Alliance for Clinical Trials in Oncology- Chicago Office
125 South Wacker Suite 1600
Chicago, IL. 60606
P: 773-702-3541
F: 312-345-0117

allianceforclinicalrialsinoncology.org

September 20, 2022

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

On September 15, 2022, the NCI Adult CIRB - Late Phase Emphasis reviewed A021703 (Version Date 08/09/22), and granted approval pending modification. The CIRB determined that the regulatory and CIRB SOP requirements for approval are met, but the CIRB requests minor, directed modifications. Our response to the CIRB's review letter received on September 16, 2022, is provided below in **bold**.

Thank you for your review. Please let us know what further information we may provide.

Sincerely,

[redacted]

[redacted]

Stipulation(s):
A response to the following is required:

Consent Form(s):

1. Page 15, under “Who will see my medical information?”, under the heading “Alliance for Clinical Trials in Oncology and Alliance Data Innovation Lab”, the description of the ICAREdata® project is incomplete. In keeping with protocol section 6.1.4, the participant needs to be informed that the project will only occur at “selected sites” and the participant should be encouraged “to ask their study team if the ICAREdata® project applies to them”. The current language suggests all participants at any site will be involved with the ICAREdata® project neither of which is true. Revise appropriately.

RESPONSE: The following information has been added to the first paragraph of the ICAREdata language under “Who will see my medical information?” “This project will only occur at selected sites. Please ask your study team if the ICAREdata® project applies to you.”

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Chicago, IL. 60606
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August 9, 2022

[redacted]

[redacted]

[redacted]

[redacted]

On July 21, 2022, we received a disapproval Letter for Amendment #03 of NCI Protocol #A021703 "Randomized Double-Blind Phase III Trial of Vitamin D3 Supplementation in Patients with Previously Untreated Metastatic Colorectal Cancer (SOLARIS)." Please see the attached response memo and revised protocol submission. The study team's responses to each review item are included in bold text, with hyperlinks to each section of the protocol containing each revision.

Please let us know what further information we may provide.

Sincerely,

[redacted]

[redacted]

[redacted]

I. Comments Requiring a Response – Major Issues:

#	Section	Comments
1.	**Global - Protocol**	Will the previously funding authorized for drug distribution within the Alliance grant be adequate to support distribution for the increase in sample size? If not, please provide the estimated amount required to support drug distribution for the additional sample size. **PI Response:** We have received approval from Alliance Foundation to cover additional drug storage/distribution for the increased sample size.
2.	8.1.12	Presently reads "Participants who undergo interventional therapy for metastases (e.g., surgical resection, radiofrequency ablation, transarterial embolization) will do so according to standard institutional practice. For participants for whom an elective surgery or procedure is contemplated, the Study Chair should be notified via email prior to any planned intervention. Participants may be allowed to continue on study post-intervention if protocol therapy has been held for ≤ 28 days, if they continue to have measurable disease per RECIST v1.1 outside of the treated metastatic lesion(s) post-intervention, and if the continuation of protocol therapy has been discussed with the Study Chair" This paragraph needs to state that all patients regardless of whether they have measurable disease post intervention will continue on study. However, the continued use of systemic therapy may differ between those with and without disease by imaging and this should be described per the study team's wish. **PI Response:** We would like to clarify that this paragraph is referring to continuing on *protocol therapy with chemotherapy + bevacizumab + vitamin D3* (as opposed to continuing "on study" as currently written) post-intervention. We agree with the Reviewer that all patients should remain on study post-intervention. We have now clarified this in the protocol.
3.	13.2.1	The statistics section has been amended to indicate that "Patients who receive surgery with curative intent will be censored for PFS at the date of surgery. The rate of surgery with curative intent will be examined, and if the rate is significantly different across arms, additional sensitivity analyses may be carried out." Given that this is a double-blinded study, it is more appropriate not to censor such patients at the date of surgery. For example, if more patients go to curative surgery on the high dose vitamin D arm, and PFS is thereby extended on that arm, that should be reflected in the PFS comparison, which won't happen if those patients are censored for PFS at the time of surgery. Please remove this change in the censoring rule. **PI Response:** We appreciate the feedback from the reviewer. We have removed the previous change in the censoring rule as suggested. Notably, we will add a sensitivity analysis to examine the robustness of the analysis results

#	Section	Comments
		by censoring the PFS at the surgery date. The protocol has been updated to reflect this change in Section 13.2.4.

I. Recommendations:

#	Section	Comments
4.	Global-Protocol	**According to our records A021703 is using TRIAD. Please confirm and add the following section if applicable.** ***Digital Radiation Therapy Data Submission Using Transfer of Images and Data*** Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred. TRIAD Access Requirements: • A valid Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) (CTEP-IAM) account. • Registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR). Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR. • TRIAD Site User role on an NCTN or ETCTN roster. • All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN. TRIAD Installation: To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at [redacted] This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration. For questions, contact TRIAD Technical Support staff via email [redacted] **PI Response:** This study does not use the Transfer of Images and Data (TRIAD).

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO ALLIANCE A021703

RANDOMIZED, DOUBLE-BLINDED PHASE III TRIAL OF VITAMIN D3 SUPPLEMENTATION IN PATIENTS WITH PREVIOUSLY UNTREATED METASTATIC COLORECTAL CANCER (SOLARIS)

[X]	**Update:**	[ ]	**Status Change:**
[X]	Eligibility changes	[ ]	Activation
[X]	Therapy / Dose Modifications / Study Calendar changes	[ ]	Closure
[X]	Informed Consent changes	[ ]	Suspension / temporary closure
[X]	Scientific / Statistical Considerations changes	[ ]	Reactivation
[X]	Data Submission / Forms changes		
[X]	Editorial / Administrative changes		
[ ]	Other:		

No recommended IRB level of review is provided by the Alliance since the CIRB is the IRB of record for this trial.

The site has 30 days after the posting of this amendment to implement it at their site. Please refer to the amendment application and CIRB guidelines for further instructions.

UPDATES TO THE PROTOCOL:

Cover Page (p. 1)

- [redacted]

Study Recourses (p. 2)

- Under the **Expedited Adverse Event Reporting** heading, the website has been updated to reflect current boilerplate language.

CTSU Address and Contact Information (Page 3)

- All text in the table has been updated with current CTSU boilerplate language.

Schema

- The abbreviated eligibility criteria has been updated to align with the changes made in Section 3.2.

Section 2.0 Objectives

- In Section 2.2.6 "Demographic and clinicopathologic characteristics" has been added to the end of the sentence.

Section 3.2 Eligibility Criteria

- In the 1st paragraph of Section 3.2.1, a new 2nd sentence has been added for clarity that reads: "A biopsy from either the primary colonic tumor and/or a metastatic site is acceptable."
- In the third paragraph of Section 3.2.3, the word "which" has been added to the 1st sentence, and a new 2nd sentence has been added which reads "No washout period is required after palliative radiation to other sites."
- In Section 3.2.7, the units have been removed from the UPC ratio and the corresponding footnote has been updated for clarity.
- In the 3rd paragraph of Section 3.2.8, the phrase "or controlled" has been added to the end of the sentence.
- In Section 3.2.10, the 2nd sentence of the 1st paragraph, the phrase "at least 7 days" has been removed.

Section 4.0 Patient Registration

- Section 4.2 and Section 4.4 have been updated to reflect current CTSU boilerplate language.

Section 5.0 Study Calendar

- The study calendar has been updated to reflect the removal of 'serum' from the creatinine collection in order to make the requirement of this collection less restrictive.
- Footnote #1 has been updated to provide clarity to the collection of the Diet and Lifestyle Questionnaire: Diet and Lifestyle Questionnaire "can be" completed "within" ≤ 4 weeks "after" enrollment.
- Footnote A has been corrected to state that a "UPC ratio" not urinalysis should be performed.
- 'I.E. every 8 weeks' has been removed from footnote C.

Section 6.0 Data and Specimen Submission

- Section 6.1.2 and Section 6.1.3 have been updated to reflect current CTSU boilerplate language.
- Section 6.1.4, has been updated with new ICAREdata language.
- In the third paragraph of Section 6.4, 'of' has been replaced with 'after.'

Section 8.1.12 Surgery/Metastasectomy

- In the third sentence of the paragraph, 'on study' has been updated to "protocol therapy with chemotherapy + bevacizumab + vitamin D3." This sentence has been revised in response to CTEP recommendation.

Section 8.2.2 Dose Modifications for mFOLFOX6 and FOLFIRI

- 'Irinotecan' has been added to the second sentence of the first paragraph.

Section 13.0 Statistical Considerations

- In the second bullet of the first paragraph in Section 13.2.1 the word "new" has been added prior to anti-cancer therapy.
- In the first paragraph, the second and third sentences of Section 13.2.2 have been updated to reflect the increase in total accrual: Based on the results from CALGB 80405, we anticipate a PFS median of approximately 10 months [27]. We plan to accrue a total of "445" patients "(approximately 222" patients per arm) in "39" months with a minimum follow-up of "13" months to achieve 273 PFS

events. The length of accrual time is based on an accrual rate of "3" patients per month "for the first 6 months, 12 patients per month for 1 year (after the first 6 months) and 14 patients per month for the remaining accrual period." This design with one interim analysis for futility only with O'Brien-Fleming type stopping boundary (Gamma family with parameter -4 for futility) will yield 90% power to detect a hazard ratio of 0.70 (median PFS of 10 vs. 14.3 months) assuming exponential survival and using a one-sided log-rank test with type I error rate of 0.05. This sample size takes into account a "27.6%" drop-out rate due to patients coming off treatment for reasons other than disease progression (e.g. surgical resection);

- A second paragraph has been added to Section 13.2.2.
- In the third paragraph of Section 13.2.4, a fifth and sixth sentence have been added.
- In Section 13.3.1, the sample size has been increased from 400 to '445.'
- In Section 13.3.2, the following two sentences have been added to further clarify the accrual increase: "We made the same assumption for the accrual rate for the original study design. In Update #03 where the sample size was increased to 445, we updated the accrual rate by using three different accrual periods in which the rate in each period is approximately the actual observed accrual rate in the study (see Section 13.2.2)."
- In Section 13.3.3, the monthly accrual rate has been updated.
- Section 13.4.1 has the following updates:
    - In the first bullet point "Unconfirmed" has been added to the beginning of the first sentence.
    - In the third bullet point, "Toxicity: As per NCI CTCAE v5.0, the term toxicity is defined as adverse events that are classified as possibly, probably, or definitely related to study treatment," has been replaced with "Adverse Event."
    - In the 5th bullet poin**t,** "Prevalence" has replaced "incidence."
    - In the 6th bullet point, "Subgroup Analyses" has replaced "Baseline 25(OH)D"; "baseline demographic and clinicopathologic factors (e.g., body mass index [<25 vs 25-30 vs. ≥30 kg/m^2], presence of liver metastases [yes vs. no], RAS mutation status [wildtype vs. mutant]). Baseline 25(OH)D" has been added to the end of the first sentence; 'of baseline 25(OH)D levels' has been removed from the 4th sentence and 6th sentences and "Comparison of PFS across arm in subgroups of interest while adjusting for baseline characteristics will also be conducted as exploratory analysis" has been added as the last sentence of the paragraph.
- In Section 13.8, the **Domestic Planned Enrollment Report** table has been updated to reflect the increased accrual and the ethnic and racial categories lists have been removed to align with the current Alliance model protocol template.

UPDATES TO THE MODEL CONSENT:

- In the "**What is the Purpose of this study**?" section the accrual was updated from 400 to 445.
- The "**Who will see my medical information section**?" has been updated with new ICARE data language.

A replacement protocol and consent document have been issued.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A021703

RANDOMIZED DOUBLE-BLIND PHASE III TRIAL OF VITAMIN D3 SUPPLEMENTATION IN PATIENTS WITH PREVIOUSLY UNTREATED METASTATIC COLORECTAL CANCER (SOLARIS)

Industry-supplied agent(s): Vitamin D3 (NSC# 375571)
Commercial agent(s): 5-fluorouracil (NSC# 19893); Leucovorin calcium (NSC# 3590); Oxaliplatin (NSC# 266046); Irinotecan (NSC# 616348); Bevacizumab (NSC# 704865)
IND #142392; IND holder: Alliance

ClinicalTrials.gov Identifier: NCT04094688

Study Chair

[redacted]

Community Oncology Co-Chair

[redacted]

Correlative Science Co-Chair

[redacted]

Imaging Co-Chair

[redacted]

GI Committee Co-Chair

[redacted]

GI Committee Co-Chair

[redacted]

ECOG-ACRIN Champion

[redacted]

NRG Champion

[redacted]

SWOG Champion

[redacted]

Primary Statistician

[redacted]

Secondary Statistician

[redacted]

Protocol Coordinator

[redacted]

Data Manager

[redacted]

Participating NCTN Groups:
Alliance/Alliance for Clinical Trials in Oncology (lead), ECOG-ACRIN / ECOG-ACRIN Cancer Research Group, NRG / NRG Oncology, SWOG / SWOG

Study Resources

Expedited Adverse Event Reporting

[redacted]

Medidata Rave® iMedidata portal

[redacted]

OPEN (Oncology Patient Enrollment Network)

[redacted]

Biospecimen Management System

[redacted]

Protocol Contacts

A021703 Nursing Contact

[redacted]

A021703 Pharmacy Liaison

[redacted]

Drug Distribution Contact

[redacted]

Alliance Biorepository at Washington University (WUSTL)

[redacted]

IROC Ohio

[redacted]

Protocol-related questions may be directed as follows:	
Questions	**Contact (via email)**
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
Questions related to IRB review:	Alliance Regulatory Inbox [redacted]
Questions regarding CTEP-AERS reporting:	Alliance Pharmacovigilance Inbox [redacted]
Questions regarding specimens/specimen submissions:	Alliance Biorepository at WUSTL
Questions regarding drug supply:	McKesson Clinical Research Services
Questions regarding drug administration:	Pharmacy Liaison

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in [redacted] and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: [redacted] receive further instruction and support. Contact the CTSU Regulatory Help Desk at [redacted] regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at [redacted] Contact the CTSU Help Desk with any OPEN related questions by phone or email: [redacted]	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website [redacted] Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log in with a CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).		
For clinical questions (i.e. patient eligibility or treatment-related) see Protocol Contacts, Page 2.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) Contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – [redacted] All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU website is located at [redacted]		

RANDOMIZED DOUBLE-BLIND PHASE III TRIAL OF VITAMIN D3 SUPPLEMENTATION IN PATIENTS WITH PREVIOUSLY UNTREATED METASTATIC COLORECTAL CANCER

Eligibility Criteria (see Section 3.2)

- Histologically confirmed locally advanced/metastatic colorectal adenocarcinoma with no planned metastasectomy
- No known dMMR or MSI-H disease
- Measurable disease per RECIST v1.1
- No prior systemic treatment for metastatic disease
- Prior neoadjuvant or adjuvant chemotherapy/radiation allowed if completed > 12 months prior to colorectal cancer recurrence
- Prior rectal chemoradiation permitted if completed ≥ 4 weeks prior to registration
- No continuous daily vitamin D ≥ 2,000 IU/day for the 12 months prior to registration
- Major surgery/open biopsy completed ≥ 4 weeks and/or minor surgery/core biopsy completed ≥ 1 weeks prior to registration.
- Not pregnant and not nursing. Women of childbearing potential must have negative pregnancy test ≤ 14 days prior to registration
- Age ≥ 18 years; ECOG PS: 0-1
- No resectable metastatic disease for which potentially curative metastasectomy is planned

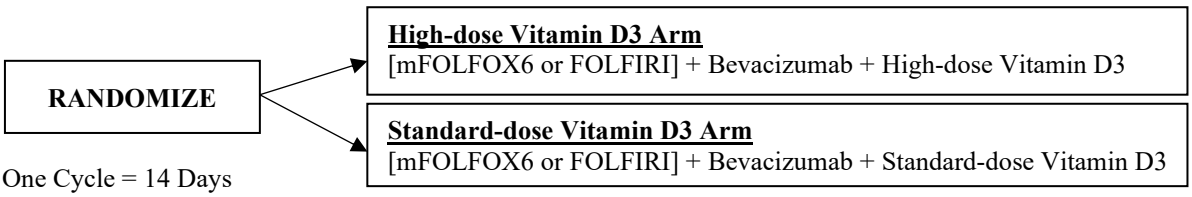
Required Initial Laboratory Values:

ANC ≥ 1500/mm^3
Platelet Count ≥ 100,000/mm^3
Hemoglobin ≥ 9 g/dL
Creatinine ≤ 1.5 x upper limit of normal (ULN) **or** Calc. CrCl > 30 mL/min
Calcium* ≤ 1.0 x ULN
Total Bilirubin** ≤ 1.5 x ULN
AST/ALT*** ≤ 2.5 x ULN
UPC Ratio ≤ 1
or Urine Protein ≤ 1+ ****

* Corrected for albumin level if albumin not WNL
** If Gilbert's disease: direct bilirubin ≤ 1.5 x ULN if patient to receive FOLFIRI; direct bilirubin ≤ 3.0 x ULN if patient to receive FOLFOX
*** AST/ALT < 5 x ULN if liver metastases
**** If both of these are above 1, then 24-hour urine must be ≤ 1 g/24 hours.

- No "currently active" second malignancy other than non-melanoma skin cancers or cervical carcinoma in situ
- No history of bleeding events, bleeding diathesis, arterial thrombotic events (incl. TIA, CVA, unstable angina requiring intervention, or MI), or clinically significant PAD ≤ 6 months of registration
- No history of uncontrolled CHF defined as NYHA Class III or greater
- No history of GI perforation ≤ 12 months of registration
- No history of malabsorption, uncontrolled vomiting or diarrhea, other GI-function-affecting disease, allergic reaction attributed to compounds similar to study agents
- No uncontrolled HTN, serious or non-healing wound, ulcer, or bone fracture, or uncontrolled intercurrent illness (incl. psychiatric illness/social situations)
- HIV-positivity allowed if on effective anti-retroviral therapy and undetectable HIV viral load ≤ 6 months of registration
- No pre-existing hypercalcemia
- No known active hyperparathyroid disease or other serious Ca^{2+} metabolism disturbance ≤ 5 years of registration
- No predisposing colonic or small bowel disorders with uncontrolled symptoms; colostomy or ileostomy allowed
- No symptomatic genitourinary stones ≤ 12 months of registration
- Treated brain metastases allowed if post-treatment imaging shows no evidence of progression ≥ 28 days prior to registration
- New/progressive brain metastases or LMD allowed if no immediate CNS-specific treatment required
- No uncontrolled seizure disorders or grade ≥ 2 peripheral neuropathy, neurosensory toxicity, or neuromotor toxicity
- Must be able to swallow oral formulations
- Concurrent use of calcium, vitamin D, thiazide diuretics, oral corticosteroids, or other anti-cancer therapy not permitted

Schema



One Cycle = 14 Days

Treatment is to continue until 5 years after registration or disease progression, unacceptable toxicity, or withdrawal of consent. Patients will be followed for survival until 5 years after registration or until death, whichever comes first.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

Chemotherapy, imaging, and clinical follow-up must be administered/performed at the registering institution. If the Group credited for enrollment is a non-Alliance Group, then other requirements from the credited Group may apply.

Table of Contents

1.0 BACKGROUND

1.1 Rationale for Trial Design

The hypothesis that vitamin D status is related to colorectal cancer (CRC) has received strong experimental support over the past two decades, based on the almost ubiquitous expression in colon cancer cells of the vitamin D receptor (VDR) and 1-α-hydroxylase (CYP27B1), which converts plasma 25(OH)D into 1,25-dihyroxycholecalciferol [1,25(OH)2D], the active metabolite [1-3]. Binding of VDR by 1,25(OH)2D leads to transcriptional activation and repression of target genes, resulting in induction of differentiation and apoptosis, and inhibition of proliferation, angiogenesis, and metastatic potential [4-10]. In vitro and in vivo data have demonstrated growth inhibition and differentiation of colon carcinoma cell lines and xenografts by administration of 1,25(OH)2D, and rat models of colorectal cancer maintained on a 1,25(OH)2D diet developed fewer tumors and metastases compared to control animals [7, 11-15]. In Apc^{min} mice, treatment with vitamin D or its synthetic analogs significantly decreased tumor burden [16]. These anti-neoplastic actions of vitamin D and the presence of 1α-hydroxylase and VDR in CRC cells suggest that 1,25(OH)2D3 can be synthesized locally within the tumor and microenvironment to yield high concentrations for autocrine and paracrine effects.

Epidemiologic data also support the vitamin D hypothesis, with multiple prospective observational studies consistently showing a significant relationship between higher plasma 25(OH)D levels and improved survival among patients with CRC [17-20]. The first such study was a prospective analysis of 304 patients with stage I-IV CRC from the Nurses' Health Study (NHS) and Health Professionals Follow-Up Study (HPFS) that reported that higher plasma 25(OH)D levels were associated with significantly improved overall survival (OS) (multivariate HR 0.52; 95% CI 0.29 to 0.94; *P* trend=0.02) [17]. In subgroup analyses, the benefit of higher plasma 25(OH)D seemed greater in stage III and IV patients compared to stage I and II patients (adjusted HR 0.40 versus 0.90, respectively, comparing extreme quartiles). This finding was subsequently confirmed in a larger cohort of mCRC patients enrolled in the phase III randomized clinical trial of first-line chemotherapy, CALGB/SWOG 80405 [21]. Among 1,043 patients in this study with available baseline plasma 25(OH)D levels, the median 25(OH)D concentration was deficient at 17.2 ng/mL. Patients with higher levels of 25(OH)D had significantly improved OS compared to those with lower levels, with a median OS of 32.6 months versus 24.5 months, comparing extreme quintiles (adjusted HR 0.65; 95% CI, 0.51-0.83; *P* trend = 0.001). Similarly, patients with higher plasma 25(OH)D levels had significantly improved PFS, with a median PFS of 12.2 months versus 10.1 months, comparing extreme quintiles (adjusted HR 0.79; 95% CI, 0.63-0.99; *P* trend=0.01).

Given the compelling preclinical and epidemiologic data above, the SUNSHINE multicenter randomized, double-blind, phase II trial was conducted to address causality in the relationship between vitamin D and CRC [22]. From 2012-2016, 139 patients with previously untreated mCRC were randomized to receive standard FOLFOX + bevacizumab chemotherapy with either a) high-dose vitamin D3 (8,000 IU/day x 2 weeks as loading dose, followed by 4,000 IU/day as maintenance dose), or b) standard-dose vitamin D3 (400 IU/day) in blinded fashion. There were several reasons for not utilizing a true placebo, including: 1) potential unwillingness of CRC participants to be randomized to a vitamin D placebo, which would negatively impact accrual; 2) known prevalence of vitamin D deficiency and insufficiency in the metastatic population; 3) the fact that vitamin D3 400 IU daily increases serum 25(OH)D levels by only 3-4 ng/mL; and 4) previous research indicating a lack of benefit of multivitamin supplements (which typically contain 400 IU of vitamin D) on outcomes in stage III colon cancer patients [23, 24]. All of these reasons support using vitamin D3 400 IU/day as an active control arm. The primary

endpoint was PFS by intent-to-treat analysis, and patients were treated until disease progression, unacceptable toxicity, or withdrawal of consent.

Baseline characteristics were well-balanced between the two arms in SUNSHINE, with slightly more ECOG performance status 1 patients randomized to high-dose vitamin D3 (58% versus 43%, *P*=0.08). Median follow-up time for the entire study population was 22.9 months at the time of database lock on September 1, 2018, and compliance with vitamin D3 was high, with a median of 98% of expected capsules taken by patients in both the high-dose and standard-dose vitamin D arms. The majority of patients discontinued study treatment for disease progression (49% receiving high-dose vitamin D3 versus 54% receiving standard-dose). Interestingly, more patients randomized to high-dose vitamin D3 came off study to pursue potentially curative surgery (17% versus 9%). The addition of high-dose vitamin D3 to chemotherapy did not result in added toxicity; in fact, there were fewer grade 3/4 events of diarrhea among patients receiving high-dose vitamin D3 compared to those receiving standard-dose vitamin D3 (1% versus 12%, *P*=0.02). In regards to the primary efficacy endpoint, the SUNSHINE trial showed that high-dose vitamin D3 significantly prolonged PFS compared to standard-dose vitamin D3. The multivariable HR for progression or death was 0.64 (one-sided 95% CI, 0-0.90; *P*=0.02) comparing high-dose to low-dose vitamin D3, with a median PFS of 13.0 (95% CI, 10.1-14.7) vs. 11.0 months (95% CI, 9.5-14.0), respectively (stratified log rank *P*=0.03). Further adjustment for primary tumor location did not change the impact of high-dose vitamin D3 on PFS (HR 0.66; 95% CI, 0-0.94; *P*=0.02). Among 128 evaluable patients, ORR was 58% vs. 63% (*P*=0.27) and disease control rate (DCR) was 100% vs. 95% (*P*=0.06), comparing high-dose to low-dose vitamin D. OS data are not yet mature, but at the time of the data lock, median OS was 24.3 (95% CI, 19.0-33.2) vs. 24.3 (95% CI, 20.3-32.4) months, respectively (log rank *P*=0.43).

Plasma 25(OH)D levels from patients enrolled on SUNSHINE are shown in Table 1. Patients in both arms were vitamin D deficient at baseline: median 16.1 ng/mL for high-dose and 18.7 ng/mL for standard-dose (*P*=0.30). At the time of the first restaging scan at approximately 8 weeks, patients randomized to standard-dose vitamin D3 did not have a significant change in their 25(OH)D levels, whereas those receiving high-dose vitamin D3 increased their levels into the sufficient range, with a median of 32 ng/mL (*P*<0.001). Similarly, at the second restaging scan at approximately 16 weeks, control arm patients had no appreciable change in their 25(OH)D levels, whereas those receiving high-dose vitamin D3 had a further small rise to median 35 ng/mL (*P*<0.001). And finally, at treatment discontinuation, plasma levels in the standard-dose arm again remained the same, and levels among patients in the high-dose arm were maintained at median 35 ng/mL (*P*<0.001). These data reveal several important insights: 1) vitamin D3 at 400 IU/day is an appropriate active control arm; 2) vitamin D3 8,000 IU/day x 2 weeks followed by 4,000 IU/day effectively raises plasma 25(OH)D levels into sufficient range; 3) mCRC patients are vitamin D deficient at baseline, and are not already using high-dose vitamin D prior to study enrollment; 4) no contamination of the control arm was seen in SUNSHINE; and 5) the high compliance rate reported by patients on SUNSHINE is now confirmed by the plasma 25(OH)D data [22].

Table 1

TIME POINT	HIGH-DOSE VITAMIN D3		STANDARD-DOSE VITAMIN D3		*P* VALUE
	No.	Median 25(OH)D (25^{th}, 75^{th} percentile) ng/mL	No.	Median 25(OH)D (25^{th}, 75^{th} percentile) ng/mL	
Baseline	63	16.1 (10.1, 23.0)	61	18.7 (13.5, 22.7)	0.30
First Restaging (After 4 Cycles)	54	32.0 (25.7, 39.5)	50	18.7 (16.1, 22.5)	<0.001
Second Restaging (After 8 Cycles)	47	35.2 (25.0, 45.4)	37	18.5 (16.0, 22.6)	<0.001
Treatment Discontinuation	43	34.9 (24.9, 44.7)	47	18.7 (13.9, 23.0)	<0.001
Change from Baseline to First Restaging	50	17.6 (9.9, 25.0)	47	-0.5 (-2.1, 3.5)	<0.001
Change from Baseline to Second Restaging	46	17.3 (7.6, 27.8)	34	-0.4 (-2.3, 4.0)	<0.001
Change from Baseline to Treatment Discontinuation	38	21.2 (6.6, 32.6)	43	0.8 (-3.2, 2.3)	<0.001

1.2 Trial Importance

Based on the positive phase II SUNSHINE data described above, a larger confirmatory phase III trial with more robust power is warranted in order to definitively determine the role of high-dose vitamin D3 supplementation in treatment of metastatic CRC. If positive, the SOLARIS phase III trial will be practice-changing and will result in incorporation of high-dose vitamin D3 into first-line chemotherapy as a new standard of care. SOLARIS will also provide investigators with an invaluable cohort of mCRC patients with associated biospecimens and lifestyle questionnaires for hypothesis-generating correlative studies related to vitamin D3, inflammation, immunity, and other pathways. The results of SOLARIS will address causality, unveil novel insights into vitamin D3 biology, and critically impact cancer care on a global scale given the availability of vitamin D3. Indeed, in an era of expensive and often toxic anti-neoplastic drugs, vitamin D3 represents an attractive and accessible treatment option with respect to both safety and cost.

2.0 OBJECTIVES

2.1 Primary Objective

To compare the progression-free survival (PFS) of patients receiving high-dose vitamin D3 in combination with standard chemotherapy (FOLFOX or FOLFIRI) and bevacizumab versus those receiving standard-dose vitamin D3 in combination with standard chemotherapy and bevacizumab.

2.2 Secondary Objectives

2.2.1 To compare the objective response rate (ORR) of patients receiving high-dose vitamin D3 in combination with standard chemotherapy + bevacizumab versus those receiving standard-dose vitamin D3 in combination with standard chemotherapy + bevacizumab.

2.2.2 To compare the overall survival (OS) of patients receiving high-dose vitamin D3 in combination with standard chemotherapy + bevacizumab versus those receiving standard-dose vitamin D3 in combination with standard chemotherapy + bevacizumab.

2.2.3 To evaluate and compare the toxicity of adding high-dose vitamin D3 versus standard-dose vitamin D3 to chemotherapy + bevacizumab.

2.2.4 To assess the influence of diet, body mass index, physical activity, and other lifestyle habits on PFS among patients with locally advanced/metastatic colorectal cancer.

2.2.5 To evaluate the incidence of vitamin D3 deficiency in participants with previously untreated metastatic colorectal cancer.

2.2.6 To compare the efficacy of high-dose vitamin D3 versus standard-dose vitamin D3 in subgroups of patients defined by baseline plasma 25(OH)D levels, demographic and clinicopathologic characteristics.

2.2.7 To evaluate the prognostic effect of highest-achieved 25(OH)D levels with PFS.

2.3 Other Objective

Results of the primary analysis will be examined for consistency, while taking into account the stratification factors and/or covariates of baseline QOL and fatigue.

2.4 Exploratory Objectives

2.4.1 To evaluate the association between germline variation in vitamin D pathway genes and plasma 25(OH)D levels, response to vitamin D3 supplementation, and patient outcome.

2.4.2 To evaluate the impact of high-dose vitamin D3 versus standard-dose vitamin D3 on the plasma Angiome, and how the Angiome modifies the association between vitamin D3 supplementation and patient outcome.

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study and for 6 months after the last dose of study treatment due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives, or double barrier method (diaphragm plus condom).

3.2 Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e. has had menses at any time in the preceding 12 consecutive months).

___ **3.2.1 Documentation of Disease:**

Histologically confirmed advanced/metastatic colorectal adenocarcinoma for which metastasectomy is not planned. A biopsy from either the primary colonic tumor and/or a metastatic site is acceptable.

No known dMMR or MSI-H disease.

___ **3.2.2 Measurable disease per RECIST v1.1 as defined in Section 11.0.**

___ **3.2.3 Prior Treatment**

No prior systemic treatment for metastatic disease.

Patients may have received prior neoadjuvant or adjuvant chemotherapy and/or chemoradiation. The last course of adjuvant therapy must have been completed > 12 months prior to colorectal cancer recurrence.

Patients may have received prior standard rectal cancer chemoradiation, which must have been completed ≥ 4 weeks prior to registration. No washout period is required after palliative radiation to other sites.

No continuous daily use of vitamin D supplements ≥ 2,000 IU per day for the 12 months prior to registration. Patients may have had continuous daily use of vitamin D supplements ≥ 2,000 IU per day if total duration < 12 months in the 12 months prior to registration. Patients may have had continuous daily use of vitamin D supplements < 2,000 IU per day for any duration prior to registration.

Patients must have completed any major surgery or open biopsy ≥ 4 weeks prior to registration and must have completed any minor surgery or core biopsy ≥ 1 week prior to registration. (Note: insertion of a vascular access device is not considered major or minor surgery.) Patients must have recovered from the effects of any surgery (e.g. wound is healed, no active infection, no drains, etc.) prior to registration.

___ **3.2.4 Not pregnant and not nursing.**

This study involves an agent that has known genotoxic, mutagenic and teratogenic effects. Therefore, for women of childbearing potential only, a negative serum or urine pregnancy test done ≤ 14 days prior to registration is required.

___ **3.2.5 Age ≥ 18 years**

___ **3.2.6 ECOG Performance Status: 0-1**

___ **3.2.7 Required Initial Laboratory Values:**

- Absolute Neutrophil Count ≥ 1,500/mm^3
- Platelet Count ≥ 100,000/mm^3
- Hemoglobin ≥ 9 g/dL
- Creatinine ≤ 1.5 x upper limit of normal (ULN)
  OR
  Calc. CrCl > 30 mL/min
- Calcium ≤ 1.0 x ULN *
- Total Bilirubin ≤ 1.5 x ULN**
- AST/ALT ≤ 2.5 x ULN ***
- UPC Ratio ≤ 1
  OR
  Urine Protein ≤ 1+ ****

* Corrected for albumin level if albumin not within institutional limits of normal

** If Gilbert's disease, use direct bilirubin instead of total bilirubin; direct bilirubin ≤ 1.5 x ULN if patient to receive FOLFIRI; direct bilirubin ≤ 3.0 x ULN if patient to receive mFOLFOX6

*** AST/ALT < 5 x ULN if clearly attributable to liver metastases

**** If both the UPC ratio and urine protein are above 1, but 24-hour urine is ≤ 1 g/24 hours, then the patient is eligible.

___ **3.2.8 Patient History**

No resectable metastatic disease for which potentially curative metastasectomy is planned.

No "currently active" second malignancy other than non-melanoma skin cancers or cervical carcinoma in situ. Patients are not considered to have a "currently active" malignancy if they have completed therapy and have been free of disease for ≥ 3 years.

No significant history of bleeding events or bleeding diathesis ≤ 6 months of registration unless the source of bleeding has been resected or controlled.

No history of arterial thrombotic events, including, but not limited to, transient ischemic attack, cerebrovascular accident, unstable angina, angina requiring surgical or medical intervention, or myocardial infarction ≤ 6 months of registration.

No history of clinically significant peripheral artery disease ≤ 6 months of registration.

No history of uncontrolled congestive heart failure defined as NYHA Class III or greater.

No history of gastrointestinal (GI) perforation ≤ 12 months of registration except for GI perforation related to a primary colorectal tumor that has since been fully resected.

No history of malabsorption, uncontrolled vomiting or diarrhea, or any other disease significantly affecting GI function that could interfere with the absorption of oral agents.

No history of allergic reaction attributed to compounds of similar chemical or biological composition to the study agents.

3.2.9 Comorbid Conditions

No uncontrolled hypertension (defined as BP >160/90).

No serious or non-healing wound, ulcer, or bone fracture.

No uncontrolled intercurrent illness, including, but not limited to, psychiatric illness/social situations that, in the opinion of the treating physician, may increase the risks associated with participation or treatment on the study or may interfere with the conduct of the study or interpretation of the study results.

Patients positive for HIV are eligible only if they meet <u>all</u> of the following:

- On effective anti-retroviral therapy
- Undetectable HIV viral load by standard clinical assay ≤ 6 months of registration

No known pre-existing hypercalcemia ≤ 6 months of registration.

No known active hyperparathyroid disease or other serious disturbance of calcium metabolism ≤ 5 years of registration.

No predisposing colonic or small bowel disorders in which symptoms are uncontrolled as indicated by > 3 watery or soft stools daily in patients without a colostomy or ileostomy. Patients with a colostomy or ileostomy are allowed per treating physician discretion.

No symptomatic genitourinary stones ≤ 12 months of registration.

Patients with treated brain metastases are eligible if follow-up imaging after CNS-directed therapy shows no evidence of progression ≥ 28 days prior to registration.

Patients with new or progressive brain metastases (active brain metastases) or leptomeningeal disease are eligible if the treating physician determines that immediate CNS-specific treatment is not required and is unlikely to be required during the first cycle of protocol-specified therapy after registration.

No uncontrolled seizure disorders.

No grade ≥ 2 peripheral neuropathy, neurosensory toxicity, or neuromotor toxicity per CTCAE v5.0 regardless of causality.

Patients must be able to swallow oral formulations of the agent.

3.2.10 Concomitant Medications

Concurrent use of supplemental calcium and/or vitamin D is not permitted. Patients must discontinue the supplement(s) prior to registration. See Section 8.1.9 for more information.

Concurrent use of thiazide diuretics (e.g. hydrochlorothiazide) is not permitted. Patients must discontinue the drug(s) or switch to an alternative anti-hypertensive agent at least 7 days prior to registration.

Chronic concomitant treatment with oral corticosteroids, lithium, phenytoin, quinidine, isoniazid, and/or rifampin are not permitted. Patients must discontinue the agent(s) at least 7 days prior to registration. Short-term use of corticosteroids as antiemetic therapy is acceptable; see Section 8.1.10 for more information.

Concurrent use of other anti-cancer therapy including chemotherapy, targeted, and/or biological agents is not permitted; see Section 8.1 for more information.

4.0 PATIENT REGISTRATION

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at [redacted]In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at [redacted]

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at [redacted]

4.2 Cancer Trials Support Unit Site Registration Procedures

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory

Office, but sites are required to contact the CTSU Regulatory Office at [redacted] to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling [redacted]

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status;
- Active status at the site(s) on the IRB/REB approval on at least one participating organization's roster;
- If using NCI CIRB, active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- Lists all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

4.2.1 Additional Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB signatory Institution (US sites only); and
- Compliance with all protocol-specific requirements (PSRs).

4.2.2 Protocol-Specific Requirements for A021703 Site Registration

This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider. To manage provider associations or to add or remove associated providers, access the Provider Association page from the Regulatory section on the CTSU members' website at [redacted] Sites must be linked to at least one Imaging and Radiation Oncology Core (IROC) provider to participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. An individual with a primary role on any roster is required to update provider associations, though all individuals at a site may view provider associations. To find who holds primary roles at your site, view the Person Roster Browser under the RUMS section on the CTSU website.

4.2.3 Downloading Site Registration Documents

- Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and their associated investigators and staff on a participating roster. To view/download site registration

forms: Log in to the CTSU members' website [redacted] using your CTEP-IAM username and password;

- Click on *Protocols* in the upper left of the screen
    - Enter the protocol number in the search field at the top of the protocol tree; or
    - Click on the By Lead Organization folder to expand, then select *Alliance*, and protocol number *A021703*.
- Click on *Documents*, *Protocol Related Documents, and* use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.4 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: [redacted] in order to receive further instruction and support.

4.2.5 Checking Site's Registration Status

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration*; and
- Enter the sites 5-character CTEP Institution Code and click on Go.
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

4.2.6 Credentialing

There are no credentialing requirements for this trial.

4.2.7 Delegation of Task Log (DTL)

Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL

Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and include a Master Task List, which describes DTL task assignments, CI signature, and CTEP registration requirements.

4.3 Patient Registration Requirements

Informed Consent: The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.

Patient-completed Booklet: The Diet and Lifestyle Questionnaire booklet will be sent to the enrolling institution at the time of each patient registration/randomization. A sample of the booklet can be found on the Alliance and CTSU websites as a separate document, and it is to be used for reference and IRB submission only. It is not to be used for patient completion.

This study includes the use of the mandatory patient-completed measure, Diet and Lifestyle Questionnaire. The Diet and Lifestyle Questionnaire is available in English. Completion of the Diet and Lifestyle Questionnaire booklet is mandatory for all patients registered to this trial who are able to speak, read, and/or understand this language.

Protected Health Information: The Diet and Lifestyle Questionnaire collected for this study will be sent directly to the Dana-Farber Cancer Institute. This booklet will be labeled with patient initials and patient study ID.

4.4 Patient Registration/Randomization Procedures

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

To receive site reimbursement for specific tests and/or bio-specimen submissions, completion dates must be entered in the OPEN Funding screen post registration. Please refer to the protocol-specific funding page on the CTSU members' website for additional information. Timely entry of completion dates is recommended as this will trigger site reimbursement.

Access OPEN at [redacted] or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at [redacted] For any additional questions, contact the CTSU Help Desk at [redacted]

4.5 Stratification Factors and Treatment Assignments

Dynamic Allocation

After a patient is registered, they will be assigned to one of the two treatment arms (treatment vs. control) in a 1:1 ratio utilizing a dynamic allocation algorithm based on method by Pocock and Simon [25]. The goal of the algorithm is to maintain arm balance with respect to the following important stratification factors:

- Chemotherapy Backbone: mFOLFOX6 vs. FOLFIRI
- Primary Tumor Location: Right (Cecum, Ascending Colon, Hepatic Flexure, Transverse Colon) vs. Left (Splenic Flexure, Descending Colon, Sigmoid Colon, Rectosigmoid Junction, Rectum)
- ECOG PS: 0 vs. 1

In order to ensure that treatment assignment is not deterministic, a level of randomness has been added to the algorithm such that patients will be assigned to the arm that leads to more imbalance 90% of the time.

5.0 STUDY CALENDAR

Pre-Study Testing Intervals:

The pre-study testing intervals are guidelines only. Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

To be completed ≤ 14 DAYS before registration: All laboratory studies, history and physical.

To be completed ≤ 28 DAYS before registration: Any scan of any type which is utilized for tumor measurement per protocol.

	Prior to registration*	Day 1 of each cycle*	Post-treatment follow up**	PD, withdrawal, or removal**
Tests & Observations				
H&P, Weight, Pulse, BP, PS	X	X	X	X
Height	X			
Adverse Event Assessment		X	X	X
Diet/Lifestyle Questionnaire	X(1)			
Patient Medication Diary		X(2)		
Registration Fatigue/ Uniscale Assessment	X(3)			
Laboratory Studies				
CBC, Differential, Platelets	X	X		
CMP	X(4)	X(4)		
Creatinine	X	X		
Albumin, Glucose	X	X		
AST, ALT, Alkaline Phosphatase, Total Bilirubin	X	X		
Serum or Urine HCG	X(5)			
UPC Ratio/Urine Protein	X	A		
CEA	X	B		X
Staging				
CT (or MRI) Chest, Abd/Pelvis	C	C	C	C
Correlative Studies: For patients who consent to participate in A021703 Biobanking				
Blood, Tissue, and/or Stool	*Baseline, during treatment, and end of treatment; see Section 6.2.*			

* Labs, tests, and observations completed prior to registration may be used for Day 1 of Cycle 1 tests if obtained ≤ 7 days prior to treatment. For subsequent cycles, labs, tests, and observations may be obtained ≤ 3 days prior to day of treatment.

** If protocol therapy is discontinued for reasons other than disease progression, then physical examination, AE assessment, and restaging scans are required every 8-16 weeks (+/- 1 week) until 5 years from registration, disease progression, or start of new anticancer therapy, whichever comes first; thereafter, survival information is required every 6 months until 5 years from registration. See also Section 12.0.

1 Diet and Lifestyle Questionnaire can be completed within ≤ 4 weeks after enrollment; see Section 4.3, Section 6.4, and Section 14.1.

2 The diary must begin the day the patient starts taking vitamin D3 and must be completed per protocol and returned to the treating institution or compliance must be documented in the medical record by any member of the care team. See Appendix II for a copy of the diary.

3 To be completed ≤ 21 days prior to treatment.

4 At minimum, CMP should include the following: sodium, potassium, carbon dioxide, chloride, BUN, calcium, magnesium, phosphorus.

5 For women of childbearing potential, to be done ≤ 14 days prior to registration; see Section 3.2.

A All patients receiving bevacizumab should have a UPC ratio or urine protein performed every other cycle starting with Cycle 1; if urine protein is ≥ 2+, 24-hour urine collection or UPC ratio needs to be obtained.

B To be obtained at baseline and then every 4 cycles thereafter (beginning prior to Cycle 5) until 5 years from registration or until evidence of disease progression or relapse. Any measurements of biochemical response should occur in conjunction with the radiographic assessments for disease status.

C Baseline scans should include a CT (or MRI) of the chest, abdomen, and pelvis performed with both IV and oral contrast if possible. Restaging scans will be performed every 4 cycles while on protocol therapy. Response assessment should include assessment of all sites of disease, and the same imaging method used at baseline should be used for all subsequent evaluations. Multiphase CT scan (chest/abdomen/pelvis) is the preferred imaging modality; equivalent modalities (MRI scan of the abdomen/pelvis with chest CT) may be used per treating physician discretion. CT scans should be of diagnostic quality and CT abdomen/pelvis performed with oral and IV contrast unless there is a medical contraindication. MRI scans should be of diagnostic quality and performed with IV contrast unless there is a medical contraindication. Scans may be obtained up to 7 days prior to the beginning of a new cycle. Supporting documentation is to be submitted per Section 6.1.5.

6.0 DATA AND SPECIMEN SUBMISSION

6.1 Data Collection and Submission

6.1.1 Data Submission Schedule

A Data Submission Schedule (DSS) is available on the Alliance study webpage, within the Case Report Forms section. The DSS is also available on the CTSU website within the study-specific Case Report Forms folder.

6.1.2 Medidata Rave

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (Lab Admin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to [redacted] for registration types and documentation required.

This study has a Delegation of Tasks Log (DTL). Therefore, those requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under *Data Management > Rave Home* and click to *accept* the invitation in the *Tasks* pane located in the upper right corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management

> Rave section at [redacted] or by contacting the CTSU Help Desk at [redacted]

6.1.3 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP For Status, and DQP Reports modules.

6.1.4 ICAREdata™

Selected sites will be participating in the ICAREdata® project. - The Integrating Clinical Trials and Real-world Endpoints data (ICAREdata) initiative is a program led by the Alliance Data Innovation Lab which is a component of the Alliance for Clinical Trials in Oncology.

The ICAREdata® project aims to expand the ability to achieve clinical research goals by providing new ways to collect data required for clinical trials. Today, virtually all clinical trials data are collected using special forms and computer applications, such as a software known as Medidata Rave. Instead of using these "add on" data collection systems, the ICAREdata project will gather study data directly from the Electronic Health Record (EHR). As with all research data collections, data collected by the ICAREdata project are stored in a secured repository.

Select institutions will be invited to participate and will receive training on the specific ICAREdata® requirements. As with all clinical trials data management, the nature of data collected using the ICAREdata methods will be specific to a particular research protocol, and might include demographic information, diagnosis, laboratory values, physician assessments, and other results, such as adverse event reports. The Data Innovation Lab will manage data collection, working with the IT department at these sites to configure the EHR to deliver mCODE (minimal common oncology data elements) data and other required outcome data in the form of structured ICAREdata questions. Clinicians will provide the study required data by answering standardized questions or data fields as part of their encounter visit with the subjects. The IT departments will also work to implement the data transfer capability from the site EHR to the Alliance Data Innovation Lab via a secure/tested extraction method.

Investigators and research staff at limited select sites that utilize the EHR research adverse events data collection tool will be asked to complete a brief voluntary survey. The research staff and investigator's email addresses at these predetermined sites will be submitted at the time of Adverse Events data collection tool training. The survey will take approximately 5 minutes to complete. It will solicit feedback on the investigators and study

staff experiences including overall staff acceptance, usability, preferences for using the tool to document any adverse events. The plan survey administration timeline is at baseline and then a select period thereafter. Ultimately, the survey will be used to gather general feedback of the usability of the tool across multiple site level stakeholders.

Data will be encrypted at-rest and in-transit using a secure interface with an established authorization protocol handled by the ICAREdata infrastructure. Alliance Data Lab staff will issue a client ID and credentials to participating ICAREdata sites that will be used to authenticate those sites for access to the ICAREdata infrastructure service/extraction method to submit data. The clinical site will be responsible for securely storing these credentials (e.g., installed on a server that an IT administrator manages) such that those staff responsible for submitting data will have the proper access. Data will be stored and maintained in HIPAA compliant data repositories (such as AWS) and access controlled by an identity server with strict management to ensure confidentiality, integrity, and availability of PHI. Strict access controls will be maintained. Only authorized Alliance Data Lab personnel will have access to the data and scope of access will be further controlled based on role and level of need to know.

Participating institutions may email the Alliance Data Innovation Lab at [redacted] with any questions.

6.1.5 Supporting Documentation to be Submitted to the Alliance

This study requires supporting documentation for diagnosis, response, progression, other. Supporting documentation will include pathology and radiology reports, and these must be submitted at the following time points:

- **Baseline:** Pathology report, radiology report
- **Restaging:** Radiology report
- **Progression:** Pathology report (if applicable), radiology report

Supporting documentation is to be submitted via Rave.

6.2 Specimen Collection and Submission

Correlative Science Manual (CSM): **The Alliance A021703 Correlative Science Manual (CSM) contains instructions for specimen collection, processing, and shipping.** The manual can be found on the study-specific webpage on the Alliance and CTSU websites. Questions regarding the CSM should be directed to the contact(s) specified in the manual.

For all patients registered to Alliance A021703: Plasma 25(OH)D level testing will be conducted using the whole blood specimens. The submission of these samples for plasma 25(OH)D testing is required for all patients registered to this study, including those who are found to be ineligible and those who do not receive protocol therapy.

For patients consented to A021703 Biobanking: All participating institutions must ask patients for their consent to participate in the biobanking for future correlative studies, although patient participation is optional. Rationale for these studies are described in Section 14.3. For patients who consent to participate, tissue, blood, and/or stool will be collected at the following time points for these future studies:

	Prior to initiation of treatment	Prior to treatment on C3D1	Prior to treatment on C5D1	Prior to treatment on C9D1	At treatment discontinuation
Mandatory for all patients registered to A021703:					
Plasma and Buffy Coats from Whole Blood	1 x 5 mL		1 x 5 mL	1 x 5 mL	1 x 5 mL
For patients consented to A021703 Biobanking, submit the following:					
Archival Tumor Tissue	X				
Plasma from Whole Blood	3 x 10 mL		3 x 10 mL	3 x 10 mL	3 x 10 mL
Serum from Whole Blood	1 x 10 mL		1 x 10 mL	1 x 10 mL	1 x 10 mL
Stool	X	X	X		X

6.3 Imaging Report Submission

Local interpretation imaging reports should be entered into Rave. Reports must be submitted from baseline to disease progression. See Section 5.0 for additional details. For patients who go off study treatment for reasons other than disease progression (i.e. toxicity) please continue to collect images until disease progression.

De-identify the patient data report using institutional procedures to remove patient name and medical record number while preserving the Alliance patient ID number and protocol number.

6.4 Diet and Lifestyle Questionnaire Completion and Submission

The patient-completed questionnaire booklet for this study will be sent to the registering institution within two (2) weeks of patient registration/randomization (see Section 4.3 for further information). A sample of the questionnaire booklet is available as a separate document on the Alliance and CTSU websites for reference and IRB submission only. **It is not to be used for patient completion**. The booklet must be given to patients to complete and patients should be instructed to return the booklet to site staff in person; it is recommended that the measure be completed during a physician visit and/or chemotherapy session. Patients must complete the questionnaire in booklet format.

Verbal administration of the measure for visually impaired patients is permitted if the measure and verbal administration of the measure is conducted in a language understandable to the patients.

The booklet is to be administered within 4 weeks after enrollment.

The Diet and Lifestyle Questionnaire is available in English. Completion of the Diet and Lifestyle Questionnaire booklet is mandatory for all patients registered to this trial who are able to speak, read, and/or understand this language. Ad-hoc translation of patient-completed measures is not permitted.

Submission of Completed Booklets: The completed booklets are to be returned to the Diet and Lifestyle Coordination Office by site staff via the pre-paid envelope provided to the following address:

[redacted]

[redacted]

7.0 TREATMENT PLAN/INTERVENTION

Protocol treatment is to begin ≤ 14 days of registration.

For questions regarding treatment, please see the study contacts page.

It is acceptable for individual chemotherapy doses to be delivered ≤ a 24-hour (business day) window before and after the protocol-defined date for Day 1 of a new cycle. For example, if the treatment due date is a Friday, the window for treatment includes the preceding Thursday through the following Monday. In addition, patients are permitted to have a new cycle of chemotherapy delayed up to 7 days for major life events (e.g., serious illness in a family member, major holiday, vacation that cannot be rescheduled) without this being considered a protocol violation. Documentation to justify this delay should be provided.

This is a randomized, double-blind trial. Blinded, patient-specific clinical supplies of high-dose vitamin D3/standard-dose vitamin D3 will be requested by the clinical site via the A021703 Vitamin D3 Order Form at the time of randomization and should arrive at the clinical site ≤ approximately 7-10 days of submitting the request (see Section 10.2).

Patients will be randomized in a 1:1 fashion to receive either chemotherapy + bevacizumab + high-dose vitamin D3 (Arm 1, experimental arm) or chemotherapy + bevacizumab + standard-dose vitamin D3 (Arm 2, control arm). Chemotherapy will consist or either mFOLFOX6 or FOLFIRI, and the regimen administered is per treating physician discretion. The chemotherapy regimen administered must remain consistent for the duration of the trial (i.e. patients cannot switch from one chemotherapy regimen to the other once protocol treatment has been initiated). **The chosen chemotherapy regimen must be declared prior to patient randomization as chemotherapy regimen is a stratification factor used in this trial; see Section 4.5.** Bevacizumab or an FDA-approved biosimilar to bevacizumab is allowed; the use of bevacizumab or a biosimilar should remain consistent for the duration of the trial for each patient. Treatment will continue until disease progression or unacceptable adverse event for a maximum period of 5 years from registration.

7.1 Chemotherapy + Bevacizumab + Vitamin D3

Protocol therapy for all patients will consist of chemotherapy (mFOLFOX6 or FOLFIRI) + bevacizumab administered intravenously starting on Day 1 of each 14-day cycle and vitamin D3 taken orally on Days 1-14 of each 14-day cycle. Administration schedules for bevacizumab with mFOLFOX6 and FOLFIRI can be found in the tables below and are provided as general guidelines only; standard institutional procedures should be followed.

Patients will be randomized in a double-blind fashion to either high-dose vitamin D3 (4,000 IU/day) or standard-dose vitamin D3 (400 IU/day) with an administration schedule as follows:

- **Arm 1 – High-dose Vitamin D3**
  - Cycle 1 (Loading Dose Period)
    - Two (2) 4,000 IU capsules by mouth for a total dose of 8,000 IU/day
      - Dispensed as one 14-count bottle of 4,000 IU capsules and one 100-count bottle of 4,000 IU capsules with instructions to take one capsule from each bottle at the same time once daily for 14 days; see Section 10.2.
  - Cycle 2 and All Subsequent Cycles

        - One (1) 4,000 IU capsule by mouth for a total dose of 4,000 IU/day
            - Dispensed as 100-count bottle of 4,000 IU capsules with instructions to take one capsule once daily; see Section 10.2. Note: the initial 100-count bottle of 4,000 IU capsules dispensed at Cycle 1 will continue to be used for subsequent cycles until a new 100-count bottle is needed.

- **Arm 2 – Standard-dose Vitamin D3**
    - Cycle 1 (Loading Dose Period)
        - One (1) 400 IU capsule and one (1) placebo capsule by mouth for a total dose of 400 IU/day
            - Dispensed as one 14-count bottle of placebo capsules and one 100-count bottle of 400 IU capsules with instructions to take one capsule from each bottle at the same time once daily for 14 days; see Section 10.2.
    - Cycle 2 and All Subsequent Cycles
        - One (1) 400 IU capsule by mouth for a total dose of 400 IU/day
            - Dispensed as 100-count bottles of 400 IU capsules with instructions to take one capsule once daily; see Section 10.2. Note: the initial 100-count bottle of 400 IU capsules dispensed at Cycle 1 will continue to be used for subsequent cycles until a new 100-count bottle is needed.

Patients will be asked to complete a Medication Diary during treatment with vitamin D3; see Appendix II.

Administration Schedule for mFOLFOX6 + Bevacizumab + Vitamin D3:

All patients must receive the specific doses listed below in the table for Cycle 1 (i.e. dose level 0); thereafter, dose modifications are per treating physician discretion and local institutional standard; see Section 8.2. Agents should be administered per local institutional standards, however, oxaliplatin and continuous-infusion 5-fluorouracil should continue to be administered for all cycles until unacceptable toxicity. If toxicity arises that requires dose modification and is thought to be related to 5-fluorouracil, treating physicians may wish to first dose-modify or discontinue the bolus administration, rather than the continuous-infusion 5-fluorouracil. Vitamin D3 can be taken either before or after chemotherapy + bevacizumab.

Agent	Dose	Route	Duration	Day	ReRx
Bevacizumab*	5 mg/kg	IV	Institutional Standard	Day 1	Every 14 Days
Oxaliplatin	85 mg/m^2	IV	Institutional Standard	Day 1	Every 14 Days
Leucovorin	400 mg/m^2	IV	Institutional Standard	Day 1	Every 14 Days
5-Fluorouracil	400 mg/m^2	IV Bolus	Institutional Standard	Day 1	Every 14 Days
5-Fluorouracil	2400 mg/m^2	CIV	Institutional Standard	Days 1-3	Every 14 Days

* Bevacizumab may be omitted on Cycle 1 Day 1 per treating physician's discretion.

Additionally, patients will take two (2) vitamin D3 capsules by mouth for Days 1-14 of Cycle 1, and then patients will take one (1) vitamin D3 capsule by mouth for Days 1-14 of Cycle 2 and all subsequent cycles.

Administration Schedule for FOLFIRI + Bevacizumab + Vitamin D3:

All patients must receive the specific doses listed below in the table for Cycle 1 (i.e. dose level 0); thereafter, dose modifications are per treating physician discretion and local institutional standard; see Section 8.2. Agents should be administered per local institutional standards, however, irinotecan and continuous-infusion 5-fluorouracil should continue to be administered for all cycles until unacceptable toxicity. If toxicity arises that requires dose modification and is thought to be related to 5-fluorouracil, treating physicians may wish to first dose-modify or discontinue the bolus administration, rather than the continuous-infusion 5-fluorouracil. Vitamin D3 can be taken either before or after chemotherapy + bevacizumab.

Agent	Dose	Route	Duration	Day	ReRx
Bevacizumab*	5 mg/kg	IV	Institutional Standard	Day 1	Every 14 Days
Irinotecan	180 mg/m^2	IV	Institutional Standard	Day 1	Every 14 Days
Leucovorin	400 mg/m^2	IV	Institutional Standard	Day 1	Every 14 Days
5-Fluorouracil	400 mg/m^2	IV Bolus	Institutional Standard	Day 1	Every 14 Days
5-Fluorouracil	2400 mg/m^2	CIV	Institutional Standard	Days 1-3	Every 14 Days

* Bevacizumab may be omitted on Cycle 1 Day 1 per treating physician's discretion.

Additionally, patients will take two (2) vitamin D3 capsules by mouth for Days 1-14 of Cycle 1, and then patients will take one (1) vitamin D3 capsule by mouth for Days 1-14 of Cycle 2 and all subsequent cycles.

In order to preserve the double-blind, plasma 25(OH)D levels should not be routinely checked while the patient is on study. Plasma 25(OH)D levels will be assayed only as part of the research blood samples collected during the study. If there are concerns related to a participant's vitamin D3 status, the Study Chair should be contacted for further discussion.

7.2 Imaging

Imaging scans should be performed at baseline and then after every 4 cycles of treatment, prior to Day 1 of the upcoming cycle (i.e., prior to Cycles 5, 9, 13, etc.). CT scans are preferred over MRI and should be used if possible (unless the patient has a medical contraindication). CT scans should be acquired at approximately 70 seconds after IV contrast administration (to ensure maximum enhancement of the liver parenchyma in most patients). The acquired images should be reconstructed using axial slice thickness < 5 mm, preferably 2.5 mm, with sagittal and coronal reformat. Thinner axial images (2.5 mm) help avoid volume averaging, which may blur metastatic margins, and enhance the measurement accuracy. The same imaging modality used at baseline must be used throughout the study to enhance consistency.

Treatment decisions will be based on local investigator/radiologist assessment of response.

8.0 DOSE AND TREATMENT MODIFICATIONS, UNBLINDING

8.1 Ancillary Therapy, Concomitant Medications, and Supportive Care

8.1.1 Patients should not receive any other treatment which would be considered treatment for the primary neoplasm or impact the primary endpoint.

This includes any surgical intervention, radiotherapy, cryotherapy, ablation, etc., performed on the primary neoplasm.

8.1.2 Patients should receive full supportive care while on this study.

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

8.1.3 Treatment with hormones or other chemotherapeutic agents may not be administered except for:

Steroids given for adrenal failure; hormones administered for non-disease-related conditions (e.g. insulin for diabetes); and intermittent use of dexamethasone as an antiemetic.

8.1.4 Antiemetics may be used at the discretion of the treating physician.

Prior to the administration of mFOLFOX6 or FOLFIRI, premedication with antiemetics, such as serotonin (5HT3) antagonists (i.e., ondansetron, granisetron) with or without dexamethasone may be used at the treating physician's discretion or according to institutional standards.

8.1.5 Diarrhea management is per the discretion of the treating physician.

Diarrhea could be managed conservatively with medications such as loperamide. Treating physicians may wish to start loperamide at the earliest sign of 1) a poorly formed or loose stool, 2) the occurrence of 1-2 more bowel movements than usual in one day, or 3) an increase in stool volume or liquidity. Treating physicians may also wish to provide patients with instructions for loperamide use at the initial treatment visit and instructions to purchase the medication over-the-counter so that they have sufficient supply on hand in case antidiarrheal support is required. Patients may be instructed to increase fluid intake to help maintain fluid and electrolyte balance during episodes of diarrhea. Local institutional standards should be used as dose modification guidelines for diarrhea.

Patients with severe diarrhea may need to be assessed for intravenous hydration and correction of electrolyte imbalances.

8.1.6 Palliative radiation therapy may not be administered.

Patients who require radiation therapy during protocol treatment will be removed from protocol therapy.

8.1.7 Alliance Policy Concerning the Use of Growth Factors

The following guidelines are applicable unless otherwise specified in the protocol.

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 33: 3199-3212, 2015 and American Society of Clinical

Oncology – American Society of Hematology Clinical Practice Guideline Update on the Use of Epoetin and Darbepoetin in Adult Patients with Cancer. J Clin Oncol 28:4996-5010, 2010.

Epoetin (EPO): Use of epoetin in this protocol is prohibited.

Filgrastim (G-CSF), tbo-filgrastim, and sargramostim (GM-CSF) are allowed.

White blood cell growth factors (including filgrastim (G-CSF), pegfilgrastim, and other FDA-approved white blood cell growth factor biologics) are allowed per treating physician discretion.

1. White blood cell growth factor treatment for patients on protocols that do not specify their use is discouraged.
2. White blood cell growth factor may not be used:
    a. To avoid dose reductions, delays or to allow for dose escalations specified in the protocol.
    b. For the treatment of febrile neutropenia the use of CSFs should not be routinely instituted as an adjunct to appropriate antibiotic therapy. However, the use of CSFs may be indicated in patients who have prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction (sepsis syndrome) or fungal infection, as per the ASCO guidelines. Investigators should therefore use their own discretion in using the CSFs in this setting. The use of CSF (filgrastim/pegfilgrastim) must be documented and reported (e.g. on CRFs per protocol requirements).
    c. If white blood cell growth factors are used, they must be obtained from commercial sources. Selection of white blood cell growth factor products should be per institutional guidelines.

8.1.8 Hypersensitivity/Infusion Reactions

Treat hypersensitivity and infusion reactions to protocol therapy as per institutional standards.

8.1.9 Supplements and Herbal Medications

Patients should not receive any supplements containing vitamin D, calcium supplements, or herbal medications/treatments while on this study.

8.1.10 Vitamin D Depleting Drugs

Patients should not receive chronic corticosteroids, lithium, phenobarbital, phenytoin, quinidine, isoniazid, and/or rifampin, all of which can cause vitamin D depletion, while on this study. Short-term corticosteroids as antiemetic therapy for chemotherapy are permitted; see Section 8.1.4.

8.1.11 Cold-induced Sensory Neuropathy

Participants should be counseled to avoid cold drinks, chewing of ice chips, and exposure to cold water or air because the neurotoxicity often seen with oxaliplatin appears to be exacerbated by exposure to cold. The period of time during which the participant is at risk for these cold-induced sensory neuropathies is not well documented. Participants should exercise caution regarding cold exposure during the treatment period. Peripheral sensory neuropathies can occur at any time after receiving oxaliplatin therapy.

8.1.12 Surgery/Metastasectomy

Participants who undergo interventional therapy for metastases (e.g., surgical resection, radiofrequency ablation, transarterial embolization) will do so according to standard institutional practice. For participants for whom an elective surgery or procedure is contemplated, the Study Chair should be notified via email prior to any planned intervention. Participants may be allowed to continue on protocol therapy with chemotherapy + bevacizumab + vitamin D3 post-intervention if protocol therapy has been held for ≤ 28 days, if they continue to have measurable disease per RECIST v1.1 outside of the treated metastatic lesion(s) post-intervention, and if the continuation of protocol therapy has been discussed with the Study Chair.

8.2 Dose Modifications

If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

If more than one of these apply, use the most stringent (i.e. the greatest dose reduction.)

AERS reporting may be required for some adverse events; see Section 9.0.

If a new cycle of chemotherapy is delayed, then bevacizumab should also be delayed.

If vitamin D3 administration is delayed, chemotherapy + bevacizumab administration may continue.

If chemotherapy + bevacizumab are delayed, then vitamin D3 should continue (provided that vitamin D3 is not the affecting agent).

If any agent is delayed due to toxicity for ≥ 4 weeks, counting from the originally scheduled day of treatment that was held, discontinue agent.

If vitamin D3 is permanently discontinued for any reason prior to disease progression, the patient will be discontinued from the study. Any further treatment will be "off study" per treating physician discretion; see Section 12.0.

If bevacizumab administration is permanently discontinued for any reason prior to disease progression, chemotherapy should be continued on Day 1 of every 14-day cycle and vitamin D3 should continue orally once daily.

If chemotherapy administration is permanently discontinued for any reason prior to disease progression, patients will not be allowed to switch to the other chemotherapy regimen. Bevacizumab administration may continue on Day 1 of every 14-day cycle and vitamin D3 administration may continue orally once daily.

If oxaliplatin or irinotecan administration is permanently discontinued for any reason prior to disease progression (e.g. grade 3 progressive sensory or motor neuropathy), 5-FU (particularly the continuous-infusion 5-fluorouracil) and leucovorin, bevacizumab, and vitamin D3 administration should continue. Oxaliplatin or irinotecan may be resumed at treating physician's discretion; however switching from one agent to the other is not permitted.

8.2.1 Dose Modifications for Vitamin D3

There will be no dose level reductions for vitamin D3 on this study, only dose delays.

8.2.1.1 Hypercalcemia

For **grade 2 hypercalcemia**, delay vitamin D3 until toxicity improves to grade ≤ 1, then resume at the same dose. If the toxicity recurs, then permanently discontinue vitamin D3.

For **grade ≥ 3 hypercalcemia**, permanently discontinue vitamin D3.

8.2.1.2 Renal and Urinary Toxicities

For **any grade renal calculi (i.e. kidney stones)**, permanently discontinue vitamin D3.

8.2.1.3 Other Non-Hematologic Toxicities

For **all other persistent grade 2 toxicities or grade ≥ 3 toxicities that are clinically significant and considered at least possibly related to vitamin D3**, delay vitamin D3 until toxicity improves to grade ≤ 1, then resume at the same dose.

For **second recurrences of persistent grade ≥ 2 toxicities that are clinically significant and considered at least possibly related to vitamin D3**, permanently discontinue vitamin D3.

8.2.2 Dose Modifications for mFOLFOX6 and FOLFIRI

Treating physicians should follow local institutional standard practice guidelines for further dose modifications related to the mFOLFOX6 and/or FOLFIRI chemotherapy regimens. Oxaliplatin, irinotecan, and continuous-infusion 5-fluorouracil should continue to be administered for all cycles until unacceptable toxicity. However, if toxicity arises that requires dose modification and is thought to be related to 5-fluorouracil, treating physicians may wish to first dose-modify or discontinue the bolus administration, rather than the continuous-infusion 5-fluorouracil.

8.2.3 Dose Modifications for Bevacizumab

Treating physicians should follow local institutional standard practice guidelines for further dose modifications related to bevacizumab.

8.2.4 Dose Modifications for Obese Patients

There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. Therefore, all dosing is to be determined solely by actual weight without any modification unless explicitly described in the protocol. This will eliminate the risk of calculation error and the possible introduction of variability in dose administration. Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation. Physicians who are uncomfortable with calculating doses based on actual body weight should recognize that doing otherwise would be a protocol violation. Physicians may consult the published guidelines of the American Society of Clinical Oncology Appropriate Chemotherapy Dosing for Obese Adult Patients with Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 30(13): 1553-1561, 2012.

8.3 Unblinding Procedures

Unblinding can be done only in cases of an emergency. Follow the directions below to unblind patient treatment. Please note that if a treatment assignment is unblinded, the patient must discontinue protocol therapy.

8.3.1 Emergency Unblinding Procedures

Examples of emergencies include 1) a life-threatening unexpected adverse event that is at least possibly related to the investigational agent and for which unblinding would influence treatment decisions; or 2) medication error, such as accidental overdose. Expected adverse events are listed in the “Toxicities” section below.

Contact the Alliance Executive Officer on call by calling [redacted] pressing 1 to speak with an operator, and then asking for pager [redacted] to return the call.

The institution must provide the following information to the Alliance Executive Officer:

- Alliance study ID (i.e. "A021703")
- Alliance patient ID number (e.g. "999999")
- Patient initials (e.g. "L,FM")
- Institution name
- Name and telephone number of treating physician
- Name and contact information of person requesting the unblinding procedure
- Name and contact information of person to inform of treatment assignment
- Reason for emergency unblinding

Please remember that emergency unblinding request may be authorized only by an Alliance Executive Officer, and emergency unblinding applies only if unblinding would influence management of the medical situation. After the Executive Officer deems unblinding is warranted, the treatment assignment will be provided to the contact person at the treating site.

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. The CTCAE is available at [redacted] Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms. Please refer the NCI Guidelines: Adverse Event Reporting Requirements for further details on AE reporting procedures.

9.1 Routine Adverse Event Reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times according to the Study Calendar in Section 5.0. For this trial, the Form, "Adverse Events" is used for routine AE reporting in Rave.

9.1.1 Solicited Adverse Events

The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment by CTCAE.

CTCAE v5.0 Term	CTCAE v5.0 System Organ Class (SOC)
Neutrophil count decreased	Investigations
Platelet count decreased	Investigations
Diarrhea	Gastrointestinal disorders

Nausea	Gastrointestinal disorders
Vomiting	Gastrointestinal disorders
Peripheral sensory neuropathy	Nervous system disorders
Hypertension	Vascular disorders

9.2 CTCAE Routine Reporting Requirements

In addition to the solicited adverse events listed in Section 9.1, the following table outlines the combinations of time points, grades and attributions of AEs that require routine reporting to the Alliance Statistics and Data Center. Questions about routine reporting should be directed to the Data Manager.

Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			a	a	a
Unlikely			a	a	a
Possible		a	a, b	a, b	a, b
Probable		a	a, b	a, b	a, b
Definite		a	a, b	a, b	a, b

a) Adverse Events: Other CRF - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date, or as part of the Clinical Follow-Up Phase.

b) Adverse Events: Late CRF - Applies to AEs occurring greater than 30 days after the patient's last treatment date.

9.3 Expedited Adverse Event Reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 will be utilized for AE reporting. The CTCAE is identified and located on the CTEP website at: [redacted] All appropriate treatment areas should have access to a copy of the CTCAE. All reactions determined to be "reportable" in an expedited manner must be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS).

For further information on the NCI requirements for SAE reporting, please refer to the 'NCI Guidelines for Investigators: Adverse Event Reporting Requirements' document published by the NCI.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

9.3.1 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE ≤ 30 Days of the Last Administration of the Investigational Agent/Intervention [1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

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

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour;
5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS ≤ 24 hours of learning of the AE, followed by a complete expedited report ≤ 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted ≤ 10 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report ≤ 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

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

9.3.2 Expedited AE Reporting Timelines Defined

"24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS ≤ 24 hours of learning of the event followed by a complete CTEP-AERS report ≤ 5 calendar days of the initial 24-hour report.

"10 calendar days" - A complete CTEP-AERS report on the AE must be submitted ≤ 10 calendar days of the investigator learning of the event.

Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions (see below).

Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under an IND.

Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

9.3.3 Additional Instructions or Exclusions to CTEP-AERS Expedited Reporting Requirements

All adverse events reported via CTEP-AERS (i.e. serious adverse events) should also be forwarded to your local IRB.

Grade ≤ 4 anemia, neutropenia, or thrombocytopenia resulting in hospitalization does not require CTEP-AERS, but should be submitted as part of study results. All other grade 3, 4, or 5 adverse events that precipitate hospitalization or prolong an existing hospitalization must be reported via CTEP-AERS.

New primary malignancies should be reported using Medidata Rave®.

Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g. radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Any death occurring within 30 days of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring greater than 30 days after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours only if it is possibly, probably, or definitely related to the investigational agent/intervention.

Pregnancy Loss:

- Pregnancy loss is defined in CTCAE as "Death in utero."
- Any Pregnancy loss should be reported expeditiously, as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC.
- A Pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.

All new malignancies must be reported via CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome/acute myelogenous leukemia, and in situ tumors.

Secondary Malignancy:

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

Second Malignancy:

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

Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.

Treatment expected adverse events include those listed in Section 10.0 and in the package insert.

CTEP-AERS reports should be submitted electronically.

10.0 DRUG INFORMATION

10.1 General Considerations

The total administered dose of chemotherapy may be rounded up or down within a range of 10% of the actual calculated dose.

It is not necessary to change the doses of standard chemotherapy drugs due to changes in weight unless the calculated dose changes by ≥10% or per institutional standard procedures.

All study agents are to be administered at the registering institution.

If the Group credited for enrollment is a non-Alliance Group, then other requirements from the credited Group may apply.

10.2 Vitamin D3 (NSC# 375571)

Investigators ordering and/or dispensing supplied agents at any time for study treatment must be currently registered with PMB, DCTD, NCI and have an active registration status. A registered investigator must co-sign for other personnel prescribing the supplied agents.

Procurement

Vitamin D3 is patient specific, and may NOT be dispensed to another patient.

Patient-specific supply may be confirmed by checking the patient ID number included on the drug invoice and drug bottles.

Vitamin D3 will be provided by Pharmavite, LLC and distributed by McKesson Clinical Research Services. Sites will procure initial and subsequent supplies of vitamin D3 by submitting the Vitamin D3 Order Form on the A021703 study page on the Alliance and CTSU websites. Submission instructions are outlined on the form.

Study drug cannot be shipped post-distribution.

McKesson Clinical Research Services will ship patient-specific, blinded drug supplies. The drug bottles will be labeled with the patient ID number. Additional details regarding drug supply can be found on the Vitamin D3 Order Form.

Formulation

Vitamin D3 and placebo will be provided as liquid gel capsules containing the following ingredients:

Ingredients	Function	Vitamin D3 400 IU (%)	Vitamin D3 4000 IU (%)	Placebo (%)
Soybean Oil, USP	Carrier	59.3375	57.6951	59.52
Gelatin, NF	Shell	27.2300	27.2300	27.23
Glycerin, USP 99.5%	Shell Plasticizer	10.0100	10.0100	10.01
Purified Water, USP	Pharmaceutical Solvent	3.2400	3.2400	3.20
Corn Oil	Carrier	0.1770	1.7702	-
Cholecalciferol	Dietary Active	0.0046	0.0456	-
Cod Liver Oil	Dietary Active	0.0009	0.0091	-

Storage and Stability

Vitamin D3 capsules must be stored in its unopened original packaging at room temperature (15-30°C) and protected from excessive heat.

Investigator's Brochure Availability

The Investigator's Brochure (IB) for vitamin D3 may be obtained by contacting the Alliance Central Protocol Operations Program Office at [redacted] Note: a Chemistry, Manufacturing, and Controls (CMC) document is being used in lieu of an IB for vitamin D3.

Preparation

Vitamin D3 will be provided in tamper-proof bottles as blinded, matched drug supplies. Local pharmacies may adhere labels directly to the bottles.

Administration

Vitamin D3 will be taken orally by mouth as described in Section 7.1.

When agents are required to be dispensed in the original manufacturer's drug product container and a site's policy dictates provision of exact quantities for dispensing purposes, removal of the extra agent from the manufacturer's container is the only way this can be satisfied and destroying the extra is allowed.

Drug Accountability

NCI Investigational Agent Accountability Record for Oral agents (manual or electronic form) should be used to document receipt, dispensing, patient's returns, and disposal of supplied vitamin D3.

Ninety days after the patient is off treatment, any expired or remaining supplies should be destroyed according to institutional procedure.

Drug Interactions

Aluminum hydroxide: Vitamin D may increase the serum concentration of aluminum hydroxide, leading to increased serum aluminum concentration.

Mineral oil: mineral oil may interfere with the absorption of vitamin D analogs, leading to decreased serum concentration of vitamin D.

Calcium salts may increase the adverse/toxic effect of vitamin D.

Thiazide and thiazide-like diuretics may enhance the hypercalcemic effect of vitamin D.

Pharmacokinetics

Vitamin D is absorbed in the small intestine and excreted to feces. It is inactive until hydroxylated hepatically to 25-hydroxyvitamin D (calcifediol, 25(OH)D), then to the active metabolite 1, 25-dihydroxyvitamin D (calcitriol) in the kidney.

The half-life of hydroxylated calcifediol is 2 to 3 weeks and calcitriol is about 4 hours.

Adverse Events

Vitamin D toxicity may occur with excessive doses; symptoms may include nausea, vomiting, loss of appetite, constipation, dehydration, fatigue, irritability, confusion, weakness and/or weight loss. Effects of vitamin D can last ≥ 2 months after therapy is discontinued.

10.3 Fluorouracil (Adrucil®, 5FU, NSC# 19893)

Procurement

Commercial supplies. Institutional pharmacy shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

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

Storage and Stability

Store intact vials at room temperature and protect from light. A slight discoloration may occur with storage but usually does not denote decomposition. If exposed to cold, a precipitate may form; gentle heating to 60ºC will dissolve the precipitate without impairing the potency. Solutions in 50 – 1000 mL 0.9% NaCl or D5W or undiluted solutions in syringes are stable for 72 hours at room temperature. Fluorouracil should not be co-administered with either diazepam,

doxorubicin, daunorubicin, idarubicin, cisplatin, or cytarabine. However, fluorouracil and leucovorin are compatible for 14 days at room temperature. Fluorouracil is compatible with vincristine, methotrexate, and cyclophosphamide

Preparation

Dilute in 50 – 1000 mL of 0.9% NaCl or D5W.

Administration

Fluorouracil may be given IV bolus or IV infusion. Refer to the treatment section for specific administration instructions. Avoid extravasation, may be an irritant.

Drug Interactions

Fluorouracil may increase effects of warfarin. Avoid ethanol (due to GI irritation). Avoid black cohosh.

Pharmacokinetics

Distribution: V_d ~ 22% of total body water; penetrates extracellular fluid, CSF, and third space fluids (e.g. pleural effusions and ascitic fluid)

Metabolism: Hepatic (90%); via a dehydrogenase enzyme; Fluorouracil must be metabolized to be active.

Half-life Elimination: Biphasic: Initial: 6-20 minutes; two metabolites, FdUMP and FUTP, have prolonged half-lives depending on the type of tissue.

Excretion: Lung (large amounts as CO_2); urine (5% as unchanged drug) in 6 hours.

Adverse Events

Consult the package insert for the most current and complete information.

<u>Common Known Potential Toxicities, > 10%:</u>

Dermatologic: Dermatitis, pruritic maculopapular rash, alopecia.

Gastrointestinal (route and schedule dependent): Heartburn, nausea, vomiting, anorexia, stomatitis, esophagitis, anorexia, diarrhea. GI toxicity (anorexia, nausea, and vomiting) is generally more severe with continuous-infusion schedules.

Emetic Potential: <1000 mg: Moderately low (10% to 30%) ≥ 1000 mg: Moderate (30% to 60%)

Hematologic: Leukopenia; Myelosuppressive (tends to be more pronounced in patients receiving bolus dosing of FU). Decreased white blood cell count with increased risk of infection; decreased platelet count with increased risk of bleeding.

Local: Irritant chemotherapy.

<u>Less Common Known Potential Toxicities, 1% - 10%:</u>

Dermatologic: Dry skin

Gastrointestinal: GI ulceration

<u>Rare Known Potential Toxicities, <1% (Limited to Important or Life-threatening):</u>

Cardiac enzyme abnormalities, chest pain, coagulopathy, dyspnea, ECG changes similar to ischemic changes, hepatotoxicity; hyperpigmentation of nail beds, face, hands, and veins used in infusion; hypotension, palmar-plantar syndrome (hand-foot syndrome), photosensitization.

Cerebellar ataxia, headache, somnolence, ataxia are seen primarily in intracarotid arterial infusions for head and neck tumors.

Nursing Guidelines

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

Administer antiemetics as indicated.

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

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

Monitor for neurologic symptoms (headache, ataxia).

Inform patient of potential alopecia.

Those patients on continuous infusion may need instruction regarding central intravenous catheters and portable intravenous or IA infusion devices.

5FU–induced conjunctivitis is a common problem. Advise patient to report any eye soreness or redness to the healthcare team.

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

10.4 Leucovorin Calcium (NSC# 3590)

Procurement

Commercial supplies. Institutional pharmacy shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

NOTE: Levoleucovorin is not the same as leucovorin calcium.

Leucovorin calcium is available as:

- Solution for Injection 100 mg/10 mL (10 mL, 30 mL)
- Lyophilized Powder for Injection 50 mg, 100 mg, 200 mg, 350 mg, 500 mg

Storage and Stability

Powder for Injection: Store at room temperature of 25°C (77°F). Protect from light. Solutions reconstituted with bacteriostatic water for injection U.S.P., must be used within 7 days. Solutions reconstituted with SWFI must be used immediately. Parenteral admixture is stable for 24 hours stored at room temperature (25°C) and for 4 days when stored under refrigeration (4°C).

Solution for Injection: Prior to dilution, store vials under refrigeration at 2°C to 8°C (36°F to 46°F). Protect from light.

Preparation

Powder for Injection: Reconstitute with SWFI or BWFI; dilute with D5W or NS for infusion. When doses > 10 mg/m^2 are required, reconstitute using sterile water for injection, not a solution containing benzyl alcohol.

Solution for Injection: Dilute in D5W or NS for infusion.

Administration

Should be administered IV infusion (2 hours) and is not intended for intrathecal use.

Combination Therapy with Fluorouracil: Fluorouracil is usually given after, or at the midpoint, of the leucovorin infusion. Leucovorin is usually administered by IV infusion. Other administration schedules have been used; refer to individual protocols.

Drug Interactions

Capecitabine: Leucovorin Calcium-Levoleucovorin may enhance the adverse/toxic effect of Capecitabine. Risk C: Monitor therapy.

Fluorouracil (Systemic): Leucovorin Calcium-Levoleucovorin may enhance the adverse/toxic effect of Fluorouracil (Systemic). This effect is associated with the ability of leucovorin or levoleucovorin to enhance the anticancer effects of fluorouracil. Risk C: Monitor therapy.

Fluorouracil (Topical): Leucovorin Calcium-Levoleucovorin may enhance the adverse/toxic effect of Fluorouracil (Topical). Risk C: Monitor therapy.

Fosphenytoin: Leucovorin Calcium-Levoleucovorin may decrease the serum concentration of Fosphenytoin. Risk C: Monitor therapy.

Glucarpidase: May decrease serum concentrations of the active metabolite(s) of Leucovorin Calcium-Levoleucovorin. Specifically, 6S-5-methyltetrahydrofolateconcentrations may be reduced. Glucarpidase may decrease the serum concentration of Leucovorin Calcium-Levoleucovorin. Management: Avoid leucovorin administration within 2 hours of glucarpidase dosing. Continue to administer the pre-glucarpidase leucovorin dose for at least the first 48 hours after glucarpidase administration, and dose based on methotrexate concentration thereafter. Risk D: Consider therapy modification.

PHENobarbital: Leucovorin Calcium-Levoleucovorin may decrease the serum concentration of PHENobarbital. Risk C: Monitor therapy.

Phenytoin: Leucovorin Calcium-Levoleucovorin may decrease the serum concentration of Phenytoin. Risk C: Monitor therapy.

Primidone: Leucovorin Calcium-Levoleucovorin may decrease the serum concentration of Primidone. Additionally, leucovorin/levoleucovorin may decrease concentrations of active metabolites of primidone (e.g. phenobarbital). Risk C: Monitor therapy.

Raltitrexed: Leucovorin Calcium-Levoleucovorin may diminish the therapeutic effect of Raltitrexed. Risk X: Avoid combination.

Tegafur: Leucovorin Calcium-Levoleucovorin may enhance the adverse/toxic effect of Tegafur. This effect is associated with the ability of leucovorin or levoleucovorin to enhance the anticancer effects of fluorouracil. Risk C: Monitor therapy.

Trimethoprim: Leucovorin Calcium-Levoleucovorin may diminish the therapeutic effect of Trimethoprim. Management: Avoid concurrent use of leucovorin or levoleucovorin with trimethoprim (plus sulfamethoxazole) for Pneumocystis jiroveci pneumonia. If trimethoprim is used for another indication, monitor closely for reduced efficacy. Risk X: Avoid combination.

Pharmacokinetics

Absorption: Oral, IM: Well absorbed

Metabolism: Intestinal mucosa and hepatically to 5-methyl-tetrahydrofolate (5MTHF; active)

Bioavailability: Saturable at oral doses >25 mg; 25 mg (97%), 50 mg (75%), 100 mg (37%)

Half-life Elimination: ~4-8 hours

Time to Peak: Oral: ~2 hours; IV: Total folates: 10 minutes; 5MTHF: ~1 hour

Excretion: Urine (primarily); feces

Adverse Events

Consult the package insert for the most current and complete information.

Dermatologic: Rash, pruritus, erythema, urticaria

Hematologic: Thrombocytosis

Respiratory: Wheezing

Miscellaneous: Allergic reactions, anaphylactoid reactions

Nursing Guidelines

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

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

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

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

10.5 Oxaliplatin (Eloxatin®, OXAL, NSC# 266046)

Procurement

Commercial supplies. Institutional pharmacy shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Commercially Available for Injection as Solution [preservative free]: 5 mg/mL (10 mL, 20 mL, and 40 mL).

Storage and Stability

Refer to package insert for complete preparation and dispensing instructions. Store intact vials in original outer carton at room temperature and do not freeze. According to the manufacturer, solutions diluted for infusion are stable up to 6 hours at room temperature or up to 24 hours under refrigeration. Oxaliplatin solution diluted with D5W to a final concentration of 0.7 mg/mL (polyolefin container) has been shown to retain >90% of its original concentration for up to 30 days when stored at room temperature or refrigerated; artificial light did not affect the concentration (Andre, 2007). As this study did not examine sterility, refrigeration would be preferred to limit microbial growth. Infusion solutions do not require protection from light.

Preparation

Do not prepare using a chloride-containing solution (e.g. NaCl). Dilution with D5W (250 or 500 mL) is required prior to administration.

Administration

Refer to the treatment section for specific administration instructions. Administer as IV infusion over 2 hours. Flush infusion line with D5W prior to administration of any concomitant

medication. Patients should receive an antiemetic premedication regimen. Cold temperature may exacerbate acute neuropathy. Avoid mucositis prophylaxis with ice chips during oxaliplatin infusion.

Drug Interactions

Increased Effect/Toxicity: Nephrotoxic agents may increase Oxaliplatin toxicity.

When administered as sequential infusions, observational studies indicate a potential for increased toxicity when platinum derivatives (carboplatin, cisplatin, oxaliplatin) are administered before taxane derivatives (docetaxel, paclitaxel).

Decreased Effect: Oxaliplatin may decrease plasma levels of digoxin

Pharmacokinetics

Distribution: V_d: 440 L

Protein Binding: >90% primarily albumin and gamma globulin (irreversible binding to platinum)

Metabolism: Nonenzymatic (rapid and extensive), forms active and inactive derivative phase: 16.8 hours

Excretion: Primarily urine (~54%); feces (~2%)

Adverse Events

Consult the package insert for the most current and complete information. Percentages reported with monotherapy.

<u>Common Known Potential Toxicities, > 10%:</u>

Central nervous system: Fatigue, fever, pain, headache, insomnia

Gastrointestinal: Nausea, diarrhea, vomiting, abdominal pain, constipation, anorexia, stomatitis

Hematologic: Anemia, thrombocytopenia, leukopenia

Hepatic: Liver enzymes increased

Neuromuscular & skeletal: Back pain, peripheral neuropathy (may be dose limiting). The most commonly observed oxaliplatin-related toxicity is acute and cumulative neurotoxicity, observed in patients treated at doses above 100 mg/m^2/cycle. This neurotoxicity has included paresthesias and dysesthesias of the hands, feet, and perioral region as well as unusual laryngopharyngeal dysesthesias characterized by a loss of sensation of breathing without any objective evidence of respiratory distress (hypoxia, laryngospasm, or bronchospasm). OXAL neurotoxicity appears to be exacerbated by exposure to cold. Patients on this study will be counseled to avoid cold drinks and exposure to cold water or air. Should a patient develop laryngopharyngeal dysesthesia, their oxygen saturation should be evaluated via a pulse oximeter; if normal, an anxiolytic agent should be given and the patient observed in the clinic until the episode has resolved. Because this syndrome may be associated with the rapidity of OXAL infusion, subsequent doses of OXAL should be administered as a 6-hour infusion (instead of the normal 2-hour infusion).

Acute and cumulative neurotoxicities are dose limiting for OXAL. The acute neurotoxicity is characterized by paresthesias and dysesthesias that may be triggered or exacerbated by exposure to cold. These symptoms occur within hours of exposure and are usually reversible over the following hours or days. Cumulative doses of OXAL above 680 mg/m^2 may produce functional impairment characterized by difficulty performing activities requiring fine sensory-motor coordination; impairment is caused by sensory rather than motor changes.

The likelihood of experiencing neurotoxicity is directly related to the total cumulative dose of OXAL administered. The relative risk of developing neurotoxicity was 10%, 50%, and 75% in patients who received total cumulative OXAL doses of 780 mg/m^2, 1,170 mg/m^2, and 1,560 mg/m^2, respectively. Both acute and cumulative neurotoxicities due to OXAL have lessened in 82% of patients within 4 to 6 months, and have completely disappeared by 6 to 8 months in 41% of patients. In addition, the likelihood that neurologic symptoms will regress has been shown to correlate inversely with cumulative dose.

Respiratory: Dyspnea, cough

Less Common Known Potential Toxicities, 1% - 10%:

Cardiovascular: Edema, chest pain, peripheral edema, flushing, thromboembolism

Central nervous system: Dizziness

Dermatologic: Rash, alopecia, hand-foot syndrome

Endocrine & metabolic: Dehydration, hypokalemia

Gastrointestinal: Dyspepsia, taste perversion, flatulence, mucositis, gastroesophageal reflux, dysphagia

Genitourinary: Dysuria

Hematologic: Neutropenia

Local: Injection site reaction

Neuromuscular & skeletal: Rigors, arthralgia

Ocular: Abnormal lacrimation

Renal: Serum creatinine increased

Respiratory: URI, rhinitis, epistaxis, pharyngitis, pharyngolaryngeal dysesthesia

Miscellaneous: Allergic reactions, hypersensitivity (includes urticaria, pruritus, facial flushing, shortness of breath, bronchospasm, diaphoresis, hypotension, syncope, hiccup

Rare Known Potential Toxicities, <1% (Limited to Important or Life-threatening):

Gastrointestinal: Life threatening enteric sepsis secondary to neutropenia and diarrhea.

Hepatic: Veno-occlusive disease of the liver is a rare serious adverse event that has occurred in association with administration of oxaliplatin and fluorouracil.

Otic: Clinical ototoxicity occurs in less than 1% of patients following oxaliplatin administration, and severe ototoxicity has not been reported.

Nursing Guidelines

GI toxicity similar to cisplatin occurs with doses above 30 mg/m^2. It can be almost constant and frequently severe, but not always dose-limiting. Monitor for nausea and vomiting and treat accordingly.

Dose-limiting side effect can be paresthesias of hands, fingers, toes, pharynx, and occasionally cramps which develops with a dose-related frequency (>90 mg/m^2). Duration of symptoms tend to be brief (less than a week) with the first course, but longer with subsequent courses. Phase I patients have reported exacerbation of paresthesias by touching cold surfaces or exposure to cold. Advise patient of these possibilities and instruct patient to report these symptoms to the

health care team. Also advise patient to refrain from operating dangerous machinery that requires fine sensory-motor coordination, if symptoms appear.

These sensory neuropathies developed after subsequent courses with increasing intensity (Grade 3 toxicity after the fourth course) and with increasing duration. In 63% of the patients tested in phase I at high doses (135-200 mg/m^2), neuropathies became long-term with slow reversal over several months. Disabling walking and handwriting difficulties, as well as mouth and throat dysesthesias and laryngospasms were seen. Instruct patient to report any swallowing difficulties or gait changes.

OXAL is incompatible with NS. Flush lines with D5W prior to and following OXAL infusion.

Low back pain is a common side effect, perhaps a form of hypersensitivity reaction. Instruct patient in good body mechanics, advise light massage, heat, etc.

Laryngopharyngeal dysesthesia (LPD) occurs in about 15% of patients and is acute, sporadic, and self-limited. It usually occurs within hours of infusion, is induced or exacerbated by exposure to cold, and presents with dyspnea and dysphagia. The incidence and severity appear to be reduced by prolonging infusion time. Instruct patient to avoid ice and cold drinks the day of infusion.

Comparison of the Symptoms and Treatment of Laryngopharyngeal Dysesthesias and Platinum Hypersensitivity Reactions

Comparison of the Symptoms and Treatment of Laryngopharyngeal Dysesthesias and Platinum Hypersensitivity Reactions		
Clinical Symptoms	**Laryngopharyngeal Dysesthesias**	**Platinum Hypersensitivity**
Dyspnea	present	present
Bronchospasm	absent	present
Laryngospasm	absent	present
Anxiety	present	present
O_2 saturation	normal	decreased
Difficulty swallowing	present (loss of sensation)	absent
Pruritus	absent	present
Urticaria/rash	absent	present
Cold-induced symptoms	yes	no
BP	normal or increased	normal or decreased
Treatment	anxiolytics, observation in a controlled clinical setting until symptoms abate or at the physicians' discretion	oxygen, steroids, epinephrine, bronchodilators; fluids and vasopressors, if appropriate

Treatment anxiolytics, observation in a controlled clinical setting until symptoms abate or at the physicians' discretion oxygen, steroids, epinephrine, bronchodilators; fluids and vasopressors, if appropriate

Alopecia is rare with OXAL alone, but is seen with 5-FU-OXAL combination. Advise patient.

Mild-moderate diarrhea has been seen – usually of short duration. Treat accordingly. See Section 8.1 for ancillary treatment.

Respiratory problems (i.e. pulmonary fibrosis, cough, dyspnea, rales, pulmonary infiltrates, hypoxia, air hunger and tachypnea) have been observed in patients administered OXAL. In rare cases, death has occurred due to pulmonary fibrosis. Please monitor and instruct the patient to report any respiratory difficulties and hold OXAL until interstitial lung disease is ruled out for cases of Grade ≥ 3. If patient is experiencing shortness of breath, a chest x-ray and assessment of oxygenation via either finger oximetry or arterial blood gas evaluation are required to confirm the absence or presence of pulmonary infiltrates and/or hypoxia (treat accordingly: no intervention, steroids, diuretics, oxygen, or assisted ventilation).

Veno-occlusive disease (VOD) is a rare but serious complication that has been reported in patients receiving oxaliplatin in combination with 5-FU. This condition can lead to hepatomegaly, splenomegaly, portal hypertension and/or esophageal varices. Instruct patients to report any jaundice, ascites, or hematemesis to the MD immediately as these could be a sign of VOD or other serious condition.

Acute vein irritation can occur with infusion. Apply heat to arm of infusion if you are using a peripheral line. However, extravasation of drug can cause severe pain, redness, soreness, and exfoliation of the skin in the affected area with loss of affected vein for a long period. If a patient has a problem with pain or sclerosis when chemotherapy is given by a peripheral line, then placement of a central line should be considered.

Hemolytic Uremic Syndrome (HUS) may result in kidney damage. Oxaliplatin is to be discontinued in cases where hematocrit is <25%, thrombocytopenia <100,000, and creatinine 1.6 mg/dL.

Patients may experience sleep disturbances, specifically insomnia. Encourage good sleep hygiene, and instruct patient to report any problems with sleep to the MD, to assess for the potential use of sleeping aids.

Cold-induced transient visual abnormalities can be experienced by patients while receiving OXAL, although the relationship to OXAL has not been completely determined. Instruct patient to report any problems with vision to the MD.

Extrapyramidal side effects and/or involuntary limb movement has been seen with OXAL administration. Patients may also experience restlessness. Instruct patient to report any of these side effects to the MD.

A bolus infusion of OXAL/CAPCIT may increase the risk of developing life-threatening enteric sepsis secondary to neutropenia and diarrhea. Patients with grade 4 ANC and grade 3 diarrhea should be closely monitored and condition reported to MD for possible hospitalization for appropriate hydration and treatment with antibiotics, appropriate for gram negative or anaerobic sepsis. Patients should be monitored closely and provided with aggressive supportive care until neutropenia and diarrhea resolve.

10.6 Irinotecan (Camptosar, NSC# 616348)

Procurement

Commercial supplies. Institutional pharmacy shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Commercially available for injection 20 mg/mL (2 mL, 5 mL) [contains sorbitol 45 mg/mL; do not use in patients with hereditary fructose intolerance].

Storage and Stability

Refer to package insert for complete preparation and dispensing instructions. Store intact vials at room temperature and protect from light. Due to the relatively acidic pH, irinotecan appears to be more stable in D5W than 0.9% NaCl. Solutions diluted in D5W are stable for 24 hours at room temperature or 48 hours under refrigeration at 2ºC to 8ºC. Solutions diluted in 0.9% NaCl may precipitate if refrigerated. Do not freeze.

Preparation

Doses should be diluted in 250-500 mL D5W or 0.9% NaCl to a final concentration of 0.12-2.8 mg/mL.

Administration

Administer by IV infusion, usually over 90 minutes.

Drug Interactions

Cytochrome P450 Effect: Substrate (major) of CYP2B6, 3A4

Increased Effect/Toxicity: CYP2B6 and CYP3A4 inhibitors may increase the levels/effects of irinotecan. Bevacizumab may increase the adverse effects of irinotecan (e.g. diarrhea, neutropenia). Ketoconazole increases the levels/effects of irinotecan and active metabolite; discontinue ketoconazole 1 week prior to irinotecan therapy; concurrent use is contraindicated.

Decreased Effect: CYP2B6 and CYP3A4 inducers may decrease the levels/effects of irinotecan.

Ethanol/Nutrition/Herb Interactions Herb/Nutraceutical: St. John's Wort decreases therapeutic effect of irinotecan; discontinue ≥ weeks prior to irinotecan therapy; concurrent use is contraindicated.

Pharmacokinetics

Distribution: Vd: 33-150 L/m^2

Protein binding, plasma: Predominantly albumin; Parent drug: 30% to 68%, SN-38 (active metabolite): ~95%

Metabolism: Primarily hepatic to SN-38 (active metabolite) by carboxylesterase enzymes; SN-38 undergoes conjugation by UDP-glucuronosyl transferase 1A1 (UGT1A1) to form a glucuronide metabolite. Conversion of irinotecan to SN-38 is decreased and glucuronidation of SN-38 is increased in patients who smoke cigarettes, resulting in lower levels of the metabolite and overall decreased systemic exposure. SN-38 is increased by UGT1A1*28 polymorphism (10% of North Americans are homozygous for UGT1A1*28 allele). Patients homozygous for the UGT1A1*28 allele are at increased risk of neutropenia; initial one-level dose reduction should be considered for both single-agent and combination regimens. The lactones of both Irinotecan and SN-38 undergo hydrolysis to inactive hydroxyl acid forms.

Half-life elimination: SN-38: Mean terminal: 10-20 hours

Time to peak: SN-38: Following 90-minute infusion: ~1 hour

Excretion: Within 24 hours: urine: Irinotecan (11% to 20%), metabolites (SN-38 < 1%, SN-38 glucuronide, 3%)

Adverse Events

Consult the package insert for the most current and complete information including U.S. Boxed Warnings pertaining to severe diarrhea and severe myelosuppression.

Common known potential toxicities, > 10%:

Cardiovascular: Vasodilation

Central nervous system: Cholinergic toxicity (includes rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing and intestinal hyperperistalsis); fever, pain, dizziness, insomnia, headache, chills

Dermatologic: Alopecia, rash

Endocrine & metabolic: Dehydration

Gastrointestinal: Late onset diarrhea, early onset diarrhea, nausea, abdominal pain, vomiting, cramps, anorexia, constipation, mucositis, weight loss, flatulence, stomatitis

Hematologic: Anemia, leukopenia, thrombocytopenia, neutropenia

Hepatic: Bilirubin increased, alkaline phosphatase increased

Neuromuscular & skeletal: Weakness, back pain

Respiratory: Dyspnea, cough, rhinitis

Miscellaneous: Diaphoresis, infection

Less common known potential toxicities, 1% - 10%:

Cardiovascular: Edema, hypotension, thromboembolic events

Central nervous system: Somnolence, confusion

Gastrointestinal: Abdominal fullness, dyspepsia

Hematologic: Neutropenic fever, hemorrhage, neutropenic infection

Hepatic: AST increased, ascites and/or jaundice

Respiratory: Pneumonia

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

ALT increased, amylase increased, anaphylactoid reaction, anaphylaxis, angina, arterial thrombosis, bleeding, Bradycardia, cardiac arrest, cerebral infarct, cerebrovascular accident, circulatory failure, colitis, deep thrombophlebitis, dysrhythmia, embolus, gastrointestinal bleeding, gastrointestinal obstruction, hepatomegaly, hiccups, hyperglycemia, hypersensitivity, hyponatremia, ileus, interstitial lung disease, intestinal perforation, ischemic colitis, lipase increased, lymphocytopenia, megacolon, MI, muscle cramps, myocardial ischemia, pancreatitis, paresthesia, peripheral vascular disorder, pulmonary embolus, pulmonary toxicity (dyspnea, fever, reticulnodular infiltrates on chest x-ray), renal failure (acute), renal impairment, syncope, thrombophlebitis, thrombosis, typhlitis, ulceration, ulcerative colitis, vertigo

Nursing Guidelines

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

Cholinergic symptoms of lacrimation, nasal congestion, diaphoresis, flushing, ABD cramping, and diarrhea can occur at the beginning, during, or immediately after the irinotecan infusion. It is suggested that the patient remain in the treatment area for a minimum of one hour following the completion of the very first irinotecan infusion. If diarrhea occurs within one hour of infusion, refer to Section 8.1.5 for management.

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

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

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

The pulmonary toxicity seen is usually manifested by dyspnea beginning 42-175 days after treatment and occurs at a cumulative dose ranging from 400-1000 mg/m^2 (median 750). Instruct patient to report any cough or SOB.

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

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

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

Advise patients of probable hair loss.

10.7 Bevacizumab (NSC# 704865)

Procurement

Commercial supplies. Institutional pharmacy shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody, consisting of 93% human and 7% murine amino acid sequences. The agent is composed of human IgG framework and murine antigen-binding complementarity-determining regions. Bevacizumab blocks the binding of VEGF to its receptors resulting in inhibition of angiogenesis.

Bevacizumab is commercially available in 100 mg or 400 mg vials (25 mg/mL).

Bevacizumab or an FDA-approved biosimilar to bevacizumab is allowed.

Storage and Stability

Bevacizumab should be stored in a refrigerator (2°C to 8°C) and should remain refrigerated until just prior to use. Do not freeze. Do not shake. The sterile single use vials contain no antibacterial preservatives; therefore, vials should be discarded eight hours after initial entry. Solutions diluted for infusion may be stored in the refrigerator for up to 8 hours.

Preparation

The calculated dose should be diluted in 100 mL of 0.9% Sodium Chloride for Injection.

Administration

Bevacizumab is administered as an intravenous infusion as outlined in Section 7.0. The initial dose can be administered over a minimum of 90 minutes. If no adverse reactions occur after the

initial dose, the second dose can be administered over a minimum of 60 minutes. If no adverse reactions occur after the second dose, all subsequent doses can be administered over a minimum of 30 minutes. If infusion-related adverse reactions occur, all subsequent infusions can be administered over the shortest period that was well tolerated.

Drug Interactions

DIC has been described in a few patients receiving bevacizumab in combination with oxaliplatin, fluorouracil and leucovorin.

When combined with chemotherapy, bevacizumab is reported to increase the risk of neutropenia over that of chemotherapy alone.

Adverse Events

Consult the package insert for the most current and complete information.

According to the package information for bevacizumab, the most serious adverse events associated with bevacizumab to date are gastrointestinal perforations/wound healing complications, hemorrhage, arterial thromboembolic events, hypertensive crises, nephrotic syndrome, and congestive heart failure.

Hypertension is among the most common adverse events associated with bevacizumab; both new hypertension and worsening of existing hypertension have been reported. Hypertensive crises have been reported in several studies, and the end organ consequences included CNS bleeding and ischemia, and congestive heart failure

Proteinuria, ranging from asymptomatic abnormal urinalysis to nephrotic syndrome, has been described in 10% or more of patients receiving bevacizumab.

Bleeding, including fatal CNS hemorrhage, has been reported. Bleeding at tumor sites or at sites of other pre-existing abnormalities (e.g., diverticulosis, hemorrhoids) has also been described. In a phase III study, fatal hemoptysis occurred in 2 of 55 patients with non-small cell lung cancer, both of whom had a history of hemoptysis. The rate of fatal hemoptysis in non-squamous NSCLC is estimated at 1-2%. Epistaxis is usually short lived and resolves without treatment, although some episodes may require medical intervention.

Thrombosis/embolism; both arterial and venous thromboses (including pulmonary embolism, mesenteric vein thrombosis, ischemic bowel, cerebral vascular accident), and myocardial infarction have been described in patients receiving bevacizumab. Fatal pulmonary embolus has also been described.

With regard to arterial thromboses (which include myocardial infarction, transient ischemic attack, cerebrovascular accident/stroke, and angina/unstable angina), recent studies indicate that the risk with bevacizumab and chemotherapy is 2-3 times (up to 5%) that of chemotherapy alone. Furthermore, certain baseline characteristics, specifically age > 65 years and prior thromboembolic event, conferred additional risk.

Hepatic Dysfunction: Reversible and marked elevations of liver function tests (total bilirubin and/or transaminase and AP) have been rarely reported when bevacizumab is used in combination with chemotherapy or concurrently with other drugs that are potentially hepatotoxic. The mechanism of such hepatic toxicities is unclear. It is possible that on rare occasions, bevacizumab may potentiate the liver side effect of a concurrent medication, although it is unclear at this time whether bevacizumab alone can cause LFT derangement.

Bowel perforation and bowel anastomotic dehiscence have been reported in clinical trials using bevacizumab alone or in combination with chemotherapy. Although these events were also related to co-existing factors such as tumor involvement, chemotherapy, recent invasive

procedures or bowel inflammation, they have occurred at an increased rate in patients receiving bevacizumab. A fatal bowel perforation has been described. GI perforation should be included in the differential diagnosis of patients receiving bevacizumab therapy presenting with abdominal pain or rectal/abdominal abscess. Partial delay in wound healing has been demonstrated in animal models treated with anti-VEGF antibodies and it is possible that bevacizumab may delay or compromise wound healing in patients.

Reversible posterior leukoencephalopathy syndrome (RPLS) or similar leukoencephalopathy syndrome: RPLS or clinical syndromes related to vasogenic edema of the white matter have been recently reported in association with bevacizumab therapy. These syndromes have been seen in < 1% of patients to date. Clinical presentations are variable and may include altered mental status, seizure and cortical visual deficit. HTN is a common risk factor and was present in most (though not all) patients on bevacizumab who developed RPLS. MRI scans are key to diagnosis and typically demonstrate vasogenic edema (hyperintensity in T2 and FLAIR images and hypointensity in T1 images) predominantly in the white matter of the posterior parietal and occipital lobes; less frequently, the anterior distributions and the gray matter may also be involved. RPLS should be in the differential diagnosis in patients presenting with unexplained mental status change, visual disturbance, seizure or other CNS findings. RPLS is potentially reversible, but timely correction of the underlying causes, including control of BP and interruption of the offending drug, is important in order to prevent progression to irreversible tissue damage.

Infusion reactions, including fever, chills, rigors, rash, urticaria, dyspnea, and hypersensitivity reactions have been reported in approximately 3% of patients.

Neutropenia: Grade 3-4 neutropenia, febrile neutropenia, or increased rate of infection were increased in studies in which bevacizumab with chemotherapy (IFL, paclitaxel and carboplatin) was compared to chemotherapy alone.

Other toxicities: Other reported or potential toxicities associated with bevacizumab include:

- Constitutional—Headache, infection without neutropenia, asthenia
- Cardiovascular—Hypotension, pericardial effusion, congestive heart failure
- Skin—Rash, urticaria
- Gastrointestinal—Nausea, vomiting, stomatitis/pharyngitis, colitis, intestinal obstruction
- Pulmonary—Pulmonary infiltration, dyspnea
- Musculoskeletal—Arthralgia, chest pain

11.0 MEASUREMENT OF EFFECT

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1).

Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline [26].

11.1 Schedule of Evaluations

For the purposes of this study, patients should be reevaluated every 8 weeks (i.e. every 4 cycles).

Supporting documentation of response should be submitted per Section 6.1.5, and radiologic images and local interpretation reports should be submitted per Section 6.3.

11.2 Definitions of Measurable and Non-measurable Disease

11.2.1 Measurable Disease

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

A superficial non-nodal lesion is measurable if its longest diameter is ≥ 1.0 cm in diameter as assessed using calipers (e.g. skin nodules) on imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

Tumor lesions in a previously irradiated area are considered measurable disease if there has been evidence of disease progression in the previously irradiated area in the 6 months prior to registration.

11.2.2 Non-measurable Disease

Non-measurable disease includes disease smaller than these dimensions or lesions considered truly non-measurable including: leptomeningeal disease, ascites, pleural or pericardial effusion, lymphangitic involvement of skin or lung.

11.3 Guidelines for Evaluation of Measurable Disease

11.3.1 Measurement Methods

All measurements should be recorded in metric notation (i.e. decimal fractions of centimeters) using a ruler or calipers.

The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during restaging. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.

Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.3.2 Acceptable Modalities for Measurable Disease

- Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less.
    - As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

11.3.3 Measurement at Follow-up Evaluation

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

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

11.4 Measurement of Treatment/Intervention Effect

11.4.1 Target Lesions & Target Lymph Nodes

Measurable lesions (as defined in Section 11.2.1) up to a maximum of 5 lesions, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. These lesions can be non-nodal or nodal (as defined in Section 11.2.1), where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

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

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

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

Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.

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

11.4.2 Non-target Lesions & Non-target Lymph Nodes

Non-measurable sites of disease are classified as non- target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with Section 11.4.3.

11.4.3 Response Criteria

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

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example,

bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

- Evaluation of Target Lesions
    - **Complete Response (CR):** All of the following must be true:
        - Disappearance of all target lesions.
        - Each target lymph node must have reduction in short axis to < 1.0 cm.
    - **Partial Response (PR):** At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (see Section 11.4.1).
    - **Progression (PD):** At least one of the following must be true:
        - At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.
        - At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (see Section 11.4.1). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.
    - **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.
- Evaluation of Non-Target Lesions & Non-target Lymph Nodes
    - **Complete Response (CR):** All of the following must be true:
        - Disappearance of all non-target lesions.
        - Each non-target lymph node must have a reduction in short axis to < 1.0 cm.
    - **Non-CR/Non-PD:** Persistence of one or more non-target lesions or non-target lymph nodes
    - **Progression (PD):** At least one of the following must be true:
        - At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.
        - Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)

11.4.4 Overall Objective Status

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

For Patients with Measurable Disease

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

* See Section 11.4.3

11.4.5 Symptomatic Deterioration

Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as "symptomatic deterioration" on the corresponding Case Report Form in Rave. Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration, and radiologic imaging should continue to be collected every 8-16 weeks (+/- 1 week) until disease progression (or start of a new anticancer therapy); see Section 5.0.

11.5 Definitions of Analysis Variables

Formal definitions of variables used in analyses can be found in the Statistical Considerations section (Section 13.0) of the protocol.

12.0 END OF TREATMENT/INTERVENTION

12.1 Duration of Protocol Treatment

Protocol treatment (intervention) is to continue until one of the criterion for discontinuation listed below has been met. Please see the study calendar (Section 5.0) and the treatment section (Section 7.0) for treatment and following up time periods.

12.2 Criteria for Discontinuation of Protocol Treatment/Intervention

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression per RECIST v1.1
- Clinical progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the protocol treatment
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Patient non-compliance
- Pregnancy
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
    - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent
- Surgical intervention, radiotherapy, cryotherapy, ablation, etc. is performed on the primary neoplasm or metastasis
- Patient is five (5) years from registration/randomization

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

12.3 Follow-up

12.3.1 Duration of Follow-up

Participants will be followed for 5 years from the date of registration/randomization or until death, whichever occurs first.

12.3.2 Follow-up for Patients who Stop Study Treatment Early

All participants who discontinued study treatment for any reason other than disease progression and all participants whose tumor progression was not documented at the end-of-study visit will continue to have tumor assessments every 8-16 weeks (+/- 7 days) until documented disease progression or until the start of additional anti-tumor therapy.

12.3.3 Follow-up for Specimen Submission

If the patient discontinues study treatment for any reason, specimens should continue to be collected and submitted after discontinuation of therapy per Section 6.2.

12.4 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

12.5 Managing Ineligible Patients and Registered Patients Who Never Receive Protocol Intervention

Definition of ineligible patient

A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible.

Follow-up for ineligible patients who continue with protocol treatment

Patients who are deemed ineligible after registering may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient continues protocol treatment. All scans, tests, and data submission are to continue as if the patient were eligible. Notification of the local IRB may be necessary per local IRB policies.

Follow-up for ineligible patients who discontinue protocol treatment

For patients who are deemed ineligible after registering to the trial, who start treatment, but then discontinue study treatment, the same data submission requirements are to be followed as for those patients who are eligible and who discontinue study treatment.

Follow-up for patients who are registered, but who never start study treatment

For all study participants who are registered to the trial but who never receive study intervention (regardless of eligibility), the follow-up requirements are specified below.

Baseline, off treatment, and post-treatment follow up (i.e., relapse, progression, and survival) data submission required. See the Data Submission Schedule accompanying the All Forms Packet.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Design

This randomized phase III trial is designed to compare progression-free survival of patients with previously untreated metastatic colorectal cancer who receive either 1) high-dose vitamin D3 in combination with standard chemotherapy (FOLFOX or FOLFIRI) + bevacizumab or 2) standard-dose vitamin D3 in combination with standard chemotherapy (FOLFOX or FOLFIRI) + bevacizumab. Patients will be randomized in a 1:1 allocation to either arm. One interim analysis for futility will be performed. It will allow stopping early for futility while controlling overall alpha level. The sample size calculation was conducted using EAST v6.4.

Efficacy analyses will be based on the intent to treat principle. Any analyses related to adverse events will be based on the safety population. All patients who were randomized and received

any amount of protocol therapy will be considered part of the safety population and evaluable for safety analysis. For the purposes of safety analysis, patients will be assigned to the treatment group for the therapy that was actually received.

13.2 Statistical Design and Analysis for the Primary Endpoint

13.2.1 Primary Endpoint

The primary endpoint of this study is progression-free survival (PFS). PFS is defined as the time from randomization to the first documentation of disease progression (per RECIST v1.1) or death. The censoring rule is as follows:

- Patients who are still alive and have not progressed will be censored for PFS at the time of their last disease assessment.
- Patients who initiate alternative (new) anti-cancer therapy will be censored for PFS at the time of their last disease assessment prior to initiation of alternative (new) anti-cancer therapy.
- Patients who are alive and have no tumor measurement post-baseline will be censored for PFS at Day 1 post-randomization.

Efficacy analyses will be based on the intent-to-treat principle. All randomized patients regardless of whether any treatment is received will be included in the analysis. Patients will be assigned to the treatment group they were randomized to regardless of actual treatment received.

13.2.2 Statistical Design

Based on the results from CALGB 80405, we anticipate a PFS median of approximately 10 months [27]. We plan to accrue a total of 445 patients (approximately 222 patients per arm) in 39 months with a minimum follow-up of 13 months to achieve 273 PFS events. The length of accrual time is based on an accrual rate of 3 patients per month for the first 6 months, 12 patients per month for 1 year (after the first 6 months) and 14 patients per month for the remaining accrual period. This design with one interim analysis for futility only with O'Brien-Fleming type stopping boundary (Gamma family with parameter -4 for futility) will yield 90% power to detect a hazard ratio of 0.70 (median PFS of 10 vs. 14.3 months) assuming exponential survival and using a one-sided log-rank test with type I error rate of 0.05. This sample size takes into account a 27.6% drop-out rate due to patients coming off treatment for reasons other than disease progression (.e.g. surgical resection).

The sample size is increased from the original 400 to 445, in Update #03, due to a higher than expected drop-out rate observed.

13.2.3 Study Operating Characteristics

The table below shows the operating characteristics assuming the PFS follows exponential survival functions. The percent of times that 1) the study would stop early due to futility and 2) the study would conclude that high-dose vitamin D3 + (FOLFOX or FOLFIRI) + bevacizumab is superior to standard dose vitamin D3 + (FOLFOX or FOLFIRI) + bevacizumab at the final analysis are tabulated by true medians of PFS and the true hazard ratio. Proportions are based on 10,000 replicates in the simulation study.

True Median PFS (Months)		True hazard ratio	% of times the study will be stopped	% of times that standard-dose vitamin D3 + (FOLFOX or FOLFIRI) +
Standard-dose vitamin D3 + (FOLFOX or	High-dose vitamin D3 + (FOLFOX or			

FOLFIRI) + bevacizumab	FOLFIRI) + bevacizumab		early for futility	bevacizumab is superior at the final analysis
10.0	14.29	0.70	1.12	89.84
10.0	13.22	0.756	3.54	74.64
10.0	12.15	0.823	9.47	48.76
10.0	11.07	0.903	21.74	21.0
10.0	10.0	1.00	41.99	4.9

13.2.4 Analysis Plan

Interim Analysis Decision Rules

One interim analysis will be performed to assess treatment futility and will be performed at the time at which 50% of the projected PFS events (137 PFS events) have occurred. The specific hazard ratios and critical p-values for declaring futility at the interim analysis is specified in the table below. When PFS crosses futility boundary, the accrual will be suspended (if still ongoing), the currently enrolled patients will be followed per protocol, and the data will be reported.

Analysis time point (% events)	Number of PFS events	Critical p-value for futility	HR for futility
50%	137	>0.568	>1.03

Final Analysis Decision Rules

The primary efficacy analysis will be performed at the time when 273 PFS events have occurred. The specific hazard ratio and critical p-values for declaring superiority or futility are specified in the table below. Specifically, at the final analysis, if p-value is less than or equal to 0.05 the high-dose vitamin D3 + (FOLFOX or FOLFIRI) + bevacizumab regimen will be deemed effective; otherwise, high-dose vitamin D3 + (FOLFOX or FOLFIRI) + bevacizumab regimen will be considered to have not met the criteria for efficacy.

Analysis time point (% events)	Number of PFS events	Critical p-value for efficacy	HR for efficacy	Critical p-value for futility	HR for futility
100% (Final)	273	0.05	0.819	0.05	0.819

Analysis Plan for Both Interim and Final Analyses: PFS will be compared between treatment arms using the un-stratified log-rank test and its one-sided p-value will be used for decision making. The HR for PFS will be estimated using a Cox proportional hazards model and the 95% CI for the HR will be provided. Results from a stratified analysis will also be provided. Kaplan-Meier methodology will be used to estimate the median PFS for each treatment arm, and Kaplan-Meier curves will be produced. Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS for each treatment arm [28]. A sensitivity analysis of PFS comparison across arms will be conducted where PFS will be censored at surgery date for patients who receive surgery with curative intent. Comparison of PFS across arms while adjusting for baseline characteristics will also be conducted as an exploratory analysis.

13.3 Sample Size, Accrual Time, and Study Duration

13.3.1 Sample Size

We anticipate randomizing a maximum of 445 patients (approximately 222 per arm) per statistical design in Section 13.2.

13.3.2 Accrual Rate and Accrual Duration

CALGB 80405 accrued approximately 30 patients per month. For this protocol, MSI-high patients will be excluded (approximately 5% prevalence rate). Thus, the accrual rate is projected to be approximately 28 patients per month. We made the same assumption for the accrual rate for the original study design. In Update #03 where the sample size was increased to 445, we updated the accrual rate by using three different accrual periods in which the rate in each period is approximately the actual observed accrual rate in the study (see Section 13.2.2). Accrual will not be halted for interim analysis. We anticipate that the study will take approximately 39 months to fully accrue if there are no major issues of patient safety and the study passes interim analysis.

13.3.3 Primary Endpoint Completion Date for ClinicalTrials.gov Reporting

For purpose of ClinicalTrials.gov reporting, the primary endpoint completion date (PECD) for this study is the time the 273rd PFS event occurs. Per design, the maximum study duration is estimated to be 52 months (39-month accrual time + 13 month follow-up) from the first patient randomized.

13.4 Supplementary Analysis Plans

13.4.1 Secondary Endpoints

- **Objective Response:** Unconfirmed objective response by RECIST v1.1 criteria will be estimated using objective response rate (ORR) where ORR is defined as the number of evaluable patients achieving a response (PR or CR per RECIST v1.1) during treatment with study therapy divided by the total number of evaluable patients. The population of evaluable patients for this analysis will be the same as the ITT population defined above. Rates of response will be compared across arms using a Chi-Square Test for Proportion. Point estimates will be generated for objective response rates within each arm along with 95% binomial confidence intervals [29].
- **Overall Survival:** Overall survival time is defined as the time from randomization to death due to any cause. Patients who are alive will be censored at last follow-up for overall survival. The distribution of survival time will be estimated using the method of Kaplan-Meier [30]. Overall survival will be compared between treatment arms using the log-rank test. OS medians, survival rates at 3 years and HR will be estimated along with 95% confidence intervals.
- **Adverse Event:** Adverse events will be evaluated via the CTCAE standard toxicity grading. Overall adverse event profiles by treatment arm will be explored and summarized. Frequency distributions, graphical techniques, and other descriptive measures will form the basis of the analysis.
- **Physical Activity & PFS:** PFS of patients receiving high-dose vitamin D3 vs. patients receiving standard-dose vitamin D3 will be compared in subgroups of physical activity (PA) levels. The levels will be defined as low PA (< 9 metabolic-equivalent task [MET]-hours/week) vs. high PA (≥ 9 MET-hours/week). The distribution of PFS time will be estimated using the method of Kaplan-Meier

within each subgroup and arm combination [30]. PFS will be compared between treatment arms using the non-stratified log-rank test in each subgroup of PA levels. PFS medians, survival rates at 3 years, and HR will be estimated along with 95% confidence intervals within each subgroup and arm combination. Interaction between PA subgroups and treatment arms will be tested using likelihood ratio test.

- **Baseline Prevalence of Vitamin D3 Deficiency:** The baseline prevalence of vitamin D3 deficiency will be defined as the number of evaluable vitamin D3 deficient patients divided by the total number of evaluable patients. The population of evaluable patients for this analysis will be all patients whose 25(OH)D level was successfully measured at baseline. Vitamin D3 deficiency is defined as 25(OH)D level < 20 ng/mL. Prevalence of vitamin D3 deficiency will be compared across arms using a Chi-Square Test for Proportion. Point estimates will be generated for vitamin D3 deficiency rates within each arm along with 95% confidence intervals [29].
- **Subgroup Analyses for PFS:** PFS of patients receiving high-dose vitamin D3 vs. patients receiving standard-dose vitamin D3 will be compared in subgroups of baseline 25(OH)D levels, baseline demographic and clinicopathologic factors (e.g., body mass index [<25 vs 25-30 vs. ≥30 kg/m^2], presence of liver metastases [yes vs. no], RAS mutation status [wildtype vs. mutant]). Baseline 25(OH)D levels will be defined as deficient (< 20 ng/mL) vs. other (≥ 20 ng/mL). The distribution of PFS time will be estimated using the method of Kaplan-Meier within each subgroup and arm combination [30]. PFS will be compared between treatment arms using the non-stratified log-rank test in each subgroup PFS medians, survival rates at 3 years, and HR will be estimated along with 95% confidence intervals within each subgroup and arm combination. Interaction between subgroups and treatment arms will be tested using likelihood ratio test. Comparison of PFS across arm in subgroups of interest while adjusting for baseline characteristics will also be conducted as exploratory analysis.
- **Prognostic Effect of Highest Achieved 25(OH)D & PFS:** PFS of patients will be compared in subgroups of highest achieved 25(OH)D levels. The levels will be defined by quartile of highest-achieved level among patients who have both baseline and at least one on-treatment 25(OH)D sample result. The distribution of PFS time will be estimated using the method of Kaplan-Meier within each subgroup [30]. PFS will be compared across quartiles using the non-stratified log-rank test. PFS medians, survival rates at 3 years, and HR will be estimated along with 95% confidence intervals. Baseline 25(OH)D will be entered into the Cox model as a covariate.

13.5 Monitoring the Study

13.5.1 Adverse Event Stopping Rule

The Study Chair and A021703 Statistician will review the accrual and safety data periodically, as well as the Alliance Group Meeting Reports, in order to identify any feasibility problems associated with accrual rates and adverse events. There is no formal adverse event stopping rule for this study.

13.5.2 Accrual Monitoring Stopping Rule

The NCI Cancer Therapy Evaluation Program (CTEP) accrual guidelines for phase III trials will be utilized for this study. The current guidelines can be found on the CTEP website [redacted]

13.6 Study Reporting

Data Safety Monitoring Board Reporting

This study will be monitored by the Alliance Data Safety Monitoring Board (DSMB), an NCI-approved functioning body. Reports containing efficacy, adverse event, and administrative information will be provided to the DSMB every six months as per NCI guidelines.

Clinical Data Update System Reporting

This study will be monitored by the Clinical Data Update System (CDUS) version 2.0. An abbreviated report containing cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reporting time points are: January 31, April 30, July 31, and October 31.

13.7 Descriptive Factors

- Tumor Biology: Metachronous, Synchronous vs. Unknown
- Primary Tumor Unresected at Study Entry: Yes vs. No
- Disease Description: Locally Advanced vs. Metastatic
- Metastatic Sites: Local lymph node vs. Distant lymph node vs. Liver vs. Abdominal wall vs. Bone vs. CNS/brain vs. Lung vs. Pelvis vs. Peritoneum vs. others

13.8 Inclusion of Women and Minorities

This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

The geographical region served by the Alliance, has a population which includes approximately 18% minorities. Based on prior Alliance studies involving similar disease sites, we expect about 15% of patients will be classified as minorities by race and about 38.75% of patients will be women. Expected sizes of racial by gender subsets for patients registered randomized to this study are shown in the following table.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	1	1			2
Asian	6	7			13
Native Hawaiian or Other Pacific Islander	1	1			2
Black or African American	19	31			50
White	135	215	10	16	376
More Than One Race			1	1	2
Total	162	255	11	17	445

14.0 CORRELATIVE AND COMPANION STUDIES

There will be a mandatory retrospective diet and lifestyle impact analysis, a mandatory retrospective plasma 25(OH)D level analysis, and optional biobanking for future correlative science studies, and all patients are encouraged (or required) to participate.

14.1 Diet and Lifestyle Questionnaire Analysis

14.1.1 Background

Epidemiologic and scientific research indicates that diet and other lifestyle factors have a significant influence on the risk of developing colorectal cancer. Consumption of red meat, alcohol, calcium, fiber, aspirin, folic acid, obesity, physical activity, and cigarette smoking are among factors that have been suggested to influence the risk of developing colorectal cancer [31-51].

Not until recently have there been data assessing the influence of these factors on treatment outcomes and survival in patients with established cancer. In CALGB 80405 (trial of either bevacizumab or cetuximab with chemotherapy [FOLFOX or FOLFIRI] for stage IV colon cancer), a self-completed questionnaire was utilized to assess diet, physical activity, smoking, medication use and family history. Multiple important findings have stemmed from this trial. However, these data were collected over a decade ago; dietary intake and physical activity patterns may have changed since then. Therefore, it is important to collect contemporary data on dietary intake, physical activity, and other modifiable factors in this study to investigate the impact of these variables on clinical outcomes.

14.1.2 Objectives

To assess the influence of diet, body mass index, physical activity, and other lifestyle habits on PFS among patients with locally advanced/metastatic colorectal cancer.

14.1.3 Methods

In this companion study, patients participating in the treatment trial will be asked to complete a 131-item validated, food-frequency questionnaire within first 6 weeks of

randomization. The questionnaire, designed by Dr. Walter Willett and colleagues for the Nurses' Health Study, has been extensively validated among both health professional and lay populations, and provides comprehensive data on over 100 micro-nutrients, with and without supplement use. This questionnaire can be self-administered. Within the questionnaire, a series of questions about leisure-time physical activity, smoking habits, alcohol intake, and other habits that have also been validated in large populations will be included. Height and weight will also be obtained as part of the clinical trial. A similar study was initiated in the preceding CALGB first-line metastatic trial (CALGB 80405) and more than 65% of eligible patients completed the questionnaire.

Validation of the Semi-quantitative Food Frequency Questionnaire (SFFQ): The current version of the questionnaire consists of 131 food items plus vitamin and mineral supplement use that collectively account for over 90% of the intake of the nutrients assessed [52-56]. For each food, a commonly used unit or portion size (e.g. one egg or slice of bread) is specified, and participants are asked how often, on average over the past year, they consumed that amount of each food. There are nine possible responses which range from never to six or more times per day. The nutrient intakes will be computed by multiplying the frequency of consumption of each food by the nutrient content of the specified portions, using composition values from Department of Agriculture sources supplemented with other data, including the components of specific vitamins and breakfast cereals. All nutrients will be adjusted for total energy intake by the residuals method [57].

In 1980, the food frequency questionnaire was administered twice to 173 individuals at an interval of approximately one year, and four one-week diet records for each subject were collected during that period. Diet records probably are the best measures of current, short-term food intake. Since the seven-day record provides information for a relatively short period of time, four one-week diet records in different seasons were collected. The mean calorie adjusted intakes from the four one-week diet records and those from the questionnaire were well-correlated [54-56]. In the 1986 diet validation study, the correlation between folate calculated from the SFFQ and red cell folate level was 0.55 [34]. Nutrients calculated from the expanded SFFQ were correlated with other corresponding biochemical indicators: plasma beta-carotene (r = 0.30-0.42), plasma vitamin E (r = 0.41-0.53), adipose linoleic acid (r = 0.35-0.37), adipose trans fatty acid (r = 0.51), and adipose N-3 fatty acids (r = 0.48-0.49) [58-61]. To evaluate further the capability of the revised 131-item questionnaire to discriminate among subjects, Willett and colleagues asked 127 individuals to complete two weeks of diet records and the semi-quantitative food frequency questionnaire in 1986. The mean calorie adjusted intakes from the diet records and those from the questionnaire were well-correlated [54].

The validity of this 131-item SFFQ was be separately assessed in 200 patients with colorectal, breast, or neuroendocrine cancer undergoing treatment with cytotoxic chemotherapy [62]. The Pearson correlation coefficients for various carotenoids as measured by the questionnaire, with the corresponding measurements in plasma specimens, ranged from 0.33 to 0.44 (all $P < .001$), adjusted for total energy intake, body mass index, age, sex, smoking status, and total plasma cholesterol. Similarly, the adjusted correlation between self-reported total vitamin E intake and plasma alpha-tocopherol was 0.34 ($P < .001$). Correlations between questionnaire and plasma measurements of trans-fat, eicosapentaenoic acid, and docosahexaenoic acid were 0.55, 0.29, and 0.42 (all $P < .001$), respectively. These levels of correlation were consistent with those reported in similar studies of self-reported diet in otherwise healthy populations. Thus, among patients with cancer receiving cytotoxic chemotherapy, questionnaire-based measurements of various

micronutrients and dietary factors appeared to predict meaningful differences in the corresponding measurements in plasma specimens.

These data indicate that the proposed self-administered dietary questionnaires provide highly informative and biologically relevant measurement of a wide variety of nutrients, thus allowing one to address the dietary hypotheses outlined in the specific aims.

In terms of other measures from the survey, Wolf et al. reported on a detailed validation study of the physical activity questionnaire among a sample of 325 participants in the Nurses' Health Study II (NHS II) (241 random cohort sample and 84 random sample of African American participants) [63]. Participants completed four 1-week activity recalls and four 7-day activity diaries over one year and then repeated the NHS II activity questionnaire. For the total activity score, the correlations of the last activity questionnaire with the diaries was 0.64 for the total cohort sample and 0.59 for the African American sample. Within the Health Professionals Follow-up Study, a parallel study of men, validity of the physical activity questionnaire was assessed among 238 randomly selected participants by comparisons with four 1-week activity diaries, four 1-week activity recalls, and resting and post exercise pulse rates [64]. Correlations with the activity diaries were 0.41 for inactivity (sitting) and 0.58 for vigorous physical activity. Vigorous activity assessed by the questionnaire was correlated with resting pulse ($r = -0.45$) and post-exercise pulse ($r = -0.41$).

14.1.4 Statistical Analysis

The primary efficacy variable for analyses will be progression-free survival (PFS). Secondary efficacy endpoint is overall survival (OS).

Exposure Definitions: For all dietary exposures including dietary and supplemental vitamin D3, intakes will be categorized into energy-adjusted quintiles, consistent with our previous studies. In addition, physical activity will be categorized into categories of MET-hours as previously defined in prior work. Body mass index (in kg/m^2) will be divided into World Health Organization categories of underweight, normal weight, overweight and obesity. Baseline characteristics of patients will be compared according to quintiles of the biomarker using Wilcoxon signed rank tests for continuous variables and chi-squared tests for categorical variables. The log-rank test and Kaplan-Meier curves will be used to compare PFS and OS across different covariate level. Cox proportional hazards models will be used to control for multiple confounders. The two-tailed P value for the linear trend test across categories will be calculated using the exposure level as a continuous variable, consistent with prior studies. In secondary analyses, we will examine how the relationship between a specific exposure level and patient outcome is modified by relevant covariates such as ECOG performance status, treatment assignment, physical activity and body mass index, among others. Tests for statistical interaction will be performed by entering into the model the cross-product term of the exposure level as a continuous variable with the covariate as a continuous or binary variable.

14.2 Plasma 25(OH)D Level Analysis

14.2.1 Background

Plasma 25(OH)D is considered the best indicator of vitamin D3 status by the institute of medicine (IOM) due to its long half-life, lack of feedback regulation of its synthesis, and because it reflects all potential sources and precursors of vitamin D3 [65]. Although significant dose-response relationships between plasma 25(OH)D and outcome have been reported, supporting biologic plausibility, the optimal plasma 25(OH)D concentration associated with a survival benefit remains unclear [17, 21]. Moreover, the kinetics of

25(OH)D response to oral vitamin D3 in mCRC patients is unknown, and may be affected by both known variables relevant to the general population (i.e., skin pigmentation, diet, season, adiposity), and issues unique to cancer patients (receipt of chemotherapy has been linked to severe vitamin D3 deficiency and attenuated response to supplementation) [66-70]. In addition, baseline 25(OH)D levels may influence the degree of response to vitamin D3, and ample data show that the dose-response relationship is not linear [71, 72]. Indeed, in our dose-finding RCT of vitamin D3 in blacks, we confirmed that higher doses resulted in higher 25(OH)D levels at three months, and lower baseline 25(OH)D predicted a larger increase in 25(OH)D with any given dose of vitamin D3 [73]. In light of the complexity of the vitamin D3 dose-response relationship, particularly in cancer patients, it is imperative to investigate the impact of vitamin D3 supplementation on 25(OH)D levels in mCRC patients within the context of prospective randomized intervention. We therefore propose to test the hypothesis that raising 25(OH)D levels with vitamin D3 results in improved survival. Moreover, we will also test the distinct hypothesis that lower baseline 25(OH)D levels are associated with worse survival, and these deficient patients are most likely to benefit from high-dose supplementation.

14.2.2 Objectives

To evaluate the incidence of vitamin D3 deficiency in participants with previously untreated metastatic colorectal cancer.

To compare the efficacy of high-dose vitamin D3 versus standard-dose vitamin D3 in subgroups of patients defined by baseline plasma 25(OH)D levels.

To evaluate the prognostic effect of highest-achieved 25(OH)D levels with PFS.

14.2.3 Methods

Plasma 25(OH)D levels will not be checked during the study, but blood will be serially collected, processed, and banked at -80ºC per standard procedures for future 25(OH)D analysis. Plasma 25(OH)D concentrations will be measured in a single batch at study completion by liquid chromatography/mass spectrometry at Heartland Assays Inc. (Ames, IA) with 10% blinded quality control (QC) samples interspersed. All laboratory staff will be blinded to patient status. The assay is validated as part of the CDC Vitamin D Standardization-Certification Program (VDSCP) and the DEQAS proficiency program, and it is calibrated to National Institute of Standards and Technology (NIST) reference ranges, as previously reported [74].

14.2.4 Statistical Analysis

We will evaluate the relationship between 1) highest-achieved plasma 25(OH)D, and 2) baseline 25(OH)D, and PFS and OS using Cox proportional hazards modeling, adjusted for assigned treatment arm and relevant clinical and biological. We will calculate P values for trend by using 25(OH)D as a continuous variable in the model. We will investigate the relationship between vitamin D3 dose and survival within subgroups defined by low vs. high baseline plasma 25(OH)D to assess for effect modification. Tests for statistical interaction will be performed by entering into the Cox model the cross-product term of vitamin D3 dose with continuous baseline 25(OH)D.

14.3 Biobanking for Future Correlative Science Studies

NOTE: Testing of banked samples will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

Note: All laboratory correlates are classified as exploratory, and the specimens requested for submission in Section 6.2 will be collected for banking-only at this time.

Blood, tissue, and stool specimens will be collected and stored for future translational research for patients who consent to participate. Future studies may include: mutation analysis, immune cell biomarker studies, ctDNA, inflammation markers/cytokines, pharmacogenetic studies, future molecular and immunohistochemical studies, and microbiome profiling from stool samples.

15.0 MONITORING PLAN

Use standard Alliance monitoring procedures.

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APPENDIX I REGISTRATION FATIGUE/UNISCALE ASSESSMENTS

Registration Fatigue/Uniscale Assessments

At patient registration, this form is to be administered by a nurse/CRA, completed by the patient, and entered into Medidata Rave at the time of registration.

If needed, this appendix can be adapted to use as a source document. A booklet containing this assessment does not exist – please do not order this booklet.

How would you describe:

your level of fatigue, on the average in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
No Fatigue										Fatigue as bad as it can be

your overall quality of life in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

APPENDIX II PATIENT MEDICATION DIARY

Patient Initials: _____ Patient ID Number: _____ Study Number: _____

Cycle #: _____

Patient Instructions

- Please fill in on the table below *every* day that you take your study medication by writing in the number of capsules you take, the date and time at which you take them, and any comments regarding that day's dose.
- Please bring these medication log (diary) sheets, the empty pill bottle(s), and any extra vitamin D3 capsules with you to all appointments.
- Vitamin D3 should be taken by mouth (orally) with or without food at the same time every day. Grapefruit/juice, pomegranate/juice, pomelos, star fruits, and Seville oranges should be avoided while on vitamin D3.
- Vitamin D3 can be taken either before or after the usual treatment on days when you receive both.
- For the first cycle of treatment only, you will be given two bottles with capsules that look identical, but each bottle will contain a different dose of vitamin D3 or a placebo. You will take two vitamin D3 capsules (one from each bottle) by mouth once a day for each day of the first cycle. This is called the "loading dose" period.
- If you miss a dose, please take the missed dose as soon as possible, but only if there are 12 or more hours remaining before the next scheduled dose.
- If you miss a dose and the next dose is due (scheduled) in less than 12 hours, then place a "**0**" for the "Number of Capsules" you took that day, and do not take the "missed" dose. Please take the next dose as scheduled.
- If vomiting occurs after taking vitamin D3, then do NOT take a replacement dose on that day (*unless* it appears that an intact or whole capsule has been vomited). Start taking vitamin D3 again with the next scheduled dose. If consistent vomiting occurs, please notify your doctor.
- Vitamin D3 capsules should be stored at room temperature; do not crush or chew capsules.

CYCLE #: _____

DAY	MEDICATION	DATE	TIME		NUMBER OF CAPSULES TAKEN	COMMENTS
Example	*Vitamin D3*	*05/01/2019*	*9:00*	*AM*	*1*	*None*
1	Vitamin D3					
2	Vitamin D3					
3	Vitamin D3					
4	Vitamin D3					
5	Vitamin D3					
6	Vitamin D3					
7	Vitamin D3					
8	Vitamin D3					
9	Vitamin D3					
10	Vitamin D3					
11	Vitamin D3					
12	Vitamin D3					
13	Vitamin D3					
14	Vitamin D3					

Comments: _____

Patient Signature: _____ Date: _____

The table below is to be completed ONLY by Site Staff (Nurse/CRP) after the cycle is completed:

Pill Bottle Returned (Circle)	Yes No
Date of Pill Count (MM/DD/YYYY)	/ /
Number of Capsules Given	
Number of Capsules Returned	
Discrepancy (Circle)	Yes No
Site Staff Initials	