A Phase 1/2, Open-Label, Dose-Escalation, and Cohort-Expansion Study Evaluating the Safety, Pharmacokinetics, and Therapeutic Activity of OBI-999 in Patients with Advanced Solid Tumors.

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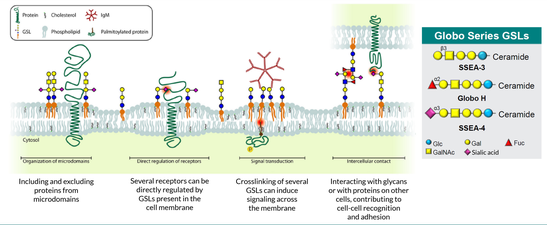
BACKGROUND

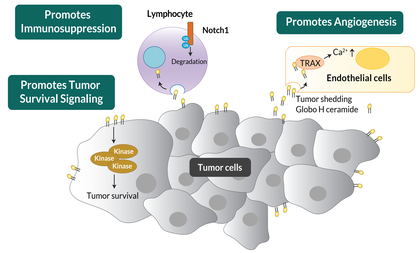
- Glycosphingolipids, glycans conjugated to a ceramide core, are essential for the recruitment of immune-related proteins to specific membrane microdomains[1,2,3]
- Aberrant glycosylation is a universal feature of cancer cells.[4]
- Globo series is a unique class of GSLs involved in early embryogenesis and tumor development[5] (**Figure 1**)
- Globo H is a glycosphingolipid found on a variety of epithelial tumors and is believed to play a role in tumor development and progression[1,2]
- Globo H is found on normal cells but highly overexpressed on many epithelial tumor cells, making it a promising target for immunotherapy

Figure 1. Glycosphingolipids and Globo Series



- Experimental data suggest that Globo H promotes immunosuppression, tumor survival signaling, and angiogenesis (**Figure 2**).[5-7] Globo H expression in tumor stem cells and its function as an immune checkpoint makes it a target for immunotherapy[8]

Figure 2. Roles of Globo H



- OBI-999 is an antibody drug conjugate (ADC) composed of a human recombinant IgG monoclonal antibody that selectively and specifically binds to GH, attached by a novel Thiobridge site specific linker to the antimitotic agent monomethyl auristatin E (MMAE). Its mechanism of action is based on tumor-selective delivery of MMAE to GH-expressing tumors with subsequent tumor cell death[9, 10]
- OBI-999 has received orphan drug designation for pancreatic and gastric cancer
- Preclinical studies demonstrated that the OBI-999 antibody binds specifically to the GH antigen, and antitumor efficacy was noted in breast, gastric, pancreatic, and lung cancer xenograft models[11] (**Figure 3,4**)

Figure 3. OBI-999 Strong Tumor Growth Inhibition in HPAC Pancreatic Cancer Xenograft Model

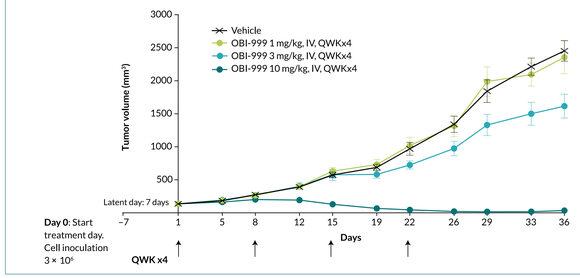
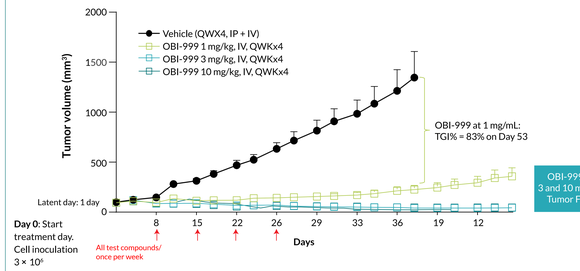


Figure 4. OBI-999 Strong Tumor Growth Inhibition in NCI-N87 Gastric Carcinoma Xenograft



- The PK of OBI-999 were determined in normal and tumor bearing mice, rats, and monkeys. Exposure of OBI-999 increased proportionally with dose. No sex difference or accumulation was seen[11]

Table 1. Pharmacokinetic Parameters of OBI-999 in Tumor-Bearing Mice

Dosage	Total Ab[a]				Intact ADC[a]				Free MMAE[b]		
	$T_{1/2}$(d)	C_{max}	AUC	CL	$T_{1/2}$(d)	C_{max}	AUC	CL	$T_{1/2}$(d)	C_{max}	AUC
5 mg/kg	3.2	80.8	158.8	30.1	2.3	73.4	164.6	30.2	3.7	1.8	4.7

Ab, antibody; ADC, antibody-drug conjugate; AUC, area under the concentration-time curve; CL, clearance; C_{max}, maximum concentration; MMAE, monomethyl auristatin E; $T_{1/2}$, half-life.
[a]For total Ab and ADC, C_{max} = μg/mL, AUC = d*μg/mL.
[b]For MMAE, C_{max} = ng/mL, AUC = d*μg/mL, CL = mL/kg/day.

Study Objectives and Endpoints

Primary Objectives

- To determine the safety and tolerability of OBI-999 when administered via IV infusion to patients with advanced solid tumors
- To determine the MTD and Recommended Phase 2 Dose (RP2D) of OBI-999

Secondary Objectives

To evaluate:

- Preliminary clinical activity profile of OBI-999 (ORR, CBR, DOR, and PFS)
- Immunogenicity of OBI-999 (anti - drug antibodies [ADAs])
- Serum PK of OBI-999 and its active metabolite MMAE

Exploratory Objectives

- Determine potential association between Globo H expression and tumor biopsies or circulating tumor cells (CTCs) and activity of OBI-999, potential association between changes in CTC counts or expression of Globo H on CTCs and activity of OBI-999
- To explore other potential predictive biomarkers of OBI-999 activity

METHODS

Main Inclusion Criteria

- Histologically or cytologically confirmed patients with advanced solid tumors
- Patients must have been treated with established standard-of-care therapy, or physicians have determined that such established therapy is not sufficiently efficacious, or patients have declined to receive standard-of-care therapy
- Measurable disease (RECIST 1.1)[12]
- ECOG 0 or 1
- Adequate organ function

Main Exclusion Criteria

- Less than 3 weeks from prior cytotoxic chemotherapy or radiation therapy; and less than 5 half-lives or 6 weeks from prior biologic therapies, prior to the first dose of OBI-999
- Sensory or motor neuropathy of ≥ Grade 1
- Unresolved toxicities from prior anticancer therapy, (not resolved to Grade 0 or 1 using NCI CTCAE version 5.0), except for alopecia and certain laboratory values
- Receipt of any prior therapy targeting Globo H
- Known untreated central nervous system metastases
- Significant clinical cardiac abnormality (e.g., clinical heart failure, unstable angina, or ejection fraction < 35%)

Study Design (Figure 5)

- Phase 1 (Dose-Escalation), OBI-999 will be given at doses of 0.4, 0.8, 1.2, 1.6, and 2.0 mg/kg (capping calculations at a maximum of 100 kg) using a 3+3 design to identify MTD and RP2D
- Phase 2 (Cohort-Expansion), patients will be treated at the MTD or possibly at a lower RP2D, as determined by the MTD, cumulative toxicities observed in phase 1, and PK results obtained during phase 1. Different dose levels, e.g., intermediate dose level lower than 2.0 mg/kg, may also be explored based on safety and PK modeling data
- All patients will receive prophylactic treatment for infusion reactions such as acetaminophen (650 mg) orally and diphenhydramine (50 mg) orally or IV
- **Patient tumor sample must have an H score of ≥100 for Globo H in an FDA IDE-approved assay (by NeoGenomics)**

Figure 5. OBI-999-001 Study Design NCT04084366

- **Subject number**: 3+3 design, up to 30 (sequential enrollment);
- **Cohorts**: 6 cohorts of escalating dose levels of 0.4, 0.8, 1.2, 1.6 and 2.0 mg/kg;
- **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.

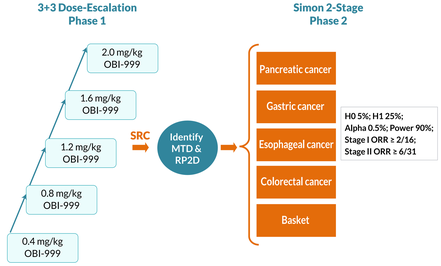
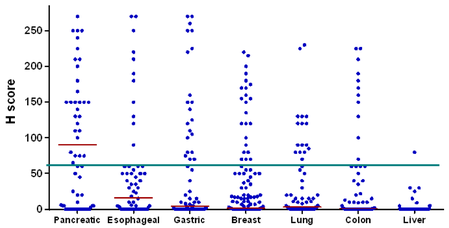


Figure 6. Frequency of Globo H Over-Expression



	Pancreatic	Esophageal	Gastric	Breast	Lung	Colon	Liver
Median	90.0	16.5	4.0	2.0	3.0	1.0	0.0
Number	72	64	73	131	77	75	70
Prevalence of H-score ≥ 100	50.0%	17.2%	24.7%	13.0%	10.4%	16.0%	0%

CONCLUSIONS

- OBI-999 shows excellent anti-tumor activity in multiple cancer types, including breast, pancreatic, lung, and gastric xenograft models that express high levels of Globo H
- This is a first in a human clinical study
- This study will be undertaken in patients with advanced cancer that has progressed on prior therapy
- The objectives of the study are to determine the MTD and RP2D in phase 1 and to seek a preliminary signal of activity across a number of tumor types known to over-express GH, using ORR as an end-point in a two-stage Simon phase 2 design

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