CLINICAL STUDY PROTOCOL

A Phase 1b Study of the OxPhos Inhibitor ME-344 Combined with Bevacizumab in Previously Treated Metastatic Colorectal Cancer

Protocol Number: ME-344-003

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IND Number: 157,739

Original Protocol: 10 August 2021 (not implemented)
Amendments 1 and 2 were not implemented

Amendment 3: 06 January 2023

SPONSOR'S PROTOCOL SIGNATURE PAGE

By signing below, the Sponsor declares that this study will be conducted in accordance with current United States (US) Food and Drug Administration Code of Federal Regulations, Good Clinical Practice (GCP) standards, the Declaration of Helsinki (Brazil 2013), and local ethical and legal requirements.

DocuSigned by:
Alejandro Ricart
Signer Name: Alejandro Ricart
Signing Reason: I approve this document
Signing Time: 09-Jan-2023 | 12:51 PST
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09-Jan-2023 | 12:51 PST

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Date

INVESTIGATOR'S SIGNATURE PAGE

By signing below, the Investigator agrees to adhere to the protocol as written and agrees that any changes to the protocol must be approved by MEI Pharma, Inc. before seeking approval from the Institutional Review Board (IRB)/Ethics Committee (IEC).

The study will be conducted in accordance with the current International Council for Harmonisation (ICH) Guidelines, the Guidelines for GCP, and local ethical and regulatory requirements.

The information contained in this protocol is proprietary and provided to me in confidence, and may not be disclosed to any other party, in any form, without prior authorization from MEI Pharma, Inc., except to the extent necessary for the conduct of the study at this study site.

Principal Investigator:

Signature	Date
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PROTOCOL SYNOPSIS

Protocol Number: ME-344-003

Title of Study:
A Phase 1b Study of the OxPhos Inhibitor ME-344 Combined with Bevacizumab in Previously Treated Metastatic Colorectal Cancer

Name of Investigational Product: ME-344
Other Co-administered drug: Bevacizumab

Study Center(s): Approximately 8 sites in the United States

Principal Investigator: Patrick M. Boland, MD

Study Population: Adults with previously treated metastatic colorectal cancer (mCRC) who have progressed on, or are intolerant to, standard chemotherapy drugs including fluoropyrimidine, oxaliplatin, irinotecan, and cetuximab/panitumumab (if clinically indicated)

Studied Period (years): 2 years	**Phase of development:**
Estimated date first subject enrolled: March 2023 Estimated date last subject completed: February 2025	Phase 1b

Study Duration: Approximately 24 months

Objectives	**Endpoints**
Primary	
• To estimate progression-free survival (PFS) at 16 weeks of treatment in subjects with mCRC administered ME-344 in combination with bevacizumab	• PFS rate at 16 weeks
Secondary	
• To evaluate the preliminary efficacy of ME-344 administered in combination with bevacizumab in subjects with mCRC	• PFS • Overall or Objective response rate (ORR) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 • Duration of Response (DOR) • Overall survival (OS)
• To determine the safety and tolerability of ME-344 administered in combination with bevacizumab	• Incidence and severity of treatment-emergent adverse events (TEAEs) and their relationship to study drug; change from baseline in physical examinations, vital signs, 12-lead electrocardiograms (ECGs), and clinical laboratory evaluations
• To evaluate the pharmacokinetics (PK)of ME-344 administered in combination with bevacizumab	• Maximum observed concentration (C_{max}), last observed quantifiable concentration (C_{last}), area under the concentration-time curve from time zero to time of last measurable concentration (AUC_{last})
Exploratory	
• To evaluate correlatives of mitochondrial metabolism	• Determine changes in isoleucine/leucine, tricarboxylic acid (TCA) cycle intermediates, short chain acyl carnitine, and nucleotide and TCA cycle intermediates

Study Design:

This is a Phase 1b open-label, multiple dose/schedule sequential study to determine the safety and efficacy of the oxidative phosphorylation (OxPhos) inhibitor ME-344 in combination with bevacizumab in subjects with recurrent mCRC.

This study will enroll subjects who have progressed or demonstrated intolerability to standard approved therapies which include fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, and cetuximab/panitumumab, programmed cell death protein 1(PD-1) inhibitors, or BRAF (v-raf murine sarcoma viral oncogene homolog B1) inhibitors (if clinically indicated) in the metastatic setting. Approximately 40 subjects will be enrolled in the study, in 2 cohorts of 20 subjects each.

This study consists of 3 periods: (i) screening, (ii) treatment, and (iii) follow-up. During screening, each potential subject will provide informed consent prior to starting any study-specific procedures. Screening assessments will be completed within 28 days prior to administration of ME-344 combined with bevacizumab.

During the treatment period, subjects enrolled in Cohort 1 will receive ME-344 at a dose of 10 mg/kg intravenously (IV) on Days 1, 8, and 15 in combination with bevacizumab at a dose of 5 mg/kg IV administered on Days 1 and 15 of each 28-day cycle.

Cohort 2 will initiate enrollment after at least 4 subjects in Cohort 1 have completed 4 cycles of therapy without evidence of disease progression (i.e., have achieved stable disease (SD) or a response), thus establishing a lack of progression in at least 4 [20%] subjects over the first 16 weeks of therapy. Subjects in Cohort 2 will receive ME-344 at a dose of 10 mg/kg IV on Days 1 and 15 combined with bevacizumab at a dose of 5 mg/kg IV administered on Days 1 and 15 of each 28-day cycle. If Cohort 1 does not meet the criteria for initiation of Cohort 2, the Safety Review Committee will determine whether or not to keep active subjects on study treatment or to close the study due to lack of efficacy.

Follow-up includes the End of Treatment (EOT) visit and survival follow-up. After patients have discontinued treatment for any reason, they will be followed every 3 months, or more frequently as needed, until withdrawal of consent, the patient is lost to follow-up, death, or defined end of study. If patients withdraw consent, they will be asked if they are willing to be contacted via telephone for survival status. If the patient refuses to be contacted, attempts to determine survival status should be made via access to public records, where permitted by local laws.

All radiographic tumor assessments, preferably computed tomography (CT), or alternatively magnetic resonance imaging (MRI), will be carried out in accordance with RECIST v1.1, and are to be performed every 8 weeks (±7 days) relative to first dose of study drug for the first 6 months, then every 3 months until 1 year, and every 4 months thereafter. Tumor assessments will be repeated until progressive disease (PD), or as per standard practice post-progression.

There is no maximum duration of treatment for this study; subjects will discontinue study drug once there is disease progression, unacceptable AEs (adverse events), withdrawal of consent, start of new anticancer therapy, or death.

Safety will be assessed via TEAEs, physical examinations, vital signs, 12-lead ECGs, and clinical laboratory evaluations (hematology, serum chemistry, coagulation [at screening for all subjects and Day 1 of every cycle for subjects on anticoagulation therapy], urinalysis). Severity grading of TEAEs will use the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0.

Blood samples for PK analysis will be collected during Cycle 1 on Days 1 and 15 pre-dose, 5 minutes after the end of infusion, and 1, 2, 3, 6, and 24 hours after the completion of the infusion.

The metabolomic correlative study will be performed on samples obtained from subjects enrolled at Rutgers Cancer Institute of New Jersey who consent to the metabolomic sample collection and analysis portion of this study. Plasma samples will be collected at timepoints specified in the Schedule of Assessments (Appendix 1). Samples will be stored at -70°C until analyzed. Specific markers of the mitochondrial oxidative phosphorylation pathway will be analyzed based on the outcomes from the planned nonclinical studies at the site.

See the Schedule of Assessments (Appendix 1) for a detailed list of study procedures and timing.

Number of Subjects (planned):

Approximately 40 subjects will be enrolled in 2 cohorts of 20 subjects each.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

Subjects must meet ALL the following inclusion criteria to qualify for the study:

1. Provide written informed consent to participate.
2. Male or female subjects ≥18 years of age.
3. Histological or cytological documentation of adenocarcinoma of the colon or rectum that is metastatic (all other histological types are excluded).
4. Measurable disease following RECIST v1.1.
5. Subjects who progressed or demonstrated intolerability to prior standard approved therapies which include fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, and cetuximab/panitumumab (if clinically indicated e.g., RAS wild-type tumors) in the advanced or metastatic setting.
6. Subjects with microsatellite instability-high/deficient mismatch repair (MSI-H/dMMR) CRC should have failed or demonstrated intolerance to prior programmed death receptor-1 (PD 1)-blocking antibody.
7. Subjects with BRAF V600E mutation should have failed or demonstrated intolerance to BRAF-targeted therapy.
8. Previous treatment with any investigational drug or anticancer treatment must be completed >28 days or 5 half-lives, whichever is longer, before the first dose of study treatment.
9. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1 (within 14 days prior to the initiation of study treatment).
10. Adequate bone marrow, liver, and renal function as assessed by the following laboratory requirements (within 7 days before Day 1):
    a. Total bilirubin ≤1.5 × the upper limit of normal (ULN).
    b. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 × ULN (5 × ULN for subjects with liver metastases).
    c. Creatinine clearance (CrCL) ≥60 mL/min as calculated using the Cockcroft-Gault equation (Appendix 2)
    d. Hemoglobin ≥8.0 g/dL.
    e. Platelet count >100,000/mm^3, absolute neutrophil count (ANC) >1500/$mm.^3$
    f. International normalized ratio (INR)/prothrombin time (PT) 1.5 × ULN (subjects who are therapeutically treated with an agent such as warfarin or heparin will be allowed to participate provided that no prior evidence of underlying abnormality in coagulation parameters exists.
    g. Urine protein <2+. Subjects discovered to have ≥2+ proteinuria on dipstick urinalysis at baseline will undergo a 24-hour urine collection and must demonstrate <2.0 g of protein in 24 hours.
11. QT-interval corrected according to Fridericia's formula (QTcF) ≤470 milliseconds (msec).
12. Women of childbearing potential and men must agree to use adequate contraception before entering the program until at least 8 weeks after the last study drug (ME-344) administration and for at least 6 months after the last dose of bevacizumab. The Investigator or designee is to advise the subject on how to achieve adequate contraception. Adequate contraception is defined in the study as any medically recommended method (or combination of methods) as per standard of care. Women of childbearing potential must have a blood or urine pregnancy test performed a maximum of 7 days before start of study treatment, and a negative result must be documented before start of study treatment. Women are considered not of childbearing potential if they have been without menses for 1 year and have follicle-stimulating hormone (FSH) levels considered to be post-menopausal.

Exclusion Criteria

Subjects must NOT meet any of the following exclusion criteria to qualify for the study:

1. Untreated brain metastases, spinal cord compression, or primary brain tumor.
2. Symptomatic brain metastases, leptomeningeal disease, spinal cord compression, or primary brain tumor. Notes: Patients previously treated or untreated for this condition who are asymptomatic in the absence of corticosteroid and anti-epileptic therapy are allowed. Brain metastases must be stable for ≥4 weeks, with imaging (e.g., MRI or CT) demonstrating no current evidence of progressive brain metastases at screening.
3. History of central nervous system (CNS) disease (excluding asymptomatic lacunar infarction) except cerebrovascular accident (CVA) >6 months with preserved performance status.
4. History of pulmonary hemorrhage/hemoptysis Grade ≥2 (defined as bright red blood of at least 2.5 mL) within 1 month prior to enrollment.
5. Evidence of uncontrolled or unstable cardiovascular disease, myocardial infarction (within 6 months), unstable angina pectoris, New York Heart Association (NYHA) classification ≥ Grade II congestive heart failure, serious arrhythmias requiring drug therapy, history of congenital long QT syndrome, congenital short QT syndrome, Torsades de Pointes, or Wolff-Parkinson-White syndrome.
6. Bevacizumab or aflibercept therapy ≤3 weeks prior to starting study treatment.
7. Peripheral neuropathy Grade ≥2.
8. Any of the following comorbidities:
    a. Uncontrolled hypertension (systolic blood pressure >150 mmHg or diastolic blood pressure >90 mmHg) despite best medical management.
    b. Uncontrolled diabetes mellitus (with HbA1c >8.5% at Screening).
    c. Active peptic ulcer.
    d. Unhealed wound (except for suturing associated with implanted port placement)
    e. Other clinically significant diseases (such as interstitial pneumonia or renal impairment)
    f. Systemic infection requiring treatment.
9. Other severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or that may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient an inappropriate candidate for the study.
10. Major surgical procedure within 28 days prior to study treatment initiation (such as open chest, thoracoscopic surgery, laparoscopic surgery), unless only colostomy is performed; open biopsy or suturing for major trauma within 14 days of study treatment initiation; or planned major surgical procedure (open chest, laparoscopy) during the study ("major surgical procedures" does not include central venous port insertion).
11. Pregnant, breastfeeding, positive pregnancy test, or women who are unwilling to use contraception; men who are unwilling to use contraception during the study.
12. Known seropositive for, or active infection with hepatitis B virus:
    - Hepatitis B surface antigen (HBsAg) positive.
    - HBsAg negative, anti-HBs positive and/or anti-HBc positive and detectable viral DNA by PCR

    Note: Subjects who are HBsAg positive and viral DNA PCR negative are eligible. These subjects should receive prophylactic therapy for hepatitis as per institutional standards.
13. Known seropositive for, or active infection with hepatitis C virus:
    - Subjects with positive hepatitis C virus (HCV) antibodies are eligible with negative PCR test for HCV.
14. Active and uncontrolled infection with human immunodeficiency virus (HIV), or with acquired immunodeficiency syndrome (AIDS), or currently taking medications for HIV that are contraindicated for concomitant use in this study.

15. Symptomatic or uncontrolled infection with human T-cell leukemia virus type 1.
16. History of other primary malignancy in the past 5 years or concurrent active malignancies (synchronous malignancies, requiring treatment; excluding malignancies that are expected to be completely cured, such as intramucosal carcinoma and carcinoma in situ, curatively treated cervical cancer in situ, non-melanoma skin cancer, superficial bladder tumors [Ta (non-invasive tumor), Tis (carcinoma in situ), and T1 (tumor invades lamina propria)], and asymptomatic localized prostate cancer with no requirement for systemic therapy or requiring only hormonal therapy and with normal prostate-specific antigen values within ≥12 months prior to enrollment). Breast cancer survivors on hormone therapy may be eligible if blood count is adequate and history of remission is >5 years ago.
17. Venous thromboembolism (unless appropriately treated and stable on anticoagulant for at least 2 weeks).
18. Arterial thrombosis or arterial thromboembolism such as myocardial infarction, transient ischemic attack, or cerebrovascular attack in the last 6 months prior to enrollment.
19. Subjects who discontinued prior treatment with bevacizumab, ziv-aflibercept, and/or ramucirumab because of severe events of hemorrhages, hypertension, fistula, perforation, arterial/venous thromboembolism, posterior reversible encephalopathy syndrome (PRES), renal injury, or proteinuria.
20. Concomitant use of strong inhibitors and strong inducers of cytochrome P450 (CYP) enzymes and transporters.

Investigational Product, Dosage, and Mode of Administration:

ME-344 will be suspended in 250 mL sterile saline and will be infused IV over 30 minutes.

Cohort 1: 10 mg/kg on Days 1, 8, and 15 of each 28-day cycle.

Cohort 2: 10 mg/kg on Days 1 and 15 of each 28-day cycle.

Co-administered Therapy, Dosage, and Mode of Administration:

Bevacizumab (Avastin®) or any U.S. approved biosimilar of bevacizumab) will be administered IV at a dose of 5 mg/kg on Days 1 and 15 of each 28-day cycle in Cohorts 1 and 2. Infusion will be based on the product's US Prescribing Information (Avastin [US Prescribing Information] September 2022 or biosimilar).

Duration of Treatment:

Subjects will continue treatment with ME-344 and bevacizumab until radiological progressive disease, based on RECIST v1.1 criteria or symptomatic deterioration per the Investigator. If the disease progresses in a subject, both drugs will be stopped. Other reasons for a subject to discontinue therapy include unacceptable toxicity, withdrawal of consent, start of new anticancer therapy, or death. Safety follow-up will conclude at the EOT visit of the study. After subjects have discontinued treatment for any reason, they will be followed every 3 months, or more frequently as needed, until withdrawal of consent, the patient is lost to follow-up, death, or defined end of study. If patients withdraw consent, they will be asked if they are willing to be contacted via telephone for survival status. If the subject refuses to be contacted, attempts to determine survival status should be made via access to public records, where permitted by local laws.

Statistical Methods:

Sample Size Justification

With a sample size of 20 subjects in each cohort, assuming the true PFS rate at 16 weeks is 30%, there is 89% chance to observe PFS rate ≥20% (i.e., ≥4 of 20 subjects progression-free).

Analysis Populations

The Intent-to-Treat (ITT) Population is defined as all enrolled subjects who receive at least one dose of ME-344.

The Efficacy Evaluable (EE) Population includes all subjects who receive at least one dose of ME-344 and have adequate Week 16 efficacy assessments or develop progression of disease (or died) prior to Week 16. The EE Population will be used as the primary analysis population for assessing response to the study drugs.

The PK Population includes all subjects who receive at least one dose of ME-344 and have at least one evaluable post-baseline ME-344 PK concentration. PK analysis will be conducted using the PK Population.

The Safety Population includes all subjects who receive at least one dose of ME-344. Safety analyses will be performed on the Safety Population.

Statistical Analysis

The primary efficacy endpoint (PFS rate at Week 16) will be evaluated using the Kaplan-Meier (KM) method when the last subject in Cohort 1 completes the efficacy assessment at Week 16 (or discontinues, develops disease progression, or dies, whichever occurs earlier). The KM estimates for median, first and third quartiles (Q1 and Q3, respectively), and the PFS rate at Week 16 will be presented.

The OS will be analyzed using the KM method.

The secondary efficacy endpoints ORR will be summarized by the number and percentage of subjects achieving ORR. The 2-sided exact 95% confidence interval (CI) based on the Clopper-Pearson method will be provided.

Safety will be assessed through the analysis of the reported incidence, severity, and relationship of TEAEs, including serious adverse events (SAEs), adverse events of special interest, AEs leading to withdrawal of study drug, and AEs related to study treatment. Change from baseline in physical examinations, vital signs, 12-lead ECGs, and clinical laboratory evaluations will be summarized.

Information regarding study drug administration, study drug compliance, and other safety variables will also be summarized or listed. Extent of exposure to study drug will be generated from the study drug administration data. Exposure data will be summarized by cohort.

All analyses will be conducted by cohort. Pooled summaries (Cohort 1 + Cohort 2) may be conducted if deemed meaningful. Subgroup analysis by baseline demographic or disease characteristics may be conducted.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC_{last}	area under the concentration-time curve from time zero to time of last measurable concentration
BRAF	B-Raf murine sarcoma viral oncogene homolog B
BUN	blood urea nitrogen
CI	confidence interval
CL	Clearance
C_{last}	last observed quantifiable concentration
C_{max}	maximum observed concentration
CNS	central nervous system
CR	complete response
CrCL	creatinine clearance
CRF	case report form
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte-associated antigen-4
CVA	cerebrovascular accident
CYP	cytochrome P450
dMMR	deficient mismatch repair
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EE	Efficacy Evaluable
EGFR	epidermal growth factor receptor

Abbreviation	Definition
EOT	End of Treatment
FOLFIRI	fluorouracil with leucovorin and irinotecan
FOLFOX	fluorouracil with leucovorin and oxaliplatin
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
hERG	human ether-à-go-go-related gene
HIV	human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	intravenous(ly)
KM	Kaplan-Meier
LDH	lactate dehydrogenase
MCH	mean corpuscular hemoglobin
mCRC	metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MSI-H	microsatellite instability-high
MSS	microsatellite stable
MTD	maximum tolerated dose
mAbs	monoclonal antibodies
mTOR	mammalian target of rapamycin
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
NYHA	New York Heart Association
ORR	Overall or Objective Response rate
OS	overall survival
OxPhos	oxidative phosphorylation

Abbreviation	Definition
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death protein 1
PFS	progression-free survival
PK	pharmacokinetic(s)
P-gp	P-glycoprotein
pMMR	mismatch repair proficient
PO	oral(ly)
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PT	prothrombin time
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
ROS	reactive oxygen species
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCLC	small cell lung cancer
SD	stable disease
SRC	Safety Review Committee
STD_{10}	severely toxic dose
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	apparent terminal elimination half-life
T_1	tumor invades lamina propria
T_a	non-invasive tumor
T_{is}	carcinoma in situ
TCA	tricarboxylic acid
TEAE	treatment-emergent adverse event
TG-1	transglutaminase-1
T^{max}	time to maximum observed concentration
ULN	upper limit of normal
US	United States
V_{dss}	volume of distribution at steady state
VEGF	vascular endothelial growth factor
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

1.1. Disease Background

Colorectal cancer is one of the most common tumors, and approximately 20–25% of patients are diagnosed in advanced Stage IV disease (Aran 2016). Colorectal cancer patients with unresectable metastases have a limited median survival of around 5 months if only treated with best supportive care (Wang 2016). Significant improvements have been made in the treatment of metastatic colorectal cancer (mCRC), particularly in the first- and second-line setting; however, it is inevitable that these patients eventually progress. Although these patients may still have good performance status after second-line therapy, third-line treatment options are limited. In the third- and later-line setting, regorafenib and trifluridine/tipiracil are available for patients with mCRC (Grothey 2013, Benson 2021). However, the PFS in the third-line setting remains at <3 months with a median OS around 8–9 months. There is, therefore, an unmet clinical need for treatment options in the third line setting for mCRC.

The rationale of continuing to target the vascular endothelial growth factor (VEGF) pathway in mCRC was confirmed when third-line monotherapy with the VEGF receptor inhibitor regorafenib improved survival in the CORRECT (Grothey 2013) and CONCUR (Li 2015) study populations. However, the efficacy of regorafenib is limited and its adverse effects, particularly fatigue and palmar-plantar erythrodysesthesia can pose management difficulties and worsen quality of life (Grothey 2013).

Tumors treated with antiangiogenic therapy can correct hypoxia and downregulate aerobic glycolysis. Tumors eventually adapt and show metabolic plasticity, switching to mitochondrial metabolism, which is mediated by adenosine monophosphate-activated protein kinase (AMPK), protein kinase A (PKA), and peroxisome proliferator-activated receptor alpha (PPARα). Because of this adaptation, mitochondrial metabolism becomes essential for tumor survival. Thus, antimitochondrial agents induce metabolic synthetic lethality in this situation (Navarro 2016).

1.2. Current Therapeutic Options

Chemotherapy: In early-stage CRC, the standard treatment includes tumor resection and adjuvant chemotherapy. In metastatic disease, the standard treatment includes various lines of chemotherapy combined with targeted therapies or immunotherapies according to tumor subtype and gene mutations identified (Benson 2021).

Three main classes of chemotherapeutic agents, fluoropyrimidine, irinotecan, and oxaliplatin, are used to treat mCRC. Fluorouracil with leucovorin and oxaliplatin (FOLFOX) and fluorouracil with leucovorin and irinotecan (FOLFIRI) are most used as the first-line treatment for patients with unresectable mCRC (Aparicio 2020). However, these treatments appear to be largely ineffective for late-stage colon cancer.

Targeted therapy: Options for patients with mCRC include agents targeting either VEGF or the epidermal growth factor receptor (EGFR) (Benson 2021, Ciardiello 2019). Specifically, bevacizumab, a humanized monoclonal antibody that inhibits VEGF, combined with fluoropyrimidine-based chemotherapy, is approved as first- and second-line treatment for patients with mCRC (Benson 2021, Ciardiello 2019). Several therapy options are available for treating patients with *RAS* wild type mCRC. The best sequence for first-to-second-line therapy is

cetuximab-based therapy, followed by a bevacizumab-based regimen (Wu 2021). Cetuximab (chimeric monoclonal antibody targeting EGFR) is used as a single agent in mCRC patients expressing EGFR who failed both irinotecan- and oxaliplatin-containing regimens or in patients who are intolerant to irinotecan-based regimens; a combination of cetuximab with irinotecan is used in patients who are refractory to irinotecan-based chemotherapy (Benson 2021, Ciardiello 2019). Panitumumab (humanized monoclonal antibody against EGFR) is approved as monotherapy for treating mCRC with disease progression after prior treatment with various chemotherapeutic agents (Benson 2021, Ciardiello 2019). However, anti-EGFR agents such as cetuximab or panitumumab are ineffective in mCRC patients with *RAS* and *RAF* (specifically *BRAF* V600E) gene mutations, as EGF receptor inhibition is unattainable because of constitutive oncogenic signaling (Benvenuti 2007, Benson 2021, Ciardiello 2019). Thus, systemic treatment options in patients with RAS mutations currently include chemotherapy with or without angiogenic agents such as bevacizumab in first-line, bevacizumab or aflibercept or ramucirumab in the second-line, followed by later-line treatment such as trifluridine/tipiracil and regorafenib (Patelli 2021, Van Cutsem 2019).

BRAF Mutation: Several therapeutic options are available for patients with BRAF-mutated mCRC, including treatment with BRAF inhibitor such as encorafenib in combination with cetuximab (Tabernero 2016, van Geel 2017, Quintela-Fandino 2020, Mauri 2021, Wu 2021).

Immunotherapy: The development of immune checkpoint inhibitors, such as anti-cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) monoclonal antibodies (mAbs) (ipilimumab, tremelimumab), anti-PD-1 mAbs (nivolumab, pembrolizumab), has dramatically changed the therapeutic scenario for mCRC with high microsatellite instability (MSI-H). For most patients with MSI-H/dMMR, the first-line treatment options include combination chemotherapy plus targeted therapy, as well as immunotherapy, whether it be PD-1 monotherapy or a combination with ipilimumab (Benson 2021). For patients with MSI-H/dMMR tumors who progress or recur after chemotherapy, pembrolizumab or nivolumab with or without low-dose ipilimumab represents a preferred second-line treatment option (Keytruda® USPI 2017, Golshani 2020). Whereas in dMMR or MSI-H mCRC, there is clear clinical evidence for a therapeutic role of immune checkpoint inhibitors, the majority of mCRC patients with mismatch repair proficient (pMMR) or microsatellite stable (MSS) tumors do not benefit from immunotherapy.

1.3. ME-344

ME-344 is a synthetic small molecule mitochondrial inhibitor based on the isoflavone ring structure. Specifically, it directly targets the OxPhos complex 1, a pathway involved in the production of adenosine triphosphate in the mitochondria. Preliminary screening studies have identified ME-344 as a candidate for development as an anticancer product, given its broad antiproliferative activity against a panel of human cancer cells representative of most major organ systems.

ME-344 was derived from a parental compound, genistein, and has been shown to disrupt signal transduction upstream and downstream of the mammalian target of rapamycin (mTOR) 1 and mTOR2.

1.3.1. Nonclinical Studies

In vitro studies in a range of cancer cell lines showed that ME-344 disrupts the mitochondrial oxidative phosphorylation via the electron transport chain thereby causing energy starvation. Two forms of ME-344 induced cell death have been identified as a result of energy starvation; caspase-independent autophagy and apoptotic cell death induced by a *BAX*-mediated loss of mitochondrial membrane potential.

Further investigation into the mechanism of antitumor activity of ME-344 was performed in sensitive and resistant lung cancer cell lines. In sensitive cell lines the drug-induced cell death was associated with increased levels of reactive oxygen species (ROS) that resulted in downstream interference with tumor cell redox homeostasis and mitochondrial function leading to tumor cell death.

In human xenograft models including sensitive NCI-H460 large cell lung cancer cells, ME-344 exhibited notable activity against tumor growth.

Further inhibition of tumor growth and cancer cell proliferation was demonstrated in an *in vivo* polyoma middle T-antigen driven murine model. ME-344, when used in combination with antiangiogenic protein tyrosine kinase inhibitors (TKI), nintedanib or regorafenib, demonstrated significant increase in tumor growth inhibition (TGI) index while single agent activity was limited. The anti-tumor efficacy of ME-344 and regorafenib, a multi-kinase inhibitor, was tested in a CT26 murine colon carcinoma xenograft model. Both drugs resulted in tumor growth delay as single agents; however, there was enhanced anti-tumor efficacy with the combination. All treatments were well tolerated with no deaths or mean body weight losses on study. The PK of IV administered ME-344 were assessed in conjunction with rat and dog repeat-dose toxicology studies. ME-344 plasma concentration profiles displayed rapid maximum concentrations followed by rapid elimination with no marked differences between sexes. The time to maximum observed concentration (T_{max}) was 0.167 hours, the first sampling point post-dose. The apparent terminal elimination half-life ($t_{½}$) in rats ranged from 0.32 to 2.25 hours depending on dose (higher dose levels generally corresponded with increasing $t_{½}$). In the dog, $t_{½}$ was less than 1 hour. Systemic exposure, as assessed by C_{max} and area under the concentration-time curve from time zero to time of AUC_{last}, was approximately dose proportional (doses ranging from 35 to 140 mg/kg).

Safety pharmacology in vitro testing with ME-344 on cloned human ether-à-go-go-related gene (hERG) potassium channels expressed in human embryonic kidney cells resulted in a half-maximal inhibitory concentration (IC_{50}) of 18.0 µM for the inhibitory effect of ME-344 on hERG potassium current. There were no changes in ECGs observed in dogs administered up to 140 mg/kg ME-344 weekly for three weeks, which resulted in group plasma C_{max} >870 µM. Furthermore, there were no microscopic findings of myocardial inflammation in male or female dogs.

The no observed adverse effect level (NOAEL) for ME-344 when administered once weekly for three weeks in female rats and dogs was 35 mg/kg and 140 mg/kg, respectively. The NOAEL in male rats and dogs was <35 mg/kg and 140 mg/kg, respectively. Treatment-related effects in both species included transient decreases in food consumption and body weight gain seen amongst animals that received 140 mg/kg. The only other potentially treatment-related effect in dogs was reduced testes organ weights in males at 140 mg/kg.

The rat was deemed the more sensitive species to ME-344 toxicities. In addition to the observations in dogs, studies in rats show decreased erythroid parameters and slightly increased leukograms, primarily at 140 mg/kg. Microscopic findings were present in the epididymides/ testes (degeneration of spermatozoa), spleen (hematopoiesis), and heart. The cardiovascular findings were mild, patchy, dose-dependent myocardial inflammatory cell infiltrates, which were not associated with any biochemical or clinical sequelae. Similar cardiovascular events were not observed in either male or female dogs. Finally, the death of one male rat, three days after receiving the first 140 mg/kg dose could potentially be attributable to ME-344 administration. As such, the 140 mg/kg dose in rats was considered the severely toxic dose in 10% of the animals (STD_{10}).

1.3.2. Clinical Studies

A Phase 1 clinical study (ME-344-001) enrolled 30 subjects with refractory solid tumors and no standard therapeutic alternatives in dose cohorts of ME-344 between 1.25 and 20 mg/kg IV weekly.

Results indicated that weekly infusions of ME-344 were generally well tolerated up to 10 mg/kg. The primary dose limiting toxicity (DLT) was peripheral neuropathy, which was observed at the 15 mg/kg and 20 mg/kg weekly dosing schedules and was generally reversible following discontinuation of study drug and appeared to be more frequent with rapid ME-344 infusion rate and in patients with pre-existing neuropathy. Other TEAEs reported for $\geq$10% of subjects (serious and non-serious) were nausea, dizziness, fatigue, vomiting, diarrhea, and asthenia. No significant effects on QTc interval, cardiac function (as assessed by echocardiography), or cardiac injury (as assessed by CK-MB and troponin) were observed. A maximum tolerated dose (MTD) of 10 mg/kg was established.

The PK analyses showed that ME-344 plasma concentrations declined in a multi-exponential fashion with a mean $t_{½}$ of approximately 6 hours. There was a linear relationship between dose and both Day 1 C_{max} levels and exposure (AUC), with good correlation between Day 1 and Day 15 results. ME-344 values for volume of distribution at steady state (V_{dss}), $t_{½}$, and clearance (CL) appeared to be dose-independent. Additionally, there were no statistical differences for CL and V_{dss} between Day 1 and Day 15.

The efficacy analyses revealed some evidence of clinical activity. Of the 30 subjects, one with small cell lung cancer (SCLC) treated at the 5 mg/kg dose level achieved a durable partial remission. In addition, 10 (33.3%) patients experienced SD, 4 of which were prolonged (41 to 89 weeks).

A Phase 1b study (ME-344-002) was conducted to evaluate the safety and tolerability of 10 mg/kg ME-344 (Days 1, 8, 15, and 22) given in combination with 4 mg/m^2 topotecan (Days 1, 8, and 15) in subjects with solid tumors. The study enrolled 46 cancer patients: 28 ovarian, 13 lung, and 5 cervical. AEs reported for >20% of subjects were predominantly gastrointestinal disorders: nausea [48%], diarrhea [46%], vomiting [39%], and constipation, [33%]); other frequently reported AEs were fatigue (65%), neutropenia (46%), hypertension (41%), decreased appetite (41%), thrombocytopenia (39%), and anemia (35%). Of the 17 subjects experiencing SAEs, only 1 had an event (diarrhea) that was considered related to ME-344 administration. Of the 6 deaths on study (i.e., during the study and within 30 days of last treatment administration) that were reported, 5 (11%) were attributed to the underlying disease,

and 1 (2%) was due to an AE (neutropenic sepsis). Peripheral neuropathy, including sensory neuropathy, has been reported in prior clinical studies of ME-344 as a single agent or in combination with topotecan.

The overall response rate (complete remission + partial remission) was 2.4% for the Efficacy Population (consisting of patients with evaluable or measurable disease at baseline who completed at least 1 cycle of treatment and either underwent at least one follow-up tumor evaluation or discontinued treatment prior to the first tumor evaluation due to clinical progression). Due to this response rate, the DOR was not applicable. In the Safety Population (all patients who received at least one dose of ME-344), median PFS was 3.0 months, and median time for OS was 3.3 months.

A placebo-controlled window of opportunity study (CNIO-BR-009) (Quintela-Fandino 2020) evaluated the pharmacodynamics of 10 mg/kg ME-344 for one cycle on Days 8, 15, and 21 of a 28-day cycle in combination with the antiangiogenic antibody bevacizumab in 41 patients with HER2-negative breast cancer. The study demonstrated a biologic activity of ME-344 as documented by a decrease in Ki67, a marker of cell proliferation, and no new safety signals were identified. The combination treatment was tolerable, with most of the AEs being Grade 1 in severity. The Grade 1 AEs were diarrhea and asthenia (25% each), and headache and nausea (15% each). Grade 2 AEs included headache (15%). There were 2 cases of Grade 3 hypertension; however, 1 of the subjects had prior Grade 3 hypertension at enrollment, which continued despite use of two antihypertensive drugs.

Additional information regarding nonclinical and clinical experience with ME-344 may be found in the Investigator's Brochure.

1.4. Study Rationale

It is hypothesized that in cases where antiangiogenics such as bevacizumab led to vascular normalization and resultant tumor tissue hypoxia, chronic high-rate glycolysis is offset, with the potential for tumors to switch to an alternative metabolic source, primarily mitochondrial energy. If this source is essential for tumor survival, it would open a therapeutic opportunity for mitochondrial inhibitors such as ME-344 to induce metabolic synthetic lethality, resulting in tumor suppression and thereby prolonging PFS. This study will assess tumor response in subjects treated concurrently with bevacizumab and ME-344.

Two schedules will be explored in this study, 10 mg/kg weekly for 3 weeks followed by a week of rest (Cohort 1) and 10 mg/kg every 2 weeks (Cohort 2), both schedules administered in 28-day cycles. In a prior Phase 1 study, the MTD was defined as 10 mg/kg weekly, which will be used in Cohort 1. The second dose regimen, 10 mg/kg every 2 weeks, will be used for Cohort 2, allowing for a more convenient bi-weekly dosing compatible with the majority of current treatment regimens for metastatic colorectal cancer.

2. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To estimate PFS at 16 weeks of treatment in subjects with mCRC administered ME-344 in combination with bevacizumab	• PFS rate at 16 weeks
Secondary	
• To evaluate the preliminary efficacy of ME-344 administered in combination with bevacizumab in subjects with mCRC	• PFS • ORR using RECIST v1.1 • DOR • OS
• To determine the safety and tolerability of ME-344 administered in combination with bevacizumab	• Incidence and severity of TEAEs and their relationship to study drug; change from baseline in physical examinations, vital signs, 12-lead ECGs, and clinical laboratory evaluations
• To evaluate the PK of ME-344 administered in combination with bevacizumab	• Maximum observed concentration (C_{max}), last observed quantifiable concentration (C_{last}), area under the concentration-time curve from time zero to time of AUC_{last}
Exploratory	
• To evaluate correlatives of mitochondrial metabolism	• Determine changes in isoleucine/leucine, TCA cycle intermediates, short chain acyl carnitine, and nucleotide and TCA cycle intermediates

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This is a Phase 1b open-label, multiple dose/schedule sequential study to determine the safety and efficacy of the OxPhos inhibitor ME-344 in combination with bevacizumab in subjects with recurrent mCRC.

This study will enroll subjects with metastatic CRC, including but not limited to subjects with RAS wild-type or mutant tumors, MSI-H/pMMR, and BRAF V600E, who have progressed or demonstrated intolerability to standard approved therapies which include fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, cetuximab/panitumumab, PD-1 inhibitors, or BRAF inhibitors (if clinically indicated), and/or checkpoint inhibitors. Approximately 40 subjects will be enrolled in the study, in 2 cohorts of 20 subjects each.

This study consists of three periods: (i) screening, (ii) treatment, and (iii) follow-up. During screening, each potential subject will provide informed consent prior to starting any study-specific procedures. Screening assessments will be completed within 28 days prior to administration of ME-344 combined with bevacizumab.

During the treatment period, subjects enrolled in Cohort 1 will receive ME-344 at a dose of 10 mg/kg IV on Days 1, 8, and 15 in combination with bevacizumab at a dose of 5 mg/kg IV administered on Days 1 and 15 of each 28-day cycle.

Cohort 2 will initiate enrollment after at least 4 subjects in Cohort 1 have completed 4 cycles of therapy without evidence of disease progression (i.e., have achieved SD or a response), thus establishing a lack of progression in at least 4 [20%] subjects over the first 16 weeks of therapy. Subjects in Cohort 2 will receive ME-344 at a dose of 10 mg/kg IV on Days 1 and 15 combined with bevacizumab at a dose of 5 mg/kg IV administered on Days 1 and 15 of each 28-day cycle. If Cohort 1 does not meet the criteria for initiation of Cohort 2, the Safety Review Committee (SRC) will determine whether or not to keep active subjects on study treatment or to close the study due to lack of efficacy.

There is no maximum duration of treatment for this study; subjects will discontinue study drug once there is disease progression, unacceptable adverse event(s) (AEs), withdrawal of consent, start of new anticancer therapy, or death.

Follow-up includes the EOT visit and survival follow-up. After patients have discontinued treatment for any reason, they will be followed every 3 months, or more frequently as needed, until withdrawal of consent, the patient is lost to follow-up, death, or defined end of study. If patients withdraw consent, they will be asked if they are willing to be contacted via telephone for survival status. If the patient refuses to be contacted, attempts to determine survival status should be made via access to public records, where permitted by the local laws.

All radiographic tumor assessments, preferably CT, or alternatively MRI, will be carried out in accordance with RECIST v1.1, and are to be performed every 8 weeks (±7 days) relative to first dose of study drug for the first 6 months, then every 3 months until 1 year, and every 4 months thereafter. Tumor assessments will be repeated until objective disease relapse, progression, or as per standard practice post-progression.

Safety will be assessed via TEAEs, physical examinations, vital signs, 12-lead ECGs, and clinical laboratory evaluations (hematology, serum chemistry, coagulation [at screening for all subjects and Day 1 of every cycle for subjects on anticoagulation therapy], urinalysis). Severity grading of TEAEs will use the NCI CTCAE v5.0.

Blood samples for PK analysis will be collected during Cycle 1 on Days 1 and 15 pre-dose, 5 minutes after the end of infusion, and 1, 2, 3, 6, and 24 hours after the completion of the infusion.

The metabolomic correlative study will be performed on samples obtained from subjects enrolled at Rutgers Cancer Institute of New Jersey who consent to the metabolomic sample collection and analysis portion of this study. Plasma samples will be collected at timepoints specified in the Schedule of Assessments (Appendix 1). Samples will be stored at -70°C until analyzed. Specific markers of the mitochondrial oxidative phosphorylation pathway will be analyzed based on the outcomes from the planned nonclinical studies at the site.

See the Schedule of Assessments (Appendix 1) for a detailed list of study procedures and timing.

Amendments 1 and 2 were not implemented.

3.2. Number of Subjects

Approximately 40 subjects will be enrolled in 2 cohorts of 20 subjects each.

3.3. Treatment Assignment

Enrollment will occur continuously into Cohort 1 until 20 subjects complete radiological assessments at 16 weeks or discontinue, progress, start new anticancer therapy, or die, whichever happens earlier.

Subjects enrolled in Cohort 1 will receive ME-344 at a dose of 10 mg/kg IV on Days 1, 8 and 15 in combination with bevacizumab at a dose of 5 mg/kg IV administered on Days 1 and 15 of each 28-day cycle.

If Cohort 1 demonstrates adequate safety, tolerability, and efficacy, Cohort 2 will open to continuous enrollment of 20 subjects.

Subjects enrolled in Cohort 2 will receive ME-344 at a dose of 10 mg/kg IV on Days 1 and 15 combined with bevacizumab at a dose of 5 mg/kg IV administered on Days 1 and 15 of each 28-day cycle.

Subjects who discontinue bevacizumab due to tolerability may continue treatment with the single agent ME-344 at the investigator's discretion, if in the investigator's opinion they benefit from single-agent treatment. Subjects with persistent proteinuria ≥2 g/24 hours must discontinue bevacizumab and ME-344. The results of the Phase I study demonstrated that ME-344 alone treatment displayed single agent activity leading to PR or SD responses in subjects with solid tumors.

3.4. Dose Adjustment Criteria

If toxicity occurs, the toxicity will be assessed utilizing the NCI CTCAE v5.0, and appropriate supportive care treatment will be administered to decrease the signs and symptoms thereof, in accordance with the toxicity management guidelines in Table 1.

No intra-patient dose escalation will be permitted.

Table 1: Toxicity Management

Adverse Reaction	Severity [a]	Drug Modification	
		Bevacizumab	ME-344
Hypertension	• Grade 3 or 4 • (Systolic BP ≥160 OR Diastolic BP ≥100)	• Hold bevacizumab until BP improves to <160/100 mmHg for one week with treatment; then resume at the same dose	• Hold ME-344 until BP improves to <160/100 mmHg; then resume at the same dose • For recurrence despite adequate use of antihypertensive medications, hold ME-344 and resume at 75% dose
	• Hypertensive crisis	• Discontinue bevacizumab	• Discontinue ME-344

Table 1: Toxicity Management (Continued)

Adverse Reaction	Severity [a]	Drug Modification	
		Bevacizumab	ME-344
	• Hypertensive encephalopathy		• Discontinue ME-344
PRES	• Any	• Discontinue bevacizumab	• Discontinue ME-344
Congestive Heart Failure	• Any	• Discontinue bevacizumab	• Discontinue ME-344
Infusion-related reaction (see additional guidance provided in Section 5.1.6)	• Severe	• If due to bevacizumab, discontinue bevacizumab	• If due to ME-344, discontinue ME-344
	• Clinically significant	• Interrupt infusion, resume at a decreased rate of infusion after symptoms resolve	• Interrupt infusion, resume at a decreased rate of infusion after symptoms resolve
	• Mild, clinically insignificant	• Decrease infusion rate	• Decrease infusion rate
Hemorrhage	• Grade 3 or 4	• Discontinue bevacizumab	• Discontinue ME-344
Renal Injury and Proteinuria	• Nephrotic syndrome; proteinuria ≥3.5 g/24 h	• Discontinue bevacizumab	• Discontinue ME-344
	• Proteinuria ≥2–3.5g/ 24 h	• Withhold bevacizumab until proteinuria <2 g/24h	• Withhold ME-344 until proteinuria <2 g/24h
Gastrointestinal Perforations and Fistulae	• Gastrointestinal perforation, any grade • Tracheoesophageal fistula, any grade • Fistula, Grade 4 • Fistula formation involving any internal organ	• Discontinue bevacizumab	• Discontinue ME-344
Wound Healing Complications	• Any	• Withhold bevacizumab until adequate wound healing	• Hold ME-344 and resume at the same dose once adequately healed
	• Necrotizing fasciitis	• Discontinue bevacizumab	• Discontinue ME-344

Table 1: Toxicity Management (Continued)

Adverse Reaction	Severity [a]	Drug Modification	
		Bevacizumab	ME-344
Neuropathy	• Grade 2	• Continue bevacizumab	• Hold ME-344 and resume at 50% dose once the AE has resolved to Grade 1
	• Grade 3-4	• Continue bevacizumab	• Discontinue ME-344
Hematologic Toxicity	• Grade 4	• Hold bevacizumab until resolution to Grade 1 or baseline; resume at the same dose	• Hold ME-344 until resolution to Grade 1 or baseline; resume at the same dose • For recurrence, hold ME-344 and resume at 50% dose
Other clinically significant nonhematologic toxicity	• Grade 3	• If related to bevacizumab; hold bevacizumab until resolution to Grade 1 or baseline; resume at the same dose	• Hold ME-344 until resolution to Grade 1 or baseline; resume at the same dose • For recurrence, hold ME-344 and resume at 50% dose
	• Grade 4	• If related to bevacizumab; hold bevacizumab until resolution to Grade 1 or baseline; resume at the same dose if considered safe by Investigator • For recurrence, discontinue bevacizumab	• Hold ME-344 until resolution to Grade 1 or baseline; resume at 50% dose
For dose modifications for other adverse reactions reported in subjects treated with bevacizumab refer to the Avastin USPI.			

Abbreviations: AE = adverse event; BP = blood pressure; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute; PRES = posterior reversible encephalopathy syndrome.

[a] Severity grading per NCI CTCAE v5.0.

3.4.1. Criteria for Withholding, Adjustment, or Discontinuing ME-344 Doses

Infusion reactions may develop with the first or any subsequent infusion of ME-344. Investigators and support staff should be alert to the signs and symptoms that are typically associated with infusions reactions. Standard medical intervention should be initiated based on the severity of symptoms and good clinical practice. Interventions may include H_1 specific antihistamines, glucocorticoids, epinephrine, bronchodilators, and general cardio-pulmonary support. Refer to Table 1 for guidance regarding infusion reaction management, and for additional guidance regarding holding or discontinuing the ME-344 dose.

3.4.2. Criteria for Withholding or Discontinuing Bevacizumab Doses

Refer to Table 1 and the bevacizumab US Prescribing Information (Avastin® [US Prescribing Information] September 2022 or biosimilar) for additional guidance on holding or discontinuing the bevacizumab dose. Except for persistent proteinuria >2+, if bevacizumab is discontinued due to intolerability the subject may continue treatment with ME-344 single agent per the investigator's discretion.

3.5. Criteria for Study Termination

Study termination is defined as the time when all study-specific assessments and data collection are completed. Upon termination of the study, the Sponsor or designee will conduct site closure activities with the Investigator or site staff (as appropriate), in accordance with applicable regulations.

The Sponsor reserves the right to temporarily suspend or terminate the study at any time for reasons including, but not limited to, safety issues or ethical reasons. The Sponsor or designee will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action, when applicable. Where required by applicable regulations, the Investigator or head of the medical institution must inform the IRB/Independent Ethics Committee (IEC).

4. SELECTION AND WITHDRAWAL OF SUBJECTS

4.1. Subject Inclusion Criteria

Subjects must meet ALL the following inclusion criteria to qualify for the study:

1. Provide written informed consent to participate.
2. Male or female subjects ≥18 years of age.
3. Histological or cytological documentation of adenocarcinoma of the colon or rectum that is metastatic (all other histological types are excluded).
4. Measurable disease following RECIST v1.1.
5. Subjects who progressed or demonstrated intolerability to prior standard approved therapies which include fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, and cetuximab/panitumumab (if clinically indicated e.g., RAS wild-type tumors) in the advanced or metastatic setting.
6. Subjects with MSI-H/dMMR CRC should have failed or demonstrated intolerance to prior programmed death receptor-1 (PD 1)-blocking antibody.
7. Subjects with BRAF V600E mutation should have failed or demonstrated intolerance to BRAF-targeted therapy.
8. Previous treatment with any investigational drug or anticancer treatment must be completed >28 days or 5 half-lives, whichever is longer, before the first dose of study treatment.

9. ECOG Performance Status score of 0 or 1 (within 14 days prior to the initiation of study treatment).
10. Adequate bone marrow, liver, and renal function as assessed by the following laboratory requirements (within 7 days before Day 1):
    a. Total bilirubin ≤1.5 × the ULN.
    b. ALT and AST ≤2.5 × ULN (5 × ULN for subjects with liver metastases).
    c. CrCL ≥60 mL/min as calculated using the Cockcroft-Gault equation (Appendix 2).
    d. Hemoglobin ≥8.0 g/dL.
    e. Platelet count >100,000/mm^3, ANC >1500/mm^3.
    f. INR/PT 1.5 × ULN (subjects who are therapeutically treated with an agent such as warfarin or heparin will be allowed to participate provided that no prior evidence of underlying abnormality in coagulation parameters exists.
    g. Urine protein <2+. Subjects discovered to have ≥2+ proteinuria on dipstick urinalysis at baseline will undergo a 24-hour urine collection and must demonstrate <2.0 g of protein in 24 hours.
11. QT-interval corrected according to Fridericia's formula (QTcF) ≤470 milliseconds (msec).
12. Women of childbearing potential and men must agree to use adequate contraception before entering the program until at least 8 weeks after the last study drug (ME-344) administration and for at least 6 months after the last dose of bevacizumab. The Investigator or designee is to advise the subject on how to achieve adequate contraception. Adequate contraception is defined in the study as any medically recommended method (or combination of methods) as per standard of care. Women of childbearing potential must have a blood or urine pregnancy test performed a maximum of 7 days before start of study treatment, and a negative result must be documented before start of study treatment. Women are considered not of childbearing potential if they have been without menses for 1 year and have follicle stimulating hormone (FSH) levels considered to be post-menopausal.

4.2. Subject Exclusion Criteria

Subjects must NOT meet any of the following exclusion criteria to qualify for the study:

1. Untreated brain metastases, spinal cord compression, or primary brain tumor.
2. Symptomatic brain metastases, leptomeningeal disease, spinal cord compression, or primary brain tumor. Notes: Patients previously treated or untreated for this condition who are asymptomatic in the absence of corticosteroid and anti-epileptic therapy are allowed. Brain metastases must be stable for ≥ 4 weeks, with imaging (e.g., MRI or CT) demonstrating no current evidence of progressive brain metastases at screening.
3. History of CNS disease (excluding asymptomatic lacunar infarction) except CVA >6 months with preserved performance status.

4. History of pulmonary hemorrhage/hemoptysis Grade ≥2 (defined as bright red blood of at least 2.5 mL) within 1 month prior to enrollment.
5. Evidence of uncontrolled or unstable cardiovascular disease, myocardial infarction (within 6 months), unstable angina pectoris, NYHA classification ≥ Grade II congestive heart failure, serious arrhythmias requiring drug therapy, history of congenital long QT syndrome, congenital short QT syndrome, Torsades de Pointes, or Wolff-Parkinson-White syndrome.
6. Bevacizumab or aflibercept therapy ≤ 3 weeks prior to starting study treatment
7. Peripheral neuropathy Grade ≥ 2
8. Any of the following comorbidities:
    a. Uncontrolled hypertension (systolic blood pressure >150 mmHg or diastolic blood pressure >90 mmHg) despite best medical management.
    b. Uncontrolled diabetes mellitus (with HbA1c >8.5% at Screening).
    c. Active peptic ulcer.
    d. Unhealed wound (except for suturing associated with implanted port placement).
    e. Other clinically significant disease (such as interstitial pneumonia or renal impairment).
    f. Systemic infection requiring treatment.
9. Other severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or that may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient an inappropriate candidate for the study.
10. Major surgical procedure within 28 days prior to study treatment initiation (such as open chest, thoracoscopic surgery, laparoscopic surgery), unless only colostomy is performed; open biopsy or suturing for major trauma within 14 days of study treatment initiation; or planned major surgical procedure (open chest, laparoscopy) during the study ("major surgical procedures" does not include central venous port insertion).
11. Pregnant, breastfeeding, positive pregnancy test, or women who are unwilling to use contraception; men who are unwilling to use contraception during the study.
12. Known seropositive for, or active infection with hepatitis B virus:
    - HBsAg positive.
    - HBsAg negative, anti-HBs positive and/or anti-HBc positive and detectable viral DNA by PCR.

Note: Subjects who are HBsAg positive and viral DNA PCR negative are eligible. These subjects should receive prophylactic therapy for hepatitis as per institutional standards.

13. Known seropositive for, or active infection with hepatitis C virus:
    - Subjects with positive hepatitis C virus (HCV) antibodies are eligible with negative PCR test for HCV.

14. Active and uncontrolled infection with HIV, or with AIDS, or currently taking medications for HIV that are contraindicated for concomitant use in this study.
15. Symptomatic or uncontrolled infection with human T-cell leukemia virus type 1.
16. History of other primary malignancy in the past 5 years or concurrent active malignancies (synchronous malignancies, requiring treatment; excluding malignancies that are expected to be completely cured, such as intramucosal carcinoma and carcinoma in situ, curatively treated cervical cancer in situ, non-melanoma skin cancer, superficial bladder tumors [Ta (non-invasive tumor), Tis (carcinoma in situ), and T1 (tumor invades lamina propria)], and asymptomatic localized prostate cancer with no requirement for systemic therapy or requiring only hormonal therapy and with normal prostate-specific antigen values within ≥12 months prior to enrollment). Breast cancer survivors on hormone therapy may be eligible if blood count is adequate and history of remission is >5 years ago.
17. Venous thromboembolism (unless appropriately treated and stable on anticoagulant for at least 2 weeks).
18. Arterial thrombosis or arterial thromboembolism such as myocardial infarction, transient ischemic attack, or cerebrovascular accident in the last 6 months prior to enrollment.
19. Subjects who discontinued prior treatment with bevacizumab, ziv-aflibercept, and/or ramucirumab because of severe events of hemorrhages, hypertension, fistula, perforation, arterial/venous thromboembolism, PRES, renal injury, or proteinuria.
20. Concomitant use of strong inhibitors and strong inducers of CYP enzymes and transporters.

4.3. Discontinuation of Treatment and Subject Withdrawal Criteria

Subjects will be discontinued from study treatment for any of the following reasons:

- Disease progression (see Section 6).
- Intolerable toxicity, including unacceptable and clinically significant laboratory values thought to be related to drug toxicity.
- Pregnancy.
- Subject request to discontinue treatment.
- Subject request to withdraw from the study.
- Conditions requiring therapeutic intervention not permitted by the protocol.
- Intercurrent illness (at the Investigator's discretion).
- Non-compliance/lost to follow-up.
- Investigator or Sponsor determines it is in the best interest of the subject.

After discontinuation from study treatment, subjects must be followed for AEs for 30 calendar days after their last dose of study medication and return for the End of Treatment (EOT) visit. All new AEs occurring during this period must be reported and followed until resolution, unless,

in the opinion of the Investigator, these AEs are not likely to improve because of the underlying disease. In such case, the Investigator must record the reason for this decision in the subject's medical record.

All subjects who have Grade ≥3 laboratory abnormalities (NCI CTCAE v5.0) at the time of discontinuation must be followed until the laboratory values have returned to Grade ≤2 or baseline, unless in the opinion of the Investigator it is not likely that these values will improve. In such case, the Investigator must record the reason for this decision in the subject's medical record.

5. STUDY DRUG MATERIALS AND MANAGEMENT AND TREATMENT OF SUBJECTS

5.1. ME-344

5.1.1. Description of the Active Pharmaceutical Ingredient

The ME-344 drug substance is a small molecule manufactured by chemical synthesis and contains no animal or plant-derived components. ME-344 is a chiral compound and is manufactured predominantly as a single stereoisomer that is dextrorotatory.

5.1.2. Description of the Study Drug Product

The drug product is an aqueous solution for IV infusion. The drug substance is formulated as a 35 mg/mL solution in 30% weight per volume (w/v) Captisol® (b-cyclodextrin sulfobutyl ethers, sodium salts) in water for injection. The drug product comprises the same formulation used in the Good Laboratory Practice (GLP) preclinical toxicology studies, and similar Captisol formulations are currently used for several marketed drugs.

5.1.3. Study Drug Packaging and Labeling

ME-344 is supplied in glass vials, packaged into boxes.

5.1.4. Study Drug Storage

The drug product is stored refrigerated (2–8°C, 36–46°F).

Any variance from these storage conditions should be reported to the Sponsor on detection, and ME-344 should be quarantined until the Sponsor authorizes usage or otherwise.

5.1.5. Study Drug Preparation

Calculate the amount of ME-344 required based on body weight at 10 mg per kg body weight, up to a maximal dose of 1000 mg (100 kg x 10 mg/kg) for subject with body weight exceeding 100 kg. Use aseptic technique for preparation. ME-344 drug for infusion should only be prepared the morning of the planned dosing date –do not prepare and store overnight. Calculate the amount of ME-344 and add to normal saline (0.9% Sodium Chloride) to bring the total volume to 250 mL. The infusion line may be primed with normal saline. Overfill of normal saline in the bag should follow institutional procedures and not be >5%. On visual inspection, the solution for

infusion should be colorless to slightly yellowish and free of particles. Ensure proper labeling of the ME-344 study drug infusion bag.

The infusion bag should be prepared the morning of infusion, protected from sunlight with infusion completed within 24 hours of reconstitution, as dictated by standard operating procedures (SOPs) at the site.

5.1.6. Study Drug Administration

ME-344 will be infused IV over up to 60 minutes.

- Cohort 1: 10 mg/kg on Days 1, 8, and 15 of each 28-day cycle.
- Cohort 2: 10 mg/kg on Days 1 and 15 of each 28-day cycle.

ME-344 will be infused 30 minutes prior to bevacizumab administration.

The following guidance may be instituted prior to administration of ME-344 if there is a concern for increased blood pressure or potential infusion reactions.

Approximately 30 minutes prior to the start of the ME-344 infusion, pre-medicate with:

- 650 mg acetaminophen orally (PO).
- 25–50 mg diphenhydramine PO or IV.
- 20 mg famotidine PO or IV or equivalent available H2 blocker.

If infusion reaction is experienced, refer to Table 1 for guidance regarding infusion reaction management.

5.1.7. Study Drug Accountability

The Investigator or designee is responsible for accountability of all used and unused ME-344 supplies at the site.

The Sponsor or its representatives must be granted access on reasonable request to check drug storage, dispensing procedures, and accountability records. All ME-344 inventories must be made available for inspection by the monitor, Sponsor or its designee, and regulatory agency inspectors upon request.

5.1.8. Study Drug Disposition

At the end of the study, ME-344 will be returned to the Sponsor or designee or destroyed. ME-344 must not be destroyed unless prior approval has been granted by the Sponsor or designee.

5.2. Bevacizumab

Bevacizumab (Avastin brand or any US-approved biosimilar) will be administered IV at a dose of 5 mg/kg on Days 1 and 15 of each 28-day cycle in Cohorts 1 and 2. To the extent possible each subject should use a single bevacizumab product throughout the trial.

Bevacizumab will be prepared for infusion per package insert instructions and/or institutional procedures.

US-licensed brand name or biosimilar bevacizumab will be sourced commercially. Refer to the US Prescribing Information (Avastin [US Prescribing Information] September 2022 or biosimilar) for further details regarding storage, handling, preparation, and administration.

5.3. Concomitant Medications

Prior and concomitant medications will be recorded from 28 days prior to Cycle 1 Day 1 until the EOT visit or start of new anticancer treatment (whichever occurs first).

5.3.1. Permitted Concomitant Medications

Premedication with antiemetics is allowed according to standard practice guidelines.

Medications considered necessary for the subject's safety and well-being may be given at the discretion of the Investigator except for those listed in Section 5.3.2.

Vaccinations, including the COVID-19 vaccine, are permitted, except for live attenuated vaccines. It is recommended that vaccinations be administered at least 2 weeks prior to Day 1 of the study.

The following medications should be used with caution:

- **Medications Which Alter Serum Electrolytes**

  Subjects requiring medications that have the potential to alter serum electrolytes (e.g., diuretics) should be monitored closely for electrolyte abnormalities, as these can contribute to the risk of QT prolongation and ventricular arrhythmias.

- **Medications Known to Prolong the QT Interval**

  Although no significant effect on QTc interval was observed in Study ME-344-001, drugs known to prolong the QT interval should be used with caution. If, after a subject has been enrolled, he/she requires the concomitant use of any of the medications that may cause QT interval prolongation (Appendix 3), study drugs will be held in the event the QTc is prolonged beyond 500 msec. If the QTc returns to ≤470 msec, the subject may resume study treatment with the approval of the Medical Monitor if no more than 2 ME-344 doses were missed.

  Ondansetron or palonosetron should be used with caution due to the possible risk of QT prolongation (Appendix 3); IV doses of 0.15 mg/kg every 4 hours for 3 doses may be used (no single IV dose should exceed 16 mg), or a single oral dose of 24 mg may be used. Prochlorperazine and Aprepitant may be used safely.

- **Sensitive In Vivo CYP Substrates or CYP Substrates with a Narrow Therapeutic Range**

  In *in vitro* studies with human liver microsomes, ME-344 inhibited all CYP enzymes tested. In subjects receiving ME-344 as an IV infusion, plasma concentrations declined rapidly and were approximately 1% of C_{max} around 6 hours after the end of infusion. Since ME-344 is administered either weekly (on Days 1, 8, and 15), or every two weeks (on Days 1 and 15) dosing regimen, the potential for clinically relevant inhibition of CYP enzymes is low. Nevertheless, concomitant use of medications that are sensitive *in vivo*

CYP substrates or CYP substrates with a narrow therapeutic range (Appendix 4) should be used with caution during the study.

5.3.2. Prohibited Concomitant Medications

The following treatments are prohibited while in this study:

- No other investigational therapy should be given to subjects.
- No other anticancer agents should be given to subjects. If such agents are required, the subject must first be withdrawn from the study.
- Herbal products and dietary supplements are not allowed throughout the study. Subjects are required stop use of these products prior to the first dose of study drug.
- Medications Metabolized via Cytochrome P450**:**

  No clinical information is available on drug-drug interactions for ME-344. Given the lack of information regarding the cytochrome P450 (CYP) enzymes responsible for the metabolism of ME-344, concomitant medications that are strong inhibitors or inducers of major CYP metabolizing enzymes are prohibited. A list of all agents (with strong modulators appearing in **bold** font) is presented in Appendix 5. Closely monitor for safety or efficacy for concomitant use of moderate inhibitors and inducers of CYP enzymes and transporters.

5.4. Treatment Compliance

Subjects will be administered study drugs under the supervision of the Investigator or designated study site personnel. Study drug dose, date of administration, and infusion start and stop times will be documented.

5.5. Randomization and Blinding

Not applicable; this is an open-label study.

6. ASSESSMENT OF EFFICACY

6.1. Tumor Response

Baseline tumor measurements by CT or MRI should be performed as close as possible to the start of treatment, but no longer than 6 weeks prior to Cycle 1 Day 1. Subjects should be re-evaluated at the Investigator's discretion, but at a minimum of every 8 weeks (±7 days) from Cycle 1 Day 1 for the first 6 months, then every 3 months until 1 year, and every 4 months thereafter. Radiologic images should be performed consistently for the areas of disease involvement taken for the study evaluation.

Assessments of disease response and progression should be made according to RECIST v1.1 (Eisenhauer 2009).

6.2. Pharmacokinetics

Blood samples for PK analysis will be collected during Cycle 1 on Days 1 and 15 pre-dose ME-344, 5 minutes after the end of infusion, and 1, 2, 3, 6, and 24 hours after the completion of the infusion.

PK parameters include:

- maximum observed concentration (C_{max}).
- last observed quantifiable concentration (C_{last}).
- area under the concentration-time curve from time zero to time of AUC_{last}.

Data from this study may be pooled with other studies and may be analyzed by other methods.

6.3. Correlatives of Mitochondrial Metabolism

Metabolomics analysis will be performed at a single center on patient plasma samples as a correlative study. Similar to ME-344, metformin is a mitochondrial Complex I inhibitor. Metabolomics analysis of tumor biopsies from ovarian cancer patients after metformin treatment revealed suppressed TCA cycle intermediates and short chain acyl carnitine, increased isoleucine/leucine, and changes in nucleotide intermediates and glutathione-related metabolites. Consistent with the metformin-induced metabolic changes, metabolomics analysis of a human acute myeloid leukemia cell line treated in vitro with ME-344 revealed changes in several pathways, including pyrimidine and purine metabolism, valine/isoleucine/leucine biosynthesis, ascorbate and aldarate metabolism, pantothenate and Co-A biosynthesis, and TCA cycle intermediates. A metabolomics analysis of plasma from type 2 diabetes mellitus (T2DM) patients treated with metformin revealed similar changes to those detected in the ovarian cancer tumor samples, supporting the analysis of plasma samples to analyze the metabolic changes induced by mitochondrial Complex I inhibitors.

Blood samples will be collected from patients at the following time points:

- Cycle 1 Day 1 (pre-dose and 6 hours post-dose).
- Cycle 1 Day 15, Cycle 2 Day 1, and Cycle 3 Day 1.

Blood will be collected in a fasting state with minimum fasting time of 4 hours. Plasma samples will be flash frozen, processed, and analyzed for metabolomics markers. It is anticipated that changes will be detected in isoleucine/leucine, TCA cycle intermediates, short chain acyl carnitine, and nucleotide and TCA cycle intermediates.

The metabolomic correlative study will be performed on samples obtained from subjects enrolled at Rutgers Cancer Institute of New Jersey who consent to the metabolomic sample collection and analysis portion of this study. Plasma samples will be collected at timepoints specified in the Schedule of Assessments (Appendix 1). Samples will be stored at -70°C until analyzed. Specific markers of the mitochondrial oxidative phosphorylation pathway will be analyzed based on the outcomes from the planned nonclinical studies at the site.

7. ASSESSMENT OF SAFETY

The Schedule of Assessments (Appendix 1) summarizes the frequency and timing of all applicable study assessments, including allowable windows for study visits and assessments/procedures. Written informed consent must be provided before any study related procedures are performed.

See Section 4.1 and Section 4.2 for eligibility criteria. Eligibility must be confirmed by the Medical Monitor prior to the first dose of study drug.

7.1. Safety Parameters

7.1.1. Demographic/Medical History

Demographic information includes age, gender, race, and ethnicity. Relevant medical history (past and concurrent) includes cancer diagnosis (and tumor locations) and history, histopathology, date and method of diagnosis, and prior antitumor therapy.

7.1.2. Vital Signs

Vital signs include blood pressure (systolic and diastolic), heart rate, and temperature.

7.1.3. Weight and Height

Weight is measured on Day 1 of each cycle, as both study drugs are dosed based on weight. Height is measured only at screening.

7.1.4. Physical Examination

Complete physical examination, including assessment of peripheral neuropathy, is required at the Screening and EOT visits. Symptom-directed physical examinations, including assessment of peripheral neuropathy will be performed at all other visits.

7.1.5. ECOG Performance Status

The scale in Appendix 6 is to be used to assess ECOG Performance Status (Oken 1982).

7.1.6. Electrocardiogram (ECG)

Subjects should be resting and semi-recumbent for triplicate ECGs. Data collection includes abnormal findings; if abnormal finding(s) are assessed as clinically significant, the finding(s) should be reported as AE(s). The Investigator is responsible for interpreting and measuring ECG data.

7.1.7. Laboratory Evaluations

Blood and urine for laboratory evaluations will be collected and analyzed at a local/site laboratory in accordance with quality laboratory standards. Hematology, serum chemistry, urinalysis, and other parameters to be tested are listed in Table 2.

Table 2: Clinical Laboratory Tests

Laboratory Test Category	Specific Laboratory Tests	
Hematology:	Hemoglobin	Neutrophils (absolute)
	Hematocrit	Monocytes
	Erythrocyte (red blood cell [RBC]) count	Eosinophils
	Quantitative platelet count	Lymphocytes
	Total leukocyte (white blood cell [WBC]) count	Basophils
	Mean corpuscular hemoglobin (MCH)	Platelets
Serum Chemistry:	Aspartate aminotransferase (AST)	Calcium
	Alanine aminotransferase (ALT)	CO2 or bicarbonate
	Alkaline phosphatase (ALP)	Blood urea nitrogen (BUN) or urea
	Albumin	Creatinine
	Total bilirubin (if total bilirubin is ≥2 × ULN with no evidence of Gilbert's syndrome, then fractionate into direct and indirect bilirubin)	Glucose
	Sodium	Chloride
	Potassium	Lipase
	Total protein	Lactate dehydrogenase (LDH)
	Phosphorus	Amylase, magnesium
Coagulation:	Activated partial thromboplastin time (aPTT)	International normalized ratio for prothrombin time (INR/PT)
Urinalysis:	pH	Blood
	Protein	Specific gravity
	Glucose	Ketones
Serology:	Hepatitis B core antibody (HBcAb)	Hepatitis C antibody
	Hepatitis B surface antibody (HBsAb)	Hepatitis C PCR (only if hepatitis C antibody is positive)
	Hepatitis B surface antigen (HBsAg)	
	Hepatitis B PCR (only if HBcAb and HBsAg are positive)	
Pregnancy	Serum beta human chorionic gonadotropin (βhCG) pregnancy test for females of childbearing potential (screening only), urine or serum test at all other visits	

8. ADVERSE EVENTS

An AE is any untoward medical event that occurs in a subject following the start of study drug administration, whether or not the event is considered drug related. An AE can therefore be any of the following:

- A pre-existing medical condition can be recorded as an AE if the condition worsens by at least one grade following the start of study drug administration and if the frequency, severity, or character of the condition worsens during the study. When recording on the electronic case report form (eCRF) it is important to capture applicable descriptors (e.g., more frequent arthritic pain).
- Disease-related out-of-range laboratory values will not be considered AEs/SAEs if there is no change from the screening laboratory values. Any deterioration in a laboratory value or other clinical test that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug or deemed clinically significant by the Investigator will be considered an AE.

AEs will be recorded using the terminology defined in the Medical Dictionary for Regulatory Activities (MedDRA).

A TEAE is defined as an AE starting or worsening in CTCAE grade after the first dose until 30 days after the last dose of study drug, or start of new anticancer therapy, whichever is earlier.

Death related to disease progression is not considered an AE. Signs and symptoms related to disease progression are not considered AEs. Anticipated fluctuations of pre-existing conditions, including the disease under study that do not represent a clinically significant exacerbation or worsening, need not be considered AEs.

Only one AE term should be recorded in the event field on the AE eCRF if a specific AE is attributable to a primary diagnosis. AEs that are secondary to other events should be identified by their primary cause with the exception of severe or serious secondary events. For example:

- If a subject initially had diarrhea and is subsequently diagnosed with colitis, this event should be consolidated to one data entry, which is colitis.
- If a subject had diarrhea that resulted in mild dehydration, only diarrhea should be reported in the eCRF.
- If a subject who had diarrhea developed acute renal failure, both acute renal failure and diarrhea will be entered separately.

For AEs, a diagnosis should be recorded on the AE eCRF rather than individual signs and symptoms (e.g., record only colitis rather than diarrhea, abdominal pain, decreased appetite). However, if a constellation of signs and symptoms cannot be medically characterized as a single diagnosis or syndrome, each individual event should be reported on the AE eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced on the AE eCRF based on a single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

8.1. Assessment of Severity

The term "severity" is used to describe the intensity of an AE. Severity will be graded according to NCI CTCAE v5.0. For AEs not covered by CTCAE, each AE will be assigned a category by the Investigator as described in Table 3.

Table 3: NCI CTCAE v5.0 Adverse Event Grading System

Grade	Comments
1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Minimal, local, or noninvasive intervention indicated, limiting age appropriate instrumental ADL[a]
3	Hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]
4	Urgent intervention indicated
5	Death related to AE

Abbreviations: ADL = activities of daily living; AE = adverse event.

[a] Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Self-care ADL refers to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

8.2. Assessment of Causality

The Investigator is obligated to assess the relationship between study drug and the occurrence of each AE. The Investigator is to use his/her best medical judgement in determining the likely relationship of the AE to ME-344 and to bevacizumab. The relationship of an AE or SAE to study drug is to be classified as either 'Related' or 'Not Related'.

8.3. Documenting Adverse Events

AEs should be documented in the source documents and entered in the subject's case report form (CRF; or eCRF) with action taken with respect to the study drug and outcome.

8.4. Clinical Laboratory Changes

Clinical laboratory measurements are reported in the subject's CRF (or eCRF). Laboratory abnormalities are to be reported as AEs only when deemed clinically significant (i.e., led to treatment interruption or discontinuation, associated with initiation of concomitant therapy, or with hospitalization).

8.5. Adverse Event Follow-up

AEs occurring on study will be followed until resolution or return to baseline. AEs leading to discontinuation of study drug will be followed for minimum of 30 days after the last dose of study drug or until resolution, whichever comes first.

8.6. Documenting Action Taken with Study Drug in Response to the AE

The Investigator will record the action taken regarding the study treatment in response to an AE:

- Dose not changed
- Dose-reduced
- Study drug interrupted
- Study drug withdrawn
- Not applicable

8.7. Outcome of Adverse Event

The Investigator will record the outcome of the AE as follows:

- Recovered/resolved
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Death
- Unknown

8.8. Serious Adverse Events

8.8.1. Definition

An SAE is an event that meets any of the following criteria:

- Adverse event resulting in death (Grade 5 toxicity)
- Life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received any study drug
- Other: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

  Examples of such events are:

  - Intensive treatment in an emergency room or at home for allergic bronchospasm
  - Blood dyscrasias or convulsions that do not result in inpatient hospitalization
  - Development of drug dependency or drug abuse

8.8.2. Definition of Terms

Life threatening: An AE is life threatening if the subject was at immediate risk of death from the event as it occurred (i.e., it does not include a reaction that if it had occurred in a more serious form might have caused death). For example, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug -induced hepatitis can be fatal.

Hospitalization: Adverse events requiring hospitalization should be considered SAEs. Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., elective surgery for a pre-existing condition that has not worsened) need not be considered AEs or SAEs. If anything, untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'non-serious' according to the usual criteria.

If there is a question as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

Disability/incapacitation: An AE is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.

8.8.3. Reporting Serious Adverse Events

All SAEs must be reported to the Sponsor or Sponsor's designee (the Pharmacovigilance contract research organization [CRO]) within 24 hours of the Investigator becoming aware of the SAE.

To report an SAE, please refer to the applicable study manual or eCRF for SAE reporting instructions.

The 4 minimum criteria for a valid SAE report include:

- Study identifier
- Subject identifier
- Event term
- Study drug

All SAEs will be reported for up to 30 days after the last dose of study drug. After 30 days post-last dose, only SAEs deemed related to study drug will be reported to the Sponsor. The Investigator must report new significant follow-up information for these events to the CRO immediately (i.e., no more than 24 hours after becoming aware of the information).

New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant (requiring therapy or hospitalization) new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

All deaths should be recorded and reported to the Sponsor. Disease progression, hospitalization to assess disease progression, and death due to disease progression as determined by the Investigator are not considered SAEs. All other causes of death must be reported as SAEs. The Investigator should make every effort to obtain and send death certificates and autopsy reports for all deaths to the Sponsor.

All SAEs also must be reported by each site to the appropriate IRB/IEC in accordance with local requirements for reporting SAEs to their IRB/IEC.

In the event of a medical emergency (requiring immediate attention regarding operation of the clinical study and/or the use of study drug), study site staff will apply appropriate medical intervention according to current standards of care and will contact the Medical Monitor or designee (e.g., CRO representative) for further consultation and guidance.

8.8.4. Sponsor Reporting to Regulatory Authorities

The Sponsor is responsible for reporting suspected unexpected serious adverse reactions (SUSARs) in an expedited manner to regulatory authorities, as required per local regulations.

The Sponsor or designee will report to the original manufacturer any SAE deemed to be related to bevacizumab and considered unexpected according to the US Prescribing Information.

8.8.5. Pregnancies

To ensure subject safety, any pregnancy in a subject on study treatment must be reported within 24 hours of learning of its occurrence. Pregnancy occurring up to 3 months after receiving the last dose of study drug must be reported.

Study drug must be discontinued in a subject who becomes pregnant. The pregnancy must be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Subjects must be followed at least 8 weeks after giving birth to a child.

Pregnancy in and of itself is not an AE; however, certain situations and/or outcomes of pregnancy can be (see below). Any pregnancies should be recorded on a Pregnancy Form and reported by the Investigator to the Sponsor or designee. Pregnancy follow-up should be recorded and should include an assessment of the possible relationship to the study drug of any pregnancy outcome

Examples of pregnancy outcomes that are SAEs include reports of:

- Congenital anomalies or developmental delay in the fetus or the child
- Fetal death or spontaneous abortion
- Suspected adverse reactions in the neonate that are classified as serious

Pregnancy case information should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes must first be obtained from the mother.

9. STATISTICS

A Statistical Analysis Plan (SAP) will be prepared and finalized before study database lock and analysis of data. Any deviations from the final SAP will be described and justified in the clinical study report. All statistical analyses will be performed using the statistical software application SAS®.

9.1. Sample Size Justification

The PFS rate >20% is considered as a positive efficacy signal to proceed to a later stage trial. With a sample size of 20 subjects in each cohort, assuming the true PFS rate at 16 weeks is 30%, there is 89% chance to observe PFS rate ≥20% (i.e., ≥4 of 20 subjects progression-free) based on binomial distribution. If 7 out of 20 subjects achieve PFS at 16 weeks (observed PFS rate of 35%), we are 90% confident that the true PFS rate >20% as the lower bound of 80% CI is 20.7%. If 12 out of 40 subjects achieve PFS at 16 weeks (observed PFS rate of 30%), we are 90% confident that the true PFS rate >20% as the lower bound of 80% CI is 20.5%.

Table 4 summarizes the 95% and 80% exact CIs when observed PFS rate are 20% to 50%, respectively.

Table 4: Observed Progression-free Survival Rate with Exact 95% and 80% Confidence Intervals

	N=20			N=40		
Observed PFS Rate	**Number of PFS Subjects**	**95% CI (%)**	**80% CI (%)**	**Number of PFS Subjects**	**95% CI (%)**	**80% CI (%)**
20%	4	5.7, 43.7	9.0, 36.1	8	9.1, 35.6	12.0, 30.4
25%	5	8.7, 49.1	12.7, 41.5	10	12.7, 41.2	16.2, 35.9
30%	6	11.9, 54.3	16.6, 46.7	12	16.6, 46.5	20.5, 41.2
35%	7	15.4, 59.2	20.7, 51.8	14	20.7, 51.7	24.9, 46.3
40%	8	19.1, 63.9	24.9, 56.7	16	24.9, 56.7	29.4, 51.4
45%	9	23.1, 68.5	29.3, 61.5	18	29.3, 61.5	34.1, 56.3
50%	10	27.2, 72.8	33.8, 66.2	20	33.8, 66.2	38.8, 61.2

If 10 (50%) of 20 subjects experience Grade ≥3 treatment-emergent neuropathy, the 95% CI for incidence rate of Grade ≥3 neuropathy will be (27.2%, 72.8%) based on exact method.

9.2. Analysis Populations

- The ITT Population is defined as all enrolled subjects who receive at least one dose of ME-344.
- The EE Population includes all subjects who receive at least one dose of ME-344 and have adequate Week 16 efficacy assessments or develop progression of disease (or died) prior to Week 16. The EE Population will be used as the primary analysis population for assessing response to the study drugs.

- The PK Population includes all subjects who receive at least one dose of ME-344 and have at least one evaluable post-baseline ME-344 PK concentration. PK analysis will be conducted using the PK Population.
- The Safety Population includes all subjects who receive at least one dose of ME-344. Safety analyses will be performed on the Safety Population.

9.3. Statistical Analysis

9.3.1. General Methodology

In general, data will be summarized using number and percentage for discrete parameters, and by descriptive statistics (number of observations, mean, standard deviation, median, minimum, and maximum) for continuous parameters.

No imputation of values for missing data will be performed.

All analyses will be conducted by cohort. Pooled summaries (Cohort 1 and Cohort 2) may be conducted if deemed meaningful. Subgroup analysis by baseline demographic or disease characteristics may be conducted.

9.3.2. Demographics, Baseline Characteristics, and Subject Disposition

Demographic and baseline disease characteristics will be summarized by cohort for the ITT Population. Data to be tabulated will include demographic features such as gender, age, race, and ethnicity, as well as disease specific status. The number and percentage of subjects who complete the study or who withdraw for any reason will be presented by cohort. Disposition of study treatment will be summarized as well for the ITT Population.

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary and summarized for the Safety Population.

9.3.3. Efficacy Analysis

The primary efficacy endpoint (PFS rate at Week 16) will be evaluated using the KM method for the ITT Population when the last subject in Cohort 1 completes the efficacy assessment at Week 16 (or discontinues, develops disease progression, starts new anticancer therapy, or dies, whichever occurs earlier). The KM estimates for median, first and third quartiles (Q1 and Q3, respectively), and the PFS rate at Week 16 will be presented. The PFS KM plot will be generated. Time-to-event (progression or death due to any cause) will be calculated from the day of first study drug dose to the first observation of progressive disease (PD) as assessed by the Investigator per RECIST v.1.1 or death from any cause. Subjects without a PD or death event will be censored at last adequate assessment date or first dose date if no adequate postbaseline assessment is available.

The OS time is defined as the time from first study drug dose to death from any cause. Subjects without a death event will be censored at the last date when the patient was known to be alive. The OS will be analyzed using the KM method.

The secondary efficacy endpoints overall response rate (ORR; defined as the proportion of patients achieving complete response [CR] or partial response [PR] per RECIST v.1.1). The 2-sided exact 95% CI based on the Clopper--Pearson method will be provided.

All efficacy analysis will be conducted by cohort. Pooled analysis (Cohort 1 + Cohort 2) may be conducted if deemed meaningful. Subgroup analysis by baseline demographic or disease characteristics may be conducted.

9.3.4. Safety Analysis

A TEAE is defined as an AE starting or worsening per CTCAE grade after the first dose until 30 days after the last dose of study drug, or start of new anticancer therapy, whichever is earlier. Safety will be assessed through the analysis of the reported incidence, severity, and relationship of TEAEs, including SAEs, adverse events of special interest, AEs leading to withdrawal of study drug, and AEs related to study treatment.

The AEs will be summarized by MedDRA coding terms, System Organ Class, and Preferred Term (PT) by cohort using the Safety Population.

Change from baseline in physical examinations, vital signs, 12-lead ECGs, and clinical laboratory evaluations will be summarized.

Information regarding study drug administration, study drug compliance, and other safety variables will also be summarized or listed. Extent of exposure to study drug will be generated from the study drug administration data. Exposure data will be summarized by cohort.

9.3.5. Pharmacokinetic Analysis

Plasma levels of ME-344 will be listed and summarized by cohort. Estimation of PK parameters will be performed by non-compartmental methods using the PK Population, with descriptive results presented by cohort. Data from this study may be pooled with data from other studies and may be analyzed by other methods.

9.3.6. Analysis of Correlatives of Mitochondrial Metabolism

The metabolomics data will be summarized if the sample assay data are available.

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

10.1. Study Monitoring

Before an investigational site can enter a patient into the study, a representative of MEI Pharma (the Sponsor) or its designee will evaluate the investigational study site to:

- Determine the adequacy of the facilities.
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

During the study, a monitor from the Sponsor or its designee will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that investigational product accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (e.g., clinic charts).
- Record and report any protocol deviations.
- Confirm AEs and SAEs have been properly recorded on CRFs, confirm any SAEs have been forwarded to the Sponsor or its designee, and confirm those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the Investigator(s) or other staff need information or advice.

10.2. Audits and Inspections

Authorized representatives of the Sponsor or its designee, regulatory authorities, or the IRB/IEC may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. The Investigator should contact the Sponsor or its designee immediately if contacted by a regulatory agency about an inspection.

10.3. Institutional Review Board (IRB)

The Investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the subject consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

10.4. Safety Review Committee

A SRC consisting of the study chair, MEI Pharma medical lead, the study Medical Monitor, the study biostatistician, and the Principal Investigators involved in the study will provide safety oversight for its conduct. The SRC will meet on a regular basis, with the first meeting occurring after the first 5 subjects complete 1 cycle of therapy, and then every 2–3 months thereafter. The SRC will review the totality of safety data, including AEs, SAEs, and laboratory results, with the primary purpose of protecting the safety of study participants, the credibility of the study, and the validity of study results. The SRC will provide their recommendation whether the combination is deemed safe, and Cohort 2 can be opened for enrollment.

11. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor or its designee may conduct a quality assurance audit. See Section 10.2 for more details regarding the audit process.

12. ETHICS

12.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Form (ICF), must be approved, or given a favorable opinion in writing by an IRB/IEC as appropriate. The Investigator must submit written approval to the Sponsor or its designee before enrollment of subjects.

The Investigator is responsible for informing the IRB/IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB/IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB/IEC upon receipt of amendments and annually, as local regulations require.

The Investigator is also responsible for providing the IRB/IEC with any reportable serious adverse drug reactions from any other study conducted with the investigational product. The Sponsor or its designee will provide this information to the Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB/IEC according to local regulations and guidelines.

12.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP and applicable regulatory requirements.

12.3. Written Informed Consent

The Investigator(s) at each study center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any study procedures.

The Investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject.

13. DATA HANDLING AND RECORDKEEPING

13.1. Inspection of Records

The Sponsor or its designee will be allowed to conduct site visits of the investigational facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts, study source documents, and other records related to study conduct.

13.2. Data Protection and Privacy

In order to verify subject eligibility criteria and ensure ongoing subject safety during the study and preserve the integrity of study data, notwithstanding source data verification at the study site, the Sponsor/CRO may request to review subject source medical data. Should the Sponsor request copies of subject medical data, the rationale for such request will be ethically and scientifically justified. Such records will promptly be destroyed by the Sponsor/CRO when the purpose of the review has been met.

13.3. Retention of Records

The Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved, for 2 years following the discontinuation of the investigational use. If it becomes necessary for the Sponsor or the regulatory authority to review any documentation relating to the study, the Investigator must permit access to such records.

14. PUBLICATION POLICY

The Sponsor intends to publish the results of this study as soon as possible following completion of data analysis. Data derived from the study are the exclusive property of the Sponsor. Authorship (both inclusion and sequence) will be determined by mutual agreement. In the event of a disagreement on authorship, the Sponsor will serve as adjudicator.

15. REFERENCES

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APPENDIX 1. SCHEDULE OF ASSESSMENTS

Assessment/Procedure	Screening	Cycles 1 and 2			Cycles ≥3			EOT	Survival Follow-up
Day(s) of Cycle	-28 to -1	1	8 [a]	15	1	8 [a]	15	30 days after last dose	Every 12 weeks after EOT
Visit Window (days)			±2	±2		±2	±2	±7	
Informed consent	X								
Medical history	X								
Physical examination [b]	X	X	X	X	X	X	X	X	
Vital signs [c]	X	X	X	X	X	X	X	X	
Height	X								
Weight	X	X			X			X	
ECOG performance status [d]	X [d]	X			X			X	
Pregnancy test [e]	X	X			X			X	
Hepatitis B & C tests [f]	X								
HIV antibody test	X								
12-lead electrocardiogram (triplicate)[g]	X	X[g]		X[g]				X	
Hematology [h]	X	X		X	X		X	X	
Serum chemistry [i]	X	X		X	X		X	X	
Coagulation [j]	X	X [j]			X [j]				
Urinalysis (dipstick) [k]	X	X		X	X		X	X	
ME-344 10 mg/kg infusion (Cohort 1)		X	X	X	X	X	X		
ME-344 10 mg/kg infusion (Cohort 2)		X		X	X		X		
Bevacizumab 5 mg/kg infusion		X		X	X		X		
PK sample collection [l]		X [l]		X [l]					
Metabolomics sample collection [m]		X		X	X				
Adverse event collection [n]		X	X	X	X	X	X	X	
Concomitant medication recording [o]	X	X	X	X	X	X	X	X	
Disease/response assessment [p]	X				X				
Survival status [q]									X

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EOT = End of Treatment; INR = international normalized ratio; IV = intravenous; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MRI = magnetic resonance imaging; PCR = polymerase chain reaction; PK = pharmacokinetic; INR/PT = International Normalized Ratio of prothrombin time; RBC = red blood cell; WBC = white blood cell.

[a] **Day 8** – ME-344 dosing and study procedures on Day 8 are only applicable to subjects in Cohort 1. No ME-344 dosing or study procedures are performed for subjects in Cohort 2.

[b] **Physical examination** – Complete physical examination, including assessment of peripheral neuropathy, is required at the Screening and EOT visits. Symptom-directed physical examinations, including assessment of peripheral neuropathy will be performed at all other visits.

[c] **Vital signs** – Blood pressure (systolic and diastolic), heart rate, and temperature.

[d] **ECOG** – Must be within 14 days of Cycle 1 Day 1.

[e] **Pregnancy test** – Serum pregnancy test for females of childbearing potential performed at screening within 7 days prior to Cycle 1 Day 1. Urine or serum test performed on Day 1 of subsequent cycles.

[f] **Hepatitis B and C tests** – Hepatitis B core antibody, hepatitis B surface antigen, and hepatitis C antibody are required. Hepatitis B PCR is required if hepatitis B core antibody and/or surface antigen is positive. Hepatitis C PCR is required if hepatitis C antibody is positive.

[g] **ECGs** are to be obtained at the end of each infusion of ME-344 on Cycle 1 Day 1 and Day 15, EOT, and as clinically indicated. ECGs to be obtained prior to collection of matching PK samples on Cycle 1 Day 1 and Day 15 only.

[h] **Hematology** – Hematology tests include WBC, ANC, RBC, hemoglobin, hematocrit, lymphocytes, eosinophils, monocytes, basophils, platelets, and MCH. Screening labs must be repeated if performed >7 days prior to Cycle 1 Day 1.

[i] **Serum chemistry** – Serum chemistry tests include glucose, BUN or urea, CO2 or bicarbonates, creatinine, sodium, potassium, chloride, calcium, ALP, AST, ALT, total bilirubin, total protein, albumin, lipase, LDH, and phosphorous. Screening labs must be repeated if performed >7 days prior to Cycle 1 Day 1.

[j] **Coagulation** – Coagulation tests include aPTT, INR/PT. Screening labs must be repeated if performed >7 days prior to Cycle 1 Day 1. For subjects on anticoagulation therapy test will be performed on Day 1 of every cycle. Close monitoring of at least weekly evaluations will be performed until INR/PT is stable based on a measurement that is prior to initiation of study treatment, as defined by the local standard.

[k] **Urinalysis** – Urinalysis tests include dipstick or urine test (pH, specific gravity, glucose, ketones, blood, and protein). Screening labs must be repeated if performed >7 days prior to Cycle 1 Day 1. If baseline urine protein is ≥2+, unless due to ureteral stents of urinary diversion, a 24-hour urine collection must be performed to confirm urinary protein excretion is<2.0 g/24 hour.

[l] **PK sampling** – Blood samples for PK analysis will be collected during Cycle 1 on Days 1 and 15 pre-dose, 5 minutes after the end of infusion, and 1, 2, 3, 6, and 24 hours after the completion of the infusion.

[m] **Metabolomics sampling –** Blood samples for metabolomics analysis will be collected (at Rutgers Cancer Institute of New Jersey) at Cycle 1 Day 1 (pre-dose and 6 hours post-dose), Cycle 1 Day 15, Cycle 2 Day 1, and Cycle 3 Day 1 in a fasting state with minimum fasting time of 4 hours.

[n] **Adverse events** – Adverse events are to be recorded from the time of the first dose of study drug on Cycle 1 Day 1 through 30 days after the last dose of study drug or start of new anticancer treatment (whichever occurs first). Any untoward occurrence related to a study procedure during screening should also be reported as an AE.

[o] **Concomitant medications** – Concomitant medications are to be recorded from 28 days prior to Cycle 1 Day 1 until the EOT visit or start of new anticancer treatment (whichever occurs first).

[p] **Disease/response assessment** – CT of the neck, chest, abdomen, and pelvis are to be obtained at screening (within 4 weeks prior to Cycle 1 Day 1) and every 8 weeks (±7 days) from Cycle 1 Day 1 for the first 6 months, then every 3 months until 1 year, and every 4 months thereafter. CT scans are to be performed using IV or oral contrast. For subjects intolerant to contrast agents, MRI scans may be used.

[q] **Survival status** – Survival information to be collected every 12 weeks following the EOT visit.

APPENDIX 2. CREATININE CLEARANCE

In the event the local laboratory does not calculate CrCL based on the most recent serum creatinine value, estimate the subject's CrCL using the serum creatinine value provided by the local laboratory, actual body weight, and the appropriate Cockcroft-Gault formula:

$$CrCL = \frac{(140 - age) \times (weight\ in\ kg)}{72 \times (serum\ creatinine\ in\ mg/dL)} \times (0.85\ if\ female)$$

If necessary, convert serum creatinine values from µmol/L to mg/dL by dividing by 88.4. For example, 100 µmol/L divided by 88.4 equals 1.131 mg/dL.

APPENDIX 3. DRUGS THAT PROLONG THE QTC INTERVAL AND/OR INDUCE TORSADES DE POINTES

Medications that have possible risk of prolonging the QT interval and/or Torsades de Pointes may have an unacceptable risk of co-administration with ME-344. Medications with a conditional risk may be used at the discretion of the Investigator.

All concomitant medications both prior to enrollment and during study conduct must be carefully reviewed and monitored. Subjects should avoid taking grapefruit juice.

Generic Name	Brand Names	Drug Class	Therapeutic Use
Alfuzosin	Uroxatral®	alpha1-blocker	benign prostatic hyperplasia
Amantadine	Symmetrel®, Symadine®	antiviral	anti-infective/ Parkinson's Disease
Amiodarone	Cordarone®, Pacerone®, Nexterone®	antiarrhythmic	abnormal heart rhythm
Amisulpride	Solian®, Supitac®, Soltus®, Amitrex®, Amazeo®	antipsychotic, atypical	psychosis
Amitriptyline	Elavil® (discontinued), Tryptomer®, Tryptizol®, Laroxyl®, Saroten®, Sarotex® Lentizol®, Endep®	antidepressant, tricyclic	depression
Amoxapine	Asendin®, Amokisan®, Asendis®, Defanyl®, Demolox®, Moxadil®	antidepressant, tetracyclic	depression
Anagrelide	Agrylin®, Xagrid®	phosphodiesterase 3 inhibitor	thrombocythemia
Apomorphine	Apokyn®, Ixense®, Spontane®, Uprima®	dopamine agonist	Parkinson's disease
Arsenic trioxide	Trisenox®	anticancer	leukemia
Atazanavir	Reyataz®	antiviral	HIV/AIDS
Azithromycin	Zithromax®, Zmax®	antibiotic	bacterial infection
Bedaquiline	Sirturo®	antibiotic	drug-resistant tuberculosis
Bortezomib	Velcade®, Bortecad®	proteasome inhibitor	multiple myeloma, lymphoma
Bosutinib	Bosulif®	tyrosine kinase inhibitor	leukemia
Chloral hydrate	Aquachloral®, Novo-Chlorhydrate®, Somnos®, Noctec®, Somnote®	sedative	sedation/insomnia
Chloroquine	Aralen®	antimalarial	malaria infection
Chlorpromazine	Thorazine®, Largactil®, Megaphen®	antipsychotic/ antiemetic	schizophrenia/nausea
Ciprofloxacin	Cipro®, Cipro-XR®, Neofloxin®	antibiotic	bacterial infection
Citalopram	Celexa®, Cipramil®	antidepressant, SSRI	depression

Generic Name	Brand Names	Drug Class	Therapeutic Use
Clarithromycin	Biaxin®, Prevpac®	antibiotic	bacterial infection
Clomipramine	Anafranil®	antidepressant, tricyclic	depression
Clozapine	Clozaril®, Fazaclo®, Versacloz®	antipsychotic, atypical	schizophrenia
Cocaine	Cocaine	local anesthetic	topical anesthetic
Crizotinib	Xalkori®	kinase inhibitor	anticancer
Dabrafenib	Tafinlar®	anticancer	melanoma
Dasatinib	Sprycel®	tyrosine kinase inhibitor	leukemia
Desipramine	Pertofrane®, Norpramine®	antidepressant, tricyclic	depression
Dexmedetomidine	Precedex®, Dexdor®, Dexdomitor®	sedative	sedation
Dihydroartemisinin +piperaquine	Eurartesim®	antimalarial	malaria
Diphenhydramine	Benadryl®, Nytol®, Unisom®, Sominex®, Dimedrol®, Daedalon®	antihistamine	allergic rhinitis, insomnia
Disopyramide	Norpace®	antiarrhythmic	abnormal heart rhythm
Dofetilide	Tikosyn®	antiarrhythmic	abnormal heart rhythm
Dolasetron	Anzemet®	antinausea	nausea, vomiting
Doxepin	Sinequan®, Silenor®, Aponal®, Adapine®, Doxal®, Deptran®, Sinquan®	antidepressant, tricyclic	depression
Dronedarone	Multaq®	antiarrhythmic	atrial fibrillation
Droperidol	Inapsine®, Droleptan®, Dridol®, Xomolix®	antipsychotic/ antiemetic	anesthesia adjunct, nausea
Eribulin	Halaven®	anticancer	metastatic breast neoplasias
Erythromycin	E.E.S.®, Robimycin®, EMycin®, Erymax®, Ery-Tab®, Eryc Ranbaxy®, Erypar®, Eryped®, Erythrocin Stearate Filmtab®, Erythrocot®, E-Base®, Erythroped®, Ilosone®, MY-E®, Pediamycin®, Zineryt®, Abboticin®, Abboticin-ES®, Erycin®, PCE Dispertab®, Stiemycine®, Acnasol®, Tiloryth®	antibiotic	bacterial infection; increase GI motility
Escitalopram	Cipralex®, Lexapro®, Nexito®, Anxiset-E® (India), Exodus® (Brazil), Esto® (Israel), Seroplex®, Elicea®, Lexamil®, Lexam®, Entact® (Greece), Losita® (Bangladesh), Reposil® (Chile), Animaxen®	antidepressant, SSRI	major depression/ anxiety disorders

Generic Name	Brand Names	Drug Class	Therapeutic Use
	(Colombia), Esitalo® (Australia), Lexamil® (South Africa)		
Famotidine	Pepcid®, Fluxid®, Quamatel®	H2-receptor antagonist	peptic ulcer/GERD
Felbamate	Felbatol	anticonvulsant	seizure
Fingolimod	Gilenya®	sphingosine phosphate receptor modulator	multiple sclerosis
Flecainide	Tambocor®, Almarytm®, Apocard®, Ecrinal®, Flécaine®	antiarrhythmic	abnormal heart rhythm
Fluconazole	Diflucan®, Trican®	antifungal	fungal infection
Fluoxetine	Prozac®, Sarafem®, Fontex®	antidepressant, SSRI	depression
Foscarnet	Foscavir®	antiviral	HIV/AIDS
Fosphenytoin	Cerebyx®, Prodilantin®	anticonvulsant	seizure
Furosemide (Frusemide)	Lasix®, Fusid®, Frumex®	diuretic	increase urine & salt loss
Galantamine	Reminyl®, Nivalin®, Razadyne-ER®,	cholinesterase inhibitor	dementia, Alzheimer's
Gemifloxacin	Factive®	antibiotic	bacterial infection
Granisetron	Kytril®, Sancuso®, Granisol®	antinausea	nausea, vomiting
Halofantrine	Halfan®	antimalarial	malaria infection
Haloperidol	Haldol® (US & UK), Aloperidin®, Bioperidolo®, Brotopon®, Dozic®, Duraperidol® (Germany), Einalon S®, Eukystol®, Halosten®, Keselan®, Linton®, Peluces®, Serenace®, Serenase®, Sigaperidol®	antipsychotic	schizophrenia, agitation
Hydrochlorothiazide	Apo-Hydro®, Aquazide H®, BP Zide®, Dichlotride®, Hydrodiuril®, HydroSaluric®, Hydrochlorot®, Microzide®, Esidrex®, Oretic®	diuretic	increase urine & salt loss
Ibutilide	Corvert®	antiarrhythmic	abnormal heart rhythm
Iloperidone	Fanapt®, Fanapta®, Zomaril®	antipsychotic, atypical	schizophrenia
Imipramine (melipramine)	Tofranil®	antidepressant, tricyclic	depression
Indapamide	Lozol®, Natrilix®, Insig®	diuretic	increase urine & salt loss
Isradipine	Dynacirc®	antihypertensive	high blood pressure
Itraconazole	Sporanox®, Onmel®	antifungal	fungal infection
Ketoconazole	Nizoral®, Sebizole®, Ketomed®, Keton®	antifungal	fungal infection
Lapatinib	Tykerb®, Tyverb®	anticancer	breast cancer, metastatic

Generic Name	Brand Names	Drug Class	Therapeutic Use
Levofloxacin	Levaquin®, Tavanic®	antibiotic	bacterial infection
Lithium	Eskalith®, Lithobid®	antimania	bipolar disorder
Methadone	Dolophine®, Symoron®, Amidone®, Methadose®, Physeptone®, Heptadon®	opiate	pain control, narcotic dependence
Mifepristone	Korlym®, Mifeprex®	progesterone antagonist	pregnancy termination
Mirabegron	Myrbetriq®	beta3 adrenergic antagonist	overactive bladder
Mirtazapine	Remeron	antidepressant, tetracyclic	depression
Moexipril/HCTZ	Uniretic®, Univasc®	antihypertensive	high blood pressure
Moxifloxacin	Avelox®, Avalox®, Avelon®	antibiotic	bacterial infection
Nicardipine	Cardene®	antihypertensive	high blood pressure
Nilotinib	Tasigna®	anticancer	leukemia
Norfloxacin	Noroxin®, Ambigram®	antibiotic	bacterial infections
Nortriptyline	Pamelor®, Sensoval®, Aventyl®, Norpress®, Allegron®, Noritren®, Nortrilen®	antidepressant, tricyclic	depression
Ofloxacin	Floxin®	antibiotic	bacterial infection
Olanzapine	Zyprexa®, Zydis®, Relprevv®	antipsychotic, atypical	schizophrenia, bipolar
Ondansetron	Zofran®, Anset®, Ondemet®, Zuplenz®, Emetron®, Ondavell®, Emeset®, Ondisolv®, Setronax®	antiemetic	nausea, vomiting
Oxytocin	Pitocin®, Syntocinon®	oxytocic	labor stimulation
Paliperidone	Invega®, Xepilon®	antipsychotic, atypical	schizophrenia
Palonosetron	Aloxi	antiemetics, selective 5-HT3 antagonist	chemotherapy-induced nausea and vomiting
Paroxetine	Paxil®, Aropax®, Pexeva®, Seroxat®, Sereupin®	antidepressant, SSRI	depression
Pasireotide	Signifor®	somatostatin analog	Cushing’s disease
Pazopanib	Votrient®	tyrosine kinase inhibitor	anticancer
Pentamidine	NebuPent®, Pentam®	antibiotic	pneumocystis pneumonia
Perflutren lipid microspheres	Definity®	imaging contrast agent	echocardiography
Pimozide	Orap®	antipsychotic	Tourette's tics
Posaconazole	Noxafil®, Posamol®	antifungal	fungal infection

Generic Name	Brand Names	Drug Class	Therapeutic Use
Procainamide (Oral off US market)	Pronestyl®, Procan®	antiarrhythmic	abnormal heart rhythm
Promethazine	Phenergan®	antipsychotic/ antiemetic	nausea
Protriptyline	Vivactil®	antidepressant, tricyclic	depression
Quetiapine	Seroquel®	antipsychotic, atypical	schizophrenia
Quinidine	Quinaglute®, Duraquin®, Quinact®, Quinidex®, Cin-Quin®, Quinora®	antiarrhythmic	abnormal heart rhythm
Quinine sulfate	Qualaquin®	antimalarial	malaria or leg cramps
Ranolazine	Ranexa®, Ranozex®	antianginal	chronic angina
Rilpivirine	Edurant®, Complera®, Eviplera®	antiviral	HIV/AIDS
Risperidone	Risperdal®	antipsychotic, atypical	schizophrenia
Ritonavir	Norvir®	antiviral	HIV/AIDS
Saquinavir	Invirase®(combo)	antiviral	HIV/AIDS
Sertraline	Zoloft®, Lustral®, Daxid®, Altruline®, Besitran®, Deprax®, Elrval®, Emergen®, Gladem®, Implicane®, Sedoran®, Sealdin®, SerivoLowfin®, Stimuloton®, Tresleen®, Sertralin Bluefish®	antidepressant, SSRI	depression
Sevoflurane	Ulane®, Sojourn®	anesthetic, general	anesthesia
Solifenacin	VESIcare®	muscle relaxant	treatment of overactive bladder
Sorafenib	Nexavar®	tyrosine kinase inhibitor	anticancer
Sotalol	Betapace®, Sotalex®, Sotacor®	antiarrhythmic	abnormal heart rhythm
Sunitinib	Sutent®	anticancer	renal cell cancer, GIST
Tacrolimus	Prograf®, Prograf®, Advagraf®, Protopic®	immunosuppressant	immune suppression
Tamoxifen	Nolvadex®(discontinued), Istubal®, Valodex®	anticancer	breast cancer
Telaprevir	Incivek®, Incivo®	antiviral	Hepatitis C
Telavancin	Vibativ®	antibiotic	bacterial infection
Telithromycin	Ketek®	antibiotic	bacterial infection
Tetrabenazine (Orphan drug in US)	Nitoman®, Xenazine®	monoamine transporter inhibitor	chorea (Huntington's disease)
Thioridazine	Mellaril®, Novoridazine®, Thioril®	antipsychotic	schizophrenia
Tizanidine	Zanaflex®, Sirdalud®	muscle relaxant	spasticity

Generic Name	Brand Names	Drug Class	Therapeutic Use
Tolterodine	Detrol®, Detrusitol®	muscle relaxant	bladder spasm
Toremifene	Fareston®	estrogen agonist/antagonist	anticancer
Trazodone	Desyrel® (discontinued 6/13), Oleptro®, Beneficat®, Deprax®, Desirel®, Molipaxin®, Thombran®, Trazorel®, Trialodine®, Trittico®, Mesyrel®	antidepressant, SARI	depression, insomnia
Trimethoprim-Sulfa	Septra®, Bactrim®, Sulfatrim®, Biseptol®, Co-trimoxazole®, Cotrim®, Septrin®, Trisul®	antibiotic	bacterial infection
Trimipramine	Surmontil®, Rhotrimine®, Stangyl®	antidepressant, tricyclic	depression
Vandetanib	Caprelsa®	anticancer	thyroid cancer
Vardenafil	Levitra®	phosphodiesterase inhibitor	vasodilator
Vemurafenib	Zelboraf®	kinase inhibitor	anticancer
Venlafaxine	Effexor®, Efexor®	antidepressant, SNRI	depression
Voriconazole	VFend®	antifungal	antifungal
Vorinostat	Zolinza®	anticancer	lymphoma
Ziprasidone	Geodon®, Zeldox®	antipsychotic, atypical	schizophrenia

APPENDIX 4. SENSITIVE IN VIVO CYP SUBSTRATES AND CYP SUBSTRATES WITH NARROW THERAPEUTIC RANGE

The following agents should be used with caution in patients enrolled in this study:

CYP Enzymes	Sensitive substrates [a]	Substrates with narrow therapeutic range [b]
CYP1A2	alosetron, caffeine, duloxetine, melatonin, ramelteon, tacrine, tizanidine	theophylline, tizanidine
CYP2B6 [c]	bupropion, efavirenz	
CYP2C8	repaglinide[d]	Paclitaxel
CYP2C9	celecoxib	warfarin, phenytoin
CYP2C19	lansoprazole, omeprazole, S-mephenytoin	S-mephenytoin
CYP3A [e]	alfentanil, aprepitant, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tolvaptan, tipranavir, triazolam, vardenafil	alfentanil, astemizole [f], cisapride [f], cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine [f]
CYP2D6	atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine, venlafaxine	Thioridazine

[a] *Sensitive CYP substrates* refers to drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a known CYP inhibitor.

[b] CYP *substrates with narrow therapeutic range* refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).

[c] The AUC of these substrates were not increased by 5-fold or more with a CYP2B6 inhibitor, but they represent the most sensitive substrates studied with available inhibitors evaluated to date.

[d] Repaglinide is also a substrate for OATP1B1, and it is only suitable as a CYP2C8 substrate if the inhibition of OATP1B1 by the investigational drug has been ruled out.

[e] Because a number of CYP3A substrates (e.g., darunavir, maraviroc) are also substrates of P-glycoprotein (P-gp), the observed increase in exposure could be due to inhibition of both CYP3A and P-gp.

[f] Withdrawn from the United States (US) market because of safety reasons.

APPENDIX 5. CYTOCHROME P450 DRUG-INTERACTIONS FOR INHIBITORS, INDUCERS, AND TRANSPORTERS

P450 Drug-Interactions Inhibitors (strong inhibitors are shown in bold font)

1A2	2B6	2C19	2C9	2D6	3A4,5,7
acyclovir amiodarone caffeine cimetidine **ciprofloxacin** **enoxacin** echinacea **enoxacin** famotidine **flutamide** **fluvoxamine** grapefruit juice lidocaine **lomefloxacin** **mexiletine** ***Mexitil*** moclobemide **norfloxacin** ofloxacin oral contraceptives perphenazine phenacetin **propafenone** ropinirole tacrine ticlopidine tocainide verapamil zileuton *Zyflo*	**clopidogrel** ***Plavix*** efavirenz fluoxetine fluvoxamine ketoconazole memantine nelfinavir oral contraceptives paroxetine ritonavir thiotepa **ticlopidine** ***Ticlid***	artemisinin chloramphenicol delavirdine efavirenz esomeprazole felbamate **fluconazole** **fluoxetine** **fluvoxamine** indomethacin inh modafinil *Provigil* omeprazole *Prilosec* oral contraceptives oxcarbazepine **ticlopidine** topiramate voriconazole	amiodarone anastrazole cimetidine delavirdine efavirenz fenofibrate *Tricor* fluconazole {fluoxetine} fluvoxamine fluvastatin isoniazid ketoconazole leflunomide modafiinil phenylbutazone {sertraline} sulfamethoxazole **sulfaphenazole** tamoxifen teniposide valproic acid voriconazole *Vfend* {zafirlukast}, {*Accolate*} 5-fluorouracil	amiodarone {amitriptyline} **bupropion** celecoxib chlorpheniramine chlorpromazine cimetidine **cinacalcet** {citalopram} chlorpheniramine clomipramine {desipramine} diphenhydramine doxepin duloxetine {fluvoxamine} **fluoxetine** **goldenseal** halofantrine haloperidol {hydroxyzine} imipramine methadone metoclopramide moclobemide **paroxetine** pimozide propafenone **quinidine/quinine** ritonavir {sertraline} **terbinafine** thioridazine ticlopidine	amiodarone amprenavir aprepitant - initially **atazanavir** **boceprevir** ***Reyataz*** {cimetidine} ciprofloxacin **clarithromycin** **delavirdine** diltiazem doxycycline echinacea enoxacin erythromycin fluconazole fluvoxamine **grapefruit juice** **imatinib** **indinavir** **itraconazole** **ketoconazole** miconazole **nefazodone** **nelfinavir** **ritonavir and boosted PIs** **saquinavir** **telithromycin** verapamil **voriconazole**
NAT2 Acetaminophen					

P450 Drug-Interactions Inducers (increase the ability of the enzyme to metabolize the substrates) (strong inducers are shown in bold font)

1A2	2B6	NAT2	2C19	2C9	2D6	3A4,5,7
carbamazepine charbroiled meat cigarette smoke cruciferous veggies esomeprazole griseofulvin insulin lansoprazole marijuana smoke moricizine omeprazole rifampin ritonavir	lopinavir/ritonavir phenobarbital phenytoin rifampin **carbamazepine**	retinoic acid	gingko biloba **rifampin** St John's Wort	aprepitant-long term barbiturates bosentan carbamazepine rifampin-chronic ritonavir and boosted protease inhibitors St John's Wort-long-term aprepitant-long term barbiturates bosentan carbamazepine	rifampin	aprepitant -long term barbiturates bosentan **carbamazepine** efavirenz felbamate glucocorticoids modafinil nafcillin nevirapine {oxcarbazepine} **phenytoin** primidone **rifampin** **St. John's Wort** pioglitazone *Actos* topiramate at >200 mg/d

Drug-Interactions Transporters

Carbamazepine	Norethindrone
Cefadroxil	Phenformin
Cefamandole	Phenobarbital
Cefazolin	Phenoxybenzamine
Cyclosporine	Prazosin
Desipramine	Probenecid
Disopyramide	Quinine
Elacridar	Rifabutin
Erythromycin	Rifampin
Gefitinib	Secobarbital
Isoniazid	Valspodar
Midazolam	Verapamil

APPENDIX 6. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS SCALE

The following scale should be used to determine ECOG performance status:

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

Source: Oken 1982.

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