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CLINICAL RESEARCH PROTOCOL

STUDY DRUG:	OBI-888
PROTOCOL NUMBER:	OBI-888-001
PROTOCOL TITLE:	A Phase I/II, Open-Label, Dose Escalation and Cohort Expansion Study Evaluating the Safety, Pharmacokinetics (PK), Pharmacodynamics (PD), and Therapeutic Activity of OBI-888 in Patients with Locally Advanced or Metastatic Solid Tumors
TRIAL REGISTRATION NUMBERS:	
National Clinical Trial Number:	NCT03573544
US FDA IND Number:	136961
SPONSOR:	OBI Pharma Inc. Ste W1907, 19F, #3, Park St, Nankang Software Park, Nangang District, Taipei 11503, Taiwan
VERSION NUMBER:	Protocol Amendment 4, Version 5.0
VERSION DATE:	08-May-2020

SPONSOR APPROVAL PAGE

Date:

Tillman Pearce, MD
Clinical Lead
Medical Department

PROTOCOL REVISION HISTORY

Version	Date	Comment
1.0	11 Dec 2017	Initial version
2.0	05 Jan 2018	a. Updated the eligibility criteria, specifically Inclusion Criterion #4 and Exclusion Criterion #15 b. Updated the DLT definitions c. Revised the clinical laboratory assessment frequency
3.0	14 Aug 2018	a. Revised the objectives and endpoints to include RP2D as a primary objective and glycan analysis as an exploratory endpoint b. Updated the eligibility criteria, specifically Inclusion Criteria #4, #7, #8; #9, and Exclusion Criteria #1, #4, #9, #11, #13, and #14 c. Updated the DLT definitions d. Updated the tumor response evaluation criteria e. Revised the PK, ADA, ECG, and radiology assessment frequency f. Replaced the DMC with an SRC
4.0	12 Jun 2019	a. Updated the study population to enroll patients with cancer types with high Globo H expression b. Added details regarding the tumor biopsy sample requirements and Globo H testing c. Revised the enrollment methodology for Part B to use a Simon two-stage design d. Revised the dosing guidelines and drug product storage conditions

Version	Date	Comment
5.0	08 May 2020	a. Removed study assessments, objectives, and endpoints pertaining to circulating tumor cells b. Clarified the duration of study treatment c. Revised pregnancy testing to allow for urine or serum testing d. Revised the eligibility criteria, specifically Inclusion Criteria #9 and #11; and Exclusion Criteria #1 and #5 e. Updated the OBI-888 drug preparation details f. Revised the physical examination, height, weight, vital sign, ECOG, ECG, hematology, serum chemistry, coagulation, urinalysis, and radiology assessment frequency g. Clarified SAE reporting requirements and that disease progression should not be reported as an AE or SAE

PROTOCOL OBI-888-001

A PHASE I/II, OPEN-LABEL, DOSE ESCALATION AND COHORT EXPANSION STUDY EVALUATING THE SAFETY, PHARMACOKINETICS (PK), PHARMACODYNAMICS (PD), AND THERAPEUTIC ACTIVITY OF OBI-888 IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC SOLID TUMORS.

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol and all other information relevant to OBI-888-001 are the confidential and proprietary information of OBI Pharma, Inc., and except as may be required by federal, state or local laws or regulation, may not be disclosed to others without prior written permission of OBI Pharma, Inc.

I have read the protocol, including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the in the Declaration of Helsinki, Federal Code of Regulations for Good Clinical Practices and International Conference on Harmonization guidelines and all applicable regulatory requirements. I will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by OBI Pharma, Inc. or specified designees. I will discuss the material with them to ensure that they are fully informed about OBI-888 and the study.

Investigator's Signature	**Date**
Name (Printed)	**Site**

1 SYNOPSIS

Title of Study:	A Phase I/II, Open-Label, Dose Escalation and Cohort Expansion Study Evaluating the Safety, Pharmacokinetics (PK), Pharmacodynamics (PD), and Therapeutic Activity of OBI-888 in Patients with Locally Advanced or Metastatic Solid Tumors.
Protocol Number:	OBI-888-001
Phase of Development:	I/II
Rationale:	Globo H is a hexasaccharide glycosphingolipid located endogenously on the outer membrane of epithelial cells and was first identified in breast cancer cells. Globo H was found to be overexpressed on the cell surface of several epithelial cancers such as breast, pancreatic, ovarian, endometrial, gastric, lung, and prostate cancers. Globo H has been associated with tumor stem cells, as a potent inducer of angiogenesis and immune suppressor through Notch signaling, rendering it a target for cancer therapy. OBI-888 is a human recombinant IgG monoclonal antibody that selectively and specifically binds to Globo H. In summary, the mechanism of action of OBI-888 includes: the induction of cancer cell death via complement dependent cytotoxicity (CDC), antibody-dependent cell mediated cytotoxicity (ADCC), and antibody dependent cellular phagocytosis (ADCP); and also it acts by the depletion of Globo-H ceramide (GHCer) resulting in anti-angiogenesis and anti-immunosuppression. Preclinical studies demonstrated that OBI-888 antibody binds specifically to Globo H antigen and antitumor efficacy was noted in preclinical breast, pancreatic, colon cancer, and lung cancer tumor xenograft models.
Study Purpose:	This is a 2-part study: Part A (Dose Escalation) is designed to establish the maximum tolerated dose (MTD) and Recommended Phase II dose (RP2D) of OBI-888 as monotherapy. Part B (Cohort Expansion) is intended to further characterize the safety and preliminary clinical activity profile of the RP2D dose of OBI-888 administered as monotherapy in patients with locally advanced or metastatic solid tumors.
Objectives:	The primary objectives are: • To evaluate the safety and tolerability of OBI-888 when administered intravenously (IV) to patients with locally advanced or metastatic solid tumors. • To determine the MTD and RP2D of OBI-888 as monotherapy. The secondary objectives are: • To evaluate the preliminary clinical activity profile (objective response rate [ORR], clinical benefit rate [CBR], duration of response [DOR], and progression-free survival [PFS]) with OBI-888. • To evaluate the immunogenicity of OBI-888 (anti-drug antibodies [ADAs]).

	• To determine the serum pharmacokinetics (PK) and pharmacodynamics (PD) of OBI-888. Exploratory objectives are: • To assess ADCC and CDC. • To identify potential predictive biomarkers. • To assess the expression of immune markers including immune checkpoints, in the tumor tissue samples. • To assess the expression of Globo H and related tumor-associated glycans in the tumor tissue .To perform glycan analysis of OBI-888.
Study Design:	This is a Phase I/II, open-label, dose escalation and cohort expansion study of OBI-888, a humanized monoclonal antibody (mAb) targeting Globo H in patients with locally advanced or metastatic solid tumors.
	<u>Part A – Dose Escalation:</u> Three cohorts of escalating dose levels of 5, 10, and 20 mg/kg will be assessed using a 3+3 design to identify MTD and RP2D. Three patients will be enrolled at the lowest dose level. If none of the 3 patients experiences a dose-limiting toxicity (DLT), the next cohort of 3 patients will be enrolled at the next higher dose level. If 1 of 3 patients in the initial dose cohort experiences a DLT, that cohort will be expanded to 6 patients. If only 1 of these 6 patients has a DLT, the next cohort of 3 patients will be enrolled at the next higher dose level. If 2 or more patients of the 3-6 patients in a cohort experience a DLT, dose escalation will cease, and the lower dose level will be designated as the MTD where no more than 1 of 6 patients has experienced at DLT. New patients will be enrolled at the previous lower (tolerated) dose level until that cohort has 6 patients. This lower dose level will be considered the MTD if ≤1 in 6 patients has a DLT. A patient who withdraws from the study within the DLT evaluation period for reasons other than drug related adverse events (AEs) will be replaced. Part A will include a **screening period** (up to 28 days) prior to the first dose of OBI-888, a **treatment period**, and a **follow-up period.** Treatment will continue until DLT, progressive disease, unacceptable toxicity, or decision by the Investigator or patient to discontinue treatment. Patients with locally advanced or metastatic solid tumors will be enrolled in Part A. <u>Part B – Expansion Cohort:</u> Once Part A (Dose Escalation) is completed, Part B will enroll a maximum of 150 additional patients with advanced solid tumors with high Globo H expression (defined as an H-score cutoff ≥ 100 using a validated immunohistochemistry [IHC] assay) across 4 disease specific cohorts and 1 basket cohort based on a Simon two-stage design. The first stage of Part B, will recruit up to 9 patients in each cohort (up to 45 patients in the first stage across all cohorts). If sufficient evidence of activity is observed in the first stage, up to 21 additional patients will be enrolled into that cohort (up to 105 patients in the second stage across all cohorts). Part B will be conducted to obtain additional safety data, characterize the PK/PD profile of OBI-888, obtain a preliminary assessment of the clinical

	activity of OBI-888 in Globo H expressing solid tumors, and inform subsequent efficacy-finding clinical development. No DLTs have been observed at any dose level tested in Part A, and the MTD has not been reached. Therefore, dosing in Part B will be initiated at the highest dose tested in Part A (20 mg/kg OBI-888). The following 5 cohorts of patients who have high expression of Globo H by a qualified laboratory assessment (ie, Globo H H-score ≥ 100 using a validated IHC assay) will be enrolled in Part B. • Cohort 1: Pancreatic cancer • Cohort 2: Esophageal cancer • Cohort 3: Gastric cancer • Cohort 4: Colorectal cancer • Cohort 5: Basket (any solid tumor type other than those included in Cohorts 1-4). All patients are required to provide a tumor biopsy sample, either unstained slides (preferred) or a formalin fixed paraffin embedded (FFPE) tissue block at the initiation of screening visit for screening of Globo H overexpression and confirmation for eligibility of patients for Part B. Patients with a confirmed and documented Globo H H-score of ≥ 100 will be eligible for the study, and will subsequently enter the 28-day screening period to complete the remaining screening procedures. Note that submission of the tumor sample for Globo H determination may be performed more than 28 days prior to the first dose (after obtaining informed consent), but the other screening evaluations must be performed within the 28-day window. Part B will include a **screening period** (up to 28 days) prior to the first dose of OBI-888, a **treatment period**, a **follow-up period**. Treatment will continue until progressive disease, unacceptable toxicity, or decision by the Investigator or patient to discontinue treatment. The safety follow-up will be conducted 28-days after the last dose of study treatment for both parts.
Selection of Patients – Inclusion Criteria:	Inclusion Criteria: Patients must meet all of the following criteria in order to be included in the study: 1. Male or female patients, 18 years of age or older at the time of consent. 2. Provide written informed consent prior to performing any study-related procedure. 3. Histologically or cytologically confirmed patients with advanced or metastatic solid tumors for both Dose Escalation and Expansion. 4. Patients must have been treated with established standard-of-care therapy, or physicians have determined that such established therapy is not sufficiently efficacious, or patients have declined to receive standard-of-care therapy. 5. Measurable disease (i.e., at least one measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.

	6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. 7. Adequate organ function defined as: o Hepatic: ▪ Serum alanine aminotransferase (ALT) ≤3 × upper limit of normal (ULN), ≤5 × ULN in the presence of liver metastases ▪ Serum aspartate aminotransferase (AST) ≤3 × ULN, ≤5 × ULN in presence of liver metastases ▪ Serum bilirubin ≤1.5 × ULN o Renal: ▪ Creatinine clearance >30 mL/minute using Cockcroft Gault equation o Hematologic: ▪ Absolute neutrophil count ≥1000/μL ▪ Platelets ≥75,000/μL ▪ Hemoglobin ≥8 g/dL 8. Patient is willing and able to comply with all protocol-required assessments, visits, and procedures, including pretreatment tumor biopsy. Archival tumor biopsies (slides or FFPE tissue block) are acceptable at baseline. 9. Females of childbearing potential must have a negative urine or serum pregnancy test prior to starting study therapy, and agree to use a reliable form of contraceptive during the study treatment period and for at least 120 days following the last dose of study drug. Subject not of childbearing potential (i.e., permanently sterilized, postmenopausal) can be included in study. Postmenopausal is defined as 12 months with no menses without an alternative medical cause. Male patients must agree to use an adequate method of contraception during the study treatment period and for at least 120 days following the last dose of study drug. 10. Cannot be breast feeding. 11. Patients in Part B (Cohort Expansion) must have a documented Globo H H-score of at least 100 from a qualified laboratory IHC assay in one of the following tumor types to be enrolled in the respective cohort: o Cohort 1: Pancreatic cancer o Cohort 2: Esophageal cancer o Cohort 3: Gastric cancer o Cohort 4: Colorectal cancer o Cohort 5: Basket (any solid tumor type other than those included in Cohorts 1 through 4)

Selection of Patients – Exclusion Criteria:	Exclusion Criteria: Patients meeting any of the following criteria are ineligible to participate in this study: 1. Less than 3 weeks, from prior cytotoxic chemotherapy or radiation therapy; and less than 5 half-lives or 3weeks from biological therapies, whichever is shorter, prior to the first dose of OBI-888. 2. Has undergone a major surgical procedure (as defined by the Investigator) or significant traumatic injury within 28 days prior to the first dose of OBI-888. 3. Presence of an active autoimmune or inflammatory disease requiring systemic treatment within the past 2 months or a documented history of clinically severe autoimmune disease that requires systemic steroids or other immunosuppressive medications. Local steroid injections, intermittent use of topical, inhaled, ophthalmologic, intra-articular, topical, or intranasal corticosteroids, or systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or equivalent would not be excluded from the study. 4. Presence of primary immunodeficiency or receiving systemic steroids of >10 mg/day of prednisone or equivalent or other immunosuppressive agents within 14 days prior to the first dose of OBI-888. 5. Has active bacterial, viral, fungal, or mycobacterial infection requiring systemic therapy, including known infection with human immunodeficiency virus (HIV) or active infection with hepatitis B virus or hepatitis C virus. Patients with HIV infection are eligible if CD4+ T-cell counts are ≥350 cells/μL; patients on antiretroviral therapy should be on an established dose for at least 4 weeks and have an HIV viral load less than 400 copies/mL prior to enrollment. 6. Patients with a history of solid organ transplant. 7. Unresolved toxicities from prior anticancer therapy, defined as having not resolved to Grade 0 or 1 (using National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] version 4.03), except for alopecia and laboratory values listed in the inclusion criteria. 8. Receipt of any prior therapy targeting Globo H. 9. Known hypersensitivity to OBI-888 or its excipients. 10. Has known untreated central nervous system metastases. Patients with treated brain metastases are eligible if there is no evidence of progression for at least 4 weeks after central nervous system-directed treatment, as ascertained by clinical examination and brain imaging (magnetic resonance imaging [MRI] or computed tomography [CT]) during the screening period. 11. Any medical co-morbidity or psychiatric illness that is life-threatening or, in the opinion of the Investigator, renders the patient unsuitable for participation in a clinical trial due to possible

	noncompliance, would place the patient at an unacceptable risk, and/or potential to affect interpretation of results of the study. 12. Is receiving any concurrent prohibited medication as listed in Section 8.6.3.
Planned Sample Size:	Up to 18 patients will be enrolled in the 3+3 dose escalation phase (Part A). The cohort expansion phase (Part B) will enroll up to 150 total patients based on a Simon two-stage design. The first stage will recruit up to 9 patients in each cohort. If at least 1 objective response is observed within the first 6 cycles of therapy, a second stage recruitment will occur with up to 21 additional patients enrolled into that cohort, for a total of up to 30 patients per cohort. If at least 4 objective responses are observed within the first 6 cycles of therapy in 30 patients, then OBI-888 will be considered worthy of further evaluation in that indication. This design is based on a level of low interest for a treatment with an ORR of 5% versus a level of high interest for a treatment with an ORR of 25%. The sample size is based on a one-sided alpha of 0.05 and 90% power. The two-stage design limits the number of patients treated using a treatment with low levels of activity.
Investigational Therapy: **Dose/ Route/ Regimen**	OBI-888 (a humanized anti-Globo H mAb). OBI-888 drug product (in final concentration 30 mg/mL) will be supplied by OBI Pharma Inc. OBI-888 will be administered as a 90-minute IV infusion on Days 1, 8, 15, and 22 of each 28-day cycle. The infusion duration may be reduced, at the Investigator's discretion, to 30-60 minutes starting with Cycle 3 if the infusions in the first two cycles are well tolerated. • For Part A (Dose Escalation), OBI-888 will be given at dose levels of 5, 10, and 20 mg/kg until the MTD is determined. • For Part B (Cohort Expansion), patients will be treated with 20 mg/kg OBI-888 since no DLTs were observed at any of the dose levels tested in Part A, and the MTD was not reached.
Reference Therapy:	None
Treatment Duration:	Patients will be treated during the treatment period until progressive disease, unacceptable toxicity, or decision by the Investigator or patient to discontinue treatment.
Criteria for Evaluation:	Safety: Safety assessments include incidence and severity of AEs and serious AEs (SAEs), clinical laboratory tests (hematology, serum chemistry, coagulation, and urinalysis), vital sign measurements, electrocardiograms (ECGs), and physical examination. Safety assessments are performed at screening and throughout the study. DLTs: A DLT is defined as the occurrence of any of the following events, within the first cycle of treatment, that are considered to be at least possibly related

	to OBI-888. All AEs unless they have been determined to be not related to study drug will be taken into consideration in determining DLTs. NCI-CTCAE version 4.03 will be the basis for the descriptive terminology and grading of AEs. DLTs are defined as: • Grade 4 neutropenia • ≥Grade 3 febrile neutropenia with or without infection. • Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding • ≥Grade 3 nausea and vomiting or diarrhea for more than 72 hours despite optimal supportive care • Any other ≥Grade 3 non-hematological AE that does not resolve before the next infusion The DLT evaluation period is the first cycle; 28 days from the start of study treatment. Immunogenicity: Immunogenicity assessments will be performed at Cycle 1 Day 1 and throughout the trial. PK: Blood samples will be collected for evaluation of serum OBI-888 concentration, to assess the accumulation of OBI-888, and to assess the attainment of steady state. The timing of the PK samples may be adjusted upon review of accumulating data. PK parameters will be calculated using a non-compartmental method from the PK samples collected on Dose 1 and will include but will not be limited to maximum serum concentration (C_{max}), total exposure (AUC), elimination half-life ($t_{1/2}$), clearance (Cl), time to reach maximum concentration (T_{max}) and volume of distribution (V_d). To assess the attainment of steady state, trough (C_{min}) concentrations and peak concentrations (end of infusion) of each dose would be obtained directly from analytical data. Pharmacometric methods may also be applied to further investigate OBI-888 exposure (e.g., accumulation of OBI-888, presence of dose- or time-dependent OBI-888 PK behavior, verification of influential factors on OBI-888 PK). Preliminary Clinical Activity Profile: Tumor response will be evaluated by the Investigator using RECIST version 1.1. Tumor status assessment will be performed pretreatment (up to 28 days prior to dosing). During the study tumor response will be assessed after every second cycle (every 8 weeks) for the first 6 months, then every 12 weeks thereafter.

Study Endpoints:	Primary endpoints: • DLTs with OBI-888 • AEs/SAEs and laboratory abnormalities as graded by NCI CTCAE version 4.03 • MTD and RP2D of OBI-888 Secondary endpoints: • Percentage of patients with ORR, CBR, DOR and PFS according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) • Percentage of patients with anti-OBI-888 antibodies (ADAs) in blood • PK and PD parameters of OBI-888 Exploratory endpoints: • Globo H and related glycan expression in tumor tissue by IHC • ADCC and CDC • Identify potential predictive markers by IHC or molecular analysis • Tumor infiltrating Lymphocytes (TILs), including natural killer (NK) cells, and programmed death – ligand 1 (PD-L1) expression in tumor tissue samples by IHC • Killer cell immunoglobulin-like receptor (KIR), human leukocyte antigen (HLA), and Fc receptor gamma genotype • Glycan analysis of OBI-888
Statistical Methods and Planned Analyses:	Analyses will be conducted by dose level in the dose escalation phase and by cohort in the expansion phase. Descriptive summaries for categorical variables will include counts and percentages. Descriptive summaries for continuous variables will include means, medians, standard deviations, minimum and maximum values. Descriptive summaries of time to event data will include medians and confidence intervals. Graphical summaries of the data may be presented. All data will be listed for all patients. Further details of the analysis, including the handling of missing data, transformations, other data handling procedures, and analytical methodology will be provided in the Statistical Analysis Plan (SAP). Additional exploratory analyses of the data will be conducted as deemed appropriate. All analyses of safety and preliminary clinical activity profile will be performed on all patients who were enrolled and received at least 1 dose of study drug. <u>Safety Analyses</u> AEs will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 or higher and assessed for severity using CTCAE version 4.03. AEs will be summarized by system organ class and preferred term and presented in decreasing order of incidence. DLTs will also be summarized by dose and cohort. Vital signs, ECG data, hematology, serum chemistry, coagulation, and urinalysis parameters from baseline and during study will be examined. Treatment-emergent changes in key laboratory parameters will be identified.

	Laboratory data will be summarized for each time point that specimens are collected. Changes from baseline for laboratory values may also be explored as specified in the SAP. PK Analyses PK parameters will be calculated using a non-compartmental method from the PK samples collected on Dose 1 and will include but is not limited to C_{max}, AUC, $t_{1/2}$, Cl, T_{max} and V_d. To assess the attainment of steady state, trough (C_{min}) concentrations and peak concentrations (end of infusion) of each dose would be obtained directly from analytical data. Summary statistics will be tabulated for the PK parameters of OBI-888 on Dose 1. Geometric means and coefficients of variation will be presented for C_{max}, AUC, $t_{1/2}$, Cl, and V_d. Median, minimum, and maximum will be presented for T_{max}. To describe the dependency on dose, scatter plots of C_{max} and AUC versus dose will be provided. Summary statistics will be tabulated for the trough (C_{min}) concentration and peak concentrations (end of infusion) by dose and study day. To assess the attainment of steady state, geometric mean C_{min} values will be plotted versus study day by dose. Pharmacometric methods may also be applied to further investigate OBI-888 exposure (e.g., accumulation of OBI-888, presence of dose- or time-dependent OBI-888 PK behavior, and verification of influential factors on OBI-888 PK). Preliminary Clinical Activity Profile Analyses ORR will be summarized as the percentage of patients with confirmed partial response (PR) or complete response (CR) according to RECIST version 1.1. CBR will be summarized as the percentage of patients with confirmed CR, PR, or stable disease (SD). DOR, defined as time from the date of reported confirmed PR or CR to the date of progression will be summarized descriptively using summary statistics. Additionally, a listing of DOR for those patients experiencing response will be provided. PFS is defined as the time from first dose of study drug until radiographically determined disease progression or death due to any cause, whichever event occurs first. Patients who are still alive or who have no progressive disease reported at analysis will be censored at their last evaluable tumor assessment. Time to progression, death, and/or censoring will be reported for all patients. Kaplan-Meier estimates and 95% confidence intervals will be presented for time-to-event endpoints such as PFS if sufficient numbers of events to calculate meaningful statistics are observed.

2 Table of Contents

2.1 In-Text Tables

2.2 In-Text Figures

3 List of Abbreviations

Abbreviation	Definition
ADAs	anti-drug antibodies
ADCC	antibody-dependent cell mediated cytotoxicity
ADCP	antibody dependent cellular phagocytosis
AE	adverse event
ALP	alkaline phosphatase
ALT (SGPT)	alanine aminotransferase (serum glutamic pyruvic transaminase)
aPTT	activated partial thromboplastin time
AST (SGOT)	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
AUC	total exposure
BUN	blood urea nitrogen
C	cycle
CBR	clinical benefit rate
CDC	complement dependent cytotoxicity
Cl	clearance
C_{max}	maximum serum concentration
CR	complete response
CFR	Code of Federal Regulations
C_{min}	trough
CRO	Contract Research Organization
CT	computed tomography
DCF	Data Clarification Form
DLT	dose-limiting toxicity
DOR	duration of response
DP	drug product
eCRF	electronic case report form
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
FFPE	formalin fixed paraffin embedded
GCP	Good Clinical Practice
GHCer	Globo-H ceramide
GMP	Good Manufacturing Practice
HIPAA	Health Insurance Portability Accountability Act
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IgM	immunoglobulin M
IHC	immunohistochemistry
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	intravenous(ly)
KIR	killer cell immunoglobulin-like receptor
LDH	lactate dehydrogenase
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer
NOAEL	no-observed-adverse-effect level
ORR	objective response rate
OS	overall survival
PD	pharmacodynamic
PD-LI	programmed death – ligand 1
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
PT	prothrombin time
Q8wk	every 8 weeks
Q12wk	every 12 weeks
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase II dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneously
SD	stable disease
SRC	safety review committee
$T_{1/2}$	half-life
TACA	tumor-associated carbohydrate antigens
TEAE	treatment-emergent adverse event
TGI	tumor growth inhibition
TIL	tumor infiltrating lymphocytes
T_{max}	time to reach maximum concentration
ULN	upper limit of normal
V_d	volume of distribution
WHO	World Health Organization

4 Introduction

4.1 Background on OBI-888

Globo H is a neutral hexasaccharide (Fucα1→2Ga1β1→3GalNAcβ1→3Ga1α1→4Ga1β1→ 4G1cβ1) glycosphingolipid, was originally isolated from the human breast cancer cell line MCF-7 (Menard, et al., 1983; Bremer, et al. 1984). Its overexpression has been seen on a variety of epithelial cell tumors such as colon, ovarian, gastric, pancreatic, endometrial, lung, prostate, and breast cancers with the use of monoclonal antibodies (mAbs), MBrl (immunoglobulin M [lgM]) (Menard, et al., 1983; Bremer, et al. 1984; Canevari, et al., 1983) and VK-9 (immunoglobulin G 3 [IgG3]) (Ragupathi, et al., 1999).

In normal tissue, Globo H is weakly expressed at the apical epithelial cells at lumen border, a site which appears to be inaccessible to the immune system. Globo H ceramide shed from tumor cells - acting as an immune checkpoint molecule to facilitate the escape of cancer cells from immune surveillance - inhibits the activation of immune cells (Tsai, et al., 2013). Incorporation of Globo H ceramide by endothelial cells results in enhanced angiogenic activity to promote tumor growth (Cheng, et al., 2014).

Due to its property, Globo H may serve as a promising target for immunotherapy for epithelial cancers. Given the finding of increased expression across a variety of cancers, Globo H can be considered an ideal target and Globo H-based anticancer therapeutics can be broadly useful treating number of oncology indications. OBI-888, a recombinant human immunoglobulin G (IgG) mAb, selectively binds to Globo H, a tumor associated carbohydrate antigen (TACA). OBI-888 is highly specific to Globo H antigen. Antibody-dependent cell mediated cytotoxicity (ADCC) is one of the mechanisms for therapeutic antibodies to kill target cancer cells. The action is initiated by ligation of FcyRIIIa on effector cells, predominantly natural killer cells, to antibodies bound to cell-associated antigens. Multiple cross-linking of the two cell types leads to pathway activation of ADCC (Richards, et al., 2008).

OBI-888 has also been shown to suppress the Globo-H ceramide (GHCer) induced T cell inactivation by Jurkat/NFAT Re Luc reporter bioassay activated by anti-CD3/CD28 antibodies. Depletion of GHCer by OBI-888 serves as a plausible route in overcoming the immunosuppression induced by the cancer cells.

Previously, Globo H-based cancer vaccines have been evaluated in clinical trials for the past several years. For example, the cancer vaccine KLH-Globo H conjugate (OBI-822/OBI-821, also known as OPT-822/OPT-821) is currently in Phase II/III clinical trials for the treatment of metastatic breast cancer (NCT01516307). It was reported that progression-free survival (PFS) and interim overall survival (OS) were significantly improved in those patients who developed a Globo H specific IgG response to the vaccine. However, several challenges have been recognized, including inconsistency in eliciting T cell-mediated immunity in cancer patients, mandatory usage of an adjuvant since TACAs in general are usually poorly immunogenic, emergence of immunotolerance to KLH and difficulties in the control of conjugate quality (Zhou, et al., 2015). In order to achieve the desired immunological response, alternate carriers of the carbohydrate antigens are being studied. In addition to the vaccine strategy, Globo H-targeted therapy targeting the epitope using mAb can be a reasonable alternative.

4.2 Nonclinical Studies

4.2.1 Anti-tumor Effect of OBI-888 in a MCF-7 Xenograft Model

In a tumor xenograft model of human breast adenocarcinoma, viable MCF-7 (ATCC HTB-22) cells were subcutaneously (SC) implanted (2.0 x 107 cells in 1:1 matrigel/media mixture at 0.2 mL/mouse) into female athymic nude mice. Supplemental injections of estradiol cyclopentyl propionate (100 µg/mouse) were administered SC between the scapulae twice weekly beginning one week prior to cell implantation, and continuing through to study completion. Intravenous administration of OBI-888 was initiated one day after tumor cell implantation (denoted as Day 1). Tumor implanted mice were divided into four treatment groups, each group containing eight animals. Intravenous injections of the vehicle (25 mM sodium citrate, pH 6.5) at 10 mL/kg and OBI-888 at 1, 3, and 10 mg/kg were administered twice weekly for 6 weeks. The tumor size was monitored and recorded for 42 days. Mortality, body weight, and signs of overt animal toxicity were recorded twice weekly for 42 days. Tumor growth inhibition (TGI) was calculated as T/C (treatment/control) x 100% and TGI (1-T/C) x 100%. T/C value $\leq$42% was considered significant antitumor activity. Two-way ANOVA followed by Bonferroni test was applied to ascertain the statistically significant difference compared to respective vehicle.

Biweekly intravenous administration of OBI-888 at 10 mg/kg was associated with significant antitumor activity (T/C value $\leq$42%, and $p < 0.05$) on Day 42, and moderate, but statistically significant ($p < 0.05$), antitumor activity from Day 19 to Day 40 compared to vehicle control group. OBI-888 at 3 mg/kg intravenous biweekly administration was associated with moderate, but statistically significant ($p < 0.05$), antitumor activity from Day 22 to Day 42 compared to vehicle control group. OBI-888 at 1 mg/kg intravenous biweekly showed slight TGI compared to vehicle control group during the study period. On Day 42, TGI was 27%, 50% and 85% for OBI-888 at 1, 3, and 10 mg/kg by intravenous administration twice weekly, respectively.

All test doses of OBI-888 were well-tolerated in animals, and were not associated with significant changes in body weight compared to the vehicle groups. No overt toxicities were observed during the study period.

4.2.2 A 7-day Single Dose Toxicity Study in Sprague-Dawley Rats

A single bolus of OBI-888 administered intravenous at 10, 60, and 300 mg/kg was assessed for its possible adverse and toxic effects in both male and female Sprague-Dawley rats over a 7-day experimental period.

OBI-888 was associated with moderate flushed skin within 60 minutes after treatment (60 and 300 mg/kg: 66%/ 44% and 100%/ 100% in male/ female rats, respectively), but normal skin color returned in a short period of time. No other significant clinical observations were observed during cage-side inspections and all treated animals survived over the 7-day study period. Moreover, body weight gains, as well as food and water consumption, were not affected by administration of OBI-888.

Compared to vehicle control, serum calcium was slightly elevated by 10 and 60 mg/kg OBI-888, and serum potassium and chloride were mildly increased by 60 mg/kg OBI-888 in male rats. These parameters were unchanged relative to vehicle control in female rats. Urinary pH, protein, urobilinogen, nitrate, leukocyte, glucose, bilirubin, ketone, specific gravity and red blood cell count (RBC) were not altered following OBI-888 administrations at terminal. The clotting times and the blood cell populations were not affected by OBI-888 injections on Day 7.

The animals of OBI-888 300 mg/kg treated groups were sacrificed and the organs were checked externally and internally and harvested for histopathological examination. Some mottled surfaces were observed in kidneys in both 300 mg/kg treated male and female rats with incidences of 100% and 33%, respectively. Non-specific lesions such as focal, tubular cysts, infarct and granulation in the kidney and an endometrial stromal polyp in the uterus were observed in OBI-888 300 mg/kg in histological data that might be related to spontaneous incidence in rats. In addition, focal inflammatory cell infiltration in the lung and diffuse acinar cell atrophy in the salivary gland were found in some OBI-888 300 mg/kg treated rats.

4.2.3 A 28-day Repeat Dose Toxicity Study in Sprague Dawley Rats Followed by a 14-day Recovery Phase

OBI-888 administered via intravenous bolus injection at dose levels of 0, 20, 60, and 200 mg/kg once weekly for a total of 4 doses (Day 1, 8, 15, and 22) was assessed for its possible adverse and toxic effects in both male and female Sprague Dawley rats over a 28-day period. The potential reversibility of any findings following a 14-day recovery period was also evaluated. The first day of dosing was designated as Day 1.

There were no OBI-888-related changes in clinical signs, body weights, food consumption, ophthalmic examinations, and functional observational battery parameters. All animals dosed with control or OBI-888 survived over the 28-day period.

There were no definitive OBI-888-related changes in hematology parameters at any dose. On Day 28, there were statistically significant increases in mean reticulocytes in males at 200 mg/kg (1.40 × control mean). Such increases were likely driven by the unusually high reticulocytes in one male rat at 200 mg/kg. This animal also had moderately decreased platelets on Day 28 (0.14 × control mean). Such high reticulocyte counts were correlated to increased hematopoiesis in histopathology assessments. These increases were considered of uncertain relationship to OBI-888 due to the single incidence of these changes and presence of microscopic correlates. At 200 mg/kg/dose, one treated male rat had increased eosinophils (2.11 × of pretreatment). Similar increases were observed in control animals; therefore, these changes were considered likely unrelated to OBI-888. On Day 28, there were statistically significant increases in mean neutrophils in females at 200 mg/kg (1.56 × control mean). The increases were likely due to generally lower mean neutrophils in the control females compared to the 200 mg/kg females (including at the pre-study time point, Day -5), and was unrelated to OBI-888. There were no definite OBI-888-related changes in clinical chemistry, coagulation, and urinalysis parameters at any dose.

The animals of all 4 OBI-888 treated groups (0, 20, 60, and 200 mg/kg) were sacrificed and the organs were checked externally and internally and harvested for histopathological examination. At terminal euthanasia, OBI-888-related higher mean absolute and/or relative organ weights were observed in the spleen of animals given 200 mg/kg/dose and in the liver of males given 200 mg/kg/dose; no definitive microscopic correlates were observed. No definitive OBI-888-related macroscopic or microscopic findings were observed. At recovery euthanasia, no OBI-888-related organ weight differences, macroscopic findings, or microscopic findings were observed.

In conclusion, administration of OBI-888 by intravenous bolus injection once weekly for 28 days was well tolerated in Sprague Dawley rats at levels of 200 mg/kg/dose. Based on these results, the no-observed-adverse-effect level (NOAEL) was considered to be 200 mg/kg/day.

4.2.4 A 28-day Repeat Dose Toxicity Study in Cynomolgus Monkeys Followed by a 14-day Recovery Phase

OBI-888 administered via intravenous (slow bolus) injection at dose levels of 0, 20, 60, and 200 mg/kg once weekly for a total of 4 doses (Day 1, 8, 15, and 22) was assessed for its possible adverse and toxic effects in both male and female cynomolgus monkeys over a 28-day period. The potential reversibility of any findings following a 14-day recovery period and its toxicokinetic characteristics were also evaluated. The first day of dosing was designated as Day-1.

No OBI-888-related clinical observations occurred during this study. All clinical observations that occurred were considered unrelated to OBI-888 because they were transient and did not persist, were considered to be related to study procedures, or were incidental findings commonly seen in laboratory-housed cynomolgus monkeys under similar study conditions. In addition, body weights, as well as qualitative food consumption, were not affected by administration of OBI-888. All animals dosed with control or OBI-888 survived until scheduled necropsy.

No OBI-888-related ocular effects occurred during this study. No OBI-888-related abnormalities in rhythm or waveform morphology were found at any dose level based on comparison of pre-dose and post-dose electrocardiographic recordings. No OBI-888-related changes in electrocardiography parameters and all the electrocardiograms (ECGs) evaluated in this study were qualitatively considered normal.

There were no definitive OBI-888-related changes in hematology parameters at any dose. On Day 28, four animals at 200 mg/kg had decreased neutrophil counts that were below the lowest control or pre-study values. These changes were considered to be of uncertain relationship to OBI-888 given the minimal magnitude of decrease below the lowest control value and the lack of microscopic correlates. OBI-888-related changes in coagulation parameters were limited to minimally increased fibrinogen in two 200 mg/kg treated female animals on Day 28. These changes were associated with mildly increased globulins and decreased albumin, suggestive of an acute phase response in these animals and were considered non-adverse. OBI-888-related changes in clinical chemistry parameters were limited to decreased albumin and increased globulins in individual animals at 200 mg/kg/dose. These changes were suggestive of a mild acute phase response, and were considered non-adverse. There were no OBI-888-related changes in urinalysis parameters occurred during the study.

The animals of all 4 OBI-888 treated groups (0, 20, 60, and 200 mg/kg) were sacrificed and the organs were checked externally and internally and harvested for histopathological examination. At terminal (Day 28) or recovery (Day 43) necropsy, there were no gross findings, organ weight changes, or microscopic findings.

Maximum serum concentrations (C_{max}) of OBI-888 occurred generally at 1 hour post-dose except for 60 mg/kg dosed animal on Day 22 where C_{max} was observed at 8 hour post-dose. Mean elimination half-life ($t_{1/2}$), when estimable, ranged from 37.2 to 42.0 hours on Day 1 and from 16.3 to 49.9 hours on Day 22. The mean clearance (Cl) was similar across the dose levels and ranged from 1.14 to 1.76 mL/hour/kg on Day 1 and from 1.43 to 2.41 mL/hour/kg on Day 22. The estimated mean volume of distribution (V_d) ranged from 33.3 to 135 mL/kg. Systemic exposure (C_{max} and total exposure [$AUC_{(0-t)}$]) to OBI-888 increased with increasing dose across the dose ranges. There was no accumulation of OBI-888 due to repeat

administration on Day 22 compared to Day 1 and mean accumulation ratios for $AUC_{(0-144)}$ ranged from 0.586 to 1.21. No gender difference was observed across dose ranges on both days.

In conclusion, administration of OBI-888 via intravenous (slow bolus) injection once weekly for a total of 4 doses (Days 1, 8, 15, and 22) was well tolerated in cynomolgus monkeys at levels of 200 mg/kg/dose. Based on these results, the NOAEL was considered to be 200 mg/kg/ dose.

4.3 Clinical Studies

4.3.1 Results from OBI-888-001

As of March 2020, a total of 17 patients with locally advanced or metastatic solid tumors have been enrolled, including 14 patients in the dose escalation phase (at doses of 5, 10, and 20 mg/kg) and 3 patients in the cohort expansion phase (at the selected recommended phase II dose [RP2D] of 20 mg/kg). The dose escalation phase is complete; no dose-limiting toxicities were reported and the maximum tolerated dose was not reached. The cohort expansion phase is ongoing, with OBI-888 administered at 20 mg/kg.

There have been 8 serious adverse events (SAEs) reported from 5 patients (from all 3 dose cohorts). All SAEs were assessed by the Investigator as unrelated to OBI-888. Two SAEs were Grade 5 (both in 1 patient), and the remaining SAEs were Grade 3 in severity. No patient has discontinued the study due to treatment related adverse events (AEs). Two (2/17, 11.7%) patients died on-study, both due to disease progression. OBI-888 in doses up to 20 mg/kg have been generally well-tolerated and no safety concerns have been noted.

In general, pharmacokinetic (PK) profiles following single-dose administration were similar across patients. Pharmacokinetic analysis showed no significant accumulation in peak concentrations (C_{max}) after multiple OBI-888 doses. However, accumulation of trough concentrations was observed in most patients (12/14, 86%). The mean trough concentrations at steady state increased with increasing OBI-888 dose (3.6 µg/mL for Cohort 1 [5 mg/kg], 5.1 µg/mL for Cohort 2 [10 mg/kg], and 11.3 µg/mL for Cohort 3 [20 mg/kg]). As expected for intravenous (IV) administration, C_{max} was achieved in most patients by the end of infusion. C_{max}/D values for each dose ranged from 0.246 to 0.275, suggesting that C_{max} was dose proportional across the doses tested. AUC_{last} exhibited higher variation across the doses tested, however, mean values of AUC_{last}/D and CL were similar across the dose groups. The mean Vz ranged from 4.4 to 5.7 L across the dose groups, which is consistent with the expected distribution volume of large protein therapeutics. The $t_{1/2}$ was similar across the dose groups (30 hours).

The incidence of anti-drug antibody (ADA) induction was 1/5 and 1/3 in Cohorts 1 and 2 respectively. ADCC and complement dependent cytotoxicity (CDC) induction activity were observed in all post-injection serum samples, showing a positive correlation with the OBI-888 serum concentrations detected in the PK study.

4.3.2 Globo H H-Score in Various Tumor Tissues

The distribution of immunohistochemistry (IHC) H-scores for Globo H observed in pancreatic, esophageal, gastric, colon, breast, lung, and liver cancers are as shown in Figure 4-1. A total of 562 specimens including tumor tissue resections and tumor tissue microarray section cores were analyzed, including 72 pancreatic cancer, 64 esophageal cancer, 73 gastric cancer, 131 breast cancer, 77 lung cancer, 75 colon cancer, and 70 liver cancer. The prevalence of Globo H cut-off varies in different cancer types and are summarized in Table 4-1.

Figure 4-1 Globo H Immunohistochemistry H-Score of Various Tumor Tissues

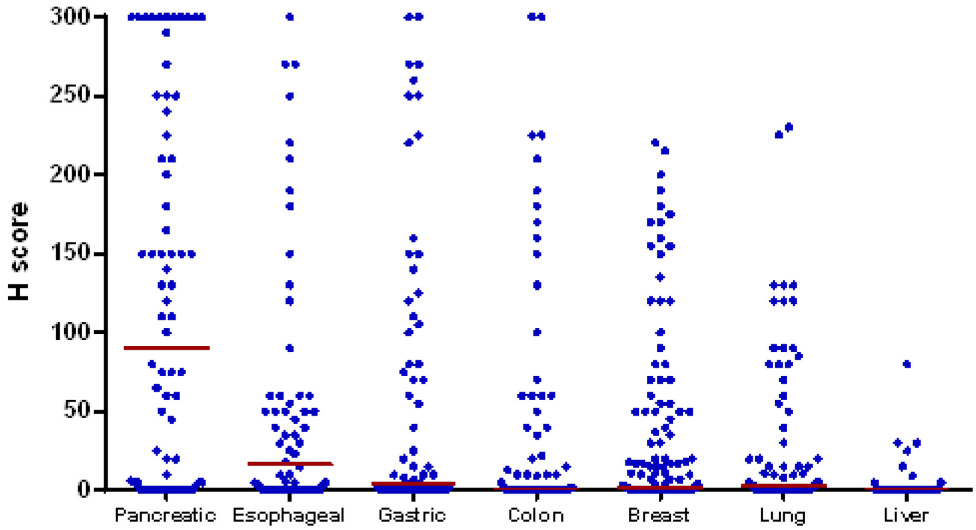

Table 4-1 Prevalence of Globo H Cut-Off in Different Cancer Types

Indication	# Evaluable Specimens	# H-score ≥1	Prevalence at H-score ≥1	# H-score ≥15	Prevalence at H-score ≥15	# H-score ≥20	Prevalence at H-score ≥20	# H-score ≥100	Prevalence at H-score ≥100
Pancreatic	72	55	76.4%	48	66.7%	48	66.7%	36	50.0%
Esophageal	64	42	65.6%	33	51.6%	31	48.4%	11	17.2%
Gastric	73	43	58.9%	30	41.1%	28	38.4%	18	24.7%
Colon	75	38	50.7%	24	32.0%	23	30.7%	12	16.0%
Breast	131	77	58.8%	49	37.4%	40	30.5%	17	13.0%
Lung	77	45	58.4%	28	36.4%	24	31.2%	8	10.4%
Liver	70	12	17.1%	5	7.1%	4	5.7%	0	0%

4.4 Clinical Risks/Benefits of OBI-888

As this is the first study in humans, there are no known clinical benefits that have been determined to be associated with the use of OBI-888. However, it is hoped that data from this clinical study and other trials sponsored by OBI Pharma will demonstrate the clinical benefits of OBI-888 in subjects with advanced or metastatic solid tumors.

4.5 Rationale

Globo H is a hexasaccharide glycosphingolipid located endogenously on the outer membrane of epithelial cells and was first identified in breast cancer cells. Globo H was found to be overexpressed on the cell surface of several epithelial cancers such as breast, pancreatic, ovarian, endometrial, gastric, lung, and prostate cancers. Globo H has been associated with tumor stem cells, as a potent inducer of angiogenesis and immune suppressor through Notch signaling, rendering it a target for cancer therapy (Cheng, et al., 2014).

The target population to be enrolled in this study will be patients with advanced or metastatic solid tumors refractory to at least one line of systemic therapy or intolerable with standard

therapy or for which no standard treatment is available. In Part B, all subjects will have Globo H expression analysis of their tumor in order to obtain a preliminary assessment of OBI-888 activity in patients whose tumors express the drug target. In this setting, while additional therapy may be available, the duration of PFS and OS could be optimized by new therapies with better efficacy and safety profile. Therefore, based on the above noted preclinical studies showing potential anti-tumor activity of OBI-888 in several tumor types, this study is conducted with the aim to offer patients the possibility of tumor shrinkage and prolongation of survival with this novel monoclonal antibody. Following the establishment of the safe dose, and PK/pharmacodynamic (PD) profile in the escalation phase, the expansion phase will be initiated to obtain additional safety data, and assess the preliminary clinical activity profile of OBI-888 administered as monotherapy in patients with locally advanced or metastatic solid tumors patients, and where we had seen signal of tumor inhibition in the preclinical trials.

The dose levels for this study resulted from calculation based on data from preclinical studies. The initial dose chosen for this study is 5 mg/kg administered every week.

This is a 2-part study: Part A (Dose Escalation) is designed to establish the maximum tolerated dose (MTD) of OBI-888 as monotherapy. Part B (Cohort Expansion) is intended to further characterize the safety and preliminary clinical activity profile of the MTD dose of OBI-888 administered as monotherapy in patients with locally advanced or metastatic solid tumors.

5 Study Objectives and Endpoints

5.1 Study Objectives

5.1.1 Primary Objectives

The primary objectives are:

- To evaluate the safety and tolerability of OBI-888 when administered IV to patients with locally advanced or metastatic solid tumors.
- To determine the MTD and RP2D of OBI-888 as monotherapy.

5.1.2 Secondary Objectives

The secondary objectives are:

- To evaluate the preliminary clinical activity profile (objective response rate [ORR], clinical benefit rate [CBR], duration of response [DOR], and progression-free survival [PFS]) of OBI-888.
- To evaluate the immunogenicity of OBI-888 (ADAs).
- To determine the serum PK and PD of OBI-888.

5.1.3 Exploratory Objectives

Exploratory objectives are:

- To assess ADCC and CDC.
- To identify potential predictive biomarkers.
- To assess the expression of immune markers including immune checkpoints, in the tumor tissue samples.
- To assess the expression of Globo H and related tumor-associated glycans in the tumor tissue
- To perform glycan analysis of OBI-888.

5.2 Study Endpoints

5.2.1 Primary Endpoints

- Dose-limiting toxicities (DLTs) with OBI-888
- AEs/SAEs and laboratory abnormalities as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03
- MTD and RP2D of OBI-888

5.2.2 Secondary Endpoints

- Percentage of patients with ORR, CBR, DOR and PFS according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1)
- Percentage of patients with anti-OBI-888 antibodies (ADAs) in blood
- PK and PD parameters of OBI-888

5.2.3 Exploratory Endpoints

- Globo H and related glycan expression in tumor tissue by IHC
- ADCC and CDC
- Identify potential predictive markers by IHC or molecular analysis
- Tumor infiltrating lymphocytes (TILs), including natural killer (NK) cells, and programmed death – ligand 1 (PD-L1) expression in tumor tissue samples by IHC

- Killer cell immunoglobulin-like receptor (KIR), human leukocyte antigen (HLA), and Fc receptor gamma genotype
- Glycan analysis of OBI-888

6 Investigational Plan

6.1 Description of Overall Study Design and Plan

This is a Phase I/II, open-label, dose escalation and cohort expansion study of OBI-888, a humanized mAb targeting Globo H, in patients with locally advanced or metastatic solid tumors.

This is a 2-part study. Part A (Dose Escalation) is designed to establish the MTD and RP2D of OBI-888. Part B (Cohort Expansion) is intended to further characterize the safety and clinical activity profile of the RP2D dose of OBI-888 administered as monotherapy in patients with locally advanced or metastatic solid tumors.

A Safety Review Committee (SRC) will review the safety data (AEs and laboratory toxicities) of each lower level dose cohort, before proceeding to the next dose level during dose escalation part. At the end of dose escalation phase, the SRC will review safety and PK data to confirm the MTD and establish RP2D, before start of the expansion cohort during the study, as specified in a separate charter.

6.1.1 Part A - Dose Escalation

The dose escalation part of the study will include 3 cohorts of escalating dose levels of 5, 10, and 20 mg/kg, using 3+3 design to identify MTD and RP2D.

Three patients will be enrolled at the lowest dose level. If none of the 3 patients experiences a DLT, the next cohort of 3 patients will be enrolled at the next higher dose level. If 1 of 3 patients in the initial dose cohort experiences a DLT, that cohort will be expanded to 6 patients. If only 1 of these 6 patients has a DLT, then the next cohort of 3 patients will be enrolled at the next higher dose level. If 2 or more patients of the 3-6 patients in a cohort experience a DLT, dose escalation will cease and that dose level will be above the MTD the highest dose where no more than 1 of 6 patients has experienced at DLT. New patients will be enrolled at the previous lower (tolerated) dose level until that cohort has 6 patients. This lower dose level will be considered the MTD if ≤1 in 6 patients has a DLT.

Subject should receive all four planned doses with OBI-888 administered during Cycle 1 to be eligible for DLT evaluation, unless they experience a DLT with any dose. A patient who withdraws from the study within the DLT evaluation period for reasons other than drug-related AE will not be included for DLT evaluation and will be replaced; but can continue to receive study treatment after slipped dose, if still eligible for treatment.

Escalation to higher OBI-888 dose cohort is not permissible during the study. After a DLT is experienced by a subjects, dose interruption, modifications or dose delays may apply, as per Investigators judgement (refer protocol Section 8.3).

6.1.2 Part B - Cohort Expansion

Once Part A (Dose Escalation) is completed, Part B will enroll a maximum of 150 additional patients with advanced solid tumors with high Globo H expression (defined as an H-score cutoff ≥ 100 using a validated IHC assay) across 4 disease specific cohorts and 1 basket cohort based

on a Simon two-stage design. The first-stage of Part B will recruit up to 9 patients in each cohort (up to 45 patients in the first stage across all cohorts). If sufficient evidence of activity is observed in the first stage, up to 21 additional patients will be enrolled into that cohort (up to 105 patient in the second stage across all cohorts).

Part B will be conducted to obtain additional safety data, characterize the PK and PD profile of OBI-888, obtain a preliminary assessment of the clinical activity of OBI-888 in Globo H expressing solid tumors, and inform subsequent efficacy-finding clinical development.

No DLTs have been observed at any dose level tested in Part A, and the MTD has not been reached. Therefore, dosing in Part B will be initiated at the highest dose tested in Part A (20 mg/kg OBI-888).

The following 5 cohorts of patients who have high expression of Globo H by a qualified laboratory assessment (ie, Globo H H-score ≥ 100 using a validated IHC assay) will be enrolled in Part B.

- Cohort 1: Pancreatic cancer
- Cohort 2: Esophageal cancer
- Cohort 3: Gastric cancer
- Cohort 4: Colorectal cancer
- Cohort 5: Basket (any solid tumor type other than those included in Cohorts 1 through 4)

All patients are required to provide a tumor biopsy sample, either unstained slides (preferred) or a formalin fixed paraffin embedded (FFPE) tissue block at the initiation of screening visit for screening of Globo H overexpression and confirmation for eligibility of patients for Part B. Patients with a confirmed and documented Globo H H-score of ≥ 100 will be eligible for the study, and will subsequently enter the 28-day screening period to complete the remaining screening procedures.

Patients will continue to receive treatment with OBI-888 until progressive disease, unacceptable toxicity, or decision by the Investigator or patient to discontinue treatment.

6.1.3 Duration of Study

The study (Part A and B) includes a **screening period** (up to 28 days) prior to the first dose of OBI-888, a **treatment period**, and a **follow-up period**. Treatment will continue until progressive disease, unacceptable toxicity, or decision by the Investigator or patient to discontinue treatment.

For Part B, pre-screening for Globo H tumor sample analysis may occur prior to the screening period for participation in the OBI-888-001 study.

The safety follow-up will be conducted 28 days after the last dose of study treatment.

6.2 Definition of Dose-Limiting Toxicities

A DLT is defined as the occurrence of any of the following events, within the first cycle of treatment, that are considered to be at least possibly related to OBI-888. All AEs unless they have been determined to be not related to study drug will be taken into consideration in determining DLTs. NCI-CTCAE version 4.03 will be the basis for the descriptive terminology and grading of AEs.

DLTs are defined as:

- Grade 4 neutropenia
- ≥Grade 3 febrile neutropenia with or without infection
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding
- ≥Grade 3 nausea and vomiting or diarrhea for more than 72 hours despite optimal supportive care
- Any other ≥Grade 3 non-hematological AE that does not resolve before the next infusion.

The DLT evaluation period is the first cycle; 28 days from start of study treatment.

6.3 Discussion of Study Design

This study will be undertaken in patients with advanced cancer that has progressed on prior therapy. In this setting, patients will be seeking to alleviate symptoms of their fatal disease and prolong life through exposure to a novel agent.

Patient safety, and a favorable risk/benefit balance, will be carefully monitored throughout and after treatment. Additionally, attention will be taken to enrolling only patients who are felt to be in sufficient condition to undertake this clinical trial, as defined by adequate performance status, suitable baseline organ function, and the Investigator's determination that there are no significant comorbid conditions which present undue risk. Nevertheless, unexpected toxicity of the investigational drug may occur, and all patients will have informed consent prior to treatment.

In terms of the study design, escalating cohorts for 5, 10, and 20 mg/kg will be assessed using a 3+3 design to identify the MTD and RP2D. Once the MTD and RP2D are established and PK/PD data are carefully evaluated, a cohort expansion will be initiated. The cohort expansion will allow for additional safety data, characterize the PK/PD profile of OBI-888, and evaluate the preliminary clinical activity profile of OBI-888 administered as monotherapy in patients with advanced or metastatic solid tumors.

7 Selection and Withdrawal of Patients

7.1 Inclusion and Exclusion Criteria

7.1.1 Inclusion Criteria

Patients must meet all of the following criteria in order to be included in the study:

1. Male or female patients, 18 years of age or older at the time of consent.
2. Provide written informed consent prior to performing any study-related procedure.
3. Histologically or cytologically confirmed patients with advanced or metastatic solid tumors will be enrolled, for both Dose Escalation and Expansion.
4. Patients must have been treated with established standard-of-care therapy, or physicians have determined that such established therapy is not sufficiently efficacious, or patients have declined to receive standard-of-care therapy.
5. Measurable disease (i.e., at least one measurable lesion per RECIST, version 1.1) (Eisenhauer, et al., 2009).
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Oken, et al., 1982).

7. Adequate organ function defined as:
    a. Hepatic:
        - Serum alanine aminotransferase (ALT) ≤3 × upper limit of normal (ULN), ≤5 × ULN in the presence of liver metastases
        - Serum aspartate aminotransferase (AST) ≤3 × ULN, ≤5 × ULN in presence of liver metastases
        - Serum bilirubin ≤1.5 × ULN (unless due to Gilbert's syndrome or hemolysis)
    b. Renal:
        - Creatinine clearance >30 mL/minute using Cockcroft Gault equation
    c. Hematologic:
        - Absolute neutrophil count ≥1000/μL
        - Platelets ≥75,000/μL
        - Hemoglobin ≥8 g/dL
8. Patient is willing and able to comply with all protocol-required assessments, visits, and procedures, including a pretreatment tumor biopsy. Archival tumor biopsies (slides or FFPE tissue block) are acceptable at baseline.
9. Females of childbearing potential must have negative serum or urine pregnancy test prior to starting study therapy, and agree to use a reliable form of contraceptive during the study treatment period and for at least 120 days following the last dose of study drug. Subject not of childbearing potential (i.e., permanently sterilized, postmenopausal) can be included in study. Postmenopausal is defined as 12 months with no menses without an alternative medical cause. Male patients must agree to use an adequate method of contraception during the study treatment period and for at least 120 days following the last dose of study drug.
10. Cannot be breast feeding.
11. Patients in Part B (Cohort Expansion) must have a documented Globo H H-score of at least 100 from a qualified laboratory IHC assay in one of the following tumor types to be enrolled in the respective cohort:
    - Cohort 1: Pancreatic cancer
    - Cohort 2: Esophageal cancer
    - Cohort 3: Gastric cancer
    - Cohort 4: Colorectal cancer
    - Cohort 5: Basket (any solid tumor type other than those included in Cohorts 1 through 4)

7.1.2 Exclusion Criteria

Patients meeting any of the following criteria are ineligible to participate in this study:

1. Less than 3 weeks, from prior cytotoxic chemotherapy or radiation therapy; and less than 5 half-lives or 3 weeks from biological therapies, whichever is shorter, prior to the first dose of OBI-888.
2. Has undergone a major surgical procedure (as defined by the Investigator) or significant traumatic injury within 28 days prior to the first dose of OBI-888.
3. Presence of an active autoimmune or inflammatory disease requiring systemic treatment

within the past 2 months or a documented history of clinically severe autoimmune disease that requires systemic steroids or other immunosuppressive medications. Local steroid injections, intermittent use of topical, inhaled, ophthalmologic, intra-articular, topical, or intranasal corticosteroids, or systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or equivalent would not be excluded from the study.

4. Presence of primary immunodeficiency or receiving systemic steroids of >10 mg/day prednisone or equivalent or other immunosuppressive agents within 14 days prior to the first dose of OBI-888.
5. Has active bacterial, viral, fungal, or mycobacterial infection requiring systemic therapy, including known infection with human immunodeficiency virus (HIV) or active infection with hepatitis B virus or hepatitis C virus. Patients with HIV infection are eligible if CD4+ T-cell counts are ≥350 cells/μL; patients on antiretroviral therapy should be on an established dose for at least 4 weeks and have an HIV viral load less than 400 copies/mL prior to enrollment.
6. Patients with a history of solid organ transplant.
7. Unresolved toxicities from prior anticancer therapy, defined as having not resolved to Grade 0 or 1 (using NCI CTCAE version 4.03), except for alopecia and laboratory values listed in the inclusion criteria.
8. Receipt of any prior therapy targeting Globo H.
9. Known hypersensitivity to OBI-888 or its excipients.
10. Has known untreated central nervous system metastases. Patients with treated brain metastases are eligible if there is no evidence of progression for at least 4 weeks after central nervous system-directed treatment, as ascertained by clinical examination and brain imaging (magnetic resonance imaging [MRI] or computed tomography [CT]) during the screening period.
11. Any medical co-morbidity or psychiatric illness that is life-threatening or, in the opinion of the Investigator, renders the patient unsuitable for participation in a clinical trial due to possible noncompliance, would place the patient at an unacceptable risk, and/or potential to affect interpretation of results of the study.
12. Is receiving any concurrent prohibited medication as listed in Section 8.6.3.

7.2 Treatment Discontinuation and Withdrawal of Subjects

A patient who withdraws from the study within the DLT evaluation period for reasons other than drug related AE will be replaced.

A patient may voluntarily withdraw or be withdrawn from the study treatment at any time for reasons including, but not limited to, the following:

- Progressive disease
- Grade 4 infusion reactions and OBI-888 related toxicity
- Dose reductions required on more than 2 occasions for toxicity related to OBI-888
- Treatment interruption for more than 2 consecutive doses for related or unrelated reasons.
- Patient withdrawal of consent: At any time, a patient's participation in the study may be terminated at his/her request or on the basis of the Investigator's clinical judgment.

- Inter-current illness: A condition, injury, or disease unrelated to the primary diagnosis that becomes apparent during treatment and necessitated the patient's termination from the study.
- General or specific changes in the patient's condition that renders him/her ineligible for further treatment according to the inclusion/exclusion criteria.
- Protocol deviation: The patient's findings or conduct fail to meet the protocol entry criteria or fail to adhere to the protocol requirements (e.g., drug noncompliance, failure to return for defined number of visits). The deviation necessitated premature termination from the study.
  Lost to follow-up: The patient stops coming for visits, and study personnel are unable to contact the patient.

7.3 Follow-Up for Drug Discontinuation/Subject Withdrawal from Study

If a patient discontinues study treatment and is withdrawn from the study for any reason, the study site must immediately notify the Sponsor. The date and the reason for study treatment discontinuation / study withdrawal must be recorded on the electronic case report form (eCRF). Patients who withdraw prematurely are to attend an early termination visit, if possible, and complete all assessments.

In the event that a patient discontinues prematurely from the study due to a treatment-emergent adverse event (TEAE) or serious TEAE, the TEAE or serious TEAE will be followed until it resolves (returns to normal or baseline values) or stabilizes, or until it is judged by the Investigator to be no longer clinically significant.

Once a patient is withdrawn from the study, the patient may not re-enter the study.

8 Treatments

8.1 Details of Study Treatment

OBI-888 (a humanized anti Globo H monoclonal antibody).

OBI-888 drug product is a colorless to light yellow liquid which is filled in a transparent Type I glass vial in solution form, with final concentration 30 mg/mL in 25 mM L-Histidine, 150 mM L-Arginine, pH 6.0, 0.02% Polysorbate 80.

All study drug will be supplied by OBI Pharma Inc., and must remain under adequate security, and proper storage condition. Do not use study drug after the expiration date, which is imprinted on the drug container.

Investigational drug solution should be prepared by mixing the OBI-888 drug product (DP) with infusion solution (0.9% saline or 5% glucose) before intravenous infusion. Refer to Appendix 1 and the Pharmacy Manual for study drug preparation instructions.

8.1.1 Packaging and Labeling

OBI-888 drug product will be packaged in carton boxes. Each box will contain ten OBI-888 vials. The labels on each kit will meet the applicable regulatory requirements for each country.

OBI-888 will be packaged and labeled according to current Good Manufacturing Practices (GMP) guidelines. Details of the packaging and labeling are provided in the Pharmacy Manual.

8.1.2 Storage

OBI-888 drug product must be stored at a temperature of 2 to 8º C. Based on the stability data available, the shelf-life of OBI-888 drug product is stable for at least 36 months at 5 ± 3°C.

8.2 Dosage Schedule

8.2.1 OBI-888 Doses

For Part A (Dose Escalation), OBI-888 will be given at doses of 5 mg/kg, 10 mg/kg and 20 mg/kg to the 3 dose cohorts.

For Part B (Cohort Expansion) subjects will be treated with 20 mg/kg OBI-888 since no DLTs have been observed at any dose level tested in Part A, and the MTD was not reached.

If during treatment a patient's body weight changes by >10% from the baseline value, the OBI-888 dose should be adjusted.

8.2.2 Regimen

OBI-888 will be administered as an IV infusion on Days 1, 8, 15, and 22 of each 28-day cycle in Part A and Part B of the study.

Treatment will continue until progressive disease, unacceptable toxicity, or decision by the Investigator or patient to discontinue treatment.

8.2.3 Duration of Infusion

OBI-888 investigational drug solution (OBI-888 drug product mixed with saline/glucose infusion solution) should be administered as IV infusion by the site staff.

The infusion should be given for a duration of approximately 90-minute (±10 minutes), for the initial two cycles (C1 and C2).

The infusion duration from Cycle 3 could be reduced, if no infusion related AEs to prior infusions occur, to 30 minutes or 60 minutes at the discretion of the Investigator.

8.3 Dose Modifications and Toxicity Management

Escalation to higher OBI-888 dose cohort is not permissible during the study.

Dose modifications for hematologic and non-hematologic toxicity and infusion reactions should be independently assessed at each visit. Recommendations for dose modifications for toxicity are provided in Table 8-1 below.

Table 8-1 OBI-888 Dose Modifications for Toxicity

Toxicity	Hold Dose	% of Full Dose after Recovery to Grade 0-1
Grade 1	Do not hold dose	100
Grade 2	Hold dose until resolution to Grade 0 or 1	75
Grade 3	Hold dose until resolution to Grade 0 or 1	75
Grade 4	Treatment should be discontinued	NA

Once the dose has been reduced for toxicity and found to be well tolerated, re-escalation may be permitted at the Investigator's discretion. If a subject requires dose reductions on more than 2 occasions for toxicity related to OBI-888, the subject should discontinue from the study.

All reasons for treatment modifications should be fully explained.

The study drug dose which is not administered within the permitted window period of ±3 days, must be skipped, and the next dose will be administered as per protocol schedule. Any skipped dose due to safety reason and if medically justified, for OBI-888 treatment related or unrelated reasons, will not be captured as a protocol deviation for this study.

Treatment interruption for more than 2 consecutive doses for related or unrelated reasons may necessitate discontinuation of study treatment.

Treatment interruption for intercurrent non-treatment related adverse events will be at the Investigator's discretion and based on the well-being of the patient. All reasons for treatment interruption and delays should be fully explained. Treatment for hematologic and non-hematologic toxicity may be implemented as clinically indicated according to institutional guidelines. Refer Table 8-2 for therapeutic antiemetic and anti-diarrheal recommendations.

Table 8-2 Therapeutic Antiemetic and Anti-Diarrheal Recommendations

Diarrhea and Abdominal Cramping	Nausea, Vomiting, or Anorexia
Dicyclomine: Recommended when the predominant issue is cramping or abdominal pain	1st line: 5HT3-inhibitors
Diphenoxylate/Atropine or/and Loperamide	2nd-line: Dexamethasone, ideally in combination with a 5HT3-inhibitor. Short term use can be very effective
	Other agents: anti-histamines; benzodiazepines; proton pump inhibitors; dopamine antagonists; cannabinoids
Hyoscine: Anti spasmodic agents helpful for abdominal cramping	
Budesonide (Entocort EC): Corticosteroid with limited systemic absorption; 9 mg once daily for up to 8-12 weeks	

8.3.1 Infusion Reactions

Signs/symptoms of infusion reactions may include: allergic reaction/hypersensitivity (including drug fever); arthralgia (joint pain); bronchospasm; cough; dizziness; dyspnea (shortness of breath); fatigue (asthenia, lethargy, malaise); headache; hypertension; hypotension; myalgia (muscle pain); nausea; pruritic/itching; rash/ desquamation; rigors/chills; sweating (diaphoresis); tachycardia; tumor pain (onset or exacerbation of tumor pain due to treatment); urticaria (hives, welts, wheals); and vomiting.

In the event of an infusion reaction, additional serum/plasma samples may be drawn at the time of the event to evaluate drug concentration and anti-drug antibody, as well as to assess levels of cytokines and/or other markers of inflammation.

Prophylactic Measures

Prior to dosing with OBI-888, patients should receive prophylactic treatment for infusion reactions consisting of acetaminophen orally and diphenhydramine (or equivalent) orally or IV 30 to 60 minutes prior to infusion of OBI-888 (recommended doses are: acetaminophen 650 mg, diphenhydramine 50 mg). If an alternative premedication regimen is thought to be required, Sponsor approval should be sought.

For patients who experience an infusion reaction despite initial premedication, additional prophylactic treatment may be added prior to subsequent doses, including an H2 blocker such as ranitidine, and/or corticosteroids.

Prophylactic treatment for infusion reactions may be withheld at the Investigator's discretion if no infusion reactions were observed with the first cycle of treatment.

Management of Infusion Reactions

In the event of an infusion reaction, the OBI-888 infusion should be interrupted and medical therapy administered according to institutional standard of care which, depending upon the severity of the event, may include but should not be limited to use of H1 and H2 inhibitors, and corticosteroids.

Patients who experience a Grade 1 or Grade 2 infusion reaction may resume the infusion of drug at a reduced infusion rate (30% to 50% slower than initial rate) on the same day following appropriate medical management. If the 4-hour window from product reconstitution to completion of infusion will be exceeded (Appendix 1), new drug may be prepared to administer the remainder of the planned dose.

Patients who experience a Grade 3 infusion reaction may be retreated at the discretion of the Investigator at the next scheduled treatment. Such patients should receive additional prophylactic medication that may include a corticosteroid, and the duration of infusion may be increased.

OBI-888 should be permanently discontinued in patients who experience a life-threatening (Grade 4) infusion reaction.

8.4 Study Treatment Assignment

Patients will be assigned to a dose level in the order of study entry.

8.5 Treatment Accountability and Compliance

All drug supplies will be provided by the Sponsor. Administration of study drugs will be supervised by study personnel to ensure compliance.

8.6 Prior and Concomitant Illnesses and Medications

8.6.1 Prior and Concomitant Illnesses

Investigators should document all prior significant illnesses that the patient has experienced prior to screening. Additional illnesses present at the time when informed consent is given and up to the time of first dosing are to be regarded as concomitant illnesses. Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs on the eCRF.

8.6.2 Prior and Concomitant Medications

All medications and other treatments taken by the patient prior to the start of the study at screening and treatments initiated during the study, must be recorded on the eCRF. The entry must include the dose, regimen, route, indication, and dates of use.

After the baseline visit, medication to treat minor illness(es) are generally permitted, including:

- Use of localized palliative radiation for pre-existing lesions to control pain, at the discretion of the physician.
- Corticosteroids use: topical, inhaled, ophthalmologic, intra-articular, or intranasal corticosteroids; systemic steroids at physiologic doses not to exceed 10 mg/day of prednisone or equivalent. For management of side effects including nausea or infusion reactions, intermittent prophylactic or therapeutic use of glucocorticoids is allowed at doses required for medical therapy administered according to institutional standard of care and at the Investigator's discretion.

8.6.3 Prohibited Medications

If there is a clinical indication for the use of one of these prohibited medications, then discontinuation from the study drug may be required.

- Anti-neoplastic therapy, whether approved or experimental, including but are not limited to: chemotherapy, immunotherapy, surgery, radiotherapy are not allowed with OBI-888. **NOTE:** Use of localized palliative radiation for pre-existing lesions to control pain may be allowed at the discretion of the physician.
- Immunosuppressive therapy (e.g., cyclosporine, rapamycin, tacrolimus, cyclophosphamide, methotrexate, etc.).
- Systemic steroids of >10 mg/day prednisone or equivalent
- Any other concurrent investigational therapy, regardless of indication.

9 Study Procedures

Table 9-1 outlines the timing of procedures, and assessments to be performed throughout the study.

The PK sampling schedule is outlined in Table 9-2 (Part A – Dose Escalation) and Table 9-3 (Part B - Expansion).

9.1 Subject Informed Consent

Prior to performing any study-related procedures, the Investigator (or his/her designated staff member) will obtain written informed consent from the patient.

9.2 Procedures by Study Period

Assessments and study procedures are to be performed as outlined in The Schedule of Assessments, Table 9-1. The PK, ADA, Biomarker, and Glycan Sampling Schedule is provided in Table 9-2 (Part A – Dose Escalation) and Table 9-3 (Part B - Expansion).

The Investigator may at his/her discretion arrange for a patient to have an unscheduled assessment, especially in the case of AEs that require follow-up or an AE considered by the Investigator to be possibly related to the use of study drug. The unscheduled visit page on the eCRF must be completed. Additional visits to follow-up positive ADA may happen after end of study (Table 9-1).

Table 9-1 Schedule of Assessments

Study Procedure	**Screening Visit****	**Treatment Period**					**EoS / ET**
Cycle (C) #	-	**Cycle 1**				**Cycle 2-13**	
Cycle # and Day		C1D1	C1D8	C1D15	C1D22		
Window period (days)	-28 to -1 days	-1*	±1	±3	±3	±3 days	±7 days
Informed consent[a]	X						
Demographics	X						
Eligibility screening	X	X					
Medical history[b]	X	X					
Physical examination[c]	X	X	X	X	X	D1 of each Cycle	X
Height, weight[d]	X	X	X	X	X	D1 of each Cycle	X
Vital signs[e]	X	X	X	X	X	D1, D8, D15, D22 of each Cycle	X
ECOG[f]	X					D1 of each Cycle	X
12-lead ECG[g]	X	X					
Pregnancy testing[h]	X						X
Tumor biopsy[i]	X**						
Hematology and Biochemistry[j]	X	X				D1 of each Cycle	X
Coagulation and Urinalysis[k]	X	X					
Drug administration[l]		X	X	X	X	D1, D8, D15, D22 of each 28 day cycle	
Pharmacokinetic sample[m]		See footnote m and Table 9-2 (Part A) and Table 9-3 (Part B)					
Immunogenicity (ADA)[n]		See footnote n and Table 9-2 (Part A) and Table 9-3 (Part B)					
Biomarkers[o]	X	See footnote o and Table 9-2 (Part A) and Table 9-3 (Part B)					
Radiology evaluations (CT or MRI)[p]	X					Q8wk (±1 wk) for the first 6 months, then Q12wk (±1 wk) thereafter	X
Concomitant medications	◄	———	———	———	———	———	►
Adverse events		◄	———	———	———	———	►

EOS/ET - End of Study/Early Termination. EoS Visit is the safety follow-up visit, conducted 28±7 days after the last OBI-888 dose. ET visit lab assessments will be conducted for subjects discontinuing study treatment, if last available tests are before 2 weeks.

*The -1 day window (1 day prior) for C1D1 is for safety laboratory assessments. Blood can be drawn 1 day prior to initiation of study drug infusion on C1D1. Safety laboratory results should be available and reviewed by the Investigator prior to the OBI-888 administration.

** All patients are required to provide a tumor biopsy sample, unstained slides (preferred) or a formalin fixed paraffin embedded (FFPE) tissue block at the initiation of screening visit for screening of Globo H overexpression and confirmation for eligibility of subjects for Part B. Patients with a confirmed and documented Globo H H-score of ≥ 100 are eligible for the study, and will subsequently enter the 28-day screening period to complete the remaining screening procedures.

Footnotes:

a. Informed consent to be obtained before any other study procedures are performed.
b. Medical history to include previous cancer therapies, cancer history, and past and ongoing concomitant illnesses.
c. A complete physical examination is required at screening and at discontinuation. Directed physical examinations may be limited to problem focused review of symptoms and major organ systems at D1 of each cycle and prior to infusion.
d. Height to be obtained at screening only. Weight obtained at D1 of each cycle, prior to infusion. If during treatment a patient's body weight changes by >10% from the baseline value, the OBI-888 dose should be adjusted.
e. Vital signs include temperature, blood pressure and pulse (at supine position) prior to every infusion. Temperature measurement will be obtained as clinically indicated.
f. ECOG performance status: at baseline, C2D1 and end of study/early termination.
g. 12-lead ECG: at screening and pre and post infusion at C1D1 (within one hour after end of infusion).
h. Pregnancy testing should be performed in females of childbearing potential only. A urine or serum pregnancy test is acceptable.
i. Tumor biopsy samples are mandatory at screening visit. Fresh (preferred) tissue or archival tissue is acceptable. A minimum of 3 slides are required for the central laboratory Globo H assay for determination of eligibility. Up to 12 unstained additional slides should be provided, depending upon availability, for the protocol-defined exploratory studies.
j. Hematology and Serum chemistry (Laboratory Assessments: Table 12-1). Blood draw is prior to OBI-888 infusion.
Hematology: hematocrit, hemoglobin, red blood cell (RBC) count, white blood count (WBC), absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet count.
Serum chemistry: sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphorus, magnesium, total protein, albumin, ALT, AST, ALP, creatine kinase, LDH, total bilirubin, and uric acid. Creatinine clearance will be calculated by Cockcroft Gault equation at the screening visit, Week 1 and EOS/early termination.
k. Coagulation, and Urinalysis (Laboratory Assessments: Table 12-1). Blood draw and urine collection is prior to OBI-888 infusion.
Coagulation: PT, aPPT, and INR.
Urinalysis: specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase as assessed by dipstick. A microscopic urinalysis (only if needed) evaluating white blood cells, red blood cells, epithelial cells, bacteria, cast and crystals
l. OBI-888 is given in cycles with each individual cycle consisting of 28 days (4-week cycle). IP is administered on a weekly basis (within cycle as C1D1, C1D8, C1D15, and C1D22; C2D1, C2D8, and so on; until progressive disease, unacceptable toxicity, or decision by the Investigator or patient to discontinue treatment.
m. Pharmacokinetic: (for analysis of serum concentration of OBI-888). Detailed schedules are provided in Table 9-2 (Part A) and Table 9-3 (Part B).
n. Immunogenicity studies (ADA): ADA samples will be collected at the same time points, along with pre-infusion only PK samples. No post-infusion ADA samples will be collected. Detailed schedules are provided in Table 9-2 (Part A) and Table 9-3 (Part B). For subjects with persistent antibodies at end of study, an additional ADA sample will be collected at 4 months after the end of study visit.
o. Biomarker: Detailed schedules are provided in Table 9-2 (Part A) and Table 9-3 (Part B).
p. Radiology (CT or MRI scan) evaluations of tumor response: Performed during screening and during the study every Q8wk (±1 wk) for the first 6 months, then every Q12wk (±1 wk) thereafter. Unscheduled scans can be performed anytime, if needed to confirm disease progression. Radiology assessment for end of study follow-up and early termination should be performed unless the patient already has radiographic confirmation of progressive disease or the last exam was ≤8 weeks prior to permanent discontinuation of study drug. The same assessment method and the same technique should be used on each patient while on study.

Table 9-2 Part A – Pharmacokinetic, ADA, Biomarker, and Glycan Sampling Schedule

Cycle (C)	Cycle 1						Cycle 2		Every 2 Cycles[e, h]	EoS / ET
Cycle Day	**D1**	**D2**	**D4**	**D8**	**D15**	**D22**	**D1, 8, 15**	**D22**	**D1**	**±7 days**
Pharmacokinetic Samples										
Before infusion	X[a]			X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X
End of infusion (90 minutes)[c]	X	X[d]	X[d]	X	X	X	X	X		
1 hour after end of infusion (150 minutes)[e]	X									
4 hours after end of infusion (330 minutes)[e]	X									
8 hours after end of infusion (570 minutes)[e]	X									
Immunogenicity studies (ADA)[f]	X			X	X	X	X	X	X	X
Glycan analysis[g]	X			X	X	X	X	X		
Biomarkers										
ADCC[i]	X				X			X	C4D1	X
CDC/ADCC[i]	X			X	X					
KIR, HLA, Fc receptor gamma genotyping[i]	X									X

ADA = antidrug antibody; ADCC = antibody-dependent cell-mediated cytotoxicity; C = cycle; CDC = complement dependent cytotoxicity; D = day; EoS/ET = End of Study/Early Termination; HLA = human leukocyte antigen; KIR = killer cell immunoglobulin-like receptor

Note: OBI-888 infusion should be administered on Days 1, 8, 15, and 22 of every 28 day cycle throughout the study treatment period.
The infusion duration of Cycle 1 and Cycle 2 are 90 minutes, and can be reduced to 30-60 minutes from Cycle 3, if there were no infusion related adverse events on prior infusions and at the discretion of the Investigator.

a. C1D1 Pre-infusion serum samples can be drawn within 1 day prior-to the infusion.

b. Pre-infusion serum samples can be collected at any time prior to the infusion on the day of the infusion.

c. Post infusion samples at the end of infusion and later (at 1, 4, and 8 hours after the end of the infusion) can be collected in a window of ±15 minutes.

d. For Cycle1 Days 2 and 4, a single sample will be collected (window ±2 hours):
   - 24 hours after end of infusion (for infusion at C1D1)
   - 72 hours after end of infusion (for infusion at C1D1)

e. If there is change of the infusion rate or interruption of infusion, the PK sampling at Day 1 are to be collected from the exact time of completion of infusion to obtain the post-infusion samples at 1, 4, 8 hour at the end of infusion. Exact time of sample collection and the reason for interruption should be documented in the eCRF.

f. ADA sample will be collected along with the pre-infusion PK samples according to the above table. No post-infusion ADA samples including C1D2 and C1D4 will be collected. For subjects with persistent antibodies at end of study, an additional ADA sample will be collected at 4 months after the end of study visit.

g. Glycan analysis: pre-infusion and end of infusion in cycle 1 and 2 only. Residual PK and ADA samples will be pooled for glycan analysis after PK and ADA data are finalized.

h. Samples to be collected on Day 1 of C4, C6, C8, C10, C12.

i. Biomarkers:

- ADCC (effector cell): pre-infusion blood sample will be collected at C1D1, C1D15, C2D22, C4D1 and end of study/early termination.
- CDC/ADCC (humoral): pre infusion and end-of-infusion blood sample will be collected at C1D1, C1D8, and C1D15.
- KIR, HLA, Fc receptor gamma genotyping: blood sample will be collected at C1D1 (pre-infusion) and end of study/early termination.

Table 9-3 Part B – Pharmacokinetic, ADA, and Biomarker Sampling Schedule

Cycle (C)	Screening	Cycle 1						Cycle 2	Every 2 cycles starting with Cycle 3 [a]	Every 2 cycles starting with Cycle 4[c]	EoS / ET
Cycle Day	**-28 to -1 days**	**D1**	**D2**	**D4**	**D8**	**D15**	**D22**	**D1**	**D1**	**D1**	**±7 days**
Pharmacokinetic Samples											
Before infusion		X[d]			X[b]	X[b]		X[b]		X[b]	
End of infusion (90 minutes)[f]		X	X[j,k]	X[k]		X					
1 hour after end of infusion (150 minutes)[e,f]		X[j]									
3 hours after end of infusion (270 minutes)[e,f]		X[j]									
6 hours after end of infusion (450 minutes)[e,f]		X[j]									
Immunogenicity studies (ADA)[g]		X						X		X	X
Glycan analysis[h]		X			X	X		X		X	X
Biomarkers											
Globo H	X[m]										
ADCC/CDC (humoral)[d,l]		X			X	X					
KIR, HLA, Fc receptor gamma genotyping[d]		X									
Multiplex IHC[n]	X										
Diagnostic marker[n]	X										
SSEA-3/SSEA-4[n]	X										
Surrogate biomarker[d,i]		X							X		

ADA = antidrug antibody; ADCC = antibody-dependent cell-mediated cytotoxicity; C = cycle; CDC = complement dependent cytotoxicity; D = day; EoS/ET = End of Study/Early Termination; HLA = human leukocyte antigen; IHC = immunohistochemistry; KIR = killer cell immunoglobulin-like receptor; SSEA = stage-specific embryonic antigens

Note: OBI-888 infusion should be administered on Days 1, 8, 15, and 22 of every 28 day cycle throughout the study treatment period.

The infusion duration of Cycle 1 and Cycle 2 are 90 minutes, and can be reduced to 30-60 minutes from Cycle 3, if there were no infusion related adverse events on prior infusions and at the discretion of the Investigator.

a. Samples to be collected on Day 1 of C3, C5, C7, C9, C11, and C13.

b. Pre-infusion serum samples can be collected at any time prior to the infusion on the day of the infusion.

c. Samples to be collected on Day 1 of C4, C6, C8, C10, and C12.

d. C1D1 Pre-infusion serum samples can be drawn within 1 day prior-to the infusion.
e. If there is change of the infusion rate or interruption of infusion, the PK sampling at Day 1 are to be collected from the exact time of completion of infusion to obtain the post-infusion samples at 1, 3, 6 hour at the end of infusion. Exact time of sample collection and the reason for interruption should be documented in the eCRF.
f. Post infusion samples at the end of infusion and later (at 1, 3, and 6 hours after the end of the infusion) can be collected in a window of ±15 minutes
g. ADA sample will be collected along with the pre-infusion PK samples according to the above table. For subjects with persistent antibodies at end of study, an additional ADA sample will be collected at 4 months after the end of study visit.
h. Glycan analysis: Residual PK and ADA samples will be pooled for glycan analysis after PK and ADA data are finalized.
i. Samples should be collected to evaluate tumor-specific biomarkers (eg, CEA for colorectal, gastric, and esophageal cancer; and CA19-9 for pancreatic cancer).
j. This intensive PK sampling will be collected only from first 3 patients in each cohort.
k. For C1D2 and C1D4, samples can be collected in a window of ±2 hours:
   - 24 hours after end of infusion (for infusion at C1D1).
   - 72 hours after end of infusion (for infusion at C1D1).
l. Blood sample will be collected pre-infusion and end-of-infusion.
m. For Part B, pre-screening for Globo H tumor sample analysis may occur prior to the screening period for participation in the OBI-888-001 study.
n. Tumor biopsy samples obtained during the initial screening visit should be used for this assessment.

10 Clinical Activity Profile Assessments

Radiology (CT or MRI scan) evaluations (±7 days) of tumor response are to be performed during screening within 28 days prior to Cycle 1 Day 1 (first dose of study medication), and thereafter during the study every 8 weeks (Q8wk; ± 1 week) for the first 6 months, then every 12 weeks (Q12wk; ± 1 week). Unscheduled scans can be performed anytime, if needed to confirm disease progression. Radiology assessment for end of study follow-up and early termination should be performed unless the last exam was ≤ 8 weeks prior to permanent discontinuation of study drug. The same assessment method and the same technique should be used on each patient while on study.

Overall tumor response and progression will be evaluated by the Investigator according to RECIST, version 1.1.

11 Pharmacokinetics

11.1 Pharmacokinetic Sampling

Blood samples for pharmacokinetic analysis of OBI-888 levels will be collected at the time points indicated in the Pharmacokinetic Sampling Schedules (Table 9-2 [Part A – Dose Escalation] and Table 9-3 [Part B – Expansion]). The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Details of PK blood sample collection, processing, storage, and shipping procedures are provided in a separate laboratory manual.

11.2 Pharmacokinetic Analytical Methodology

The concentration of study drug will be determined from the serum samples using a validated analytical method. Details of the method validation and sample analysis will be included with the final clinical study report.

PK parameters will be calculated using a non-compartmental method from the PK samples collected on Dose 1 and will include C_{max}, total exposure (AUC), $t_{1/2}$, Cl, and V_d. To assess the attainment of steady state, trough (C_{min}) concentrations and peak concentrations (end of infusion) of each dose would be obtained directly from analytical data.

Pharmacometric methods may also be applied to further investigate OBI-888 exposure (e.g., accumulation of OBI-888, presence of dose- or time-dependent OBI-888 PK behavior, verification of influential factors on OBI-888 PK).

12 Safety Assessments

Safety assessments (vital signs, physical examinations, ECG recording, AEs, clinical laboratory results [routine hematology, serum chemistry, coagulation, and urinalysis]) are to be performed at protocol-specified visits, as specified in the Schedule of Assessments, Table 9-1.

12.1 Vital Signs

Vital signs (body temperature, heart rate, systolic and diastolic blood pressure measurements) will be evaluated at the visits indicated in the Schedule of Assessments (Table 9-1). All vital signs will be measured after the patient has been resting in a supine position for at least

5 minutes. Blood pressure measurements are to be taken in the same arm for the duration of the study. Temperature measurement will be obtained as clinically indicated.

Body weight (without shoes) will be recorded whenever vital signs are recorded, and height (without shoes) will be recorded at screening only.

Vital sign measurements will be repeated if clinically significant or machine/equipment errors occur. Out-of-range blood pressure, respiratory rate or heart rate measurements will be repeated at the Investigator's discretion. Any confirmed, clinically significant vital sign measurements must be recorded as AEs.

12.2 Physical Examination

A complete physical examination (head, eyes, ears, nose, throat [HEENT], heart, lungs, abdomen, skin, cervical and axillary lymph nodes, neurological, and musculoskeletal systems) will be performed at screening and early termination. Medical history will be recorded at screening, including smoking history, if applicable.

A limited physical examination to verify continued patient eligibility and to follow up any change in medical history will be performed at the visits indicated in the Schedule of Assessments (Table 9-1). Symptom-driven limited physical examinations will be performed as clinically indicated at any study visit. All changes not present at baseline or described in the past medical history and identified as clinically noteworthy must be recorded as AEs.

Medical history will include previous cancer therapies, cancer history, and past and ongoing concomitant illnesses.

12.3 Electrocardiogram

A 12-lead resting ECG will be obtained at the visits indicated in the Schedule of Assessments (Table 9-1).

At screening, the Investigator will examine the ECG traces for signs of cardiac disease that could exclude the patient from the study. An assessment of normal or abnormal will be recorded and if the ECG is considered abnormal, the abnormality will be documented on the eCRF. ECGs will be repeated if clinically significant abnormalities are observed or artifacts are present.

12.4 Laboratory Assessments

Laboratory assessment samples (Table 12-1) are to be obtained at designated visits as detailed in the Schedule of Assessments (Table 9-1).

Table 12-1 Laboratory Assessments

Hematology	**Serum chemistry**	**Urine analysis (dipstick)**
Hemoglobin Hematocrit Platelet count Red blood cell (RBC) count White blood cell (WBC) count with differential	Albumin Alanine aminotransferase (ALT) Alkaline phosphatase (ALP) Aspartate aminotransferase (AST) Blood urea nitrogen (BUN) or Urea Bicarbonate Creatinine Creatine kinase Electrolytes (Na, K, Cl, Ca, P, Mg) Glucose Lactate dehydrogenase (LDH) Total bilirubin Total protein Uric acid	Appearance Blood pH Protein Glucose Ketones Nitrite Leukocyte esterase Specific gravity Urobilinogen Bilirubin Microscopic, as needed
Coagulation		
Prothrombin time (PT), International Normalized Ratio (INR) Activated partial thromboplastin time (aPTT)		
Serum or Urine Pregnancy test: A pregnancy test will be performed on all female patients of child-bearing potential at the screening visit and early termination visit.		

The routine safety laboratory testing will be performed at the local laboratory following the lab's guidelines. PK, ADA and biomarkers will be analyzed at a qualified laboratory facility Urine samples will be analyzed by dipstick, and a microscopic analysis will be performed if the results of dipstick indicate abnormalities to be further investigated. All laboratory reports must be reviewed, signed, and dated by the Investigator. Any laboratory test result considered by the Investigator to be clinically significant should be considered an AE (clinically significant AEs include those that require an intervention). Clinically significant abnormal values occurring during the study will be followed until repeat test results return to normal, stabilize, or are no longer clinically significant.

12.5 Adverse Events

12.5.1 Adverse Events

An AE is any symptom, physical sign, syndrome, or disease that either emerges during the study or, if present at screening, worsens during the study, regardless of the suspected cause of the event. All medical and psychiatric conditions (except those related to the indication under study) present at screening will be documented in the medical history eCRF. Changes in these conditions and new symptoms, physical signs, syndromes, or diseases should be noted on the AE eCRF during the rest of the study. Clinically significant laboratory abnormalities should also be recorded as AEs. Surgical procedures that were planned before the patient enrolled in the study are not considered AEs if the conditions were known before study inclusion; the medical condition should be reported in the patient's medical history.

Patients will be instructed to report AEs at each study visit. All AEs are to be followed until resolution or until a stable clinical endpoint is reached.

Each AE is to be documented on the eCRF with reference to date of onset, duration, incidence, severity, relationship to study drug, action taken with study drug, treatment of event, and outcome. Furthermore, each AE is to be classified as being serious or non-serious. Changes in AEs and resolution dates are to be documented on the eCRF.

For the purpose of this study, the period of observation for collection of AEs extends from the time the patient receives the first dose of study treatment (Cycle 1 Day 1) until 28 days after end of treatment. Follow-up of the AE, even after the date of therapy discontinuation, is required if the AE persists until the event resolves or stabilizes at a level acceptable to the Investigator.

Specific guidelines for classifying AEs by intensity (Grade) and relationship to study drug are given in Table 12-2 and Table 12-3. The severity of AEs will be graded according to the NCI CTCAE version 4.03 (Grades 1 to 5).

Table 12-2 Classification of Adverse Events by Intensity (NCI CTCAE Grade)

MILD (Grade 1): An event that is easily tolerated by the patient, causing minimal discomfort, and not interfering with everyday activities.
MODERATE (Grade 2): An event that is sufficiently discomforting to interfere with normal everyday activities.
SEVERE (Grade 3): An event that prevents normal everyday activities.
LIFE-THREATENING (Grade 4)
DEATH (Grade 5)

Table 12-3 Classification of Adverse Events by Relationship to Study Drug

UNRELATED: This category applies to those AEs that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.).
UNLIKELY: This category applies to those AEs that are judged to be unrelated to the test drug, but for which no extraneous cause may be found. An AE may be considered unlikely to be related to study drug if or when it meets 2 of the following criteria: (1) it does not follow a reasonable temporal sequence from administration of the test drug; (2) it could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; (3) it does not follow a known pattern of response to the test drug; or (4) it does not reappear or worsen when the drug is re-administered.
POSSIBLY: This category applies to those AEs for which a connection with the test drug administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; or (3) it follows a known pattern of response to the test drug.
PROBABLY: This category applies to those AEs that the Investigator feels with a high degree of certainty are related to the test drug. An AE may be considered probably related if or when it meets 3 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; (3) it disappears or decreases on cessation or reduction in dose (note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; for example, as in bone marrow depression, fixed drug eruptions, or tardive dyskinesia); or (4) it follows a known pattern of response to the test drug.
DEFINITELY: This category applies to those AEs that the Investigator feels are incontrovertibly related to test drug. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; (3) it disappears or decreases on cessation or reduction in dose and recurs with re-exposure to drug (if re-challenge occurs); and (4) it follows a known pattern of response to the test drug.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted. If the intensity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

The severity of AEs will be graded according to the NCI CTCAE version 4.03 (Grades 1 to 5).

12.5.2 Serious Adverse Events

An AE is considered "serious" if in the view of either the Investigator or Sponsor, it meets one or more of the following criteria:

- Is fatal
- Is life-threatening
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly/birth defect

Other important medical events that may not be immediately life-threatening or result in death or hospitalization, based upon appropriate medical judgment, are considered SAEs if they are thought to jeopardize the patient and/or require medical or surgical intervention to prevent one of the outcomes defining a SAE.

Since SAEs are critically important for the identification of significant safety problems, it is important to take into account both the Investigator's and the Sponsor's assessment. If either the Sponsor or the Investigator believes that an event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting.

Hospitalization is not considered an SAE and should not be reported if it is for social reasons in the absence of an AE, or for diagnostic or study-related procedures.

Disease progression is considered an expected event in this patient population, and should not be considered an AE or SAE. However, any medical event/condition that is untoward in the context of disease progression and/or for the specific patient's disease course should be reported as an AE and assessed accordingly by the investigator.

Progression of disease with a fatal outcome does not need to be reported as an AE. However the applicable protocol CRF page(s) pertaining to death should be completed immediately in order to record the disease progression/death.

12.5.3 Serious Adverse Event Reporting

An SAE occurring after receiving OBI-888 or within 28 days of stopping the treatment must be reported to the contracted contract research organization (CRO) and will be communicated to the Sponsor. Any such SAE due to any cause, whether or not related to the study drug, must be reported within 24 hours of occurrence or when the Investigator becomes aware of the event. The Investigator must send the SAE information to the Sponsor/contracted CRO using the electronic data system (preferred method), by filling out a paper SAE reporting form (to be sent via electronic mail or dedicated fax line), or by telephone line. SAEs occurring after signing of the informed consent before and before receiving OBI-888 should be reported only if the SAE was directly related to a screening procedure.

If the Investigator contacts the contracted CRO by telephone, then a written report must follow within 24 hours and is to include a full description of the event and sequelae in the AE report page of the eCRF.

The event must also be recorded on the standard AE eCRF. Preliminary reports of SAEs must be followed by detailed descriptions later on, including clear and anonymized photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. SAE reports must be made whether or not the Investigator considers the event to be related to the investigational drug.

Appropriate remedial measures should be taken to treat the SAE, and the response should be recorded. Clinical, laboratory, and diagnostic measures should be employed as needed in order to determine the etiology of the problem. The Investigator must report all additional follow-up evaluations to the contracted CRO within 10 calendar days. All SAEs will be followed until the Investigator and Sponsor agree the event is satisfactorily resolved.

Any SAE that is not resolved by the end of the study or upon discontinuation of the patient's participation in the study is to be followed until it either resolves, stabilizes, returns to baseline values (if a baseline value is available), or is shown to not be attributable to the study drug or procedures.

12.5.4 Pregnancy

Female patients of child-bearing potential must have a negative pregnancy test at the screening (serum/urine) and the end of study/early termination visit (serum/urine). Following

administration of study drug, any known cases of pregnancy in female patients will be reported until the patient completes or withdraws from the study. The pregnancy will be reported immediately by phone and by faxing/emailing a completed Pregnancy Report to the Sponsor (or designee) within 24 hours of knowledge of the event. The pregnancy will not be processed as an SAE; however the Investigator will follow the patient until completion of the pregnancy and must assess the outcome in the shortest possible time but not more than 30 days after completion of the pregnancy. The Investigator should notify the Sponsor (or designee) of the pregnancy outcome by submitting a follow-up Pregnancy Report. If the outcome of the pregnancy meets the criteria for immediate classification of an SAE (e.g., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator will report the event by phone and by faxing a completed SAE form to the Sponsor (or designee) within 24 hours of knowledge of the event.

12.5.5 Overdose

The Investigator must immediately notify the Sponsor of any occurrence of overdose with study drug.

12.6 ECOG Performance Status

ECOG performance status will be evaluated at the visits indicated in the Schedule of Assessments (Table 9-1). A summary of ECOG performance status is provided in Table 12-4.

Table 12-4 ECOG Performance Status

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

12.7 Immunogenicity

Safety assessment will also include evaluation of immunogenicity (ADAs). Immunogenicity assessments are to be performed as outlined in Table 9-2 (Part A – Dose Escalation) and Table 9-3 (Part B - Expansion).

If a subject is found to be ADA-positive at the end-of-study, the persistence of the ADA will be evaluated by collecting one more sample, 4 months later after the last study visit. The serum from each time point will test for anti-OBI-888 antibody concentration by a validated ELISA based assay.

13 Exploratory Analyses

13.1 Blood Samples

Blood samples will be collected as outlined in Table 9-2 (Part A – Dose Escalation) and Table 9-3 (Part B - Expansion), and analyzed for ADCC (effector cell), ADCC/CDC (humoral) activities, and potential biomarkers which may include KIR, HLA, Fc receptor gamma (FcγR) genotyping activities.

13.2 Tumor Tissue Samples

Tumor tissue biopsy or tissue samples will be collected at time of screening in both escalation and expansion phases of the study from all patients. Fresh (preferred) tissue (ie, unstained slides) or archival tissue (ie, FFPE tissue block) is acceptable. All attempts should be made to obtain fresh biopsy specimens. However, if historical sample is available, they should be retained along with histology/pathology report, if possible. All fresh biopsy specimens or historical samples should be sent to the central laboratory for testing.

A minimum of 3 slides are required for the central laboratory Globo H assay for determination of eligibility. Up to 12 unstained additional slides should be provided, depending upon availability, for the protocol-defined exploratory studies. The tumor biopsy samples mandated at baseline are to be used for Globo H testing by IHC to clarify the mechanism of action of OBI-888. They will also be used to examine the expression of immune markers such as TILs, including NK cells, and immune checkpoints such as PD-L1, by IHC, as well as to evaluate expression of additional tumor associated glycans.

Globo H expression by IHC assay will be determined at a qualified laboratory using the tumor biopsy sample. Patients who have a confirmed and documented Globo H H-score of ≥ 100 are eligible for the study, and will continue with completion of the screening procedures over a period of 28 days prior to the first dose of OBI-888. Note that submission of the tumor sample for Globo H determination may be performed more than 28 days prior to the first dose (after obtaining informed consent), but the other screening evaluations must be performed within the 28-day window.

13.3 Glycan Analysis of OBI-888

Glycan analysis of the Fc portion of OBI-888 mAb will be performed in the pre-infusion and end of infusion samples in the first two cycles of treatment (see Table 9-2 [Part A – Dose Escalation] and Table 9-3 [Part B – Expansion]). Residual samples from the PK and ADA analyses samples will be pooled for glycan analysis after PK and ADA data are finalized.

Fc-glycans and the terminal sugars of Fc-glycans have been shown to be critical for the safety, PK and efficacy (ADCC) of mAb. If the Fc-glycans are completely hydrolyzed, the mAb may lose its ADCC activity and anti-tumor efficacy. Modification of Fc-glycans and glycosylation patterns may influence the PD and PK behavior of OBI-888. Therefore, these exploratory glycan analysis data on OBI-888 may be used to correlate with its clinical efficacy.

14 Statistical Analysis

A Statistical Analysis Plan (SAP) will be prepared after the protocol is approved. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will serve as a compliment to the protocol and supersedes it in case of differences.

The statistical evaluation will be performed using the Statistical Analysis Software (SAS®) Version 9.4 or higher (SAS Institute, Cary, NC).

Analyses will be conducted by dose level in the dose escalation phase and by cohort in the expansion phase. Descriptive summaries for categorical variables will include counts and percentages. Descriptive summaries for continuous variables will include means, medians, standard deviations, minimum and maximum values. Descriptive summaries of time to event data will include medians and confidence intervals. Graphical summaries of the data may be presented. All data will be listed for all patients.

Further details of the analysis, including the handling of missing data, transformations, other data handling procedures, and analytical methodology will be provided in the SAP. Additional exploratory analyses of the data will be conducted as deemed appropriate.

14.1 Determination of Sample Size

This is a 2-part study: Part A Dose Escalation and Part B Cohort Expansion.

Up to 18 patients will be enrolled in the 3+3 dose escalation phase (Part A).

The cohort expansion phase (Part B) will enroll up to 150 total patients based on a Simon two-stage design. The first stage will recruit up to 9 patients in each cohort. If at least 1 objective response is observed within the first 6 cycles of therapy, a second stage recruitment will occur with up to 21 additional patients enrolled into that cohort, for a total of up to 30 patients per cohort. If at least 4 objective responses are observed within the first 6 cycles of therapy in 30 patients, then OBI-888 will be considered worthy of further evaluation in that indication. This design is based on a level of low interest for a treatment with an ORR of 5% versus a level of high interest for a treatment with an ORR of 25%. The sample size is based on a one sided alpha of 0.05 and 90% power. The two-stage design limits the number of patients treated for a treatment with low levels of activity.

14.2 Analysis of Populations

The population to be analyzed will include all enrolled patients who receive at least 1 dose of study drug. This population will be used for all analysis on the safety and clinical activity profile.

14.3 Preliminary Clinical Activity Profile Analysis

ORR will be summarized as the percentage of patients with confirmed partial response (PR) or complete response (CR) according to RECIST version 1.1. CBR will be summarized as the percentage of patients with confirmed CR, PR, or stable disease (SD). DOR, defined as time from the date of reported confirmed PR or CR to the date of progression will be summarized descriptively using summary statistics. Additionally, a listing of DOR for those patients experiencing response will be provided. PFS is defined as the time from first dose of study drug until radiographically determined disease progression or death due to any cause, whichever

event occurs first. Patients who are still alive or who have no progressive disease reported at analysis will be censored at their last evaluable tumor assessment.

Time to progression, death, and/or censoring will be reported for all patients. Kaplan Meier estimates and 95% confidence intervals will be presented for time to event endpoints such as PFS if sufficient numbers of events to calculate meaningful statistics are observed.

14.4 Pharmacokinetic Analysis

PK parameters will be calculated using a non-compartmental method from the PK samples collected on Dose 1 and will include C_{max}, total exposure (AUC), $t_{1/2}$, Cl, T_{max}, and V_d. To assess the attainment of steady state, trough (C_{min}) concentrations and peak concentrations (end of infusion) of each dose would be obtained directly from analytical data.

Summary statistics will be tabulated for the PK parameters of OBI-888 on Dose 1. Geometric means and coefficients of variation will be presented for C_{max}, AUC, $t_{1/2}$, Cl, and V_d. Median, minimum, and maximum will be presented for T_{max}.

To describe the dependency on dose, scatter plots of C_{max} and AUC versus dose will be provided. Summary statistics will be tabulated for the trough (C_{min}) concentration and peak concentrations (end of infusion) by dose and study day. To assess the attainment of steady state, geometric mean C_{min} values will be plotted versus study day by dose.

Pharmacometric methods may also be applied to further investigate OBI-888 exposure (e.g., accumulation of OBI-888, presence of dose- or time-dependent OBI-888 PK behavior, verification of influential factors on OBI-888 PK).

Based on the PK data (PK profile of first dose, steady-state trough serum concentrations, $C_{trough,}$ or $C_{min,ss}$) and targeted concentration (IC_{50} in xenograft model), a PK modeling will be carried out for various dose regimens including 15 mg/kg weekly, 15 mg/kg every 2 weeks, or 15 mg/kg q3 weeks. Simulated C_{trough} of desired regimen should be above the targeted serum concentration. The steady-state trough serum concentrations should be above 2.4 ug/mL, from the preclinical xenograft model exhibiting IC_{50} (trough level at 50% tumor inhibition) of 2.4 ug/mL.

14.5 Safety Analysis

AEs will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 or higher and assessed for severity using CTCAE version 4.03. AEs will be summarized by system organ class and preferred term and presented in decreasing order of incidence. DLTs will also be summarized by dose and cohort. The incidence of TEAEs (events with onset dates on or after the start of the study drug) will be included in incidence tables. Events with missing onset dates will be included as treatment-emergent. If a patient experiences more than 1 occurrence of the same AE, the occurrence with the greatest severity and the closest association with the study drug will be used in the summary tables. SAEs and AEs causing discontinuation will be tabulated. All AEs will be listed by patient, along with information regarding onset, duration, relationship and severity to study drug, action taken with study drug, treatment of event, and outcome.

Vital signs, ECG data, hematology, serum chemistry, coagulation, and urinalysis parameters from baseline and during study will be examined. Treatment emergent changes in key laboratory parameters will be identified. Clinical laboratory data and vital signs will be

summarized for each time point evaluated using descriptive statistics including mean values and mean change from baseline values, as well as numbers of patients with values outside limits of the normal range at each time point.

Summary tables will be provided for concomitant medications initiated prior to study enrollment or during the study period.

14.6 Safety Review Committee (SRC)

The SRC for OBI-888-001 study will comprise of the clinical lead, medical monitor and the study Investigator(s) or designee. The SRC will act in an advisory capacity to monitor patient safety and efficacy during the trial.

This Committee will convene after each cohort completes the first cycle of treatment during the dose escalation phase, to review safety data (AEs and laboratory toxicities) to determine whether DLTs have occurred. Based on DLTs in Part A with consideration of available PK and PD data, RP2D for Part B (Cohort Expansion) will be recommended by SRC. The Committee will convene at regular intervals during the conduct of the Cohort Expansion portion of the study to assess safety and activity.

14.7 Interim Analysis

Not applicable. There is no interim analysis planned for this study.

15 Study Management

15.1 Approval and Consent

15.1.1 Regulatory Guidelines

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the Code of Federal Regulations (CFR), and in compliance with good clinical practices (GCP) guidelines.

15.1.2 Institutional Review Board/Independent Ethics Committee

Conduct of the study must be approved by an appropriately constituted Institutional Review Board (IRB)/Independent Ethics Committee (IEC). Approval is required for the study protocol, Investigator's Brochure (IB), protocol amendments, informed consent forms (ICFs), and patient information sheets.

15.1.3 Informed Consent

For each study patient, written informed consent will be obtained prior to any protocol-related activities. As part of this procedure, the Principal Investigator or one of his/her associates must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the patient is aware of the potential risks, inconveniences, or adverse effects that may occur. The patient should be informed that he/she may withdraw from the study at any time, and the patient will receive all information that is required by local regulations and International Conference on Harmonization (ICH) guidelines. The Principal Investigator will provide the Sponsor or its representative with a copy of the IRB/IEC-approved ICF prior to the start of the study.

15.2 Data Handling

Any data to be recorded directly on the CRFs (to be considered as source data) will be identified at the start of the study. Data reported on the CRF that are derived from source documents should be consistent with the source documents, or the discrepancies must be explained.

Concomitant medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List. AEs will be coded using the MedDRA terminology.

Clinical data will be entered on eCRFs for transmission to the Sponsor. Data on eCRFs transmitted via the web-based data system must correspond to and be supported by source documentation maintained at the study site, unless the study site makes direct data entry to the databases for which no other original or source documentation is maintained. In such cases, the study site should document which eCRFs are patient to direct data entry and should have in place procedures to obtain and retain copies of the information submitted by direct data entry. All study forms and records transmitted to the Sponsor must carry only coded identifiers such that personally identifying information is not transmitted. The primary method of data transmittal is via the secure, internet-based electronic data capture (EDC) system. Access to the EDC system is available to authorized users via the study's Internet web site, where an assigned username and password are required for access.

Any changes made to data after collection will be made through the use of Data Clarification Forms (DCF). The eCRFs will be considered complete when all missing and/or incorrect data have been resolved.

15.3 Source Documents

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data or other activities in a clinical study necessary for the reconstruction and evaluation of the study.

15.4 Record Retention

Study records and source documents must be preserved for at least 15 years after the completion or discontinuation of/withdrawal from the study or 2 years after the last approval of a marketing application in an ICH region, whichever is the longer time period.

The Investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of patient health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR, Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 [HIPAA] Privacy Regulation). The Investigator shall ensure that study patients authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the Sponsor.

15.5 Monitoring

The study will be monitored to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.

On-site and remote (if available) monitoring visits will be made at appropriate times during the study. Clinical monitors must have direct access to source documentation in order to check the completeness, clarity, and consistency of the data recorded in the eCRFs for each patient.

The Investigator will make available to the clinical monitor source documents and medical records necessary to complete eCRFs. In addition, the Investigator will work closely with the clinical monitor and, as needed, provide them appropriate evidence that the conduct of the study is being done in accordance with applicable regulations and GCP guidelines.

15.6 Quality Control and Quality Assurance

The Sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, and reliability of the study data presented to the Sponsor lies with the Investigator generating the data.

The Sponsor will arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, Standard Operating Procedures, GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions. Quality assurance procedures will be performed at study sites and during data management to assure that safety and preliminary clinical activity profile data are adequate and well documented.

15.7 Protocol Amendment and Protocol Deviation

15.7.1 Protocol Amendment

Amendments to the protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no impact on the safety of patients or the conduct of the study will be classed as administrative amendments and will be submitted to the IRB/IEC for information only. The Sponsor will ensure that acknowledgement is received and filed. Amendments that are classed as substantial amendments must be submitted to the appropriate Regulatory Authorities and the IRBs/IECs for approval.

15.7.2 Protocol Deviations

Should a protocol deviation occur, the Sponsor must be informed as soon as possible. Protocol deviations and/or violations and the reasons for which they occurred will be included in the clinical study report. Reporting of protocol deviations to the IRB/IEC and in accordance with applicable Regulatory Authority requirements is an Investigator responsibility.

15.8 Ethical Considerations

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the CFR, and in compliance with GCP guidelines.

IRBs/IECs will review and approve this protocol and the ICF. All patients are required to give written informed consent prior to participation in the study.

15.9 Financing and Insurance

Prior to the study commencing, the Sponsor (or its designee) and the Investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement that will be signed by the Investigator (or the institution signatory) and the Sponsor (or its designee).

The Investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The Sponsor will provide insurance coverage for the clinical study as required by national regulations.

15.10 Publication Policy and Disclosure of Data

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the Investigator and others performing the clinical study will be patient to the terms of a clinical study agreement that will be agreed between the Institution and the Sponsor or their designee. With respect to such rights, the Sponsor or its designee will solely own all rights and interests in any materials, data, and intellectual property rights developed by Investigators and others performing the clinical study described in this protocol, patient to the terms of any such agreement. In order to facilitate such ownership, Investigators will be required to assign all such inventions either to their Institution or directly to the Sponsor or its designee, as will be set forth in the clinical study agreement.

16 References

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17 Appendices

17.1 Appendix 1 Drug Preparation Instruction for OBI-888

1. **OBI-888**
   - Dosage intravenous infusion: according to clinical protocol Section 8.2 Dosage Schedule. The dosage will include dose levels of 5, 10, and 20 mg/kg.
2. **Storage Condition:**
   - OBI-888 vials are to be stored at 2-8ºC.
3. **Investigational Drugs:**
   - OBI-888 fill concentration and volume: 30 mg/mL, 5 mL/vial in 10 mL vial.

     Contents: 30 mg/mL OBI-888 in 25 mM L-Histidine, 150 mM L-Arginine, pH 6.0, 0.02% Polysorbate 80.

At time of treatment, calculate the volume of OBI-888 DP needed according the treatment dosage. Withdraw the volume from OBI-888 DP vial by using a sterile syringe and add the volume into an infusion bag containing 500 mL 0.9% Saline or 5% glucose. Mix infusion bag by gently inverting the bag 4~5 times. **Do not shake the infusion bag vigorously**.

Drug product should be reconstituted within 1 hour after removal from the refrigerator. The combined OBI-888 and infusion solution, 0.9% normal saline or 5% glucose, is stable up to 48 hours from the time of reconstitution at room temperature. The administration of the drug must be completed within 4 hours after reconstitution to minimize potential microbial growth. If reconstitution and administration are not possible within the above time limits, the combined product should be destroyed according to the institutional pharmacy Standard Operating Procedure and documented in the drug accountability records.

4. Illustration of Drug Preparation Procedures

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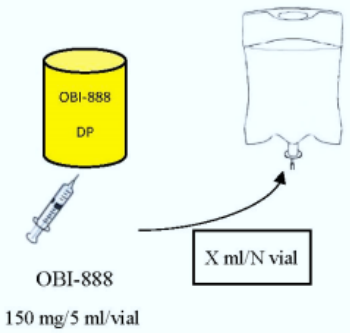
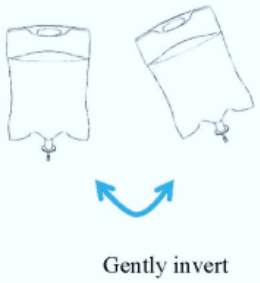
OBI-888 Drug Preparation Instruction Sheet

Determine the dose of OBI-888 DP.

Calculate the volume (X mL) of the OBI-888 DP solution needed by the following equation:

$$\text{X mL} = \frac{\text{Weight (Kg of Patient)} \times \text{dose of OBI-888 (mg/kg)}}{\text{30 mg/mL}}$$

Description of Drug Preparation Procedures	Illustration of Drug Preparation Procedures
Step1. Withdraw **X mL** from OBI-888 DP vial (s) and add the OBI-888 DP into a **500 mL** saline /glucose infusion bag.	
Step2. Mix infusion bag by gently inverting the bag 4~5 times. **Note: Do not shake the infusion bag vigorously.**	
Step3. Intravenous infusion into a subject over 90 minutes after reconstitution.