CLINICAL PROTOCOL

An Open-Label Study to Assess the Safety, Tolerability, and Efficacy of Active Immunotherapy with Dose Escalation and Cohort Expansion of OBI-833 (Globo H-CRM197) in Advanced/Metastatic Gastric, Lung, Colorectal, or Breast Cancer Subjects

Product Name:	**OBI-833/OBI-821**
Protocol Number:	**OBI-833-001**
Protocol Version:	**Version 10.3 – 30/Jul/2020 (US and Taiwan)**
US IND Number:	**16138**
Sponsor:	**OBI Pharma, Inc.** Room W1907, 19F, 3 Yuan Qu Street (Nankang Software Park), Taipei 115, Taiwan R.O.C. 6020 Cornerstone Court West, Suite #200 San Diego, CA 92121 U.S.A.

Additional Study Contact Information will be provided in a separate document.

Signature Page and Revision History

Lance Ou 31 Jul 2020

Lance Ou, R.Ph., Ph.D.
Associate Director
Clinical Development

Date

Chen-En Tsai 31 Jul 2020

Chen-En Tsai, MD, PhD
Vice President
Medical Affairs and Clinical Development

Date

Sponsor Address:
OBI Pharma, Inc.
Ste W1907, 19F, #3, Park St,
Nankang Software Park, Nangang District,
Taipei 11503, Taiwan

OBI Pharma USA, Inc.
6020 Cornerstone Court W, Suite 200
San Diego, CA92121, USA

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SYNOPSIS

Name of Company:	OBI Pharma, Inc.
Name of Compound:	OBI-833 (Globo H-CRM197) and OBI-821 (Adjuvant) [OBI-833/OBI-821]
Study Title:	An Open-Label Study to Assess the Safety, Tolerability, and Efficacy of Active Immunotherapy with Dose Escalation and Cohort Expansion of OBI-833 (Globo H-CRM197) in Advanced/Metastatic Gastric, Lung, Colorectal, or Breast Cancer Subjects
Phase of Development:	US and Taiwan–arm of multi-national Phase I dose escalation and cohort expansion study
Objectives:	• To evaluate the safety and tolerability of OBI-833/OBI-821 in subjects with advanced/metastatic gastric, lung, colorectal, or breast cancer • To assess humoral immune responses (anti-Globo H IgG and IgM production) following subcutaneous administration of OBI-833/OBI-821 • Tumor response (per RECIST 1.1 criteria)
Endpoints:	Primary: Safety and Tolerability Secondary: Immune response (anti-Globo H IgG and IgM production) Tumor response (per RECIST 1.1 criteria)
Design:	Open label, non-randomized dose escalation and cohort expansion trial.
Dose Groups and Treatments:	This study consists of dose escalation phase and cohort expansion phase. A standard 3+3 trial design will be used for OBI-833/OBI-821 dose escalation phase. The dosing of OBI-833 will be divided into 3 cohorts: • Cohort 1: OBI-833 (equivalent to 10 μg Globo H)/100 μg OBI-821 • Cohort 2: OBI-833 (equivalent to 30 μg Globo H)/100 μg OBI-821 • Cohort 3: OBI-833 (equivalent to 100 μg Globo H)/100 μg OBI-821 Upon all of the dose escalation phase subjects completing 5 injections of OBI-833/OBI-821, OBI Scientific Committee justified safety, efficacy and immune response data of all the dose escalation phase subjects and recommend 30μg of OBI-833 as the dose level for cohort expansion phase in lung cancer (Non-Small Cell Lung Cancer, NSCLC). Up to 14 NSCLC subjects will be enrolled in the cohort expansion phase.
Route of Administration	• Subcutaneous (sc)

Dosing Frequency and Study Duration:	[Dose Escalation Phase] Each subject in dose escalation phase will be given a total of 10 doses of OBI-833/OBI-821 subcutaneously at Weeks 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24 (Visits 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10, respectively). Post treatment, subjects will be continually evaluated for safety and immune response every 4 weeks until the end of the study, which is 12 weeks after the last dose (i.e., Week 36). Subsequently, subjects will be followed for survival every 8 weeks up to 12 months after the end of the study. [Cohort Expansion Phase] In cohort expansion phase, subjects will be given OBI-833/OBI-821 at Weeks 1, 2, 3, 4, 6, 8, 12, 16, 20, 24, and every 8 weeks thereafter (Visits 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and every 8 weeks thereafter) until disease progression or up to 1 year after the last subject receives the first dose of study treatment. For the subjects discontinued treatment because of disease progression, subjects will be continually evaluated for safety and immune response every 8 weeks until the end of the study, which is 24 weeks after the last dose. Subjects may continue to be treated at discretion of the investigator after disease progression. The following clinical situations should be conformed for continuous injection after disease progression (FDA Guidance for Industry, 2011): — Subjects continue to meet all other study protocol eligibility criteria. — All drug-related toxicities resolved to the baseline level. — No deterioration of subject performance status. — Does not delay imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases). For the subjects who are eligible and willing to continue injection after disease progression, subjects will be treated with OBI-833/OBI-821 every 8 weeks for additional 3 injections, which is a total of 24 weeks after disease progression, to evaluate clinical and immune responses. Subsequently, subjects will be followed up for survival after End of Study.
Dose Limiting Toxicity (DLT)	An event in the dose escalation phase subjects will be considered a dose limiting toxicity (DLT) if it occurs within the first 6 weeks after the administration of OBI-833/OBI-821 and meets the following criteria: - Any Grade 3 or Grade 4 toxicities considered at least possibly related to the investigational drug.
Selection Criteria:	**Inclusion Criteria:** 1. Subjects ≥21 years of age 2. **[Dose Escalation Phase]** Histologically or cytologically confirmed diagnosis of gastric, lung, colorectal or breast cancer on file **[Cohort Expansion Phase]** Histologically or cytologically confirmed diagnosis of Globo H-positive NSCLC 3. **[Dose Escalation Phase]** Subjects with recurrent or metastatic incurable disease that failed to

	respond to at least one line of anticancer standard therapy and for which standard treatment is no longer effective or tolerable. **[Cohort Expansion Phase]** Subjects with metastatic NSCLC who have achieved stable disease (SD), or partial response (PR) status after at least 1 regimen of anticancer therapy (i.e., chemotherapy, or targeted therapy, or PD-1/PD-L1 antagonists either alone or in combination), and there are no standard treatments available except permitted Target or PD-1/PD-L1 therapies as listed in section 7.1 (i.e., add on with ongoing first line Targeted therapy or PD-1/PD-L1 therapy). 4. Measurable disease (i.e., present with at least one measurable lesion per RECIST, version 1.1 [Eisenhauer 2009]). 5. **[Dose Escalation Phase]** No known central nervous system (CNS) metastases or neurological symptoms possibly related to active CNS metastasis in Dose Escalation Phase. **[Cohort Expansion Phase]** Subjects with asymptomatic CNS metastases for at least four weeks before study drug treatment 6. Performance status: ECOG ≤ 1 7. Organ Function Requirements – Subjects must have adequate organ functions as defined below: - AST/ALT ≤ 3X ULN (upper limit of normal) - AST/ALT ≤ 5X ULN [with underlying liver metastasis] - Total bilirubin ≤ 2.0 X ULN - Serum creatinine ≤ 1.5X ULN - ANC ≥ 1500 /μL - Platelets > 100,000/μL 8. Subjects of child-bearing potential must agree to use acceptable contraceptive methods during treatment and until the end of the study. 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. 9. Ability to understand and the willingness to sign a written informed consent document according to institutional guidelines.
Selection Criteria:	**Exclusion Criteria** 1. Patients who have not received standard chemotherapy, hormonal or targeted therapy for their underlying advanced/metastatic cancer. 2. Subjects who are pregnant or breast-feeding at entry. 3. Subjects with splenectomy. 4. Subjects with known or clinically manifest, symptomatic CNS metastases in **Dose Escalation Phase**. 5. Subjects with HIV infection, active hepatitis B infection or active hepatitis C infection. 6. Subjects with any autoimmune or other disorders requiring iv/oral steroids or immunosuppressive or immunomodulatory therapies. - e.g., Type 1 juvenile onset diabetes mellitus, antibody positive for rheumatoid arthritis, Grave's disease, Hashimoto's thyroiditis, lupus, scleroderma, systemic vasculitis, hemolytic anemia, immune

	mediated thrombocytopenia, Crohn's disease, Ulcerative colitis or psoriasis etc. 7. Subjects with any known uncontrolled inter-current illness including ongoing or active infections, symptomatic congestive heart failure (NYHA>2), unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements. 8. **[Dose Escalation Phase]** Subjects with any of the following MEDICATIONS within 4 weeks prior to IP treatment, except permitted therapies as listed in section 7.1: - Chemotherapeutic Agent - Immunotherapy [mAbs, Interferons, Cytokines (except GCSF)] - Immunosuppressants (e.g., cyclosporin, rapamycin, tacrolimus, rituximab, alemtuzumab, natalizumab, etc.). - IV/oral steroids except single prophylactic use in CT/MRI scan or other one-time use in approved indications. The interval between IV/oral steroids administration and first dose of OBI-833/OBI-821 must be more than pharmacological duration or 5 half-lives of administered steroids, whichever is longer. Uses of inhaled and topical steroids are allowed. - Another investigational drug **[Cohort Expansion Phase]** Subjects with any of the following MEDICATIONS within 4 weeks prior to IP treatment, except permitted therapies as listed in section 7.1: - Chemotherapeutic Agent - Immunotherapy [Interferons, Cytokines] (except PD-1/PD-L1 antagonists) - Immunosuppressants (e.g., cyclosporin, rapamycin, tacrolimus, rituximab, alemtuzumab, natalizumab, cyclophosphamide, etc.). - IV/oral steroids except single prophylactic use in CT/MRI scan or other one-time use in approved indications. The interval between IV/oral steroids administration and first dose of OBI-833/OBI-821 must be more than pharmacological duration or 5 half-lives of administered steroids, whichever is longer. Uses of inhaled and topical (except on injection site) steroids are allowed. - Another investigational drug 9. Subjects with pleural effusions and/or ascites, due to malignancy, requiring paracentesis every 2 weeks or more frequently. 10. Subjects with any known severe allergies (e.g., anaphylaxis) to any active or inactive ingredients in the study drugs.
Study Evaluation and Assessment:	**[Dose Escalation Phase]** • Tumor status confirmation: Full body CT scans (chest, abdomen, and pelvis) will be performed at screening and then every 12 weeks till the end of the study. • Safety and toxicity (adverse events) will be evaluated at each visit, i.e., Weeks 1, 2, 3, 4, 6, 8, 12, 16, 20, 24, 28, 32, and 36 (End of Study). • Hematology, serum chemistry and urine analysis will be conducted at each visit, i.e., Weeks 1, 2, 3, 4, 6, 8, 12, 16, 20, 24, 28, 32, and 36.

	• Immunology test for anti-Globo H IgG and IgM will be conducted at Weeks 1, 3, 4, 6, 8, 12, 16, 20, 24, 28, 32, and 36. • Tumor-specific antigen testing (CEA for all enrolled subjects) to be performed prior to treatment and every 12 weeks until the end of the study. **[Cohort Expansion Phase]** • Tumor status confirmation: Full body CT scans (chest, abdomen, and pelvis) will be performed at screening, Weeks 12, 24 and then every 8 weeks until disease progression or up to 1 year after the last subject receives the first dose of study treatment. For the continuous injection subjects after disease progression, subjects will perform tumor assessment every 8 weeks until end of study. • Safety and toxicity (adverse events) will be evaluated at each visit till the end of the study. • Hematology, serum chemistry and urine analysis will be conducted at each visit till the end of the study. • Immunology test for anti-Globo H IgG and IgM will be conducted at Weeks 1, 3, 4, 6, 8, 12, 16, 20, 24, and every visit thereafter till the end of the study. • Tumor-specific antigen testing (CEA and CYFRA 21-1 for all enrolled subjects in selected sites) to be performed at screening, Weeks 12, 24, every 8 weeks thereafter until disease progression and end of study visit.
Exploratory Analysis	**[Dose Escalation Phase]** Exploratory tests for the following biomarkers will be conducted at Weeks 1, 3, 4, 6, 8, 12, 16, 20, 24, 28, 32, and 36: • IHC for Globo H, SSEA-3, SSEA-4 and PD-L1 (Week 1; from paraffinated material of original surgery specimens) • Monitoring of immune response of anti-Globo H, anti-SSEA-3, and anti-SSEA-4 antibody production. • CTC (Week 1, 6 and 28 only) • ADCC and CDC • T cell and B cell responses (Weeks 12, 16, 20 and 24) **[Cohort Expansion Phase]** Exploratory tests for the following biomarkers will be conducted at Screening, Weeks 1, 2, 3, 4, 6, 8, 12, 16, 20, 24, and every 8 weeks thereafter until end of study: • IHC for Globo H, SSEA-3, SSEA-4, and PD-L1 (Screening; from fresh prepared (preferred) or paraffinated material of original surgery specimens) • Monitor immune response of anti-Globo H, anti-SSEA-3, and anti-SSEA-4 antibody production. • CTC (Week 1, 8, 64 and End of Study/Early Termination)

	• ADCC and CDC • T cell and B cell responses (at Weeks 8 or after until PTP1) (4 continue visits after either anti-Globo H, anti-SSEA-3, or anti-SSEA-4 IgG reaches 20 μg/ml in the serum) • B/T cell immunogenomic analysis (Screening, Weeks 6, 12, 20, 64, and every 8 weeks till 8 weeks after 1st disease progression) • Ex vivo Immunogenicity Analysis (Screening visit) • Cobas EGFR Mutation Tests will be conducted at Weeks 1, 12, 40 and post treatment period 1 and End of Study for all subjects with known EGFR mutations in selected Taiwan sites. Cobas EGFR Mutation Tests will also be conducted at Early Termination visit for the early termination subjects other than PD.
Study Management:	**[Dose Escalation Phase]** • After completing 5 injections of OBI-833/OBI-821 (i.e., at Visit 5, Week 6) in the first 3 or 6 subjects at the lower dose cohort in dose escalation phase, if there are no subjects of the first 3 or there are less than 2 subjects of the first 6 who develop DLT, enrollment can be started in the next higher dose cohort. • Any subject who develops any DLT will be discontinued from study treatment. • All subjects who have a Grade 3 or 4 clinical or laboratory abnormality at the time of withdrawal from the study must be followed until resolution to Grade 2 or less, unless it is unlikely to improve because of underlying disease. • If there is more than 1 subject of the first 6 who develop DLT in dose escalation phase, then dose escalation will be suspended until a full review by the Data and Safety Monitoring Board. Recommendation for dose reduction will result from the discussion of emerging safety data by the DSMB. If dose reduction is required for the subjects in Cohort 1 (10μg cohort), the study will be suspended temporally and can only be resumed to further enroll Cohort 1 subject without dose reduction if justified by recommendation of the DSMB upon analysis of emerging safety data. A Data and Safety Monitoring Board will be established to assist the Sponsor in monitoring subject safety, risk/benefit, and decision for dose escalation, dose reduction and termination of the study. • Patients who prematurely withdraw from dose escalation phase will be replaced. To meet the replacement a subject should fulfill the following criteria: 1) Not receives a total of 5 OBI-833/OBI-821 injections, during the dose escalation phase; and 2) Reason of not completing 5 injections is other than development of related adverse event or a DLT (eg. noncompliance or withdrew of consent). • OBI Scientific Committee justified safety, efficacy and immune response data of all the dose escalation phase subjects and recommend 30μg of OBI-833 as the dose level for cohort expansion phase in lung cancer (NSCLC).

[Cohort Expansion Phase]

- Patients will be treated until disease progression, intolerable toxicity, withdrawal of consent, or up to 1 year after the last subject receives the first dose of study treatment. Patients will then enter the post-treatment period and follow-up phase.
- Subjects may continue for treatment at discretion of the investigator after disease progression. The following clinical situations should be conformed for continuous injection after disease progression:
  - — Subjects continue to meet all other study protocol eligibility criteria
  - — All drug-related toxicities resolved to the baseline level
  - — No deterioration of subject performance status
  - — Does not delay imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases)

  For the subjects discontinued treatment because of disease progression, subjects will be continually evaluated for safety and immune response every 8 weeks until end of the study, which is 24 weeks after the last dose. For the subjects who are eligible and willing continuous injection after disease progression, subjects will be treated with OBI-833/OBI-821 every 8 weeks for additional 3 injections, which is a total of 24 weeks after disease progression, to evaluate clinical and immune responses. Subsequently, subjects will be followed up for survival every 12 weeks up to 24 weeks after End of Study.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
ALC	absolute lymphocyte count
ALK	Anaplastic Lymphoma Kinase
ALT (SGPT)	serum glutamic pyruvic transaminase
ANCA	antineutrophil cytoplasmic antibody
AST (SGOT)	serum glutamic oxaloacetic transaminase
BUN	blood urea nitrogen
CDC	complement dependent cytotoxicity
CA	cancer antigen
CEA	carcinoembryonic antigen
CNS	central nervous system
CR	complete response
CRF	case report form
CRM197	active and nontoxic form of diphtheria toxin (DT) called cross-reacting material 197 (CRM197)
CT	computerized tomography
CTC	circulating tumor cell
CTCAE	common terminology criteria for adverse events
CYFRA 21-1	cytokeratin fragment 21-1
DLT	dose limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EF	ejection fraction
EGFR	Epidermal Growth Factor Receptor
ESR	erythrocyte sedimentation rate
FACS	fluorescence-activated cell sorting
FDA	Food and Drug Administration
Gb5	Globo H precursor Gb5, also called stage specific embryonic antigen-3 (SSEA-3)
GCSF	granulocyte colony stimulating factor
GM-CSF	granulocyte macrophage colony stimulating factor
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis B virus
HIV	human immunodeficiency virus
ICF	informed consent form
ICH-GCP	International Conference of Harmonization - Good Clinical Practice
IHC	Immunohistochemistry
IRB	Institutional Review Broad
KLH	keyhole limpet hemocyanin
LDH	lactate dehydrogenase
LVEF	left ventricular ejection fraction
mABs	monoclonal antibodies
MRI	magnetic resonance imaging
MSKCC	Memorial-Sloan Kettering Cancer Center
MUGA	multiple gated acquisition scan

NCI	National Cancer Institute
NK cell	natural killer cell
NKT cell	natural killer T cell
NOAEL	no observed adverse effect level
NSCLC	non-small cell lung cancer
OS	overall survival
PBS	phosphate buffer saline
PD	progressive disease
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PR	partial response
RBC	red blood cell counts
RECIST	response evaluation criteria in solid tumors
RF	rheumatoid factor
SAEs	serious adverse event(s)
SC	subcutaneous
SD	stable disease
SOP	standard operating procedure
SSEA	stage specific embryonic antigen
SSEA-3	Globo H precursor Gb5, also called stage specific embryonic antigen-3
SSEA-4	sialyl Gb5, also called stage specific embryonic antigen-4
TKI	Tyrosine Kinase Inhibitor
ULN	upper limit of normal
WBC	white blood cell counts
WHO	World Health Organization

1 GOALS AND OBJECTIVES

1.1 Primary Objective

- To evaluate the safety and tolerability of OBI-833/OBI-821 in subjects with advanced/metastatic gastric, lung, colorectal, or breast cancer.

1.2 Secondary Objective

- To assess humoral immune responses (anti-Globo H IgG and IgM production) following subcutaneous administration of OBI-833/OBI-821
- Tumor response (per RECIST 1.1 criteria)

1.3 Exploratory Objective

- To assess other immune responses as measured by exploratory analysis of anti-Globo H, anti-SSEA-3 and anti-SSEA-4 antibodies, CTC, ADCC, and CDC.
- To assess Globo H, SSEA-3, SSEA-4, and PD-L1 expression in tumor tissue samples.
- To assess Cellular immune responses (T cell and B cell responses).

2 BACKGROUND AND RATIONALE FOR DEVELOPMENT

2.1 Cancer Immunotherapy

Recent advances in the aspects of cellular immunology and tumor–host immune interactions, have led to the development of effective immune-based therapies capable of reducing tumor size in patients with metastatic cancer. Currently, there are three main approaches to cancer immunotherapy, a non-specific stimulation of immune reactions by stimulating effector cells and/or inhibiting regulatory cells, an active immunization to enhance specific anti-tumor reactions, known as cancer vaccines, and a passive transfer of anti-tumor antibodies or activated immune cells with antitumor activity, also known as adoptive immunotherapy (DeVita et al. 2008).

Cancer immunotherapy is based on the theory that tumor specific antigens can be recognized when processed by, and presented to, a properly trained immune system. The malignant cells are commonly characterized by the appearance of large and unusual protein and carbohydrate motifs on their cell surfaces which distinguish them from their normal cell counterparts (Rabinovich et al. 1994). The identification of tumor-associated antigens recognized by cellular or humoral effectors of the immune system has opened new perspectives for cancer therapy. In the past two decades several monoclonal antibodies have provided sufficient efficacy and safety data to gain regulatory approval for passive immunotherapy of cancer. These include edrecolomab (Mab 17-1A), rituximab (anti-CD20), trastuzumab (Herceptin), gemtuzamab zogamicin (Mylotarg), and alemtuzumab (CAMPATH-1, anti-CD52).

Recently, ch14.18, a chimeric monoclonal antibody against GD2, has been shown to improve survival of high risk neuroblastoma patients in a Phase III trial, making this the first effective anti-cancer antibody targeting carbohydrate antigens (Yu et al. 2010). In addition to passive immunotherapy with these monoclonal antibodies, active immunotherapy of human cancer is a rapidly growing experimental area targeting peptidic as well as carbohydrate tumor-associated antigens. The biotechnology and pharmaceutical industries have only recently successfully developed cancer vaccines. In 2006, Gardasil was approved in the U.S, and it is the first cancer preventive vaccine against the human papillomavirus that causes cervical cancer and genital warts. In July 2007, Northwest Biotherapeutics received approval of its personalized therapeutic vaccine for brain cancer (DCVax®-Brain) in Switzerland. In April 2009, the Russian Ministry of Public Health issued a registration certificate for the use of Oncophage® (vitespen) in the treatment of kidney cancer patients at intermediate risk for disease recurrence (*http://www.antigenics.com/news/2008/0408.phtml*). These successful cases are encouraging in reaffirming the development of Globo H as an immunotherapeutic target for solid tumors such as breast, gastric, lung, colorectal, ovarian, pancreatic and possibly other cancer types.

In adjuvant immunization trials, the primary target is the "minimal residual disease" which consists of a small number of tumor cells or early micrometastases that may persist for long periods after apparent resection of all residual tumors (Zhang et al. 1996; Zhang et al. 1997a; Zhang et al. 1997b; Zhang et al. 1998). Active immunotherapy with therapeutic vaccines is a good strategy to target minimal residual disease and prevent relapse by inducing antibodies of sufficient titer against tumor antigens to eliminate residual tumor cells from the peritoneal cavity, blood and lymphatic systems, and to inhibit micrometastases. However, the immune response to cancer antigens is suppressed in cancer patients (Sotomayor et al. 1996; Pawelec et al. 1997; Khong and Restifo 2002). In the past few years, methods have been developed to synthesize antigens that mimic natural cancer antigens (Musselli et al. 2001) which are conjugated to a potent immunogen as a carrier and co-administered with an immuno-stimulatory molecule as an adjuvant that can reliably provoke an immune response.

Many of the more tumor-restricted monoclonal antibodies derived by immunization of mice with human tumor cells have been directed against carbohydrate antigens expressed at the cell surface (Menard et al. 1983; Zhang et al. 1997a). Cell surface carbohydrates are characteristic of different stages of normal development and differentiation; distinct carbohydrates are expressed in tissue- and cell-specific manners during those processes. Several carbohydrate antigens (Livingston 1995a; Livingston et al. 1997; Livingston and Ragupathi 1997) have proven to be promising targets for immunotherapy. Immunization against carbohydrate antigens conjugated to immuno-stimulatory molecules results in humoral antibody response, primarily an IgM antibody response. These antibodies are known to induce complement dependent cytotoxicity (CDC), inflammation, and phagocytosis of tumor cells by the reticulo-endothelial system (opsonization).

In addition to CDC, IgG antibodies of subclasses IgG1 and IgG3 in humans can also induce antibody dependent cell mediated cytotoxicity (ADCC). They are ideally suited for eradication of residual tumor cells and systemic or intraperitoneal micrometastases which have been well-documented in a variety of mouse experiments. Carbohydrate antigens have been chosen as targets for active immunotherapy include Globo H (Ragupathi et al. 1997; Slovin et al. 1999;

Allen et al. 2001; Gilewski et al. 2001), GM2 (White et al. 1991; Livingston et al. 1994a; Livingston et al. 1994b; Livingston 1995b; Helling et al. 1995; Chapman et al. 2000a; Chapman et al. 2000b), GD2 (Livingston 1998), GD3 (Helling et al. 1994; McCaffery et al. 1996; Ragupathi et al. 2000), sTn (MacLean et al. 1993; Longenecker et al. 1993; Longenecker et al. 1994; Sandmaier et al. 1999) and Tn (Allen et al. 2001).

Sialyl-Tn (sTn) is a disaccharide tumor associated antigen expressed on the MUC1 mucin on a number of human cancer cells and is associated with more aggressive disease. Theratope® vaccine (Biomira, Inc., Edmonton, Alberta, Canada and Merck KGaA of Darmstadt, Germany) is a cancer vaccine which consists of a synthetic STn antigen conjugated to KLH (Keyhole limpet hemocyanin) combined with an immunostimulant (adjuvant) DetoxTM derived from bacteria. A Phase III trial of Theratope® vaccine (sTn-KLH) vs KLH in 1,030 women with metastatic breast cancer showed that Theratope® vaccine was well tolerated with minimal toxicity. The most common adverse effects were induration and erythema at the site of injection. While the results of this trial did not meet the primary endpoints of time to disease progression and overall survival, a subsequent *post-hoc* analysis showed that women who received concurrent endocrine and Theratope® vaccine treatment had a significant overall survival benefit versus those who received endocrine therapy alone (Ibrahim et al. 2013).

2.2 Globo H Expression in Solid Tumors

Cancer cells contain unique tumor associated carbohydrate antigens (TACAs) that are not common to most of the host cell surfaces. The expression level of cell surface carbohydrate antigens is often significantly increased on carcinogenic transformation (Zhang et al. 1997a; Zhang et al. 1997b). Thus, TACAs offer the potential for a targeted immunotherapeutic approach to the treatment of certain forms of cancer. Among TACA, great interest has been focused on the immunogenic potential of Globo H, the terminal hexasaccharide portion of the glycolipid. Globo H is highly expressed in epithelial cancers such as breast cancer, ovarian cancer, endometrial cancer, gastric cancer, colon cancer, pancreatic cancer, lung cancer, and prostate cancer (Zhang et al. 1997b); it is expressed on the cancer cell surface as a glycolipid and possibly as a glycoprotein (Miotti et al. 1989).

Globo H is also expressed at lower levels on some normal luminal surfaces (Zhang et al. 1998). However, the antigen is predominantly localized to the apical cells at secretory borders—sites that appear to be inaccessible to immune surveillance. In Phase I trials discussed below, Globo H antigen expressed at the secretory borders of normal epithelial tissues induced neither tolerance nor autoimmunity once antibodies were elicited, suggesting that the antigens are sequestered from the immune system.

Recent work has shown that Globo H and the Globo series Stage-Specific Embryonic Antigen 3 (SSEA-3) and Stage-Specific Embryonic Antigen 4 (SSEA-4) are expressed on epithelial cancer cells and corresponding cancerous stem cells (Chang et al. 2008b; Lou et al. 2014). SSEA-3 (Gb5) is a penta-saccharide precursor of Globo H, and is also known as stage-specific embryonic antigen SSEA-3. Until recently, SSEA-3 and SSEA-4 have been known as markers for human embryonic stem cells that can be observed only in stem cells during the embryonic development stage (Chang et al. 2008b; Lou et al. 2014). Finding of Globo H, SSEA-3 and SSEA-4 on the cancer stem cells suggests that, in principle, the Globo H-protein conjugated

immunotherapy not only targets the cancer cells, but also the cancer stem cells, for eradication. The same study also revealed Globo H expression in 25/41 breast cancer specimens (61.0%) and SSEA-3 expression in 31/40 (77.5%) various tumors (Chang et el. 2008a).

It is noteworthy that similar to Globo H, SSEA-3 and SSEA-4 expression in normal tissues was predominantly at the secretory borders of epithelium (Chang et al. 2008b) where access to the immune system is restricted. Immunization of mice with Globo H-KLH and Globo H-CRM197 induced antibodies reactive with Globo H, SSEA-3, and SSEA-4, suggesting that a Globo H-based vaccine will target tumor cells expressing Globo H, SSEA-3, and SSEA-4 (Huang et al. 2013).

Recent data have shown that Globo H, SSEA-3 and SSEA-4 (so-called Globo Series TACAs) are highly expressed on human cancer specimens from various solid tumor types. These data show Globo H expression in 73/80 breast cancer specimens (91.3%), SSEA-3 expression in 79/79 (100%) tumors, and SSEA-4 expression in 80/80 (100%) (Dr. A. Yu, Taiwan unpublished data). This research also showed Globo H expression in 71/74 (95.9%), SSEA-3 expression in 76/79 (96.2%), and SSEA-4 expression in 72/81 (88.9%) gastric cancer specimens. In addition, the data also revealed high Globo series expression in lung cancer samples with Globo H expression in 61/61 (100%), SSEA-3 expression in 62/63 (98.4%), and SSEA-4 expression in 61/62 (98.4%) of the samples analyzed. (Data submitted for publication by Dr. A. Yu at Chang Gung Memorial Hospital, Taiwan)

Globo series TACAs are also highly expressed in colon cancer. A recent publication showed that Globo H is expressed in different colon cancer cell lines (6/7, 85.7%), SSEA-3 is expressed on colon cancer cell lines (0/7; 0%), and SSEA-4 is expressed on colon cancer cell lines (5/7; 71.4%) (Lou et al. 2014).

In this phase 1 clinical trial, the proposed plan is to enroll subjects with advanced/metastatic incurable gastric, breast, colorectal or lung cancer and subsequently evaluate the expression levels in the Globo series TACAs.

2.3 OBI-833 (Globo H-CRM197) Immunological Profile

Recent studies have revealed that the expression of some glycans, such as Globo H and SSEA-3 and SSEA-4, was observed on breast cancer cells and breast cancer stem cells (BCSCs) (Chang et al. 2008b; Huang et al. 2013; Lou et al. 2014). All these findings support a rationale for the development of carbohydrate-based vaccines based on these cancer-specific glycans. Notably, the recent study indicated Globo H-CRM197 vaccine elicited more IgG antibodies, which are more selective for Globo H and the Globo series epitopes including SSEA-3 and SSEA-4, all of which were specifically overexpressed on breast cancer cells and breast cancer stem cells with SSEA-4 at the highest level (>90%) (Chang et al. 2008b).

Globo H has been evaluated as the target of active immunotherapy in a few clinical trials including the ongoing Phase II (US) / Phase III (Taiwan) clinical trial of OBI-822/OBI-821 (Protocol No. OPT-822-001) under the US BB-IND 14,719 sponsored by OBI Pharma, Inc. The rationale for designing Globo-H conjugated to CRM-197 (a diphtheria toxin mutant) vaccine is based on the theory that tumor specific carbohydrate antigens can be recognized

when processed and presented to a properly trained immune system. Immunization against these carbohydrate antigens results in a humoral antibody response. These antibodies are known to induce complement mediated cytotoxicity (CDC), inflammation, and phagocytosis of tumor cells by the reticuloendothelial system (opsonization). In addition to CDC, IgG antibodies of subclasses IgG1 and IgG3 in humans can also induce antibody dependent cell mediated cytotoxicity (ADCC). They are ideally suited for eradication of tumor cells and systemic metastases, which renders promises for OBI-833 to be used as a potential cancer vaccine.

2.4 Nonclinical Pharmacology

OBI-833 is a glycoprotein conjugate comprised of a carbohydrate tumor antigen, Globo H, covalently linked to an inactive and nontoxic form of diphtheria toxin (DT) called cross-reacting material 197 (CRM197) as a carrier protein. It is intended to evoke an immune response against cancer cells by co-administering a natural cancer antigen, Globo H, conjugated to a potent immuno-stimulatory adjuvant, CRM-197.

OBI-821 is a saponin-based adjuvant derived from the bark of the *Quillaja saponaria* (QS) Molina tree. OBI-821 is structurally similar to QS-21 based on the comparison of physicochemical data. Both OBI-821 and QS-21 exist as mixtures of isomers. OBI-821 serves as an immunological adjuvant that could potentiate the humoral antibody response to OBI-833.

In order to characterize the immunogenic potential of the antigen/adjuvant combination, OBI-833/OBI-821 was tested in three pharmacology studies, including an immunogenicity study, an LL/2 tumor bearing mice model study, and a combination therapy study with gemcitabine.

The pharmacology studies showed that active immunotherapy with OBI-833/OBI-821 can effectively stimulate anti-Globo H IgM and IgG responses in an *in vivo* murine model. Mouse vaccinated with OBI-833/OBI-821 can significantly inhibit tumor growth rate in an *in vivo* subcutaneous Globo H positive tumor implant model. It was also observed that the treatment of standard chemotherapeutic agent, gemcitabine, followed by vaccinated with OBI-833/OBI-821, did not affect the production of anti-Globo H IgM and IgG antibodies induced by OBI-833/OBI-821.

Overall, these nonclinical pharmacology studies provided sound rationale to support clinical investigation of OBI-833/OBI-821.

Detailed information on the nonclinical pharmacology studies of OBI-833/OBI-821 is provided in the Investigator's Brochure.

2.5 Toxicology

The safety of OBI-833/OBI-821 vaccine was initially evaluated in a non-GLP 4-week repeat-dose rat toxicology study, in which OBI-833/OBI-821 at 2 doses (equivalent to 30 μg or 90 μg of Globo H) were administered once weekly via subcutaneous injection to Sprague Dawley rats for 4 weeks. OBI-833/OBI-821 was well tolerated without observation of adverse effects.

An additional toxicology study of OBI-833/OBI-821, a GLP 17-week repeat-dose rat toxicology study with an interim analysis at 11 weeks, was conducted to evaluate 10 subcutaneous injections in cancer patients in the planned Phase I clinical trial. The potential toxicity of the test article, OBI-833, and adjuvant, OBI-821, was assessed for separate administration or as a co-formulation via subcutaneous injection once weekly to Sprague Dawley rats for 17 weeks (Dosing Phase). In addition, reversibility, persistence, or delayed occurrence of any effects were assessed in a 4-week recovery period after the Dosing Phase. The doses of OBI-833/OBI-821 in the toxicology study (equivalent to 30 μg and 100 μg Globo H, and 100 μg of OBI-821) were selected based on the planned clinical dose range of Phase I study. The only observation caused by OBI-833 administration in combination with the adjuvant OBI-821 once weekly for 11 weeks in rats was minimal enhancement of the local irritation that the adjuvant produced at the injection sites. Injection site irritations were resolved clinically within a week and resolved microscopically within three weeks post-administration.

The toxicology studies demonstrated the safety and immunogenicity of the vaccine/adjuvant combination of OBI-833/OBI-821 and showed that the vaccine was well-tolerated at doses above that of the proposed clinical doses, on a per kg body-weight basis. All findings noted in the 4-week non-GLP and in the 11-week interim analysis of the 17-week GLP repeated dose toxicology studies in rats were not considered adverse and were likely due to inflammatory/immunostimulatory responses to the adjuvant, OBI-821.

Detailed information on the toxicology studies of OBI-833/OBI-821 are provided in the Investigator's Brochure.

2.6 Rationale for Trial Design

The primary purpose of the clinical trial is to investigate safety and tolerability of OBI-833/OBI-821 in subjects with advanced/metastatic incurable gastric, lung, colorectal, or breast cancer. Meanwhile, the humoral immune responses, i.e., anti-Globo H IgG and IgM production following administration of OBI-833/OBI-821 will be assessed as the secondary objective of this study. Exploratory analysis of other immune responses such as Globo H, SSEA-3, SSEA-4, PD-L1 expression in tumor tissue samples, anti-Globo H, anti-SSEA-3, anti-SSEA-4 antibodies, CTC, ADCC, CDC will be conducted as appropriate.

Upon the completion of 5 injections of OBI-833/OBI-821 in subjects in the dose escalation phase, OBI Scientific Committee justified safety, efficacy and immune response data of all the dose escalation phase subjects and recommend 30 μg dose of OBI-833 and lung cancer (Non-Small Cell Lung Cancer) for cohort expansion. Up to 14 lung cancers subjects are to be enrolled in the cohort expansion phase.

OBI-833/OBI-821 showed a delayed antibody response in a previous dose escalation phase 1 study. In this situation, clinical progression may occur before the treatment has had sufficient time to be effective. Thus, continuous injection after disease progression will be the potential approach to address this issue. Therefore, clinical progression that is asymptomatic and/or is not likely to result in life-threatening complications with further progression (e.g., new onset Central Nervous System (CNS) metastases) may allow the continuous administration of OBI-833/OBI-

821 at the discretion of investigator and subjects should be fully informed for the subsequent treatment (FDA Guidance for Industry, Clinical Considerations for Therapeutic Cancer Vaccines, 2011).

2.7 Rationale for Starting Dose

The initial planned starting dose in this First in Human clinical trial is 10 µg of OBI-833 (in Globo H equivalent) in combination with the adjuvant, 100 µg of OBI-821. Based on the reported NOAEL following 11 weekly SC injections of 100 µg of OBI-833 plus 100 µg of OBI-821, the highest dose evaluated in the 17 week toxicology study in rats, this dose of OBI-833/OBI-821 (100 µg/100 µg) was chosen as the highest anticipated human dose in the proposed Phase I clinical study. This proposed dosing plan is consistent with the FDA Guidance for developmental toxicity studies for preventive and therapeutic vaccines for infectious disease indications, and the proposed WHO 2013 Guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines.

3 ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

1. Subjects ≥21 years of age
2. **[Dose Escalation Phase]**

   Histologically or cytologically confirmed diagnosis of gastric, lung, colorectal or breast cancer on file

   [Cohort Expansion Phase]

   Histologically or cytologically confirmed diagnosis of Globo H-positive NSCLC
3. **[Dose Escalation Phase]**
   Subjects with recurrent or metastatic incurable disease that failed to respond to at least one line of standard anticancer therapy and for which standard treatment is no longer effective or tolerable.
   [Cohort Expansion Phase]
   Subjects with metastatic NSCLC who have achieved stable disease (SD), or partial response (PR) status after at least 1 regimen of anticancer therapy (i.e., chemotherapy, or targeted therapy, or PD-1/PD-L1 antagonists either alone or in combination), and there are no standard treatments available except permitted Target or PD-1/PD-L1 therapies as listed in section 7.1 (i.e., add on with first line ongoing Targeted therapy or PD-1/PD-L1 therapy).
4. Measurable disease (i.e., present with at least one measurable lesion per RECIST, version 1.1 [Eisenhauer 2009]).
5. **[Dose Escalation Phase]**

   No known central nervous system (CNS) metastases or neurological symptoms possibly related to active CNS metastasis in Dose Escalation Phase.

   [Cohort Expansion Phase]

   Subjects with asymptomatic CNS metastases for at least four weeks before study drug treatment

6. Performance status: ECOG ≤ 1
7. Organ Function Requirements – Subjects must have adequate organ functions as defined below:
   - AST/ALT ≤ 3X ULN (upper limit of normal)
   - AST/ALT ≤ 5X ULN [with underlying liver metastasis]
   - Total bilirubin ≤ 2.0 X ULN
   - Serum creatinine ≤ 1.5X ULN
   - ANC ≥ 1500 /µL
   - Platelets > 100,000/µL
8. Subjects of child-bearing potential must agree to use acceptable contraceptive methods during treatment and until the end of the study. 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.
9. Ability to understand and the willingness to sign a written informed consent document according to institutional guidelines.

3.2 Exclusion Criteria

1. Patients who have not received standard chemotherapy, hormonal or targeted therapy for their underlying cancer.
2. Subjects are pregnant or breast-feeding at entry.
3. Subjects with splenectomy.
4. Subjects with known or clinically manifest, symptomatic CNS metastases in **Dose Escalation Phase**.
5. Subjects with HIV infection, active hepatitis B infection or active hepatitis C infection.
6. Subjects with any autoimmune or other disorders requiring IV/oral steroids or immunosuppressive or immunomodulatory therapies.
   - e.g., Type 1 juvenile onset diabetes mellitus, antibody positive for rheumatoid arthritis, Grave's disease, Hashimoto's thyroiditis, lupus, scleroderma, systemic vasculitis, hemolytic anemia, immune mediated thrombocytopenia, Crohn's disease, Ulcerative colitis or psoriasis etc.
7. Subjects with any known uncontrolled inter-current illness including ongoing or active infections, symptomatic congestive heart failure (NYHA>2), unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
8. **[Dose Escalation Phase]**
   Subjects with any of the following MEDICATIONS within 4 weeks prior to IP treatment, except permitted therapies as listed in section 7.1:
   - Chemotherapeutic Agents
   - Immunotherapy [mAbs, Interferons, Cytokines (except GCSF)]

- Immunosuppressants (e.g., cyclosporin, rapamycin, tacrolimus, rituximab, alemtuzumab, natalizumab, etc.).
- IV/oral steroids except single prophylactic use in CT/MRI scan or other one-time use in approved indications. The interval between IV/oral steroids administration and first dose of OBI-833/OBI-821 must be more than pharmacological duration or 5 half-lives of administered steroids whichever is the longer. Uses of inhaled and topical steroids are allowed.
- Another investigational drug.

[Cohort Expansion Phase]
Subjects with any of the following MEDICATIONS within 4 weeks prior to IP treatment, except permitted therapies as listed in section 7.1:

- Chemotherapeutic Agents
- Immunotherapy [Interferons, Cytokines] (except PD-1/PD-L1 antagonists)
- Immunosuppressants (e.g., cyclosporin, rapamycin, tacrolimus, rituximab, alemtuzumab, natalizumab, cyclophosphamide, etc.).
- IV/oral steroids except single prophylactic use in CT/MRI scan or other one-time use in approved indications. The interval between IV/oral steroids administration and first dose of OBI-833/OBI-821 must be more than pharmacological duration or 5 half-lives of administered steroids whichever is longer. Uses of inhaled and topical steroids (except on injection sites) are allowed.
- Another investigational drug.

9. Subjects with pleural effusions and/or ascites, due to malignancy, requiring paracentesis every 2 weeks or more frequently.
10. Subjects with any known severe allergies (e.g., anaphylaxis) to any active or inactive ingredients in the study drugs.

4 TREATMENT PLAN

4.1 Subject Enrollment and Dose Escalation Procedure

This is a Phase I, open-label, non-randomized study with two phases: dose escalation phase and cohort expansion phase. Both phases evaluate safety and tolerability of OBI-833.

A standard 3+3 trial design will be used for OBI-833/OBI-821 dose escalation phase. The dosing of OBI-833 will be divided into 3 cohorts:

- Cohort 1: OBI-833 (equivalent to 10 μg Globo H)/100 μg OBI-821
- Cohort 2: OBI-833 (equivalent to 30 μg Globo H)/100 μg OBI-821
- Cohort 3: OBI-833 (equivalent to 100 μg Globo H)/100 μg OBI-821

In the dose escalation phase, the first three subjects of 10 μg dose cohort (Cohort 1) should be enrolled sequentially with at least a 24-hour interval. If there is no DLT observed in any of

these subjects, the trial will proceed to enroll subjects into the 30 μg dose cohort (Cohort 2). If one out of the first three Cohort 1 subjects develops a DLT, an additional three subjects will be further enrolled. If less than 2 of the 6 subjects (i.e. only 1 of the 6 subjects) develop DLT, dose escalation to 30 μg will be proceeded. If more than 1 of 6 subjects develop DLT, the study will be suspended temporally and can only be resumed to further enroll Cohort 1 subject without dose reduction justified by recommendation of the DSMB upon analysis of emerging safety data.

For 30 μg dose cohort (Cohort 2), firstly three patients will be enrolled. If there is no DLT observed in any of these subjects, the trial will proceed to enroll subjects into the 100 μg dose cohort (Cohort 3). If one out of the first three Cohort 2 subjects develops a DLT, an additional three subjects will be further enrolled. If less than 2 of the 6 subjects (i.e. only 1 of the 6 subjects) develop DLT, dose escalation to 100μg will be proceeded. If more than 1 of 6 subjects suffer from DLT, Data and Safety Monitoring Board will review the safety data to recommend if the study should be suspended or de-escalate to previous 10μg cohort to complete a maximum of 6 subjects.

For 100 μg dose cohort (Cohort 3), firstly three subjects will be enrolled in this cohorts. If one out of the first three Cohort 3 subjects develops a DLT, an additional three subjects will be further enrolled. If none of the first three or less than 2 of the 6 subjects experience DLT at the 100 μg dose level, then this dose will be maximum dose for escalation phase. If more than 1 of 6 subjects experience DLT at this dose level, study will be suspended temperately and DSMB will review safety data to recommend if the study should be de-escalate to 30 μg to complete a maximum of 6 subjects.

Upon the completion of 5 injections of OBI-833/OBI-821 in subjects in the dose escalation phase, OBI Scientific Committee justified safety, efficacy and immune response data of all the dose escalation phase subjects and recommend 30 μg dose of OBI-833 for cohort expansion.

OBI Scientific Committee also examined the data of all the dose escalation phase subjects and preclinical efficacy data to evaluate the type of cancers to benefit from OBI-833/OBI-821 treatment. OBI Scientific Committee determined that lung cancer (Non-Small Cell Lung Cancer) subjects with SD or PR tumor status are to be enrolled for preliminary antitumor activity evaluation. Up to 14 subjects are to be enrolled in the cohort expansion phase.

The total number of subjects to be enrolled in the study is thus flexible: a maximum number of 18 subjects can be enrolled in the dose escalation phase; and a maximum number of 14 subjects can be enrolled in the cohort expansion phase. A maximum of total 32 subjects can be enrolled in this Phase I study.

Dose modification may be considered, as justified by emerging safety data. Subject tumor biopsy/tissue samples will be collected at Week 1 using fresh prepared or paraffinated material from original surgery specimens to test for expression level of Globo H, SSEA-3, SSEA-4 and PDL-1 for data analysis purpose. IHC data is not for eligibility criteria for Dose Escalation Phase but only Globo-H^+ NSCLC subjects will be enrolled in Cohort Expansion Phase.

Subjects who are eligible for participation in this study will be enrolled into the dose cohort that is open at the time the subject is registered for enrollment in Dose Escalation Phase.

For each subject in dose escalation phase, maximum of 10 doses of OBI-833 (equivalent to 10, 30 or 100μg of Globo H)/OBI-821 (100μg) will be administered subcutaneously at Weeks 1, 2, 3, 4, 6, 8 , 12, 16, 20, and 24 (Visits 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10, respectively). Patients who prematurely withdraw from dose escalation phase will be replaced. To meet the replacement a subject should fulfill the following criteria: 1) Not receives a total of 5 OBI-833/OBI-821 injections, during the dose escalation phase; and 2) Reason of not completing 5 injections is other than development of related adverse event or a DLT (e.g., noncompliance or withdrew of consent).

For Cohort Expansion Phase, patients will be treated subcutaneously at Weeks 1, 2, 3, 4, 6, 8, 12, 16, 20, 24 and every 8 weeks until disease progression, intolerable toxicity, withdrawal of consent, or up to 1 year after the last subject receives the first dose of study treatment. Subjects may continue treatment after disease progression at discretion of the investigator. The following clinical situations should be conformed for continued injection after disease progression (FDA Guidance for Industry, 2011):

— Subjects continue to meet all other study protocol eligibility criteria.

—All drug-related toxicities resolved to the baseline level.

— No deterioration of subject performance status.

— Does not delay imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases).

For the subjects discontinued treatment because of disease progression, subjects will be continually evaluated for safety and immune response every 8 weeks until the end of the study, which is 24 weeks after the last dose. For the subjects who are eligible and willing to continue injection after disease progression, subjects will be treated with OBI-833/OBI-821 every 8 weeks for additional 3 injections, which is a total of 24 weeks after disease progression, to evaluate clinical and immune responses. Subsequently, subjects will be followed up for survival every 12 weeks up to 24 weeks after End of Study.

Week 1 is defined as the visit with the first sc administration of investigational drug. Blood samples will be collected for routine blood test (part of safety assessment) and evaluation of immune responses at various weeks as indicated in the Time and Events Schedule (Table 1 and 2). Following the last dose of study drug, subjects will be evaluated for safety and immune response every 4 weeks for dose escalation phase or 8 weeks for cohort expansion phase until the end of the study (“End of Study”), which is 12 or 24 weeks after the last dose administration. For subjects eligible for continued injection after disease progression should be fully informed the foreseeable risks or discomforts and other alternative treatment options.

4.2 OBI-833/OBI-821 Administration Schedule and Procedure

For each dose administration, a vial of OBI-833 drug product and a vial of OBI-821 drug product will be used. The dosing solution will be prepared by mixing the two components prior to injection. The mixing instruction for each dose level of OBI-833/OBI-821 is shown in Appendix I.

- For dose escalation phase, enrolled subjects will be treated for a maximum of 10 doses of OBI-833/OBI-821 (sc) at Weeks 1, 2, 3, 4, 6, 8, 12, 16, 20, and 24 (Visit 1 to Visit 10). For Cohort Expansion Phase, subjects will be treated until disease progression.
- A dose of 10 µg OBI-833/100 µg OBI-821, 30 µg OBI-833/100 µg OBI-821 or 100 µg OBI-833/100 µg OBI-821 mixture will be injected subcutaneously according to respective cohorts 1, 2, and 3 in escalation phase and 30 µg OBI-833/100 µg OBI-821 in cohort expansion phase.
- Administration of OBI-833/OBI-821 combination should be completed within 2 hours after mixing.
- Subcutaneous injection (sc) over the arm (left or right) is preferable.
- If axillary lymph nodes were removed, avoid injections on the same arm.
- If axillary lymph nodes on both sides (left and right) were removed, injections can be made on the thigh (left or right).
- If local reaction occurs, rotate or alternate the injection site around the arms and thighs to minimize injection site irritation.

5 STUDY PROCEDURES

5.1 Screening Phase – Prior to First Dosing of the Investigational Drug (Screening Visit)

A signed Informed Consent Form will be properly obtained following a full explanation of the study protocol and prior to conducting any study related procedures.

For Dose Escalation Phase, the screening/baseline evaluations are to be conducted within 28 days prior to first dosing of the investigational drug. All entry/eligibility assessment must be performed prior to first dosing of the investigational drug.

- Record demographics.
- Obtain significant medical history, other underlying disease/condition and history along the previous 12 months.
- Confirm eligibility criteria (meeting all inclusion criteria, not having any exclusion criteria).
- Perform physical examination including vital signs (blood pressure, respiratory rate, pulse, and body temperature), height, weight, and ECOG performance status.
- Conduct urine pregnancy test. In case of positive results, the subject will not be eligible for the study.
- Conduct routine urinalysis - pH, protein, glucose, specific gravity, ketone, bilirubin, and urobilinogen. Analysis of urinary sediments (RBC, WBC, epithelial casts, hyaline casts, and bacterial) is optional.
- Conduct hematology test - includes hemoglobin, hematocrit, WBC, RBC, platelet, differentials, RF and ESR.

- Conduct serum chemistry analysis - includes sodium, potassium, chloride, calcium, magnesium, BUN, creatinine, ALT, AST, alkaline phosphatase, total protein, albumin, total bilirubin, LDH, amylase, lipase, cholesterol, triglycerides, cortisol, T3, T4, free T4, and TSH.
- Conduct HBV (e.g., HBsAg, HBeAg, and if clinically indicated, HBcAb and/or HBV DNA), HCV (e.g., anti-HCV) testing. Conduct HIV testing if no historical data are available. Optional tests (e.g., viral load) can be ordered based on lab test results and Investigator's clinical judgment for suspected active infection on follow-up visits. Antiviral agents are allowed for the treatment and management of viral infections. However, interferon therapy is not allowed, and if indicated, the subject needs to be excluded from the study.
- Perform 12-Lead ECG.
- Perform Tumor Assessment:
  - Full body CT scans (chest, abdomen, and pelvis) will be performed at screening and used as the baseline scan. If full body CT scan has been performed within 4 weeks before the screening exam (the date consent form sign by patient), then this previously performed scan can be used as the baseline scan.
  - To identify and record lesions to be evaluated for response based on RECIST 1.1 criteria.
  - Imaging will be assessed by the study site radiologist or delegated investigators.
  - For cohort expansion phase, an interval of at least 6 weeks is required for Stable Disease (SD) status; an interval of at least 4 weeks is required for Partial Response (PR) status.
- Record use of concomitant medications.
- Perform re-testing of lab assessments: a re-test may be allowed after 1 week (or by Investigators' judgment) from the initial lab test to re-confirm the subject's organ function or condition. However, the assessment needs to be conducted within the specified screening period prior to first dosing of the investigational drug.
- Perform pre-treatment tumor-specific antigen testing: CEA for all enrolled subjects.

For Cohort Expansion Phase, the screening/baseline evaluations are to be conducted within 35 days prior to first dosing of the investigational drug. All entry/eligibility assessment must be performed prior to first dosing of the investigational drug.

- Obtain tumor biopsy/tissue samples of primary site (and distant metastases if possible) which will be tested for Globo H, SSEA-3, SSEA-4 and PD-L1 expression by immunohistochemistry (specified in Section 5.8 "Other Study Procedures"). Although fresh specimens are preferred, most subjects should have historical tumor tissue specimens available, which can be submitted to the central lab for testing. If tumor tissue samples are not available, fresh tumor tissue samples should be acquired. For Cohort Expansion Phase, fresh/archived tumor biopsies to test Globo H expression are essential.
- Record demographics.

- Obtain significant medical history, other underlying disease/condition and history along the previous 12 months.
- Confirm eligibility criteria (meeting all inclusion criteria, not having any exclusion criteria).
- Perform physical examination including vital signs (blood pressure, respiratory rate, pulse, and body temperature), height, weight, and ECOG performance status.
- Conduct urine pregnancy test. In case of positive results, the subject will not be eligible for the study.
- Conduct routine urinalysis - pH, protein, glucose, specific gravity, ketone, bilirubin, and urobilinogen. Analysis of urinary sediments (RBC, WBC, epithelial casts, hyaline casts, and bacterial) is optional.
- Conduct hematology test - includes hemoglobin, hematocrit, WBC, RBC, platelet, differentials, RF and ESR.
- Conduct serum chemistry analysis - includes sodium, potassium, chloride, calcium, magnesium, BUN, creatinine, ALT, AST, alkaline phosphatase, total protein, albumin, total bilirubin, LDH, amylase, lipase, cholesterol, triglycerides, cortisol, T3, T4, free T4, and TSH.
- Conduct HBV (e.g., HBsAg, HBeAg, and if clinically indicated, HBcAb and/or HBV DNA), HCV (e.g., anti-HCV) testing. Conduct HIV testing if no historical data are available. Optional tests (e.g., viral load) can be ordered based on lab test results and Investigator's clinical judgment for suspected active infection on follow-up visits. Antiviral agents are allowed for the treatment and management of viral infections. However, interferon therapy is not allowed, and if indicated, the subject needs to be excluded from the study.
- Perform 12-Lead ECG.
- Perform Tumor Assessment:
    - Full body CT scans (chest, abdomen, and pelvis) will be performed at screening and used as the baseline scan. If full body CT scan has been performed within 4 weeks of the screening exam (the date consent form sign by patient), then this previously performed scan can be used as the baseline scan.
    - To identify and record lesions to be evaluated for response based on RECIST 1.1 criteria.
    - Imaging will be assessed by the study site radiologist or delegated investigators.
    - For cohort expansion phase, an interval of at least 6 weeks is required for Stable Disease (SD) status; an interval of at least 4 weeks is required for Partial Response (PR) status.
- Record use of concomitant medications.
- Perform re-testing of lab assessments: a re-test may be allowed after 1 week (or by Investigators' judgment) from the initial lab test to re-confirm the subject's organ function or condition. However, the assessment needs to be conducted within the specified screening period prior to first dosing of the investigational drug.
- Perform pre-treatment tumor-specific antigen testing: CEA and CYFRA21-1 for all enrolled subjects in selected sites.

- Collect blood samples for exploratory analysis of the B/T cell immunogenomic and Ex vivo immunogenicity analysis in selected Taiwan sites.

5.2 Treatment Period: Week 1 – Visit 1

Eligible subject will be treated with the first dose of the investigational drug according to the assigned cohort/dosage that is currently enrolling at the time the subject is eligible for enrollment (Section 4.1).

For Cohort 1 in dose escalation phase, OBI-833 (equivalent to 10μg Globo H)/OBI-821 (100μg) will be administered subcutaneously (sc). Subjects enrolled in Cohort 2 will be administered OBI-833 (equivalent to 30μg Globo H)/OBI-821 (100μg) subcutaneously (sc); while subjects in Cohort 3 will be administered OBI-833 (equivalent to 100μg Globo H)/OBI-821 (100μg) subcutaneously (sc). For cohort expansion, OBI-833 (equivalent to 30μg Globo H)/OBI-821 (100μg) will be administered.

The following evaluations are to be conducted during Week 1 (visits as specified below):

- Perform physical examination including vital signs (blood pressure, respiratory rate, pulse, and body temperature) and weight prior to administration of investigational drug.
- Conduct routine urinalysis - pH, protein, glucose, specific gravity, ketone, bilirubin, and urobilinogen prior to administration of investigational drug. Analysis of urinary sediments (RBC, WBC, epithelial casts, hyaline casts, and bacterial) is optional.
- Conduct hematology test - includes hemoglobin, hematocrit, WBC, RBC, platelet, differentials, RF, and ESR prior to administration of investigational drug.
- Conduct serum chemistry analysis - includes sodium, potassium, chloride, calcium, magnesium, BUN, creatinine, ALT, AST, alkaline phosphatase, total protein, albumin, total bilirubin, LDH, amylase, lipase, cholesterol, triglycerides, cortisol, T3, T4, free T4, and TSH, prior to administration of investigational drug.
- Collect blood samples for the measurement of anti-Globo H IgG and IgM titers prior to administration of investigational drug.
- For Dose Escalation Phase only: Obtain tumor biopsy/tissue samples of primary site (and distant metastases if possible) which will be tested for Globo H, SSEA-3, SSEA-4 and PD-L1 expression by immunohistochemistry (specified in Section 5.8 “Other Study Procedures”). Although fresh specimens are preferred, most subjects should have historical tumor tissue specimens available, which can be submitted to the central lab for testing. If tumor tissue samples are not available, fresh tumor tissue samples should be acquired prior to administration of investigational drug. However, in cases where tumor biopsies may not be possible, subjects are not required to submit tissue samples.
- Collect blood samples for exploratory analysis of the following biomarkers prior to administration of investigational drug:
    - Monitoring of immune response of anti-Globo H, anti-SSEA-3 and anti-SSEA-4 antibody production.
    - CTC (only in selected Taiwan sites)

  - ADCC and CDC
- Administer investigational drug subcutaneously.
- Record use of concomitant medications.
- Monitor and record adverse events assessed by NCI CTCAE v4.0 post administration of investigational drug.
- Collect blood sample for the subjects with known EGFR mutations to be analyzed in the Cobas EGFR Mutation Tests in cohort expansion phase

5.3 Treatment Period Week 2 to Week 4 (Visit 2 to Visit 4)

Investigational drug will be administered subcutaneously at Weeks 2, 3 and 4 (Visits 2, 3 and 4, respectively).

The following evaluations are to be conducted during Weeks 2 to 4 (Visit 2 - Visit 4 as specified below):

- Perform physical examination including vital signs (blood pressure, respiratory rate, pulse, and body temperature) and weight - Weeks 2, 3 and 4 (Visits 2, 3 and 4) prior to administration of investigational drug.
- Conduct routine urinalysis - pH, protein, glucose, specific gravity, ketone, bilirubin, and urobilinogen prior to administration of investigational drug. Analysis of urinary sediments (RBC, WBC, epithelial casts, hyaline casts, and bacterial) is optional - Weeks 2, 3 and 4 (Visits 2, 3 and 4) prior to administration of investigational drug.
- Conduct hematology test - includes hemoglobin, hematocrit, WBC, RBC, platelet, differentials, RF, and ESR - Weeks 2, 3 and 4 (Visits 2, 3 and 4) prior to administration of investigational drug.
- Conduct serum chemistry analysis - includes sodium, potassium, chloride, calcium, magnesium, BUN, creatinine, ALT, AST, alkaline phosphatase, total protein, albumin, total bilirubin, LDH, amylase, lipase, cholesterol, triglycerides, cortisol, T3, T4, free T4, and TSH - Weeks 2, 3 and 4 (Visits 2, 3 and 4) prior to administration of investigational drug.
- Collect blood samples for the measurement of anti-Globo H IgG and IgM - Weeks 3 and 4 (Visits 3 and 4), prior to administration of investigational drug.
- Collect blood samples for exploratory analysis of the following biomarkers – Weeks 3 and 4 (Visits 3 and 4), prior to administration of investigational drug:
  - Monitoring of immune response of anti-Globo H, anti-SSEA-3 and anti-SSEA-4 antibody production.
  - ADCC and CDC
- Perform 12-Lead ECG – Week 4 (Visit 4) only for Dose Escalation Phase, prior to administration of investigational drug.
- Administer investigational drug subcutaneously – Weeks 2, 3 and 4 (Visits 2, 3 and 4).
- Record use of concomitant medications – Weeks 2, 3, and 4 (Visits 2, 3, and 4)

- Monitor and record adverse events assessed by NCI CTCAE v4.0 – Weeks 2, 3, and 4 (Visits 2, 3, and 4).

5.4 Treatment Period: Week 6 to Week 24 (Visit 5 to Visit 10) or Disease Progression

[Dose Escalation Phase]

Investigational drug will be administered subcutaneously at Weeks 6, 8, 12, 16, 20, and 24 (Visit 5 to Visit 10, respectively).

The following evaluations are to be conducted at these weeks (or visits):

- Perform physical examination including vital signs (blood pressure, respiratory rate, pulse, and body temperature) and weight – Weeks 6, 8, 12, 16, 20, and 24 (Visit 5 – Visit 10); assessments to be performed prior to administration of investigational drug.
- Conduct routine urinalysis - pH, protein, glucose, specific gravity, ketone, bilirubin, and urobilinogen. Analysis of urinary sediments (RBC, WBC, epithelial casts, hyaline casts, and bacterial) is optional – Weeks 6, 8, 12, 16, 20, and 24 (Visit 5 - Visit 10); assessments to be performed prior to administration of investigational drug.
- Conduct hematology test - includes hemoglobin, hematocrit, WBC, RBC, platelet, differentials, RF, and ESR – Weeks 6, 8, 12, 16, 20, and 24 (Visit 5 - Visit 10); assessments to be performed prior to administration of investigational drug.
- Conduct serum chemistry analysis - includes sodium, potassium, chloride, calcium, magnesium, BUN, creatinine, ALT, AST, alkaline phosphatase, total protein, albumin, total bilirubin, LDH, amylase, lipase, cholesterol, triglycerides, cortisol, T3, T4, free T4, and TSH – Week 6, 8, 12, 16, 20, and 24 (Visit 5 – Visit 10); assessments to be performed prior to administration of investigational drug. Collect blood samples for measurement of anti-Globo H IgG and IgM titer – Weeks 6, 8, 12, 16, 20, and 24 (Visit 5 - Visit 10); samples to be collected prior to administration of investigational drug.
- Collect blood samples for exploratory analysis for the following biomarkers – Weeks 6, 8, 12, 16, 20 and 24 (Visit 5 - Visit 10) prior to administration of investigational drug:
    - Monitoring of immune response of anti-Globo H, anti-SSEA-3 and anti-SSEA-4 antibody production.
    - ADCC and CDC
- Collect blood samples for exploratory analysis for the following biomarkers – Week 6 (Visit 5) prior to administration of investigational drug:
    - CTC (only in selected Taiwan sites)
- Collect blood sample for exploratory cellular immune response – Weeks 12, 16, 20 and 24 (Visit 7 - Visit 10) prior to administration of investigational drug:
    - T cell and B cell immune response in selected Taiwan sites

- Perform tumor assessment according to the RECIST 1.1 criteria, including CT scan as required, every 12 weeks – Weeks 12 and 24 (Visits 7 and 10, respectively) prior to administration of investigational drug.
- Perform tumor-specific antigen testing (CEA for all enrolled subjects) every 12 weeks – Weeks 12 and 24 (Visits 7 and 10, respectively)
- Perform 12-Lead ECG at Weeks 12 and 20 (Visits 7 and 9, respectively) only, assessments to be performed prior to administration of investigational drug.
- Administer investigational drug subcutaneously – Weeks 6, 8, 12, 16, 20, and 24 (Visit 5 - Visit 10).
- Record use of concomitant medications – every Visit (Visit 5 - Visit 10).
- Monitor and record adverse events assessed by NCI CTCAE v4.0 – every Visit (Visit 5 - Visit 10).

[Cohort Expansion Phase]

Investigational drug will be administered subcutaneously at Weeks 6, 8, 12, 16, 20, 24, and every 8 weeks thereafter until disease progression.

- Perform physical examination including vital signs (blood pressure, respiratory rate, pulse, and body temperature) and weight – Weeks 6, 8, 12, 16, 20, 24 and every 8 weeks until disease progression; assessments to be performed prior to administration of investigational drug.
- Conduct routine urinalysis - pH, protein, glucose, specific gravity, ketone, bilirubin, and urobilinogen. Analysis of urinary sediments (RBC, WBC, epithelial casts, hyaline casts, and bacterial) is optional – Weeks 6, 8, 12, 16, 20, 24 and every 8 weeks until disease progression; assessments to be performed prior to administration of investigational drug.
- Conduct hematology test - includes hemoglobin, hematocrit, WBC, RBC, platelet, differentials, RF, and ESR – Weeks 6, 8, 12, 16, 20, 24 and every 8 weeks until disease progression; assessments to be performed prior to administration of investigational drug.
- Conduct serum chemistry analysis - includes sodium, potassium, chloride, calcium, magnesium, BUN, creatinine, ALT, AST, alkaline phosphatase, total protein, albumin, total bilirubin, LDH, amylase, lipase, cholesterol, triglycerides, cortisol, T3, T4, free T4, and TSH – Week 6, 8, 12, 16, 20, 24 and every 8 weeks until disease progression; assessments to be performed prior to administration of investigational drug. Collect blood samples for measurement of anti-Globo H IgG and IgM titer – Weeks 6, 8, 12, 16, 20, 24 and every 8 weeks until disease progression; samples to be collected prior to administration of investigational drug.
- Collect blood samples for exploratory analysis for the following biomarkers – Weeks 6, 8, 12, 16, 20 24 and every 8 weeks until disease progression prior to administration of investigational drug:
    - Monitoring of immune response of anti-Globo H, anti-SSEA-3 and anti-SSEA-4 antibody production.
    - ADCC and CDC

- Collect blood samples for exploratory analysis for the following biomarkers—Dose Escalation Phase: Week 6 (Visit 5) or Cohort Expansion Phase: Week 8, 64 (visits 6, 15) prior to administration of investigational drug:
    - CTC (only in selected Taiwan sites)
- Collect blood sample for exploratory cellular immune response only if either anti-Globo H, anti-SSEA-3, or anti-SSEA-4 serum concentration reaches 20 μg/ml – 4 continue visits prior to administration of investigational drug (Week 8 (Visits 6) or after):
    - T cell and B cell immune response in selected Taiwan sites
- Collect blood samples for exploratory analysis for the following biomarkers—Week 6, 12, 20, 64, and every 8 weeks until 8 weeks after the 1st disease progression (Visits 5, 7, 9, 15, and every 8 weeks until 8 weeks after the 1st disease progression) prior to administration of investigational drug:
    - B/T cell immunogenomic analysis in selected Taiwan sites
- Perform tumor assessment according to the RECIST 1.1 criteria, including CT scan as required, every 12 weeks—Weeks 12, 24 and every 8 weeks until disease progression prior to administration of investigational drug.
- Perform tumor-specific antigen testing (CEA and CYFRA21-1 for all enrolled subjects in selected sites) every 12 weeks—Weeks 12, 24 and every 8 weeks until disease progression
- Perform 12-Lead ECG at Weeks 12 and 8 weeks after final injection or disease progression, assessments to be performed prior to administration of investigational drug.
- Administer investigational drug subcutaneously—Weeks 6, 8, 12, 16, 20, 24, and every 8 weeks until disease progression.
- Record use of concomitant medications—every visit until disease progression.
- Monitor and record adverse events assessed by NCI CTCAE v4.0—every visit until disease progression.
- Collect blood sample at weeks 12 and 40 for the subjects with known EGFR mutations to be analyzed in the Cobas EGFR Mutation Tests

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5.5 Post Treatment Period to End of Study: Week 28 to Week 36 (Visit 11 to Visit 13) for Dose Escalation Phase; after disease progression for Cohort Expansion Phase

The following evaluations are to be conducted every 4 weeks for Dose Escalation Phase or every 8 weeks for Cohort Expansion Phase until the end of the study ("End of Study"), which is 12 weeks (Dose Escalation Phase) or 24 weeks (Cohort Expansion Phase) after the last subcutaneous dose of the investigational drug.

- Perform physical examination including vital signs (blood pressure, respiratory rate, pulse, and body temperature) and weight.
- Conduct routine urinalysis - pH, protein, glucose, specific gravity, ketone, bilirubin, and urobilinogen. Analysis of urinary sediments (RBC, WBC, epithelial casts, hyaline casts, and bacterial) is optional.

- Conduct hematology test - includes hemoglobin, hematocrit, WBC, RBC, platelet, differentials, RF and ESR.
- Conduct serum chemistry analysis - includes sodium, potassium, chloride, calcium, magnesium, BUN, creatinine, ALT, AST, alkaline phosphatase, total protein, albumin, total bilirubin, LDH, amylase, lipase, cholesterol, triglycerides, cortisol, T3, T4, free T4, and TSH.
- Collect blood samples for measurement of anti-Globo H IgG and IgM titer.
- Collect blood samples for exploratory analysis for the following biomarkers:
    - Monitoring of immune response of anti-Globo H, anti-SSEA-3 and anti-SSEA-4 antibody production.
    - ADCC and CDC
- Collect blood samples for exploratory analysis for the following biomarkers – Dose Escalation Phase: Week 28 (Visit 11) or Cohort Expansion Phase: End of study:
    - CTC (only in selected Taiwan sites)
- Collect blood sample for exploratory cellular immune response only if either anti-Globo H, anti-SSEA-3, or anti-SSEA-4 serum concentration reaches 20 μg/ml – 4 continue visits prior to administration of investigational drug (8-Week after the last injection; PTP1):
    - T cell and B cell immune response in selected Taiwan sites
- Collect blood samples for exploratory analysis for the following biomarkers— Cohort Expansion Phase: 8 weeks after 1st disease progression:
    - B/T cell immunogenomic analysis (only in selected Taiwan sites)
- Perform tumor assessment according to the RECIST 1.1 criteria at weeks 36 (Visit 13) for Dose Escalation Phase or at every visit for the continuous injection subjects after disease progression in Cohort Expansion Phase. If the data of CT assessment are available within 6 weeks prior to the scheduled visit, the assessment of CT may not be performed based on the investigator's discretion.
- Perform tumor-specific antigen testing (CEA for all enrolled subjects) at weeks 36 (Visit 13) for Dose Escalation Phase or End of Study visit for Cohort Expansion Phase in selected sites (CEA and CYFRA21-1).
- Perform 12-lead ECG at the visits described in Table 1 and 2.
- Record uses of concomitant medications every visit.
- Monitor and record adverse events assessed by NCI CTCAE v4.0 every visit.
- Administer investigational drug subcutaneously every visit for the continuous injection subjects after disease progression in Cohort Expansion Phase
- Collect blood sample at post treatment period 1 and End of Study for the subjects with known EGFR mutations to be analyzed in the Cobas EGFR Mutation Tests in cohort expansion phase

5.6 Follow-Up Period (Up to 12 Months Following End of Study, i.e., Weeks 44 to 84)

Unless the subject meets the off study criteria (Section 11.2), all surviving subjects will be followed up for survival status by phone contact or subjects' clinic visit, every 8 weeks for Dose Escalation Phase or 12 weeks for Cohort Expansion Phase for up to 48 weeks or 24 weeks, respectively, following the End of Study/ Early Termination visit.

5.7 Early Termination

Subjects, who prematurely terminated study treatment or evaluation for any reasons other than disease progression except continuous in post treatment period will only need to complete Early Termination Visit for the following evaluations before discontinuation from the study or continuing onto the follow-up phase. Disease progressive subjects who are not willing to continue into the post-treatment period will the perform EoS visit. If lab data is available within 1 week prior to EoS/EoT, lab tests can be waived. Surviving subjects will then enter Follow-up period to follow up survival status by phone contact or subjects' clinic visit 12 weeks for Cohort Expansion Phase for up to 24 weeks.

- Perform physical examination and measure vital signs (blood pressure, respiratory rate, pulse, and body temperature), Weight.
- Conduct routine urinalysis - pH, protein, glucose, specific gravity, ketone, bilirubin, and urobilinogen. Analysis of urinary sediments (RBC, WBC, epithelial casts, hyaline casts, and bacterial) is optional.
- Conduct hematology test - includes hemoglobin, hematocrit, WBC, RBC, platelet, differentials, RF, and ESR.
- Conduct serum chemistry analysis - includes sodium, potassium, chloride, calcium, magnesium, BUN, creatinine, ALT, AST, alkaline phosphatase, total protein, albumin, total bilirubin, LDH, amylase, lipase, cholesterol, triglycerides, cortisol, T3, T4, free T4, and TSH.
- Collect blood samples for measurement of anti-Globo H IgG and IgM titer.
- Collect blood samples for exploratory analysis for the following biomarkers:
    - Monitoring of immune response of anti-Globo H, anti-SSEA-3 and anti-SSEA-4 antibody production.
    - CTC (only in selected Taiwan sites)
    - ADCC and CDC
- Perform 12-Lead ECG.
- Perform Tumor assessment according to RECIST 1.1 criteria including CT scan as required. If the data of CT assessment are available within 6 weeks prior to the ET visit, the assessment of CT may not be performed based on the investigator's discretion.
- Perform tumor-specific antigen testing (CEA and CYFRA21-1 for all enrolled subjects in selected sites)
- Record adverse events assessed by NCI CTCAE v4.0.

- Record use of concomitant medications.
- Subjects, who discontinued the study treatment or evaluation (before End of Study) for reasons other than disease progression, will be followed up for disease status by clinic visit, until Disease Progression. Same evaluations will be conducted as those defined in the Post-Treatment Period.
- EGFR will be analyzed for the early termination subjects other than PD.

5.8 Other Study Procedures

Tumor tissue samples (and histology/pathology report, if possible) will be collected at Week 1 prior to administration of the investigational drug and be submitted to a central laboratory to test the expression levels of Globo H, SSEA-3, SSEA-4, and PD-L1 by immunohistochemistry, as well as other tumor markers that may be expressed in the lung, gastric, colorectal or breast tumors. Note that, subject tumor biopsy/tissue samples will be collected to test the expression levels of Globo H, SSEA-3, SSEA-4, and/or PD-L1 will be conducted at Week 1 for data analysis purpose and not for eligibility criteria in Dose Escalation Phase. Tumor biopsy/tissue samples are mandatory for Cohort Expansion subjects to test Globo H and other tumor markers such as SSEA-3, SSEA-4, and/or PD-L1 are for data analysis purposes. Globo H expression levels will be collected and tested at screening visit for eligibility.

Blood samples will be collected at various visits shown in Table 1 and 2 and stored with the intention of performing scientific research or immunological analysis on humoral and cellular mediated immune responses, and immunogenicity of the vaccine, using in-house glycan chip and Quantitative ELISA to detect immune response and monitor tumor response by biomarkers.

These tests will include measurement of anti-Globo H IgG and IgM production. Blood samples will also be collected for exploratory analysis of various biomarkers as follows:

- Monitoring of immune response of anti-Globo H, anti-SSEA-3 and anti-SSEA-4 antibody production.
- CTC (only in selected Taiwan sites)
- ADCC and CDC
- T cell and B cell immune response (in selected Taiwan sites)
- B/T cell immunogenomic analysis (in selected Taiwan sites)
- Ex vivo immunogenicity analysis (in selected Taiwan sites)
- Cobas EGFR Mutation Tests (in selected Taiwan sites)

Tissue and blood samples will be analyzed using qualified assays by contracted laboratories under the supervision of OBI Pharma, Inc.

In order to evaluate the treatment response and the therapeutic mechanism of immunotherapies to specific tumor biology, blood and tumor samples need to be stored for present and relevant future studies in order to further explore the anti-tumor immune mechanism against specific tumor biology.

Future studies will be carried out during and after the end of the clinical trial. This may be due to any trends or results that could potentially raise further questions and hypotheses leading to crucial findings and breakthroughs in cancer treatment.

The required study procedures are summarized in the Time and Events Schedule, Table 1 below.

Table 1 Time and Event Schedule for Dose Escalation Phase

Phases Visit ID	Screening	Treatment Period										Post Treatment Period			Follow-Up	Early Termination*
														End of Study		
	Screening Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13		
Corresponding Week		**1**	**2**	**3**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**44-84**	
Visit window (Day)	**		(±3)					(±7)				(±7)			(±7)	N/A
Informed Consent	X															
Demographics & Medical History	X															
Inclusion/Exclusion Criteria	X															
Physical Examination[1] & Vital Signs	X	X	X									X	X	X		X
ECG[2]	X				X			X		X		X		X		X
Urine Pregnancy Test[3]	X															
HIV, HBV and HCV Test[4]	X															
Survival															X	
Treatments																
Registration & Cohort Assignment		X														
Administer Investigational Drug[5]		X	X	X	X	X	X	X	X	X	X					
Laboratory Assessments																
Urine Analysis[6] Hematology[7] Serum Chemistry[8]	X	X	X									X	X	X		X

Table 1. Time and Event Schedule for Dose Escalation Phase (Continued)

Phases Visit ID	Screening	Treatment Period										Post Treatment Period			Follow-Up	Early Termination*
														End of Study		
	Screening Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13		
Corresponding Week		**1**	**2**	**3**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**44-84**	
Visit window (Day)	**		(±3)					(±7)				(±7)			(±7)	N/A
Laboratory Assessment (cont'd)																
Tumor sample for IHC [9]		X														
Blood samples for anti-Globo H IgG and IgM[10]		X		X	X	X	X	X	X	X	X	X	X	X		X
Blood for exploratory analysis of biomarkers[11]		X		X	X	X	X	X	X	X	X	X	X	X		X
Other Assessments																
Adverse Events [12]		X	X									X	X	X		X
Concomitant Medications[13]	X	X	X									X	X	X		X
Tumor Assessment[14]	X							X			X			X		X
Tumor Specific Antigen[15]	X							X			X			X		X
Cellular immune responses[16]								X	X	X	X					

* Early termination is defined as the time point at which the subject withdraws from the study before completing all required treatments and evaluations (i.e., Week 36). These assessments should be obtained when the subject permanently discontinues the study treatment or continuing onto the follow-up phase; however, imaging (e.g., CT scans) does not need to be acquired again if last imaging was done within 4 weeks.
Subjects, who discontinued the study treatment or evaluation (before End of Study) for reasons other than disease progression, will be followed up for disease status by clinic visit, until Disease Progression. Same evaluations will be conducted as those defined in the Post-Treatment Period

**If screening assessment is performed within 7 days prior to Visit 1 at the same laboratory, urine analysis, hematology, and serum chemistry are not required at Visit 1.

1. Includes ECOG performance score, weight, and height at screening. Includes weight at treatment period, post treatment period and early termination visit. Vital signs include blood pressure, respiratory rate, pulse and body temperature.
2. An ECG will be performed at the time of screening, at Weeks 4, 12, 20, 28 and 36 (Visits 4, 7, 9, and 11, and End of Study, respectively) or at the early termination visit (if subject is discontinued prior to Week 36 (End of Study). For any subject who experienced a significant cardiovascular-related medical event, e.g., tachycardia, unscheduled tests will be conducted per Investigator's judgment.
3. Urine pregnancy test is to be performed only on subjects of child bearing potential. Follow up pregnancy testing during the study period will be performed at the Investigator's discretion.

4. Conduct HBV (e.g., HBsAg, HBeAg, and if clinically indicated, HBcAb and/or HBV DNA), HCV (e.g., anti-HCV) testing. Conduct HIV testing if no historical data are available. Optional tests (e.g., viral load) can be ordered for suspected active infection at follow-up visits based on the Investigator's clinical judgment.
5. Vital signs (blood pressure, respiratory rate, pulse and temperature) and inspection of injection sites will be monitored at 0-5 minutes, at 15-30 minutes, and then at 2 hour (±30 minutes) after injection. For every Cohorts, the first three subjects should be hospitalized following first dose of the investigational drug injection, vital signs and inspection of injection sites will be monitored after injection of investigational drug for following time point: at 0-5 minutes, at 15-30 minutes, at 2 hour (±30 minutes), at 4 hour (±30 minutes), at 6 hour (±30 minutes), before bed and before discharge.
6. Conduct routine urinalysis - pH, protein, glucose, specific gravity, ketone, bilirubin, and urobilinogen. Analysis of urinary sediments (RBC, WBC, epithelial casts, hyaline casts, and bacterial) is optional.
7. Hematology includes hemoglobin, hematocrit, WBC, RBC, platelet, differentials, RF, and ESR.
8. Serum chemistry includes sodium, potassium, chloride, calcium, magnesium, BUN, creatinine, ALT, AST, alkaline phosphatase, total protein, albumin, total bilirubin, LDH, amylase, lipase, cholesterol, triglycerides, cortisol, T3, T4, free T4, and TSH.
9. Tumor biopsy/tissue samples of primary site (and distant metastases if possible) will be collected for Globo H, SSEA-3, SSEA-4 and PD-L1 expression by immunohistochemistry (specified in Section 5.8 "Other Study Procedures"). Although fresh specimens are preferred, most subjects should have historical tumor tissue specimens available, which can be submitted to the central lab for testing. If tumor tissue samples are not available, fresh tumor tissue samples should be acquired. However, in cases where tumor biopsies may not be possible, subjects are not required to submit tissue samples.
10. Samples will be collected for analysis of Anti-Globo H IgG and IgM titers by a conventional method.
11. Samples will be collected for exploratory analysis of the following biomarkers and immunological responses: Anti-SSEA-3and antiSSEA-4 antibody titers by in-house development kit, Anti-Globo H, anti-SSEA-3 and anti-SSEA-4 antibodies by glycan array and Quantitative ELISA as well as ADCC and CDC. Samples will only be collected at visits 1, 5, 11 (weeks 1, 6, 28) and early termination for exploratory analysis of CTC in selected Taiwan sites.
12. Adverse events will be assessed by NCI CTCAE v4.0. For the subject who withdraws treatment during the treatment period, adverse events should be recorded through 28 days after the last administration of investigational drug (OBI-833/OBI-821).
13. Concomitant drugs should be recorded including any medication taken within 28 days prior to 1st dosing of the investigational drug. For the subject who withdraws the study during the treatment period, concomitant drug should be recorded until 28 days after the last administration of investigational drug.
14. Tumor assessment will be according to the RECIST 1.1 criteria, including CT scan as required. CT scan will be performed at designated times during treatment. The window period for CT scans is +/– 7 days from the planned visit per protocol schedule. If the data of CT assessment are available within 6 weeks prior to the scheduled visit, the assessment of CT may not be performed based on the investigator's discretion. Unscheduled tumor assessments can also be performed at the Investigator's discretion. Methodology used to assess tumors during the study period should be consistent with the methodology used at baseline/screening. For subjects where CT scans are contraindicated, MRIs can be performed instead.
15. Tumor-specific antigen testing (CEA for all enrolled subjects) to be performed prior to treatment and every 12 weeks until the end of the study.
16. Whole blood sample will be collected to test induced B and T cell responses in selected Taiwan sites.

Table 2 Time and Event Schedule for Cohort Expansion Phase

Phases Visit ID	**Screening**	**Treatment Period**											**Post Treatment Period**			**Follow-Up**	**Early Termination**
															End of Study		
	Screening Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11~Final Injection	PTP 1	PTP 2			
Corresponding Week		**1**	**2**	**3**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**q8 weeks**	8 wks after final injection or 8 wks for continuous injection	16 wks after final injection or 16 wks for continuous injection	24 wks after final injection or 24 wks for continuous injection	**24 wks after End of Study**	
Visit window (Day)	**		(±3)					(±7)				(±7)	(±7)			(±7)	
Informed Consent	X																
Tumor sample for IHC[1]	X																
Demographics & Medical History	X																
Inclusion/Exclusion Criteria	X																
Physical Examination[2] & Vital Signs	X	X	X									X	X	X	X		X
ECG[3]	X							X					X		X		X
Urine Pregnancy Test[4]	X																
HIV, HBV and HCV Test[5]	X																
Survival																X	
Treatments																	
Administer Investigational Drug[6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Laboratory Assessments																	
Urine Analysis[7] Hematology[8] Serum Chemistry[9]	X	X	X									X	X	X	X		X

Table 2. Time and Event Schedule for Cohort Expansion Phase (Continued)

Phases / Visit ID	Screening	Treatment Period											Post Treatment Period			Follow-Up	Early Termination
															End of Study		
	Screening Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11~Final Injection	PTP 1	PTP 2			
Corresponding Week		**1**	**2**	**3**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**q8 weeks**	8 wks after final injection or 8 wks for continuous injection	16 wks after final injection or 16 wks for continuous injection	24 wks after final injection or 24 wks for continuous injection	**24 wks after End of Study**	
Visit window (Day)	**		(±3)					(±7)				(±7)	(±7)			(±7)	
Laboratory Assessment (cont'd)																	
Blood samples for anti-Globo H IgG and IgM[10]		X		X	X	X	X	X	X	X	X	X	X	X	X		X
Blood for exploratory analysis of biomarkers[11]		X		X	X	X	X	X	X	X	X	X	X	X	X		X
Other Assessments																	
Adverse Events [12]		X	X										X	X	X		X
Concomitant Medications[13]	X	X	X										X	X	X		X
Tumor Assessment[14]	X							X			X	X	X[18]	X[18]	X[18]		X[21]
Tumor Specific Antigen[15]	X							X			X	X			X		X
Cellular immune responses[16]							4 continue visits after either anti-Globo H, SSEA-3, SSEA-4 IgG serum concentration reaches 20 μg/ml										
Immunogenomic[17]	X					X		X		X		X***	X***				
Ex vivo Immunogenicity[19]	X																
Cobas EGFR Mutation Tests[20]		X						X				X	X		X		X*

*For the early termination subjects other than PD.
**If screening assessment is performed within 7 days prior to Visit 1 at the same laboratory, urine analysis, hematology, and serum chemistry are not required at Visit 1.
***Only starts after Weeks 64, and every 8 weeks thereafter till 8 weeks after 1st disease progression

1. Tumor biopsy/tissue samples of primary site (and distant metastases if possible) will be collected for Globo H, SSEA-3, SSEA-4 and PD-L1 expression by immunohistochemistry (specified in Section 5.8 "Other Study Procedures") at Screening visit. Although fresh specimens are preferred, most subjects should have historical tumor tissue specimens available, which can be submitted to the central lab for testing. If tumor tissue samples are not available, fresh tumor tissue samples should be acquired. Only Globo H positive subjects are eligible.
2. Includes ECOG performance score, weight, and height at screening. Includes weight at treatment period, post treatment period and early termination visit. Vital signs include blood pressure, respiratory rate, pulse, and body temperature.
3. An ECG will be performed at the time of screening, at Weeks 12, and 8 weeks after final injection as well as EoS visit. For any subject who experienced a significant cardiovascular-related medical event, e.g., tachycardia, unscheduled tests will be conducted per Investigator's judgment.
4. Urine pregnancy test is to be performed only on subjects of child bearing potential. Follow up pregnancy testing during the study period will be performed at the Investigator's discretion.
5. Conduct HBV (e.g., HBsAg, HBeAg, and if clinically indicated, HBcAb and/or HBV DNA), HCV (e.g., anti-HCV) testing. Conduct HIV testing if no historical data are available. Optional tests (e.g., viral load) can be ordered for suspected active infection at follow-up visits based on the Investigator's clinical judgment
6. Vital signs (blood pressure, respiratory rate, pulse and temperature) and inspection of injection sites will be monitored at 0-5 minutes, at 15-30 minutes, and then at 2 hour (±30 minutes) after injection.
7. Conduct routine urinalysis - pH, protein, glucose, specific gravity, ketone, bilirubin, and urobilinogen. Analysis of urinary sediments (RBC, WBC, epithelial casts, hyaline casts, and bacterial) is optional.
8. Hematology includes hemoglobin, hematocrit, WBC, RBC, platelet, differentials, RF, and ESR.
9. Serum chemistry includes sodium, potassium, chloride, calcium, magnesium, BUN, creatinine, ALT, AST, alkaline phosphatase, total protein, albumin, total bilirubin, LDH, amylase, lipase, cholesterol, triglycerides, cortisol, T3, T4, free T4, and TSH.
10. Samples will be collected for analysis of Anti-Globo H IgG and IgM titers by a conventional method.
11. Samples will be collected for exploratory analysis of the following biomarkers and immunological responses: Anti-SSEA-3and antiSSEA-4 antibody titers by in-house development kit, Anti-Globo H, anti-SSEA-3 and anti-SSEA-4 antibodies by glycan array and Quantitative ELISA as well as ADCC and CDC. Samples will only be collected at visits 1, 6, 15, and End of Study/Early Termination (weeks 1, 8, 64, and End of Study/Early Termination) for exploratory analysis of CTC in selected Taiwan sites.
12. Adverse events will be assessed by NCI CTCAE v4.0. For the subject who withdraws treatment during the treatment period, adverse events should be recorded through 28 days after the last administration of investigational drug.
13. Concomitant drugs should be recorded including any medication taken within 28 days prior to 1st dosing of the investigational drug. For the subject who withdraws the study during the treatment period, concomitant drug should be recorded until 28 days after the last administration of investigational drug.
14. Tumor assessment will be according to the RECIST 1.1 criteria, including CT scan as required. CT scan will be performed at designated times during treatment. The window period for CT scans is +/– 7 days from the planned visit per protocol schedule. If the data of CT assessment are available within 6 weeks prior to the scheduled visit, the assessment of CT may not be performed based on the investigator's discretion. Unscheduled tumor assessments can also be performed at the Investigator's discretion. Methodology used to assess tumors during the study period should be consistent with the methodology used at baseline/screening. For subjects where CT scans are contraindicated, MRIs can be performed instead. Brain CT/MRI can be evaluated per Investigator's judgement.
15. Tumor-specific antigen testing (CEA and CYFRA21-1 for all enrolled subjects in selected sites) to be performed prior to treatment at Weeks 12, 24,and every 8 weeks until disease progression and end of study visit.
16. Whole blood sample will be collected to test induced B and T cell responses in selected Taiwan sites.
17. Whole blood sample will be collected to test B and T cell Immunogenomic Analysis in selected Taiwan sites.
18. Only for the subjects who are eligible to continuous injection after disease progression.
19. Whole blood sample will be collected to test Ex vivo Immunogenicity Analysis in selected Taiwan sites.
20. Cobas EGFR Mutation Tests will be conducted at Weeks 1, 12, 40, post treatment period 1 and End of Study for all subjects with known EGFR mutations in selected Taiwan sites.
21. If tumor assessment was performed within 30 days prior to early termination visit, tumor assessment is not required. The data of tumor assessment within 30 days prior to early termination visit is acceptable for Early Termination visit.

6 MANAGEMENT OF TOXICITY AND TREATMENT DISCONTINUATION

6.1 General Management

Vital signs (blood pressure, respiratory rate, pulse and temperature) and inspection of injection sites will be monitored at 0-5 minutes, at 15-30 minutes, and then at 2 hour (±30 minutes) after each injection of investigational drug.

For cohort in dose escalation phase, the first three subjects should be hospitalized following first dose of the investigational drug injection, vital signs and inspection of injection sites will be monitored after injection of investigational drug for following time point: at 0-5 minutes, at 15-30 minutes, at 2 hour (±30 minutes), at 4 hour (±30 minutes), at 6 hour (±30 minutes), before bed and before discharge.

6.2 Management of Drug-Induced Toxicities

Risks to the patients will be mitigated with careful clinical monitoring and evaluation of laboratory safety parameters.

The most likely adverse effects anticipated in this study are local skin reaction at the injection site, fever, chills and sweats as a direct effect of active immunotherapy. These adverse effects seldom require therapy; but anti-pruritics may be used only if symptomatic. If necessary, NSAIDs may be used to control fever and pain, but steroids are prohibited. Pre-medication with anti-pruritics or steroids is prohibited. The study treatment will continue despite these symptoms.

Slight to moderate dermal edema and erythema were observed in animal studies although these were not considered adverse effects. Investigators should treat these conditions per their normal practice. Subjects will be instructed to notify the Investigator if they experience drainage of fluid, injection-site reaction with break in skin and blue-black discoloration and swelling.

Less common but more severe allergic reactions include severe bronchospasm and anaphylaxis. In the presence of these conditions, treatment should be immediately discontinued and the subject treated with epinephrine, steroids, oxygen, volume support, or other bronchodilators and supportive care as needed. The study treatment will be discontinued and the subject will be continuously monitored and may be withdrawn from the study.

Autoimmune disorder may occur since low level of Globo H is expressed by epithelial cells. However, the likelihood of autoimmune disorder is rare since Globo H expression is confined to the apical epithelial cells at lumen borders, a site which appears not to be accessible to the immune system. Immune complex disease as manifested by skin, joint, renal or other changes could occur, but these should be rare in the absence of prior exposure to Globo H.

Treatment will be discontinued, if there is evidence of frequent toxicities associated with severe epithelial cell injury. If any SAE's require the use of immunosuppressive therapies (e.g., cyclosporin, rapamycin, tacrolimus, rituximab, alemzutumab, natalizumab, iv/oral steroid, etc.) or immunomodulatory therapies (e.g., plasmapheresis, intravenous immunoglobulins), then the subject should be terminated from the treatment, and continue to be followed up until disease progression, early termination or end of study.

6.3 Definition and Management of Dose Limiting Toxicity

- An event in dose escalation phase will be considered a dose limiting toxicity (DLT) if it occurs within the first 6 weeks after the administration of OBI-833/OBI-821 and meets the following criteria:
  - Any Grade 3 or Grade 4 toxicities considered at least possibly related to the investigational drug.

- Any subject who develops a DLT will be terminated from study treatment.
- All subjects who have a Grade 3 or 4 clinical or laboratory abnormality at the time of withdrawal from the study must be followed until resolution to Grade 2 or less, unless it is unlikely to improve because of underlying disease.
- If there is any subject of the first 3 or there is more than 1 subject of the first 6 who develop DLT, then the dose escalation will be suspended until a full review by the Data and Safety Monitoring Board. Dose modification, such as a 50% dose reduction for the next dose cohort, may be considered, as justified by emerging safety data. If dose reduction is required for the subjects in cohort 1 (10 μg Cohort), study will be suspended temporally. Data and Safety Monitoring Board will review the emerging safety data and instruct if the study can be resumed and continue to enroll Cohort 1 subject without dose reduction.

6.4 Guidelines for Individual Subject Study Treatment (OBI-833/OBI-821) Discontinuation

- In the event of a ≥ Grade 3 immune-associated AE or emergent SAE as listed below, the subject is required to discontinue study drug treatment. The Data and Safety Monitoring Board will be notified of these events and safety reporting to the various health authorities will follow each country's respective health agency guidelines.
  - Auto-immune diseases included but not limited to severe Guillain-Barré Syndrome (GBS) or chronic inflammatory demyelinating polyneuropathy (CIDP).
  - Encephalopathy or any other significant CNS involvement.
  - Anaphylaxis or respiratory failure requiring intubation and/or ventilator support.
  - Indication for emergency intervention and life-threatening consequences such as malignant hypertension, shock leading to vital organ impairment, severe cardiac arrhythmias, etc.
  - Vasculitis leading to severe ischemia and vascular neuropathy.
  - Nephritis leading to severe renal impairment.
  - Hepatitis leading to severe hepatic dysfunction.
  - Adrenal insufficiency – life threatening adrenal crisis.
  - Severe pancreatitis.
  - Thyroiditis leading to ≥ grade 4 hyperthyroidism or hypothyroidism.
  - Autoimmune hemolytic anemia.
  - And any other potential life threatening or disabling adverse events attributable to the study drug in the opinion of the Investigator and medical monitor.
- Immune related AEs that would NOT be considered emergent or serious, and may NOT require study treatment discontinuation may include:

  - Inflammation that can be attributable to a local antitumor reaction at tumor sites or in draining lymph nodes. This includes inflammatory reactions at sites of tumor resections or exposed to radiation therapy.
- If toxicity occurs regardless of investigational drug administration that does not meet study treatment discontinuation criteria:
  - The investigational drug administration may be delayed for up to 2 consecutive weeks.
  - In the event that the administration of the investigational drug is delayed for more than 2 consecutive weeks, then the Investigator should confer with the Sponsor's Medical Monitor to discuss the appropriateness of continued treatment.
- All subjects in both phases who discontinue study treatment prematurely should undergo the early termination procedures as described in Section 5.7.
- A Data and Safety Monitoring Board will be established to assist Sponsor in monitoring the subject safety, risk/benefit, dose escalation, dose reduction and termination of the study.

7 TREATMENTS PERMITTED AND PROHIBITED DURING STUDY

7.1 Permitted Treatments during Study

[Dose Escalation Phase]

1. Analgesics: Non-steroidal anti-inflammatory drugs (NSAID), analgesics other than NSAID (like aspirin), and opiates may be used for pain control.
2. GCSF and Hematopoietic growth factors will be allowed **in the dose escalation phase if deemed necessary by physicians**.
3. Antihistamine (H1 and H2) and decongestant: cetirizine HCl, fexofenadine HCl, levocetirizine, and pseudoephedrine.
4. Antiemetic and anti-pruritics therapy.
5. Therapy with bisphosphonates (e.g., to treat bone metastases), is at the discretion of the investigator.

[Cohort Expansion Phase]

1. Analgesics: Non-steroidal anti-inflammatory drugs (NSAID), analgesics other than NSAID (like aspirin), and opiates may be used for pain control.
2. Antihistamine (H1 and H2) and decongestant: diphenhydramine, hydroxyzine, cimetidine, ranitidine, famotidine, cetirizine HCl, fexofenadine HCl, levocetirizine, and pseudoephedrine.
3. Antiemetic (eg., ondansetron) and anti-pruritics (eg., diphenhydramine or hydroxyzine) therapy.
4. Therapy with bisphosphonates (e.g., to treat bone metastases), is at the discretion of the investigator.
5. EGFR/ALK TKIs (e.g., gefitinib, erlotinib, afatinib and crizotinib), EGFR mAb (Necitumumab), bevacizumab and PD-1/PD-L1 inhibitors (e.g., pembrolizumab and nivolumab)

7.2 Prohibited Treatments during Study

The following treatments are prohibited during the Treatment and Post-treatment periods of the study until End of Study (Appendix II):

[Dose Escalation Phase]

1. Anti-cancer treatment: no other anti-cancer therapy is allowed during the study. The list of other chemotherapy agents, chemotherapeutic agents, active or passive immunotherapy, includes, but is not limited to:
    - Chemotherapeutic agents: antimetabolites, alkylating agents, vinca alkaloid, epipodophyllotoxins, taxanes, camptothecins, antitumor antibiotics, nitrosoureas folate analogue metabolic inhibitor, and miscellaneous cytotoxic agents.
    - Surgery
    - Radiotherapy
2. Biologic Agents: Monoclonal antibodies, Interferons and Interleukins
3. Immunotherapy: cyclosporin, rapamycin, tacrolimus, rituximab, alemtuzumab, natalizumab etc.
4. Steroids: iv/oral steroids except single prophylactic use in CT/MRI scan or other one-time use in approved indications. The interval between iv/oral steroids administration and first dose of OBI-833/OBI-821 must be more than pharmacological duration or 5 half-lives of administered steroids whichever is the longer.
    - Uses of inhaled and topical steroids are allowed.
5. Tyrosine kinase inhibitors
6. Alternative and complementary medicine may affect immune system
7. Other investigational drugs

[Cohort Expansion Phase]

1. Anti-cancer treatment: The list of chemotherapy agents, active or passive immunotherapy (Appendix II), includes, but is not limited to:
    - Chemotherapeutic agents: antimetabolites, alkylating agents, vinca alkaloid, epipodophyllotoxins, taxanes, camptothecins, antitumor antibiotics, nitrosoureas folate analogue metabolic inhibitor, and miscellaneous cytotoxic agents. EGFR/ALK TKIs are permitted.
    - Surgery
    - Radiotherapy
2. Biologic Agents: Interferons, Interleukins, Denosumab (RANKL inhibitor), GCSF and Hematopoietic growth factors
3. Immunotherapy: cyclosporin, rapamycin, tacrolimus, rituximab, alemtuzumab, natalizumab, cyclophosphamide, etc (except PD-1/PD-L1 antagonists).
4. Steroids: iv/oral steroids except single prophylactic use in CT/MRI scan or other one-time use in approved indications. The interval between iv/oral steroids administration and first dose of OBI-833/OBI-821 must be more than pharmacological duration or 5 half-lives of administered steroids whichever is the longer.
    - Topical (except injection sites) and inhaled steroid use is allowed

5. Alternative and complementary medicine may affect immune system.
6. Other investigational drugs

7. Subjects who continuous treatment after disease progression are allowed to concomitant use of all approved anti-cancer therapies

8 INVESTIGATIONAL DRUG INFORMATION

8.1 OBI-833 (Globo H-CRM197)

Formulation:

OBI-833 is supplied as a sterile lyophilized powder drug product in single-use 2 mL amber borosilicate glass serum vials. Each vial contains 150 μg Globo H linked with CRM197 along with potassium phosphate buffered saline, Sucrose, and polysorbate 80**.**

The physical appearance specification for the drug product is lyophilized cake/powder. The reconstituted solution of OBI-833 drug product is a clear liquid.

Supplier:

OBI-833 will be supplied by OBI Pharma, Inc.

Source and Pharmacology:

OBI-833 is a glycoconjugate comprised of a carbohydrate tumor antigen, Globo H, which is covalently linked to the carrier protein, an inactive and nontoxic form of diphtheria toxin (DT) called cross-reacting material 197 (CRM197).

Immunization of mice with Globo H-CRM197 (DT) induced antibodies reactive with Globo H, SSEA-3, and SSEA-4, suggesting that a Globo H-based vaccine will target tumor cells expressing Globo H, SSEA-3, and SSEA-4. More specifically, as Globo H, SSEA-3, and SSEA-4 are found to be expressed in human tissues of breast cancer, hepatocellular cancer (HCC), lung cancer, oral cancer, gastric and pancreatic cancers, it is postulated that the anti-Globo H, SSEA-3 and SSEA-4 antibodies generated from immunization of OBI-833/OBI-821 can target tumor cells in aforementioned cancer types.

8.2 OBI-821

Formulation:

OBI-821 is lyophilized powder/cake in individual 2 mL amber borosilicate glass serum vial containing 125 μg OBI-821, sodium phosphate buffered saline, and Trehalose.

Supplier:

OBI-821 will be supplied by OBI Pharma, Inc.

Source and Pharmacology:

OBI-821 is a saponin based adjuvant derived from the bark of the *Quillaja saponaria* Molina tree. OBI-821 is a purified saponin, which is structurally similar to descriptions found in the literature for another adjuvant, QS-21. OBI-821 exists as a mixture of isomers. The primary component is designated as OBI-821-V1A, with the balance being a group of closely related analogs.

OBI-821 has been shown to stimulate a variety of immunological activities including antigen-specific antibody to carbohydrate tumor antigen conjugated to a carrier protein. OBI-821 also augments the induction of major histocompatibility complex (MHC)-restricted class I cytotoxic T lymphocytes to subunit antigen vaccines, as well as antigen-specific cellular proliferation.

8.3 Clinical Trial Material (CTM) Supply, Packaging, Labeling and Storage

All CTM will be supplied by OBI Pharma, and must remain under adequate security, storage condition. Do not use any CTM after the expiration date, which is labeled on the investigational drug container.

Investigational Drug Supply

- OBI-833 (equivalent to 150 µg Globo-H) and OBI-821 (125 µg) are provided in separate single-use vials. OBI-821 is mixed with OBI-833 at the time of each injection (within 2 hours after mixing). Following the injections, the leftover OBI-833/OBI-821 mixtures are not recyclable.
- Each injection dose consists of a mixture of 100 µg OBI-821 and OBI-833 containing 10 µg, 30 µg, or 100 µg of Globo H equivalents. OBI-833 drug product is reconstituted in water and mixed with reconstituted OBI-821 immediately. The freshly combined OBI-833/OBI-821 mixture is administered by subcutaneous injection. See Appendix I for detailed procedure for preparation and mixing of OBI-833 and OBI-821 for injection.

Packaging and Labeling

- Packaging and the contents of the label will be in accordance with all applicable regulatory requirements.

Investigational Drug Storage

- OBI-833 and OBI-821 are provided in separate single-use vials. OBI-821 is to be mixed with OBI-833 at time of injections. The recommended storage temperature for both OBI-833 and OBI-821 drug product vials are between 2–8°C.

9 STUDY ENDPOINT

9.1 Primary Endpoints

The primary endpoint is safety and tolerability of OBI-833/OBI-821 assessed by adverse events, changes in laboratory values, and changes in vital signs and physical exam results.

9.2 Secondary Endpoints

- Immune response as assessed by anti-Globo H IgG and IgM production.
- Tumor response per RECIST 1.1 criteria.

9.3 Safety Assessment

- Toxicity and adverse events will be assessed by NCI CTCAE v4.0 following subcutaneous doses of OBI-833/OBI-821 immunization.
- Safety and toxicity will be assessed according to the dose of OBI-833/OBI-821 the subjects received and on all subjects who received at least one dose of OBI-833/OBI-821. Every effort should be made to follow up all subjects and all scheduled evaluations should be performed until study closure or the death of the subjects irrespective of withdrawals from the treatments.
- Any clinically significant abnormalities persisting at the end of the study/early termination will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

9.4 Safety Variables

- Toxicity & adverse events (as assessed by NCI CTCAE v4.0).
- Safety laboratory examination (Urinalysis, hematology and serum chemistry).
- Vital signs (blood pressure, respiratory rate, pulse and temperature).
- Liver and renal functions.
- Physical exam.
- ECG.

10 RESPONSE CRITERIA

Criteria for Tumor Response by RECIST 1.1:

RECIST 1.1 will be used as the guideline for the analysis of this study. Images will be taken from the chest, abdomen and pelvis area. A Baseline/Screening tumor burden will be obtained by evaluating the entire organ systems included in the body systems imaged. This tumor burden will be categorized as either Measurable (Target Lesions) or Non-Measurable (Non-Target Lesions) (see Section 10.1). The purpose of establishing this Baseline/Screening is to allow for subsequent assessment of on-treatment response.

10.1 Definitions for Measurability of Tumor Lesions

Measurable:

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness recommended to be in between 2.5 mm and 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.
- Malignant lymph nodes:

To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be in between 2.5 mm and 5 mm). At baseline and during follow-up, only the short axis will be measured and followed See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually NOT considered measurable unless there has been demonstrated progression in the lesion.

Non-Measurable:

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions.

Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

10.2 Recording Tumor Lesions

When more than 1 measurable lesion is present at baseline all lesions up to a maximum of **5 lesions total** (and a maximum of **2 lesions** per organ) representative of all involved organs should be identified as **target lesions** and will be recorded and measured at baseline (this means in instances where subjects have only 1 or 2 organ sites involved a maximum of 2 and 4 lesions respectively will be recorded).

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as **non-target lesions** and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'.

In addition, it is possible to record multiple non target lesions involving the same organ as a single item on the case record form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

10.3 Response Evaluation

Target Lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum-diameters while on study. Measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks.
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- At each time point, the presence or absence of new lesions will be assessed.

Non-Target Lesions

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
- Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Table 3 Overall Response Table

Target Lesions	Non-Target Lesions	New Lesions[1]	Time Point Response
CR	CR	No	CR
CR	SD	No	PR
CR	UE	No	PR[2]
PR	UE	No	PR[2]
PR	CR	No	PR
PR	SD	No	PR
SD	UE	No	SD
SD	CR	No	SD
SD	SD	No	SD
PD	ANY	Yes/No	PD
ANY	Unequivocal PD/PD	Yes/No	PD
ANY	ANY	Yes	PD
UE	Non-PD	No	UE
CR	NA[4]	No	CR
PR	NA[4]	No	PR
SD	NA[4]	No	SD
NA[3]	SD	No	SD
NA[3]	CR	No	CR
NA[3]	UE	No	UE
NA[3]	NA[4]	No	UE

1 Identification of new lesions at a post-baseline time point will result in time point response of PD. If an identified new lesion subsequently becomes UE, the time point response will be recorded as PD unless the new lesion has proven to have resolved.

2 If a non-target lesion is classified as UE, a designation of PR may be assigned based on information from the target lesions.

3 No target lesions identified at baseline.

4 No non-target lesions identified at baseline.

5 CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, UE = unable to evaluate, and NA = not applicable.

11 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

11.1 Criteria for Removal from Protocol Therapy

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

- Evidence of disease progression based on RECIST 1.1 Criteria (see Section 10) in dose escalation phase.
- Noncompliance.
- Subject voluntarily withdrew his/her consent.
- Subject develops a DLT.

- Extraordinary medical circumstances: Subject who, in the opinion of the Investigator, should be discontinued for their well-being or if at any time the treatments prescribed by this protocol are detrimental to the subject's health, the subject may be withdrawn from the study (see Section 5). In this event, reasons for withdrawal should be clearly documented.
- If subject becomes pregnant or requires breast-feeding during the Treatment period.
- Subjects who are off protocol therapy instead of disease progression will need to complete End of Study Visit.
- All surviving subjects will be followed up for survival status by phone contact or subjects' clinic visit every 12 weeks for up to 24 weeks.

11.2 Off Study Criteria

- Death.
- Lost to follow-up: After Investigators or study staff have attempted to reach the subject at least 2 times over a 4-week period and failed, the subject may then be considered lost to follow-up.
- Withdrawal of consent: Subject decides to voluntarily withdraw from the study **AND** refuses collection of follow-up information.

12 STATISTICAL CONSIDERATIONS

12.1 Hypotheses

No formal statistical hypotheses will be tested.

12.2 Target Sample Size

A maximum number of 18 subjects can be enrolled in the dose escalation phase; and a maximum number of 14 subjects can be enrolled in the cohort expansion phase. A maximum of total 32 subjects can be enrolled in this Phase I study. The sample sizes for the study are not driven by statistical considerations. The study is considered as pilot and exploratory in nature to evaluate the potential dose-response relationship to facilitate dose selection for subsequent studies.

12.3 Safety and Toxicity

Toxicity graded by the US NCI Common Toxicity Criteria Version 4.0 in conjunction with MedDRA (Medical Dictionary for Regulatory Affairs) will be employed to evaluate the safety profile of the study treatments. Safety variables to be evaluated are listed in Section 9.4.

12.4 Statistical Methods

12.4.1 Analytical Sets

- The Safety Population is the group of subjects who received at least one dose of investigational product and had at least one post-dose safety assessment.

- The Immune Response Population is the group of subjects who received at least one dose of investigational product and had anti-Globo H IgG or IgM production.

- The Tumor Response Population will include all enrolled subjects.

12.4.2 Premature Termination and Missing Values

All available data will be displayed and utilized in data analysis. Subjects prematurely terminating the study treatment will be summarized. Listings of subjects with premature termination will be provided with the dates and reasons for termination. Missing data will not be replaced by any estimated or imputed values.

12.4.3 Baseline

The baselines for clinical findings, laboratory evaluations, vital signs, physical examination, ECG, and performance status, as detailed in Table 1 and 2– Treatment and Post Treatment Periods, will be evaluated at entry.

12.4.4 Interim Analysis

No interim analysis will be performed.

12.5 Safety Analysis

12.5.1 Adverse Events

Adverse events will be regarded as Treatment Emergent (TEAE) if they started on or after the date and time of administration of the first dose of study drug, or if they were present prior to the administration of the first dose of study drug and increased in severity during the study.

Adverse Events (AEs) will be coded using the standard Medical Dictionary for Regulatory Activities (MedDRA) dictionary and grouped by system organ class and preferred term and events. TEAEs will be summarized by frequency and proportion of total subjects, by system organ class and preferred terms. Separate summaries will be given for: all events, events by CTC grade, and events by relationship to study drug. All AEs will be provided in data listings.

Subjects who died during the study will be summarized and listed. Subjects with Serious Adverse Events (SAEs) will be summarized and listed. AEs leading to discontinuation or leading to modification of drug dose will be summarized.

12.5.2 Clinical Laboratory Parameters

Each laboratory analyses will be summarized using descriptive statistics mean (standard deviation), median (range, min, max). Change from baseline will also be summarized. The incidence of markedly abnormal lab values will be provided.

12.5.3 Other Safety Parameters

Other safety parameters such as vital signs, ECGs, concomitant medications and study drug exposure will be summarized via summary tables and descriptive statistics.

12.6 Immune Response Analysis

The results of anti-Globo H IgG and IgM titer determined by ELISA at each assessment time point per dose cohort will be summarized using descriptive statistics. Change from baseline (Week 1) will also be summarized. The maximal response, time to maximal response and the area under the response curve for each IgG type may be determined to aid the evaluation of potential dose-response relationship.

The immune response may also be analyzed and summarized based on the solid tumor cancer type as appropriate, or based on the IHC results of Globo H, SSEA-3, SSEA-4 and PD-L1 antigen at baseline (Week 1 or screening).

12.7 Exploratory Analysis of Other Biomarkers

The results of exploratory analysis of other biomarkers (Anti-SSEA-3, anti-SSEA-4 antibodies, CTC, ADCC, CDC) at each assessment time point per dose cohort will be summarized using descriptive statistics. Change from baseline (Week 1) will also be summarized. Cellular immune responses (B cells and T cells) will be analyzed for 4 continuous visits after either serum anti-Globo H, anti-SSEA-3, or anti-SSEA-4 IgG reaches 20 μg/ml after Week 8. B/T cell immunogenomic analysis will be conducted at Screening, Weeks 6, 12, 20, 64, and every 8 weeks until 8 weeks after 1st disease progression. Ex vivo immunogenicity Analysis will be conducted at screening visit. Anti-Globo H, anti-SSEA-3 and anti-SSEA-4 antibody will be evaluated by Quantitative ELISA and glycan array. Cobas EGFR Mutation Tests will be conducted at Weeks 1, 12, 40 and post treatment period 1 for all subjects with known EGFR mutations in selected Taiwan sites.

13 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Timely, accurate, and complete reporting and analysis of safety information from clinical trials are crucial for the protection of subjects, Investigators, and the Sponsor, and is mandated by regulatory agencies worldwide. The sponsor has established standard operating procedures (SOPs) in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical trials sponsored by OBI Pharma, Inc. or its affiliates will be conducted in accordance with those procedures.

The investigator and/or delegated site staff is responsible for detecting, documenting and reporting events that meet the definition of an Adverse Event (AE) or Serious Adverse Event (SAE). During the study when there is a cohort safety evaluation, the investigator or site staff will be responsible for detecting, documenting and reporting all AEs and SAEs. AEs and SAEs will be collected from the start of dosing of OBI-833/OBI-821 and until the End of Study.

13.1 Adverse Events

Based on ICH guidelines, an adverse event (AE) is defined as any untoward medical occurrence in a clinical study subject administered a medicinal product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the investigational drug. This includes any

occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Treatment-Related AEs

A treatment-related AE is an event that is considered associated with the use of a study treatment (OBI-833/OBI-821) if the attribution is possibly, probably, or definitely related by the definitions listed in Section 13.3.

Adverse events (AEs) and toxicities will be assessed throughout the study and graded according to US NCI Common Toxicity Criteria, Version 4.0, developed by the Cancer Therapy Evaluation Program at the National Cancer Institute. The criteria for unacceptable toxicities should include any ≥ Grade 4 toxicity, with the exception of local skin reactions, fever, chilling, sweats, urticaria, and/or pruritis since these are common side effects of antibody/adjuvant administration, are reversible, and controlled by supportive management. Theoretically, immune complex disease as manifested by skin, joint, renal, or other manifestations could occur, but these should be rare in the absence of prior exposure to mouse protein. These will be an indication to stop therapy in the affected subjects, but accrual of new subjects may continue.

In general, Grade 1 (Mild) and Grade 2 (Moderate) adverse events are considered acceptable. Grade 3 AEs are Severe but reversible or medically manageable conditions involving major organ and organ function. Grade 4 AEs are Life-threatening consequences; urgent intervention indicated.

Any adverse event must be recorded in the subject medical records and on the eCRFs. The onset and end dates, severity, duration, effect on investigational drug administration (e.g., discontinuation), relationship to investigational drug, and administration of any other drug(s) for treatment of AEs will be recorded for each adverse event.

Subjects will be questioned and/or examined by the Investigator or his/her designee for evidence of adverse events. The questioning of subjects with regard to the possible occurrence of adverse events will be generalized as, “How have you been feeling since your last visit?” The presence or absence of specific adverse events should not be solicited from subjects.

13.2 Anticipated Adverse Events

Previous reports and clinical studies on Globo H did not present with any drug-related serious adverse effects. Adverse effects were generally mild to moderate with the most common adverse effects been mild flu-like symptoms and transient local skin reactions at the subcutaneous injection site. However, possibilities of an allergic or autoimmune reaction may occur, as with all immunotherapy and vaccines. When serious toxicities due to immunotherapy treatment do occur, please follow the guidelines for treatment discontinuation in Section 6.

13.3 Assessment of Relationship to Treatment

The Investigator must assess the relationship of any adverse event to the use of investigational drug, based on available information, using the following guidelines:

- Not related:

With no temporal relationship with administration of the investigational drug. May have negative dechallenge and rechallenge information. Typically explained by extraneous factors (e.g., concomitant disease, environmental factors, or other medications or chemicals).

- Unlikely related:

With a temporal relationship to administration of the investigational drug that makes a causal relationship improbable, and in which other medications, chemicals, or underlying disease provide plausible explanations.

- Possibly related:

With a reasonable time sequence to administration of the investigational drug, but which could also be explained by concurrent disease or other medications or chemicals. Information on treatment withdrawal may be lacking or unclear.

- Probably related:

With a reasonable time sequence to administration of the investigational drug, unlikely to be attributed to concurrent disease or other medications or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge).

- Definitely related:

Occurs in a plausible time relationship to administration of the investigational drug, and which concurrent disease or other medications or chemicals cannot explain. The response to withdrawal of the treatment should be clinically plausible.

13.4 Serious Adverse Events

Based on ICH guidelines, a SAE is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- Results in persistent or significant disability/incapacity
- Requires inpatient hospitalization or results in prolongation of ER visit (≥24hrs).
- Results in congenital abnormally/birth defect
- Are medically significant*

*Any important medical events that may not be immediately life-threatening or result in death or hospitalization (≥24hrs) but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available

- The event can be attributed to another agent(s) other than the study treatment(s) or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Any event requiring hospitalization (or results in prolongation of hospitalization) that occurs during the course of a subject's participation in a clinical study must be reported as a SAE except hospitalizations for the following:

- Social reasons in the absence of an AE
- Surgery or procedure planned before entry into the study (must be documented in the CRF)
- Elective hospitalization for treatment of disease (e.g., subjects be treated with the first dose of the investigational drug)

Disease progression should not be recorded as an AE or SAE term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the SAE definition (see Section 13.5).

13.5 Reporting of Serious Adverse Events

OBI Pharma, Inc. or its designee must be notified of the occurrence of all serious adverse events whether or not deemed drug related or expected within 24 hours of awareness of the event by the Investigator. This reporting timeframe also applies to serious adverse events follow up report for new information update.

Serious adverse events (SAEs) require immediate notification to OBI Pharma, Inc. or its designee starting from the date of first dosing and until the last follow up visit in the post-treatment period. For subjects who withdraw treatment during the treatment period, the serious adverse events should be reported to OBI Pharma, Inc. through 28 days after the last administration of study product.

However, if any serious adverse events occurred after the reporting period defined above, it is required to be reported within 24 hours of awareness if a causal relationship is suspected.

As for health authority, all serious adverse events report will be submitted and followed per local regulations

The sponsor (OBI Pharma Inc.) will also be responsible for compliance with applicable portions of the USA Public Health Service Act, the Federal Food, Drug, and Cosmetic Act, and the Code of Federal Regulations (CFR). These responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the product by fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the product that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and submitting annual progress reports (21 CFR 312.33).

13.6 Pregnancy

If it is subsequently discovered that a subject is pregnant during the study period, study treatment will be permanently discontinued in an appropriate manner.

The Investigator must notify OBI Pharma, Inc. or its designee of this event within 24 hours of awareness.

The pregnancy events require immediate notification to OBI Pharma, Inc. or its designee starting from the date of first dosing until the last follow up visit in the post-treatment period. For the subject who withdraws the study during the treatment period, the pregnancy events should be reported to OBI Pharma, Inc. until 28 days after the last administration of study product.

In addition, the Investigator must report to OBI Pharma, Inc. or its designee follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome.

13.7 Data and Safety Monitoring Board

A Data and Safety Monitoring Board will be established to assist the Sponsor in monitoring subject safety, risk/benefit, and decision for dose escalation, dose modification and termination of the study.

14 STUDY ADMINISTRATION AND MONITORING

14.1 Institutional Review Board Approval

This proposed study must have the approval of a properly constituted Institutional Review Board (IRB). Investigator will obtain written and dated approval from the IRB for the protocol, protocol amendment, informed consent forms, recruitment materials and any other written information to be provided to the subjects.

14.2 Informed Consent Forms

Each subject (or a legally authorized representative) must give written consent (and sign other locally required documents) according to local requirements after the nature of the study has been fully explained. The consent form must be signed prior to performance of any study-related activity. The consent form that is used must be approved both by the sponsor and by the reviewing IEC/IRB. The informed consent should be in accordance with the current revision of the Declaration of Helsinki, current International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines, and OBI Pharma, Inc. or its designee's policy.

The Investigator or person obtaining consent according to the institutional policies and procedures must explain to potential subjects or their legal representatives the aims, methods, reasonably anticipated benefits and potential hazards of the trial and any discomfort the subjects may experience. Subjects will be informed that they are free not to participate in the trial and that they may withdraw consent to participate at any time. They will be told which alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that their records may be examined by competent authorities and authorized persons but that personal information will be treated as strictly confidential and will

not be publicly available. Subjects must be given the opportunity to ask questions. After this explanation and before entry into the trial, consent should be appropriately recorded by means of the subject's or his/her legal representative's dated signature. If a subject and his/her legal representative are unable to read, the consenting process will be conducted according to the institution policies and procedures.

The subject should receive a signed and dated copy of the informed consent form. A copy of the signed informed consent form (including amended consents) must be given to the subject prior to the study participation. The Investigator must keep each subject's signed consent form(s) on file and readily available for review by the monitor and for inspection by the regulatory agency at any time.

14.3 Study Conduct and Monitoring

All aspect of the study will be conducted under ICH and Good Clinical Practice guidelines. It will be monitored by qualified individuals designated by the sponsor. Monitoring will be conducted according to Good Clinical Practice and standard operating procedures for compliance with applicable government regulations. The Investigator will agree to the monitor's access to the clinical supplies, dispensing, and storage area, and to the clinical files of the study subjects, and if requested, agrees to assist the monitor.

14.4 Case Report Forms

Data from this study will be entered in electronic Case Report Forms (eCRFs) using a validated Electronic Data Capture (EDC) system will be employed by the Sponsor via a designated Contract Research Organization (CRO). Site personnel will receive detailed training on completion of the eCRFs. All data entered will be reviewed electronically at a central location and any discrepancies or clarifications will be corrected during routine on-site clinical monitoring. Concomitant medications entered into the database will be coded using the WHO Drug Reference List. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

It is the Investigator's responsibility to ensure completion of all applicable eCRFs and to review and approve all eCRFs according to instructions by the Sponsor designated CRO.

14.5 Source Documents

In addition to routine monitoring, the study may be evaluated by an auditor designated by OBI Pharma, Inc. or its designee, or by government inspectors who need to be allowed access to the original medical records, and all the study documents.

14.6 Retention of Documents

It is the responsibility of the Investigator and his/her staff to maintain a comprehensive and centralized filing system for all documentation relevant to the protocol. Such documentation includes:

- Cases report forms must be accurate and up to date.

- Subject log records that list all subjects who have been screened for study entry, including reasons why a subject is ineligible.
- Subject drug inventory records including records for the total number of investigational drug vials prepared and dispensed for study subject.
- Clinical supplies shipment forms must be signed and dated.
- Informed consent forms: Signed consent forms from each subject must be available and verified for proper documentation and approval.

The protocol, protocol amendment, the regulatory authority approval, IRB approval, sponsor and CRO correspondence and any other documents pertaining to the conduct of the protocol, must be kept on file by the Investigator.

These documents should be retained by the Investigator according to ICH-GCP guideline and local regulations.

14.7 Quality Control and Quality Assurance

To ensure accurate, complete, and reliable data, OBI Pharma, Inc. or its representatives will conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. The monitors will review source documents and ensure the data recorded in eCRF are accurate.

The site may be subjected to review by the IRB and/or to quality assurance audits performed by OBI Pharma, Inc. or its representatives.

14.8 Drug Accountability

It is the responsibility of the clinical Investigator to ensure that all study drug received at the site will be inventoried and accounted for throughout the study and recorded in the drug accountability forms maintained in the Trial Center File. The drug accountability will be verified by the monitor during on site monitoring visits. Study drug will be stored in a limited access area according to temperature specifications detailed in this protocol.

The Investigator will confirm that all original containers are retained and stored according to the institutional policy, until these containers are inventoried by the sponsor. Original containers will not be retained and stored if not allowable according to institutional policy. Unless otherwise instructed by the sponsor, the Investigator agrees at the end of the study to return all retained containers of study drug to the sponsor as instructed by the site manager. A pharmacist of the medical center or the authorized personnel designated by the Investigator will fill out the drug accountability records. All entries must be legible and complete.

OBI Pharma, Inc. or its designee will ensure proper disposition of original containers empty or full with returned or unused study drug. Appropriate documentation will be maintained. If OBI Pharma, Inc. authorizes destruction at the trial site, the Investigator must ensure that the materials are destroyed in compliance with applicable regulation policy, according to the institution's destruction policy and any instructions provided by OBI Pharma, Inc.

14.9 Study Completion/Discontinuation/Termination

- The following situations are regarded as study completion:

  - Successful completion of the trial at the center;
  - The required number of subjects for the trial has been recruited;
- Study termination can occur at any time either by the Sponsor or by the Investigator, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. Reasons for such action taken by the Sponsor may include, but are not limited to:
  - Failure of the Investigator to comply with the protocol, the Sponsor's procedures or GCP guidelines;
  - Ethical concerns;
  - Safety and/or toxicity concerns;
  - Sufficient data suggesting lack of efficacy;
  - Inadequate recruitment of subjects by the Investigator.

14.10 Use of Information and Publication

Please refer to the Clinical Study Agreement.

15 REFERENCES

1. Allen JR, Harris CR, and Danishefsky SJ (2001) Pursuit of optimal carbohydrate-based anticancer vaccines: preparation of a multiantigenic unimolecular glycopeptide containing the Tn, MBr1, and Lewis(y) antigens. J. Am. Chem. Soc. 123: 1890-7
2. Chang, K., Kuo, W., Wang, M. (2008a). The Epidemiology of Breast Cancer in Taiwan. J. Chinese Oncol. 24(2), 85-93
3. Chang WW, Lee CH, Lee P, Lin J, Hsu CW, Hung JT, Lin JJ, Yu JC, Shao L, Yu J, Wong CH, and Yu AL. (2008b). Expression of Globo H and SSEA3 in breast cancer stem cells and the involvement of fucosyltransferases 1 and 2 in Globo H synthesis. PNAS (V.105, No. 33): 11667–11672
4. Chapman PB, Morrissey DM, Panageas KS, Hamilton WB, Zhan C, Destro AN, Williams L, Israel RJ, Livingston PO (2000a) Induction of antibodies against G_{M2} ganglioside by immunizing melanoma patients using G_{M2}-KLH + QS21 vaccine: a dose-response study. Clin. Cancer Res. 6: 874-879.
5. Chapman PB, Morrisey D, Panageas KS, Williams L, Lewis JJ, Israel RJ, Hamilton WB, Livingston PO (2000b) Vaccination with a bivalent G(M2) and G(D2) ganglioside conjugate vaccine: a trial comparing doses of G(D2)-keyhole limpet hemocyanin. Clin. Cancer Res. 6:4658-62
6. Devita, Hellman, and Rosenburg (2008). Cancer: Principles and Practice of Oncology. 8th Edition.
7. Gilewski T, Ragupathi G, Bhuta S, Williams LJ, Musselli C, Zhang XF, Bornmann WG, Spassova M, Bencsath KP, Panageas KS, Chin J, Hudis CA, Norton L, Houghton AN, Livingston PO, Danishefsky SJ. (2001) Immunization of metastatic breast cancer patients with a fully synthetic globo H conjugate: a phase I trial. Proc Natl Acad Sci U S A 98:3270-5
8. Helling F, Shang A, Calves M, Zhang S, Ren S, Yu RK, Oettgen HF, Livingston PO (1994) Increased immunogenicity of G_{D3} conjugate vaccines: comparison of various carrier proteins and selection of G_{D3}-KLH for further testing. Cancer Res. 54: 197-203.
9. Helling F, Zhang S, Shang A, Adluri S, Calves M, Koganty R, Longenecker BM, Yao T-J, Oettgen HF, Livingston PO (1995) G_{M2}-KLH conjugate vaccine: increased immunogenicity in melanoma patients after administration with immunological adjuvant QS-21. Cancer Res. 55: 2783-2788.
10. Huang YL, Hung JT, Cheung SK, Lee HY, Chu KC, Li ST, Lin YC, Ren CT, Cheng TJ, Hsu TL, Yu AL, Wu CY, Wong CH (2013). Carbohydrate-based vaccines with a glycolipid adjuvant for breast cancer. Proc. Natl. Acad. Sci. 110: 2517-2522.
11. Ibrahim NK, Murray JL, Zhou D, Mittendorf EA, Sample D, Tautchin M, Miles D (2013) Survival advantage in patients with metastatic breast cancer receiving endocrine therapy plus sialyl Tn-KLH vaccine: post hoc analysis of a large randomized trial. J. Cancer 4: 577-584.
12. Khong HT and Restifo NP (2002) Natural selection of tumor variants in the generation of "tumor escape" phenotypes. Nat. Immunol. 3: 999-1005.
13. Livingston PO (1995a) Augmenting the immunogenicity of carbohydrate tumor antigens. Seminars in Can. Biol. 6:357-366.
14. Livingston PO (1995b) Approaches to augmenting the immunogenicity of melanoma gangiosides: from whole melanoma cells to gangioside-KHL conjugate vaccines. Immunol. Reviews 145:148-166.

15. Livingston PO (1998) Ganglioside vaccines with emphasis on G_{M2}. Semin. Oncol. 25: 636-645.
16. Livingston PO, Adluri S, Helling F, Yao T-J, Kensil CR, Newman MJ, and Marciani D (1994a) Phase 1 trial of immunological adjuvant QS-21 with a GM2 ganglioside-keyhole limpet haemocyanin conjugate vaccine in patients with malignant melanoma. Vaccine 12:1275-1280.
17. Livingston PO, Wong GYC, Adluri S, Tao Y, Padavan M, Parente R, Hanlon C, Jones Calves M, Helling F, Ritter G, Oettgen HF, Old LJ (1994b) Improved survival in stage III melanoma patients with G_{M2} antibodies: a randomized trial of adjuvant vaccination with G_{M2} ganglioside. J. Clin. Oncol. 12: 1036-1044.
18. Livingston PO, Zhang S, Lloyd KO (1997) Carbohydrate vaccines that induce antibodies against cancer. 1. Rationale. Cancer Immunol. Immunother. 45: 1-9.
19. Livingston PO & Ragupathi G. (1997) Carbohydrate vaccines that induce antibodies against cancer. 2. Previous experience and future plans. Cancer Immunol. Immunother. 45: 10-19.
20. Longenecker BM, Reddish M, Koganty R, and MacLean GD (1993) Immune responses of mice and human breast cancer patients following immunization with synthetic sialyl-Tn conjugated to KLH plus detox adjuvant. Ann. N. Y. Acad. Sci. 690: 276-91
21. Longenecker BM, Reddish M, Koganty R, and MacLean GD (1994) Specificity of the IgG response in mice and human breast cancer patients following immunization against synthetic sialyl-Tn, an epitope with possible functional significance in metastasis. Adv. Exp. Med. Biol. 353: 105-24.
22. Lou YW, Wang PY, Yeh SC, Chuang PK, Li ST, Wu CY, Khoo KH, Hsiao M, Hsu TL, Wong CH (2014) Stage-specific embryonic antigen-4 as a potential therapeutic target in glioblastoma multiforme and other cancers. Proc. Natl. Acad. Sci. 111:2482-2487.
23. MacLean GD, Reddish M, Koganty RR, Wong T, Gandhi S, Smolenski M, Samuel J, Nabholtz JM, Longenecker BM (1993) Immunization of breast cancer patients using a synthetic sialyl-Tn glycoconjugate plus Detox adjuvant. Cancer Immunol. Immunother. 36: 215-22
24. McCaffery M, Yao T-J, Williams L, Livingston PO, Houghton AN, Chapman PB (1996) Enhanced immunogenicity of BEC2 anti-idiotypic monoclonal antibody that mimics G_{D3} ganglioside when combined with adjuvant. Clin. Cancer Res. 2: 679-686.
25. Menard S, Tagliabue E, Canevari S, Fossati G, Colnaghni MI (1983) Generation of monoclonal antibodies reacting with normal and cancer cells of human breast. Cancer Res. 43:1295-1300.
26. Miotti S, Leoni F, Canevari S, Sonnino S, Colnaghi MI (1989) Immunoblotting detection of carbohydrate epitopes in glycolipids and glycoproteins of tumor origin. In: Oettgen HF, ed. Gangliosides and Cancer. Weinheim: VCH Verlagsgesellschaft, pp 169-176.
27. Musselli C, Livingston PO, Ragupathi G (2001) Keyhole limpet hemocyanin conjugate vaccines against cancer: the Memorial Sloan Kettering experience. J. Cancer Res. Clin. Oncol. 127 Suppl 2:R20-6
28. Pawelec G, Zeuthen J, Kiessling R (1997) Escape from host-antitumor immunity. Crit. Rev. Oncog. 8: 111-41
29. Rabinovich NR, McInnes P, Klein DL, Hall BF. (1994) Vaccine technologies: view to future. Science 265: 1401-1404
30. Ragupathi G, Meyers M, Adluri S, Howard L, Musselli L, Livingston PO (2000) Induction of antibodies against G_{D3} ganglioside in melanoma patients by vaccination with G_{D3}-lactone-KLH conjugate plus immunological adjuvant QS-21. Int. J. Cancer 85: 659-666.

31. Ragupathi, G., Park, T. K., Zhang, S., Kim, I. J., Graber, L., Adluri, R., Lloyd, K. O., Danishefsky, S. J. & Livingston, P. O. (1997) Immunization of mice with a fully synthetic globo H antigen results in antibodies against human cancer cells: A combined chemical-immunological approach to the fashioning of an anticancer vaccine. Angew. Chem. Int. Ed. Engl. 36: 125-128
32. Sandmaier BM, Oparin DV, Holmberg LA, Reddish MA, MacLean GD, Longenecker BM (1999) Evidence of a cellular immune response against sialyl-Tn in breast and ovarian cancer patients after high-dose chemotherapy, stem cell rescue, and immunization with Theratope STn-KLH cancer vaccine. J. Immunother. 22: 54-66.
33. Slovin SF, Ragupathi G, Adluri S, Ungers G, Terry K, Kim S, Spassova M, Bornmann WG, Fazzari M, Dantis L, Olkiewicz K, Lloyd KO, Livingston PO, Danishefsky SJ, Scher HI. (1999) Carbohydrate vaccines in cancer: immunogenicity of a fully synthetic globo H hexasaccharide conjugate in man. Proc Natl Acad Sci U S A 96:5710-5
34. Sotomayor EM, Borrello I, Levitsky HI (1996) Tolerance and cancer: a critical issue in tumor immunology. Crit. Rev. Oncog. 7:433-56.
35. White AC, Cloutier P, Coughlin RT (1991) A purified saponin acts as an adjuvant for a T-independent antigen. Adv. Exp. Med. Biol. 303: 207-210.
36. Yu AL, Gilman AL, Ozkaynak MF, London WB, Kreissman SG, Chen HX, Smith M, Anderson B, Villablanca JG, Matthay KK, Shimada H, Grupp SA, Seeger R, Reynolds CP, Buxton A, Reisfeld RA, Gillies SD, Cohn SL, Maris JM, Sondel PM. (2010) Anti-GD2 Antibody with GM-CSF, IL2 and Isotretinoin for Neuroblastoma. New Eng. J. Med. 363:1324-34.
37. Zhang S, Graeber LA. Helling F, Ragupathi G, Adluri S, Lloyd KO, Livingston PO (1996) Augmenting the immunogenicity of synthetic MUC1 peptide vaccine in mine. Cancer Res. 56:3315-3319.
38. Zhang, S., Cordon-Cardo, C., Zhang, H. S., Reuter, V. E., Adluri, S., Hamilton, W. B., Lloyd, K. O. & Livingston, P. O. (1997a) Selection of tumor antigens as targets for immune attack using immunohistochemistry: I. Focus on gangliosides. Int. J. Cancer 73, 42-49.
39. Zhang S, Zhang HS, Cordon-Cardo C, Reiter VS, Singhal AK, Lloyd KO, Livingston PO. (1997b) Selection of tumor antigens as targets for immune attack using immunohistochemistry: II. Blood group-related antigens. Int. J. Cancer, 73, 50-56.
40. Zhang, S., Zhang, H. S., Reuter, V. E., Slovin, S. F., Scher, H. I. & Livingston, P. (1998) Expression of potential target antigens for immunotherapy on primary and metastatic prostate cancers. Clin. Cancer Res. 4, 295-302.
41. Guidance for Industry-Clinical Considerations for Therapeutic Cancer Vaacines. US Department of Health and Human Services, FDA, CBER, October 2011.

16 APPENDICES

APPENDIX I: OBI-833 AND OBI-821 MIXING INSTRUCTION FOR SUBCUTANEOUS ADMINISTRATION

1. **Storage Condition: Both** OBI-833 and OBI-821 vials are to be stored at 2-8° C.

2. **Study Cohorts**
   - Cohort 1: OBI-833 (equivalent to 10 μg Globo H)/100 μg OBI-821
   - Cohort 2: OBI-833 (equivalent to 30 μg Globo H)/100 μg OBI-821
   - Cohort 3: OBI-833 (equivalent to 100 μg Globo H)/100 μg OBI-821

3. **Investigational Drugs:**

   Orange Vial (OBI-821)

   Contents: 125 μg OBI-821 in sodium phosphate buffered saline, and Trehalose. At time of treatment, with a syringe, add 0.5 mL or 0.9 mL of water for injection to Orange Vial (OBI-821) to obtain OBI-821 solution: **Fully dissolve** the contents of the vial (Orange Vial)) by gently inverting the vial 4-5 times. **Do not shake the vial vigorously.** According to drug mixing procedures for three cohorts, OBI-821 is mixed with OBI-833 immediately for injection after re-constituted with WFI.

Dosing Cohort	Water for Injection (mL) added to Orange vial
Cohort 1: OBI-833 (equivalent to 10 μg Globo H)/100 μg OBI-821	0.9
Cohort 2: OBI-833 (equivalent to 30 μg Globo H)/100 μg OBI-821	0.5
Cohort 3: OBI-833 (equivalent to 100 μg Globo H)/100 μg OBI-821	0.5

   Green Vial (OBI-833)

   Contents: 150 μg Globo H linked with CRM197 with potassium phosphate buffered saline, Sucrose, and polysorbate 80**.**

   At time of treatment, with a syringe, add, according to the respective cohort, 1.2 mL or 2.0mL of water for injection to Green Vial to obtain OBI-833 solution. **Fully dissolve** the contents of the vial (Green Vial) by gently inverting the vial 4-5 times. **Do not shake the vial vigorously**. According to drug mixing procedures for three cohorts, OBI-833 is mixed with OBI-821 immediately for injection after re-constituted with WFI.

Dosing Cohort	Water for Injection (mL) added to Green Vial
Cohort 1: OBI-833 (equivalent to 10 μg Globo H)/100 μg OBI-821	1.2
Cohort 2: OBI-833 (equivalent to 30 μg Globo H)/100 μg OBI-821	2.0
Cohort 3: OBI-833 (equivalent to 100 μg Globo H)/100 μg OBI-821	1.2

At the time of treatment, withdraw the contents of Green vial (OBI-833) and the appropriate amount of water for injection according to the table below and transfer into Orange Vial (OBI-821). Mix the contents of the Orange Vial (OBI-821) by gently inverting the vial 4-5 times. **Do not shake the vial vigorously.** At this point, Orange Vial (OBI-821) contains the Treatment (OBI-833 plus OBI-821) is ready for injection into the study subject. Withdraw the appropriate volume from Orange Vial (OBI-821) containing the Treatment for injection.

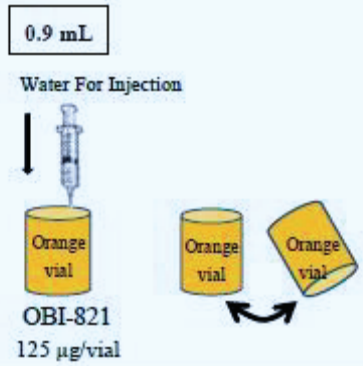
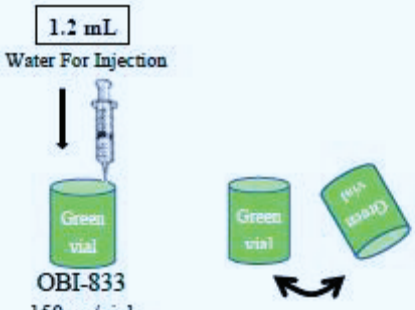
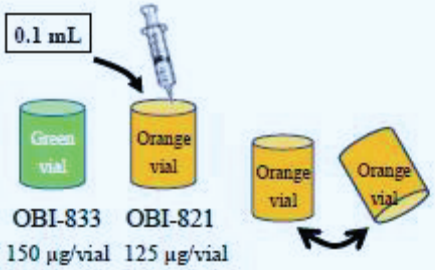
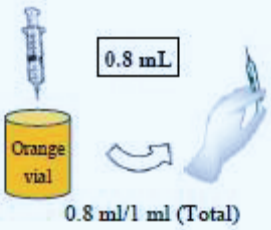
Dosing Cohort	**Volume of Green Vial (mL) to be added to Orange Vial (OBI-821)**	**Total Volume Administered (mL) from Orange Vial (OBI-821)**
Cohort 1: OBI-833 (equivalent to 10 μg Globo H)/100 μg OBI-821	0.1	0.8
Cohort 2: OBI-833 (equivalent to 30 μg Globo H)/100 μg OBI-821	0.5	0.8
Cohort 3: OBI-833 (equivalent to 100 μg Globo H)/100 μg OBI-821	1.0	1.2

*WFI=Water for Injection

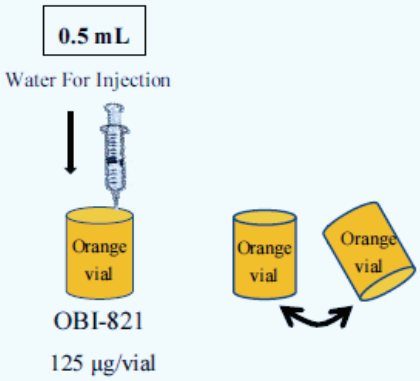
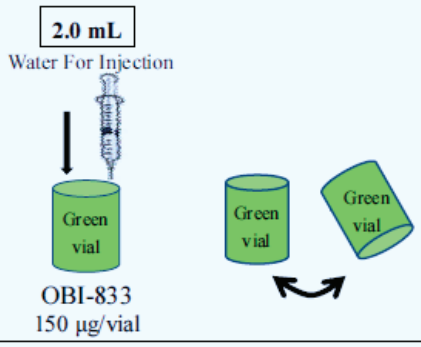
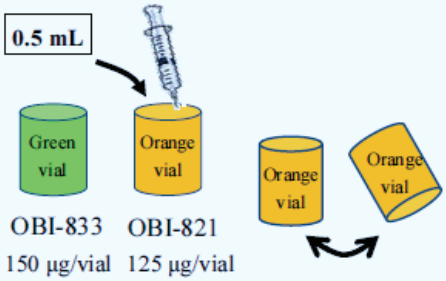
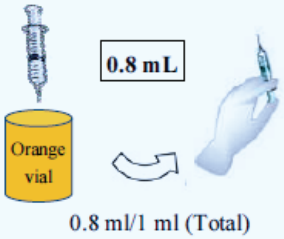
It is highly recommended that **the administration of the combined product should occur within 2 hours from reconstitution** to minimize potential microbial growth. If administration is not possible within 2 hours from reconstitution, the combined product should be destroyed according to the institutional pharmacy Standard Operating Procedure and documented in the drug accountability records.

4. Illustration of Drug Mixing Procedures:

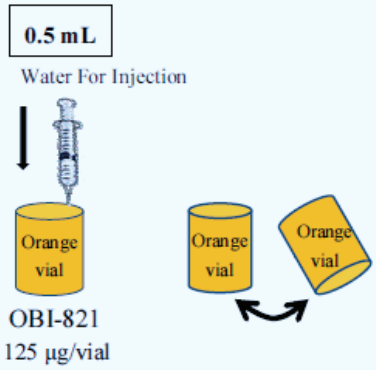
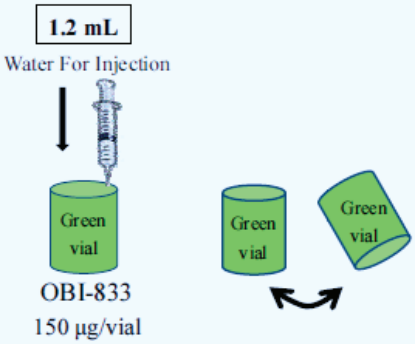
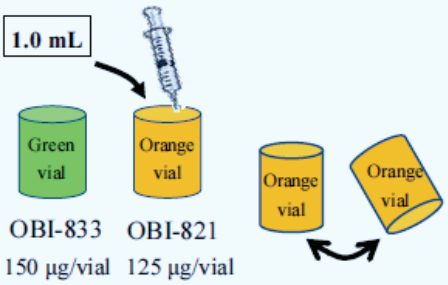
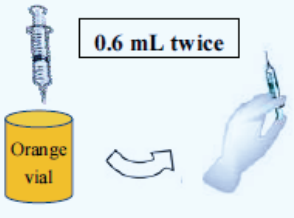
OBI-833 10 µg +OBI-821 100 µg

Description of Drug Preparation Procedures	Illustration of Drug Preparation Procedures
The outer box of MED ID includes four labeled syringes and an inner box. The orange label vial (OBI-821) and green label vial (OBI-833), are packaged in the inner box.	
Step1. Add **0.9 mL** Water For Injection into orange label vial (OBI-821) by using *1.0 mL syringe* labeled with step 1. Gently inverting the orange label vial 4~5 times and make sure the OBI-821 is fully dissolved.	
Step2. Add **1.2 mL** Water For Injection into green label vial (OBI-833) by using *3.0 mL syringe* labeled with step 2. Mix green label vial by gently inverting the green label vial 4~5 times and make sure the OBI-833 is fully dissolved.	
Step3. Transfer **0.1 mL** from green label vial to orange label vial by using *0.5 mL syringe* labeled with step 3. Mix orange label vial by gently inverting the orange label vial 4~5 times.	
Step4. Withdraw **0.8 mL** from orange label vial by using *1.0 mL syringe* labeled with step 4, and inject subcutaneously into a subject within 2 hours after reconstitution.	

OBI-833 30 µg +OBI-821 100 µg

Description of Drug Preparation Procedures	Illustration of Drug Preparation Procedures
The outer box of MED ID includes four labeled syringes and an inner box. The orange label vial (OBI-821) and green label vial (OBI-833), are packaged in the inner box.	
Step1. Add **0.5 mL** Water For Injection into orange label vial (OBI-821) by using *1.0 mL syringe* labeled with step 1. Gently inverting the orange label vial 4~5 times and make sure the OBI-821 is fully dissolved.	
Step2. Add **2.0 mL** Water For Injection into green label vial (OBI-833) by using *3.0 mL syringe* labeled with step 2. Mix green label vial by gently inverting the green label vial 4~5 times and make sure the OBI-833 is fully dissolved.	
Step3. Transfer **0.5 mL** from green label vial to orange label vial by using *1.0 mL syringe* labeled with step 3. Mix orange label vial by gently inverting the orange label vial 4~5 times.	
Step4. Withdraw **0.8 mL** from orange label vial by using *1.0 mL syringe* labeled with step 4, and inject subcutaneously into a subject within 2 hours after reconstitution.	

OBI-833 100 µg +OBI-821 100 µg

Description of Drug Preparation Procedures	Illustration of Drug Preparation Procedures
The outer box of MED ID includes four labeled syringes and an inner box. The orange label vial (OBI-821) and green label vial (OBI-833), are packaged in the inner box.	
Step1. Add **0.5 mL** Water For Injection into orange label vial (OBI-821) by using *1.0 mL syringe* labeled with step 1. Gently inverting the orange label vial 4~5 times and make sure the OBI-821 is fully dissolved.	
Step2. Add **1.2 mL** Water For Injection into green label vial (OBI-833) by using *3.0 mL syringe* labeled with step 2. Mix green label vial by gently inverting the green label vial 4~5 times and make sure the OBI-833 is fully dissolved.	
Step3. Transfer **1.0 mL** from green label vial to orange label vial by using *1.0 mL syringe* labeled with step 3. Mix orange label vial by gently inverting the orange label vial 4~5 times.	
Step4. Withdraw **0.6 mL** from orange label vial by using *1.0 mL syringe* labeled with step 4, and inject subcutaneously into a subject **twice** within 2 hours after reconstitution.	

APPENDIX II: PROHIBITED CONCOMITANT MEDICATION

[Dose Escalation Phase]

Chemotherapeutic Agents:	
Antimetabolites	Miscellaneous cytotoxic agents
Vinca alkaloid	Alkylating agents
Epipodophyllotoxins	Antitumor antibiotics
Taxanes	Nitrosoureas
Camptothecins	
Biologic Agents:	
Monoclonal antibodies (trastuzumab, cetuximab, etc.)	
Interferons	
Interleukins	
Immunotherapy	
cyclosporin, rapamycin, tacrolimus, rituximab, PD-1/PD-L1 antagonists	
IV/oral steroid except single prophylactic use in CT/MRI scan, or other one-time use in approved indications. Inhaled and topical use of steroids are allowed.	
Hormone therapy	
Estrogen receptor antagonists, selective estrogen receptor inhibitors and aromatase inhibitors	
Target therapy	
Tyrosine kinase inhibitors and monoclonal antibodies	
Other non-cancer vaccine therapy	
Washout period for concomitant vaccines is two weeks prior to IP treatment.	
Alternative and complementary medicine may affect immune system	

[Cohort Expansion Phase]

Chemotherapeutic Agents:	
Antimetabolites	Miscellaneous cytotoxic agents
Vinca alkaloid	Alkylating agents
Epipodophyllotoxins	Antitumor antibiotics
Taxanes	Nitrosoureas
Camptothecins	
Biologic Agents:	
Monoclonal antibodies (except necitumumab and bevacizumab)	

Interferons Interleukins
Immunotherapy cyclosporin, rapamycin, tacrolimus, rituximab (except PD-1/PD-L1 antagonists) IV/oral steroid except single prophylactic use in CT/MRI scan, or other one-time use in approved indications. Inhaled and topical use of steroids are allowed.
Other non-cancer vaccine therapy Washout period for concomitant vaccines is two weeks prior to IP treatment.
Alternative and complementary medicine may affect immune system
Subjects who continuous treatment after disease progression are allowed to concomitant use of all approved anti-cancer therapies

APPENDIX III: ECOG PERFORMANCE STATUS AND RECIST 1.1 GUIDELINE

1. ECOG Performance

These scales and criteria are used by doctors and researchers to assess how a subject's disease is progressing, assess how the disease affects the daily living abilities of the subject, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light 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

* As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

2. RECIST 1.1 Guideline

Please find the reference published in Eur J Cancer.:

E.A. Eisenhauer, P. Therasse, J. Bogaerts et al., "New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (Version 1.1)," European Journal of Cancer, 45 (3) 228-247 (2009).

http://ctep.cancer.gov/protocoldevelopment/docs/recist_guideline.pdf