OBI PHARMA

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

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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.[3,4]
- 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

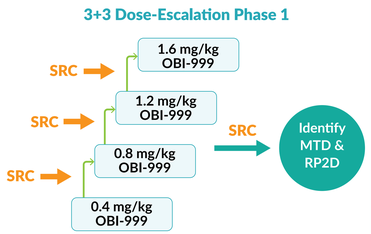
- At least 3 weeks from prior cytotoxic chemotherapy or radiation therapy to first dose or ≥5 half-lives or 3 weeks from prior biologic therapies to first dose.
- Major surgery or significant traumatic injury within 28 days prior to first dose.
- Grade ≥2 sensory or motor neuropathy.
- Prior therapy 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

- **Subject number:** Up to 30 (sequential enrollment)
- **Cohorts:** 4 cohorts of escalating dose levels of 0.4, 0.8, 1.2, and 1.6 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



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

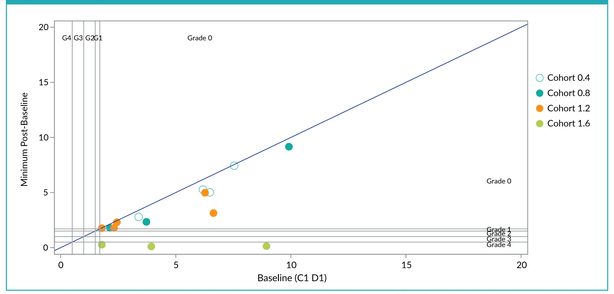
Variable	Cohort 1 0.4 mg/kg (N=3)	Cohort 2 0.8 mg/kg (N=3)	Cohort 3 1.2 mg/kg (N=6)	Cohort 4 1.6 mg/kg (N=3)	Total (N=15)
Females, n (%)	1 (33.3)	0	3 (50.0)	2 (66.7)	6 (40.0)
Age, years					
N	3	3	6	3	15
Mean (SD)	53.6 (13.45)	70.3 (5.13)	55.1 (9.31)	54.7 (18.9)	57.8 (12.71)
Median	60	69	54.5	48	58
Min, 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

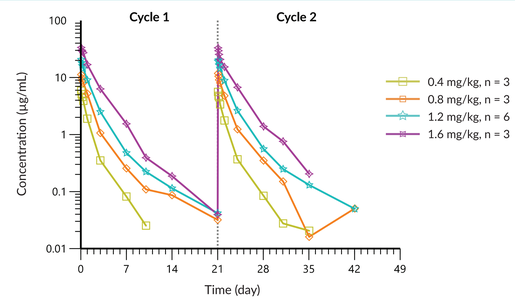


Solid diagonal represents no change; verical and horizontal lines are borders between CTCAE grades. Vertical distance from the diagonal represents magnitude of change; above the diagonal is an increase, below a decrease. For analytes where the reference range varied by age/sex, the lowest value was used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

Pharmacokinetics

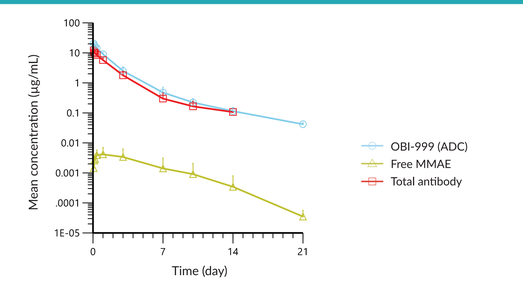
- The mean concentration-time profiles of OBI-999 at Cycle 1 and Cycle 2 are illustrated in **Figure 3.**

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

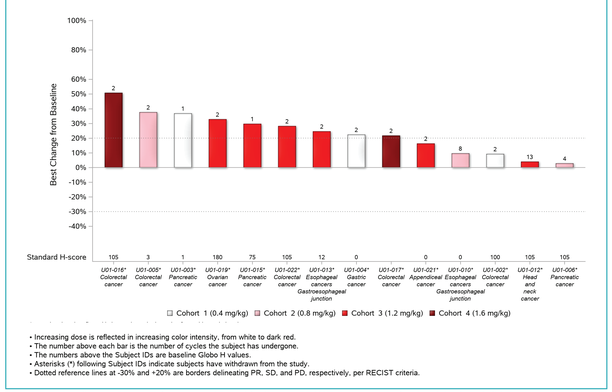


ADC, antibody-drug conjugate; MMAE, monomethyl auristatin E.

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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