OBI Pharma, Inc.

Global Innovator in Immuno-Oncology and Targeted Cancer Therapies

Advancing in the Clinic!

QIC CEO Week 2023

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Safe Harbor Statement

This presentation contains certain forward-looking statements.

These forward-looking statements may be identified by words such as ‘believes,’ ‘expects,’ ‘anticipates,’ ‘projects,’ ‘intends,’ ‘should,’ ‘seeks,’ ‘estimates,’ ‘future,’ or similar expressions or by discussion of, among other things, strategy, goals, plans, or intentions. Various factors may cause actual results to differ materially in the future from those reflected in forward-looking statements contained in this presentation, among others:

1. Pricing and product initiatives of competitors
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3. Delay or inability in obtaining regulatory approvals or bringing products to market
4. Fluctuations in currency exchange rates and general financial market conditions
5. Uncertainties in the discovery, development, or marketing of new products or new uses of existing products, including without limitation negative results of clinical trials or research projects, unexpected side effects of pipeline or marketed products
6. Increased government pricing pressures
7. Interruptions in production
8. Loss of or inability to obtain adequate protection for intellectual property rights
9. Litigation
10. Loss of key executives or other employees
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Any statements regarding earnings growth is not a profit forecast and should not be interpreted to mean that OBI’s earnings or earnings per share for this year or any subsequent period will necessarily match or exceed published earnings or earnings per share forecasts of OBI Pharma, Inc.

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Agenda

1. **Company Introduction**
2. **Globo H Science Leadership**
   - Novel I-O Pipeline
3. **AKR1C3 Science Leadership**
   - Novel Pro-drug
4. **Key Milestones and Inflection Points**

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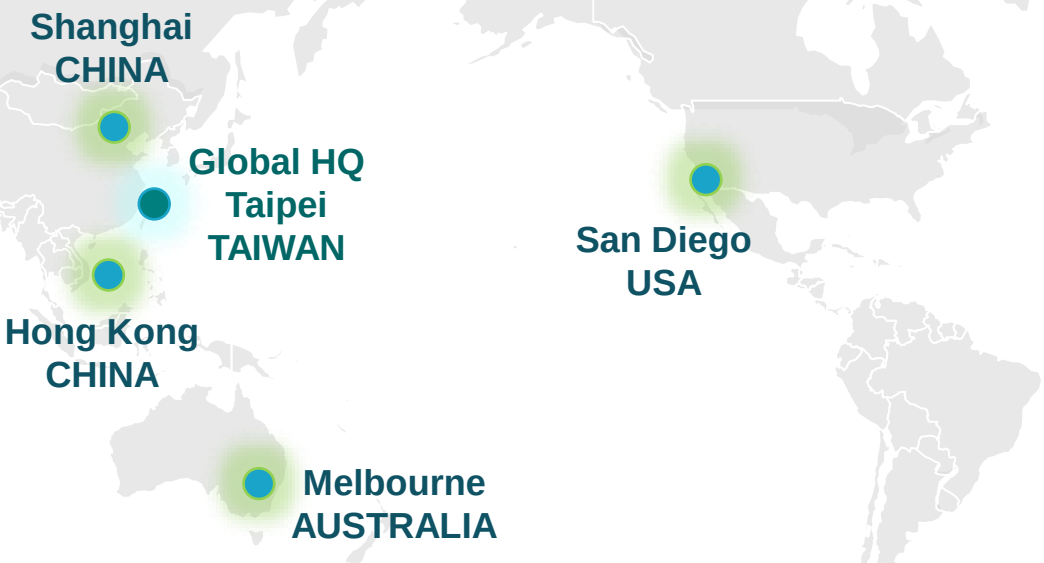
OBI Pharma, Inc. (TPEx: 4174.TWO)

www.obipharma.com

Founded:	**April 29, 2002**
IPO on TPEx:	**March 23, 2015**
Market Cap 20 Apr, ’23:	**~US$ 660M (~NT$ 19.8B)**
Fund Raised at IPO:	**~US$ 200M (~NT$ 6.2B)**
Net Cash on Hand:	**~US$ 90M**
Employees:	**129**



OBI data on file

Experienced Global Management Team

Yen Yun, MD, PhD
Chairman & CEO

Kevin Poulos
Chief Commercial Officer

Wayne Saville, MD
Chief Medical Officer

Frank Chen
Chief Financial Officer

Ming-Tain Lai, PhD
Chief Science Officer

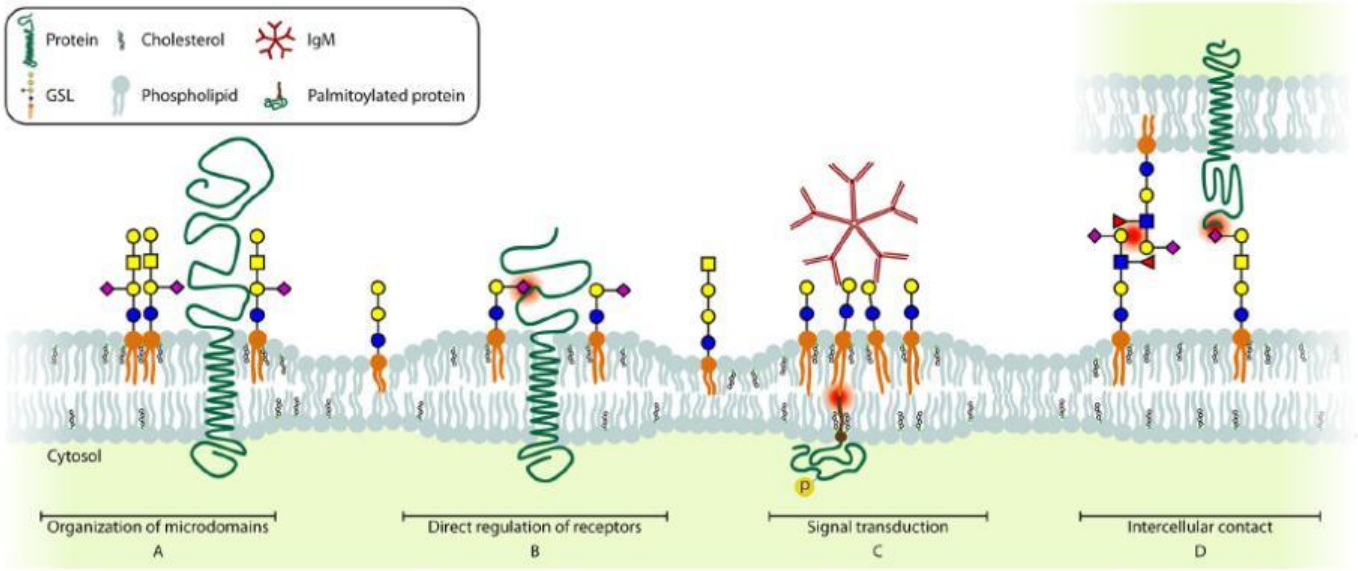
Mitch Che
Chief Operating Officer

David Hallinan, PhD
VP Regulatory Affairs

Agenda

1. Company Introduction
2. Globo H Science Leadership
   - Novel I-O Pipeline
3. AKR1C3 Science Leadership
   - Novel Pro-drug
4. Key Milestones and Inflection Points

Functions of Glycosphingolipids (GSLs)



A
Including and excluding proteins from microdomains

B
Several receptors can be directly regulated by GSLs present in the cell membrane

C
Crosslinking of several GSLs can induce signaling across the membrane

D
Interacting with glycans or with proteins on other cells, contributing to cell-cell recognition and adhesion

Zhang T, et al. *Front Immunol.* 2019 Jan 29;10:90.

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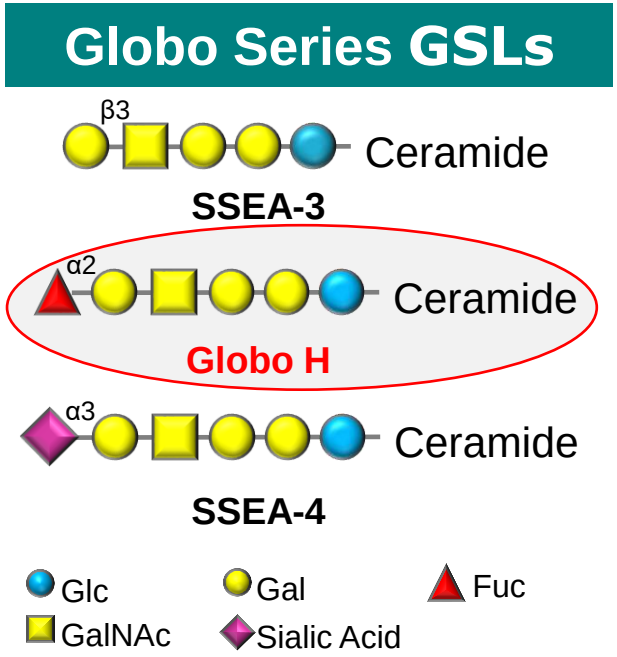
Glycans, Glycosphingolipids and Cancer

- Glycans and glycosphingolipids (GSLs) play a crucial role in tumor progression
- Aberrant glycosylation is a hallmark of cancer cells
- GSLs are glycans conjugated to a lipid (ceramide) core
- Globo series is a unique class of GSLs involved in early embryogenesis and tumor development



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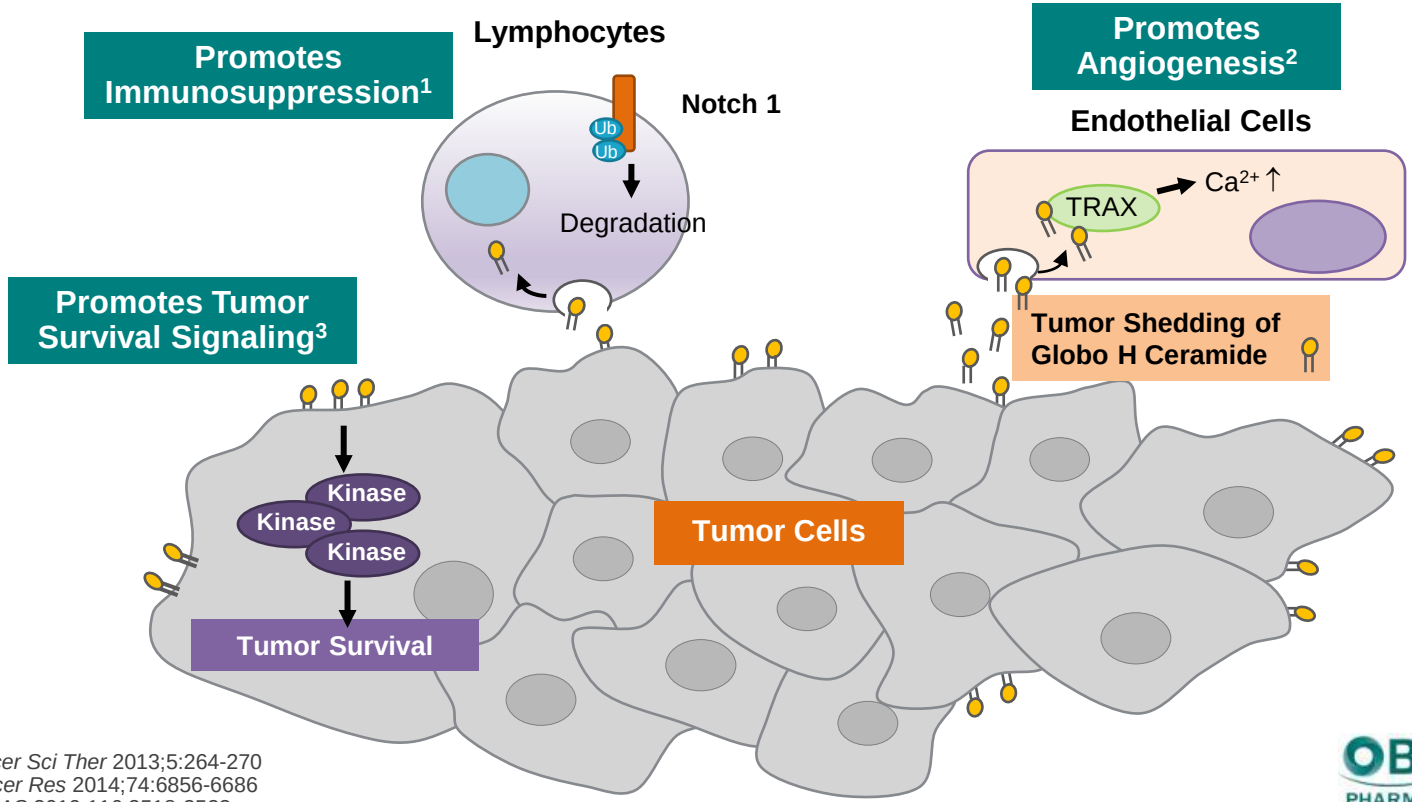
Potential Roles of Globo H in Immunosuppression, Angiogenesis, and Cancer Cell Survival Signaling



1 Tsai YC, *et al*. *J Cancer Sci Ther* 2013;5:264-270
2 Cheng JY, *et al*. *Cancer Res* 2014;74:6856-6686
3 Chuang PK, *et al. PNAS* 2019;116:3518-3523

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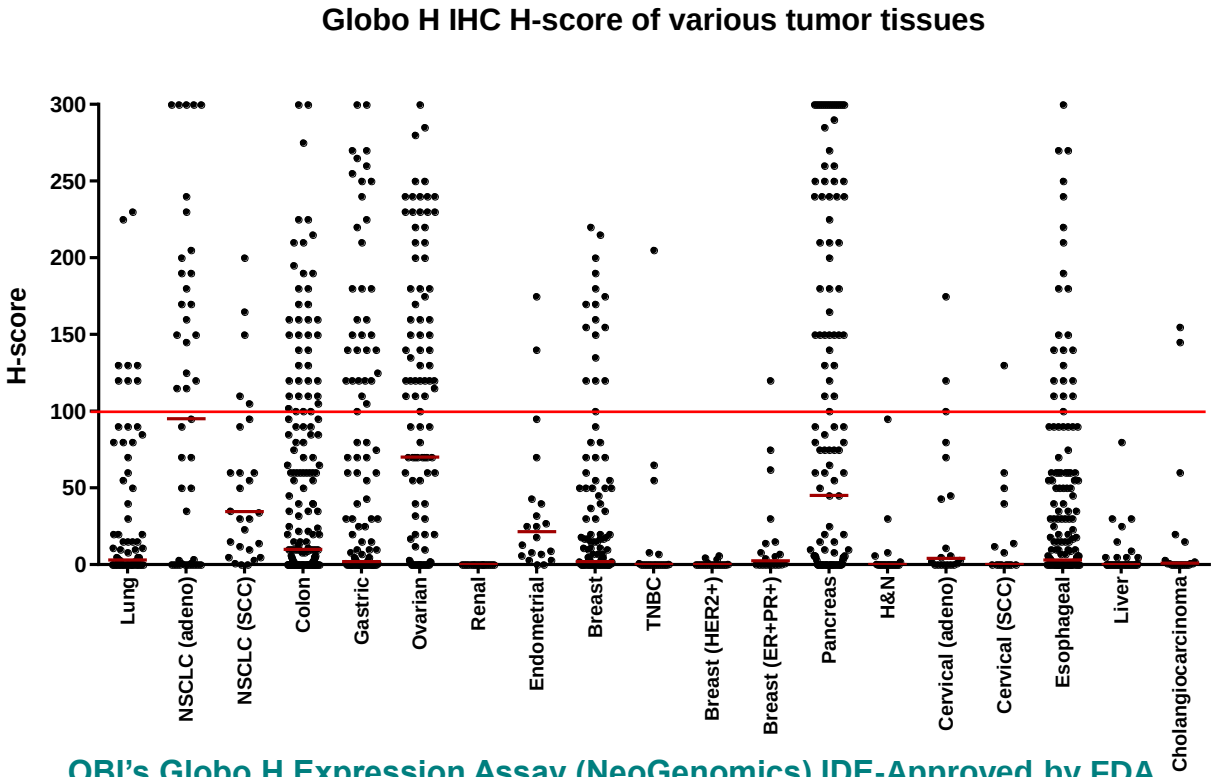
High Globo H Expression in Common Cancers



Cancer	# Evaluable Specimens	Prevalence at H-score ≥100
NSCLC (adeno)	45	49%
Ovarian	118	33%
Pancreatic	139	32%
Gastric	133	26%
Colon	191	21%
NSCLC (SCC)	28	18%
Cervical (adeno)	20	15%
Breast	131	13%
Esophageal	186	12%
Lung	77	10%
Endometrial	20	10%
Cholangio-carcinoma	20	10%

OBI's Globo H Expression Assay (NeoGenomics) IDE-Approved by FDA

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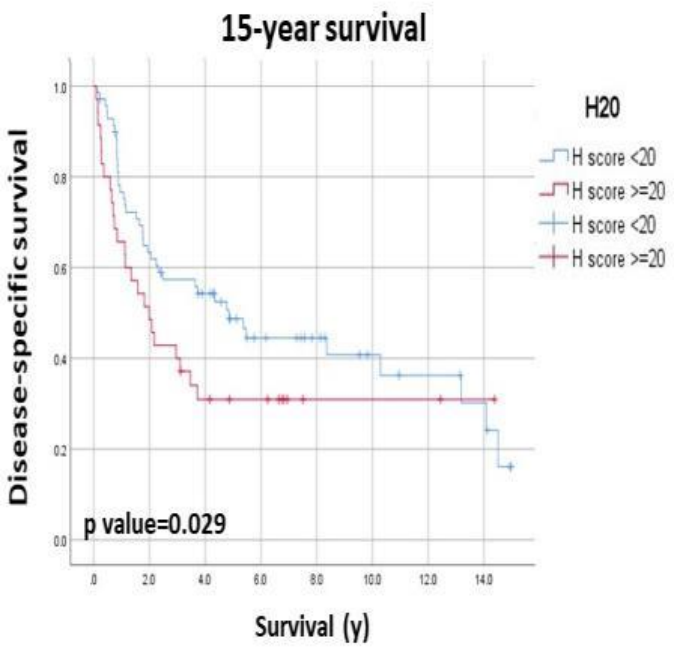
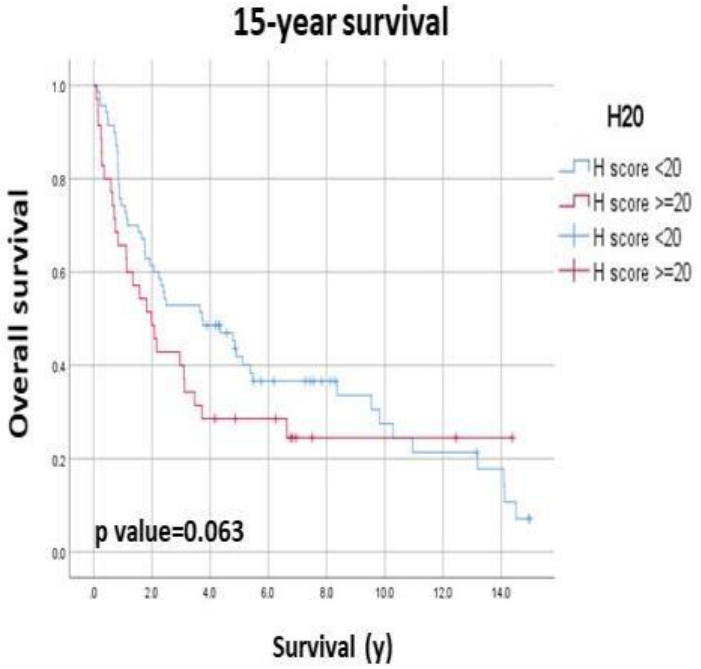
Globo H expression associates with poor survival in gastric cancer

Disease specific survival (DSS)

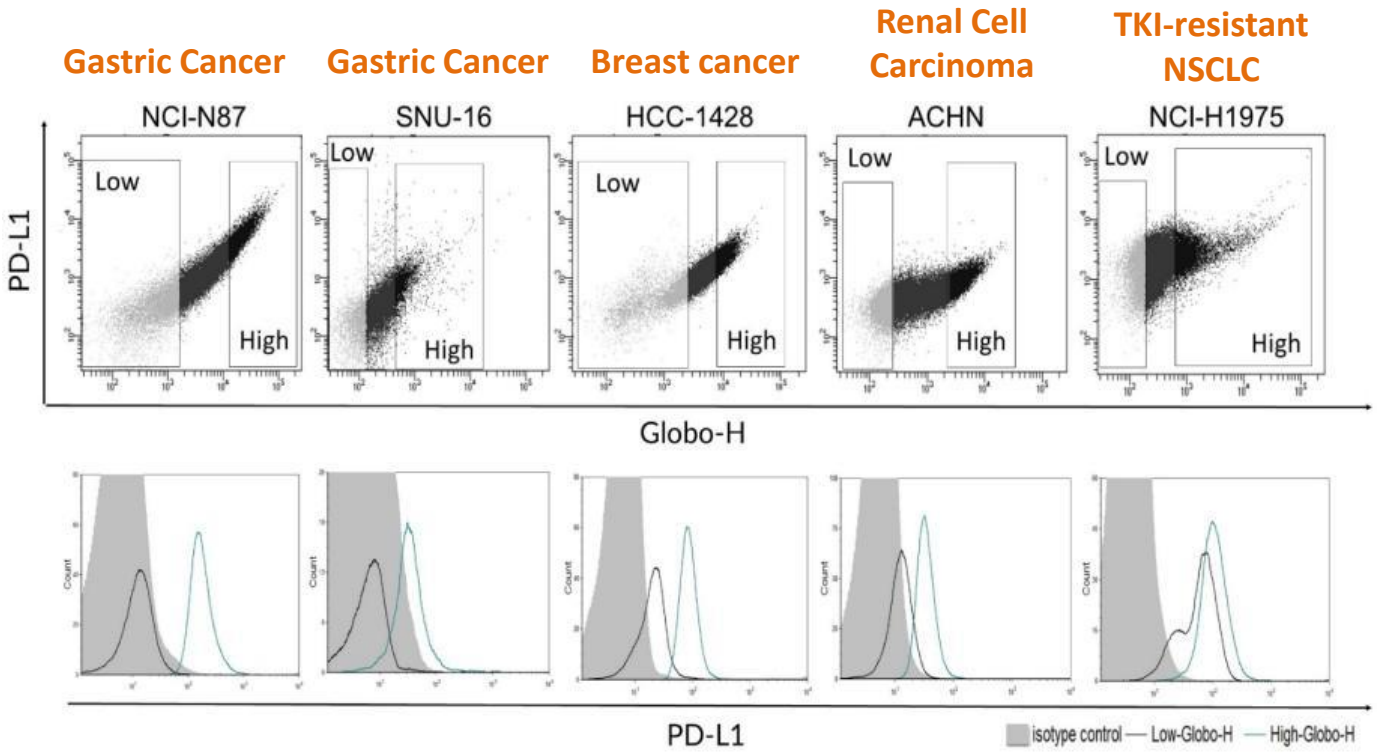


Overall survival (OS)



AACR 2022 Poster #6138

High Globo H expression correlates with higher levels of PD-L1 protein in cancer cells



OBI Pharma's Innovative Cancer Pipeline

Stage of Development

PRODUCT	TYPE	TARGET	CANCER	DISCOVERY	PRE-CLINICAL	PHASE 1	PHASE 2	PHASE 3
Adagloxad Simolenin	Vaccine	Globo H	Breast (TNBC)	GLORIA Global Phase 3 TNBC Study				
OBI-999	ADC	Globo H	Multiple Cancers					
OBI-833	Vaccine	Globo H	Multiple Cancers					
OBI-3424	Prodrug	AKR1C3	Multiple Cancers					
OBI-866	Vaccine	SSEA-4	Multiple Cancers					
R992	ADC	TROP-2	Multiple Cancers					

OBI licensing rights:

- Adagloxad Simelenin: OBI owns global rights
- OBI-999: OBI owns ex-China rights
- OBI-833: OBI owns ex-China rights
- OBI-3424: OBI owns ex-Asia rights
- OBI-866:OBI owns global rights
- R-992: OBI owns ex-China rights

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Adagloxad Simolenin

First-in-Class Active Immunotherapy Stimulating anti-Globo H Antibodies

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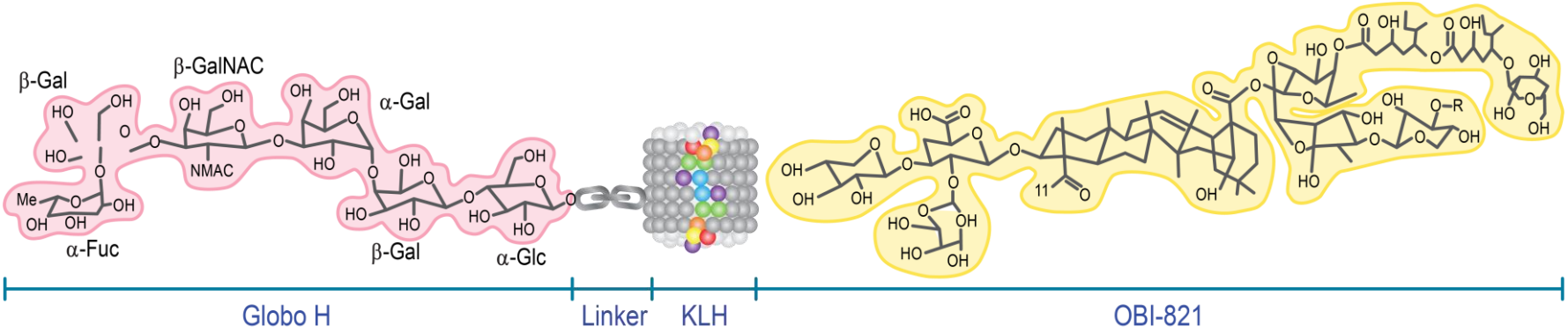
Adagloxad Simolenin (A-S): Globo H Vaccine



Adagloxad simolenin is comprised of a synthetic tumor antigen, **Globo H**, conjugated to a hemocyanin carrier protein (**KLH**) derived from the keyhole limpet

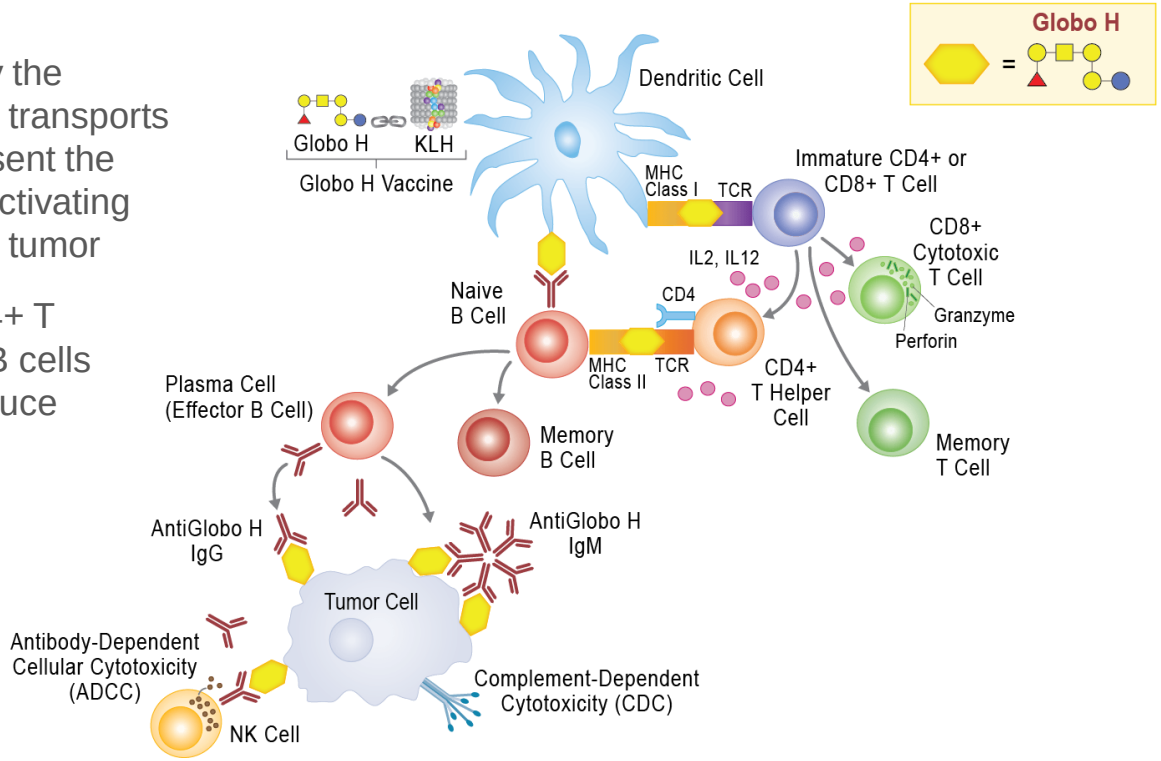
It is administered with **OBI-821—**a saponin-based immune adjuvant purified from *Quillaja saponaria* tree bark—that induces humoral and cell-mediated responses

Quillaja saponaria

Huang, C-H et al. *J Immunother Cancer*. 2020; 8:e000342.

MOA of Therapeutic Vaccine Adagloxad Simolenin

- Globo H antigen is phagocytosed by the dendritic cell which processes it and transports it to the lymph node where they present the antigen to immature CD8+ T cells, activating them so that they can migrate to the tumor
- The dendritic cells also activate CD4+ T helper cells to support activation of B cells which become Plasma Cells and induce anti-Globo IgG and IgM
- IgM and IgG antibodies recognize Globo H expressed on the tumor cell surface and recruit complements to attack the tumor cells (IgM) and guide NK cells to destroy the tumor (IgG)



Adagloxad Simolenin Int'l Phase 2 Metastatic Breast Cancer study published in *JITC Peer reviewed journal*

Open access Original research

Journal for ImmunoTherapy of Cancer

Globo H-KLH vaccine adagloxad simolenin (OBI-822)/OBI-821 in patients with metastatic breast cancer: phase II randomized, placebo-controlled study

Chiun-Sheng Huang,[1] Alice L Yu,[2,3] Ling-Ming Tseng,[4,5] Louis W C Chow,[6] Ming-Feng Hou,[7] Sara A Hurvitz,[8] Richard B Schwab,[9] James L Murray,[10] Hsien-Kun Chang,[11] Hong-Tai Chang,[12] Shin-Cheh Chen,[13] Sung-Bae Kim,[14] Jung-Tung Hung,[15] Shir-Hwa Ueng,[15] Su-Hua Lee,[16] Chwen-Cheng Chen,[17] Hope S Rugo [18]

ABSTRACT

Purpose This randomized, double-blind, placebo-controlled, parallel-group, phase II trial assessed the efficacy and safety of adagloxad simolenin (OBI-822; a Globo H epitope covalently linked to keyhole limpet hemocyanin (KLH)) with adjuvant OBI-821 in metastatic breast cancer (MBC).

Conclusion AS/OBI-821 did not improve PFS in patients with previously treated MBC. However, humoral immune response to Globo H correlated with improved PFS in AS/OBI-821 recipients, leading the way to further marker-driven studies. Treatment was well tolerated.

Huang et al. *J Immunother Ca* 2020;8:e000342

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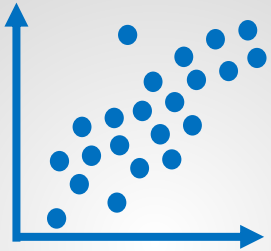
Learnings From Adagloxad Simolenin Phase II Trial in Patients with Metastatic Breast Cancer (MBC)

Higher Globo H tumor expression correlated with improved PFS



Higher anti-Globo H IgG levels correlated with improved PFS

Patients receiving full treatment had improved PFS

Next study: Homogenous, e.g., TNBC, and earlier stage patients with high Globo H

These learnings have been applied to the development of the protocol for the Global Phase 3 GLORIA Trial in TNBC patients expressing Globo H

PFS, progression-free survival.
Clinicaltrials.gov. Trial of Active Immunotherapy With Globo H-KLH (OPT-822) in Metastatic Breast Cancer Subjects. NCT01516307

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GLORIA

Phase 3, Randomized, Open-Label Study of the Anti-Globo H Vaccine Adagloxad Simolenin (OBI-822)/OBI-821 in the Adjuvant Treatment of Patients with High-Risk, Early-Stage Globo H-Positive Triple-Negative Breast Cancer

Clinicaltrials.gov. Study of Adagloxad Simolenin (OBI-822)/OBI-821 in the Adjuvant Treatment of Patients With Globo H Positive TNBC NCT03562637

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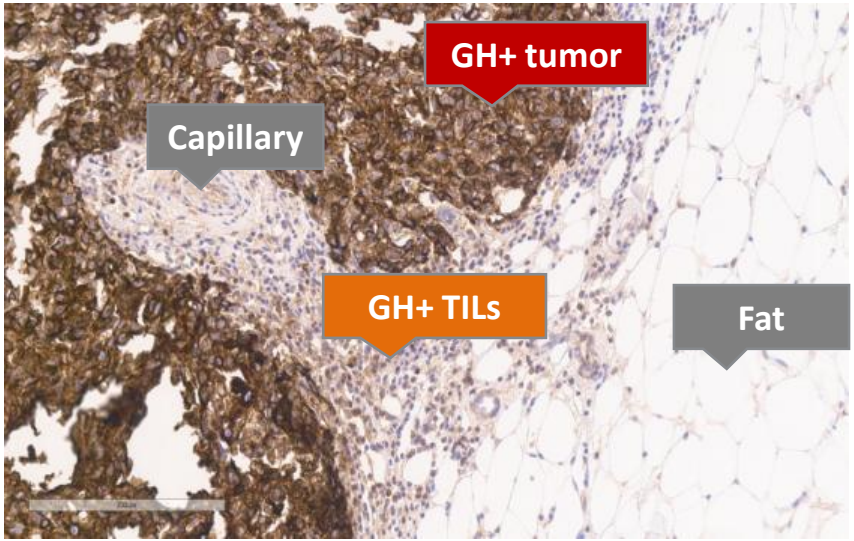
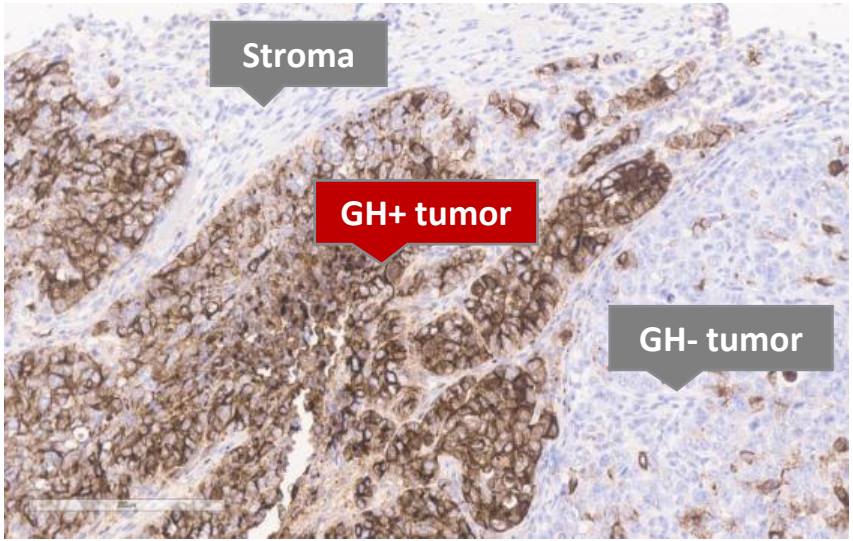
Globo H Expression in Triple Negative Breast Cancer



White 57-year-old female with infiltrating ductal carcinoma
H-score = 300



White 59-year-old female with papillary carcinoma
H-score = 185

GH expression level was assessed, and results are presented using an H-score system (0 to 300)

H-score = (% of weak intensity x 1) + (% of moderate intensity x 2) + (% of strong intensity x 3)

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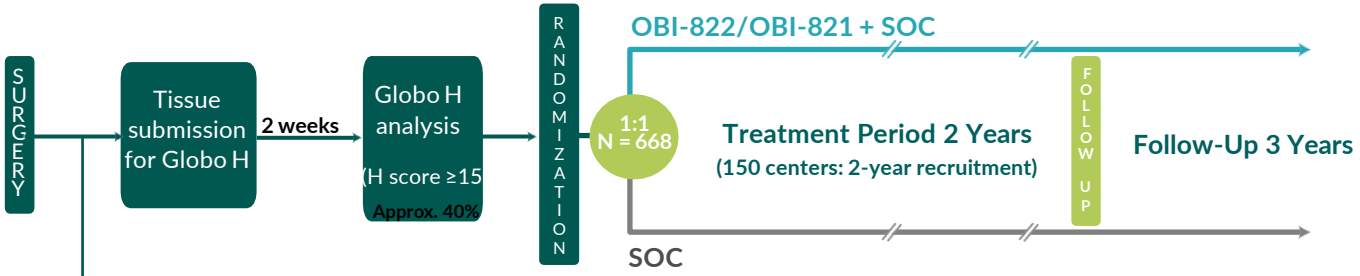
GLORIA Phase 3 TNBC Study Design



Key Eligibility Criteria

- Histologically documented TNBC (ER/PR ≤5% cells)
- High risk defined as:
  - ≥1 cm residual primary or ≥1 residual axillary node after adequate neoadjuvant chemotherapy
    or
  - Pathological Stage IIB or III disease treated with adequate adjuvant chemotherapy alone
- Received ≥4 cycles of standard taxane- and/or anthracycline-based chemotherapy

Primary Endpoint: IDFS

- 187 events required (3-year IDFS HR 0.66)
- 80% power; two-sided alpha 0.05

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GLORIA Phase 3 TNBC Study Objectives

Primary Objective

- To determine the effect of adagloxad simolenin (AS) treatment on improving IDFS in the study population

Secondary Objectives

- To determine the impact of AS treatment in the study population, on:
  - Overall Survival (OS)
  - Quality of Life (QoL)
  - Breast cancer-free interval (BCFI)
  - Distant disease-free survival (DDFS)
- To determine safety and tolerability of AS in the study population

Exploratory Objectives

- To explore the association between the anti-Globo H antibody response to AS and IDFS and OS
- To evaluate the impact of tumor expression of Globo H on IDFS and OS
- To identify patient baseline characteristics and demographics that may be predictive of treatment outcomes with AS
- To explore the association between baseline characteristics, including tumor pathological, molecular and immune features, and tumor expression of Globo H

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The GLORIA Study: A Phase 3, Randomized, Open-Label Study of the Anti–Globo H Vaccine Adagloxad Simolenin/OBI-821 in the Adjuvant Treatment of Patients With High-Risk, Early-Stage, Globo H–Positive, Triple-Negative Breast Cancer

GLORIA
Phase 3 Trial in TNBC

TPS-611
ASCO 2022

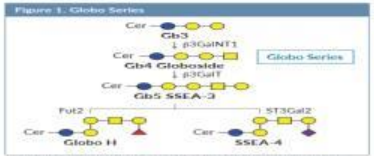
Hope S. Rugo[1], Javier Cortes[2], Carlos H. Barrios[3], Paula Cabrera[4], Binghe Xu[5], Chiun-Sheng Huang[6], Sung-Bae Kim[7], Michelle Melisko[1], Rita Nanda[8], Tadeusz Pienkowski[9], Bernardo L. Rapoport[10], Priyanka Sharma[11], Richard Schwab[12], Pei Hsu[13]

[1]Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA, USA; [2]International Breast Cancer Center (IBCC), Quiron Group, Barcelona, Spain; [3] Centro de Pesquisa Clínica, Hospital São Lucas, Porto Alegre, Brazil; [4]Instituto Nacional de Cancerologia, Mexico City, Mexico; [5]National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences (CAMS), and Peking Union Medical College (PUMC), Beijing, China; [6]National Taiwan University Hospital, Taipei City, Taiwan; [7]Asan Medical Center, Seoul, Republic of Korea; [8]University of Chicago Medicine, Chicago, IL, USA; [9]Central Clinical Hospital of the MSWiA, Warsaw, Poland; [10]Medical Oncology Center of Rosebank and Linkelfield Park Hospital, Johannesburg, South Africa; [11]University of Kansas Medical Center, Kansas City, KS; [12]University of California, San Diego School of Medicine, San Diego, CA, USA; [13]OBI Pharma, Inc., Taipei City, Taiwan

BACKGROUND

- Changes in glycosylation are associated with oncogenic transformation, and tumor cells display a wide range of aberrant glycosylation
- Lipid glycosylation results in the Lacto, Ganglio, and Globo series glycosphingolipids (GSLs) linked with ceramides in the cell surface membrane
- Globo series GSLs (stage-specific embryonic antigen (SSEA)-3, SSEA-4, and Globo H) are expressed on a wide range of tumor cells and are thought to be involved in early embryogenesis, tumor progression and metastasis, and immune suppression (**Figure 1**)

Figure 1. Globo Series



β3GalNT, β1,3-galactosyltransferase; β3GalNT1, β1,3-N-acetylgalactosaminyltransferase 1; cer, ceramide; Fut2, fucosyltransferase 2; Gb, globoside; SSEA, stage-specific embryonic antigen; ST3Gal2 ST3 beta-galactoside alpha-2,3-sialyltransferase 2.

Globo H Expression in Patients With Breast Cancer

- A validated immunohistochemistry (IHC) assay (NeoGenomics) approved by the US FDA for use in clinical trials, measures the intensity and extent of Globo H expression microscopically using an H-score, defined as the sum of the products of the staining intensity (score of 0-3) multiplied by the percentage of cells (0-100) stained at a given intensity (**Figure 2**)
- 420 patients with triple-negative breast cancer (TNBC) have been screened across 4 separate clinical trials. 173 (41%) had an H-score of ≥15 (median 70) and in those patients 69/173 (40%) had an H-score of ≥100.

Figure 2. Globo H Expression in Patients With TNBC

GH expression level was assessed, and results are presented using an H-score system (0-300)

H-score = (% of weak intensity × 1) +
(% of moderate intensity × 2) +
(% of strong intensity × 3)

57-year-old female with infiltrating ductal carcinoma; H-score = 300

59-year-old female with papillary carcinoma; H-score = 185

GH, Globo H; GH+, GH-negative; GH+, GH-positive; TIL, tumor-infiltrating lymphocyte; TNBC, triple-negative breast cancer.

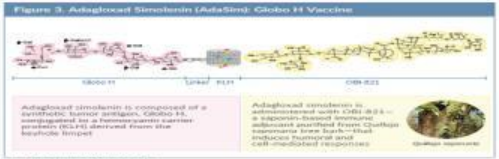
Triple-Negative Breast Cancer

- 10-20% of primary breast cancers are triple-negative breast cancers (TNBC), a heterogeneous group of tumors with the highest distant metastasis rate and lowest overall survival of all breast cancer subtypes[1]
- Patients with early-stage TNBC achieving a pathological complete response (pCR) after neoadjuvant chemotherapy demonstrate excellent recurrence-free and overall survival,[2] whereas patients with significant residual cancer burden after neoadjuvant chemotherapy have poor long-term outcomes[3]
- The presence and levels of stromal tumor-infiltrating lymphocytes (sTILs) have emerged as additional predictors of therapy response and disease-free and overall survival[4] In TNBC; the presence of sTILs in residual disease after neoadjuvant chemotherapy has also been found to be prognostic, especially in patients with large residual tumor burden[4]
- Higher pCR rates are also achieved with the addition of immune checkpoint inhibitors to neoadjuvant chemotherapy[2,5]

Globo H Conjugate Vaccine

- Adagloxad Simolenin (AdaSim) is administered with the saponin adjuvant OBI-821 as a therapeutic vaccine targeting the tumor-associated carbohydrate antigen (TACA) Globo H ceramide (**Figure 3**)

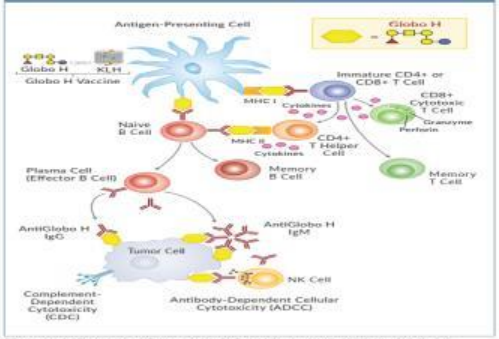
Figure 3. Adagloxad Simolenin (AdaSim): Globo H Vaccine



KLH, keyhole limpet hemocyanin.

- Following administration, the Globo H antigen is phagocytosed by dendritic cells, which process it and transport it to the lymph nodes where it activates an immature cluster of differentiation (CD)8+ T cells
- Dendritic cells also activate CD4+ T helper cells to support activation of B cells, which become plasma cells and induce anti-Globo immunoglobulin G (IgG) and immunoglobulin M (IgM)
- IgM and IgG antibodies recognize Globo H expressed on the tumor cell surface and recruit complements to attack the tumor cells (IgM) and guide natural killer cells to destroy the tumor (IgG) (**Figure 4**)

Figure 4. MOA of Therapeutic Vaccine Adagloxad Simolenin



CD, cluster of differentiation; IgG, immunoglobulin G; IgM, immunoglobulin M; KLH, keyhole limpet hemocyanin; MHC, major histocompatibility complex; MOA, mechanism of action; NK, natural killer.

THE GLORIA STUDY

The GLORIA Study is presently enrolling patients in 13 countries. Of the 119 sites identified, 84 sites have been activated. A total of 900 patients have been prescreened as of May 2, 2022.

The protocol was recently amended with respect to patient eligibility and the definition of standard of care (SOC). Patients must have recovered from surgery and completed all planned neoadjuvant and/or adjuvant multiagent chemotherapy and/or radiation therapy. SOC in the AdaSim/OBI-821 arm is concomitant therapy of capecitabine or immune checkpoint inhibitor (in the US only). In the SOC arm, patients will receive SOC therapy consisting of observation alone, or adjuvant capecitabine alone, or immune checkpoint inhibitor alone (in the US only).

THE GLORIA PHASE 3 STUDY DESIGN (NCT03562637)

A phase 3, randomized, open-label study of the anti-Globo H vaccine AdaSim /OBI-821 in the adjuvant treatment of patients with high-risk, early-stage Globo H–positive TNBC

BCFI, breast cancer–free index; DDFS, distant disease-free survival; IDFS, invasive disease-free survival; OS, overall survival; QoL, quality of life; SOC, standard of care.

Primary Endpoint: Invasive Disease-Free Survival

- 187 events required (3-year invasive disease free survival [IDFS]; hazard ratio, 0.66)
- 80% power; 2-sided alpha 0.05

Patients who complete the treatment phase without invasive disease recurrence should proceed to the IDFS follow-up phase

Key Eligibility Criteria

Key Inclusion Criteria	Key Exclusion Criteria
Histologically documented primary, localized, invasive TNBC High-risk patients with no evidence of disease after completing standard treatment and meeting one of the following criteria: • Neoadjuvant chemotherapy followed by definitive surgery: – Residual invasive disease ≥1 cm in breast or ≥1 positive axillary node • Definitive surgery followed by adjuvant chemotherapy: pathological prognostic stage IIB, IIIA, IIIB, or IIIC (8th Ed AJCC) Must have completed ≤4 cycles of taxane and anthracycline-based chemotherapy, or taxane-containing regimen only if the patient is ineligible for anthracycline treatment in the neoadjuvant or adjuvant setting Globo H IHC H-score ≥15 from tumor tissue obtained at the time of definitive surgery or initial diagnosis (only if surgical tumor tissue sample is not available) ECOG PS ≤1	Previous history of invasive breast cancer within 10 years; history of other malignancies within 5 years • Received any or other anticancer vaccines – Neoadjuvant receipt of immune checkpoint inhibitors will not be exclusionary • Concomitant treatment with anticancer therapy other than capecitabine or checkpoint inhibitor, or other investigational therapy, if expected during the study Active autoimmune disease that requires systemic immunosuppressive/ immunomodulatory therapy Prior receipt of a glycoconjugate vaccine for cancer immunotherapy

AJCC, American Joint Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; TNBC, triple-negative breast cancer.

- Randomization must occur within 16 weeks after definitive surgery and radiation therapy
- Concurrent capecitabine or checkpoint inhibition allowed

Stratification

Neoadjuvant vs Adjuvant only

If Neoadjuvant:

1. American Joint Committee on Cancer (AJCC) postneoadjuvant therapy pathological (yp) N status according to the 8th edition of the *AJCC Cancer Staging Manual* (ypNX/N0 I vs ypN1 vs ypN2/N3)
2. Receipt of adjuvant SOC therapy (capecitabine; immune checkpoint inhibitor) (Yes vs No)
3. Region (United States vs Mexico/Latin America vs Asia-Pacific vs China vs Eastern Europe vs Western Europe)

If Adjuvant:

1. AJCC pathological prognostic stage according to the 8th edition of the *AJCC Cancer Staging Manual* (stages IIB/IIIA vs IIIB/IIIC)
2. Region (United States vs Mexico/ Latin America vs Asia-Pacific vs China vs Eastern Europe vs Western Europe)

Patients who complete the treatment phase without invasive disease recurrence should proceed to the IDFS follow-up phase

Study Objectives

Primary Objective

To determine the effect of AdaSim/OBI-821 treatment on IDFS in the study population

Secondary Objectives

- To determine the impact of AdaSim/OBI-821 treatment, on:
  - Overall survival (OS)
  - Quality of life (QoL)
  - Breast cancer–free interval
  - Distant disease-free survival
- To determine safety and tolerability of AdaSim/OBI-821 in the study population

Exploratory Objectives

- To explore the association between the anti-Globo H antibody response to AdaSim/ OBI-821 and IDFS and OS
- To evaluate the impact of tumor expression of Globo H on IDFS and OS
- To identify patient baseline characteristics and demographics that may be predictive of treatment outcomes with AdaSim/OBI-821
- To explore the association between baseline characteristics, including tumor pathological, molecular, and immune features, and tumor expression of Globo H

SUMMARY

- Patients with TNBC and residual disease after neoadjuvant chemotherapy have a poor prognosis
- Globo H is a glycosphingolipid expressed in early embryogenesis and aberrantly overexpressed in TNBC, including in cancer stem cells
- Globo H is thought to be involved with embryogenesis, tumor progression and metastasis, and immune suppression
- When administered with the adjuvant OBI-821, AdaSim results in IgM and IgG anti-Globo H humoral responses
- The phase 3 GLORIA Study is evaluating the effectiveness of AdaSim/OBI-821 as adjuvant therapy in patients with early-stage TNBC that has a high risk of progression
- In addition to safety, efficacy, and QoL, the study will evaluate the relationship between aberrant Globo H expression and baseline characteristics such as tumor pathology and immune factors

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Presented at 2022 American Society of Clinical Oncology (ASCO) Annual Meeting, June 3-7, Chicago, IL

Adagloxad Simolenin Global Phase 3 Trial Investigator Site Locations

OBI data on file

OBI-833

Cancer Vaccine Targeting Tumor Expression of Globo H

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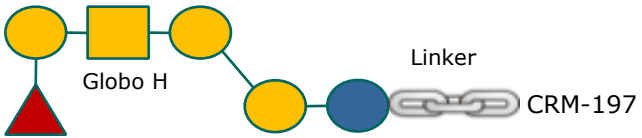
OBI-833

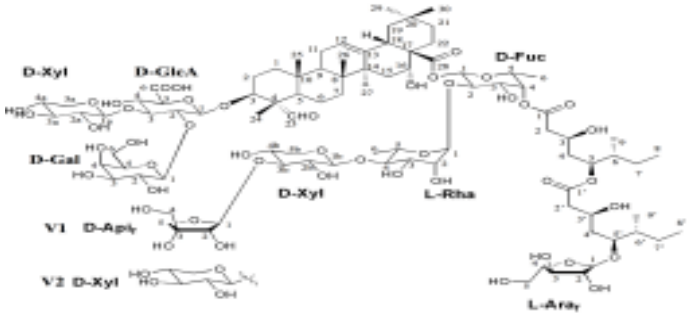
OBI-833 + the saponin adjuvant OBI-821 is a therapeutic vaccine targeting Globo H ceramide in a variety of epithelial tumors

Innovative Glycoprotein



+

Saponin adjuvant OBI-821



OBI-833

Comprises a fully synthetic tumor antigen (Globo H) conjugated to a protein carrier (CRM-197)

OBI-821

Induces humoral and cell-mediated immune responses

OBI data on file

Encouraging Phase 1 NSCLC cohort expansion results

- OBI-833 demonstrated a favorable safety profile.
- OBI-833 elicited a **beneficial immune response** in NSCLC patients and rendered some TKI-treated patients **durable stable disease status**.
- The median progression-free survival was 38.1 weeks.
- 11 of the 14 patients were **co-treated with an EGFR TKI** in the study. Eight of them remained in stable disease status for over 6 months.
- Two patients were treated with OBI-833 for **over 2 years**; one of the patient showed tumor size reduction by 27% after 16 months of OBI-833 treatment.
- 50% patients had high Globo H (H Score > 100) expression.
- Phase 2 study in preparation.

OBI data on file

OBI-833 P1 study published at ESMO

A Phase 1 Cohort Expansion Trial of OBI-833 in Non-Small Cell Lung Cancer Patients

Ching-Liang Ho[1], Kang-Yun Lee[2], Her-Shyong Shiah[3], Chia-Chi Lin[4], Chien-Chih Ou[5], Chen-En Tsai[6], Pan-Chyr Yang[7]

[1] Division of Hematology/Oncology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan [2] Division of Thoracic Medicine, Taipei Medical University Shuang Ho Hospital, Taipei, Taiwan [3] Department of Hematology and Oncology, Taipei Medical University Hospital, Taipei, Taiwan
[4] Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan [5] Department of Clinical Development, OBI Pharma, Taipei, Taiwan [6] Department of Medical Affairs and Clinical Development, OBI Pharma, Taipei, Taiwan [7] Department of Internal Medicine, National Taiwan University, Taipei, Taiwan

Introduction

- Globo H, a glycan initially isolated from the MCF-7 breast cancer cell line, is overexpressed in a variety of epithelial cell tumors such as colon, ovarian, gastric, pancreatic, lung, prostate, and breast cancers, and has limited expression in normal tissue.
- Experimental data suggest that Globo H promotes immunosuppression, tumor survival signaling, and angiogenesis.
- Globo H expression in tumor cells and its function as a potential immune checkpoint make it a target for immunotherapy.
- OBI-833, a novel cancer active immunotherapy, comprises of a synthetic Globo H conjugated with a recombinant CRM 197.

Background

- Lung cancer is the leading cause of cancer-related deaths worldwide (Jemal et al, 2009) and non-small cell lung cancer (NSCLC) accounts for 80-85% of all lung cancers (Sher et al, 2008; Wang et al, 2011).
- Mutations in the epidermal growth factor receptor (EGFR) gene are commonly observed in NSCLC, particularly in tumors of adenocarcinoma histology. *EGFR* mutation frequency was 47.9% in Asian patients, as compared with 19.2% in Western patients.
- Globo H is highly expressed in epithelial cancers such as lung cancer, breast cancer, prostate cancer (Zhang et al, 1997b) and pancreatic, gastric and esophageal cancer (AACR; 2020. Abstract nr 2946)
- OBI-833 is a novel cancer vaccine targeting Globo H. Results of the dose-escalation trial showed a favorable safety profile and supported the cohort expansion trial in NSCLC patients at a dose of 30 μg.
- Patients with Globo H-positive metastatic NSCLC who had achieved stable disease (SD) or partial response (PR) after at least one regimen of anticancer therapy were enrolled. For patients who were on the targeted therapy, OBI-833 was added to their ongoing therapies. Humoral immune responses and relevant tumor biomarkers were monitored.

Disposition

	Number of Patients Cohort Expansion
Screened	24
Enrolled Population	14
Safety Population	14
	Number of Study Discontinuation
Disease Progression	11
SUSAR*	1
Withdrawal of Consent	0

*Grade 4 acute pancreatitis, possibly related

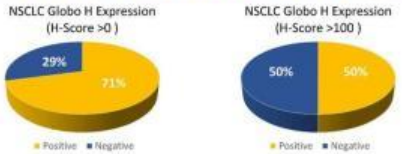
Adverse Events

- As of June 2020, a total of 126 AEs were reported, of which 79 were considered as treatment related AEs. Most of them were injection site reactions. Among the 3 reported SAEs, one was treatment-related, which was Grade 4 acute pancreatitis, and two were non-treatment related.
- Injection site reactions were less than Grade 2, occurred on the day of injection, recovered within 2-3 days without medical treatment, and usually recurred after each subsequent injection.

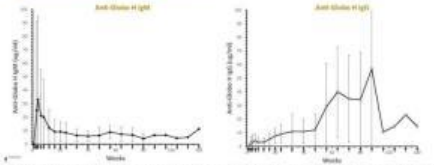
Summary of Serious Adverse Events

Subject ID	SAE (Preferred Term)	Severity	Relationship
034-005	Ascites	Grade 3	Not-related
034-008	Pneumonia	Grade 5	Not-related
034-006	Acute pancreatitis	Grade 4	Possibly-related

Globo H Expression in 24 Screened Subjects

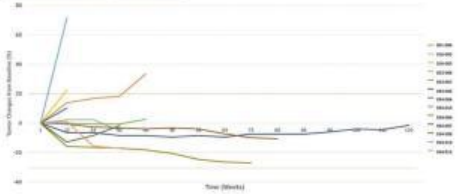


Antibody Responses



93% and 64% of patients showed positive blood anti-Globo H IgM and IgG results, respectively. The positivity was defined as the anti-Globo H IgM or IgG concentration ≥ 3 μg/mL at least once during the study period.

Tumor Responses



Swimmer Plot of Time to Progression

Median PFS was 31 weeks (range, 3~108). Six of the 11 EGFR TKI-treated patients had SD for over six months. One patient has been treated for more than two years and his treatment is still ongoing. Of note, one patient's tumor size had reduced by 27% after 16 months of OBI-833 treatment.

Conclusions

- OBI-833 can elicit a beneficial immune response in NSCLC patients and rendered durable stable disease status for some TKI-treated patients.
- Further development of OBI-833 in *EGFR*-mutated NSCLC patients to assess the potential benefits of combination therapy of OBI-833 with TKIs is ongoing.

OBI-999

Antibody-Drug Conjugate (ADC) Targeting Tumor Expression of Globo H

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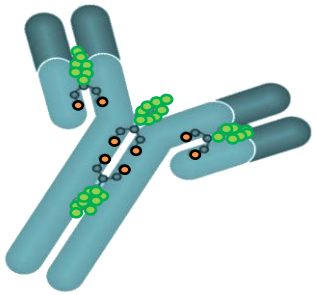
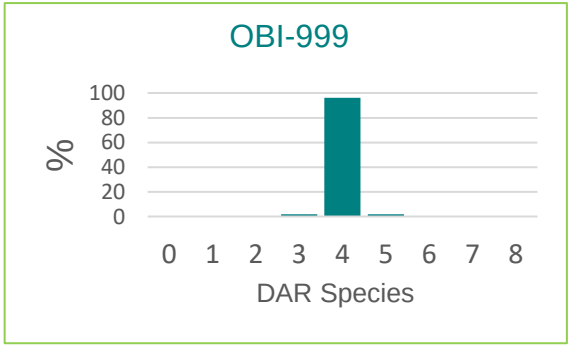
OBI-999 Targeting Tumor-Specific Globo H

Proprietary Novel Site-Specific Linker Technology ThioBridge®

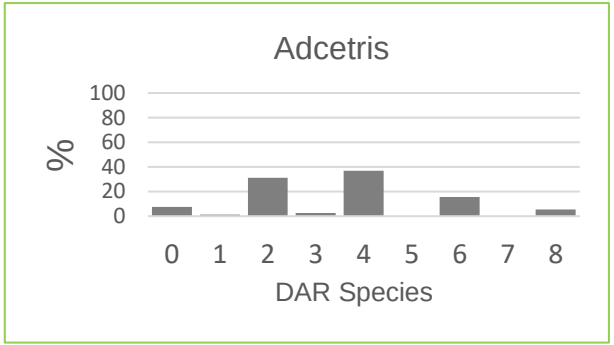


Maintains the stability of the antibody and a consistent drug-to-antibody ratio (DAR)

Improved Homogeneity vs Adcetris



DAR4>95%



DAR2 & DAR4 (majority)

	OBI-999	Adcetris
Target / Linker / Payload	**Globo H Ab / Thiobrige / vc-PAB-MMAE**	**CD30 Ab / Maleimide / vc-MMAE**
Linker	**Thiobridge** (proprietary)	**Maleimide** (generic)
Conjugation technology	**Site specific**	**Random**

OBI data on file. ThioBridge® is the registered trademark of Abzena

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OBI-999 Strong Anti-Tumor Effects in 4 Cancer Models

CANCER TYPE	TUMOR MODEL	TREATMENT DURATION	ANTI-TUMOR EFFECT AT TOP DOSE
Pancreatic	**HPAC**	QW x 4	**Tumor Free**
Gastric	**NCI-N87**	QW x 4	**Tumor Free** (achieved at both 3 and 10 mg/kg)
Lung PDX	**LU-01-0266**	QW x 4	**Tumor Free**
Breast	**MCF7**	QW x 6 or Q3W x 2	**Tumor Free**

PDX, patient-derived xenograft; TGI, tumor growth inhibition; QW, every week; Q3W, every 3 weeks.

Yang, MC *et al*. *AACR 2019*. Abstract No. 4814. OBI Data on File.

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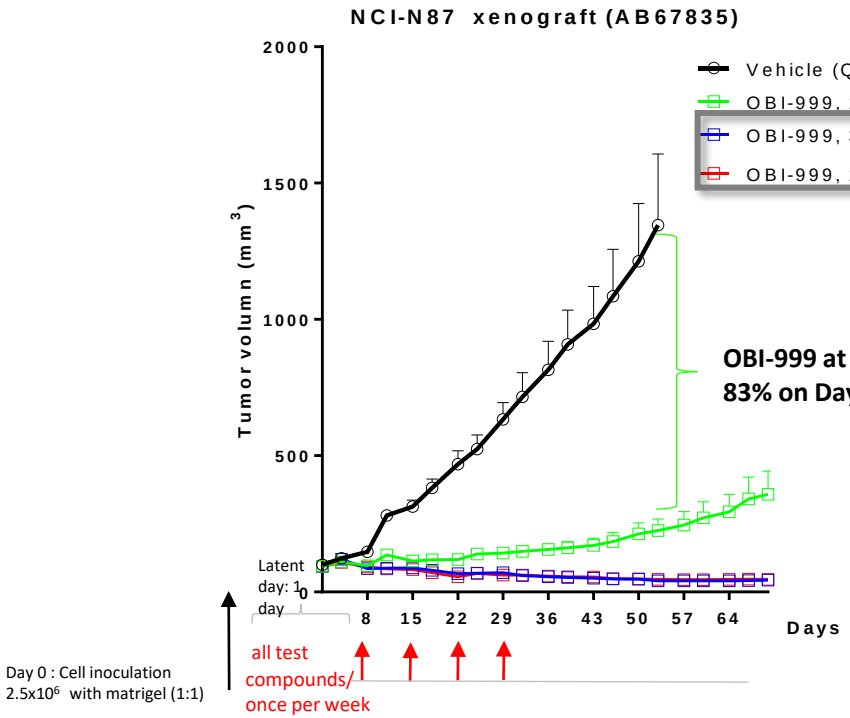
OBI-999 Strong tumor growth inhibition in NCI-N87 Gastric carcinoma xenograft

Globo H expression: 57%.



OBI-999 at 1 mTGI% = 83% on Day 53 g/mL:

Orphan Drug Designation approved by US FDA

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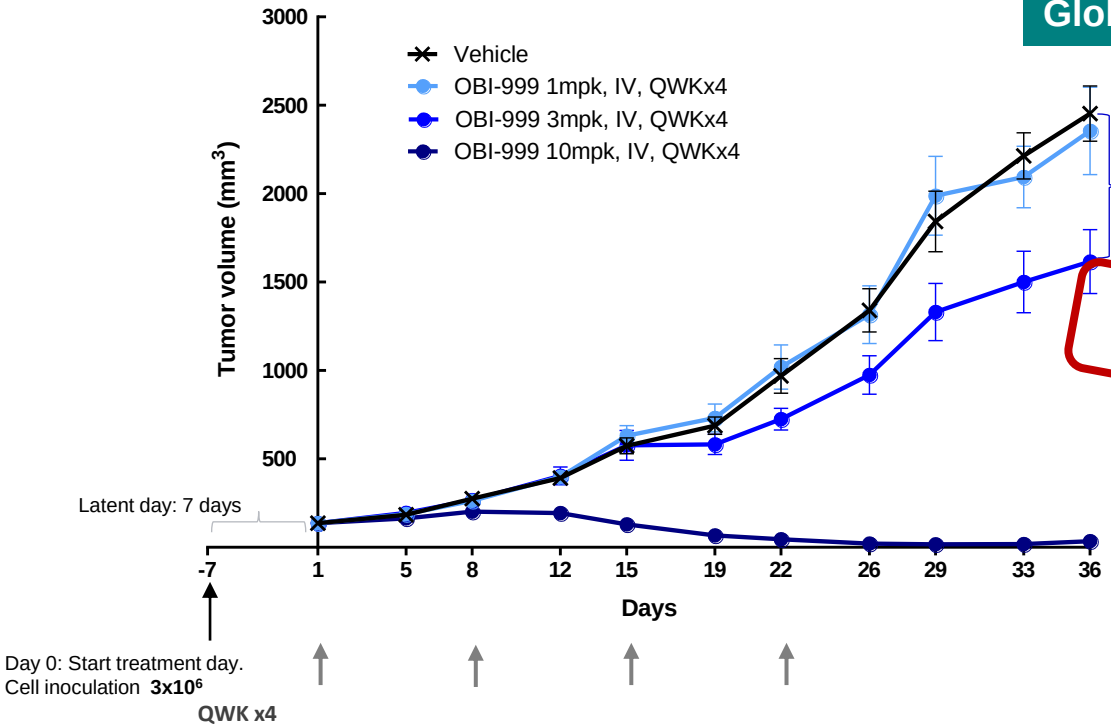
OBI-999 Strong tumor growth inhibition in HPAC pancreatic cancer xenograft model

HPAC xenograft (OBI-20180927)



Globo H expression: 97%.

OBI-999 at 3 mg/kg:
TGI 36.1% on Day 36

Orphan Drug Designation approved by US FDA

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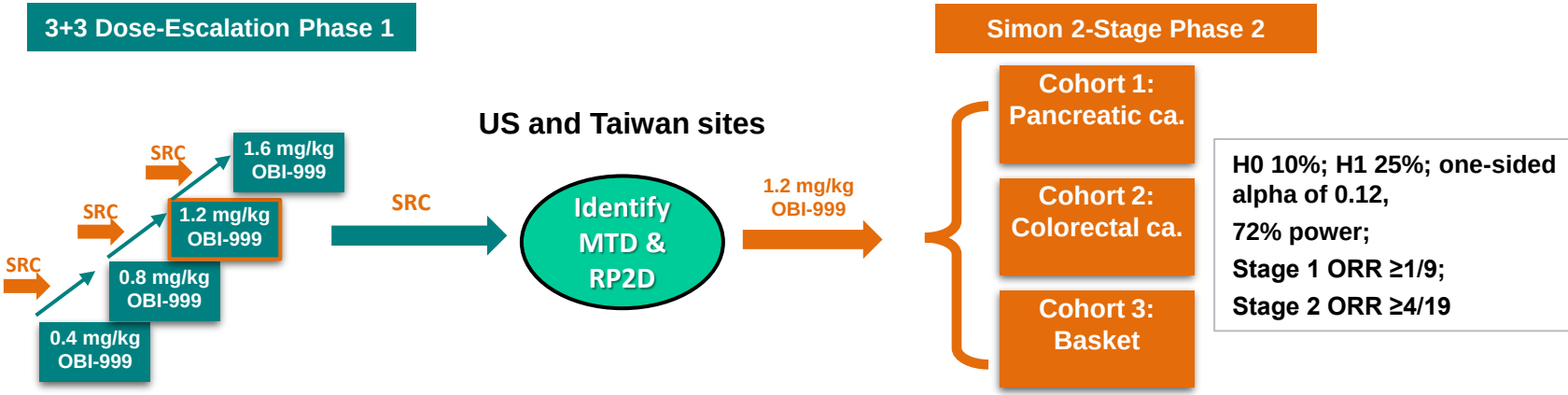
Initiation Phase 2 portion of study November 2021

- Subject number: 3+3 design, up to 30 (sequential enrollment);
- Treatment cycle: 21-day cycle up to 35 cycles (approximately 2 years);
- SRC: review safety and PK data after each cohort completes the 1st cycle.
- Patient tumor sample must have an **H score of ≥100** for Globo H in an **FDA IDE-approved assay** (NeoGenomics)



- Primary objectives:
  - Safety and tolerability of OBI-999
  - MTD and PR2D
- Secondary objectives:
  - ORR, CBR, DOR, PFS
  - ADAs
  - PK
- Exploratory objectives:
  - Tumor Tissue Samples: Globo H testing

ASCO 2020 Poster # 387

First-in-Human Study of OBI-999, a Globo H–Targeting Antibody–Drug Conjugate, in Patients With Advanced Solid Tumors

Apostolia Maria Tsimberidou[1], Henry Hiep Vo[1], Jennifer Beck[1], Chi-Sheng Shia[2], Pei Hsu[2], Tillman E. Pearce[3]

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OBI PHARMA
3029
ASCO 2022

INTRODUCTION

- Aberrant glycosylation is a hallmark of cancer.[1]
- Globo H, a glycosphingolipid (GSL), is overexpressed on a variety of cancer cells, including cancer stem cells, suggesting its potential role as a drug target for tumor eradication.[2]
- OBI-999, a novel humanized monoclonal immunoglobulin G1 antibody conjugated with MMAE, selectively and specifically binds to Globo H.
- MMAE, a synthetic analog of dolastatin 10, is an ultrapotent antimitotic agent that causes cell cycle arrest by inhibiting the polymerization of tubulin.[2,4]
- Antibody–drug conjugates (ADCs) such as OBI-999 enhance the antitumor efficacy of therapeutic antibodies while reducing the systemic toxicity of highly potent chemotherapeutic agents.[3]

Study Objectives

We conducted a Phase 1, first-in-human trial of OBI-999 in patients with advanced solid tumors and evaluated the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of OBI-999 as a single agent (NCT04084366).

PATIENTS AND METHODS

Major Inclusion Criteria

- Patients ≥18 years of age
- Histologically or cytologically confirmed advanced solid tumors that had been previously treated with standard of care therapy and it was determined by their physicians that such therapy was no longer effective, or patients had declined to receive further standard of care treatments.
- Measurable disease as per Response Evaluation Criteria in Solid Tumors (RECIST v1.1).
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.
- Adequate hematologic, hepatic, and renal function.

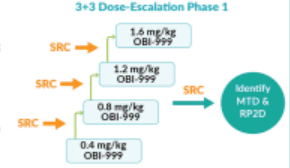
Major Exclusion Criteria

- At least 3 weeks from prior cytotoxic chemotherapy or radiation therapy to first dose or ≥5 half-lives or 3 weeks from prior biologic therapies to first dose.
- Major surgery or significant traumatic injury within 28 days prior to first dose.
- Grade ≥2 sensory or motor neuropathy.
- Prior therapy targeting Globo H.
- Life-threatening medical comorbidity.
- Concurrent antineoplastic therapy, immunosuppressive therapy, systemic corticosteroids of >10 mg/day prednisone or equivalent, strong cytochrome P450 family 3 subfamily A member 4 inhibitors/inducers, or clinical inhibitors of P-glycoprotein.

Study Design

OBI-999 was administered at doses of 0.4, 0.8, 1.2, and 1.6 mg/kg on day 1 of each 21-day cycle, using a "3+3" design to identify the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D).

Figure 1. OBI-999 Study Design



MTD, maximum tolerated dose; PK, pharmacokinetics; RP2D, recommended Phase 2 dose; SRC, Safety Review Committee.

Treatment

- OBI-999 was administered by intravenous infusion over 60 minutes. The starting dose of OBI-999 was 0.4 mg/kg on day 1 of each 21-day cycle. The MTD was defined as the dose level where ≥1 of 6 patients experienced a dose-limiting toxicity (DLT). Treatment was discontinued for disease progression, grade 4 infusion reaction, OBI-999-related toxicity, >2 dose reductions due to OBI-999-related toxicities, treatment interruption in >2 consecutive doses, withdrawal of consent, protocol deviation, and intercurrent illness

RESULTS

- From November 25, 2019, to March 19, 2021, 22 patients were screened, and 15 patients received ≥1 dose of OBI-999.
- Patient demographics and baseline characteristics are listed in **Table 1**

Table 1. Demographics and Baseline Characteristics

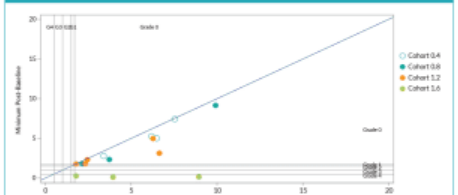
Variable	Cohort 1 0.4 mg/kg (N=3)	Cohort 2 0.8 mg/kg (N=3)	Cohort 3 1.2 mg/kg (N=6)	Cohort 4 1.6 mg/kg (N=3)	Total (N=15)
Females, n (%)	1 (33.3)	0	3 (50.0)	2 (66.7)	6 (40.0)
Age, years					
N	3	3	6	3	15
Mean (SD)	53.6 (13.45)	70.3 (5.13)	55.1 (9.31)	54.7 (18.9)	57.8 (12.71)
Median	60	69	54.5	48	58
Min, Max	35, 66	66, 76	43, 69	40, 76	35, 76
ECOG, n (%)					
1	3 (100.0)	3 (100.0)	6 (100.0)	3 (100.0)	15 (100.0)
Number of Previous Systemic Therapies, n (%)					
Median (range)					
1	0	1 (33.3)	0	0	1 (6.7)
2	1 (33.3)	0	4 (60.0)	0	5 (33.3)
≥ 3	2 (66.7)	2 (66.7)	2 (40.0)	3 (100)	9 (60.0)
Tumor Type(s), n (%)					
Colorectal cancer	2 (66.7)	1 (33.3)	0	2 (66.7)	5 (33.3)
Esophageal cancers/ Gastroesophageal junction	0	1 (33.3)	1 (16.7)	1 (33.3)	3 (20.0)
Gastric cancer	0	0	1	0	1 (6.7)
Head and neck cancer	0	0	1 (16.7)	0	1 (6.7)
Appendiceal cancer	0	0	1 (16.7)	0	1 (0.1)
Ovarian cancer	0	0	1 (16.7)	0	1 (6.7)
Pancreatic cancer	1 (33.3)	1 (33.3)	1 (16.7)	0	3 (20.0)
Globo H H-Score					
n	3	3	6	2	14
Mean (SD)	33.7 (57.4)	36 (59.8)	78.7 (66.4)	102.5 (3.5)	63.3 (59.0)
Median	1	3	90	102.5	87.5
Min, Max	0, 100	0, 105	0, 180	100, 105	0, 180
Globo H, n (%)					
Negative (H-score <99)	2 (67)	2 (67)	3 (60)	0	7 (50)
Positive (H-score ≥100)	1 (33)	1 (33)	3 (60)	2 (100)	7 (50)
Insufficient tissue	0	0	0	1	1

ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation; yr, year.

Safety and Tolerability

- The most common treatment-emergent adverse events (TEAEs) were neutropenia of any grade (n = 3, 20%) and anemia (n = 2, 13%).
- No peripheral neuropathy and no clinically significant ocular events were observed despite MMAE being known to be associated with peripheral neuropathy.
- No DLT was noted in the first 3 dose-escalation cohorts (3 patients, each). In the 4th dose-escalation cohort (1.6 mg/kg), a patient developed grade 4 neutropenia lasting for 11 days after the first dose of OBI-999. The other 2 patients treated in the 1.6 mg/kg cohort also developed grade 4 neutropenia. Therefore, this dose level (1.6 mg/kg) was considered to exceed the MTD. Subsequently, 3 additional patients were treated at the lower dose level (1.2 mg/kg). No grade 4 neutropenia was noted in patients treated with dose levels of OBI-999 of up to 1.2 mg/kg, and it was determined to be the RP2D.
- Changes in neutrophil counts from baseline to the minimum value observed post-baseline are shown in **Figure 2**.

Figure 2. Change in neutrophil count from baseline to minimum observed post-baseline value

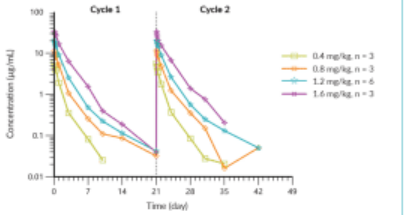


Solid diagonal represents no change; vertical and horizontal lines are borders between CTCAE grades. Vertical distance from the diagonal represents magnitude of change; above the diagonal is an increase, below a decrease. For analytes where the reference range varied by age/sex, the lowest value was used to create the borders.

Pharmacokinetics

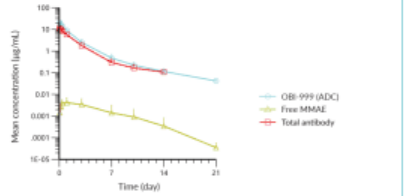
- The mean concentration-time profiles of OBI-999 at Cycle 1 and Cycle 2 are illustrated in **Figure 3**.

Figure 3. Mean Concentration-Time Profile of OBI-999 at Cycle 1 and Cycle 2



- The mean concentration-time profile of total antibody (TAb), antibody-drug conjugate (ADC), and unconjugated MMAE after the first cycle of OBI-999 1.2 mg/kg on day 1 of each 21-day cycle is illustrated in **Figure 4**. Peak TAb and OBI-999 concentrations typically occurred immediately after the infusion. OBI-999 concentrations declined in a manner similar to that of TAb and remained detectable at later time points.

Figure 4. Peak TAb and OBI-999 concentrations

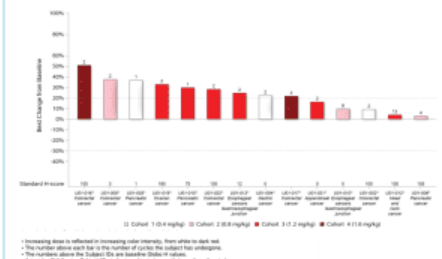


ADC, antibody-drug conjugate; MMAE, monomethyl auristatin E.

Pharmacodynamics

- Globo H expression analysis was performed on 15 tumor tissue specimens using a validated automated immunohistochemistry (IHC) assay (NeoGenomics®). One specimen was not considered evaluable due to the presence of <100 viable tumor cells. Globo H H-scores are listed for each patient with an adequate sample in **Figure 5**.
- A total of 14 patients were evaluable for tumor response, with the best response being stable disease (SD) in 5 patients (36%), lasting for 13, 8, 4, 2 and 2 cycles. All patients discontinued the study drug. The primary reason for treatment discontinuation was disease progression (by RECIST v1.1), which was reported for 12 (80%) patients; the remaining two (13%) patients discontinued treatment due to physician decision.

Figure 5. Antitumor Activity in Patients Treated With OBI-999 at Post-Baseline Scans



PD, progressive disease; PR, partial response; SD, stable disease; RECIST, Response Evaluation Criteria in Solid Tumors.

CONCLUSIONS

- At a dose of 1.2 mg/kg administered on day 1 of 21-day cycles, OBI-999 was generally safe and well tolerated and was determined to be the MTD/RP2D.
- The peak total antibody and OBI-999 concentrations typically occurred immediately after the infusion.
- OBI-999 concentrations declined in a manner similar to that of the peak total antibody and remained detectable at later timepoints.
- OBI-999 exhibited non-linear PK from 0.4 mg/kg to 1.6 mg/kg, with lower clearance at higher doses.
- Circulating MMAE levels were low relative to ADC, with serum exposure of MMAE around 0.1% that of the ADC.
- The most common TEAEs were neutropenia of any grade (n = 3, 20%) and anemia (n = 2, 13%).
- The majority of TEAEs were mild or moderate in severity.
- No peripheral neuropathy and no clinically significant ocular events were observed despite MMAE being known to be associated with peripheral neuropathy.
- We are conducting a Phase 2 dose-expansion study in patients with advanced metastatic pancreatic cancer and other epithelial carcinomas at a dose of 1.2 mg/kg. Patients who have experienced disease progression following surgery and/or systemic therapy and have no standard of care options are eligible if their tumor expresses high levels of Globo H (>100) using a US FDA-approved, validated IHC assay (NeoGenomics®).

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Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting, June 3-7, 2022, Chicago, IL

OBI-999 and Keytruda combo synergy poster at AACR 2023

OBI PHARMA

Poster 5946

OBI-999, an anti-Globo H antibody drug conjugate, exhibits synergistic anti-tumor effect in combination with pembrolizumab

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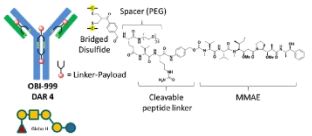
Background

Globo H, a glycosphingolipid, is highly expressed in a variety of epithelial tumors with a limited expression in normal tissues. OBI-999 is an anti-Globo H antibody drug conjugate, which consists of a Globo H-specific monoclonal antibody conjugated with monomethyl auristatin E (MMAE) through a cleavable linker. MMAE is known to induce immunogenic cell death (ICD). ICD involves the activation of cytotoxic T lymphocyte-driven adaptive immunity with long-term immunological memory. Given the capability of inducing ICD and creating more accessible tumor microenvironment, this study aims to investigate whether OBI-999 in combination with pembrolizumab can have synergistic antitumor effect in animal models. Results showed that OBI-999 and pembrolizumab had a significant synergistic efficacy in various animal models. OBI-999 is currently in Phase 1/2 clinical trial for advanced solid tumors (NCT04084366).

Methods

The ICD effects of OBI-999 were examined *in vitro* by incubation of the Globo H expression cells with OBI-999 followed by the detection of damaging-associated molecular patterns (DAMPs) such as calreticulin (CRT), high mobility group box 1 (HMGB1), and ATP. The ICD-related immunity induced by OBI-999 was assessed *in vivo* using advanced severe immunodeficient mice that were reconstituted with human peripheral blood mononuclear cells (PBMCs). Antitumor effect of OBI-999 in combination with pembrolizumab was evaluated in several cancer types of xenograft tumor models using PBMC-humanized mice.

Structure of OBI-999



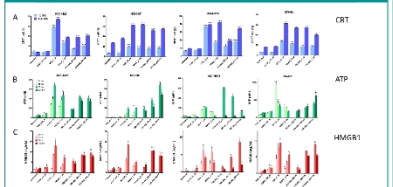
OBI-999 consists of a Globo H targeting antibody plus a novel linker ThioBridge® and a tubulin inhibitor payload MMAE. The ThioBridge® is designed to form site-specific disulfide bonds through cross-linking to the reduced cysteines in the Fab and hinge regions of the antibody rendering a homogeneous drug-antibody ratio (DAR).

ThioBridge® is the registered trademark of Abzena

Results

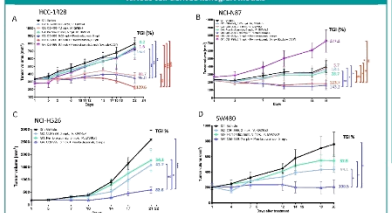
Incubation of OBI-999 with high Globo H expression cancer cell lines (HCC-1428, NCI-N87, and NCI-H526) and mid Globo H expression cancer cell line (SW480) induced the release of a panel of DAMPs including CRT, ATP, and HMGB1 in dose- and time-dependent manners. The detection of the hallmark DAMPs indicated that OBI-999 induced ICD *in vitro*. Furthermore, OBI-999 showed a synergistic antitumor effect in combination with pembrolizumab in several xenograft tumor models using PBMC-humanized mice. In high Globo H expression human breast cancer cell line HCC-1428 xenograft model, OBI-999 (0.05 mg/kg; once a week) plus pembrolizumab (5 mg/kg; twice a week) exhibited significantly stronger inhibition on tumor growth (TGI 95.0%) compared to the treatment with OBI-999 (TGI 16.3%) or pembrolizumab (TGI 8.2%) alone. Similar synergistic effects of the combination therapy were observed in other cancer types of xenograft models as well, including gastric cancer (NCI-N87), small cell lung cancer (NCI-H526) and colorectal cancer (SW480). Analysis of tumor-infiltrating lymphocytes (TILs) in HCC-1428 xenograft model showed that OBI-999 combined with pembrolizumab treatment induced the populations of cytotoxic CD8 T-cells and mature dendritic cells. In addition, pembrolizumab treatment decreased PD-1 expression on CD8 and CD4 cells, and OBI-999 treatment decreased PD-L1 expression on tumor cells, which reversed the exhausted status of immune cells and alleviate the immunosuppression microenvironment.

Figure 1. OBI-999 induced immunogenic cell death as shown by a panel of DAMPs



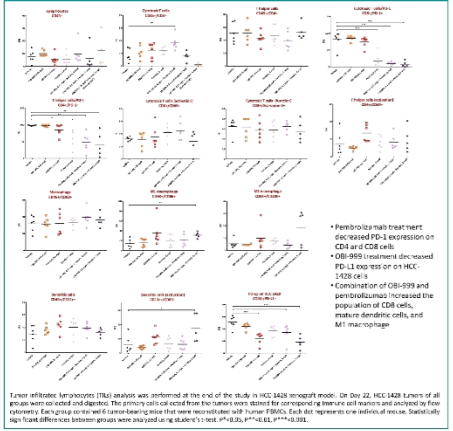
OBI-999 induced a panel of damage-associated molecular patterns (DAMP) *in vitro*. (A) Ecto-calreticulin (CRT) was detected by flow cytometry on HCC-1428, NCI-N87, NCI-H526, and SW480 cells after treatment with various concentrations of OBI-999 for 72 or 120 hours. (B) Extracellular ATP was measured in the culture supernatant after cells were incubated with OBI-999 for 72 or 120 hours. (C) High mobility group box 1 (HMGB1) was detected by ELISA in all tested cell lines after OBI-999 treatment for 72 or 120 hours. Doxorubicin was used as a positive control and cisplatin as a negative control for ICD induction. Data are presented as mean ± S.D. Significant difference between treated and control was analyzed by Student's t-test. *p < 0.05, **p < 0.01, ***p < 0.001.

Figure 2. Combination of OBI-999 and pembrolizumab showed synergistic antitumor effect in various cell-derived xenograft models



OBI-999 in combination with pembrolizumab showed synergistic antitumor effect in PBMC humanized mice that carried tumor xenograft of: (A) human breast cancer HCC-1428; (B) human gastric cancer NCI-N87; (C) human lung cancer NCI-H526; and (D) human colon cancer SW480. The anti-cancer effect was evaluated through CD8+ cells (Animal 6). Human PBMCs (2×10^6) mixed with tumor cells were implanted subcutaneously in the left flank of advanced severe immunodeficient mice. CD8+ T cells were removed by magnetic beads before injected into mice in the CD8 depletion groups. OBI-999 was administered intravenously once a week for 3 or 4 weeks as indicated. Pembrolizumab was given intraperitoneally twice a week for 2 or 3 weeks. Each group contained 6 mice. Data are presented as mean ± S.E. Significant difference between groups was analyzed by Student's t-test. *p < 0.05, **p < 0.01, ***p < 0.001.

Figure 3. Immune cells infiltration and activation in HCC-1428 tumors after OBI-999/pembrolizumab treatment



- Pembrolizumab treatment decreased PD-1 expression on CD4 and CD8 cells
- OBI-999 treatment decreased PD-L1 expression on HCC-1428 cells
- Combination of OBI-999 and pembrolizumab increased the population of CD8 cells, mature dendritic cells, and M1 macrophage

Tumor infiltrates lymphocytes (TILs) analysis was performed at the end of the study in HCC-1428 xenograft model. On Day 22, HCC-1428 tumors of all groups were collected and digested. The primary cells collected from the tumors were stained for corresponding immune cell markers and analyzed by flow cytometry. Each group contained 6 tumor-bearing mice that were reconstituted with human PBMCs. Each dot represents one individual mouse. Statistically significant differences between groups were analyzed using student's t-test. #*=0.05, #***=0.01, #****=0.001.

Conclusions

- OBI-999 exhibited synergistic antitumor effect with pembrolizumab in various xenograft models
- The synergistic effect may be attributed to the capability of OBI-999 to induce immunogenic cell death
- Tumor-infiltrating lymphocytes and activated dendritic cells suggested a tumor microenvironment that favors the function of immune checkpoint inhibitors like pembrolizumab
- A combination therapy of OBI-999 with anti-PD-1 in clinical study is warranted

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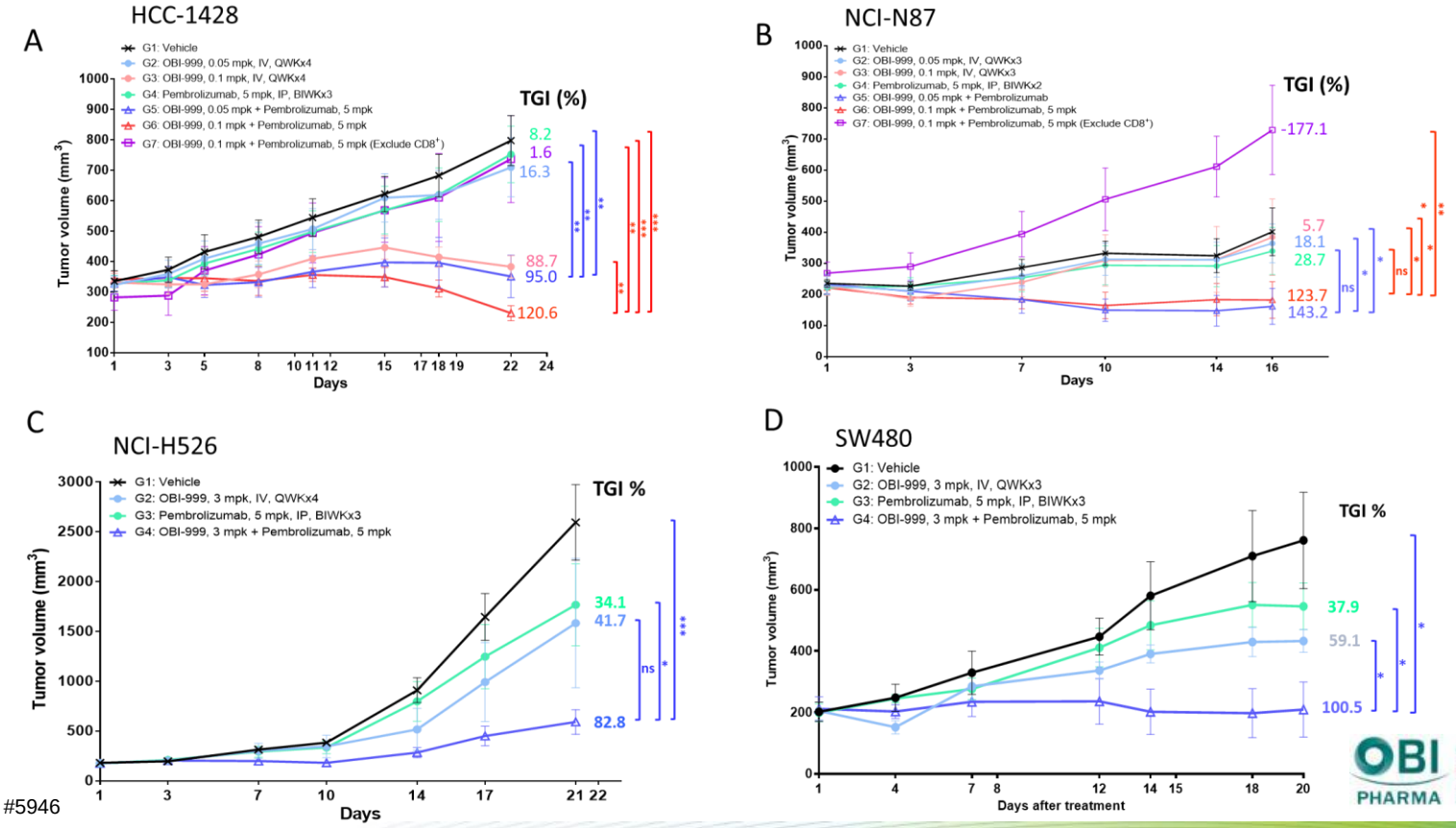
Combination of OBI-999 and pembrolizumab showed synergistic antitumor effect in four cancer models (breast, gastric, lung, colon)



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Agenda

1. Company Introduction
2. Globo H Science Leadership
   - Novel I-O Pipeline
3. AKR1C3 Science Leadership
   - Novel Pro-drug
4. Key Milestones and Inflection Points

OBI-3424

Small Molecule Prodrug Targeting Tumors Expressing the AKR1C3 Enzyme

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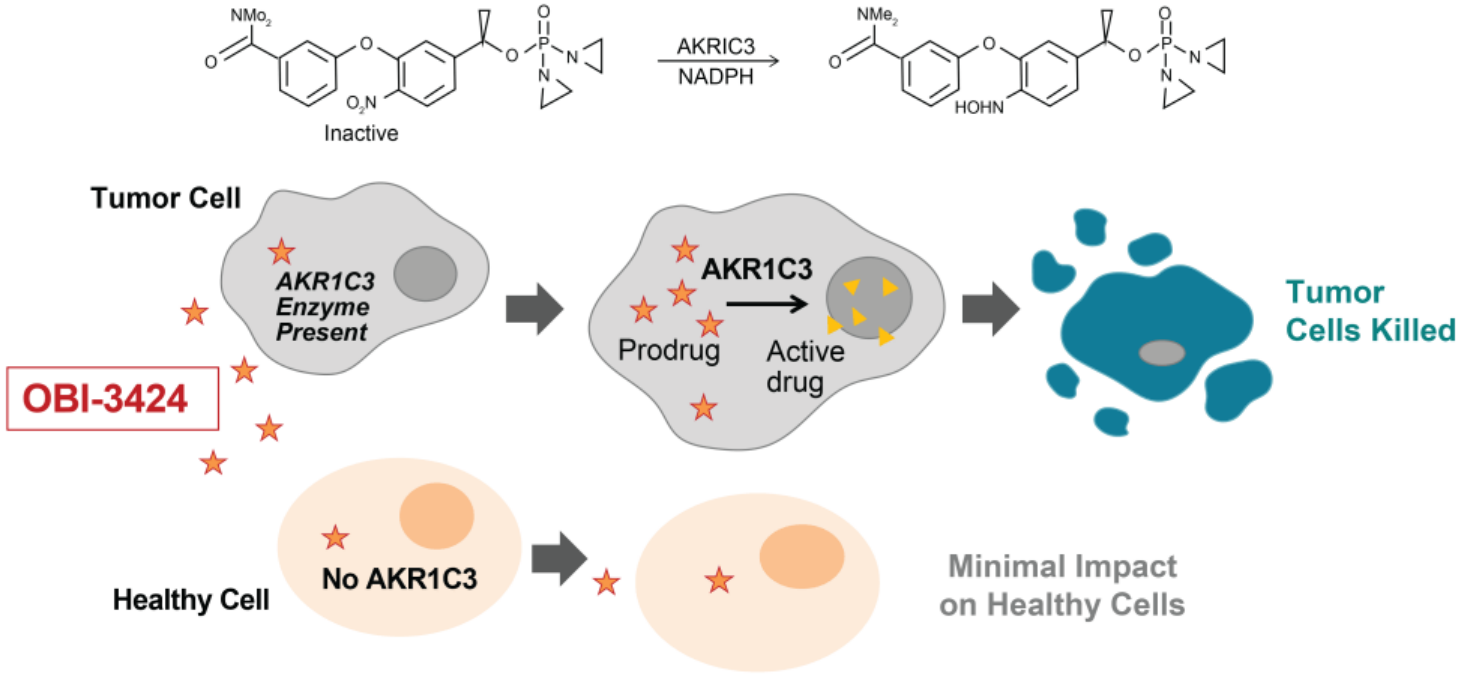
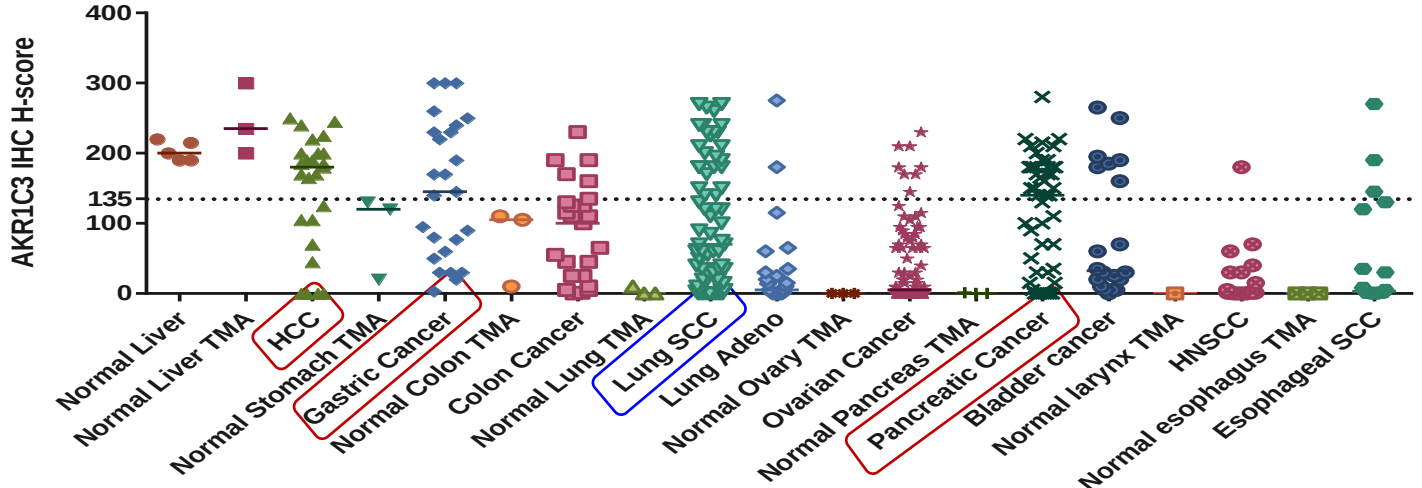
The Prodrug OBI-3424 Is Converted to Active Drug in AKR1C3 Expressing Tumor Cells



AKR1C3 Prevalence in 10 Cancer Types

Prevalence of H-score ≥135



Median	200	235	180	120	145	105	100	0	70	5	0	5	0	140	32.5	0	1.5	0	3
N	5	3	25	3	25	3	25	3	75	25	3	100	3	49	20	1	20	3	20
Prevalence* (%)	100	100	64	0	56	0	24	0	36	8	0	8	0	55	35	0	5	0	15

OBI Data on file. Immunohistochemistry (IHC) staining assay was used to survey the expression levels in various human tissue types.

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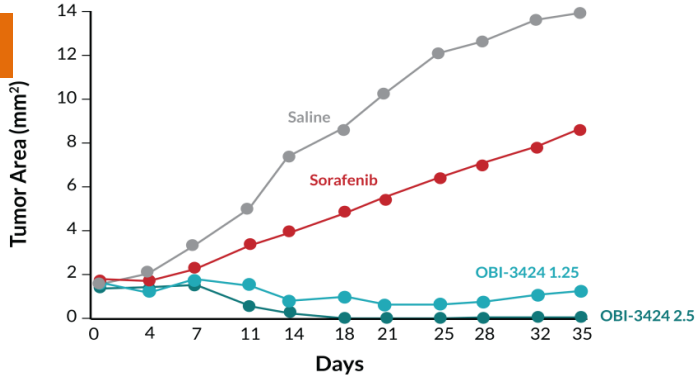
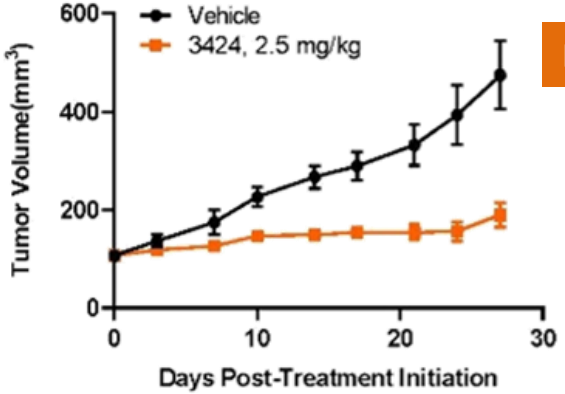
OBI-3434 also demonstrated strong anti-tumor activity against **Liver**, **Pancreatic**, **Gastric** and **Lung** cancers

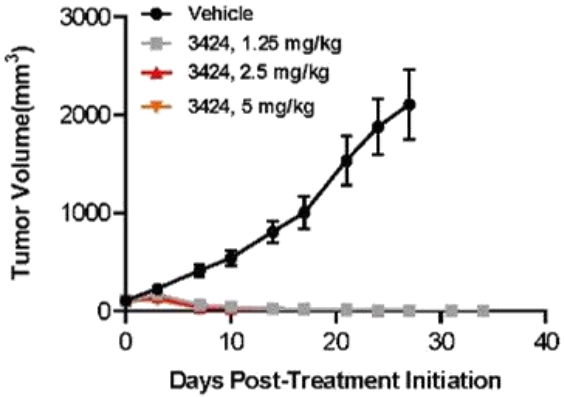
Liver Cancer



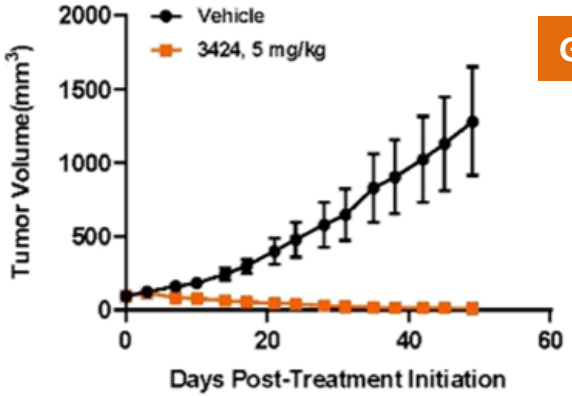
Pancreatic Cancer



Lung Cancer



Gastric Cancer



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AACR 2021 Poster #1220

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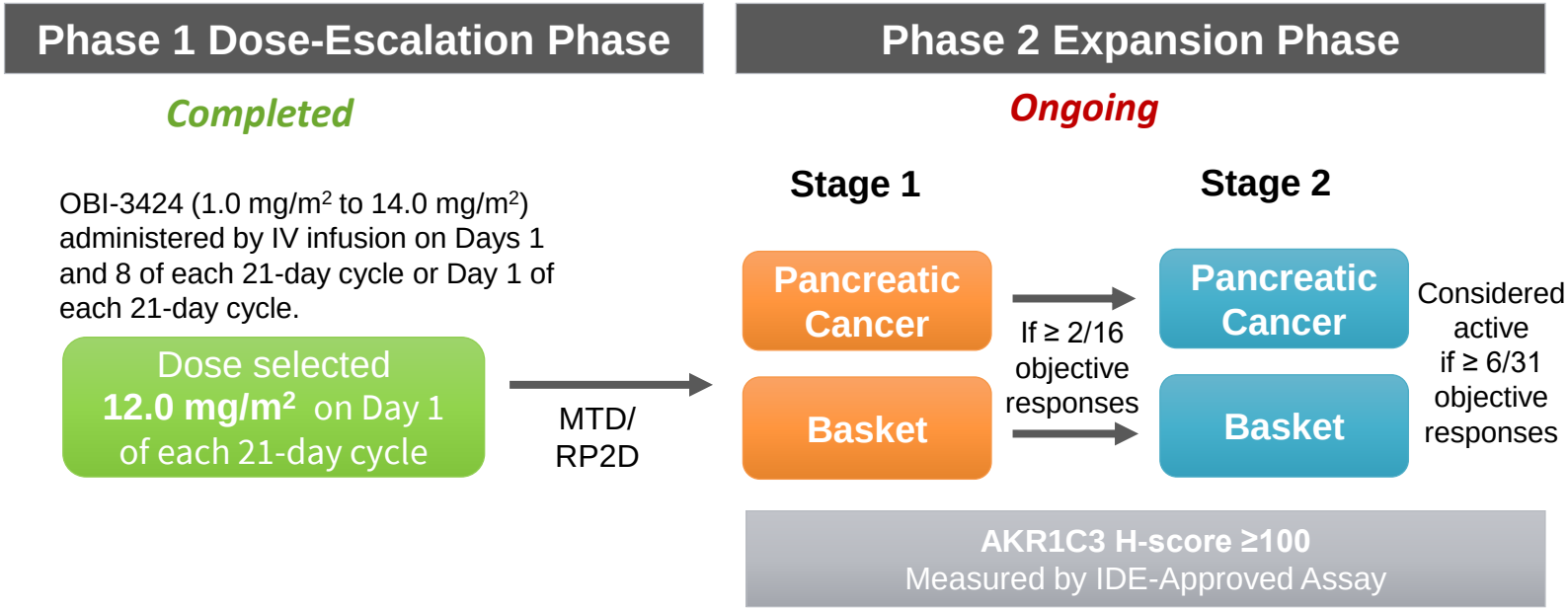
OBI-3424-001: Study Schematic and Current Status



ASCO 2020 Poster #387.
ASCO 2022 Poster #3030.
ClinicalTrials.gov Identifier: NCT03592264

OBI PHARMA

3030

ASCO 2022

Safety, Pharmacokinetics, and Clinical Activity of OBI-3424, an AKR1C3 Activated Prodrug, in Patients With Advanced or Metastatic Solid Tumors: A Phase 1 Dose-Escalation Study

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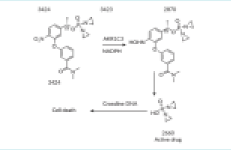
INTRODUCTION

- Aldo-keto reductases (AKRs) are a superfamily of NAD(P)(H)-dependent oxidoreductases that primarily catalyze the reduction of aldehydes and ketones to their corresponding alcohols.[2,3]
- AKR family 1 member C3 (AKR1C3) is involved in the synthesis of steroid hormones and prostaglandins, activating mechanisms that are involved in cell proliferation.[2,3]
- AKR1C3 is overexpressed in various solid tumors (breast, prostate, endometrium, gastrointestinal, pancreas, liver, and kidney) and hematologic malignancies, and the intensity of AKR1C3 expression is strikingly elevated in certain tumors relative to normal tissues.[2]
- AKR1C3 plays a role in carbonyl metabolism and has the capability of reducing carbonyl-containing anticancer drugs, such as doxorubicin, into the related alcohols, thereby destroying their anticancer effect.[3,4,5]
- OBI-3424 is a highly potent DNA-alkylating prodrug that is selectively activated by AKR1C3 (**Figure 1**).
- In the presence of NADPH, OBI-3424 is reduced by AKR1C3 to an intermediate that spontaneously hydrolyzes to the cytotoxic moiety OBI-2660, an aziridine bisalkylating agent that causes cross-linking of DNA at the N7 (or O6) position of guanine and subsequent tumor cell death.[1]
- The cytotoxicity of OBI-3424 is highly AKR1C3 dependent, and this selective mode of activation distinguishes OBI-3424 from traditional prodrug alkylating agents.
- We report the results of a Phase 1, first-in-human trial of OBI-3424 in patients with advanced solid tumors (NCT03592264).

Figure 1. Structure and Mechanism of Action of OBI-3424



AKR1C3, aldo-keto reductase family 1 member C3.

Study Objectives

- Safety and tolerability of single-agent OBI-3424 administered intravenously (IV).
- Dose-limiting toxicities (DLTs), maximum tolerated dose (MTD), and recommended Phase 2 dose (RP2D) of OBI-3424 administered as a single agent.
- Pharmacokinetics of OBI-3424 in plasma and urine.

PATIENTS AND METHODS

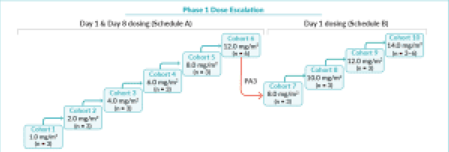
Eligibility Criteria

- Patients ≥18 years of age.
- Histologically or cytologically confirmed advanced solid tumors for which standard curative or palliative measures did not exist or were no longer effective.
- Exclusion criteria included prior radiotherapy to >25% of the bone marrow; symptomatic brain metastases; other malignancies treated within the last 3 years; active infection; radiation therapy, surgery, chemotherapy, targeted therapy, hormones, or investigational drug/device within 28 days of study entry; or concomitant use of strong cytochrome P450 family 3 subfamily A member 4 inhibitors/inducers or naproxen.

Study Design

- The initial dose escalation part of the study (OBI-3424 1, 2, 4, 6, 8 and 12 mg/m² IV on days 1 and 8 every 3 weeks, Schedule A) was followed by an amended dose escalation phase (OBI-3424 8, 10, 12, and 14 mg/m² IV on day 1 every 3 weeks, Schedule B) (**Figure 2**).

Figure 2. Study Design: A standard 3+3 dose-escalation design was used.



PA3, Protocol amendment #3

- "3+3" design.
- The MTD was defined as the dose level where <2 of 6 patients experienced a DLT.
- Treatment was discontinued if there was clinically significant deterioration of the patient's condition; disease progression; noncompliance/protocol violation; pregnancy; unacceptable toxicity, or consent withdrawal.

Patient Monitoring

- Radiologic assessments of tumor response by computed tomography (CT) scan were conducted at baseline and after every 2 cycles.
- Tumor response was measured using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1).
- Toxicities were assessed using the National Cancer Institute Common Toxicity Criteria version 5.
- A DLT was defined as the occurrence of any event within the first cycle of treatment that was considered possibly related to OBI-3424.

RESULTS

Patient Demographics

The most common tumor types were prostate cancer (8 of 39, 21%) and colorectal cancer (5 of 39, 13%) (**Table 1**).

Table 1. Patient Demographics and Baseline Characteristics

Variable	Day 1 and Day 8 Dosing: Cohort 1 1.0 mg/m² (n=3)	Cohort 2 2.0 mg/m² (n=3)	Cohort 3 4.0 mg/m² (n=3)	Cohort 4 6.0 mg/m² (n=3)	Cohort 5 8.0 mg/m² (n=3)	Cohort 6 12.0 mg/m² (n=6)	Day 1 Dosing: Cohort 7 8.0 mg/m² (n=3)	Cohort 8 10.0 mg/m² (n=3)	Cohort 9 12.0 mg/m² (n=6)	Cohort 10 14.0 mg/m² (n=6)	Total (N=39)
Females, n (%)	1 (33.3)	1 (33.3)	3 (100.0)	1 (33.3)	0	1 (16.7)	1 (33.3)	3 (100.0)	3 (50.0)	3 (50.0)	17 (43.6)
Age, n	3	3	3	3	3	6	3	3	6	6	39
Mean, yr (SD)	71.3 (2.08)	64.3 (9.07)	58.3 (17.21)	53 (5.57)	65 (8.89)	68.3 (7.99)	54.7 (13.65)	60.7 (11.02)	59.8 (11.36)	68.2 (6.62)	63.1 (10.25)
Median, yr	72	68	64	54	68	67.5	57	66	60	68.5	67
Min, max, yr	69, 73	54, 71	39, 72	47, 58	55, 72	55, 78	40, 67	48, 68	45, 75	59, 76	39, 78
ECOG PS, n (%)											
0	0	0	1 (33.3)	0	0	1 (16.7)	2 (66.7)	0	1 (16.7)	2 (33.3)	7 (17.9)
1	3 (100.0)	2 (66.7)	2 (66.7)	3 (100.0)	3 (100.0)	5 (83.3)	1 (33.3)	3 (100.0)	5 (83.3)	4 (66.7)	31 (79.5)
Missing	0	1 (33.3)	0	0	0	0	0	0	0	0	1 (2.6)
Tumor Type, n (%)											
Breast	0	0	0	0	0	0	0	0	0	1 (16.7)	1 (2.6)
Colorectal	0	0	0	1 (33.3)	0	0	0	0	1 (16.7)	3 (50.0)	5 (12.8)
Hepatocellular carcinoma	2 (66.7)	0	0	0	0	0	0	0	1 (16.7)	0	3 (7.7)
Lung	0	0	1 (33.3)	0	0	0	0	0	0	0	1 (2.6)
Melanoma	0	0	0	0	0	0	0	0	1 (16.7)	0	1 (2.6)
Ovarian	0	1 (33.3)	0	0	0	0	0	0	0	0	1 (2.6)
Prostate	0	2 (66.7)	0	0	1 (33.3)	3 (50.0)	2 (66.7)	0	0	0	8 (20.5)
Squamous cell carcinoma	0	0	0	0	2 (66.7)	0	0	0	0	0	2 (5.1)
Other	1 (33.3)	0	2 (66.7)	2 (66.7)	0	3 (50.0)	1 (33.3)	3 (100.0)	3 (50.0)	2 (33.3)	17 (43.6)
Stage, n (%)											
Stage 3	0	0	0	0	0	0	0	0	1 (16.7)	0	1 (2.6)
Stage 4	3 (100.0)	2 (66.7)	3 (100.0)	3 (100.0)	3 (100.0)	6 (100.0)	3 (100.0)	3 (100.0)	5 (83.3)	6 (100.0)	37 (94.9)
Unknown	0	1 (33.3)	0	0	0	0	0	0	0	0	1 (2.6)

ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation; yr, year.

Safety and Tolerability

- The median number of doses administered was 4 (range, 1-38).
- Treatment-related adverse events (TEAEs) occurred in 32 (82%) of the 39 patients (**Table 2**).
- The most common AEs were anemia (25/39, 64%), thrombocytopenia/platelet count decreased (21/39, 54%), nausea (10/39, 26%), and fatigue (8/39, 21%).
- There were no fatal TEAEs; 5 patients reported a treatment-related serious AE: 4 patients with Grade >3 anemia in Cohort 6 (12 mg/m²) and 1 patient in Cohort 8 (10mg/m²)

Table 2. Patient Incidence* of Treatment-Emergent Adverse Events (AEs)

Preferred Term, n (%)	Day 1 and Day 8 Dosing: Cohort 1 1.0 mg/m² (n=3)	Cohort 2 2.0 mg/m² (n=3)	Cohort 3 4.0 mg/m² (n=3)	Cohort 4 6.0 mg/m² (n=3)	Cohort 5 8.0 mg/m² (n=3)	Cohort 6 12.0 mg/m² (n=6)	Day 1 Dosing: Cohort 7 8.0 mg/m² (n=3)	Cohort 8 10.0 mg/m² (n=3)	Cohort 9 12.0 mg/m² (n=6)	Cohort 10 14.0 mg/m² (n=6)	Total (N=39)
Patients reporting any treatment-emergent AE	2 (66.7)	0	2 (66.7)	1 (33.3)	3 (100.0)	6 (100.0)	3 (100.0)	3 (100.0)	6 (100.0)	6 (100.0)	32 (82.1)
Patients reporting any grade ≥3 treatment-emergent AE	0	0	1 (33.3)	1 (33.3)	1 (33.3)	6 (100.0)	2 (66.7)	2 (66.7)	2 (33.3)	4 (66.7)	19 (48.7)
Treatment-emergent AEs in >10% of patients											
Anemia	0	0	1 (33.3)	1 (33.3)	1 (33.3)	6 (100.0)	3 (100.0)	2 (66.7)	5 (83.3)	6 (100.0)	25 (64.1)
Thrombocytopenia	0	0	0	0	0	0	0	0	0	2 (33.3)	2 (5.1)
Platelet count decreased	0	0	0	0	2 (66.7)	6 (100)	1 (33.3)	1 (33.3)	4 (66.7)	5 (83.3)	19 (48.7)
Lymphocytopenia	0	0	0	1 (33.3)	0	2 (33.3)	1 (33.3)	1 (33.3)	0	2 (33.3)	7 (17.9)
Leukopenia	0	0	0	0	0	1 (16.7)	0	0	3 (50.0)	3 (50.0)	7 (17.9)
Neutropenia	0	0	1 (33.3)	0	0	1 (16.7)	0	0	2 (33.3)	2 (33.3)	6 (15.4)
Nausea	1 (33.3)	0	1 (33.3)	1 (33.3)	0	0	1 (33.3)	2 (66.7)	2 (33.3)	2 (33.3)	10 (25.6)
Diarrhea	0	0	0	0	0	2 (33.3)	0	0	2 (33.3)	1 (16.7)	5 (12.8)
Vomiting	0	0	1 (33.3)	0	0	3 (50.0)	0	0	0	1 (16.7)	5 (12.8)
Fatigue	1 (33.3)	0	0	1 (33.3)	1 (33.3)	1 (16.7)	0	2 (66.7)	2 (33.3)	0	8 (20.5)
Decreased appetite	0	0	0	0	0	3 (50.0)	0	0	0	1 (16.7)	4 (10.3)
Dyspnea	0	0	0	0	0	1 (16.7)	0	1 (33.3)	0	2 (33.3)	4 (10.3)

*Patients reporting multiple AEs in the same System Organ Class or Preferred Term are counted only once in that row

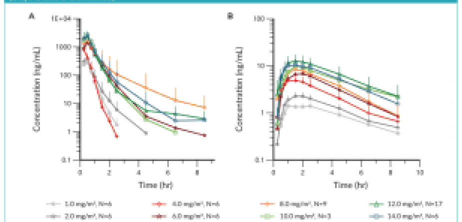
Dose-Limiting Toxicity and Maximum Tolerated Dose

- In Schedule A (days 1 and 8 every 3 weeks), OBI-3424 was well tolerated at doses of up to 8.0 mg/m². Given that the platelet count nadirs were occurring on day 15 or day 21, the schedule of administration was modified for Schedule B (day 1 every 3 weeks) (**Figure 2**).
- Treatment with OBI-3424 at doses of ≥8 mg/m² using Schedule A and 12 mg/m² using Schedule B was associated with clinically significant decreases in hemoglobin levels and platelet counts, corresponding to the observed increase in the incidence of anemia and thrombocytopenia in these dosing cohorts.
- OBI-3424 administered on day 1 every 3 weeks was tolerated at doses up to 14 mg/m²; the MTD was not reached.
- The RP2D and regimen of OBI-3424 were determined to be 12 mg/m² on day 1 every 3 weeks (**Schedule B**).

Pharmacokinetics

- OBI-3424 and OBI-2660 (a circulating metabolite of OBI-3424) concentrations were analyzed from blood samples collected on day 1 of cycle 1 (pretreatment); 15 minutes after infusion begins; at the end of infusion (EOI); and 15, 30, 60, and 90 minutes and 2, 4, 6, and 8 hours post-treatment.
- Mean plasma concentration versus time profiles of single doses of OBI-3424 and OBI-2660 are illustrated in **Figure 3**.
- OBI-3424 and OBI-2660 pharmacokinetic parameters are summarized in **Table 3**.
- Maximum serum concentrations (C_{max}) of OBI-3424 generally occurred at the end of the 30-minute drug infusion. Time to maximum concentration of OBI-2660 was observed to be slightly delayed compared with OBI-3424, with C_{max} achieved between 1.33 and 1.75 hours after the start of drug infusion.
- The half-life of OBI-3424 was short (0.20 to 0.74 hours), while OBI-2660 had a longer half-life (1.87 to 3.48 hours).
- Mean clearance ranged from 4.8 to 8.8 L/h/m² and volume of distribution ranged from 2.4 to 4.3 L/m² for OBI-3424.
- No accumulation of exposure (C_{max} and area under the concentration-time curve) between 2 doses (cycle 1 day 1 and cycle 1 day 8) was observed for either OBI-3424 and OBI-2660.

Figure 3. Pharmacokinetic Profiles of OBI-3424 (A) and OBI-2660 (B) During Cycle 1 (Days 1 and 8 Combined)



OBI-3424 and OBI-2660 pharmacokinetic parameters are summarized in **Table 3**.

Table 3. Mean Plasma Pharmacokinetic Parameters for OBI-3424 and OBI-2660 in Cycle 1 – Days 1 and 8 Combined

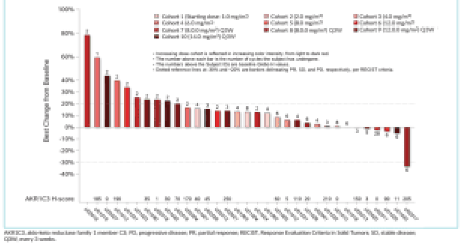
Dose Level (mg/m²)	T_{max} (h) OBI-3424	T_{max} (h) OBI-2660	C_{max} (ng/mL) OBI-3424	C_{max} (ng/mL) OBI-2660	AUC_{0-t} (h*ng/mL) OBI-3424	AUC_{0-t} (h*ng/mL) OBI-2660	$T_{1/2}$ (h) OBI-3424	$T_{1/2}$ (h) OBI-2660	CL (L/h/m²) OBI-3424	V_{ss} (L/m²) OBI-3424
1	0.46 (0.10)	1.75 (0.61)	289.30 (56.10)	1.70 (0.80)	257.10 (46.10)	7.30 (1.90)	0.29 (0.04)	3.08 (1.21)	4.74 (0.87)	2.45 (0.40)
2	0.50 0.00	1.67 (0.26)	375.80 (161.40)	2.30 (0.50)	298.00 (156.50)	10.00 (2.20)	0.31 (0.14)	2.48 (0.76)	8.85 (5.25)	4.13 (1.67)
4	0.33 (0.13)	1.33 (0.41)	803.50 (500.70)	5.00 (1.10)	650.90 (391.60)	19.30 (6.70)	0.21 (0.04)	2.00 (0.24)	7.74 (3.29)	2.68 (1.69)
6	0.50 0.00	1.75 (0.27)	1360.30 (247.10)	6.80 (0.40)	1278.10 (230.00)	27.40 (3.50)	0.74 (0.39)	2.09 (0.44)	4.84 (1.03)	3.72 (0.83)
8	0.42 (0.13)	1.44 (0.30)	1613.10 (419.80)	8.50 (1.60)	1678.40 (1302.00)	32.80 (8.90)	0.67 (0.33)	1.87 (0.35)	6.53 (2.92)	3.97 (1.06)
10	0.50 0.00	1.67 (0.29)	2654.70 (426.40)	10.10 (1.10)	2037.00 (316.20)	29.20 (18.30)	0.57 (0.24)	2.99 (0.10)	4.92 (0.83)	3.06 (0.50)
12	0.44 (0.17)	1.53 (0.37)	2481.90 (1132.70)	13.10 (4.20)	2159.40 (1089.10)	56.60 (21.40)	0.55 (0.34)	2.41 (0.69)	8.20 (7.98)	4.33 (4.67)
14	0.42 (0.13)	1.75 (0.52)	2619.20 (878.00)	11.20 (2.70)	2131.80 (955.10)	45.60 (9.80)	0.55 (0.27)	2.46 (0.78)	8.49 (5.67)	4.31 (1.22)

Data expressed as mean (SD).
CL, clearance; AUC_{0-t}, area under the concentration-time curve from time 0 to the last measurable concentration; C_{max}, time to maximum concentration; SD, standard deviation; $T_{1/2}$, half-life; T_{max}, time to maximum concentration; Vdss, volume of distribution at steady state.

Antitumor Activity

- Best response by RECIST v1.1 is shown in Figure 4. Of 33 patients who were evaluable for response assessment, one patient with cholangiocarcinoma in Cohort 8 (10 mg/m² Q3W) had a partial response (PR), 21 (54%) had stable disease (SD), and the remaining 11 (28%) patients had progressive disease. Six patients ended the study before the first post-treatment response assessment.
- AKR1C3 expression was assessed by a validated automated immunohistochemistry assay in tumor tissue of 32 patients. In nine patients, tumor cells were insufficient for testing. AKR1C3 H-scores are listed in **Figure 4**.

Figure 4. Antitumor Activity in Patients Treated With OBI-3424 at Post-Baseline Scans



AKR1C3, aldo-keto reductase family 1 member C3; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; Q3W, every 3 weeks.

CONCLUSIONS

- OBI-3424 was tolerated at doses of up to 14.0 mg/m² on day 1 every 3 weeks. No DLT occurred at the maximum administered dose, and thus MTD was not determined.
- All patients who received OBI-3424 at the dose of 12.0 mg/m² on days 1 and 8 every 3 weeks experienced anemia and/or thrombocytopenia, requiring dose reductions and blood transfusions.
- The most common AEs were anemia (64%), thrombocytopenia/platelet count decreased (48.7%), nausea (26%), and fatigue (21%); including 5 patients who experienced a treatment-emergent serious AE (Grade >3 anemia).
- OBI-3424 exhibited linear pharmacokinetics and dose proportionality from 1.0 mg/m² to 14.0 mg/m² without marked accumulation after repeated dosing, indicating that there was no evidence of cumulative toxicity.
- Best confirmed response to OBI-3424 treatment was PR.
- A Phase 2 dose-expansion study of single-agent OBI-3424 is currently enrolling patients with locally advanced/metastatic hepatocellular carcinoma, pancreatic cancer, and other epithelial carcinomas with high AKR1C3 expression.

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Presented at American Society of Clinical Oncology (ASCO) Annual Meeting, June 3-7, 2022, Chicago, IL

OBI-3424 and pembrolizumab combo in multiple cancers

OBI PHARMA

Poster#6111

OBI-3424, an AKR1C3-activated prodrug, exhibits *in vivo* synergistic anti-tumor effect in combination with pembrolizumab by induction of immunogenic cell death

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OBI Pharma, Inc. Taipei, Taiwan

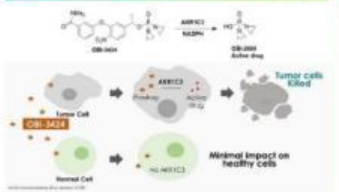
Background

OBI-3424 is a prodrug of nitrogen mustard that is selectively cleaved by AKR1C3 to release an active, cytotoxic aziridine, which forms DNA crosslinks and cause cell death. Immunogenic cell death (ICD) involves the activation of cytotoxic T lymphocyte-driven adaptive immunity with long-term immunological memory. This study aims to investigate whether OBI-3424 can induce ICD and create a tumor microenvironment that benefits the combination therapy of OBI-3424 with immune checkpoint inhibitors. OBI-3424 is currently in Phase 1/2 clinical trials for solid tumor and acute lymphoblastic leukemia (NCT03592264 and NCT04315324).

Methods

OBI-3424 induced ICD was examined in vitro by incubation of the prodrug with AKR1C3 positive cells followed by the detection of damaging-associated molecular patterns (DAMPs). The ICD-related immunity was assessed in vivo using advanced severe immunodeficient mice that were engrafted with human peripheral blood mononuclear cells (PBMCs). Anti-tumor effect of OBI-3424 in combination with pembrolizumab was evaluated in a xenograft model using PBMC-humanized mice.

Structure and Mechanism of action of OBI-3424

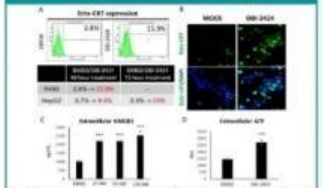


OBI-3424 is a chemically synthesized potent nitrogen mustard, which is selectively cleaved to the cytotoxic aziridine (OBI-2660) by AKR1C3 in the presence of NADPH. The active molecule OBI-3660 released by OBI-3424 is similar to the chemotherapeutic drugs thiotepa and mitomycin C, which leads to alkylation and cross-linking of DNA at the N7 (or O6) position of guanine.

Results

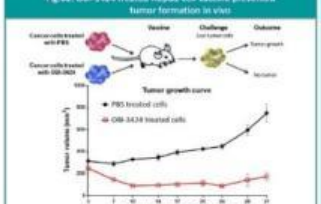
Incubation of OBI-3424 with AKR1C3 positive cells H460 and HepG2 induced the release of DAMPs including calreticulin, HMGB1, and ATP, in dose- and time-dependent manners (Fig.01). The detection of the DAMPs indicated that OBI-3424 induced ICD *in vitro*. The OBI-3424-induced ICD and its related immunity were also assessed *in vivo*. PBMC-humanized mice were immunized with OBI-3424- or PBS-treated HepG2 cells and then challenged with live HepG2 cells. No tumor growth was noted in mice that were immunized with OBI-3424-treated cells, indicating that the dying HepG2 cells induced by OBI-3424 elicited an adaptive, tumor-specific immune response (Fig.02). Furthermore, OBI-3424 showed a synergistic anti-tumor effect in combination with pembrolizumab in HepG2 xenograft model using PBMC-humanized mice. OBI-3424 plus pembrolizumab exhibited significantly stronger inhibition on tumor growth (TGI 77.2%) when compared with the treatment of OBI-3424 (TGI 27.8%) or pembrolizumab (TGI -15.3%) alone (Fig.03). Moreover, the combo benefits were totally diminished when CD8 T cells were excluded from the PBMC, which indicated that OBI-3424 treatment could further activate CD8 T cells to attack tumors and the combo benefits were CD8 T cell dependents. Analysis of tumor-infiltrating lymphocytes (TILs) showed that OBI-3424 treatment induced the populations of activated cytotoxic CD8 T-cells (CD45+/CD8+/CD69+ and CD45+/CD8+/Granzyme), activated helper CD4 T-cells (CD45+/CD4+/CD69+), and mature dendritic cells (CD11b+/CD86+) (Fig.05). In addition, OBI-3424 treatment also increased PD-1 expression on CD8 and CD4 cells, which in turn potentiated the anti-tumor effect of pembrolizumab (Fig.05).

Fig.01. OBI-3424 elicits DAMP molecules in vitro



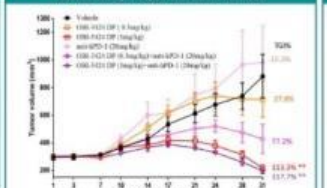
OBI-3424 elicits ICD in vitro. (A) Ecto-calreticulin (CRT) detected by flow cytometry on H460 and HepG2 after treatment with 100nM OBI-3424 for 48 or 72 hours. (B) Immunofluorescent staining of CRT (green) in H460 treated with100nM OBI-3424. Blue, nuclei. Scale bar, 50 μm. (C) ELISA of HMGB1 in the culture supernatant from H460 treated with OBI-3424 25, 50 and 100nM. (D) Extracellular ATP was measured in the culture supernatant after H460 cells were treated with OBI-3424 100nM. Data represent mean ± S.D. *p < 0.05, **p < 0.01, ***p < 0.001. Statistical analysis: Student's t-test

Fig.02. OBI-3424 treated HepG2 cell vaccine prevented tumor formation in vivo



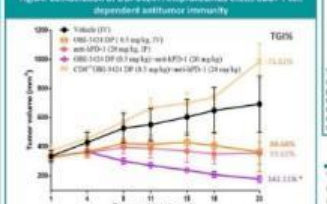
Vaccination of OBI-3424-treated HepG2 cells prevented tumor growth in vivo. HepG2 cells vaccine were prepared by treating cancer cells with PBS or OBI-3424 (5 μM) for 96 hours. The treated cells were implanted subcutaneously into the left flanks of advanced immunodeficient mice that were reconstituted with human PBMC one day earlier. Seven days later, repeated the implantation of the treated cells. Fourteen days later, live and untreated HepG2 cells were implanted subcutaneously into the right flanks of the mice.

Fig.03. Combination of OBI-3424 with Pembrolizumab exhibits strong additive efficacy in HepG2 humanized mice model



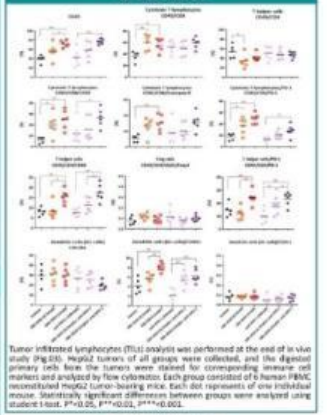
OBI-3424 was administered intravenously once weekly for 4 weeks. Anti-PD1 antibody (pembrolizumab) was given intraperitoneally twice weekly for 4 weeks. Each group consisted of 6 human PBMC reconstituted HepG2 tumor-bearing mice. Data points represent group mean tumor volume ± standard error of mean (SEM). Statistically significant differences between groups were analyzed using student t-test. P*<0.05, P**<0.01, P***<0.001.

Fig.04. Combination of OBI-3424+Pembrolizumab elicits CD8+ T cell dependent antitumor immunity



OBI-3424 was administered intravenously once weekly for 2 weeks. Anti-PD1 antibody (pembrolizumab) was given intraperitoneally twice weekly for 2 weeks. CD8 T cells were depleted by magnetic beads before injected into mice in CD8-/- group. Each group consisted of 6 human PBMC reconstituted HepG2 tumor-bearing mice. Data points represent group mean tumor volume ± standard error of mean (SEM). Statistically significant differences between groups were analyzed using student t-test. P*<0.05, P**<0.01, P***<0.001.

Fig.05. Immune cells infiltration and activation under the treatment of OBI-3424 ± anti-PD-1



Tumor infiltrated lymphocytes (TILs) analysis was performed at the end of in vivo study (Fig.03). HepG2 tumors of all groups were collected, and the digested primary cells from the tumors were stained for corresponding immune cell markers and analyzed by flow cytometer. Each group consisted of 6 human PBMC reconstituted HepG2 tumor-bearing mice. Each dot represents of one individual mouse. Statistically significant differences between groups were analyzed using student t-test. P*<0.05, P**<0.01, P***<0.001.

Conclusion

We demonstrated that OBI-3424 was able to induce ICD as shown by the release of DAMPs in vitro and tumor-specific immunity in vivo. OBI-3424 also created a tumor microenvironment that enhances the function of pembrolizumab, supported by the synergistic effect in animals with the cotreatment of the two drugs. The results suggest that a combination therapy of OBI-3424 and anti-PD-1 in human clinical study is warranted. OBI-3424 is currently in Phase 1/2 clinical trials for solid tumor and acute lymphoblastic leukemia (NCT03592264 and NCT04315324).

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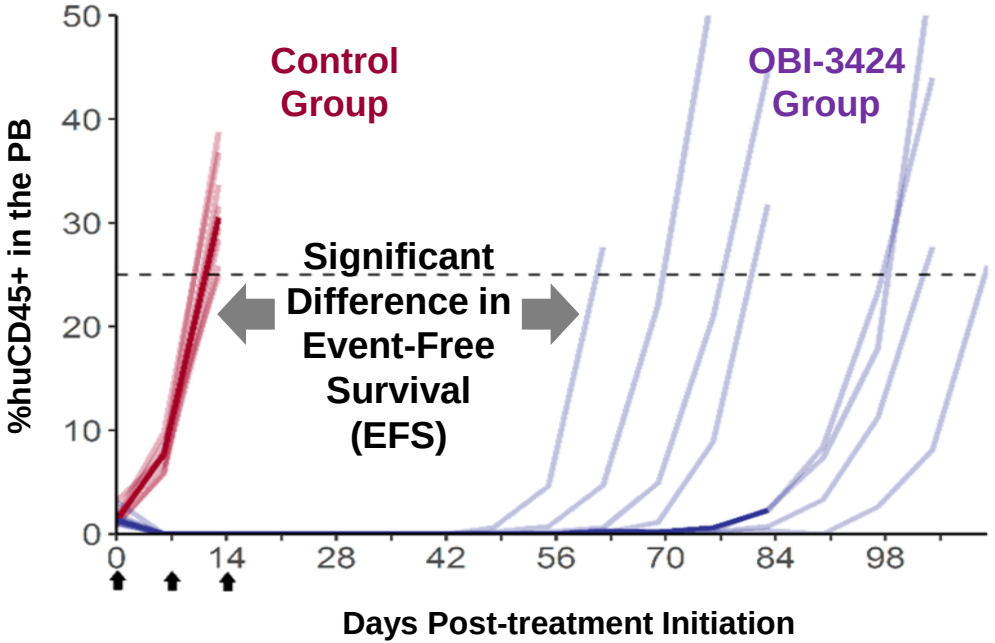
Significant Reduction in Leukemia Bone Marrow Infiltration With OBI-3424 in PDX Model (T-ALL 31)



"OBI-3424 is one of the most effective drugs we have ever tested against T-ALL in over 12 years of evaluating drugs at the Children's Cancer Institute using preclinical models of childhood ALL"

Prof Richard B. Lock
Head of the Leukemia Biology Program
Children's Cancer Institute in Australia

Data presented at the 2018 AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics. Abstract number: LB-B16. Clin Cancer Res April 23 2019 **DOI:** 10.1158/1078-0432.CCR-19-0551

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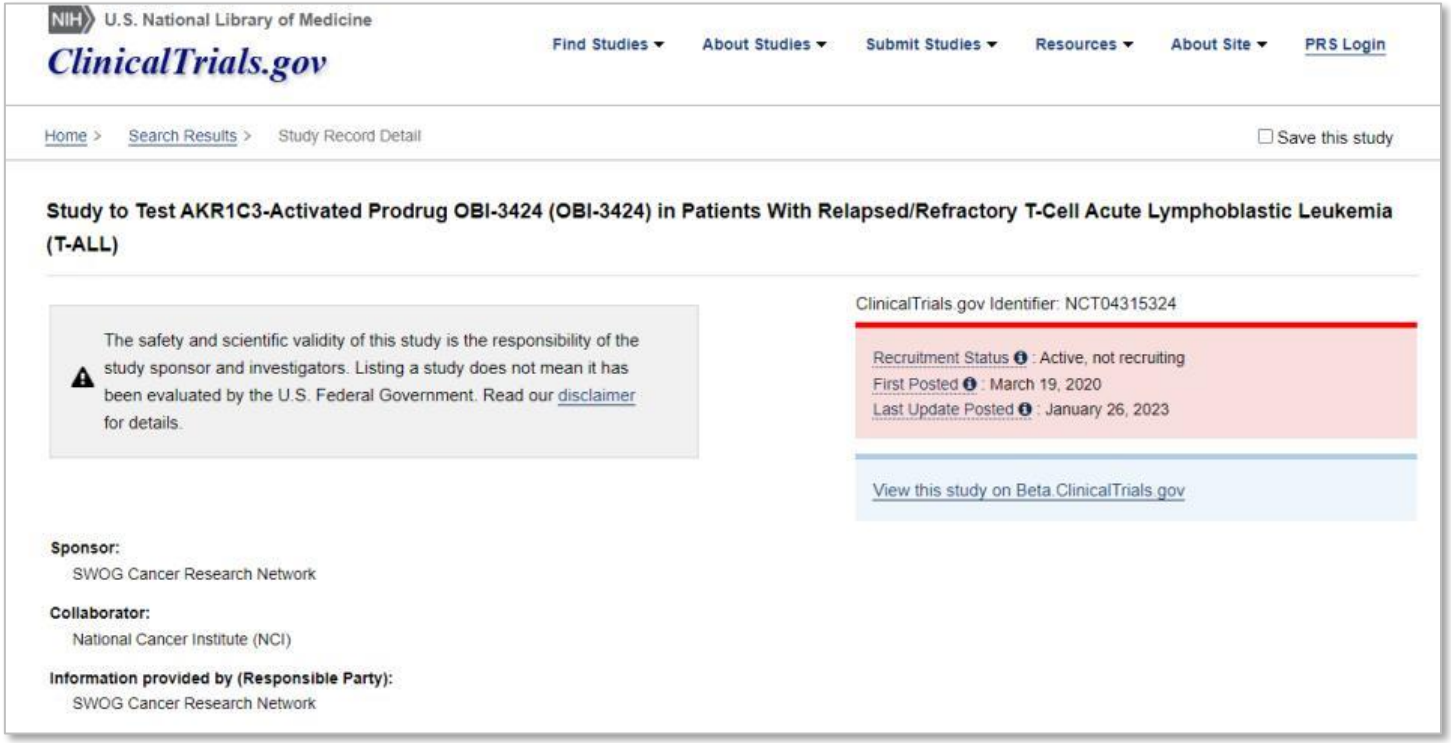
OBI-3424 Phase 2 T-ALL Study sponsored by SWOG ongoing



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Study to Test AKR1C3-Activated Prodrug OBI-3424 (OBI-3424) in Patients With Relapsed/Refractory T-Cell Acute Lymphoblastic Leukemia (T-ALL)

⚠ The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT04315324

Recruitment Status : Active, not recruiting
First Posted : March 19, 2020
Last Update Posted : January 26, 2023

View this study on Beta.ClinicalTrials.gov

Sponsor:
SWOG Cancer Research Network

Collaborator:
National Cancer Institute (NCI)

Information provided by (Responsible Party):
SWOG Cancer Research Network

ClinicalTrials.gov Identifier: NCT04315324. A Phase II Study of AKR1C3-Activated Prodrug OBI-3424 (OBI-3424) in Patients With Relapsed/Refractory T-Cell Acute Lymphoblastic Leukemia (T-ALL)

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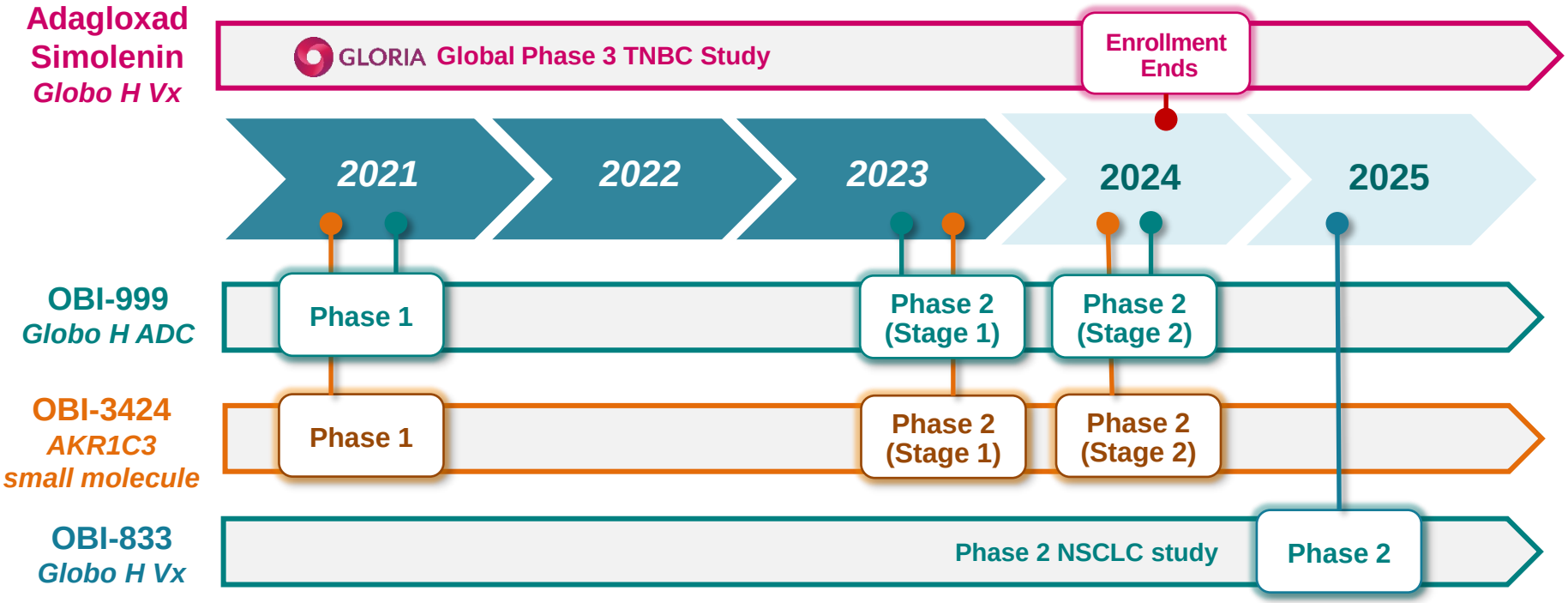
Agenda

1. Company Introduction
2. Globo H Science Leadership
   - Novel I-O Pipeline
3. AKR1C3 Science Leadership
   - Novel Pro-drug
4. Key Milestones and Inflection Points

Projected Clinical Data in 2023-25
1st-in-class Oncology products



OBI Data on File * Projected.

OBI Partnering Strategy
Innovative Cancer Portfolio

Solidify commercial licensing and/or scientific study collaborations to maximize our portfolio value

- ***Regional or Global Licensing***
- ***Commercial partnerships***
- ***R & D combination study collaborations***
- ***Strategic alliances***

Globo Series / Globo H Immunotherapies

Globo Series Vaccines	Globo H ADC
Adagloxad Simolenin[1] OBI 833[2]	OBI-999[2]

AKR1C3 Targeted Therapy

DNA Alkylating Prodrug
OBI-3424[3]

1 OBI owns worldwide rights.
2 OBI owns ex-China rights.
3 OBI owns worldwide rights other than China, HK, Macao, Taiwan, Japan, S. Korea, Singapore, Malaysia, Thailand, Turkey, and India.

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Thank You

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