SeattleGenetics

Protocol Number:	SGN22E-001
Version:	Amendment 6; 05-Dec-2019
Protocol Title:	A single-arm, open-label, multicenter study of enfortumab vedotin (ASG-22CE) for treatment of patients with locally advanced or metastatic urothelial cancer who previously received immune checkpoint inhibitor (CPI) therapy.
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PROTOCOL SYNOPSIS

Protocol Number SGN22E-001 **Version** Amendment 6; 05-Dec-2019 **Phase** 2	**Product Name** Enfortumab vedotin (ASG-22CE) **Study Sponsor** Seattle Genetics, Inc. 21823 30th Drive SE Bothell, WA 98021, USA **IND Sponsor** Astellas Pharma Global Development, Inc. (APGD) 1 Astellas Way Northbrook, IL 60062, USA

Protocol Title

A single-arm, open-label, multicenter study of enfortumab vedotin (ASG-22CE) for treatment of patients with locally advanced or metastatic urothelial cancer who previously received immune checkpoint inhibitor (CPI) therapy.

Study Objectives

Primary:

- To determine the antitumor activity of single-agent enfortumab vedotin as measured by confirmed objective response rate (ORR) in patients with locally advanced or metastatic urothelial cancer who have previously received systemic therapy with a CPI and either previously received platinum-containing chemotherapy or are platinum-naïve and cisplatin-ineligible

Secondary:

- To assess duration of response (DOR)
- To assess disease control rate (DCR)
- To assess progression-free survival (PFS)
- To assess overall survival (OS)
- To assess the safety and tolerability of enfortumab vedotin
- To assess the pharmacokinetics (PK) of enfortumab vedotin
- To assess the incidence of antitherapeutic antibodies (ATA)

Additional:

- To explore potential correlations between biomarkers and clinical outcomes
- To evaluate the treatment effect of enfortumab vedotin on quality of life (QoL)

Study Population

The population to be studied includes patients with locally advanced or metastatic urothelial cancer who previously received therapy with CPI, with measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. Patients who received CPI therapy in the neoadjuvant/adjuvant setting and had recurrent or progressive disease (PD) either during therapy or within 3 months of therapy completion are eligible. Patients must also be either:

1) Platinum-treated (Cohort 1): Patients who received prior treatment with platinum-containing chemotherapy defined as those who received platinum in the adjuvant/neoadjuvant setting and had recurrent or progressive disease within 12 months of completion OR received treatment with platinum in the locally advanced (defined as unresectable with curative intent) or metastatic setting;

OR

2) Platinum-naïve and cisplatin ineligible (Cohort 2): Patients who have not received prior platinum-containing or other chemotherapy in the locally advanced or metastatic setting and are ineligible for treatment with cisplatin at time of enrollment. Patients who received platinum in the adjuvant/neoadjuvant setting and did not progress within 12 months of completion will be considered platinum-naïve.

Patients must have PD during or following their most recent therapy. Eligible patients must be ≥18 years of age, and legally an adult according to local regulation. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status score of ≤1 for Cohort 1, or ECOG ≤2 for Cohort 2. Patients must have an anticipated life expectancy of ≥3 months as assessed by the investigator. Patients must have adequate baseline hematologic, hepatic, and renal function.

Patients must not have ongoing sensory or motor neuropathy (Grade 2 or higher), or active central nervous system metastases. Patients must not have been previously enrolled in an enfortumab vedotin study or previously treated with other monomethyl auristatin E (MMAE)-based antibody-drug conjugates (ADCs). There are no limits for prior lines of therapy, including taxanes. Patients must not have a history of another malignancy within 3 years, or any evidence of residual disease from a previously diagnosed malignancy. Patients are also excluded if they are currently receiving systemic antimicrobial treatment for active infection or high dose steroids. Patients with uncontrolled diabetes are excluded. Uncontrolled diabetes is defined as hemoglobin A1C (HbA1c) ≥8% or HbA1c 7–<8% with associated diabetes symptoms (polyuria or polydipsia) that are not otherwise explained. Patients must not have uncontrolled tumor-related bone pain or impending spinal cord compression. Patients requiring pain medication must be on a stable regimen at the time of enrollment (a minimum of 2 weeks).

Number of Planned Patients

Approximately 200 patients will be enrolled in this study, including approximately 100 or more platinum-treated patients (Cohort 1), and up to approximately 100 platinum-naïve and cisplatin-ineligible patients (Cohort 2).

Study Design

This is a single-arm, open-label, multicenter trial designed to assess the efficacy and safety of enfortumab vedotin as a single agent in locally advanced or metastatic urothelial cancer patients who have previously received systemic therapy with a CPI. For the purpose of this study a CPI is defined as a programmed cell death protein 1 (PD-1) inhibitor or programmed death-ligand 1 (PD-L1) inhibitor (including, but not limited to: atezolizumab, pembrolizumab, durvalumab, avelumab, and nivolumab). Patients must either have received prior treatment with platinum-containing chemotherapy (Cohort 1) or received no prior treatment with platinum-containing or other chemotherapy and are ineligible for treatment with cisplatin at time of enrollment (Cohort 2).

Enfortumab vedotin at a dose of 1.25 mg/kg will be administered as an intravenous (IV) infusion over approximately 30 minutes on Days 1, 8, and 15 of each 28-day cycle. Patients will continue to receive study treatment until disease progression, unacceptable toxicity, investigator decision, consent withdrawal, start of a subsequent anticancer therapy, pregnancy, or study termination by the sponsor. After discontinuation of study treatment, patients will be followed every 8 weeks (±1 week) for response assessments, ECOG performance status, and physical exams. After 1 year of on study, the frequency of follow-up exams including response assessments will be reduced to every 12 weeks (±1 week). Patients that have progressed or begun subsequent anticancer therapy will be contacted every 8 weeks (±1 week) up to 1 year on study, and every 12 weeks (±1 week) thereafter to obtain information on subsequent anticancer therapy, and survival status until death, study closure, or withdrawal of consent, whichever occurs first. The study will be closed 5 years after enrollment of the last patient, or when no patients remain in long-term follow-up, whichever occurs first. Additionally, the sponsor may terminate the study at any time.

On a periodic basis, an independent data monitoring committee (IDMC) will monitor the safety of patients participating in this trial. The IDMC will be responsible for evaluating the results of safety analyses and will make recommendations to the sponsor.

An ongoing real-time review of patient safety and serious adverse events (SAEs) will also be conducted by the sponsor's Drug Safety Department.

Test Product, Dose, and Mode of Administration

Enfortumab vedotin 1.25 mg/kg will be administered as an IV infusion over approximately 30 minutes on Day 1, 8, and 15 of each 28-day cycle.

Duration of Treatment

Patients may continue on study treatment until disease progression, unacceptable toxicity, investigator decision, consent withdrawal, start of a subsequent anticancer therapy, pregnancy, or study termination by the sponsor.

Efficacy Assessments

Measures of anticancer activity will be assessed by computed tomography (CT) scans with contrast approximately every 8 weeks (±1 week). After 1 year on study, response assessments will be reduced to every 12 weeks (±1 week). The schedule of response assessments should not be adjusted for dose delays/interruptions or other reasons for changes in the timing of a patient's study activities; timepoints for response assessments should be calculated from Cycle 1 Day 1 during treatment. For patients who cannot receive CT scans with contrast, other protocol-specified imaging methods may be used. Patients must be evaluated using the same imaging method throughout the study for efficacy assessments. CT scans with contrast at the minimum will include the chest, abdomen, and pelvis. Other regions should be scanned if the patient has known or suspected disease in that region. Responses (complete response [CR] or partial response [PR]) will be confirmed with repeat scans 4 weeks (+1 week window) after first documentation of response. The determination of antitumor activity will be based on confirmed objective response assessments as defined by RECIST Version 1.1. Response and progression will be assessed by an independent review facility (IRF). The investigator will make treatment decisions based on site assessments of scans by RECIST.

Patients who discontinue study treatment for reasons other than objective disease progression by RECIST will continue to receive scans 8 weeks (±1 week) after the previous response assessment scan and every 8 weeks (±1 week) following the previous scan thereafter. After 1 year on study the frequency of response assessments will be reduced to every 12 weeks (±1 week). The tumor assessments will continue until the patient has radiologically-confirmed progression per the investigator, initiates a new anticancer therapy, dies, withdraws consent, or the study closes, whichever comes first.

Pharmacokinetic and ATA Assessments

Blood samples for PK and ATA will be collected throughout the study. Qualified or validated assays will be used to measure the concentrations of enfortumab vedotin ADC, total antibody (TAb), and MMAE in serum or plasma and assess ATA.

Biomarker Assessments

Samples for exploratory biomarkers will be collected at protocol-specified timepoints. Biomarker assessments will not be used for patient selection. Biomarker assessments in tumor tissue may include, but will not be limited to, tumor expression of Nectin-4 protein, messenger ribonucleic acid (mRNA) expression, markers of disease subtype, and markers of the immune microenvironment in tumor. Assessments in blood samples may include, but will not be limited to, markers of immune function, including abundance and phenotype of immune cell subsets, circulating tumor DNA (ctDNA), and abundance of cytokines. Methods of analysis may include immunohistochemistry (IHC), next generation sequencing, polymerase chain reaction (PCR), mutation and gene expression profiling, T-cell receptor beta chain sequencing, flow cytometry, and immunoassays.

Safety Assessments

Safety assessments will be based on the information collected through the safety surveillance process and will include the data from recorded adverse events (AEs) including SAEs, recording of concomitant medication, physical examination findings, cardiac monitoring, and laboratory tests.

Quality of Life Assessments

Patient reported outcomes (PRO) assessments will be used to obtain QoL information at protocol-specified timepoints. The following validated tools will be used: European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) and EuroQol 5-dimensions (EQ-5D).

Statistical Methods

Analysis for primary endpoint:

The primary endpoint of this study is the confirmed ORR per IRF. The ORR is defined as the proportion of patients with confirmed CR or PR according to RECIST Version 1.1. The ORR per IRF and its exact 2-sided 95% confidence interval (CI) using the Clopper-Pearson method (Clopper 1934) will be calculated.

There are 2 cohorts of CPI-treated patients in the study: Cohort 1) platinum-treated patients as defined in the study population above, and Cohort 2) platinum-naïve and cisplatin-ineligible patients also defined in the study population above . The primary endpoint will be analyzed separately for each cohort and may be analyzed for all patients, combining both Cohorts 1 and 2.

The primary analysis on Cohort 1 (platinum-treated patients) will be conducted when enrollment is completed in Cohort 1, and all patients in the cohort have been followed for at least 6 months, or have discontinued from study, or had 30 days safety follow-up after PD, whichever comes first. Analysis for Cohort 2 will occur at 4 timepoints: 1) at the time of analysis of Cohort 1, 2) when approximately 50 patients in Cohort 2 have had the opportunity to be followed for approximately 8 months from the first dose of enfortumab vedotin, 3) when approximately 70 patients in Cohort 2 have had the opportunity to be followed for approximately 8 months from the first dose of enfortumab vedotin, and 4) when all patients in Cohort 2 have had the opportunity to be followed for approximately 8 months from the first dose of enfortumab vedotin. All patients may also be analyzed at the time of analysis of Cohort 1 and/or Cohort 2.

The primary analysis of efficacy endpoints will be based on the full analysis set, including all patients who enrolled and received any amount of enfortumab vedotin. At the time of the interim analyses for Cohort 2, additional analyses of efficacy endpoints will be performed based on the efficacy evaluable set, including all patients in the full analysis set who started treatment with enfortumab vedotin at least 8 months before the analysis data cutoff.

Sample size:

The study is designed to estimate the confirmed ORR in patients receiving enfortumab vedotin and to detect an improvement in the ORR compared with a historical response rate of 10%. Approximately 200 patients will be enrolled in this study to ensure collection of sufficient efficacy and safety data, including approximately 100 or more platinum-treated patients (Cohort 1), and up to approximately 100 platinum-naïve and cisplatin-ineligible patients (Cohort 2). Using the estimate of approximately 100 patients Cohort 1, the study will have 98% power to detect a 15% increase in ORR from 10% to 25% and 81% power to detect a 10% increase in ORR from 10% to 20%, at one-sided significant level of 0.025, based on exact methods using EAST®, Version 6.0, by Cytel Inc.

The confirmed ORR and 95% exact CI in Cohort 2 will be summarized at 4 timepoints: 1) at the time of analysis of Cohort 1, 2) when approximately 50 patients in Cohort 2 have had the opportunity to be followed for approximately 8 months from the first dose of enfortumab vedotin, 3) when approximately 70 patients in Cohort 2 have had the opportunity to be followed for approximately 8 months from the first dose of enfortumab vedotin, and 4) when all patients treated in Cohort 2 have had the opportunity to be followed for approximately 8 months from the first dose of enfortumab vedotin.

For illustration purposes, below is the summary of expected 95% CIs for Cohort 2 at various analysis timepoints, assuming a 30% observed ORR:

Number of Patients	Expected 95% Confidence Interval
N=20	12%–54%
N=50	18%–45%
N=70	20%–42%
N=100	21%–40%

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ADC	antibody-drug conjugate
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATA	antitherapeutic antibodies
BSC	best supportive care
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CNS	central nervous system
CPI	checkpoint inhibitor
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CT	computed tomography
ctDNA	Circulating tumor DNA
DCR	disease control rate
DCR_{16}	disease control rate at 16 weeks
DLT	dose-limiting toxicity
DOR	duration of response
ECD	extracellular domain
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EORTC	European Organization for the Research and Treatment of Cancer
EOT	end of treatment
EQ-5D	EuroQol 5-dimensions
FDA	Food and Drug Administration
HbA1c	hemoglobin A1c
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
Ig	immunoglobulin
IHC	immunohistochemistry
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
IRF	independent review facility
IRR	infusion-related reaction
IV	intravenous
LFT	liver function test
MMAE	monomethyl auristatin E
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NCI CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death protein 1

PD-L1	programmed death-ligand 1
PFS	progression-free survival
PK	pharmacokinetics
PP	per-protocol
PR	partial response
PRO	patient reported outcomes
PT	prothrombin time
PTT	partial thromboplastin time
QLQ-C30	EORTC Quality of Life Questionnaire
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
TAb	total antibody
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
vc	valine-citrulline

1 INTRODUCTION

1.1 Urothelial Cancer

According to the International Agency for Research on Cancer urothelial cancer kills more than 165,000 patients annually and is the ninth most common cancer overall worldwide. Approximately 151,000 new cases of urothelial cancer are diagnosed annually in Europe, with 52,000 deaths per year. Over 22,000 new cases are diagnosed annually in Japan, with 7,600 deaths per year (Cancer Today, http://gco.iarc.fr/today/. Accessed Jan 31, 2017). According to National Cancer Institute estimates, approximately 77,000 new cases of urothelial cancer were diagnosed in 2016, and more than 16,000 people died from the disease in the United States (US) alone (National Cancer Institute 2016). Metastatic urothelial cancer has a 5-year mortality rate exceeding 85%.

First-line therapy for metastatic urothelial cancer in patients with sufficient renal function consists of cisplatin-based combinations, like methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) and gemcitabine with cisplatin, which demonstrate an overall response rate up to 50%, including approximately 10%–15% complete responses (CRs) (Bellmunt 2011). Despite initial chemosensitivity, patients are not cured and the outcome of metastatic urothelial cancer after these regimens is poor: median time to progression is only 7 months and median overall survival (OS) is 14 months. Approximately 15% of patients experience 5-year survival and the prognosis is particularly poor among patients with visceral metastases for whom the 5-year OS rate is 7% (von der Maase 2005).

Almost half of urothelial cancer patients are unfit for cisplatin-containing chemotherapy due to impaired renal function, poor performance status or comorbidity (Dash 2006). In this setting, long term survival is even lower (De Santis 2009). In April 2017, the Food and Drug Administration (FDA) approved the anti-programmed death-ligand 1 (PD-L1) immune checkpoint inhibitor (CPI) atezolizumab (TECENTRIQ®) as first line treatment for patients ineligible for cisplatin. The accelerated approval was based on an open-label single arm study that showed long durations of response, indicating activity in this difficult-to-treat population, with an objective response rate (ORR) of 23% that was similar across varying levels of target expression. The median OS for these patients was 15.9 months, although this is a single arm study and any OS benefit will need to be confirmed in a randomized experience (Balar 2017).

Pembrolizumab (Keytruda®) received accelerated approval from the FDA in May 2017 as first line treatment for patients ineligible for cisplatin. The approval was based on an open label single arm study in 370 patients showing an ORR of 29% (Keytruda Prescribing Information, Merck, May 2017).

Other options for first line cisplatin-ineligible patients typically include carboplatin-based regimens or single-agent taxane or gemcitabine (Cathomas 2015).

1.2 Second-Line Therapy Options for Metastatic Urothelial Cancer

Few options are available for second-line treatment of metastatic disease. In the European Union, the small-molecule tubulin inhibitor vinflunine (Javlor®) was authorized in 2009 based on modest activity (overall response rate 9%), moderate survival benefit of 2 months (6.9 months for vinflunine + best supportive care [BSC] vs 4.6 months for BSC alone, hazard ratio 0.88), and a favorable safety profile (Bellmunt 2009). In May 2016, the FDA provided accelerated approval of atezolizumab as the first salvage therapy following platinum agents for locally advanced or metastatic urothelial carcinoma in the US, followed by EU approval in September 2017. In February 2017, nivolumab (Opdivo®) became the second immunotherapy granted accelerated approval by the FDA, which was followed by EU approval in June 2017. In March and May 2017, the FDA granted accelerated approval for avelumab (Bavencio®) and durvalumab (Imfinzi™), respectively, both PD-L1 blocking antibodies indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. . Pembrolizumab received regular approval from the FDA in May 2017 as second-line treatment (Keytruda Prescribing Information, Merck, May 2017). The approval was based on the first randomized experience reported for a CPI in the locally advanced or metastatic post-platinum urothelial cancer setting, a phase 3 study in 542 patients showing an OS of 10.3 months as compared to 7.4 months with taxane chemotherapy or vinflunine. Additionally, ORR was 21% for pembrolizumab and 11% for chemotherapy. No statistically significant difference in progression-free survival (PFS) between the two arms was observed (Bellmunt 2017). EU approval for the same indication was granted in September 2017 and Japanese approval in January 2018. Other programmed cell death protein 1 (PD-1) and PD-L1 inhibitors are currently being evaluated in clinical trials for urothelial cancer, as first and second-line therapy (Mullane 2016).

While CPIs offer a new approach to treatment of metastatic urothelial cancer, tumor responses have occurred in a minority of patients and the improvement in long-term survival is only a few months. For example, in May 2017, Roche announced that a confirmatory phase 3 trial of second-line atezolizumab had failed to meet its primary endpoint of OS (Roche, press release "Roche provides update on phase III study of Tecentriq [atezolizumab] in people with previously treated advanced bladder cancer," 10-May-2017). Most patients with locally advanced or metastatic urothelial cancer do not respond to CPIs and many who do respond ultimately develop disease progression (Rosenberg 2016). Novel treatments are still needed, particularly for patients who have not responded to CPIs or who have progressed following CPI therapy.

Currently, no therapies are approved for patients previously treated with a CPI. Although taxanes are not approved in this setting, they are a common choice for third line treatment (and were a standard second-line treatment before atezolizumab was approved). Taxanes have response rates of approximately 10% as second-line therapy, with progression-free survival (PFS) and OS of only 3.3 months and 7.4 months, respectively (Bellmunt 2017). No

data are currently available regarding the clinical activity of taxanes in the third line setting after CPI therapy.

The lack of approved therapies for patients with metastatic urothelial cancer after treatment with a CPI and the limited activity observed with second-line chemotherapy adequately demonstrate that this population has significant unmet medical need. This patient population appears appropriate for this phase 2 study.

1.3 Nectin-4

Nectin-4 is a 66 kDa type I transmembrane protein that belongs to the nectin family of adhesion molecules. It is composed of an extracellular domain (ECD) containing 3 immunoglobulin (Ig)-like subdomains, a transmembrane helix, and an intracellular region (Takai 2008a). Nectins are thought to mediate Ca^{2+}-independent cell-cell adhesion via both homophilic and heterophilic trans-interactions at adherens junctions where they can recruit cadherins and modulate cytoskeletal rearrangements (Rikitake 2008). Sequence identity of Nectin-4 to other Nectin family members is low and ranges between 25%–30% in the ECD (Reymond 2001).

The 3 Ig-like subdomains in the ECD of Nectin-4 are designated V, C1 and C2. The C1 domain is responsible for cis-interaction (homodimerization), while V domains of most Nectin molecules contribute to trans-interaction and cell-cell adhesion (Mandai 2015; Takai 2008b).

Nectin-4 was originally identified by bioinformatics and cloned from human trachea (Reymond 2001). Nectin-4 was identified as markedly upregulated in urothelial cancer using suppression subtractive hybridization on a pool of urothelial cancer specimens. Characterization of expression in multiple tumor specimens, both at the ribonucleic acid (RNA) level and by immunohistochemistry (IHC), also demonstrated high levels of Nectin-4 in breast, pancreatic, lung, and other cancers (Challita-Eid 2016).

1.4 Nectin-4 as a Target in Metastatic Urothelial Cancer

Nectin-4 has been found to be expressed in multiple cancers, particularly urothelial, breast, lung, pancreatic, and ovarian cancers. Higher levels of expression are associated with disease progression and/or poor prognosis (Fabre-Lafay 2007).

Although no longer required for metastatic urothelial cancer patients prior to enrollment, in an ongoing phase 1 study of enfortumab vedotin in multiple cancer types including metastatic urothelial cancer (Study ASG-22CE-13-2), patients were initially prescreened for Nectin-4 expression. Nectin-4 expression is still assessed in archival tissue, though metastatic urothelial cancer patients may enroll regardless of Nectin-4 expression. An H-score, derived from the intensity of staining with anti-Nectin-4 antibody and the percentage of cells expressing Nectin-4 in the tumor tissue, was determined for each screened patient. H-score values range between 0 (no expression) and 300 (maximal expression).

Of 186 patients with metastatic urothelial cancer whose tumor tissue was screened using a central Clinical Laboratory Improvement Amendments laboratory-validated test, more than 97% had detectable Nectin-4 expression. Ninety-three percent of these patients met the initial criterion for enrollment in the phase 1 study (H-score ≥150). The median H-score was 280.

Based upon the prevalence of high Nectin-4 expression in this population of metastatic urothelial cancer patients, this phase 2 study does not include an eligibility requirement for a minimum level of Nectin-4 expression. However, Nectin-4 expression will be assessed with tumor tissue collected at screening.

1.5 Enfortumab Vedotin

Enfortumab vedotin is a Nectin-4 targeted monoclonal antibody (AGS-22C3) covalently linked to the microtubule-disrupting agent monomethyl auristatin E (MMAE). Enfortumab vedotin consists of three functional subunits:

- A fully human IgG1K antibody (AGS-22C3)
- The microtubule-disrupting agent MMAE
- A protease-cleavable maleimidocaproyl-valine-citrulline (vc) linker that covalently attaches MMAE to AGS-22C3

Enfortumab vedotin binds the V domain of Nectin-4 (Challita-Eid 2016). In the presumed mechanism of action, the drug binds Nectin-4 protein on the cell surface and is internalized, causing proteolytic cleavage of the vc linker and intracellular release of MMAE. Free MMAE subsequently disrupts tubulin polymerization and leads to mitotic arrest.

1.6 Rationale for Enfortumab Vedotin in Metastatic Urothelial Cancer, Clinical Safety and Efficacy

A phase 1 dose escalation and expansion study with enfortumab vedotin monotherapy in patients with metastatic urothelial cancer and other malignant solid tumors is ongoing (Study ASG-22CE-13-2). In this study, patients received doses of enfortumab vedotin ranging from 0.5 to 1.25 mg/kg on Days 1, 8, and 15 of each 28-day cycle.

As of the data cut-off date of 02 October 2017, 140 metastatic urothelial cancer patients had been enrolled in the phase 1 study. Interim data suggest that enfortumab vedotin is generally well tolerated at doses up to 1.25 mg/kg, and induces multiple objective responses in this patient population.

Among metastatic urothelial cancer patients, 137 (98%) experienced a treatment-emergent adverse event (TEAE), and 122 (87%) of these patients' TEAEs were deemed possibly or probably related to study drug by the investigator. The most common TEAEs among metastatic urothelial cancer patients were fatigue (49%), nausea (45%), decreased appetite (39%), alopecia (37%), diarrhea (36%), dysgeusia (31%), pruritus (29%), anemia (26%), abdominal pain (24%), constipation (24%), vomiting (24%), and weight decreased (20%).

Drug doses were reduced in 18 out of 140 metastatic urothelial cancer patients (13%) due to adverse events (AEs), including 16 out of 97 patients (17%) in the 1.25 mg/kg dose group. Drug was withdrawn in 26 out of 140 (19%) metastatic urothelial cancer patients due to AEs, including 13 out of 97 (13%) from the 1.25 mg/kg dose group. Across all dose levels, drug was withdrawn from 12 out of 140 (9%) metastatic urothelial cancer patients due to AEs deemed possibly or probably related to enfortumab vedotin. In the 1.25 mg/kg dose group, drug was withdrawn from 6 out of 97 (6%) metastatic urothelial cancer patients due to AEs deemed as possibly or probably related to enfortumab vedotin. TEAEs leading to study drug discontinuation among urothelial cancer patients included peripheral neuropathy, urosepsis, increased aspartate aminotransferase (AST), acute kidney injury, and increased blood creatinine in 2 patients each.

Fifty-five metastatic urothelial cancer patients (39%) experienced at least one treatment emergent serious adverse event (SAE). Sixteen patients (11%) had SAEs that were deemed by the investigator to be possibly or probably related to treatment. At the 1.25 mg/kg dose level, 31 out of 97 patients (32%) had at least one treatment emergent SAE. Nine patients (9%) had SAEs that were deemed by the investigator to be possibly or probably related to treatment. As of the 02 October 2017 data cut-off date, there were 6 fatal TEAEs in the metastatic urothelial cancer patients during this study, and 2 were deemed to be drug-related.

As of the 02 October 2017 data cut-off date, 1 of the related fatal events in Study ASG-22CE-13-2 was reported in conjunction with serious hyperglycemia. Following the data cut-off date, 2 additional treatment-related fatal events associated with serious hyperglycemia were reported in October 2017. All active enfortumab vedotin study protocols were immediately amended to address this new safety information (See Appendix H Amendment 1). No additional treatment-related fatal events have been reported as of 15 March 2018.

A summary of the clinical and nonclinical safety data relevant to the investigational product and its study in human subjects are provided in the Investigator's Brochure. Based upon the totality of the safety data available the observed safety profile supports further clinical development of enfortumab vedotin in metastatic urothelial cancer patients.

Enfortumab vedotin shows encouraging antitumor activity in patients with metastatic urothelial cancer with either post-baseline imaging or who had discontinued treatment before imaging. As of the data cut-off date of 02 October 2017, there were 5 CRs and 50 partial responses (PRs) (ORR=45%, 55 of 121 patients) across dose levels. The ORR at 1.25 mg/kg (the dose level for the present study) was 54% (42 out of 78 patients). Disease control (CR + PR + stable disease [SD]) was reached in 69% of metastatic urothelial cancer patients (84 of 121 patients), including 71% in the 1.25 mg/kg dose group (55 of 78 patients).

Enfortumab vedotin also shows promising antitumor activity in metastatic urothelial cancer patients previously treated with CPIs who had either post-baseline imaging or had discontinued treatment before imaging. Across dose levels, the ORR was 50% (35 out of 70 patients), and at 1.25 mg/kg the ORR was 53% (29 out of 55 patients). Disease control

was reached in 73% (51 of 70 patients), including 75% (41 of 55 patients) of the 1.25 mg/kg dose group.

Confirmed ORR was 27% across all dose levels (33 of 121 patients) and 32% at 1.25 mg/kg (25 of 78 patients). In patients previously treated with a CPI, the confirmed ORR was 31% (17 out of 55 patients) at 1.25 mg/kg.

This phase 2 study is designed to further investigate the encouraging clinical safety and efficacy data observed in the ongoing phase 1 trial of enfortumab vedotin in metastatic urothelial cancer patients, including patients previously treated with CPIs.

Clinical data to date support a favorable benefit-risk ratio for enfortumab vedotin in patients with locally advanced or metastatic urothelial carcinoma who previously received CPI therapy. To assure an ongoing favorable benefit-risk assessment for subjects enrolled into the study, an Independent Data Monitoring Committee (IDMC) will be utilized to monitor safety data and may request interim efficacy data, if needed.

2 OBJECTIVES

2.1 Primary Objective

- To determine the antitumor activity of single-agent enfortumab vedotin as measured by confirmed ORR in patients with locally advanced or metastatic urothelial cancer who have previously received systemic therapy with a CPI and either previously received platinum-containing chemotherapy or are platinum-naïve and cisplatin-ineligible

2.2 Secondary Objectives

- To assess DOR
- To assess disease control rate (DCR)
- To assess PFS
- To assess OS
- To assess the safety and tolerability of enfortumab vedotin
- To assess the pharmacokinetics (PK) of enfortumab vedotin
- To assess the incidence of antitherapeutic antibodies (ATA)

2.3 Additional Objectives

- To explore potential correlations between biomarkers and clinical outcomes
- To evaluate the treatment effect of enfortumab vedotin on quality of life (QoL)

2.4 Endpoints

2.4.1 Primary Endpoint

- The primary efficacy endpoint of this study is ORR (confirmed CR or PR per Response Evaluation Criteria in Solid Tumors [RECIST] Version 1.1) as determined by an independent review facility (IRF)

2.4.2 Secondary Endpoints

- DOR (confirmed CR or PR) per IRF
- DCR_{16} (disease control rate [CR, PR or SD] at 16 weeks) per IRF
- PFS per IRF
- ORR per investigator assessment
- DOR per investigator assessment
- DCR_{16} per investigator assessment
- PFS per investigator assessment
- OS
- Type, incidence, severity, seriousness, and relatedness of AEs
- Laboratory abnormalities
- Selected plasma or serum PK parameters of enfortumab vedotin, MMAE, and total antibody (TAb)
- Incidence of ATA to enfortumab vedotin

2.4.3 Additional Endpoints

- Biomarkers of biological and clinical activity, including Nectin-4 expression
- Patient reported outcomes (PRO) per the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30)
- PRO per EuroQol 5-dimensions (EQ-5D), including health utility values, and visual analog scale

3 INVESTIGATIONAL PLAN

3.1 Summary of Study Design

This is a single-arm, open-label, multicenter trial designed to assess the efficacy and safety of enfortumab vedotin as a single agent in locally advanced or metastatic urothelial cancer patients who have previously received systemic therapy with a CPI. Patients must also either have received prior treatment with platinum-containing chemotherapy (Cohort 1) or received

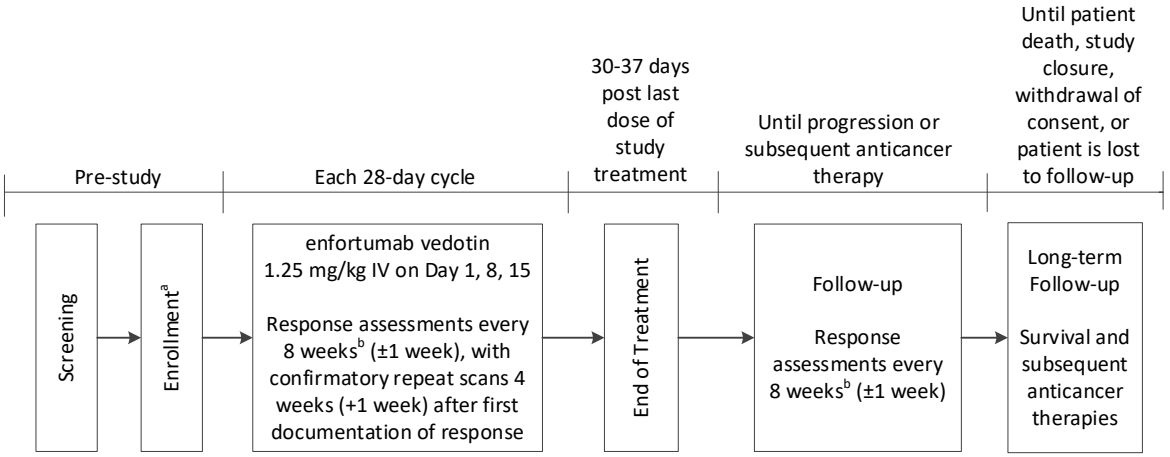
no prior platinum-containing or other chemotherapy and are ineligible for treatment with cisplatin at time of enrollment. (Cohort 2). Patients must have progressive disease (PD) during or following their most recent therapy. There are no limits for prior lines of therapy, including taxanes.

Enfortumab vedotin at a dose of 1.25 mg/kg will be administered as an intravenous (IV) infusion over approximately 30 minutes on Days 1, 8, and 15 of each 28-day cycle. Measures of anticancer activity will be assessed by computed tomography (CT scans with contrast, unless contraindicated) every 8 weeks (±1 week) timed from Cycle 1 Day 1 during treatment. After 1 year on study the frequency of response assessments will be reduced to every 12 weeks (±1 week). Patients will continue to receive study treatment until disease progression, unacceptable toxicity, investigator decision, consent withdrawal, start of subsequent anticancer therapy, pregnancy, or study termination by the sponsor. After discontinuation of study treatment, patients will be followed every 8 weeks (±1 week) for response assessments, Eastern Cooperative Oncology Group (ECOG) performance status, and physical exams. After 1 year on study the frequency of follow up visits including response assessments will be reduced to every 12 weeks (±1 week). Patients that have radiologically-confirmed disease progression (per RECIST 1.1 as determined by the investigator) or have begun subsequent anticancer therapy will be contacted every 8 weeks (±1 week) up to 1 year on study, and every 12 weeks (±1 week) thereafter to obtain information on subsequent anticancer therapy, and survival status until death, study closure, withdrawal of consent, or patient is lost to follow-up, whichever occurs first (see Figure 1). The study will be closed 5 years after enrollment of the last patient, or when no patients remain in long-term follow-up, whichever occurs first. Additionally, the sponsor may terminate the study at any time.

On a periodic basis, an IDMC will monitor the safety of patients participating in this trial. The IDMC will be responsible for evaluating the results of safety analyses and will make recommendations to the sponsor. The IDMC may also request efficacy data, if needed, to evaluate risk/benefit before making recommendations. The IDMC will make recommendations to either continue the study unchanged, to modify the study, or to discontinue the study. If corneal AEs are observed in <15% of the first 60 enrolled patients (from Cohorts 1 and/or 2) and if the events are generally low grade or asymptomatic, the IDMC may make a recommendation to cease Cycle 2 Day 22 and/or Cycle 6 Day 22 slit lamp exams for the remaining patients if warranted based on review of the cumulative ocular safety data. The IDMC will communicate the recommendations to the sponsor. The final decision to act on the IDMC recommendations will be made by the sponsor. The IDMC recommended to cease Cycle 2 Day 22 and Cycle 6 Day 22 slit lamp exams in Jul 2018 and Aug 2019, respectively.

An ongoing real-time review of patient safety and SAEs will also be conducted by the sponsor's Drug Safety Department.

Figure 1: Study schema



a There are 2 cohorts of CPI-treated patients in the study: Cohort 1) platinum-treated patients, and Cohort 2) platinum-naïve/cisplatin-ineligible patients.
b After 1 year on study, the frequency of response assessments will be reduced to every 12 weeks (±1 week).

3.2 Discussion and Rationale for Study Design

This study will enroll patients who have previously received CPI therapy. Based on prior treatment patterns, taxanes or vinflunine are anticipated to be the next line of therapy to address post-CPI relapsed disease, but response rates are expected to be only 9%–13% (Bellmunt 2017; Bellmunt 2009; Choueiri 2012; McCaffrey 1997). Data presented from a recent study of patients treated with docetaxel after platinum and CPI therapy showed a 10.5% ORR (n=2/19) (Drakaki 2018). Recently, 10% has been used as the historical response rate expected for both platinum pre-treated second-line and cisplatin ineligible first-line patients (Balar 2017; Rosenberg 2016). Given that patients enrolled in the current study have a poor prognosis and represent an area of unmet medical need, the lower bound of the exact 95% confidence interval (CI) for ORR that excludes a historical response rate of 10% is considered to be a meaningful improvement over currently available therapies with the proposed enrollment of approximately 100 patients.

The primary endpoint of this study, confirmed ORR, is a direct measure of antitumor activity and is an acceptable surrogate endpoint (FDA Guidance for Industry "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics"). To further assess the significance of ORR in this study, the durability of response will be evaluated as a secondary endpoint. Furthermore, standardized RECIST (Version 1.1, see Appendix D) criteria (Eisenhauer 2009) will be employed by investigators and the IRF to evaluate responses. Responses will be confirmed per IRF with repeat scans 4 weeks (+1 week) after initial documentation of response.

ORR may be evaluated in a single-arm study when it is defined as the sum of PR plus CR (FDA Guidance for Industry "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics"). Moreover, to ensure consistent unbiased application of the RECIST criteria in this open-label study, all imaging assessments performed to confirm disease status at study

entry and to assess responses during the study will be submitted to an independent third-party imaging core laboratory.

3.2.1 Method of Assigning Patients to Treatment Groups

This is a single-arm study in which all patients will receive 1.25 mg/kg enfortumab vedotin administered as an IV infusion over approximately 30 minutes on Day 1, 8, and 15 of each 28-day treatment cycle.

3.2.2 Rationale for Selection of Doses

Enfortumab vedotin will be administered at a dose of 1.25 mg/kg as an IV infusion over approximately 30 minutes on Days 1, 8, and 15 of each 28-day cycle. This dose and regimen has demonstrated an acceptable safety profile and encouraging antitumor activity in the phase 1 study (Study ASG-22CE-13-2).

In the phase 1 study, enfortumab vedotin was administered on Days 1, 8, and 15 of every 28-day treatment cycle. The study tested escalating dose levels of 0.5, 0.75, 1, and 1.25 mg/kg, with expansion cohorts at the 0.75, 1, and 1.25 mg/kg dose levels. A maximum tolerated dose was not reached in this study.

As of the 02 October 2017 data cut-off date, at the 1 mg/kg dose level, increased alanine aminotransferase levels was the only dose-limiting toxicity observed (1 out of 14). No DLT was observed at 1.25 mg/kg and doses above 1.25 mg/kg were not tested. Incidence of some of the most frequent drug-related AEs, such as decreased appetite, alopecia, diarrhea and rash, although primarily Grades 1–2 and clinically manageable, increased with increasing dose levels among patients with urothelial cancer. The most common study drug-related AE, fatigue, occurred in 21%, 33%, and 43% of urothelial cancer patients in the 0.75, 1, and 1.25 mg/kg dose groups, respectively. Similarly, study-drug related nausea, alopecia, decreased appetite, and diarrhea were all more common in the 1.25 mg/kg dose group than the 0.75 mg/kg dose group. Moreover, dose reductions due to AEs were more frequent for the 1.25 mg/kg vs lower dose levels. Safety assessments of metastatic urothelial cancer patients (N=140) showed that frequency of all TEAEs were comparable across all dose levels. AEs leading to withdrawal and Grade 3–4 TEAEs were less frequent in the 1.25 mg/kg dose level than at lower dose levels.

While all doses of enfortumab vedotin demonstrated activity, the 1.25 mg/kg dose was associated with the highest activity and had an acceptable safety profile. The confirmed ORR in patients with metastatic urothelial cancer treated at the 1.25 mg/kg dose was 32% (25 out of 78 patients) versus 19% (8 out of 43) for patients treated with doses less than 1.25 mg/kg.

Based on PK data from the phase 1 study (Study ASG-22CE-13-2), the half-life of enfortumab vedotin is ~1–2 days. No notable (<30%) intra-cycle accumulation of antibody-drug conjugate (ADC) was observed with the current dosing regimen (on Days 1, 8, and 15 of every 28-day cycle) at any dose level. Minimal (<50%) intra-cycle accumulation of MMAE was observed. It is anticipated that the dosing schedule in the study will maintain

ADC exposures over each 28-day cycle, contributing to a favorable balance of activity and safety, as observed in the phase 1 trial (Study ASG-22CE-13-2).

In summary, the dose regimen of 1.25 mg/kg on Days 1, 8, and 15 of each 28-day cycle proposed for the phase 2 study has demonstrated an acceptable safety profile and encouraging clinical activity that was higher than at lower dose levels.

3.2.3 Blinding

This is an open-label, single-arm study.

4 STUDY POPULATION

All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular patient. Patients must meet all of the enrollment criteria to be eligible for this study. Eligibility criteria may not be waived by the investigator and are subject to review in the event of a good clinical practice audit and/or health regulatory authority inspection.

4.1 Inclusion Criteria

1. Patients must have histologically documented urothelial (previously known as transitional cell) carcinoma (i.e., cancer of the bladder, renal pelvis, ureter, or urethra). Patients with squamous differentiation or mixed cell types are eligible. Patients with resectable locally advanced disease are ineligible.

2. Patient must have received prior treatment with a CPI in the locally advanced or metastatic urothelial cancer setting. Patients who received CPI therapy in the neoadjuvant/adjuvant setting and had recurrent or progressive disease either during therapy or within 3 months of therapy completion are eligible. A CPI is defined as a PD-1 inhibitor or PD-L1 inhibitor (including, but not limited to: atezolizumab, pembrolizumab, durvalumab, avelumab, and nivolumab).

3. Patients must be one of the following:

    a. Platinum-treated (Cohort 1): Patients who received prior treatment with platinum-containing chemotherapy defined as those who received platinum in the adjuvant/neoadjuvant setting and had recurrent or progressive disease within 12 months of completion OR received treatment with platinum in the locally advanced (defined as unresectable with curative intent) or metastatic setting;

    OR

    b. Platinum-naïve and cisplatin ineligible (Cohort 2): Patients who have not received prior treatment with platinum-containing or other chemotherapy in the locally advanced or metastatic setting and are ineligible for treatment with cisplatin at time of enrollment due to one of the following: ECOG performance status score of 2; impaired renal function (defined as creatinine clearance [CrCl] ≥30 and <60 mL/min),

or a ≥ Grade 2 hearing loss. Patients who received platinum in the adjuvant/neoadjuvant setting and did not progress within 12 months of completion will be considered platinum-naïve.

4. Patients must have had progression or recurrence of urothelial cancer during or following receipt of most recent therapy.
5. Tumor tissue samples must be available for submission to the sponsor prior to study treatment.
6. Legally an adult according to local regulation at the time of signing informed consent, and minimum age of 18 years.
7. Patients must have measurable disease according to RECIST (Version 1.1) (Eisenhauer 2009). Lesions in a prior radiation field must have progressed subsequent to radiotherapy to be considered measurable.
8. An ECOG performance status score of ≤1 for Cohort 1, or ≤2 for Cohort 2.
9. The following baseline laboratory data, assessed locally (no transfusions are permitted within 2 weeks prior to screening):
   - absolute neutrophil count $\geq 1.0 \times 10^9$/L
   - platelet count $\geq 100 \times 10^9$/L
   - hemoglobin ≥9 g/dL
   - serum bilirubin ≤1.5 × upper limit of normal (ULN) or ≤3 × ULN for patients with Gilbert's disease
   - CrCl ≥30 mL/min as measured by 24-hour urine collection or estimated by the Cockcroft-Gault criteria
   - alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 × ULN
10. Female patient must either:
    - Be of nonchildbearing potential:
      - Postmenopausal* (defined as at least 1 year without any menses) prior to screening, or
      - Documented surgically sterile (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy, bilateral tubal occlusion)

      *Those who are amenorrheic due to an alternative medical cause are not considered postmenopausal and must follow the criteria for childbearing potential patients
    - Or, if of childbearing potential,
      - Agree not to try to become pregnant during the study and for at least 6 months after the final study drug administration,

- And have a negative urine or serum pregnancy test within 7 days prior to Day 1 (Females with false positive results and documented verification of negative pregnancy status are eligible for participation),
- And if heterosexually active, agree to abstinence (if in line with the usual preferred lifestyle of the patient) or consistently use a condom plus 1 form of highly effective birth control[†] per locally accepted standards starting at screening and throughout the study period and for at least 6 months after the final study drug administration

11. Female patient must agree not to breastfeed or donate ova starting at screening and throughout the study period, and for at least 6 months after the final study drug administration.

12. A sexually active male patient with female partner(s) who are of childbearing potential is eligible if:

    - Agree to abstinence (if in line with the usual preferred lifestyle of the patient) or to use a male condom starting at screening and continue throughout study treatment and for at least 6 months after the final study drug administration. If the male patient has not had a vasectomy or is not sterile as defined below their female partner(s) is utilizing 1 form of highly effective birth control[†] per locally accepted standards starting at screening and continuing throughout study treatment and for at least 6 months after the male patient receives their final study drug administration.

13. Male patient must not donate sperm starting at screening and throughout the study period, and for at least 6 months after the final study drug administration.

14. Male patient with a pregnant or breastfeeding partner(s) must agree to abstinence or use a condom for the duration of the pregnancy or time their partner is breastfeeding throughout the study period and for at least 6 months after the final study drug administration.

    [†]Highly effective forms of birth control include:
    - Consistent and correct usage of established hormonal contraceptives that inhibit ovulation
    - Established intrauterine device (IUD) or intrauterine hormone releasing system (IUS)
    - Vasectomy (a vasectomy is a highly effective contraception method provided the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used)
    - Male is sterile due to a bilateral orchiectomy or radical cystoprostatectomy/removal of seminal vesicles

15. The patient must provide written informed consent.

16. Patients must have an anticipated life expectancy of ≥3 months as assessed by the investigator.

4.2 Exclusion Criteria

1. Ongoing sensory or motor neuropathy Grade ≥2.
2. Active central nervous system (CNS) metastases. Patients with treated CNS metastases are permitted on study if all the following are true:
   - CNS metastases have been clinically stable for at least 6 weeks prior to screening and baseline scans show no evidence of new or enlarged metastasis
   - If requiring steroid treatment for CNS metastases, the patient is on a stable dose ≤20 mg/day of prednisone or equivalent for at least 2 weeks
   - Patient does not have leptomeningeal disease
3. Ongoing clinically significant toxicity (Grade 2 or higher) associated with prior treatment (including systemic therapy, radiotherapy or surgery). Patients with ≤ Grade 2 hypothyroidism or panhypopituitarism related to treatment with PD-1 and PD-L1 inhibitors may be enrolled. Patients on hormone replacement therapy may be enrolled if on a stable dose. Patients with ≥ Grade 3 immunotherapy-related hypothyroidism or panhypopituitarism are excluded. Patients with immunotherapy related myocarditis, colitis, uveitis, or pneumonitis are excluded. Patients with other immunotherapy related adverse events requiring high doses of steroids (>20 mg/day of prednisone or equivalent) are excluded.
4. Prior enrollment in an enfortumab vedotin study or prior treatment with other MMAE-based ADCs.
5. History of another malignancy within 3 years before the first dose of study drug, or any evidence of residual disease from a previously diagnosed malignancy. Patients with nonmelanoma skin cancer, localized prostate cancer treated with curative intent with no evidence of progression, low-risk or very low-risk (per standard guidelines) localized prostate cancer under active surveillance/watchful waiting without intent to treat, or carcinoma in situ of any type (if complete resection was performed) are allowed.
6. Currently receiving systemic antimicrobial treatment for active infection (viral, bacterial, or fungal) at the time of first dose of enfortumab vedotin. Routine antimicrobial prophylaxis is permitted.
7. Patients with a positive hepatitis B surface antigen and/or antihepatitis B core antibody. Patients with a negative polymerase chain reaction (PCR) assay are permitted with appropriate antiviral prophylaxis.
8. Active hepatitis C infection or known human immunodeficiency virus (HIV) infection. Patients who have been treated for hepatitis C infection are permitted if they have documented sustained virologic response of ≥12 weeks.
9. Documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, myocardial infarction, or cardiac symptoms (including congestive heart

failure) consistent with New York Heart Association Class III-IV (see Appendix C) within 6 months prior to the first dose of enfortumab vedotin.

10. Radiotherapy or major surgery within 2 weeks prior to first dose of study drug.
11. Chemotherapy, biologics, investigational agents, and/or antitumor treatment with immunotherapy that is not completed 2 weeks prior to first dose of study drug.
12. Known hypersensitivity to enfortumab vedotin or to any excipient contained in the drug formulation of enfortumab vedotin (including histidine, trehalose dihydrate, and polysorbate 20).
13. Patients with active keratitis or corneal ulcerations. Patients with superficial punctate keratitis are allowed if the disorder is being adequately treated in the opinion of the investigator.
14. Other underlying medical condition that, in the opinion of the investigator, would impair the ability of the patient to receive or tolerate the planned treatment and follow-up.
15. Patients with uncontrolled diabetes. Uncontrolled diabetes is defined as hemoglobin A1c (HbA1c) ≥8% or HbA1c 7–<8% with associated diabetes symptoms (polyuria or polydipsia) that are not otherwise explained.
16. Uncontrolled tumor-related bone pain or impending spinal cord compression. Patients requiring pain medication must be on a stable regimen at the time of enrollment (a minimum of 2 weeks).

4.3 Removal of Patients From Therapy or Assessment

Seattle Genetics or their designee must be notified if a patient is withdrawn from study treatment or from the study. The reason(s) for withdrawal must be documented in the patient's medical records and case report form (CRF).

4.3.1 Discontinuation of Study Treatment

A patient's study treatment may be discontinued for any of the following reasons:

- PD
- AE
- Investigator decision
- Patient decision, non-AE
- Study termination by sponsor
- Other, non-AE
- Pregnancy

Patients who discontinue from study treatment will remain on study for follow-up unless they withdraw consent.

4.3.2 Patient Withdrawal From Study

Any patient may be discontinued from the study for any of the following reasons:

- Patient withdrawal of consent
- Study termination by sponsor
- Lost to follow-up
- Death
- Other

5 TREATMENTS

5.1 Treatments Administered

Patients in this study will receive enfortumab vedotin 1.25 mg/kg administered as an IV infusion over approximately 30 minutes on Days 1, 8, and 15 of every 28-day cycle.

5.2 Investigational Study Drug

Detailed information describing the preparation, administration, and storage of enfortumab vedotin is located in the Pharmacy Binder.

5.2.1 Description

Enfortumab vedotin is generated by conjugation of a chemical intermediate that contains both the MMAE and linker subunits, to cysteine residues of the antibody. The resulting ADC contains an average of 3.8 drug molecules per antibody. The enfortumab vedotin drug product is a sterile, preservative free, white to off-white lyophilized powder to be reconstituted for IV administration. Enfortumab vedotin is supplied in 30 mg single-dose vials. Please refer to the Pharmacy Binder for further information.

5.2.2 Dose and Administration

Enfortumab vedotin at a dose of 1.25 mg/kg will be administered as an IV infusion over approximately 30 minutes on Days 1, 8, and 15 of every 28-day cycle. In the absence of infusion-related reactions (IRRs), the infusion rate for all patients should be calculated in order to achieve an approximate 30-minute infusion period. Enfortumab vedotin must not be administered as an IV push or bolus. Enfortumab vedotin should not be mixed with other medications. At least 1 week must elapse between doses of enfortumab vedotin.

Weight-based dosing is calculated using the patient's actual body weight. **An exception to weight-based dosing is made for patients weighing greater than 100 kg; doses will be based on 100 kg for these individuals. The maximum dose permitted on this study is 125 mg.**

Doses must be adjusted for patients who experience a ≥10% change in weight from baseline, or previous cycle. Patient weight must be measured during all relevant assessment windows as described in the schedule of events. Other dose adjustments for changes in body weight <10% are permitted per institutional standard.

The injection site should be monitored closely for redness, swelling, pain, and infection during and at any time after administration. Patients should be advised to report redness or discomfort promptly at the time of administration or after infusion. Institutional guidelines will be followed for the administration of chemotherapy agents and precautions taken to prevent extravasation per institutional standards and as described in "Chemotherapy and Biotherapy Guidelines and Recommendations for Practice" (Polovich 2014) and "Management of Chemotherapy Extravasation: ESMO-EONS Clinical Practice Guidelines" (Perez Fidalgo 2012).

The patient should be observed during administration of enfortumab vedotin and for at least 60 minutes following the infusion during the first 3 cycles. All supportive measures consistent with optimal subject care should be given throughout the study according to institutional standards.

5.2.3 Dose Modifications

Intrapatient dose reduction to 1 mg/kg (dose level –1), and to 0.75 mg/kg (dose level –2) will be allowed depending on the type and severity of toxicity. Patients requiring a dose reduction may be re-escalated by 1 dose level (e.g., patients reduced to 0.75 mg/kg may only be re-escalated to 1 mg/kg) provided the toxicity does not require study drug discontinuation and has returned to baseline or ≤ Grade 1. If the toxicity recurs, re-escalation will not be permitted. Patients with ≥ Grade 2 corneal AEs will not be permitted to dose re-escalate.

Enfortumab vedotin should not be administered to patients with known CrCl <30 mL/min. Dose modification recommendations for enfortumab vedotin-associated toxicity are presented in Table 1 and Table 2.

If toxicities occur on Day 1 of any cycle and require the enfortumab vedotin dose to be held, then the start of the cycle may be delayed. If toxicities occur on Days 8 or 15 of any cycle and require the dose to be held >2 days, then the dose(s) must be eliminated, rather than delayed. If a patient only receives enfortumab vedotin on Day 1 and needs to skip Days 8 and 15, the patient could resume the next cycle as early as Day 22 (new Day 1) if the toxicity has resolved by that time.

Intrapatient dose reduction or delay for other enfortumab vedotin-associated toxicity is permitted at the discretion of the site investigator. Dose delays may last up to 8 weeks (2 cycles). Dose delays for patients who are responding to treatment may be extended beyond 8 weeks, if the patient's toxicity does not otherwise require permanent discontinuation. Patients may not receive other investigational drugs, radiotherapy (except palliative radiotherapy as described in Section 5.3.2), or systemic antineoplastic therapy during dose delays. If there is a dose delay, the schedule for response assessments will not be adjusted and will continue to be timed from Cycle 1 Day 1 during treatment.

Table 1: Recommended dose modifications for enfortumab vedotin-associated hematologic toxicity

Grade 1	Grade 2	Grade 3	Grade 4
Continue at same dose level.	Continue at same dose level. For Grade 2 thrombocytopenia, withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose level.	Withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose level or consider dose reduction by 1 dose level. Transfusions or growth factors may be used as indicated per institutional guidelines.	Withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then reduce dose by 1 dose level and resume treatment, or discontinue at the discretion of the investigator. Transfusions or growth factors may be used as indicated per institutional guidelines. For anemia, treatment discontinuation should be strongly considered.

Table 2: Recommended dose modifications for enfortumab vedotin-associated nonhematologic toxicity

Grade 1	Grade 2	Grade 3	Grade 4
Continue at same dose level. If ocular symptoms and/or changes in vision are identified, the patient should be evaluated by a qualified optometrist or ophthalmologist.	Continue at same dose level, except in the event of Grade 2 neuropathy or corneal AEs. For Grade 2 neuropathy or corneal AEs, withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose level. For the second occurrence of Grade 2 neuropathy or corneal AEs, withhold dose until toxicity is ≤ Grade 1, then reduce the dose by 1 dose level and resume treatment. If ocular symptoms and/or changes in vision are identified, the patient should be evaluated by a qualified optometrist or ophthalmologist.	Withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose level or consider dose reduction by 1 dose level.[a] For Grade 3 neuropathy or corneal AEs, discontinue treatment. For Grade 3 hyperglycemia/elevated blood glucose withhold enfortumab vedotin treatment. Resume treatment once hyperglycemia/elevated blood glucose has improved to ≤ Grade 2 and patient is clinically and metabolically stable. If ocular symptoms and/or changes in vision are identified, the patient should be evaluated by a qualified optometrist or ophthalmologist.	For Grade 4 AEs, discontinue treatment.[a] Grade 4 vomiting and/or diarrhea that improves to ≤ Grade 2 within 72 hours with supportive management does not require discontinuation.

a Grade 3/4 electrolyte imbalances/laboratory abnormalities, except hyperglycemia, that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset do not require discontinuation (e.g., Grade 4 hyponatremia). Grade 3 rash that is not limiting self-care activities of daily living or associated with infection requiring systemic antibiotics does not require treatment interruption, provided symptoms are not severe and can be managed with supportive treatment.

See Section 5.4.1 for recommended management of infusion reactions. See Section 5.4.2 for recommended management of hyperglycemia. See Section 5.4.3 for recommended management of rash.

5.2.3.1 Treatment Discontinuation Recommendations Related to Liver Safety

In the absence of an explanation for increased liver function tests (LFTs), such as viral hepatitis, preexisting or acute liver disease, or exposure to other agents associated with liver injury, the patient may be discontinued from the study treatment. The investigator may determine that it is not in the patient's best interest to continue study treatment. Discontinuation of treatment should be considered if:

- ALT or AST >8 × ULN
- ALT or AST >5 × ULN for more than 2 weeks
- ALT or AST >3 × ULN and total bilirubin >2 × ULN or international normalized ratio (INR) >1.5 (if INR testing is applicable/evaluated)
- ALT or AST >3 × ULN with the appearance of symptoms suggestive of liver injury (e.g., right upper quadrant pain or tenderness) and/or eosinophilia (>5%)

These treatment discontinuation recommendations are based on the FDA Guidance for Industry (Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009). The recommendations are a basic guide to the investigator based on accumulated clinical experience with drugs in development, and are not specific to clinical experience with enfortumab vedotin.

See Appendix E for recommended liver safety monitoring and assessment criteria in patients with Grade 2 or greater elevations in ALT, AST, or bilirubin.

5.2.4 Storage and Handling

Refrigeration should be set at 2–8°C for storage of vials and solutions containing enfortumab vedotin. The controlled location must be accessible only to the pharmacist, the investigator, or a duly designated person. Study drug must be reconstituted before administration. Please refer to the Pharmacy Binder for information regarding stability of reconstituted study drug.

The effect of light on the study drug has not been assessed; therefore, it is recommended that vials of enfortumab vedotin lyophilized powder, reconstituted drug product and/or dosing solutions be protected from light until the time of use.

Do not shake reconstituted vials of the study drug.

Any partially used vials or prepared dosing solutions should be destroyed by the site according to institutional drug disposal procedures. Unused vials should be destroyed by the site or returned to the sponsor after authorization by the sponsor or designee. Drug accountability procedures are provided in the Pharmacy Binder.

5.2.5 Packaging and Labeling

Refer to the Pharmacy Binder for information regarding packaging and labeling.

5.2.6 Preparation

Recommended safety measures for handling and preparation include masks, protective clothing, gloves (double glove with nitrile gloves), and vertical laminar airflow safety cabinets.

Detailed drug preparation instructions are provided in the Pharmacy Binder.

5.3 Concomitant Therapy

All concomitant medications and blood products will be recorded from Day 1 (predose) through the safety reporting period (30 days after the last study treatment). Any concomitant medication given for a study protocol-related adverse event should be recorded from the time of informed consent.

5.3.1 Required Concomitant Therapy

There are no required concomitant therapies.

5.3.2 Allowed Concomitant Therapy

Concomitant chronic prednisone (or equivalent) may be used at a dose of ≤20 mg/day. Higher doses of prednisone (or equivalent) are permitted for limited duration to treat acute conditions that arise during the study as medically indicated. The use of anti-emetics are permitted. Premedications for IRRs per Section 5.4.1 are permitted.

Therapy to manage enfortumab vedotin-associated toxicity as recommended in Section 5.2.3 are permitted, including growth factors, and transfusions.

Patients who are receiving strong CYP3A4 inhibitors or P-glycoprotein (P-gp) inhibitors concomitantly with enfortumab vedotin should be closely monitored for adverse reactions.

Routine prophylaxis with vaccines is permitted; it is recommended that vaccines used do not contain live micro-organisms.

Palliative radiotherapy on a non-target bone lesion that is not progressing is allowed after 3 cycles of treatment; must be administered after the initial response assessment and repeat scans described in Section 7.2. This will not be considered a subsequent anticancer therapy, but must not interfere with the assessment of tumor target lesions. Treatment with enfortumab vedotin should be interrupted during palliative radiotherapy.

Patients with a positive hepatitis B surface antigen and/or antihepatitis B core antibody and a negative PCR assay at baseline should receive appropriate antiviral prophylaxis or regular surveillance monitoring as per local or institutional guidelines.

5.3.3 Prohibited Concomitant Therapy

Patients may not receive other investigational drugs, radiotherapy (except palliative radiotherapy as described in Section 5.3.2), or systemic anti-neoplastic therapy during the treatment period. Patients who receive prohibited concomitant therapy must be discontinued from the study.

5.4 Management of Adverse Reactions

5.4.1 Management of Infusion Reactions

An IRR may occur during the infusion of study treatment. The infusion should be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. All supportive measures consistent with optimal patient care should be given throughout the study according to institutional standards. Supportive measures may include administering medications for IRRs.

Patients who have experienced an IRR may be premedicated for subsequent infusions. Premedication may include pain medication (e.g., acetaminophen or equivalent), an antihistamine (e.g., diphenhydramine hydrochloride), and a corticosteroid administered 30–60 minutes prior to each infusion or according to institutional standards. Should a patient experience IRRs in the setting of premedication, continued treatment with enfortumab vedotin must be discussed with the medical monitor prior to the next planned dose.

If anaphylaxis occurs, study treatment administration should be immediately and permanently discontinued.

5.4.2 Management of Hyperglycemia

Investigators should monitor blood glucose levels and are advised to perform additional assessments if any symptoms of hyperglycemia are observed, including a thorough evaluation for infection. In addition, if steroids are used to treat any other condition, blood glucose levels may require additional monitoring. If elevated blood glucose levels are observed, patients should be treated according to local standard of care and referral to endocrinology may be considered.

Patients, especially those with a history of or ongoing diabetes mellitus or hyperglycemia, should be advised to immediately notify their physician if their glucose level becomes difficult to control or if they experience symptoms suggestive of hyperglycemia such as frequent urination, increased thirst, blurred vision, fatigue, and headache.

Patients who enter the study with an elevated HbA1c (≥6.5%) at baseline should be referred to an appropriate provider during Cycle 1 for glucose management. Blood glucose should be checked prior to each dosing and dose should be withheld for blood glucose >250 mg/dL (Grade 3 or higher), regardless of relatedness to enfortumab vedotin. Dosing may continue once the patient's blood glucose has improved to ≤250 mg/dL (≤ Grade 2) and the patient is clinically and metabolically stable. Patients with blood glucose >500 mg/dL (Grade 4) considered unrelated to enfortumab vedotin may continue dosing once the patient's blood glucose has improved to ≤250 mg/dL (≤ Grade 2) and the patient is clinically and metabolically stable. Blood glucose >500 mg/dL (Grade 4) considered related to enfortumab vedotin requires treatment discontinuation. If a patient experiences new onset diabetes mellitus, evaluate patients with a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide to assess for new onset type 1 diabetes in the setting of prior CPI.

5.4.3 Management of Rash

In the phase 1 study (Study ASG-22CE-13-2), rash and similar dermatologic AEs were common among patients treated with enfortumab vedotin, and were seen more frequently at the highest dose. Although the exact etiology of dermatologic toxicities associated with enfortumab vedotin is unclear at this time, due to the expression of Nectin-4 in the skin, rash may be an on-target toxicity. The most common dermatological AEs reported in ASG-22CE-13-2 were drug eruption, rash, skin exfoliation, skin pigmentation disorder, and rash maculo-papular. Most occurred during Cycle 1, and some were associated with pruritus. Almost all were mild, with the exception of two events of rash reported as Grade 3 in the 1 mg/kg dose group. None required discontinuation of study drug and one event of Grade 1 papular rash at 1.25 mg/kg required a dose reduction. Mild rash related to enfortumab vedotin should be treated using local supportive care as needed. Topical corticosteroids have been used along with antihistamines for pruritus as needed. Grade 3 rash that is not limiting self-care activities of daily living or associated with infection requiring systemic antibiotics does not require treatment interruption, provided symptoms are not severe and can be managed with supportive treatment.

5.5 Treatment Compliance

Study drug administration will be performed by study site staff and documented in source documents and the CRF.

6 STUDY ACTIVITIES

6.1 Schedule of Events

Adverse events and concomitant medications will be recorded from Day 1 (predose) through the safety reporting period (30 days after the last study treatment, see Section 7.7.1.3). Day 1 is the first day of treatment with study drug in each cycle. Any study protocol-related AE (defined in Section 7.7.1.1) as well as any concomitant medications given for treatment of the adverse event, should be recorded from the time of informed consent. A schedule of events is provided in Appendix A. Study activities are listed by visit in this section and descriptions of all study assessments are presented in Section 7.

Local laboratory testing should be performed on all dosing days. All local laboratory results must be reviewed prior to study drug administration in order to determine whether to proceed with dosing or whether dose modification is required.

6.2 Screening Visit (Days –28 to Day 1)

- Informed consent
- Study eligibility per inclusion/exclusion criteria
- Medical history (see Section 7.1)
- Acquire and submit tumor specimen (see Section 7.4.2). Either archival tissue or pre-treatment fresh tumor tissue (obtained from a fresh biopsy) is acceptable.
- Complete eye examination (see Section 7.7.7)

- Brain scan (magnetic resonance imaging [MRI] with gadolinium preferred; if contraindicated, see Appendix F) to determine eligibility with respect to CNS metastases)
- Bone scan
- CT scan with contrast (if contraindicated, see Appendix F), including chest, abdomen, and pelvis. Other regions should be scanned if the patient has known or suspected disease in that region.
- INR/prothrombin time (PT) and partial thromboplastin time (PTT)
- Serology for hepatitis B surface antigen and antihepatitis B core antibody
- Serology for antihepatitis C antibody. If positive, follow up with PCR testing.
- Urinalysis (with reflexive microscopy)
- HbA1c. If HbA1c is elevated (≥6.5%), refer patient to appropriate provider during Cycle 1 for glucose management.

6.2.1 Baseline Visit (Days –7 to Day 1)

- Pregnancy test (either serum or urine) for females of childbearing potential (see Section 7.7.2)
- Physical exam (including weight; see Section 7.7.3)
- Collect height
- Vital signs (see Section 7.7.4)
- Complete blood count (CBC) with differential (see Section 7.7.2)
- Serum chemistry panel (see Section 7.7.2)
- CrCl (see Section 7.7.2)
- ECOG performance status (see Section 7.7.5)
- Electrocardiogram (ECG) (see Section 7.7.6)

6.3 Treatment Period (Day 1 to Day 22)

6.3.1 Day 1 (±2 days)

- Predose (to occur on day of dosing unless noted below)
  - QLQ-C30 (see Section 7.6.1)
  - EQ-5D (see Section 7.6.2)
  - Pregnancy test (either serum or urine) for females of childbearing potential
  - Physical exam (including weight; may be conducted the day prior to dosing)
  - Vital signs
  - CBC with differential (may be collected the day prior to dosing)
  - Serum chemistry panel (may be collected the day prior to dosing)
  - ECOG performance status (may be conducted the day prior to dosing)
  - Blood samples for PK assessments (within 24 hours prior to dose; Cycles 1–4 and every even-numbered cycle thereafter; see Table 3)

- Blood samples for ATA assessments (within 24 hours prior to dose; Cycles 1–4 and every even-numbered cycle thereafter; see Table 3)
- Blood samples for biomarker assessments (within 24 hours prior to dose; Cycles 1–4; see Table 3)

- Enfortumab vedotin administration (see Section 5.2.2)
- Postdose
  - Blood samples for PK assessments (Cycles 1–2; see Table 3)

If Baseline Visit activities occur within 1 day prior to Cycle 1, Day 1, the following assessments do not need to be repeated at the Cycle 1 Day 1 visit: physical exam (including weight), vital signs, ECOG performance status, serum chemistry panel, and CBC with differential. If the baseline pregnancy test occurs within 7 days prior to Cycle 1 Day 1, the pregnancy test does not need to be repeated at the Cycle 1 Day 1 visit.

6.3.2 Day 3

- Blood samples for PK assessments (±24 hours; Cycles 1 and 2)
- Blood samples for biomarker assessments (±24 hours; Cycle 1)

6.3.3 Day 8 (+2 days)

- Predose (to occur on day of dosing unless noted below)
  - Vital signs
  - CBC with differential (may be collected the day prior to dosing)
  - Serum chemistry panel (may be collected the day prior to dosing)
  - Blood samples for PK assessments (within 24 hours prior to dose; Cycles 1 and 2)
  - Blood samples for biomarker assessments (within 24 hours prior to dose; Cycle 1)
- Enfortumab vedotin administration. At least 1 week must elapse between doses of enfortumab vedotin.
- Postdose
  - Blood samples for PK assessments (Cycles 1 and 2)

6.3.4 Day 15 (+2 days)

- Predose (to occur on day of dosing unless noted below)
  - Vital signs
  - CBC with differential (may be collected the day prior to dosing)
  - Serum chemistry panel (may be collected the day prior to dosing)
  - Blood samples for PK assessments (within 24 hours prior to dose; Cycles 1 and 2)
  - Blood samples for biomarker assessments (within 24 hours prior to dose; Cycle 1)
- Enfortumab vedotin administration. At least 1 week must elapse between doses of enfortumab vedotin.
- Postdose

- Blood samples for PK assessments (Cycles 1 and 2)

6.3.5 Day 17

- Blood samples for PK assessments (-24/+48 hours; Cycles 1 and 2)

6.3.6 Day 22

- Blood samples for PK assessments (Cycles 1 and 2 [±48 hours])
- CT scan with contrast (if contraindicated, see Appendix F) of the chest, abdomen, pelvis and any other region of known or suspected disease (every 8 weeks [±1 week] from Cycle 1 Day 1 during treatment, with repeat scans 4 weeks [+1 week] after first documentation of response). Brain and/or bone scans should also be repeated at this timepoint if metastases were identified at baseline, or if metastasis is suspected. After 1 year on study the frequency of scans will be reduced to every 12 weeks (±1 week). Following confirmation scans, response assessments should continue with the previous scan schedule (i.e., the schedule should not be adjusted). If there is a dose delay due to toxicity, the schedule for response assessments will not be adjusted and will continue to be timed from Cycle 1 Day 1 during treatment. Tumor imaging should also be performed whenever disease progression is suspected.

6.4 End of Treatment Visit (30 to 37 days after last dose of study drug)

EOT visits should occur 30 to 37 days after the last dose of study drug unless delayed due to an AE. However, EOT evaluations must be performed before initiation of a new therapy for cancer, with the exception of the slit lamp examination. If EOT evaluations are completed before 30 days after the last study treatment, the patient will be contacted 30 to 37 days following the last treatment to assess for adverse events.

- QLQ-C30
- EQ-5D
- Slit lamp examination (for patients who experience corneal adverse events during the study). Performed ≥4 weeks from last dose.
- Pregnancy test (either serum or urine) for females of childbearing potential
- Physical exam (including weight)
- Vital signs
- CBC with differential
- Serum chemistry panel
- ECOG performance status
- ECG
- Blood samples for PK and ATA assessments
- Blood samples for biomarker assessments
- CT scan with contrast (if contraindicated, see Appendix F) of the chest, abdomen, pelvis and any other region of known or suspected disease. Responses will be confirmed with repeat scans at 4 weeks after first documentation of response

(+1 week). Following confirmation scans, response assessments should continue with the previous scan schedule (i.e., the schedule should not be adjusted and should all be timed every 8 weeks [±1 week] from Cycle 1 Day 1 during treatment). Tumor imaging should also be performed whenever disease progression is suspected. Bone and/or brain scans should also be repeated at this timepoint if metastases were identified at baseline, or if metastasis is suspected. Scans not required if previous scan conducted <4 weeks prior to EOT.

6.5 Every Month for 6 Months After End of Treatment Visit (±1 week)

- Pregnancy test (either serum or urine) for females of childbearing potential

6.6 Follow-up (Every 8 Weeks [±1 week])

Prior to initiation of subsequent anticancer therapy or radiologically-confirmed disease progression (per investigator according to RECIST), patients will have the assessments listed below done 8 weeks (±1 week) after the previous response assessment scan and every 8 weeks (±1 week) following the previous visit thereafter until radiologically-confirmed disease progression (per investigator according to RECIST), initiation of a new anticancer therapy, patient death, study closure, or withdrawal of consent, whichever comes first. After 1 year on study the frequency of visits including response assessments will be reduced to every 12 weeks (±1 week).

- Physical exam
- ECOG performance status
- CT scan with contrast (if contraindicated, see Appendix F) of the chest, abdomen, pelvis and any other region of known or suspected disease (with repeat scans 4 weeks [+1 week] after first documentation of response). Brain and/or bone scans should also be repeated at this timepoint if metastases were identified at baseline, or if metastasis is suspected. Following confirmation scans, response assessments should continue with the previous scan schedule (i.e., the schedule should not be adjusted). Tumor imaging should also be performed whenever disease progression is suspected.

6.7 Long-term Follow-up (Every 8 Weeks [±1 week])

After initiation of subsequent anticancer therapy or radiologically-confirmed disease progression (per investigator according to RECIST), patients will be contacted every 8 weeks (±1 week) after EOT (or 8 weeks from previous protocol visit, whichever is later) for survival status and collection of subsequent anticancer therapy information until death, study closure, or withdrawal of consent, or patient is lost to follow-up, whichever occurs first. After 1 year on study, the frequency of contacts will be reduced to every 12 weeks (±1 week).

6.8 End of Study/End of Follow-up

The study will be closed 5 years after enrollment of the last patient, or when no patients remain in long-term follow-up, whichever occurs first. Additionally, the sponsor may terminate the study at any time.

The date the patient met criteria for study discontinuation and the reason for study discontinuation will be recorded.

7 STUDY ASSESSMENTS

7.1 Screening/Baseline Assessments

Only patients who meet all inclusion and exclusion criteria specified in Section 4 will be enrolled in this study. Enrollment status and date will be recorded in CRF.

Patient medical history includes a thorough review of significant past medical history, current conditions, tobacco history, any treatment for prior malignancies and response to prior treatment, and any concomitant medications.

A complete eye examination, brain scan, bone scan, CT scan with contrast for baseline response efficacy assessment, INR/PT/PTT, serology for hepatitis B and C, urinalysis with reflexive microscopic analysis, HbA1c, and pregnancy test (either urine or serum, for females of childbearing potential) are required for all patients at screening.

7.2 Response/Efficacy Assessments

Measures of anticancer activity will be assessed by CT scans with contrast approximately every 8 weeks (±1 week). After 1 year on study, response assessments will be reduced to every 12 weeks (±1 week). The schedule of response assessments should not be adjusted for dose delays/interruptions or other reasons for changes in the timing of a patient's study activities; timepoints for response assessments should be calculated from Cycle 1 Day 1 during treatment. For patients who cannot receive CT scans with contrast, other acceptable imaging methods are detailed in Appendix F (Scanning and Contrast Guidelines). For brain scans, MRI with gadolinium is the preferred method of assessment; however, other imaging methods are detailed in Appendix F if contrast is contraindicated. Patients must be evaluated using the same imaging method throughout the study for efficacy assessments. CT scans with contrast at the minimum will include the chest, abdomen, and pelvis. Other regions should be scanned if the patient has known or suspected disease in that region. Brain and/or bone scans should also be repeated at response assessment timepoints if bone metastases were identified at baseline, or if metastasis is known or suspected. Responses (CR or PR) will be confirmed with repeat scans 4 weeks (+1 week window) after first documentation of response. The schedule for response assessments should not be adjusted after the confirmatory scan (e.g., CR at Week 8, confirmatory scans at Week 12, next assessment due at Week 16). Tumor imaging should also be performed whenever disease progression is suspected.

Patients who discontinue study treatment for reasons other than objective disease progression by RECIST Version 1.1 (see Appendix D) will continue to receive CT scans with contrast 8 weeks (±1 week) after the previous response assessment scan and every 8 weeks (±1 week) following the previous scan thereafter. After 1 year on study the frequency of response assessments will be reduced to every 12 weeks (±1 week). The tumor assessments will continue until the patient has radiologically-confirmed disease progression per RECIST as determined by the investigator, initiates a new anticancer therapy, dies or withdraws consent,

or the study closes, whichever comes first. The determination of antitumor activity will be based on confirmed objective response assessments as defined by RECIST Version 1.1 (see Appendix D) (Eisenhauer 2009). Patients who do not have at least 2 (initial response and confirmation scan) post-baseline response assessments will be counted as non-responders. The investigator will make treatment decisions based on site assessments of scans by RECIST. Clinical response of CR, PR, SD, or PD will be determined at each assessment. Response and progression will also be assessed by an IRF.

Survival status will be updated every 8 weeks (±1 week) after EOT (or 8 weeks from previous protocol visit, whichever is later) until death, study closure, or withdrawal of consent, whichever occurs first. After 1 year on study the frequency of survival status updates will be reduced to every 12 weeks (±1 week).

Patients' clinical data must be available for CRF source verification. Tumor images will be submitted to a central imaging lab.

7.3 Pharmacokinetic and ATA Assessments

Blood samples for PK and ATA will be collected throughout the study per the sample collection schedule provided in Table 3. Validated or qualified assays will be used to measure the concentrations of enfortumab vedotin ADC, TAb, and MMAE in serum or plasma. PK samples will be collected and archived for possible analysis of other enfortumab vedotin-related species, such as circulating metabolites of MMAE. A qualified assay will be used to determine the levels of ATA in serum.

Refer to the Central Laboratory Manual for information on collection, processing, storage, and shipment of sample.

7.4 Biomarker Studies

Samples for exploratory biomarkers will be collected at protocol-specified timepoints (see Table 3 and Appendix A). Biomarker assessments will not be used for patient selection.

Methods of analysis may include IHC, next generation sequencing, PCR, mutation and gene expression profiling; T-cell receptor beta chain sequencing, flow cytometry and immunoassays.

7.4.1 Biomarkers in Blood

The primary effects of enfortumab vedotin on urothelial carcinoma tumor cells may lead to changes in the activation state of local, tumor-associated and peripheral immune cells. Biomarker assessments in blood samples may include but may not be limited to: markers of immune function, including abundance and phenotype of immune cell subsets, circulating tumor DNA (ctDNA), and abundance of cytokines. These may provide insight into treatment-related changes in activation state of peripheral immune system associated with enfortumab vedotin-induced tumor cell death.

Table 3: Pharmacokinetic, ATA, and biomarker blood sample collection timepoints

	Study Day	Time	Window	Relative Time	Blood						
							Biomarkers				
							Plasma			PBMC	
					PK	ATA	Cytokines	Research 1	Research 2	Immuno-phenotyping	Research
Cycles 1 and 2	Day 1	Pre-dose	within 24 hr	START of infusion	X	X	X	X	X	X	X
		End of infusion	within 15 min	END of infusion	X						
	Day 3	48 hr	±24 hr	END of Day 1 infusion	X		X[a]		X[a]	X[a]	X[a]
	Day 8	Pre-dose	within 24 hr	START of infusion	X		X[a]	X[a]	X[a]	X[a]	X[a]
		End of infusion	within 15 min	END of infusion	X						
	Day 15	Pre-dose	within 24 hr	START of infusion	X		X[a]		X[a]	X[a]	X[a]
		End of infusion	within 15 min	END of infusion	X						
	Day 17	48 hr	–24 hr/+48 hr	END of Day 15 infusion	X						
	Day 22	168 hr	±48 hr	END of Day 15 infusion	X						
Subsequent dosing cycles	Day 1	Pre-dose	within 24 hr	START of infusion	X[b]	X[b]	X[c]	X[c]	X[c]	X[c]	X[c]
End of Treatment (within 30–37 days of last dose)					X	X	X	X	X	X	X

a Cycle 1 only
b Cycles 3 and 4 and every even-numbered cycle thereafter
c Cycles 3 and 4 only

7.4.2 Biomarkers in Pre-Treatment Tumor Tissue

To better understand relationships between pre-treatment urothelial carcinoma biological characteristics, and patient outcome, submission of a tumor block or freshly sectioned, unstained charged slides (at least 10 slides are mandatory unless prior approval is obtained from the sponsor) of pretreatment tumor tissue are required. Either archival tissue or pre-treatment fresh tumor tissue (obtained from a fresh biopsy) is acceptable. See the Laboratory Manual for details.

Biomarker assessments in tumor tissue may include, but not be limited to:

- Tumor expression of Nectin-4 protein
- Messenger ribonucleic acid (mRNA) expression
- Markers of disease subtype (e.g., The Cancer Genome Atlas [TCGA] subtypes)
- Tumor mutational burden
- Markers of the tumor immune microenvironment

7.5 Biospecimen Repository

In the US only, for patients who provide additional consent, remaining de-identified unused blood and/or tissue will be retained by the sponsors and used for future research, including but not limited to the evaluation of targets for novel therapeutic agents, the biology of ADC sensitivity and resistance mechanisms, and the identification of biomarkers for ADCs. Blood and tissue samples donated for future research will be retained for a period of up to 25 years. If additional consent is not provided, any remaining biological samples will be destroyed following study completion and when the samples are no longer required to be maintained for potential regulatory submissions.

7.6 Quality of Life

Two validated tools will be used: the QLQ-C30, and the EQ-5D.

If possible, PRO assessments should be completed before any other procedures at the study visits noted in the schedule of events (Appendix A).

7.6.1 EORTC Core Quality of Life Questionnaire, QLQ-C30

The QLQ-C30 was developed to measure aspects of QoL pertinent to patients with a broad range of cancers who are participating in clinical trials (Aaronson 1993; Sneeuw 1998). The current version of the core instrument (QLQ-C30, Version 3) is a 30-item questionnaire consisting of the following:

- 5 functional domains (physical, role, cognitive, emotional, social);
- 3 symptom scales (fatigue, pain, nausea & vomiting);

- Single items for symptoms (shortness of breath, loss of appetite, sleep disturbance, constipation, diarrhea) and financial impact of the disease; and
- 2 global items (health, overall QoL).

7.6.2 EuroQol-5 Dimensions

The EQ-5D is a standardized instrument developed by the EuroQol Group for use as a generic, preference-based measure of health outcomes. It is applicable to a wide range of health conditions and treatments and provides a simple descriptive profile and a single index value for health status. The EQ-5D is a 5-item self-reported measure of functioning and well-being, which assesses 5 dimensions of health, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension comprises 3 levels (no problems, some/moderate problems, extreme problems). A unique EQ-5D health state is defined by combining 1 level from each of the 5 dimensions. This questionnaire also records the respondent's self-rated health status on a vertical graduated (0 to 100) visual analogue scale. Responses to the 5 items will also be converted to a weighted health state index (utility score) based on values derived from general population samples. The EQ-5D is recommended for use in cost-effectiveness analyses commonly employed in health technology assessments by the Washington Panel on Cost Effectiveness in Health and Medicine (Gold 1996).

7.7 Safety Assessments

The assessment of safety during the course of this study will consist of the surveillance and recording of AEs including SAEs, recording of concomitant medication, and measurements of protocol-specified physical examination findings, cardiac monitoring, and laboratory tests.

Safety will be monitored over the course of the study by an IDMC as described in Section 9.3.10.

7.7.1 Adverse Events

7.7.1.1 Definitions

Adverse Event

According to the International Council for Harmonisation (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 Code of Federal Regulations (CFR) 312.32, Investigational New Drug (IND) Safety Reporting, an AE is any untoward medical occurrence in a patient or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

The following information should be considered when determining whether or not to record a test result, medical condition, or other incident on the Adverse Events and Pre-existing Conditions CRF:

- From the time of informed consent through the day prior to study Day 1, only study protocol-related AEs should be recorded. A protocol-related AE is defined as an untoward medical event occurring as a result of a protocol mandated procedure.
- All medical conditions present or ongoing predose on study Day 1 should be recorded.
- All AEs (regardless of relationship to study drug) should be recorded from study Day 1 (pre-dose) through the end of the safety reporting period (see Section 7.7.1.3). Complications that occur in association with any procedure (e.g., biopsy) should be recorded as AEs whether or not the procedure was protocol mandated.
- Changes in medical conditions and AEs, including changes in severity, frequency, or character, during the safety reporting period should be recorded.
- In general, an abnormal laboratory value should not be recorded as an AE unless it is associated with clinical signs or symptoms, requires an intervention, results in a SAE, or results in study termination or interruption/discontinuation of study treatment. When recording an AE resulting from a laboratory abnormality, the resulting medical condition rather than the abnormality itself should be recorded (e.g., record "anemia" rather than "low hemoglobin").

Serious Adverse Events

An AE should be classified as an SAE if it meets one of the following criteria:

Fatal:	AE resulted in death
Life threatening:	The AEs placed the patient at immediate risk of death. This classification does not apply to an AE that hypothetically might cause death if it were more severe.
Hospitalization:	The AE resulted in hospitalization or prolonged an existing inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed consent in the study or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization. Pre-planned hospitalizations for therapeutic, diagnostic, or surgical procedures of the underlying cancer or study target disease that did not worsen during the clinical trial need not be captured as SAEs.
Disabling/incapacitating:	An AE that resulted in a persistent or significant incapacity or substantial disruption of the patient's ability to conduct normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a patient exposed to the molecule or study treatment regimen before conception or during pregnancy.
Medically significant:	The AE did not meet any of the above criteria, but could have jeopardized the patient and might have required medical or surgical intervention to prevent one of the outcomes listed above or involves suspected transmission via a medicinal product of an infectious agent.

Adverse Event Severity

AE severity should be graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03. These criteria are provided in the study manual.

AE severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the sponsor for defining regulatory reporting obligations (see definition for SAEs, above).

Relationship of the Adverse Event to Study Treatment

The relationship of each AE to enfortumab vedotin should be evaluated by the investigator using the following criteria:

Related:	There is evidence to suggest a causal relationship between the drug and the AE, such as: • A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome) • One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)
Unrelated:	Another cause of the AE is more plausible (e.g., due to underlying disease or occurs commonly in the study population), or a temporal sequence cannot be established with the onset of the AE and administration of the study treatment, or a causal relationship is considered biologically implausible

7.7.1.2 Procedures for Eliciting and Recording Adverse Events

Investigator and study personnel will report all AEs and SAEs whether elicited during patient questioning, discovered during physical examination, laboratory testing and/or other means by recording them on the CRF and/or SAE form, as appropriate.

Eliciting Adverse Events

An open-ended or non-directed method of questioning should be used at each study visit to elicit the reporting of AEs.

Recording Adverse Events

The following information should be recorded on the Adverse Events and Pre-existing Conditions CRF:

- Description including onset and resolution dates
- Whether it met SAE criteria
- Severity
- Relationship to study treatment or other causality
- Outcome

Diagnosis vs Signs or Symptoms

In general, the use of a unifying diagnosis is preferred to the listing out of individual symptoms. Grouping of symptoms into a diagnosis should only be done if each component sign and/or symptom is a medically confirmed component of a diagnosis as evidenced by standard medical textbooks. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, report the individual symptom as a separate adverse event.

Important exceptions for this study are adverse reactions associated with the infusion of study drug. For IRRs, record the NCI CTCAE term of 'infusion related reaction' with an overall level of severity (per NCI CTCAE). In addition, record each sign or symptom of the reaction as an individual AE. If multiple signs or symptoms occur with a given infusion-related event, each sign or symptom should be recorded separately with its level of severity.

Recording Serious Adverse Events

For SAEs, record the event(s) on both the CRF and an SAE form.

The following should be considered when recording SAEs:

- Death is an outcome of an event. The event that resulted in the death should be recorded and reported on both an SAE form and CRF.
- For hospitalizations, surgical, or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the narrative as part of the action taken in response to the illness.

Progression of the Underlying Cancer

Do not report radiographic signs of disease progression (e.g., 'tumor progression' or 'metastases') as an AE (this data is captured in the efficacy assessment). Report the symptoms and signs of disease progression (e.g., "fatigue", "dyspnea") as AEs; do not report disease progression as the AE term.

For disease progression with a fatal outcome, report the immediate cause of death as the event term. If the immediate cause of death cannot be determined and it is thought by the investigator to be related to disease progression, report the AE using the term 'disease progression' with a fatal outcome.

Pregnancy

Notification to Drug Safety: Complete a Pregnancy Report Form for all pregnancies that occur from the time of first study drug dose until 6 months after the last dose of study drug(s) including any pregnancies that occur in the partner of a male study patient. Only report pregnancies that occur in a male patient's partner if the estimated date of conception is after the male patient's first study drug dose. Email or fax to the sponsor's Drug Safety Department within 48 hours of becoming aware of a pregnancy. All pregnancies will be

monitored for the full duration; all perinatal and neonatal outcomes should be reported. Infants should be followed for a minimum of 8 weeks.

Collection of data on the CRF: All pregnancies (as described above) that occur within 30 days of the last dose of study drug(s) will also be recorded on the Adverse Events and Pre-Existing Conditions CRF.

Abortion, whether accidental, therapeutic, or spontaneous, should be reported as an SAE. Congenital anomalies or birth defects, as defined by the 'serious' criterion above (see definitions Section 7.7.1.1) should be reported as SAEs.

Corneal Adverse Events

Corneal ulcer or keratitis AEs ≥ Grade 2 should be graded within their respective categories. Grade 1 corneal ulcer or keratitis AEs should be graded per "Eye disorders – Other, specify" criteria. Other corneal AEs should be recorded and graded per "Eye disorders – Other, specify" criteria.

Adverse Events of Possible Hepatic Origin

If an AE is accompanied by increases in LFT values (e.g, AST, ALT, bilirubin, etc.) or is suspected to be due to hepatic dysfunction, see Appendix E for detailed information on recommended monitoring and assessment of liver abnormalities. See Section 5.2.3.1 for treatment discontinuation recommendations related to hepatic safety.

Patients with AEs of hepatic origin accompanied by LFT abnormalities should be carefully monitored.

7.7.1.3 Reporting Periods for Adverse Events and Serious Adverse Events

The safety reporting period for all AEs and SAEs is from study Day 1 (predose) through 30 days after the last study treatment. However, all study protocol-related AEs are to be recorded from the time of informed consent. All SAEs that occur after the safety reporting period and are considered study treatment-related in the opinion of the investigator should also be reported to the sponsor.

SAEs will be followed until significant changes return to baseline, the event stabilizes (recovering/resolving) or is no longer considered clinically significant by the investigator, or the patient dies or withdraws consent. All non-serious AEs will be followed through the safety reporting period. Certain non-serious AEs of clinical interest may be followed (including collection of relevant concomitant medications) until resolution, return to baseline, study closure, or the events become chronic to the extent that they are adequately characterized.

7.7.1.4 Serious Adverse Events Require Immediate Reporting

Within 24 hours of observing or learning of an SAE, investigators are to report the event to the sponsor, regardless of the relationship of the event to the study treatment regimen.

For initial SAE reports, available case details are to be recorded on an SAE form. At a minimum, the following should be included:

- Patient number
- Date of event onset
- Description of the event
- Study treatment, if known

The completed SAE form and SAE Fax Cover Sheet are to be emailed or faxed to the study sponsor's Drug Safety Department or designee within 24 hours (see email or fax number[s] specified on the SAE report form).

Relevant follow-up information is to be submitted to the study sponsor as soon as it becomes available.

7.7.1.5 Sponsor Safety Reporting to Regulatory Authorities

Investigators are required to report all SAEs, including anticipated SAEs, to the study sponsor (see Section 7.7.1.4).

The study sponsors will report all SAEs to regulatory authorities as applicable and as required per local regulatory reporting requirements. In the US, endpoints that assess disease-related mortality or major morbidity, as well as other SAEs that are not study endpoints but are known consequences of the underlying disease or condition that are anticipated to occur in the study population, should not be reported to the FDA as individual IND safety reports per the final rule amending the IND safety reporting requirements under 21 CFR 312.32 and the FDA's guidance Safety Assessment for IND Safety Reporting Guidance for Industry (draft guidance December 2015).

In this study, the SAEs that do not require individual IND safety reports to the FDA are progression of the underlying cancer. These anticipated SAEs will be reviewed periodically by an IDMC and Seattle Genetics Drug Safety Department. If upon review, an SAE is occurring at a higher rate than that which would be expected for the study population, then an IND safety report for the SAE will be submitted to the FDA.

7.7.2 Clinical Laboratory Tests

Samples will be drawn for central and local labs.

Local laboratory testing will include institutional standard tests for study eligibility, evaluating safety, and making clinical decisions. Local laboratory testing should be performed on all dosing days. All local laboratory results must be reviewed prior to study drug administration in order to determine whether to proceed with dosing or whether dose modification is required.

The following laboratory assessments will be performed by the central lab to evaluate safety at scheduled timepoints (see Appendix A) during the course of the study:

- The serum chemistry panel is to include the following tests: albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen, calcium, creatinine, chloride, glucose, lactate dehydrogenase (LDH), phosphorus, potassium, sodium, total bilirubin, amylase, lipase, and uric acid.
- The CBC with differential is to include the following tests: white blood cell count with five-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), platelet count, hemoglobin, and hematocrit.

The following laboratory assessment(s) will be performed by local laboratories at scheduled timepoints (see Appendix A) during the course of the study:

- CrCl at baseline using the Cockcroft-Gault criteria or 24-hour urine collection
- Standard urinalysis (with reflexive microscopy)
- INR/PT/PTT
- A serum or urine beta human chorionic gonadotropin (β-hCG) pregnancy test for females of childbearing potential
- HbA1c
- Serology for hepatitis B surface antigen and antihepatitis B core antibody
- Serology for antihepatitis C antibody. If positive, follow up with PCR testing

7.7.3 Physical Examination Including Weight

Physical examinations should include assessments of the following body parts/systems: abdomen, extremities, head, heart, lungs, neck, and neurological. Height will be collected at the Baseline visit. Weight will be collected at specified timepoints (see Appendix A), but does not need to be collected at visits following EOT.

7.7.4 Vital Signs

Vital sign measurements will be performed to include heart rate (bpm), diastolic and systolic blood pressure (mmHg), and temperature. Vital sign values will be recorded, and any diagnosis associated with clinically significant abnormal vital signs will be recorded as an adverse event or pre-existing condition.

7.7.5 ECOG Performance Status

ECOG performance status (Appendix B) will be evaluated at protocol-specified timepoints.

7.7.6 Cardiac Monitoring

ECGs will be conducted at baseline and at the EOT visit. Additional ECGs should be conducted if clinically indicated. Routine 12-lead ECGs will be performed after the patient has been in a supine position for at least 5 minutes. The ECG assessments should be performed prior to obtaining the PK and biomarker samples if possible.

7.7.7 Eye Examination

Patients will have a complete eye examination at baseline performed by a qualified ophthalmologist or optometrist, including but not limited to: uncorrected, corrected and best corrected visual acuity, slit lamp, tonometry examination, and dilated fundus examination. EOT slit lamp examinations are required for all patients who experience corneal adverse events during the study. EOT slit lamp examinations must be performed ≥4 weeks from last dose. Additional eye examinations are to be conducted as clinically indicated.

7.8 Post-treatment Assessments

7.8.1 Follow-up Assessments

Patients who discontinue study treatment will continue to receive physical exams (no weight collection is required), ECOG assessment, and response assessments every 8 weeks (±1 week) after the previous response assessment scan and every 8 weeks (±1 week) following the previous visit thereafter until radiologically-confirmed disease progression (per RECIST as determined by the investigator), initiation of a new anticancer therapy, patient death, study closure, or withdrawal of consent, whichever comes first. After 1 year on study the frequency of follow-up visits will be reduced to every 12 weeks (±1 week).

7.8.2 Long-term follow-up Assessments

After radiologically-confirmed progression (per RECIST as determined by the investigator) or initiation of a new anticancer therapy, patients will be contacted every 8 weeks (±1 week) after EOT (or 8 weeks from previous protocol visit, whichever is later) to obtain information on subsequent anticancer therapy and survival status. Long-term follow-up will continue until patient death, study closure, withdrawal of consent, or patient is lost to follow-up, whichever occurs first. After 1 year on study the frequency of long-term follow-up visits will be reduced to every 12 weeks (±1 week).

7.9 Appropriateness of Measurements

The safety measures that will be used in this trial are considered standard procedures for evaluating the potential adverse effects of study medications.

The determination of antitumor activity will be based on confirmed objective response assessments as defined by RECIST Version 1.1 (see Appendix D) (Eisenhauer 2009) and treatment decisions by the Investigator will be based on these assessments. These criteria are considered standard in oncological practice for this type of neoplasm, and the intervals of evaluation in this protocol are appropriate for disease management.

Immunogenicity is commonly assessed for biologics; therefore, standard tests will be performed to detect the possible presence of specific antibodies to enfortumab vedotin.

Pharmacokinetic assessments are also common in clinical studies to help characterize dose-exposure-response relationships.

Exploratory biomarker measurements in peripheral blood samples enable correlation with PK assessments and are common in clinical studies. Assessments conducted on pretreatment tumor tissue are similarly common. Both peripheral blood and tumor biomarker samples will be assessed using commonly employed, standard tests.

8 DATA QUALITY CONTROL AND QUALITY ASSURANCE

8.1 Site Training and Monitoring Procedures

A study manual with instructions for study compliance and CRF completion will be provided. Prior to the enrollment of patients at the site, Seattle Genetics or its designated clinical and medical personnel will review the following items with the investigator and clinic staff:

- The protocol, study objectives, eligibility requirements, study procedures, registration, and withdrawal processes
- Current Investigator's Brochure
- Recording and reporting AEs and SAEs
- Enrollment goals and study timelines
- The CRF completion process and source documentation requirements
- Monitoring requirements
- Institutional review board/independent ethics committee (IRB/IEC) review and approval process
- Informed consent process
- Good clinical practice guidelines and related regulatory documentation requirements
- Key study team roles and responsibilities
- Investigational product storage, accountability, labeling, dispensing, and record keeping
- Patient coding
- Study samples/specimen collection, handling and shipping
- Protocol compliance
- Clinical study supplies and record keeping, document retention, and administrative requirements

Monitoring visits will occur periodically, with frequency dependent on the rate of enrollment and workload at each site. During monitoring visits, the Seattle Genetics representative, Astellas Pharma Global Development representative, or designated contract research organization will review regulatory documentation, CRFs, source documentation, and

investigational product storage, preparation, and accountability. The CRFs will be reviewed for completeness, adherence to the provided guidelines, and accuracy compared to the source documents. The investigators must ensure that the monitor is allowed to inspect all source documents pertinent to study patients, and must cooperate with the monitor to ensure that any problems noted in the course of the trial are resolved. The investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by Seattle Genetics or its designated monitors or collaborators, and by quality assurance auditors, or representatives of regulatory authorities.

8.2 Data Management Procedures

Seattle Genetics will provide CRF Completion Guidelines for electronic CRF (eCRF) data entry. Study specific data management procedures will be maintained in the data management plan. Queries resulting from edit checks and/or data verification procedures will be posted electronically in the eCRF.

8.3 Access to Source Data

The investigator will permit the sponsor's representatives to monitor the study as frequently as the sponsor deems necessary to determine that protocol adherence and data recording are satisfactory. Appropriate measures to protect patient confidentiality are to be employed during monitoring. The CRFs and related source documents will be reviewed in detail by the monitor at each site visit. Original source documents or certified copies are needed for review. This review includes inspection of data acquired as a requirement for participation in this study and other medical records as required to confirm that the information contained in the CRFs, such as disease assessments, AEs, and concomitant medications, is complete and correct. Other study records, such as correspondence with the sponsor and the IRB/IEC and screening and drug accountability logs will also be inspected. All source data and study records must also be available for inspection by representatives of regulatory authorities and IRB/IEC.

8.4 Accuracy and Reliability of Data

Steps to be taken to assure the accuracy and reliability of data include:

- The selection of qualified investigators and appropriate study centers.
- Review of protocol procedures with the investigators and associated personnel prior to the study.
- Periodic monitoring visits by the designated monitor(s).
- CRFs will be reviewed for accuracy and completeness by the designated monitor(s) during monitoring visits to the study centers. Any discrepancies will be resolved with the investigator or designees as appropriate.

8.5 Quality Assurance Procedures

Research and Development Quality or its designee may conduct audits at the clinical site or other study-related facilities and organizations. Audit reports will be retained by Research and Development Quality of Seattle Genetics as part of the written record.

8.6 Data Handling and Record Keeping

8.6.1 Data Handling

It is the investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports. Data reported on the CRF that is derived from source documents should be consistent with the source documents or the discrepancies should be explained.

Any change or correction to a CRF will be maintained in an audit trail within the electronic data capture system. Data changes may only be made by those individuals so authorized. The investigator should retain records of the changes and corrections, written and/or electronic.

8.6.2 Investigator Record Retention

The investigator shall retain study drug disposition records and all source documentation (such as original ECG tracings, laboratory reports, inpatient or office patient records) for the maximum period required by the country and institution in which the study will be conducted, or for the period specified by Seattle Genetics, whichever is longer. The investigator must contact Seattle Genetics prior to destroying any records associated with the study. If the investigator withdraws from the study (due to relocation, retirement, etc.), the records shall be transferred to a mutually agreed upon designee, such as another investigator or IRB/IEC. Notice of such transfer will be provided in writing prior to the transfer to Seattle Genetics.

9 DATA ANALYSIS METHODS

9.1 Determination of Sample Size

The study is designed to estimate the confirmed ORR in patients receiving enfortumab vedotin and to detect an improvement in the ORR compared with a historical 10% response rate. The rationale for the historical response rate is provided in Section 3.2.

Approximately 200 patients will be enrolled in this study to ensure collection of sufficient efficacy and safety data, including approximately 100 or more platinum-treated patients as defined in the eligibility criteria in Section 4.1 (Cohort 1), and up to approximately 100 platinum-naïve and cisplatin-ineligible patients also defined in the eligibility criteria in Section 4.1 (Cohort 2). Using the estimate of approximately 100 patients in Cohort 1, the study will have 98% power to detect a 15% increase in ORR from 10% to 25% and 81% power to detect a 10% increase in ORR from 10% to 20%, at one-sided significance level of 0.025, based on exact methods using EAST®, Version 6.0, by Cytel Inc.

The confirmed ORR and 95% exact CI in Cohort 2 will be summarized at 4 timepoints: 1) at the time of analysis of Cohort 1, 2) when approximately 50 patients in Cohort 2 have had the opportunity to be followed for approximately 8 months from the first dose of enfortumab vedotin, 3) when approximately 70 patients in Cohort 2 have had the opportunity to be followed for approximately 8 months from the first dose of enfortumab vedotin, and 4) when all patients in Cohort 2 have had the opportunity to be followed for approximately 8 months from the first dose of enfortumab vedotin.

For illustration purposes, below is the summary of expected 95% CIs for Cohort 2 at various analysis timepoints, assuming a 30% observed ORR:

Number of Patients	Expected 95% Confidence Interval
N=20	12%–54%
N=50	18%–45%
N=70	20%–42%
N=100	21%–40%

Slit lamp examinations will be conducted on at least the first 60 enrolled patients (from Cohorts 1 and/or 2) on Cycle 2 Day 22 (±1 week) and Cycle 6 Day 22 (±1 week). If corneal AEs are observed in <15% of the first 60 enrolled patients and if the events are generally low grade or asymptomatic, the IDMC may make a recommendation to cease Cycle 2 Day 22 and/or Cycle 6 Day 22 slit lamp exams for the remaining patients if warranted based on review of the cumulative ocular safety data. Based on the results from the Phase 1 study (Study ASG-22CE-13-2), as of the data cut-off date of 14 November 2016, there were 3 patients who reported experiencing corneal adverse events out of 33 patients on 1.25 kg/mg of enfortumab vedotin. Assuming an event rate of 9% (3/33), with a sample size of 60, the probability of observing >3 events (5%) is 80.0% and the probability of observing <9 events (15%) is 91.2%. If the event rate is higher, the probability of observing <9 events is decreased. For example, if the event rate is 20%, the probability of observing <9 events is decreased to 12.7%. Based on the analysis described above and the review of cumulative ocular safety data, the IDMC recommended that the Cycle 2 Day 22 and Cycle 6 Day 22 slit lamp exams be discontinued in Jul 2018 and Aug 2019, respectively.

Sample size calculations were performed using EAST®, Version 6.0, by Cytel Inc.

9.2 Study Endpoint Definitions

9.2.1 Objective Response Rate

The primary endpoint of this study is the confirmed ORR per IRF. The ORR is defined as the proportion of patients with confirmed CR or PR according to RECIST Version 1.1 (see Appendix D) (Eisenhauer 2009). Patients who do not have at least 2 (initial response and confirmation scan) post-baseline response assessments as described in Section 7.2 of the protocol will be counted as non-responders.

In addition, ORR per investigator will be analyzed as a secondary endpoint.

9.2.2 Duration of Response

The DOR is defined as the time from first documentation of objective response (CR or PR that is subsequently confirmed) to the first documentation of PD (per RECIST Version 1.1) or to death due to any cause, whichever comes first.

DOR data will be censored as described below:

- Patients who do not have PD and are still on study at the time of an analysis will be censored at the date of the last disease assessment documenting absence of PD;
- Patients who have started an antitumor treatment other than the study treatment (with the exception of palliative radiotherapy as described in Section 5.3.2) prior to documentation of PD will be censored at the date of the last disease assessment prior to start of new therapy;
- Patients who are removed from the study prior to documentation of PD will be censored at the date of the last disease assessment documenting absence of PD.

DOR will only be calculated for the patients achieving a confirmed CR or PR.

9.2.3 Disease Control Rate at Week 16

DCR_{16} per IRF is defined as the proportion of patients with CR, PR, or SD at Week 16 visit, based on IRF assessment. Responses do not need to be confirmed to be scored as responders for the purpose of determining DCR_{16}. Patients whose disease response cannot be assessed as CR, PR, or SD at Week 16 or later will be scored as non-responders for calculating the DCR. An exception is patients who have a CR, PR, or SD subsequent to Week 16, but who miss Week 16; these patients will be counted as having disease control at Week 16.

In addition, DCR_{16} per investigator will be also summarized.

9.2.4 Progression-free Survival

PFS is defined as the time from start of study treatment to first documentation of objective tumor progression (PD per RECIST Version 1.1), or to death due to any cause, whichever comes first.

The same censoring rules outlined in Section 9.2.2 for DOR will be applied to PFS. Patients lacking an evaluation of tumor response after their first dose will have their event time censored at Day 1.

9.2.5 Overall Survival

OS is defined as the time from start of study treatment to date of death due to any cause. In the absence of death, OS will be censored at the last date the patient is known to be alive.

9.3 Statistical and Analytical Plans

The statistical and analytical plans presented below summarize the more complete plans to be detailed in the statistical analysis plan (SAP). A change to the data analysis methods

described in the protocol will require a protocol amendment only if it alters a principal feature of the protocol. The SAP will be finalized prior to database lock. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

9.3.1 General Considerations

In general, descriptive statistics will be presented that include the number of observations, mean, median, standard deviation, minimum and maximum for continuous variables, and the number and percentages (of non-missing) per category for categorical variables.

Unless otherwise specified, CIs will be calculated at 2-sided 95% level.

The 2-sided 95% exact CI using Clopper-Pearson method (Clopper 1934) will be calculated for the response rates where applicable (e.g., ORR).

For time-to-event endpoints, the median survival time will be estimated using the Kaplan-Meier method; the associated 95% CI will be calculated based on the complementary log-log transformation (Collett 1994).

Unless otherwise specified, summaries and analyses will be provided by cohort (i.e., platinum-treated and platinum-naïve and cisplatin-ineligible). Summaries and analyses may also be provided overall.

9.3.1.1 Randomization and Blinding

This is a single-arm, open-label study. No randomization will be utilized.

9.3.1.2 Adjustments for Covariates

No adjustment for covariates is planned in the analyses.

9.3.1.3 Handling of Dropouts and Missing Data

With the exception of time-to-event endpoints, no imputation will be conducted for missing data unless otherwise specified.

9.3.1.4 Multicenter Studies

There are multiple centers in this study, however it is not anticipated that any center will accrue enough patients to warrant an analysis by center.

9.3.1.5 Multiple Comparisons and Multiplicity

No multiple comparisons are planned and no alpha adjustment is needed because only one primary endpoint will be tested in this single arm study.

9.3.1.6 Data Transformations and Derivations

Time variables based on two dates, e.g., Start Date and End Date, will be calculated as (End Date – Start Date + 1) (in days) unless otherwise specified in the planned analysis section.

Unless otherwise specified, baseline values used in all analyses will be the most recent non-missing measurement prior to the first dose of study drug.

9.3.1.7 Analysis Sets

The full analysis set will include all patients who are enrolled and receive any amount of enfortumab vedotin in the study. A patient is considered enrolled if he/she has met all criteria for participation in the study and has Seattle Genetics approval as documented in the eCRF. The full analysis set will be used as the primary dataset for efficacy analysis. Patient demographics and baseline disease characteristics will be summarized based on the full analysis set.

The safety analysis set will include all patients who receive any amount of enfortumab vedotin. The safety analysis set will be used for all safety analyses.

The efficacy evaluable set will include all patients in the full analysis set who started treatment with enfortumab vedotin at least 8 months before the analysis data cutoff. The efficacy evaluable set will be used for the additional analyses of efficacy endpoints at the time of the interim analyses of Cohort 2 to allow adequate follow up for a stable estimate of ORR and DOR.

The PK analysis set will include all patients who received enfortumab vedotin and from whom at least one blood sample was collected and assayed for enfortumab vedotin, MMAE, or TAb concentration. Corresponding records of the time of dosing and sample collection must also be available for all enfortumab vedotin, MMAE, and TAb concentration data. The PK analysis set will be used for PK analyses.

Additional analysis sets of patients may be defined in the SAP.

9.3.1.8 Examination of Subgroups

As exploratory analyses, subgroup analyses may be conducted for selected endpoints. Subgroups may include but are not limited to the following:

- Number of Bellmunt risk factors (ECOG performance status >0; hemoglobin level <10 g/dL; presence of liver metastases) (Bellmunt 2010)
- Number of prior systemic therapies
- Best response to prior CPI therapy
- Liver metastasis at baseline

9.3.1.9 Timing of Analyses

The primary analysis on Cohort 1 (platinum-treated patients) will be conducted when enrollment is completed in Cohort 1, and all patients in the cohort have been followed for at least 6 months, or have discontinued from study, or had 30 days safety follow-up after PD, whichever comes first. Analysis for Cohort 2 will occur at 4 timepoints: 1) at the time of analysis of Cohort 1, 2) when approximately 50 patients in Cohort 2 have had the opportunity to be followed for approximately 8 months from the first dose of enfortumab vedotin, 3) when approximately 70 patients in Cohort 2 have had the opportunity to be followed for

approximately 8 months from the first dose of enfortumab vedotin, and 4) when all patients in Cohort 2 have had the opportunity to be followed for approximately 8 months from the first dose of enfortumab vedotin. All patients may also be analyzed at the time of analysis of Cohort 1 and/or Cohort 2.

Additional cutoff dates may be defined and corresponding database locks may occur to allow for more precise estimates of time-to-event endpoints.

9.3.2 Patient Disposition

An accounting of study patients by disposition will be tabulated and the number of patients in each analysis set will be summarized. Patients who discontinue study treatment and patients who withdraw from the study will be summarized with reason for discontinuation or withdrawal using the full analysis set.

9.3.3 Patient Characteristics

Demographics and other baseline characteristics will be summarized using the full analysis set. Details will be provided in the SAP.

9.3.4 Treatment Administration

Treatment administration will be summarized for safety analysis set. Summary statistics for duration of therapy (weeks) and the number of cycles per patient will be presented, as well as the number and percentage of patients who were treated at each cycle and completed each cycle. Details will be provided in the SAP.

9.3.5 Efficacy Analyses

The primary analysis of efficacy endpoints will be based on the full analysis set. At the time of the interim analysis for Cohort 2, the efficacy evaluable set will be used for the additional analyses of efficacy endpoints to allow adequate follow up for a stable estimate of ORR and DOR.

9.3.5.1 Primary Efficacy Analyses

The primary endpoint of this study is the confirmed ORR per IRF. The ORR is defined as the proportion of patients with confirmed CR or PR according to RECIST Version 1.1 (see Appendix D) (Eisenhauer 2009). Patients who do not have at least 2 (initial response and confirmation scan) post-baseline response assessments as described in Section 7.2 of the protocol will be counted as non-responders.

The ORR per IRF and its exact 2-sided 95% CI using the Clopper-Pearson method (Clopper 1934) will be calculated.

There are 2 cohorts of CPI-treated patients in the study: Cohort 1) platinum-treated patients, and Cohort 2) platinum-naïve and cisplatin-ineligible patients. The primary endpoint will be analyzed separately for each cohort and may be analyzed for all patients, combining both Cohorts 1 and 2.

9.3.5.2 Secondary Efficacy Analyses

The analyses on secondary endpoints, confirmed ORR per investigator, DCR_{16} per IRF, and DCR_{16} per investigator assessment will be summarized, and their exact 2-sided 95% CIs using the Clopper-Pearson method (Clopper 1934) will be calculated.

Secondary endpoints, such as DOR per IRF, DOR per investigator, PFS per IRF, PFS per investigator, and OS, are time-to-event endpoints, and they will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. Details on the censoring algorithm will be provided in the SAP.

9.3.6 Pharmacokinetic and ATA Analyses

Plasma enfortumab vedotin ADC, TAb, and MMAE concentrations will be summarized with descriptive statistics at each PK sampling timepoint using the PK analysis set. These data may be combined with data from previous studies for population PK and PK/pharmacodynamics analyses. The relationship between enfortumab vedotin PK and pharmacodynamics endpoints, safety, or efficacy may be explored.

The incidence of ATA will be summarized by visit and overall using the safety analysis set.

9.3.7 Quality of Life Analyses

The PRO based on EQ-5D, and QLQ-C30 will be summarized over time with descriptive statistics by visit, using the full analysis set.

9.3.8 Biomarker Analyses

Relationships of biomarker parameters (e.g., pre-treatment values, absolute and relative changes from pre-treatment) to efficacy, safety, and pharmacokinetic parameters will be explored. Relationships and associated data that are determined to be of interest will be summarized. Details of these analyses will be described separately.

9.3.9 Safety Analyses

The safety analysis set will be used to summarize all safety endpoints.

9.3.9.1 Extent of Exposure

Duration of treatment, number of cycles, total dose and dose intensity will be summarized. Dose modifications will also be summarized. Details will be provided in the SAP.

9.3.9.2 Adverse Events

An overview of AEs will provide a tabulation of the incidence of all AEs, treatment-emergent AEs, treatment-related AEs, Grade 3 and higher AEs, SAEs, treatment-related SAEs, deaths, and AEs leading to study treatment discontinuation. Adverse events will be defined as treatment emergent if they are newly occurring or worsened following study treatment.

AEs will be classified by system organ class and preferred tem using the Medical Dictionary for Regulatory Activities (MedDRA) and graded using NCI CTCAE, Version 4.03.

The incidence of AEs will be summarized by system organ class, preferred term, severity and relationship to study drug. In the event of multiple occurrences of the same AE in one patient, the AE will be counted once as the occurrence for the maximum grade. AEs leading to premature discontinuation of study drug will be summarized and listed in the same manner.

All AEs will be listed.

9.3.9.3 Deaths and Serious Adverse Events

SAEs will be listed and summarized in the same manner as all AEs. Events with a fatal outcome will be listed.

9.3.9.4 Clinical Laboratory Results

Summary statistics for lab values and for change from baseline will be tabulated as appropriate by scheduled visit. Laboratory values will be listed with grade per NCI CTCAE v4.03 and flagged when values are outside the normal reference range.

9.3.9.5 Other Safety Analyses

ECOG Status

ECOG status will be summarized for each visit. Shifts from baseline to the best and worst postbaseline score may be tabulated.

ECG

ECG status (normal, abnormal clinically significant, or abnormal not clinically significant) may be summarized for each scheduled and unscheduled ECG, and shifts from baseline may be tabulated.

9.3.10 Interim Analyses

An IDMC will periodically monitor the trial for safety. The IDMC will review expedited SAEs as they are received. Further details will be provided in the IDMC Charter.

In addition, an ongoing real-time review of SAEs will be conducted by Seattle Genetics Pharmacovigilance.

Additionally, available data for Cohort 2 will be summarized at the time of the primary analysis of Cohort 1 (e.g., the estimated ORR and its 2-sided 95% exact Clopper-Pearson CI), after approximately 50 patients in Cohort 2 have had the opportunity to be followed for approximately 8 months from the first dose of enfortumab vedotin, and after approximately 70 patients in Cohort 2 have had the opportunity to be followed for approximately 8 months from the first dose of enfortumab vedotin. All patients may also be analyzed at the time of analysis of Cohort 1 and/or Cohort 2.

10 INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

This study will be conducted in accordance with the Note for Guidance on Good Clinical Practice (ICH Harmonised Tripartite Guideline E6 [R1]; FDA CFR [21 CFR § 50, 56, 312]), Declaration of Helsinki (Brazil 2013), and all applicable regulatory requirements.

10.1 Informed Consent

The investigator is responsible for ensuring that the risks and benefits of study participation are presented to the patient in simple terms using the IRB/IEC approved informed consent document and for ensuring patients are re-consented when the informed consent document is updated during the study, if required. The investigator will ensure that written informed consent is obtained from each patient, or legally acceptable representative, if applicable to this study, by obtaining the signature and date on the informed consent document prior to the performance of protocol evaluations or procedures.

If informed consent is obtained from a legally acceptable representative for a patient who is unable to provide informed consent at study entry (if applicable), but the patient is later able to provide informed consent, the investigator must obtain written informed consent from the patient.

10.2 Ethical Review

The investigator will provide the sponsor or its designee with documentation of the IRB/IEC approval of the protocol and the informed consent document before the study may begin at the investigative site(s). The name and address of the reviewing ethics committee are provided in the investigator file.

The investigator will supply the following to the investigative site's IRB/IEC:

- Protocol and amendments
- Informed consent document and updates
- Clinical Investigator's Brochure and updates
- Relevant curricula vitae, if required
- Required safety and SAE reports
- Any additional submissions required by the site's IRB/IEC

The investigator must provide the following documentation to the sponsor or its designee:

- The IRB/IEC periodic (e.g., quarterly, annual) re-approval of the protocol.
- The IRB/IEC approvals of any amendments to the protocol or revisions to the informed consent document.
- The IRB/IEC receipt of safety and SAE reports, as appropriate.

10.3 Regulatory Considerations

This study will be conducted in accordance with the protocol and ethical principles stated in the applicable guidelines on good clinical practice, and all applicable local and/or regional laws, rules, and regulations.

10.3.1 Investigator Information

The contact information and qualifications of the principal investigator and subinvestigators and name and address of the research facilities are included in the investigator file.

10.3.2 Protocol Amendments and Study Termination

Any investigator-initiated changes to the protocol (with the exception of changes to eliminate an immediate hazard to a study patient) must be approved by the sponsor prior to seeking approval from the IRB/IEC, and prior to implementing. The investigator is responsible for enrolling patients who have met protocol eligibility criteria. Protocol deviations must be reported to the sponsor and the local IRB/IEC in accordance with IRB/IEC policies.

The sponsor may terminate the study at any time. The IRB/IEC must be advised in writing of study completion or early termination.

10.4 Study Documentation, Privacy and Records Retention

To protect the safety of participants in the study and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide the sponsor, its licensees and collaborators, applicable regulatory agencies, and applicable IRB/IEC with direct access to original source documents or certified copies.

Records containing patient medical information must be handled in accordance with local and national laws, rules, and regulations and consistent with the terms of the patient authorization contained in the informed consent document for the study (the Authorization). Care should be taken to ensure that such records are not shared with any person or for any purpose not contemplated by the Authorization. Furthermore, CRFs and other documents to be transferred to the sponsor should be completed in strict accordance with the instructions provided by the sponsor, including the instructions regarding the coding of patient identities.

In compliance with local and/or regional regulations, this trial may be registered and trial results may be posted on public registries, such as ClinicalTrials.gov.

10.5 Clinical Trial Agreement

Payments by the sponsor to investigators and institutions conducting the trial, requirements for investigators' insurance, the publication policy for clinical trial data, and other requirements are specified in the clinical trial agreement.

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APPENDIX A: SCHEDULE OF EVENTS

		Screening/ Baseline		Enrollment	Every 28-day cycle						EOT	Follow-up	LTFU
	Day	D –28 to 1	D –7 to 1	Within 7D of 1st dose	D1	D3[A]	D8	D15	D17[A]	D22	Within 30–37d of last dose[B]	Every 8 weeks	Every 8 weeks
	Visit window				±2d	±24h	+2d	+2d	–24h /+48h			±7 d	±7 d
Screening/baseline assessments	Inclusion/exclusion, medical history	X		Submit confirmation of eligibility prior to treatment									
	Informed consent	X											
	Acquire and submit tumor specimen[C]	X											
	Complete eye examination[D]	X											
	Slit lamp eye examination[D]										X[O]		
	Brain scan	X								X[E]	X[E]	X[E]	
	Bone scan	X								X[E]	X[E]	X[E]	
	INR/PT/PTT	X											
	Hepatitis B and C screening	X											
	Urinalysis with microscopic analysis	X											
	HbA1c[N]	X											
	Pregnancy test (females of childbearing potential)[F]		X		X						X		
Safety assessments	Physical exam (including weight)[P]		X		X[G]						X	X[H]	
	Height		X										
	Vital signs		X		X[G]		X	X			X		
	CBC with differential[P]		X		X[G]		X	X			X		
	Chemistry panel[P]		X		X[G]		X	X			X		
	CrCl		X										
	ECOG performance status[P]		X		X[G]						X	X[H]	
	ECG		X								X		
	Concomitant medications	Related to study procedures from time of informed consent			Collect from Day 1 predose through 30 days post last study treatment								
	Adverse event collection												
PRO/QoL	QLQ-C30 and EQ-5D				X						X		
Treatment	Study drug administration[I]				X		X	X					
PK/ATA/biomarker	Blood sample collection	See PK, ATA and Biomarker Table (Table 3) for sample collection details											
Response assessment	CT scan with contrast of chest, abdomen, pelvis and any other region of known or suspected disease[Q]	X								X[J,K]	X[J,L]	X[H,J]	
	Survival status												X[M]

Footnotes

A Cycles 1 and 2. See PK, ATA and Biomarker Table (Table 3) for sample collection details.
B EOT evaluations must be obtained before the initiation of subsequent anticancer therapy, with the exception of slit lamp examinations. If EOT evaluations are completed before 30 days following the last study treatment, conduct a phone screen 30–37 days following the patient's last study treatment to ensure that no changes in AE profile have occurred.
C Pretreatment tumor tissue (from primary or metastatic site) for biomarker studies must be available for submission to the sponsor prior to study treatment. A minimum of 10 freshly sectioned, unstained charged slides are required. Either archival tissue or pre-treatment fresh tumor tissue (obtained from a fresh biopsy) is acceptable.
D Repeated as clinically indicated throughout the study.
E Repeated at disease assessment timepoints if disease present at baseline, or as clinically indicated throughout the study.
F Either serum or urine pregnancy test. Not required for Cycle 1 if baseline assessment performed within 7 days. Repeat every month (±1 week) for 6 months after EOT.
G Not required for Cycle 1 if baseline assessments performed within 1 day.
H Patients who discontinue study treatment for reasons other than objective disease progression by RECIST Version 1.1 will continue to have physical exams (no weight collection is required), ECOG, and response assessments 8 weeks (±1 week) after the previous response assessment scan and every 8 weeks (±1 week) following the previous visit thereafter. After 1 year on study the frequency of follow-up visits and response assessments will be reduced to every 12 weeks (±1 week). The tumor assessments will continue until the patient has radiologically-confirmed disease progression per RECIST as determined by the investigator, initiates a new anticancer therapy, patient death, study closure, or withdrawal of consent, whichever comes first.
I At least 1 week must elapse between doses of enfortumab vedotin.
J Responses will be confirmed with repeat scans at 4 weeks after first documentation of response (+1 week). Following confirmation scans, response assessments should continue with the previous scan schedule (i.e., the schedule should not be adjusted). Tumor imaging should also be performed whenever disease progression is suspected.
K Response assessment will be performed every 8 weeks (±1 week). After 1 year on study, response assessments will be reduced to every 12 weeks (±1 week). The schedule of response assessments should not be adjusted for dose delays/interupptions or other reasons for changes in the timing of a patient's study activities; timepoints for response assessments should be calculated from Cycle 1 Day 1 during treatment.
L Not required if conducted <4 weeks prior to EOT.
M Contact patient for survival status and collection of subsequent anticancer treatment information every 8 weeks (±1 week) after EOT (or 8 weeks from previous protocol visit, whichever is later) until death, study closure, or withdrawal of consent, or patient is lost to follow-up, whichever occurs first. After 1 year on study the frequency of follow-up contacts will be reduced to every 12 weeks (±1 week).
N If HbA1c is elevated (≥6.5%), refer patient to appropriate provider during Cycle 1 for glucose management.
O EOT slit lamp examination required for all patients who experience corneal adverse events during the study and must be performed ≥4 weeks from last dose.
P May be collected or conducted up to 1 day prior to dosing. Local laboratory results must be reviewed prior to study drug administration in order to determine whether to proceed with dosing or whether dose modification is required.
Q If contrast is contraindicated, see Appendix F.

APPENDIX B: PERFORMANCE STATUS SCALES CONVERSION

Karnofsky		Lansky		ECOG	
Percent	Description	Percent	Description	Score	Description
100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.	0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.		
80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly.	1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
70	Cares for self, unable to carry on normal activity or to do active work.	70	Both greater restriction of, and less time spent in, play activity.		
60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.	2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet active play and activities.		
40	Disabled, requires special care and assistance.	40	Mostly in bed, participates in quiet activities.	3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed, needs assistance even for quiet play.		
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping, play entirely limited to very passive activities.	4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
10	Moribund, fatal processes progressing rapidly.	10	No play, does not get out of bed.		
0	Dead.	0	Dead.	5	Dead.

APPENDIX C: NEW YORK HEART ASSOCIATION CLASSIFICATION

A Functional and Therapeutic Classification for Prescription of Physical Activity for Cardiac Patients

Class I:	patients with no limitation of activities; they suffer no symptoms from ordinary activities.
Class II:	patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.
Class III:	patients with marked limitation of activity; they are comfortable only at rest.
Class IV:	patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

On-line source:
http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp

APPENDIX D: RECIST CRITERIA SUMMARY (VERSION 1.1)

Response Evaluation Criteria in Solid Tumors	
Term	Definition
Complete response (CR)	Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to <10 mm.
Partial response (PR)	A ≥30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 0.5 cm. The appearance of one or more new lesions is also considered progression.
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
Measurable lesion	Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10 mm by CT scan (CT slice thickness no greater than 5 mm). A lymph node must be ≥15 mm in short axis when assessed by CT scan to be considered measurable.

From RECIST Version 1.1 (Eisenhauer 2009)

A response (CR or PR) will be considered confirmed if the following disease assessment (at least 4 weeks after the initial response) still shows response (CR or PR). In cases where the initial response is followed by SD, it will be considered as confirmed if the SD is later followed by PR or CR. For example, if a patient had PR in week 8, SD in week 12, and PR in week 16, this PR will be considered as confirmed.

APPENDIX E: LIVER SAFETY MONITORING AND ASSESSMENT

The following recommendations are from the Food and Drug Administration (FDA) Guidance for Industry titled "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" issued July 2009.

Any patient with an increase of serum aminotransferases to >3 × upper limit of normal (ULN) or bilirubin >2 × ULN should undergo detailed testing for liver enzymes (including at least alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], and total bilirubin [TBL]). To confirm the abnormality, testing should be repeated within 72 hours of notification of the test results.

Definition of Liver Abnormalities

Confirmed liver abnormalities will be characterized as Moderate and Severe:

Moderate:

- ALT or AST >3 × ULN **OR** Total Bilirubin >2 × ULN

Severe:

- ALT or AST >3 × ULN **AND** Total Bilirubin >2 × ULN (*See Hy's Law Definition)
- ALT or AST >8 × ULN
- ALT or AST >5 × ULN for more than 2 weeks
- ALT or AST >3 × ULN and International Normalized Ratio (INR) >1.5 (if INR testing is applicable/evaluated)
- ALT or AST >3 × ULN with the appearance of symptoms suggestive of liver injury (e.g., right upper quadrant pain or tenderness) and/or eosinophilia (>5%)

The investigator may determine that abnormal liver function results, other than as described above, may qualify as moderate or severe abnormalities and require additional monitoring and follow-up.

*Hy's Law Definition: Drug-induced jaundice caused by hepatocellular injury, without a significant obstructive component, has a high rate of bad outcomes, from 10 to 50% mortality (or transplant). The 2 "requirements" for Hy's Law are: 1) Evidence that a drug can cause hepatocellular-type injury, generally shown by an increase in transaminase elevations higher 3 × ULN ("2 × ULN elevations are too common in treated and untreated patients to be discriminating"). 2) Cases of increased bilirubin (at least 2 × ULN) with concurrent transaminase elevations at least 3 × ULN and no evidence of intra- or extra-hepatic bilirubin obstruction (elevated ALP) or Gilbert's syndrome (Temple 2006).

Follow-up Procedures

Confirmed moderate and severe abnormalities in hepatic functions should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical

examination and laboratory tests. Patients with confirmed abnormal liver function testing should be followed as described below.

Confirmed moderately abnormal liver function tests (LFTs) should be repeated 2 to 3 times weekly then weekly or less if abnormalities stabilize or the study drug has been discontinued and the patient is asymptomatic.

Severe hepatic liver function abnormalities as defined above, in the absence of another etiology, may be considered an important medical event and may be reported as a SAE. The sponsor should be contacted and informed of all patients for whom severe hepatic liver function abnormalities possibly attributable to study drug are observed.

To further assess abnormal hepatic laboratory finding, it is recommended that the investigator:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Illnesses and conditions such as hypotensive events, and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Nonalcoholic steatohepatitis is seen in obese hyperlipoproteinemic and/or diabetic patients, and may be associated with fluctuating aminotransferase levels.
- Obtain a history of concomitant drug use (including nonprescription medication, complementary and alternative medications), alcohol use, recreational drug use and special diets
- Obtain a history of exposure to environmental chemical agents.
- Based on the patient's history, other testing may be appropriate including:
    - Acute viral hepatitis (A, B, C, D, E or other infectious agents),
    - Ultrasound or other imaging to assess biliary tract disease,
    - Other laboratory tests including INR, direct bilirubin.
- Consider gastroenterology or hepatology consultations.

Conduct additional testing as determined by the investigator to further evaluate possible etiology.

See Section 5.2.3.1 for treatment discontinuation recommendations related to hepatic safety.

APPENDIX F: SCANNING AND CONTRAST GUIDELINES

In decreasing order of preference

Brain Scan

1. Brain MRI with gadolinium

If gadolinium is medically contraindicated:

2. Brain MRI without gadolinium
3. Brain CT with IV contrast
4. Brain CT without IV contrast

Chest-Abdomen-Pelvis Scans:

1. Chest-Abdomen-Pelvis CT with IV contrast

If iodine media is medically contraindicated:

2. Chest CT without IV contrast and Abdomen-Pelvis MRI with gadolinium
3. Chest-Abdomen-Pelvis CT without IV contrast (oral contrast is recommended)
4. Chest-Abdomen-Pelvis MRI with gadolinium

CT Oral Contrast

1. Radio opaque agents (e.g., iodine and barium based agents)
2. Radio-lucent agents (whole milk, VoLumen®, water)

Important: Imaging modality, anatomical coverage and acquisition parameters should remain consistent across all imaging visits for each patient.

APPENDIX G: INVESTIGATOR SIGNATURE PAGE

Investigator Statement and Signature

I have read the attached protocol entitled "A single-arm, open-label, multicenter study of enfortumab vedotin (ASG-22CE) for treatment of patients with locally advanced or metastatic urothelial cancer who previously received immune checkpoint inhibitor (CPI) therapy"

I understand and agree to the provisions of the protocol, and I accept the responsibilities listed above in my role as principal investigator for the study.

Investigator Signature	Date
Investigator Name, Printed	

APPENDIX H: DOCUMENT HISTORY

Version	Date
Original	24-May-2017
Amendment 1	14-Nov-2017
Amendment 2	13-Feb-2018
Amendment 3	13-Apr-2018
Amendment 4	16-Apr-2018
Amendment 5	14-Nov-2018
Amendment 6	05-Dec-2019

Summary of Changes in Amendment 1

Section(s)	Change	Rationale
Title page	Added study name, EudraCT Number, and updated study medical monitor	Administrative changes
Synopsis and 4.2	Added exclusion criterion: 15. Patients with uncontrolled diabetes. Uncontrolled diabetes is defined as hemoglobin A1C (HbA1c) ≥8% or HbA1c 7–<8% with associated diabetes symptoms (polyuria or polydipsia) that are not otherwise explained.	Adds an exclusion criterion for patients with uncontrolled diabetes
5.2.2	Revised text as follows: **An exception to weight-based dosing is made for patients weighing greater than ~~120~~ 100 kg; doses will be based on ~~120~~ 100 kg for these individuals. The maximum dose permitted on this study is ~~150~~ 125 mg.**	Revises cap on weight-based dosing from 120 kg to 100 kg
5.2.3	Added text as follows to Table 2, Grade 3 column: For Grade 3 hyperglycemia/elevated blood glucose withhold enfortumab vedotin treatment. Resume treatment once hyperglycemia/elevated blood glucose has improved to ≤ Grade 2 and patient is clinically and metabolically stable. Added text to refer to Management of Hyperglycemia section: See Section 5.4.2 for recommended management of hyperglycemia.	Provides dose modification guidance for hyperglycemia.
5.4.2	Added Management of Hyperglycemia section as follows: Investigators should monitor blood glucose levels and are advised to perform additional assessments if any symptoms of hyperglycemia are observed, including a thorough evaluation for infection. In addition, if steroids are used to treat any other condition, blood glucose levels	Adds new section on management of hyperglycemia

Section(s)	Change	Rationale
	may require additional monitoring. If elevated blood glucose levels are observed, patients should be treated according to local standard of care and referral to endocrinology may be considered. Patients, especially those with a history of or ongoing diabetes mellitus or hyperglycemia, should be advised to immediately notify their physician if their glucose level becomes difficult to control or if they experience symptoms suggestive of hyperglycemia such as frequent urination, increased thirst, blurred vision, fatigue, and headache. Patients who enter the study with an elevated HbA1c (≥6.5%) at baseline should be referred to an appropriate provider during Cycle 1 for glucose management. Blood glucose should be checked prior to each dosing and dose should be withheld for blood glucose >250 ml/dL (Grade 3 or higher). Dosing may continue once the patient's blood glucose has improved to ≤ Grade 2 and patient is clinically and metabolically stable.	
6.2, 7.1, 7.7.2, and Appendix A	Added assessment at screening: HbA1c: If HbA1c is elevated (≥6.5%), refer patient to appropriate provider during Cycle 1 for glucose management.	Adds HbA1c at screening, with guidelines for glucose management if elevated.

Summary of Changes in Amendment 2

Section(s)	Change	Rationale
3.1, 6.3.6, 7.7.7, 9.1, and Appendix A	Added Cycle 6 (±1 week) slit lamp examinations for at least the first 60 enrolled patients. Clarified that end of treatment (EOT) slit lamp exams will be performed for all patients who experience a corneal adverse event on study.	Added per Food and Drug Administration (FDA) request Clarification
5.4.2	Revised the text as follows: Blood glucose >250 ~~mL~~mg/dL	Error correction

Summary of Changes in Amendment 3

Section(s)	Change	Rationale
1.6	Updated section with 2-Oct-2017 data cut-off date for ASG-22CE-13-2. Added text to explicitly state benefit-risk statement as follows: Clinical data to date support a favorable benefit-risk ratio for enfortumab vedotin in patients with locally advanced or metastatic urothelial carcinoma who previously received CPI therapy. To assure an ongoing favorable benefit-risk assessment for subjects enrolled into the study, an Independent Data Monitoring Committee (IDMC) will be utilized to monitor safety data and may request interim efficacy data, if needed.	Updates section to match current Investigator's Brochure edition data cut. Adds benefit-risk statement per regulatory agency request under the Voluntary Harmonisation Procedure (VHP).
4.2	Added text to exclusion criteria 3 as follows: Patients with immunotherapy related myocarditis, colitis, uveitis, or pneumonitis are excluded.	Excludes patients with immunotherapy related myocarditits per regulatory agency request under VHP.
Synopsis, 3.1, 4.3.1	Added pregnancy to list of reasons for treatment discontinuation.	Per regulatory agency request under VHP
5.2.2	Added text regarding drug administration setting as follows: The patient should be observed during administration of enfortumab vedotin and for at least 60 minutes following the infusion during the first 3 cycles. All supportive measures consistent with optimal subject care should be given throughout the study according to institutional standards.	Adds administration monitoring per regulatory agency request under VHP.
6.5 and Appendix A	Added a pregnancy test monthly (±1 week) for 6 months after end of treatment (EOT) for patients of childbearing potential	Per regulatory agency request under VHP.

Summary of Changes in Amendment 4

Section(s)	Change	Rationale
1.2	Updated the second-line therapy options for metastatic urothelial cancer.	To provide current regulatory approvals and data for the various treatment options for urothelial cancer.
Synopsis and 2.1	Revised primary objective as follows: • To determine the antitumor activity of single-agent enfortumab vedotin as measured by confirmed objective response rate (ORR) in patients with locally advanced or metastatic urothelial cancer who tohave previously received systemic therapy with a CPI and either previously received platinum-containing chemotherapy or are platinum-naïve and cisplatin-ineligible	To align with revisions to the inclusion criteria that further differentiate patients who received prior platinum-containing chemotherapy from those who are platinum-naïve and cisplatin-ineligible.
Synopsis and 3.1	Revised summary of the study design and the study schema to reflect changes in other sections.	To align with revisions to the inclusion criteria, efficacy assessments (methods and timing), and cohorts from which the corneal events will be evaluated.
3.2	Added efficacy data from a recent study of patients treated with docetaxel after platinum and CPI therapy.	To provide additional support for rationale for the current study design.
3.2.2	Updated section with 2-Oct-2017 data cut-off date for ASG-22CE-13-2.	Updates section to match current IB edition data cut.
Synopsis and 4.1	Revised inclusion criterion 1 as follows: 1. Patients must have histologically ~~or cytologically~~ documented ~~locally advanced or metastatic~~ urothelial (previously known as transitional cell) carcinoma ~~of the urothelium~~ (i.e., cancer of the bladder, renal pelvis, ureter, or urethra).	To align with current disease terminology.
Synopsis and 4.1	Revised inclusion criterion 2 as follows: 2. Patient must have received prior treatment with a CPI in the locally advanced or metastatic urothelial cancer setting. Patients who received CPI therapy in the neoadjuvant/adjuvant setting and had recurrent or	To clarify the eligibility requirements for prior CPI therapy.

Section(s)	Change	Rationale
	progressive disease either during therapy or within 3 months of therapy completion are eligible. A CPI is defined as a PD-1 inhibitor or PD-L1 inhibitor (including, but not limited to: atezolizumab, pembrolizumab, durvalumab, avelumab, and nivolumab).	
Synopsis and 4.1	Revised inclusion criterion 3 as follows: 3. Patients must ~~either have~~ be one of the following: a.Platinum-treated (Cohort 1): Patients who received prior treatment with platinum-containing chemotherapy ~~or be~~ defined as those who received platinum in the adjuvant/neoadjuvant setting and had recurrent or progressive disease within 12 months of completion OR received treatment with platinum in the locally advanced (defined as unresectable with curative intent) or metastatic setting; OR b.Platinum-naïve and cisplatin ineligible (Cohort 2): Patients who have not received prior treatment with platinum-containing or other chemotherapy in the locally advanced or metastatic setting and are ineligible for treatment with cisplatin at time of enrollment due to one of the following: impaired renal function (defined as creatinine clearance [CrCl] ≥30 and <60 mL/min), or a hearing loss of 25 decibels (dB) at two contiguous frequencies. ~~If~~ Patients who received platinum ~~was administered~~ in the adjuvant/neoadjuvant setting ~~patient must have progressed~~ and did not progress within 12 months of completion will be considered platinum-naïve.	To further differentiate patients who received prior platinum-containing chemotherapy from those who are platinum-naïve and cisplatin-ineligible.
4.1 and 7.7.2	Revised inclusion criterion 9 by adding that CrCl could be measured by 24-hour urine collection.	To allow flexibility in the method for measuring CrCl.
Synopsis and 4.2	Revised exclusion criterion 4 as follows:	To ensure no crossover of patients between enfortumab vedotin studies.

Section(s)	Change	Rationale
	4. Prior ~~treatment with~~ enrollment in an enfortumab vedotin study or prior treatment with other MMAE-based ADCs.	
4.2	Revised exclusion criterion 13 as follows: 13. Patients with active keratitis or corneal ulcerations. Patients with superficial punctate keratitis are allowed if the disorder is being adequately treated in the opinion of the investigator.	To allow patients on study with superficial punctate keratitis whose disorder is being adequately treated in the opinion of the investigator.
Synopsis and 4.2	Added exclusion criterion 16 as follows: 16. Uncontrolled tumor-related bone pain or impending spinal cord compression. Patients requiring pain medication must be on a stable regimen at the time of enrollment (a minimum of 2 weeks).	To exclude patients with uncontrolled tumor-related bone pain or impending spinal cord compression and to ensure that those who have pain being controlled pain medication have been on a stable regimen for a minimum of 2 weeks at the time of enrollment.
Synopsis and 4.3.1	Added pregnancy to list of reasons for discontinuation of study treatment	Updates to align with other enfortumab vedotin studies, based on regulatory feedback and for patient safety
5.2.2	Added the following language to the dose and administration instructions: The injection site should be monitored closely for redness, swelling, pain, and infection during and at any time after administration. Patients should be advised to report redness or discomfort promptly at the time of administration or after infusion. Institutional guidelines will be followed for the administration of chemotherapy agents and precautions taken to prevent extravasation per institutional standards and as described in "Chemotherapy and Biotherapy Guidelines and Recommendations for Practice" (Polovich 2014) and "Management of Chemotherapy Extravasation: ESMO-EONS Clinical Practice Guidelines" (Perez Fidalgo 2012).	To ensure that injection sites are monitored for potential adverse reactions and provide guidelines for managing extravasation if it occurs.
5.2.3	Revised dose modifications by adding dose re-escalation parameters for patients who are dose reduced, adding that enfortumab vedotin should not be administered to patients with CrCl < 30 mL/min (if known), and adding parameters for dose delays and eliminations depending	To ensure patient safety.

Section(s)	Change	Rationale
	on the timing of toxicities relative to dosing days. Clarified that dose reduction or delay for other enfortumab vedotin-associated toxicity does not need medical monitor involvement, but can be done at the discretion of the site investigator. Also clarified that dose delays for *any* patient may be extended beyond 8 weeks without the approval of the medical monitor if the toxicity does not require permanent discontinuation. Added an exception to allow patients to receive palliative radiotherapy during a dose delay.	
5.2.3, Table 1	Revised recommended dose modifications for enfortumab vedotin-associated hematologic toxicity to allow discontinuations at the discretion of the investigator for Grade 4 hematologic toxicity rather than requiring discussion with the sponsor. Also clarified that discontinuation is strongly recommended for Grade 4 anemia.	To ensure patient safety.
5.2.3, Table 2	Revised recommended dose modifications for enfortumab vedotin-associated nonhematologic toxicity to ensure that treatment is discontinued for any Grade 4 nonhematologic adverse event except for Grade 4 vomiting and/or diarrhea that improves to ≤ Grade 2 within 72 hours with supportive management. Clarified that for Grade 3 neuropathy or corneal AEs, treatment should be discontinued regardless of investigator discetion or sponsor approval. Added that if ocular symptoms and/or changes in vision are identified (Grades 1 – 3), the patient should be evaluated by a qualified optometrist or ophthalmologist. Also clarified the following: Grade 3/4 electrolyte imbalances/laboratory abnormalities, except hyperglycemia, that are not associated with clinical sequelae and are corrected with supplementation/ appropriate management within 72 hours of their onset do not require discontinuation (e.g., Grade 4 hyponatremia). Grade 3 rash that is not limiting self-care activities of daily living or associated with infection requiring systemic antibiotics does not require	To ensure patient safety.

Section(s)	Change	Rationale
	treatment interruption, provided symptoms are not severe and can be managed with supportive treatment. In addition, patients with Grade 4 nausea and/or diarrhea resolved within 72 hours with supportive management do not require discontinuation.	
Synopsis and 5.2.3, 6.3.6, 6.4, 6.6, and 7.2	Clarified throughout the protocol that response assessments will not be adjusted for dose delays or other changes in timing of study activities and will all be timed from Cycle 1 Day 1 during treatment.	To ensure that the timing of response assessments is consistent across patients and applicable to the course of the disease under study.
5.3.2, 5.3.3, and 9.2.2	Added allowed concomitant therapy with palliative radiotherapy for a non-target bone lesion.	To provide an option for additional disease management that will not interfere with measurement of the investigational agent's activity.
5.3.3	Clarified that patients who receive prohibited concomitant therapy must be discontinued from the study.	To ensure that patients who receive prohibited concomitant therapy do not continue on study.
5.4.2	Added additional instructions for the management of hyperglycemia as follows: Blood glucose >500 mg/dL (Grade 4) considered related to enfortumab vedotin requires treatment discontinuation. If a patient experiences new onset diabetes mellitus, evaluate patients with a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide to assess for new onset type 1 diabetes in the setting of prior CPI.	To ensure patient safety.
5.4.3	Added management of rash as follows: In the phase 1 study (Study ASG-22CE-13-2), rash and similar dermatologic AEs were common among patients treated with enfortumab vedotin, and were seen more frequently at the highest dose. Although the exact etiology of dermatologic toxicities associated with enfortumab vedotin is unclear at this time, due to the expression of Nectin-4 in the skin, rash maybe an on-target toxicity. The most common dermatological AEs reported in ASG 22CE-13-2 were drug eruption, rash, skin exfoliation, skin pigmentation disorder, and rash	To ensure patient safety.

Section(s)	Change	Rationale
	maculo-papular. Most occurred during Cycle 1, and some were associated with pruritus. Almost all were mild, with the exception of two events of rash reported as Grade 3 in the 1 mg/kg dose group. None required discontinuation of study drug and one event of Grade 1 papular rash at 1.25 mg/kg required a dose reduction. Mild rash related to enfortumab vedotin should be treated using local supportive care as needed. Topical corticosteroids have been used along with antihistamines for pruritus as needed. Grade 3 rash that is not limiting self-care activities of daily living or associated with infection requiring systemic antibiotics does not require treatment interruption, provided symptoms are not severe and can be managed with supportive treatment.	
Synopsis, 6.2, 6.3.6, 6.4, 6.6, 7.1, and 7.2, and Appendix A	Clarified that brain scans are to be performed using an MRI with gadolinium unless contraindicated and that CT scans with contrast are to be done for other parts of the body unless contrast is contraindicated. For patients for whom contrast is contraindicated, additional guidelines for scanning have been provided in Appendix F. Also clarified that brain scans will be performed if metastases were identified at baseline or if metastasis is suspected.	To ensure consistent methodologies used in performing disease assessments and to provide alternatives for patients for whom contrast is contraindicated.
6.2	Clarified that serology for *antihepatitis C antibody* is to be done during screening and that *if positive, follow up with PCR testing*.	Clarification.
6.3.1, 6.3.3, and 6.3.4, and Appendix A	Clarified that on Days 1, 8, and 15 of each treatment period CBC with differential and the serum chemistry panel may be collected the day prior to dosing.	Clarification.
6.6 and 6.7	Moved duration of the study from Section 6.6 Long-term Follow-up to Section 6.7 End of Study/End of Follow-up	To place duration of the study in the appropriate section of the protocol
Synopsis and 7.2	Replaced ‘protocol-specified timepoints’ with the actual timing of the response assessments: Measures of anticancer activity will be assessed by CT scans with contrast approximately every 8 weeks (±1 week). After 1	To ensure clarity of the timing of the response assessments and to align with other protocol sections

Section(s)	Change	Rationale
	year on study, response assessments will be reduced to every 12 weeks (±1 week).	
7.3	Added example of possible analysis on archived samples: other enfortumab vedotin related species, such as circulating metabolites of MMAE.	Clarification
Synopsis and 7.4	Changed enzyme-linked immunosorbent assay (ELISA) to immunoassays.	Because other immunoassays may be used rather than just ELISA.
Synopsis and 7.4.1	Added circulating tumor DNA (ctDNA) to the biomarker assessments.	To allow testing of ctDNA.
7.4.2	Removed examples of messenger ribonucleic acid (mRNA) expression (e.g., Nectin-4) and examples of markers of the tumor immune microenvironment (e.g., PD-L1, CD4, CD8). Also added tumor mutational burden to the biomarker assessments.	Because other mRNA may be tested rather than only Nectin-4 and because other markers of the tumor immune microenvironment may be tested rather than only PD-L1, CD4, and CD8. Added tumor mutational burden to allow testing of that biomarker.
7.7.2	Added the following local laboratory assessment: serology for hepatitis B surface antigen and antihepatitis B core antibody	To allow testing for hepatitis B.
7.7.7	Added that eye examinations may be performed by a qualified optometrist and clarified that uncorrected, corrected and best correct visual acuity are to be examined.	Clarification.
7.7.7 and 9.1, and Appendix A	Added the cohorts from which the corneal events will be evaluated.	Clarification.
Synopsis and 9.1, 9.3.1.9, and 9.3.10	Increased enrollment from 120 to 200 patients and defined Cohort 1 as patients who received prior platinum-containing chemotherapy (100 or more patients), and Cohort 2 as patients who are platinum-naïve and cisplatin-ineligible (up to approximately 100 patients). Based on the increased sample size and addition of separate cohorts of patients, statistical analysis details were updated as well as the timepoints at which analyses will be performed.	To ensure collection of sufficient efficacy and safety data and to ensure that a sufficient number of patients are analyzed.

Section(s)	Change	Rationale
Synopsis and 9.3.1 and 9.3.5.1	Based on the addition of separate cohorts of patients, summaries and analyses will be provided by cohort (i.e., platinum-treated and platinum-naïve and cisplatin-ineligible). Summaries and analyses may also be provided overall.	To clarify that all analyses will now be performed by cohort and may be performed overall.
9.3.1.7	Clarified that the intent-to-treat (ITT) analysis set will include all patients who are enrolled and receive any amount of enfortumab vedotin in the study.	Clarification.
9.3.1.8	Added from the statistical analysis plan (SAP) to the protocol the important subgroup of metastatic sites at baseline: lymph node only, liver. Also updated subgroups based on revisions to eligibility criteria. Also added best response achieved to prior CPI therapy for urothelial cancer (e.g., patients with PD), which will also be added to the SAP	To add one of the previously defined subgroups from the SAP to the protocol and to align subgroups with the other revisions made in this amendment for eligibility. To also add the new subgroup analysis for response to prior CPI therapy to further characterize the patient population.
Appendix A	Revised based on revisions made in this amendment	To align with changes made for this amendment
Appendix D	Added to the definition of measurable lesions that a lymph node that must be ≥15 mm in short axis when assessed by CT scan to be considered measurable.	To align with the published RECIST Version 1.1.
Appendix F	Added Scanning and Contrast Guidelines.	To provide protocol-specified options for scanning for all patients and options for those for whom contrast is contraindicated.

Summary of Changes in Amendment 5

Section(s)	Change	Rationale
Title page	Replaced [redacted] with [redacted] as Medical Monitor	Administrative change
Synopsis, 4.1	Revised Study Population to allow ECOG performance status 2 patients into the study in Cohort 2. Revised Inclusion Criterion #8 as follows: An ECOG Performance Status score of ≤~~0 or~~ 1 for Cohort 1, or ≤2 for Cohort 2.	Revises population of Cohort 2 to allow ECOG performance status 2 patients
Synopsis, 4.1	Revised Study Population to require an anticipated life expectancy of ≥3 months. Add new Inclusion Criterion #16: Patients must have an anticipated life expectancy of ≥3 months as assessed by the investigator.	Revises inclusion criteria to require that all patients must have a life expectancy of ≥3 months as assessed by the investigator
Synopsis, 7.3, 9.3.6	Revised text on PK assessments to add measurement of total antibody (TAb)	Error correction
Synopsis, 9.1, 9.3.1.9, 9.3.10	Revised Statistical Methods section as follows: Analysis for Cohort 2 will occur at 3 timepoints: 1) at the time of analysis of Cohort 1, 2) when approximately 50 patients in Cohort 2 have ~~been~~ had the opportunity to be followed for at least 6 months, and 3) when all patients in Cohort 2 have ~~been~~ had the opportunity to be followed for at least 6 months~~, or have discontinued from study, or had 30 days safety follow-up after PD~~. Revised Statistical Methods section as follows: The confirmed ORR and 95% exact CI in Cohort 2 will be summarized at 3 timepoints: 1) at the time of analysis of Cohort 1, 2) when approximately 50 patients in Cohort 2 have ~~been~~ had the opportunity to be followed for at least 6 months, and 3) when all patients treated in Cohort 2 have ~~been~~ had the opportunity to be followed for at	Clarifies timing of and description for Cohort 2 analyses

Section(s)	Change	Rationale
	least 6 months~~, or have discontinued from study, or had 30 days safety follow-up after PD~~.	
2.4	Corrected definitions for ORR and DOR as follows: ORR (confirmed CR ~~and~~or PR per Response Evaluation Criteria in Solid Tumors [RECIST] Version 1.1) DOR (confirmed CR ~~and~~or PR)	Clarification that either a confirmed CR or confirmed PR would qualify toward the analysis of ORR and DOR
2.4.2	Added total antibody to secondary endpoint regarding PK	Error correction
4.1	Revised definition of cisplatin-ineligible in Inclusion Criterion #3b as follows: …ineligible for treatment with cisplatin at time of enrollment due to one of the following: ECOG performance status score of 2; impaired renal function (defined as creatinine clearance [CrCl] ≥30 and <60 mL/min), or a ≥ Grade 2 hearing loss ~~of 25 decibels (dB) at two contiguous frequencies~~.	Revises cisplatin-ineligibility definition to include ECOG peformance status 2 patients Revises cisplatin-ineligibility definition regarding hearing loss
4.2	Revised Exclusion Criterion #3 as follows: Patients with ≤ Grade 2 hypothyroidism or panhypopituitarism related to treatment with PD-1 and PD-L1 inhibitors may be enrolled. Patients on hormone replacement therapy may be enrolled if on a stable dose. Patients with ≥ Grade 3 immunotherapy-related hypothyroidism or panhypopituitarism are excluded.	Clarifies the conditions under which patients with immunotherapy related hypothyroidism and panhypopituitarism may be enrolled on or excluded from the study
5.2.3	Deleted the following text from the Table 2 footnote: ~~In addition, patients with Grade 4 nausea and/or diarrhea resolved within 72 hours with supportive management do not require discontinuation.~~	Removes potentially redundant and incorrect footnote
5.3.2	Revised P-pg to P-glycoprotein (P-gp)	Error correction
5.4.2	Revised the text as follows: Blood glucose should be checked prior to each dosing and dose should be withheld for blood glucose >250 mg/dL (Grade 3 or higher), regardless of relatedness to enfortumab vedotin. Dosing may continue once the patient's blood glucose has improved to ≤250	Clarifies hyperglycemia conditions under which dosing should be held, and under which treatment should be discontinued

Section(s)	Change	Rationale
	mg/dL (≤ Grade 2) and the patient is clinically and metabolically stable. Patients with blood glucose >500 mg/dL (Grade 4) considered unrelated to enfortumab vedotin may continue dosing once the patient's blood glucose has improved to ≤250 mg/dL (≤ Grade 2) and the patient is clinically and metabolically stable. Blood glucose >500 mg/dL (Grade 4) considered related to enfortumab vedotin requires treatment discontinuation.	
6.3.1, Appendix A	Revised Day 1 procedures as follows: Physical exam (including weight; may be conducted the day prior to dosing) ECOG performance status (may be conducted the day prior to dosing)	Allows additional flexibility for conducting the physical exam and ECOG performance status the day before Day 1 dosing.
7.7.1.3	Revised the definition of Adverse Events of Clinical Interest as follows: Certain non-serious AEs of clinical interest may be followed (including collection of relevant concomitant medications) until resolution, return to baseline, ~~or~~study closure, or the events become chronic to the extent that they are adequately characterized.	Allows for the collection of concomitant medications for Adverse Events of Clinical Interest. Limits the requirement to follow these events if the AE stabilizes.
9.2.2	Added the following text to the definition of duration of response: (per RECIST Version 1.1)	Clarifies that progressive disease per RECIST v1.1 is considered an event in the calculation of duration of response
9.2.4	Removed the following text: ~~For patients who are enrolled but fail to receive study treatment, the enrollment date will be used as the starting point in the calculation in PFS.~~	Removes irrelevant language; these patients will not be considered part of the full analysis set
9.2.5	Removed the following text: ~~For patients who are enrolled but fail to receive study treatment, the enrollment dates will be used as the starting point in the calculation in OS.~~	Removes irrelevant language; these patients will not be considered part of the full analysis set

Section(s)	Change	Rationale
	Revised the following text: In the absence of ~~confirmation of~~ death, OS will be censored at the last date the patient is known to be alive.	Updates for accuracy
9.3.1.7, 9.3.2, 9.3.3, 9.3.5, 9.3.7	Revised the name of the intent to treat analysis set to the full analysis set.	Revises the analysis set name to be consistent with ICH E9 guidance
9.3.1.7, 9.3.5	Removed the per protocol analysis set. Revised the PK analysis set as follows: The PK analysis set will include all patients who received enfortumab vedotin and from whom at least one blood sample was collected and assayed for enfortumab vedotin, MMAE, or TAb concentration. Corresponding records of the time of dosing and sample collection must also be available for all enfortumab vedotin, MMAE, and TAb concentration data. ~~Enrolled patients with sufficient administered dose and plasma concentration data to reliably estimate PK parameters as determined by a clinical pharmacologist.~~ The PK analysis set will be used for PK analyses.	Removes irrelevant language; sensitivity analyses will not be performed, and the per protocol analysis set is not needed Updates PK analysis set with currently planned analyses
9.3.1.8	Revised the planned subgroup analyses as follows: Number of prior systemic therapies ~~(e.g., number, CPI type, PD-1 vs. PD-L1)~~ Best response ~~achived~~ to prior CPI therapy ~~for urothelial cancer (e.g., patients with PD)~~ Liver ~~Visceral metastases vs non-visceral metastases~~ metastasis at baseline ~~Metastatic sites at baseline: lymph node only, liver~~ ~~Nectin-4 expression~~	Simplifies the planned subgroup analyses
9.3.10	Removed the following text: ~~No formal interim analyses are planned.~~	Updates for accuracy

Summary of Changes in Amendment 6

Section(s)	Change	Rationale
Title page	Replaced [redacted] with [redacted] as Medical Monitor	Administrative change
Synopsis	Added text as follows: The primary analysis of efficacy endpoints will be based on the full analysis set, including all patients who enrolled and received any amount of enfortumab vedotin.	Updates the synopsis to better reflect the statistical methodology presented in the body of the protocol.
Synopsis, 9.3.1.7, 9.3.5	Defined the 'efficacy-evaluable set' to include all patients who started treatment with enfortumab vedotin at least 8 months before the analysis data cutoff. Specified in the protocol that at the time of Cohort 2 interim analysis, additional analyses of the efficacy endpoints will be performed based on the efficacy-evaluable set to allow adequate follow up for a stable estimate of ORR and DOR.	Defines a population that allows adequate follow up for response endpoints at the time of the interim analysis
Synopsis, 9.1, 9.3.1.9, 9.3.10	Revised the timing of Cohort 2 interim analysis and final analysis to when patients have had the opportunity to be followed for approximately 8 months from the first dose of enfortumab vedotin. Added additional interim analysis for Cohort 2 after approximately 70 subjects have been followed for approximately 8 months from the first dose of enfortumab vedotin. Added a row for this interim analysis in the synopsis table for the expected 95% confidence interval: N=70 20% - 42%	Clarifies the timing of Cohort 2 analyses to allow adequate follow up for response endpoints

Synopsis, 9.3.5.1	Removed the following text: ~~The primary efficacy analysis will be performed by testing the null hypothesis of ORR being less than or equal to 10% against the alternative hypothesis that ORR is greater than 10% at overall 1-sided 2.5% level of significance, i.e., H_0: P≤0.10 vs H_a: P>0.10.~~ ~~Within each cohort, the study will be considered successful if the lower bound of the 2-sided 95% exact Clopper-Pearson CI for ORR is greater than 10%, so that the null hypothesis that the ORR is less than or equal to 10% can be rejected.~~	Updated to reflect current feedback from the FDA.
3.1, 6.3.6, 7.7.7, Appendix A	Removed Cycle 2 Day 22 and Cycle 6 Day 22 slit lamp exams from study activities and the Schedule of Events.	Slit lamp exams are no longer required per IDMC recommendation as of Jul 2018 and Aug 2019. This revision clarifies that these exams are no longer required.
3.2	Revised the text as follows: Given that patients enrolled in the current study have a poor prognosis and represent an area of unmet medical need, the lower bound of the exact 95% confidence interval (CI) for ORR that excludes a historical response rate of 10% ~~an ORR of greater than 10% as measured by the lower bound of the 95% confidence interval (CI)~~ is considered to be a meaningful improvement over currently available therapies with the proposed enrollment of approximately 100 patients.	Clarification.
5.3, 6.1, 7.7.1.3, Appendix A	Revised the safety reporting period from: The safety reporting period for all AEs and SAEs is from study Day 1 (predose) through the EOT visit or 30 days after the last study treatment, whichever is later. To: The safety reporting period for all AEs and SAEs is from study Day 1 (predose) through 30 days after the last study treatment.	Provides a definitive safety reporting period for the study, eliminating ambiguity around subjects who have no EOT visit.

5.3.2	Added the following text: Patients with a positive hepatitis B surface antigen and/or antihepatitis B core antibody and a negative PCR assay at baseline should receive appropriate antiviral prophylaxis or regular surveillance monitoring as per local or institutional guidelines.	Adds that antiviral prophylaxis for hepatis B virus (HBV) is permitted, and clarifies that local or institutional guidelines in treatment or surveillance monitoring of PCR negative HBV may be followed.
6.1, 7.7.2 and Appendix A	Added the following text: Local laboratory testing should be performed on all dosing days. All local laboratory results must be reviewed prior to study drug administration in order to determine whether to proceed with dosing or whether dose modification is required.	Clarifies that local labs are required for each dosing day, and that lab results should be available before dosing, for patient safety.