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

11 June 2024

STATISTICAL ANALYSIS PLAN

Protocol 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
Protocol Number:	2020-PT049
Phase:	Phase I/II
Sponsor:	XBiotech USA, Inc. 5217 Winnebago Lane Austin, Texas 78744 U.S.A. Phone: 512-386-2900
Document Number	Final v1.0
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2 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Only abbreviations and terms relevant to the SAP are repeated herein. The reader is referred to the protocol for the complete and comprehensive list of abbreviations and definitions of terms for the study.

Abbreviation	Definition
ADaM	Analysis data Model
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
CBR	Clinical Benefit Response
CDISC	Clinical Data Interchange Standards Consortium
CFB	Change from baseline
CI	Confidence Interval
CR	Complete Response
CRP	C-Reactive Protein
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DEXA	Dual-energy X-ray
DLT	Dose limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ESR	Erythrocyte Sedimentation Rate
FU	Fluorouracil
ICH	International Conference on Harmonization
KPS	Karnofsky performance status
LBM	Lean body mass
LV	Leucovorin
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified ITT
MMRM	Mixed Model for Repeated Measures
MTD	Maximum tolerated dose
NCI	National Cancer Institute
ORR	Objective Response Rate
OS	Overall survival
PD	Pharmacodynamics
PFS	Progression Free Survival
PI-SAF	Phase I Safety Analysis Set
PII-SAF	Phase II Safety Analysis Set
PK	Pharmacokinetics
PT	Preferred Term
PR	Partial Response
QOL	Quality of life
REML	Restricted Maximum Likelihood
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
TEAE	Treatment-emergent adverse event

Abbreviation	Definition
TESAE	Treatment-emergent serious adverse event
TTF	Time to treatment failure
WHO-DD	World Health Organization – Drug Dictionary

3 INTRODUCTION

3.1 Preface

This document presents the statistical analysis plan (SAP) for XBiotech USA, Inc. Study 2020-PT049 (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).

Reference materials for this statistical plan include protocol v3.1 for Study 2020-PT049 (13Oct2021) and Guidance for Industry: E9 Statistical Principles for Clinical Trials (1998).

The SAP described hereafter is an *a priori* plan. Any changes to this SAP will be finalized and approved prior to study unblinding. Statistical programming may occur as study data accumulate so that analysis programs are ready at study completion. However, early programming will rely on data randomly linked to subjects, effectively rendering program output meaningless.

3.2 Purpose of Analyses

The purposes of the planned analyses described in this SAP are to identify the maximum tolerated dose (MTD) of XB2001 or maximum XB2001 dose studied if no Dose Limited Toxicities (DLTs) are observed in Phase I and the safety, tolerability, as well as the clinical activities of XB2001 at the MTD or the maximum dose studied in patients with advanced pancreatic cancer in Phase II. Pharmacokinetics (PK)/pharmacodynamics (PD) analyses will be specified in a separate document and will not be included in this SAP. Results from the analyses completed will be included in the final clinical study report for Study 2020-PT049 and may also be utilized for regulatory submissions, manuscripts, or other clinical development activities.

Post-hoc exploratory analyses not identified in this SAP may be performed to further examine the study data. Exploratory analyses will be clearly identified in the final clinical study report. Additional analyses not prospectively identified in this SAP may also be completed for publications, or regulatory or funding inquiries. These analyses, if performed, may not be reported in the clinical study report but will be fully documented in the document containing the additional analyses.

3.3 Summary of Statistical Analysis Changes to the Protocol

The analyses described in this analysis plan are consistent with the analyses described in the Study protocol 2020-PT049.

4 STUDY OBJECTIVES AND ENDPOINTS

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. The 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 I will be the dose of XB2001 used in Phase II 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 (PFS): defined as the time frame from treatment initiation to first progression based on RECIST 1.1 criteria or death from any cause, whichever occurs first.
- Overall Survival (OS): defined as the time frame from treatment initiation to death from any cause.
- Objective Response Rate (ORR): defined as the proportion of subjects with best overall response of complete response (CR) or partial response (PR). ORR will be determined via every 8-week imaging.
- Time to Treatment Failure (TTF): defined as time from treatment initiation to treatment discontinuation for any reason, including disease progression, treatment toxicity, or death.
- Clinical Benefit Response (CBR): CBR is a composite measure consisting of change in lean body mass (LBM) and change in quality of life (QOL). A positive CBR will be defined as stabilization or positive (≥ 0 kg) change in 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 the EORTC QLQ-C30.
- Quality of Life assessed through the cancer-specific EORTC QLQ-C30 questionnaire
- Number of Serious Adverse Events (SAEs)
- Incidence of Grade 3-4 Diarrhea
- Duration of hospitalizations
- Assessment of Pharmacokinetics (PK)
- Number of treatment cycles received
- Reduction in (CD14+CD16+IL-1α+) triple positive tumor associated monocytes in peripheral blood

Exploratory Endpoints (Phase II only):

- Symptom questionnaire
- Cardiac related adverse events

5 STUDY METHODS

5.1 General Study Design

This trial will include two phases (Phase I and Phase II). Phase I is an open label, dose escalation study to determine 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 II portion of this study will proceed only after completion of Phase I, 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 II of the trial will be the MTD, as determined in Phase I of the trial. If DLTs aren't observed at the maximum XB2001 dose studied in Phase I, the dose of XB2001 used for Phase II of the trial will be the maximum dose studied in Phase I.

Dose Escalation (Phase I):

- 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/m^2 intravenously over 90 minutes, followed by LV l + d racemic 400 mg/m^2 intravenously over 30 minutes, followed by 5-FU 2400 mg/m^2 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: 250 mg (dose cohort 1), 500 mg (dose cohort 2), and 1000 mg (dose cohort 3).

- Dose Escalation Rules:

  XB2001 will be dose escalated and a traditional 3+3 design will be used. The MTD or the maximum dose studied (if no DLTs are observed over the dose range) of XB2001 will be assessed for the combination with the 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 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 this 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 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 a DLT, MTD will be exceeded and the lower dose level will be considered to be the MTD.

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 II portion.

Subjects enrolled in the Phase I 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 of protocol 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 II portion of the study and will be randomized in a 1:1 fashion to receive either XB2001 administered in combination with ONIVYDE + 5-FU + LV or placebo in combination with ONIVYDE + 5-FU + LV.

The Phase II portion will be a randomized, double-blind, placebo-controlled study to establish the safety and tolerability of XB2001 administered in combination with ONIVYDE + 5-FU + LV 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 Phase II portion of 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 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 the UGT1A1*28 allele will receive the first cycle of therapy at a 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 of the protocol 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 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 who were homozygous for the UGT1A1*28 allele will receive the first cycle of therapy at a 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 of the protocol 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 the Visit 3 DLT assessment (Phase 1 subjects) or Visit 13 (Phase II 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.

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

The study calendars are shown in Table 1, Table 2 and Table 3.

Table 1 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	

		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
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 postinfusion 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.

Table 2 Study Calendars – Phase II Portion

		Cycle1	Cycle2	Cycle3	Cycle4	Cycle5	Cycle6	Cycle7	Cycle8	Cycle9	Cycle10	Cycle11	Cycle12	Follow Up[12]	OLE Visits[12]
Visit (V)	**Screening**	**V1 (Baseline)**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	
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

		Cycle1	Cycle2	Cycle3	Cycle4	Cycle5	Cycle6	Cycle7	Cycle8	Cycle9	Cycle10	Cycle11	Cycle12	Follow Up[12]	OLE Visits[12]
Visit (V)	**Screening**	**V1 (Baseline)**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	
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
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									
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 ***MUST BE COMPLETED WITHIN 72 HOURS PRIOR TO VISIT*															
DEXA Scan		X						X							
Tumor Measurements[7]	X[8]							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.
[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.

Table 3 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.

5.2 Randomization and Blinding

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. Only study team members working at the drug depot or administering the treatment assignments will be unblinded.

6 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).

The sample size in Phase II 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 (reduction in [CD14+CD16+IL-1α+] triple positive tumor associated monocytes).

6.1 Analysis Sets

There will be four (4) analysis sets defined for this study.

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

6.2 Management of Analysis Data

6.2.1 Data Handling

Unscheduled or repeated laboratory results will not be analyzed for the summary of continuous values but will be included in the laboratory shift tables as follows: Unscheduled tests will be included with the time of the nearest regularly scheduled test. If there is a scheduled test and one or more unscheduled tests assigned to the same time point, the most conservative test (i.e., a test with low or high results) will be used. Repeated tests will be included only if they reflect abnormal (low or high) results and if the corresponding original results are normal. All laboratory values, for all visits, will be provided in by subject listings.

6.2.2 Missing Data

Unless otherwise specified, there will be no substitutions made to accommodate missing data points. All data recorded on the case report forms will be included in data listings that will accompany the clinical study report.

6.2.2.1 Handling of Missing Date Values

Partial or Missing Dates

The following conventions will be used to impute missing portions of dates for adverse events and concomitant medications, if warranted. Note that the imputed values outlined here may not always provide the most conservative date. In those circumstances, the imputed value may be replaced by a date that will lead to a more conservative analysis.

1. Start Dates
   1) If the year is unknown, then the date will not be imputed and will be assigned a missing value.
   2) If the month is unknown, then:
      i. If the year matches the first dose date year, then impute the month and day of the first dose date.
      ii. Otherwise, assign 'January.'
   3) If the day is unknown, then:
      i. If the month and year match the first dose date month and year, then impute the day of the first dose date.
      ii. Otherwise, assign the first day of the month.

2. Stop Dates
   1) If the year is unknown, then the date will not be imputed and will be assigned a missing value.
   2) If the month is unknown, then assign 'December.'
   3) If the day is unknown, then assign the last day of the month.

6.2.2.2 Handling of Missing Efficacy Data

Missing data of efficacy will be handled and censored as follows:

Subjects without a death report will be censored at the date of last survival confirmation in the OS analysis. Subjects without any data after baseline will be censored at the date of randomization.

For the ORR analysis, subjects who are included in the analysis without any measurable disease at baseline or any tumor assessment after baseline will be considered a non-responder.

For the TTF analysis, subjects without treatment failure at the time of the analysis will be censored at the last dose date.

For the PFS analysis, subjects who have no baseline tumor assessment and no death, or no adequate post-baseline tumor assessment and no death will be censored at the date of randomization. Subjects who have no documented Progressive Disease or death before the data cut-off date will be censored at the date of last adequate tumor assessment date.

6.2.2.3 Adverse Events

If the relationship of an AE is missing, it will be considered treatment related. Missing AE severity will be coded as severe.

6.2.3 Handling of Early Termination Visit Information

If a subject is terminated early from this study, the early termination visit data will be analyzed at the closest scheduled visit. If the closest visit has valid data, the early termination data will be assigned to the next available visit.

6.2.4 Coding Conventions for Events and Medications

All adverse events and medical history will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA Version 27.0) system for reporting (preferred term and body system).

Prior and Concomitant medications will be coded using WHO-DD (Drug Dictionary) (Version Mar 2024).

6.2.5 Analysis Software

Data manipulation, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.4 or higher) for Windows. If the use of other software is warranted, the final clinical study report will detail what software was used and for what purposes.

6.2.6 Study Data

All study data will be formulated into regulatory compliant data sets to provide transparency, traceability, and integrity of trial analysis results from the collection source. Observed study data will be mapped to the CDISC Study Data Tabulation Model (SDTM) and serve as the source data from the trial. All study analyses will be completed using analysis data sets that are derived from the SDTM and follow the CDISC Analysis Data Model (ADaM) architecture. All planned analyses will be performed using the ADaM data sets developed for this study.

6.3 Planned Study Analyses

6.3.1 Statistical Summaries: Descriptive and Inferential

Data from Phase I and Phase II will be analyzed and reported separately. Phase I analyses will be performed by cohort and in total for the applicable population. Phase II analyses will be performed by treatment arm and in total for the applicable population.

Descriptive summaries of variables will be provided as appropriate. For continuous variables, the number of non-missing values (n) and the median, mean, standard deviation (SD), minimum, and maximum will be tabulated by treatment. For categorical variables, the counts and proportion will be tabulated by treatment. Confidence intervals (CIs) will be provided as appropriate. Expansion of descriptive table categories within and/or across each treatment may occur.

Change from baseline (CFB) scores will be calculated as the post-baseline measurement minus the baseline value.

All collected data and all derived data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or figures but will be included in the data listings.

6.3.2 Interim Analyses and Data Monitoring

No interim analysis will be performed.

6.4 Statistical Tests

All p-values provided will be rounded to and displayed in four decimals. If a p-value less than 0.0001 occurs, it will be shown in tables as <0.0001.

6.5 Multiplicity

No adjustment for multiplicity will be performed.

7 SUMMARY OF STUDY DATA

7.1 Subject Disposition

A summary of the analysis sets includes the number and percentage of subjects for the following categories: subjects screened, subjects randomized (Phase II only), number and percentage of subjects in the PI-SAF and PII-SAF sets, number and percentage of subjects in the mITT set (Phase II only). All percentages will be based on the number of subjects in the PI-SAF set (Phase I) or randomized (Phase II).

End of study information will also be summarized, including the number and percentage of subjects completing the study and the number and percentage of subjects who prematurely

discontinued the study with reasons for withdrawal. All percentages will be based on the number of subjects in the PI-SAF set (Phase I) or PII-SAF set (Phase II).

A by-subject data listing of study completion information including the reason for premature study withdrawal, if applicable, will be presented.

7.2 Protocol Deviations

All protocol deviations will be presented in a data listing, with a flag to indicate if a deviation was considered major. A summary table will be generated based on the classification of protocol deviations.

7.3 Demographics and Baseline Characteristics

Subject demographic data and baseline characteristics will be tabulated and summarized descriptively by dose cohort/treatment arm and overall, for the PI-SAF and PII-SAF sets. All missing data will be presented as part of a missing category, if appropriate. Individual subject demographics and baseline characteristics will be provided in listings.

Demographic and baseline characteristics will include:

- age (years),
- sex (male, female),
  - ✓ If Female, the childbearing potential (Yes, No-Post Menopausal, No-Surgical Sterilization)
- ethnicity (Hispanic or Latino, Not Hispanic or Latino),
- race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other),
- baseline weight (kg), baseline height (cm), and baseline body mass index (BMI) in kg/m^2,
- Eastern Cooperative Oncology Group performance score (ECOG PS),
- Karnofsky performance status (KPS).

7.4 Medical and Surgical History

Medical and surgical history will be summarized separately for the PI-SAF and PII-SAF sets as follows:

- The number and percentage of subjects with at least one medical/surgical history record will be presented.

- The number and percentage of subjects with at least one medical/surgical history record within each primary system organ class (SOC) and preferred term (PT) will be presented. The summary will be sorted using the internationally agreed order for SOC and using

descending order of overall numerical counts for PT. Where terms tie, these will be sorted alphabetically.

Subject medical and surgical history data including specific details will be presented in a listing.

7.5 Prior and Concomitant Medications

The prior medications are defined as any medication that starts and ends prior to the first dose of study drug. Concomitant medication is defined as any medication taken on or after the day of first dose of study drug. If the start date of a medication is missing/incomplete and the end date is prior to the first dose of study drug, the medication will be assumed to be a prior medication. If the start date of a medication is missing/incomplete and the end date is on or after the first dose of study drug, the medication will be assumed to be a concomitant medication. If both the start date and end date are missing/incomplete, and it is not clear when the medication was taken, the medication will be considered concomitant.

Prior and concomitant medications will be summarized separately for the PI-SAF and PII-SAF sets as follows:

The number and percentage of subjects with at least one prior or concomitant medication will be presented.

The number and percentages of subjects with at least one prior or concomitant medication within each Anatomical Group (Anatomical Therapeutic Chemical (ATC) level 4), and PT will be presented. The summary will be sorted using numerical counts by descending order of ATC, then descending order of PT in the total column. For tied terms, these will be sorted alphabetically.

Prior and concomitant medications data including specific details will be presented in a listing.

7.6 Non-drug therapy

Non-drug therapy data including specific details will be presented in a listing.

7.7 Prior anti-neoplastic therapy

Prior anti-neoplastic therapy will be summarized for the PI-SAF and PII-SAF sets.

The number and percentage of subjects who received any prior anti-neoplastic medication, radiotherapy or surgery will be summarized.

The summary of prior anti-neoplastic medications will include the line of therapy, agent type at last treatment, and type of therapy at last treatment.

The summary of prior anti-neoplastic radiotherapy will include the locations/body sites (including all locations recorded for each subject).

The summary of prior anti-neoplastic surgery will include the procedure at last surgery and residual disease at last surgery.

All prior anti-neoplastic medication, radiotherapy and surgery will be listed.

7.8 Other Baseline Analyses

Detailed information of drug allergies, social history (smoking/drinking history), infectious disease history (HIV, HCV, HBV, Tuberculosis), and surgical history will be provided in subject level listings.

8 SAFETY ANALYSES

8.1 Treatment Exposure

Treatment exposure will be summarized for the PI-SAF and PII-SAF sets.

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

Duration of exposure to study treatment (*days*) = (last date of exposure to study treatment) – (date of first administration of study treatment) + 1 day.

Patient level listings of all doses administered on treatment will be provided.

8.2 Dose Limiting Toxicities

The primary objective of the Phase I dose-escalation part of this study is to assess the DLT and identify the MTD or maximum XB2001 dose studied if no DTLs are observed.

DLTs will be summarized for the PI-SAF set. A summary table of the number and percentage of subjects with DLTs by dose cohort and overall will be provided. DLTs will also be summarized by primary SOC and PT.

Subject level listing of all DLTs will be provided.

8.3 Adverse Events

All AE analyses will be conducted using the PI-SAF and PII-SAF sets.

Tabular summaries of AEs will be provided for those events that are considered treatment emergent, where treatment-emergent AE (TEAE) is defined as any AE with onset or worsening on or after the first dose of study drug through the last study visit. In general, if a missing/incomplete start date is not clearly prior to initiation of treatment, then the AE will be considered a TEAE. If the AE end date is prior to the initiation of treatment, the AE will not be considered a TEAE.

The number and percentage of subjects with any TEAEs will be displayed by SOC and PT for each dose cohort/treatment arm. Within each SOC/PT, subjects will be counted only once if they had more than one event reported during the treatment period.

TEAEs will also be summarized by greatest reported severity for each event PT. The severity of all AEs will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Counts indicate subjects reporting one or more TEAEs that map to the severity grade classification for each PT. At each level of summarization (SOC or PT) subjects are only counted once and the worst severity case of repeated instances of the same TEAE will be used in tabulations. TEAEs will also be summarized by strongest investigator assessment of relationship to study drug in a similar manner. Related TEAEs include any TEAEs with relationship of definitely, probably, or possibly related.

All AEs including those that are not treatment emergent will be listed individually by subject.

An overall summary will display the number and percentage of subjects who experience at least one TEAEs in each of the following categories:

- Any TEAE
- TEAEs related to study drug
- TEAEs related to ONIVYDE
- TEAEs related to 5-FU+LV
- Maximum severity of TEAE
- Treatment-emergent serious adverse events (TESAEs)
- TEAEs with Fatal Outcome
- TEAEs leading to discontinuation (temporary or permanent) or interruption of study drug
- Related TEAEs leading to discontinuation (temporary or permanent) or interruption of study drug

The following summary tables will be presented for TEAE data:

- TEAEs by SOC and PT
- TEAEs by maximum severity, SOC, and PT
- TEAEs by maximum relationship to study drug, SOC, and PT
- TEAEs leading to discontinuation (temporary or permanent) or interruption of study drug by SOC and PT
- TESAEs by SOC and PT
- Study drug related TEAEs by SOC and PT
- ONIVYDE related TEAEs by SOC and PT

- 5-FU+LV related TEAEs by SOC and PT
- Study drug related TEAEs leading to discontinuation (temporary or permanent) or interruption of study drug by SOC and PT
- Grade 3-5 TEAEs by SOC and PT
- Cardiac related TEAEs by PT
- Grade 3 or 4 diarrhea TEAEs

8.4 Deaths, Serious Adverse Events and Other Significant Adverse Events

8.4.1 Deaths

All deaths, regardless of causality, will be provided in listings and written clinical narratives.

8.4.2 Serious Adverse Events

The number and percentage of subjects with TESAEs will be displayed by SOC and PT, and relationship to study drug. Within each PT, subjects will be counted only once if they had more than one TESAE event reported during the treatment period.

Clinical narratives for each TESAE observed will be written to include important data and safety findings related to the individual TESAE and included in the final clinical study report.

A listing will be produced for all subjects who reported serious TEAEs.

8.4.3 Adverse Events Leading to Discontinuation/Interruption of Study Drug

The number and percentage of subjects with TEAEs leading to discontinuation (temporary or permanent), or interruption, of study drug will be displayed by SOC and PT for each dose cohort/treatment arm. Within each PT, subjects will be counted only once if they had more than one TEAE leading to discontinuation (temporary or permanent), or interruption, of study drug reported during the treatment period.

A listing will be produced for all subjects who discontinued study drug due to TEAEs.

8.4.4 Cardiac Related Adverse Events

The number and percentage of subjects with cardiac related TEAE will be displayed by SOC and PT for each treatment arm in Phase II. Within each PT, subjects will be counted only once if they had more than one cardiac related TEAE.

A listing will be produced for all subjects who reported cardiac related TEAEs.

8.4.5 Grade 3 to 4 Diarrhea Adverse Events

The number and percentage of subjects with grade 3-4 diarrhea TEAEs will be summarized for each treatment arm in Phase II.

A listing will be produced for all subjects who reported grade 3-4 diarrhea TEAEs.

8.4.6 Grade 2 or Higher Laboratory Adverse Events

A listing will be produced for all subjects who reported grade 2 or higher laboratory TEAEs.

8.5 Clinical Laboratory Evaluations

Clinical laboratory results, including clinical chemistry; hematology; inflammation markers: C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR) labs; and urinalysis will be summarized for each dose cohort/treatment arm by time point for the observed value as well as for the change from baseline value. In addition, laboratory shift summary tables will be provided for all laboratory parameters where low/normal/high or abnormal/normal status can be ascertained. All analyses will be conducted using the PI-SAF and PII-SAF sets.

Listings of individual laboratory parameters by visit with normal ranges, and abnormality assessments will also be completed.

8.6 Vital Signs

Vital sign results will be summarized descriptively for each dose cohort/treatment arm by time point for the observed value as well as for the change from baseline value. All vital sign data by subject will be presented in a listing. Unscheduled visit results will not be summarized but will be included in subject data listings. All analyses will be conducted using the PI-SAF and PII-SAF sets.

8.7 Physical Examinations

A shift summary table will be provided for all physical examination parameters. A by subject listing will be provided to display all physical examination information. All analyses will be conducted using the PI-SAF and PII-SAF sets.

8.8 Hospitalizations

A summary table will be provided including the number of hospitalizations and the duration of hospitalizations (days) by treatment arm for the PII-SAF set.

A by subject listing will be provided to display all hospitalization information.

8.9 Other Safety Measures

Electrocardiogram (ECG) parameters and pregnancy test data will be provided in subject level listings.

No other safety analyses have been prospectively defined. If, however, after study results are reviewed, or Sponsor recommend additional safety parameters or analyses be completed, they will be fully described and documented in the final clinical study report. The SAP does not need to be amended to complete any other safety measures identified as post-hoc.

9 EFFICACY ANALYSES

Efficacy analyses will be conducted for Phase II based on the mITT set.

9.1 Progression-free Survival

PFS is defined as the time from treatment initiation to first progression based on RECIST 1.1 criteria or death from any cause, whichever occurs first. Subjects who have no baseline tumor assessment and no death, or no adequate post-baseline tumor assessment and no death will be censored at the date of randomization. Subjects who have no documented Progressive Disease or death before the data cut-off date will be censored at the date of the last adequate tumor assessment date.

Comparison between treatment arms will be performed using a log-rank test. A Cox proportional hazards regression model will be used to estimate the HR (ties will be handled with Efron's method), and its 95% CI. Kaplan-Meier methods will be used to estimate the 25th, 50th, and 75th quartiles and their 95% CIs. A Kaplan-Meier curve will be provided to visually describe PFS changes over time.

9.2 Overall Survival (OS)

OS is defined as the duration from the date of treatment initiation to death from any cause. Subjects who are alive at the time of analysis will be censored at the last known date alive. Subjects without any data after baseline will be censored on the randomization day.

The analysis method for OS will be the same as that for PFS.

9.3 Objective Response Rate (ORR)

ORR is defined as the best overall response of CR or PR. ORR will be determined via every 8-week imaging. Subjects without any measurable disease at baseline or any tumor assessment after baseline will be considered as non-responders. A Pearson Chi-square test (or Fisher's exact test) will be used to compare the ORR between arms. The Newcombe (score) method will be used to calculate 95% CI for ORR difference between arms. The Wilson (score) method will be used to calculate the 95% CI of each arm. Analyses will be performed at Weeks 8, 16, and 24.

9.4 Time to Treatment Failure

TTF, is defined as time from treatment initiation to treatment discontinuation for any reason, including disease progression, treatment toxicity, or death. Subjects without treatment failure at the time of analysis will be censored at the last dose date.

The analysis method for TTF will be the same as that for PFS.

9.5 Clinical Benefit Response

The CBR is a composite measure consisting of change in lean body mass (LBM) and change in quality of life (QOL) from baseline to Week 8.

A positive CBR will be defined as stabilization or positive (≥ 0 kg) change in LBM - as assessed by DEXA scan, and improvement or no worsening (≥ 0 score points change) on any two of the three symptom scale measures (fatigue, pain, or 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.

The analysis method for CBR will be the same as that for ORR.

9.6 Patient Reported Outcome

EORTC QLQ-C30

The EORTC QLQ-C30 is a valid and reliable self-reported questionnaire, it includes 30 items resulting in 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning). 1 global health status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single item symptoms (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The EORTC QLC-C30 will be scored according to the EORTC scoring manual and all of the scales and single-item measures will be linearly transformed so that each score has a range of 0-100.

Subjects showing stabilization or improvement from baseline (≤ 0 change) on any two of the three symptom scales (pain, fatigue, appetite loss) will be considered responders. Subjects experiencing a reduction or worsening, or have data missing at a visit, will be defined as non-responders. The response rate of EORTC QLQ-C30 Symptom Scales will be evaluated at Weeks 8, 16, and 24. The analysis method will be the same as that for ORR.

Additionally, observed values as well as the change from baseline values in all scales will be summarized descriptively by time point and treatment arm.

Scales will be analyzed using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) with fixed effects for treatment, week, and the treatment-by-week interaction; and with baseline score as a covariate. The outcome variable will be change from baseline scores. Study week will be included in the model as a categorical variable (Weeks 8,

16, and 24) along with the treatment-by-week interaction. Least squares means will be used to compare treatments. Pairwise treatment comparisons will be performed at each week. An unstructured covariance matrix will be utilized. The Kenward Roger method will be used for computing the denominator degrees of freedom for the tests of fixed effects.

Symptom Questionnaire

The symptom questionnaire is a patient reported outcome questionnaire and will be assessed at Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22. 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.

Observed values as well as the change from baseline values of symptom questionnaire scores will be summarized descriptively by time point and treatment arm.

10 OTHER ANALYSES

PK/PD analyses and clinical correlate analyses (CD14+CD16+IL-1α+ levels) will be described in a separate document.

11 REPORTING CONVENTIONS

The following reporting conventions will be adopted for the presentation of study data. These conventions will enhance the review process and help to standardize presentation with common notations.

11.1 General Reporting Conventions

- All tables and data listings will be developed in Landscape Orientation, unless presented as part of the text in a Clinical Study Report (CSR).
- Figures will be presented in Landscape Orientation, unless presented as part of the text in a CSR.
- Legends will be used for all figures with more than one variable or item displayed.
- Figures will be presented in color with treatment groups distinguished by different symbols and colors. Lines in figures should be wide enough to view the line after being photocopied.
- Specialized text styles, such as bolding, italics, borders, shading, superscripted and subscripted text will not be used in tables, figures, and data listings unless they add significant value to the table, figure, or data listing.
- Only standard keyboard characters should be used in tables and data listings. Special characters, such as non-printable control characters, printer specific, or

font specific characters, will not be used on a table, figure, or data listing. Hexadecimal character representations are allowed (e.g.,μ,α,β).

- All titles will be centered on a page. The International Conference on Harmonization (ICH) numbering convention is to be used for all tables, figures, and data listings. The study number (Study 2020-PT049) will be indicated in all titles.
- All footnotes will be left justified and the bottom of a page. Footnote s must be present on the page where they are first referenced. Footnotes should be used sparingly and must add value to the table, figure, or data listing. If more than four footnote lines are planned, then a cover page may be used to display footnotes.
- Missing values for both numeric and character variables will be presented as blanks in a table or data listing. A zero (0) may be used if appropriate to identify when the frequency of a variable is not observed.
- All date values will be presented as YYYY-MM-DD (e.g., 2013-05-17) ISO 8601 format.
- All observed time values will be presented using a 24-hour clock HH:MM:SS format (e.g., 01:35:45 or 11:26). Seconds should only be reported if they were measured as part of the study, also in ISO 8601 format.
- Time durations will be reported in mixed HHh MMm SSs notation (e.g., 5h 32m, or 27h 52m 31s). The use of decimal notation to present (display) time durations should be avoided (e.g., 0.083h = 5m) unless it is necessary to show the computation of time differences in a table, figure, or data listing, in which case both notations may be used to display the time duration.
- All tables, figures, and data listings will have the Table, Listing, or Graph status (DRAFT, FINAL), and a date/time stamp on the bottom of each output.
- All analysis programs developed for a table, figure, or data listing display will be self-contained to facilitate transfer of programs to multiple computing environments and transfer to a regulatory agency (if requested).

11.2 Population Summary Conventions

- Population(s) represented on the tables or data listings will be clearly identified in the last title of the Table as “Population: <name of population>” and will be identical in name to that identified in the protocol or SAP.
- Consistent terminology will be used to define and identify a population.
- Sub-population(s) or special population(s) descriptions will provide sufficient detail to ensure comprehension of the population used for analysis in a table or figure.
- Population sizes may be presented for each treatment or dosing category as totals in the column header as (N=xxxx), where appropriate.

- Population sizes shown with summary statistics are the samples sizes (n) of subjects with non-missing values.
- All population summaries for categorical variables will include all categories that were planned and for which the subjects may have had a response. Percentages corresponding to null categories (cells) will be suppressed.
- All population summaries for continuous variables will include N, mean, SD, minimum, and maximum. Other summaries (e.g., number missing, median, quartiles, 5%, 95% intervals, coefficient of variation (CV) or %CV) may be used as appropriate.
- All percentages are rounded and reported to xx.x%. A percentage of 100% will be reported as 100%. No value of 0% will be reported. Any computation of the percentage that results in 0% is to be presented as a blank.
- Population summaries that include p-values will report the p-value to four decimal places with a leading zero (0.0001). All p-values reported on default output from statistical software (i.e., SAS® Software version) may be reported at the default level of precision. P-values <0.0001 should be reported as <0.0001 not 0.0000. Any post-hoc changes to reporting conventions will be identified in the study report but will not necessitate a protocol or SAP amendment.