PROTOCOL TITLE

Phase I/II randomized, double-blind, placebo-controlled trial (1-BETTER) examining XB2001 (anti-IL-1-α True Human antibody) in combination with ONIVYDE + 5-Fluorouracil + Leucovorin in advance pancreatic cancer.

NCT NUMBER

NCT04825288

13 October 2021

Trial Protocol

A Phase I/II randomized, double-blind, placebo-controlled trial (1-BETTER) examining XB2001 (anti-IL-1α True Human antibody) in combination with ONIVYDE + 5-Fluorouracil + Leucovorin in advanced pancreatic cancer

SPONSOR

XBiotech USA Inc

13 October 2021

TABLE OF CONTENTS

BASIC INFORMATION

Study Title: A Phase I/II randomized, double-blind, placebo-controlled trial (1-BETTER) examining XB2001 (anti-IL-1α True Human antibody) in combination with ONIVYDE + 5-Fluorouracil + Leucovorin in advanced pancreatic cancer

Investigational Product:	XB2001
IND Number:	153686
Protocol Version / Date:	3.1/ 13 October 2021
Protocol Number:	2020-PT049
Sponsor:	XBiotech USA, Inc. 5217 Winnebago Lane Austin, Texas 78744 U.S.A. Phone: 512-386-2900
Study Chair:	[redacted]

INVESTIGATOR/SPONSOR SIGNATURES

Study Title: A Phase I/II randomized, double-blind, placebo-controlled trial (1-BETTER) examining XB2001 (anti-IL-1α True Human antibody) in combination with ONIVYDE + 5-Fluorouracil + Leucovorin (+folinic acid) in advanced pancreatic cancer

Protocol Version / Date: 3.1 / 13 October 2021

Protocol Number: 2020-PT049

Study Investigator Signature: I have read the protocol. I understand the contents and intend to comply fully with all requirements and the applicable current local and international regulations and guidelines. No changes will be made without formal authorization by XBiotech USA, Inc., in the form of a protocol amendment.

Investigator Signature:

_____
Printed name of Investigator

_____
Signature

_____
Date

Sponsor Signature: XBiotech USA, Inc.

_____
Printed name

_____
Signature

_____
Date

CLINICAL PROTOCOL SYNOPSIS

Name of Investigational Product: XB2001 (an anti-IL-1α True Human antibody)
Title of Study: A Phase I/II randomized, double-blind, placebo-controlled trial (1-BETTER) examining XB2001 (anti-IL-1α True Human antibody) in combination with ONIVYDE + 5-Fluorouracil + Leucovorin (+folinic acid) in advanced pancreatic cancer
Sponsor: XBiotech USA, Inc.
Study Chair: [redacted]
Number of Planned Subjects: **Phase 1 Portion:** 9 to 18 **Phase 2 portion:** 60
Study Design: This trial will include two phases (phase 1 and phase 2). Phase 1 is an open label, dose escalation study to determine dose limiting toxicities (DLTs) of XB2001 in at least nine patients with metastatic pancreatic cancer, treated with concurrent 5 Fluorouracil (5-FU), leucovorin (LV), and ONIVYDE in the second- or third-line setting. The phase 2 portion of this study will proceed only after completion of phase 1, and the related full safety analysis. It will entail enrollment of 60 patients who will be randomized on a 1:1 basis to XB2001 plus ONIVYDE+LV+5-FU (Arm 1), or placebo plus ONIVYDE + LV + 5-FU (Arm 2). The dose of XB2001 used in phase 2 of the trial will be the maximum tolerated dose (MTD), as determined in phase 1 of the trial. If dose-limiting toxicities aren't observed at the maximum XB2001 dose studied in phase 1, the dose of XB2001 used for phase 2 of the trial will be the maximum dose studied in phase 1.
Study Duration: **Phase 1:**Approximately 58 days per patient, including a screening period of up to 30 days, followed by two treatment cycles, 14 days each, of intravenous XB2001, 5-FU, LV, and ONIVYDE. During the 28 days corresponding to the treatment cycles patients will be stringently monitored and assessed for DLTs. **Phase II:** Approximately 28 weeks per patient, including a screening period of up to 30 days followed by a 24-week period, during which patients will receive up to 12 cycles of treatment.
Dosage and Administration: ***Phase 1 Portion:*** ***The Phase 1 consists of two cycles of XB2001 in Combination Therapy.*** For the first cycle of therapy, subjects will receive a single intravenous dose of XB2001 followed by ONIVYDE 70 mg/m^2

intravenously over 90 minutes, followed by leucovorin l + d racemic 400 mg/m^2 intravenously over 30 minutes, followed by 5-Fluorouracil 2400mg/m^2 intravenously over 46 hours.

- Subjects who are homozygous for UGT1A1*28 allele will receive ONIVYDE at a reduced dose of 50 mg/m^2 during cycle 1 of treatment. If they have no significant drug related toxicity after the first administration of ONIVYDE, the dose may be increased to 70 mg/m^2 with subsequent treatment cycles.
- For cycle 2 of therapy, subjects will receive a single intravenous dose of XB2001 at the same dose they received with cycle 1, followed by ONIVYDE 70 mg/m2 intravenously over 90 minutes, followed by leucovorin l + d racemic 400 mg/m^2 intravenously over 30 minutes, followed by 5-Fluorouracil 2400mg/m^2 intravenously over 46 hours.

There will be 3 sequential XB2001 dose levels: 250mg (dose cohort 1), 500mg (dose cohort 2), and 1000mg (dose cohort 3). Cohort 2 will only begin enrolling after cohort 1 has completed therapy and a full data safety assessment has been completed. Cohort 3 will only begin enrollment after cohort 2 has completed treatment and a full data safety analysis has been conducted. DLTs for patients treated in phase 1 of the study will be assessed through completion of cycle 2 of treatment, for a total of 28 days.

Phase 2 Portion:

ARM 1: XB2001 + ONIVYDE + 5-FU + LV combination therapy administered for 12 cycles of treatment

- Arm 1 Treatment Cycle: Subjects randomized to Arm 1 of the phase 2 study will receive the following treatments every 2 weeks: XB2001 at MTD, or at the maximum dose studied if MTD is not observed, as an intravenous infusion over up to 60 minutes, followed by ONIVYDE 70 mg/m^2 intravenously over 90 minutes, followed by leucovorin l + d racemic 400 mg/m^2 intravenously over 30 minutes, followed by 5-Fluorouracil 2400mg/m^2 intravenously over 46 hours. Therapy will be administered every 2 weeks (2 weeks = 1 cycle).Subjects who are homozygous for UGT1A1*28 allele receive the first cycle of ONIVYDE therapy at reduced dose of 50 mg/m^2. If tolerated, the dose of ONIVYDE may be increased to 70 mg/m^2 with subsequent cycles.
- If ONIVYDE is withheld or discontinued for adverse reactions, patients will no longer be treated with XB2001. They will continue to be followed for assessment of primary and secondary endpoints. However, they will not be treated on protocol, as investigators will be allowed to treat patients as they see fit.

ARM 2: Placebo + ONIVYDE + 5-FU + LV combination therapy administered for 12 cycles of treatment

- *Arm 2 Treatment Cycle:* Subjects randomized to this arm will receive the following treatments every 2 weeks: Placebo as an intravenous infusion over up to 60 minutes, followed by ONIVYDE 70 mg/m^2 intravenously over 90 minutes, followed by leucovorin l + d racemic 400 mg/m^2 intravenously over 30 minutes, followed by 5-fluorouracil 2400 mg/m^2 intravenously over 46 hours. Therapy will be administered every 2 weeks (2 weeks = 1 cycle).
  - Subjects homozygous for UGT1A1*28 allele receive the first cycle of ONIVYDE therapy at a reduced dose of 50 mg/m^2. If no significant drug related toxicity after the first administration of ONIVYDE is noted, the dose may be increased to 70 mg/m^2 for subsequent cycles.
  - If ONIVYDE is withheld or discontinued for adverse reactions, patients will no longer be treated with XB2001. They will continue to be followed for assessment of primary and secondary endpoints. However, they will not be treated on protocol, as investigators will be allowed to treat patients as they see fit.

**** One treatment cycle is defined as 2 weeks**. Study treatment will be administered for up to 12 cycles over a 24-week treatment period

Study Objectives:

Phase I and Phase II Primary Endpoints:

- Primary Endpoint of Phase I: To identify the maximum tolerated XB2001 dose (MTD), or maximum XB2001 dose studied if no DLTs are observed. DLT and MTD of XB2001 will be assessed in combination with ONIVYDE + LV + 5-FU, when given as second- or third-line treatment of subjects with advanced pancreatic adenocarcinoma. The MTD identified in phase 1 will be the dose of XB2001 used in phase 2 of the study.
- Primary Endpoint of Phase 2: Safety and tolerability of XB2001 at the MTD, or the maximum dose studied in phase 1.

Secondary Endpoints (phase 2 portion):

- Progression Free Survival
  - Progression Free Survival (PFS), as defined by the time frame from treatment initiation to first progression based on RECIST 1.1 criteria.
- Overall Survival (OS)

- Overall Survival (OS), defined as time from treatment initiation to death.

- Objective Response Rate (ORR):
  - Objective response rate (ORR), designated as complete remission, partial remission, stable disease, or progressive disease. ORR will be determined via every 8-week imaging.

- Time to Treatment Failure
  - Time to Treatment Failure, defined as time from treatment initiation to treatment discontinuation resulting from progression or side effects.

- Percentage of Subjects with Clinical Benefit Response (CBR).
- CBR is a composite measure consisting of change in lean body mass (LBM) and change in quality of life (QOL).
  - CBR will be assessed every 8 weeks while patients are on treatment.
  - A positive CBR will be defined as stabilization or positive (≥0 kg) change in lean body mass (LBM)—as assessed by dual-energy X-ray absorptiometry (DEXA) scan, and improvement or no worsening (≥0 score point change) on any two of the three symptom scale measures (fatigue, pain, appetite) of EORTC QLQ-C30.
- Quality of Life assessed through the cancer-specific EORTC QLQ-C30 questionnaire
  - Time Frame: Baseline to weeks 8, 16 and 24.
- Number of Serious Adverse Events (SAEs)
- Incidence of Grade 3-4 Diarrhea
- Duration of hospitalizations
  - Time Frame: Baseline to weeks 4, 8, 12, 16, 20 and 24.
- Assessment of Pharmacokinetics (PK)
- Number of treatment cycles received.
- Reduction in (CD14+CD16+IL-1α+) triple positive tumor associated monocytes in peripheral blood
  - Time Frame: Baseline to week 2 (post infusion at visit 2).

Exploratory Endpoints (phase II):

- Results of a symptom questionnaire will be summarized by treatment arm and compared over time.
- Comparison of cardiac related adverse events in each treatment arm.

Key Inclusion and Exclusion Criteria:

Inclusion

- Histologically or cytologically confirmed pancreatic adenocarcinoma of exocrine pancreas that is metastatic, unresectable, or recurrent
- At least one measurable lesion according to Response Evaluation Criteria in Solid Tumor V1.1
- Documented disease progression after one prior gemcitabine-based therapy OR one FOLFIRINOX and gemcitabine containing therapy
- Eastern Cooperative Oncology Group (ECOG) performance of 0 or 1 or Karnofsky performance status (KPS) ≥ 70
- Adequate hepatic, renal and bone marrow function

Exclusion

- Clinically significant decrease in performance status within 2 weeks of the intended first dose administration
- Clinically significant GI disorder, including but not limited to, inflammatory bowel disease, recurrent ischemic colitis, etc.
- Severe arterial thromboembolic events less than 6 months before inclusion. Venous thromboemolism, including pulmonary embolism and deep venous thrombosis, does not exclude patients from enrollment
- Severe hypersensitivity to 5-FU
- Use of warfarin within 4 weeks of screening or any time during the study
- Prior Whole Brain Radiation Therapy (WBRT) to treat pancratic cancer brain metastases or any brain metastases
- NYHA Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled blood pressure (defined as ≥ 160/100 mm Hg)
- Use of strong CYP3A4 inducers or inhibitors and/or UGT1A1 inhibitors within 14 days prior to Visit 1/Baseline visit
- Life expectancy, in the absence of treatment, of less than or equal to 90 days, based on the principal investigator's best judgment

Abbreviations

ADA	Anti-Drug Antibody
AE	Adverse Event
ALT	Alanine Aminotransferase (ALT, SGPT)
PT/aPTT	Prothrombin Time/Activated Partial Thromboplastin Time
ALP	Alkaline Phosphate
BMI	Body Mass Index
BP	Blood Pressure
BSA	Body Surface Area
CBC	Complete Blood Count
CBR	Clinical Benefit Response
CI	Confidence Interval
CH	Heavy chain constant region
CL	Light chain constant region
eCRF	Electronic Case Report Form
CRA	Clinical Research Associate
CRP	C-Reactive Protein
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limited Toxicity(ies)
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ELISA	Enzyme-Linked Immunosorbent Assay
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B Surface Antigen
HIV	Human Immunodeficiency Virus
IAs	Interim Analysts
IAC	Interim Analysis Committee
IFN-γ	Interferon Gamma
IgG	Immunoglobulin G
IL-6	Interleukin-6

IL-1α	Interleukin-1α
IL-1β	Interleukin-1β
IL-1RA	Interleukin-1 Receptor Antagonist
IRB	Institutional Review Board
MTD	Maximum Tolerated Dose
mPAC	Metastatic Pancreatic Cancer
NSAID	Non-Steroidal Anti-inflammatory Drug
ORR	Objective Response Rate
OS	Overall Survival
PD	Pharmacodynamics
PK	Pharmacokinetics
PFS	Progression Free Survival
pI	Isoelectric Point
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
TNF	Tumor Necrosis Factor
TTF	Time to Treatment Failure
ULN	Upper Limit of Normal
UV	Ultraviolet
VAS	Visual Analog Scale
WOCBP	Women of childbearing potential

1. BACKGROUND

1.1 OVERVIEW

XBiotech USA, Inc. has identified a True Human monoclonal antibody, XB2001, that blocks the biological activity of IL-1α with a high degree of affinity and specificity. IL-1α is a key mediator of inflammatory responses and is implicated in the pathophysiology of various diseases, including cancer, cardiovascular and rheumatologic diseases. Ample evidence supports targeting IL-1α to block pathological inflammatory processes associated with many diseases.

XB2001 is a recombinant human IgG4 monoclonal antibody specific for human interleukin-1α (IL-1α). The entire XB2001 heavy and light chain sequences are identical to those found in naturally-occurring human peripheral repertoire, originally expressed by a peripheral blood B lymphocyte obtained from a healthy anti-IL-1α immune individual. No *in vitro* affinity maturation or modifications have been made to improve its natural binding affinity (~60 pM). True human antibodies, such as XB2001, essentially are non-immunogenic in humans and thus be optimal in terms of safety, activity and pharmacokinetics. XBiotech has conducted 15 clinical studies to date using a previous anti-IL-1α True Human antibody[1,2,3,4,5,6,7,8,9]. These studies were conducted in a variety of diseases, tested numerous doses and formulations of the IL-1α antibody, and have included intravenous and subcutaneous formulations and several different dose levels and dosing schedules. Targeting IL-1α was safe and very well tolerated in all of these studies[5,6,7,10].

A first-in-man phase 1 study and two phase 3 studies sponsored by XBiotech have been completed with a previous generation anti-IL-1α True Human monoclonal antibody in oncology: Advanced Cancers [NCT01021072], Advanced Colorectal Cancer [NCT01767857], and symptomatic colorectal cancer [NCT02138422][5,6].

1.2 DISEASE BACKGROUND

Advanced metastatic pancreatic adenocarcinoma (mPAC) is increasing in incidence and has a five-year survival rate of less than 5% and median overall survival of 4-6 months[10]. Responsible for only 2.5% of all new cancer diagnoses, pancreatic cancer will be second leading cause of cancer-related mortality in the United States in 2030[11].

1.3 CURRENT TREATMENT OPTIONS

Approximately 85% of patients with pancreatica adenocarcinoma have limited treatment options. These patients often suffer from significant loss of appetite and weight is common at presentation[12]. First-line treatment options include[13]:

- FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin)
- Gemcitabine alone or combined with nab-paclitaxel (Abraxane)

Patients with good performance status, ECOG 0-1, are typically treated with FOLFIRINOX first-line, whereas some patients receive gemcitabine/abraxane if they have a lower performance status. Or there is concern they will not tolerate FOLFRINOX. Olaparib is used in the maintenance setting in first-line treatment of advanced pancreatic cancer patients with BRCA1 or BRCA2 mutations.

Second-line treatment for patients treated with FOLFRINOX is typically gemcitabine/abraxane. For patients treated with gemcitabine/abracane first-line, second-line options are imited, and include 5-Fluorouracil, Leucovorin, and ONIVYDE.

Several drugs, such as novel cytotoxics, stromal-depleting agents, signal transduction inhibitors, and immunotherapies, are currently being tested in advanced pancreatic cancer patients[14]. However, treatment of such patients remain a large unmet need.

1.4 NOVEL THERAPY

The infusion of cytotoxic agents results in systemic injury. Some of the injury relates to the mechanism of action, whether DNA intercalation, topoisomerase inhibition or disruption of microtubule function. However, while the direct metabolic toxicity is primarily of acute importance clinically, consequences of ensuing inflammatory responses to cytotoxic agents may have more impact on the efficacy and durability of therapy and outcomes. Cellular and tissue insult from cytotoxic agents result in upregulation of inflammatory pathways associated with injury, including activation of leukocytes, vascular endothelium and stromal cells of the tumor microenvironment. A key trigger in the inflammatory response both at the tumor microenvironment, in the vasculature and overall systemically may be IL-1α.

XB2001 is a naturally occurring antibody that neutralizes IL-1α and is a safe and promising approach to block inflammation that occurs with advanced malignancies and chemotherapy. IL-1α induces upregulation of VEGF and angiogenesis in the tumor microenvironment; IL-1α also acts to recruit infiltration by

leukocytes (such as myeloid suppressor cells) that can suppress anti-tumor immunity; systemically, IL-1α can mediate metabolic dysregulation, fatigue, anorexia, and anxiety through the hypothalamic-pituitary-adrenal axis. IL-1α is thus a central player in paraneoplastic inflammation.

XB2001 is the second molecule developed by XBiotech to specifically target interleukin-1α (IL-1α). By targeting a key pathway in paraneoplastic inflammation, previous clinical findings targeting IL-1α has shown anti-tumor activity while at the same time treating disease-related symptoms. The highly regulated expression of IL-1α makes it a safe target with excellent tolerability profile, and is an ideal treatment option in a vulnerable advanced cancer population, and highly suitable as an adjunct in combination with cytotoxic therapies.

1.5 STUDY AGENTS: CLINICAL EVIDENCE

Nanoliposomal irinotecan (nal-IRI "ONIVYDE") plus 5-fluorouracil (5FU) and folinic acid (FA) were recently approved as second- or third-line treatment for pancreatic cancer. In a pivotal phase 3 trial, patients were randomized to single agent 5-fluorouracil vs the combination of 5-fluorouracil and ONIVYDE[14]. After 313 events, median overall survival in patients assigned nanoliposomal irinotecan plus 5FU/FA was 6.1 months (95% CI 4·8–8·9) vs 4.2 months (3·3–5·3) with 5FU/FA alone (hazard ratio 0·67, 95% CI 0·49–0·92; p=0·012). This combination was particularly effective in patients able to tolerate 80% of the recommended dose and receive at least 6 weeks of chemotherapy. The grade 3 or 4 adverse events that occurred most frequently in the 117 patients assigned nanoliposomal irinotecan plus 5FU and folinic acid were neutropenia (32 [27%]), diarrhea (15 [13%]), vomiting (13 [11%]), and fatigue (16 [14%]).

A previous generation anti-IL-1α antibody has been shown to be safe and effective in several clinical studies of patients who have not responded to standard chemotherapy. A phase 3 study was conducted comparing anti-IL-1α therapy to best supportive care in 309 patients with metastatic colorectal cancer who had failed all available chemotherapy[6]. The study's primary endpoint was a composite measure of lean body mass, pain, fatigue and anorexia, symptoms that are independent risk factors for survival in colorectal cancer [REF..7/2/16PR]. Patients receiving anti-IL-1α treatment achieved 33% response rate compared to 19% for placebo (p=0.0045). In addition, clinical response correlated with a remarkable 2.7-fold increase in overall survival. Treatment corelates included a significant improvement in control of paraneoplastic thrombocytosis and reduced systemic inflammation (as measured by serum IL-6). There was also a 26% relative reduction in the number of SAEs in the treatment arm (p=0.062); and the mean duration of hospitalization between treatment and placebo groups was 10.2 vs 16.8 days (p=0.0151).

Results using a previous generation anti-IL-1α antibody in a Phase I study were recently presented at ASCO (NCT03207724). The study evaluated IL-1α antagonism in combination with nanoliposomal irinotecan (Nal-Iri) and 5-fluorouracil (5FU)/folinic acid (FA) in patients diagnosed with advanced pancreatic adenocarcinoma and with weight loss who failed gemcitabine-based chemotherapy. The study's primary endpoint was identifying maximum tolerated dose with secondary endpoints including change in lean body mass, quality of life measures, overall and progression free survival, CRP and CAP 19-9 levels, and objective measures of functionality. Therapy was exceedingly well-tolerated at all dose levels including the maximum dose level of 12mg/kg of antibody (2400mg/m2 5-FU; 400mg/m2 folinic acid; 70mg/m2 nanoliposomal irinotecan). The treatment regimen resulted in unexpected tolerability, including lower than expected incidence of serious diarrhea. In addition, progression free and overall survival were substantially greater than seen in the Phase III study for the ONIVYDE-5-FU combination alone.

1.6 STUDY RATIONALE

Chemotherapy related and paraneoplastic related acute and chronic inflammatory responses, respectively, are the cause of significant morbidity and are largely unmanaged by targeted anti-inflammatory therapy during cancer treatment. XB2001 neutralizes IL-1α and can provide a highly targeted block of a key inflammatory pathway that is involved both in response to injury of healthy tissue from cytotoxic therapy and paraneoplastic inflammation that supports tumor growth, spread and morbidity.

Therefore, in this study we will randomize mPAC subjects undergoing cytotoxic chemotherapy with ONIVYDE and 5-FU to received either XB2001 or placebo. XB2001, given in combination with ONIVYDE, 5-Fluorouracil, and Leucovorin, may provide needed benefits to subjects. This includes overall improvement in quality of life and performance status, a reduction in steroid use and adverse events (including a reduction in the number and duration of hospitalizations), more treatment cycles and improved progression free and overall survival.

1.6.1 DEXA Scan Rationale

Microvasculature perfusing the hypothalamus is fenestrated by neuronal processes of pro-opiomelanocortin (*POMC*) *neurons*. The POMC neurons penetrating into the lumen of the vessel are exposed to moieties in

the blood. Interleukin-1 receptor (IL-1R) is displayed on the surface of the neuronal processes of the POMC neurons and can thus be innervated by IL-1a, enabling IL-1a that may be circulating in association with activated platelets, neutrophil traps or activate monocytes, to mediate direct modulation of the central nervous system (CNS). The IL-1R signaling through the POMC neurons of hypothalamus can regulate appetite, metabolism, and wellbeing[15,16,17]. In times of acute stress (such as trauma or illness), these neurons are able to sense "danger" and drive physiological mechanisms that provide enhanced ability to respond to stress, including breakdown of muscle protein for the mobilization of amino acid substrates to provide for gluconeogenesis. When the "danger" signal is chronic, as it is in cancer, this process may drive pathologic muscle wasting, including loss of crucial cardiac and diaphragmatic muscle.

Treatment with XB2001 is expected to reduce IL-1α mediated signaling. The primary endpoint of the study is measure of tumor-associated IL-1a expressing monocytes that may be involved in the process of metabolic dysregulation. XB2001 could potentially help attenuate IL-1 signals through the POMC pathway and interrupt in part the underlying wasting phenotype associated with malignancy.

Previous clinical studies in advanced cancer have reported benefits with an anti-IL-1a antagonist that include reduced wasting. Dual energy X-ray absorptiometry (DEXA) is a means of measuring body composition. In a previous double-blind placebo controlled clinical study, cancer subjects receiving 8 weeks of anti-IL-1a antibody monotherapy showed significant improvement in clinical performance, which involved a composite measure including DEXA assessment of lean mass[18]. In the study, the DEXA assessment at 8 weeks was a crucial parameter for identifying subjects with good clinical outcomes. DEXA requires only extremely low exposure to X-ray radiation, and represents a safe, simple and reliable means of monitoring lean mass in cancer subjects. In this study, we will be using DEXA scan measures at 8 weeks to assess muscle integrity of subjects at what has been determined in previous studies to be a critical timepoint in therapy.

2. INVESTIGATIONAL PRODUCT

2.1 ACTIVE INGREDIENT, PHARMACOLOGIC CLASS, STRUCTURE

[redacted]

[redacted]

[redacted]

It is important to point out that affinity maturation had already taken place in the human host, and therefore no *in vitro* affinity maturation was required to increase the natural binding affinity of XB2001. In addition, the IgG4 heavy chain and kappa light chain constant regions have not been modified in any way in vitro. These two features should make for a drug product with reduced potential for immunogenicity.

2.2 DRUG PRODUCT (XB2001 100MG/ML) DESCRIPTION

XB2001 100mg/ml

[redacted]

2.3 STORAGE

The recommended storage condition for drug product in vials is upright, at 2-8°C, protected from light. The drug product diluted using the normal saline should be used for infusion within 8 hours. The diluted bag can be stored either at 2-8ºC or at room temperature (not exceeding 25ºC). If the bag is held at 2-8ºC, move the bag to room temperature at least 30 minutes to 1 hour prior to administration so that the drug product is warmed up to room temperature prior to infusion.

2.4 STABILITY

The drug product is formulated in a buffer in which most of the tonicity comes from [redacted] rather than salt. [redacted] is an effective stabilizer against oxidation and aggregation, as well as thermal and mechanical stress.

2.5 DOSING AND METHODS OF ADMINISTRATION

Treatments will continue until disease progression, unacceptable toxicity or study completion.
For safety information on all treatments please see section 10.7.

2.5.1. Doses

2.5.1.1 XB2001

Administer study drug/ placebo ***PRIOR*** to chemo (ONIVYDE, Leucovorin and 5-Fluorouracil). Dependent on phase and cohort, XB2001 will be administered at 250 mg, 500 mg and 1000 mg doses by intravenous infusion prior to chemotherapy infusions at each cycle (14 days).

One vial of XB2001 (2.5, 5 or 10 mL at 100 mg/ml depending on phase and/or cohort) should be diluted in normal saline prior to infusion as instructed in the pharmacy manual. The drug product should then be mixed by gently inverting the bag ten times.

After priming the infusion set lines, the delivery pump should be programmed to deliver 100 mL of the diluted drug product over up to a 1-hour period (60 ± 15 minutes), with the subject being monitored for signs of an infusion reaction. The infusion should be chased with a minimum of 30mL of normal saline to deliver any product that may be held up in the dead volume of the infusion set.

2.5.1.2 Nanoliposomal Irinotecan (ONIVYDE, Mm398)

DO NOT SUBSTITUTE ONIVYDE for other drugs containing irinotecan HCl. Administer ONIVYDE **AFTER** XB2001 and **PRIOR** to leucovorin and fluorouracil.

The dose of ONIVYDE is 70 mg/m^2 administered by intravenous infusion over 90 minutes every 2 weeks. The recommended starting dose of ONIVYDE in subjects known to be homozygous for the UGT1A1*28 allele is 50 mg/m^2 administered by intravenous infusion over 90 minutes. Increase the dose of ONIVYDE to 70 mg/m^2 as tolerated in subsequent cycles. There is no recommended dose of ONIVYDE for subjects with serum bilirubin above the upper limit of normal.

Premedication

Administer a corticosteroid and an anti-emetic 30 minutes prior to ONIVYDE infusion

Please refer to package insert for full prescribing information.

2.5.1.3 5-Fluorouracil (5-FU)

5-FU will be administered at 2400 mg/m^2 by intravenous infusion over 46 hours every two weeks during treatment period.

2.5.1.4 Leucovorin (Folinic Acid, LV)

Leucovorin 1 + d racemic[1] form will be administered at 400 mg/m^2 by intravenous infusion over 30 minutes every two weeks during the treatment period.

Please refer to package insert for full prescribing information.

Due to the drug shortage of Leucovorin secondary to the COVID-19 pandemic, it is appropriate to substitute Levoleucovorin as a replacement for Leucovorin. Levoleucovorin is a folate analog containing the active isomer of leucovorin and can be used interchangeably with Leucovorin once you receive Sponsor's written approval.

2.5.2 Dosage Modifications

Toxicities may warrant dosage adjustments. The toxicity of each cycle must be recorded prior to the administration of a subsequent cycle and graded according to the NCI CTCAE (Version 5.0). All dose reductions should be based on the worst preceding toxicity.

2.5.2.1 XB2001 Dose Modifications

Once established in Phase I, subjects in phase II will continue to receive MTD (or the maximum dose studied if MTD is not observed) of XB2001 while on study. Subjects who are experiencing unacceptable toxicities should discontinue treatment and be removed from study (see section 6.4). If ONIVYDE/LV/5-FU treatment is permanently discontinued, XB2001 treatment will also be discontinued, and subject will be removed from study. All treatments can be withheld for 1 cycle (2 weeks). If treatments are withheld for >1 consecutive cycles or >2 total cycles (i.e. non-consecutively) throughout the study, subjects will be removed from study.

[1] Commercially available leucovorin is composed of a 1:1 racemic mixture of the dextrorotary and levorotary isomers

Subjects who require > 2 dose reductions (ONIVYDE) should be withdrawn from study.

2.5.2.2 ONIVYDE Dose Modifications

<table>
<tr><th>Toxicity NCI CTCAE v5.0</th><th>Directions</th><th>ONIVYDE adjustment in subjects receiving 70 mg/m^2</th><th>Subjects homozygous for UGT1A1*28 without previous increase to 70 mg/m^2</th></tr>
<tr><td>Grade 2 Diarrhea</td><td colspan="3">Withhold ONIVYDE. Administer loperamide for late diarrhea of any severity.
Administer atropine, if not contraindicated, for early diarrhea of any severity.</td></tr>
<tr><td rowspan="6">Grade 3 or 4 Diarrhea</td><td rowspan="6">Withhold ONIVYDE
Initiate loperamide for late onset diarrhea of any severity.
Administer intravenous or subcutaneous atropine 0.25 to 1 mg (unless contraindicated) for early onset diarrhea of any severity.
Upon recover to ≤ Grade 1, resume ONIVYDE at:</td><td colspan="2"><u>First Occurrence</u></td></tr>
<tr><td>50 mg/m^2</td><td>43 mg/m^2</td></tr>
<tr><td colspan="2"><u>Second Occurrence</u></td></tr>
<tr><td>43 mg/m^2</td><td>35 mg/m^2</td></tr>
<tr><td colspan="2"><u>Third Occurrence</u></td></tr>
<tr><td colspan="2">Discontinue ONIVYDE</td></tr>
</table>

<table>
<tr><th>Toxicity NCI CTCAE v5.0</th><th>Directions</th><th>ONIVYDE adjustment in subjects receiving 70 mg/m^2</th><th>Subjects homozygous for UGT1A1*28 without previous increase to 70 mg/m^2</th></tr>
<tr><td rowspan="6">Grade 3 or 4 Adverse Reactions</td><td rowspan="6">Withhold ONIVYDE
Upon recover to ≤ Grade 1, resume ONIVYDE at:</td><td colspan="2"><u>First Occurrence</u></td></tr>
<tr><td>50 mg/m^2</td><td>43 mg/m^2</td></tr>
<tr><td colspan="2"><u>Second Occurrence</u></td></tr>
<tr><td>43 mg/m^2</td><td>35 mg/m^2</td></tr>
<tr><td colspan="2"><u>Third Occurrence</u></td></tr>
<tr><td colspan="2">Discontinue ONIVYDE</td></tr>
<tr><td>Interstitial Lung Disease</td><td colspan="3"><u>First Occurrence</u>: Discontinue ONIVYDE</td></tr>
<tr><td>Anaphylactic Reaction</td><td colspan="3"><u>First Occurrence</u>: Discontinue ONIVYDE</td></tr>
</table>

Withhold ONIVYDE for absolute neutrophil count (ANC) below 1500/mm^3 or neutropenic fever. Upon recovery to ANC ≥ 1500/mm^3, reduce ONIVYDE dose for Grade 3-4 neutropenia or neutropenic fever.

2.5.2.3 5-Fluorouracil Dose Modifications

If ONIVYDE is withheld or discontinued for adverse reactions, 5-FU will also be withheld or discontinued. If the dose of ONIVYDE is reduced for adverse reactions, the dose of 5-FU will be reduced by 25%.

Withhold 5-FU for any of the following:

- Development of angina, myocardial infarction/ischemia, arrhythmia, or heart failure in subjects with no history of coronary artery disease or myocardial dysfunction
- Hyperammonemic encephalopathy
- Acute cerebellar syndrome, confusion, disorientation, ataxia, or visual disturbances
- Grade 3 or 4 diarrhea
- Grade 2 palmar-plantar erythrodysesthesia (hand-foot syndrome)
- Grade 3 or 4 mucositis
- Grade 4 myelosuppression

Upon resolution or improvement to Grade 1 diarrhea, mucositis, myelosuppression, or palmar-plantar erythrodysesthesia, resume 5-FU administration at a reduced dose (initial reduced dose will be 2000 mg/m^2 continuous infusion; second reduced dose will be 1800 mg/m^2 continuous infusion).

2.5.2.4 Leucovorin Dose Modifications

No dose reduction of leucovorin is recommended. If 5-FU treatment is withheld, leucovorin will also be withheld.

2.5.3 Administration Schedule

Phase I

Subjects will receive two treatment cycles (total of 28 days) in which they will be given one intravenous dose of XB2001 prior to receiving ONIVYDE 70 mg/m^2 intravenously over 90 minutes, followed by leucovorin l + d racemic 400 mg/m^2 intravenously over 30 minutes, followed by 5-Fluorouracil 2400 mg/m^2 intravenously over 46 hours at each cycle.

- Subjects who are homozygous for UGT1A1*28 allele will receive once cycle of ONIVYDE therapy at reduced dose of 50 mg/m^2.

*There will be 3 sequential XB2001 dose levels: 250 mg (dose cohort 1), 500 mg (dose cohort 2), and 1000 mg (dose cohort 3).

Phase II

XB2001 + ONIVYDE + LV + 5-FU Administration Schedule: Subjects randomized to this arm will receive the following treatments every 2 weeks: XB2001 MTD (or the maximum dose studied if MTD is not observed) as an intravenous infusion over up to 60 minutes, followed by ONIVYDE 70 mg/m^2 intravenously over 90 minutes, followed by leucovorin l + d racemic 400 mg/m^2 intravenously over 30 minutes, followed by 5-Fluorouracil 2400 mg/m^2 intravenously over 46 hours.

Placebo + ONIVYDE + LV + 5-FU Administration Schedule: Subjects randomized to this arm will receive the following treatments every 2 weeks: Placebo as an intravenous infusion over up to 60 minutes, followed by ONIVYDE 70 mg/m^2 intravenously over 90 minutes, followed by leucovorin l + d racemic 400 mg/m^2 intravenously over 30 minutes, followed by 5-fluorouracil 2400 mg/m^2 intravenously over 46 hours. One cycle of treatment is defined as two weeks.

2.6 AGENT ORDERING

The clinical site's pharmacy will order study drug from XBiotech's contract drug distributor as needed and will be responsible for procuring Standard of Care chemotherapy treatments.

2.7 POTENTIAL DRUG INTERACTIONS

There are no known drug interactions with XB2001.

2.8 RESTRICTED & PROHIBITED THERAPIES & PROCEDURES

2.8.1 Restricted Therapies while on Study

- Live virus vaccines;
- Chemotherapy agents other than those specified in this protocol;
- Radiotherapy;
- Strong CYP3A4 inducers or inhibitors (see more information in paragraph below);
- Strong UGT1A1 inhibitors (see more information in paragraph below)

ONIVYDE is known to interact with CYP3A4 inducers (e.g., rifampin, phenytoin, carbamazepine, rifabutin, rifapentine, phenobarbital, St John's wort); CYP3A4 inhibitors (e.g., clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, voriconazole) or UGT1A1 inhibitors (e.g., atazanafir, gemfibrozil, indinavir). The use of strong CYP3A4 inducers or inhibitors and strong UTG1A1 inhibitors should be avoided. Subjects on strong CYP3A4 inducers or inhibitors and/or strong UTG1A1 inhibitors should discontinue at least 14 days prior to starting ONIVYDE. If possible, non-enzyme-inducing therapies may be substituted at least 14 days prior to starting ONIVYDE.

In the event that it becomes medically necessary for a subject to be treated with a restricted therapy during the study, this should be recorded on both the source documentation and EDC as a concomitant therapy, however the subject may continue on trial as scheduled if both the PI and Medical Monitor are in agreement.

2.8.2 Prohibited Therapies & Procedures while on Study

- Investigational Agents
- Immunotherapies/biologics, including agents that inhibit tumor necrosis factor (TNF), interleukin 1 (IL-1), epidermal growth factor receptor (EGFR) and Programmed cell death protein 1 (PD-1).
- Whipple procedure, (patient should not be enrolled if, in the investigators judgment, the patient is likely to require Whipple procedure within 8 weeks from the start of study).
- Whole brain irradiation (patient's with brain metastasis should not be enrolled if in the investigators judgment the patient is likely to require whole brain irradiation within 8 weeks from the start of therapy).
- Distal and/or total pancreatectomy (patient should not be enrolled if, in the investigators judgment, the patient is likely to require procedure within 8 weeks from the start of study).

2.9 PERMITTED THERAPIES

Subjects are permitted to use insulin or other anti-diabetics to control blood sugar, any recommended analgesics, medications to reduce/control the side effects of chemotherapy, and anti-infectives/antibiotics.

Subjects will be premedicated with standard corticosteroids and an antiemetic 30 minutes prior to ONIVYDE administration, per package insert and must be documented in the concomitant medications. Supportive medications will be prescribed for nausea/vomiting/diarrhea/etc. as clinically indicated. All therapies will be captured in the source and on the concomitant medications eCRF.

3. STUDY DESIGN AND OBJECTIVES

Study Title: A Phase I/II randomized, double-blind, placebo-controlled trial (1-BETTER) examining XB2001 (anti-IL-1α True Human antibody) in combination with ONIVYDE + 5-FU/LV (+ folinic acid) in advanced pancreatic cancer

Sponsor: XBiotech USA, Inc.

Study Chair: [redacted]

Sample Size: Approximately 69 subjects will be enrolled in the USA (at least 9 subjects in the open label phase I and 60 subjects in the randomized phase II portion).

Approximate Duration:

This trial will include 2 phases. Phase I, will be an open label, dose escalation study establishing the Maximum Tolerated Dose (MTD) or maximum dose studied (if no dose limiting toxicities are observed over the dose range) of XB2001 in at least nine subjects with metastatic pancreatic adenocarcinoma who are receiving ONIVYDE + Leucovorin l + d racemic + 5-Fluorouracil chemotherapy treatment. The duration for each patient in the Phase I portion will be 28 days (2 treatment cycles) in which they will be given one intravenous dose of XB2001 (at the same dose level that they enrolled to) prior to receiving ONIVYDE + Leucovorin l + d racemic + 5-Fluorouracil chemotherapy treatment at each visit and assessed

for Dose Limited Toxicities (DLT). Phase II will be implemented following the completion of the Phase I and declaration of the MTD or maximum dose studied (if no dose limiting toxicities are observed over the dose range). The duration of subject participation in the randomized, double-blind, placebo-controlled Phase II portion of the trial is approximately 28 weeks: including a screening period of up to 30 days, and 24-week treatment period. All study subjects can continue treatment with XB2001 along with ONIVYDE + 5-FU + LV in an open label extension, for as long as they are judged to be benefitting clinically and have had no unacceptable toxicities.

Study Objectives:

Phase I and Phase II Primary Endpoints:

- Primary Endpoint of Phase I: To identify the maximum tolerated XB2001 dose (MTD) or maximum XB2001 dose studied if no DLTs are observed. DLT and MTD of XB2001 will be assessed in combination with ONIVYDE + LV + 5-FU, when given as second- or third-line treatment of subjects with advanced pancreatic adenocarcinoma. The MTD identified in phase 1 will be the dose of XB2001 used in phase 2 of the study.
- Primary Endpoint of Phase II: Safety and tolerability of XB2001 at the MTD, or the maximum dose studied.

Secondary Endpoints (Phase II only):

- Progression Free Survival
    - Progression Free Survival (PFS), as defined by the time frame from treatment initiation to first progression based on RECIST 1.1 criteria.
- Overall Survival (OS)
    - Overall Survival (OS), defined as time from treatment initiation to death. Objective Response Rate,, determined via every 8-week imaging assessments,
    - Time to Treatment Failure
    - Time to Treatment Failure, defined as time from treatment initiation to treatment discontinuation resulting from progression or side effects Percentage of Subjects with Clinical Benefit Response (CBR)
- CBR is a composite measure consisting of change in lean body mass (LBM) and change in quality of life (QOL).
    - CBR will be assessed every 8 weeks while patients are on treatment.

    - A positive CBR will be defined as stabilization or positive (≥0 kg) change in lean body mass (LBM)—as assessed by dual-energy X-ray absorptiometry (DEXA) scan, and improvement or no worsening (≥0 score point change) on any two of the three symptom scale measures (fatigue, pain, appetite) of EORTC QLQ-C30.
- Quality of Life assessed through the cancer-specific EORTC QLQ-C30 questionnaire
    - Time Frame: Baseline to weeks 8, 16 and 24.
- Number of Serious Adverse Events (SAEs)
- Incidence of Grade 3-4 Diarrhea
- Duration of hospitalizations
    - Time Frame: Baseline to weeks 4, 8, 12, 16, 20 and 24.
- Assessment of Pharmacokinetics (PK)
- Number of Treatment Cycles
- Reduction in (CD14+CD16+IL-1α+) triple positive tumor associated monocytes in peripheral blood
    - Time Frame: Baseline to week 2 (post infusion at visit 2).

Exploratory Endpoints (Phase II only):

- Results of a symptom questionnaire will be summarized by treatment arm at various post-infusion time points and compared over time.
- Cardiotoxicity measured by the number of required ECGs and cardiotoxicity related adverse events summarized by treatment arm and compared over time.

Trial Design:

Dose Escalation (Phase 1):

- After enrollment subjects will receive two treatment cycles (a total of 28 days) in which they will be given one intravenous dose of XB2001 prior to receiving ONIVYDE 70 mg/m2 intravenously over 90 minutes, followed by leucovorin l + d racemic 400 mg/m2 intravenously over 30 minutes, followed by 5-Fluorouracil 2400 mg/m2 intravenously over 46 hours at each cycle.
    - Subjects who were homozygous for UGT1A1*28 allele will receive the cycle of ONIVYDE therapy at reduced dose of 50 mg/m^2.
- There will be 3 sequential dose levels: 250mg (dose cohort 1), 500mg (dose cohort 2), and 1000mg (dose cohort 3).

- Dose Escalation Rules:
    - XB2001 will be dose escalated and a traditional 3:3 design will be used. The maximum tolerated dose (MTD) or the maximum dose studied (if no dose limiting toxicities are observed over the dose range) of XB2001 will be assessed for the combination with ONIVYDE + LV + 5-FU chemotherapy regimen. The MTD or maximum dose studied will be the Recommended Phase II Dose (RP2D).
    - The dose of XB2001 will be escalated in sequential cohorts of three subjects each. Dose-escalation will continue if none of three subjects experience a dose-limiting toxicity (DLT) (defined below).
    - A dose cohort will be expanded to six subjects if one of the first three subjects experience an apparent DLT during the first or second treatment cycles (28 days).
    - Due to the fact that this chemotherapy regimen is an established treatment for these patient population, only the dose for XB2001 will be changed according to observed DLTs.
    - Enrollment to next higher dose-cohort (i.e. from level 1 to level 2 or from level 2 to level 3) will be withheld until the last enrolled patient in the previous dose-cohort has reached the end of second cycle (i.e. no sooner than 28 days from the start of the first cycle).
    - The maximum tolerated dose (MTD) of XB2001 is defined as the highest dose level at which no more than one out of six subjects experience a DLT. If two or more out of six subjects within the same cohort encounter DLT, MTD will be exceeded and the lower dose level will be considered to be the MTD. Adverse events (AEs) will be defined by Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.
    - DLTs will be evaluated during the first and second treatment cycles (28 days) and defined as follows: a) inability to deliver all scheduled doses during cycle due to an unexpected drug-related toxicity and/or b) inability to deliver the intended dose of XB2001 in the cycle due to drug-related toxicity (DLT is defined as any grade 3-4 adverse events that are deemed possibly related to the combination regimen unless there is a toxicity clearly attributable exclusively to another single component of the combination). Criteria for positive safety evaluation is completion of two treatment cycles or early discontinuation due to DLT.
    - Subjects who do not finish two cycles due to AEs other than DLTs will be replaced as described above.

- An event will be classified as "Not Suspected" when a causal relationship between AE and study drug is unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provided sufficient explanation for the observed event. An event will be classified as Suspected when a causal relationship between AE and study drug is possible, and other medications, therapeutic interventions, or underlying conditions do not provide sufficient explanation for the observed event.

- After a MTD or maximum dose studied has been declared, the study will progress to the Phase 2 portion.

Subjects enrolled in the phase 1 portion of the study can continue treatment with XB2001 along with ONIVYDE + 5-FU + LV for as long as they are judged to be benefitting clinically and have had no unacceptable toxicities. Subjects will continue at the dose level for which they were enrolled until the MTD or the maximum dose studied has been established, at which point they can increase to the MTD or the maximum dose studied dose level. Subjects will continue to have assessments outlined in section 6 while on study.

Dose Expansion (Phase II):

An additional 60 subjects with advanced pancreatic cancer will be enrolled at the MTD or the maximum dose studied in a double-blind, placebo-controlled Phase 2 portion of the study and will be randomized in a 1:1 fashion to receive either XB2001 administered in combination with ONIVYDE + Leucovorin l + d racemic + 5-Fluorouracil or placebo in combination with ONIVYDE + Leucovorin l + d racemic + 5-Fluorouracil.

The Phase II will be a randomized, double-blind, placebo-controlled study to establish the safety and tolerability of XB2001 administered in combination with ONIVYDE + Leucovorin l + d racemic + 5-Fluorouracil in adults with advanced metastatic pancreatic cancer. Subjects will be assessed for study eligibility at the initial screening visit after providing informed consent. Thirty days are allowed in the screening window to complete all screening procedures and randomize the subject. During the screening period, certain treatments will be washed out, as applicable, according to eligibility requirements. Imaging for tumor measurements required at screening within 28 days of randomization and should be performed as close as possible to treatment start. Subjects who fail initially may be re-screened once based on the investigator discretion but only if inclusion/exclusion are met at time of re-screening.

The study is approximately 28 weeks (4-week screening period and 24-week treatment period) for all subjects. Subjects who meet eligibility criteria at screening will be randomized in a 1:1 fashion to one of two treatment arms:

ARM 1: XB2001 + ONIVYDE + LV + 5-FU combination therapy administered for up to 12 cycles of treatment

- *Arm 1 Treatment Cycle*: Subjects randomized to this arm will receive the following treatments every 2 weeks: XB2001 MTD or the maximum dose studied as an intravenous infusion over up to 60 minutes (+15), followed by ONIVYDE 70 mg/m^2 intravenously over 90 minutes, followed by leucovorin l + d racemic 400 mg/m^2 intravenously over 30 minutes, followed by 5-Fluorouracil 2400mg/m^2 intravenously over 46 hours. Therapy will be administered every 2 weeks (2 weeks = 1 cycle).
    - Subjects who are homozygous for UGT1A1*28 allele receive first cycle of therapy at reduced dose of 50 mg/m^2. If no significant drug related toxicity after first administration of ONIVYDE is noted, the dose may be increased to 70 mg/m^2 for subsequent cycles, as tolerated.
    - Please see section 2.5.2 for dose modifications.

ARM 2: Placebo + ONIVYDE + LV + 5-FU combination therapy administered for 12 cycles of treatment

- *Arm 2 Treatment Cycle:* Subjects randomized to this arm will receive the following treatments every 2 weeks: Placebo as an intravenous infusion over up to 60 minutes (+15), followed by ONIVYDE 70 mg/m^2 intravenously over 90 minutes, followed by leucovorin l + d racemic 400 mg/m^2 intravenously over 30 minutes, followed by 5-fluorouracil 2400 mg/m^2 intravenously over 46 hours. Therapy will be administered every 2 weeks (2 weeks = 1 cycle).
    - Subjects who were homozygous for UGT1A1*28 allele receive first cycle of therapy at reduced dose of 50 mg/m^2. If no significant drug related toxicity after first administration of ONIVYDE is noted, the dose may be increased to 70 mg/m^2 for subsequent cycles, as tolerated.
    - Please see section 2.5.2 for dose modifications

One treatment cycle is defined as 2 weeks. Study treatment will be administered for 12 cycles of treatment over the 24-week treatment period. Subjects will be monitored for a minimum of 30 minutes (+/- 10 minutes) after the first 3 infusions of XB2001 or placebo for safety. After completion of visit 3 DLT assessment (phase 1 subjects) or visit 13 (phase 2 subjects) subjects in both portions can continue treatment with XB2001 in an open label extension, for as long as are judged by the investigator to be benefitting clinically and have had no unacceptable toxicities.

During the 24-week treatment period, subjects will attend clinical study visits on weeks they are receiving treatment, as well as the final visit 13. Visit 13 (week 24) will be a follow up visit and the completion of cycle 12. Clinical assessments, collection of samples for routine laboratory tests and XB2001

concentrations, radiology assessments, and safety testing will be performed at specified clinic visits. After completion of the 28-week study period, data will be locked, unblinded, and analyzed for safety and efficacy endpoints for both arms. Subjects from both arms can continue treatment with XB2001 along with ONIVYDE + 5-FU + LV indefinitely in an open label extension, for as long as they are judged to be benefitting clinically and have had no unacceptable toxicities. In addition to end of study analyses following database lock, an additional database lock may be performed at Week 8 for interim analyses utilizing unblinded safety and efficacy data, to help plan as the study progresses future development activities. If interim analyses are performed, a Data and Safety Monitoring Board (DSMB) will be established to conduct such analyses and will consist of at least one clinician and a statistician, one of whom will chair the committee, and may also include other members as required. In addition, if interim analyses occur a DSMB charter will define the organization and roles and responsibilities of the committee, possible recommendations or requests, and the communication process following reviews. Results from the Week 8 database lock and/or interim analyses will not be disseminated to investigators or subjects participating in the study. In addition, results of the interim analyses will not be disseminated to individuals associated with the conduct of the study.

Subjects will be monitored at a follow-up visit (Visit 13) for safety and clinical assessments after completing the 24-week treatment period.

4. ELIGIBILITY CRITERIA

4.1 INCLUSION CRITERIA

Subjects are included in the study if they meet all of the following criteria:

1. Written informed consent provided by the patient.
2. Age ≥18 years.
3. Histologically or cytologically confirmed pancreatic adenocarcinoma of exocrine pancreas that is metastatic, unresectable, or recurrent.
4. At least one measurable lesion according to Response Evaluation Criteria in Solid Tumor. (RECIST v1.1)
5. Documented disease progression after one prior gemcitabine-based therapy OR one FOLFIRINOX and gemcitabine containing therapy.
6. Eastern Cooperative Oncology Group (ECOG) performance of 0 or 1 or Karnofsky performance status (KPS) ≥ 70.
7. Adequate hepatic, renal and bone marrow function within 4 weeks prior to registration defined as:
    - Serum total bilirubin ≤ upper normal limit (UNL)
    - Serum albumin ≥ 3.0 g/dL
    - Aspartate aminotransferase (AST) & alanine aminotransferase (ALT) ≤ 3 x UNL (≤ 5 x UNL is acceptable if liver metastases are present)
    - CLcr > 30 ml/min (calculated by Cockcroft-Gault method)
    - Leukocytes ≥ 3000/mL
    - Absolute neutrophil count ≥ 1500 mm^3
    - Platelets ≥ 100,000 mm^3; must not have had transfusion in the prior 2 weeks
    - Hemoglobin ≥ 9 g/dL; must not have had transfusion in the prior 2 weeks
8. Full understanding of the study protocol procedures and willingness to comply with them.
9. Normal ECG or ECG without any clinically significant findings with QTc < 470 ms.
10. For women of childbearing potential (WOCBP), a negative serum pregnancy test result at Screening.
11. In case of female subjects of childbearing potential, willingness to use one method of contraception of high efficacy during the entire study period. These methods can include but not limited to hormonal contraceptives, intrauterine devices, condoms, diaphragms etc. Women of non-childbearing potential include those considered to have a medical history that indicates that pregnancy is not a reasonable risk, including post-menopausal women and those with a history of hysterectomy or surgically sterilized.

12. If you are a male participating in this clinical research study, you should not get a sexual partner pregnant during your participation in this research study as the effect of the study drug on sperm is not known. The male contraception methods can include but not limited to mechanical methods (abstinence, withdrawal, non-vaginal intercourse) or contemporary methods comprising condoms and vasectomy.
13. At least 14 days since the last cancer treatment including: chemotherapy, radiation therapy, surgery, hormonal therapy prior to baseline visit.

4.2 EXCLUSION CRITERIA:

Subjects with ANY of the following will be excluded from the study:

1. History of treatment with XB2001 for any reason.
2. Clinically significant GI disorders.
3. Severe arterial thromboembolic events less than 6 months before inclusion. Venous thromboemolism, including pulmonary embolism and deep venous thrombosis, does not exclude patients from enrollment.
4. Severe hypersensitivity to 5-FU.
5. Use of warfarin within 4 weeks of screening or any time during the study.
6. Prior Whole Brain Radiation Therapy (WBRT).
7. Evidence of brain metastases.
8. NYHA Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled blood pressure (defined as ≥ 160/100 mm Hg).
9. Active infection or uncontrolled fever.
10. Clinically significant decrease in performance status (medical records) within 2 weeks of intended first dose administration.
11. Any other severe concomitant disease, disorder, or condition that could interfere with patient's safety, ability to participate, or interpretation of study results.
12. Malignancies other than metastatic pancreatic adenocarcinoma within the last 3 years before study start, except for cervical carcinoma in situ, treated basal or squamous cell carcinoma.
13. Investigational therapy administered within 4 weeks, or within a time interval less than at least 5 half-lives of the investigational agent, whichever was longer, prior to the first scheduled day of dosing in this study.
14. Pregnant or breastfeeding subjects
15. Known or suspected history of immunosuppression, including history of invasive opportunistic infections (e.g. tuberculosis [TB], histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis,

aspergillosis) despite infection resolution.

16. History of interstitial lung disease.
17. Stage C Child-Pugh liver cirrhosis.
18. Use of strong CYP3A4 inducers or inhibitors and/or strong UGT1A1 inhibitors within 14 days prior to Visit 1/Baseline visit.
19. Current use, or up to 14 days use prior to Visit1/Baseline visit, of an immunotherapy and live virus vaccines.
20. Participant must not have received colony stimulating factors (eg, granulocyte colony-stimulating factor, granulocyte macrophage colony stimulating factor, or recombinant erythropoietin) within 4 weeks prior initiating protocol therapy.
21. Participant has had any known Grade 3 or 4 anemia, neutropenia or thrombocytopenia due to prior chemotherapy that persisted > 4 weeks and was related to the most recent treatment.
22. Subjects that, in the investigator's judgement, are likely to require whole brain irradiation, Whipple procedure, or distal and/or total pancreatectomy within 8 weeks from start of study.
23. Life expectancy, in the absence of treatment, of less than or equal to 90 days, based on the principal investigator's best judgment.

5. PROCEDURES AND ASSESSMENTS

5.1 LABORATORY AND CLINICAL EVALUATIONS

At specified visits (see Section 6), all subjects will undergo routine clinical assessment including medical history review, physical examination, and collection of vital signs (temperature, blood pressure, heart rate and respiratory rate).

In order to determine study eligibility, assess patient safety, routine and protocol defined blood samples will be collected at multiple time points (see Section 6) including: complete metabolic panel (CMP), complete blood count (CBC), inflammatory markers, serum pregnancy test (screening only) for women of childbearing potential.

Blood samples will also be collected for PK/PD, ADA/PD and $CD14^+/CD16^+/IL\text{-}1\alpha^+$ staining, throughout the study as defined in Section 6. Missed sample collection(s) for PK/PD, ADA/PD and $CD14^+/CD16^+/IL\text{-}1\alpha^+$ staining will not result in a protocol deviation.

An ECG should be completed at Screening prior to randomization.

5.2 TUMOR MEASUREMENTS

Response Evaluation Criteria in Solid Tumor (RECIST) 1.1

- RECIST is a standard way to measure the response of a tumor to treatment. It provides objective criteria to determine whether a tumor disappears, shrinks, stays the same or gets bigger. RECIST 1.1 will be used to assess tumor progression. This is referred to as complete response (CR), partial response (PR), progressive disease (PD) and stable disease (SD). At baseline, tumor lesions will be categorized as measurable or non-measurable as follows:
    - Measurable
        - Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement) with a minimum size of 10mm by CT scan or MRI.
    - Non-Measurable
        - All other lesions, including small lesions (i.e. longest diameter is < 10mm) as well as truly non-measurable lesions.
    - All measurements should be recorded in metric notation. Imaging for baseline/inclusion assessment should be done at least 4 weeks prior to randomization and as close to the first treatment as possible.
    - The same method of assessment and technique should be used to characterize and identify each reported lesion for the duration of the study.
    - When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured during screening.
    - Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

- A sum of the diameters (longest for non-nodal lesions, shortest for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

- All other lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (CRF).

- Response Criteria – Evaluation of Target Lesions:
  - *Complete Response (CR):* Disappearance of all target lesions.
  - *Partial Response (PR):* at least 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
  - *Progressive Disease (PD):* At least 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (including baseline). In addition, the sum must also demonstrate an absolute increase of at least 5mm. Note: the appearance of one or more new lesions is also considered progression.
  - *Stable Disease (SD):* Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD, taking as reference the smallest sum on the study.
- Response Criteria – Evaluation of Non-Target Lesions:
  - *Complete Response (CR):* Disappearance of all non-target lesions and normalization of tumor marker level.
  - *Non-CR/Non-PD:* Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above normal limits.
  - *Progressive Disease (PD):* Unequivocal progression of existing non-target lesions.
    - When patient also has measurable disease. In this setting, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall

tumor burden has increased sufficiently to merit discontinuation of therapy.

- The circumstance of a patient only having non-measurable disease will not apply as they are required to have at least one measurable lesion.

- For more information and detailed description of all other relevant circumstances please refer to RECIST guidelines (version 1.1)[24].
  - Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal).
  - The smaller of these measures is the short axis. Nodal lesions with shorter perpendicular axis of ≥ 15mm should be measured as target and reported.
  - The longest diameter for non-nodal lesions should be measured.
  - A sum of diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters.

5.2.1 Imaging for Tumor Measurements

All imaging must be done prior to any other assessments related to a study visit. Required imaging (DEXA, CT and/or MRI) can be done within 72 hours prior to the visit.

Either computerized tomography (CT) (preferred) or magnetic resonance imaging (MRI) imaging will be done at specified visits (see Section 6) to evaluate tumor response. The same modality that is chosen for the initial tumor assessment must be used for the duration of the study. The lesions should be measured/assessed. The choice of modality should be based primarily on the type of scan that the patient has previously received as their standard of care.

Standardization of imaging requirements and image acquisition patterns allow for optimal comparability of subjects. Scanner quality control is highly recommended and should follow standard manufacturer and facility maintenance schedule using commercial phantoms. Thus, the following protocols for image acquisition of CT and MRI for subjects where RECIST assessment will be performed.

- Computerized tomography (CT)
    - Image quality control for CT includes an analysis of image noise and uniformity, CT number, and spatial resolution.
    - The frequency of quality control is also variable and should focus on clinically relevant scanning parameters.
    - Dose analysis should follow the ALARA principle, 'As Low As Reasonably Achievable', which refers to making every reasonable effort to maintain radiation exposures as far below the dose limits as possible.
    - CT scans of the chest, abdomen, and pelvis should be contiguous throughout all the anatomic region of interest. The minimum size of the measurable lesion at baseline should be no less than double the slice thickness and also have a minimum size of 10mm. As lesions potentially decrease in size at follow-up visits, they should still be measured. Lesions which are reported as too small to measure should be assigned a default measurement of 5mm if they are still visible.
    - Acquisition parameters
        - *Anatomic coverage:* Optimal anatomic coverage for most solid tumors is the chest, abdomen, and pelvis. Coverage should encompass all areas of unknown predilection for metastases and should additionally investigate areas that may be involved based on signs and symptoms of individual subjects. Because a lesion later identified in a body part not scanned at baseline would be considered a new lesion representing PD, careful consideration should be given to the extent of imaging coverage at baseline and subsequent follow-up time points.
        - *IV contrast administration:* Administration (dose and rate) of IV contrast and timing may vary depending on anatomical region, tumor type, CT scanning equipment, CT acquisition protocol, type of venous access, and condition of the patient, but should be consistent to provide for optimal visualization and measurement of metastases. To account for these variabilities, an adequate volume of suitable contrast should be given so that the metastases are demonstrated to best effect and a consistent method should be used on subsequent examinations (refer to institutional guidelines for best practice). For subjects who develop contraindications to contrast after baseline, MRI should be

performed. If patient is determined unable to undergo MRI, the subject must be considered non-evaluable and as a no-responder for object response.

- *Slice thickness and reconstruction interval:* It is recommended that CT scans be performed at 5mm contiguous slice thickness or less. If institution performs medically acceptable scans at slice thickness greater that 5mm, the minimum lesions at baseline should be twice the slice thickness of the baseline scans.
- *Alternative contrast agents:* Prohibited.

- Magnetic resonance imaging (MRI)
  - The technical specifications of the scanning sequences should be optimized for the evaluation to the type and site of the disease.
  - Generally, axial imaging of the abdomen and pelvis with T1 and T2 weighted imaging along with gadolinium enhanced imaging should be performed.
  - The field view, matrix, number of excitations, phase encode steps, use of fat suppression, and fast sequences should be optimized for the specific body part being imaged as well as the scanner utilized.
  - The same type of scanner and image acquisition protocol should be used for the duration of the study.

5.3 Dual-Energy X-Ray Absorptiometry (DEXA)

- Must be done prior to CT imaging and all other assessments related to study visit. DEXA can be completed within 72 hours prior to the visit. Intravenous and oral contrast will prevent proper DEXA imaging.
- At specified time points (see Section 6), subjects will undergo DEXA scans to assess change in lean body mass.

5.4 EFFICACY ASSESSMENTS

Objective Response Rate (ORR)

- ORR will be defined by the percent of subjects in the study with a best overall response of CR or PR as assessed by the investigator (per RECIST 1.1). Assessment and documentation of tumor

response must be completed prior to administration of treatment at each specified time point (see Section 6).

- Confirmation of response is not required, as the control arm serves as an appropriate means of interpretation of data. The best overall response will be recorded from randomization until progression or end of study and is defined as the best response achieved across all time points.
- Subjects with insufficient data for response classification will be classified as 'Not Evaluable' for best overall response, and as a non-responder for objective response in the ITT population.

Overall Survival (OS)

- Overall survival (OS) will be defined as the duration from the date of randomization until death. Subjects who are alive at the end of follow-up will be censored and survival time will be defined as time from randomization to censor date.

Time to Treatment Failure (TTF)

- Time to treatment failure (TTF) is defined as a composite endpoint measuring time from randomization to discontinuation of treatment for any reason, including disease progression, treatment toxicity, or death**.**

Clinical Benefit Response (CBR)

- CBR will be evaluated at specified time points (see Section 6) is defined as a composite measure consisting of change in lean body mass (stabilization or positive (≥ 0kg) change) – as assessed by DEXA imaging, and improvement or no worsening (≥ 0 score point change) on two of the three symptom scale measures (fatigue, pain, appetite) of the EORTC QLQ-C30.

Progression Free Survival (PFS)

- PFS will be evaluated following the formal database lock, or during an interim analysis, if applicable. PFS is defined as the time from date of randomization to the date of disease progression or death (any cause). Disease progression can include clinical progression, in which it is deemed by the investigator that the patient is coming off study due to the progression of underlying disease. Clinical or radiological (RECIST 1.1) progression will suffice as disease progression.
- Subjects with two or more consecutive missing response assessments prior to a visit with documented progression (or death) will be censored at the last date of tumor assessment when the patient was documented to be progression free.

EORTC-QLQ-C30 (Version 3.0)

- EORTC-QLQ-C30 is a patient reported outcome questionnaire and will be assessed at specified time points (see Section 6). This assessment consists of 15 subscales in 3 independent domains: global health-related quality of life (HRQL), functional scales (cognitive, emotional, physical, role, and social functioning), and symptom scales (appetite loss, constipation, diarrhea, dyspnea, fatigue, insomnia, nausea and vomiting, and pain).
- Improvement is indicated by subjects showing stabilization or improvement from baseline (≤ 0 change) on any two of the three symptom scales (pain, fatigue, appetite).

Symptom Questionnaire

- The symptom questionnaire is a patient reported outcome questionnaire and will be assessed at specified time points (see Section 6). This assessment contains several questions related to symptoms the patient is feeling at that moment. It will be answered by the patient within 24 hours following the completion of the 5-FU infusion. The appropriate site staff will administer the questionnaire over the phone and record patient answers on source documentation. Missing data for this questionnaire will not result in a protocol deviation.

5.5 PHARMACOKINETICS (PK)

In order to assess PK, serum/plasma samples will be collected at multiple time points pre or post infusion (see Section 6).

Treatment emergent anti-drug antibodies (ADA) will also be evaluated throughout the study (see Section 6).

5.6 PHARMACODYNAMICS (PD) & CLINICAL CORRELATES

$CD14^+/CD16^+/IL\text{-}1\alpha^+$ staining of PBMC will be performed as time points defined in Section 6 to evaluate PD of XB2001.

The following tests may also be performed to assess the PD properties of the XB2001:

- Cytokine biomarkers (including IL-6, IL-1RA)
- Other relevant biomarkers

6. TREATMENT PLAN

6.1 VISIT DESCRIPTIONS

Assessments/procedures at a clinic should be performed in the following order:

Imaging assessments, which can be completed within 72 hours prior to visit date, must be performed in the following order at any visit that has both these procedures:

1. DEXA
2. MRI/CT

Other Assessments:

1. Patient Reported Outcomes (with the exception of post-infusion questionnaires).
2. Investigator assessments (performed only by adequately trained investigators or sub-investigators; the same investigator or sub-investigator should perform all the evaluations for a given patient throughout the entire study period).
3. Safety and laboratory assessments.
4. Administration of study drug.

   **Vitals, Blood Draws and collection of safety information will vary based on visit, please refer to study procedures section.*

6.2 STUDY PROCEDURES

6.2.1 Study Procedures Phase I portion

******For study visits requiring radiology (DEXA, CT or MRI)-All radiology can be completed within <u>72 hours</u> prior to the visit and must be completed prior to all other assessments for that visit, please ensure these assessments are scheduled accordingly******

Screening (maximum 30 days; begins when informed consent is signed)

- Informed consent
- Review of Inclusion and Exclusion criteria
- Obtainment of medical history and demographics
- Height, weight, and BMI

Radiology

- Tumor Measurements (used for Baseline):
    - Tumor measurements for Screening, which will also be used for Baseline, ***must be done within 28 days of Visit 1/Baseline.***
    - Assessments can include CT or MRI, and the same modality that is chosen for the initial tumor assessment must be used for the duration of the study. The choice of modality should be based primarily on the type of scan that the patient has previously received as their standard of care.

Safety

- Concomitant medications/treatments
- Physical examination
- Electrocardiogram
- Collection of vital signs (Temperature, blood pressure, heart rate and respiratory rate)

Laboratory

- These labs (referred to collectively as "safety labs" from visit 1 to end of study) are monitored throughout the study:
    - Chemistry (CMP): Albumin, Alkaline Phosphatase, ALT, AST, GGT, Bicarbonate (CO_2), Calcium, Chloride, Creatinine, Glucose, Potassium, Sodium, Total Bilirubin, Total Protein, Blood Urea Nitrogen (BUN)
    - Hematology: Complete Blood Count (CBC) with Differential and Platelets

- These labs (referred to collectively as "CRP-ESR Labs" from visit 1 to end of study) are monitored throughout the study:
    - Inflammation Markers: C-Reactive Protein (CRP), and Erythrocyte Sedimentation Rate (ESR)
- Urinalysis (bilirubin, pH, protein, glucose, red and white blood cells)
- These are only required at screening:
    - Serum Pregnancy for women of childbearing potential

<u>Visit 1 (Week 0, Infusion visit 1, must occur within 30 days of signing Informed Consent)</u>

****Baseline for Tumor Measurements will be those used for screening, AS LONG AS IT OCCURRED WITHIN 28 DAYS OF BASELINE VISIT****

Pre-Infusion:

- Enrollment
- Weight, and BMI

Radiology

- DEXA scan

Efficacy

- EORTC-QLQ-C30 assessment

Safety

- Physical examination
- Collection of vital signs
- Collection of AEs/SAEs
- Concomitant medications/treatments

Laboratory

- Safety Labs (see Screening procedures for details)
- Urinalysis (see Screening procedures for details)
- Urine pregnancy test for women of childbearing potential

- Blood draw for ADA/PD.

Infusion:

- Complete Dispensing form in EDC
- Order of intravenous infusions (please see section 2 for instructions):
    - Administration of XB2001
    - *Laboratory blood draw: Collection of PK/PD samples 30 minutes post-infusion (+/- 10 minutes) of XB2001. Collection must be done prior to initiation of chemotherapy.*
    - Administration of ONIVYDE
    - Administration of Leucovorin
    - Administration of 5-FU

Post-Infusion:

- Vital signs and AEs/SAEs will be collected at 30 minutes post-infusion (+/- 10 minutes)
- Blood draw for PK/PD

Visit 2 (Week 2, Infusion visit 2)

Pre-Infusion:

- Weight, and BMI

Efficacy

- EORTC-QLQ-C30 assessment

Safety

- Physical examination
- Collection of vital signs
- Collection of AEs/SAEs
- Confirm any DLTs

- Concomitant medications/treatments

Laboratory

- Safety Labs (see Screening procedures for details)
- Urinalysis (see Screening procedures for details)
- Urine pregnancy test for women of childbearing potential
- Blood draw for PK/PD and ADA/PD.

Infusion:

- Complete Dispensing form in EDC
- Order of intravenous infusions (please see section 2 for instructions):
    - Administration of XB2001
    - Administration of ONIVYDE
    - Administration of Leucovorin
    - Administration of 5-FU

Post-Infusion:

- Vital signs and AEs/SAEs will be collected at 30 minutes post-infusion (+/- 10 minutes)

<u>Visit 3 (Follow Up Visit, Week 4):</u>

Safety

- Physical examination
- Collection of vital signs
- Collection of AEs/SAEs
- Confirm any DLTs
- Concomitant medications/treatments

Laboratory

- Safety Labs
- Urine pregnancy test for women of childbearing potential (only if subject is participating in OLE)

- Blood draw for PK/PD and ADA/PD.

*** <u>Only If subject is participating in OLE</u>:**

Infusion:

- Weight, and BMI
- Complete Dispensing form in EDC
- Order of intravenous infusions (please see section 2 for instructions):
    - Administration of XB2001
    - Administration of ONIVYDE
    - Administration of Leucovorin
    - Administration of 5-FU

<u>Any Future Visits (Open Label Extension) (to occur every 14 days):</u>

Subjects who have completed visit 3 of the phase 1 portion are eligible to participate in the open label extension. Subjects who had experienced a DLT up to follow-up visit (over 28 days) are not eligible to participate in OLE.

Weight, and BMI will be taken at each infusion visit to be used to calculate the chemotherapy dose.

Radiology (DEXA, CT, MRI) and EORTC-QLQ-30 will be completed every 8 weeks for subjects who remain on study in the open label extension.

Pre-Infusion:

- Weight, and BMI

Radiology (can be completed within 72 hours of the visit)

- DEXA scan (only performed every 8 weeks)
- Tumor Measurements (only performed every 8 weeks)

Efficacy

- EORTC-QLQ-C30 assessment

Safety

- Physical examination
- Collection of vital signs
- Collection of AEs/SAEs
- Concomitant medications/treatments

Laboratory

- Safety Labs
- Urine pregnancy test for women of childbearing potential

Infusion:

- Complete Dispensing form in EDC
- Order of intravenous infusions (please see section 2 for instructions):
    - Administration of XB2001
    - Administration of ONIVYDE
    - Administration of Leucovorin
    - Administration of 5-FU

6.2.2 Study Procedures Phase II

Cycle, Visit, Week Reference for PhaseII:

Completion of	Equates to	
CYCLE	Visit	Week
1	2	2
2	3	4
3	4	6
4	5	8
5	6	10
6	7	12
7	8	14
8	9	16
9	10	18
10	11	20
11	12	22
12	13	24

For study visits requiring radiology (DEXA, CT or MRI)-All radiology can be completed within 72 hours prior to the visit and must be completed prior to all other assessments for that visit, please ensure these assessments are scheduled accordingly

Blood Samples for PK/PD & ADA/PD and for CD14+/CD16+/IL-1α+ staining are collected at applicable visits throughout the study.

Screening (maximum 30 days; begins when informed consent is signed)

- Informed consent
- Review of Inclusion and Exclusion criteria
- Obtainment of medical history and demographics
- Height, weight and BMI

Radiology

- Tumor Measurements (used for Baseline):
    - Tumor measurements for Screening, which will also be used for Baseline, ***must be done within 28 days of Visit 1/Baseline.***
    - Assessments can include CT or MRI, and the same modality that is chosen for the initial tumor assessment must be used for the duration of the study. The choice of modality should be based primarily on the type of scan that the patient has previously received as their standard of care.

Safety

- Concomitant medications/treatments
- Physical examination
- Electrocardiogram
- Collection of vital signs (Temperature, blood pressure, heart rate and respiratory rate)

Laboratory

- These labs (referred to collectively as "safety labs" from visit 1 to end of study) are monitored throughout the study:

- Chemistry (CMP): Albumin, Alkaline Phosphatase, ALT, AST, GGT, Bicarbonate (CO_2), Calcium, Chloride, Creatinine, Glucose, Potassium, Sodium, Total Bilirubin, Total Protein, Blood Urea Nitrogen (BUN)
- Hematology: Complete Blood Count (CBC) with Differential and Platelets

- These labs (referred to collectively as "CRP-ESR Labs" from visit 1 to end of study) are monitored throughout the study:
  - Inflammation Markers: C-Reactive Protein (CRP), and Erythrocyte Sedimentation Rate (ESR)

- Urinalysis (bilirubin, pH, protein, glucose, red and white blood cells)
- These are only required at screening:
  - Serum Pregnancy for women of childbearing potential

Baseline, Visit 1 (Week 0; Start of Cycle 1; must occur within 30 days of signing Informed Consent)

****Baseline for Tumor Measurements will be those used for screening, AS LONG AS IT OCCURRED WITHIN 28 DAYS OF BASELINE VISIT****

Pre-Infusion:

- Weight and BMI
- Randomization

Radiology

- DEXA scan (can be completed within 72 hours of visit)

Efficacy

- EORTC-QLQ-C30 assessment
- Symptom questionnaire (appropriate study staff will record patient answers over the phone on source documentation within 24 hours post-5-FU infusion)

Safety

- Physical examination

- Collection of vital signs
- Collection of AEs/SAEs
- Concomitant medications/treatments

Laboratory

- Safety Labs (see Screening procedures for details)
- Urinalysis (see Screening procedures for details)
- Urine pregnancy test for women of childbearing potential
- Laboratory blood draw: Collection of ADA/PD and $CD14^+/CD16^+/IL\text{-}1\alpha^+$ staining samples

Infusion:

- Complete Dispensing form in EDC
- Order of intravenous infusions (please see section 2 for instructions):
  - Administration of XB2001 or placebo
  - *Laboratory blood draw: Collection of PK/PD samples 30 minutes post-infusion (+/- 10 minutes) of XB2001/Placebo.* ***Collection must be done prior to initiation of chemotherapy.***
  - Administration of ONIVYDE
  - Administration of Leucovorin
  - Administration of 5-FU

Post-Infusion:

- Vital signs and AEs/SAEs will be collected at 30 minutes post-infusion (+/- 10 minutes)
- Symptom questionnaire (appropriate study staff will record patient answers over the phone on source documentation within 24 hours post-5-FU infusion)

******PK/PD SAMPLES WILL ALSO BE COLLECTED ON DAY 4 (+/- 1 day) AND DAY 7 (+/- 1 day) FOLLOWING INITIAL INFUSION OF XB2001/PLACEBO******

Visit 2 (Week 2; Start of Cycle 2):

Pre-Infusion:

- Weight and BMI

Safety

- Physical examination
- Collection of vital signs
- Collection of AEs/SAEs
- Concomitant medications/treatments

Laboratory

- Safety Labs
- Urine pregnancy test for women of childbearing potential
- Collection of PK/PD, ADA/PD samples

Infusion:

- Complete Dispensing form in EDC
- Order of intravenous infusions (please see section 2 for instructions):
  - Administration of XB2001 or placebo
  - *Laboratory blood draw: Collection of $CD14^+/CD16^+/IL\text{-}1\alpha^+$ staining samples 30 minutes post-infusion (+/- 10 minutes) of XB2001/Placebo.* ***Collection must be done prior to initiation of chemotherapy.***
  - Administration of ONIVYDE
  - Administration of Leucovorin
  - Administration of 5-FU

Post-Infusion:

- Vital signs and AEs/SAEs will be collected at 30 minutes post-infusion (+/- 10 minutes)
- Symptom questionnaire (appropriate study staff will record patient answers over the phone on source documentation within 24 hours post-5-FU infusion)

Visit 3 (Week 4; Start of Cycle 3):

Pre-Infusion:

- Weight and BMI

Safety

- Physical examination
- Collection of vital signs
- Collection of AEs/SAEs
- Concomitant medications/treatments

Laboratory

- Safety Labs
- Urine pregnancy test for women of childbearing potential
- Collection of PK/PD, ADA/PD samples

Infusion:

- Complete Dispensing form in EDC
- Order of intravenous infusions (please see section 2 for instructions):
  - Administration of XB2001 or placebo
  - Administration of ONIVYDE
  - Administration of Leucovorin
  - Administration of 5-FU

Post-Infusion:

- Vital signs and AEs/SAEs will be collected at 30 minutes post-infusion (+/- 10 minutes)
- Symptom questionnaire (appropriate study staff will record patient answers over the phone on source documentation within 24 hours post-5-FU infusion)

Visit 4: (Week 6; Start of Cycle 4)

Pre-Infusion:

- Weight and BMI

Safety

- Physical examination
- Collection of vital signs
- Collection of AEs/SAEs
- Concomitant medications/treatments

Laboratory

- Safety Labs
- Urine pregnancy test for women of childbearing potential
- Collection of PK/PD, ADA/PD samples

Infusion:

- Complete Dispensing form in EDC
- Order of intravenous infusions (please see section 2 for instructions):
    - Administration of XB2001 or placebo
    - Administration of ONIVYDE
    - Administration of Leucovorin
    - Administration of 5-FU

Post-Infusion:

- Symptom questionnaire (appropriate study staff will record patient answers over the phone on source documentation within 24 hours post-5-FU infusion)

Visit 5 (Week 8; Start of Cycle 5):

Pre-Infusion:

- Weight and BMI

Radiology (can be completed within 72 hours prior to visit)

- DEXA scan
- Tumor Measurements

Efficacy

- EORTC-QLQ-C30 assessment

Safety

- Physical examination
- Collection of vital signs
- Collection of AEs/SAEs
- Concomitant medications/treatments

Laboratory

- Safety Labs
- CRP-ESR Labs
- Urine pregnancy test for women of childbearing potential

Infusion:

- Complete Dispensing form in EDC
- Order of intravenous infusions (please see section 2 for instructions):
  - Administration of XB2001 or placebo
  - Administration of ONIVYDE
  - Administration of Leucovorin
  - Administration of 5-FU

Post-Infusion:

- Symptom questionnaire (appropriate study staff will record patient answers over the phone on source documentation within 24 hours post-5-FU infusion)

Visit 6 (Week 10; Start of Cycle 6):

Pre-Infusion:

- Weight and BMI

Safety

- Physical examination
- Collection of vital signs
- Collection of AEs/SAEs

- Concomitant medications/treatments

Laboratory

- Safety Labs
- Urine pregnancy test for women of childbearing potential
- Collection of PK/PD, ADA/PD samples

Infusion:

- Complete Dispensing form in EDC
- Order of intravenous infusions (please see section 2 for instructions):
    - Administration of XB2001 or placebo
    - Administration of ONIVYDE
    - Administration of Leucovorin
    - Administration of 5-FU

Post-Infusion:

- Symptom questionnaire (appropriate study staff will record patient answers over the phone on source documentation within 24 hours post-5-FU infusion)

Visit 7 (Week 12; Start of Cycle 7):

Pre-Infusion:

- Weight and BMI

Safety

- Physical examination
- Collection of vital signs
- Collection of AEs/SAEs
- Concomitant medications/treatments

Laboratory

- Safety Labs
- Urinalysis

- Urine pregnancy test for women of childbearing potential

Infusion:

- Complete Dispensing form in EDC
- Order of intravenous infusions (please see section 2 for instructions):
    - Administration of XB2001 or placebo
    - Administration of ONIVYDE
    - Administration of Leucovorin
    - Administration of 5-FU

Post-Infusion:

- Symptom questionnaire (appropriate study staff will record patient answers over the phone on source documentation within 24 hours post-5-FU infusion)

Visit 8 (Week 14; Start of Cycle 8):

Pre-Infusion:

- Weight and BMI

Safety

- Physical examination
- Collection of vital signs
- Collection of AEs/SAEs
- Concomitant medications/treatments

Laboratory

- Safety Labs
- Urine pregnancy test for women of childbearing potential
- Collection of PK/PD, ADA/PD samples

Infusion:

- Complete Dispensing form in EDC
- Order of intravenous infusions (please see section 2 for instructions):
    - Administration of XB2001 or placebo

- Administration of ONIVYDE
- Administration of Leucovorin
- Administration of 5-FU

Post-Infusion:

- Symptom questionnaire (appropriate study staff will record patient answers over the phone on source documentation within 24 hours post-5-FU infusion)

Visit 9 (Week 16; Start of Cycle 9):

Pre-Infusion:

- Weight and BMI

Radiology (can be completed within 72 hours prior to visit)

- Tumor Measurements

Efficacy

- EORTC-QLQ-C30 assessment

Safety

- Physical examination
- Collection of vital signs
- Collection of AEs/SAEs
- Concomitant medications/treatments

Laboratory

- Safety Labs
- CRP-ESR Labs
- Urine pregnancy test for women of childbearing potential

Infusion:

- Complete Dispensing form in EDC
- Order of intravenous infusions (please see section 2 for instructions):
  - Administration of XB2001 or placebo

- Administration of ONIVYDE
- Administration of Leucovorin
- Administration of 5-FU

Post-Infusion:

- Symptom questionnaire (appropriate study staff will record patient answers over the phone on source documentation within 24 hours post-5-FU infusion)

Visit 10 (Week 18; Start of Cycle 10):

Pre-Infusion:

- Weight and BMI

Safety

- Physical examination
- Collection of vital signs
- Collection of AEs/SAEs
- Concomitant medications/treatments

Laboratory

- Safety Labs
- Urine pregnancy test for women of childbearing potential

Infusion:

- Complete Dispensing form in EDC
- Order of intravenous infusions (please see section 2 for instructions):
  - Administration of XB2001 or placebo
  - Administration of ONIVYDE
  - Administration of Leucovorin
  - Administration of 5-FU

Post-Infusion:

- Symptom questionnaire (appropriate study staff will record patient answers over the phone on source documentation within 24 hours post-5-FU infusion)

Visit 11 (Week 20; Start of Cycle 11):

Pre-Infusion:

- Weight and BMI

Safety

- Physical examination
- Collection of vital signs
- Collection of AEs/SAEs
- Concomitant medications/treatments

Laboratory

- Safety Labs
- Urine pregnancy test for women of childbearing potential

Infusion:

- Complete Dispensing form in EDC
- Order of intravenous infusions (please see section 2 for instructions):
  - Administration of XB2001 or placebo
  - Administration of ONIVYDE
  - Administration of Leucovorin
  - Administration of 5-FU

Post-Infusion:

- Symptom questionnaire (appropriate study staff will record patient answers over the phone on source documentation within 24 hours post-5-FU infusion)

Visit 12 (Week 22; Start of Cycle 12):

Pre-Infusion:

- Weight and BMI

Safety

- Physical examination
- Collection of vital signs

- Collection of AEs/SAEs
- Concomitant medications/treatments

Laboratory

- Safety Labs
- Urine pregnancy test for women of childbearing potential

Infusion:

- Complete Dispensing form in EDC
- Order of intravenous infusions (please see section 2 for instructions):
    - Administration of XB2001 or placebo
    - Administration of ONIVYDE
    - Administration of Leucovorin
    - Administration of 5-FU

Post-Infusion:

- Symptom questionnaire (appropriate study staff will record patient answers over the phone on source documentation within 24 hours post-5-FU infusion)

<u>Follow Up; Visit 13 (Week 24; Completion of Cycle 12):</u>

Radiology (can be completed within 72 hours prior to visit)

- Tumor Measurements

Efficacy

- EORTC-QLQ-C30 assessment

Safety

- Physical examination
- Collection of vital signs
- Collection of AEs/SAEs
- Concomitant medications/treatments

Laboratory

- Safety Labs

- CRP-ESR Labs
- Urinalysis
- Urine pregnancy test for women of childbearing potential

Open Label Extension Visits; To Occur Every 14 Days):

Subjects who have completed visit 13 in the phase 2 portion are eligible to participate in the open label extension.

Pre-Infusion:

- Weight, and BMI

Safety

- Collection of AEs/SAEs
- Concomitant medications/treatments

Infusion:

Complete Dispensing form in EDC

- Order of intravenous infusions (please see section 2 for instructions):
    - Administration of XB2001
    - Administration of ONIVYDE
    - Administration of Leucovorin
    - Administration of 5-FU

Post Infusion:

- Vital signs and AEs/SAEs will be collected at 30 minutes post-infusion (+/- 10 minutes) only for first 3 visits for subjects who received placebo during study.

6.3 STUDY CALENDARS

(PHASE I PORTION)

		Infusion Visit 1	Infusion Visit 2	Follow Up Visit	OLE Visits[10]
Visit (V)	**Screening**	**V1**	**V2**	**V3**	
Week (W)		**W0**	**W2**	**W4**	
Day (D)	**-30 to -1**	**D0**	**D[1]**	**D[1]**	**D[1]**
Visit Window (d)[1]	+5d	±3d	±3d	±3d	±3d
Screening/Baseline[2]					
Informed Consent	X				
Inclusion/Exclusion	X				
Medical History/ Demographics	X				
Height, Weight, BMI	X				
Enrollment		X			
Treatment[3, 4]					
Administer Study Drug		X	X	X[14]	X
Weight, BMI[5a]		X	X	X[14]	X
Administer ONIVYDE		X	X	X[14]	X
Administer Leucovorin		X	X	X[14]	X
Administer 5-Fluorouracil		X	X	X[14]	X
Con Meds/Treatments[5b]	X	X	X	X	X
Efficacy[4]					
EORTC-QLQ-C30		X	X		X[11]
Safety[4]					
Physical Examination	X	X	X	X	X
Electrocardiogram	X				
Vital Signs[9]	X	X[6]	X	X	X
AEs/SAEs		X[6]	X[6]	X[6]	X[6]
DLTs			X	X	
Laboratory Testing[4]					
Safety Labs	X	X	X	X	X
CRP-ESR Labs	X				
Urinalysis	X	X	X		
Urine Pregnancy Test (WOCBP only)	Serum	X	X	X[14]	X
PK/ADA/PD					
PK/PD		X[12]	X[13]	X[13]	
ADA/PD		X[13]	X[13]	X[13]	
Radiology ***MUST BE COMPLETED WITHIN 72 HOURS PRIOR TO VISIT*					
DEXA Scan		X			X[11]
Tumor Measurements[7]	X[8]				X[11]

	[1] Visit Window for each visit subsequent to V1/Baseline will be calculated from baseline visit (day 0).
	[2] 30 days are allowed to complete all screening procedures, **WITH THE EXCEPTION OF TUMOR MEASUREMENTS WHICH MUST BE DONE WITHIN 28 DAYS OF BASELINE VISIT.**
	[3] Subjects will be randomized to dosing cohort 1, 2 or 3 and will follow corresponding treatment plan.
	[4] Order of assessments and procedures is: radiology, patient reported assessments (with the exception of post-infusion symptom questionnaires), investigator assessments, safety and laboratory assessments and administration of study drug, administration of chemotherapy. All must be completed prior to the administration of the treatment regimen. *Vitals, Blood Draws and collection of safety information will vary based on visit, please refer to study procedures section.*
	[5a] Weight and BMI are to be collected pre-infusion at the infusion visits.
	[5b] Concomitant medications within 30 days before screening until 7 days after the last administration of the study drug must be recorded for the purpose of drug-drug and drug-disease interaction evaluation and signal detection.
	[6] Vital signs and AEs/SAEs will be collected 30 minutes (+/- 10 minutes) post-infusion of XB2001.
	[7] Assessments can include CT or MRI, and the same modality that is chosen for the initial tumor assessment must be used for the duration of the study. The choice of modality should be based primarily on the type of scan that the patient has previously received as their standard of care.
	[8] Imaging required for tumor measurements during screening must be done within 28 days of baseline visit. For those who remain on study in the open-label phase, all other required imaging can be completed within 72 hours prior to the applicable visit.
	[9] Vital signs to be collected: Temperature, blood pressure, heart rate and respiratory rate.
	[10] Performed only if patient is deemed to be benefiting from treatment and continues on study.
	[11] Radiology (DEXA, CT, MRI) and EORTC-QLQ-30 will be completed every 8 weeks for subjects who remain on study in the open label extension.
	[12] Samples must be collected 30 minutes (+/- 10 minutes) post-infusion of XB2001 but prior to administration of chemotherapy.
	[13] Samples must be collected prior to infusion of XB2001.
	[14] To occur only if subject is participating in the OLE.

(PHASE II PORTION)

Visit (V)	Screening	Cycle 1 V1 (Baseline)	Cycle 2 V2	Cycle 3 V3	Cycle 4 V4	Cycle 5 V5	Cycle 6 V6	Cycle 7 V7	Cycle 8 V8	Cycle 9 V9	Cycle 10 V10	Cycle 11 V11	Cycle 12 V12	Follow up[12] V13	OLE Visits[12]
Week (W)		W0	W2	W4	W6	W8	W10	W12	W14	W16	W18	W20	W22	W24	
Day (D)	-30 to -1	D0	D[1]	D[1]	D[1]	D[1]	D[1]	D[1]	D[1]	D[1]	D[1]	D[1]	D[1]	D[1]	D[1]
Visit Window (d)[1]	+5d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d
Screening/Baseline[2]															
Informed Consent	X														
Inclusion/Exclusion	X														
Medical History/ Demographics	X														
Height, Weight, BMI	X														
Randomization		X													
Treatment[3a, 4]															
Administer Study Drug/Placebo		X	X	X	X	X	X	X	X	X	X	X	X		X
Weight, BMI[3b]		X	X	X	X	X	X	X	X	X	X	X	X		X
Administer ONIVYDE		X	X	X	X	X	X	X	X	X	X	X	X		X
Administer Leucovorin		X	X	X	X	X	X	X	X	X	X	X	X		X
Administer 5-Fluorouracil		X	X	X	X	X	X	X	X	X	X	X	X		X
Efficacy[4]															
EORTC-QLQ-C30		X				X				X				X	
Symptom Questionnaire[13]		X	X	X	X	X	X	X	X	X	X	X	X		
Safety[4]															
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Electrocardiogram[14]	X														
Vital Signs[9]	X	X[6]	X[6]	X[6]	X	X	X	X	X	X	X	X	X	X	X[6]
AEs/SAEs		X[6]	X[6]	X[6]	X	X	X	X	X	X	X	X	X	X	X[6]
Con Meds/Treatments[5]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Laboratory Testing[4]															
Safety Labs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CRP-ESR Labs	X					X				X				X	
Urinalysis	X	X						X						X	
Urine Pregnancy Test (WOCBP only)	Serum	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK/PD		X[10]	X[11]	X[11]	X[11]		X[11]		X[11]						
ADA/PD		X[11]	X[11]	X[11]	X[11]		X[11]		X[11]						
CD14$^+$/CD16$^+$/IL-1α$^+$ staining		X[11]	X[10]												
Radiology ***CAN BE COMPLETED WITHIN 72 HOURS PRIOR TO EACH APPLICABLE VISIT* **															
DEXA Scan		X				X									
Tumor Measurements[7]	X[8]					X				X				X	

[1] Visit Window for each visit subsequent to V1/Baseline will be calculated from baseline visit (day 0).

[2] 30 days are allowed to complete all screening procedures, **WITH THE EXCEPTION OF TUMOR MEASUREMENTS WHICH MUST BE DONE WITHIN 28 DAYS OF BASELINE VISIT.**

[3a] Subjects will be randomized to arms 1 or 2 and will follow the corresponding treatment plan.
[3b] Weight and BMI are to be collected pre-infusion at the infusion visits.
[4] Order of assessments and procedures is: radiology, patient reported assessments (with the exception of post-infusion symptom questionnaires), investigator assessments, safety and laboratory assessments, administration of study drug and administration of chemotherapy. All must be completed prior to the administration of the treatment regimen. *Vitals, Blood Draws and collection of safety information will vary based on visit, please refer to study procedures section.*
[5] Concomitant medications within 30 days before screening until 14 days after the last administration of the study drug must be recorded for the purpose of drug-drug and drug-disease interaction evaluation and signal detection.
[6] Vital signs and AEs/SAEs also will be collected 30 minutes (+/- 10 minutes) post-infusion of XB2001/placebo. Subjects participating in OLE who received placebo while on study will have vital signs and AEs/SAEs collected 30 minutes (+/- 10 minutes) post-infusion for 1st 3 infusions.
[7] Tumor measurements will be performed at screening and at week 8, 16, and 24. Assessments can include CT or MRI, and the same modality that is chosen for the initial tumor assessment must be used for the duration of the study. The choice of modality should be based primarily on the type of scan that the patient has previously received as their standard of care. For study visits requiring radiology (DEXA, CT or MRI)-All radiology can be completed within 72 hours prior to the visit and must be completed prior to all other assessments for that visit.
[8] Imaging required for tumor measurements during screening must be done within 28 days of baseline visit. All other required imaging can be completed within 72 hours prior to the applicable visit.
[9] Vital signs to be collected: Temperature, blood pressure, heart rate and respiratory rate.
[10] Samples must be collected 30 minutes (+/- 10 minutes) post-infusion of XB2001/Placebo but prior to administration of chemotherapy on visit 1 as well as Day 4 (+/-1 day) and Day 7 (+/- 1 day).
[11] Samples must be collected prior to infusion of XB2001/Placebo .
[12]Completion of cycle 12. All subjects are eligible to participate in an open-label crossover phase and receive XB2001 along with ONIVYDE + 5-FU + LV as long as they are deemed to be benefitting from therapy and want to continue XB2001 treatment.
[13] Symptom questionnaire will be given pre and post-infusion at Visit 1 **ONLY**. Questionnaire will be given 24 hourspost 5-FU injection.
[14] Any additional ECGs will only be conducted if they are required as standard of care.
[15] Missed samples will not result in a protocol deviation.

6.3.1 Unscheduled and Early Termination Visits

Study Procedure	Unscheduled Visit[2] (if applicable)	Early Termination (if applicable)
Treatment:[3]		
Con Meds/Treatments	X	X
Efficacy:[1]		
EORTC-QLQ-C30	X	X
Safety:[1]		
Vital Signs	X	X
Physical Examination	X	X
AEs/SAEs	X	X
Laboratory Testing:[1]		
Safety Labs	X	X
CRP-ESR Labs	X	X
Urinalysis	X	X
Pregnancy Test (WOCBP only)	Urine/Serum	Serum
PK/PD/ADA:[1]		
PK/PD and ADA/PD (serum/plasma)	X	X
[1] Assessments/procedures should be conducted in the following order: patient assessments, investigator assessments, safety and laboratory assignments.		
[2] During an unscheduled visit, any of the study procedures noted may be performed, but not all are required.		
[3] Concomitant medications within 30 days before screening until 7 days after the last administration of the study drug must be recorded for the purpose of drug-drug and drug-disease interaction evaluation and signal detection.		

6.4 DISCONTINUATION OF THERAPY

If a patient is discontinued from study, the reason for discontinuation/withdrawal must be clearly documented in the source documentation and the EDC. Every effort should be made by the investigative site to have subjects who discontinue early from study complete all assessments included in the Early Termination visit included in the study calendar provided in section 6. All subjects will be unblinded after clinical database lock.

Study therapy MUST immediately be discontinued for any the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason).
- Any clinical adverse event, laboratory abnormality, inter-current illness, or clinical progression of disease which, in the opinion of the Principal Investigator, indicates that continued participation in the study is not in the best interest of the subject.
- ONIVYDE + Leucovorin + 5-Fluorouracil chemotherapy treatment is discontinued.
- Pregnancy. Subject may be able to continue on study if pregnancy is terminated and PI approved continuation in study.
- Termination of the study by the sponsor.
- Imprisonment or the compulsory detention for medical treatment.
- Initiating treatment with prohibited therapies (see section 2.8.2).
- Death of the subject.

6.5 TRIAL STOPPING RULES

Sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted to investigators/ institutions and the regulatory authority(ies) in advance of the intended termination or suspension. The IRB/EC will also be promptly informed and provided with the reason(s) for the termination or suspension by the Sponsor or by the Investigator or/institution, as specified by the applicable regulatory requirement(s). The investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to Sponsor 30 days in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If Sponsor terminates the study for safety reasons, Sponsor will immediately notify the investigator by phone and subsequently provide written instructions for study termination.

6.6 EMERGENCY UNBLINDING

Subjects and investigators will be unblinded to their treatment allocation after database lock. In the event of an emergency that would require the investigator to be aware of the treatment allocation prior to the end of the trial, the investigator can obtain this information, on a per subject basis, after consultation with the Sponsor's Medical Monitor, if possible. Every effort should be made to consult with the Medical Monitor prior to emergency unblinding. Events that qualify for emergency unblinding are as follows:

- A grade 3 or greater AE which are "probably or definitely" related to study drug AND only if **treatment assignment information is deemed essential for the management of the event**. This type of reaction would require that the patient receive no further doses and is followed until the resolution of the toxicity.
- Any suspected, unexpected, serious adverse reaction (SUSAR) AND only if **treatment assignment information is deemed essential for the management of the event**.
- Pregnancy. Subject may be able to continue on study if pregnancy is terminated and PI approves continuation in study.

7. CORRELATIVE STUDIES

7.1 PHARMACOKINETICS (PK)/ ANTI-DRUG ANTIBODY (ADA)/ PHARMACODYNAMICS (PD)/ BIOMARKER SAMPLE COLLECTION

Patient blood will be drawn into blood collection tubes at each collection time point per the study protocol for PK/ADA/PD & potential biomarker analysis. These samples will be processed by the collection lab if needed per the study laboratory flowchart. The whole blood or the obtained plasma/serum will be sent to XBiotech for analysis. Missing PK/ADA/PD samples will not result in a protocol deviation.

An enzyme-linked immunosorbent assay (ELISA) has been developed to specifically measure XB2001 levels (PK) in human plasma. The presence of treatment-emergent antibodies against XB2001 (ADA) will also be evaluated. Additionally, samples will be assessed for pharmacodynamic and biomarker analysis.

8. ASSESSMENT OF SAFETY

Safety will be assessed by monitoring adverse events, vital signs, and clinical laboratory measurements. Adverse events will be monitored from visit 1 (week 0) (post-infusion) through visit 13 (week 24). Any serious adverse events whether related or not to study drug will be followed up until resolution, which typically includes improvement of the severity (eg: grade 3 to 2), resolved with sequalae or death.

Subjects who come off trial for any reason after being randomized in the study will be contacted (unless the subject withdrew consent) at regular intervals (4-6 weeks) by phone to check the resolution status of the SAEs or determine date of death. Once the trial has been completed, any subjects who have been lost to follow up will be queried against any applicable national databases to determine date of death.

Study drug, XB2001, will be administered under close observation in a facility equipped to handle anaphylaxis or infusion site reactions. Vital signs and AE assessments will be done at 30 minutes (+/- 10 minutes) post-infusion for visits 1, 2 and 3.

Any grade 3 or greater adverse event or infusion site reaction must be reported to the sponsor within 24 hours of learning of the event.

9. STUDY VARIABLES

9.1 DEMOGRAPHIC AND DISEASE CHARACTERISTICS

Demographic characteristics will include standard demography (age, sex, race, height, weight, and BMI) medical history and medication history for each subject. Characteristics of the subjects with pancreatic cancer, including AEs, SAEs, duration of hospitalization(s), tumor measurements, survival assessments, quality of life as measured by EORTC QLQ-C30, and change in Lean Body Mass, will be assessed. Baseline is defined as the visit 1 (week 0), pre-infusion assessments.

10. ADVERSE EVENTS

10.1 DEFINITION OF ADVERSE EVENT (AE)

An adverse event is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including laboratory findings), symptom, or disease temporally associated with the use of XB2001, whether or not it is apparently related to XB2001;
- A concurrent illness;
- An exacerbation, or an unexpected increase in frequency or intensity of a preexisting condition, including intermittent or episodic conditions;
- A significant or unexpected worsening of the condition/indication under investigation;
- A suspected interaction between the investigational drug and concomitant medications;
- An abnormal laboratory finding (including radiological interpretations, histopathological findings, etc.).

10.2 DEFINITION OF SERIOUS ADVERSE EVENT (SAE)

An adverse event is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening adverse event;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Congenital anomaly/birth defect;
- An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring

intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Note that seriousness and severity should not be confused. A subject could experience a severe headache that would not qualify as an SAE, while another might experience a mild stroke that, while not severe, would be considered serious.

10.3 RECORDING OF ADVERSE EVENTS

All untoward events occurring between visit 1 (week 0) (post-infusion) and the end of study (or if subject terminates from study early, two weeks after the last infusion of the treatment regimen) should be recorded on the eCRF, regardless of whether they are considered related to study drug.

All AEs should be recorded in a standard medical terminology as concisely as possible. The AE recorded should not be a procedure or a clinical/laboratory measurement but should reflect the event leading to the procedure or the cause of the clinical/laboratory abnormality, if known. Whenever possible, AEs should be evaluated and recorded as a diagnosis, rather than individual signs and symptoms. However, if a definitive diagnosis is not possible, the individual signs and symptoms should be recorded. Any AE that worsens in intensity, or becomes serious, should be recorded as a new event.

10.4 EVALUATING ADVERSE EVENTS

All AEs will be graded according to the CTCAE version 5.0.

10.5 ASSESSMENT OF CAUSALITY

Investigators are required to assess the relationship, if any, of each AE or SAE to the investigational drug using clinical judgment to determine the degree of certainty with which an AE can be attributed to the investigational drug. Alternative causes, such as natural history of the underlying disease, other risk factors, and the temporal relationship of the event to the administration of the study medication must be considered.

Relationship to study drug is summarized as follows:

- **Not Related:** There is another obvious cause of the AE
- **Unlikely to be related:** There is another more likely cause of the AE

- **Possibly related:** The AE could have been due to the investigational drug
- **Probably related:** The AE is probably attributable to the investigational drug
- **Definitely related:** The AE is most likely attributable to the investigational drug

10.6 REPORTING REQUIREMENTS

Any grade 3 or greater adverse event and injection site reaction must be reported to the sponsor within 24 hours of learning of the event.

All serious adverse events (SAEs) should be reported to the Sponsor on the initial SAE report forms within 24 hours of knowledge of the event. These immediate reports should be followed promptly by detailed, written reports (follow-up SAE reports). The subject should be followed up with until stabilization of the reported SAE, either with full satisfactory resolution or resolution with sequelae, or until death of the subject. Before declaring the subject is lost to follow-up, three unsuccessful attempts at contact should be made and recorded on the SAE form. The immediate and follow-up reports should identify subjects by unique code numbers (generated by the safety database) assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The Investigator should also submit SAEs to the IRB/EC according to their IRB/EC guidelines [ICH-GCP E6]. Drug-related Serious Adverse Events will be reported to the FDA by XBiotech's Medical Safety Officer according to 21 CFR 312.32.

10.7 REFERENCE SAFETY INFORMATION: POTENTIAL ADVERSE REACTIONS

10.7.1 XB2001

More than 1,100 subjects have been treated using a previous anti-IL-1α antibody in subjects with advanced solid tumors, advanced hematologic malignancies, metastatic colorectal cancer, peripheral vascular disease, type II diabetes, acne vulgaris, plaque psoriasis, pyoderma gangrenosum, atopic dermatitis and hidradenitis suppurativa. Over 2,000 doses (N=309) of previous anti-IL-1α antibody were administered at 7.5 mg/kg to refractory, metastatic CRC subjects with cancer associated symptoms at baseline (ECOG performance status 1 and 2). In this study, the most common AEs reported (>10%) were abdominal pain, peripheral edema, fatigue, anemia, constipation, decrease in weight, asthenia, decreased appetite, and nausea. The majority of these events were grade 1 or 2 and appeared to be related to the underlying CRC. The prevalence of these events was similar in the treatment and placebo groups. Two infusion reactions were reported in this trial, and they were not serious or severe (grade I or II).

XB2001 is a recombinant human IgG4 monoclonal antibody specific for human interleukin-1α (IL-1α). As such, it is an immunomodulator that has anti-inflammatory and anti-neoplastic properties. Other agents that could be considered in the same pharmacologic class include biologic agents that target IL-1 receptor antagonist and IL-1β. Potential risks for agents in this class include infusion or injection site reactions and risk of infection.

XB2001 is considered to be a True Human monoclonal antibody. Unlike previous generations of humanized or fully human antibodies, the entire XB2001 heavy and light chain sequences are identical to those found in naturally-occurring human IgG4κ, with the light and heavy chain variable regions being identical to those originally expressed by a peripheral blood B lymphocyte that was obtained from a healthy individual. No *in vitro* affinity maturation or modifications have been made to improve its natural binding affinity (~60 pM). We believe that a true human antibody should be effectively non-immunogenic in humans and thus exhibit optimal activity and pharmacokinetics.

The mechanism behind infusion reactions is not clear in all cases. It may involve a reaction against the antibody products themselves, or, against some minor residual component from the manufacturing process (i.e. host cell proteins). To date, after administration to over 800 subjects, and over 5,000 doses across all trials, the risk of infusion reaction remains extremely low. In order to mitigate this class-specific risk, monitoring is encouraged for at least 1 hour after the end of the initial XB2001 infusion. Availability of resuscitation equipment must be ensured. Pre-medication with antihistamines or corticosteroids is not required.

For the purposes of expedited safety reporting in clinical trials, the following should be considered expected events:

- Infusion Related Reactions
- Injection Site Reactions

10.7.2 ONIVYDE

Severe Neutropenia

ONIVYDE can cause severe or life-threatening neutropenia and fatal neutropenic sepsis. In a clinical study, the incidence of fatal neutropenic sepsis was 0.8% among subjects receiving ONIVYDE, occurring

in one of 117 subjects in the ONIVYDE plus fluorouracil/leucovorin (ONIVYDE/5-FU/LV) arm and one of 147 subjects receiving ONIVYDE as a single agent. Severe or life-threatening neutropenia occurred in 20% of subjects receiving ONIVYDE/5-FU/LV compared to 2% of subjects receiving fluorouracil/leucovorin alone (5-FU/LV). Grade 3 or 4 neutropenic fever/neutropenic sepsis occurred in 3% of subjects receiving ONIVYDE/5-FU/LV, and did not occur in subjects receiving 5-FU/LV.

In subjects receiving ONIVYDE/5-FU/LV, the incidence of Grade 3 or 4 neutropenia was higher among Asian subjects [18 of 33 (55%)] compared to White subjects [13 of 73 (18%)]. Neutropenic fever/neutropenic sepsis was reported in 6% of Asian subjects compared to 1% of White subjects.

Monitor complete blood cell counts on Days 1 and 8 of every cycle and more frequently if clinically indicated. Withhold ONIVYDE if the absolute neutrophil count (ANC) is below 1500/mm3 or if neutropenic fever occurs. Resume ONIVYDE when the ANC is 1500/mm3 or above. Reduce ONIVYDE dose for Grade 3-4 neutropenia or neutropenic fever following recovery in subsequent cycles.

Severe Diarrhea

ONIVYDE can cause severe and life-threatening diarrhea. Do not administer ONIVYDE to subjects with bowel obstruction.

Severe or life-threatening diarrhea followed one of two patterns: late onset diarrhea (onset more than 24 hours following chemotherapy) and early onset diarrhea (onset within 24 hours of chemotherapy, sometimes occurring with other symptoms of cholinergic reaction). An individual patient may experience both early and late-onset diarrhea.

In a clinical study, Grade 3 or 4 diarrhea occurred in 13% receiving ONIVYDE/5-FU/LV compared to 4% receiving 5-FU/LV. The incidence of Grade 3 or 4 late onset diarrhea was 9% in subjects receiving ONIVYDE/5-FU/LV, compared to 4% in subjects receiving 5-FU/LV. The incidence of Grade 3 or 4 early onset diarrhea was 3% in subjects receiving ONIVYDE/5-FU/LV, compared to no Grade 3 or 4 early onset diarrhea in subjects receiving 5-FU/LV. Of subjects receiving ONIVYDE/5-FU/LV in Study 1, 34% received loperamide for late-onset diarrhea and 26% received atropine for early-onset diarrhea. Withhold ONIVYDE for Grade 2-4 diarrhea. Initiate loperamide for late onset diarrhea of any severity. Administer intravenous or subcutaneous atropine 0.25 to 1 mg (unless clinically contraindicated) for early onset diarrhea of any severity. Following recovery to Grade 1 diarrhea, resume ONIVYDE at a reduced dose *[see section 2.5.2]*.

Interstitial Lung Disease

Irinotecan HCl can cause severe and fatal interstitial lung disease (ILD). Withhold ONIVYDE in subjects with new or progressive dyspnea, cough, and fever, pending diagnostic evaluation. Discontinue ONIVYDE in subjects with a confirmed diagnosis of ILD.

Severe Hypersensitivity Reaction

Irinotecan HCl can cause severe hypersensitivity reactions, including anaphylactic reactions. Permanently discontinue ONIVYDE in subjects who experience a severe hypersensitivity reaction.

Embryo-Fetal Toxicity

Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE, ONIVYDE can cause fetal harm when administered to a pregnant woman. Embryotoxicity and teratogenicity were observed following treatment with irinotecan HCl, at doses resulting in irinotecan exposures lower than those achieved with ONIVYDE 70 mg/m2 in humans, administered to pregnant rats and rabbits during organogenesis. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ONIVYDE and for one month following the final dose.

10.7.3 Fluorouracil

Increased Risk of Serious or Fatal Adverse Reactions in Subjects with Low or Absent Dipyrimidine Dehydrogenase (DPD) Activity

Based on postmarketing reports, subjects with certain homozygous or certain compound heterozygous mutations in the DPD gene that result in complete or near complete absence of DPD activity are at increased risk for acute early-onset of toxicity and severe, life-threatening, or fatal adverse reactions caused by fluorouracil (e.g., mucositis, diarrhea, neutropenia, and neurotoxicity). Subjects with partial DPD activity may also have increased risk of severe, life-threatening, or fatal adverse reactions caused by fluorouracil.

Withhold or permanently discontinue fluorouracil based on clinical assessment of the onset, duration and severity of the observed toxicities in subjects with evidence of acute early-onset or unusually severe toxicity, which may indicate near complete or total absence of DPD activity. No fluorouracil dose has been proven safe for subjects with complete absence of DPD activity. There is insufficient data to recommend a specific dose in subjects with partial DPD activity as measured by any specific test.

Cardiotoxicity

Fluorouracil can cause cardiotoxicity, including angina, myocardial infarction/ischemia, arrhythmia, and

heart failure, based on postmarketing reports. Reported risk factors for cardiotoxicity are administration by continuous infusion rather than intravenous bolus and presence of coronary artery disease. Withhold fluorouracil for cardiotoxicity. The risks of resumption of fluorouracil in subjects with cardiotoxicity that has resolved have not been established.

Hyperammonemic Encephalopathy

Fluorouracil can cause hyperammonemic encephalopathy in the absence of liver disease or other identifiable cause, based on postmarketing reports. Signs or symptoms of hyperammonemic encephalopathy began within 72 hours after initiation of fluorouracil infusion; these included altered mental status, confusion, disorientation, coma, or ataxia, in the presence of concomitant elevated serum ammonia level. Withhold fluorouracil for hyperammonemic encephalopathy and initiate ammonia-lowering therapy. The risks of resumption of fluorouracil in subjects with hyperammonemic encephalopathy that has resolved have not been established.

Neurologic Toxicity

Fluorouracil can cause neurologic toxicity, including acute cerebellar syndrome and other neurologic events, based on postmarketing reports. Neurologic symptoms included confusion, disorientation, ataxia, or visual disturbances. Withhold fluorouracil for neurologic toxicity. There are insufficient data on the risks of resumption of fluorouracil in subjects with neurologic toxicity that has resolved.

Diarrhea

Fluorouracil can cause severe diarrhea. Withhold fluorouracil for Grade 3 or 4 diarrhea until resolved or decreased in intensity to Grade 1, then resume fluorouracil at a reduced dose. Administer fluids, electrolyte replacement, or antidiarrheal treatments as necessary.

Palmar-Plantar Erythrodysesthesia (Hand-Foot Syndrome)

Fluorouracil can cause palmar-plantar erythrodysesthesia, also known as hand-foot syndrome (HFS). Symptoms of HFS include a tingling sensation, pain, swelling, and erythema with tenderness, and desquamation. HFS occurs more commonly when fluorouracil is administered as a continuous infusion than when fluorouracil is administered as a bolus injection and has been reported to occur more frequently in subjects with previous exposure to chemotherapy. HFS is generally observed after 8-9 weeks of fluorouracil administration but may occur earlier. Institute supportive measures for symptomatic relief of

HFS. Withhold fluorouracil administration for Grade 2 or 3 HFS; resume fluorouracil at a reduced dose when HFS is completely resolved or decreased in severity to Grade 1.

Myelosuppression

Fluorouracil can cause severe and fatal myelosuppression which may include neutropenia, thrombocytopenia, and anemia. The nadir in neutrophil counts commonly occurs between 9 and 14 days after fluorouracil administration. Obtain complete blood counts prior to each treatment cycle, weekly if administered on a weekly or similar schedule, and as needed. Withhold fluorouracil until Grade 4 myelosuppression resolves; resume fluorouracil at a reduced dose when myelosuppression has resolved or improved to Grade 1 in severity.

Mucositis

Mucositis, stomatitis or esophagopharyngitis, which may lead to mucosal sloughing or ulceration, can occur with fluorouracil. The incidence is reported to be higher with administration of fluorouracil by intravenous bolus compared with administration by continuous infusion. Withhold fluorouracil administration for Grade 3 or 4 mucositis; resume fluorouracil at a reduced dose once mucositis has resolved or decreased in severity to Grade 1.

Increased Risk of Elevated International Normalized Ratio (INR) with Warfarin

Clinically significant elevations in coagulation parameters have been reported during concomitant use of warfarin and fluorouracil. Closely monitor subjects receiving concomitant coumarin-derivative anticoagulants such as warfarin for INR or prothrombin time in order to adjust the anticoagulant dose accordingly.

Embryofetal Toxicity

Based on its mechanism of action, fluorouracil can cause fetal harm when administered to a pregnant woman. In animal studies, administration of fluorouracil at doses lower than a human dose of 12 mg/kg caused teratogenicity. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during and for 3 months following cessation of therapy with fluorouracil.

11. STATISTICAL PLAN

11.1 DETERMINATION OF SAMPLE SIZE

The study will enroll approximately 30 subjects each in treatment and placebo arms. The sample size will provide an opportunity to observe reasonably strong trends in clinical endpoints and will provide 80% power to observe a statistically significant pharmacodynamic effect for XB2001 activity[25] (reduction in [CD14+CD16+IL-1α+] triple positive tumor associated monocytes).[26]

11.2 RANDOMIZATION

A centralized block randomization schedule with a 1:1 allocation ratio will be utilized using an electronic randomization system. Subjects will be randomly assigned to Arms 1 or 2. The randomization schedule will not be stratified by any factors.

11.3 ANALYSIS SETS

- The safety analysis set (SAF) population will consist of all subjects who receive at least one dose of study medication and will be analyzed as treated. The SAF population will be the primary analysis population for all safety analyses.
- The modified intent-to-treat (mITT) population will consist of all randomized and treated subjects and will be analyzed as randomized. The mITT population will be the primary analysis population for all efficacy analyses.

11.4 PATIENT DISPOSITION

A listing of all subjects prematurely discontinued from the study, along with reasons for discontinuation will be provided. In addition, the total number of subjects for each of the following categories will be summarized.

- The total number of screened subjects: met the inclusion criteria regarding the target indication and signed the informed consent
- The total number of subjects in each analysis set (SAF, and mITT populations)

- The total number of subjects who complete the study and discontinued the study, and the reasons for discontinuation

11.5 STATISTICAL METHODS

Continuous data will be summarized for each treatment group using the number of observations available (N), means, standard deviation (SD), minimums, medians, and maximums. Categorical data will be summarized for each treatment group using counts and percentages. Confidence intervals (CIs) will be provided as appropriate. All statistical tests will be two-sided unless otherwise noted. Full details of all analyses will be provided in the statistical analysis plan (SAP).

11.5.1 Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group.

11.5.2 Safety Analysis

The primary objective of this study is to evaluate the safety and tolerability of XB2001. Safety endpoints will be evaluated by monitoring adverse events from clinical and laboratory reporting. The safety analysis will be based on the SAF population. A summary of safety results will be presented for each treatment group.

11.5.2.1 Analysis of Adverse Events

- Adverse events reported in this study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary (version 24.0 or newer). Coding will be to lowest level terms. The verbatim text, the PT, and the primary SOC will be listed in patient listings.
- Pre-treatment AEs are defined as those that develop or worsen in severity from the time the patient provides informed consent, prior to the first dose of study drug. Treatment emergent AEs (TEAEs) are defined as AEs that develop or worsen in severity following the first dose of study drug through the last study visit.
- TEAEs will be grouped by MedDRA System Organ Class (SOC) and Preferred Term (PT) within SOC and will be presented for each treatment group. The number and percentage of subjects experiencing AEs and TEAEs will be summarized by seriousness (SAEs, including the total number of SAEs), severity (grades 1-5), and

relationship. The number of subjects with grade 3 or 4 diarrhea TEAEs will also be summarized.

11.5.2.2 Other Safety

- Vital Signs
    - Vital sign parameters (Temperature, blood pressure, heart rate and respiratory rate) will be summarized descriptively by treatment group using actual values and change from baseline values.
- Laboratory Tests
    - Clinical laboratory values will be converted to standard international units. Clinical laboratory (as described in the treatment plan) data will be listed for each subject. Laboratory data will be summarized descriptively by treatment group using actual values and change from baseline values. A listing will be provided for subjects with grade 2 or greater laboratory AEs.
- Hospitalizations
    - The number of hospitalizations and the duration of hospitalizations (days) will be summarized by treatment group.

11.5.3 Efficacy Analysis

In addition to the analyses that will be performed following the formal database lock at the end of the study, an additional database lock may be performed at Week 8, and interim analyses utilizing unblinded efficacy data available as the study progresses, may also be conducted to help plan potential future development activities. If interim analyses are performed, an internal interim analysis committee (IAC) will be established to review the interim data and formulate recommended decisions/actions. The IAC will consist of at least a clinician and a statistician (neither of whom are involved in study conduct or compound development), one of whom will chair the committee, and may also include other members as required by the nature of the IAs. Details will be provided in a separate IAC charter, which will define the organization and roles and responsibilities of the committee, possible recommendations or requests, and the communication process following IA reviews. Results from the Week 8 DBL and/or interim analyses will not be disseminated to investigators or subjects participating in the study. In addition, results of the interim analyses will not be disseminated to individuals associated with the conduct of the study. Full details on the analyses will be provided in the SAP.

Overall Survival (OS)

- OS will be defined as the duration from the date of randomization until death. Subjects who are alive at the analysis time point the will be censored, and survival time will be defined as time from randomization to the censoring date. Subjects, who are lost to follow-up or discontinued, will be censored at the time of last contact.
- OS will be summarized using Kaplan-Meier methods and the two treatment groups will be compared using an unadjusted log-rank test. Stratified log-rank tests or Cox proportional hazards regression models may also be performed. Kaplan-Meier curves will be produced.

Progression Free Survival (PFS)

- PFS will be defined as time from randomization to disease progression (see section 5.4) or death. Subjects surviving without disease progression at the end of study will be censored. Subjects, who are lost to follow-up or discontinued, will be censored at the time of last contact.
- PFS will be summarized using Kaplan-Meier methods and the two treatment groups will be compared using an unadjusted log-rank test. Stratified log-rank tests or Cox proportional hazards regression models may also be performed. Kaplan-Meier curves will be produced.

Objective Response Rate (ORR)

- The ORR will be estimated by dividing the total number of confirmed complete response (CR) and partial response (PR) by the total number of subjects in the mITT population.
- Exact 95% confidence intervals for the response rate in each treatment arm will be calculated. Best overall response (BOR), determined from the sequence of cycle responses assessed, will be used for analysis purposes. Response rates will be compared between treatment groups using a Pearson Chi-square test and Wald 95% CI will be reported. Analyses will be performed at week 8, 16, and 24.

Time to Treatment Failure (TTF)

- TTF will be defined as time from randomization to treatment failure. Subjects without treatment failure at the end of study will be censored. Subjects, who are lost to follow-up or discontinued, will be censored at the time of last contact.

- TTF will be summarized using Kaplan-Meier methods and the two treatment groups will be compared using an unadjusted log-rank test. Stratified log-rank tests or Cox proportional hazards regression models may also be performed. Kaplan-Meier curves will be produced.

Clinical Benefit Response (CBR)

- The CBR response (yes or no) will be defined as a composite measure consisting of change in lean body mass (LBM) and change in quality of life from baseline to week 8. The CBR will be defined as a stabilization or positive (≥ 0 kg) change in lean body mass (LBM)—as assessed by dual-energy X-ray absorptiometry (DEXA) scan, and improvement or no worsening (≥ 0 score point change) on any two of the three symptom scale measures (fatigue, pain, appetite) of EORTC QLQ-C30. The number and percentage of subjects with CBR will be provided at week 8. Subjects missing the follow-up assessments will be considered non-responders.
- Exact 95% confidence intervals for the response rate in each treatment group will be calculated. Response rates will be compared between treatment groups using a Pearson Chi-square test and Wald 95% CI will be reported.

EORTC QLQ-C30

- The EORTC survey results will be converted to domain specific scores using the prescribed algorithm. Subjects showing stabilization or improvement from baseline (≤ 0 change) on any two of the three symptom scales (pain, fatigue, appetite) will be considered responders. Subjects experiencing a reduction or worsening, or have data missing at a visit, will be defined as non-responders.
- Exact 95% confidence intervals for the response rate in each treatment group will be calculated. Responder rates will be compared at week 8, 16 and 24 using Pearson Chi-square tests.

Absolute change for each domain specific score will be summarized descriptively and will be compared between the treatment groups using a mixed model for repeated measures (MMRM) (SAS MIXED procedure) with treatment group.

11.5.4 Pharmacokinetics (PK), Pharmacodynamics (PD) and Clinical Correlate Analysis

Descriptive statistics of PK and PD concentrations and parameters will be presented as well as CD14+CD16+IL-1α+ levels.

11.5.5 Treatment Exposure

The number and percentage of subjects exposed to study drug along with duration of exposure will be summarized descriptively by treatment group.

12. STUDY MANAGEMENT AND ADMINISTRATION

12.1 ETHICAL CONDUCT OF STUDY (GCP)

The guidelines of the World Medical Association Declaration of Helsinki in its revised edition (64th WMA General Assembly, Fortaleza, Brazil, October 2013), the guidelines of ICH GCP E6 (R2), as well as the demands of national drug and data protection laws and other applicable regulatory requirements, will be strictly followed. Approval will be obtained from the appropriate regulatory authorities before sites are initiated.

12.2 IRB AND EC APPROVAL

Prior to initiation of the study, the protocol, the informed consent form, the subject information sheet(s), details of the subject recruitment procedures and any other relevant study documentation will be submitted to the responsible IRB or Ethics Committee (EC). The Investigator will report promptly to the IRB/EC any new information that may adversely affect the safety of subjects or the conduct of the study. Similarly, the Investigator will submit written summaries of the study status to the IRB/EC annually, or more frequently if requested by the IRB/EC. Upon completion of the study, the Investigator will provide the IRB/EC with a brief report of the outcome of the study, if required.

12.3 PROTOCOL MODIFICATIONS

Modifications of the signed protocol are only possible by approved protocol amendments and with the agreement of all responsible persons. The procedure for approval of a protocol amendment is identical to that for approval of the protocol. The IRB/EC must be informed of all protocol amendments and should be asked for its opinion as to whether a full re-evaluation of the ethical aspects of the study is necessary by the committee. This should be fully documented. The Investigator must not implement any deviation from or change to the protocol, without discussion with an agreement by the study Sponsor and prior review and documented approval/favorable opinion of the amendment from the relevant IRB/EC, except where it is necessary to eliminate an immediate hazard to study subjects, or where the change(s) involves only

logistical or administrative aspects of the study (e.g., change in CRA(s), change of telephone number(s)). Protocol amendments will be submitted to the appropriate authority(ies) as required by the applicable regulatory requirement(s).

12.4 SUBJECT INFORMATION AND CONSENT

The Investigator is responsible for ensuring that no subject will receive any study-related examination or activity before that subject has given an IRB/EC approved informed consent. The subject must give written consent after the receipt of detailed information. The verbal explanation will cover all the elements specified in the written information provided for the subject. The Investigator will inform the subject of the aims, methods, anticipated benefits and potential hazards of the study, including any discomfort it may entail. The subject must be given every opportunity to clarify any points he/she does not understand and if necessary, ask for more information. At the end of the interview, the subject may be given time to reflect if this is required, or if the subject requests more time. Subjects and/or legal guardian forms will be kept and archived by the Investigator in the Investigator's study file. It should be emphasized that the subject is at liberty to withdraw their consent to participate at any time, without penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give, or withdraw, written informed consent may not be included or continued in this study, but this will not impact their subsequent care. The Investigator will notify in writing each subject's primary care physician (or equivalent) of the subject's intent to participate in the study.

12.5 DATA PROTECTION AND CONFIDENTIALITY

By signing the final protocol, every participating Investigator agrees to keep all information and results concerning the study and the investigational product confidential. The confidentiality obligation applies to all personnel involved at the investigational site. The Investigator must ensure that each participant's anonymity will be maintained in accordance with applicable laws. On eCRFs or other documents submitted to the Sponsor, subjects should not be identified by their name, but by subject ID number. The Investigator should keep a separate log of ID numbers, names and addresses. Documents that contain the names associated with these ID numbers (e.g., written consent/assent forms), are not for submission to the Sponsor and should be maintained by the Investigator in strict confidence except to the extent necessary to allow auditing by regulatory authorities, auditing or monitoring by the Institutional Review Board/EC, the Sponsor personnel or their affiliates and designees (such as CRAs).

Copies of radiological scans and autopsy reports (and other documents), if applicable, that may be requested by the Sponsor should be de-identified. The Investigator shall obtain all such permissions and authorizations as may be necessary or desirable to allow the collection and use of information protected under federal privacy laws and state privacy laws, including permission/authorization for monitoring and analysis (including re-analysis in combination with results of other studies), for regulatory submission purposes and for applicable reporting (if any) required to be made by Sponsor, its affiliates and their designee.

12.6 STUDY REPORT AND PUBLICATIONS

A final integrated clinical/statistical report will be prepared that is compliant with the ICH Harmonized Tripartite Guideline: Structure and Content of Clinical Study Reports (E3). The results of this study will be published and/or presented at scientific meetings in a timely manner. The publication policy is described in the contract between the Sponsor and Investigator.

12.7 STUDY FILES AND RETENTION OF RECORDS

Copies of all study documents should be retained by the Investigator until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product, in accordance with 21 CFR 312.62. These documents should be retained for a longer period however, if required by regulatory requirements or by agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained. The final database will be archived according to the regulatory requirements.

12.8 CASE REPORT FORMS

Data for this protocol will be captured electronically in an Electronic Data Capture (EDC) system. Designated study personnel will be provided unique usernames and passwords. Each study personnel will have specific access within the electronic data collection system based on their role. The EDC system contains an audit trail associated with each individual's unique password that will document date and time of data entry and revisions. All protocol-specified data is to be entered into the EDC system in a timely manner for review and audit by XBiotech. All data is to be entered such that it will allow accurate interpretation and tabulation. It is the Investigator's responsibility to ensure that all discontinued orders or

changes in study or other medications entered into the database correspond to entries in the subject's medical records (i.e. source documents) and to acknowledge accurate completion of the eCRF.

12.9 DRUG ACCOUNTABILITY

IMP accountability and chain of custody logs at every site for each randomized subject (per visit) must be kept current and should contain the following information:

- Subject identification number
- PI name and site information
- Study protocol details
- IMP preparation, unit type, date(s) and time(s) of administration
- Quantity of used and unused IMP with lot number(s) and/or with unique identifiers
- IMP disposition related to subject treatment
- IMP destroyed per site's destruction process
- IMP returned/prepared for return to sponsor/depot

The Investigator (or pharmacist, as appropriate) must maintain records of the delivery of the study medication to the study site, the inventory at the site, the usage for each subject, and destruction. The inventory must be available for monitoring, auditing or inspection.

12.10 INSPECTIONS

Investigator sites, the study database and study documentation may be subject to quality assurance audits during the course of the study either by the Sponsor or their appointed representatives. In addition, regulatory bodies at their discretion may conduct inspections. The Investigator shall permit the authorized Sponsor, agents of the Sponsor, and regulatory agency employees to enter and inspect any site where the drug or records pertaining to the drug are held, and to inspect all records relating to an investigation, including subject records. The Sponsor will not, however, copy any source data from the patient's dossier. Completed eCRFs must be made available by the Investigator for review by the Sponsor, agents of the Sponsor, the CRA and the regulatory agencies. To ensure the accuracy of data submitted, it is mandatory that representatives of the Sponsor and of the regulatory agencies have direct access to source documents (e.g., subject medical records, charts, laboratory reports, etc.). Subject confidentiality will be protected at

all times.

12.11 ACCESS TO INFORMATION FOR MONITORING

CRAs will establish and maintain regular contact between the Investigator and the Sponsor. CRAs will evaluate the competence the study center, informing the Sponsor about any problems relating to facilities, technical equipment or medical staff. During the study, CRAs will check that written informed consent has been obtained from all subjects correctly and that data are recorded correctly and completely. CRAs are also entitled to compare entries in eCRFs with corresponding source data and to inform the Investigator of any errors or omissions. CRAs will also monitor adherence to the protocol at the Investigator site. They will arrange for the supply of investigational product and ensure appropriate storage conditions are maintained. The CRA will make written reports to the Sponsor on each occasion when contact with the Investigator is made, regardless of whether it is by phone or in person. During monitoring visits, entries in the eCRFs will be compared with the original source documents. The Investigator must agree to meet with the CRA at regular intervals and to cooperate in resolving any queries or findings made during the monitoring process.

REFERENCES

[1] Coleman KM, Gudjonsson JE, Stecher M. Open-Label Trial of MABp1, a True Human Monoclonal Antibody Targeting Interleukin 1α, for the Treatment of Psoriasis. JAMA Dermatol. 2015 May;151(5):555-6. doi: 10.1001/jamadermatol.2014.5391.

[2] Carrasco D, Stecher M, Lefebvre GC, Logan AC, Moy R. An Open Label, Phase 2 Study of MABp1 Monotherapy for the Treatment of Acne Vulgaris and Psychiatric Comorbidity. J Drugs Dermatol. 2015 Jun;14(6):560-4.

[3] Kanni T et al. MABp1 Targeting Interleukin-1Alpha for Moderate to Severe Hidradenitis Suppurativa not Eligible for Adalimumab: A Randomized Study. J Invest Dermatol. 2017 Nov 9.

[4] Gottlieb A. et al. A Phase II Open-Label Study of Bermekimab in Subjects with Hidradenitis Suppurativa Shows Resolution of Inflammatory Lesions and Pain. J Invest Dermatol. 2020 Aug;140(8):1538-1545.e2. doi: 10.1016/j.jid.2019.10.024. Epub 2020 Jan 29.

[5] Hong DS. et al. MABp1, a first-in-class true human antibody targeting interleukin-1α in refractory cancers: an open-label, phase 1 dose-escalation and expansion study. Lancet Oncol. 2014 May;15(6):656-66. doi: 10.1016/S1470-2045(14)70155-X. Epub 2014 Apr 17.

[6] Hickish T. et al. MABp1 as a novel antibody treatment for advanced colorectal cancer: a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol. 2017 Feb;18(2):192-201. doi: 10.1016/S1470-2045(17)30006-2. Epub 2017 Jan 14.

[7] Hong DS. et al. Xilonix, a novel true human antibody targeting the inflammatory cytokine interleukin-1 alpha, in non-small cell lung cancer. Invest New Drugs. 2015 Jun;33(3):621-31. doi: 10.1007/s10637-015-0226-6. Epub 2015 Mar 31.

[8] El Sayed H. et al. A randomized Phase II study of Xilonix, a targeted therapy against interleukin 1α, for the prevention of superficial femoral artery restenosis after percutaneous revascularization. J Vasc Surg. 2016 Jan;63(1):133-41.e1. doi: 10.1016/j.jvs.2015.08.069. Epub 2015 Oct 1.

[9] Timper K. et al. Safety, pharmacokinetics, and preliminary efficacy of a specific anti-IL-1alpha therapeutic antibody (MABp1) in subjects with type 2 diabetes mellitus. J Diabetes Complications. Sep-Oct 2015;29(7):955-60.doi: 10.1016/j.jdiacomp.2015.05.019. Epub 2015 Jun 3.

[10] Carrato, A., Falcone, A., Ducreux, M. et al. A Systematic Review of the Burden of Pancreatic Cancer in Europe: Real-World Impact on Survival, Quality of Life and Costs. J Gastrointest Canc 46, 201–211 (2015). https://doi.org/10.1007/s12029-015-9724-1.

[11] Rahib L. et al. Projecting Cancer Incidence and Deaths to 2030: The Unexpected Burden of Thyroid, Liver, and Pancreas Cancers in the United States. DOI: 10.1158/0008-5472.CAN-14-0155 Published June 2014.

[12] Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. Lancet. 2011;378(9791):607-620. doi:10.1016/S0140-6736(10)62307-0.

[13] Pancreatic Cancer: Types of Treatment. https://www.cancer.net/cancer-types/pancreatic-cancer/types-treatment

[14] Wang-Gillam, A., et al., Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. Lancet, 2016. **387**(10018): p. 545-57.

[15] Ching S, et al. Endothelial-Specific Knockdown of Interleukin-1 (IL-1) Type 1 Receptor Differentially Alters CNS Responses to IL-1 Depending on Its Route of Administration. The Journal of Neuroscienc, September 26, 2007; 27(39): 10476-10486.

[16] Teresa M. Reyes and Paul E. Sawchenko. Involvement of the Arcuate Nucleus of the Hypothalamus in Interleukin-1-Induced Anorexia. The Journal of Neuroscience, June 15, 2002, 22(12):5091–5099.

[17] Braun T. et al. Central Nervous System Inflammation Induces Muscle Atrophy Via Activation of the Hypothalamic-Pituitary-Adrenal Axis. J. Exp. Med. 2011 21; 208(12): 2449-63.

[18] Hickish et al. MABp1 as a novel antibody treatment for advanced colorectal cancer: a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol. 2017 Feb; 18(2): 192-201.

[19] Jang et al. Mass spectrometric quantification of neutral and sialylated N-glycans from a recombinant therapeutic glycoprotein produced in Chinese hamster ovary cell lines. Anal. Biochem. 386 (2009) 228-236.

[20] Miossec. Anti-interleukin 1α autoantibodies. Ann Rheum Dis 2002; 61: 577-579.

[21] Gallay et al. Characterization and detection of naturally occurring antibodies against IL-1α and IL-1β in normal human plasma. Eur Cytokine Network 1991; 2: 329-338.

[22] Müller et al. Autoantibodies to IL-1α in sera from umbilical cords, children, and adults, and from subjects with juvenile chronic arthritis. Scand J Rheumatol. 1996; 25 (3): 164-7.

[23] Svenson et al. Distribution and characterization of autoantibodies to interleukin 1 alpha in normal human sera. Scand J Immunol. 1990: 32 (6): 695-701.

[24] Eisenhauer E.A. et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1); *Eur J Cancer*. 2009 Jan;45(2):228-47. doi: 10.1016/j.ejca.2008.10.026.

[25] Kapellos et al. Human Monocyte Subsets and Phenotypes in Major Chronic Inflammatory Diseases. Front Immunol. (2019) 30;10:2035.

[26] Sidibe et al. Angiogenic factor-driven inflammation promotes extravasation of human proangiogenic monocytes to tumours. Nature Communications (2018) 9:355.