** Symptoms of heart failure or the angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Adapted from:
The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

Appendix C Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

RECIST version 1.1 will be used in this trial for assessment of tumor response. The information in this appendix has been adapted from the published criteria and is provided as a reference. Please refer to the published criteria for additional information. Questions regarding the criteria should be directed to the lead PI. The published criteria can be accessed at:

https://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf

RECIST 1.1 RESPONSE EVALUATION	
EVALUATION OF TARGET LESIONS	
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
EVALUATION OF NON-TARGET LESIONS	
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD)	Unequivocal progression (refer to the published criteria for details) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Equivocal Progression:

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected. Refer to the published criteria for additional information regarding the determination of ‘unequivocal’ and ‘equivocal’ progression.

Method of Assessment:

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Selection of Target and Non-Target Lesions:

When more than one measurable lesion is present at baseline, all measurable lesions up to a maximum of five measurable lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance, the next largest lesion that can be measured reproducibly should be selected.

Pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression.'

Measurable Tumor Lesions:

Measurable disease per RECIST 1.1 is defined as the presence of at least one measurable lesion. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm; see Appendix II of the published criteria for information on imaging guidance).
- 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion.

Measurability of Malignant Lymph Nodes:

To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis of these nodes will be measured and followed. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

Non-Measurable Tumor Lesions:

All lesions that do not meet the above definition of measurable lesions/nodes, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis) as well as truly non-measurable lesions are considered non-measurable disease. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Cystic Lesions:

Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

Adapted from:

E.A. Eisenhower, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan; 45(2):228-47.

Appendix D Common Terminology Criteria for Adverse Events (CTCAE) v5.0

The descriptions and grading scales found in the revised National Cancer Institute's Common Terminology Criteria for Adverse Events version 5.0 (NCI-CTCAE v5.0) will be used to assess adverse events for this trial. NCI-CTCAE v5.0 is available at the following link: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

Refer to Section 10.0 for additional details on adverse events assessment and reporting.

Appendix E Cockcroft-Gault Equation for Creatinine Clearance

The Cockcroft and Gault formula for creatinine clearance is recommended as an estimate of glomerular filtration rate (GFR) for assisting with drug dosing decisions in renal impairment.

For Females:

$$\text{Creatinine Clearance} = \frac{0.85 \times (140 - \text{age in years}) \times (\text{weight in kg})}{72 \times (\text{serum creatinine in mg/dL})}$$

OR

$$\frac{0.85 \times (140 - \text{age in years}) \times (\text{weight in kg})}{0.814 \times (\text{serum creatinine in } \mu\text{mol/L})}$$

Adapted from: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

Appendix F Summary of Changes

Protocol Amendment 1—December 11, 2020			
Section	**Prior Version**	**Amendment 1 Revisions**	**Rationale**
Cover page	IND number: TBD	IND number: 153324	Administrative update to add IND number
Cover page and throughout	Protocol version/date: August 6, 2020 (Initial version)	Protocol version/date: December 11, 2020 (Amendment 1)	Administrative update
Table of Contents	N/A	Updates the Table of Contents	Administrative update
Inclusion Criterion 3.1.8 Appendix E (Cockcroft-Gault Equation for Creatinine Clearance)	Inclusion criterion 3.1.8 required serum creatinine ≤ 1.5 x ULN at study entry	Inclusion criterion 3.1.8 has been revised to require creatinine clearance ≥ 60 mL/min at study entry, as calculated per the Cockcroft-Gault formula. Appendix E has been added to reference the formula.	Revision in response to the following **FDA** reviewer comment: *"Modify inclusion criteria to use creatinine clearance calculated using Cockcroft-Gault Equation rather than serum creatinine."*
Inclusion Criterion 3.1.9	For subjects with a known history of human immunodeficiency virus (HIV), the HIV viral load must be undetectable for ≥ 6 months prior to registration, and subjects must be receiving effective anti-retroviral HIV therapy, if indicated. *NOTE: HIV testing is not required for subjects without a known history of HIV, unless mandated by a local health authority.*	For subjects with a known history of human immunodeficiency virus (HIV), the HIV viral load must be undetectable for ≥ 6 months prior to registration, and subjects must be receiving effective anti-retroviral HIV therapy, if indicated. *NOTE: HIV testing is not required for subjects without a known history of HIV, unless mandated by a local health authority.* *NOTE: Use of strong CYP3A4 inhibitors/inducers is prohibited (refer to Section 4.4.3 and Exclusion Criterion 3.2.7). Subjects who are using concurrent strong CYP3A4 inhibitors/inducers (e.g., ritonavir, cobicistat) as part of their anti-retroviral therapy (ART) regimen may be switched to an alternative ART regimen (with minimal drug-drug interaction profile) before study participation; however, they are excluded from the study if their regimen*	Revision in response to the following **FDA** reviewer comment: *"Refer to the following guidance: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cancer-clinical-trial-eligibility-criteria-patients-hiv-hepatitis-b-virus-or-hepatitis-c-virus."*

Section	Prior Version	Amendment 1 Revisions	Rationale
		cannot be altered.	
Table 4.2.4 (Definition of DLT)	The DLT criteria for non-hematologic toxicity were as follows: • ≥ Grade 3 treatment-related* toxicity despite the use of adequate/maximal medical interventions and/or prophylaxis as dictated by local institutional clinical practices or the judgment of the treating Investigator, EXCEPT: – nausea, vomiting, or diarrhea (lasting <3 days or without supportive care measures) – alopecia – fatigue – hypersensitivity reaction • Any Grade non-hematologic toxicity that is treatment-related* and which results in a >14 day delay in Cycle 2 Day 1 dosing • Any Grade non-hematologic toxicity that is treatment-related* and which results in a >14 day delay in Cycle 2 Day 1 dosing Footnote: * Treatment-related is defined as any toxicity that is possibly, probably or definitely related to either bevacizumab or irinotecan liposome.	The DLT criteria for non-hematologic toxicity have been revised as follows: • ≥ Grade 3 treatment-related* non-hematologic toxicity despite the use of adequate/maximal medical interventions and/or prophylaxis as dictated by local institutional clinical practices or the judgment of the treating Investigator, EXCEPT: – those that are clearly and incontrovertibly due to disease progression or extraneous causes – ≥ Grade 3 fatigue lasting < 7 days • Any Grade non-hematologic toxicity that is treatment-related* and which results in a >14 day delay in Cycle 2 Day 1 dosing • An elevated alanine or aspartate aminotransferase (ALT or AST) lab value that is ≥ 3X the ULN, and at the same time, an elevated serum total bilirubin lab value that is ≥ 2X the ULN, and at the same time, an alkaline phosphatase (ALP) lab value that is < 2X the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing. Footnote: * Treatment-related is defined as any toxicity that is possibly, probably or definitely related to either bevacizumab or irinotecan liposome.	Revision in response to the following **FDA** reviewer comment: *"Modify your DLT criteria to include:* *a. Hy's law* *b. Grade 3 or higher fatigue ≥ 7 days should be considered at DLT* c. *Any grade ≥3 treatment related non-hematologic toxicity despite the use of adequate/ maximal medical interventions EXCEPT those that are clearly and incontrovertibly due to disease progression or extraneous causes."*
Section 5.0 (Study Procedures and Schedule of Assessments)	N/A	Adds a physical exam to the End of Treatment Visit. Adds a comprehensive chemistry panel to the Safety Follow Up Visit	Addition of assessments for safety monitoring

Section	Prior Version	Amendment 1 Revisions	Rationale
Section 11.1.1	N/A	Adds Section 11.1.1 to describe provisions for consenting subjects with limited proficiency in English: For potential study patients with limited proficiency in English, a short form consent document (written in the language understood by the patient) will be used during the initial consent process. In addition, the services of an interpreter who is fluent in both English and the language understood by the potential study patient will be used to explain the contents of the long form consent document (written in English). If the patient enrolls, they will be reconsented using an IRB-approved long form consent document that has been translated to the language understood by the patient, when it is available. The process will be conducted in accordance with guidelines and policies of the IRB of record.	Revision in response to the following **IRB** reviewer comment: *"What are the provisions for non-English speakers?"*
Appendix F (Summary of Changes)	N/A	Adds a 'Summary of Changes' to summarize protocol revisions	Administrative update
Throughout	N/A	Adjusts formatting and style to accommodate protocol revisions. Corrects typographical errors.	Administrative update.

Protocol Amendment 2—November 30, 2021

Section	Revision	Rationale
Cover page & throughout	Updates protocol version/date from December 11, 2020 (Amendment 1) to November 30, 2021 (Amendment 2)	Administrative update
Table of Contents & Throughout	Updates page numbers on the bottom of each page and in the Table of Contents	Administrative update

Section	Revision	Rationale
Inclusion criterion 3.1.14	Addition of bolded text: For subjects with hypertension, hypertension must be well controlled on medication. *NOTE: For the purposes of determining eligibility only, uncontrolled hypertension **at baseline** is defined as a consistent **baseline** bp of ≥ 140 mmHg systolic **and**/or ≥ 90 mmHg diastolic, on initial and repeat checks**. (A repeat check is only required if the initial check is ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic.)***	Revises language to clarify that baseline blood pressure checks only need to be repeated in cases where the bp is ≥ 140 mmHg systolic of ≥ 90 mmHg diastolic.
Exclusion criterion 3.2.1	Deletion of strikethrough text: Exclusions for receipt of prior systemic anti-cancer therapy: • Subjects must not have received any prior irinotecan-based therapies. • Subjects must not have received more than 3 prior platinum-based chemotherapy regimens. • Subjects must not have received more than 2 prior non-platinum, cytotoxic chemotherapy regimens. *Note: Prior receipt of ~~non-VEGF-targeting~~ biological therapies is permitted. These may include but are not limited to hormonal therapies, immunotherapies, monoclonal antibodies (mAbs), tyrosine kinase inhibitors (TKIs), poly (ADP-ribose) polymerase (PARP) inhibitors, or other targeted agents. Refer to the below exclusion criterion for washout rules.*	Administrative update to correct discrepancy. Revises language to align with exclusion criterion 3.2.2, where prior receipt of VEGF-targeting therapies is permitted, provided such agents are not administered within 3 months prior to registration
Exclusion criterion 3.2.2 & Applicable repetitive sections throughout	Deletion of strikethrough text and addition of bolded text: Exclusions for washout from prior systemic anti-cancer therapy: • Subjects must not have received chemotherapy, immunotherapy, monoclonal antibody (mAb) therapy, hormonal therapy, or other targeted therapy within ≤ 14 days prior to registration. • Subjects must not have received investigational agents or investigational devices within ≤ 14 days prior to registration. • Subjects must not have received VEGF-targeting agents, including bevacizumab, within ≤ ~~6 months~~ **3 months** prior to registration.	Revises washout from prior bevacizumab therapy from 6 months to 3 months per PI request. Six months is unnecessarily long and is an accrual barrier.
Exclusion criterion 3.2.6 & Applicable repetitive sections throughout	Deletion of strikethrough text and addition of bolded text: Subjects must not have received hematologic growth factors and/or blood products (transfusions) within ≤ ~~28 days~~ **14 days** prior to registration.	Revises washout from prior hematologic growth factors and/or blood products from 28 days to 14 days per PI request. Twenty eight days is unnecessarily long for this patient population and is an accrual barrier.

Section	Revision	Rationale
Exclusion criterion 3.2.9	Deletion of strikethrough text and addition of bolded text: Subjects must not have **current clinical symptoms of bowel obstruction or** a history of bowel obstruction within ≤ 6 months prior to registration. ~~Subjects also must not have:~~ • ~~Current evidence of tumor recto-sigmoid involvement by pelvic examination~~ • ~~Current tumor bowel involvement on CT scan~~ • ~~Current clinical symptoms of bowel obstruction~~	Revises the exclusion criterion regarding tumor bowel involvement for clarity, per PI request.
Section 4.6.1 (Short Term Safety Follow Up Phase) & Section 5.0 (Study Procedures and Schedule of Assessments)	Deletion of strikethrough text and addition of bolded text to Section 4.6.1. Addition of bolded text to footnote 20 of Section 5.0. ~~All subjects who have received at least 1 dose of either irinotecan liposome or bevacizumab will have an EOT visit 0-7 days after the last dose of trial therapy and prior to initiation of subsequent therapy.~~ **Subjects who have received at least 1 dose of either irinotecan liposome or bevacizumab will have an end of treatment (EOT) visit ≤14 days after the decision to permanently discontinue trial therapy. If feasible, it is recommended that the EOT visit occur prior to the initiation of subsequent therapy. *EXCEPTION: The EOT visit is not required if it would fall within ≤ 14 days of the safety follow up visit; in these cases, the EOT visit may be skipped, and instead the patient may proceed to the safety follow up visit.***	Extends the window for the end of treatment visit to accommodate flexibility in patient scheduling.
Section 5.0 (Study Procedures and Schedule of Assessments)	Deletion of strikethrough text and addition of bolded text: Study Procedures and Schedule of Assessments Table, Footnote 9: For subjects with hypertension at baseline, hypertension must be well controlled ~~(well controlled is defined as < 160 mmHg systolic and < 100 mmHg diastolic on initial and repeat checks)~~ **[uncontrolled at baseline is defined as a baseline bp of ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic on initial and repeat checks (A repeat check is only required if the initial check is ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic)]** on medication within ≤ 28 days prior to registration. Refer to Inclusion Criterion 3.1.14 for details.	Corrects discrepancy. Revises the definition of 'uncontrolled baseline hypertension' in footnote 9 of Section 5.0 to align with the definition as it is written in Section 3.1.14.
Section 5.0 (Study Procedures and Schedule of Assessments)	Deletion of strikethrough text and addition of bolded text: Study Procedures and Schedule of Assessments Table, Footnote 17: Abbreviation for hepatitis B virus = ~~HBC~~ **HBV**	Administrative update. Corrects typographical error.

Section	Revision	Rationale
Table 4.3.3 (Prohibited Medications and Therapies)	Addition of bolded text: Hematologic growth factors and blood products (transfusions): Not permitted while receiving trial therapy **for subjects participating in the safety lead-in portion of the study.** Should a subject **who is participating in the safety lead-in portion of the study** require the use of these agents while receiving trial therapy, trial therapy must be discontinued. ***(Note: These agents are permitted for subjects who are not participating in the safety lead-in.)***	Per PI request, removes hematologic growth factors and/or blood products from the list of prohibited medications for patients who are not participating in the safety lead-in portion of the trial. Use of these agents is reasonable in this patient population after the safety lead-in has been completed.
Section 4.6.1 (Short Term Safety Follow Up Phase) & Section 4.6.2 (Long Term Follow Up Phase)	Addition of bolded text. 4.6.1—Safety Follow Up Visit: Refer to Section 5.0 for details on the assessments that are to be conducted at the safety follow up visit. All subjects who have received at least 1 dose of either irinotecan liposome or bevacizumab will have a safety follow up visit approximately 30 days (± 7 days) after the last dose of study medication. Subjects will be followed for toxicity and concomitant medication use through this visit. In addition, subjects who are removed from treatment for unacceptable adverse events will be followed **clinically (per standard of care)** until resolution or stabilization of the adverse event**, or as indicated**. **After completion of the Safety Follow Up Visit, patients who have discontinued trial therapy for reasons other than disease progression will proceed to the Long Term Follow Up Phase of the study (Section 4.6.2). Patients who have discontinued trial therapy due to disease progression will discontinue study participation upon completion of the Safety Follow Up Visit (i.e., Long Term Follow Up Phase is not required).** **NOTE: Subjects experiencing ongoing drug-related toxicity at the time of the Safety Follow Up Visit may continue to be followed clinically (per standard of care) until resolution or stabilization of the adverse event, or as indicated.** 4.6.2—Long Term Follow Up Phase: Following the last dose of trial therapy, subjects **who have not yet progressed** will be followed for up to 3 years, or until progression, initiation of subsequent anti-cancer therapy, withdrawal, or death; whichever occurs first. As outlined in Section 5.0, follow every 3 months (± 14 days) for 1 year post-last dose, then every 6 months (± 30 days) thereafter, for up to a total of 3 years.	Administrative revision to add clarifying language. Clarifies that the Long Term Follow Up Phase of the study is only for patients who have not yet progressed.
Section 7.5 (Definitions)	Deletion of strikethrough text and addition of bolded text: DOR is defined as the time that elapses between the first day of documented response to trial therapy and subsequent disease progression. For DOR analysis, response is defined as complete response (CR) **or** partial response (PR) ~~or stable disease (SD)~~ per RECIST 1.1 criteria; and disease progression is defined as progressive disease (PD) per RECIST 1.1 criteria. Refer to Section 7.2.3 for additional details.	Administrative update to correct discrepancy. Corrects error in definition of “duration of response” to align with Section 7.2.3.

Section	Revision	Rationale
Section 10.3.2.4 (Reporting to Ipsen)	Addition of bolded text: The Coordinating Center will send the initial completed SAE form within 24 hours of notification via email to Ipsen (drugsafety.USA@ipsen.com)... **…For questions regarding the reporting process, please contact Ipsen:** • **Pharmacovigilance Telephone Call Center (24 hours/7 days): 855-463-5127** • **Pharmacovigilance Fax: 855-631-0644** • **General and Emergency email: drugsafety.USA@Ipsen.com** • **Affiliate general Pharmacovigilance mailbox: pharmacovigilance.USA@ipsen.com**	Administrative update. Adds additional contact information for Ipsen's Pharmacovigilance Team.
Throughout	Grammatical and formatting edits.	Administrative update

Protocol Amendment 3—January 20, 2022

Section	Revision	Rationale
Cover page & throughout	Updates protocol version/date from November 30, 2021 (Amendment 2) to January 20, 2022 (Amendment 3)	Administrative update
Table of Contents & Throughout	Updates page numbers on the bottom of each page and in the Table of Contents	Administrative update
Inclusion criterion 3.1.16	Deletion of strikethrough text and addition of bolded text: Females of reproductive potential must agree to use adequate contraception (abstinence or two methods of birth control, such as a barrier method in combination with hormonal contraception) while receiving trial therapy and for ~~6 months~~ **7 months** following completion of trial therapy.	Increases the required contraception timeframe for females from 6 months post-therapy to 7 months post-therapy, to align with the current Invesgiator's brochure (version 15, dated December 2021) for irinotecan liposome injection.
Section 5.0 (Study Procedures and Schedule of Assessments Table)	Deletion of strikethrough text and addition of bolded text: Footnote 4: Prior to registration, females of reproductive potential must agree to use adequate contraception (abstinence or two methods of birth control, such as a barrier method in combination with hormonal contraception) while receiving trial therapy and for ~~6 months~~ **7 months** following completion of trial therapy.	Increases the required contraception timeframe for females from 6 months post-therapy to 7 months post-therapy, to align with the current Invesgiator's brochure (version 15, dated December 2021) for irinotecan liposome injection.

Section	Revision	Rationale
Exclusion criterion 3.2.15	Addition of bolded text: Subjects must not have received a live vaccine within ≤ 30 days prior to registration. *NOTE: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines and are not allowed.* ***If a subject receives SARS-CoV-2 vaccinations (COVID-19 vaccinations) during study participation, it is the responsibility of the investigator to determine the suitability of the vaccine being given with the information provided by the manufacturer.***	Provides guidance for SARS-CoV-2 (COVID-19) vaccinations, to align with the current Invesgiator's brochure (version 15, dated December 2021) for irinotecan liposome injection.
Table 4.4.3 (Prohibited Medications and Therapies)	Live vaccines: Not permitted within ≤ 30 days prior to registration or while receiving trial therapy. Should a subject require the use of these agents while receiving trial therapy, trial therapy must be discontinued. *NOTE: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines and are not allowed.* ***If a subject receives SARS-CoV-2 vaccinations (COVID-19 vaccinations) during study participation, it is the responsibility of the investigator to determine the suitability of the vaccine being given with the information provided by the manufacturer.***	Provides guidance for SARS-CoV-2 (COVID-19) vaccinations, to align with the current Invesgiator's brochure (version 15, dated December 2021) for irinotecan liposome injection.
Section 9.2.8 (Irinotecan Liposome Injection—Incompatibilities)	Deletion of strikethrough text and addition of bolded text: Incompatibilities—None known. Irinotecan liposome injection has been tested for compatibility with ~~limited~~ **a number of** materials, and no compatibility issues have been identified. **Infusion sets without inline filters are recommended for use. However, an infusion set with an in-line filter that has a pore size of at least 0.2 µm is compatible for use.** ~~The following materials were tested:~~ ~~• Infusion sets (without in-line filter) made of PVC or polyethylene lined~~ ~~• IV bags made of PVC or coextruded film of polyolefin/polyamide~~	Updates information regarding compatibility of irinotecan liposome injection with infusion sets, to align with the current Investigator's brochure for irinotecan liposome injection.
Appendix F (Summary of Changes)	Adds a summary of revisions for protocol amendment 3	Administrative update

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