UNC LINEBERGER
CLINICAL ONCOLOGY RESEARCH PROGRAM
UNVERSITY OF NORTH CAROLINA AT CHAPEL HILL

PROTOCOL AMENDMENT #05

LCCC 1317: GENIC, A Genotype-directed Phase II Study of Irinotecan Dosing in Metastatic Colorectal Cancer (mCRC) Patients Receiving FOLFIRI + Bevacizumab

AMENDMENT INCORPORATES (check all that apply):

_X_ Editorial, administrative changes
___ Scientific changes (IRB approval)
___ Therapy changes (IRB approval)
___ Eligibility Changes (IRB approval)

Summary of Changes:

1. Section 4.3 – clarify that Bevacizumab initiation may be delayed until cycle 2 day 1 at the discretion of the investigator in case of prior minor surgery.
2. Section 6.0, Time and Events Table – a five business day window for when the clinician should complete the PRO-CTCAE Clinician Form was added to footnote #11.
3. Section 9.1 – the Clinician or a designee (such as the study coordinator) may complete the PRO-CTCAE Clinician Form on Day 15. Additionally, mandatory participation in the PRO-CTCAE sub-study is not required for non-English speaking patients and they will not be asked to participate.
4. Section 9.6.2 – a designee may complete the PRO-CTCAE Clinician Form on Day 15.
5. Section 12.8 (Appendix H) – the PRO-CTCAE Clinician Form signature line was revised to indicate a designee may sign as well as the investigator.

THE ATTACHED VERSION DATED JULY 11, 2018 INCORPORATES THE ABOVE REVISIONS

ATTACH TO THE FRONT OF EVERY COPY OF PROTOCOL

UNC LINEBERGER
CLINICAL ONCOLOGY RESEARCH PROGRAM
UNVERSITY OF NORTH CAROLINA AT CHAPEL HILL

PROTOCOL AMENDMENT #04

LCCC 1317: GENIC, A Genotype-directed Phase II Study of Irinotecan Dosing in Metastatic Colorectal Cancer (mCRC) Patients Receiving FOLFIRI + Bevacizumab

AMENDMENT INCORPORATES (check all that apply):
X__Editorial, administrative changes
X__Scientific changes (IRB approval)
X__Therapy changes (IRB approval)
___Eligibility Changes (IRB approval)

Summary of Changes:

1. Main Consent v10/11/17 - Updates the consent risk language for FOLFIRI and include cardiac risks for 5FU
2. Section 4.2.2 - Clarifies that infusion times are provided as an approximate guide but may vary per institutional guidelines
3. Section 4.3 - Clarifies that stopping and/or dropping irinotecan is allowed after 4 cycles at treating physician's discretion as warranted by disease status and side effects (ex. low tumor burden while experiencing significant AEs related to irino)
4. Section 4.3 - Clarifies that leucovorin can be omitted at treating physician's discretion
5. Section 4.3 - Bevacizumab initiation may be delayed until cycle 1 day at the discretion of the investigator in case of prior minor surgery.
6. Section 4.3.2 Footnote 6 - Clarifies that dose modifications are only required for clinically significant grade 3-4 adverse events (ex not required for asymptomatic electrolyte disturbances)
7. Section 6.1 - Clarifies that UGT1A1 genotyping is determined from germline sequencing and once collected per protocol is not subject to a collection window.

THE ATTACHED VERSION DATED October 04, 2017 INCORPORATES THE ABOVE REVISIONS

ATTACH TO THE FRONT OF EVERY COPY OF PROTOCOL

UNC LINEBERGER
CLINICAL ONCOLOGY RESEARCH PROGRAM
UNVERSITY OF NORTH CAROLINA AT CHAPEL HILL

PROTOCOL AMENDMENT #03

LCCC 1317: GENIC, A Genotype-directed Phase II Study of Irinotecan Dosing in Metastatic Colorectal Cancer (mCRC) Patients Receiving FOLFIRI + Bevacizumab

AMENDMENT INCORPORATES (check all that apply):
X__Editorial, administrative changes
___Scientific changes (IRB approval)
X__Therapy changes (IRB approval)
___Eligibility Changes (IRB approval)

Summary of Changes:

- Sect 4.3.2 FOLFIRI Dose Modifications: revised to provide additional guidance for grade 3 and 4 neutropenia and grade 2 mucositis

THE ATTACHED VERSION DATED December 09, 2015 INCORPORATES THE ABOVE REVISIONS

ATTACH TO THE FRONT OF EVERY COPY OF PROTOCOL

UNC LINEBERGER
CLINICAL ONCOLOGY RESEARCH PROGRAM
UNVERSITY OF NORTH CAROLINA AT CHAPEL HILL

PROTOCOL AMENDMENT # 02

LCCC 1317: GENIC, A Genotype-directed Phase II Study of Irinotecan Dosing in Metastatic Colorectal Cancer (mCRC) Patients Receiving FOLFIRI + Bevacizumab

AMENDMENT INCORPORATES (check all that apply):
X Editorial, administrative changes
X Scientific changes (IRB approval)
Therapy changes (IRB approval)
X Eligibility Changes (IRB approval)

Summary of Changes

1. Title revised to read: "GENIC, A Genotype-directed Phase II Study of Irinotecan Dosing in Metastatic Colorectal Cancer (mCRC) Patients Receiving FOLFIRI + Bevacizumab."
2. Section 9.1 Background , Appendices G and H: Recall interval (days) for PROCTCAE questionnaires revised from "previous 7 days" to "previous 14 days".
3. Remove Anna Snavely and add Allison Deal as statistician of record.
4. Section 3.2.6. Added statement "Addition or increase of standard of care antihypertensive regimen to control hypertension is allowed."
5. Section 6.1 Time and events table: HISTORY footnote 4. The day 1 and 15 "History" collected by study coordinator /personnel to assess adverse events, this revision also occurs in Sections 6.3.1, 6.3.2 and 6.4.
6. Section 6.3.1, 6.3.2 and 6.4 Concomitant Medications: we are not collecting concomitant medication information, section is revised to state "review for prohibited concomitant medications".
7. Change exclusion 3.2.1.6 to:

   3.2.16 Proteinuria as demonstrated by:
   Urine protein: creatinine (UPC) ratio ≥ 1.0 at screening (patients discovered to have a UPC >=1 should undergo a 24 hour urine collection and must demonstrate ≤ 1g of protein in 24 hours to be eligible).
   OR
   "Urine dipstick for proteinuria ≥ 2+ (patients discovered to have ≥2+ proteinuria on dipstick urinalysis may either undergo Urine protein: creatinine (UPC) testing, and may participate if ratio <1. 0 or should undergo a 24 hour urine collection and must demonstrate ≤ 1g of protein in 24 hours to be eligible)
8. Revised link in 12.6 Appendix F to http://medicine.iupui.edu/clinpharm/ddis/

THE ATTACHED VERSION DATED February 10, 2015 INCORPORATES THE ABOVE REVISIONS

ATTACH TO THE FRONT OF EVERY COPY OF PROTOCOL

PROTOCOL AMENDMENT #_01

LCCC 1317: Genotype-directed Phase II Study of Irinotecan Dosing in Metastatic Colorectal Cancer (mCRC) Patients Receiving FOLFIRI + Bevacizumab

AMENDMENT INCORPORATES (check all that apply):
X__Editorial, administrative changes
X__Scientific changes (IRB approval)
___ Therapy changes (IRB approval)
X__Eligibility Changes (IRB approval)

AMENDMENT RATIONALE AND SUMMARY:

Sections: 3.0, 6.0, 9.0, 10.3.2, 10.4.2, 12.7 Appendix G and 12.8 Appendix H -
This amendment was driven by incorporation of a sub-study in LCCC1317. This PRO-CTCAE sub-study will evaluate the feasibility of a proposed system of collecting Patient Reported Outcomes (PRO) and corresponding clinician assessed symptomatic adverse events of interest in the LCCC 1317 population across multiple participating sites. This change is reflected in the study synopsis, eligibility criterion 3.1.9, the Time and Events table, study assessment sections 6.2-6.3, in sections 10.3-10.4, and in detail in section 9.0.

Title Page: Added investigators for the PRO-CTCAE sub-study: William A. Wood, MD, MPH; Ethan Basch, MD

Sections: 6.1, 6.3.1, 6.3.3, 6.6.2, 6.6.3 - In addition, the volume of blood for exploratory correlative studies within LCCC1317 was increased from 5mL to 10mLs (D1 cycle 1, and every odd numbered cycle thereafter), and from 5 to 5-7mLs (D1 cycle 1).

Sections: 1.4, 3.1.9 and 3.2.2 - Modified eligibility criteria for LCCC1317 to exclude Asian patients from study because genotyping assay used does not test for *6 allele, which is more common in Asian patients. Patients with this allele would be classified as *1 carriers, placing them at increased risk of irinotecan-induced toxicity. Added reference #28.

THE ATTACHED VERSION DATED MAY 2, 2014 INCORPORATES THE ABOVE REVISIONS

ATTACH TO THE FRONT OF EVERY COPY OF PROTOCOL

UNC LINEBERGER
CLINICAL ONCOLOGY RESEARCH PROGRAM
UNVERSITY OF NORTH CAROLINA AT CHAPEL HILL

LCCC 1317: GENIC, A Genotype-directed Phase II Study of Irinotecan Dosing in Metastatic Colorectal Cancer (mCRC) Patients Receiving FOLFIRI + Bevacizumab

Principal Investigator
Hanna K. Sanoff, MD, MPH
University of North Carolina at Chapel Hill
Department of Medicine, Division of Hematology/Oncology
170 Manning Drive, CB 7305, Chapel Hill, NC 27599
[redacted]

Co-Principal Investigator
Federico Innocenti, MD, PhD

PRO-CTCAE Sub-Study Investigators
William A. Wood, MD, MPH
Ethan Basch, MD

Biostatistician
Allison Deal, MS
UNC Lineberger Comprehensive Cancer Center, Room 20-024
[redacted]

Clinical Protocol Office
Lineberger Comprehensive Cancer Center
The University of North Carolina at Chapel Hill
450 West Drive, 3rd Floor, CB# 7295
Chapel Hill, NC 27599-7295

University of North Carolina Cancer Network (UNCCN) Study Coordinator:
Phone: 919-966-7359 Fax: 919-966-4300

Sponsor: Lineberger Comprehensive Cancer Center
Funding Source: University Cancer Research Fund (UCRF)

Version: Amendment 01 dated May 2, 2014
Amendment 02 dated February 10, 2015
Amendment 03 dated December 09, 2015
Amendment 04 dated October 04, 2017
Amendment 05 dated July 11, 2018

UNC LINEBERGER
CLINICAL ONCOLOGY RESEARCH PROGRAM
UNVERSITY OF NORTH CAROLINA AT CHAPEL HILL

LCCC 1317: GENIC, A Genotype-directed Phase II Study of Irinotecan Dosing in Metastatic Colorectal Cancer (mCRC) Patients Receiving FOLFIRI + Bevacizumab

Principal Investigator
Hanna K. Sanoff, MD, MPH
University of North Carolina at Chapel Hill
Department of Medicine, Division of Hematology/Oncology
170 Manning Drive, CB 7305, Chapel Hill, NC 27599
[redacted]

Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name:_____

PI Signature: _____

Date:_____

TABLE OF CONTENTS

1.0 BACKGROUND AND RATIONALE 1

1.1 Study Synopsis 1

1.2 Colorectal Cancer Therapy 1

1.3 Irinotecan in mCRC 2

1.4 Rationale 5

2.0 OBJECTIVES 6

2.1 Primary Objective 6

2.2 Secondary Objectives 6

2.3 Exploratory Objective 6

2.4 Endpoints 6

3.0 PATIENT ELIGIBILITY 7

3.1 Inclusion Criteria 7

3.2 Exclusion Criteria 7

4.0 TREATMENT PLAN 9

4.1 Schema 9

4.2 Treatment Dosage and Administration 10

4.3 Toxicities and Dosing Delays/Dose Modifications 11

4.4 Concomitant Medications/Treatments 17

4.5 Duration of Therapy 18

4.6 Duration of Follow Up 18

4.7 Removal of Patients from Protocol Therapy 18

4.8 Study Withdrawal 19

5.0 DRUG INFORMATION 19

5.1 Irinotecan (Camptosar®) 19

5.2 5-Fluorouracil (5-FU) 21

5.3 Leucovorin 23

5.4 Bevacizumab (Avastin®) 24

6.0 EVALUATIONS AND ASSESSMENTS 28

6.1 Time and Events Table 28

6.2 Pre-Study Assessments 30

6.3 On Study Assessments 31

6.4 End of Treatment Visit 31

6.5 Post-Treatment/Follow-up Assessments 32

6.6 Correlative Studies 32

6.7 Assessment of Safety 33

6.8 Assessment of Efficacy Based on RECIST 1.1 33

7.0 ADVERSE EVENTS 36

7.1 Definitions 37

7.2 Documentation of non-serious AEs or SARs 38

7.3 SAEs or Serious SARs 39

7.4 Data and Safety Monitoring Plan 40

8.0 STATISTICAL CONSIDERATIONS FOR LCCC 1317 41

8.1 Study Design 41

8.2 Sample Size, Stopping Rule and Safety Rule 41

8.3 Data Analysis Plans 42

9.0 PRO-CTCAE Sub-study 43

9.1 Background 43

9.2 Primary Objectives 44

9.3 Secondary Objectives 44

9.4 Exploratory Objectives 45

9.5 Primary Endpoints 45

9.6 Methods 45

9.7 Statistical Considerations 46

10.0 STUDY MANAGEMENT 47

10.1 Institutional Review Board (IRB) Approval and Consent 48

10.2 Required Documentation 48

10.3 Registration Procedures 49

10.4 Data Management and Monitoring 49

10.5 Auditing 50

10.6 Adherence to the Protocol 50

10.7 Amendments to the Protocol 52

10.8 Record Retention 52

10.9 Obligations of Investigators 53

11.0 REFERENCES 54

12.0 APPENDICES 57

12.1 Appendix A ECOG Performance Status 57

12.2 Appendix B List of Prohibited Drugs and Prohibited Juices and Fruits 58

12.3 Appendix C New York Heart Association Functional Classification 59

12.4 Appendix D List of Drugs to be Used with Caution 60

12.5 Appendix E Dietetic and pharmacologic guidelines for the treatment of drug induced diarrhea 61

12.6 Appendix F: Patient Handout: Prohibited Medications or Those to be used with Caution 67

12.7 Appendix G: Subset of PRO-CTCAE Questions 69

12.8 Appendix H: PRO-CTCAE Clinician Form 70

1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

This phase II multicenter clinical trial will use a genotype-guided dosing strategy for irinotecan to prospectively analyze efficacy in 100 metastatic colorectal cancer patients (mCRC) receiving FOLFIRI (5-fluorouracil (5-FU), leucovorin, irinotecan) plus bevacizumab. Irinotecan is detoxified and excreted primarily by glucuronidation in the liver via the isoenzyme uridine diphosphate glucuronosyl transferase (UGT1A1). Common variants in UGT1A1 alter the rate of glucuronidation and thus alter exposure to irinotecan.

The UGT1A1 *28 allele results in slower irinotecan glucuronidation, and thus greater exposure to its active metabolite SN-38. At the standard irinotecan dose used in FOLFIRI (180 mg/m^2; established prior to our understanding of the importance of genotype in the rate of this drug's metabolism), there is a small increased risk of neutropenia in *28 homozygotes. However, the risk of clinically important consequences of neutropenia, such as febrile neutropenia and infection, are not significantly increased. Patients with other genotypes have a quite low risk of adverse effects suggesting patients with these low risk genotypes may tolerate higher doses of irinotecan in FOLFIRI. This finding was demonstrated in a phase I study in which *1/*28 and *1/*1 genotypes were able to tolerate escalating doses of irinotecan up to 260 mg/m^2 and 310 mg/m^2, respectively.

The central hypothesis of this trial is that increasing the irinotecan dose in *1/*28 and *1/*1 genotypes will increase the overall benefit of FOLFIRI for patients with mCRC as these two groups are likely under-dosed with the current dosing regimen. Eligible patients will be genotyped for UGT1A1 and assigned into 1 of 3 different dosing groups, based on their relative rate of metabolism. The primary objective of this trial is to estimate progression-free survival (PFS), and secondary objectives include characterization of toxicity and objective response rate (OR; complete response (CR) + partial response (PR)).

A sub-study of LCCC1317 is described in section 9.0. This sub-study will evaluate the feasibility of a proposed system of collecting Patient Reported Outcomes (PRO) and corresponding clinician assessed symptomatic adverse events of interest in the LCCC 1317 population across multiple participating sites. This sub-study will be mandatory for all patients enrolled in LCCC1317 at UNC, and for all patients at Affiliate sites that elect to participate in this optional sub-study.

1.2 Colorectal Cancer Therapy

Worldwide, colorectal cancer is the fourth most commonly diagnosed malignant disease, with more than 500,000 deaths estimated every year. In the US, colorectal cancer is the third most common malignant disease and the second

most frequent cause of cancer-related death, with more than 50,000 deaths anticipated in 2013. [1]

Acceptable first-line chemotherapy regimens for mCRC include FOLFIRI or FOLFOX (5-FU, leucovorin, oxaliplatin. [2, 3] Bevacizumab, the humanized monoclonal antibody against vascular endothelial growth factor (VEGF) approved for use in combination with chemotherapy for the treatment of mCRC, is routinely used in combination with FOLFIRI or FOLFOX for first-line treatment. [4-6]

Epidermal growth factor receptor (EGFR)-targeted therapies (ie, cetuximab and panitumumab) are occasionally used in first-line therapy in combination with FOLFIRI or FOLFOX (as an alternative to bevacizumab). However, they should only be used after KRAS genotyping of tumor tissue, as neither agent is effective in persons with KRAS mutated disease. [7-9]

Unfortunately, regardless of whether FOLFIRI or a FOLFOX regimen with or without bevacizumab or EGFR-targeted therapy is used as first-line treatment, all patients progress and will require second-line and likely subsequent treatments. [2, 3, 6] This highlights the need for innovative systemic therapies or innovative approaches in patients with mCRC.

1.3 Irinotecan in mCRC

The most commonly used dose of irinotecan within FOLFIRI is 180 mg/m^2 every two weeks [2, 10] however, dose-finding studies during the early development of irinotecan were conducted before knowledge of the genetic basis of irinotecan associated severe toxicity. When dosed based on body surface area and without regard to genotype, the rate of grade 3/4 neutropenia and diarrhea across all cycles in patients receiving FOLFIRI as first-line treatment of mCRC is reported to be 24% and 14%, respectively, with a 7% incidence of febrile neutropenia. [2]

There is extensive clinical experience in non-genotypically selected patients (e.g. including *28 homozygotes) with irinotecan at doses of 350 mg/m^2 alone [11] (and in combination with other chemotherapy [12-14]. Single agent doses of irinotecan up to 500 mg/m^{2}every 21 days were tolerated in a non-genotypically selected patient population.[15]All of these regimens were deemed to have clinically acceptable toxicity.

1.3.1 Irinotecan Metabolism and Relationship to Toxicity

Irinotecan exists as the pro-drug CPT-11 that is converted to its active metabolite, SN-38. This active metabolite is 100-1000x more cytotoxic than CPT-11, and is detoxified and excreted primarily by glucuronidation in the liver via the enzyme UGT1A1. [16] UGT1A1 is polymorphic, with variability in the number of TA amino acid repeats in the UGT1A1 promoter region, ranging from 5-8. Six repeats are the most common, also denoted as *1. The 7 TA repeat polymorphism is referred to as *28.[17]

The UGT1A1*1 allele and *28 allele were reported at a rate of ~45% each in one study of 250 white patients, with the remainder (~10%) homozygous for *28.[18] This *28/*28 genotype is associated with up to a 70% reduction in enzyme activity, higher SN-38 concentrations and a subsequent increased risk of toxicity, particularly neutropenia. [18, 19]

In a study of 86 advanced cancer patients receiving irinotecan monotherapy, an increased SN-38 area under the concentration-time curve (AUC) and the *28/*28 genotype were significantly associated with a lower absolute neutrophil count nadir ($p < 0.0001$). [20] A study in 60 cancer patients receiving irinotecan monotherapy (350 mg/m^2 every 3 weeks) demonstrated a relative risk of 9.3 for grade 4 neutropenia in *28/*28 patients versus *1/*28 and *1/*1 patients.[21]

A meta-analysis including 10 cohorts of patients (for a total of 821 patients) demonstrated a significant increase in grade 3/4 neutropenia for *28/*28 patients at medium (150-250 mg/m^2) and high doses (>250 mg/m^2) of irinotecan (odds ratios of 3.22 and 27.8, respectively), as compared to the *1/*1 or *1/*28 genotype groups.[19]

As a result of these findings, the current US package insert for irinotecan (Camptosar®) includes homozygosity of the UGT1A1*28 allele as a risk factor for severe neutropenia and recommends consideration of initial dose reduction in these patients; a specific recommendation on dose is not provided. Few oncologists follow this practice as the strength of the relationship between genotype and toxicity is not clear, the data are not consistent, and other factors are clearly involved in determining toxicity.[22] In the largest trial included in the meta-analysis (250 patients, >90% of whom received standard-dose FOLFIRI) Toffoli et al reported 13.6% grade ≥3 neutropenia in those homozygous for *28 in cycle 1, as compared to 5.3% of the *28 heterozygotes and 1.7% in the *1/*1 group. While there was a significant association between the *28/*28 genotype and ≥Grade 3 hematologic toxicity in cycle 1 as compared to the *1/*1 genotype, no significant association was seen with irinotecan-associated non-hematologic toxicities (including diarrhea or vomiting) in cycle 1, or in either category of toxicities across the full course of treatment.[18]

A key finding was the low rates of toxicity in the *28 heterozygotes and the *1 groups, rates considerably lower than those reported earlier when results were not stratified by genotype.[2]

1.3.2 Safety and Clinical Activity Associated with Genotypic Dosing of Irinotecan within FOLFIRI

Safety

The guiding principle for dose escalation in phase I trials is to avoid unnecessary exposure of patients to sub-therapeutic doses of an agent while preserving safety and maintaining rapid accrual. [23] Our hypothesis that current irinotecan doses

are suboptimal in some patient groups was tested in a dose-escalation study of mCRC patients treated with FOLFIRI alone. [17] Excluding patients with UGT1A1 *28/*28, irinotecan doses of 370 and 310 mg/m^2 administered every 2 weeks were safely tolerated in *1/*1 and *1/*28 patients, respectively. The most common grade ≥3 observed toxicities in cycle 1 across all dose levels and when both genotype groups were combined included neutropenia (23%) and diarrhea (7%); across all cycles the corresponding toxicities were neutropenia (35%) and diarrhea (14%). This rate of diarrhea is similar to the incidence reported when results are not stratified by genotype. [2] Also of particular importance in this UGT1A1 guided dose-escalation trial, although incidence of neutropenia is higher, the rate of febrile neutropenia was no higher than expected with current FOLFIRI dosing at 6%. [17]

Similar results were obtained in a subsequent study, demonstrating an irinotecan maximum tolerated dose (MTD) of 390, 340, and 130 mg/m^2 when used within the FOLFIRI regimen every 2 weeks in *1/*1, *1/*28, and *28/*28 patients, respectively.[24] The most common grade 3/4 toxicity reported in cycle 1 across all dose levels in the *1/*1 genotype included diarrhea (10%), asthenia (24%) and neutropenia (22%). In the *1/*28 genotype they were diarrhea (5%), asthenia (11%) and neutropenia (26%). The *28/*28 genotype experienced higher levels of these toxicities in cycle 1, despite receiving lower doses: diarrhea (21%), asthenia (21%), and neutropenia (29%). There were no reports of febrile neutropenia in any of the groups. While higher than for the other genotypes, the level of ≥grade 3 neutropenia reported in the *28/*28 is lower than that reported for FOLFOX [2], while the rate of diarrhea is comparable to that reported for the regimen IFL (with 5-FU and irinotecan dosed weekly at lower doses for 4 weeks of every 6 week cycle), the standard of care regimen for mCRC for many years.[5]

These data, along with the meta-analysis summarized in section 1.3.1 support the proposed dosing of irinotecan in LCCC1317, outlined below and in the Schema.

Clinical Activity

While the phase I studies just reviewed were designed to establish the safety of genotypic dosing, response rates and time to progression (TTP) were also explored.

When the data are grouped by dose, OR was similar between the 2 studies. In the study by Toffoli et al, the OR in patients treated at the MTD and higher (≥ 310 mg/m^2 in *1/*28 patients and ≥ 370 mg/m^2 in *1/*1 patients) was significantly greater than in patients treated at doses below the MTD (65% versus 25%, respectively).[17] TTP was not different between these two groups. In a similar posthoc analysis by Marcuello et al [24], patients were grouped into 2 cohorts based on the median dose received. Of patients treated with ≥ 260 mg/m^2 and < 260 mg/m^{2}of irinotecan, 67% and 24% respectively achieved an OR. Furthermore, the median TTP was higher in patients treated with ≥ 260 mg/m^2

irinotecan (16 months) than in patients treated with < 260 mg/m^2 of irinotecan (7 months) (p=0.003). Although efficacy was a secondary endpoint, the results are suggestive of a beneficial effect of FOLFIRI when higher irinotecan dosing is administered in *1/*1 and *1/*28 patients.

1.3.3 Safety Associated with Genotypic Dosing of Irinotecan within FOLFIRI+Bevacizumab

Safety

The addition of bevacizumab to FOLFIRI is effective, commonly used, and generally well tolerated, with 22-26% and 5-11% experiencing ≥grade 3 neutropenia and diarrhea respectively, in controlled clinical trials.[25, 26] Because of the frequent use of bevacizumab alongside FOLFIRI, a similar genotype-guided dose-escalation study in patients receiving FOLFIRI plus bevacizumab is currently ongoing in the *1/*1 and *1/*28 groups. At the 260 mg/m^2 dose in *1/*28 patients, only 2 dose limiting toxicities (DLTs) were observed among 10 treated patients.

At the 310 mg/m^2 dose in *1/*1 patients, only 2 DLTs were observed among 10 treated patients.[27] Based on these safety data, we have elected to use these 2 doses in the present trial.

1.4 Rationale

In the treatment of mCRC, irinotecan is typically prescribed at the same standard dose to all patients normalized by body surface area (BSA), as testing for UGT1A1*28 is not currently standard of care in most centers.

Robust phase I data support the safety and tolerability of higher than standard doses in *1/*1 and *1/*28 patients.[17, 24] These phase I data also suggest that genotype-guided dosing may result in considerable improvement in chemotherapy efficacy among patients with greater UGT1A1 activity (*1/*1 and *1/*28) treated with irinotecan (90% of white patients).

In our proposed study, eligible patients will be genotyped for UGT1A1 (required) and assigned into 1 of 3 different irinotecan dosing groups:*1/*1, *1/*28, *28/*28. The UGT1A1 genotyping assay does not test for the rare *6 allele present almost exclusively in people of Asian descent. The *6 allele confers UGT1A1 deficiency similar to *28. With the current genotyping assay, Asian carriers of the *6 allele would be classified as *1. In order to ensure safety of Asian patients, they will not be eligible for this trial. [28]

Patients will be requested to consent to genetic testing of available archival tumor tissue. An additional blood sample on D1 of treatment will also be requested for pharmacogenomic and other genetic testing in addition to status of UGT1A1.

Our phase II multicenter single arm study will prospectively analyze efficacy in mCRC patients receiving genotype-based dosing of irinotecan within the

FOLFIRI + bevacizumab regimen. We hypothesize that genotype-based dosing will result in improved regimen efficacy as demonstrated by prolonged PFS compared with historical controls (median 10.5 months).[29, 30] Such promising efficacy would warrant a large, phase III randomized trial designed with adequate power to determine if genotype-guided irinotecan dosing in FOLFIRI + bevacizumab should become standard of care.

2.0 OBJECTIVES

2.1 Primary Objective

Estimate PFS in previously untreated mCRC patients receiving FOLFIRI + bevacizumab when irinotecan dose is based on UGT1A1 genotype

2.2 Secondary Objectives

2.2.1 Evaluate the toxicity profile when irinotecan is dosed according to UGT1A1 genotype

2.2.2 Estimate OR (CR+PR) in previously untreated mCRC patients receiving FOLFIRI + bevacizumab when irinotecan dose is based on UGT1A1 genotype

2.2.3 Estimate OS in previously untreated mCRC patients receiving FOLFIRI + bevacizumab when irinotecan dose is based on UGT1A1 genotype

2.3 Exploratory Objective

2.3.1 [redacted]

2.4 Endpoints

2.4.1 Primary Endpoint

PFS is defined as time from day 1 (D1) of treatment to progression or death from any cause.

2.4.2 Secondary Endpoints

- Toxicity will be classified and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE, version 4.0)
- OR will be defined per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1)
- OS is defined as the time from D1 of treatment to death from any cause

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

Subjects must meet all of the inclusion criteria to participate in this study:

3.1.1 IRB-approved informed consent obtained and signed

3.1.2 Age ≥ 18 years

3.1.3 Histological or cytological documentation of adenocarcinoma of the colon or rectum

3.1.4 Measurable or non-measurable (but evaluable) disease as defined via RECIST 1.1

3.1.5 Metastatic disease not amenable to surgical resection with curative intent

3.1.6 No prior chemotherapy for metastatic disease

3.1.7 Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 (see section 12.1, Appendix A)

3.1.8 Adequate bone marrow, renal and hepatic function, as evidenced by the following:

- absolute neutrophil count (ANC) ≥1,500/mm^3
- platelets ≥100,000/mm^3
- hemoglobin ≥9.0 g/dL
- serum creatinine ≤1.5 x upper limit of normal (ULN)
- AST and ALT ≤3x ULN (≤5.0 × ULN for patients with liver involvement of their cancer
- Bilirubin ≤1.5 X ULN
- Alkaline phosphatase ≤3 x ULN (≤5 x ULN with liver involvement of their cancer)

3.1.9 Willing to comply with study procedures

3.1.10 Negative pregnancy test (urine or serum), within 7 day prior to Day 1 of FOLFIRI in women of childbearing potential

3.1.11 Women of childbearing potential and male subjects must agree to use adequate contraception for the duration of study participation. Adequate contraception is defined as any medically recommended method (or combination of methods) as per standard of care.

3.2 Exclusion Criteria

All subjects meeting any of the exclusion criteria at baseline will be excluded from study participation:

3.2.1 UGT1A1 genotype other than *1/*1, *1/*28, or *28/*28

3.2.2 Patients of Asian descent. The current genotyping assay classifies patients who are carriers of the Asian *6 allele as *1 carriers.

3.2.3 Known dihydropyrimidine dehydrogenase (DPD) deficiency

3.2.4 Prior treatment with irinotecan and/or bevacizumab

3.2.5 Unable or unwilling to discontinue (and substitute if necessary) use of prohibited drugs for at least 14 days (fruits and juices for at least 7 days) prior to Day 1 of FOLFIRI + bevacizumab initiation (see section 12.2, Appendix B, for list of prohibited drugs)

3.2.6 Inadequately controlled hypertension (defined as systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg.) To control hypertension, the addition or increase of standard of care antihypertensive regimen is allowed.

3.2.7 Prior history of hypertensive encephalopathy

3.2.8 Active cardiac disease including any of the following:

- New York Heart Association (NYHA) Grade II or greater congestive heart failure (see section 12.3, Appendix C)
- History of myocardial infarction or unstable angina within 6 months prior to Day 1
- History of stroke or transient ischemic attack within 6 months prior to Day 1 of FOLFIRI + bevacizumab initiation

3.2.9 Significant vascular disease (e.g., aortic aneurysm, requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to Day 1 of FOLFIRI + bevacizumab initiation

3.2.10 History of hemoptysis (≥ 1/2 teaspoon of bright red blood per episode) within 1 month prior to Day 1 of FOLFIRI + bevacizumab initiation

3.2.11 Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation)

3.2.12 Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to Day 1 of FOLFIRI + bevacizumab initiation or anticipation of need for major surgical procedure during the course of the study

3.2.13 Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to Day 1 of FOLFIRI + bevacizumab initiation

3.2.14 History of abdominal fistula or gastrointestinal perforation within 6 months prior to Day 1 of FOLFIRI + bevacizumab initiation

3.2.15 Serious, non-healing wound, active ulcer, or untreated bone fracture

3.2.16 Proteinuria as demonstrated by:

Urine protein: creatinine (UPC) ratio ≥ 1.0 at screening (patients discovered to have a UPC >=1 should undergo a 24 hour urine collection and must demonstrate ≤ 1g of protein in 24 hours to be eligible)

OR

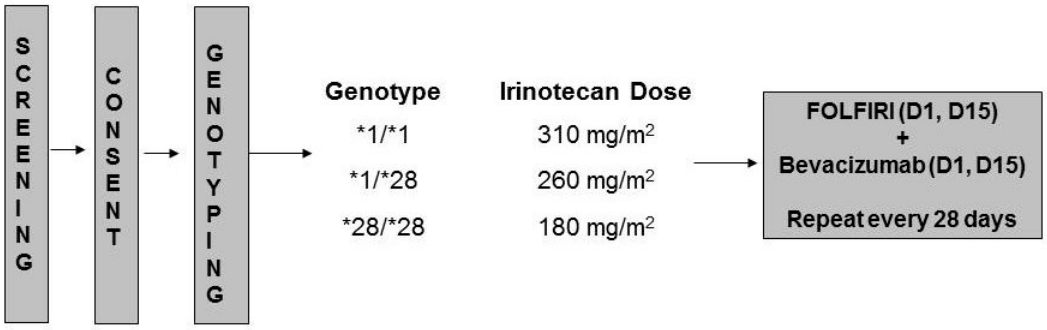
Urine dipstick for proteinuria ≥ 2+ (patients discovered to have ≥2+ proteinuria on dipstick urinalysis may either undergo Urine protein: creatinine (UPC) testing, and may participate if ratio <1. 0 or should undergo a 24 hour urine collection and must demonstrate ≤ 1g of protein in 24 hours to be eligible)

3.2.17 Any serious uncontrolled medical disorder that would impair the ability of the subject to receive protocol-driven therapy

3.2.18 Other anti-cancer or investigational therapy while patients are on study therapy

4.0 TREATMENT PLAN

4.1 Schema



This Phase II multi-center, single arm study is designed to estimate PFS in untreated mCRC patients receiving FOLFIRI + bevacizumab when irinotecan dose is based on UGT1A1 genotype. Patients will be assigned to one of 3 dose levels of irinotecan based on genotyping results, as part of the FOLFIRI + bevacizumab chemotherapy regimen. Patients will continue on treatment until tumor progression, unacceptable toxicity, consent withdrawal, or withdrawal from the study at the discretion of the investigator. Archival tissue will be requested from all patients at the time of enrollment for genetic sequencing. An additional blood sample will be requested D1 of treatment for pharmacogenomic and other genetic studies beyond UGT1A1 testing.

4.2 Treatment Dosage and Administration

4.2.1 Premedication and Hydration

Premedication should be provided per institutional guidelines. It is recommended that premedication include antiemetic agents. An example of a typical premedication regimen includes oral dexamethasone 12 mg and a 5HT3 receptor antagonist, e.g., oral ondansetron 24 mg, both administered 30 minutes prior to irinotecan therapy. Unless contraindicated, atropine 0.4 mg IV as needed for diarrhea every 2 hours during or after irinotecan and prochlorperazine 10 mg PO/IV every 6 hours as needed for nausea/vomiting may be prescribed. Since diarrhea may be severe and delayed >24 hours with irinotecan, loperamide 4 mg PO may be prescribed for the patient to take at the onset of diarrhea, followed by loperamide 2 mg PO as needed every 2 hours until diarrhea-free for 12 hours. See Appendix E, section 12.5 for additional information. Hydration during FOLFIRI should be provided per institutional guidelines.

4.2.2 FOLFIRI + Bevacizumab Administration

Drug	Dose & Route	Schedule[a]
Irinotecan[b]	Dose dependent on genotype: IV over 90 minutes	Day 1 and Day 15
Leucovorin (LV)[b]	200-400[c] mg/m^2 IV over 2 hours	Day 1 and Day 15
5-FU	400 mg/m^2 IV bolus followed by 2400 mg/m^2 IV over 46 hours	Day 1 and Day 15
Bevacizumab	5 mg/kg IV infused as per institutional policy	Day 1 and Day 15

[a]Repeat cycles every 28 days
[b]Both irinotecan and leucovorin should be administered prior to 5-FU;
[c]Levo-leucovorin may be substituted (if use, dose should be half (50%) of the planned dose of leucovorin); folate analogs may also be omitted at the discretion of the investigator

Irinotecan will be given every two weeks as an approximately 90-minute intravenous (IV) infusion. Leucovorin or levo-leucovorin may be initiated 30 minutes prior to starting irinotecan and both administered via a Y-connector to save infusion time at the discretion of each study site. Then 5-FU will be administered as an initial 400 mg/m^2 IV bolus over 2-5 minutes followed by an IV continuous infusion of 2,400 mg/m^2 over 46 hours. Bevacizumab will be administered at a dose of 5 mg/kg IV at an infusion duration per institutional policy. The aforementioned infusion durations are provided as a guideline. Infusions of these standard of care agents should be performed per institutional guidelines. Deviations from these guidelines are not considered protocol violations.

Irinotecan dose will depend upon the patient genotype: *1/*1 patients will receive 310 mg/m^2; *1/*28 patients will receive 260 mg/m^2; *28/*28 patients will receive the standard of care dose of 180 mg/m^2. Each cycle is 28 days, with irinotecan, LV, 5-FU, and bevacizumab administrations on day 1 and 15 of every cycle.

Treatment will be continued until disease progression or unacceptable toxicity.

4.3 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of any toxicity according to the Time and Events table (section 6.1). Toxicity will be assessed according to the NCI CTCAE v. 4.0.

If a patient experiences ≥2 AEs simultaneously that require different dose reductions, the lowest dose (or greatest dose reduction) should be used.

Treatment may be delayed ≤4 weeks from the expected day of the next treatment for any reason. Subjects whose treatment is delayed will proceed with the next cycle of treatment at the dose level recommended according to tables below, provided ≤4 weeks has elapsed beyond when their next treatment was due. If >4 weeks has elapsed, the agent(s) held must be discontinued. Provided patients remain on either irinotecan or 5-FU, patients will remain on protocol therapy. If both of these agents are discontinued, patients will come off of protocol therapy and be followed-up per protocol.

NOTE:

- If a dose of FOLFIRI is held or delayed for toxicity reasons, the original day and cycle numbering should be maintained. For example, if cycle 2 D15 FOLFIRI is held and re-started on Day 21, this visit will be considered cycle 2 D15.
- Leucovorin can be omitted at treating physician's discretion
- Irinotecan may be discontinued after cycle 4 at treating physician's discretion as warranted by disease status and adverse side effects.
- Bevacizumab initiation may be delayed until cycle 2 day 1 at the discretion of the investigator in case of prior minor surgery.

4.3.1 FOLFIRI Dose Levels

For FOLFIRI dose reductions, please refer to the following table.

FOLFIRI DOSING & DOSE LEVELS FOR ***1/*1 GENOTYPE**			
Agent	**Initial Dose**	**Level (-1)**	**Level (-2)**
Irinotecan	310 mg/m^2	260 mg/m^2	180 mg/m^2
Leucovorin[a]	400 mg/m^{2a}	320 mg/m^{2a}	240 mg/m^{2a}
5-FU bolus	400 mg/m^2	320 mg/m^2	240 mg/m^2
5-FU infusion	2400 mg/m^2	2000 mg/m^2	1600 mg/m^2

[a] May substitute with levoleucovorin at half (50%) of planned dose of leucovorin, or omit folate analogs at discretion of the investigator

FOLFIRI DOSING & DOSE LEVELS FOR ***1/*28 GENOTYPE**			
Agent	**Initial Dose**	**Level (-1)**	**Level (-2)**
Irinotecan	260 mg/m^2	180 mg/m^2	140 mg/m^2
Leucovorin[a]	400 mg/m^{2a}	320 mg/m^{2a}	240 mg/m^{2a}
5-FU bolus	400 mg/m^2	320 mg/m^2	240 mg/m^2
5-FU infusion	2400 mg/m^2	2000 mg/m^2	1600 mg/m^2
[a] May substitute with levoleucovorin at half (50%) of planned dose of leucovorin, or omit folate analogs at discretion of the investigator			

FOLFIRI DOSING & DOSE LEVELS FOR ***28/*28 GENOTYPE**			
Agent	**Initial Dose**	**Level (-1)**	**Level (-2)**
Irinotecan	180 mg/m^2	140 mg/m^2	110 mg/m^2
Leucovorin[a]	400 mg/m^{2a}	320 mg/m^{2a}	240 mg/m^{2a}
5-FU bolus	400 mg/m^2	320 mg/m^2	240 mg/m^2
5-FU infusion	2400 mg/m^2	2000 mg/m^2	1600 mg/m^2
[a] May substitute with levoleucovorin at half (50%) of planned dose of leucovorin, or omit folate analogs at discretion of the investigator			

4.3.2 FOLFIRI Dose Modifications

On Day 1 or Day 15	**Toxicity**	**Dose Level for Subsequent FOLFIRI**	
If ANC <1.0, hold treatment that day.[2] Re-check weekly. Resume per table if ANC ≥1.0	**Neutropenia[1]**	**Irinotecan**	**5-FU**
	Grade 2	↓1 dose level of each for rest of cycle. May resume prior dose level at the beginning of subsequent cycle if ANC >=1.5[7]	
	Grade 3	↓1 dose level of each for rest of cycle. If G-CSF is initiated, may resume prior dose level at the beginning of subsequent cycle if ANC >=1.5[7] at investigator discretion	
	Grade 4[8]	↓1-2[3] dose levels of each for rest of cycle. If G-CSF is initiated, may resume prior dose level at the beginning of subsequent cycle if ANC >=1.5[7] at investigator discretion	
	Febrile neutropenia	↓1 dose level & begin G-CSF	↓1 dose level & begin G-CSF

If platelets <75K, hold treatment that day.[2] Re-check weekly. Resume per table if platelets ≥75K	**Thrombocytopenia**	**Irinotecan**	**5-FU**
	Grade 2	↓1 dose level of each for rest of cycle. May resume prior dose level at the beginning of subsequent cycle if plts>=100,000[7]	
	Grade 3	↓1 dose level	↓1 dose level
	Grade 4	↓1-2[3] dose levels	↓1-2[3] dose levels

If mucositis >Grade 2, hold treatment that day.[2] Re-check weekly. Resume per table if mucositis Grade 0-1.	**Mucositis**	**Irinotecan**	**5-FU**
	Grade 2	Maintain dose	↓1 dose level for the rest of cycle. May resume prior dose level at the beginning of the next cycle if grade 0-1.
	Grade 3	Maintain dose	↓1 dose level
	Grade 4	Maintain dose	↓2 dose levels

On Day 1 or Day 15	**Toxicity**	**Dose Level for Subsequent FOLFIRI**	
If diarrhea[4] >Grade 2, hold treatment for that day.[2] Re-check weekly. Resume per table if diarrhea is ≤Grade 2.	**Diarrhea**	**Irinotecan**	**5-FU**
	Grade 2	↓1[3] dose level of each for rest of cycle[7]	
	Grade 3[8]	↓1 dose level	↓1 dose level
	Grade 4[8]	↓1-2[3] dose levels	↓1-2[3] dose levels

If HFSR >Grade 2, hold treatment for that day.[2] Re-check weekly. Resume per table if HFSR ≤Grade 1.	**HFSR[5]**	**Irinotecan**	**5-FU**
	Grade 3	Maintain dose	1 dose level

Hold[2] dose of suspected offending agent(s), re-check weekly. Resume per table once toxicity resolves to ≤Grade 2	**Other non specified[6]**	**Irinotecan**	**5-FU**
	≥Grade 3	↓1 dose level	↓1 dose level

Footnotes

[1] Prophylactic use of G-CSF and other hematopoietic growth factors are prohibited prior to and following cycle 1 day 1. They may be used for subsequent doses beginning after cycle 1 day 15 at the investigator's discretion. Also see section 4.4.4.

[2]Hold offending agent(s) as identified in table

[3]At discretion of investigator

[4]See section 4.3.3

[5]Hand-foot skin reaction

[6]Do not adjust doses for nausea and vomiting unless they persist for >48 hours despite maximum antiemetic support, or grade 3-4 adverse effects deemed not clinically significant (e.g. asymptomatic electrolyte disorders amenable to repletion).

[7]For next cycle, resume at the previous dose levels provided ANC ≥1.5 and platelets ≥ 100,000K at discretion of investigator

[8]Patients experiencing either grade 4 neutropenia or ≥grade 3 diarrhea that requires a >14 day dose delay in cycle 1 will have repeat UGT1A1 genotype testing at UNC, as well as at an outside CLIA-certified laboratory

4.3.3 Management of Irinotecan-associated Diarrhea

It is recommended that patients be provided loperamide tablets (or prescription) at the start of their treatment. Patients should be instructed to treat diarrhea with loperamide at its earliest occurrence (any grade), and to observe the recommended dietary modifications as outlined in section 12.5. This appendix also includes pharmacologic guidelines for the treatment of cancer treatment-induced diarrhea.

Subjects should be instructed to first notify their physician/healthcare provider at onset of diarrhea of any severity and to start supportive care immediately at the first episode of diarrhea (i.e., unformed stool).

An assessment of diarrhea frequency, consistency and duration as well as knowledge of other symptoms such as fever, cramping, pain, nausea, vomiting, dizziness and thirst should be taken at baseline. Consequently subjects at high risk of diarrhea can be identified. Subjects should be educated on signs and symptoms of diarrhea with instructions to report any changes in bowel patterns to the physician.

If subjects present with diarrhea, obtain information on food (solid and liquid) and over the counter (OTC) medication, including herbal supplements, taken during the treatment period.

For grade 3 or 4 diarrhea, or for < grade 3 diarrhea with complicating features (e.g. severe cramping, severe nausea/vomiting, decreased performance status, grade 3 or 4 neutropenia, sepsis, fever, frank bleeding, dehydration), hydrate aggressively with IV fluids as appropriate and consider octreotide therapy. Begin antibiotic therapy as needed for diarrhea lasting longer than 24 hours or if there is fever or neutropenia. Maintain adequate hydration and begin dietary modifications according to institutional guidelines for diarrhea management. In addition, patients experiencing ≥grade 3 diarrhea leading to >14 days dose delay in cycle 1 will have repeat UGT1A1 genotype testing at UNC, as well as at an outside CLIA-certified laboratory.

4.3.4 Bevacizumab Toxicity Management

There are no reductions in the bevacizumab dose. If adverse events occur that require holding bevacizumab, the dose will remain the same once treatment resumes provided these events do not require discontinuation of the agent (see table below).

Any toxicity associated or possibly associated with bevacizumab treatment should be managed according to standard medical practice.

4.3.5 Blood Pressure

Standard practice guidelines should be followed for determining initiation and continued infusion of bevacizumab based on blood pressure. Hypertension should be managed with appropriate antihypertensive medication. If unmanageable toxicity including events such as medically uncontrolled hypertension of hypertensive encephalopathy occurs because of bevacizumab at any time during the study, treatment with bevacizumab should be discontinued.

4.3.6 Other Bevacizumab-associated Toxicities

Adverse events requiring delays or permanent discontinuation of bevacizumab are listed in the table below.

Event	Grade;Description	Action
Hypertension	3	Hold until ≤Grade 2 and begin or increase antihypertensive medication. If must hold for >4 weeks, discontinue bevacizumab
	4[a]	Discontinue
Hemorrhage	3; non-pulmonary and non-CNS hemorrhage	Subjects who are also receiving full-dose anticoagulation will be discontinued from bevacizumab All other subjects will have bevacizumab held until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence. Subjects who experience a repeat Grade 3 hemorrhagic event will be discontinued from receiving bevacizumab.
	4; non-pulmonary and non-CNS hemorrhage	Discontinue bevacizumab
	1; pulmonary or CNS hemorrhage	Subjects who are also receiving full-dose anticoagulation will be discontinued from bevacizumab All other subjects will have bevacizumab held until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy.

		• There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence.
	2, 3 or 4; pulmonary or CNS hemorrhage	Discontinue bevacizumab
Venous Thrombosis	3 or 4	Hold bevacizumab until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is >2 weeks, bevacizumab may be resumed during the period of full-dose anticoagulation if all of the following criteria are met: • The subject must have an in-range INR (usually between 2 and 3) if on warfarin; low-molecular weight heparin (LMWH), warfarin, or other anticoagulant dosing must be stable prior to restarting bevacizumab treatment. • The subject must not have had a Grade 3 or 4 hemorrhagic event while on anticoagulation.
Arterial Thromboembolic event[b]	Any grade	Discontinue bevacizumab
Congestive Heart Failure	3	Hold bevacizumab until resolution to ≤Grade 1
	4	Discontinue bevacizumab
Proteinuria	≥3	At discretion of investigator
GI Perforation		Discontinue bevacizumab
Fistula	Any grade (tracheoesophageal fistula)	Discontinue bevacizumab
	4	Discontinue bevacizumab
Bowel Obstruction	1	Continue patient on study for partial obstruction NOT requiring medical intervention
	2	Hold bevacizumab for partial obstruction requiring medical intervention; patient may restart upon completion
	3/4	Hold bevacizumab for complete obstruction. If surgery is necessary, patient may restart bevacizumab after full recovery from surgery, at investigator's discretion.
Wound dehiscence	Any; requiring medical or surgical	Discontinue bevacizumab

	therapy	
Reversible Posterior Leukoencephalo-pathy	Any; confirmed by MRI	Discontinue bevacizumab
Other unspecified bevacizumab-related AEs	3	Hold bevacizumab until recovery to ≤Grade 1
	4	Discontinue bevacizumab
[a]Including hypertensive encephalopathy [b]New onset, worsening or unstable angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, or any other arterial thromboembolic event		

4.4 Concomitant Medications/Treatments

Standard of care prophylactic antiemetics should be given per institutional standard.

Patients will be instructed not to take any additional medications (including OTC products) during the course of the study without prior consultation with the investigator. At each visit, the investigator will ask the patient about any new medications he/she is taking or has taken since starting the study therapy.

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient is permitted with the following exceptions:

4.4.1 Concomitant Palliative Radiotherapy

Concomitant radiation for palliation is allowed provided that target lesions are not included in radiation field, and no more than 10% of the bone marrow is irradiated.

4.4.2 Prohibited Drugs

CYP3A4 Inhibitors and Inducers

In addition to conversion to the active metabolite SN-38, irinotecan is also metabolized by CYP3A4 and 3A5 to inactive metabolites. Patients unable or unwilling to discontinue (and substitute if necessary) use of CYP3A4 inducing drugs and strong CYP3A4 inhibiting drugs are ineligible for LCCC1317 as these can significantly change plasma concentrations of irinotecan and its active metabolites. Patients must not have received any of the prohibited drugs for at least 14 days prior to Day 1 of FOLFIRI (see section 12.2, Appendix B) for list of prohibited drugs). See http://medicine.iupui.edu/clinpharm/ddis/table.asp for a frequently updated list of inducers and strong inhibitors of CYP3A4.

CYP3A4 and UGT1A1 Inhibitors

Coadministration of atazanavir sulfate, a CYP3A4 and UGT1A1 inhibitor has the potential to increase systemic exposure to SN-38, the active metabolite of irinotecan. Therefore it is prohibited for patients enrolled into this study.

4.4.3 Drugs to be Used with Caution

Weak and moderate inhibitors of CYP3A4 should also be used with caution as they may potentially increase the plasma concentrations of irinotecan. Such concomitant medications should be avoided, if possible. See Appendix D (section 12.4) for a list of drugs to be used with caution. In addition, see http://medicine.iupui.edu/clinpharm/ddis/table.asp for a list of weak and moderate CYP3A4 inhibitors that should also be used with caution.

4.4.4 Hematopoietic Growth Factors

Prophylactic use of G-CSF (filgrastim or pegfilgrastim) and other hematopoietic growth factors are prohibited prior to or following cycle 1 day 1. Prophylaxis may be used for subsequent doses beginning after cycle 1 day 15 at the investigator's discretion provided they are not substituted for a required dose reduction. Filgrastim or pegfilgrastim should be implemented for any episode of febrile neutropenia.

4.5 Duration of Therapy

In the absence of treatment delays due to toxicities, protocol-directed treatment may continue until:

- Disease progression
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Both 5-FU and irinotecan have been discontinued
- Pregnancy
- Patient decides to withdraw from study treatment, **OR**
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

4.6 Duration of Follow Up

Patients will be followed for up to 5 years after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable AEs will be followed until resolution or stabilization of the event(s).

4.7 Removal of Patients from Protocol Therapy

Patients will be removed from protocol therapy and the PI notified when any of the criteria listed in section 4.5 apply. The reason for discontinuation of protocol therapy will be documented on the eCRF.

In case a patient decides to prematurely discontinue protocol therapy ("refuses treatment"), the patient should be asked if she or he may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.

Excessive patient withdrawals from protocol therapy or from the study can render the study un-interpretable; therefore, unnecessary withdrawal of patients should be avoided.

4.8 Study Withdrawal

If a patient decides to withdraw from the study (and not just from protocol therapy) all efforts should be made to complete and report study assessments as thoroughly as possible. The investigator should contact the patient or a responsible relative by telephone or through a personal visit to establish as completely as possible the reason for the study withdrawal. A complete final evaluation at the time of the patient's study withdrawal should be made with an explanation of why the patient is withdrawing from the study. If the reason for removal of a patient from the study is an adverse event, the principal specific event will be recorded on the eCRF.

5.0 DRUG INFORMATION

5.1 Irinotecan (Camptosar®)

Irinotecan hydrochloride is a semisynthetic derivative of camptothecin and is an antineoplastic agent of the topoisomerase I inhibitor class. It is indicated for the treatment of metastatic CRC in combination with 5-FU and leucovorin.

5.1.1 Irinotecan Supply and Supplier

Irinotecan as Camptosar® is available from Pfizer in single-dose amber glass vials containing 40 mg/2 mL or 100mg/5mL, and must be diluted prior to intravenous infusion. See Full Prescribing Information at: https://www.pfizeroncology.com/sites/pop/PDFs/uspi_camptosar.pdf for complete information. Commercially available supplies of either Camptosar® or generic irinotecan will be used for this study.

5.1.2 Preparation, Storage and Stability

The appropriate dose of irinotecan (see section 4.3) should be reconstituted, diluted, and stored according to the package insert provided by the manufacturer and according to local pharmaceutical regulations.

5.1.3 Premedication

Patients should be prescribed medications to prevent and treat nausea and vomiting per institutional guidelines. One recommended option is provided in section 4.2.1.

5.1.4 Dosage and Administration

See section 4.2.

5.1.5 Handling and Disposal

To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing irinotecan. This includes all handling activities in clinical settings, pharmacies, storerooms, and home healthcare settings, including during unpacking and inspection, transport within a facility, and dose preparation and administration. If a solution of irinotecan contacts the skin, wash the skin immediately and thoroughly with soap and water. If irinotecan contacts the mucous membranes, flush thoroughly with water. Procedures for proper handling and disposal of anti-cancer drugs should be considered.

5.1.6 Adverse Events Associated With Irinotecan

Incidence rates of AEs associated with irinotecan are provided in the product's Full Prescribing Information (https://www.pfizeroncology.com/sites/pop/PDFs/uspi_camptosar.pdf). Some of the AEs expected with irinotecan treatment are listed below.

Nausea, vomiting, and diarrhea are common AEs following treatment with irinotecan, and can be severe. When observed, nausea and vomiting usually occur during or shortly after infusion of irinotecan.

Diarrhea: Irinotecan can induce both early and late forms of diarrhea that appear to be mediated by different mechanisms. Early diarrhea (occurring during or shortly after infusion of irinotecan) is cholinergic in nature. It is usually transient and only infrequently is severe. It may be accompanied by cholinergic symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping. Early diarrhea and other cholinergic symptoms may be prevented or ameliorated by administration of atropine. Late diarrhea (generally occurring more than 24 hours after administration of irinotecan) can be life-threatening since it may be prolonged and may lead to dehydration, electrolyte imbalance, or sepsis. Late diarrhea should be treated promptly with loperamide. Patients with diarrhea should be carefully monitored, given fluid and electrolyte replacement if they become dehydrated, and given antibiotic support if they develop ileus, fever, or severe neutropenia.

Hepatic: In the clinical studies evaluating the weekly dosage schedule, NCI CTCAE Grade 3 or 4 liver enzyme abnormalities were observed in fewer than 10% of patients. These events typically occur in patients with known hepatic metastases.

Hematologic: Irinotecan commonly causes neutropenia, leukopenia (including lymphocytopenia), and anemia. Deaths due to sepsis following severe neutropenia have been reported in patients receiving irinotecan. Individuals who are homozygous for the UGT1A1*28 allele (approximately 10% of North American population) are at increased risk for neutropenia following initiation of irinotecan treatment. Serious thrombocytopenia is uncommon.

Body as a Whole: Asthenia, fever, and abdominal pain are generally the most common events of this type.

Hypersensitivity: Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have been observed.

Colitis/Ileus: Cases of colitis complicated by ulceration, bleeding, ileus, and infections have been observed. Patients experiencing ileus should receive prompt antibiotic support.

Renal Impairment/Renal Failure: Rare cases of renal impairment and acute renal failure have been identified, usually in patients who became volume depleted from severe vomiting and/or diarrhea.

Thromboembolism: Thromboembolic events have been observed in patients receiving irinotecan; the specific cause of these events has not been determined.

Respiratory: In clinical studies, ≥Grade 3 dyspnea was reported in 4% of patients. Of note, over half of these patients had lung metastases. Interstitial pulmonary disease, which can be fatal, is uncommon. Risk factors include preexisting lung disease, use of pneumotoxic drugs, radiation therapy, and colony stimulating factors.

5.1.7 Drug Interactions

Exposure to irinotecan and its active metabolite SN-38 is substantially reduced when patients are concomitantly receiving CYP3A4 enzyme-inducing drugs such as the anti-convulsants phenytoin, phenobarbital, or carbamazepine, as well as other agents such as St. John's Wort. Strong inhibitors of CYP3A4 enzymes such as the anti-fungal ketoconazole and the HIV anti-retrovirals (e.g., atazanavir), have increased exposure to irinotecan and SN-38 and should be avoided in patients receiving irinotecan. See https://www.pfizeroncology.com/sites/pop/PDFs/uspi_camptosar.pdf for further information. See section 4.4.2 for further information on prohibited concomitant drugs, and section 4.4.3 regarding drugs to be used with caution.

5.2 5-Fluorouracil (5-FU)

5-FU is an antineoplastic anti-metabolite that interferes with the synthesis of DNA and, to a lesser extent, RNA by blocking the methylation reaction of deoxyuridylic acid to thymidylic acid. It is indicated for the treatment of metastatic CRC.

5.2.1 Supply and Supplier

The following information was taken from the prescribing information for Teva USA's Adrucil® (5-FU). Additional details may be found at: http://www.tevausa.com/assets/base/products/pi/Adrucil_PI.pdf.

Each 10 mL contains 500 mg of FU (50 mg/mL) and sodium hydroxide to adjust pH to approximately 9.2. Commercially available supplies of either Adrucil® or another generic 5-FU will be used for this study.

5.2.2 Preparation, Storage and Stability

The appropriate dose of 5-FU should be reconstituted, diluted, and stored according to the package insert provided by the manufacturer and according to local pharmaceutical regulations.

5.2.3 Premedication/Hydration

Patients should receive premedication and hydration per institutional guidelines for FOLFIRI.

5.2.4 Dosage and Administration

See section 4.2 for additional details.

5.2.5 Handling and Disposal

To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing 5-FU. This includes all handling activities in clinical settings, pharmacies, storerooms, and home healthcare settings, including during unpacking and inspection, transport within a facility, and dose preparation and administration. If a solution of 5-FU contacts the skin, wash the skin immediately and thoroughly with soap and water. Procedures for proper handling and disposal of anti-cancer drugs should be considered.

5.2.6 Adverse Events Associated with 5-FU

The most common toxicities seen with 5-FU therapy include stomatitis, esophagopharyngitis (which may result in sloughing and ulceration), diarrhea, anorexia, nausea, and vomiting. Neutropenia commonly follows treatment, with white count nadir observed between days 9 and 14 following therapy. Mild alopecia has been reported, though is usually not complete. Dermatitis, in the form of a pruritic maculopapular rash that usually appears on the extremities and (less frequently) trunk, is generally reversible and responsive to symptomatic treatment. This dermatitis may be increased with sun exposure.

Other less common adverse reactions are:
Hematologic: pancytopenia, thrombocytopenia, agranulocytosis, anemia.
Cardiovascular: myocardial ischemia, angina.
Gastrointestinal: gastrointestinal ulceration and bleeding.
Allergic Reactions: anaphylaxis and generalized allergic reactions.
Neurologic: acute cerebellar syndrome (which may persist following discontinuance of treatment), nystagmus, headache.
Dermatologic: dry skin; fissuring; photosensitivity, as manifested by erythema or increased pigmentation of the skin; vein pigmentation; palmar-plantar

erythrodysesthesia syndrome, as manifested by tingling of the hands and feet followed by pain, erythema and swelling.
Ophthalmic: lacrimal duct stenosis, visual changes, lacrimation, photophobia.
Psychiatric: disorientation, confusion, euphoria.
Miscellaneous: thrombophlebitis, epistaxis, nail changes (including loss of nails)

5.3 Leucovorin

Leucovorin, also known as folinic acid or citrovorum factor, is a chemically reduced derivative of folic acid. Leucovorin is readily converted to another reduced folate, 5,10-methylenetetrahydrofolate, which acts to stabilize the binding of fluorodeoxyuridylic acid to thymidylate synthase, thereby enhancing the inhibition of this enzyme. It is used to enhance the effects of fluoropyrimidines such as 5-FU.

5.3.1 Supply and Supplier

The following information was taken from the prescribing information for Teva USA's leucovorin calcium. Additional details may be found at: http://www.tevausa.com/assets/base/products/pi/Leucovorin_PI_9-2007.pdf. Leucovorin calcium is commercially available as a sterile, single-use vial containing either 100 mg or 350 mg each. Commercially available supplies of generic leucovorin calcium will be obtained from Teva or another manufacturer and used for this study. See section 4.2.2 regarding potential omission of folate analogs, or substitution of levo-leucovorin for leucovorin.

5.3.2 Preparation, Storage and Stability

The appropriate dose of leucovorin (see section 4.3) should be reconstituted and diluted and stored according to the package insert provided by the manufacturer and according to local pharmaceutical regulations.

5.3.3 Dosage and Administration

See section 4.2 for additional information.

5.3.4 Adverse Events Associated with Leucovorin

Leucovorin should not be used for pernicious anemia and other megaloblastic anemias secondary to the lack of vitamin B12. A hematologic remission may occur while neurologic manifestations continue to progress.

Leucovorin enhances the toxicity of 5-FU. When these drugs are administered concurrently in the treatment of advanced colorectal cancer, as they are in this study, gastrointestinal toxicities (particularly stomatitis and diarrhea) are observed more commonly and may be more severe and of prolonged duration. Seizures and/or syncope have been reported rarely in patients with cancer receiving leucovorin, usually in combination with fluoropyrimidine administration, and most commonly in those with CNS metastases or other predisposing factors; however, a causal relationship has not been established.

Allergic sensitization, including anaphylactoid reactions and urticaria, has been reported following administration of leucovorin.

5.3.5 Drug Interactions

Folic acid in large amounts may counteract the antiepileptic effect of phenobarbital, phenytoin, and primidone, and increase the frequency of seizures in susceptible pediatric patients.

5.4 Bevacizumab (Avastin®)

Bevacizumab, a humanized monoclonal antibody, is a vascular endothelial growth factor-specific angiogenesis inhibitor indicated for the treatment of mCRC in combination with 5-FU, 5-FU + irinotecan or 5-FU + oxaliplatin, for non-small cell lung cancer, glioblastoma, and for metastatic renal cell carcinoma.

5.4.1 Bevacizumab Supply and Supplier

Bevacizumab as Avastin® is available from Genentech in 100mg and 400mg single-use vials, and must be diluted prior to intravenous infusion. See Full Prescribing Information at: www.gene.com. Commercially available supplies of Avastin® will be used for this study.

5.4.2 Preparation, Storage and Stability

The appropriate dose of bevacizumab (see section 4.2.2) should be diluted, and stored according to the package insert provided by the manufacturer and according to local pharmaceutical regulations.

5.4.3 Premedication

Patients should be prescribed medications to prevent and treat nausea and vomiting per institutional guidelines.

5.4.4 Dosage and Administration

See section 4.2.2.

5.4.5 Adverse Events Associated With Bevacizumab

The most common (>10%) adverse reactions associated with bevacizumab include epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain, and exfoliative dermatitis. See the Avastin® prescribing information for more detailed information. In addition to the Warnings and Precautions outlined below, other adverse events of note include venous thromboembolic events, neutropenia and infection, and congestive heart failure.

Venous Thromboembolic Events (VTE)

The overall incidence of Grade 3-4 VTEs in a controlled study in mCRC was 15.1% in patients receiving irinotecan, bolus 5FU and leucovorin (IFL) plus

bevacizumab and 13.6% in the placebo arm. More patients in the bevacizumab containing arm experienced deep vein thrombosis (34 vs.19 patients) and intra-abdominal venous thrombosis (10 vs. 5 patients).

The risk of developing a second thromboembolic event while on bevacizumab and oral anticoagulants was evaluated in two randomized studies. In Study 1, 53 patients (14%) on the IFL and bevacizumab arm and 30 patients (8%) in the IFL and placebo arm received full dose warfarin following a VTE. Among these patients, an additional thromboembolic event occurred in 21% of the bevacizumab arm and 3% of patients receiving IFL alone. In a second, randomized, 4-arm study in 1401 patients with mCRC, prospectively evaluating the incidence of VTE (all grades), the overall incidence of first VTE was higher in the bevacizumab containing arms (13.5%) than the chemotherapy alone arms (9.6%). Among the 116 patients treated with anticoagulants following an initial VTE event (73 in the bevacizumab plus chemotherapy arms and 43 in the chemotherapy alone arms), the overall incidence of subsequent VTEs was also higher among the bevacizumab treated patients (31.5% vs. 25.6%). In this subgroup of patients treated with anticoagulants, the overall incidence of bleeding, the majority of which were Grade 1, was higher in the bevacizumab treated arms than the chemotherapy arms (27.4% vs. 20.9%).

Neutropenia and Infection
The incidence of neutropenia and febrile neutropenia is greater in patients receiving IFL+ bevacizumab compared to chemotherapy alone. Specifically, the incidence of Grade 3 or 4 neutropenia was higher in mCRC patients receiving IFL plus bevacizumab (21%) than in patients on chemotherapy alone (14%).

Congestive Heart Failure
The incidence of Grade ≥3 left ventricular dysfunction was 1.0% in patients receiving bevazicumab compared to 0.6% in the control arm across indications.

The prescribing information contains more detailed information on the following Warnings and Precautions.

Gastrointestinal Perforations
Serious and sometimes fatal gastrointestinal perforation occurs more frequently in bevacizumab treated patients compared to controls. The incidence of gastrointestinal perforation ranged from 0.3 to 2.4% across clinical studies. The typical presentation may include abdominal pain, nausea, emesis, constipation, and fever. Perforation can be complicated by intra-abdominal abscess and fistula formation. The majority of cases occurred within the first 50 days of initiation of the drug.

Surgery and Wound Healing Complications
Bevacizumab impairs wound healing in animal models. In clinical

trials, administration of bevacizumab was not allowed until at least 28 days after surgery. In a controlled clinical trial, the incidence of wound healing complications, including serious and fatal complications, was 15% in patients with mCRC who underwent surgery during the course of bevacizumab versus 4% in the control group. The appropriate interval between the last dose of this agent and elective surgery is unknown; however, its half-life is estimated to be 20 days. Necrotizing fasciitis including fatal cases, has been reported in patients treated with bevacizumab, usually secondary to wound healing complications, gastrointestinal perforation or fistula formation.

Hemorrhage
Bevacizumab can result in two distinct patterns of bleeding: minor hemorrhage, most commonly Grade 1 epistaxis; and serious, and in some cases fatal, hemorrhagic events. Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding occurred up to five-fold more frequently in patients receiving bevacizumab than in patients receiving only chemotherapy. Across indications, the incidence of Grade ≥3 hemorrhagic events among patients receiving bevacizumab ranged from 1.2 to 4.6%.

Non-Gastrointestinal Fistula Formation
Serious and sometimes fatal non-gastrointestinal fistula formation involving tracheo-esophageal, bronchopleural, biliary, vaginal, renal and bladder sites occurs at a higher incidence in bevacizumab-treated patients compared to controls. The incidence of non-gastrointestinal perforation was ≤0.3% in clinical studies. Most events occurred within the first 6 months of therapy.

Arterial Thromboembolic Events
Serious, sometimes fatal, arterial thromboembolic events (ATE) including cerebral infarction, transient ischemic attacks, myocardial infarction, angina, and a variety of other ATE occurred at a higher incidence in patients receiving bevacizumab compared to those in the control arm. Across indications, the incidence of Grade ≥3 ATE in the bevacizumab containing arms was 2.6% compared to 0.8% in the control arms. When combined with chemotherapy, the risk of developing an ATE during therapy was increased in patients with a history of arterial thromboembolism, or age greater than 65 years.

Hypertension
The incidence of severe hypertension is increased in patients receiving bevacizumab as compared to controls. Across clinical studies the incidence of Grade 3 or 4 hypertension ranged from 5-18%.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
RPLS has been reported to occur in <0.1% of patients in clinical studies. The onset of symptoms occurred from 16 hours to 1 year after initiation of bevacizumab. RPLS is a neurological disorder that can present with headache,

seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present.

Proteinuria

The incidence and severity of proteinuria is increased in patients receiving bevacizumab as compared to controls. Nephrotic syndrome occurred in <1% of patients receiving bevacizumab in clinical trials, in some instances with fatal outcome.

Infusion Reactions

Infusion reactions reported in the clinical trials and post-marketing experience include hypertension, hypertensive crises associated with neurologic signs and symptoms, wheezing, oxygen desaturation, Grade 3 hypersensitivity, chest pain, headaches, rigors, and diaphoresis. In clinical studies, infusion reactions with the first dose of bevacizumab were uncommon (<3%) and severe reactions occurred in 0.2% of patients.

Ovarian Failure

The incidence of ovarian failure was higher (34% vs. 2%) in premenopausal women receiving bevacizumab in combination with modified (m)FOLFOX chemotherapy as compared to those receiving mFOLFOX chemotherapy alone for adjuvant treatment for colorectal cancer.

6.0 EVALUATIONS AND ASSESSMENTS

6.1 Time and Events Table

	Pre-Study[1]	Day 1 each cycle[1]	Day 15 each cycle[1]	Day 1 every other cycle	Treatment Discontinuation[2]	Follow-up[3]
Informed Consent	X					
History[4]	X	X	X		X	X
Physical exam	X	X			X	X
ECOG Performance Status	X	X			X	X
Pregnancy Test[5]	X[5]					
CBC w/diff, serum chemistries[6]	X	X	X		X	
LFTs[6]	X	X	X		X	
Urinalysis	X[7]	X[7]				
UGT1A1 testing[8] (required)	X					
Tumor measurement and CEA blood test[9]	X[9]			X[9]	X[9]	
Concomitant Meds	X	Throughout study				
FOLFIRI Initiation		X	X			
Bevacizumab dose		X	X			
Toxicity Assessment	Throughout study					
Request archival tissue	X[10]					
Blood sample for correlatives		X[10] (cycle 1 only)		X[10]		
PRO-CTCAE sub-study[11]	X[11]	X[11]	X[11]			
Survival						X

Key to Footnotes

[1]Scans within 28 days prior to Day 1 of FOLFIRI; other evaluations may be within 2 weeks unless otherwise noted; for D1 cycle 1 evaluation, if screening (baseline) evaluations were performed within 7 days of D1 of treatment, these do not need to be repeated. A window of +/- 3 days will apply to all study visits. UGT1A1 genotyping is determined from germline sequencing and once collected per protocol is not subject to a collection window.

[2]This visit should occur in patients when treatment stops for whatever reason (toxicity, progression, and at discretion of the investigator)

[3]Follow-up contacts every 3 months +/- 15 days after treatment discontinuation for up to 2 years and then every 6 months +/- 15 days for the following 3 years or until death (whichever is first) and may be conducted via telephone. See section 6.5.1 for information to be collected. Patients who have on ongoing Grade 4 AE or SAE at the time of discontinuation from treatment will continue to be followed until the event is resolved or deemed irreversible by the investigator.

[4]Complete history at baseline only, thereafter focused history on symptoms/toxicity, study coordinator /personnel to assess adverse events.

[5]Urine or serum B-HCG, within 7 day prior to Day 1 of FOLFIRI and only if clinically appropriate.

[6]Serum chemistries to include Na, K, Cl, Mg, creatinine, BUN; liver function tests (LFTs) to include AST, ALT, total bilirubin, alkaline phosphatase

[7]Perform urinalysis (UA) at baseline to determine urine protein: creatinine (UPC) ratio ≥ 1.0 at screening or perform a urine dipstick for proteinuria; see exclusion criteria 3.2.16. UA on D1 of each cycle to be performed at the discretion of the investigator, and per institutional policy

[8] Collect 5-7 mL of whole blood using a purple top (EDTA) tube; see section 6.6 for additional information

[9]Tumor measurements within 5 days prior to D1 every 2 cycles starting with cycle 3 to include CT/MRI scans of chest, abdomen and pelvis---any additional suspected sites of disease should be evaluated per treating physician discretion; CEA=carcinoembryonic antigen; tumor imaging at treatment discontinuation to be done at treatment discontinuation at discretion of investigator. If tumor assessments are available for patients who have not yet experienced progressive disease (PD) at the time treatment is discontinued, the follow-up tumor evaluations will be documented in the eCRF until PD or death is confirmed, or until another treatment is initiated.

[10]Request archival tissue from all patients, and collect two blood samples (1 x 5-7mLs and 1 x 10mLs each in purple top) for genetic testing on C1D1. Starting with cycle 3,

collect blood sample (10 mLs in purple top) for additional correlatives every odd numbered cycle. See section 6.6.2 and the laboratory manual for additional details.

[11] See sections 6.2, 6.3 and 9.0 for details.

6.2 Pre-Study Assessments

The assessments required as part of screening can be completed in one or more visits, as long as the assessments are completed within the time frames listed in the Key to the Time and Events table.

Clinical evaluation: complete history, comprehensive physical examination (to also include vital signs, height, and weight), ECOG performance status
Laboratory studies:

- **Pregnancy Test**: Serum or urine pregnancy test is required for all women of childbearing potential at screening, within 7 days prior to the first dose of FOLFIRI
- **Hematology**: CBC with differential
- **Serum Chemistries**: Na, K, Cl, Mg, creatinine, BUN
- **LFTs**: AST, ALT, total bilirubin, alkaline phosphatase
- **Urinalysis or urine dipstick**
- **CEA blood test**
- **UGT1A1 (**required; see section 6.6)

Tumor measurement: Tumor imaging should remain consistent throughout study, and should include CT/MRI scans of chest, abdomen and pelvis, and any additional suspected sites of disease.
Concomitant medications: Documentation of all concomitant medications, and in particular any drugs that strongly inhibit or induce CYP3A4. **NOTE**: Patients will be given a list of medications they should not be taking while on this study (see section 12.6, Appendix F). Patients will be instructed to bring this list with them for all study visits for review by their study team and for all visits to healthcare professionals (e.g., primary care physicians, consultants) while on study.
Archival tissue: Initiate collection of archival tissue from those patients who consent to this optional collection.
Toxicity: Toxicity will be assessed according to the NCI CTCAE v. 4.0.
PRO-CTCAE: Register patient into PRO-Core (see section 10.4.2) if site participating in PRO-CTCAE sub-study (see section 9.0); train patient in completing PRO-CTCAE questionnaire prior to or on D1 of cycle 1.

LCCC 1317 amendment 05 CLINIC

6.3 On Study Assessments

6.3.1 Day 1 of Each Cycle

Clinical evaluation: focused history on symptoms/toxicity, study coordinator /personnel to assess adverse events, comprehensive physical examination (to also include vital signs and weight), ECOG performance status

Laboratory studies:

- **Hematology**: CBC with differential
- **Serum Chemistries**: Na, K, Cl, Mg, creatinine, BUN
- **LFTs**: AST, ALT, total bilirubin, alkaline phosphatase
- **Urinalysis or urine dipstick:** (at discretion of investigator)
- **Cycle 1 only:** Two blood samples (1 x5-7 mLs and 1x10mLs in purple top tube (see section 6.6) for correlative studies

Concomitant medications: review for prohibited concomitant medications

Toxicity: Toxicity will be assessed according to the NCI CTCAE v. 4.0.

PRO-CTCAE: See section 9.0; patient to complete PRO-CTCAE questionnaire, and research personnel to ensure completion of PRO-CTCAE Report Form (see section 12.7 Appendices G and H).

6.3.2 Day 15 of Each Cycle

Clinical evaluation: focused history on symptoms/toxicity, study coordinator /personnel to assess adverse events.

Laboratory studies:

- **Hematology**: CBC with differential
- **Serum Chemistries**: Na, K, Cl, Mg, creatinine, BUN
- **LFTs**: AST, ALT, total bilirubin, alkaline phosphatase

Concomitant medications: review for prohibited concomitant medications

Toxicity: Toxicity will be assessed according to the NCI CTCAE v. 4.0.

PRO-CTCAE: See section 9.0; patient to complete PRO-CTCAE questionnaire, and research personnel to ensure completion of PRO-CTCAE Report Form.

6.3.3 Day 1 of Every Other Cycle (starting with cycle 3)

Tumor measurement: Tumor imaging should remain consistent throughout study, and should include CT/MRI scans of chest, abdomen and pelvis, and any additional suspected sites of disease.

Correlative studies: 10mLs blood in purple top tube (see section 6.6) for correlative studies.

6.4 End of Treatment Visit

This visit should occur, at discretion of investigator, in patients when they stop treatment, whether due to disease progression or unmanageable toxicity.

Clinical evaluation: Focused history on symptoms/toxicity, study coordinator /personnel to assess adverse events, comprehensive physical exam to include vital signs and weight, ECOG performance status
Laboratory studies: Hematology: CBC with differential, CEA blood test, Na, K, Cl, Mg, creatinine, BUN, AST, ALT, total bilirubin, alkaline phosphatase
Tumor measurement: For patients who discontinue for reasons other than disease progression, tumor measurements should take place. Tumor imaging should remain consistent throughout study, and should include CT/MRI scans of chest, abdomen and pelvis, and any additional suspected sites of disease.
Concomitant medications: review for prohibited concomitant medications
Toxicity: Patients who have an ongoing Grade 4 AE or SAE at the time of discontinuation from treatment will continue to be followed until the event is resolved or deemed irreversible by the investigator.

6.5 Post-Treatment/Follow-up Assessments

Summary of all phone conversation must be documented in the medical record.

6.5.1 Follow-up

Follow-up visits should occur every 3 months +/- 15 days after treatment discontinuation for up to 2 years and then every 6 months +/- 15 days for the following 3 years or until death (whichever is first) and may be conducted via telephone.

After study drug treatment ends, anti-cancer medications taken by the patient should be documented in the eCRF if this information is available.

If tumor assessments are available for patients who have not yet experienced progressive disease (PD), enter the follow-up tumor evaluations in the eCRF until PD is confirmed.

Patients who withdraw consent from study drug treatment should enter the follow-up period (unless consent to follow-up is specifically withdrawn).

6.6 Correlative Studies

In addition to required UGT1A1 testing, with additional optional consent, other correlative studies on archival tissue and blood will be conducted. Correlative studies may include exploratory DNA-based (germline - genotyping of candidate variants, high-density SNP chip genotyping and genome sequencing; tumor - methylation, sequencing, genotyping of candidate variants) and RNA-based analyses (RNA-seq, expression arrays), or other biomarker analyses.

6.6.1 UGT1A1 Testing (Required)

Collect 5-7 mL of whole blood using a purple top (EDTA) tube and bring or ship to UNC McClendon Clinical Laboratories. The blood should be received by McClendon within 24 hours of collection but can be stored under refrigeration if

it will be >24 hours. Additional details on storage and shipment are provided in the LCCC1317 laboratory manual. Any blood remaining after the DNA is isolated and residual DNA will be forwarded or shipped to UNC as per the LCCC1317 laboratory manual.

6.6.2 Archival Tumor Tissue and D1 cycle 1 blood collection (Optional)

The tissue specimens (blocks or slides) should be requested at the time of study enrollment from patients who consent to this. A blood sample (5-7mLs) for additional correlative studies beyond UGT1A1 will be collected on D1 of cycle 1. Tissue and blood will be stored in UNC's Tissue Procurement Facility until genetic testing is initiated. Detailed information on processing, shipping and storage of these samples will be provided in the LCCC1317 laboratory manual. Any specimens remaining after protocol directed studies are complete will be stored for future research related to cancer in patients who consent to this storage.

6.6.3 D1 Every Odd Numbered Cycle (Optional)

An additional 10 mL blood sample for additional genetic studies will be collected on D1 of cycle 1 and every odd numbered cycle. Blood will be stored in UNC's Tissue Procurement Facility until genetic testing for sequencing of cell free DNA (cfDNA) is initiated. Detailed information on processing, shipping and storage of these samples will be provided in the LCCC1317 laboratory manual. Any specimens remaining after protocol directed studies are complete will be stored for future research related to cancer in patients who consent to this storage.

6.7 Assessment of Safety

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of any toxicity according to the Time and Events table (section 6.0). Toxicity will be assessed according to the NCI CTCAE v. 4.0.

6.8 Assessment of Efficacy Based on RECIST 1.1

Patients who have received at least 2 cycles of therapy and have their disease re-evaluated at 2 months will be evaluable for assessment of the primary objective (PFS). Patients who drop out of the study prior to this point will not be evaluable for the primary objective unless they meet criteria for disease progression prior to this initial disease assessment, and have completed at least 2 doses (1 cycle) of FOLFIRI.

6.8.1 Assessment of Disease-Tumor Measurement Based on RECIST 1.1

See the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 (Eur J Cancer 45;2009:228-247) for additional details on RECIST1.1.

Measurable disease will be defined as the presence of at least one measurable lesion that can be accurately measured in at least one dimension with the longest diameter a minimum size of:

- ≥10mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10mm 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.

For malignant lymph nodes to be considered pathologically enlarged and measurable, a lymph node must be ≥15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5mm). At baseline and in follow-up, only the short axis will be measured and followed.

All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions, will be considered non-measurable. Lesions considered truly non-measurable include leptomeningeal disease; ascites; pleural/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.

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment. 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. Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesions is recommended.

6.8.2 Baseline Documentation of Target and Non-Target Lesions

All measurable lesions up to a maximum of 5 lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longer diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, only the short axis is

added into the sum. The baseline sum diameters will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

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

6.8.3 Evaluation of Target Lesions using RECIST 1.1 Criteria

NOTE: In addition to the information below, also see section 4.3.2 in the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1[31] for special notes on the assessment of target lesions.

Complete response (CR)−Disappearance of all target lesions. Any pathological lymph node (LN) (whether target or non-target) must have decreased in short axis to <10mm.

Partial response (PR)−At least a 30% decrease in the sum of the longest diameter (LD) of the target lesions taking as reference the baseline sum LD.

Progressive disease (PD)−At least a 20% increase in the sum of the LD of the target lesions taking as reference the smallest sum LD recorded since the treatment started including baseline 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 5mm. The appearance of one or more new lesions also constitutes PD.

Stable disease (SD)−Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD since the treatment started.

6.8.4 Evaluation of Non-Target Lesions using RECIST 1.1 Criteria

Complete response (CR)−Disappearance of all non-target lesions and normalization of tumor marker levels. All LN must be non-pathological in size (<10mm short axis).

Non-complete response (non-CR)/non-progression (non-PD)−Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.

Progressive disease (PD)−Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

6.8.5 Evaluation of Best Overall Response using RECIST 1.1 Criteria

The best overall response is the best response recorded from the start of the study treatment until the end of treatment provided the confirmation criteria are met. To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat studies that should be performed > 4 weeks after the criteria for response are first met. If a CR/PR cannot be confirmed the original "response" should be considered stable disease. The best overall response will be defined according to the following table:

Overall Response First Time Point	Overall Response Subsequent Time Point	BEST Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR[1]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE[2]	SD provided minimum criteria for SD duration met, otherwise, NE[2]
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE[2]	SD provided minimum criteria for SD duration met, otherwise, NE[2]
NE	NE[2]	NE[2]

[1] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

[2] NE=inevaluable

7.0 ADVERSE EVENTS

7.1 Definitions

7.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence (e.g., an abnormal laboratory finding, symptom, or disease temporally associated with the use of a drug) in a patient or clinical investigation subject administered a pharmaceutical product 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 a medicinal product, whether or not related to the medicinal product.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) need not be considered AEs and should not be recorded as an AE. Disease progression should not be recorded as an AE, unless it is attributable by the investigator to the study therapy.

7.1.2 Suspected Adverse Reaction (SAR)

A suspected adverse reaction (SAR) is any AE for which there is a *reasonable possibility* that the drug is the cause. *Reasonable possibility* means that there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Causality assessment to a study drug is a medical judgment made in consideration of the following factors: temporal relationship of the AE to study drug exposure, known mechanism of action or side effect profile of study treatment, other recent or concomitant drug exposures, normal clinical course of the disease under investigation, and any other underlying or concurrent medical conditions. Other factors to consider in considering drug as the cause of the AE:

- Single occurrence of an uncommon event known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event not commonly associated with drug exposure, but otherwise uncommon in the population (e.g., tendon rupture); often more than once occurrence from one or multiple studies would be needed before the sponsor could determine that there is *reasonable possibility* that the drug caused the event.
- An aggregate analysis of specific events observed in a clinical trial that indicates the events occur more frequently in the drug treatment group than in a concurrent or historical control group

7.1.3 Unexpected AE or SAR

An AE or SAR is considered <u>unexpected if</u> the specificity or severity of it is not consistent with the applicable product information (e.g., Investigator's Brochure

(IB) for an unapproved investigational product or package insert/summary of product characteristics for an approved product). Unexpected also refers to AEs or SARs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.4 Serious AE or SAR

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

- Death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Requires inpatient hospitalization (>24 hours) or prolongation of existing hospitalization;*
- Results in congenital anomaly/birth defect;
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. For reporting purposes, also consider the occurrences of pregnancy as an event which must be reported as an important medical event.

*Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.

Pregnancy that occurs during the study must also be reported as an SAE.

7.2 Documentation of non-serious AEs or SARs

For non-serious AEs or SARs, documentation must begin from day 1 of study treatment and continue through the 30 day follow-up period after treatment is discontinued.

Collected information should be recorded in the Case Report Forms (CRF) for that patient. Please include a description of the event, its severity or toxicity grade, onset and resolved dates (if applicable), and the relationship to the study drug. Documentation should occur at least monthly.

7.3 SAEs or Serious SARs

7.3.1 Timing

After informed consent but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g. SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run-in).

For any other experience or condition that meets the definition of an SAE or a serious SAR, recording of the event must begin from day 1 of study treatment and continue through the 30 day follow-up period after treatment is discontinued.

7.3.2 Documentation and Notification

These events (SAEs or Serious SARs) must be recorded in the SAE console within Oncore™ for that patient within 24 hours of learning of its occurrence. For Affiliate sites, an email must also be sent to the NCCN Study Coordinator indicating that an SAE or Serious SAR has been entered into Oncore (email contact will be provided at study start-up).

7.3.3 Reporting

IRB Reporting Requirements:

UNC**:**

- UNC will submit an aggregated list of all SAEs to the UNC IRB annually at the time of study renewal according to the UNC IRB policies and procedures.
- The UNC-IRB will be notified of all SAEs that qualify as an Unanticipated Problem per the UNC IRB Policies using the IRB's web-based reporting system (see section 10.6) within 7 days of the Investigator becoming aware of the problem.

Affiliate sites:

- For affiliate sites using a local IRB of record, please submit adverse events per local IRB policy.
- For affiliate sites relying on the UNC-IRB, an aggregated list of all SAEs will be submitted to the UNC IRB annually at the time of study renewal according to the UNC IRB policies and procedures. In addition, any SAEs that qualify as an Unanticipated Problem will be entered into Oncore and reported to the UNC IRB by the UNCCN Study Coordinator using the IRB's web-based reporting system (see section 10.6) within 7 days of the Investigator becoming aware of the problem.

Pregnancy

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on study, or within 28 days of the subject's last dose of study should be

recorded as SAEs. The patient is to be discontinued immediately from the study. For Affiliate sites, the pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the UNCCN Study Coordinator immediately via facsimile to 919-966-4300. The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must document the outcome of the pregnancy (either normal or abnormal outcome). If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE.

7.4 Data and Safety Monitoring Plan

The Principal Investigator will provide continuous monitoring of patient safety in this trial with periodic reporting to the Data and Safety Monitoring Committee (DSMC).

Meetings/teleconferences will be held at a frequency dependent on study accrual, and in consultation with the study Biostatistician. These meetings will include the investigators as well as protocol nurses, clinical research associates, regulatory associates, data managers, biostatisticians, and any other relevant personnel the principal investigators may deem appropriate. At these meetings, the research team will discuss all issues relevant to study progress, including enrollment, safety, regulatory issues, and data collection.

The team will produce summaries or minutes of these meetings. These summaries will be available for inspection when requested by any of the regulatory bodies charged with the safety of human subjects and the integrity of data including, but not limited to, the oversight (Office of Human Research Ethics (OHRE) Biomedical IRB, the Oncology Protocol Review Committee (PRC) or the North Carolina TraCS Institute Data and Safety Monitoring Board (DSMB).

The UNC LCCC Data and Safety Monitoring Committee (DSMC) will review the study on a regular (quarterly to annually) basis, with the frequency of review based on risk and complexity as determined by the UNC Protocol Review Committee. The UNC PI will be responsible for submitting the following information for review: 1) safety and accrual data including the number of patients treated; 2) significant developments reported in the literature that may affect the safety of participants or the ethics of the study; 3) preliminary response data; and 4) summaries of team meetings that have occurred since the last report. Findings of the DSMC review will be disseminated by memo to the UNC PI, PRC, and the UNC IRB and DSMB.

8.0 STATISTICAL CONSIDERATIONS FOR LCCC 1317

8.1 Study Design

This is a single arm, non-randomized, phase II study to evaluate the efficacy and safety of irinotecan dosed according to UGT1A1 genotype in mCRC patients receiving FOLFIRI + bevacizumab. The primary objective is to estimate PFS in this group of patients receiving irinotecan dose based on UGT1A1 genotype. Secondary objectives include evaluating the safety of this genotype-directed approach, and estimating OR and OS in this group of patients. An exploration of associations between tumor and host genetic profiles and response or toxicity will also be performed.

8.2 Sample Size, Stopping Rule and Safety Rule

Based on historical data, the median PFS for patients receiving FOLFIRI + bevacizumab is between 9.7-10.4 months when irinotecan dose is based on BSA, as per current standard of care. From the two previous phase I studies described earlier [17, 24], we expect to see an improvement in median PFS of 3.5 months (to 14 months from 10.5 months) using the genotype-directed approach. The sample size for this trial, therefore, is based on testing the null hypothesis that the median PFS is 10.5 against a one-sided alternative (assuming an exponential distribution). Specifically, 86 patients are required to detect a change in median PFS from 10.5 to 14 months, assuming a one-sided, 0.05 level test, with 80% power, 24 months of accrual, and 24 months of follow-up (One Sample Survival; swogstat.org). We plan to enroll 100 patients to ensure 86 patients are evaluable for the primary endpoint of PFS.

Sequential boundaries will be used to suspend the trial if excessive gastrointestinal toxicity is seen during cycle 1. If the study reaches a stopping boundary, it may be terminated by the PI, or submitted to the DSMC with a description of the toxicities and a rationale for why the study should be continued. Using the NCI CTCAE v. 4.0, diarrhea ≥ grade 3 or grade 2 diarrhea that persists >48 hours despite maximum supportive care will be counted in the toxicity rate for the purposes of early stopping. The accrual will be halted if the number of patients experiencing the GI toxicity just defined is equal to or exceeds b_n out of n patients who have been monitored for toxicity in cycle 1 (see Stopping Rule table below). This is a Pocock type stopping boundary that assumes that a toxicity rate of 0.30 is acceptable, but anything >30% is unacceptable. If the true toxicity rate is equal to 0.30, the probability of crossing the boundary is 0.05.

Stopping Rule

Number of Patients, n	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Boundary, b_n	-	-	-	4	5	6	6	7	7	8	8	9	9	9	10	10	11	11	12	12
Number of Patients, n	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40

Boundary, b_n	12	13	13	14	14	15	15	15	16	16	17	17	17	18	18	19	19	19	20	20
Number of Patients, n	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60
Boundary, b_n	20	21	21	22	22	22	23	23	24	24	24	25	25	25	26	26	27	27	27	28
Number of Patients, n	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80
Boundary, b_n	28	28	29	29	30	30	30	31	31	31	32	32	32	33	33	34	34	34	35	35
Number of Patients, n	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
Boundary, b_n	35	36	36	36	37	37	38	38	38	39	39	39	40	40	40	41	41	41	42	42

Similarly, sequential boundaries will be used to guide use of prophylactic growth factors if excessive febrile neutropenia or ≥grade 3 infection (using the NCI CTCAE v. 4.0) related to neutropenia in cycle 1 is seen related to genotypic dosing of irinotecan. If the study reaches a pre-defined boundary, the PI will amend the trial incorporating the use of pegfilgrastim (Neulasta®) prophylactically prior to cycle 1 in subsequent patients. The decision to use pegfilgrastim in all patients or a subset (ie, based on genotype) will be made by the PI based on the toxicity profile. The decision about the use of pegfilgrastim will be made if the number of patients with the specified toxicities in cycle 1 is equal to or exceeds b_n out of n patients who have been monitored for toxicity (see Safety Rule table below). This is a Pocock type stopping boundary that assumes that a toxicity rate of 0.20 is acceptable, but anything >20% is unacceptable. If the true toxicity rate is equal to 0.20, the probability of crossing the boundary is 0.05. This level of acceptable febrile neutropenia prior to prophylactic use of growth factors is also in accordance with the American Society of Clinical Oncology (ASCO) guidelines on use of growth factors.[32]

Safety Rule

Number of Patients, n	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Boundary, b_n	-	-	3	4	4	5	5	6	6	6	7	7	7	8	8	8	9	9	9	10
Number of Patients, n	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
Boundary, b_n	10	10	11	11	11	11	12	12	12	13	13	13	13	14	14	14	15	15	15	15
Number of Patients, n	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60
Boundary, b_n	16	16	16	16	17	17	17	18	18	18	18	19	19	19	19	20	20	20	21	21
Number of Patients, n	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80
Boundary, b_n	21	21	22	22	22	22	23	23	23	23	24	24	24	24	25	25	25	25	26	26
Number of Patients, n	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
Boundary, b_n	26	26	27	27	27	27	28	28	28	28	29	29	29	29	30	30	30	30	31	31

8.3 Data Analysis Plans

PFS and OS will be summarized for patients receiving genotype-directed dosing using the method of Kaplan and Meier. Median PFS and OS will be reported

along with their corresponding 95% confidence intervals. Frequency tables will be used to summarize toxicity data and any other patient characteristics of interest. OR will be reported along with an exact 95% confidence interval.

Cox models and logistic regression models may also be used to adjust for additional covariates as sample size permits.

Analyses of potential biomarkers will be exploratory and descriptive in nature. For associations between genetic alterations and response, Fisher's exact tests will be used.

9.0 PRO-CTCAE Sub-study

9.1 Background

The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) characterizes signs, symptoms and diseases by type and grade (severity) and is frequently used for investigator reporting of adverse events in oncology clinical trials.[33] A systematic approach to eliciting information on side effects experienced by patients may provide a more comprehensive picture of these adverse effects within a population, as well as improve safety, symptom management and patient satisfaction.[34, 35] A set of questions was developed to facilitate direct patient reporting of symptomatic adverse events, with the ultimate goal of improving the accuracy and timeliness of grading this subset of adverse events(see http://appliedresearch.cancer.gov/pro-ctcae/?&url=/tools/pro-ctcae.html; accessed April 30, 2014). These questions comprise the Patient Reported Outcomes (PRO) version of the CTCAE (the PRO-CTCAE). To date, 80 of the symptoms listed in the CTCAE have been modified for patient self-reporting and validated through literature reviews, expert consensus and cognitive interviews with patients [33].

A system incorporating PRO-CTCAE into overall toxicity assessment should be easy to use, focus on clinically relevant issues and report output to clinicians in an accessible format. [36] In this PRO-CTCAE sub-study, we plan to evaluate the feasibility of a proposed system of collecting PRO-CTCAE and corresponding clinician assessed symptomatic AEs of interest (on the PRO-CTCAE Clinician Form; see section 12.8, Appendix H) in the LCCC 1317 population across multiple participating sites. Thirteen symptomatic adverse events to be scored by patients (using the PRO-CTCAE questionnaire) and clinicians (using the NCI CTCAE v4.0 criteria) were chosen for this sub-study based on likely symptomatic toxicities seen with the FOLFIRI+bevacizumab combination.

Patients will be asked about symptom frequency, severity and interference with usual activities over the last 14 days (see appendix G, section 12.7) on D1 and D15 of each cycle. The PRO-CTCAE information being collected is for research purposes only. Therefore, patients will be advised to directly discuss any

symptoms of concern with their clinicians during conduct of the parent study. Clinicians will also grade the same symptoms based on the NCI CTCAE v4.0 on D1 and D15 of each cycle. Either the Clinician or a designee (such as the study coordinator) may complete the Clinician portion of the questionnaire on D15.

This sub-study will be mandatory for all patients enrolled in LCCC1317 at UNC, and for all patients at Affiliate sites that elect to participate in this optional sub-study. Non-English speaking patients are not required to participate and will not be asked to participate. Once feasibility is established, future studies will be designed to compare the documentation and use of routine clinician assessed CTCAEs within clinical trials with the method outlined in this sub-study.

9.2 Primary Objectives

9.2.1 Estimate the proportion of patients who complete all the PRO-CTCAE questions at least 80% of the time the patient questionnaire is available (on D1 and D15 of each cycle) in the parent trial (1317)

9.2.2 Estimate the proportion of patients with completed PRO-CTCAE Clinician Forms (i.e., both patient and clinician fully completed) at least 80% of the time the patient questionnaire is available (on D1 and D15 of each cycle) in the parent trial (1317)

9.3 Secondary Objectives

9.3.1 Estimate concordance between PRO-CTCAE grades of toxicity and investigator-assigned CTCAE grades of toxicity for each symptom of interest separately

9.3.2 Compare proportion of patients with PRO-CTCAE maximum score (≥2 for diarrhea, ≥3 for all other symptoms) to proportion of patients with investigator-

assigned CTCAE maximum score (≥2 for diarrhea, ≥3 for all other symptoms) for each symptom separately

9.3.3 Compare time to first PRO-CTCAE score of ≥2 for diarrhea, ≥3 for all other symptoms to time to first investigator-assigned CTCAE score of ≥2 for diarrhea, ≥3 for all other symptoms

9.4 Exploratory Objectives

9.4.1 [redacted]

9.5 Primary Endpoints

9.5.1 The patient component of the toxicity assessment process defined in this study will be considered feasible if at least 80% of patients complete all the questions at least 80% of the time. The PRO-CTCAE (26 questions) are a subset of the complete PRO-CTCAE questions, and are mapped to 13 symptoms.

9.5.2 The toxicity assessment process defined in this study will be considered feasible if at least 80% of patients have completed PRO-CTCAE Clinician Forms (i.e., both patient and clinician fully completed) at least 80% of the time.

9.6 Methods

9.6.1 Patient Registration and Training

At participating sites at baseline, all patients will be registered into PRO-Core (see section 10.4.2) by research personnel. Following registration and prior to or on D1 of cycle 1, patients will be trained on completion of the questionnaire either via the iPad (to be made available to each participating site) or on paper. Registration and training of each patient is anticipated to take approximately 15 minutes. Site study staff will convey to the patient that the information regarding symptoms collected by the PRO-CTCAE self-report are for research purposes only. Study staff must advise patients to directly discuss any concerning symptoms with their doctor.

9.6.2 D1 and D15 of each cycle

Also see Time and Events Table and Study Assessments (sections 6.0 through 6.3). Starting with D1 of cycle 1, and continuing on each D1 and D15 study visit during treatment (under LCCC1317), patients will respond to the 26 PRO-CTCAE questions ideally on the iPad, or on paper if necessary (see Appendix G, section 12.7, for the list of questions patients will complete at each visit). We anticipate this will take patients approximately 10 minutes to complete each time.

If done on the iPad, patient responses will be converted to a PRO-CTCAE grade for each symptom, which will then automatically populate the PRO-CTCAE Clinician Form. If done on paper, research personnel will either: (1) convert patient responses to a PRO-CTCAE grade using a simple scoring system (research personnel will be trained on this scoring system at study start-up) and then transfer the grades by hand to the PRO-CTCAE Clinician Form or (2) enter the patient responses into PRO-Core to generate a PRO-CTCAE Clinician Form with patient grades.

Research staff will then present the PRO-CTCAE Clinician Form (populated with patient grades) to the clinician (or designee on D15)for completion of clinician-assessed CTCAE grade. (**NOTE:** Research personnel should consult clinician investigator for any noted discrepancies between the clinician-assessed grade on the PRO-CTCAE Report Form and clinic notes). The decision regarding dose modifications based on toxicity (Yes/No) will also be documented on the PRO-CTCAE Clinician Form by research personnel. Data from the completed PRO-CTCAE Clinician Form will be entered by research personnel into PRO-Core (see section 10.4.2).

9.7 Statistical Considerations

9.7.1 Sample Size

There are two primary feasibility objectives for this sub study: (1) to estimate the proportion of patients who complete all the PRO-CTCAE questions at least 80% of the time the patient questionnaire is available (on D1 and D15 of each cycle) in the parent trial (1317) and (2) to estimate the proportion of patients with completed PRO-CTCAE Clinician Forms (i.e., both patient and clinician fully completed) at least 80% of the time the patient questionnaire is available (on D1 and D15 of each cycle) in the parent trial (1317). Patients will be evaluable for these objectives if they enroll in LCCC1317 and are treated at UNC or at a site that agrees to participate in the sub-study. We plan to enroll 100 patients in LCCC1317. The number of patients included in the sub-study will depend on site participation. The table below includes precision estimates (exact 95% confidence intervals for a proportion of 50% and maximum half-widths) for various potential sample sizes. For example, if there are 90 patients evaluable for the sub-study, we will be able to estimate both proportions of interest within at least 10.7%.

Sample Size (n)	Exact 95% CI	Maximum Half-Width
100	(39.8%, 60.2%)	10.2%
90	(39.3%, 60.7%)	10.7%
80	(38.6%, 61.4%)	11.4%

9.7.2 Data Analysis Plans

The proportion of patients who complete all the PRO-CTCAE questions at least 80% of the time the patient questionnaire is available (on D1 and D15 of each cycle) and the proportion of patients with completed PRO-CTCAE Clinician Forms (i.e., both patient and clinician fully completed) at least 80% of the time the patient questionnaire is available will both be estimated and reported along with exact 95% confidence intervals. Each patient will have a different number of possible questionnaires available because the questionnaires will only be available on D1 and D15 of each cycle as long at the patient is on treatment in LCCC1317. Therefore, "80% of the time" will be calculated for each patient individually based on that patient's number of possible questionnaires. The first primary objective addresses the feasibility of the patient component of the toxicity assessment process. We will consider having patients report their own symptoms using this process feasible if at least 80% of patients complete all the questions at least 80% of the time. The second primary objective addresses the feasibility of the overall process of collecting PRO-CTCAE and corresponding clinician assessed symptomatic AEs of interest in the LCCC 1317 population across multiple participating sites. The overall process will be considered feasible if at least 80% of patients have completed PRO-CTCAE Clinician Forms (i.e., both patient and clinician fully completed) at least 80% of the time. The denominator for both proportions will be all patients included in the sub-study (enrolled at UNC or an Affiliate site agreeing to participate in the sub-study).

The weighted Kappa statistic will be used to estimate concordance between PRO-CTCAE grades of toxicity and investigator-assigned CTCAE grades of toxicity for each symptom of interest as documented on the PRO-CTCAE Clinician Forms. The blocked bootstrap will be used to estimate standard errors to account for the fact that toxicity assessments are made at multiple time-points. McNemar's tests will be used to compare the proportion of patients with a PRO-CTCAE maximum score (≥2 for diarrhea, ≥3 for all other symptoms) to the proportion of patients with investigator-assigned CTCAE maximum score (≥2 for diarrhea, ≥3 for all other symptoms) for each symptom. Time to first PRO-CTCAE score of ≥2 for diarrhea, ≥3 for all other symptoms and time to first investigator-assigned CTCAE score of ≥2 for diarrhea, ≥3 for all other symptoms (with time measured from D1 of cycle 1) will be estimated using the method of Kaplan and Meier and will be compared using the log-rank test.

Fisher's exact tests will be used to explore the association between patient-reported toxicities of ≥ grade 2 diarrhea or ≥ grade 3 for all other symptoms and dose modifications (as reported on the PRO-CTCAE Clinician Forms) and to explore the association between patient reported maximum score (≥2 for diarrhea, ≥3 for all other symptoms) and irinotecan starting dose. The bootstrap method will be used as appropriate to account for correlation.

10.0 STUDY MANAGEMENT

10.1 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 patient 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 patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

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

10.2 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Protocol Office (CPO) at the University of North Carolina.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any sub-investigators who will be involved in the study.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation (NOTE: this is required if UNC holds the IND. Otherwise, the Investigator's signature documenting understanding of the protocol and providing commitment that this trial will be conducted according to all stipulations of the protocol is sufficient to ensure compliance.)
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

10.3 Registration Procedures

10.3.1 LCCC1317

All UNC patients must be registered with the CPO at the University of North Carolina before enrollment to study. For UNC patients, prior to registration, eligibility criteria must be confirmed with the UNC Study Coordinator. To register a patient, call the Oncology Protocol Office at 919-966-4432 Monday through Friday, 9:00AM-5:00PM.

For Affiliate patients, please contact the UNCCN Study Coordinator for the potential subject (direct line 919-966-7359), Monday through Friday, 9:00AM-5:00PM. To register a patient, please fax registration forms and eligibility documents to 919-966-4300.

10.3.2 PRO-CTCAE Sub-study

At participating sites at baseline, all patients will be registered into the PRO-Core by research personnel at each site (see section 10.4.2).

10.4 Data Management and Monitoring

10.4.1 LCCC1317

The CPO UNCCN of the UNC LCCC will serve as the coordinating center for this trial. Data for LCCC1317 will be collected through a web based clinical research platform, OnCore®. Other study institutions will be given a password to directly enter their own data onto the web site via electronic case report forms (eCRFs). UNCCN personnel will coordinate and manage data for quality control assurance and integrity.

All data will be collected and entered into OnCore® by Clinical Research Associates (CRAs) from UNC LCCC and participating institutions. The investigators at each site will allow monitors to review all source documents supporting data entered into OnCore®. The UNCCN Data Coordinator can be reached at 919-843-2742 or 1-877-668-0683.

10.4.2 PRO-CTCAE Sub-study

Data from the PRO-CTCAE sub-study will be entered into PRO-Core. The PRO-Core (Patient-Reported Outcomes Core Facility) is a shared resource that builds electronic questionnaires and other tools for use in cancer outcomes research. The PRO-Core is housed in the Cancer Outcomes Research Program, Lineberger Comprehensive Cancer Center, University of North Carolina. PRO-Core features include development and administration of surveys via the web or interactive voice response (IVR) automated telephone systems, as well as study participant tracking and computer-assisted telephone interviewing (CATI). Data are stored in a secure enterprise-level Oracle database managed by the ITS Research Computing group at UNC, and web servers are hosted by the UNC Center for

Bioinformatics. Data transmitted between the server and end-users are encrypted using SSL, and all databases are encrypted.

PRO-Core Faculty Director: Antonia Bennett (avbenn@email.unc.edu)
PRO-Core Director of Systems Development: Mattias Jonsson (jonsson@unc.edu)

PRO-Core: http://pro.unc.edu/
ITS Research Computing: http://its.unc.edu/research/its-research-computing/
UNC Center for Bioinformatics: http://bioinformatics.unc.edu/

10.5 Auditing

As an investigator initiated study, this trial will also be audited by the Lineberger Cancer Center audit committee every six or twelve months, depending on the participation of affiliate sites.

10.6 Adherence to the Protocol

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

10.6.1 Emergency Modifications

UNC and Affiliate investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior UNC or their respective institution's IRB/IEC approval/favorable opinion.

For Institutions Relying on UNC's IRB:
For any such emergency modification implemented, a UNC IRB modification form must be completed by UNC Research Personnel within five (5) business days of making the change.

For Institutions Relying on Their Own IRB:
For Affiliate investigators relying on their own institution's IRB, as soon as possible after the modification has been made, the implemented deviation or change and the reasons for it should be submitted to:

- To UNC Principal Investigator for agreement
- The Affiliate institution's IRB for review and approval. (Once IRB's response is received, this should be forwarded to the UNCCN Regulatory Associate).

10.6.2 Single Patient/Subject Exceptions

For Institutions Relying on UNC's IRB:

Any request to enroll a single subject who does not meet all the eligibility criteria of this study requires the approval of the UNC Principal Investigator and the UNC IRB.

For Institutions Relying on Their Own IRB:
Any request to enroll a single subject who does not meet all the eligibility criteria of this study requires the approval of the UNC Principal Investigator and the participating institution's IRB, per its policy. Please forward the IRB response to the UNCCN Regulatory Associate by facsimile or via email within 10 business days after the original submission.

10.6.3 Other Protocol Deviations/Violations

According to UNC's IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance meets any of the following criteria:

- Has harmed or increased the risk of harm to one or more research participants.
- 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.

If a deviation or violation occurs please follow the guidelines below:

For Institutions Relying on UNC's IRB:
Protocol Deviations: UNC or Affiliate personnel will record the deviation in OnCore®, and report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Violations should be reported by UNC personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

For Institutions Relying on Their Own IRB:

In addition to adhering to the policies regarding protocol compliance set forth by your institution's IRB, the following is also required:

Protocol Deviations: In the event a deviation from protocol procedures is identified, record the deviation in OnCore®.

Protocol Violations: Any protocol violation that occurs must be reported to your IRB per institutional policies and reported to the UNCCN Study Coordinator within 5 days. UNC-CH will determine if the violation affects the safety of the patient and integrity of the data. Once your institution's IRB response is received, please forward to the UNCCN Regulatory Associate.

Unanticipated Problems:
Affiliate Sites:
Any events that meet the criteria for "Unanticipated Problems (UPs)" as defined by UNC's IRB must also be reported to the UNCCN Study Coordinator. The UNCCN Study Coordinator will report the event to the UNC IRB using the IRB's web-based reporting system. Examples of such UPs include a lost or stolen laptop computer that contains sensitive study information.

UNC
Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB must be reported by the Study Coordinator using the IRB's web-based reporting system.

10.7 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at UNC. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

For Institutions Relying on UNC's IRB:
The written amendment, and if required the amended consent form, must be sent to UNC's IRB for approval prior to implementation.

For Institutions Relying on Their Own IRB:
Investigators must submit the UNC IRB approved amendment to their institution's IRB for approval. For multi-center studies, any affiliate site must submit their informed consent revisions to the UNCCN Regulatory Associate prior to submission to their IRB.

10.8 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and

regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

10.9 Obligations of Investigators

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 Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator 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 and entered into the eCRFs. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all eCRFs will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

11.0 REFERENCES

1. Society, A.C. *Cancer Facts & Figures 2013*. 2013.
2. Tournigand, C., et al., *FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study.* J Clin Oncol, 2004. **22**(2): p. 229-37.
3. Colucci, G., et al., *Phase III randomized trial of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer: a multicenter study of the Gruppo Oncologico Dell'Italia Meridionale.* J Clin Oncol, 2005. **23**(22): p. 4866-75.
4. Kabbinavar, F.F., et al., *Combined analysis of efficacy: the addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer.* J Clin Oncol, 2005. **23**(16): p. 3706-12.
5. Hurwitz, H., et al., *Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer.* N Engl J Med, 2004. **350**(23): p. 2335-42.
6. Saltz, L.B., et al., *Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study.* J Clin Oncol, 2008. **26**(12): p. 2013-9.
7. Van Cutsem, E., et al., *Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer.* N Engl J Med, 2009. **360**(14): p. 1408-17.
8. Lievre, A., et al., *KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab.* J Clin Oncol, 2008. **26**(3): p. 374-9.
9. NCCN, *NCCN Practice Guidelines for Colong Cancer*, 2013.
10. Ducreux, M., et al., *Irinotecan combined with bolus fluorouracil, continuous infusion fluorouracil, and high-dose leucovorin every two weeks (LV5FU2 regimen): a clinical dose-finding and pharmacokinetic study in patients with pretreated metastatic colorectal cancer.* J Clin Oncol, 1999. **17**(9): p. 2901-8.
11. Fuchs, C.S., et al., *Phase III comparison of two irinotecan dosing regimens in second-line therapy of metastatic colorectal cancer.* J Clin Oncol, 2003. **21**(5): p. 807-14.
12. Stevenson, J.P., et al., *Phase I clinical and pharmacogenetic trial of irinotecan and raltitrexed administered every 21 days to patients with cancer.* J Clin Oncol, 2001. **19**(20): p. 4081-7.
13. Falcone, A., et al., *Sequence effect of irinotecan and fluorouracil treatment on pharmacokinetics and toxicity in chemotherapy-naive metastatic colorectal cancer patients.* J Clin Oncol, 2001. **19**(15): p. 3456-62.
14. Van Cutsem, E., et al., *A phase II study of irinotecan alternated with five days bolus of 5-fluorouracil and leucovorin in first-line chemotherapy of metastatic colorectal cancer.* Ann Oncol, 1998. **9**(11): p. 1199-204.
15. Merrouche, Y., et al., *High dose-intensity of irinotecan administered every 3 weeks in advanced cancer patients: a feasibility study.* J Clin Oncol, 1997. **15**(3): p. 1080-6.
16. Kawato, Y., et al., *Intracellular roles of SN-38, a metabolite of the camptothecin derivative CPT-11, in the antitumor effect of CPT-11.* Cancer Res, 1991. **51**(16): p. 4187-91.

17. Toffoli, G., et al., *Genotype-driven phase I study of irinotecan administered in combination with fluorouracil/leucovorin in patients with metastatic colorectal cancer.* J Clin Oncol, 2010. **28**(5): p. 866-71.
18. Toffoli, G., et al., *The role of UGT1A1*28 polymorphism in the pharmacodynamics and pharmacokinetics of irinotecan in patients with metastatic colorectal cancer.* J Clin Oncol, 2006. **24**(19): p. 3061-8.
19. Hoskins, J.M., et al., *UGT1A1*28 genotype and irinotecan-induced neutropenia: dose matters.* J Natl Cancer Inst, 2007. **99**(17): p. 1290-5.
20. Ramchandani, R.P., et al., *The role of SN-38 exposure, UGT1A1*28 polymorphism, and baseline bilirubin level in predicting severe irinotecan toxicity.* J Clin Pharmacol, 2007. **47**(1): p. 78-86.
21. Innocenti, F., et al., *Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan.* J Clin Oncol, 2004. **22**(8): p. 1382-8.
22. Deeken, J.F., R. Slack, and J.L. Marshall, *Irinotecan and uridine diphosphate glucuronosyltransferase 1A1 pharmacogenetics: to test or not to test, that is the question.* Cancer, 2008. **113**(7): p. 1502-10.
23. Le Tourneau, C., J.J. Lee, and L.L. Siu, *Dose escalation methods in phase I cancer clinical trials.* J Natl Cancer Inst, 2009. **101**(10): p. 708-20.
24. Marcuello, E., et al., *A genotype-directed phase I-IV dose-finding study of irinotecan in combination with fluorouracil/leucovorin as first-line treatment in advanced colorectal cancer.* Br J Cancer, 2011. **105**(1): p. 53-7.
25. Pectasides, D., et al., *XELIRI-bevacizumab versus FOLFIRI-bevacizumab as first-line treatment in patients with metastatic colorectal cancer: a Hellenic Cooperative Oncology Group phase III trial with collateral biomarker analysis.* BMC Cancer, 2012. **12**: p. 271.
26. Ducreux, M., et al., *Efficacy and safety of bevacizumab-based combination regimens in patients with previously untreated metastatic colorectal cancer: final results from a randomised phase II study of bevacizumab plus 5-fluorouracil, leucovorin plus irinotecan versus bevacizumab plus capecitabine plus irinotecan (FNCLCC ACCORD 13/0503 study).* Eur J Cancer, 2013. **49**(6): p. 1236-45.
27. Sharma M, T.G., Buonadonna A et al, *A UGT1A1 genotype-guided dosing study of irinotecan in metastatic colorectal cancer (mCRC) patients (pts).* ASCO Gastrointestinal Cancer Symposium (in press), 2014 (in press).
28. Cheng, L., et al., *UGT1A1*6 polymorphisms are correlated with irinotecan-induced toxicity: a system review and meta-analysis in Asians.* Cancer Chemother Pharmacol, 2014. **73**(3): p. 551-60.
29. Falcone A, C.C., Masi G et al, *FOLFOXIRI/bevacizumab (bev) versus FOLFIRI/bev as first-line treatment in unresectable metastatic colorectal cancer (mCRC) patients (pts): Results of the phase III TRIBE trial by GONO group.* J Clin ONcol, 2013. **31**: p. 3505.
30. Heinemann V, v.W.L., Decker T et al, *Randomized comparison of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment of KRAS wild-type metastatic colorectal cancer: German AIO study KRK-0306 (FIRE-3).* J Clin Oncol, 2013. **31**: p. abstract LBA3506.

31. Eisenhauer, E.A., et al., *New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).* Eur J Cancer, 2009. **45**(2): p. 228-47.
32. Smith, T.J., et al., *2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline.* J Clin Oncol, 2006. **24**(19): p. 3187-205.
33. Hay, J.L., et al., *Cognitive interviewing of the US National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE).* Qual Life Res, 2014. **23**(1): p. 257-69.
34. Basch, E., *Systematic collection of patient-reported adverse drug reactions: a path to patient-centred pharmacovigilance.* Drug Saf, 2013. **36**(4): p. 277-8.
35. Basch, E., A. Bennett, and M.C. Pietanza, *Use of patient-reported outcomes to improve the predictive accuracy of clinician-reported adverse events.* J Natl Cancer Inst, 2011. **103**(24): p. 1808-10.
36. Jensen, R.E., et al., *Review of Electronic Patient-Reported Outcomes Systems Used in Cancer Clinical Care.* J Oncol Pract, 2013.

12.0 APPENDICES

12.1 Appendix A ECOG Performance Status

Grade	Description
0	Fully active, able to carry on all pre-diseases performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g. light housework, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Death

12.2 Appendix B List of Prohibited Drugs and Prohibited Juices and Fruits

The following drugs are prohibited in the 14 days prior to first dose of FOLFIRI through end of study therapy.

Strong CYP3A4,5,7 inhibitors	CYP3A4 inducers*	CYP3A4 and UGT1A1 Inhibitor
clarithromycin	avasimibe	atazanavir
conivaptan	barbiturates	
indinavir	bosentan	
itraconazole	carbamazepine	
ketoconazole	efavirenz	
lopinavir	etravirine	
mibefradil	modafenil	
nefazodone	nafcillin	
nelfinavir	nevirapine	
posaconazole	oxcarbazepine	
ritonavir	phenobarbital	
saquinavir	phenytoin	
telithromycin	pioglitazone	
troleandomycin	rifabutin	
voriconazole	rifapentine	
	rifampin	
	St. John's wort	
	talviraline	
	tipranavir	
	topiramate	
	troglitazone	

This database of CYP inhibitors was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and from the University of Washington's Drug Interaction Database based on *in vitro* studies. This database of CYP inducers was compiled from the FDA's "Guidance for Industry, Drug Interaction Studies;" from the Indiana University School of Medicine's "Clinically Relevant" Table; and from Pursche et al. 2008 Curr Clin Pharm. 3:198-203.

*Systemic glucocorticoids eliminated from list of prohibited CYP3A4 inducers as dexamethasone does not appear to alter the pharmacokinetics of irinotecan (see pfizer.com, Camptosar® prescribing information).

All juices/fruits listed are prohibited in the 7 days prior to first dose of FOLFIRI: **grapefruits, grapefruit juices, grapefruit hybrids, Seville oranges, pummelos, and exotic citrus fruits**

12.3 Appendix C New York Heart Association Functional Classification

Class	NYHA Functional Classification
I	Subjects have cardiac disease but *without* the resulting *limitations* of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Subjects have cardiac disease resulting in *slight limitation* of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Subjects have cardiac disease resulting in *marked limitation* of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Subjects have cardiac disease resulting in *inability* to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

12.4 Appendix D List of Drugs to be Used with Caution

Moderate CYP3A4,5,7 inhibitors
amprenavir
aprepitant
atazanavir
cimetidine
ciprofloxacin
darunavir
diltiazem
elvitegravir
erythromycin
fluconazole
fosamprenavir
imatinib
tipranavir
tofisopam
verapamil
This database of CYP inhibitors was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and from the University of Washington's Drug Interaction Database based on *in vitro* studies.

12.5 Appendix E Dietetic and pharmacologic guidelines for the treatment of drug induced diarrhea

Patients receiving iriontecan are at risk of developing diarrhea and should be managed early and appropriately to avoid potential escalation in severity, duration or complications as well as treatment delays or dose reductions. Patients should be educated about the risks of developing diarrhea, and encouraged to contact the site to report and discuss the severity of diarrhea including the appropriate course of treatment.

The following recommendations are based on available guidelines for the management of cancer treatment induced diarrhea (Wadler et al 1998, Kornblau et al. 2000, Benson et al. 2004).

Table 1 NCI CTCAE (Version 4) grading of diarrhea

Grade	Definition
1	increase of < 4 stools/day over baseline; mild increase in ostomy output compared to baseline
2	Increase of 4-6 stools/day over baseline, moderate increase in ostomy output compared to baseline
3	increase of ≥7 stools/day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL
4	Life threatening consequences; urgent intervention indicated

Management

Evaluate diarrhea

- Obtain history of onset and duration of diarrhea including a description of the number of stools and stool composition (e.g. watery, blood or mucus in stool)
- Assess patient for fever, abdominal pain/cramps, distension, bloating, nausea, vomiting, dizziness, weakness (i.e., rule out risk for sepsis, bowel obstruction, dehydration)
- Determine if diarrhea is complicated vs. uncomplicated
- Obtain medication and dietary profile (i.e. to identify any diarrheogenic agents)

Table 2 Uncomplicated vs. complicated diarrhea

Uncomplicated	Complicated
Grade 1-2 diarrhea with no complicating signs and symptoms	Grade 3-4 diarrhea Grade 1-2 with the following complicating signs or symptoms: Moderate to severe cramping Grade ≥ 2 nausea/vomiting Decreased performance status Fever Sepsis Neutropenia Frank bleeding Dehydration

Rule out other or concomitant causes

Other or concomitant causes of diarrhea such as medications (e.g. stool softeners, laxatives, antacids), infections (e.g. C difficile, Candida species), partial bowel obstruction, malabsorption, fecal impaction, short bowel syndrome, endocrine dysfunction, dietary factors (high fiber diet, lactulose, etc.) should be ruled out. Consider appropriate tests and diarrhea work up as outlined below.

General recommendations

- Stop all lactose-containing products, alcohol
- Stop laxatives, bulk fiber (Metamucil®, Procter & Gamble), and stool softeners (docusate sodium; Colace®, Roberts)
- Stop high-osmolar food supplements such as Ensure® Plus and Jevity® Plus (with fiber)
- Drink 8 to 10 large glasses of clear liquids per day [water, Pedialyte® (Ross), Gatorade® (Quaker), broth]
- Eat frequent small meals (bananas, rice, applesauce, Ensure®, toast)

It is further recommended that patients be provided loperamide tablets (or prescription) with the start of study treatment. When provided with loperamide, it is mandatory that patients are instructed on the correct use in order to manage signs or symptoms of diarrhea at home (e.g. initial administration of 4 mg, then 2 mg every 4 hours at the first sign of loose stool or symptoms of abdominal pain; do not exceed 16 mg/day). At each study visit, each patient should be specifically questioned regarding any experience of diarrhea or diarrhea related symptoms. If symptoms were experienced, then the healthcare provider should question the patient regarding the actions taken for these symptoms. Note that high dose loperamide can result in paralytic ileus.

Medications

Loperamide is usually indicated for Grade 1 and 2 diarrhea. The standard dose is 4 mg followed by 2 mg every 4 hrs or after each unformed stool (maximum 16 mg/day). This dose may be increased in patients with mild to moderate diarrhea (Grade 1 or 2) that persists for more than 24 hours ("high dose loperamide"). The dose is 4 mg to start, followed by 2 mg every 2 hours (maximum 16 mg/day). Loperamide should be discontinued after a 12 hour diarrhea-free interval.

Diphenoxylate hydrochloride and **atropine sulfate** may be used in place of loperamide as first-line treatment for diarrhea at the discretion of the treating physician. It may not be expected that this would be sufficient for the management of Grade 3 or 4 diarrhea.

Octreotide may be considered for unresolved Grade 1-2 after 24 hours high-dose loperamide +/- diphenoxylate/atropine (48 hrs. total treatment with loperamide) or Grade 3-4 diarrhea. These patients usually require hospitalization.

Opiates may be considered as second-line treatment option for unresolved Grade 1 to 2 or Grade 3 to 4 diarrhea such as Opium tincture (deodorized tincture of opium or opium 10% tincture) or Paregoric (Camphorated Tincture of Opium®). Note that due to the differences in morphine content, special care must be taken to avoid potential overdose. Opium tincture is 25 times more concentrated (at 10 mg/mL of morphine) than Paregoric (at 0.4 mg/mL). Opioids should be stopped 24h after resolution of diarrhea. If opium tincture is not available, administration of codeine phosphate can be considered as an alternative.

Antibiotics (e.g. fluoroquinolones) should be considered (prophylactically or concomitantly), particularly in the case of persistent diarrhea, severe neutropenia or fever.

Treatment of uncomplicated grade 1or 2 diarrhea

The recommended algorithm for management of uncomplicated grade 1 or 2 diarrhea is summarized in the following table:

Table 3 Treatment of uncomplicated grade 1 or 2 diarrhea

Timeline		Treatment
Initial Treatment		Standard dose of loperamide (initial administration 4 mg, then 2 mg every 4 hours or after each unformed stool; max 16 mg/day) ***NOTE:*** *Diphenoxylate hydrochloride and atropine sulfate may be used in place of loperamide as first-line treatment for diarrhea.*
Re-assessment 12-24 hours after initial onset of diarrhea	If diarrhea resolved	Continue instructions for dietary modification and gradually add solid foods to diet Discontinue loperamide after 12-hours diarrhea-free interval
	If diarrhea unresolved	Diarrhea Grade 1-2 (uncomplicated) Escalate to high dose loperamide (2 mg every 2 hours or after each unformed stool; max 16 mg/day) Monitor patient condition (to rule out dehydration, sepsis, ileus) Observe patient for response to antidiarrheal treatment and reassess 12 to 24 hours later Consider oral antibiotics Progression to complicated Grade 1-2 (e.g. presence of fever, dehydration, neutropenia) or Grade 3-4 with or without symptoms See below for treatment guidance.
Re-assessment 24-48 hours after the initial onset of diarrhea	If diarrhea resolved	Continue instructions for dietary modification and gradually add solid foods to diet Discontinue loperamide and/or other treatment after 12-hours diarrhea-free interval *NOTE: Use of high-dose loperamide can result in paralytic ileus*
	If diarrhea unresolved	Unresolved Grade 1-2 after 24 hours high-dose loperamide (48 hrs total treatment with loperamide) or progression to Grade 3-4 Evaluate patient in an office/outpatient center for a medical/laboratory check and selected workup (see 'Diarrhea workup' within this section for additional recommended tests); Hospitalization may need to be considered Replace fluids and electrolytes as appropriate Discontinue loperamide and begin a second-line agent which can be an opiate or octreotide acetate **Opiates** Opium tincture (deodorized tincture of opium or opium 10% tincture) or Paregoric (Camphorated Tincture of Opium®) ***NOTE:*** *Due to the differences in morphine content, special care must be taken to avoid potential overdose. Opium tincture is 25 times more concentrated (at 10 mg/mL of morphine) than Paregoric (at 0.4 mg/mL). Opioids should be stopped 24h after resolution of diarrhea.* *If opium tincture is not available administration of codeine phosphate can be considered as an alternative.* **Octreotide** Recommended dose of octreotide is 100-150 µg SC TID (every 8 hours). Treatment should be administered until patient is free of symptoms for 24 hours.

Treatment of grade 3-4 or complicated diarrhea regardless of grade

Severe diarrhea Grade 3 or 4 or complicated Grade 1 or 2 diarrhea may require hospitalization, and assessment of CBC, electrolytes and stool workup (e.g. cultures to exclude infectious causes) are recommended. Octreotide is the preferred anti-diarrheogenic agent (100-150 µg SC TID – every 8 hours; up to 500 µg TID). High dose loperamide (initial 4 mg, then 2 mg every 2 hours; maximum 16 mg/d) or opioids (e.g. opium tincture or dihydrocodeine tartrate tablets/injections) or atropine/diphenoxylate may be considered; however, they may not be sufficient for persistent, complicated or Grade 3 to 4 diarrhea. Thus, patients should be assessed for effectiveness of the anti-diarrheal therapy closely and switched to octreotide as indicated. Start IV fluids and antibiotics as clinically indicated with monitoring of the patient's condition.

Treatment of diarrhea grade 3/4 or complicated diarrhea grade 1-2

- Admit to hospital
- Administer IV fluids and electrolytes as needed
- Administer SC octreotide acetate (100-150 µg TID – every 8 hours)
- Stop loperamide and opiates if not already stopped
- If there is no improvement in the diarrhea after 24 hrs, dose escalate octreotide acetate up to 500 µg TID SC until diarrhea is controlled
- Medical/laboratory check and selected workup if patient does not need hospitalization (see 'Diarrhea workup' within this section for additional recommended tests)
- Monitor/Continue IV fluids and antibiotics as needed. Treatment should be discontinued within 24 hours after the resolution of diarrhea
- For study drug dose adjustment/delay see the respective protocol section

Diarrhea workup

If applicable and as necessary, appropriate tests should be performed (AGA Technical Review 1999).

Spot stool analysis

- Collect stool separating it from urine (special containers, analyze immediately, exceptionally freeze samples)
- Blood
- Fecal leukocytes (Wright's staining and microscopy) or
- Clostridium difficile toxin
- Fecal cultures including Salmonella spp., Campylobacter spp., Giardia, Entamoeba, Cryptosporidium (which can lead to opportunistic infections in immonunosuppressed patients), plus Shigella and pathogenic E. coli - enterotoxigenic, enterohemorrhagic etc., possibly Aeromonas, Pleisiomonas (if suspected exposure to contaminated water)

Endoscopic examinations

Endoscopic examinations may be considered **only if absolutely necessary**. The bowel is likely to be fragile with evidence of colitis and thus great care and caution must be exercised in undertaking these invasive procedures.

- Gastroscopy to obtain jejunal fluid - re. bacterial overgrowth for cultures and biopsy of proximal jejunum to assess extent of inflammatory jejunitis
- Sigmoidoscopy - reassessment of colitis

References

AGA Technical Review on the Evaluation and Management of Chronic Diarrhea (1999) Gastroenterol; 116: 1464-1486.

Benson AB, Ajani JA, Catalano RB, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea (2004) Journal of Clinical Oncology; 22: 2918-2926.

Kornblau S, Bensen AB, Catalano R, et al (2000) Management of Cancer Treatment–Related Diarrhea: Issues and Therapeutic Strategies. Journal of Pain and Symptom Management 19:118-129.

Wadler S, Bensen AB, Engelking C, et al (1998) Recommended guidelines for the treatment of chemotherapy induced diarrhea. Journal of Clinical Oncology; 16: 3169-3178.

12.6 Appendix F: Patient Handout: Prohibited Medications or Those to be used with Caution

One of the medications you are receiving during this clinical trial is **irinotecan**. **Irinotecan** interacts with some drugs that are processed by your liver. Because of this, it is very important to tell your study doctors about all of your medicines before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the-counter remedy), or anything that you buy from the health food store or grocery store (herbal supplement). Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you**.

- **Irinotecan** is processed by a certain enzyme in the liver called CYP3A4. Drugs that increase the activity of this enzyme are called "inducers," and drugs that decrease the activity of this enzyme are called "inhibitors." **Irinotecan** must be used very carefully with other medicines that are **inducers** or **inhibitors** of CYP3A4.
- You and healthcare providers who prescribe drugs for you must be careful about adding or removing any drug in this category.
- Before you start the study, your study doctor will work with your regular prescriber to switch the prohibited medications listed on the next page if you are taking them.
- Your regular prescribers should look at this web site: http://medicine.iupui.edu/clinpharm/ddis/ [1] to see if any medicine they want to prescribe is on a list of drugs to avoid. Your study doctor may also have a list of medications for you to show your regular prescribers instead of, or in addition to, this website.
- If you drink grapefruit juice or eat grapefruit, Seville oranges, pummelos or exotic citrus fruits you should avoid these until the study is over.
- Other medicines can be a problem with your study drugs.
    - You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
    - Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor's name is _____ and he or she can be contacted at _____.

Prohibited Drugs	
atazanavir	phenobarbital
avasimibe	phenytoin
barbiturates	pioglitazone
bosentan	posaconazole
carbamazepine	rifabutin
clarithromycin	rifapentine
conivaptan	rifampin
efavirenz	ritonavir
etravirine	saquinavir
indinavir	St. John's wort
itraconazole	talviraline
ketoconazole	tipranavir
lopinavir	topiramate
mibefradil	telithromycin
modafenil	troglitazone
nafcillin	troleandomycin
nefazodone	voriconazole
nelfinavir	
nevirapine	
oxcarbazepine	

References

1. Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). "http://medicine.iupui.edu/clinpharm/ddis/clinical-table/"

12.7 Appendix G: Subset of PRO-CTCAE Questions

See next page

1. In the last 14 days, how OFTEN did you have **LOOSE OR WATERY STOOLS (DIARRHEA)**:

- Never / Rarely / Occasionally / Frequently / Almost constantly

2. In the last 14 days, what was the SEVERITY of your **CONSTIPATION** at its WORST:

- None / Mild / Moderate / Severe / Very severe

3. In the last 14 days, what was the SEVERITY of your **DIFFICULTY SWALLOWING** at its WORST:

- None / Mild / Moderate / Severe / Very severe

4. In the last 14 days, what was the SEVERITY of your **MOUTH OR THROAT SORES** at their WORST:

- None / Mild / Moderate / Severe / Very severe

5. In the last 14 days, how much did **MOUTH OR THROAT SORES** INTERFERE with your usual or daily activities:

- Not at all / A little bit / Somewhat / Quite a bit / Very much

6. In the last 14 days, what was the SEVERITY of your **FATIGUE, TIREDNESS, OR LACK OF ENERGY** at its WORST:

- None / Mild / Moderate / Severe / Very severe

7. In the last 14 days, how much did **FATIGUE, TIREDNESS, OR LACK OF ENERGY** INTERFERE with your usual or daily activities:

- Not at all / A little bit / Somewhat / Quite a bit / Very much

8. In the last 14 days, what was the SEVERITY of your **DECREASED APPETITE** at its WORST:

- None / Mild / Moderate / Severe / Very severe

9. In the last 14 days, how much did **DECREASED APPETITE** INTERFERE with your usual or daily activities:

- Not at all / A little bit / Somewhat / Quite a bit / Very much

10. In the last 14 days, what was the SEVERITY of your **SHORTNESS OF BREATH** at its WORST:

- None / Mild / Moderate / Severe / Very severe

11. In the last 14 days, how much did **SHORTNESS OF BREATH** INTERFERE with your usual or daily activities:

- Not at all / A little bit / Somewhat / Quite a bit / Very much

12. In the last 14 days, what was the SEVERITY of your **INSOMNIA (INCLUDING DIFFICULTY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY)** at its WORST:

- None / Mild / Moderate / Severe / Very severe

13. In the last 14 days, how much did **INSOMNIA (INCLUDING DIFFICULTY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY)** INTERFERE with your usual daily activities:

- Not at all / A little bit / Somewhat / Quite a bit / Very much

14. In the last 14 days, how OFTEN did you have **NAUSEA**:

- Never / Rarely / Occasionally / Frequently / Almost constantly

15. In the last 14 days, what was the SEVERITY of your **NAUSEA** at its WORST:
- None / Mild / Moderate / Severe / Very severe

16. In the last 14 days, how OFTEN did you have **VOMITING**:
- Never / Rarely / Occasionally / Frequently / Almost constantly

17. In the last 14 days, what was the SEVERITY of your **VOMITING** at its WORST:
- None / Mild / Moderate / Severe / Very severe

18. In the last 14 days, how OFTEN did you have **PAIN**:
- Never / Rarely / Occasionally / Frequently / Almost constantly

19. In the last 14 days, what was the SEVERITY of your **PAIN** at its WORST:
- None / Mild / Moderate / Severe / Very severe

20. In the last 14 days, how much did **PAIN** INTERFERE with your usual or daily activities:
- Not at all / A little bit / Somewhat / Quite a bit / Very much

21. In the last 14 days, how OFTEN did you have **PAIN IN THE ABDOMEN (BELLY AREA):**
- Never / Rarely / Occasionally / Frequently / Almost constantly

22. In the last 14 days, what was the SEVERITY of your **PAIN IN THE ABDOMEN (BELLY AREA)** at its WORST:
- None / Mild / Moderate / Severe / Very severe

23. In the last 14 days, how much did **PAIN IN THE ABDOMEN (BELLY AREA)** INTEFERE with your usual or daily activities:
- Not at all / A little bit / Somewhat / Quite a bit / Very much

24. In the last 14 days, how OFTEN did you have a **HEADACHE**:
- Never / Rarely / Occasionally / Frequently / Almost constantly

25. In the last 14 days, what was the SEVERITY of your **HEADACHE** at its WORST:
- None / Mild / Moderate / Severe / Very severe

26. In the last 14 days, how much did your **HEADACHE** INTERFERE with your usual or daily activities:
- Not at all / A little bit / Somewhat / Quite a bit / Very much

12.8 Appendix H: PRO-CTCAE Clinician Form

See next page

(Symptom Questions Provided for Clinician Scoring and Reference; Patients to complete Patient Questionnaire)	Patient Score (calculate)	Clinician Score	Dose Modification Based on this assessment? (circle)
Diarrhea In the last 14 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA): **Never/Rarely/Occasionally/Frequently/Almost Constantly**			**Y/N**
Constipation In the last 14 days what was the SEVERITY of your CONSTIPATION at its WORST: **None/Mild/Moderate/Severe/Very Severe**			**Y/N**
Dysphagia In the last 14 days, what was the SEVERITY of your DIFFICULTY SWALLOWING at its WORST: **None/Mild/Moderate/Severe/Very severe**			**Y/N**
Mucositis a. In the last 14 days, what was the SEVERITY of your MOUTH OR THROAT SORES at their WORST: **None/Mild/Moderate/Severe/Very Severe** b. In the last 14 days, how much did MOUTH OR THROAT SORES INTERFERE with your usual or daily activities: **Not at all/A little bit/Somewhat/Quite a bit/ Very much**			**Y/N**
Fatigue a. In the last 14 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST: **None/Mild/Moderate/Severe/Very Severe** b. In the last 14 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities: **Not at all/A little bit/Somewhat/Quite a bit/Very Much**			**Y/N**
Anorexia a. In the last 14 days, what was the SEVERITY of your DECREASED APPETITE at its WORST: **None/Mild/Moderate/Severe/Very severe** b. In the last 14 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities: **Not at all/A little bit/Somewhat/Quite a bit/Very much**			**Y/N**

(Symptom Questions Provided for Clinician Scoring and Reference; Patients to complete Patient Questionnaire)	Patient Score (calculate)	Clinician Score	Dose Modification Based on this assessment? (circle)
Dyspnea a. In the last 14 days, what was the SEVERITY of your SHORTNESS OF BREATH at its WORST: **None/Mild/Moderate/Severe/Very severe** b. In the last 14 days, how much did SHORTNESS OF BREATH INTERFERE with your usual or daily activities: **Not at all/A little bit/Somewhat/Quite a bit/Very much**			**Y/N**
Insomnia a. In the last 14 days, what was the SEVERITY of your INSOMNIA (INCLDUING DIFFICULT FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY) at its WORST: **None/Mild/Moderate/Severe/Very severe** b. In the last 14 days, how much did INSOMNIA (INCLUDING DIFFICULTY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY) INTERFERE with your usual daily activities: **Not at all/A little bit/Somewhat/Quite a bit/Very much**			**Y/N**
Nausea a. In the last 14 days, how OFTEN did you have NAUSEA: **Never/Rarely/Occasionally/Frequently/Almost constantly** b. In the last 14 days, what was the SEVERITY of your NAUSEA at its WORST: **None/Mild/Moderate/Severe/Very severe**			**Y/N**
Vomiting a. In the last 14 days, how OFTEN did you have VOMITING: **Never/Rarely/Occasionally/Frequently/Almost constantly** b. In the last 14 days, what was the SEVERITY of your VOMITING at its WORST; **None/Mild/Moderate/Severe/Very severe**			**Y/N**

(Symptom Questions Provided for Clinician Scoring and Reference; Patients to complete Patient Questionnaire)	Patient Score (calculate)	Clinician Score	Dose Modification Based on this assessment? (circle)
Pain a. In the last 14 days, how OFTEN did you have PAIN: **Never/Rarely/Occasionally/Frequently/Almost constantly** b. In the last 14 days, what was the SEVERITY of your PAIN at its WORST: **None/Mild/Moderate/Severe/Very severe** c. In the last 14 days, how much did PAIN INTERFERE with your usual daily activities: **Not at all/A little bit/Somewhat/Quite a bit/Very much**			**Y/N**
Abdominal pain a. In the last 14 days, how OFTEN did you have PAIN IN THE ABDOMEN (BELLY AREA): **Never/Rarely/Occasionally/Frequently/Almost constantly** b. In the last 14 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA) at its WORST: **None/Mild/Moderate/Severe/Very severe** c. In the last 14 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities: **Not at all/A little bit/Somewhat/Quite a bit/Very much**			**Y/N**
Headache a. In the last 14 days, how OFTEN did you have a HEADACHE: **Never/Rarely/Occasionally/Frequently/Almost constantly** b. In the last 14 days, what was the SEVERITY of your HEADACHE at its WORST: **None/Mild/Moderate/Severe/Very severe** c. In the last 14 days, how much did your HEADACHE INTERFERE with your usual or daily activities: **Not at all/A little bit/Somewhat/Quite a bit/Very much**			**Y/N**

Investigator (or Designee) Signature: _____