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Daniel P Petrylak
Yale University
Joel Picus
Washington University School of Medicine in St. Louis
et al.

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Phase I Dose-Escalation Study of the Safety and Pharmacokinetics of AGS15E Monotherapy in Patients with Metastatic Urothelial Carcinoma

Daniel P. Petrylak[1], Bernhard J. Eigl[2], Saby George[3], Elisabeth I. Heath[4], Sebastien J. Hotte[5], David D. Chism[6], Lisle M. Nabell[7], Joel Picus[8], Susanna Y. Cheng[9], Leonard J. Appleman[10], Guru P. Sonpavde[11,12], Alicia K. Morgans[13], Pourya Pourhosseini[14], Ruishan Wu[15], Laura Standley[15], Ruslan Croitoru[15], and Evan Y. Yu[16]

ABSTRACT

Purpose: Effective treatment of locally advanced or metastatic urothelial carcinoma (mUC) remains an unmet need. Antibody–drug conjugates (ADC) providing targeted drug delivery have shown antitumor activity in this setting. AGS15E is an investigational ADC that delivers the cytotoxic drug monomethyl auristatin E to cells expressing SLITRK6, a UC-associated antigen.

Patients and Methods: This was a multicenter, single-arm, phase I dose-escalation and expansion trial of AGS15E in patients with mUC (NCT01963052). During dose escalation, AGS15E was administered intravenously at six levels (0.10, 0.25, 0.50, 0.75, 1.00, 1.25 mg/kg), employing a continual reassessment method to determine dose-limiting toxicities (DLT) and the recommended phase II dose (RP2D) for the dose-expansion cohort. The primary objective was to evaluate the safety and pharmacokinetics of AGS15E in patients with and without prior chemotherapy and with prior checkpoint inhibitor (CPI) therapy. Best overall response was also examined.

Results: Ninety-three patients were recruited, including 33 patients previously treated with CPI. The most common treatment-emergent adverse events were fatigue (54.8%), nausea (37.6%), and decreased appetite (35.5%). Peripheral neuropathy and ocular toxicities occurred at doses of ≥0.75 mg/kg. AGS15E increased in a dose-proportional manner after single- and multiple-dose administration; accumulation was low. Five DLT occurred from 0.50 to 1.25 mg/kg. The RP2D was assessed at 1.00 mg/kg; the objective response rate (ORR) was 35.7% at this dose level. The ORR in the total population and CPI-exposed subgroup were 18.3% and 27.3%, respectively.

Conclusions: DLT with AGS15E were observed at 0.75, 1.00, and 1.25 mg/kg, with an RP2D of 1.00 mg/kg being determined.

Introduction

Bladder cancer is the 10th most frequently diagnosed cancer worldwide (1, 2), with urothelial carcinoma accounting for approximately 90% of bladder cancer cases. Although the all-stage 5-year overall survival (OS) rate for urothelial carcinoma is approximately 80% (1), the 5-year OS rate for metastatic urothelial carcinoma (mUC) is approximately 5%.

The standard-of-care, first-line treatments for patients with advanced or mUC are cisplatin-based combinations (2). In patients who are ineligible or unfit for cisplatin, regimens such as carboplatin and gemcitabine are available (2, 3), as well as the recent accelerated approval of the combination of enfortumab vedotin (EV) plus pembrolizumab (4, 5). Objective response rates (ORR) of 40% to 60% and disease control rates (DCR) close to 80% are seen with first-line chemotherapy in mUC (2). However, due to chemotherapy resistance, long-term survival is poor in this setting (2, 6).

Patients who are ineligible for cisplatin-based chemotherapy, or whose disease progresses on platinum-containing chemotherapy, may subsequently receive checkpoint inhibitors (CPI), including three that are currently approved by the FDA for the treatment of locally advanced or mUC in patients progressing during or after platinum-containing chemotherapy (pembrolizumab, nivolumab, and avelumab; ref 1). The combination of CPI with platinum-based chemotherapy does not appear to provide a survival benefit in these patients, whereas the use of maintenance CPI therapy in responding patients improves survival (7, 8).

Effective treatment of locally advanced or mUC, beyond first- or second-line therapy, remains an unmet need. The lack of effective therapies for advanced urothelial carcinoma has spurred investigation of antibody–drug conjugates (ADC) that enable targeted drug delivery. The FDA has approved the ADC EV and sacituzumab govitecan (SG) for patients with locally advanced or mUC previously treated with platinum-based chemotherapy and CPI (5, 9, 10); EV is also approved for cisplatin-ineligible patients after prior systemic therapy (5).

[1]Yale School of Medicine, New Haven, Connecticut. [2]BC Cancer, Vancouver, British Columbia, Canada. [3]Roswell Park Cancer Institute, Buffalo, New York. [4]Karmanos Cancer Institute, Detroit, Michigan. [5]Department of Oncology, McMaster University, Hamilton, Ontario, Canada. [6]Thompson Cancer Survival Center, Knoxville, Tennessee. [7]O'Neal Comprehensive Cancer Center, Birmingham, Alabama. [8]Siteman Cancer Center, Washington University School of Medicine, St. Louis, Missouri. [9]Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada. [10]UPMC Hillman Cancer Center, Pittsburgh, Pennsylvania. [11]Advent Health Cancer Institute, Orlando, Florida. [12]University of Central Florida, Orlando, Florida. [13]Dana-Farber Cancer Institute, Boston, Massachusetts. [14]Seagen, Woodinville, Washington. [15]Astellas Pharma Global Development, Inc., Northbrook, Illinois. [16]Division of Medical Oncology, Seattle Cancer Care Alliance, Seattle, Washington.

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Corresponding Authors: Daniel P. Petrylak, Yale School of Medicine, 35 Park Street, Ste North Pavilion 4, New Haven, CT 06511. E-mail: daniel.petrylak@yale.edu; and Evan Y. Yu, Fred Hutchinson Cancer Center and University of Washington, 825 Eastlake Avenue East, Seattle, WA 98109. E-mail: evanyu@uw.edu

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Translational Relevance

Despite the introduction of checkpoint inhibitor (CPI) therapies in recent years, patients with locally advanced or metastatic urothelial carcinoma (mUC) have limited treatment options and poor outcomes. Antibody–drug conjugates (ADC) such as enfortumab vedotin and sacituzumab govitecan have shown promising outcomes in mUC. AGS15E is an investigational ADC that delivers the cytotoxic drug monomethyl auristatin E to cells expressing SLITRK6, a highly expressed urothelial carcinoma tumor antigen, regardless of disease stage. This multicenter, phase I trial investigated the safety, pharmacokinetics, and antitumor activity of AGS15E in mUC, to address the unmet need in this population. The safety profile of AGS15E was manageable and similar to those of other ADC. Antitumor responses were observed in the overall study population as well as in patients with prior CPI exposure. As the first ADC targeting SLITRK6 in clinical development, AGS15E demonstrated antitumor activity and a safety profile consistent with other ADC.

AGS15E is an investigational ADC that delivers the cytotoxic drug monomethyl auristatin E (MMAE) to cells expressing SLITRK6, a neuronal transmembrane protein and tumor antigen. SLITRK6 has limited expression in normal tissues and high expression in both urothelial carcinoma (90%) and mUC (100%), regardless of tumor stage, making it a suitable target in this setting (11). Upon binding to SLITRK6, the ADC is internalized and the valine-citrulline linker undergoes proteolytic cleavage by cathepsin B. This releases the small molecule microtubule-disrupting agent, MMAE, inside the cell, disrupting tubulin polymerization and leading to apoptosis (11, 12). Preclinical toxicology studies were conducted in monkeys and rats to determine the starting dose of AGS15E (data on file). A no observed effect level of 1.00 mg/kg AGS15E was determined in monkeys, and a no observed adverse effect level (NOAEL) of 1.00 mg/kg was observed in female rats. NOAEL could not be determined in male rats due to nonreversible testicular changes. Following ICH S9 guidance for anticancer pharmaceuticals, one-sixth of the highest nonseverely toxic dose of 1.00 mg/kg equates to 0.17 mg/kg, approximating the selected starting dose of 0.10 mg/kg in this study. Here, we report the results of a phase I, dose-escalation and expansion study, conducted to examine the safety and pharmacokinetic (PK) profile of AGS15E in patients with mUC.

Patients and Methods

Study design

This was a single-arm, open-label, phase I, dose-escalation adaptive trial employing a continual reassessment method (CRM), followed by expansion cohorts (NCT01963052). Patients with mUC were recruited at 11 study centers in North America (eight United States, three Canada) into three distinct cohorts (parts A, B, and C). The study consisted of a dose-escalation and a dose-expansion phase, the escalation phase determining the recommended phase II dose (RP2D) to be carried forward into the expansion phase. Patients from part A took part in the escalation phase, where sequential dose-escalation using a CRM determined the preliminary RP2D and the maximum tolerated dose (MTD). Patients from parts A, B, and C took part in the dose-expansion phase that evaluated the antitumor activity and safety of AGS15E at a single-dose level. Part B was a dose-expansion cohort where patients were enrolled below the RP2D, and part C (added after a protocol amendment) was an additional dose-expansion cohort that enrolled patients who had received previous CPI therapy in the metastatic setting.

Patients ≥18 years with histologically confirmed transitional cell carcinoma of the urothelium [cancer of the bladder, renal pelvis, ureter, or urethra, with measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1] were enrolled; patients with urothelial carcinoma with squamous differentiation or mixed cell types were also eligible. Additional inclusion criteria by study cohort are shown in Supplementary Table S1. Exclusion criteria across all cohorts included any preexisting grade ≥2 sensory or motor neuropathy or uncontrolled central nervous system metastases and treatment with any anticancer therapy within 14 days prior to the first dose of study drug.

All patients received a single 30-minute intravenous infusion of AGS15E once a week for 3 weeks (days 1, 8, and 15) of every 4-week cycle, until disease progression, treatment intolerance, or another per-protocol discontinuation criterion was met. The dose-limiting toxicity (DLT)-evaluable population consisted of patients who had completed study assessments through predose cycle 2, day 1 or experienced a DLT during the review period. Patients in the expansion phase were not included in the DLT-evaluable population.

In part A, patients were sequentially assigned to one of six dose levels (0.10, 0.25, 0.50, 0.75, 1.00, 1.25 mg/kg) until the first patient experienced a grade ≥2 adverse event (AE) related to the study drug during cycle 1. Two additional patients were enrolled at this dose if a grade ≥2 AE occurred during cycle 1; the dose was escalated if no DLT was observed after the enrollment of three patients at a given dose level. After observation of the first DLT, dose assignment was guided by CRM. In part B, three patients were enrolled at the dose below the preliminary RP2D. Following completion of the 4-week safety review for these patients, a data review team meeting was held to determine if the dose could be escalated. Patients in part C received the preliminary RP2D dose determined in part A.

The study was conducted in compliance with the protocol approved by an institutional review board (IRB) or independent ethics committee and in accordance with International Conference on Harmonisation on Good Clinical Practice and all applicable laws and regulations, including the Declaration of Helsinki. An IRB-approved written informed consent was signed and dated by each patient prior to participation in the study.

Study endpoints and assessments

The primary objective was the evaluation of the safety and PK of AGS15E in patients with mUC. The primary safety endpoint was the incidence of AE including DLT, grade 3 and 4 AE, treatment-related AE, serious AE, and AE requiring discontinuation of AGS15E. All AE were graded using NCI Common Terminology Criteria for Adverse Events (CTCAE; v4.03). Primary PK endpoints included assessments for total antibody (TAb) levels, AGS15E, and MMAE. Samples were collected during the treatment period and at the safety follow-up, and blood was collected predose for each additional cycle. Serum concentrations of AGS15E (ADC) and TAb were measured using a validated ELISA, with a quantitative range of 2.5 to 40.0 ng/mL. The plasma concentrations of MMAE were determined using a validated liquid chromatography with a tandem mass spectrometry (LC-MS/MS) assay with a concentration range of 5 to 2,000 pg/mL. Antibodies to AGS15E were detected using an electrochemiluminescence assay. All patients were screened for antidrug antibody (ADA) formation, and any patient with an antibody titer >4 underwent a confirmatory assay to determine ADA formation to the unconjugated monoclonal antibody (AGS15C) and the ADC (AGS15E). SLITRK6

expression levels were measured in archival tumor tissue at baseline. Secondary endpoints included the incidence of a tumor response as measured by best overall response (BOR). This was defined as either a complete or partial response (CR/PR) per RECIST v1.1, confirmed ≥28 days later per investigator's assessment and central review. Other response parameters included ORR, DCR [% of patients who experienced a best response of CR, PR, or stable disease (including patients with unconfirmed CR or PR classified as stable disease)], progression-free survival (PFS), and duration of response (DOR). Assessment of disease progression was performed every 8 weeks (±7 days) by RECIST v1.1 and included both local and central review; if CR or PR occurred per local review, a confirmatory scan was performed ≥4 weeks since the previous scan, preferably at week 5.

Clinical laboratory evaluations, electrocardiograms, and vital signs assessments were carried out according to the assessment schedule. On days of AGS15E administration, vital signs were taken within 30 minutes before the infusion, upon completion of the infusion, and at 30 and 60 minutes postinfusion. As ocular AE can occur with tubulin inhibitor-containing ADC, eye examinations were also carried out at baseline and during cycle 2.

Statistical analyses

The planned sample size for this study was up to 155 patients. Because this was the first-in-human study of AGS15E, no prior estimate of the underlying DLT rate existed. The MTD (RP2D) by the CRM method was defined as the dose with a DLT rate of 0.2. On the basis of existing toxicology data and study design simulations conducted to estimate the MTD, it was determined if the true MTD was 0.50 mg/kg with this dosing frequency, the probability of correctly estimating the MTD with an enrollment of 45 patients would be 65% based on the Bayesian CRM design. Additional patients could be enrolled to further evaluate the first cycle and multicycle toxicity profile of AGS15E, resulting in a total of approximately 80 patients in part A. No sample size or power calculations were performed for part B and part C. Baseline characteristics, safety, and antitumor activity were assessed in the full analysis set (FAS), which included all patients who received ≥ one dose of AGS15E. PFS and DOR were summarized using descriptive statistics and the Kaplan-Meier method with 95% CI. Summary statistics were employed to capture BOR, ORR, and DCR. The PK analysis set included patients who received AGS15E and had ≥ one blood sample assayed for AGS15E serum/plasma concentrations. PK data were analyzed using noncompartmental methods and descriptive statistics; mean plasma concentration-over-time plots were generated. All statistical analyses were performed using SAS (v9.3 or later; SAS Institute, Inc., Cary).

Data availability

Researchers may request access to anonymized participant level data, trial level data and protocols from Astellas sponsored clinical trials at www.clinicalstudydatarequest.com. For the Astellas criteria on data sharing see: https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx

To request trial data, please visit https://www.clinicalstudydatarequest.com/SearchAllPostings.aspx and select "click here to submit an enquiry." Astellas will review all requests on a case-by-case basis.

Results

Patient population

The total study population included 93 patients (**Table 1**; Supplementary Table S2), including 33 patients who had previous CPI exposure and one patient who was ineligible for cisplatin-containing treatment. Due to a protocol deviation, the one patient enrolled in part B received the RP2D (instead of one dose level below the RP2D, per protocol) and was analyzed in the 1.00-mg/kg dose cohort. Most patients were male (79.6%), and the median age was 67.0 years (range, 30–82 years; **Table 1**). The most common sites of metastases were the lymph nodes (66.7%), lungs (39.8%), and liver (29.0%). A large proportion of patients had high (H-score 201–300; $n = 39/93$, 41.9%) or moderate (H-score 101–200; $n = 23/93$, 24.7%) SLITRK6 expression levels, as measured by H-score (Supplementary Table S3).

Median treatment duration was 16.4 weeks (range, 2–138) in the total study population, with a median of 10 infusions per patient (range, 1–58).

Safety and tolerability

During the escalation phase, 47 patients from part A received AGS15E at doses of 0.10 mg/kg ($n = 1$, 2.1%), 0.25 mg/kg ($n = 3$, 6.4%), 0.50 mg/kg ($n = 8$, 17.0%), 0.75 mg/kg ($n = 14$, 29.8%), 1.00 mg/kg ($n = 14$, 29.8%), and 1.25 mg/kg ($n = 7$, 14.9%). Of the 44 patients who were evaluable for DLT, 11.4% (5/44) experienced a DLT during dose escalation at 0.50-mg/kg ($n = 1$), 0.75-mg/kg ($n = 2$), and 1.25-mg/kg ($n = 2$) dose levels. Among DLT-evaluable patients, 12 had previous CPI exposure, of whom one patient from the 1.25-mg/kg dose group experienced a DLT (neutropenia). Mean treatment duration was 21 weeks, with a median of nine infusions per patient (range, 1–48) for patients in part A. Both the MTD determined by the data review team, and the RP2D determined during the escalation phase were 1.00 mg/kg. In the expansion phase, 46 patients from parts A ($n = 32$), B ($n = 1$), and C ($n = 13$) received the RP2D of 1.00 mg/kg AGS15E.

The most common treatment-emergent AE (TEAE) across the total study population were fatigue (54.8%, 51/93), nausea (37.6%, 35/93) decreased appetite (35.5%, 33/93), constipation (31.2%, 29/93), diarrhea (30.1%, 28/93), dysgeusia (25.8%, 24/93), vomiting (23.7%, 22/93), and urinary tract infection (20.4%, 19/93; **Fig. 1**, **Table 2**; Supplementary Table S4). Grades 1, 2, and 3 TEAE were experienced by 5.4% (5/93), 32.3% (30/93), and 35.5% (33/93) of patients, respectively. TEAE of severity grade 3 and above in ≥5% of patients in the expansion cohort included anemia ($n = 5$, 5.4%) and fatigue ($n = 5$, 5.4%). The most common primary reason for treatment discontinuation was disease progression (as per RECIST v1.1), seen in 61.3% ($n = 57/93$) of patients (Supplementary Fig. S1). A total of 78.3% (73/93) of patients completed the safety follow-up 28 days after final AGS15E infusion.

During dose escalation, 48.9% (23/47) of patients reported serious TEAE. Most were reported in a single patient each, except febrile neutropenia ($n = 2$), urinary tract infection ($n = 3$), malignant neoplasm progression ($n = 2$), and acute renal failure ($n = 4$). Four patients experienced fatal TEAE, which were not considered possibly related to the study drug during dose escalation (suicide, $n = 1$; dyspnea, $n = 1$; disease progression, $n = 2$).

During dose expansion, 37.6% (35/93) of patients experienced serious AE, most of which were reported by one patient each. Across the total study population, 10.8% (10/93) reported at least one serious TEAE considered at least possibly related to the study drug. Six patients experienced fatal TEAE during dose expansion (cardiac arrest, $n = 1$; coronary artery disease, $n = 1$; acute renal failure, $n = 1$; pulmonary embolism, $n = 1$; disease progression, $n = 2$), two of which (cardiac arrest, $n = 1$; acute renal failure, $n = 1$) were considered at least possibly related to the study drug.

Although no AE of special interest were prespecified for AGS15E, peripheral neuropathy and ocular toxicity have been

Table 1. Patient demographics and baseline clinical characteristics (FAS).

Characteristics	Part A		Parts A, B, C	Part C	
	RP2D[a] 1.00 mg/kg ($n = 46$)	Total ($n = 79$)	RP2D[a] 1.00 mg/kg ($n = 60$)	1.00 mg ($n = 13$)	Total[b] ($n = 93$)
Age, y					
Mean (SD)	65.7 (9.49)	64.7 (10.02)	65.4 (9.81)	64.1 (11.55)	64.6 (10.13)
Median (range)	67.5 (37; 82)	67.0 (30; 82)	67.0 (37; 82)	66.0 (39; 81)	67.0 (30; 82)
Age category (y), *n* (%)					
<65	18 (39.1)	36 (45.6)	25 (41.7)	6 (46.2)	43 (46.2)
≥65	28 (60.9)	43 (54.4)	35 (58.3)	7 (53.8)	50 (53.8)
≥75	8 (17.4)	10 (12.7)	9 (15.0)	1 (7.7)	11 (11.8)
Sex, *n* (%)					
Male	35 (76.1)	65 (82.3)	44 (73.3)	8 (61.5)	74 (79.6)
Female	11 (23.9)	14 (17.7)	16 (26.7)	5 (38.5)	19 (20.4)
Race, *n* (%)					
White	44 (95.7)	77 (97.5)	57 (95.0)	12 (92.3)	90 (96.8)
Asian	2 (4.3)	2 (2.5)	3 (5.0)	1 (7.7)	3 (3.2)
Ethnicity, *n* (%)					
Not Hispanic or Latino	46 (100.0)	78 (98.7)	59 (98.3)	12 (92.3)	91 (97.8)
Hispanic or Latino	0	1 (1.3)	1 (1.7)	1 (7.7)	2 (2.2)
ECOG PS, *n* (%)[c]					
0	15 (32.6)	22 (27.8)	17 (28.3)	2 (15.4)	24 (25.8)
1	31 (67.4)	57 (72.2)	43 (71.7)	11 (84.6)	69 (74.2)
Primary tumor site, *n* (%)					
Bladder	32 (69.6)	54 (68.4)	42 (70.0)	10 (76.9)	64 (68.8)
Renal pelvis	9 (19.6)	16 (20.3)	10 (16.7)	1 (7.7)	17 (18.3)
Ureter	5 (10.9)	7 (8.9)	8 (13.3)	2 (15.4)	10 (10.8)
Urethra	0	2 (2.5)	0	0	2 (2.2)
Disease stage at initial diagnosis, *n* (%)					
I	6 (13.0)	11 (13.9)	7 (11.7)	1 (7.7)	12 (12.9)
II	8 (17.4)	13 (16.5)	8 (13.3)	0	13 (14.0)
III	4 (8.7)	11 (13.9)	8 (13.3)	3 (23.1)	15 (16.1)
IV	17 (37.0)	27 (34.2)	20 (33.3)	3 (23.1)	30 (32.3)
Unknown	11 (23.9)	17 (21.5)	17 (28.3)	6 (46.2)	23 (24.7)
Sites of metastasis at baseline, *n* (%)					
Primary tumor/recurrence	7 (15.2)	7 (8.9)	9 (15.0)	2 (15.4)	9 (9.7)
Lymph node	27 (58.7)	50 (63.3)	40 (66.7)	12 (92.3)	63 (67.7)
Lung	19 (41.3)	33 (41.8)	23 (38.3)	4 (30.8)	37 (39.8)
Liver	13 (28.3)	24 (30.4)	16 (26.7)	3 (23.1)	27 (29.0)
Bone	8 (17.4)	15 (19.0)	10 (16.7)	2 (15.4)	17 (18.3)
Other	24 (52.2)	48 (60.8)	32 (53.3)	8 (61.5)	56 (60.2)
Has a bladder (yes), *n* (%)	26 (56.5)	47 (59.5)	36 (60.0)	9 (69.2)	57 (61.3)
Years since initial diagnosis					
Mean (SD)	4.24 (3.998)	4.01 (3.530)	3.82 (3.914)	2.55 (3.489)	3.77 (3.537)
Median (min; max)	2.92 (0.6; 19.8)	2.76 (0.6; 19.8)	2.22 (0.4; 19.8)	1.72 (0.4; 14.0)	2.58 (0.4; 19.8)
Years since metastatic disease					
Mean (SD)	1.86 (2.372)	1.73 (1.967)	1.63 (2.129)	0.93 (0.500)	1.60 (1.848)
Median (min; max)	1.00 (0.1; 14.4)	1.25 (0.1; 14.4)	0.96 (0.1; 14.4)	0.95 (0.3; 1.9)	1.11 (0.1; 14.4)
Histological type, *n* (%)					
Transitional cell carcinoma	28 (60.9)	58 (73.4)	36 (60.0)	7 (53.8)	66 (71.0)
Urothelial cells mixed	7 (15.2)	9 (11.4)	8 (13.3)	1 (7.7)	10 (10.8)
Squamous cell differentiation	1 (2.2)	2 (2.5)	2 (3.3)	1 (7.7)	3 (3.2)
Other	10 (21.7)	10 (12.7)	14 (23.3)	4 (30.8)	14 (15.1)
Prior therapy, *n* (%)					
Prior systemic therapy	45 (97.8)	78 (98.7)	58 (96.7)	13 (100.0)	91 (97.8)
0 lines	5 (10.9)	7 (8.9)	8 (13.3)	2 (15.4)	10 (10.8)
1 line	21 (45.7)	30 (38.0)	23 (38.3)	2 (15.4)	32 (34.4)
≥2 lines	20 (43.5)	42 (53.2)	29 (48.3)	9 (69.2)	51 (54.8)
Type of prior system therapy, *n* (%)[d]					
Cytotoxic therapy	41 (89.1)	73 (92.4)	53 (88.3)	12 (92.3)	85 (91.4)
Immunotherapy	12 (26.1)	28 (35.4)	22 (36.7)	10 (76.9)	38 (40.9)
Targeted therapy	3 (6.5)	7 (8.9)	4 (6.7)	1 (7.7)	8 (8.6)
Other	8 (17.4)	13 (16.5)	8 (13.3)	0	13 (14.0)

(Continued on the following page)

Table 1. Patient demographics and baseline clinical characteristics (FAS). (Cont'd)

Characteristics	Part A RP2D[a] 1.00 mg/kg (*n* = 46)	Part A Total (*n* = 79)	Parts A, B, C RP2D[a] 1.00 mg/kg (*n* = 60)	Part C 1.00 mg (*n* = 13)	Total[b] (*n* = 93)
Time from last CPI to first dose[e]					
n	12	20	24	12	32
<8 wk	6 (50.0)	10 (50.0)	12 (50.0)	6 (50.0)	16 (50.0)
≥8 wk	6 (50.0)	10 (50.0)	12 (50.0)	6 (50.0)	16 (50.0)
<12 wk	7 (58.3)	13 (65.0)	14 (58.3)	7 (58.3)	20 (62.5)
≥12 wk	5 (41.7)	7 (35.0)	10 (41.7)	5 (41.7)	12 (37.5)

Note: All patients who consented and received at least one infusion of AGS15E (FAS). Percentages are based on the number of patients in each dose group.
Abbreviation: PS, performance status.
[a]All RP2D 1.00 mg/kg population refers to all patients included in the escalation and expansion phase receiving an AGS15E dose of 1.00 mg/kg.
[b]The total population refers to all patients included in the escalation and expansion phase regardless of AGS15E dose received.
[c]Patients with an ECOG PS of 2 could be included under part B. Since the only patient included in part B had an ECOG PS score of 1, no patient with an ECOG PS score of 2 was included in this study.
[d]Patients may be counted in more than one row.
[e]Percentages calculated using number of patients exposed to CPI. One patient in part C was not included in this table due to data collection error; this patient received a CPI as the most recent prior treatment.

listed as potential risks. Eye disorders possibly related to the study drug were reported in 29% (27/93) of patients in the total study population. The most frequent eye disorders were blurred vision (15.1%, 14/93) and dry eye (5.4%, 5/93). Most eye disorders were grade 1 or 2, with two patients experiencing a grade 3 event (diplopia, $n = 1$; blurred vision, $n = 1$). Peripheral neuropathy and ocular toxicities occurred at doses of 0.75 mg/kg AGS15E or higher, with peripheral sensory neuropathy occurring in 17.2% (16/93) of patients, unspecified peripheral neuropathy in 15.1% (14/93), peripheral motor neuropathy in 7.5% (7/93), and peripheral sensorimotor neuropathy in 1.1% (1/93). Most peripheral neuropathy events were grade 1 and 2; two (2.2%) patients each reported both grade 3 peripheral motor neuropathy and grade 3 peripheral sensory neuropathy.

Pharmacokinetics and pharmacodynamics

AGS15E ADC (**Fig. 2A**), MMAE (**Fig. 2B**), and TAb (**Fig. 2C**) increased in a dose-proportional manner after single-dose (day 1) and multiple-dose (day 15) administration. The C_{max} of AGS15E ADC and TAb was reached 1 to 5 hours postinfusion, and peak MMAE (median t_{max}) was reached at approximately 1 day (day 1 and 1 hour; range, 0.106–3.04 hour) postinfusion. Serum concentrations of AGS15E ADC and TAb decreased in a multiexponential manner postinfusion, and MMAE concentrations decreased in a linear manner. The accumulation ratio (R_{ac}) was low for AGS15E ADC (range, 1.16–1.58), MMAE (1.16–1.79), and TAb (1.39–1.74) after multiple-dose administration (Supplementary Tables S5–S13).

All 93 patients were screened for ADA formation; 17.0% (8/47) were reactive for ADA during dose escalation and 5.4% (5/93) were reactive

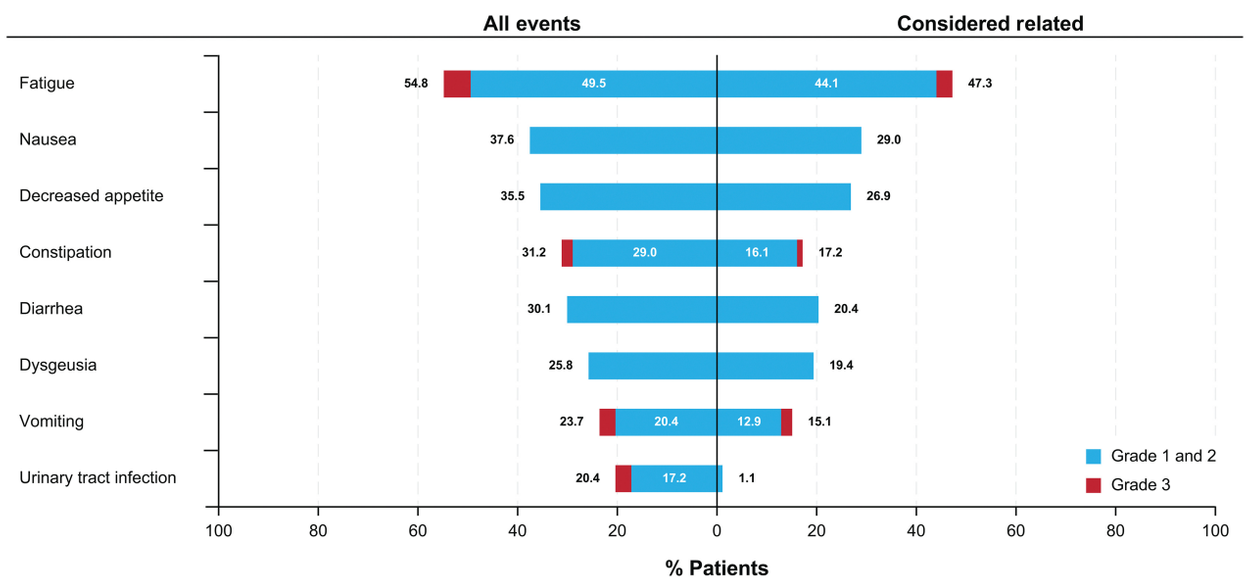

Figure 1.
TEAE (≥20% incidence). Includes all patients from the total study population.

Table 2. TEAE (≥15% patients) by SOC and PT: parts A, B, and C, expansion phase.

	AGS15E dose level (mg/kg)				
	Part A			Parts A, B, C	
MedDRA (v16.0), SOC/PT, *n* (%) of Patients	Expansion 1.00 (*n* = 32)	Combined[a] 1.00 (*n* = 46)	Total[b] (*n* = 79)	Combined[a] 1.00 (*n* = 60)	Total[b] (*n* = 93)
Overall	32 (100.0)	45 (97.8)	77 (97.5)	58 (96.7)	90 (96.8)
Blood and lymphatic system disorders	4 (12.5)	7 (15.2)	17 (21.5)	9 (15.0)	19 (20.4)
Eye disorders	11 (34.4)	17 (37.0)	22 (27.8)	25 (41.7)	30 (32.3)
Vision blurred	7 (21.9)	10 (21.7)	12 (15.2)	14 (23.3)	16 (17.2)
Gastrointestinal disorders	26 (81.3)	38 (82.6)	63 (79.7)	48 (80.0)	73 (78.5)
Abdominal pain	5 (15.6)	5 (10.9)	12 (15.2)	8 (13.3)	15 (16.1)
Constipation	12 (37.5)	16 (34.8)	28 (35.4)	17 (28.3)	29 (31.2)
Diarrhea	11 (34.4)	13 (28.3)	22 (27.8)	19 (31.7)	28 (30.1)
Nausea	15 (46.9)	18 (39.1)	28 (35.4)	25 (41.7)	35 (37.6)
Vomiting	8 (25.0)	9 (19.6)	16 (20.3)	15 (25.0)	22 (23.7)
General disorders and administration site conditions	22 (68.8)	35 (76.1)	57 (72.2)	44 (73.3)	66 (71.0)
Fatigue	17 (53.1)	28 (60.9)	45 (57.0)	34 (56.7)	51 (54.8)
Pyrexia	6 (18.8)	8 (17.4)	12 (15.2)	12 (20.0)	16 (17.2)
Infections and infestations	15 (46.9)	23 (50.0)	35 (44.3)	26 (43.3)	38 (40.9)
Urinary tract infection	8 (25.0)	12 (26.1)	17 (21.5)	14 (23.3)	19 (20.4)
Investigations	13 (40.6)	19 (41.3)	34 (43.0)	28 (46.7)	43 (46.2)
Weight decreased	9 (28.1)	10 (21.7)	14 (17.7)	14 (23.3)	18 (19.4)
Metabolism and nutrition disorders	18 (56.3)	28 (60.9)	47 (59.5)	38 (63.3)	57 (61.3)
Decreased appetite	12 (37.5)	19 (41.3)	27 (34.2)	25 (41.7)	33 (35.5)
Musculoskeletal and connective tissue disorders	20 (62.5)	28 (60.9)	44 (55.7)	36 (60.0)	52 (55.9)
Arthralgia	5 (15.6)	10 (21.7)	14 (17.7)	12 (20.0)	16 (17.2)
Back pain	6 (18.8)	8 (17.4)	11 (13.9)	12 (20.0)	15 (16.1)
Pain in extremity	9 (28.1)	13 (28.3)	16 (20.3)	14 (23.3)	17 (18.3)
Nervous system disorders	22 (68.8)	31 (67.4)	47 (59.5)	40 (66.7)	56 (60.2)
Dysgeusia	9 (28.1)	13 (28.3)	21 (26.6)	16 (26.7)	24 (25.8)
Headache	7 (21.9)	9 (19.6)	11 (13.9)	12 (20.0)	14 (15.1)
Neuropathy peripheral	8 (25.0)	11 (23.9)	14 (17.7)	14 (23.3)	17 (18.3)
Peripheral sensory neuropathy	9 (28.1)	12 (26.1)	14 (17.7)	16 (26.7)	18 (19.4)
Psychiatric disorders	8 (25.0)	14 (30.4)	22 (27.8)	16 (26.7)	24 (25.8)
Respiratory, thoracic, and mediastinal disorders	12 (37.5)	17 (37.0)	31 (39.2)	23 (38.3)	37 (39.8)

Note: All patients who consented and received at least one infusion of AGS15E (FAS). Percentages are based on the number of patients in each dose group. Patients are counted once within each SOC and each PT.

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, system organ class.

[a]The combined 1.00 mg/kg population refers to all patients included in the escalation and expansion phase receiving an AGS15E dose of 1.00 mg/kg.

[b]The total population refers to all patients included in the escalation and expansion phase regardless of AGS15E dose received.

for ADA during dose expansion. Of these patients, 46.2% (6/13) were confirmed reactive, and the remaining 53.8% (7/13) were not confirmed reactive at any time point.

Antitumor activity

During dose escalation, one patient had a confirmed CR after receiving 1.00 mg/kg AGS15E; 17.0% (8/47 patients) had a confirmed PR, and 10.6% (5/47) had an unconfirmed PR (Supplementary Table S14). In addition, a confirmed CR/PR of 35.7% (n = 5/14; 95% CI, 12.8%–64.9%) was seen at 1.00 mg/kg compared with rates of 12.5% (95% CI, 0.3%–52.7%) and 14.3% (95% CI, 1.8%–42.8%) at 0.50 mg/kg and 0.75 mg/kg, respectively (Supplementary Table S14). No patients had a confirmed CR during dose expansion, although 12.5% (4/32) of patients in part A and 30.8% (4/13) in part C had a confirmed PR (Supplementary Table S14). The confirmed CR/PR in all patients treated at 1.00 mg/kg across dose escalation and expansion was 21.7% (n = 13/60, 95% CI, 12.1%–34.2%). Additionally, BOR was shown to correlate with maximum percent reduction from baseline in total tumor burden, with the largest reduction in total tumor burden (target lesion diameter) observed in patients at dose levels of ≥0.75 mg/kg (**Fig. 3A**). Stable disease appeared to correlate with length of time on treatment (**Fig. 3B**).

Across the total study population, the confirmed ORR was 18.3% (17/93), the DCR was 62.4% (58/93), and stable disease was observed in 32.3% (30/93) of patients. At the 1.00-mg/kg dose level, 21.7% of patients had a confirmed response (**Table 3**; Supplementary Table S14, Supplementary Table S15). Responses in patients with previous CPI exposure were similar to but slightly higher than those without prior CPI exposure; confirmed ORR and DCR in the CPI-exposed population were 27.3% (9/33) and 69.7% (23/33), respectively. Median confirmed DOR in the total study population was 24.71 weeks [95% CI, 16–not estimable (NE)] and 23.86 weeks (95% CI, 16–NE) for patients previously exposed to CPI. Median PFS was 16.0 weeks (n = 93; 95% CI, 13.71–23.14) across the total study population, 16.14 weeks (n = 60; 95% CI, 13.29–24.00) in patients receiving 1.00 mg/kg, and 20 weeks (n = 33; 95% CI, 11.43–24.14) in patients with previous CPI exposure (Supplementary Fig. S2). SLITRK6 expression as determined by immunohistochemistry H-score did not correlate with confirmed BOR (Supplementary Fig. S3).

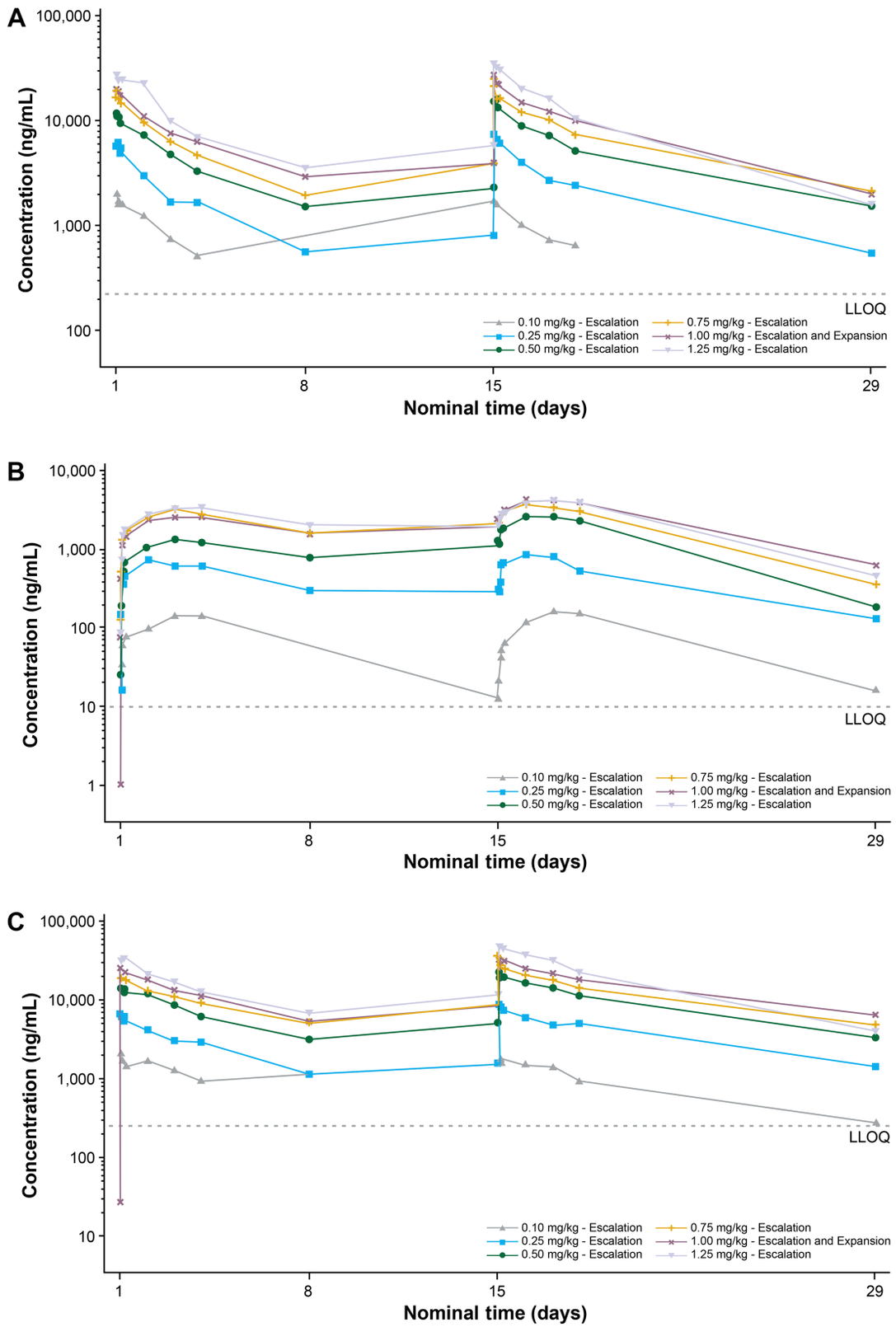

Figure 2.

Mean serum concentration–time profiles of AGS15E ADC (**A**), MMAE (**B**), and TAb (**C**) after single (day 1) and multiple (day 15) dosing in cycle 1 by dose group (semi-log scale plot) PK analysis set. LLOQ, lower limit of quantification.

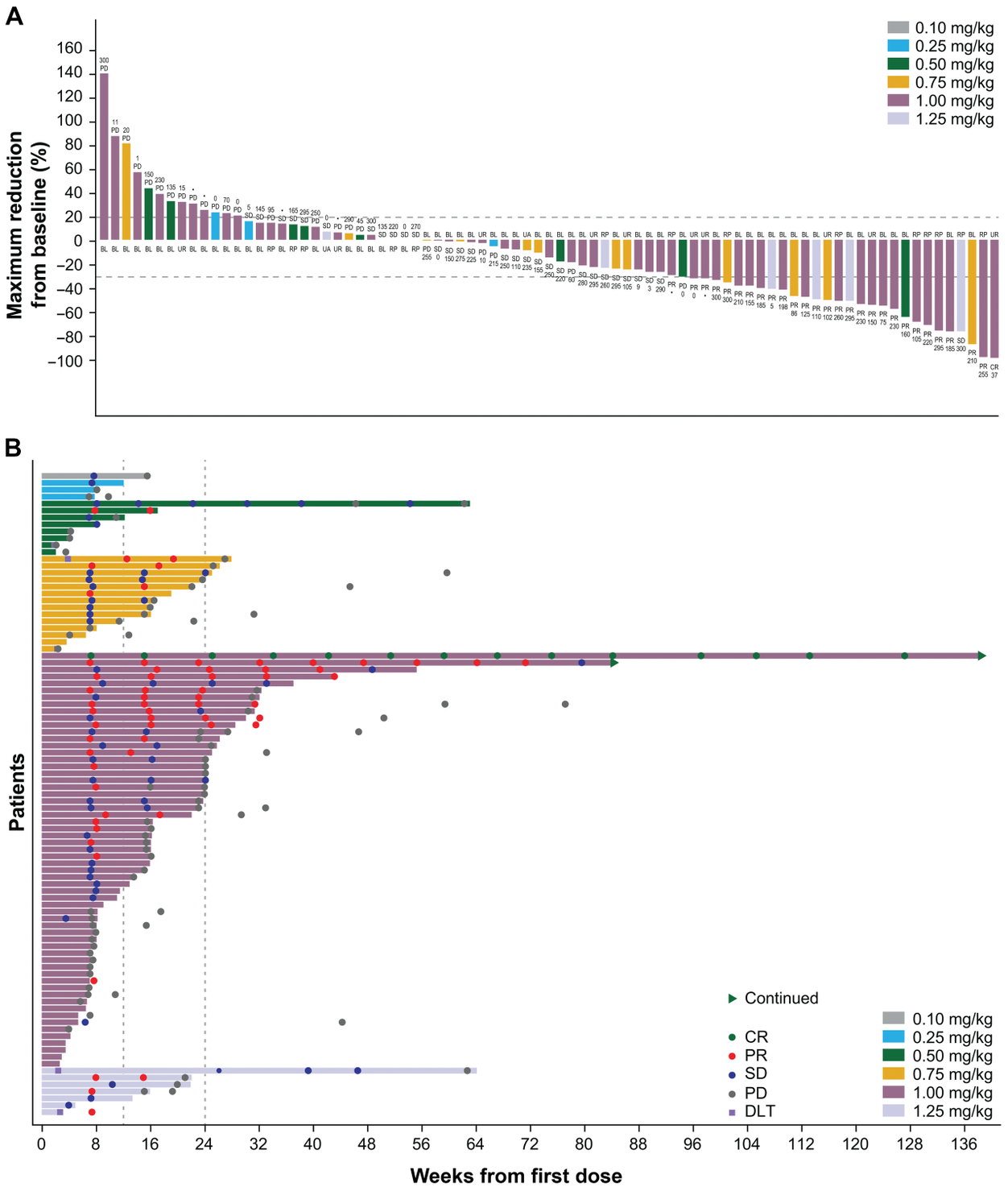

Figure 3.

A, Maximum percent reduction from baseline in total tumor burden by BOR (parts A, B, and C; FAS). All patients who consented and received at least one infusion of AGS15E (FAS). H-score is shown above or below the BOR. Maximum reduction is defined as patient's best response in sum of target lesion diameters from baseline, based on radiological evidence of measurable disease. Bars below 0 represent tumor burden reduction. BOR of SD with a minimum duration of 7 weeks from cycle 1, day 1 is required. Patients with no postbaseline radiologic disease assessment or measurement of tumor burden (at baseline or postbaseline) are excluded from the graph. Patients with nonevaluable BOR are also excluded from the graph. Investigator's assessment of BOR is annotated for each patient according to RECIST v.1.1. **B,** Duration of treatment (parts A, B, and C; FAS). All patients who consented and received at least one infusion of AGS15E (FAS). Duration of treatment is defined as (date the decision is made to end treatment or data cutoff date if patient is still on treatment) – (first dose date + 1 day)/7. BL, bladder; BOR, best overall response; CR, complete response; DLT, dose-limiting toxicity; FAS, full analysis set; OS, other site; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; RP, renal pelvis; SD, stable disease; UA, urethra; UR, ureter.

Table 3. BOR and ORR with confirmation; parts A, B, and C, expansion phase.

	AGS15E dose level (mg/kg)				
	Part A			Parts A, B, C	
	Expansion 1.00 ($n = 32$)	Combined[a] 1.00 ($n = 46$)	Total[b] ($n = 79$)	Combined[a] 1.00 ($n = 60$)	Total[b] ($n = 93$)
BOR, *n* (%)					
Confirmed CR	0	1 (2.2)	1 (1.3)	1 (1.7)	1 (1.1)
Confirmed PR	4 (12.5)	8 (17.4)	12 (15.2)	12 (20.0)	16 (17.2)
Unconfirmed PR	4 (12.5)	5 (10.9)	9 (11.4)	7 (11.7)	11 (11.8)
Stable disease[c]	9 (28.1)	12 (26.1)	26 (32.9)	16 (26.7)	30 (32.3)
PD	8 (25.0)	12 (26.1)	21 (26.6)	16 (26.7)	25 (26.9)
NE	7 (21.9)	8 (17.4)	10 (12.7)	8 (13.3)	10 (10.8)
ORR, *n* (%)					
Confirmed CR + PR, *n* (%)	4 (12.5)	9 (19.6)	13 (16.5)	13 (21.7)	17 (18.3)
95% CI[d]	3.5, 29.0	9.4, 33.9	9.1, 26.5	12.1, 34.2	11.0, 27.6
Duration on study, weeks[e,f]					
n	4	9	13	13	17
Median (min; max)	38.14 (30.1; 84.3)	35.57 (26.1; 138.4)	30.14 (17.1; 138.4)	33.29 (26.1; 138.4)	32.14 (17.1; 138.4)
Duration on treatment, weeks[e,f]					
n	4	9	13	13	17
Median (min; max)	36.64 (25.1; 84.3)	31.57 (22.1; 138.4)	28.00 (17.1; 138.4)	31.57 (22.1; 138.4)	30.14 (17.1; 138.4)

Note: All patients who consented and received at least one infusion of AGS15E (FAS). Percentages are based on the number of patients in each dose group.
Abbreviations: NA, not applicable; NE, not evaluable; ORR, overall response rate; PD, progressive disease.
[a]The combined 1.00 mg/kg population refers to all patients included in the escalation and expansion phase receiving an AGS15E dose of 1.00 mg/kg.
[b]The total population refers to all patients included in the escalation and expansion phase regardless of AGS15E dose received.
[c]Best response of stable disease with a minimum duration of 7 weeks from cycle 1, day 1 is required.
[d]Exact 95% CI based on Clopper-Pearson method.
[e]Duration on treatment = (date decision made to end treatment or data cutoff date if patient is still on study - first dose date + 1 day)/7.
[f]Duration on study for treatment portion and duration on treatment pertain to ORR and DCR patients, respectively.

Discussion

Despite the introduction of CPI therapies in recent years, outcomes have remained poor in patients with locally advanced or mUC and treatment options are limited (13–16). However, ADC such as EV and SG have shown more promising outcomes (10, 13, 17). This open-label, phase I study assessed the safety, PK profile, immunogenicity, and antitumor activity of AGS15E in patients with mUC, with a view to addressing the unmet need in this setting.

In this study, the RP2D of AGS15E was established at 1.00 mg/kg. There was no prior estimate for the underlying rate of DLT for AGS15E because this was the first study in humans using this agent. However, in a previous study of another ADC (EV) in patients with mUC, two patients experienced a DLT at the 1.00-mg/kg dose level; no other DLT occurred in the study (18). This is consistent with the DLT observed in the current study, which occurred at 0.5 mg/kg ($n = 1$), 0.75 mg/kg ($n = 2$), and 1.25 mg/kg ($n = 2$).

Antitumor responses were observed at doses of ≥0.5 mg/kg. The safety profile of AGS15E was consistent with that of microtubule-disrupting ADC, with 96.8% (90/93) of patients in the total study population reporting at least one TEAE, most of which were of grade 1 and 2 severity. Higher doses of AGS15E may correlate with more patients reporting diarrhea, nausea, and vomiting, but patient numbers in individual dose groups were too small to draw meaningful conclusions. Serious AE were reported in 10.8% (10/93) of patients and fatal TEAE in 10.8% (10/93), including two that may have been related to the study drug. Visual/ocular changes (eg, corneal damage/keratopathy) and peripheral neuropathy have previously been reported in patients treated with other tubulin inhibitor-containing ADC due to the mechanism of MMAE, with the majority being mild and reversible (19). Similarly, ocular toxicity events in this study were of mostly grade 1 and 2 severity and did not lead to treatment discontinuation. Few differences were seen in the safety profile between patient subgroups with regard to CPI exposure, other than a higher incidence of blurred vision in patients with previous CPI exposure compared with those without (33.3% vs. 17.2%, respectively). Concentrations of AGS15E ADC, MMAE, and TAb increased in an approximately dose-proportional manner after single- and multiple-dose administration. Following multiple doses for each analyte, the mean $t_{1/2}$ was 2 to 8 days and accumulation was low. In addition, only a small percentage of patients (6.5%, 6/93) were confirmed reactive for ADA, suggesting there is no correlation between dose and ADA formation.

AGS15E shows encouraging antitumor activity with a confirmed ORR in the total study population of 18% and a median PFS of 16 weeks. A trend toward increased response with higher doses was observed, with a confirmed CR/PR of 35.7% at 1.00 mg/kg compared with confirmed CR/PRs of 12.5% and 14.3% at 0.50 mg/kg and 0.75 mg/kg, respectively. The confirmed CR/PR in all patients treated at 1.00 mg/kg across dose escalation and expansion was 21.7% and was 30.8% for those with previous CPI therapy. These response rates and survival times are comparable to those seen in other ADC in this setting, including patients with previous CPI exposure. For example, preliminary data from the phase II TROPHY study of SG, an ADC targeting trophoblastic cell-surface antigen 2, showed 113 patients with locally advanced or mUC who had progressed after CPI or platinum therapy to have an ORR of 27% (95% CI, 19.5%–36.6%) and a median PFS of 5.4 months (range, 2.4–8.9 months; ref 17).

In a phase III trial of EV (an ADC targeting Nectin-4) in patients with mUC, the confirmed overall response was 40.6% (95% CI, 34.9%–46.5%) in the EV group and 17.9% (95% CI, 13.7%–22.8%) in the chemotherapy group (13). Similarities between EV and AGS15E may be explained by their target expression, with moderate or high Nectin-4 and SLITRK6 expression in 60% to 69% of urothelial tumors (Supplementary Table S3). In addition, pooled results from two phase II trials of disitamab vedotin showed promising efficacy in HER2-positive mUC patients, with a confirmed ORR of 50.5% (95% CI, 40.6%–60.3%) across the study population and 55.6% in patients with previous CPI therapy (20).

Study limitations include small sample size in parts A (escalation, $n = 1$–14), B ($n = 1$), and C ($n = 13$), removing statistical power to detect significant differences between groups, and a predominantly male (79.6%) and white (96.8%) study population. In addition, given the nearly universal expression of SLITRK6 across urothelial carcinoma tumors, biomarker-based selection was not employed. However, future work considering SLITRK6 genotype or expression levels may help identify patient subgroups who may benefit from AGS15E therapy.

Authors' Disclosures

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Authors' Contributions

D.P. Petrylak: Conceptualization, data curation, formal analysis. **B.J. Eigl:** Conceptualization, data curation. **S. George:** Resources, investigation, writing–review and editing. **E.I. Heath:** Conceptualization, data curation, formal analysis. **S.J. Hotte:** Resources, data curation, formal analysis, investigation, methodology, writing–original draft, writing–review and editing. **D.D. Chism:** Conceptualization, data curation. **L.M. Nabell:** Conceptualization, data curation. **J. Picus:** Resources, data curation, investigation, writing–original draft, project administration, writing–review and editing. **S.Y. Cheng:** Conceptualization, data curation. **L.J. Appleman:** Conceptualization, data curation. **G.P. Sonpavde:** Conceptualization. **A.K. Morgans:** Conceptualization. **P. Pourhosseini:** Formal analysis. **R. Wu:** Formal analysis. **L. Standley:** Supervision, project administration. **R. Croitoru:** Formal analysis. **E.Y. Yu:** Conceptualization, data curation, supervision, writing–review and editing.

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Note

Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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