CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of GS-5745 as Monotherapy and in Combination with Chemotherapy in Subjects with Advanced Solid Tumors	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404	
IND No.:	116561	
EudraCT Number:	Not Applicable	
Indication:	Solid Tumors	
Protocol ID:	GS-US-296-0101	
Gilead Sciences Medical Monitor:	Name: Telephone: Fax:	PPD PPD PPD
Protocol Version/Date:	Original: Amendment 1: Amendment 2: Amendment 3: Amendment 4: Amendment 5: Amendment 6:	17 December 2012 07 February 2013 27 March 2013 27 May 2014 04 September 2015 16 May 2016 01 August 2016

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Study Title:	A Phase 1 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of GS-5745 as Monotherapy and in Combination with Chemotherapy in Subjects with Advanced Solid Tumors
IND Number:	116561
EudraCT Number:	Not Applicable
Study Centers Planned:	Approximately 25 centers in the United States (US)
Primary Objectives:	• To determine the maximum tolerated dose (MTD) of GS-5745 monotherapy in subjects with advanced solid tumors • To characterize the safety and tolerability of GS-5745 as monotherapy and in combination with various chemotherapy regimens in subjects with select tumor types
Secondary Objectives:	• To characterize the pharmacokinetics (PK) of GS-5745 • To evaluate the formation of anti-GS-5745 antibodies [redacted]
Exploratory Objective:	[redacted]
Study Design:	This is an open-label, multicenter, sequential dose-escalation, and expansion study to evaluate the safety, tolerability, PK, and pharmacodynamics of GS-5745 alone and in combination with chemotherapy. The study will be conducted in 2 parts (Part A and Part B).

Part A:

Cohorts of subjects with advanced solid tumors who have failed or are intolerant to standard therapy or for whom no standard therapy exists will be sequentially enrolled at progressively higher dose levels to receive GS-5745 as monotherapy via intravenous (IV) infusion every 2 weeks (Q2W). Dose escalation [3 + 3] will be performed with cohort sizes of 3 to 6 subjects. A single subject will initially be enrolled into the first dosing cohort to evaluate any unexpected adverse effects. Provided that there are no significant safety signals up to 24 hours postdose, the remaining 2 subjects will be dosed. The starting dose will be 200 mg. Subsequent doses of 600 and 1800 mg are planned. The safety and tolerability of each dose level will be assessed after all subjects in the cohort have been followed for at least 28 days after the first infusion of GS-5745. Cohort dose escalation will occur if no subjects experience dose limiting toxicities (DLTs) during the first 28 days of study drug dosing. If one subject within the initial cohort of 3 subjects experiences a DLT during the first 28 days of study drug dosing, an additional 3 subjects will be enrolled at the same dose level. If no DLTs are observed in the additional 3 subjects, dose escalation will occur. If 2 or more subjects experience DLTs within the first 28 days, dose de-escalation to an intermediate dose will occur. Specifically, if 2 or more subjects experience DLTs at 1800 mg, then 1200 mg will be explored, and if 2 or more subjects experience DLTs at 600 mg, then 400 mg will be explored. The maximum tolerated dose (MTD) is the highest dose level with a subject incidence of DLTs during the first 28 days of study drug dosing of 0 or 1 out of 6.

After determination of MTD, Part B will commence. During the conduct of Part B, up to 3 additional cohorts consisting of no more than 10 subjects each may be studied with GS-5745 at monotherapy doses up to MTD given every 2 weeks to obtain additional information on PK and pharmacodynamics.

A DLT is a toxicity defined below considered possibly related to GS-5745 occurring during the DLT assessment window (Day 1 through Day 29) in each dose escalation cohort.

- Grade 4 neutropenia (absolute neutrophil count [ANC] < 500/μL) for > 7 days, or febrile neutropenia (ANC < 1000/μL with fever > 101 °F [38.5 °C])
- Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia associated with bleeding

- Grade 3 or 4 non-hematologic toxicity (excluding rash, nausea, diarrhea, and vomiting if controlled with standard supportive care)
- Treatment delay of ≥ 14 days due to unresolved toxicity
- Non-hematologic toxicity of ≥ Grade 2 (at any time during treatment) that, in the judgment of the investigators and the Medical Monitor, is dose-limiting
- For certain toxicities, such as laboratory assessments without a clear clinical correlate, a discussion between the investigator, Medical Monitor, and the Sponsor may take place to determine whether this adverse event (AE) should be assessed as a DLT necessitating dose reduction.

Part B:

The dose expansion will begin once all subjects in the dose escalation portion of Part A have completed the 28-day DLT period. Between 115 to 295 subjects with advanced pancreatic adenocarcinoma (Cohort 4), lung adenocarcinoma (Cohort 5), lung squamous cell carcinoma (Cohort 6), esophagogastric adenocarcinoma (Cohort 7), colorectal cancer (CRC) in the first-line setting (Cohort 8), CRC in the second-line setting (Cohort 9), or breast cancer (Cohort 10) will be enrolled to receive GS-5745 via IV every 2 to 3 weeks in combination with chemotherapy. Thirty-five subjects will be enrolled in Cohort 4, 10 subjects each in Cohorts 5 and 6, and 15 subjects each in Cohorts 7 through 10. During the conduct of Part B, a maximum of 25 additional subjects in each cohort may be enrolled to obtain information on safety, PK, pharmacodynamics, and tumor response.

The cohort dose levels for GS-5745 in Part B are presented below and will be based on the MTD determined in Part A.

	Doses to be Used in Part B (mg)	
MTD from Part A (mg)	**Q2W**	**Q3W**
200	133	200
400	267	400
600	400	600
1200	800	1200
1800	800	1200

Q2W = every 2 weeks; Q3W = every 3 weeks

The planned number of subjects and dosing intervals for Parts A and B are presented below.

Cohort	No. Subjects	GS-5745 Dose (mg)	Dosing Interval
Part A: Dose Escalation			
1	3 to 6	200	Q2W
2	3 to 6	600	Q2W
3	6	1800	Q2W
Part B: Dose Expansion			
4	35	Based on MTD from Part A (see table above)	Q2W
5	10 to 35		Q3W
6	10 to 35		Q3W
7	15 to 40		Q2W
8	15 to 55*		Q2W
9	15 to 55**		Q2W
10	15 to 40		Q2W

Q2W = every 2 weeks; Q3W = every 3 weeks

* For Cohort 8 (first-line CRC), the sample size of 40 subjects was initially planned. In amendment 5, the dose of bevacizumab is corrected to be 5 mg/kg Q2W. Up to 15 subjects who previously started bevacizumab treatment at other dose levels will be replaced. Therefore, a total of up to 55 subjects may be enrolled in Cohort 8.

** For Cohort 9 (second-line CRC), the sample size of 40 subjects was initially planned. In amendment 5, the dose of bevacizumab is corrected to be 5 mg/kg Q2W. Up to 15 subjects who previously started bevacizumab treatment at other dose levels will be replaced. Therefore, a total of up to 55 subjects may be enrolled in Cohort 9.

Number of Subjects Planned:

Up to 343 subjects will be enrolled. Part A will comprise between 12 to 48 subjects; Part B will comprise between 115 to 295 subjects.

Target Population:

Part A: Adult subjects with a histologically or cytologically confirmed advanced malignant solid tumor that is refractory to or intolerant of standard therapy or for which no standard therapy is available

Part B: Adult subjects with histologically or cytologically confirmed advanced pancreatic adenocarcinoma, non-small cell lung cancer (NSCLC), esophagogastric adenocarcinoma, CRC, or breast cancer who are candidates for chemotherapy treatment

Duration of Treatment:

Until disease progression, unacceptable toxicity, withdrawal of consent, or other reasons specified in Section 6.4

Diagnosis and Eligibility Criteria:

Inclusion Criteria

Subjects must meet *all* of the following inclusion criteria to be eligible for participation in this study:

1) Male or female ≥ 18 years of age
2) Part A: Histologically or cytologically confirmed advanced malignant solid tumor that is refractory to or intolerant of standard therapy or for which no standard therapy is available
3) Part B: Pancreatic Adenocarcinoma (Cohort 4)
    a) Presence of histologically confirmed inoperable locally advanced or metastatic pancreatic adenocarcinoma
4) Part B: NSCLC (Cohorts 5 and 6)
    a) Stage IIIB with malignant pleural effusion/pleural seeding or stage IV histologically confirmed NSCLC
    b) Absence of known epidermal growth factor receptor (EGFR) mutation
    c) Absence of known translocation or inversion events involving the ALK gene locus (resulting in EML4-ALK fusion)
5) Part B: Esophagogastric Adenocarcinoma (Cohort 7)
    a) Histologically confirmed inoperable advanced gastric adenocarcinoma (including adenocarcinoma of the gastroesophageal junction) or relapsed gastric adenocarcinoma
    b) Human epidermal growth factor receptor 2 (HER2)-negative tumor (primary tumor or metastatic lesion)
6) Part B: Colorectal Cancer (Cohort 8)
    a) Histologically confirmed inoperable advanced adenocarcinoma of the colon or rectum
    b) Radiographically measureable disease
    c) No prior cytotoxic chemotherapy to treat their metastatic disease
7) Part B: Colorectal Cancer (Cohort 9)
    a) Histologically confirmed inoperable advanced adenocarcinoma of the colon or rectum
    b) Radiographically measureable disease
    c) Received first-line combination therapy containing oxaliplatin and fluoropyrimidine with or without bevacizumab for metastatic disease with documented evidence of disease progression during or after treatment completion

8) Part B: Breast Cancer (Cohort 10)
   a) Histologically or cytologically confirmed metastatic breast cancer
   b) Radiographically measureable disease (bone-only, central nervous system [CNS], lymphangitic pulmonary metastases, and previously irradiated tumors without subsequent progression are considered nonmeasurable for the purposes of this study)
   c) Previous hormonal therapy for metastatic breast cancer or cytotoxic adjuvant chemotherapy is allowed
   d) Subjects who have received taxane-based adjuvant therapy are required to have had a disease-free interval of at least 12 months after completion of taxane therapy
   e) Treatment with weekly single-agent paclitaxel is appropriate in the opinion of the treating physician (eg, hormone-receptor negative disease, hormone therapy unresponsive)
   f) HER-2 negative tumor (primary tumor or metastatic lesion)
9) All acute toxic effects of any prior antitumor therapy resolved to Grade ≤ 1 before the start of study drug dosing (with the exception of alopecia [Grade 1 or 2 permitted] and neurotoxicity [Grade 1 or 2 permitted]).
10) Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1
11) Life expectancy of > 3 months in the opinion of the investigator
12) Adequate organ function defined as follows:
   a) Hematologic: platelets ≥ 100×10^9/L; hemoglobin ≥ 9.0 g/dL; ANC ≥ 1.5×10^9/L
   b) Hepatic: aspartate aminotransferase (AST) / alanine aminotransferase (ALT) ≤ 2.5 × upper limit of normal (ULN) (if liver metastases are present, ≤ 5 × ULN); total or conjugated bilirubin ≤ 1.5 × ULN
   c) Renal: serum creatinine ≤ 1.5 × ULN

13) Coagulation: international normalized ratio (INR) ≤ 1.6 (unless receiving anticoagulation therapy). Subjects on full-dose oral anticoagulation must be on a stable dose (minimum duration 14 days). If receiving warfarin, the subject must have an INR ≤ 3.0 and no active bleeding (ie, no bleeding within 14 days prior to first dose of study drug). Subjects on low molecular weight heparin will be allowed.

14) For female subjects of childbearing potential, willingness to use a protocol-recommended method of contraception (see Section 7.12) from the screening visit throughout the study treatment period and for 30 days following the last dose of GS-5745. ***Note: a female subject is considered to be of childbearing potential unless she has had a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy; has medically documented ovarian failure (with serum estradiol and follicle-stimulating hormone [FSH] levels within the institutional postmenopausal range and a negative serum or urine β-HCG), or is menopausal (age ≥ 55 years with amenorrhea for ≥ 6 months).***

15) For male subjects of childbearing potential having intercourse with females of childbearing potential, willingness to use a protocol-recommended method of contraception from the start of study drug, throughout the study treatment period, and for 90 days following the last dose of GS-5745, and to refrain from sperm donation from the start of study drug, throughout the study treatment period, and for 90 days following the last dose of GS-5745. ***Note: A male subject is considered able to father a child unless he has had a bilateral vasectomy with documented aspermia or a bilateral orchiectomy, or has ongoing testicular suppression with a depot luteinizing hormone-releasing hormone (LH-RH) agonist (eg, goserelin acetate [Zoladex®]), leuprolide acetate [Lupron®]), or triptorelin pamoate [Trelstar®]).***

16) Willingness to comply with scheduled visits, drug administration plan, imaging studies, laboratory tests, other study procedures, and study restrictions

17) Evidence of a signed informed consent form

Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria will not be enrolled in this study:

1) History or evidence of clinically significant disorder, condition, or disease that, in the opinion of the investigator and Medical Monitor would pose a risk to subject safety or interfere with the study evaluations, procedures, or completion
2) Pregnant or lactating
3) Subject with known CNS metastases, unless metastases are treated and stable and the subject does not require systemic steroids
4) Part B: Small cell lung cancer
5) Part B: Diagnosis of pancreatic islet cell neoplasm
6) Part B: With the exception of Cohort 9, subjects who have received prior cytotoxic chemotherapy to treat their metastatic disease
7) Myocardial infarction, symptomatic congestive heart failure (New York Heart Association Classification > Class II), unstable angina, or serious uncontrolled cardiac arrhythmia within the last 6 months of study Day 1
8) History of major surgery within 28 days prior to enrollment
9) Serious systemic fungal, bacterial, viral, or other infection that is not controlled or requires IV antibiotics
10) Anti-tumor therapy (chemotherapy, antibody therapy, molecular targeted therapy) within 28 days or 5 half-lives, whichever is shorter, of study drug dosing (6 weeks for nitrosoureas, mitomycin C, or molecular agents with $t_{1/2}$ > 10 days); concurrent use of hormone therapy for breast or prostate cancer is permitted
11) Clinically significant bleeding within 28 days of Day 1
12) Subjects known to be positive for human immunodeficiency virus (HIV), hepatitis C, or hepatitis B

Study Procedures/ Frequency:

Screening

Screening (for Parts A and B) will commence with obtaining the subject's signed informed consent and will occur up to 28 days prior to the first dosing of study drug on Day 1. Screening procedures will include the following: medical history review; physical examination; vital signs; 12-lead electrocardiogram (ECG); ECOG performance status; prior/concomitant medication review; blood collection for pregnancy test (females), chemistry, hematology, and coagulation; AE assessment, and computed tomography (CT) or magnetic resonance imaging (MRI) (scans obtained as part of standard medical practice up to 28 days prior to Day 1 of Cycle 1 are acceptable). Baseline tumor lesions will be measured and characterized prior to Cycle 1 Day 1 to assess the subject disease status prior to beginning treatment.

Treatment

Part A

Subjects meeting eligibility will receive GS-5745 by IV infusion over approximately 30 minutes every 2 weeks. Safety and efficacy assessments will occur on an outpatient basis including assessment of tumor response, physical examination, vital signs, ECG, collection of blood samples (for routine safety laboratory assessments, GS-5745 PK, anti-GS-5745 antibody, tumor markers, and biomarkers at applicable visits), urine pregnancy (prior to each infusion of GS-5745 in women of childbearing potential), and assessment of AEs. In addition, subjects will undergo CT or MRI scans every 8 weeks.

A subject who does not show evidence of disease progression by clinical assessment or by CT or MRI may continue receiving GS-5745 every 2 weeks until disease progression (clinical or radiographic), unacceptable toxicity, withdrawal of consent, or other reasons specified in Section 6.4.

Part B

Subjects with pancreatic adenocarcinoma, esophagogastric adenocarcinoma, CRC, or breast cancer will receive GS-5745 by IV infusion over approximately 30 minutes every 2 weeks in addition to the 28-day cycle chemotherapy (gemcitabine and nab-paclitaxel for pancreatic; mFOLFOX6 for esophagogastric; mFOLFOX6 and bevacizumab for first-line CRC; FOLFIRI and bevacizumab for second-line CRC; paclitaxel for breast) as described in the Reference Therapy Section below.

	Subjects with NSCLC will receive GS-5745 by IV infusion over approximately 30 minutes every 3 weeks (Q3W) in addition to the 21-day cycle chemotherapy (carboplatin and pemetrexed in subjects with lung adenocarcinoma; carboplatin and paclitaxel in subjects with lung squamous cell carcinoma) as described in the Reference Therapy Section below. Safety and efficacy assessments will occur on an outpatient basis including assessment of tumor response, physical examination, vital signs, ECG, collection of blood samples (for routine safety laboratory assessments, GS-5745 PK, anti-GS-5745 antibody, tumor markers, and biomarkers at applicable visits), urine pregnancy (prior to each infusion of GS-5745 in women of childbearing potential), and assessment of AEs. A CT or MRI scan will be performed during the last week of even-numbered cycles (ie, Cycles 2, 4, 6, etc.) for subjects with pancreatic adenocarcinoma, esophagogastric adenocarcinoma, CRC, and breast cancer and during the last week of every third cycle (ie, Cycles 3, 6, 9, etc.) for subjects with NSCLC. **Continuation of Treatment** In Parts A and B, study drug dosing will continue in the absence of disease progression or toxicity warranting discontinuation of therapy.
Test Product, Dose, and Mode of Administration:	GS-5745 is formulated as a sterile, aqueous buffered solution and is stored at 2 to 8 °C in single-use 10 mL vials. Prior to administration, single and/or multiple vials of GS-5745 will be diluted into a sterile IV bag / solution. Subjects will be administered GS-5745 IV over approximately 30 minutes. **Part A:** subjects will be administered GS-5745 IV every 2 weeks. **Part B:** subjects will be administered GS-5745 IV every 2 weeks (pancreatic, esophagogastric, CRC, and breast) or every 3 weeks (lung).

Reference Therapy, Dose, and Mode of Administration:	Part B Only **Pancreatic Adenocarcinoma:** Gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15 of a 28-day treatment cycle and nab-paclitaxel 125 mg/m^2 IV on Days 1, 8, and 15 of a 28-day treatment cycle. **NSCLC:** Carboplatin IV dosed to an area under the concentration-time curve of 6 mg/mL•min (AUC 6) on Day 1 of each 21-day treatment cycle and pemetrexed 500 mg/m^2 IV on Day 1 of each 21-day treatment cycle in subjects with lung adenocarcinoma. Chemotherapy will consist of carboplatin IV dosed to an area under the concentration-time curve of 6 mg/mL•min (AUC 6) on Day 1 of each 21-day treatment cycle and paclitaxel 200 mg/m^2 IV on Day 1 of each 21-day treatment cycle in subjects with lung squamous cell carcinoma. Subjects who have not had disease progression after 4 cycles of treatment may have some of their treatment reduced based upon the investigator's assessment of what is in the subject's best interests. However, dosing with GS-5745 should be continued per protocol. **Esophagogastric Adenocarcinoma:** mFOLFOX6 on Days 1 and 15 of each 28-day treatment cycle. The mFOLFOX6 dosing regimen will consist of *l*-leucovorin (LV) 200 mg/m^2 or *dl*-LV 400 mg/m^2 and oxaliplatin 85 mg/m^2 followed by bolus 5-FU 400 mg/m^2 and a 46-hour infusion of 5-FU 2400 mg/m^2. Administration of mFOLFOX6 will immediately follow administration of GS-5745 on Day 1 of each cycle. **First-Line CRC:** mFOLFOX6 on Days 1 and 15 of each 28-day treatment cycle and bevacizumab 5 mg/kg IV on Days 1 and 15 of each 28-day treatment cycle; mFOLFOX6 dosing described above. **Second-Line CRC:** FOLFIRI on Days 1 and 15 of each 28-day treatment cycle and bevacizumab 5 mg/kg IV on Days 1 and 15 of each 28-day treatment cycle. The FOLFIRI dosing regimen will consist of *l*-LV 200 mg/m^2 or *dl*-LV 400 mg/m^2 as a 2-hour infusion, and irinotecan 180 mg/m^2 given as a 90-minute infusion in 500 mL dextrose 5% via a Y-connector, followed by bolus 5-FU 400 mg/m^2 and a 46-hour infusion of 5-FU 2400 mg/m^2. **Breast Cancer:** Paclitaxel 80 mg/m^2 IV over 1 hour on Days 1, 8, and 15 of each 28-day treatment cycle.
Criteria for Evaluation:	
Safety:	Safety will be evaluated by assessment of clinical laboratory tests, physical examinations, 12-lead ECGs, vital sign measurements, and by the documentation of AEs.
PK:	The PK parameters calculated will include: C_{max}, AUC, CL, and $t_{1/2}$.

Statistical Methods:

Descriptive statistics, including means, medians, standard deviations, and ranges will be calculated for continuous variables, and categorical data will be summarized using frequency counts and percentages.

Sample Size

Parts A and B: Part A will comprise 12 to 48 subjects and Part B will comprise 115 to 295 subjects (including up to 15 replacement subjects for Cohort 8 and Cohort 9, respectively). The sample size is based on practical considerations and is consistent with this type of study.

Ten subjects each will be enrolled in Cohorts 5 and 6, and 15 subjects each in Cohorts 7, 8, 9 and 10. A maximum of 25 additional subjects in each cohort may be enrolled to obtain information on safety, PK, pharmacodynamics, and tumor response.

Cohort 4 (Pancreatic Adenocarcinoma): With the assumption of an overall response rate of 40%, the 90% confidence interval (CI) would be 19% to 64% with a sample size of 15, and 26% to 55% with a sample size of 35. A total of 35 subjects will be enrolled in Cohort 4.

Cohort 8 (First-Line CRC): With the assumption of an ORR of 60%, the 90% CI would be 36% to 81% with sample size of 15, and 46% to 73% with a sample size of 40.

Cohort 9 (Second-Line CRC): With the assumption of an ORR of 25%, the 90% CI would be 10% to 51% with sample size of 15, and 14% to 39% with a sample size of 40.

Cohort 10 (Breast Cancer): With the assumption of an ORR of 40%, the 90% CI would be 19% to 64% with sample size of 15, and 27% to 54% with a sample size of 40.

This study will be conducted in accordance with the guidelines of Good Clinical Practices (GCPs) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

5-FU	5-fluorouracil
AB0041	murine anti-human MMP9 monoclonal antibody
AB0046	murine anti-human MMP9 monoclonal antibody
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{0\text{-}last} + (C_{last}/\lambda_z)$
AUC_{last}	area under the concentration versus time curve to the last measurable concentration
AUC_{tau}	area under the concentration versus time curve over the dosing interval
BUN	blood urea nitrogen
CA-125	cancer antigen-125
CA 19-9	carbohydrate antigen 19-9
CBC	complete blood count
CEA	carcinoembryonic antigen
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
CI	confidence interval
CL	clearance
C_{last}	last observed quantifiable drug concentration
C_{max}	the maximum observed drug concentration
CNS	central nervous system
ConMed	concomitant medication
CR	complete response
CRC	colorectal cancer
CRO	contract research organization
CT	computed tomography scan
C_{tau}	observed drug concentration at the end of the dosing interval
CTCAE	Common Terminology Criteria for Adverse Events
Da	dalton
dL	deciliter
DSPH	Drug Safety and Public Health
ECG	electrocardiogram
ECM	extracellular matrix

ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form(s)
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
EML4	echinoderm microtubule associated protein like 4
EOI	end of infusion
EOS	end-of-study
EudraCT	European clinical trials database
FDA	(United States) Food and Drug Administration
FDP	fibrin degradation products
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice (Guidelines)
Gilead	Gilead Sciences, Inc.
β-HCG	beta human chorionic gonadotropin
HED	human equivalent dose
HER2	human epidermal growth factor receptor 2
HLGT	high-level group term
HLT	high-level term
hr	hour
HSP	hysterosalpingogram
HUS	hemolytic uremic syndrome
ICF	informed consent form
ICH	International Conference on Harmonisation
IHC	immunohistochemistry
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
INR	international normalized ratio
IRB	institutional review board
ISH	in situ hybridization
IUD	intrauterine device
IV	intravenous
IxRS	interactive voice/web response system
Kg	kilogram
LLT	lower-level term
LV	leucovorin
m	meter
MedDRA	Medical Dictionary for Regulatory Activities
mFOLFOX6	5-FU, leucovorin, and oxaliplatin
mg	milligram
mL	milliliter

mm	millimeter
MMP	matrix metalloproteinase
MRI	magnetic resonance image
MSS	musculoskeletal syndrome
MTD	maximum tolerated dose
MW	molecular weight
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGAL	neutrophil gelatinase-associated lipocalin
NOAEL	no-observed adverse effect levels
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PE	physical examination
PFS	progression-free survival
PK	pharmacokinetic
PLT	platelet(s)
PR	partial response
PSA	prostate-specific antigen
PT	prothrombin time
PTT	partial thrombin time
Q2W	every two weeks
Q3W	every three weeks
QRS	electrocardiographic deflection between the beginning of the Q wave and termination of the S wave representing time for ventricular depolarization
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave representing the time for both ventricular depolarization and repolarization to occur
QTc	QT interval corrected for heart rate
RECIST	Response Evaluation Criteria in Solid Tumors
SADR	serious adverse drug reaction
SAE	serious adverse event
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TIMP	tissue inhibitors of metalloproteinases
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
$T_{1/2}$	estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
UC	ulcerative colitis

ULN	upper limit of the normal range
US	United States
USP	United States Pharmacopoeia
VEGF	vasoactive endothelial growth factor
WBC	white blood cell count
wks	weeks
Zn	zinc
λ_z	terminal elimination rate constant; estimated by linear regression of the terminal elimination phase of the log concentration versus time curve of the drug

1. INTRODUCTION

1.1. Background

Matrix metalloproteinases (MMPs) comprise a family of at least 23 Zn^{2+}-dependent proteases which are primarily involved in the degradation and remodeling of the extracellular matrix (ECM) and basement membranes in many normal as well as pathologic biological processes. They are typically grouped based on their structure or their primary substrates and include the gelatinases, collagenases, stromelysins, matrilysins, an elastase, and membrane-type MMPs, a group of cell surface tethered proteases {Hu et al 2007}, {Mott et al 2004}. The gelatinases comprise MMP2 and MMP9, sometimes referred to as type IV collagenases, which are named for their ability to degrade type IV collagen and gelatin, a denatured form of collagen {Kridel et al 2001}, {Chen et al 2002}. The contrasting roles of MMP9 and MMP2 have been revealed in a variety of studies which support a more ubiquitous expression pattern and associated role for MMP2 in normal tissue homeostasis, compared with disease-induced and pathology-associated expression and activity of MMP9 {Hu et al 2007}, {Garg et al 2009}, {Itoh et al 2002}, {Agrawal et al 2006}, {Dubois et al 1999}, {Li et al 2009}, {Miyazaki et al 2011}, {Castaneda et al 2005}, {Naito et al 2005}, {Santana et al 2006}. Additional substrates have been identified for MMP9, and the active enzyme can release cytokines, growth factors, and bioactive fragments, which in turn modulate inflammation, neovascularization, and matrix remodeling {Hijova 2005}. MMP9 is an inducible MMP that is secreted as a zymogen and activated in a "cysteine switch" mechanism by the cleavage of the peptidoglycan binding domain {Van Wart et al 1990}. While activation of MMP9 appears to be carried out by other MMPs, the protease's activity is also regulated by the binding of tissue inhibitors of metalloproteinases (TIMPs), primarily by TIMP1 {Imai et al 1995}, {Vempati et al 2007}, {Olson et al 1997}. Elevated MMP9 expression in diseased tissue and plasma is associated with several human diseases. The health and largely normal development of the MMP9 knockout mouse has enabled evaluation in a variety of disease models, and these data support a significant role for MMP9 in a variety of inflammatory, fibrotic, and oncologic processes {Hu et al 2007}, {Itoh et al 2002}, {Dubois et al 1999}, {Itoh et al 1999}, {Opdenakker et al 2003}.

More recent studies in the MMP field have revealed diversity in the functional roles of MMPs in disease and normal homeostasis, suggesting a therapeutic opportunity for selective inhibitors. Despite their structural similarities, expression analysis in human disease and data from knockout mice reveal contrasting roles for MMP9 and MMP2 regulation and activity in normal homeostasis and in disease. MMP9 expression is restricted to limited cell types in healthy tissues whereas MMP2 is found to be more constitutively expressed {Hu et al 2007}. The disease-associated induction and functions of MMP9 render it an attractive therapeutic target.

1.1.1. MMP9 Expression in Oncology

Matrix metalloproteinase 9 is expressed by tumor epithelia as well as infiltrating macrophages, other inflammatory cells, fibroblastic stroma, and tumor-associated endothelial cells. Expression of MMP9 by tumor epithelia in particular has been implicated in many pro-tumorigenic processes and is associated either with loss of tumor suppressor or gain of oncogenic activity, as

a temporal response to either changes in local tumor environment, or during processes such as invasion and proliferation. A selection bias was applied for tumors in which MMP9 expression by tumor cells was consistently evident. Immunohistochemical and transcript analysis across multiple tumor types demonstrate heterogeneous MMP9 expression across samples, and within different regions or sections of the same case. MMP2 expression was also assessed in a subset of tumors (lung, gastric, colorectal). While expression of MMP2 was observed, MMP9 showed a more consistent pattern of upregulation in tumor tissues compared with healthy tissues.

1.2. General Information

GS-5745 is a humanized high-affinity monoclonal antibody selective for MMP9. GS-5745 was derived from the murine anti-human MMP9 monoclonal antibody, AB0041, and shares the same binding characteristics. GS-5745 and AB0041 cross-react with and inhibit rat and cynomolgus monkey MMP9, but not murine MMP9. AB0046, which cross-reacts with and inhibits murine MMP9, was generated via immunization in MMP9 knockout mice. Epitope mapping analysis revealed that AB0046 binds a similar region in murine MMP9 to that bound by GS-5745 and AB0041 in human MMP9.

1.2.1. Preclinical Pharmacology and Toxicology

Pharmacology

The therapeutic potential of inhibitory antibodies targeting human MMP9 (AB0041) and mouse MMP9 (AB0046) was evaluated in a surgical orthotopic xenograft mouse model of colorectal carcinoma in which tumors were derived from the human tumor cell line HCT116. In this treatment model, selective inhibition of MMP9 using a cocktail of anti-human MMP9 and anti-mouse MMP9 antibodies significantly reduced growth of the primary tumor and reduced the incidence of metastases in 4 independent studies. Treatment with anti-human-MMP9 antibody alone yielded tumor growth reduction similar to treatment with both anti-human-MMP9 and anti-mouse-MMP9 antibodies, suggesting an important role for tumor epithelial-derived MMP9 in primary tumor outgrowth. However, targeting of stromal MMP9 was necessary for maximum efficacy with respect to incidence of metastases, highlighting the disease-associated role of other cellular sources of MMP9 in tumorigenesis.

The major dose limiting toxicity (DLT) observed in clinical studies with pan-MMP inhibitors, such as marimastat, was musculoskeletal syndrome (MSS) consisting of tendonitis manifested by joint stiffness, edema, reduced mobility, and skin discoloration. A study to evaluate the potential of an anti-MMP9 antibody to induce MSS was conducted in Lewis rats. Unlike the pan-MMP inhibitor, Marimastat, AB0041 did not induce any evidence of MSS or other toxicities in this MSS model.

Further details on non-clinical pharmacology are available in the GS-5745 Investigator's Brochure.

Toxicology

The toxicology program consists of a human-tissue cross-reactivity study, 4-week repeat-dose IV toxicity studies with 4-week recovery in both rats and monkeys, and 26-week toxicity studies in both rats and monkeys that included both IV and subcutaneous (SC) routes. Rat and rabbit embryo fetal development studies and a rat fertility study have been also concluded.

In the human-tissue cross-reactivity study, no specific GS-5745 staining was observed in normal human tissues. In the 4-week repeat-dose toxicity studies, findings associated with GS-5745 were limited to non-adverse reversible physeal hypertrophy in rats and reversible increased adrenal gland weight in female monkeys at all doses. The increased adrenal weight was associated with slight hypertrophy of the zona fasciculata in a single female monkey dosed at 100 mg/kg. The physeal hypertrophy in rats is likely directly attributable to inhibition of MMP9, as similar findings were observed in MMP9 null mice {Vu et al 1998} and in children with mutations in MMP9 and MMP13 {Lausch et al 2009}. In both mice and children, this is a transient finding that spontaneously regresses as the bone matures. The physeal hypertrophy noted in rats is not considered relevant to adult humans because the growth plates are closed and longitudinal bone growth is no longer ongoing in adults. In the 26-week studies, there were no findings of toxicological concern in rats or cynomolgus monkeys following weekly IV or SC administration at the highest tested doses of 100 mg/kg/dose (IV) and 150 mg/kg/dose (SC). These doses represent the no-observed-adverse-effect-level (NOAEL) in the rat and monkey in these chronic studies. At doses of GS-5745 up to 100 mg/kg IV, no test article-related maternal or fetal effects were observed in rats and rabbits, and no test article-related effects were observed on male or female fertility in rats.

Further details on the toxicology program are available in the GS-5745 Investigator's Brochure.

1.2.2. Summary of Phase 1 Study of GS-5745 as Monotherapy and in Combination with Chemotherapy in Subjects with Advanced Solid Tumors (Study GS-US-296-0101)

As of 16 April 2015, 100 subjects had received up to 30 infusions of GS-5745 at the following strengths: 200 mg (n = 4), 600 mg (n = 3), 800 mg (n = 67), 1200 mg (n = 20), and 1800 mg (n = 6) as monotherapy or in combination with chemotherapy (800 and 1200 mg). Preliminary safety data for this ongoing study are provided herein. Table 1-1 and Table 1-2 summarize the treatment-emergent adverse events (AEs) reported by > 15% of subjects overall in Parts A and B of the study, respectively. The most common treatment-emergent AEs after monotherapy treatment were nausea, dyspnea, and fatigue. The most common treatment-emergent AEs after combination treatment of GS-5745 and chemotherapy were fatigue, nausea, and diarrhoea. There is currently no evidence of musculoskeletal symptoms associated with GS-5745 treatment.
A total of 106 serious adverse events (SAEs) involving 40 subjects were reported. The most common SAEs were pyrexia (n =5), dyspnea (n = 4), vomiting (n = 4), anemia (n = 3), atrial fibrillation (n = 3), deep vein thrombosis (n = 3), diarrhoea (n = 3), hypokalemia (n = 3), nausea (n = 3), and pneumonia (n = 3). Three SAEs were reported with a fatal outcome: duodenal perforation in a subject with pancreatic adenocarcinoma, which was considered by the investigator to be unrelated to GS-5745, gemcitabine, or paclitaxel; neutropenia in a subject with

lung adenocarcinoma, which was considered by the investigators to be related to carboplatin and unrelated to GS-5745 or pemetrexed; and septic shock in a subject with esophagogastric adenocarcinoma, which was considered by the investigators to be unrelated to GS-5745, oxaliplatin, leucovorin, or 5-FU. Overall, GS-5745 appears to be safe and well-tolerated at multiple doses up to 1800 mg every 2 weeks (Q2W) in subjects with advanced solid tumors.

In the pancreatic adenocarcinoma cohort, 33 subjects treated with GS-5745, gemcitabine, and nab-paclitaxel have had baseline and post-treatment scans. The best overall responses based on investigator assessment were, partial response (PR) in 14 subjects, stable disease (SD) in 13 subjects, and progressive disease (PD) in 6 subjects, resulting in a response rate of 42% and disease stabilization rate of 82%. 36.1% of these subjects remain on study and continue to receive treatment with GS-5745, gemcitabine, and nab-paclitaxel.

In the esophagogastric adenocarcinoma cohort, 19 subjects treated with GS-5745 and mFOLFOX6 have had baseline and post-treatment scans. The best overall responses based on investigator assessment were complete response (CR) in 1 subject, PR in 10 subjects, SD in 7 subjects, and PD in 1 subject resulting in a response rate of 58% and disease stabilization rate of 95%. A majority of these subjects remain on study and continue to receive treatment with GS-5745 and mFOLFOX6.

Preliminary evaluation of serum markers of MMP9 enzymatic activity, including neo-epitope products of collagen cleavage by MMP9, demonstrate a decrease in several of the markers between Cycle 1 Day 1 predose and Cycle 2 Day 1 in a majority of subjects. These markers include the breakdown products of C1M, C3M, C4M2, and laminin.

Additional safety and efficacy data regarding GS-5745 is available in the Investigator's Brochure.

Table 1-1. GS-US-296-0101: Treatment-Emergent Adverse Events Occurring in > 15% of Monotherapy Subjects Overall by Dose Cohort

Adverse Events by SOC and PT	Cohort 1 200 mg N = 4 n (%)	Cohort 2 600 mg N = 3 n (%)	Cohort 3 1800 mg N = 6 n (%)	Total N = 13 n (%)
Gastrointestinal Disorders	2 (50.0)	2 (66.7)	2 (33.3)	6 (46.2)
Nausea	1 (25.0)	2 (66.7)	2 (33.3)	5 (38.5)
Vomiting	1 (25.0)	0	2 (33.3)	3 (23.1)
Diarrhoea	2 (50.0)	0	0	2 (15.4)
General Disorders and Administration Site Conditions	2 (50.0)	2 (66.7)	1 (16.7)	5 (38.5)
Fatigue	2 (50.0)	2 (66.7)	0	4 (30.8)
Asthenia	1 (25.0)	1 (33.3)	0	2 (15.4)
Chest Discomfort	1 (25.0)	0	1 (16.7)	2 (15.4)
Musculoskeletal and Connective Tissue Disorders	1 (25.0)	1 (33.3)	3 (50.0)	5 (38.4)
Arthralgia	0	1 (33.3)	1 (16.7)	2 (15.4)
Nervous System Disorders	1 (25.0)	1 (33.3)	2 (33.3)	4 (30.8)
Dizziness	1 (25.0)	1 (33.3)	1 (16.7)	3 (23.1)
Respiratory, Thoracic, and Mediastinal Disorders	1 (25.0)	0	3 (50.0)	4 (30.8)
Dyspnoea	1 (25.0)	0	3 (50.0)	4 (30.8)
Cough	1 (25.0)	0	2 (33.3)	3 (23.1)

PT = preferred term; SOC = system organ class
Adverse events were mapped according to MedDRA 17.0. Subjects were counted only once for each PT. Subjects with multiple PTs within an SOC were counted only once for that SOC.

Table 1-2. GS-US-296-0101: Treatment-Emergent Adverse Events Occurring in > 15% of Combination Therapy Subjects Overall by Dose Cohort

Adverse Events by SOC and PT	Cohort 4 800 mg N = 36 n (%)	Cohort 5 1200 mg N = 10 n (%)	Cohort 6 1200 mg N = 10 n (%)	Cohort 7 800 mg N = 31 n (%)	Total N = 87 n (%)
Blood and Lymphatic System Disorders	20 (55.6)	10 (100)	5 (50.0)	16 (51.6)	51 (58.6)
Neutropenia	11 (30.6)	4 (40.0)	2 (20.0)	10 (32.3)	27 (31.0)
Anaemia	8 (22.2)	8 (80.0)	3 (30.0)	6 (19.4)	25 (28.7)
Thrombocytopenia	9 (25.0)	2 (20.0)	1 (10.0)	6 (19.4)	18 (20.7)
Gastrointestinal Disorders	30 (83.3)	7 (70.0)	9 (90.0)	21 (67.7)	67 (77.0)
Nausea	15 (41.7)	3 (30.0)	5 (50.0)	15 (48.4)	38 (43.7)
Diarrhoea	15 (41.7)	4 (40.0)	3 (30.0)	11 (35.5)	33 (37.9)
Constipation	9 (25.0)	1 (10.0)	4 (40.0)	8 (25.8)	22 (25.3)
Vomiting	10 (27.8)	1 (10.0)	3 (30.0)	4 (12.9)	18 (20.7)
General Disorders and Administration Site Conditions	34 (94.4)	7 (70.0)	8 (80.0)	16 (51.6)	65 (74.7)
Fatigue	26 (72.2)	5 (50.0)	7 (70.0)	11 (35.5)	49 (56.3)
Oedema Peripheral	18 (50.0)	2 (20.0)	0	5 (16.1)	25 (28.7)
Pyrexia	10 (27.8)	1 (10.0)	1 (10.0)	3 (9.7)	15 (17.2)
Metabolism and Nutrition Disorders	21 (58.3)	3 (30.0)	5 (50.0)	13 (41.9)	42 (48.3)
Decreased Appetite	11 (30.6)	1 (10.0)	2 (20.0)	4 (12.9)	18 (20.7)
Nervous System Disorders	24 (66.7)	3 (30.0)	6 (60.0)	15 (48.4)	48 (55.2)
Neuropathy Peripheral	10 (27.8)	0	4 (40.0)	9 (29.0)	23 (26.4)
Dysgeusia	10 (27.8)	1 (10.0)	1 (10.0)	5 (16.1)	17 (19.5)
Respiratory, Thoracic and Mediastinal Disorders	19 (52.8)	6 (60.0)	10 (100)	13 (41.9)	48 (55.2)
Dyspnoea	5 (13.9)	3 (30.0)	3 (30.0)	5 (16.1)	16 (18.4)
Cough	10 (27.8)	1 (10.0)	2 (20.0)	2 (6.5)	15 (17.2)
Skin and Subcutaneous Tissue Disorders	28 (77.8)	5 (50.0)	6 (60.0)	10 (32.3)	49 (56.3)
Alopecia	20 (55.6)	2 (20.0)	5 (50.0)	2 (6.5)	29 (33.3)
Rash	8 (22.2)	2 (20.0)	1 (10.0)	4 (12.9)	15 (17.2)

PT = preferred term; SOC = system organ class
Adverse were mapped according to MedDRA 17.1. Subjects were counted only once for each PT. Subjects with multiple PTs within an SOC were counted only once for that SOC.

1.2.3. Rationale for Dose Selection

Estimated safety margins for GS-5745 based on the NOAELs determined in the repeat-dose toxicity studies are presented in Table 1-3. The proposed human starting dose is 200 mg every 2 weeks. Given the large safety margins (~33-fold) based on dose, the nonclinical toxicology studies are considered adequate for supporting the proposed study in oncology subjects. In addition, the observed exposures (AUC) at the NOAELs in the 4-week repeat dose rat and monkey studies are expected to be 18- and 44-fold higher, respectively, than the predicted human exposure at the starting dose of 200 mg Q2W in oncology subjects. The observed exposures (AUC) at the NOAELs in the 26-week IV repeat dose rat and monkey studies are expected to be 8- and 24-fold higher, respectively, than the predicted human exposure at a dose of 800 mg Q2W in oncology subjects (Table 1-4). Exposure margins at 1200 mg every 3 weeks (Q3W) are expected to be similar.

The doses for evaluation are expected to provide a wide range of exposures over a 9-fold dose range, using planned 3-fold (0.5 log) dose increments conventionally used in first-in-human studies and supported by overall nonclinical safety data. The GS-5745 doses of 800 mg Q2W or 1200 mg Q3W are expected to reach pharmacokinetic (PK) linearity (or target saturation) at trough concentrations.

Table 1-3. Estimated Safety Margins for GS-5745 Based on Human Equivalent Dose and Projected Exposure at the Highest Proposed Human Dose

Species	NOAEL (mg/kg/dose)	HED[a] (mg/kg/dose)	Day 21 $AUC_{0\text{-}336hr}$[b] (µg•hr/mL)	Safety/Exposure Margins	
				HED[c]	AUC[d]
Rat	100	100	438,000	33	18
Monkey	100	100	1,062,000	33	44

HED = human equivalent dose

a Because GS-5745 is a biologic with a MW of ~144,000 Da, the HED is normalized based on mg/kg rather than body surface area (FDA Guidance, 2005 Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers).

b Mean combined male and female $AUC_{0\text{-}168hr(7\ days)} \times 2$ to estimate $AUC_{0\text{-}336hr(14\ days)}$ to allow comparison with projected human efficacious steady state $AUC_{0\text{-}336hr(14\ days)}$.

c Based on a starting dose of 200 mg (~3 mg/kg in a 66-kg patient) Q2W.

d Based on a starting dose of 200 mg (~3 mg/kg in a 66-kg patient) Q2W with a projected steady state $AUC_{0\text{-}336hr(14\ days)}$ of 24,200 µg•hr/mL.

Table 1-4. Estimated Exposure Margins for Intravenous GS-5745 800 mg, Every Other Week

Species	Duration of Dosing	Route	NOAEL (mg/kg/week)	GS-5745 $AUC_{(0\text{-}336h)}$ (µg•h/mL)	Predicted Exposure Margin[c]
Rat	26 weeks	IV	100	538,000[a]	8.5
Monkey	26 weeks	IV	100	1,531,000[b]	24.3
Rat	26 weeks	SC	150	202,000[a]	3.2
Monkey	26 weeks	SC	150	1,438,000[b]	22.8

h = hour(s); IV = intravenous; SC = subcutaneous
a PK data are from Week 24 of the 26-week repeat-dose rat study ($AUC_{(0\text{-}336h)} = AUC_{(0\text{-}168h)} \times 2$).
b PK data are from Week 25 of the 26-week repeat dose monkey study ($AUC_{(0\text{-}336h)} = AUC_{(0\text{-}168h)} \times 2$).
c Based on an estimated human AUC_{inf} of 63040 µg•h/mL following every-other-week administration of GS-5745 800 mg. Value extrapolated using AUC_{inf} at 1800 mg assuming dose proportionality (Study GS-US-296-0101).

Further details on the non-clinical toxicology and PK of GS-5745 are available in the Investigator's Brochure.

1.2.4. Clinical Trials of GS-5745

In addition to the clinical development program in solid tumors, GS-5745 is being developed for the treatment of inflammatory bowel disease, rheumatoid arthritis, cystic fibrosis, and chronic obstructive pulmonary disease. Details of the clinical studies of these diseases is available in the appropriate sections of the Investigator's Brochure.

1.3. Rationale for Evaluating GS-5745 in Select Solid Tumors

Expression patterns of MMP9, previous clinical experience with a pan-MMP inhibitor, and data on correlation of MMP9 expression and survival are the basis for evaluating GS-5745 in combination with chemotherapy in pancreatic adenocarcinoma, non-small cell lung cancer (NSCLC), and esophagogastric adenocarcinoma. The expression of MMP9 in tumor epithelia as assessed by in situ hybridization (ISH, RNA) and immunohistochemistry (IHC, protein) is evident in a majority of patients with these tumor types. Elevated MMP9 levels (protein or RNA) have been significantly correlated with worse overall survival (OS). In addition, elevated expression of MMP9 has been directly implicated as a pathologic consequence of function of tumor suppressors such as KISS1, RUNX3, RECK, NDRG2, and KAI1/CD82; the loss of these tumor suppressors is associated with these tumor types.

Although Phase 3 clinical trials of previous MMP inhibitors have failed to meet their primary endpoints in advanced cancer, one trial highlighted the potential benefit of MMP inhibition in cancer. In a randomized trial of 369 subjects with gastric cancer, marimastat-treated subjects trended toward better survival ($p = 0.07$) with a statistically significant benefit in favor of marimastat for progression-free survival (PFS, $p = 0.009$). A significant survival benefit was identified at study completion in the pre-defined subgroup of 123 subjects who had received prior chemotherapy ($p = 0.043$) {Bramhall et al 2002}.

1.4. Rationale for Chemotherapy Regimens in Part B

Following the conduct of this study, the next studies of GS-5745 will be randomized, placebo-controlled Phase 2 trials or randomized, placebo-controlled Phase 3 registration trials in combination with chemotherapy. The purpose of Part B is to obtain safety data with GS-5745 when combined with commonly used, standard chemotherapy regimens for diseases in which GS-5745 is most likely to be efficacious: pancreatic adenocarcinoma, NSCLC, colorectal cancer (CRC), breast cancer, and esophagogastric adenocarcinoma.

The GS-5745 infusion schedules (Q2W in pancreatic adenocarcinoma, esophagogastric adenocarcinoma, CRC, and breast cancer, and Q3W in NSCLC) have been proposed to align with the standard of care chemotherapy schedules.

1.4.1. Pancreatic Adenocarcinoma

Gemcitabine is still commonly used as first-line therapy in pancreatic adenocarcinoma. The combination chemotherapy regimen of FOLFIRINOX demonstrated improved survival compared with gemcitabine but was much more toxic and its use is restricted to patients with excellent performance status {Conroy et al 2011}. A study evaluating the addition of nab-paclitaxel to gemcitabine reported increased median OS of 1.8 months relative to gemcitabine alone. We anticipate that randomized Phase 2 trials of GS-5745 in pancreatic adenocarcinoma will use gemcitabine in combination with nab-paclitaxel. Given the tolerability issues and limited applicability of the FOLFIRINOX regimen, it will not be studied in combination with GS-5745 in Part B.

1.4.2. Non-Small Cell Lung Cancer

Platinum agents (cisplatin and carboplatin) are the backbone of therapy for metastatic NSCLC that is epidermal growth factor (EGFR) mutation negative and EML4-ALK mutation negative. First-line cytotoxic combination chemotherapy includes a platinum agent with paclitaxel, gemcitabine, docetaxel, vinorelbine, irinotecan, or pemetrexed. In the United States (US), the standard regimen is carboplatin and paclitaxel in patients with squamous cell carcinoma. Carboplatin and pemetrexed is commonly used in first-line lung adenocarcinoma patients not eligible for bevacizumab. In Part B, GS-5745 will be combined with carboplatin and paclitaxel (squamous) or carboplatin and pemetrexed (adenocarcinoma) to cover the 2 populations that may be evaluated in Phase 2 randomized studies in NSCLC.

1.4.3. Esophagogastric Adenocarcinoma

Treatment of metastatic human epidermal growth factor receptor 2 (HER2) negative esophagogastric adenocarcinoma consists of combination chemotherapy with a triplet or doublet cytotoxic regimen. The triplet regimen of docetaxel/cisplatin/5-FU is the only approved combination in the US. Because of significant toxicity, this combination is reserved for patients who are medically fit and have good performance status. The National Comprehensive Cancer Network (NCCN) guidelines for the treatment of metastatic disease in the first-line setting recommend a 2-drug regimen. A common regimen includes a fluoropyrimidine (5-FU or capecitabine) and

platinum agent (cisplatin or oxaliplatin). There are no definitive studies demonstrating the superiority of either fluoropyrimine or platinum over the other. An mFOLFOX6 regimen is commonly used and generally acceptable in the first-line setting to treat advanced esophagogastric adenocarcinoma and will be evaluated in Part B in combination with GS-5745.

1.4.4. Colorectal Cancer

The current management of metastatic CRC in the first- and second-line settings involves combination chemotherapy with active agents including 5-FU/LV, oxaliplatin, irinotecan, and bevacizumab, among others. Although the NCCN guidelines for the treatment of CRC divide treatment regimens into discrete lines of therapy (initial therapy, therapy after first progression, etc.), current management of the disease considers the active treatment regimens as a continuum of care and it is recommended that patients receive all active agents at some point during their treatment course.

The FOLFOX regimen is a well-studied and commonly used initial treatment regimen for patients with metastatic CRC since multiple studies demonstrated superiority of FOLFOX over LV/FU and LV/FU bolus plus irinotecan {Goldberg et al 2004}, {de Gramont et al 2000}. The addition of the anti- vasoactive endothelial growth factor (VEGF) monoclonal antibody, bevacizumab, to oxaliplatin-based combination chemotherapy resulted in a statistically significant improvement in PFS (9.4 months vs. 8 months for placebo) {Saltz et al 2008}, and the addition of bevacizumab to FOLFOX has become established as a first-line therapy for metastatic CRC. The occurrence of sensory neuropathy is one of the limiting toxicities of oxaliplatin-based combination chemotherapy, and is significant because it may cause patients who are continuing to respond to treatment to discontinue therapy. One potential approach to avoiding the problem of oxaliplatin neurotoxicity is to limit oxaliplatin administration to 6 to 8 cycles, while continuing 5-FU/LV (and bevacizumab, if used), with the possibility of reintroducing oxaliplatin again (if it was discontinued due to neurotoxicity and not disease progression). This “stop-and-go” approach was found to be equivalent to continued therapy in the OPTIMOX1 trial {Tournigand et al 2006}, and is recommended in the most current NCCN guidelines.

For patients receiving oxaliplatin-based chemotherapy (eg, FOLFOX) in the first-line setting, the use of irinotecan-based combination therapy such as FOLFIRI is recommended at the time of initial progression. The FOLFIRI regimen has been shown in multiple Phase 3 trials to be an effective treatment in both the first- and second-line settings {Fuchs et al 2007}. While the order in which patients receive oxaliplatin-based therapy and irinotecan-based therapy has been shown to be unimportant, exposure to both FOLFOX and FOLFIRI regimens during the treatment course for metastatic CRC patients has led to median OS exceeding 20 months for this disease {Tournigand et al 2004}. In addition, the continuation of bevacizumab treatment after initial progression on combination chemotherapy + bevacizumab shows continued benefit in the setting of progressive disease {Grothey et al 2008}.

1.4.5. Breast Cancer

Chemotherapy for patients with metastatic breast cancer is used for patients who are not candidates for hormone therapy (eg, hormone receptor negative disease) or in those with disease that is no longer responsive to hormone therapy. Taxanes are among the most active agents for the treatment of metastatic breast cancer, and have been extensively studied in multiple clinical trials. The Cancer and Leukemia Group B (CALGB) performed a randomized comparison of weekly vs. Q3W paclitaxel which demonstrated that weekly paclitaxel is more effective than Q3W administration for the treatment of metastatic breast cancer. Weekly paclitaxel showed superior response rate (RR; 42% vs. 29%, unadjusted odds ratio [OR] 1.75; $p = 0.0004$), time to progression (TTP; median, 9 vs. 5 months; adjusted HR 1.43; $p < 0.0001$), and survival (median, 24 vs. 12 months; adjusted HR 1.28; $p = 0.0092$) {Seidman et al 2008}. However, Grade 3 neuropathy was more common with weekly dosing (24% vs. 12%; $p = 0.0003$). The superiority of weekly paclitaxel was corroborated by the results of a 2010 meta-analysis, which showed that compared with Q3W treatment, weekly administration of paclitaxel resulted in an improvement in OS (HR 0.78, 95% CI: 0.67, 0.89) {Mauri et al 2010}.

2. OBJECTIVES

The primary objectives of this study are:

- To determine the maximum tolerated dose (MTD) of GS-5745 monotherapy in subjects with advanced solid tumors
- To characterize the safety and tolerability of GS-5745 as monotherapy and in combination with various chemotherapy regimens in subjects with select tumor types

The secondary objectives of this study are:

- To characterize the PK of GS-5745
- To evaluate the formation of anti-GS-5745 antibodies

[redacted]

[redacted]

The exploratory objective of this study is:

[redacted]

3. STUDY DESIGN

3.1. Overview

This is an open-label, multicenter, sequential dose-escalation and expansion study to evaluate the safety, tolerability, PK, and pharmacodynamics of GS-5745 alone and in combination with chemotherapy. The study will be conducted in 2 parts (Parts A and B).

3.1.1. Part A

Cohorts of subjects with advanced solid tumors who have failed or are intolerant to standard therapy or for whom no standard therapy exists will be sequentially enrolled at progressively higher dose levels to receive GS-5745 as monotherapy via intravenous (IV) infusion Q2W. Dose escalation [3 + 3] will be performed with cohort sizes of 3 to 6 subjects. A single subject will initially be enrolled into the first dosing cohort to evaluate any unexpected adverse effects. Provided that there are no significant safety signals up to 24 hours postdose, the remaining 2 subjects will be dosed. The starting dose will be 200 mg. Subsequent doses of 600 mg and 1800 mg are planned. The safety and tolerability of each dose level will be assessed after all subjects in the cohort have been followed for at least 28 days after the first infusion of GS-5745. Cohort dose escalation will occur if no subjects experience a DLT during the first 28 days of study drug dosing. If 1 subject within the initial cohort of 3 subjects experiences a DLT during the first 28 days of study drug dosing, an additional 3 subjects will be enrolled at the same dose level. If no DLTs are observed in the additional 3 subjects, dose escalation will occur. If 2 or more subjects experience DLTs within the first 28 days, dose de-escalation to an intermediate dose will occur. Specifically, if 2 or more subjects experience DLTs at 1800 mg, then 1200 mg will be explored. If 2 or more subjects experience DLTs at 600 mg, then 400 mg will be explored. The MTD is the highest dose level with a subject incidence of DLTs during the first 28 days of study drug dosing of 0 or 1 out of 6.

After determination of MTD, Part B will commence. During the conduct of Part B, up to 3 additional cohorts consisting of no more than 10 subjects each may be studied with GS-5745 at monotherapy doses up to the MTD given Q2W to obtain additional information on PK and pharmacodynamics.

A DLT is a toxicity defined below considered possibly related to GS-5745 occurring during the DLT assessment window (Day 1 through Day 29) in each dose escalation cohort.

- Grade 4 neutropenia (absolute neutrophil count [ANC] < 500/μL) for > 7 days, or febrile neutropenia (ANC < 1000/μL with fever > 101 °F [38.5 °C])
- Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia associated with bleeding
- Grade 3 or 4 non-hematologic toxicity (excluding rash, nausea, diarrhea, and vomiting if controlled with standard supportive care)

- Treatment delay of ≥ 14 days due to unresolved toxicity
- Non-hematologic toxicity of ≥ Grade 2 (at any time during treatment) that, in the judgment of the investigators and the Medical Monitor, is dose-limiting.
- For certain toxicities such as laboratory assessments without a clear clinical correlate, a discussion between the investigator, Medical Monitor, and the Sponsor may take place to determine if this AE should be assessed as a DLT necessitating dose reduction.

3.1.2. Part B

The dose expansion will begin once all subjects in the dose escalation portion of Part A have completed the 28-day DLT period. Approximately 115 to 295 subjects with advanced pancreatic adenocarcinoma (Cohort 4), lung adenocarcinoma (Cohort 5), lung squamous cell carcinoma (Cohort 6), and esophagogastric adenocarcinoma (Cohort 7), CRC in the first-line (Cohort 8), CRC in the second-line (Cohort 9), or breast cancer (Cohort 10) will be enrolled to receive GS-5745 IV every 2 to 3 weeks in combination with chemotherapy. Thirty-five subjects will be enrolled in Cohort 4; ten subjects each in Cohorts 5 and 6, and 15 subjects each in Cohorts 7 through 10. During the conduct of Part B, up to a maximum of 25 additional subjects in each cohort may be enrolled to obtain information on safety, PK, pharmacodynamics, and tumor response.

Table 3-1. Dose and Regimen for GS-5745 in Parts A and B

Cohort	Number of Subjects	GS-5745 Dose (mg)	Dosing Interval (Wks)
Part A: Dose Escalation			
1	3 to 6	200	Q2W
2	3 to 6	600	Q2W
3	6	1800	Q2W
Part B: Dose Expansion			
4	35	Based on MTD from Part A (see Table 3-2)	Q2W
5	10 to 35		Q3W
6	10 to 35		Q3W
7	15 to 40		Q2W
8	15 to 55*		Q2W
9	15 to 55 **		Q2W
10	15 to 40		Q2W

* For Cohort 8 (first-line CRC), the sample size of 40 subjects was initially planned. In amendment 5, the dose of bevacizumab is corrected to be 5 mg/kg Q2W. Up to 15 subjects who previously started bevacizumab treatment at other dose levels will be replaced. Therefore, a total of up to 55 subjects may be enrolled in Cohort 8.

** For Cohort 9 (second-line CRC), the sample size of 40 subjects was initially planned. In amendment 5, the dose of bevacizumab is corrected to be 5 mg/kg Q2W. Up to 15 subjects who previously started bevacizumab treatment at other dose levels will be replaced. Therefore, a total of up to 55 subjects may be enrolled in Cohort 9.

As described in Table 3-2, the cohort dose levels for GS-5745 in Part B will be based on the MTD determined in Part A. Dose reduction of GS-5745 is not permitted for subjects enrolled in Part B.

Table 3-2. Dose and Regimen of GS-5745 for Part B Based on the MTD Determined in Part A

MTD from Part A (mg)	Doses to be Used in Part B (mg)	
	Q2W	Q3W
200	133	200
400	267	400
600	400	600
1200	800	1200
1800	800	1200

3.2. Treatment Plan and Regimen

3.2.1. Part A

Subjects meeting eligibility will receive GS-5745 by IV infusion over approximately 30 minutes Q2W. Safety and efficacy assessments will occur on an outpatient basis, and will include the following: assessment of tumor response, physical examinations, vital signs, electrocardiograms (ECGs), collection of blood samples (for routine safety laboratory analyses, GS-5745 PK, anti-GS-5745 antibody, tumor markers, and biomarkers at applicable visits), urine pregnancy (prior to each infusion of GS-5745 in women of childbearing potential), and assessment of AEs. In addition, subjects will undergo computed tomography (CT) or magnetic resonance imaging (MRI) scans every 8 weeks.

A subject who does not show evidence of disease progression by clinical assessment or by CT or MRI may continue receiving GS-5745 Q2W until disease progression (clinical or radiographic), unacceptable toxicity, withdrawal of consent, or other reasons specified in Section 6.4.

3.2.2. Part B

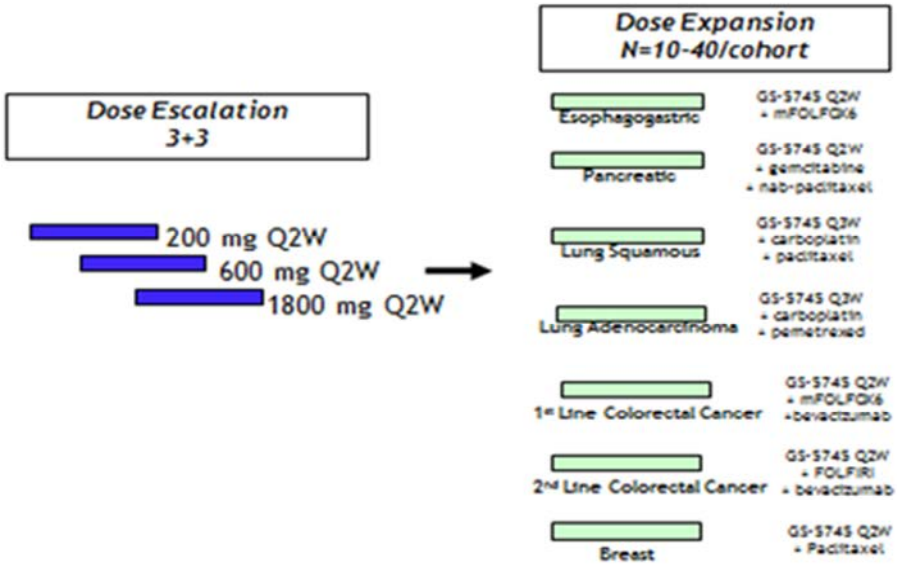
Subjects with pancreatic adenocarcinoma, esophagogastric adenocarcinoma, CRC, or breast cancer will receive GS-5745 by IV infusion over approximately 30 minutes Q2W in addition to the 28-day cycle chemotherapy (gemcitabine and nab-paclitaxel for pancreatic adenocarcinoma; mFOLFOX6 for esophagogastric adenocarcinoma; mFOLFOX6 and bevacizumab for first-line CRC; FOLFIRI and bevacizumab for second-line CRC; and paclitaxel for breast cancer). Subjects with NSCLC will receive GS-5745 by IV infusion over approximately 30 minutes Q3W in addition to the 21-day cycle chemotherapy (carboplatin and pemetrexed in subjects with lung adenocarcinoma; carboplatin and paclitaxel in subjects with lung squamous cell carcinoma). Safety and efficacy assessments will occur on an outpatient basis and will include the following:

assessment of tumor response, physical examinations, vital signs, ECGs, collection of blood samples (for routine safety laboratory assessments, GS-5745 PK, anti-GS-5745 antibody, tumor markers, and biomarkers at applicable visits), urine pregnancy (prior to each infusion of GS-5745 in women of childbearing potential), and assessment of AEs. A CT or MRI scan will be performed during the last week of even-numbered cycles (ie, Cycles 2, 4, 6, etc.) for subjects with pancreatic adenocarcinoma, esophagogastric adenocarcinoma, CRC, and breast cancer, and during the last week of every third cycle (ie, Cycles 3, 6, 9, etc.) for subjects with NSCLC.

Study drug dosing will continue in the absence of disease progression or toxicity warranting discontinuation of therapy.

Dose reduction of GS-5745 is not permitted for subjects enrolled in Part B.

Figure 3-1. Study Schema



4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Up to 343 subjects who meet the eligibility criteria will be enrolled. Part A will comprise approximately 12 to 48 subjects, and Part B will comprise between 115 to 295 subjects.

4.2. Inclusion Criteria

Subjects must meet *all* of the following inclusion criteria to be eligible for participation in this study.

1) Male or female ≥ 18 years of age

2) Part A: histologically or cytologically confirmed advanced malignant solid tumor that is refractory to or intolerant of standard therapy or for which no standard therapy is available

3) Part B: Pancreatic Adenocarcinoma

    a) Presence of histologically confirmed inoperable locally advanced or metastatic pancreatic adenocarcinoma

4) Part B: NSCLC

    a) Stage IIIB with malignant pleural effusion/pleural seeding or stage IV histologically confirmed NSCLC

    b) Absence of known Epidermal Growth Factor Receptor (EGFR) mutation

    c) Absence of known translocation or inversion events involving the ALK gene locus (resulting in EML4-ALK fusion)

5) Part B: Esophagogastric Adenocarcinoma

    a) Histologically confirmed inoperable advanced gastric adenocarcinoma (including adenocarcinoma of the gastroesophageal junction) or relapsed gastric adenocarcinoma

    b) Human Epidermal Growth Factor Receptor 2 (HER2)-negative tumor (primary tumor or metastatic lesion)

6) Part B: CRC (Cohort 8)

    a) Histologically confirmed inoperable advanced adenocarcinoma of the colon or rectum

    b) Radiographically measureable disease

    c) No prior cytotoxic chemotherapy to treat their metastatic disease

7) Part B: CRC (Cohort 9)

   a) Histologically confirmed inoperable advanced adenocarcinoma of the colon or rectum

   b) Radiographically measureable disease

   c) Received first-line combination therapy containing oxaliplatin and fluoropyrimidine with or without bevacizumab for metastatic disease with documented evidence of disease progression during or after treatment completion

8) Part B: Breast Cancer (Cohort 10)

   a) Histologically or cytologically confirmed metastatic breast cancer

   b) Radiographically measureable disease (bone-only, central nervous system [CNS], lymphangitic pulmonary metastases, and previously irradiated tumors without subsequent progression are considered nonmeasurable for the purposes of this study)

   c) Previous hormonal therapy for metastatic breast cancer or cytotoxic adjuvant chemotherapy is allowed

   d) Patients who have received taxane-based adjuvant therapy are required to have had a disease-free interval of at least 12 months after completion of taxane therapy

   e) Patients for whom treatment with weekly single-agent paclitaxel is appropriate in the opinion of the treating physician (eg, hormone-receptor negative disease, hormone therapy unresponsive)

   f) HER-2 negative tumor (primary tumor or metastatic lesion)

9) All acute toxic effects of any prior antitumor therapy resolved to Grade ≤ 1 before the start of study drug dosing (with the exception of alopecia [Grade 1 or 2 permitted] and neurotoxicity [Grade 1 or 2 permitted]).

10) Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 1

11) Life expectancy of > 3 months in the opinion of the investigator

12) Adequate organ function defined as follows:

   a) Hematologic: platelets ≥ 100×10^9/L; hemoglobin ≥ 9.0 g/dL; ANC ≥ 1.5×10^9/L

   b) Hepatic: aspartate aminotransferase (AST) / alanine aminotransferase (ALT) ≤ 2.5 × upper limit of normal (ULN) (if liver metastases are present, ≤ 5 × ULN); total or conjugated bilirubin ≤ 1.5 × ULN

   c) Renal: Serum Creatinine ≤ 1.5 × ULN

13) Coagulation: International Normalized Ratio (INR) ≤ 1.6 (unless receiving anticoagulation therapy). Subjects on full-dose oral anticoagulation must be on a stable dose (minimum duration 14 days). If receiving warfarin, the subject must have an INR ≤ 3.0 and no active bleeding (ie, no bleeding within 14 days prior to first dose of study drug). Subjects on low molecular weight heparin will be allowed.

14) For female subjects of childbearing potential, willingness to use a protocol-recommended method of contraception (see Section 7.12) from the screening visit throughout the study treatment period and for 30 days following the last dose of GS-5745. ***Note: A female subject is considered to be of childbearing potential unless she has had a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy; has medically documented ovarian failure (with serum estradiol and follicle-stimulating hormone [FSH] levels within the institutional postmenopausal range and a negative serum or urine β-HCG), or is menopausal (age ≥ 55 years with amenorrhea for ≥ 6 months).***

15) For male subjects of childbearing potential having intercourse with females of childbearing potential, willingness to use a protocol-recommended method of contraception from the start of study drug, throughout the study treatment period, and for 90 days following the last dose of GS-5745, and to refrain from sperm donation from the start of study drug, throughout the study treatment period, and for 90 days following the last dose of GS-5745. ***Note: A male subject is considered able to father a child unless he has had a bilateral vasectomy with documented aspermia or a bilateral orchiectomy, or has ongoing testicular suppression with a depot luteinizing hormone-releasing hormone (LH-RH) agonist (eg, goserelin acetate [Zoladex®]), leuprolide acetate [Lupron®]), or triptorelin pamoate [Trelstar®]).***

16) Willingness to comply with scheduled visits, drug administration plan, imaging studies, laboratory tests, other study procedures, and study restrictions

17) Evidence of a signed informed consent form

4.3. Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study.

1) History or evidence of clinically significant disorder, condition, or disease that, in the opinion of the investigator and Medical Monitor would pose a risk to subject safety or interfere with the study evaluations, procedures, or completion

2) Pregnant or lactating

3) Subject with known CNS metastases, unless metastases are treated and stable and the subject does not require systemic steroids

4) For Part B, small cell lung cancer

5) For Part B, diagnosis of pancreatic islet cell neoplasm

6) For Part B, with the exception of Cohort 9, subjects who have received prior cytotoxic chemotherapy to treat their metastatic disease

7) Myocardial infarction, symptomatic congestive heart failure (New York Heart Association Classification > Class II), unstable angina, or serious uncontrolled cardiac arrhythmia within the last 6 months of study Day 1

8) History of major surgery within 28 days prior to enrollment

9) Serious systemic fungal, bacterial, viral, or other infection that is not controlled or requires IV antibiotics

10) Anti-tumor therapy (chemotherapy, antibody therapy, molecular targeted therapy) within 28 days or 5 half-lives, whichever is shorter, of study drug dosing (6 weeks for nitrosoureas, mitomycin C, or molecular agents with $t_{1/2}$ > 10 days); concurrent use of hormone therapy for breast or prostate cancer is permitted

11) Clinically significant bleeding within 28 days of Day 1

12) Subjects known to be positive for human immunodeficiency virus (HIV), hepatitis C, or hepatitis B

4.4. Excluded Medication

During the course of the clinical trial, study subjects are anticipated to continue the use of prescribed medications identified during the screening procedures, consistent with study inclusion and exclusion criteria.

Non-study anticancer chemotherapy, radiation therapy or immunotherapy (approved or investigational) are not permitted during the trial. If administered, the subject may be removed from the trial.

Concurrent use of hormone therapy for breast or prostate cancer is permitted.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Enrollment

It is the responsibility of the investigator to ensure that subjects are eligible for the study prior to enrollment. Subjects will be assigned a unique screening number at the time of consent.

Once eligibility is confirmed subjects will be assigned a unique subject number. This is an open-label study.

All baseline tests and procedures must be completed prior to the administration of the first dose of study drug on Day 1. Once a subject number is assigned to a subject, it will not be reassigned to another subject.

5.2. Description and Handling of GS-5745

5.2.1. Formulation

GS-5745 is formulated as a sterile, aqueous buffered solution and is stored at 2 to 8 °C in single-use 10 mL vials.

5.2.2. Packaging, Labeling, Storage, and Handling

GS-5745 solution will be supplied in 10-mL glass vials with elastomeric stoppers and aluminum overseals with flip-off caps. GS-5745 drug product is shipped and stored at 2 °C to 8 °C.

All labels for study drug vials to be distributed to centers in the US will meet all applicable requirements of the US Food and Drug Administration (FDA) and other local regulations as applicable.

Gilead or designated distribution depots will distribute study drug vials to sites as per current Good Manufacturing Practices (cGMP) requirements.

5.3. Dosage and Administration of GS-5745

The target dose of GS-5745 will be prepared by diluting a single and/or multiple vials of GS-5745 into a sterile IV bag / solution.

Study drug will be administered via IV infusion over approximately 30 (± 5) minutes at the research clinic by a qualified staff member. The investigator or a qualified designee must be present during administration. Subjects should be observed following end of infusion and discharged at the discretion of the investigator or qualified designee.

Dose reduction of GS-5745 is not permitted for subjects enrolled in Part B.

Documentation of the GS-5745 administration will be noted on the electronic case report form (eCRF) and in the source documentation.

Details of preparing and administering study drug are included in the Pharmacy Binder provided by Gilead.

5.4. Dosage and Administration of Chemotherapy

Chemotherapy will be administered after study drug dosing according to the following dose and schedule:

Pancreatic Adenocarcinoma: gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15 of a 28-day treatment cycle and nab-paclitaxel 125 mg/m^2 IV on Days 1, 8, and 15 of a 28-day treatment cycle. Administration of gemcitabine and nab-paclitaxel will immediately follow administration of GS-5745 on Days 1 and 15 of each cycle.

NSCLC: carboplatin IV dosed to an area under the concentration-time curve of 6 mg/mL•min (AUC 6) on Day 1 of each 21-day treatment cycle, and pemetrexed 500 mg/m^2 IV on Day 1 of each 21-day treatment cycle in subjects with lung adenocarcinoma. Chemotherapy will consist of carboplatin IV dosed to AUC 6 on Day 1 of each 21-day treatment cycle and paclitaxel 200 mg/m^2 IV on Day 1 of each 21-day treatment cycle in subjects with lung squamous cell carcinoma. Administration of chemotherapies will immediately follow administration of GS-5745 on Day 1 of each cycle. Subjects who have not had disease progression after 4 cycles of treatment may have some of their treatment reduced based upon the investigator's assessment of what is in the subject's best interests. However, dosing with GS-5745 should be continued per protocol.

Esophagogastric Adenocarcinoma: mFOLFOX6 on Days 1 and 15 of each 28-day treatment cycle. The mFOLFOX6 dosing regimen will consist of *l*-leucovorin (LV) 200 mg/m^2 or *dl*-LV 400 mg/m^2 and oxaliplatin 85 mg/m^2 followed by bolus 5-FU 400 mg/m^2 and a 46-hour infusion of 5-FU 2400 mg/m^2. Administration of mFOLFOX6 will immediately follow administration of GS-5745 on Day 1 of each cycle. Administration of mFOLFOX6 will immediately follow administration of GS-5745 on Day 1 of each cycle. Administration of mFOLFOX6 will immediately follow administration of GS-5745 on Day 1 of each cycle.

First-Line CRC: mFOLFOX6 on Days 1 and 15 of each 28-day treatment cycle and bevacizumab at 5 mg/kg IV on Days 1 and 15 of each 28-day treatment cycle. The mFOLFOX6 dosing is described above.

Second-Line CRC: FOLFIRI on Days 1 and 15 of each 28-day treatment cycle and bevacizumab at 5 mg/kg IV on Days 1 and 15 of each 28-day treatment cycle. The FOLFIRI dosing regimen will consist of *l*-LV 200 mg/m^2 or *dl*-LV 400 mg/m^2 as a 2-hour infusion, and irinotecan 180 mg/m^2 given as a 90-minute infusion in 500 mL dextrose 5% via a Y-connector, followed by bolus 5-FU 400 mg/m^2 and a 46-hour infusion of 5-FU 2400 mg/m^2.

Breast Cancer: Paclitaxel 80 mg/m^2 IV over 1 hour on Days 1, 8, and 15 of each 28-day treatment cycle.

Dose reductions or discontinuation may be required based on emerging toxicities and should follow guidelines specified in the package insert and in Section 6.7. Dosing of gemcitabine, nab-paclitaxel, carboplatin, paclitaxel, pemetrexed, 5-FU, leucovorin, and oxaliplatin will be documented on the eCRF (and/or the interactive voice/web response system [IxRS] as applicable). Patients with weight changes +/- 10% compared to screening weight may have their BSA recalculated and the dose of drugs (other than GS-5745) modified to reflect weight changes according to local practice.

Documentation of chemotherapy administration will be noted on the eCRF and in the source documentation.

Please refer to the product package inserts for additional information.

5.4.1. Study Drug Accountability

The investigator or designee (eg, pharmacist) is responsible for ensuring adequate accountability of all used and unused investigational medicinal product during the study. This includes acknowledgement of receipt of each shipment of study drug (quantity and condition) and tracking of vials assigned/utilized for subject dosing.

Investigational Drug Accountability records will be provided to each study site to:

- Record the date of receipt and quantity of study drug.
- Record the date of dispensation, subject identifier, and study drug vial number(s) dispensed (if applicable).

Dispensing records will include the initials of the person dispensing the study drug or supplies.

5.4.2. Study Drug Return or Disposal

The study drug should be disposed of at the site as per local standard operating procedures. Please see Section 9.1.7 for additional instructions.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are described herein and presented in tabular form in Appendix 2 to Appendix 8. Any deviation from protocol procedures should be noted in the source documents and the Sponsor or Contract Research Organization (CRO) should be notified.

Subjects who fail to meet eligibility or complete the initial Screening will be permitted to rescreen provided that the reason for screen failure has been resolved and no new exclusions have been identified. If the subject is rescreened > 30 days from their original screening date (date of informed consent), all screening activities, including informed consent, need to be repeated.

6.1. Subject Enrollment and Treatment Assignment – Part A

6.1.1. Screening Visit

Subjects will be screened within 28 days before enrollment to determine eligibility for participation in the study.

The following procedures will be conducted at Screening:

- Obtain written informed consent
- Medical history (including review of disease under study, prior surgeries, and prior anti-cancer therapies)
- Review prior/concomitant medication
- Complete physical examination including height and weight
- Vital signs including blood pressure, respiratory rate, pulse, and temperature
- 12-lead ECG
- ECOG Performance Status
- Obtain blood and/or urine samples for:
  - Chemistry (see Section 6.8.10)
  - Hematology (see Section 6.8.10)
  - Coagulation (see Section 6.8.10)
  - Serum pregnancy test (females of childbearing potential)

- Serum and plasma biomarkers (see Section 6.8.12.2)
- Urinalysis

- CT or MRI (scans taken as part of standard medical practice within 4 weeks of Day 1 are acceptable)
- Record any AEs occurring after signing of the consent form
- Register subject visit in IxRS

6.1.2. Treatment Assessments

6.1.2.1. Day 1

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic on Day 1 to conduct study-required procedures prior to dosing.

The following procedures will be conducted on Day 1:

Pre-dose:

- Modified physical examination capturing changes from prior examinations, and weight
- Vital signs, including blood pressure, respiratory rate, pulse, and temperature
- 12-lead ECG
- ECOG Performance Status
- Obtain blood and/or urine samples for:
  - Chemistry (see Section 6.8.10)
  - Hematology (see Section 6.8.10)
  - Coagulation (see Section 6.8.10)
  - GS-5745 concentration
  - Anti-GS-5745 antibody
  - Serum and plasma biomarkers (see Section 6.8.12.2)
  - Urine pregnancy test (females of childbearing potential)
  - Urinalysis

- Collect archival tumor tissue specimen as applicable; efforts to acquire a tissue sample should begin on Day 1
- Review of AEs and concomitant medications
- Register subject visit in IxRS

Dosing:

- Administer GS-5745 via IV infusion over approximately 30 (± 5) minutes

Post-dose: End of Infusion (EOI):

- Vital signs including blood pressure, respiratory rate, pulse, and temperature
- 12-lead ECG
- Obtain blood samples for GS-5745 concentration (± 10 minutes)
- Review of AEs

Post-dose: Approximately 6 Hours (± 10 minutes) After EOI:

- Vital signs including blood pressure, respiratory rate, pulse, and temperature
- 12-lead ECG
- Obtain blood samples for GS-5745 concentration (± 10 minutes)
- Review of AEs

6.1.2.2. Day 2 (24 Hours After EOI ± 2 Hours), Day 3 (48 Hours After EOI ± 4 Hours), and Day 5 (96 Hours After EOI ± 4 Hours)

The following procedures will be conducted on Days 2, 3, and 5:

- Vital signs including blood pressure, respiratory rate, pulse, and temperature
- ECOG Performance Status
- Obtain blood samples for GS-5745 concentration
- Review of AEs and concomitant medications

6.1.2.3. Day 8 (168 Hours After EOI ± 4 Hours)

The following procedures will be conducted on Day 8:

- Modified physical examination capturing changes from prior examinations, and weight
- Vital signs including blood pressure, respiratory rate, pulse, and temperature
- ECOG Performance Status
- Obtain blood samples for:
  - Chemistry (see Section 6.8.10)
  - Hematology (see Section 6.8.10)
  - GS-5745 concentration
- Review of AEs and concomitant medications

6.1.2.4. Day 15, Day 29, and Day 43

The following procedures will be conducted on Days 15 (± 1 day), 29 (± 1 day), and 43 (± 2 days):

Pre-dose:

- Modified physical examination capturing changes from prior examinations, and weight
- Vital signs including blood pressure, respiratory rate, pulse, and temperature
- 12-lead ECG
- ECOG Performance Status
- Obtain blood and/or urine samples for:
  - Chemistry (see Section 6.8.10)
  - Hematology (see Section 6.8.10)
  - Coagulation (see Section 6.8.10)
  - GS-5745 concentration
  - Anti-GS-5745 antibody (Day 43 only)
  - Serum and plasma biomarkers (Days 15 and 43 only) (see Section 6.8.12.2)

- Urine pregnancy test (females of childbearing potential)
- Urinalysis

- Review of AEs and concomitant medications
- Register subject visit in IxRS

Dosing:

- Administer GS-5745 via IV infusion over approximately 30 (± 5) minutes

Post-dose: EOI:

- Vital signs including blood pressure, respiratory rate, pulse, and temperature
- 12-lead ECG (Day 43 only)
- Obtain blood samples for GS-5745 concentration (± 10 minutes)
- Review of AEs

For all subjects in Part A, the Day 29 visit is the end of the DLT assessment window. In order for a subject to be evaluable for the DLT observation, the subject must have received the first 2 doses of GS-5745, completed all safety procedures through Day 29, or have experienced a DLT prior to Day 29.

6.1.2.5. Day 57

The following procedures will be conducted on Day 57 (± 2 days):

Pre-dose:

- Modified physical examination capturing changes from prior examinations, and weight
- Vital signs including blood pressure, respiratory rate, pulse, and temperature
- 12-lead ECG
- ECOG Performance Status
- CT or MRI
- Obtain blood and/or urine samples for:
  - Chemistry (see Section 6.8.10)
  - Hematology (see Section 6.8.10)
  - Coagulation (see Section 6.8.10)
  - GS-5745 concentration

- Serum and plasma biomarkers (see Section 6.8.12.2)
- Urine pregnancy test (females of childbearing potential)
- Urinalysis

- Review of AEs and concomitant medications
- Register subject visit in IxRS

Dosing:

- Administer GS-5745 via IV infusion over approximately 30 (± 5) minutes

6.1.3. Continuation of Treatment

A subject who does not show evidence of disease progression by clinical assessment or by CT or MRI may continue receiving GS-5745 Q2W until disease progression (clinical or radiographic), unacceptable toxicity, withdrawal of consent, or other reasons specified in Section 6.4.

6.1.3.1. Every 2 Weeks (from Day 57)

For subjects continuing treatment, the following procedures will be conducted Q2W (± 2 days) from the Day 57 visit:

Pre-dose:

- Vital signs including blood pressure, respiratory rate, pulse, and temperature
- ECOG Performance Status
- Obtain blood and/or urine samples for:
  - Chemistry (see Section 6.8.10)
  - Hematology (see Section 6.8.10)
  - Coagulation (see Section 6.8.10)
  - Urine pregnancy test (females of childbearing potential)
  - Urinalysis
- Review of AEs and concomitant medications
- Register subject visit in IxRS

Dosing:

- Administer GS-5745 via IV infusion over approximately 30 (± 5) minutes

6.1.3.2. Every 8 Weeks (from Day 57): Assessment of Tumor Response

For subjects continuing treatment, the following procedures will be conducted every 8 weeks (± 5 days) from the Day 57 visit:

- CT or MRI
- Obtain blood and/or urine samples for:
  - Chemistry (see Section 6.8.10)
  - Hematology (see Section 6.8.10)
  - Coagulation (see Section 6.8.10)
  - GS-5745 concentration
  - Anti-GS-5745 antibody
  - Serum and plasma biomarkers (see Section 6.8.12.2)
- Review of AEs and concomitant medications

6.1.4. End-of-Study Visit

The following procedures will be conducted at the End-of-Study visit:

- Modified physical examination capturing changes from prior examinations, and weight
- Vital signs including blood pressure, respiratory rate, pulse, and temperature
- 12-lead ECG
- ECOG Performance Status
- Obtain blood and/or urine samples for:
  - Chemistry (see Section 6.8.10)
  - Hematology (see Section 6.8.10)
  - Coagulation (see Section 6.8.10)
  - GS-5745 concentration
  - Anti-GS-5745 antibody
  - Serum and plasma biomarkers (see Section 6.8.12.2)

- Urine pregnancy test (females of childbearing potential)
- Urinalysis

- CT or MRI (if not conducted within the previous 4 weeks)
- Review of AEs and concomitant medications
- Register subject visit in IxRS

6.1.5. Follow-up Visits

6.1.5.1. Post-Study Telephone Call

Subjects will be contacted by telephone 30 days (± 2 days) after the last dose of GS-5745 to assess AEs. For subjects who come off study for reasons other than disease progression, the site should also obtain information on post-study anti-cancer therapies, surgeries, and date of definitive disease progression (if known).

6.2. Subject Enrollment and Treatment Assignment – Part B

6.2.1. Screening Visit

Subjects will be screened within 28 days before enrollment to determine eligibility for participation in the study.

The following procedures will be conducted at Screening:

- Obtain written informed consent
- Medical history (including review of disease under study, prior surgeries, and prior anti-cancer therapies)
- Review prior/concomitant medication
- Complete physical examination including height and weight
- Vital signs including blood pressure, respiratory rate, pulse, and temperature
- 12-lead ECG
- ECOG Performance Status
- Obtain blood and/or urine samples for:
  - Chemistry (see Section 6.8.10)
  - Hematology (see Section 6.8.10)

— Coagulation (see Section 6.8.10)

— Serum pregnancy test (females of childbearing potential)

CCI [redacted]

— Urinalysis

- Obtain stool sample (can be collected any time prior to first dose, CRC cohort only, see Section 6.8.12.3)
- CT or MRI (scans taken as part of standard medical practice within 4 weeks of Day 1 are acceptable)
- Record any AEs occurring after signing of the consent form
- Register subject visit in IxRS

6.2.2. Cycle-Based Assessments

6.2.2.1. Day 1 of Each 28-Day Cycle (for Pancreatic Adenocarcinoma, Esophagogastric Adenocarcinoma, CRC, and Breast Cancer) or Day 1 of Each 21-Day Cycle (for NSCLC)

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic on Day 1 to conduct study-required procedures prior to dosing.

The following procedures will be conducted on Day 1 of each cycle:

Pre-dose:

- Modified physical examination capturing changes from prior examinations, and weight
- Vital signs including blood pressure, respiratory rate, pulse, and temperature
- 12-lead ECG
- ECOG Performance Status
- Obtain blood and/or urine samples for:

— Chemistry (see Section 6.8.10)

— Hematology (see Section 6.8.10)

— Coagulation (see Section 6.8.10)

- GS-5745 concentration
- Anti-GS-5745 antibody
- Serum and plasma biomarkers (Day 1 of cycles as specified in the laboratory manual; see Section 6.8.12.2)
- Urine pregnancy test (females of childbearing potential)
- Urinalysis

- Collect archival tumor tissue specimen as applicable; efforts to acquire a tissue sample should begin on Day 1 of Cycle 1
- Review of AEs and concomitant medications
- Register subject visit in IxRS

Dosing:

- Administer GS-5745 via IV infusion over approximately 30 (± 5) minutes followed by chemotherapy (see Section 5.4)
- Obtain blood samples for:
  - GS-5745 concentration (at the end of GS-5745 infusion for Cycle 1 and Cycle 3 only)

6.2.2.2. Day 8 of Each 28-Day Cycle (for Pancreatic Adenocarcinoma and Breast Cancer Only)

For subjects who continue to receive gemcitabine ± nab-paclitaxel (Pancreatic Adenocarcinoma) and Paclitaxel (Breast Cancer) in subsequent cycles, the following procedures will be conducted on Day 8 (± 2 days) of each cycle:

- Vital signs including blood pressure, respiratory rate, pulse, and temperature
- Obtain blood samples for hematology (see Section 6.8.10)
- Review of AEs and concomitant medications

Dosing:

- Administer chemotherapy (see Section 5.4).

6.2.2.3. Day 15 of Each 28-Day Cycle (for Pancreatic Adenocarcinoma, Esophagogastric Adenocarcinoma, CRC, and Breast Cancer)

The following procedures will be conducted on Day 15 (± 2 days) of each cycle:

- Vital signs including blood pressure, respiratory rate, pulse, and temperature
- ECOG Performance Status
- Obtain blood and/or urine samples for:
  - Chemistry (see Section 6.8.10)
  - Hematology (see Section 6.8.10)
  - GS-5745 concentration
  - Serum and plasma biomarkers (Cycle 1 Day 15 only; see Section 6.8.12.2)
  - Urine pregnancy test (females of childbearing potential)
- Review of AEs and concomitant medications
- Register subject visit in IxRS

Dosing:

- Administer GS-5745 via IV infusion over approximately 30 minutes (± 5 minutes) followed by chemotherapy (see Section 5.4).

6.2.2.4. Cycle 2 Day 15 (+ 14 Days / - 7 Days)

- Obtain tumor tissue biopsy (from subjects with breast cancer only)
- Obtain stool sample (from subjects with CRC only)

6.2.2.5. Assessment of Tumor Response

Assessment of tumor response by CT scan or MRI will be performed during the last week of even-numbered cycles (ie, Cycles 2, 4, 6, etc.) for subjects with pancreatic adenocarcinoma, esophagogastric adenocarcinoma, CRC, and breast cancer, and during the last week of every third cycle (ie, Cycles 3, 6, 9, etc.) for subjects with NSCLC.

6.2.3. Continuation of Treatment

Study drug dosing will continue in the absence of disease progression or toxicity warranting discontinuation of therapy.

6.2.4. End-of-Study Visit

The following procedures will be conducted at the End-of-Study visit:

- Modified physical examination capturing changes from prior examinations, and weight
- Vital signs including blood pressure, respiratory rate, pulse, and temperature
- ECOG Performance Status
- Obtain blood and/or urine samples for:
  - Chemistry (see Section 6.8.10)
  - Hematology (see Section 6.8.10)
  - Coagulation (see Section 6.8.8)
  - GS-5745 concentration
  - Anti-GS-5745 antibody
  - Serum and plasma biomarkers (see Section 6.8.12.2)
  - Urine pregnancy test (females of childbearing potential)
  - Urinalysis
- [redacted]
- CT or MRI (if not conducted within the previous 4 weeks)
- Review of AEs and concomitant medications
- Register subject visit in IxRS

6.2.5. Follow-up Visits

6.2.5.1. Post-Study Phone Call

Subjects will be contacted by phone 30 days (± 2 days) after the last dose of GS-5745 to assess AEs. For subjects who come off study for reasons other than disease progression, the site should also obtain information on post-study anti-cancer therapies, surgeries, and date of definitive disease progression (if known).

6.2.5.2. Long-term Follow-up

Long-term follow-up (LTFU) begins after the EOS visit, or the last visit on study if EOS does not occur. Subjects will be contacted via phone call every 3 months for determination survival status and record of any other anti-cancer therapy or cancer related surgery for up to 5 years after the EOS visit.

Subjects who are not deceased by the time the Sponsor has made the determination the study will end will receive a final follow-up phone call to assess survival status and to communicate the Sponsor's decision to end the study.

The investigator will make every effort to contact the subject or a close relative or caretaker by phone to collect survival information. The investigator should show due diligence by documenting in the source documents steps taken to contact the subject (ie, dates of phone calls, registered letters, etc).

6.3. Assessments for Premature Discontinuation of Study Drug

In order to assess PFS, if a subject discontinues study drug (for example, as a result of an AE), every attempt should be made to keep the subject in the study to collect tumor assessments (CT/MRI), chemistry, and hematology until disease progression and according to the following schedule: every 8 weeks for Part A, during the last week of even-numbered cycles (ie, Cycles 2, 4, 6, etc.) for Part B subjects with pancreatic adenocarcinoma, esophagogastric adenocarcinoma, CRC, and breast cancer, and during the last week of every third cycle (ie, Cycles 3, 6, 9, etc.) for Part B subjects with NSCLC.

If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

6.4. Criteria for Discontinuation of Study Drug

Study medication may be discontinued in the following instances:

- Documented progression of malignant disease
- Pregnancy
- Investigator discretion (the reason for investigator decision to discontinue study drug must be recorded on the eCRF)
- Non-compliance with study drug
- Protocol violation
- Withdrawal of consent (the reason for withdrawal of consent, if known, must be recorded on the eCRF)

- Lost to follow-up
- Study termination by the Sponsor
- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree
- Unacceptable toxicity, as defined in the toxicity management section of the protocol, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest; if toxicity is related to chemotherapy, the subject may continue GS-5745 alone.

6.5. Criteria for Removal from Study

Subjects may be removed from the study for the following reasons:

- Documented progression of malignant disease
- Death
- Pregnancy
- Investigator discretion (if progression of disease has not been documented, the reason for removal from study must be recorded on the eCRF)
- Non-compliance with study drug
- Subject never dosed with study drug
- Protocol violation
- Withdrawal of consent (if progression of disease has not been documented, the reason for withdrawal of consent, if provided by the subject, must be recorded on the eCRF)
- Lost to follow-up
- Study termination by the Sponsor

6.6. Replacement of Subjects

In Part A, if a subject is withdrawn from the study for any reason other than a DLT prior to completion of the DLT assessment window, a replacement subject will be enrolled at the same dose level as the replaced subject. To be evaluable for the DLT observation, a subject in Part A must receive the first 2 doses of GS-5745, complete all safety procedures through Day 29, or experience a DLT prior to Day 29.

6.7. Dose Interruption and Reduction

If an AE is attributed to only 1 drug (ie, study drug or chemotherapy), the investigator's discretion will be used to determine whether the drug not attributed to the AE will be withheld based on the investigator's assessment of risk-benefit of withholding 1 or both drugs.

6.7.1. GS-5745

If a subject experiences a DLT (see Section 7.4 for the definition of a DLT), GS-5745 treatment will be postponed until the toxicity is resolved to Grade 0 or 1 (as defined by the Common Terminology Criteria for Adverse Events [CTCAE], version 4.03) or returns to the subject's baseline value. If the toxicity is resolved to Grade 0 or 1, or returns to the subject's baseline value within 28 days from the start of the event, the subject may resume GS-5745 at 50% of the originally assigned dose level. If the subject experiences a recurrence of the toxicity meeting criteria for DLT after restarting study drug or if the toxicity does not resolve within 28 days, treatment with GS-5745 will be discontinued. Alternatively, if there is no recurrence of the toxicity, the dose of GS-5745 may be increased to 100% of the originally assigned level after discussion with the Medical Monitor.

In Part B, subjects in whom chemotherapy administration must be delayed > 3 weeks or permanently discontinued may continue to receive GS-5745 every 2 to 3 weeks in the absence of disease progression.

If the subject was not receiving GS-5745 at the time disease progression was documented (eg, due to reversible toxicity), after discussion with the Medical Monitor, GS-5745 may be re-started if the criteria for resuming treatment as described in Section 6.7.1 are met and the investigator feels it is in the subject's best interest to do so.

6.7.2. Gemcitabine and Nab-Paclitaxel

Dose reduction for gemcitabine and nab-paclitaxel should be made according to the system showing the greatest degree of toxicity. Toxicities will be graded using the NCI CTCAE (version 4.03). Two dose levels are permitted according to the criteria in Appendix 9. If a toxicity requiring dose modification occurs following the second dose reduction of either chemotherapy, further treatment should be discontinued. Any further dose modification requires prior Gilead approval.

Table 6-1. Dose Reduction Levels[a] for Gemcitabine and Nab-Paclitaxel

	Dose Level		
Drug	**Starting Dose**	**-1**	**-2[b]**
Gemcitabine	1000 mg/m^2	800 mg/m^2	600 mg/m^2
Nab-Paclitaxel	125 mg/m^2	100 mg/m^2	75 mg/m^2

a Dose reductions may or may not be concomitant. Please refer to Appendix 9 (Appendix Table 1 and Appendix Table 2) for specific recommendations regarding dose modifications for Day 1 of each cycle for hematologic and non-hematologic toxicity, respectively. Please refer to Appendix 9 (Appendix Table 3 and Appendix Table 4) for specific recommendations regarding dose modifications within a cycle for hematologic and non-hematologic toxicities, respectively.
b A maximum of 2 dose level reductions are allowed.

Subjects experiencing study drug-related toxicities that require a delay in scheduled gemcitabine or nab-paclitaxel dosing for ≥ 21 days will be discontinued from further chemotherapy treatment in this study (except for peripheral neuropathy). When a dose reduction is required, no dose re-escalation will be permitted for the duration of study treatment.

Dose Modifications at Day 1

In the event dose modifications are required at the beginning of a cycle due to AEs or hematologic toxicities, doses of gemcitabine and nab-paclitaxel may be adjusted as detailed in Appendix 9, Appendix Table 1 and Appendix Table 2.

Dose Adjustments Within a Treatment Cycle

In the event that a subject must have treatment delayed within a treatment cycle due to toxicities, those doses held during a cycle will not be made up. Dose modifications due to AEs or hematologic toxicities as represented by the blood counts and toxicities within a treatment cycle should be adjusted as outlined in Appendix 9, Appendix Table 3 and Appendix Table 4.

Peripheral Neuropathy

Nab-paclitaxel treatment should be withheld in subjects who experience ≥ Grade 3 peripheral neuropathy. Gemcitabine administration can continue during this period. Nab-paclitaxel treatment may be resumed at the next lower dose level in subsequent cycles after the peripheral neuropathy improves to ≤ Grade 1. Subjects experiencing peripheral neuropathy that requires a delay in scheduled nab-paclitaxel dosing for ≥ 21 days will discontinue nab-paclitaxel treatment. The time to resolution to Grade ≤ 1 should be the AE duration used for AE reporting.

For more information, please refer to the prescribing information. Local practices and guidelines may be followed.

6.7.3. Carboplatin

Dose reduction for carboplatin is frequently required for hematologic toxicities. As per the prescribing information, carboplatin dose should be reduced 75% in subjects with platelets $< 50 \times 10^9$/L and neutrophil count $< 0.5 \times 10^9$/L.

For more information, please refer to the prescribing information. Local practices and guidelines may be followed.

6.7.4. Paclitaxel

Dose reduction for paclitaxel is frequently required for hematologic toxicities. As per the prescribing information, the following dosage reduction guidelines are recommended. Paclitaxel therapy should not be administered to subjects with baseline neutrophil counts $< 1.5 \times 10^9$/L. Subjects should not be re-treated with subsequent cycles of paclitaxel until neutrophils recover to a level $> 1.5 \times 10^9$/L and platelets recover to a level $> 100 \times 10^9$/L. In the case of severe neutropenia ($< 0.5 \times 10^9$/L for 7 days or more) during a course of paclitaxel therapy, the dose should be reduced 20% for subsequent courses of therapy.

For more information, please refer to the prescribing information. Local practices and guidelines may be followed.

6.7.5. Pemetrexed

Per the prescribing information, dose adjustments at the start of a subsequent cycle should be based on nadir hematologic counts or maximum non-hematologic toxicity from the preceding cycle of therapy. Treatment may be delayed to allow sufficient time for recovery. Upon recovery, subjects should be retreated using the guidelines in Table 6-2 and Table 6-3.

Table 6-2. Dose Reduction for Pemetrexed – Hematologic Toxicities

Nadir ANC < 500/mm^3 and nadir platelets ≥ 50,000/mm^3	75% of previous dose
Nadir platelets < 50,000/mm^3 without bleeding regardless of nadir ANC	75% of previous dose
Nadir platelets < 50,000/mm^3 with bleeding, regardless of nadir ANC	50% of previous dose

If a subject develops non-hematologic toxicities (excluding neurotoxicity) ≥ Grade 3, treatment should be withheld until resolution to less than or equal to the subject's pre-therapy value. Treatment should be resumed according to guidelines in Table 6-3.

Table 6-3. Dose Reduction for Pemetrexed – Non-Hematologic Toxicities[a]

	Dose of Pemetrexed (mg/m^2)
Any Grade 3 or 4 Toxicities Except Mucositis	75% of previous dose
Any Diarrhea Requiring Hospitalization (Irrespective of Grade) or Grade 3 or 4 Diarrhea	75% of previous dose
Grade 3 or 4 Mucositis	50% of previous dose

a NCI CTCAE version 4.03

Pemetrexed therapy should be discontinued if a subject experiences any hematologic or non-hematologic Grade 3 or 4 toxicity after 2 dose reductions, or immediately if Grade 3 or 4 neurotoxicity is observed.

For more information, please refer to the prescribing information. Local practices and guidelines may be followed.

6.7.6. mFOLFOX6

Recommended dose reduction for the components of mFOLFOX6 is described in Table 6-4 and is based on the AE table described in Appendix 10. Sites may also follow their institutional practice for dose reductions. Leucovorin doses may be adjusted per institutional guidelines in the event of a supply shortage.

Table 6-4. Dose Reduction Levels[a] for mFOLFOX6

Drug	Dose Level		
	Starting Dose	**-1**	**-2[a]**
Oxaliplatin	85 mg/m^2	65 mg/m^2	50 mg/m^2
5-FU Bolus	400 mg/m^2	OMIT	OMIT
5-FU Continuous Infusion over 46 to 48 Hours	2400 mg/m^2	1900 mg/m^2	1500 mg/m^2
dl-Leucovorin/l-Leucovorin[c]	400/200 mg/m^2	100%	100%

a If an AE is believed likely to be due to 1 drug, it is permissible to decrease dose of that drug.
Further dose levels (−3, −4, etc.) will be 20% dose reductions from the previous level for oxaliplatin and 5-FU continuous infusion. In addition, the bolus dose of 5-FU will continue to be omitted, and the leucovorin dose will remain unadjusted (100%). Dosing of leucovorin will remain fixed at 100% of recommended dose.

6.7.6.1. Modifications for the First 2 Cycles

Follow the modifications in Appendix 10 for the first **2** cycles, until individual treatment tolerance can be ascertained. Thereafter, these modifications should be regarded as guidelines to prevent side effects from exceeding a mild-to-moderate level, and minimize the incidence and duration of debilitating side effects.

If multiple AEs are seen, administer dose based on greatest reduction required for any single AE observed.

Subjects should be assessed clinically for AEs prior to, during, and after each infusion.

6.7.6.2. Implications of Dose Reductions for Subsequent Cycles

If the subject experiences a significant AE requiring a dose reduction at the start of the next cycle, then the dose will remain lowered for all subsequent cycles.

For more information, please refer to the prescribing information. Local practices and guidelines may be followed.

6.7.7. FOLFIRI

FOLFIRI consists of 5-FU, leucovorin, and irinotecan**.** Dose reductions for neutropenia, diarrhea, or thrombocytopenia are frequently required. Appendix 10, Appendix Table 7 provides the starting dose and modified dose levels for the individual components of FOLFIRI.

Table 6-5. Starting Dose and Modified Dose Levels (mg/m^2)

Drug	Dose Level		
	Starting Dose	**-1**	**-2**
Irinotecan	180	150	120
l-LV/dl-LV	200/400	200/400	200/400
5-FU Bolus	400	320	240
5-FU Infusion	2400	2000	1500

6.8. Description of Study Procedures

6.8.1. Medical History

A complete medical history will be obtained by the investigator or designee. Medical history will include information on the subject's significant past medical events (eg, prior hospitalizations or surgeries), a review of the disease under study, prior anti-cancer therapies, and any concurrent medical illnesses.

6.8.2. Physical Examination

The investigator or qualified designee will perform a physical examination at screening and time points outlined in the Study Procedures Tables (Appendix 2 to Appendix 8). Pre-dose abnormal findings will be reported on the medical history page of the eCRF. Any changes from the pre-dose baseline physical examination which represent a clinically significant deterioration will be documented on the AE page of the eCRF.

Weight (without shoes) should be measured with each physical examination and reported in kilograms.

Height (without shoes) should be measured at Screening only and reported in centimeters.

6.8.3. Vital Signs

Vital signs, including blood pressure, respiratory rate, pulse, and temperature will be measured at the time points listed in the Study Procedures Tables in Appendix 2 to Appendix 8. All measurements will be recorded on the appropriate eCRF page with appropriate source documentation. Any abnormal measurements may be repeated and reported as AEs if appropriate. All measures of blood pressure will be performed using standard sphygmomanometry. Measurements of blood pressure should be taken per institutional guidelines.

6.8.4. Electrocardiogram

Twelve (12)-lead ECGs reporting ventricular rate, PR, QRS, QT, and QTc intervals will be obtained at the time points outlined in the Study Procedures Tables (Appendix 2 to Appendix 8).

The investigator or qualified designee will review all ECGs. The ECG tracings will be maintained in the source documentation of each subject and the appropriate data reported on the eCRF.

6.8.5. ECOG Performance Status

The ECOG Performance Status will be performed at the time points listed in the Study Procedures Tables in Appendix 2 to Appendix 8 and in accordance with Table 6-6.

Table 6-6. 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, eg, light house work, 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 et al 1982}

6.8.6. Prior and Concomitant Medications

At screening, all medication taken up to 30 days prior to the screening visit will be recorded on the eCRF. At each study visit, the site will capture any and all medications taken by the subject since the last visit or during the visit (as applicable). Concomitant medications include prescription and non-prescription medications, pre-infusion medications (eg, anti-emetics), and vitamins and minerals.

In addition, supportive therapies given during the course of the study (eg, blood transfusion, growth factor) should be collected and recorded on the eCRF.

6.8.7. Adverse Events

Subjects will be assessed for AEs per guidelines in the CTCAE (version 4.03) at the time points outlined in the Study Procedures Tables (Appendix 2 to Appendix 8). Any AEs reported after informed consent is obtained and throughout the study will be recorded on the eCRF with appropriate source documentation. The site will contact the study subject by phone 30 days after the last dose of study drug to assess AEs.

Please refer to Section 7 for additional information on AE reporting.

6.8.8. CT or MRI

Computed tomography scans will be obtained to document metastatic disease, identify target lesions as described in RECIST (version 1.1), and to assess response and disease progression. In subjects who cannot tolerate iodinated contrast, a CT of the lung without contrast and MRI of the abdomen should be performed. Imaging by CT scan (with contrast) or MRI will be performed at Screening (within 4 weeks before Day 1 if the scan was performed as part of standard medical practice) and at the time points outlined in the Study Procedures Tables (Appendix 2 to Appendix 8).

The same radiographic procedure and specification (eg, the same contrast agent, slice thickness, etc.) used to define measurable lesions must be used throughout the study for each subject. Any subject with symptoms suggestive of disease progression should be evaluated for tumor response

at the time the symptoms occur. Tumor burden will be characterized at baseline and subsequent response assessments will be carried out according to the RECIST (version 1.1) criteria.

6.8.9. Independent Radiology Review

An independent radiology review (IRR) committee will be established to provide a blinded review of radiographic data in order to provide independent interpretation of changes in tumor status. The IRR will include board-certified radiologist(s) and will be managed by a contract research organization (CRO) selected by Gilead. The review of radiographic data by the IRR will be performed on an ongoing basis. The specifics of the IRR's processes and reading methods will be described in an independent review charter developed by the contracted imaging facility in conjunction with Gilead.

6.8.10. Blood and Urine Samples

Blood and urine (for pregnancy and urinalysis) for laboratory safety tests will be collected according to the Study Procedures Tables (Appendix 2 to Appendix 8). The date and time of blood and urine collection will be recorded in the subject's source documentation. The tests will be analyzed using standard procedures. White blood cell differentials will be reported as absolute counts. All laboratory tests must be reviewed for clinical significance by the investigator or qualified designee.

Day 1 pre-dose samples may be drawn up to 2 days prior to the Day 1 visit.

The analytes listed in Table 6-7 will be tested.

Table 6-7. Blood and Urine Samples Collected During the Course of the Study

<table>
<tr><th>Serum Chemistry</th><th>Hematology</th><th>Other</th></tr>
<tr><td rowspan="4">Sodium
Potassium
Chloride
Glucose
BUN
Creatinine
ALT
AST
Alkaline phosphatase
Total bilirubin
Total protein
Albumin
Calcium
Magnesium
Phosphate
Creatinine</td><td>White Blood Cell (WBC) Count
Hemoglobin
Hematocrit
Platelet Count
ANC
Neutrophils
Lymphocytes
Monocytes</td><td rowspan="4">GS-5745 concentration
Anti-GS-5745 antibody
Serum and Plasma Biomarkers</td></tr>
<tr><td>Coagulation</td></tr>
<tr><td>PT/INR
aPTT</td></tr>
<tr><td>Pregnancy Testing</td><td>Urine</td></tr>
<tr><td>Serum Qualitative β-HCG (females)
Urine Pregnancy (females)</td><td>Urinalysis</td><td></td></tr>
</table>

6.8.11. Pregnancy Test for Females of Childbearing Potential

All female subjects of childbearing potential (as defined in Section 4.2) will have a serum pregnancy test at Screening and a urine pregnancy test prior to each dose of GS-5745 and at the End-of-Study visit. The results must be confirmed as negative prior to administration of study drug on the respective days the test is performed.

6.8.12. Biomarkers

CCI

[redacted]

CCI

[redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

CCI [redacted]

Table 6-8. Biomarker Objectives and Testing, CRC and Breast Cancer Subjects

Sample Type	Objective	Tests Outlined Below May Include, but Are Not Limited to, the Following:
Blood	To evaluate pharmacodynamics of GS-5745	MMP9 cleavage products (eg, C1M)
	To evaluate the effect of GS-5745 and other study drugs on circulating markers correlated with immune activation, MMP9 substrates and MMP family members	Circulating chemokines and inflammatory cytokines (eg, interleukin 6 [IL-6], interferon gamma [IFN-γ], CXCL10, VEGF, MMP2)
	To evaluate disease burden and investigate mutations and patterns of gene expression	Quantification and sequencing of blood-based tumor DNA, RNA or other descriptive analyses (circulating tumor cells or cell-free fraction)
Stool	To evaluate the gut microbiome and other markers	Microbiome complexity may be determined through 16s rRNA sequencing and other MMP9-related biomarkers may be evaluated for CRC subjects only
Tissue Biopsy: Archival Tissue	To evaluate baseline biomarkers that associate with GS-5745 plus combination therapy activity	MMP9 and other relevant proteins by IHC (eg PDL1, infiltrating immune cells), gene expression patterns (RNA), DNA somatic mutations MSI, MSS and CIMP status to be determined for CRC subjects only
Tissue Biopsy Week 6 (C2D15)	To evaluate biomarkers for which change from baseline associates with GS-5745 plus combination therapy activity	MMP9 and other relevant markers by IHC (eg, PDL1, immune cells), gene expression patterns (RNA) for breast cancer subjects only
CCI [redacted]		

CCI [redacted]

6.8.14. Biologic Samples for Optional Future Research

CCI [redacted]

[redacted]

6.8.15. Unscheduled Procedures

Unscheduled procedures, including, but not limited to, vital signs, 12-lead ECG, and CT or MRI, will be recorded on the applicable eCRFs.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Adverse Events

An AE is any untoward medical occurrence in a clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs also include the following:

- All AEs that occur from the study screening visit onwards and throughout the duration of the study, including the follow-up off study medication period should be recorded as an AE
- Pre- or post-treatment complications that occur as a result of protocol-mandated procedure (eg, such as venipuncture or biopsy) during or after screening (before the administration of study investigational medicinal product)
- Any pre-existing condition that increases in severity, or changes in nature during or as a consequence of the study investigational medicinal product phase of a human clinical trial, will also be considered an AE
- Complications and termination of pregnancy (see Section 7.13 for additional information)

An AE does not include the following:

- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, transfusion) performed; the condition that leads to the procedure is an AE
- Pre-existing diseases or conditions or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history eCRF.
- Uncomplicated pregnancy
- An induced elective abortion to terminate a pregnancy without medical reason

7.2. Serious Adverse Events

A serious adverse event (SAE) is defined as follows:

Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening situation (subject is at **immediate** risk of death)
- In-patient hospitalization or prolongation of existing hospitalization (excluding those for study therapy or placement of an indwelling catheter, unless associated with other SAEs)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received investigational medicinal product
- Other: medically significant events that may not be immediately life-threatening or result in death or hospitalization, but based upon appropriate medical and scientific judgment, may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

  Examples of such events are as follows:

  — Intensive treatment in an emergency room or at home for allergic bronchospasm

  — Blood dyscrasias or convulsions that do not result in hospitalization

  — Development of drug dependency or drug abuse

Clarification of Serious Adverse Events

- Death is an outcome of an AE, and not an AE in itself.
- An SAE may occur even if the subject was not on investigational medicinal product at the time of occurrence of the event. Dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE.
- "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is a SAE.

- "In-patient hospitalization" means the subject is formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department.

- The investigator should attempt to establish a diagnosis of the event on the basis of signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms.

Disease Progression and Death Related to Disease Progression

- To maintain the integrity of the study, disease progression and death from disease progression should be reported as SAEs by the investigator only if it is assessed that the study drugs caused or contributed to the disease progression (ie, by a means other than lack of effect). Unrelated disease progression should be captured on the eCRF.

- In addition, events that are indicative of the following disease- related SAEs that are assessed as unrelated to study drugs, will not be reported as expedited reports by Gilead during the study:

  — Progression of malignancy being studied

  — Death related to disease progression

These events will be exempt from global expedited reporting requirements for the duration of the study as they are the primary endpoints of this study. They will be reported as appropriate in the final clinical study report as well as any relevant aggregate safety report.

7.3. Describing Adverse Event Relationship to Study Drug and Study Procedures

The relationship of an AE or SAE to investigational medicinal product should be assessed using clinical judgment, describing the event as either unrelated (No) or related (Yes) consistent with the following definitions:

- **No:** Evidence exists that the AE has an etiology other than the investigational medicinal product. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

- **Yes:** A temporal relationship exists between the AE onset and administration of the investigational medicinal product that cannot be readily explained by the subject's clinical state or concomitant therapies. Furthermore, the AE appears with some degree of certainty to be related, based on the known therapeutic and pharmacologic actions or AE profile of the investigational medicinal product. In case of cessation or reduction of the dose the AE may abate or resolve and it may reappear upon re-challenge.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

The relationship of an AE or SAE to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using clinical judgment, describing the event as either unrelated (No) or related (Yes) consistent with the following definitions:

- **No:** Evidence exists that the AE has an etiology other than the study procedure.
- **Yes:** A temporal relationship exists between the AE onset and a protocol-mandated procedure that cannot be readily explained by the subject's clinical state or concomitant therapies. Furthermore, the AE appears with some degree of certainty to be related to the study procedure based on the known potential complications of that procedure.

7.4. Dose Escalation and Stopping Rules for Part A

In the dose escalation phase of the study (Part A), subjects will be assigned sequentially to cohorts of up to 6 subjects each. Three subjects will initially be enrolled in each cohort for DLT observation. Three additional subjects will be enrolled in each cohort in the event that a DLT is observed and/or additional safety, PK, or pharmacodynamic data are needed. The DLT observation period ends on Day 29 for all subjects in Part A. In order for a subject to be evaluable for the DLT observation, the subject must have received the first 2 doses of GS-5745, completed all safety procedures through Day 29, or have experienced a DLT prior to Day 29.

The starting dose of GS-5745 in Part A is 200 mg. A single subject will initially be enrolled into the first dosing cohort to evaluate any unexpected adverse effects. Provided that there are no significant safety signals up to 24 hours post-dose, the remaining 2 subjects will be dosed.

The safety data will be reviewed once all 3 subjects in a given cohort complete study Day 29. The decision to proceed to the next dose level will be made by the Investigators in conjunction with the Gilead study team after careful consideration and review of all available safety and laboratory findings. Dose escalation decisions will be made in accordance with a standard 3 + 3 design using the following rules:

1) If no DLT is observed within the first 28 days in the initial 3 subjects of a cohort, then dose escalation to the next higher dose level cohort will occur.

2) If one DLT is observed within the first 28 days in the initial 3 subjects of a cohort, then 3 additional subjects will be enrolled in that cohort. If no further DLT(s) are observed in the 6 subjects, then dose escalation to the next higher dose level cohort will occur. If DLTs are experienced by 2 or more study subjects in a cohort during the defined DLT period, dose de-escalation will occur to an intermediate dose (1200 mg and 400 mg as described in Section 3.1).

The MTD is defined as the highest dose level with a subject incidence of DLTs during the first 28 days of study drug dosing of 0 or 1 out of 6.

The assessment of a DLT will follow the guidelines provided in the CTCAE (version 4.03). These criteria are available online at:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

If an AE is not specified in the CTCAE, the severity grading of the AE should be recorded and graded as follows:

- **Mild (Grade 1):** Awareness of signs or symptoms, but easily tolerated;
- **Moderate (Grade 2):** Discomfort sufficient to cause interference with usual activities;
- **Severe (Grade 3 or 4):** Incapacitation with inability to work or perform usual activities.

Grade 5 (death) is an outcome and will not be recorded as a severity.

A DLT is a toxicity defined below considered possibly related to GS-5745 occurring during the DLT assessment window (Day 1 through Day 29) in each dose escalation cohort.

- Grade 4 neutropenia (ANC < 500/μL) for > 7 days, or febrile neutropenia (ANC < 1000/μL with fever > 101 °F [38.5 °C])
- Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia associated with bleeding
- Grade 3 or 4 non-hematologic toxicity (excluding rash, nausea, diarrhea, and vomiting if controlled with standard supportive care)
- Treatment delay of ≥ 14 days due to unresolved toxicity
- Non-hematologic toxicity of ≥ Grade 2 (at any time during treatment) that, in the judgment of the investigators and the Medical Monitor, is dose-limiting.
- For certain toxicities such as laboratory assessments without a clear clinical correlate, a discussion between the Investigator, Medical Monitor, and the Sponsor may take place to determine if this AE should be assessed as a DLT necessitating dose reduction.

7.5. Adverse Drug Reactions

An adverse drug reaction (ADR) is defined as an AE that is considered causally related to an investigational medicinal product. A serious ADR (SADR) is an ADR which meets the seriousness criteria.

7.6. Unexpected Adverse Event

An unexpected AE is defined as an event that has a nature or severity, or specificity that is not consistent with the applicable Investigator's Brochure or that is symptomatically and pathophysiologically related to a known toxicity but differs because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator's Brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure only listed

cerebral vascular accidents. “Unexpected,” as used in this definition, refers to an adverse drug experience that has not been previously observed and reported rather than an experience that has not been anticipated based on the pharmacological properties of the study drug.

7.7. Grading of the Severity of an Adverse Event

The severity grading of AEs will be assessed as Grade 1, 2, 3, 4 or 5 using the CTCAE (version 4.03). For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

The distinction between the seriousness and the severity of an AE should be noted. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed above.

7.8. Special Situations Reports

7.8.1. Definition of Special Situations

Special situation reports include pregnancy reports, reports of medication error, abuse, misuse, or overdose, and reports of adverse reactions associated with product complaints.

A pregnancy report is used to report pregnancies following maternal or paternal exposure to the product.

Medication error is any preventable event that can cause or lead to inappropriate medication use or patient harm while the medication is in the control of a healthcare professional, patient or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a patient accompanied by harmful, physical, and/or psychological effects.

Misuse is defined as any use of a medicinal product in a way that the product is intentionally and inappropriately used not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as a dose taken (accidentally or intentionally) exceeding the dose as prescribed by the protocol or the maximal recommended daily dose as stated in the Product Labeling (as it applies to the daily dose for the subject/patient in question).

In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s) or the investigator has reason to suspect that the subject has taken the additional dose(s).

Product complaint is defined as any written or verbal report arising from potential deviations in the manufacture, packaging or distribution of the product.

Instructions for reporting Special Situation Reports are described in Section 7.9.2.

7.9. Reporting Requirements

7.9.1. Site Reporting Requirements for Adverse Events

Classification of an event as serious or non-serious (see Sections 7.1 and 7.2) determines the reporting procedures to be followed by the site.

Site reporting requirements for AEs are summarized in Table 7-1.

Table 7-1. Site Reporting Requirements for Adverse Events

Classification	Reporting Time	Reporting Action
Serious	Within 24 hours	Fax report on designated SAE Report Form to Gilead DSPH, and to the site IRB, as per local IRB requirements; include copies of relevant source documents (eg, progress notes, autopsy reports, laboratory and diagnostic test results, discharge summaries) in communication to Gilead DSPH.
	Per eCRF submission procedure	Record and submit information on appropriate eCRFs
Non-serious	Per eCRF submission procedure	Record and submit information on appropriate eCRFs

For SAEs, in addition to completing the AE portion of the eCRF, the SAE Report Form must also be completed. The information in the AE portion of the eCRF page and the SAE Report Form(s) must match or be reconciled. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms.

Particularly for fatal or life-threatening events, copies of progress notes, autopsy reports, laboratory and diagnostic test results, discharge summaries, and other relevant documents should be e-mailed or faxed when requested and applicable. Follow-up information to the SAE should be clearly documented as “follow up” in the SAE Report Form and must be faxed to these same parties. Gilead or the CRO may request additional information from the investigator to ensure the timely completion of accurate safety reports.

The subject’s name, address, and other personal identity information should be obscured on any source documents (eg, progress notes, nurses’ notes, laboratory and diagnostic test results, discharge summaries). Only the subject’s study number, initials, or date of birth are to be provided.

The SAE Report Form must be communicated to the Gilead Drug Safety and Public Health (DSPH) and to the site IRB (if required by local regulations) within 24 hours. In the rare event that the investigator does not become aware of the occurrence of a SAE immediately (for example, if a subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and to document his/her first awareness of the AE.

Follow-up of AEs will continue through the last day on study or until the investigator and Gilead Sciences, or its designee, determine that the subject's condition is stable. Gilead Sciences may request that certain AEs be followed until resolution.

Contact information for reporting SAEs to Gilead is provided in Table 7-2:

Table 7-2. Contact Information for Reporting Serious Adverse Events

Gilead Drug Safety and Public Health (DSPH):	**Fax:** PPD **E-mail:** PPD

7.9.2. Special Situation Reporting Instructions

Instructions for Reporting Pregnancies:

- The Investigator should report all pregnancies to Gilead DSPH using the Pregnancy Report form within 24 hours of becoming aware of the pregnancy as outlined in Section 7.13. Contact information for reporting pregnancies is provided in Table 7-2.

Instructions for Reporting Other Special Situations:

- All other Special Situation reports must be reported on the Special Situation Report Form and forwarded to Gilead DSPH within 24 hours using the contact information provided in Table 7-2.

- All clinical sequelae in relation to Special Situation reports will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management and outcome will be reported, when available

7.9.3. Gilead Sciences Reporting Requirements for Adverse Events

Depending on relevant legislation or regulations in different regions and countries, Gilead Sciences may be required to expedite reports to regulatory authorities for the following types of AEs: SAEs including events related to study procedures; SADRs; and suspected, unexpected, serious adverse reactions (SUSARs).

Each SAE report received from the investigator will be evaluated by Gilead Sciences DSPH who will assess the seriousness of the event (see Section 7.2), the relationship to participation in the study (Section 7.3), and the expectedness of the event (see Section 7.6). For regulatory reporting purposes, expectedness will be determined by Gilead Sciences DSPH using reference safety information specified in the Investigator's Brochure.

Gilead Sciences or its designee will also provide all investigators and the Data Monitoring Committee (if applicable) a safety letter e-mail, fax, or overnight mail notifying them of a SUSAR. Investigators will be requested to provide written notification of the SUSAR to the IRB as soon as is practical, consistent with local regulatory requirements and local institutional policy.

7.9.4. Post-Study Reporting Requirements

All AEs and SAEs including deaths, regardless of cause or relationship, must be reported for subjects on study through the last study visit and the 30-day follow-up phone call.

Any SAEs and deaths that occur after the End of Study visit but within 30 days of the last dose of investigational medicinal product, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the 30 day time period. However, if the investigator learns of any SAEs that occur after study participation and the event is deemed relevant to the use of investigational medicinal products, he/she should promptly document and report the event to Gilead Sciences DSPH.

7.10. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to investigational medicinal product interruption or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, X-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1 and 7.2, respectively. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (ie, anemia) not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the CTCAE (version 4.03).

For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.11. Toxicity Management

Treatment-emergent toxicities will be noted by the Investigator and brought to the attention of the Gilead Sciences Medical Monitor or designee. Whether or not considered treatment-related, all subjects experiencing AEs must be monitored periodically until symptoms subside, any abnormal laboratory values have resolved or returned to baseline levels or they are considered irreversible, or until there is a satisfactory explanation for the changes observed.

Grade 3 or 4 clinically significant laboratory abnormalities should be confirmed by repeat testing as soon as practical to do so, and preferably within 3 calendar days after receipt of the original test results.

Any questions regarding toxicity management should be directed to the Gilead Medical Monitor or designee.

7.12. Contraception Requirements

Although there are no adequate and well-controlled studies of gemcitabine, nab-paclitaxel, paclitaxel, carboplatin, pemetrexed, oxaliplatin, or fluorouracil in pregnant women, based on animal studies these drugs can cause fetal harm when administered to a pregnant woman.

There are no adequate and well-controlled clinical studies of leucovorin in pregnant women, and formal animal reproductive toxicity studies have not been conducted.

The risks of treatment with GS-5745 during pregnancy have not been evaluated in humans. The potential for genotoxicity is not expected, given that GS-5745 is a monoclonal antibody. In both the rat and rabbit definitive embryo-fetal developmental toxicity studies, there were no GS-5745-related effects on embryo-fetal survival and growth and no fetal anomalies. In a fertility study in male and female rats, no test article-related effects on reproductive performance and intrauterine survival were observed at any dosage level. In addition, male and female reproductive organ weights were unaffected by GS-5745 at all dose levels. There were no test article-related effects on spermatogenic endpoints at any dose level. The animal peri/post-natal study is ongoing.

Women of childbearing potential should be informed of the potential risk and use highly effective methods of birth control during treatment with GS-5745 from screening until 30 days after the end of relevant systemic exposure. A clinically relevant interaction between GS-5745 and contraceptive steroids is not expected because of their distinct metabolic pathways and therefore, hormonal contraception may be used as part of the birth control methods. If females are using hormonal agents for contraception, the safety and/or efficacy may be affected by possible drug-drug interaction. However, it is recommended that the subject continue the hormonal agent and that a non-hormonal method (or methods) be used concurrently. If females utilize hormonal agents as one of their contraceptive methods, the same hormonal method must have been used for at least 3 months before study dosing.

Women of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test at the Baseline/Day 1 visit prior to drug administration. At minimum, a pregnancy test will be performed at the end of relevant systemic exposure. In the event of a delayed menstrual period (over 1 month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is true even for women of childbearing potential with infrequent or irregular periods.

It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure of the male subject's seminal fluid. Therefore, male subjects with female partners of childbearing potential must use condoms during treatment until the end of relevant systemic exposure.

Please refer to the latest version of the GS-5745 Investigator's Brochure for additional information, as well as the prescribing information for gemcitabine, nab-paclitaxel, paclitaxel, carboplatin, pemetrexed, oxaliplatin, leucovorin, and fluorouracil.

In the context of this protocol, a female subject is considered to be of childbearing potential unless she has had a hysterectomy, a bilateral tubal ligation, or a bilateral oophorectomy; has medically documented ovarian failure (with serum estradiol and FSH levels within the institutional postmenopausal range and a negative serum or urine β-HCG); or is menopausal (age ≥ 55 years with amenorrhea for ≥ 6 months).

Sexually active females of childbearing potential must agree to use a protocol-recommended method of contraception during heterosexual intercourse from screening until 30 days following discontinuation of GS-5745. In addition, please refer to the latest prescribing information for contraception requirements concerning gemcitabine, nab-paclitaxel, paclitaxel, carboplatin, pemetrexed, oxaliplatin, leucovorin, and fluorouracil.

Protocol-recommended contraceptive methods are described in Table 7-3. If tubal sterilization is via the Essure procedure, verification of tubal blockage by hysterosalpingogram (HSP) must be performed approximately 3 months after micro-insertion. Prior to verification, Essure is not considered a reliable form of contraception and the contraception methods described below must be used.

Lactating females must discontinue nursing before investigational medicinal product administration.

Male subjects who are sexually active are required to use barrier contraception (condom with spermicide) during heterosexual intercourse from screening through to study completion and for 90 days from the last dose of GS-5745. In addition, please refer to the latest prescribing information for contraception requirements concerning gemcitabine, nab-paclitaxel, paclitaxel, carboplatin, pemetrexed, oxaliplatin , leucovorin, and fluorouracil..

Males must also refrain from sperm donation from the start of study drugs, throughout the study treatment period, and for 90 days following the last dose of GS-5745. In addition, please refer to the latest prescribing information for contraception requirements concerning gemcitabine, nab-paclitaxel, paclitaxel, carboplatin, pemetrexed, oxaliplatin , leucovorin, and fluorouracil..

Table 7-3. Protocol-Recommended Contraceptive Methods

Single Methods	Combination Methods
Intra-Uterine Devices (IUDs) Tubal Sterilization Vasectomy	**Estrogen and Progesterone** • Oral contraceptives plus condom/spermicide • Transdermal patch plus condom/spermicide • Vaginal ring plus condom/spermicide **Progesterone + Barrier** • Injection plus condom/spermicide • Implant plus condom/spermicide **Two Barrier Methods** • Female barrier/spermicide (ie, Diaphragm or other cervical caps) plus male condom

The Gilead Medical Monitor or designee should be consulted regarding any questions relating to childbearing status or contraception.

7.13. Procedures to be Followed in the Event of Pregnancy

Each female subject should be instructed to discontinue further study therapy and inform the investigator **immediately** if she becomes pregnant at any time between the initiation of study drug until 30 days (or 90 days for the partner of male subjects) after last receiving study drugs. The investigator must report any pregnancy to Gilead DSPH within 24 hours of the time the investigator becomes aware of the pregnancy.

The investigator should counsel the subject regarding the possible effects of investigational medicinal product exposure on the fetus and the need to inform the study site of the outcome of the pregnancy.

All pregnancies of study subjects and female partners of male subjects that occur during the study and follow-up period should be reported using the Pregnancy Report eCRF. Monitoring of the pregnancy in both female study subjects and female partner of male study subjects should continue until the conclusion of the pregnancy. The outcome of the pregnancy should be reported on the Pregnancy Outcome Report eCRF within 5 days of the conclusion of the pregnancy. If the end of the pregnancy occurs after the study is completed, the outcome should be reported directly to Gilead DSPH (facsimile: PPD e-mail: PPD

Neither the pregnancy itself nor an induced elective abortion to terminate the pregnancy without medical reasons is considered an AE; such occurrences should be reported on the appropriate pregnancy report forms. However, if the outcome of the pregnancy meets the criteria for classification as an SAE (ie, spontaneous abortion, induced abortion due to complications, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the investigator should follow the procedures for reporting SAEs, ie, report the event to Gilead DSPH by telephone and follow up by submission of the appropriate AE eCRFs.

Pregnancy outcomes that are classified as SAEs include:

- Any spontaneous abortion, including miscarriage and missed abortion.
- An induced therapeutic abortion to terminate any pregnancy due to complications or other medical reasons. The underlying medical reason for this procedure should be recorded as the AE term.
- All neonatal deaths that occur within 1 month of birth, regardless of causality. In addition, any infant death after 1 month that the investigator assesses as possibly related to the in utero exposure to the study drug should also be reported as a SAE.

In the case of a live birth, the "normality" of the newborn can be assessed at time of birth (ie, there is no required minimum follow-up of a presumably normal infant before the Pregnancy Outcome Report eCRF can be completed).

The “normality” of an aborted fetus can be assessed by gross visual inspection unless there are pre-abortion laboratory findings suggestive of a congenital anomaly, in which case pathologic examination should be requested.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Objectives

The primary objectives of this study are:

- To determine the MTD of GS-5745 monotherapy in subjects with advanced solid tumors
- To characterize the safety and tolerability of GS-5745 as monotherapy and in combination with various chemotherapy regimens in subjects with select tumor types

The secondary objectives of this study are:

- To characterize the PK of GS-5745
- To evaluate the formation of anti-GS-5745 antibodies

CCI [redacted]

CCI [redacted]

The exploratory objective of this study is:

CCI [redacted]

8.1.2. Primary Endpoint

Safety will be evaluated by incidence of AEs, assessment of clinical laboratory test findings, physical examination, 12-lead ECG, and vital signs measurements.

8.1.3. Exploratory Endpoints

CCI [redacted]

8.2. Analysis Conventions

Descriptive statistics including means, medians, standard deviations, and ranges will be calculated for continuous variables, and categorical data will be summarized using frequency counts and percentages.

8.2.1. Analysis Sets

8.2.1.1. Safety Analysis Set

The Safety Analysis Set includes all subjects who receive at least 1 infusion at any dose of GS-5745. This analysis set will be used for both the safety and efficacy analyses.

Determination of the MTD in Part A will be in DLT-evaluable subjects (ie, subjects in the Safety Analysis Set who received the first 2 doses of GS-5745, completed all safety procedures through Day 29, or experienced a DLT prior to Day 29).

For Cohort 8 (first-line CRC) and Cohort 9 (second-line CRC), subjects initially dosed with bevacizumab 10 mg/kg Q2W will be replaced. The safety and efficacy data of these subjects will be listed but will not be included in the summary of safety or efficacy evaluations.

8.2.1.2. Pharmacokinetic/Pharmacodynamic Analysis Set

The Pharmacokinetic/Pharmacodynamic (PK/PD) Analysis Set include subjects in the Safety Analysis Set who have the necessary baseline and on-study measurements to provide interpretable results for specific parameters of interest.

8.2.2. Subject Groups

In Part A, 3 proposed dose level cohorts (200 mg, 600 mg, and 1800 mg) will be enrolled. In Part B, 7 cohorts (pancreatic adenocarcinoma, lung adenocarcinoma, lung squamous cell carcinoma, and esophagogastric adenocarcinoma, first-line CRC, second-line CRC, and breast cancer) will be enrolled. Intermediate dose cohorts (400 mg and 1200 mg) will be enrolled if $\geq$ 2 DLTs are observed in the proposed dose level cohorts.

8.2.3. Data Handling Conventions

In general, values for missing data will not be imputed. However, a missing pre-treatment laboratory result would be treated as normal (ie, no toxicity grade) for the laboratory abnormality summary.

All available data for subjects that do not complete the study will be included in data listings.

8.3. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized for the safety analysis set by dose level (Part A) and tumor type (Part B) using standard descriptive summaries or categorical summaries, as appropriate.

8.4. Safety Analysis

Safety will be evaluated for all subjects in the Safety Analysis Set through assessment of clinical laboratory test findings, physical examinations, 12-lead ECGs, vital sign measurements, and by the documentation of AEs.

Concomitant medication intake will also be recorded and coded to the corresponding WHO drug term and displayed in data listings.

Safety data will be listed by subject and summarized by dose level (Part A) and tumor type (Part B), and by frequency of treatment-emergent AEs and laboratory abnormalities.

All safety data collected on or after the date of the first dose of study drug through to completion of the follow-up evaluation will be summarized.

Data for the pre-treatment period will be included in data listings.

In Part B, safety data provided in the form of data listings will be reviewed by the Medical Monitor on an ongoing basis (at least monthly while subjects are actively enrolling). The Sponsor will organize regularly scheduled calls with the clinical sites to discuss study updates, safety data, and ongoing clinical experience with GS-5745.

8.4.1. Extent of Exposure

Dosing information for individual subjects will be listed and summarized by dose level (Part A) and tumor type (Part B).

8.4.2. Adverse Events

Adverse events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) (http://www.meddramsso.com) with descriptions by System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT). AEs will be summarized on the basis of the date of onset of the event. All AEs will be listed by subject.

A treatment-emergent AE will be defined as any AE that begins on or after the date of first study drug administration and within 30 days after last study drug administration.

Separate listings and summaries will be prepared for all subjects and by dose level (Part A) and tumor type (Part B) for the following types of treatment-emergent AEs:

- Study-drug-related AEs
- AEs that are Grade ≥ 3 in severity
- AEs leading to study drug interruption and/or dose modification
- AEs leading to study drug discontinuation
- Serious AEs (with categorization of the primary reason that the AE is considered serious, eg, death, hospitalization, etc)

8.4.3. Laboratory Evaluations

All laboratory data will be listed and summarized based on observed values. Reference ranges provided by the laboratory for each parameter will be used to evaluate the clinical significance of laboratory test results. Values falling outside of the relevant reference range will be flagged, as appropriate, in the data listings.

Selected laboratory data will be summarized (eg, n, mean, SD, median, Q1, Q3, minimum, and maximum) by dose level (Part A) and tumor type (Part B) at scheduled visits and for corresponding change from baseline.

Hematologic, serum biochemistry, and coagulation data will be programmatically graded according to CTCAE (version 4.03) severity grade, when applicable. For parameters for which a CTCAE (version 4.03) scale does not exist, reference ranges from the central laboratory will be used to determine programmatically if a laboratory parameter is below, within, or above the normal range for the subject's age, sex, etc. Separate listings and summaries will be prepared for laboratory abnormalities that are Grade ≥ 3 in severity.

The incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any time post-baseline up to and including 30 days after the last dose of study drug administration, will be summarized by dose level (Part A) and tumor type (Part B). If baseline data are missing, then any graded abnormality (ie, at least Grade 1) will be considered treatment-emergent.

Laboratory abnormalities that occur before the first dose of study drug or after the subject has been discontinued from treatment for at least 30 days will be included in data listings.

8.5. Exploratory Analysis

Objective response rate by tumor type (Part B) will be presented with corresponding two-sided [redacted]

CCI [redacted]

8.6. Pharmacokinetics Analysis

Pharmacokinetic parameters will be listed and summarized for GS-5745 using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, % coefficient of variation, standard deviation, median, Q1, Q3, minimum, and maximum). GS-5745 concentrations over time will be plotted in semi logarithmic and linear formats as mean ± standard deviation. Relevant PK parameters will be determined using standard non-compartmental methods with the linear up-log down trapezoidal rule utilizing a PK data analysis program (eg, WinNonlin® or equivalent). The following PK parameters will be calculated for GS-5745, as applicable: C_{max}, C_{last}, T_{max}, T_{last}, λ_z, AUC_{last}, AUC_{inf}, CL, V, and $T_{1/2}$. The relationship between PK and pharmacodynamics may be explored as appropriate.

8.7. Sample Size

The sample size of the study will depend on the number of dose levels evaluated and the emerging GS-5745-related toxicities. Part A will comprise 12 to 48 subjects and Part B will comprise 115 to 295 subjects (35 subjects in Cohort 4 [pancreatic], 10 subjects each in Cohort 5 [lung adenocarcinoma] and Cohort 6 [lung squamous cell carcinoma], and 15 subjects each in Cohort 7 [esophagogastric], Cohort 8 [first-line CRC], Cohort 9 [second-line CRC] and Cohort 10 [breast cancer]. Up to a maximum of 25 additional subjects in each cohort may be enrolled to obtain information on safety, PK, pharmacodynamics, and tumor response. For Cohort 4, with the assumption of an observed ORR of 40%, the 90% CI would be 19% to 64% with a sample size of 15, and 26% to 55% with a sample size of 35. This sample size also includes up to 15 replacement subjects for Cohort 8 and Cohort 9, respectively.

For Cohort 8 (first-line CRC), with the assumption of an ORR of 60%, the 90% CI would be 36% to 81% with sample size of 15, and 46% to73% with a sample size of 40.

For Cohort 9 (second-line CRC), with the assumption of an ORR of 25%, the 90% CI would be 10% to 51% with sample size of 15, and 14% to 39% with a sample size of 40.

For Cohort 10 (breast cancer), with the assumption of an ORR of 40%, the 90% CI would be 19% to 64% with sample size of 15, and 27% to 54% with a sample size of 40.The sample size is based on practical considerations and is consistent for this type of study.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. For studies conducted under a United States IND, the investigator will ensure that the basic principles of "Good Clinical Practice," as outlined in 21 CFR 312, subpart D "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998, are adhered to.

9.1.2. Institutional Review Board (IRB) Approval

This protocol and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IRB. Approval from the IRB must be obtained **before** starting the study and should be documented in a letter to the investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of IRB approval must also be submitted to the IRB for approval before implementation.

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must utilize an IRB-approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person obtaining consent.

9.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, and an identification code (ie, not names) should be recorded on any form or biological sample submitted to the Sponsor, IRB, or laboratory. The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial.

The investigator agrees that all information received from Gilead, including but not limited to the Investigator's Brochure, this protocol, eCRFs, the investigational new drug, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.5. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRF and query forms, IRB and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data are listed in the Source Data Verification Plan, and should include sequential notes containing at least the following information for each subject:

- subject identification (name, date of birth, gender)
- documentation that subject meets eligibility criteria, ie, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria)
- participation in trial (including trial number)
- trial discussed and date of informed consent
- dates of all visits
- documentation that protocol specific procedures were performed
- results of efficacy parameters, as required by the protocol
- start and end date (including dose regimen) of trial medication (preferably drug dispensing and return should be documented as well)
- record of all AEs and other safety parameters (start and end date, and preferably including causality and intensity)
- concomitant medication (including start and end date, dose if relevant; dose changes should be motivated)
- date of trial completion and reason for early discontinuation, if applicable

All clinical study documents must be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region (ie, United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storage outside of the site.

Please see Section 6.8.12 for information on storage of biological samples at the conclusion of the study.

9.1.6. Electronic Case Report Forms

For each subject enrolled, an eCRF must be completed and signed by the principal investigator or sub-investigator (as appropriate) within a reasonable time period after data collection. If a subject withdraws from the study, the reason must be noted on the eCRF. If a subject is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

9.1.7. Study Drug Accountability and Return

Where possible, IMP should be destroyed at the site. At the start of the study, the study monitor will evaluate each study center's IMP disposal procedures and provide appropriate instruction for disposal or return of unused IMP supplies. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused IMP supplies as long as performed in accordance with the site's SOP. This can occur only after the study monitor has performed drug accountability during an on-site monitoring visit.

A copy of the site's IMP Disposal SOP or written procedure (signed and dated by the principal investigator or designee) will be obtained for Gilead site files. If the site does not have acceptable procedures in place, arrangements will be made between the site and Gilead (or Gilead's representative) for return of unused study drug supplies.

If IMP is destroyed on site, the investigator must maintain accurate records for all IMPs destroyed. Upon study completion, copies of the IMP accountability records must be filed at the site. Another copy will be returned to Gilead.

The study monitor will review IMP supplies and associated records at periodic intervals

9.1.8. Inspections

The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from Gilead or its representatives, to IRBs or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead. All protocol modifications must be submitted to the IRB in accordance with local requirements. Approval must be obtained before changes can be implemented.

9.2.2. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies). Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

After conclusion of the study and without prior written approval from Gilead, investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media ***only after the following conditions have been met:***

- the results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form; or
- the study has been completed at all study sites for at least 2 years.

No such communication, presentation, or publication will include Gilead' confidential information (see Section 9.1.4).

The investigator will submit any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation. The investigator will comply with Gilead' request to delete references to its

confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, eg, attendance at Investigator's Meetings. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical trial payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with ICH GCP guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded on the eCRFs for consistency.

The monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered. The monitor should have access to any subject records needed to verify the entries on the eCRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead Medical Monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both the Sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies) and IRB(s). In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404

STUDY ACKNOWLEDGEMENT

A Phase 1 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of GS-5745 as Monotherapy and in Combination with Chemotherapy in Subjects with Advanced Solid Tumors

GS-US-296-0101, Amendment 6, 01 August 2016

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD

Name (Printed)
Author

PPD

Signature

24/AUG/2016.

Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Study Procedures Table (Part A)

Week		**1**						**2**	**3**		**5**		**7**		**9**	**Q2W[l]**	**Q8W[m]**	**EOS[n]**
Day	**-28 to -1**	**1**			**2**	**3**	**5**	**8**	**15**		**29**		**43**		**57**			
Window									**± 1**		**± 1**		**± 2**		**± 2**	**± 2**	**± 5**	
Hours (Relative to Dosing)		**Pre-dose**	**EOI**	**6**	**24 ± 2**	**48 ± 4**	**96 ± 4**	**168 ± 4**	**Pre-dose**	**EOI**	**Pre-dose**	**EOI**	**Pre-dose**	**EOI**				
Study Assessments																		
Informed Consent	X																	
Medical History[a]	X																	
Physical Exam[b]	X	X						X	X		X		X		X			X
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
12-Lead ECG	X	X	X	X					X		X		X	X	X			X
ECOG Performance Status	X	X			X	X	X	X	X		X		X		X	X		X
Prior/Concomitant Meds[d]	X	X			X	X	X	X	X		X		X		X	X	X	X
AEs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CT or MRI[f]	X														X		X	X
Collect Archival Tumor Tissue (if Available)[g]		X																
Register Subject Visit in IxRS	X	X							X		X		X		X	X		X
Sample Collection																		
Chemistry	X	X[j]						X	X		X		X		X	X	X[k]	X
Hematology	X	X[j]						X	X		X		X		X	X	X[k]	X
Coagulation	X	X[j]							X		X		X		X	X		X
Urinalysis	X	X[j]							X		X		X		X	X		X
Pregnancy Test[h]	X	X[j]							X		X		X		X	X		X
GS-5745 Concentration[i]		X[j]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X

Week		**1**						**2**	**3**		**5**		**7**		**9**	**Q2W[l]**	**Q8W[m]**	**EOS[n]**
Day	**-28 to -1**	**1**			**2**	**3**	**5**	**8**	**15**		**29**		**43**		**57**			
Window									**± 1**		**± 1**		**± 2**		**± 2**	**± 2**	**± 5**	
Hours (Relative to Dosing)		**Pre-dose**	**EOI**	**6**	**24 ± 2**	**48 ± 4**	**96 ± 4**	**168 ± 4**	**Pre-dose**	**EOI**	**Pre-dose**	**EOI**	**Pre-dose**	**EOI**				
Anti-GS-5745 Antibody		X[j]											X				X	X
Serum and Plasma Biomarkers	X	X[j]							X				X		X		X	X
Study Drug Dosing																		
GS-5745 IV Dosing			X							X		X		X	X	X		

EOI = end of infusion; EOS = End-of-Study (visit); PE = physical examination; Q2W = every 2 weeks; Q8W = every 8 weeks

a Medical history includes significant past medical events (eg, prior hospitalizations or surgeries), a review of the disease under study, prior anti-cancer therapies, and any concurrent medical illnesses.

b A complete physical examination (PE) will be performed at Screening. A modified PE capturing changes from prior examinations will be performed at subsequent applicable visits. Weight (without shoes) should be measured at each PE and reported in kilograms. Height (without shoes) should be measured at Screening only and reported in centimeters.

c Vital signs include blood pressure, respiratory rate, pulse, and temperature. Measurements of blood pressure should be taken per institutional guidelines.

d Prior/concomitant medications include all medication taken up to 30 days prior to Screening, any and all medications taken during the course of the study, and supportive therapies given during the course of the study (eg, blood transfusion, growth factor).

e AEs will be assessed before and after GS-5745 dosing during applicable visits.

f Tumor evaluation by CT or MRI will be performed during screening (within 4 weeks of Day 1) and every 8 weeks thereafter. The same radiographic procedure used to define measurable lesions must be used throughout the study for each subject. CT or MRI should be conducted at the EOS visit if not conducted within the previous 4 weeks. If a subject discontinues study drug (for example, as a result of an AE), every attempt should be made to keep the subject in the study to collect tumor assessments (CT/MRI), chemistry, and hematology every 8 weeks until disease progression.

g Unstained slides (10 to 12) from archival tumor tissues prepared within 2 weeks of shipment to Gilead or its designee will be requested after Day 1.

h For females of childbearing potential, a serum pregnancy test will be performed at Screening and urine pregnancy tests will be performed prior to each dose of GS-5745 and at the EOS visit.

i Blood samples to measure GS-5745 concentration will be collected pre- and post-dose at each applicable visit.

j Day 1 pre-dose samples for the specified assessments may be drawn up to 2 days prior to the Day 1 visit.

k If a subject discontinues study drug (for example, as a result of an AE), every attempt should be made to keep the subject in the study to collect tumor assessments (CT/MRI), chemistry, and hematology every 8 weeks until disease progression.

l A subject who does not show evidence of disease progression by clinical assessment or by CT or MRI may continue receiving GS-5745 Q2W until disease progression (clinical or radiographic), unacceptable toxicity, withdrawal of consent, or other reasons specified in Section 6.3. Q2W visits will occur every 2 weeks (± 2 days) from the Day 57 visit.

m Q8W visits will occur every 8 weeks (± 5 days) from the Day 57 visit.

n Subjects will be contacted by phone 30 days (± 2 days) after the last dose of GS-5745 to assess AEs. For subjects who come off study for reasons other than PD, the site should also obtain information on post-study anti-cancer therapies, surgeries, and date of definitive disease progression.

Appendix 3. Study Procedures Table (Part B – Pancreatic Adenocarcinoma)

Study Phase	Screening	Each Cycle (28 Days)			Every 2 Cycles	EOS[l]	LTFU Every 3 months
Cycle Day	**Screening**	**1**	**8**	**15**		**N/A**	**N/A**
Window	**−28**	**0[m]**	**± 2**	**± 2**		**N/A**	**N/A**
Treatment Day	**−28**	**1**	**8**	**15**		**N/A**	**N/A**
Study Assessments							
Informed Consent	X						
Medical History[a]	X						
Physical Exam[b]	X	X				X	
Vital Signs[c]	X	X	X	X		X	
12-Lead ECG	X	X					
ECOG Performance Status	X	X		X		X	
Prior/Concomitant Meds[d]	X	X	X	X		X	
AEs[e]	X	X	X	X		X	
CT or MRI[f]	X				X[k]	X	
Collect Archival Tumor Tissue (if Available)[g]		X					
Register Subject Visit in IxRS	X	X		X		X	
Sample Collection							
Chemistry	X	X[j]		X	X[k]	X	
Hematology	X	X[j]	X	X	X[k]	X	
Coagulation	X	X[j]				X	
Urinalysis	X	X[j]				X	
Pregnancy Test[h]	X	X[j]		X		X	
GS-5745 Concentration[i]		X		X		X	
Anti-GS-5745 Antibody		X[j]				X	

Study Phase	Screening	Each Cycle (28 Days)			Every 2 Cycles	EOS[l]	LTFU Every 3 months
Cycle Day	**Screening**	**1**	**8**	**15**		**N/A**	**N/A**
Window	**−28**	**0[m]**	**± 2**	**± 2**		**N/A**	**N/A**
Treatment Day	**−28**	**1**	**8**	**15**		**N/A**	**N/A**
Serum and Plasma Biomarkers	X	X[j]				X	
Overall Survival							X
Study Drug Dosing / Chemotherapy							
GS-5745 IV Dosing		X		X			
Gemcitabine Dosing		X	X	X			
Nab-Paclitaxel Dosing		X	X	X			

EOS = End-of-Study (visit); PE = physical examination

a Medical history includes significant past medical events (eg, prior hospitalizations or surgeries), a review of the disease under study, prior anti-cancer therapies, and any concurrent medical illnesses.

b A complete PE will be performed at Screening. A modified PE capturing changes from prior exams will be performed at subsequent applicable visits. Weight (without shoes) should be measured at each PE and reported in kilograms. Height (without shoes) should be measured at Screening only and reported in centimeters.

c Vital signs include blood pressure, respiratory rate, pulse, and temperature. Measurements of blood pressure should be taken per institutional guidelines.

d Prior/concomitant medications include all medication taken up to 30 days prior to Screening, any and all medications taken during the course of the study, and supportive therapies given during the course of the study (eg, blood transfusion, growth factor).

e AEs will be assessed before and after GS-5745 and gemcitabine dosing during applicable visits. The site will call subjects 30 days after the last dose of GS-5745 to assess AEs and SAEs.

f Tumor evaluation by CT or MRI will be performed during screening (within 4 weeks of Day 1) and during the last week of even-numbered cycles (ie, Cycles 2, 4, 6, etc.). The same radiographic procedure used to define measurable lesions must be used throughout the study for each subject. CT or MRI should be conducted at the EOS visit if not conducted within the previous 4 weeks. If a subject discontinues study drug (for example, as a result of an AE), every attempt should be made to keep the subject in the study to collect tumor assessments (CT/MRI), chemistry, and hematology during the last week of even-numbered cycles (ie, Cycles 2, 4, 6, etc.) until disease progression.

g Unstained slides (10 to 12) from archival tumor tissues prepared within 2 weeks of shipment to Gilead or its designee will be requested after Day 1 of Cycle 1 only.

h For females of childbearing potential, a serum pregnancy test will be performed at Screening and urine pregnancy tests will be performed prior to each dose of GS-5745 and at the EOS visit.

i Blood samples to measure GS-5745 concentration will be collected pre-dose on Day 1 and Day 15 of each cycle.

j Day 1 pre-dose samples for the specified assessments may be drawn up to 2 days prior to the Day 1 visit.

k If a subject discontinues study drug (for example, as a result of an AE), every attempt should be made to keep the subject in the study to collect tumor assessments (CT/MRI), chemistry, and hematology during the last week of even-numbered cycles (ie, Cycles 2, 4, 6, etc.) until disease progression.

l Subjects will be contacted by phone 30 days (± 2 days) after the last dose of GS-5745 to assess AEs. For subjects who come off study for reasons other than disease progression, the site should also obtain information on post-study anti-cancer therapies, surgeries, and date of definitive disease progression.

m A ± 2 day window applies to visits following Cycle 1 Day 1. There is no window for Cycle 1 Day 1.

Appendix 4. Study Procedures Table (Part B – Esophagogastric Adenocarcinoma)

Study Phase	Screening	Each Cycle (28 Days)		Every 2 Cycles	EOS[m]	LTFU Every 3 months
Cycle Day	**Screening**	**1**	**15**		**N/A**	**N/A**
Window	**−28**	**0[n]**	**± 2**		**N/A**	**N/A**
Treatment Day	**−28**	**1**	**15**		**N/A**	**N/A**
Study Assessments						
Informed Consent	X					
Medical History[a]	X					
Physical Exam[b]	X	X			X	
Vital Signs[c]	X	X	X		X	
12-Lead ECG	X	X				
ECOG Performance Status	X	X	X		X	
Prior/Concomitant Meds[d]	X	X	X		X	
AEs[e]	X	X	X		X	
CT or MRI[f]	X			X[l]	X	
Collect Archival Tumor Tissue (if Available)[g]		X				
Register Subject Visit in IxRS	X	X	X		X	
Sample Collection						
Chemistry	X	X[k]	X	X[l]	X	
Hematology	X	X[k]	X	X[l]	X	
Coagulation	X	X[k]			X	
Urinalysis	X	X[k]			X	
Pregnancy Test[h]	X	X[k]	X		X	
GS-5745 Concentration[i]		X	X		X	
Anti-GS-5745 Antibody		X[k]			X	

Study Phase	Screening	Each Cycle (28 Days)		Every 2 Cycles	EOS[m]	LTFU Every 3 months
Cycle Day	**Screening**	**1**	**15**		**N/A**	**N/A**
Window	**−28**	**0[n]**	**± 2**		**N/A**	**N/A**
Treatment Day	**−28**	**1**	**15**		**N/A**	**N/A**
Serum and Plasma Biomarkers	X	X[k]			X	
Overall Survival						X
Study Drug Dosing / Chemotherapy						
GS-5745 IV Dosing		X	X			
mFOLFOX6 Dosing[j]		X	X			

EOS = End-of-Study (visit); PE = physical examination

a Medical history includes significant past medical events (eg, prior hospitalizations or surgeries), a review of the disease under study, prior anti-cancer therapies, and any concurrent medical illnesses.

b A complete PE will be performed at Screening. A modified PE capturing changes from prior exams will be performed at subsequent applicable visits. Weight (without shoes) should be measured at each PE and reported in kilograms. Height (without shoes) should be measured at Screening only and reported in centimeters.

c Vital signs include blood pressure, respiratory rate, pulse, and temperature. Measurements of blood pressure should be taken per institutional guidelines.

d Prior/concomitant medications include all medication taken up to 30 days prior to Screening, any and all medications taken during the course of the study, and supportive therapies given during the course of the study (eg, blood transfusion, growth factor).

e AEs will be assessed before and after GS-5745 and mFOLFOX6 dosing during applicable visits. The site will call subjects 30 days after the last dose of GS-5745 to assess AEs and SAEs.

f Tumor evaluation by CT or MRI will be performed during screening (within 4 weeks of Day 1) and during the last week of even-numbered cycles (ie, Cycles 2, 4, 6, etc.). The same radiographic procedure used to define measurable lesions must be used throughout the study for each subject. CT or MRI should be conducted at the EOS visit if not conducted within the previous 4 weeks. If a subject discontinues study drug (for example, as a result of an AE), every attempt should be made to keep the subject in the study to collect tumor assessments (CT/MRI), chemistry, and hematology during the last week of even-numbered cycles (ie, Cycles 2, 4, 6, etc.) until disease progression.

g Unstained slides (10 to 12) from archival tumor tissues prepared within 2 weeks of shipment to Gilead or its designee will be requested after Day 1 of Cycle 1 only.

h For females of childbearing potential, a serum pregnancy test will be performed at Screening and urine pregnancy tests will be performed prior to each dose of GS-5745 and at the EOS visit.

i Blood samples to measure GS-5745 concentration will be collected pre-dose on Day 1 and Day 15 of each cycle.

j mFOLFOX6 dosing regimen will consist of *l*-LV 200 mg/m^2 or *dl*-LV 400 mg/m^2 and oxaliplatin 85 mg/m^2 followed by bolus 5-FU 400 mg/m^2 and a 46-hour infusion 5-FU 2400 mg/m^2.

k Day 1 pre-dose samples for the specified assessments may be drawn up to 2 days prior to the Day 1 visit.

l If a subject discontinues study drug (for example, as a result of an AE), every attempt should be made to keep the subject in the study to collect tumor assessments (CT/MRI), chemistry, and hematology during the last week of even-numbered cycles (ie, Cycles 2, 4, 6, etc.) until disease progression.

m Subjects will be contacted by phone 30 days (± 2 days) after the last dose of GS-5745 to assess AEs. For subjects who come off study for reasons other than disease progression, the site should also obtain information on post-study anti-cancer therapies, surgeries, and date of definitive disease progression

n A ± 2 day window applies to visits following Cycle 1 Day 1. There is no window for Cycle 1 Day 1.

Appendix 5. Study Procedures Table (Part B – NSCLC)

Study Phase	Screening	Each Cycle (21 Days)	Every 3 Cycles	EOS[l]	LTFU Every 3 Months
Cycle Day	**Screening**	**1**		**N/A**	**N/A**
Window	**−28**	**± 2**		**N/A**	**N/A**
Treatment Day	**−28**	**1**		**N/A**	**N/A**
Study Assessments					
Informed Consent	X				
Medical History[a]	X				
Physical Exam[b]	X	X		X	
Vital Signs[c]	X	X		X	
12-Lead ECG	X	X			
ECOG Performance Status	X	X		X	
Prior/Concomitant Meds	X	X		X	
AEs[d]	X	X		X	
CT or MRI[e]	X		X[k]	X	
Collect Archival Tumor Tissue (if Available)[f]		X			
Register Subject Visit in IxRS	X	X		X	
Sample Collection					
Chemistry	X	X[j]	X[k]	X	
Hematology	X	X[j]	X[k]	X	
Coagulation	X	X[j]		X	
Urinalysis	X	X[j]		X	
Pregnancy test[g]	X	X[j]		X	
GS-5745 Concentration[h]		X		X	
Anti-GS-5745 Antibody		X[j]		X	

Study Phase	Screening	Each Cycle (21 Days)	Every 3 Cycles	EOS[l]	LTFU Every 3 Months
Cycle Day	**Screening**	**1**		**N/A**	**N/A**
Window	**−28**	**± 2**		**N/A**	**N/A**
Treatment Day	**−28**	**1**		**N/A**	**N/A**
Serum and Plasma Biomarkers	X	X[j]		X	
Overall Survival					X
Study Drug Dosing / Chemotherapy					
GS-5745 IV Dosing		X			
Chemotherapy Dosing[i]		X			

EOS = End-of-Study (visit); PE = physical examination

a Medical history includes significant past medical events (eg, prior hospitalizations or surgeries), a review of the disease under study, prior anti-cancer therapies, and any concurrent medical illnesses.

b A complete PE will be performed at Screening. A modified PE capturing changes from prior exams will be performed at subsequent applicable visits. Weight (without shoes) should be measured at each PE and reported in kilograms. Height (without shoes) should be measured at Screening only and reported in centimeters.

c Vital signs include blood pressure, respiratory rate, pulse, and temperature. Measurements of blood pressure should be taken per institutional guidelines.

d AEs will be assessed before and after GS-5745 dosing during applicable visits. The site will call subjects 30 days after the last dose of GS-5745 to assess AEs and SAEs.

e Tumor evaluation by CT or MRI will be performed during screening (within 4 weeks of Day 1) and during the last week of every third cycle (ie, Cycles 3, 6, 9, etc.). The same radiographic procedure used to define measurable lesions must be used throughout the study for each subject. CT or MRI should be conducted at the EOS visit if not conducted within the previous 4 weeks. If a subject discontinues study drug (for example, as a result of an AE), every attempt should be made to keep the subject in the study to collect tumor assessments (CT/MRI), chemistry, and hematology during the last week of every third cycle (ie, Cycles 3, 6, 9, etc.) until disease progression.

f Unstained slides (10 to 12) from archival tumor tissues prepared within 2 weeks of shipment to Gilead or its designee will be requested after Day 1 of Cycle 1 only.

g For females of childbearing potential, a serum pregnancy test will be performed at Screening and urine pregnancy tests will be performed prior to each dose of GS-5745 and at the EOS visit.

h Blood samples to measure GS-5745 concentration will be collected pre-dose on Day 1 of each cycle.

i NSCLC chemotherapy regimen: carboplatin IV dosed to AUC 6 on Day 1 of each 21-day treatment cycle and pemetrexed 500 mg/m^2 IV on Day 1 of each 21-day treatment cycle in subjects with lung adenocarcinoma. Chemotherapy will consist of carboplatin IV dosed to AUC 6 on Day 1 of each 21-day treatment cycle and paclitaxel 200 mg/m^2 IV on Day 1 of each 21-day treatment cycle in subjects with lung squamous cell carcinoma. Subjects who have not had disease progression after 4 cycles of treatment may have some of their treatment reduced based upon the investigator's assessment of what is in the subject's best interests. However, dosing with GS-5745 should be continued per protocol.

j Day 1 pre-dose samples for the specified assessments may be drawn up to 2 days prior to the Day 1 visit.

k If a subject discontinues study drug (for example, as a result of an AE), every attempt should be made to keep the subject in the study to collect tumor assessments (CT/MRI), chemistry, and hematology during the last week of every third cycle (ie, Cycles 3, 6, 9, etc.) until disease progression.

l Subjects will be contacted by phone 30 days (± 2 days) after the last dose of GS-5745 to assess AEs. For subjects who come off study for reasons other than disease progression, the site should also obtain information on post-study anti-cancer therapies, surgeries, and date of definitive disease progression.

Appendix 6. Study Procedures Table (Part B – CRC, First-Line)

Study Phase	Screening	Each Cycle (28 Days)		Cycle 2	Cycle 3	Every 2 Cycles	EOS[m]	LTFU Every 3 Months
Cycle Day	**Screening**	**1**	**15**	**15**	**1**		**N/A**	**N/A**
Window	**−28**	**0[r]**	**± 2**	**+14 Days / −7 Days**			**N/A**	**N/A**
Treatment Day	**−28**	**1**	**15**				**N/A**	**N/A**
Study Assessments								
Informed Consent	X							
Medical History[a]	X							
Physical Exam[b]	X	X					X	
Vital Signs[c]	X	X	X				X	
12-Lead ECG	X	X						
ECOG Performance Status	X	X	X				X	
Prior/Concomitant Meds[d]	X	X	X				X	
AEs[e]	X	X	X				X	
CT or MRI[f]	X					X[l]	X	
Collect Archival Tumor Tissue (if Available)[g]		X[g]						
Register Subject Visit in IxRS	X	X	X				X	
Sample Collection								
Chemistry	X	X[k]	X			X[l]	X	
Hematology	X	X[k]	X			X[l]	X	
Coagulation	X	X[k]					X	
Urinalysis	X	X[k]					X	
Pregnancy Test[h]	X	X[k]	X				X	

Study Phase	Screening	Each Cycle (28 Days)		Cycle 2	Cycle 3	Every 2 Cycles	EOS[m]	LTFU Every 3 Months
Cycle Day	**Screening**	**1**	**15**	**15**	**1**		**N/A**	**N/A**
Window	**−28**	**0[r]**	**± 2**	**+14 Days / −7 Days**			**N/A**	**N/A**
Treatment Day	**−28**	**1**	**15**				**N/A**	**N/A**
GS-5745 Concentration[i]		X	X		X		X	
Anti-GS-5745 Antibody		X[k]					X	
Serum and Plasma Biomarkers		X[k,n]	X[n]				X[n]	
CCI								
Stool Sample	X[o]			X[o]				
CCI								
Overall Survival								X
Study Drug Dosing / Chemotherapy								
GS-5745 IV Dosing		X	X					
mFOLFOX6/Bev Dosing[j]		X	X					

EOS = End-of-Study (visit); PE = physical examination

a Medical history includes significant past medical events (eg, prior hospitalizations or surgeries), a review of the disease under study, prior anti-cancer therapies, and any concurrent medical illnesses.

b A complete PE will be performed at Screening. A modified PE capturing changes from prior exams will be performed at subsequent applicable visits. Weight (without shoes) should be measured at each PE and reported in kilograms. Height (without shoes) should be measured at Screening only and reported in centimeters.

c Vital signs include blood pressure, respiratory rate, pulse, and temperature. Measurements of blood pressure should be taken per institutional guidelines.

d Prior/concomitant medications include all medication taken up to 30 days prior to Screening, any and all medications taken during the course of the study, and supportive therapies given during the course of the study (eg, blood transfusion, growth factor).

e AEs will be assessed before and after GS-5745 and mFOLFOX6 dosing during applicable visits. The site will call subjects 30 days after the last dose of GS-5745 to assess AEs and SAEs.

f Tumor evaluation by CT or MRI will be performed during screening (within 4 weeks of Day 1) and during the last week of even-numbered cycles (ie, Cycles 2, 4, 6, etc.). The same radiographic procedure used to define measurable lesions must be used throughout the study for each subject. CT or MRI should be conducted at the EOS visit if not conducted within the previous 4 weeks. If a subject discontinues study drug (for example, as a result of an AE), every attempt should be made to keep the subject in the study to collect tumor assessments (CT/MRI), chemistry, and hematology during the last week of even-numbered cycles (ie, Cycles 2, 4, 6, etc.) until disease progression.

g Unstained slides (5×10 micron and 10×5 micron) from archival tumor tissues prepared within 2 weeks of shipment to Gilead or its designee will be requested after Day 1 of Cycle 1 only.

h For females of childbearing potential, a serum pregnancy test will be performed at Screening and urine pregnancy tests will be performed prior to each dose of GS-5745 and at the EOS visit.

i Blood samples to measure GS-5745 concentration will be collected pre-dose on Day 1 and Day 15 of each cycle, end of GS-5745 infusion on Day 1 of Cycle 1 and Cycle 3, and at the EOS visit.

j mFOLFOX6 and bevacizumab dosing regimen on Days 1 and 15 of each 28-day treatment cycle will consist of: bevacizumab at 5 mg/kg IV and mFOLFOX6 dosing regimen will consist of l-leucovorin (LV) 200 mg/m2 or dl-LV 400 mg/m2 and oxaliplatin 85 mg/m2 followed by bolus 5 FU 400 mg/m2 and a 46-hour infusion of 5-FU 2400 mg/m2

k Day 1 pre-dose samples for the specified assessments may be drawn up to 2 days prior to the Day 1 visit.

l If a subject discontinues study drug (for example, as a result of an AE), every attempt should be made to keep the subject in the study to collect tumor assessments (CT/MRI), chemistry, and hematology during the last week of even-numbered cycles (ie, Cycles 2, 4, 6, etc.) until disease progression.

m Subjects will be contacted by phone 30 days (± 2 days) after the last dose of GS-5745 to assess AEs. For subjects who come off study for reasons other than disease progression, the site should also obtain information on post-study anti-cancer therapies, surgeries, and date of definitive disease progression.

n Blood samples for biomarkers should be drawn pre-dose on all specified visits. Note that Day 15 is only required for Cycle 1 and that a blood sample at EOS is required if due to disease progression. The exact schedule of blood draws is outlined in the laboratory manual.

o A stool sample is required at study start and can be collected any time within the screening window prior to first dose. An additional stool sample at Cycle 2 Day 15 (+14 days/−7 days) is requested.

q [redacted]

r A ± 2 day window applies to visits following Cycle 1 Day 1. There is no window for Cycle 1 Day 1.

Appendix 7. Study Procedures Table (Part B – CRC, Second-Line)

Study Phase	Screening	Each Cycle (28 Days)		Cycle 2	Cycle 3	Every 2 Cycles	EOS[m]	LTFU Every 3 Months
Cycle Day	**Screening**	**1**	**15**	**15**	**1**		**N/A**	**N/A**
Window	**-28**	**0[r]**	**±2**	**+14 Days / −7 Days**			**N/A**	**N/A**
Treatment Day	**-28**	**1**	**15**				**N/A**	**N/A**
Study Assessments								
Informed Consent	X							
Medical History[a]	X							
Physical Exam[b]	X	X					X	
Vital Signs[c]	X	X	X				X	
12-Lead ECG	X	X						
ECOG Performance Status	X	X	X				X	
Prior/Concomitant Meds[d]	X	X	X				X	
AEs[e]	X	X	X				X	
CT or MRI[f]	X					X[l]	X	
Collect Archival Tumor Tissue (if Available)[g]		X						
Register Subject Visit in IxRS	X	X	X				X	
Sample Collection								
Chemistry	X	X[k]	X			X[l]	X	
Hematology	X	X[k]	X			X[l]	X	
Coagulation	X	X[k]					X	
Urinalysis	X	X[k]					X	
Pregnancy Test[h]	X	X[k]	X				X	

Study Phase	Screening	Each Cycle (28 Days)		Cycle 2	Cycle 3	Every 2 Cycles	EOS[m]	LTFU Every 3 Months
Cycle Day	**Screening**	**1**	**15**	**15**	**1**		**N/A**	**N/A**
Window	**-28**	**0[r]**	**±2**	**+14 Days / −7 Days**			**N/A**	**N/A**
Treatment Day	**-28**	**1**	**15**				**N/A**	**N/A**
GS-5745 Concentration[i]		X	X		X		X	
Anti-GS-5745 Antibody		X[k]					X	
Serum and Plasma Biomarkers		X[k,n]	X[n]				X[n]	
CCI								
Stool Sample	X[o]			X[o]				
CCI								
Overall Survival								X
Study Drug Dosing / Chemotherapy								
GS-5745 IV Dosing		X	X					
FOLFIRI/Bev Dosing[j]		X	X					

EOS = End-of-Study (visit); PE = physical examination

a Medical history includes significant past medical events (eg, prior hospitalizations or surgeries), a review of the disease under study, prior anti-cancer therapies, and any concurrent medical illnesses.

b A complete PE will be performed at Screening. A modified PE capturing changes from prior exams will be performed at subsequent applicable visits. Weight (without shoes) should be measured at each PE and reported in kilograms. Height (without shoes) should be measured at Screening only and reported in centimeters.

c Vital signs include blood pressure, respiratory rate, pulse, and temperature. Measurements of blood pressure should be taken per institutional guidelines.

d Prior/concomitant medications include all medication taken up to 30 days prior to Screening, any and all medications taken during the course of the study, and supportive therapies given during the course of the study (eg, blood transfusion, growth factor).

e AEs will be assessed before and after GS-5745 and FOLFIRI dosing during applicable visits. The site will call subjects 30 days after the last dose of GS-5745 to assess AEs and SAEs.

f Tumor evaluation by CT or MRI will be performed during screening (within 4 weeks of Day 1) and during the last week of even-numbered cycles (ie, Cycles 2, 4, 6, etc.). The same radiographic procedure used to define measurable lesions must be used throughout the study for each subject. CT or MRI should be conducted at the EOS visit if not conducted within the previous 4 weeks. If a subject discontinues study drug (for example, as a result of an AE), every attempt should be made to keep the subject in the study to collect tumor assessments (CT/MRI), chemistry, and hematology during the last week of even-numbered cycles (ie, Cycles 2, 4, 6, etc.) until disease progression.

g Unstained slides (10 to 12) from archival tumor tissues prepared within 2 weeks of shipment to Gilead or its designee will be requested after Day 1 of Cycle 1 only.

h For females of childbearing potential, a serum pregnancy test will be performed at Screening and urine pregnancy tests will be performed prior to each dose of GS-5745 and at the EOS visit.

i Blood samples to measure GS-5745 concentration will be collected pre-dose on Day 1 and Day 15 of each cycle, end of GS-5745 infusion on Day 1 of Cycle 1 and Cycle 3, and at the EOS visit.

j FOLFIRI and bevacizumab dosing regimen on Days 1 and 15 of each 28-day treatment cycle will consist of: bevacizumab at 5 mg/kg IV, and FOLFIRI at l-LV 200 mg/m^2 or dl LV 400 mg/m^2 as a 2-hour infusion, and irinotecan 180 mg/m^2 given as a 90-minute infusion in 500 mL dextrose 5% via a Y-connector, followed by bolus 5-FU 400 mg/m^2 and a 46-hour infusion 5-FU 2400 mg/m^2.

k Day 1 pre-dose samples for the specified assessments may be drawn up to 2 days prior to the Day 1 visit.

l If a subject discontinues study drug (for example, as a result of an AE), every attempt should be made to keep the subject in the study to collect tumor assessments (CT/MRI), chemistry, and hematology during the last week of even-numbered cycles (ie, Cycles 2, 4, 6, etc.) until disease progression

m Subjects will be contacted by phone 30 days (± 2 days) after the last dose of GS-5745 to assess AEs. For subjects who come off study for reasons other than disease progression, the site should also obtain information on post-study anti-cancer therapies, surgeries, and date of definitive disease progression.

n Blood samples for biomarkers should be drawn pre-dose on all specified visits. Note that Day 15 is only required for Cycle 1 and that a blood sample at EOS is required if due to disease progression. The exact schedule of blood draws is outlined in the laboratory manual.

o A stool sample is required at study start and can be collected any time within the screening window prior to first dose. An additional stool sample at Cycle 2 Day 15 (+14 days/−7 days) is requested.

[redacted]

r A ± 2 day window applies to visits following Cycle 1 Day 1. There is no window for Cycle 1 Day 1.

Appendix 8. Study Procedures Table (Part B – Breast Cancer)

Study Phase	Screening	Each Cycle (28 Days)			Cycle 2	Cycle 3	Every 2 Cycles	EOS[m]	LTFU
Cycle Day	**Screening**	**1**	**8**	**15**	**15**	**1**		**N/A**	**N/A**
Window	**−28**	**0[q]**	**± 2**	**± 2**	**+14 Days / −7 Days**			**N/A**	**N/A**
Treatment Day	**−28**	**1**	**8**	**15**				**N/A**	**N/A**
Study Assessments									
Informed Consent	X								
Medical History[a]	X								
Physical Exam[b]	X	X						X	
Vital Signs[c]	X	X	X	X				X	
12-Lead ECG	X	X							
ECOG Performance Status	X	X		X				X	
Prior/Concomitant Meds[d]	X	X	X	X				X	
AEs[e]	X	X	X	X				X	
CT or MRI[f]	X						X[l]	X	
Collect Archival Tumor Tissue (if Available)[g]		X							
Register Subject Visit in IxRS	X	X		X				X	
Sample Collection									
Chemistry	X	X[k]		X			X[l]	X	
Hematology	X	X[k]	X	X			X[l]	X	
Coagulation	X	X[k]						X	
Urinalysis	X	X[k]						X	

Study Phase	Screening	Each Cycle (28 Days)			Cycle 2	Cycle 3	Every 2 Cycles	EOS[m]	LTFU
Cycle Day	**Screening**	**1**	**8**	**15**	**15**	**1**		**N/A**	**N/A**
Window	**−28**	**0[q]**	**± 2**	**± 2**	**+14 Days / −7 Days**			**N/A**	**N/A**
Treatment Day	**−28**	**1**	**8**	**15**				**N/A**	**N/A**
Pregnancy Test[h]	X	X[k]		X				X	
GS-5745 Concentration[i]		X		X		X		X	
Anti-GS-5745 Antibody		X[k]						X	
Serum and Plasma Biomarkers		X[k,n]		X[n]				X[n]	
CCI									
Overall Survival									X
Study Drug Dosing / Chemotherapy									
GS-5745 IV Dosing		X		X					
Paclitaxel[j]		X	X	X					

EOS = End-of-Study (visit); PE = physical examination

a Medical history includes significant past medical events (eg, prior hospitalizations or surgeries), a review of the disease under study, prior anti-cancer therapies, and any concurrent medical illnesses.

b A complete PE will be performed at Screening. A modified PE capturing changes from prior exams will be performed at subsequent applicable visits. Weight (without shoes) should be measured at each PE and reported in kilograms. Height (without shoes) should be measured at Screening only and reported in centimeters.

c Vital signs include blood pressure, respiratory rate, pulse, and temperature. Measurements of blood pressure should be taken per institutional guidelines.

d Prior/concomitant medications include all medication taken up to 30 days prior to Screening, any and all medications taken during the course of the study, and supportive therapies given during the course of the study (eg, blood transfusion, growth factor).

e AEs will be assessed before and after GS-5745 and Paclitaxel dosing during applicable visits. The site will call subjects 30 days after the last dose of GS-5745 to assess AEs and SAEs.

f Tumor evaluation by CT or MRI will be performed during screening (within 4 weeks of Day 1) and during the last week of even-numbered cycles (ie, Cycles 2, 4, 6, etc.). The same radiographic procedure used to define measurable lesions must be used throughout the study for each subject. CT or MRI should be conducted at the EOS visit if not conducted within the previous 4 weeks. If a subject discontinues study drug (for example, as a result of an AE), every attempt should be made to keep the subject in the study to collect tumor assessments (CT/MRI), chemistry, and hematology during the last week of even-numbered cycles (ie, Cycles 2, 4, 6, etc.) until disease progression.

g Unstained slides (10 to 12) from archival tumor tissues prepared within 2 weeks of shipment to Gilead or its designee will be requested after Day 1 of Cycle 1 only.

h For females of childbearing potential, a serum pregnancy test will be performed at Screening and urine pregnancy tests will be performed prior to each dose of GS-5745 and at the EOS visit.

i Blood samples to measure GS-5745 concentration will be collected pre-dose on Day 1 and Day 15 of each cycle, end of GS-5745 infusion on Day 1 of Cycle 1 and Cycle 3, and at the EOS visit.

j Paclitaxel dosing regimen will consist of Paclitaxel 80 mg/m^2 IV.

k Day 1 pre-dose samples for the specified assessments may be drawn up to 2 days prior to the Day 1 visit.

l If a subject discontinues study drug (for example, as a result of an AE), every attempt should be made to keep the subject in the study to collect tumor assessments (CT/MRI), chemistry, and hematology during the last week of even-numbered cycles (ie, Cycles 2, 4, 6, etc.) until disease progression.

m Subjects will be contacted by phone 30 days (± 2 days) after the last dose of GS-5745 to assess AEs. For subjects who come off study for reasons other than disease progression, the site should also obtain information on post-study anti-cancer therapies, surgeries, and date of definitive disease progression.

n Blood samples for biomarkers should be drawn pre-dose on all specified visits. Note that Day 15 is only required for Cycle 1 and that a blood sample at EOS is required if due to disease progression. The exact schedule of blood draws is outlined in the laboratory manual.

[redacted]

q A ± 2 day window applies to visits following Cycle 1 Day 1. There is no window for Cycle 1 Day 1.

Appendix 9. Dose Modification Tables for Gemcitabine and Nab-Paclitaxel

Appendix Table 1. Dose Modifications for Day 1 of Each Cycle (Hematologic Toxicity)

Treatment Day Counts and Toxicity			
ANC		**Platelets**	**Timing**
$\geq 1.5 \times 10^9$/L	And	$\geq 100 \times 10^9$/L	Treat on time
$< 1.5 \times 10^9$/L	Or	$< 100 \times 10^9$/L	Delay by 1 week intervals until recovery

Appendix Table 2. Dose Modifications for Day 1 of Each Cycle (Non-Hematologic Toxicity)

Non-Hematologic Toxicity and/or Dose Hold with Previous Cycle	
Toxicity/Dose Held	**Gemcitabine/Gemcitabine + Nab-Paclitaxel Dose this Cycle**
Grade 0, 1, or 2 Toxicity	Same as Day 1 of previous cycle (except for Grade 2 cutaneous toxicity where doses of gemcitabine and nab-paclitaxel should both be reduced to next lower dose level
Grade 3 Toxicity[a]	Decrease gemcitabine and nab-paclitaxel to next lower dose level
Grade 4 Toxicity[a,b]	Off chemotherapy treatment
Dose Held in 2 Previous Consecutive Cycles	Decrease gemcitabine to next lower dose level and continue throughout the rest of treatment

a If the toxicity only affects neuropathy, then only nab-paclitaxel should be reduced.
b Pulmonary embolism if mild or asymptomatic will be exempt from this requirement.

Appendix Table 3. Dose Modifications for Hematologic Toxicity within a Cycle

Day 8 Blood Counts	Day 8 Nab-P	Day 8 Gem	Day 15 Blood Counts	Day 8 Nab-P	Day 8 Gem	Any Day Nab-P	Any Day Gem
ANC > 1000 and Platelets ≥ 75,000	100%	100%	ANC > 1000 and Platelets ≥ 75,000	100%			
			ANC 500-1000 or Platelets 50,000 -74,999	Full Dose (treat on time)			
			ANC < 500 or Platelets < 50,000	Hold			
ANC 500-1000[a] or Platelets 50,000-74,999	Decrease dose by 1 level (treat on time)		ANC > 1000 and Platelets ≥ 75,000	Return to Previous Level (treat on time)			
			ANC 500-1000 or Platelets 50,000-74,999	Same Dose (as Day 8, treat on time)			
			ANC < 500 or Platelets < 50,000	Hold			
ANC < 500[b] or Platelets < 50,000	Hold	Hold	ANC > 1000 and Platelets ≥ 75,000	Decrease Day 8 by 1 level (treat on time)			
			ANC 500-1000 or Platelets 50,000-74,999	Decrease Day 8 by 1 level (treat on time)			
			ANC < 500 or Platelets < 50,000	Hold			
Febrile Neutropenia (Grade 3 or 4)[d]						Hold. Upon resuming dosing, decrease to next lower dose level and do not re-escalate throughout rest of treatment.	
Recurrent Febrile Neutropenia (Grade 3 or 4)[a]						Decrease to next lower dose level and do not re-escalate throughout the rest of treatment.	Decrease 2 dose levels (to 600 mg/m^2) and do not re-escalate throughout the rest of treatment.

a Gem = gemcitabine; Nab-P = nab-paclitaxel
b If the subject does not experience resolution of neutropenia within 21 days, chemotherapy treatment will be discontinued.
c Febrile subjects (regardless of neutrophil count) should have their chemotherapy treatment interrupted. Blood counts must have returned to baseline levels before resuming chemotherapy treatment. A full sepsis diagnostic work-up should be performed while continuing broad spectrum antibiotics. If cultures are positive, the antibiotic treatment may or may not be changed, depending on the sensitivity profile of the isolated organism. Subjects with persisting fever after 3 weeks, despite uninterrupted antibiotic treatment, will discontinue chemotherapy treatment.
d Pulmonary embolism if mild or asymptomatic, will be exempt from this requirement.

Appendix Table 4. Dose Modifications for Non-Hematologic Toxicity within a Cycle

CTCAE Grade	Percent of Day 1 Gemcitabine + Nab-Paclitaxel
Grade 0 to 2 (and Grade 3 Nausea/Vomiting)	100%
Grade 3 (Except Nausea/Vomiting)	Hold either one or both drugs[a] until resolution to ≤ Grade 1, then resume treatment at the next lower dose level.
Grade 4	Hold

a This decision as to which drug should be modified will depend upon the type of non-hematologic toxicity seen and which course is medically most sound in the judgment of the investigator.

Pulmonary embolism (a Grade 4 toxicity in the CTCAE tables) if mild or asymptomatic, will be exempt from this requirement.

Appendix 10. Dose Modification Tables for mFOLFOX6

Appendix Table 5. Recommended Dose Modifications for Oxaliplatin + 5-Fluorouracil/Leucovorin[a]

CTCAE v. 4.03 System Organ Class[a]	Adverse Event[b]	Dose Level for Subsequent Cycles Based on Interval AEs	At Time of Retreatment
All Adverse Events < 1		Maintain dose level	Maintain dose level
Blood and Lymphatic System Disorders:	**Hemolytic uremic syndrome (HUS)[c]** > Grade 3	Discontinue oxaliplatin	Discontinue oxaliplatin
Investigations:	**Neutrophil count decreased**		If ANC < 1500 at start of cycle, hold and check weekly then treat based on interval adverse event. If ANC < 1500 after 4 weeks, discontinue therapy.
	Grade 1 (ANC < LLN - 1500/mm^3)	Maintain dose level	
	Grade 2 (ANC < 1500 - 1000/mm^3)	Maintain dose level	
	Grade 3 (ANC < 1000 - 500/mm^3)	Omit 5-FU bolus AND ↓ 1 oxaliplatin dose level	
	Grade 4 (ANC < 500/mm^3)	Omit bolus 5-FU and ↓ both infusional 5-FU and oxaliplatin 1 dose level	
	Platelet count decreased		If PLT < 75,000 at start of cycle, hold and check weekly then treat based on interval adverse event. If PLT < 75,000 after 4 weeks, discontinue therapy.
	Grade 1 (PLT < LLN - 75,000/mm^3)	Maintain dose level	
	Grade 2 (PLT < 75,000 - 50,000/mm^3)	Maintain dose level	
	Grade 3 (PLT < 50,000 - 25,000/mm^3)	Omit 5-FU bolus AND ↓ 1 oxaliplatin dose level	
	Grade 4 (PLT < 25,000/mm^3)	Omit 5-FU bolus AND ↓ 2 oxaliplatin dose levels	
Gastrointestinal Disorders:	**Diarrhea**		If Grade ≥ 2 at start of cycle, hold and check weekly then treat based on interval adverse event. If Grade ≥ 2 after 4 weeks, discontinue therapy.
	Grades 1, 2	Maintain dose level	
	Grade 3	↓ One 5-FU dose level	
	Grade 4	↓ Both 5-FU and oxaliplatin 1 dose level	
	Mucositis oral		
	Grades 1, 2	Maintain dose level	
	Grade 3	↓ One 5-FU dose level	
	Grade 4	↓ One 5-FU dose level	

CTCAE v. 4.03 System Organ Class[a]	Adverse Event[b]	Dose Level for Subsequent Cycles Based on Interval AEs	At Time of Retreatment
	Vomiting		
	Grades 1, 2	Maintain dose level	
	Grade 3	↓ 1 oxaliplatin dose level	
	Grade 4	↓ Both 5-FU and oxaliplatin 1 dose level	
Metabolism and Nutrition Disorders:	**Hypomagnesaemia**	Dose reduction is not required for hypomagnesaemia unless symptoms are present. If Grade ≥ 2 after 4 weeks, discontinue therapy.	
Neurology:	Do not use CTCAE.	See Appendix 10, Appendix Table 6 for AE scale and oxaliplatin dose modifications.	
Respiratory, Thoracic, and Mediastinal Disorders:	**Cough** ≥ Grade 3 **Dyspnea** ≥ Grade 3 **Hypoxia** ≥ Grade 3 **Pneumonitis** ≥ Grade 3	Hold oxaliplatin until interstitial lung disease is ruled out. If interstitial lung disease, oxaliplatin should be permanently discontinued.	
Other Non-Hematologic AEs[d,e]:	Grades 1, 2	Maintain dose level	
	Grades 3, 4	↓ 1 5-FU dose level	

a The dose of leucovorin will not be adjusted due to AEs. It should remain at 400 mg/m^2 dl-leucovorin or 200 mg/m^2 of l-leucovorin for all courses. Leucovorin will be given immediately prior to each 5-FU dose; thus, if 5-FU is delayed, leucovorin will be delayed. Leucovorin doses may be adjusted per institutional guidelines in the event of a supply shortage.

b For ≤ NCI CTCAE v. 4.03 Grade 2 toxicity not described, maintain dose level of agent.

c Recommended evaluation of suspected HUS: Evaluation should include CBC differential, platelets, PT, PTT, fibrinogen, FDP, Anti thrombin III, Von Willebrand factor, anti-nuclear antibody, rheumatoid factor, Compliment Cascade C3, C4, and CH_{50}, anti-platelet antibodies, platelet-associated IgG, and circulating immune complexes. Renal evaluation should include creatinine, BUN, and urinalysis with microscopic examination. Other laboratory and hematologic evaluations as appropriate should also be obtained, including peripheral blood smear and free hemoglobin.

d Exceptions: fatigue, anorexia, nausea/vomiting if can be controlled by antiemetics, and viral infections.

e Dose modifications for other non-hematologic adverse events at the start of subsequent courses of therapy, and at time of retreatment are also based on NCI CTCAE v. 4.03 criteria.

Appendix Table 6. Oxaliplatin[a] Dose Modifications for Non-CTCAE Neurologic Adverse Events

Adverse Events	Duration of Adverse Event		Persistent[b] Between Cycles
	1 − 7 Days	> 7 Days	
Paresthesias/Dysesthesias			
Paresthesias/dysesthesias[c] of short duration that resolve and do not interfere with function (Grade 1)	No change	No change	No change
Paresthesias/dysesthesias[c] interfering with function, but not activities of daily living (ADL) (Grade 2)	No change	No change	↓ 1 oxaliplatin dose level
Paresthesias/dysesthesias[c] with pain or with functional impairment that also interfere with ADL (Grade 3)	First time: ↓ 1 oxaliplatin dose level Second time: ↓ 1 oxaliplatin dose level	First time: ↓ 1 oxaliplatin dose level Second time: ↓ 1 oxaliplatin dose level	Discontinue
Persistent paresthesias/dysesthesias that are disabling or life-threatening (Grade 4)	Discontinue	Discontinue	Discontinue
Laryngeal Dysesthesias (investigator discretion used for grading):			
Grade 0 = none Grade 1 = mild	No change	↑ duration of infusion to 6 hours	↑ duration of infusion to 6 hours
Grade 2 = moderate Also recommended is administration of benzodiazepine and patient education. Management of patient if ≥ Grade 2 laryngeal dysesthesias occurs while treatment is being administered.	Stop oxaliplatin infusion. Administer benzodiazepine and give patient reassurance. At the discretion of the investigator, the infusion can be restarted at 1/3 the original rate of infusion.		
Grade 3 = severe			

a If oxaliplatin is discontinued, continue other study agents unless adverse events preclude their continuation.
b Not resolved by the beginning of the next cycle.
c May be cold-induced.

Each cycle consists of two 14-day courses of FOLFIRI plus study drug. A new course of therapy should not begin until the granulocyte count has recovered to ≥ 1500/mm^3, the platelet count has recovered to ≥ 100,000/mm^3, and treatment-related diarrhea is fully resolved. Subjects should return to pre-treatment bowel function without requiring antidiarrhea medications for at least 24 hours before the next chemotherapy administration. Treatment should be delayed 1 week, and if necessary 2 weeks, to allow for recovery from treatment related toxicities.

Dose modifications for subsequent courses of therapy will be carried out for Grade 3 and 4 neutropenia/hematologic toxicity and Grade 2, 3 and 4 non-hematologic toxicities. Subjects who require persistent 1- or 2-week delays for the resolution of recurring Grade 1 toxicities, may have their dose reduced by 1 dose level to permit administration of FOLFIRI every 2 weeks, at the investigator's discretion.

If the subject has not recovered after a 2-week delay or requires more than 2 dose reductions, consideration should be given to discontinuing FOLFIRI therapy and continuing treatment with GS-5745 alone.

Appendix Table 7. Recommended Dose Modifications for FOLFIRI

Toxicity NCI CTCAE Grade[a] (Value)	During a 2-Week Course of FOLFIRI Therapy or at the Time the Next Course of FOLFIRI is to Start
Neutropenia	
1 (1500 to 1999/mm^3)	Maintain dose level
2 (1000 to 1499/mm^3)	Omit dose until resolved to ≤ Grade 1, maintain dose level
3 (500 to 999/mm^3)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
4 (< 500/mm^3)	Omit dose until resolved to ≤ Grade 1, then ↓ 2 dose levels
Neutropenic Fever	Omit dose until resolved, then ↓ 2 dose levels
Other Hematologic Toxicities	Dose modifications for leukopenia or thrombocytopenia are also based on NCI CTCAE toxicity criteria and are the same as recommended for neutropenia above.
Diarrhea	
1 (2-3 stools/day > pretx[b])	Delay dose until resolved to baseline, then give same dose
2 (4-6 stools/day > pretx)	Omit dose until resolved to baseline, then ↓ 1 dose level
3 (7-9 stools/day > pretx)	Omit dose until resolved to baseline, then ↓ 1 dose level
4 (≥ 10 stools/day > pretx)	Omit dose until resolved to baseline, then ↓ 2 dose levels
Other Non-Hematologic Toxicities[c]	
1	Maintain dose level
2	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
3	Omit dose until resolved to ≤ Grade 2, then ↓ 1 dose level
4	Omit dose until resolved to ≤ Grade 2, then ↓ 2 dose levels
	For mucositis/stomatitis decrease only 5-FU, not irinotecan

a National Cancer Institute's Common Terminology Criteria for Adverse Events, v 4.03
b Pre-treatment
c Excludes alopecia, anorexia, asthenia