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

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

PURPOSE OBI-999 is a novel antibody-drug conjugate comprising the Globo H–targeting antibody (OBI-888) linked to the cytotoxic payload monomethyl auristatin E. OBI-999 demonstrated excellent dose-dependent tumor growth inhibition in breast, gastric, and pancreatic cancer xenograft models as well as a lung cancer patient–derived xenograft model. We conducted a phase I study of OBI-999 monotherapy in patients with advanced cancer (ClinicalTrials.gov identifier: NCT04084366).

PATIENTS AND METHODS OBI-999 was administered intravenously at doses of 0.4, 0.8, 1.2, and 1.6 mg/kg every 21 days as part of a 3 + 3 trial design. Primary end points were the incidence of dose-limiting toxicities and adverse events and determination of the maximum tolerated dose (MTD)/recommended phase II dose.

RESULTS Fifteen adult patients were treated. OBI-999 was well tolerated up to 1.2 mg/kg, the maximum tolerated dose. The most common treatment-emergent adverse events were neutropenia and anemia. OBI-999 exhibited nonlinear pharmacokinetics at all doses, with lower clearance at higher doses. The three patients treated at the 1.6 mg/kg dose level developed grade 4 neutropenia during cycles 1 and 2. Five (33.3%) patients had stable disease (SD) including one patient with adenoid cystic carcinoma of the oropharynx with SD for 13 cycles and one patient with gastroesophageal junction adenocarcinoma with SD for eight cycles. OBI-999 was well tolerated; however, dose-dependent, noncumulative neutropenia was dose-limiting.

CONCLUSION The recommended phase II dose was determined to be 1.2 mg/kg once every 3 weeks. A phase II cohort-expansion study is now enrolling patients with pancreatic, colorectal, and other cancers expressing high levels of Globo H.

JCO Precis Oncol 7:e2200496. © 2023 by American Society of Clinical Oncology

INTRODUCTION

Globo H, a glycosphingolipid, is overexpressed in a variety of cancers of epithelial origin, including gastric, pancreatic, ovarian, endometrial, lung, prostate, and breast cancers, as shown by immunohistochemical analysis of tumor specimens,[1] as well as in esophageal, colon, and oral cancers, as shown by flow cytometric analysis of these cell lines.[2] Globo H shed by cancer cells appears to support carcinogenesis via protection from apoptosis, suppression of immune cell activity, and promotion of angiogenesis.[1] Globo H has also been observed in cancer stem cells, suggesting its potential role as a drug target for tumor eradication.[3] In certain normal tissues, Globo H is weakly expressed in apical epithelial cells at lumen borders, where access of the immune system is restricted.[1]

OBI-999, a novel humanized monoclonal immunoglobulin G1 antibody conjugated with monomethyl auristatin E (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.[4,5] MMAE is connected to the monoclonal antibody by a ThioBridge conjugate Val-Cit-PAB linker (Abzena, San Diego, CA), which is stable in extracellular fluid (Fig 1). Upon binding to the cancer cell antigen, OBI-999 is internalized and trafficked to lysosomes, where the linker is cleaved by cathepsin B, releasing the antimitotic MMAE. 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.[6]

In preclinical studies, OBI-999 was shown to bind specifically to Globo H–expressing tumor cells and become internalized and trafficked to endosomes (in approximately 2.5 hours) and then to lysosomes, where OBI-999 is processed to release the drug payload, MMAE. OBI-999 has shown low nanomolar cytotoxicity in tumor cells with high Globo H expression

ASSOCIATED CONTENT

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on December 7, 2022 and published at ascopubs.org/journal/po on January 26, 2023: DOI https://doi.org/10.1200/PO.22.00496

CONTEXT

Key Objective

Patients with advanced/metastatic solid tumors have a poor prognosis. Agents targeting tumor-associated antigens are needed. Globo H, overexpressed on many epithelial cancer cells with limited expression on healthy cells, is an ideal target for novel treatments. This phase I dose-escalation study of antibody-drug conjugate (ADC) OBI-999 evaluated the maximum tolerated dose and the recommended phase II dose to be used in the phase II cohort expansion study.

Knowledge Generated

Maximum tolerated dose was determined to be 1.2 mg/kg. The pharmacokinetic and adverse effect profiles, and the preliminary efficacy of this novel ADC have been established. Future studies will further elucidate the clinical value of OBI-999.

Relevance

A huge unmet need exists for treatments targeting novel antigens. Globo H, overexpressed on many solid tumors, is a viable target for antibody-based therapies. ADCs deliver high doses of cytotoxic payloads to target tumor cells, maximizing the dose while reducing the risk of adverse effects.

and exhibited a bystander killing effect on tumor cells with minimal Globo H expression.[7] Furthermore, after treatment, OBI-999 and free MMAE gradually accumulated in the tumor but decreased quickly in normal tissues in animal studies. Excellent dose-dependent tumor growth inhibition by OBI-999 was demonstrated in animal models using Globo H–expressing cancer cells.[7]

We report the initial results of a first-in-human, phase I study of OBI-999 in patients with advanced solid tumors. We evaluated the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of OBI-999 as a single agent.

PATIENTS AND METHODS

Eligibility

Patients were age ≥ 18 years and had histologically or cytologically confirmed advanced solid tumors that had been previously treated with standard-of-care therapy and their physicians had determined that such therapy was no longer effective, or patients had declined to receive further standard-of-care treatments. Other eligibility criteria are listed in the Data Supplement.

The study was conducted at The University of Texas MD Anderson Cancer Center and approved by its institutional review board. All patients provided written informed consent stating that they were aware of the investigational nature of the study. The study was conducted in accordance with ethical principles of the International Council on Harmonisation Guideline for Good Clinical Practice, the Declaration of Helsinki, and applicable local regulations, and was registered at ClinicalTrials.gov (NCT04084366).

Study Design

This was a phase I, first-in-human, open-label, sequential dose-escalation study (Fig 2). The primary end points were the incidence of dose-limiting toxicities (DLTs) and treatment-emergent adverse events (TEAEs) and determination of the maximum tolerated dose (MTD)/recommended phase II dose (RP2D). Secondary end points were characterization of the OBI-999 pharmacokinetic profile and tumor response as assessed by RECIST v1.1.

Treatment

OBI-999 was administered by intravenous infusion over 60 minutes. The starting dose of 0.4 mg/kg on day 1 of each 21-day cycle was based on toxicologic, pharmacologic, and pharmacokinetic data obtained in cynomolgus monkeys. A standard 3 + 3 dose-escalation design was used, and doses of 0.8, 1.2, and 1.6 mg/kg were also administered on day 1 of each 21-day cycle (Fig 2). The MTD was defined as the dose level at which < two of six patients experienced a DLT. The definition of DLT, reasons for treatment discontinuation, and patient monitoring are described in the Data Supplement.

Tumor response was measured using RECIST v1.1.[8] Stable disease lasting ≥ 4 months was considered clinical benefit.[9,10] Patients in whom tumor measurements increased by ≥ 20% from baseline or who developed new metastatic lesions were considered to have progressive disease and treatment was discontinued.

Pharmacokinetics, pharmacodynamics, biomarkers, and immunogenicity are described in the Data Supplement.

Statistical Analysis

The sample size in this study was determined empirically, and there was no formal hypothesis testing. Categorical and continuous data were summarized with frequencies and percentages or descriptive statistics, respectively. All patients who received ≥ 1 dose of OBI-999 (N = 15) were included in the safety analyses; the efficacy population included all patients in the safety population with a baseline assessment and ≥ 1 postbaseline tumor assessment (N = 14).

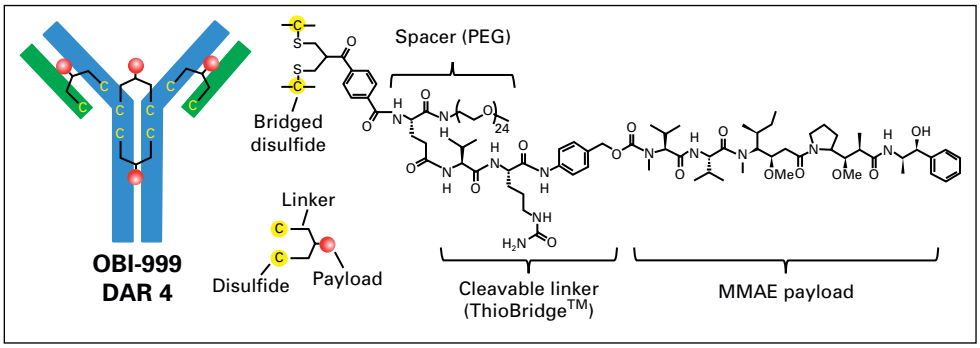

FIG 1. Structure of OBI-999. The cathepsin cleavable ThioBridge linker and MMAE payload are conjugated to cysteine residues on the parental antibody OBI-888 as illustrated. DAR, drug-to-antibody ratio; MMAE, monomethyl auristatin E; PEG, pegylated.

RESULTS

Patient Enrollment

From November 25, 2019, to March 19, 2021, 22 patients were screened, and 15 patients received ≥ 1 dose of OBI-999. The remaining seven patients were not treated because of inability to comply with protocol requirements (n = 1), comorbidities rendering them unsuitable for participation in the study (n = 3: partial bowel obstruction, n = 1; gastric bleeding, n = 1; extensive ascites/worsening performance status, n = 1), or consent withdrawal (n = 3).

Patient Demographics

Patient demographics and baseline characteristics are listed in Table 1. The median age was 58 years (range, 35-76 years). Patients were predominantly male (9/15; 60%), had an ECOG performance status of 1 (15/15; 100%), and had received ≥ 2 prior therapies (14/15; 93.3%). The most common tumor types were colorectal cancer (4/15; 26.7%), esophageal/gastroesophageal junction cancers (3/15; 20%), and pancreatic cancer (3/15; 20%). Fresh (n = 8) and archival (n = 7) tissue samples were used to assess Globo H expression. Five samples were from primary sites and 10 samples were from metastatic sites. Fifty percent of patients (7/14) had limited (H-score < 100) or zero Globo H expression and the mean Globo H H-score was 63.3. Detailed baseline data are included in Data Supplement.

Safety and Tolerability

The median duration of treatment with OBI-999 was 5.9 weeks (range, 2.4-39.9 weeks). The median number of

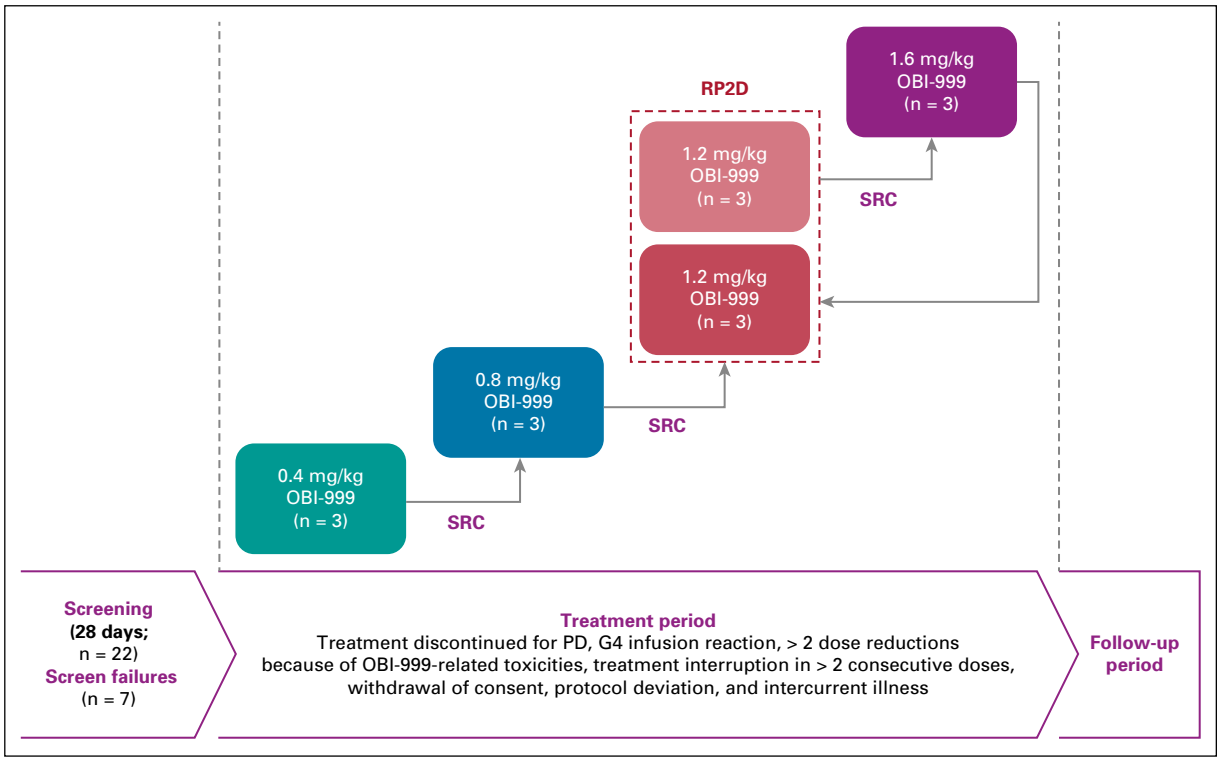

FIG 2. Study design and patient disposition. OBI-999 was administered at doses of 0.4, 0.8, 1.2, and 1.6 mg/kg on day 1 of each 21-day cycle, using escalating cohorts in a 3 + 3 design to identify the MTD and the RP2D. MTD, maximum tolerated dose; R2PD, recommended phase II dose; SRC, Safety Review Committee.

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, No. (%)	1 (33.3)	0	3 (50.0)	2 (66.7)	6 (40.0)
Age, years					
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 PS, No. (%)					
1	3 (100.0)	3 (100.0)	6 (100.0)	3 (100.0)	15 (100.0)
Previous systemic therapies, No. (%)					
1	0	1 (33.3)	0	0	1 (6.7)
2	1 (33.3)	0	4 (66.7)	0	5 (33.3)
≥ 3	2 (66.7)	2 (66.7)	2 (33.3)	3 (100)	9 (60.0)
Tumor type(s), No. (%)					
Colorectal cancer	2 (66.7)	1 (33.3)	0	2 (66.7)	5 (33.3)
Esophageal/GEJ cancers	0	1 (33.3)	1 (16.7)	1 (33.3)	3 (20.0)
Gastric cancer	0	0	1 (16.7)	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 (13.3)
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					
No.	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, No. (%)					
Negative (H-score ≤ 99)	2 (66.7)	2 (66.7)	3 (50.0)	0	7 (50.0)
Positive (H-score ≥ 100)	1 (33.3)	1 (33.3)	3 (50.0)	2 (66.7)	7 (50.0)
Insufficient sample	0	0	0	1	1

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; SD, standard deviation.

doses given was 2 (range, 1-13 doses). Of 15 patients, 6 (40%) experienced possibly or definitely drug-related AEs. Grade ≥ 3 TEAEs are listed in Table 2. TEAEs, drug-related AEs, and outcomes are described in the Data Supplement. No DLT was noted in the first three dose-escalation cohorts (three patients each).

In the fourth dose-escalation cohort (1.6 mg/kg; n = 3), the third patient (ID 018) developed grade 4 neutropenia after the first dose of OBI-999 that lasted for 11 days and constituted a DLT (see Dose-Limiting Toxicity and Maximum Tolerated Dose sections in the Data Supplement).

This patient (ID 018) had experienced a sinus infection that required hospitalization for 2 days (cycle 1 day 3 until cycle 1 day 5). Her absolute neutrophil count was 1,500/μL on cycle 1 day 5. The patient reported to the emergency center on cycle 1 day 12 with complaints of swollen glands and generalized pain. Testing was negative for COVID-19 disease upon arrival. On admission, her absolute neutrophil count was 340/μL and she was found to have acute kidney injury (creatinine, 1.64 mg/dL; uric acid, 11.7 mg/dL). Renal ultrasound was negative for hydronephrosis, and the nephrologists attributed the acute kidney injury to septic acute tubular necrosis and/or tumor lysis syndrome. A respiratory viral panel was negative. Urine culture was positive for normal site flora. Blood cultures were positive for *Staphylococcus epidermidis* skin flora. She was started on linezolid and Zosyn.

The patient's baseline characteristics and medical history were as follows: a woman in her forties with metastatic poorly differentiated adenocarcinoma of the gastroesophageal junction with extensive liver metastases who was heavily pretreated, and her disease had progressed after multiple prior treatments that included bleomycin, cisplatin, and etoposide combination therapy for 1 month followed by cisplatin, docetaxel, and 5FU combination therapy for

TABLE 2. Grade 3/4 TEAEs

TEAE[a], No. (%)	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)
Blood and lymphatic system disorders					
Neutropenia	0	0	0	3 (100)	3 (20.0)
Anemia	1 (25.0)	0	0	1 (33.3)	2 (13.3)
Investigations					
Blood creatinine level increased	0	0	0	1 (33.3)	1 (6.7)
Metabolism and nutrition disorders					
Hyperuricemia	0	0	0	1 (33.3)	1 (6.7)
Hypocalcemia	0	0	0	1 (33.3)	1 (6.7)
General disorders and administration site conditions					
Multiple organ dysfunction syndrome	0	0	0	1 (33.3)	1 (6.7)
Infections and infestations					
Septic shock	0	0	0	1 (33.3)	1 (6.7)
Renal and urinary disorders					
Acute kidney injury	0	0	0	1 (33.3)	1 (6.7)
Respiratory, thoracic, and mediastinal disorders					
Respiratory distress	0	0	0	1 (33.3)	1 (6.7)

Abbreviation: TEAE, treatment-emergent adverse event.

[a]If a patient reports multiple adverse events with the same preferred term, the patient is counted only once in that row. Includes adverse events possibly related or definitely related to the study drug.

13 months and paclitaxel and ramucirumab for 2 months. The patient had multiple comorbidities that included morbid obesity (weight 107.1 kg/height 163.5 cm), hypertension, sinus tachycardia, hepatic steatosis, and increased liver enzymes. According to the study protocol, OBI-999 was to be given at doses of 0.4, 0.8, 1.2, and 1.6 mg/kg (capping the calculation at a maximum of 100 kg) until the MTD and RP2D were determined. At the time of approval, the patient weighed 107.1 kg and she received 160 mg (1.5 mg/kg). The patient's renal insufficiency deteriorated to grade 4. During hospitalization, the patient was transferred to the intensive care unit (ICU) and declined dialysis. The development of renal insufficiency was considered to be secondary to the development of sepsis and it was not attributed to the study drug. The clinical deterioration of the patient combined with an increase in direct bilirubin (3.5 mg/dL) was attributed to progressive metastatic disease to the liver; notably, an ultrasound of the liver revealed hepatic steatosis with metastases. The patient died of progressive disease on cycle 1, day 20.

The other two patients treated in the 1.6 mg/kg cohort also developed grade 4 neutropenia (the first patient [ID 016] during cycle 1, and the second patient [ID 017] during cycle 2). Therefore, this dose level (1.6 mg/kg) was considered to have exceeded the MTD, and subsequently, three additional patients were treated at the lower dose level (1.2 mg/kg). No grade 4 neutropenia was noted in patients treated at dose levels of up to 1.2 mg/kg OBI-999.

Treatment-emergent anemia of grade ≥ 3 was noted in one patient (ID 022) treated in the 1.2 mg/kg cohort and in one patient (ID 018) treated in the 1.6 mg/kg cohort. However, the anemia was considered multifactorial; in addition to the study drug, it was also attributed to cancer and to the drawing of blood samples for routine testing/pharmacokinetic studies. Changes in neutrophil counts from baseline to the minimum value observed postbaseline are shown in Figure 3.

Thirteen (87%) of the 15 patients had ophthalmology assessments. No treatment-emergent ophthalmologic abnormalities were identified in follow-up assessments compared with baseline. All patients used topical lubrication throughout the study period.

DLT

The patient (ID 018) who developed grade 4 neutropenia lasting for 11 days after the first dose of OBI-999 had normal baseline neutrophil counts. This event was attributed to OBI-999 and was considered a DLT (see Safety and Tolerability). No other DLTs were noted.

MTD

OBI-999 administered at 1.2 mg/kg on day 1 of a 21-day cycle was well tolerated, and this dose was determined to be the MTD and the RP2D.

Pharmacokinetics

The mean concentration-time profiles of OBI-999 during cycle 1 and cycle 2 are illustrated in the Data Supplement.

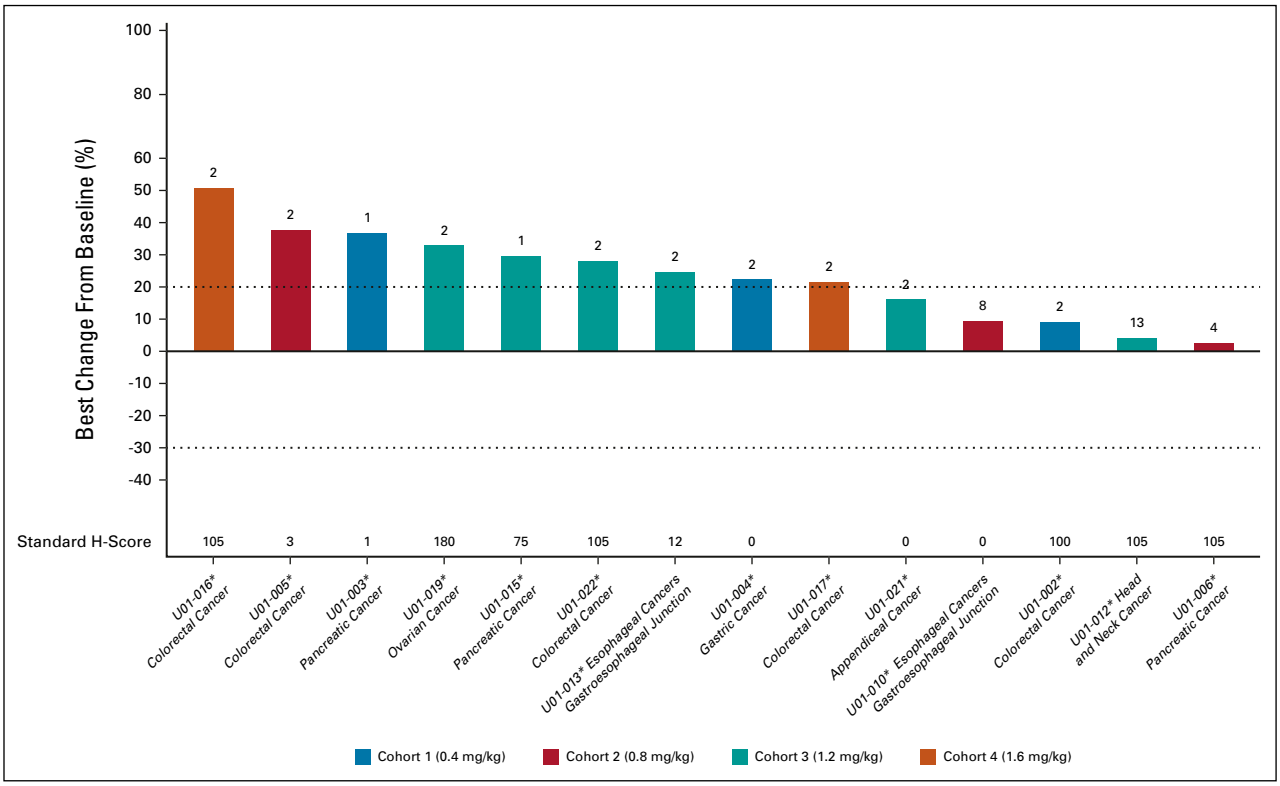

FIG 3. Antitumor activity at postbaseline scans in patients treated with OBI-999. The number above each bar is the number of cycles of treatment received by each patient. Baseline Globo H expression is shown as the H-score above each patient ID number. Dotted reference lines at –30% and +20% are borders delineating partial response, stable disease, and progressive disease, respectively, per RECIST criteria.

OBI-999 exposure following the first dose generally increased with increasing dose, and no accumulation was observed from cycle 1 to cycle 2 across all doses studied. The mean concentration-time profile of total antibody (TAb), ADC, and unconjugated MMAE after the first cycle of OBI-999 at the RP2D (1.2 mg/kg on day 1 of each 21-day cycle) is illustrated in the Data Supplement. Peak TAb and OBI-999 concentrations typically occurred immediately after the infusion. OBI-999 concentrations declined in a manner similar to TAb concentrations and remained detectable at later time points. Mean pharmacokinetic parameters are summarized using descriptive statistics in Table 3.

OBI-999 and TAb exhibited nonlinear pharmacokinetics; specifically, their clearance rates decreased with increasing dose at dose levels ranging from 0.4 mg/kg to 1.2 mg/kg and appeared to approach linearity at higher doses (1.2-1.6 mg/kg). For unconjugated MMAE, the time to reach the peak concentration ranged from 0.38 days to 7 days after infusion. The variability of the maximum concentration and area under the concentration-time curve was rather high across patients. The mean terminal half-life of unconjugated MMAE was similar to that of ADC, with mean values ranging from 2.66 days to 3.51 days.

The incidence of antidrug antibodies postbaseline to OBI-999 was 13.3% (2/15 evaluable patients) across all dosing groups.

Pharmacodynamics

Although Globo H expression was not a requirement for entry in the study, tissue samples (either primary or metastatic sites) were acquired from all 15 patients and analyzed for Globo H expression. Tumor tissue from one patient had < 100 viable tumor cells for analysis, and therefore, a Globo H H-score could not be determined. The Globo H H-scores for each evaluable patient are shown across the x axis in Figure 3. Overall, the median Globo H H-score was 87.5 (range, 0-180) across 14 patients with an adequate tissue sample to enable a Globo H assessment. Of these patients, 6/14 (43%) had an H-score of < 15 and 7/14 (50%) had an H-score of ≥ 100. There was no significant difference in Globo H expression between biopsy samples from primary sites and metastatic sites (Wilcoxon-Mann-Whitney test, P value = .636).

Antitumor Activity

Overall, 14 patients were evaluable for tumor response, with the best response being SD in five patients (36%). One patient with adenoid cystic carcinoma of the oropharynx previously treated with paclitaxel, radiotherapy, cisplatin, doxorubicin, and cyclophosphamide who received 1.2 mg/kg OBI-999 had SD (best RECIST response, 3% increase in the sum of the longest diameter of the tumor) and remained on

TABLE 3. Mean Pharmacokinetic Parameters of Total Antibody, OBI-999, and Unconjugated MMAE Following First Cycle of OBI-999

Dose	No.	T_{max}, day (SD)	C_{max}, μg/mL (SD)	AUC_{inf}, day × μg/mL (SD)	$T_{1/2}$, day (SD)	CL, L/day (SD)	Vd_{ss}, L (SD)
Total antibody, mg/kg							
0.4	3	0.06 (0.00)	3.0 (0.2)	2.9 (0.2)	0.72 (0.08)	10.6 (4.6)	10.8 (3.9)
0.8	3	0.06 (0.00)	6.7 (1.3)	9.2 (4.2)	1.37 (0.86)	7.5 (3.7)	10.9 (1.1)
1.2	6	0.06 (0.00)	12.1 (2.8)	19.1 (3.5)	1.79 (0.82)	4.2 (0.9)	9.0 (1.6)
1.6	3	0.06 (0.00)	22.3 (4.8)	40.9 (16.3)	1.96 (0.72)	4.0 (1.5)	9.5 (1.5)
OBI-999, mg/kg							
0.4	3	0.06 (0.00)	5.9 (0.7)	6.1 (1.1)	1.79 (0.53)	5.3 (2.5)	8.2 (4.0)
0.8	3	0.06 (0.00)	11.3 (2.4)	16.0 (7.0)	3.92 (1.58)	4.2 (2.0)	8.0 (0.4)
1.2	6	0.06 (0.00)	20.6 (2.8)	30.5 (4.6)	3.37 (1.43)	2.7 (0.7)	6.4 (1.5)
1.6	3	0.06 (0.00)	33.7 (4.7)	60.9 (24.2)	2.03 (0.67)	2.6 (0.8)	5.7 (1.2)
MMAE, mg/kg							
0.4	3	0.79 (0.36)	0.0027 (0.0015)	0.0128 (0.0085)	2.66 (0.76)	—	—
0.8	3	0.38 (0.00)	0.0039 (0.0039)	0.0167 (0.0115)	3.51 (0.02)	—	—
1.2	6	0.69 (0.34)	0.0046 (0.0026)	0.0264 (0.0227)	2.88 (0.57)	—	—
1.6	3	2.79 (3.66)	0.0076 (0.0060)	0.0574 (0.0414)	2.77 (1.30)	—	—

Abbreviations: AUC_{inf}, area under the concentration-time curve from time 0 to infinity; CL, clearance; C_{max}, maximum concentration; MMAE, monomethyl auristatin E; SD, standard deviation; $T_{1/2}$, half-life; T_{max}, maximum time; Vd_{ss}, volume of distribution at steady state.

study for 13 cycles. Another patient with gastroesophageal junction adenocarcinoma who received the 0.8 mg/kg OBI-999 dose experienced SD for eight cycles. In the remaining three patients, one with pancreatic cancer had SD for four cycles and two patients (one with colorectal cancer and one with appendiceal cancer) had SD for two cycles. The remaining 9 (64%) patients had progressive disease. Best tumor responses are shown for each patient in Figure 3. Of the 14 patients evaluable for tumor response, the Globo H H-score was assessed in 13 patients (one patient had inadequate tissue for analysis). The five patients with SD had Globo H H-scores of 105, 105, 100, 0, and 0. In the remaining eight patients with progressive disease, the Globo H H-scores were 0, 1, 3, 12, 75, 105, 105, and 180.

Patient Outcomes

All 15 patients discontinued the study. The primary reason for treatment discontinuation was disease progression (by RECIST v1.1), which was reported for 11/15 (73.3%) patients; 3/15 (20%) discontinued treatment owing to clinical progression, and 1/15 (6.7%) withdrew consent.

DISCUSSION

In this phase I, first-in-human, open-label, sequential dose-escalation study of OBI-999, a Globo H–targeted ADC, we identified 1.2 mg/kg administered on day 1 of 21-day cycles as the MTD/RP2D. OBI-999 exhibited nonlinear pharmacokinetics 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 approximately 0.1% that of ADC. However, disproportionately high MMAE exposure in the 1.6 mg/kg cohort was observed.

The most common TEAEs throughout the duration of the study were neutropenia and anemia. The majority of TEAEs were mild or moderate in severity (Data Supplement). At the 1.2 mg/kg dose level, OBI-999 was generally safe and well tolerated. Three of three patients treated at the 1.6 mg/kg dose level experienced grade 4 neutropenia. Of those patients, only one patient was considered to have experienced a DLT event; the remaining two patients treated at the 1.6 mg/kg dose level experienced grade 4 neutropenia for fewer than 7 days and therefore did not meet the criteria for a DLT. Nevertheless, the MTD/RP2D was determined to be 1.2 mg/kg.

In contrast to approved ADCs with MMAE as a payload, in which peripheral sensory neuropathy is a common TEAE,[11,12] no peripheral neuropathy or deterioration of pre-existing peripheral neuropathy was observed in this study. Ophthalmologic assessments at baseline and during the study showed there were no clinically significant ocular events.

A comparison of our results with data from published studies of patients treated with other FDA-approved ADCs is shown in the Data Supplement. Among these studies, the most commonly reported AEs (≥ 20%) were neutropenia, anemia, and thrombocytopenia. Disease stabilization and objective responses were noted in selected studies.

It is encouraging that five patients experienced SD despite limited Globo H expression, including one patient with adenoid cystic carcinoma of the oropharynx treated at a dose level of 1.2 mg/kg OBI-999 who had a 3% increase in tumor measurements by RECIST v1.1 and remained on study for 13 cycles and one patient with esophageal adenocarcinoma who received 0.8 mg/kg OBI-999 and remained on study for eight cycles (Data Supplement). Globo H testing was not required

for study entry, and most patients had no or limited Globo H expression, which might, in part, explain the lack of objective response to OBI-999 in this study. Three of five patients with SD had a Globo H H-score ≥ 100. Of the remaining eight evaluable patients with progressive disease, three patients had a Globo H H-score ≥ 100 (Fig 3). These results should be interpreted with caution because of the small number of patients and the use of archival tissue to assess the score in some of these patients. One patient (ID 010) whose Globo H H-score was 0 had SD by RECIST and remained on study for eight cycles; however, the tumor tissue was obtained before his last oxaliplatin and 5-FU combination therapy. The patient had previously received radiation therapy, which has been shown to affect antigen expression.[13] There are no published data on the impact of chemotherapy on Globo H expression.

To further confirm the antitumor activity of OBI-999, prescreening of Globo H expression in tumor samples before OBI-999 administration is warranted in future studies.

In conclusion, OBI-999 as monotherapy was generally safe and well tolerated. The MTD/RP2D was 1.2 mg/kg administered on day 1 of a 21-day cycle. OBI-999 exhibited a nonlinear pharmacokinetic profile with lower clearance at higher doses. Disease stabilization was noted in several patients with advanced metastatic cancer who had previously experienced progressive disease on standard treatments. Because Globo H is overexpressed in approximately 50% of pancreatic tumors[7] and patients with this disease need additional treatment options, we are conducting a phase II study of OBI-999 in patients with advanced/metastatic pancreatic cancer, as well as with hepatocellular carcinoma, and other epithelial carcinomas. Patients with pancreatic cancer are eligible if their disease has progressed after surgery and/or systemic chemotherapy and they have no standard-of-care options. Strong Globo H expression as determined by our validated immunohistochemical assay is required for entry into the study (ClinicalTrials.gov identifier: NCT04084366).

AFFILIATIONS

[1]Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX
[2]OBI Pharma Inc, Taipei City, Taiwan
[3]OBI Pharma USA, Inc, San Diego, CA

CORRESPONDING AUTHOR

Apostolia Maria Tsimberidou, MD, The University of Texas MD Anderson Cancer Center, Department of Investigational Cancer Therapeutics, Unit 455, 1515 Holcombe Boulevard, Houston, TX 77030; e-mail: atsimber@mdanderson.org.

PRIOR PRESENTATION

The results of this clinical trial were presented as a poster at the ASCO Annual Meeting, Chicago, IL, June 3-7, 2022.

SUPPORT

Supported by OBI Pharma, Inc (Taipei, Taiwan).

AUTHOR CONTRIBUTIONS

Conception and design: Apostolia Maria Tsimberidou, Tillman E. Pearce
Administrative support: Apostolia Maria Tsimberidou
Provision of study materials or patients: Apostolia Maria Tsimberidou, Jennifer Beck
Collection and assembly of data: Apostolia Maria Tsimberidou, Henry Hiep Vo, Jennifer Beck, Tillman E. Pearce
Data analysis and interpretation: Apostolia Maria Tsimberidou, Henry Hiep Vo, Chi-Sheng Shia, Pei Hsu, Tillman E. Pearce
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/po/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Apostolia Maria Tsimberidou
Consulting or Advisory Role: Vincerx Pharma, Diaccurate, NEX-I, BrYet, Bioeclipse, Macrogenic
Research Funding: IMMATICS (Inst), Karus Therapeutics (Inst), OBI Pharma (Inst), Tempus (Inst), Parker Institute for Cancer Immunotherapy (Inst), Agenus (Inst), Novocure (Inst), Tvardi Therapeutics (Inst)

Pei Hsu
Employment: OBI Pharma

Tillman E. Pearce
Employment: OBI Pharma, Abivax, InterVenn Biosciences
Leadership: OBI Pharma, CureBiotech, InterVenn Biosciences
Stock and Other Ownership Interests: OBI Pharma
Travel, Accommodations, Expenses: OBI Pharma

No other potential conflicts of interest were reported.

ACKNOWLEDGMENT

The authors thank the investigators, coordinators, and study site personnel, as well as the patients and their families for participation in this study. The authors also acknowledge Leslie Chu, PhD, whose assistance in writing this manuscript was funded by OBI Pharma USA, Inc.

REFERENCES

1. Zhang S, Cordon-Cardo C, Zhang HS, et al. Selection of tumor antigens as targets for immune attack using immunohistochemistry: I. Focus on gangliosides. Int J Cancer 73:42-49, 1997
2. Lou YW, Wang PY, Yeh SC, et al. Stage-specific embryonic antigen-4 as a potential therapeutic target in glioblastoma multiforme and other cancers. Proc Natl Acad Sci USA 111:2482-2487, 2014
3. Chang WW, Lee CH, Lee P, et al. Expression of Globo H and SSEA3 in breast cancer stem cells and the involvement of fucosyl transferases 1 and 2 in Globo H synthesis. Proc Natl Acad Sci USA 105:11667-11672, 2008
4. Francisco JA, Cerveny CG, Meyer DL, et al. cAC10-vcMMAE, an anti-CD30-monomethyl auristatin E conjugate with potent and selective antitumor activity. Blood 102:1458-1465, 2003
5. Doronina SO, Toki BE, Torgov MY, et al. Development of potent monoclonal antibody auristatin conjugates for cancer therapy. Nat Biotechnol 21:778-784, 2003
6. Alley SC, Okeley NM, Senter PD. Antibody–drug conjugates: Targeted drug delivery for cancer. Curr Opin Chem Biol 14:529-537, 2010
7. Yang MC, Shia CS, Li WF, et al. Preclinical studies of OBI-999: A novel Globo H–targeting antibody–drug conjugate. Mol Cancer Ther 20:1121-1132, 2021
8. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45:228-247, 2009
9. Tolcher AW: Stable disease is a valid end point in clinical trials. Cancer J 15:374-378, 2009
10. Villaruz LC, Socinski MA: The clinical viewpoint: Definitions, limitations of RECIST, practical considerations of measurement. Clin Cancer Res 19:2629-2636, 2013
11. Rosenberg J Sridhar SS, Zhang J, et al. EV-101: A phase I study of single-agent enfortumab vedotin in patients with nectin-4-positive solid tumors, including metastatic urothelial carcinoma. J Clin Oncol 38:1041-1049, 2020
12. Younes A, Bartlett NL, Leonard JP, et al. Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. N Engl J Med 363:1812-1821, 2010
13. Spiotto M, Fu Y-X, Weichselbaum RR: The intersection of radiotherapy and immunotherapy: Mechanisms and clinical implications. Sci Immunol 1:EAAG1266, 2016