Protocol Number:	SGN22E-003
Version:	Amendment 09; 29-Sep-2023
Protocol Title:	An open-label, randomized, controlled phase 3 study of enfortumab vedotin in combination with pembrolizumab versus chemotherapy alone in previously untreated locally advanced or metastatic urothelial cancer
Study Name:	EV-302
Investigational Product:	Enfortumab vedotin
Brief Title:	Enfortumab vedotin and pembrolizumab vs chemotherapy alone in untreated locally advanced or metastatic urothelial cancer
Phase:	3
IND Number:	116360
EU CT Number:	2023-503421-19
Sponsor:	Seagen Inc. 21823 30th Drive SE Bothell, WA 98021, USA
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PROTOCOL SYNOPSIS

Protocol Number SGN22E-003 **Version** Amendment 09; 29-Sep-2023 **Phase** 3	**Product Name** Enfortumab vedotin **Sponsor** Seagen Inc. 21823 30th Drive SE Bothell, WA 98021, USA

Protocol Title

An open-label, randomized, controlled phase 3 study of enfortumab vedotin in combination with pembrolizumab versus chemotherapy alone in previously untreated locally advanced or metastatic urothelial cancer

Study Objectives

Primary Objectives	Corresponding Dual Primary Endpoints
• To compare progression-free survival (PFS) between the experimental arm (enfortumab vedotin + pembrolizumab [Arm A]) and the control arm (gemcitabine + cisplatin or carboplatin [Arm B]) by blinded independent central review (BICR)	• PFS per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 by BICR
• To compare overall survival (OS) between the experimental arm (Arm A) and the control arm (Arm B)	• OS
Secondary Objectives	Corresponding Secondary Endpoints
• To compare the objective response rate (ORR) between the experimental arm (Arm A) and the control arm (Arm B) by BICR	• ORR per RECIST v1.1 by BICR
• To compare time to pain progression (TTPP) from the subject perspective between the experimental arm (Arm A) and the control arm (Arm B)	• TTPP
• To compare average change in pain from the subject perspective between the experimental arm (Arm A) and the control arm (Arm B)	• Mean change from baseline in worst pain at Week 26
• To evaluate PFS between the experimental arm (Arm A) and the control arm (Arm B) by investigator assessment	• PFS per RECIST v1.1 by investigator assessment
• To evaluate ORR between the experimental arm (Arm A) and the control arm (Arm B) by investigator assessment	• ORR per RECIST v1.1 by investigator assessment

• To evaluate the duration of response (DOR) between the experimental arm (Arm A) and the control arm (Arm B)	• DOR per RECIST v1.1 by BICR • DOR per RECIST v1.1 by investigator assessment
• To evaluate the disease control rate (DCR) between the experimental arm (Arm A) and the control arm (Arm B)	• DCR per RECIST v1.1 by BICR • DCR per RECIST v1.1 by investigator assessment
• To evaluate the impact of study treatment on quality of life (QOL), functioning, and symptoms from the subject perspective	• Mean scores and change from baseline of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Core 30 (QLQ-C30), and EuroQOL 5-dimensions (EQ-5D-5L) visual analogue scale (VAS), and utility scores
• To evaluate the safety profile of each treatment regimen	• Type, incidence, relatedness, severity and seriousness of adverse events (AEs) • Type, incidence and severity of laboratory abnormalities • Treatment discontinuation rate due to AEs
Exploratory Objectives	Corresponding Exploratory Endpoints
• To assess PFS, ORR, and DOR per the modified RECIST v1.1 for immune-based therapeutics (iRECIST) in Arm A	• PFS, ORR, and DOR per iRECIST by investigator assessment in Arm A
• To assess subject reported health resource utilization (HRU)	• Cumulative incidence of HRU as reported by subject
• To assess the pharmacokinetics (PKs) of enfortumab vedotin and monomethyl auristatin E (MMAE) • To assess the development of anti-therapeutic antibody (ATA) to enfortumab vedotin	• Plasma or serum concentrations of enfortumab vedotin and MMAE • Incidence of ATA to enfortumab vedotin
• To assess biomarkers of biological activity, resistance, and predictive biomarkers of response	• Exploratory biomarkers of clinical activity

Study Population

The population to be studied includes subjects with histologically documented, unresectable, previously untreated locally advanced or metastatic urothelial cancer (UC) and measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Eligible subjects must be ≥18 years of age, and must have an anticipated life expectancy of ≥12 weeks as assessed by the investigator. Subjects must not have received prior systemic therapy with the exceptions of neoadjuvant or adjuvant chemotherapy following cystectomy with recurrence >12 months from completion of therapy. Subjects must have an Eastern Cooperative Oncology Group (ECOG) Performance Status Score of 0, 1, or 2, with adequate baseline hematologic, hepatic, and renal function. In addition, subjects must be considered eligible to receive cisplatin- or carboplatin-based chemotherapy and pembrolizumab, in the investigator's judgment.

Subjects with locally advanced urothelial cancer (UC) that is resectable with curative intent are not eligible. Subjects must not have received previous treatment with enfortumab vedotin or other monomethyl auristatin E (MMAE)-based antibody-drug conjugates (ADCs), or a checkpoint inhibitor, defined as a programmed cell death protein-1 (PD-1) inhibitor or programmed cell death ligand-1 (PD-L1) inhibitor (including, but not limited to, atezolizumab, pembrolizumab, nivolumab, durvalumab, or avelumab). Subjects must not have ongoing sensory or

motor neuropathy (Grade 2 or higher) or active central nervous system (CNS) metastases. Subjects must not have a history of another malignancy within 3 years or any evidence of residual disease from a previously diagnosed malignancy. Subjects are also excluded if they are currently receiving systemic antimicrobial treatment for active infection or high dose steroids. Subjects 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.

Number of Planned Subjects

Approximately 860 subjects (approximately 430 subjects per arm) will be randomized in the global portion of this study. After enrollment of the global portion of the study is completed, the study may remain open to enrollment in China alone until approximately 130 subjects in China (including those randomized in the global portion and China portion) have been randomized.

Study Design

This is a phase 3 open-label, 2-arm randomized, controlled multicenter study to evaluate the combination of enfortumab vedotin + pembrolizumab versus standard of care gemcitabine + platinum-containing chemotherapy, in subjects with previously untreated locally advanced or metastatic UC. The study is designed to assess the dual primary endpoints of progression-free survival (PFS) and overall survival (OS) of experimental Arm A (enfortumab vedotin + pembrolizumab) compared to control Arm B (gemcitabine + cisplatin or carboplatin). Subjects will be randomized in a 1:1 manner to one of the study arms with the following stratification factors: cisplatin eligibility (eligible or ineligible), PD-L1 expression (high or low), and liver metastases (present or absent).

Subjects in Arm A will receive enfortumab vedotin at 1.25 mg/kg, administered as an intravenous (IV) infusion on Days 1 and 8 of every 3-week cycle, and pembrolizumab 200 mg as an IV infusion on Day 1 of every 3-week cycle, after completion of the enfortumab vedotin infusion.

Subjects in Arm B will receive gemcitabine at 1000 mg/m^2 as an IV infusion on Days 1 and 8 of every 3-week cycle. Cisplatin (70 mg/m^2) or carboplatin (area under the curve [AUC] 4.5, or AUC of 5 according to local guidelines) will be administered on Day 1 of every 3-week cycle, with adequate pre- and post-hydration, by IV infusion per institutional standards.

Response will be assessed by computed tomography (CT) scans with contrast (unless contraindicated) every 9 weeks (±1 week) timed from the randomization date. For subjects who cannot receive CT scans with contrast, other protocol-specified imaging methods may be used Appendix C). Brain scans should be repeated at this time point in subjects with a history of CNS metastasis or signs/symptoms of CNS metastasis. Bone imaging should also be repeated at this time point in subjects with a history of skeletal metastasis or suspicion of skeletal metastases based on imaging or symptoms. Objective responses will be confirmed per RECIST v1.1 with repeat scans done at the next scheduled response assessment per protocol after first documentation of response. Subsequent response assessments should be performed every 9 weeks (±1 week) until 18 months after randomization, then every 12 weeks (±1 week). Tumor imaging should also be performed, and blinded independent central review (BICR) evaluation triggered, whenever disease progression is suspected.

Subjects may continue on study treatment until progressive disease (BICR-confirmed or clinical progression [see Section 7.3]), an adverse event (AE), pregnancy, investigator decision, start of a subsequent anticancer therapy, subject decision (non-AE), study termination by the sponsor, completion of the maximum number of drug cycles allowed, or other reason unrelated to an AE (see Section 4.3). Treatment beyond disease progression per RECIST v1.1 may be considered in subjects in study Arm A (enfortumab vedotin [EV] + pembrolizumab) who are deriving clinical benefit as defined in Section 5.8. Subjects treated beyond disease progression per RECIST v1.1 may continue until confirmed disease progression per modified RECIST 1.1 for immune-based therapeutics (iRECIST) as assessed by the investigator (Seymour 2017) (Appendix K). Confirmatory scans must be performed 4 to 9 weeks after disease progression per RECIST v1.1 by BICR. Treatment with gemcitabine and treatment with platinum-containing chemotherapy may be given up to 6 cycles. Treatment with pembrolizumab will be discontinued once the subject has received a maximum of 35 administrations (approximately 2 years). There is no upper limit to the number of cycles of enfortumab vedotin permitted. Palliative radiotherapy on a nontarget bone lesion that is not progressing

is permitted and will not be considered a subsequent anticancer therapy; however, radiotherapy on any new or progressing lesion, per RECIST v1.1 as assessed by the investigator or after BICR-confirmed progression, will be considered a subsequent anticancer therapy and subjects will not be permitted to resume study treatment. Surgical resection for curative intent during study treatment may be permitted in subjects with favorable tumor response after discussion with the medical monitor.

Subjects who discontinue treatment for reasons other than disease progression or consent withdrawal will continue to receive response assessments every 9 weeks (±1 week) for the first 18 months timed from the randomization date, and every 12 weeks (±1 week) thereafter, until the subject has radiologically-confirmed disease progression per RECIST v1.1 guidelines as determined by BICR, dies, withdraws consent, or the study closes, whichever occurs first. Subjects who initiate a subsequent anticancer therapy but do not have disease progression per BICR will continue to receive response assessments until radiologically-confirmed progression per BICR, death, consent withdrawal, or the study closes, whichever occurs first. After discontinuation of study treatment, all randomized subjects will be followed every 12 weeks (±1 week) to obtain information on subsequent anticancer therapy, and to assess survival status until death, study closure, lost to follow-up, or subject withdraws consent, whichever occurs first.

Safety will be monitored over the course of the study by an Independent Data Monitoring Committee (IDMC).

Investigational Product, Dose, and Mode of Administration

Enfortumab vedotin (Arm A)

Enfortumab vedotin 1.25 mg/kg will be administered as an IV infusion over approximately 30 minutes on Days 1 and 8 of every 3-week cycle.

Pembrolizumab (Arm A)

Pembrolizumab 200 mg will be administered as an IV infusion after completion of the enfortumab vedotin Arm A. Infusion on Day 1 of every 3-week cycle.

Cisplatin (Arm B)

On Day 1 (or Day 2 if required per institutional guidelines) of each 3-week cycle, cisplatin 70 mg/m^2 will be administered (with adequate pre- and post-hydration) as an IV infusion per institutional standards. The body surface area used to calculate cisplatin dose may be capped per institutional standards.

Carboplatin (Arm B)

On Day 1 of each 3-week cycle, carboplatin at AUC 4.5, or AUC of 5 according to local guidelines, will be administered (with adequate pre- and post-hydration) as an IV infusion per institutional standards. Body weight used to calculate carboplatin may be capped as per institutional standards.

Gemcitabine (Arm B)

On Days 1 and 8 of each 3-week cycle, gemcitabine at 1000 mg/m^2 will be administered as an IV infusion.

Duration of Treatment

Subjects should continue on study treatment until one of the following protocol-defined reasons for treatment discontinuation occur: progressive disease (BICR-confirmed or clinical progression [see Section 7.3]), an AE, pregnancy, investigator decision, start of a subsequent anticancer therapy, subject decision(non-AE), study termination by the sponsor, completion of the maximum number of drug cycles allowed, or other reason unrelated to an AE.

Pembrolizumab may be administered for up to a maximum of 35 cycles.

Cisplatin, carboplatin, and/or gemcitabine may be administered for up to a maximum of 6 cycles.

Maintenance therapy (eg, avelumab) may be used following completion and/or discontinuation of platinum-containing therapy, if locally available, and provided the subject is deemed appropriate by the investigator (see Section 4.3.1).

Enfortumab vedotin may be administered for an unlimited number of cycles until a protocol defined reason for treatment discontinuation occurs. In Arm A, subjects who experience an unacceptable AE that is attributable only to pembrolizumab may continue on enfortumab vedotin monotherapy until a protocol-defined reason for treatment discontinuation. Subjects who experience an unacceptable AE that is attributable only to enfortumab vedotin may continue on pembrolizumab monotherapy up to a maximum of 35 cycles.

In Arm B, subjects who experience an unacceptable AE that is attributable only to platinum-containing chemotherapy may continue on gemcitabine monotherapy for up to 6 cycles. Subjects who experience an unacceptable AE that is attributable only to gemcitabine may continue on platinum-containing chemotherapy for up to 6 cycles.

Efficacy Assessments

Computed tomography scans with contrast (unless contraindicated), including chest, abdomen, and pelvis at the minimum, will be used to assess antitumor activity at protocol-specified time points. Subjects must receive the same imaging method throughout the study for response assessments. For subjects who cannot receive CT scans with contrast, other protocol-specified imaging methods may be used (see Appendix C). Bone imaging and/or brain scans should be repeated at disease assessment time points, and as clinically indicated throughout the study, in subjects with a history of skeletal metastasis or suspicion of skeletal metastasis based on imaging or symptoms, or a history of CNS metastasis or signs/symptoms of CNS metastasis. Objective responses will be confirmed per RECIST v1.1 by BICR with repeat scans done at the next scheduled scan per protocol, after first documentation of response.

Pharmacokinetic and Immunogenicity Assessments

Blood samples for pharmacokinetic (PK) and anti-therapeutic antibody (ATA) analyses will be collected for Arm A only, at specific time points. Validated or qualified assays will be used to measure the concentrations of enfortumab vedotin and MMAE in serum or plasma. A validated assay will be used to determine ATA for enfortumab vedotin in serum. Pharmacokinetic and ATA samples for pembrolizumab will be collected.

Biomarker Assessments

Biomarker assessments will be performed from archival or fresh tumor tissue, peripheral blood and urine. Subjects will be stratified by PD-L1 status, as determined by the Dako/Agilent PD-L1 immunohistochemistry (IHC) 22C3 PharmDx on tumor biospecimens. Other biomarker assessments may include central assessment of Nectin-4 expression by IHC, and Next Generation Sequencing for assessment of tumor subtyping and mutations associated with response to enfortumab vedotin in metastatic UC.

Safety Assessments

Safety assessments will include surveillance and recording of AEs, including serious adverse events (SAEs), concomitant medications, physical examination findings, vital signs, protocol-specified laboratory tests, ECOG status, electrocardiograms (ECGs), ophthalmologic examination findings and pregnancy testing. Safety will be monitored over the course of the study by the IDMC.

Other Assessments

Patient-reported outcome (PRO) assessments will include quality of life (QOL) measures, both general and oncology specific (EuroQOL 5-dimensions [EQ-5D-5L] and European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Core 30 [QLQ-C30] Questionnaire, respectively), as well as outcome specific PROs around pain (Brief Pain Inventory-Short Form [BPI-SF]). Impact on pain may also be correlated to pain medication use collected in the case report form (CRF). A health resource utilization (HRU) questionnaire will also aim to measure clinical burden outside of the clinical trial setting.

Statistical Methods

Stratification

Subject will be stratified based on the following variables:

1. Cisplatin eligibility (eligible or ineligible)
2. PD-L1 expression by IHC (High [combined positive score (CPS) ≥10] or Low [CPS <10])
3. Liver metastases (present or absent)

Multiplicity

The proposed 2-arm study will have dual primary endpoints of PFS and OS. The study can be considered positive if enfortumab vedotin plus pembrolizumab (Arm A) is superior to the control arm (Arm B) in either PFS or OS. A graphical approach with group sequential testing outlined in Maurer and Bretz (Maurer 2013) will be used to strongly control the family-wise type I error rate at a two-sided 5% level.

The initial alpha allocation for the dual primary endpoints of PFS and OS are 0.5% and 4.5%, respectively. If only 1 of the primary endpoints is statistically significant at the specified level, alpha recycling will be applied to evaluate the other primary endpoint at the 5% significance level.

When the null hypotheses for PFS and OS are both rejected, selected secondary endpoints will be tested in the following order using a gatekeeping testing strategy:

1. ORR by BICR
2. Time to pain progression (TTPP)
3. Mean change from baseline in worst pain at Week 26

Each test will be at the 5% significance level (2-sided) as long as all preceding null hypotheses are rejected. These secondary endpoints will only be tested once at either the OS interim or final analysis after the null hypotheses for PFS and OS are both rejected, and the test statistics for inferential testing will be computed from the data at the time of OS interim analysis (IA). In the event that only the null hypothesis for PFS is rejected and the superiority boundary for OS has not been crossed at the time of OS IA, these secondary endpoints will not be tested and will only be analyzed descriptively.

Sample Size Considerations

Approximately 860 subjects will be randomized in a 1:1 ratio to one of the study arms.

With 430 subjects per arm, the estimated number of OS events between Arm A and Arm B is 489, providing 93% power to demonstrate superiority at a two-sided alpha of 4.5% with 1 IA around 72.8% information fraction under the following assumptions:

4. OS curves follow piecewise exponential distribution with a reduced hazard rate (50% of the initial rate) starting from 24 months
5. hazard ratio (HR) of OS is 0.73 between the experimental and control arms
6. median OS for the control arm is 15.3 months
7. an enrollment period of 30 months
8. a yearly dropout rate of 5%

The number of PFS events between the 2 arms is estimated to be 526 events, providing 90% power to demonstrate superiority at a two-sided alpha of 0.5% with 430 subjects per arm based on the following assumptions:

1. PFS curves follow piecewise exponential distribution with a reduced hazard rate (20% of the initial rate) starting from 15 months
2. HR of PFS is 0.70 between the experimental and the control arms
3. median PFS for the control arm is 7 months
4. an enrollment period of 30 months
5. a yearly dropout rate of 5%

To evaluate the consistency of efficacy and safety in a China subpopulation compared with the global population, after completion of enrollment in the global portion, subjects in China may continue to be randomized in a 1:1 ratio to either the experimental arm or the control arm until the planned sample size of approximately 130 subjects in China is reached, including those randomized in the global portion and China portion. Subjects in China randomized after completion of enrollment in the global portion will not be included in the analysis of the global portion.

Timing of Analyses

A single planned analysis (final analysis) for PFS will take place when approximately 526 PFS events or 356 OS events (72.8% information fraction) in the intent-to-treat (ITT) analysis set have occurred, whichever is later.

Two analyses are planned for OS. OS IA is planned at the time of the final PFS analysis. At IA, the OS events in total will be approximately356 (about 72.8% of information). O'Brien-Fleming boundaries will be used to calculate the rejection boundaries based on the actual information fraction observed. The final OS analysis is planned when approximately 489 OS events have occurred in total.

Analysis Methods

Efficacy

The ITT analysis set will be used for the primary analysis of OS and PFS. All subjects who are randomized will be included in the ITT analysis set. For primary endpoints of OS and PFS, a log-rank test stratified by randomization stratification factors will be used to compare the experimental arm to the control arm. The estimated HR and corresponding 95% confidence interval from the stratified Cox proportional hazards regression model will also be presented. The median survival time will be estimated using the Kaplan-Meier method and will be reported along with the corresponding 95% confidence interval by treatment arm. Similar estimation methods will be used for the other time-to-event endpoints. Duration of response (DOR) will be summarized descriptively by Kaplan-Meier methods for subjects with a confirmed response (complete response or partial response per RECIST v1.1). ORR, DCR, and DOR will be analyzed using the response evaluable set.

Objective response rate and disease control rate will be estimated for each arm based on the response evaluable set. P-value comparing between experimental arm and the control arm using the Cochran Mantel-Haenszel test stratified by randomization stratification factors will be reported.

Safety

The frequency of AEs and SAEs will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term. In addition, summary statistics or listings will be provided for the following safety parameters: laboratory values, vital sign measurements, ECGs, and ECOG performance status.

Pharmacokinetics

Descriptive statistics will be provided for antibody drug-conjugate and unconjugated drug (MMAE) concentrations in Arm A and Arm C at each PK sampling time point. Any additional PK and PK/pharmacodynamic analyses may be described in a separate analysis plan and presented in a separate report.

Pembrolizumab PK and immunogenicity analyses will be performed only if required. If pembrolizumab analysis are performed, the PK and immunogenicity results will be presented in a separate report.

The incidence of ATA will be summarized.

Patient-Reported Outcomes

Completion and compliance rates along with change from baseline for each domain of the PROs, including EQRTC QLQ-C30, EQ-5D-5L, and BPI-SF will be summarized. Cumulative incidence of HRU, including length of stay, hospitalizations, and emergency room (ER) visits will be summarized by treatment arm and by cycle. Additionally, TTPP and mean changes from baseline in worst pain at Week 26 will be evaluated.

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1L	first-line
2L	second-line
ADC	antibody-drug conjugate
AE	adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin
AST	aspartate aminotransferase
ATAs	Anti-therapeutic antibodies
AUC	area under the curve
β-hCG	beta human chorionic gonadotropin
BICR	blinded independent central review
BPI-SF	Brief Pain Inventory – Short Form
CBC	complete blood count
CD3ζ	CD3 zeta
CI	confidence interval
CNS	central nervous system
CPS	combined positive score
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CRO	Contract Research Organization
CT	computed tomography
CTA	Clinical Trial Agreement
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DCR	disease control rate
DILI	drug-induced liver injury
DKA	diabetic ketoacidosis
DLT	dose-limiting toxicity
DOR	duration of response
ECD	extracellular domain
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group

eCRF	electronic case report form
EDC	electronic data capture
EORTC	European Organisation for Research and Treatment of Cancer
EOT	end of treatment
ePROs	electronic patient-reported outcomes
EQ-5D-5L	EuroQOL 5-dimensions
EU	European Union
EV	enfortumab vedotin
FA	final analysis
FAS	full analysis set
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin embedded
GFR	glomerular filtration rate
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HR	hazard ratio
HRU	health resource utilization
IA	interim analysis
ICD	immunogenic cell death
ICH	International Council for Harmonisation
iCPD	confirmed immune progressive disease
IDMC	Independent Data Monitor Committee
IEC	independent ethics committee
Ig	immunoglobulin
IHC	immunohistochemistry
ILD	interstitial lung disease
imAE	immune-mediated adverse events
IND	investigational new drug
INR	international normalized ratio
iRECIST	modified RECIST 1.1 for immune-based therapeutics
IRB	institutional review board
IRR	infusion related reaction
IRT	Interactive Response Technology
ITT	intent-to-treat
iUPD	unconfirmed immune progressive disease
IV	intravenous

LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	monomethyl auristatin E
MMRM	mixed model for repeated measures
mOS	median overall survival
mPFS	median progression-free survival
MRI	magnetic resonance imaging
mUC	metastatic urothelial cancer
MUGA	multiple-gated acquisition
MVAC	methotrexate, vinblastine, doxorubicin, cisplatin
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NLT	new lesions-target
NLNT	new lesion-non-target
NSAID	nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein-1
PD-L1	programmed cell death ligand-1
PD-L2	programmed cell death ligand-2
Pembro	pembrolizumab
PFS	progression-free survival
PK	pharmacokinetic
PKCθ	protein kinase C-theta
PN	peripheral neuropathy
PO	by mouth
PR	partial response
PRO	patient-reported outcome
PT	prothrombin time
PTT	partial thromboplastin time
QLQ-C30	Quality of Life Core 30
QOL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid

SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SJS	Stevens-Johnson Syndrome
SmPC	Summary of Product Characteristics
SMQ	standardized MedDRA query
SOC	system organ class
SSQ	sponsor specified query
SUSARs	suspected unexpected serious adverse reactions
T1DM	type 1 diabetes mellitus
TEAE	treatment-emergent adverse events
TEN	toxic epidermal necrolysis
TTPP	time to pain progression
UC	urothelial cancer
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia
VAS	Visual Analogue Scale
VHP	Voluntary Harmonization Procedure
WHO	World Health Organization
ZAP70	zeta-chain-associated protein kinase

1. INTRODUCTION

1.1. Urothelial Cancer

Bladder cancer, the most common form of urothelial cancer (UC), is estimated to kill nearly 200,000 patients globally on an annual basis, including more than 65,000 in Europe and 18,000 in the United States (US) (Bray 2018; Ferlay 2018; Siegel 2019). Annual diagnoses of new cases of bladder cancer are estimated to be more than 549,000 worldwide, including more than 197,000 in Europe and 81,000 in the US (Bray 2018; Ferlay 2018; Siegel 2019). Those patients with metastatic UC represent a population with significant unmet medical need, as the 5-year mortality rate for this disease exceeds 85% (von der Maase 2005).

1.1.1. Metastatic Urothelial Cancer

First-line (1L) therapy for locally advanced and metastatic UC in patients with sufficient renal function consists of cisplatin-based combinations, like methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) or gemcitabine plus cisplatin, which demonstrate an objective response rate (ORR) of up to 55%, including approximately 12% complete responses (CRs) (von der Maase 2000). Despite initial chemosensitivity, most patients are not cured and the outcome of metastatic UC after these regimens is poor: median time to progression is 7 months and median overall survival (mOS) is 14 months. Long-term survival is poor (approximately 15%) and the prognosis is particularly grim for patients with visceral metastases, for whom the 5-year survival rate is 7% (von der Maase 2000; von der Maase 2005; Bellmunt 2011).

Unfortunately, more than 50% of patients with UC are cisplatin-ineligible due to poor renal function, poor performance status, or co-morbidities (De Santis 2012). An even higher unmet need exists in this population. For these cisplatin-ineligible patients, carboplatin is the platinum-containing therapy of choice. Carboplatin is also an alkylating agent, similar to cisplatin, but with less nephrotoxicity, neurotoxicity, and ototoxicity (Dogliotti 2007). In first-line therapy for cisplatin-ineligible metastatic UC in patients, response rates to treatment with carboplatin monotherapy range from 8%–18% (Bamias 2006). In the European Organisation for Research and Treatment of Cancer (EORTC) 30986 trial, carboplatin combined with gemcitabine in a cisplatin-ineligible patient population resulted in a confirmed ORR of 36.1%. Median progression-free survival (mPFS) was 5.8 months and median OS was 9.3 months (De Santis 2012). The modest efficacy reported for available platinum-containing therapies highlights the need for additional treatment options for patients with metastatic UC. Programmed cell death protein-1 (PD-1)/programmed cell death ligand-1 (PD-L1) inhibitors have demonstrated a survival benefit compared to chemotherapy in the management of late-line metastatic UC. Randomized phase 3 trials have been reported for both atezolizumab (Tecentriq®) and pembrolizumab (Keytruda®) in the second-line (2L+) metastatic UC setting. In the IMvigor211 trial, median OS was not significantly different between the 2 arms (11.1 months vs. 10.6 months, respectively) (Powles 2018). KEYNOTE-045 studied pembrolizumab vs. investigator's choice of chemotherapy in metastatic UC patients who had recurred or progressed following platinum-containing chemotherapy. This study demonstrated a statistically significant improvement in OS (10.3 months vs. 7.4 months) when comparing the pembrolizumab arm to the chemotherapy arm (Bellmunt 2017).

In the US, both atezolizumab (Tecentriq®) and pembrolizumab (Keytruda®) have also received accelerated approvals for first-line use in cisplatin-ineligible UC patients based on open-label, single-arm studies that showed ORRs of 24% and 29%, respectively (Tecentriq® Prescribing Information, Genentech, Apr 2017) (Keytruda® Prescribing Information, May 2017). This was followed by European Union (EU) approval in September 2017. In May 2018, the Food and Drug Administration (FDA) issued an alert regarding decreased survival in patients with low expression of PD-L1 being treated in the first-line setting with pembrolizumab or atezolizumab monotherapy, compared with platinum-containing chemotherapy. Subsequent prescribing information for pembrolizumab and atezolizumab were revised to require high PD-L1 expression in first-line metastatic UC patients who are not eligible for cisplatin-containing chemotherapy. This development has further limited the options for metastatic UC patients with low expression of PD-L1.

Avelumab (BAVENCIO®) received approval in the US as a maintenance treatment following first-line platinum-containing chemotherapy based on a randomized, open-label study. Improvement in mOS compared to best supportive care was shown in patients with stable disease (21.4 months vs 14.3 months, respectively) (BAVENCIO® US Prescribing Information, EMD Serono, Nov 2020). This study did not address patients that received fewer than 4 cycles of platinum-containing therapy and only evaluated patients with disease control. The study also randomized at the start of maintenance and did not evaluate avelumab maintenance treatment compared to use of a PD-1/PD-L1 inhibitor at progression (second-line).

1.2. Nectin-4 as a Target in Urothelial Cancer

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 three immunoglobulin (Ig)-like subdomains, a transmembrane helix, and an intracellular region (Takai 2008a). Nectins are thought to mediate Ca2+-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 from 25% to 30% in the ECD (Reymond 2001).

The three 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 (Takai 2008b; Mandai 2015).

Nectin-4 was originally identified by bioinformatics and cloned from human trachea (Reymond 2001). In humans, Nectin-4 is normally expressed in keratinocytes of the skin, sweat glands, hair follicles, transitional epithelium of the bladder, salivary gland ducts, esophagus, breast, and stomach (Challita-Eid 2016). Nectin-4 was identified as markedly upregulated in UC using suppression subtractive hybridization on a pool of UC specimens. Immunohistochemical characterization of expression in multiple tumor specimens demonstrated high levels of Nectin-4 in bladder, breast, pancreatic, lung, ovarian and other cancers (Challita-Eid 2016).

1.3. Enfortumab Vedotin

Enfortumab vedotin (EV) is an antibody-drug conjugate (ADC) comprised of a fully human anti-Nectin-4 IgG1 kappa monoclonal antibody (mAb) conjugated to the small molecule

microtubule disrupting agent, monomethyl auristatin E (MMAE), via a protease cleavable maleimidocaproyl valine-citrulline linker. Conjugation takes place on cysteine residues that comprise the interchain disulfide bonds of the antibody to yield a product with a drug to antibody ratio of approximately 3.8. Nectin-4 is a 66 kDa type I transmembrane protein that belongs to the Nectin family of adhesion molecules. Nectins are thought to mediate Ca^{2+} independent cell-cell adhesion via both homophilic and heterophilic transinteractions at adherens junctions and support a wide range of biological functions, including cell movement, proliferation, polarization, survival and differentiation. Nectin-4 is expressed in multiple cancers, particularly urothelial, breast, lung, pancreatic, and ovarian cancers (Challita-Eid 2016). Higher levels of expression are associated with disease progression and/or poor prognosis in some cancers (Fabre-Lafay 2007). The high expression level of Nectin-4 on UC cells makes it an ideal therapeutic target.

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

Information about mode of action, chemical structure, and posology of enfortumab vedotin are provided in the Investigator's Brochure.

1.3.1. Enfortumab Vedotin Monotherapy in Urothelial Cancer

EV monotherapy is being evaluated in multiple phase 1, phase 2, and phase 3 studies. Study EV-101 is a phase 1 study to evaluate the safety and pharmacokinetics (PKs) of escalating doses of enfortumab vedotin given as monotherapy in subjects with metastatic UC and other malignant solid tumors that express Nectin-4 (Rosenberg 2018). EV-101 identified 1.25 mg/kg of enfortumab vedotin as the recommended monotherapy dose in metastatic UC. Study EV-201 is an ongoing phase 2, single-arm, open-label, 2-cohort study to evaluate enfortumab vedotin monotherapy in subjects with locally advanced or metastatic UC who have previously received systemic therapy with a PD-1/PD-L1 inhibitor. Subjects in Cohort 1 have previously received platinum-containing chemotherapy, and subjects in Cohort 2 are platinum-naïve and are not eligible for cisplatin (Rosenberg 2018). Study EV-301 is an ongoing phase 3 randomized controlled trial comparing enfortumab vedotin monotherapy and chemotherapy in subjects with locally advanced or metastatic UC who previously received platinum-containing chemotherapy and a checkpoint inhibitor.

The totality of EV monotherapy data to date demonstrate a manageable safety profile and significant activity in subjects with heavily pre-treated metastatic UC, where currently available therapies in the 2L setting achieve ORRs of approximately 10% with chemotherapy and 20% with anti-PD-1/PD-L1 antibodies (Bellmunt 2017).

EV-101 (ASG-22CE-13-2)

As of the 25 Oct 2018 data cutoff, 112 subjects with metastatic UC treated with enfortumab vedotin at 1.25 mg/kg (metastatic UC Total Analysis Set), ORR was 43% (95% confidence interval [CI]: 33.6, 52.5), with 5 subjects (4.5%) achieving CR, and a median duration of response (DOR) of 7.4 months (95% CI: 5.6, 9.6). The median OS was 12.3 months (95% CI: 9.3, 15.3).

In the safety population of all subjects who received any amount of enfortumab vedotin (n=201), the most common treatment-emergent adverse events (TEAEs) of any grade were fatigue (56%), nausea (45%), decreased appetite (43%), and alopecia (41%). The incidence of Grade 3 or higher TEAEs was 59%, and those reported in ≥5% of subjects included anemia (7%), hyperglycemia (7%), hyponatremia (6%), urinary tract infection (5%), and sepsis (5%). Serious adverse events (SAEs) were reported for 88 subjects (44%). The incidence of TEAEs leading to withdrawal of study drug was 24%, with 9% reported as possibly related to study drug. Twelve subjects (6%) died due to TEAEs; of these, 4 were reported as possibly related to study drug (diabetic ketoacidosis [DKA], multiple organ dysfunction syndrome, respiratory failure, and urinary tract obstruction).

Adverse events (AEs) of special interest (AESI), which included peripheral neuropathy (PN), rash, hyperglycemia, and infusion-related reaction (IRR) were prespecified for analysis as composite terms (employing either Medical Dictionary for Regulatory Activities [MedDRA] SMQ or sponsor specified query [SSQ]). The incidence of events in the category of PN was 45.8% and no SAEs were reported. In the category of rash, the incidence was 48%; of which 94.5% were Grade 2 or lower. SAEs in the category of rash included dermatitis bullous, eczema, rash maculo-papular, and rash vesicular (1 subject each), and were all considered drug related. In the category of hyperglycemia, the incidence was 15%; of which 93.5% were Grade 2 or lower. Six subjects (3%) had hyperglycemia events considered SAEs. One subject (0.5%) had an SAE of diabetic ketoacidosis, which was considered by the investigator to be related to study drug and led to death. The category of IRR includes systemic and local site reactions. The IRR event incidence was 2.5%; 99.5% of which were Grade 2 or lower. The sole subject with a Grade 3 event in this category experienced a serious event of infusion site extravasation.

EV-201 (SGN22E-001)

As of the data cutoff date of 01 Mar 2019, for subjects previously treated with a PD-1/PD-L1 inhibitor and platinum-containing chemotherapy (Cohort 1), treatment with enfortumab vedotin resulted in an ORR per blinded independent central review (BICR) of 44% (95% CI: 35.1, 53.2), including a CR for 15 subjects (12%). Activity was observed in subjects with poor prognostic features such as liver metastases (ORR 38%; 95% CI: 24.7, 52.8) and prior PD-1/PD-L1 non-response (ORR 41%; 95% CI: 31.3, 51.3). Responses to enfortumab vedotin were observed in subjects with both high (PD-L1 combined positive score [CPS] ≥10%) and low PD-L1 expression, with an ORR 36% and 47%, respectively. Observed responses were durable, with median response duration of 7.6 months (95% CI: 6.34, not reached; range: 0.95 months, 11.3+ months). Median progression-free survival (PFS) was 5.8 months (95% CI: 4.9 months, 7.5 months) and median OS was 11.7 months (95% CI: 9.1 months, not reached).

AEs (n=125) were consistent with those previously reported in the enfortumab vedotin clinical development program. The most common TEAEs of any grade in were fatigue (55%), decreased appetite (52%), alopecia (50%), nausea (45%), peripheral sensory neuropathy (43%), diarrhea (42%), and dysgeusia (42%). The incidence of Grade 3 or higher TEAEs was 73%, and those reported in >5% of subjects included anemia (14%), neutropenia (9%), hyperglycemia (7%), and fatigue and hyponatremia (6% each). SAEs were reported for 58 subjects (46%). The incidence of TEAEs leading to withdrawal of treatment was 16%, with peripheral sensory neuropathy as the most common reason for treatment withdrawal (6%). Seven subjects (6%) died due to TEAEs; none of these deaths were considered treatment-related. One subject died of interstitial

lung disease that was considered related to study treatment; the event did not meet the definition of a TEAE because it occurred >30 days after the last dose of enfortumab vedotin. This case was confounded by high dose steroid use and suspected *Pneumocystis jiroveci* pneumonia.

The incidence of AESIs in the category of PN was 56%. The majority of subjects with treatment-emergent PN had events of Grade 2 or lower, irrespective of pre-existing PN. Most events were sensory and 6% of subjects discontinued due to AE of sensory neuropathy. Fourteen of 70 subjects (20%) had resolution of all events and an additional 19 subjects (27%) had resolution or improvement in at least some events at the time of last follow-up. In the category of treatment-emergent rash, there was a 51% incidence. The majority of subjects with rash (77%) had events of Grade 2 or lower. Serious events of rash occurred in 4 subjects, including 1 reported event of Stevens-Johnson syndrome, which ultimately resolved. Overall, 72% of subjects with rash events had resolution of all events and 22% had resolution or improvement as of the last follow-up. In the category of treatment-emergent hyperglycemia, the incidence was 16%, with 50% Grade 2 or lower. As of the last follow-up, 60% of subjects with hyperglycemia had resolution of all events and an additional 15% had resolution or improvement in some hyperglycemia events. In the category of treatment-emergent IRR, the incidence was 6%. Four subjects (3%) experienced systemic IRRs which were Grade 2 or lower. All subjects recovered and no IRR events resulted in treatment discontinuation. Local site reactions included 3 subjects with infusion site extravasation. Two of the infusion site extravasation events were SAEs. All of the events resolved.

Cohort 2 is currently ongoing for subjects previously treated with a PD-1/PD-L1 inhibitor without platinum-containing chemotherapy and who are cisplatin-ineligible.

These activity/efficacy data for enfortumab vedotin in a disease setting with high unmet need, together with acceptable safety, support a favorable benefit-risk assessment for enfortumab vedotin monotherapy in treatment of patients with locally advanced or metastatic UC.

A complete summary of the clinical and nonclinical data relevant to the investigational product and its study in subjects is provided in the enfortumab vedotin Investigator's Brochure.

1.4. Pembrolizumab

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and programmed cell death-ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Pembrolizumab has been approved for first-line treatment of patients with locally advanced or metastatic bladder cancer who are not eligible for cisplatin-containing therapy and whose tumors express PD-L1 (CPS ≥10) as determined by an FDA-approved test (Dako/Agilent 22C3 PD-L1 PharmDx), or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

It is also approved for the treatment of patients with locally advanced or metastatic UC who have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant treatment.

For more details on specific indications and background information, refer to the Investigator's Brochure.

1.4.1. Pharmaceutical and Therapeutic Background

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (Okazaki 2001; Greenwald 2005).

The structure of murine PD-1 has been resolved (Zhang 2004). PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade (Okazaki 2001; Chemnitz 2004; Sheppard 2004; Riley 2009). The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins (Parry 2005; Francisco 2010). As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in locally advanced or metastatic UC.

1.5. Enfortumab Vedotin and Pembrolizumab in Combination

PD-1/PD-L1 inhibitors unleash the antitumor activity of T-lymphocytes by targeting the T-cell inhibition pathway (Sonpavde 2017), and have shown effective antitumor activity as a single agent in locally advanced or metastatic UC. Although these agents are able to induce durable responses, most patients do not respond to PD-1/PD-L1 monotherapy. Combining PD-1/PD-L1 inhibitors with a novel therapy, such as enfortumab vedotin, may be beneficial. Data from preclinical studies of brentuximab vedotin (a CD30-directed ADC comprising the same linker and MMAE payload as enfortumab vedotin), shows potential to induce immunogenic cell death (ICD), antigen presentation, and tumor immune infiltration (Gardai 2015). These results suggest that the effects are due to MMAE. Treatment with brentuximab vedotin in vitro and in preclinical models has been shown to induce hallmarks of ICD. ICD is characterized by induction of the endoplasmic reticulum stress response and subsequent surface presentation of danger-associated molecular patterns immune stimulatory molecules. These danger-associated molecular patterns induce innate immune migration and activation within the tumor microenvironment(Cao 2017; Cao 2018).

Based on the potential enhancement of immune response, it is hypothesized that combining enfortumab vedotin with a PD-(L)-1 inhibitor will result in improved response leading to

prolonged progression-free survival (PFS) and OS in patients with locally advanced or metastatic UC.

Common AEs associated with enfortumab vedotin are reviewed in Section 1.3. Pembrolizumab is generally well tolerated as a monotherapy. The most common adverse reactions reported for at least 20% of pembrolizumab-treated subjects in either of the 2 trials on which regular approval and accelerated approval were recently granted (KEYNOTE-045 and KEYNOTE-052) included fatigue, musculoskeletal pain, pruritus, decreased appetite, nausea, diarrhea, constipation, and rash. Discontinuation of pembrolizumab secondary to adverse reactions occurred in 8% to 11% of subjects, dose interruptions occurred in approximately 20% of subjects, and serious adverse reactions occurred in approximately 40% of subjects. Immune-mediated adverse events (imAEs), including pneumonitis, colitis, hepatitis, and endocrinopathies, were reported in the trials and were managed according to guidelines now outlined in the label (Pembrolizumab Prescribing Information, 2019). Based on these safety data, it was hypothesized there may be minimal overlapping toxicity between enfortumab vedotin and pembrolizumab.

1.5.1. EV-103 (SGN22E-002)

Study EV-103 is an ongoing phase 1b study evaluating the safety and antitumor activity of the combination of enfortumab vedotin with pembrolizumab and/or chemotherapy in subjects with locally advanced or metastatic UC. The combination regimens are evaluated in separate cohorts in EV-103 to inform dosing and proposed experimental arms in the planned EV-302 study. The subject population enrolled in EV-103 approximates the planned study population of EV-302, with the exception that enfortumab vedotin + pembrolizumab cohorts in EV-103 were restricted to subjects who were ineligible for cisplatin chemotherapy. Separate cohorts evaluated enfortumab vedotin in doublet combinations with pembrolizumab, cisplatin, and carboplatin. An additional cohort is evaluating the triplet combination of enfortumab vedotin, pembrolizumab and platinum-containing (cisplatin or carboplatin) chemotherapy. The study also included a dose escalation phase to evaluate the safe dose of enfortumab vedotin when combined with the standard, approved dose of pembrolizumab.

All cohorts received enfortumab vedotin dosed at 1.25 mg/kg on Days 1 and 8 of every 21-day cycle. Cohorts evaluating enfortumab vedotin plus cisplatin (n=7) or carboplatin chemotherapy (n=11, 10 of which were dose-limiting toxicity [DLT] evaluable) established the safety of enfortumab vedotin combined with cisplatin or carboplatin. The recommended dose of enfortumab vedotin in combination with pembrolizumab for the expansion parts was determined to be 1.25 mg/kg. An additional cohort enrolled a 1L metastatic UC population that received enfortumab vedotin 1.25 mg/kg in combination with pembrolizumab and either cisplatin or carboplatin, depending on the subject's eligibility for cisplatin, as defined in the protocol. As of the data cut-off of 28 May 2020, a total of 55 subjects were enrolled in the cohort, and 51 received treatment. Of the 51 subjects that were treated, 28 received enfortumab vedotin + cisplatin + pembrolizumab (median follow-up 6 months) and 23 received enfortumab vedotin + carboplatin + pembrolizumab (median follow-up 8 months). Given the limited follow-up time that is available, efficacy data for this cohort is still immature. However, the initial experience with enfortumab vedotin combined with platinum chemotherapy and pembrolizumab has demonstrated a manageable safety profile with no new safety signals identified.

Preliminary Safety (Enfortumab vedotin + Pembrolizumab)

As of the data cut-off date of 13 Oct 2020, preliminary safety data in the first 45 subjects treated with enfortumab vedotin at 1.25 mg/kg in combination with pembrolizumab in the first-line setting showed that 43 subjects (96%) experienced at least 1 treatment-related AE. The most common treatment-related AEs (occurring in ≥20% of subjects overall) were peripheral sensory neuropathy (56%), fatigue (51%), alopecia (49%), diarrhea (47%), decreased appetite (40%), rash maculo-papular (36%), dysgeusia, pruritus (33% each), nausea (29%), decreased weight (24%), dry skin (22%), anemia, ALT increased, and AST increased (20% each). Increased lipase occurred in 18% of subjects overall. Of note, increase lipase events were all reported as non-clinically significant. A total of 29 subjects (64%) experienced at least one Grade 3 or higher treatment-related AE, the most common being increased lipase (18%), fatigue, rash maculo-papular (11% each), increased amylase, neutropenia, anemia, hyperglycemia (9% each), increased transaminases (7%), acute kidney injury, dehydration, dermatitis bullous, diarrhea, hypokalemia, hyponatremia, myositis, and peripheral sensory neuropathy (4% each). Seven (16%) subjects had treatment-related serious AEs and 11 (24%) discontinued study treatment due to treatment-related AEs. The most common reason for treatment-related discontinuation was peripheral sensory neuropathy for 4 subjects. There was 1 treatment-related death (multiple organ dysfunction syndrome) reported by investigator as possibly related to treatment with several confounding factors including concomitant acute onset of atrial fibrillation, corticosteroids, and amiodarone. Regarding the treatment-related AESIs assessed during the study, the rates of PN (62% of subjects), rash (67%), and hyperglycemia (11%) as well as the median time to first onset (respectively of 2.4 months [range: 0.66,12], 0.7 months [range: 0.13,15.7], 0.5 months [range: 0.33,3.48]) were similar to that with enfortumab vedotin monotherapy in post-platinum, post-PD-1/PD-L1 inhibitor metastatic UC subjects (EV-201, Cohort 1 in (Rosenberg 2019b)

The safety profile of enfortumab vedotin in combination with pembrolizumab to date appears tolerable and manageable. Among AEs of interest, identified risks as a composite term include PN, rash, and extravasation site reactions, all reported at similar rates and severity as that for enfortumab vedotin therapy alone.

Combination of enfortumab vedotin with pembrolizumab did not notably alter the immune mediated toxicities known to be associated with pembrolizumab monotherapy.

Preliminary Efficacy (Enfortumab vedotin + Pembrolizumab)

The preliminary efficacy data of enfortumab vedotin 1.25 mg/kg in combination with pembrolizumab in the first-line setting are summarized in Table 1. As of the data cut-off of 13 Oct 2020, of the 45 subjects in the full analysis set (FAS) who received enfortumab vedotin 1.25 mg/kg in combination with pembrolizumab in the first-line setting, the confirmed ORR by investigator assessment per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 was 73.3% (95% CI: 58.1, 85.4), including 7 (16%) CRs and 26 (58%) partial responses (PRs). In addition, 9 subjects (20%) had the best overall response of stable disease (SD) and the disease control rate (DCR) (CR, PR, or SD) was 93% (95% CI: 81.7, 98.6).

Table 1: Summary of best overall response by investigator assessment per RECIST v1.1-full analysis set: 1L enfortumab vedotin 1.25 mg/kg + pembrolizumab

	1L EV 1.25 mg/kg + Pembro (N=45)
Best Overall Response[a], n (%)	
Complete Response (CR)	7 (16)
Partial Response (PR)	26 (58)
Stable Disease (SD)	9 (20)
Progressive Disease (PD)	1 (2)
Not Evaluable (NE)	2 (4)
Objective Response Rate (CR or PR), n (%)	33 (73)
95% CI[b] for ORR	(58.1, 85.4)
Disease Control Rate (CR, PR or SD), n (%)	42 (93)
95% CI[b] for DCR	(81.7, 98.6)

a Best overall response according to RECIST v1.1
b Computed using the Clopper-Pearson method (Clopper 1934)
Data cutoff: 13-Oct-2020

The majority of subjects (93%) treated with the enfortumab vedotin and pembrolizumab combination had reduction in target lesion from baseline. The majority of responses per RECIST v1.1 occurred at the first tumor assessment (Week 9) and were confirmed in subsequent assessments. As of the data cut of 13-Oct-2020, responses sustained beyond 12 months have been observed.

In first-line cisplatin-ineligible subjects with locally advanced or metastatic UC, enfortumab vedotin + pembrolizumab demonstrates encouraging efficacy with a tolerable and manageable safety profile. The confirmed ORR per investigator assessment for enfortumab vedotin + pembrolizumab observed to date in Study EV-103 suggests the potential for clinically meaningful efficacy relative to pembrolizumab alone (24% ORR on the KEYNOTE-052 trial, (Balar 2017)). Responses were achieved rapidly; the majority of responses occurred at the first tumor assessment (Week 9) and have remained durable based on available follow-up data.

In summary, the initial experience with enfortumab vedotin in combination with pembrolizumab suggests that the safety profile is manageable and tolerable. Safety and efficacy data for this combination support a favorable benefit-risk assessment and support further exploration of enfortumab vedotin combinations with pembrolizumab and in conjunction with other active agents.

1.6. Enfortumab Vedotin, Chemotherapy, and Pembrolizumab in Previously Untreated Locally Advanced or Metastatic Urothelial Carcinoma

Platinum-containing agents, such as cisplatin and carboplatin, are a well-established component of the standard of care for many solid malignancies, including advanced urothelial carcinoma that is no longer amenable to local treatments, such as surgery and/or radiotherapy. Overall,

chemotherapy combinations have led to modest improvements in outcomes for patients with advanced UC (Loehrer 1992; von der Maase 2000; De Santis 2012).

The established activity of platinum-containing chemotherapy along with the promising activity of the PD-(L)1-inhibitors in metastatic UC provide the rationale for combining enfortumab vedotin with pembrolizumab and chemotherapy to treat advanced UC. As previously described, enfortumab vedotin monotherapy has a distinct mechanism of action from pembrolizumab and the chemotherapeutic agents.

Gemcitabine (2′2′-difluorodeoxycytidine) is a cytosine analog that has shown activity against many types of solid tumors, including metastatic UC. Gemcitabine in first-line metastatic UC has demonstrated activity when combined with platinum-containing agents, however its individual activity is modest. As monotherapy in first-line cisplatin-ineligible metastatic UC, a response rate of 43% was seen, however the responses were short-lived and median OS was only 5.4 months (Culine 2011). Given this, replacing gemcitabine with enfortumab vedotin plus pembrolizumab in combination with platinum-containing drugs offers an opportunity for enhanced efficacy while maintaining tolerability.

The combination chemotherapy agents (cisplatin, carboplatin, and gemcitabine) will be used at standard doses every 3 weeks given that the targeted populations of subjects are not considered heavily pretreated (first-line setting and/or clear pre-study requirements) and they are used in the current standard of care (GC combination treatment). A complete summary of the clinical and nonclinical data relevant to the investigational product and its study in human subjects is provided in the Investigator's Brochure.

The EV-103 study is evaluating the safety and preliminary anti-tumor activity of enfortumab vedotin plus pembrolizumab and platinum containing chemotherapy as outlined in Section 1.5.1. Preliminary data indicates similar efficacy to the enfortumab vedotin plus pembrolizumab combination.

1.7. Assessment of Benefit-Risk

Apart from cisplatin-containing regimens, no other treatment to date has demonstrated an OS advantage for first-line metastatic UC, leaving a substantial therapeutic gap for the majority of the population that is unable to receive cisplatin chemotherapy. Even for the patients that are able to receive cisplatin, long-term survival is limited to less than 15% of patients treated (von der Maase 2000; Rosenberg 2019a). Carboplatin-containing regimens are commonly used in cisplatin-ineligible patients. In first-line therapy for cisplatin-ineligible metastatic UC patients, response rates to treatment with carboplatin monotherapy range from 8%–18% (Bamias 2006). In the EORTC 30986 trial, carboplatin combined with gemcitabine in a cisplatin-ineligible patient population resulted in a confirmed ORR of 36.1%. Median PFS was 5.8 months and median OS was 9.3 months (De Santis 2012). Treatment with platinum-containing chemotherapy regimens is accompanied by significant toxicities and poor long-term outcomes.

Although pembrolizumab and atezolizumab are approved for use in the first-line cisplatin-ineligible metastatic UC population, the use is restricted to those with high tumor PD-L1 expression. Patients with newly diagnosed or newly recurrent metastatic UC represent an area of unmet medical need. Novel therapies and combinations that demonstrate benefit in a

biomarker-unselected population are needed to improve outcomes in the first-line metastatic UC population.

Two recent studies evaluated combinations of platinum-containing regimens with PD-1/PD-L1 inhibitors in 1L metastatic UC. KEYNOTE-361 (platinum + gemcitabine + pembrolizumab) recently reported that despite a trend toward improved survival, the study did not show a statistically significant improvement in OS or PFS for subjects with mUC treated with pembrolizumab in combination with chemotherapy compared to chemotherapy alone (Powles 2021). IMvigor130, which evaluated platinum + gemcitabine + atezolizumab versus platinum + gemcitabine + placebo, demonstrated a statistically significant improvement in PFS and a trend toward improvement in OS that did not meet significance at the interim OS analysis. The study showed a modest 1.9-month improvement in the median PFS and at the time of the OS interim analysis (IA), the median OS for the platinum + gemcitabine + atezolizumab arm was 16 months compared to 13.4 months in the control arm (Galsky 2020).

Preliminary clinical data from the EV-103 trial show the enfortumab vedotin + platinum + pembrolizumab combination to be manageable and tolerable. Preliminary data from efficacy evaluable subjects in the cohort suggest comparable response rates and tumor reduction to the enfortumab vedotin + pembrolizumab data. Overall, these data supported inclusion of the enfortumab vedotin + pembrolizumab + platinum arm within EV-302. Nevertheless, given the limited activity of the PD-1/PD-L1 and platinum combinations, and the increasingly promising efficacy and safety of enfortumab vedotin + pembrolizumab, the sponsor has elected not to further pursue the enfortumab vedotin + platinum + pembrolizumab combination within the EV-302 trial. The EV-302 trial will evaluate enfortumab vedotin + pembrolizumab versus platinum + gemcitabine in subjects with previously untreated, locally advanced or metastatic UC. Subjects randomized to the enfortumab vedotin + platinum + pembrolizumab combination in earlier versions of the protocol will be allowed to continue with the combination or to discontinue the platinum drug and continue with enfortumab vedotin + pembrolizumab (see Appendix M).

The clinical data on the combination of enfortumab vedotin with pembrolizumab support a favorable benefit-risk ratio for patients with locally advanced or metastatic UC in the first-line setting. The EV-103 data show enfortumab vedotin and pembrolizumab to be tolerable, with manageable toxicities. Among AESIs, identified risks as a composite term include PN, rash, and extravasation site reactions, all reported at similar rates and severity as that for enfortumab vedotin therapy alone. Combination of enfortumab vedotin with pembrolizumab did not notably alter the immune mediated toxicities known to be associated with pembrolizumab monotherapy. The events reported in this combination appear to be consistent in type and severity. Clinical efficacy has been observed in the enfortumab vedotin plus pembrolizumab single-arm combination cohort and this doublet offers the potential to demonstrate improved progression-free and OS outcomes compared to the standard of care.

2. OBJECTIVES

This study will evaluate the efficacy, safety, and PK of enfortumab vedotin in combination with pembrolizumab versus standard of care gemcitabine plus platinum-containing chemotherapy in subjects with previously untreated locally advanced or metastatic UC. Specific objectives and corresponding endpoints for the study are summarized in Table 2.

Table 2: Objectives and corresponding endpoints

Primary Objectives	Corresponding Dual Primary Endpoints
• To compare PFS between the experimental arm (enfortumab vedotin + pembrolizumab [Arm A]) and the control arm (gemcitabine + cisplatin or carboplatin [Arm B]) by blinded independent central review (BICR)	• PFS per RECIST v1.1 by BICR
• To compare overall survival (OS) between the experimental arm (Arm A) and the control arm (Arm B)	• OS
Secondary Objectives	**Corresponding Secondary Endpoints**
• To compare ORR between the experimental arm (Arm A) and the control arm (Arm B) by BICR	• ORR per RECIST v1.1 by BICR
• To compare time to pain progression (TTPP) from the subject perspective between the experimental arm (Arm A) and the control arm (Arm B)	• TTPP
• To compare average change in pain from the subject perspective between the experimental arm (Arm A) and the control arm (Arm B)	• Mean change from baseline in worst pain at Week 26
• To evaluate PFS between the experimental arm (Arm A) and the control arm (Arm B) by investigator assessment	• PFS per RECIST v1.1 by investigator assessment
• To evaluate ORR between the experimental arm (Arm A) and the control arm (Arm B) by investigator assessment	• ORR per RECIST v1.1 by investigator assessment
• To evaluate DOR) the experimental arm (Arm A) and the control arm (Arm B)	• DOR per RECIST v1.1 by BICR • DOR per RECIST v1.1 by investigator assessment
• To evaluate DCR between the experimental arm (Arm A) and the control arm (Arm B)	• DCR per RECIST v1.1 by BICR • DCR per RECIST v1.1 by investigator assessment
• To evaluate the impact of study treatment on quality of life (QOL), functioning, and symptoms from the subject perspective	• Mean scores and change from baseline of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Core 30 (QLQ-C30), and EuroQOL 5-dimensions (EQ-5D-5L), visual analogue scale (VAS), and utility scores
• To evaluate the safety profile of each treatment regimen	• Type, incidence, relatedness, severity and seriousness of AEs • Type, incidence and severity of laboratory abnormalities • Treatment discontinuation rate due to AEs
Exploratory Objectives	**Corresponding Exploratory Endpoints**

• To assess PFS, ORR, and DOR per the modified RECIST v1.1 for immune-based therapeutics (iRECIST) in Arm A	• PFS, ORR, and DOR per iRECIST by investigator assessment in Arm A
• To assess subject reported health resource utilization (HRU)	• Cumulative incidence of HRU as reported by subject
• To assess the pharmacokinetics of enfortumab vedotin and MMAE • To assess the development of anti-therapeutic antibody (ATA) to enfortumab vedotin	• Plasma or serum concentrations of enfortumab vedotin and MMAE • Incidence of ATA to enfortumab vedotin
• To assess biomarkers of biological activity, resistance, and predictive biomarkers of response	• Exploratory biomarkers of clinical activity

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

This is a global phase 3 open-label, 2-arm randomized multicenter study to evaluate the combination of enfortumab vedotin + pembrolizumab versus standard of care gemcitabine + platinum-containing chemotherapy, in subjects with previously untreated locally advanced or metastatic UC. See Figure 1.

Subjects will be enrolled regardless of PD-L1 expression status, however, PD-L1 status (high or low) will be a stratification factor for randomization. The study is designed to assess the dual primary endpoints of PFS and OS of experimental Arm A (enfortumab vedotin + pembrolizumab) compared to control Arm B (gemcitabine + cisplatin or carboplatin).

A total of 860 subjects will be randomized in a 1:1 manner to one of the study arms with the following stratification factors: cisplatin eligibility (eligible or ineligible), PD-L1 expression (high or low), and liver metastases (present or absent).

Subjects in Arm A will receive enfortumab vedotin at 1.25 mg/kg, administered as an IV infusion on Days 1 and 8 of every 3-week cycle, and pembrolizumab 200 mg as an IV infusion on Day 1 of every 3-week cycle, after completion of the enfortumab vedotin infusion.

Subjects in Arm B will receive gemcitabine at 1000 mg/m^2 as an IV infusion on Days 1 and 8 of every 3-week cycle, and either cisplatin (70 mg/m^2) or carboplatin (area under the curve [AUC] 4.5, or AUC 5 according to local guidelines) on Day 1 of every 3-week cycle, with adequate pre- and post-hydration, by IV infusion per institutional standards.

Response will be assessed by computed tomography (CT) scans with contrast (unless contraindicated) every 9 weeks (±1 week) timed from the randomization date. For subjects who cannot receive CT scans with contrast, other protocol-specified imaging methods may be used (Appendix C). Brain scans should be repeated at this time point in subjects with a history of central nervous system (CNS) metastasis or signs/symptoms of CNS metastasis. Bone imaging should also be repeated at this time point in subjects with a history of skeletal metastasis or suspicion of skeletal metastasis based on imaging or symptoms. Objective responses will be confirmed per RECIST v1.1 (Eisenhauer 2009) (Appendix J) with repeat scans at the next scheduled response assessment per protocol after first documentation of response. Subsequent

response assessments should be performed every 9 weeks (±1 week) until 18 months after randomization, then every 12 weeks (±1 week). Response assessment should also be performed, and BICR evaluation triggered, whenever disease progression is suspected.

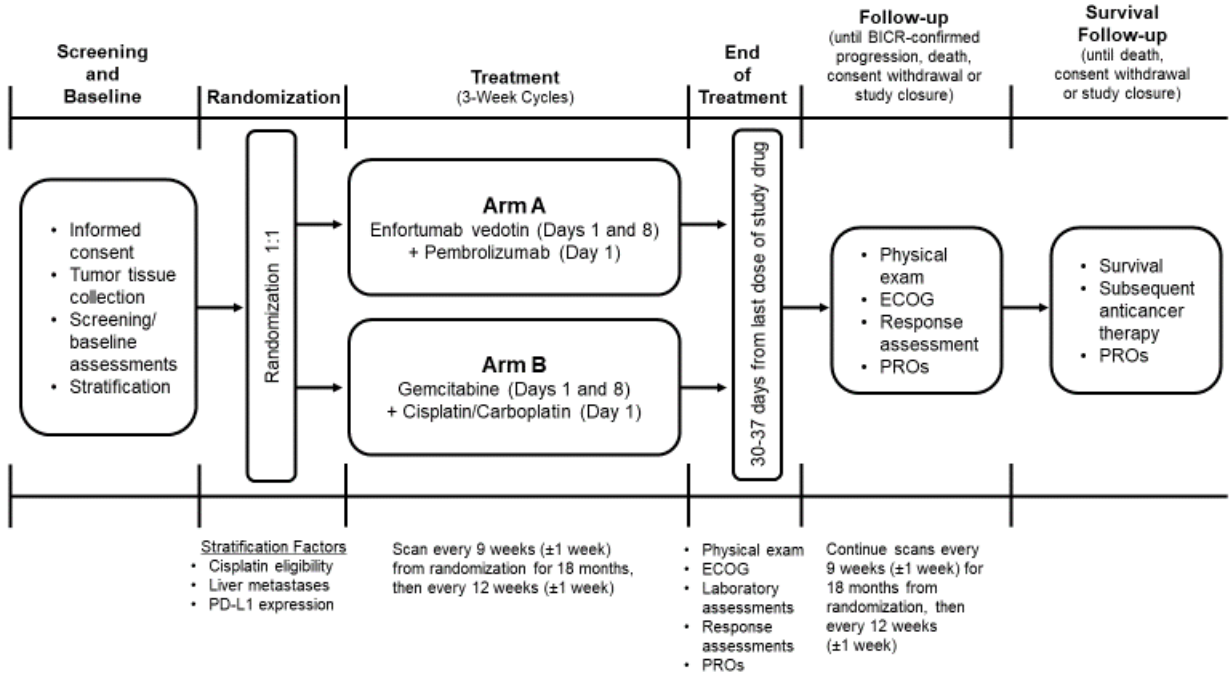
Subjects may continue on study treatment until progressive disease (BICR-confirmed or clinical progression [see Section 7.3]), an AE, pregnancy, investigator decision, start of a subsequent anticancer therapy, subject decision (non-AE), study termination by the sponsor, completion of the maximum number of drug cycles allowed, or other reason unrelated to an AE. Treatment beyond disease progression per RECIST v1.1 may be considered for subjects in study Arm A (EV + pembrolizumab) who are deriving clinical benefit as defined in Section 5.8. Subjects treated beyond disease progression per RECIST v1.1 may continue until confirmed disease progression per modified RECIST 1.1 for immune-based therapeutics (iRECIST) as assessed by the investigator (Seymour 2017) (Appendix K). Confirmatory scans must be performed 4 to 9 weeks after disease progression per RECIST v1.1 by BICR. Treatment with gemcitabine and treatment with platinum-containing chemotherapy may be given up to 6 cycles. Treatment with pembrolizumab will be discontinued once the subject has received a maximum of 35 administrations of pembrolizumab (approximately 2 years). There is no upper limit to the number of cycles of enfortumab vedotin permitted. To date in metastatic UC, enfortumab vedotin has been administered until disease progression or an unacceptable AE.

Palliative radiotherapy on a nontarget bone lesion that is not progressing is permitted and will not be considered a subsequent anticancer therapy; however, radiotherapy on any new or progressing lesion, per RECIST v1.1 as assessed by the investigator or after BICR-confirmed progression, will be considered a subsequent anticancer therapy and subjects will not be permitted to resume study treatment. Surgical resection for curative intent during study treatment may be permitted in subjects with favorable tumor response after discussion with the medical monitor.

Subjects who discontinue treatment for reasons other than disease progression or consent withdrawal will continue to receive response assessments every 9 weeks (±1 week) for the first 18 months timed from the randomization date, and every 12 weeks (±1 week) thereafter, until the subject has radiologically-confirmed disease progression per RECIST v1.1 guidelines as determined by BICR, dies, withdraws consent, or the study closes, whichever occurs first. After discontinuation of study treatment, all randomized subjects will be followed every 12 weeks (±1 week) to obtain information on subsequent anticancer therapy, and to assess survival status until death, study closure, lost to follow-up, or subject withdraws consent, whichever occurs first.

Crossover to the experimental arm of the trial (Arm A) will not be permitted for subjects in the control arm (Arm B). On a periodic basis, an Independent Data Monitoring Committee (IDMC) will monitor the safety of subjects participating in this trial. The IDMC will be responsible for evaluating the results of safety analyses and will make recommendations to the sponsor. Additional details will be described in a separate IDMC charter.

Figure 1: Study design



3.1.1. China Portion of the Study

After completion of enrollment in the global portion, subjects in China may continue to be randomized in a 1:1 ratio to either the experimental arm or the control arm until the planned sample size of approximately 130 subjects in China is reached.

3.2. Discussion and Rationale for Study Design

As outlined in Section 1, despite the availability of cisplatin-containing chemotherapy which offers a survival benefit in the first-line metastatic UC setting, the majority of patients receiving cisplatin chemotherapy do not achieve long-term disease-free survival and for patients ineligible for cisplatin, outcomes are even worse (De Santis 2012; Rosenberg 2019a). This global phase 3, randomized study evaluates enfortumab vedotin administered in combination with pembrolizumab versus chemotherapy alone in previously untreated locally advanced or metastatic UC. The study will enroll an all-comer first-line locally advanced or metastatic UC population without pre-selection based on a tissue biomarker.

3.2.1. Rationale for Endpoints

OS is a well-established endpoint for oncology drug approvals in metastatic UC. Both cisplatin-containing chemotherapy and pembrolizumab have demonstrated an OS benefit in metastatic UC (Loehrer 1992; von der Maase 2000; Bellmunt 2017). However, the OS endpoint may be impacted by subsequent therapies or non-cancer related causes of death (eg, accidents, comorbidities, and natural deaths in the elderly). The effect of later lines of treatments on the OS results are of concern for studies conducted in the earlier lines of treatment, as is the case for the EV-302 study in 1L metastatic UC. Multiple PD-1/PD-L1 inhibitors are approved in the post

platinum-containing setting, and enfortumab vedotin monotherapy is under development in later lines of therapy as well. OS also generally requires larger sample sizes and longer follow-up time, potentially delaying the time to availability of an active treatment to subjects. The sponsors, therefore, are planning to test for superiority in the PFS endpoint, in addition to the OS endpoint. PFS may better isolate effects of the study treatment without as much influence by external factors such as subsequent treatments and "cross-over" in the control arm. PFS can also be viewed as a measure of clinical benefit to patients, whereby prolonging the time to progression of cancer would have a direct impact on an individual patient's sense of well-being, as well as delaying the need for subsequent treatments with the associated side-effects. Of note, quality of life (QOL) data and patient-reported outcomes (PROs) will also be collected in this study to better understand the impact of improved PFS on subjects' daily lives.

With these considerations in mind, the sponsors have designated both PFS and OS as dual primary endpoints in the EV-302 study design, providing the opportunity to robustly evaluate the clinical benefit of enfortumab vedotin and pembrolizumab over the standard of care.

3.2.2. Rationale for Study Population

3.2.2.1. Rationale for Enrollment of a Biomarker-Unselected Population

The current trial will enroll an all-comer population with no preselection for tumor-specific biomarkers, including Nectin-4 and PD-L1 expression. The rationale for this approach is supported by data from the phase 1 and phase 2 trials of enfortumab vedotin, which showed no evidence to support an expression-response relationship between either Nectin-4 or PD-L1 and enfortumab vedotin therapy.

Subjects in the ongoing EV-201 and EV-301 studies investigating EV monotherapy in second-line and third-line metastatic UC, as well as study EV-103 investigating EV combinations in first-line metastatic UC, are all enrolled in an unselected manner with regard to the biomarkers Nectin-4 and PD-L1.

In the EV-101 (ASG 22CE-13-2) phase 1 study, more than 97% of archival tumor samples from screened subjects expressed Nectin-4 using a immunohistochemistry (IHC) assay with a median H-score of 280 out of a maximum of 300 (Petrylak 2017). Based upon the observed prevalence of high Nectin-4 expression, the protocol for phase 1 study EV-101 was amended to eliminate the enrollment requirement for H-score ≥150 in metastatic UC subjects.

In the EV-201 trial, there was no pre-selection by Nectin-4 expression and Nectin-4 expression was detectable by IHC in tumor biopsies from all treated subjects who had adequate tumor tissue for testing. The vast majority of subjects had high Nectin-4 expression levels, with a median H-score of 290 out of 300 (Rosenberg 2019b).

In the EV-201 study, PD-L1 levels at baseline were assessed by a validated 22C3 PD-L1 IHC assay. Of the 120 subjects, previously treated with both platinum-containing chemotherapy and a PD-1/PD-L1 inhibitor (Cohort 1), who had evaluable PD-L1 expression data, 65% had a CPS <10 and 35% had a CPS ≥10. Responses to enfortumab vedotin were observed in subjects with both high and low PD-L1 expression, with an ORR of 36% and 47%, respectively (Petrylak 2019). In the EV-201 trial, responses were observed regardless of PD-L1 expression level.

In the ongoing study EV-103 in 1L metastatic UC, subjects are enrolled regardless of PD-L1 expression. As of the data cut-off date of 08 Oct 2019, an ORR of 73.3% has been observed, which further supports enrollment of a PD-L1-unselected first-line metastatic UC population. Forty-two percent (42%) of subjects had low PD-L1 expression (CPS <10), 31% had high PD-L1 expression (CPS ≥10), and 27% were not evaluable. Responses were observed regardless of expression level.

Given the current understanding that PD-L1 expression is important for the use of pembrolizumab monotherapy in 1L metastatic UC, and of uncertain relevance when pembrolizumab is used in combination with cytotoxic agents, PD-L1 expression (high [CPS ≥10] versus low [CPS <10] as determined by the Dako/Agilent PD-L1 IHC 22C3 PharmDx assay) will be included as a stratification factor in the EV-302 study. Baseline tumor PD-L1 expression will be assessed in all subjects prior to randomization to evaluate any predictive or prognostic role for PD-L1 expression in this study.

3.2.3. Rationale for Control Arm Selection and Stratification Factors

Gemcitabine plus cisplatin is a preferred first-line regimen for patients with locally advanced or metastatic UC who are cisplatin eligible (von der Maase 2000). For patients who are cisplatin ineligible, gemcitabine plus carboplatin is a preferred regimen (De Santis 2012). Contemporary phase 3 trials conducted by the EORTC cooperative group with gemcitabine plus platinum-containing chemotherapy control arms include EORTC 30987 using gemcitabine plus cisplatin (Bellmunt 2012) and EORTC 30986 using gemcitabine plus carboplatin (De Santis 2012). More recently, the CALGB cooperative group presented data from the 90601 trial, including gemcitabine plus cisplatin control arm (Rosenberg 2019a). Several additional recent and ongoing phase 3 studies use gemcitabine plus platinum-containing chemotherapy in control arms, including the DANUBE study (NCT02516241), NILE (NCT03682068), KEYNOTE-361 (NCT02853305), IMvigor130 (NCT02807636), and CheckMate901 (NCT03036098).

Together, these data support the use of gemcitabine plus cisplatin or carboplatin, the current standard of care for 1L treatment of subjects with locally advanced or metastatic UC, as the control arm for the current study.

Stratification Factors

Given the different outcomes observed between the cisplatin-eligible and the cisplatin-ineligible 1L metastatic UC populations, cisplatin eligibility will be included as a stratification factor to ensure balance across treatment arms. Investigators will determine a subject's cisplatin-eligibility at the time of enrollment, per protocol. A subject may be considered cisplatin-ineligible provided they meet at least one of the following criteria: glomerular filtration rate (GFR) <60 mL/min, Eastern Cooperative Oncology Group (ECOG) or World Health Organization (WHO) performance status of 2, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade ≥2 audiometric hearing loss, or New York Heart Association (NYHA) Class III heart failure. Subjects will be stratified by cisplatin eligibility for randomization, with the intent to support approval for both cisplatin-eligible and cisplatin-ineligible (carboplatin-eligible) subject populations. Subjects will be stratified by PD-L1 expression into either PD-L1 high (CPS ≥10) or PD-L1 low (CPS <10) categories according to the Dako/Agilent PD-L1 IHC 22C3 PharmDx. Additional stratification factors

include presence or absence of liver metastases at randomization, which is an established prognostic factor in patients with metastatic UC (Bajorin 1999) (Sonpavde 2016).

3.2.4. Method of Assigning Subjects to Treatment Groups

Subjects will be randomized in a 1:1 manner to 1 of the 2 treatment arms based on the following stratification factors: cisplatin eligibility (eligible or ineligible), PD-L1 expression (high or low), and liver metastases (present or absent). Interactive Response Technology (IRT) will be used for randomization.

3.2.5. Rationale for Selection of Doses

Enfortumab vedotin administered at 1.25 mg/kg on Days 1, 8, and 15 of every 28-day cycle is the approved dose and schedule for locally advanced or metastatic UC in second-line subjects who have previously received a PD-1/PD-L1 inhibitor and platinum-containing chemotherapy (PADCEV® Prescribing Information, Seagen, December 2019). Based on PK data from previous studies, the half-life of enfortumab vedotin is approximately 3 to 4 days. No notable intra-cycle accumulation (<30%) of ADC was observed with this monotherapy dosing regimen at any dose level. Minimal intra-cycle accumulation (<50%) of MMAE was observed.

In this combination study, additional drugs in the regimen (pembrolizumab, gemcitabine and platinum-containing chemotherapy) are administered in a 21-day cycle. Enfortumab vedotin is administered on Days 1 and 8 of a 21-day cycle. When comparing the same dose level, the average weekly total exposure of enfortumab vedotin following administration on Days 1 and 8 of each 21-day cycle is predicted to be similar to that observed for dosing on Days 1, 8, and 15 of a 28-day cycle. Thus, it is anticipated that the dosing schedule in the current combination study will achieve ADC exposures over each 3-week cycle that may lead to a favorable balance of antitumor activity and safety similar to that observed in the phase 1 Study EV-101. Similar to the monotherapy dosing regimen, no to minimal accumulation of ADC and MMAE, respectively, is expected on the 21-day cycle.

Enfortumab vedotin will be administered at a dose of 1.25 mg/kg as an IV infusion over approximately 30 minutes on Days 1 and 8 of each 3-week cycle.

The dose of pembrolizumab for this study will be 200 mg administered on Day 1 of each 21-day cycle in combination with enfortumab vedotin. This is the approved dose and schedule for pembrolizumab for urothelial cancer in both first-line cisplatin-ineligible patients and second-line patients (Keytruda Prescribing Information, June 2019).

The safety and antitumor activity of enfortumab vedotin 1.25 mg/kg administered on Days 1 and 8 of every 21-day cycle in combination with pembrolizumab is currently being evaluated in the ongoing EV-103 trial outlined in Section 1.5. Early safety data shows the combination to be tolerable and consistent with the AE profiles for each individual agent.

Gemcitabine 1000 mg/m^2 will be administered on Days 1 and 8 of each 21-day cycle. Either cisplatin 70 mg/m^2 or carboplatin AUC=4.5 (or AUC=5 according to local guidelines) will be administered on Day 1 of each 21-day cycle. Cisplatin and gemcitabine at these doses have been tested in both 21-day and 28-day cycles with similar efficacy outcomes (von der Maase 2000; Rosenberg 2019a). The 21-day cycle has been a preferred schedule when tested in combination with other agents administered on a 21-day schedule (Rosenberg 2019a); (KEYNOTE-361

NCT02853305). The carboplatin and gemcitabine regimen at this dose and schedule was established as a standard of care for the cisplatin-ineligible population (De Santis 2012).

3.2.6. Blinding and Unblinding

This trial evaluates the experimental arm (enfortumab vedotin plus pembrolizumab) compared to the standard-of-care control arm (platinum-containing chemotherapy plus gemcitabine). As the control arm contains agents not contained in the experimental arm, blinding with placebo-control would be difficult and could complicate the ability to assess attribution of overlapping toxicities. Given this, the study will be conducted in an open-label fashion. Although this is an open-label study, to maintain trial integrity, until database lock and study unblinding for the pre-planned analyses, analyses or summaries by treatment assignment are only planned for the purpose of the IDMC monitoring and will be conducted by an external vendor. The primary endpoint of PFS along with response-based secondary endpoints will be assessed by BICR. Additional details will be provided in a separate document.

3.3. Overall End of Study

The study will end 5 years after enrollment of the last subject, or when no subjects remain in survival follow-up. Additionally, the sponsor may terminate the study at any time.

4. STUDY POPULATION

Subjects with previously untreated locally advanced or metastatic UC. Subjects must meet all of the enrollment criteria to be eligible for this study. Eligibility criteria may not be waived 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. Subjects must have histologically documented, unresectable locally advanced or metastatic urothelial carcinoma (ie, cancer of the bladder, renal pelvis, ureter, or urethra). Subjects with squamous or sarcomatoid differentiation or mixed cell types are eligible.
2. Subjects must have measurable disease by investigator assessment according to RECIST v1.1 (Appendix J).
    a. Subjects with prior definitive radiation therapy must have measurable disease per RECIST v1.1 that is outside the radiation field or has demonstrated unequivocal progression since completion of radiation therapy
3. Subjects must not have received prior systemic therapy for locally advanced or metastatic urothelial carcinoma with the following exceptions:
    a. Subjects that received neoadjuvant chemotherapy with recurrence >12 months from completion of therapy are permitted
    b. Subjects that received adjuvant chemotherapy following cystectomy with recurrence >12 months from completion of therapy are permitted
4. Subjects must be considered eligible to receive cisplatin- or carboplatin-containing chemotherapy, in the investigator's judgment.

a. Subjects will be considered cisplatin-ineligible, and will receive carboplatin, if they meet at least one of the following criteria:

   i. GFR <60 mL/min but ≥30 mL/min (measured by the Cockcroft-Gault formula, Modification of Diet in Renal Disease [MDRD] or 24-hour urine)

      - Subjects with a GFR ≥50 mL/min and no other cisplatin ineligibility criteria may be considered cisplatin-eligible based on the investigator's clinical judgment

   ii. ECOG or WHO performance status of 2 (refer to Inclusion 7 for additional criteria for ECOG 2 subjects)

   iii. NCI CTCAE Grade ≥2 audiometric hearing loss

   iv. NYHA Class III heart failure

5. Subjects must be age 18 years or older.
6. Archival tumor tissue comprising muscle-invasive urothelial carcinoma, or a biopsy of metastatic urothelial carcinoma must be provided for PD-L1 testing prior to randomization. If adequate archival tumor sample is not available, or evaluable, a new biopsy sample may be performed (see Section 7.5).
7. Subjects must have an ECOG Performance Status score of 0, 1, or 2 (see Appendix B for conversion of performance status using Karnofsky, if applicable).
   a. Subjects with ECOG performance status of 2 must additionally meet the following criteria:

      i. Hemoglobin ≥10 g/dL

      ii. GFR ≥50 mL/min

      iii. May not have NYHA Class III heart failure

8. Subjects must have adequate hematologic and organ function as defined by the baseline laboratory values in Table 3.

Table 3: Baseline laboratory values

System	Laboratory Value
Hematological	
ANC	≥1500/μL
Platelets	≥100,000/μL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L
Renal	
Measured or calculated[a] creatinine clearance (CrCl) (GFR can also be used in place of creatinine or CrCl)	≥30 mL/min
Hepatic	
Total bilirubin	≤1.5× ULN OR direct bilirubin ≤ ULN for subjects with total bilirubin levels >1.5× ULN ≤3× ULN for subjects with Gilbert's disease
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for subjects with liver metastases
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin (aPTT)	≤1.5 × ULN unless subject is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulation

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

a Creatinine clearance should be calculated via either Cockcroft-Gault, Modification of Diet in Renal Disease (MDRD) equations or 24h urine, per institutional standard. The same method should be used consistently for a subject over the course of the study with the exception of carboplatin dose calculation where Cockcroft-Gault method should be used in all subjects.

9. A female subject of childbearing potential is anyone born female who has experienced menarche and who has not undergone surgical sterilization (eg, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or has not completed menopause. Menopause is defined clinically as 12 months of amenorrhea in a person over age 45 in the absence of other biological, physiological, or pharmacological causes. Female subjects of childbearing potential must meet the following conditions:

   - Agree not to try to become pregnant during the study and for at least 6 months after the final dose of study drug.
   - Must have a negative urine or serum pregnancy test (minimum sensitivity of 25 mIU/mL or equivalent units of beta human chorionic gonadotropin [β-hCG]) within 1 day prior to administration of study drug. Female subjects with false positive results and documented verification of negative pregnancy status are eligible for participation.

- If heterosexually active, must consistently use highly effective methods of birth control, with a failure rate of less than 1% (as described in Appendix L) starting at screening, throughout the study period, and for at least 6 months after the final dose of study drug.
- Female subjects 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 dose of study drug.

10. A male subject who can father children is anyone born male who has testes and who has not undergone surgical sterilization (eg, vasectomy followed by a clinical test proving that the procedure was effective). Male subjects who can father children, must meet the following conditions:
    - Must not donate sperm starting at screening and throughout the study period, and for at least 6 months after the final dose of study drug. Male subjects will be informed about the negative risk to reproductive function and fertility from the study treatment. Prior to treatment male subjects should be advised to seek information on fertility preservation and sperm cryoconservation.
    - Must consistently use highly effective methods of birth control, with a failure rate of less than 1% (as described in Appendix L) starting at screening and continue throughout study period and for at least 6 months after the final dose of study drug.
    - Male subjects with a pregnant or breastfeeding partner(s) must consistently use one of 2 contraception options for preventing secondary exposure to seminal fluid (as described in Appendix L) for the duration of the pregnancy or time partner is breastfeeding throughout the study period and for at least 6 months after the final dose of study drug.
11. Subjects must provide written informed consent.

4.2. Exclusion Criteria

1. Subjects who have previously received enfortumab vedotin or other MMAE-based ADCs.
2. Subjects who have received prior treatment with a PD-(L)-1 inhibitor for any malignancy, including earlier stage UC, defined as a PD-1 inhibitor or PD-L1 inhibitor (including, but not limited to, atezolizumab, pembrolizumab, nivolumab, durvalumab, or avelumab).
3. Subjects who have previously received any prior treatment with an agent directed to another stimulatory or co inhibitory T-cell receptor (including but not limited to CD137 agonists, CTLA-4 inhibitors, or OX-40 agonists).
4. Subjects who have received anti-cancer treatment with chemotherapy, biologics, or investigational agents not otherwise prohibited by exclusion criteria 1–3 that is not completed 4 weeks prior to first dose of study treatment (ongoing hormonal/anti hormonal treatment, eg, for breast cancer, is allowed, provided that the subject is eligible per exclusion criterion 14).

5. Subjects with uncontrolled diabetes. Uncontrolled diabetes is defined as hemoglobin A1c (HbA1c) ≥8% or HbA1c 7% to <8% with associated diabetes symptoms (polyuria or polydipsia) that are not otherwise explained.
6. Subjects with an estimated life expectancy <12 weeks
7. Subjects with ongoing sensory or motor neuropathy Grade 2 or higher.
8. Subjects with active CNS metastases. Subjects with treated CNS metastases are permitted on study if all of the following are true: a) CNS metastases have been clinically stable for at least 4 weeks prior to screening and baseline scans show no evidence of new or enlarged metastasis; b) the subject is on a stable dose of ≤10 mg/day of prednisone or equivalent for at least 2 weeks (if requiring steroid treatment); c) subject does not have leptomeningeal disease.
9. Subjects with ongoing clinically significant toxicity associated with prior treatment (including radiotherapy or surgery) that has not resolved to ≤ Grade 1 or returned to baseline.
10. Currently receiving systemic antimicrobial treatment for active infection (viral, bacterial, or fungal) at the time of randomization. Routine antimicrobial prophylaxis is permitted.
11. Subjects who have known active hepatitis B (defined as HBsAg reactive) or known active hepatitis C virus (defined as HCV RNA [qualitative] detected) infection, testing for hepatitis B and hepatitis C is required if mandated by country health authority. Subjects who have been curatively treated for hepatitis C infection are permitted if they have documented sustained virologic response of 12 weeks.
12. Has a known history of human immunodeficiency virus (HIV) infection. Testing is not required unless mandated by the local health authority.
13. Subjects with conditions requiring high doses of steroids (>10 mg/day of prednisone or equivalent) or other immunosuppressive medications are excluded. Inhaled or topical steroids are permitted in the absence of active autoimmune disease. Physiologic replacement doses of corticosteroids are permitted for subjects with adrenal insufficiency.
14. Subjects with a history of another invasive malignancy within 3 years before the first dose of study drug, or any evidence of residual disease from a previously diagnosed malignancy. Subjects with nonmelanoma skin cancer or carcinoma in situ of any type (if complete resection was performed) are allowed.
    a. A history of prostate cancer (T2NXMX or lower with Gleason score ≤7) treated with definitive intent (surgically or with radiation therapy) at least 1 year prior to study entry is acceptable, provided that the subject is considered prostate cancer-free and the following criteria are met:
        i. Participants who have undergone radical prostatectomy must have undetectable PSA for >1 year and at screening.
        ii. Participants who have had radiation must have a PSA doubling time >1 year (based on at least 3 values determined >1 month apart) and a total PSA value that does not meet Phoenix criteria for biochemical recurrence (ie, <2.0 ng/mL above nadir).

b. Participants with untreated low-risk prostate cancer (Gleason score ≤6) on active surveillance with PSA doubling time >1 year (based on at least 3 values determined >1 month apart) are also eligible.

15. Subjects with a documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, myocardial infarction, or cardiac symptoms consistent with NYHA Class IV within 6 months prior to randomization (Appendix D).
16. Subjects who have received radiotherapy within 2 weeks prior to randomization. Subject must have recovered adequately from the toxicity from the intervention prior to starting study treatment.
17. Subjects who have received major surgery within 4 weeks prior to randomization. Subject must have recovered adequately from complications from the intervention prior to starting study treatment.
18. Subjects with known severe (≥ Grade 3) hypersensitivity to any enfortumab vedotin excipient contained in the drug formulation of enfortumab vedotin (including histidine, trehalose dihydrate, and polysorbate 20). Subjects with known severe (≥ Grade 3) hypersensitivity to any pembrolizumab excipient contained in the drug formulations of pembrolizumab. Subjects with known severe (≥ Grade 3) hypersensitivity to the platinum agent selected by the investigator for study treatment. Subjects with known severe (≥ Grade 3) hypersensitivity to the gemcitabine.
19. Subjects with active keratitis or corneal ulcerations. Subjects with superficial punctate keratitis are allowed if the disorder is being adequately treated in the opinion of the investigator.
20. History of autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs).
    a. Replacement therapy (eg, thyroxine, insulin, physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
    b. Brief (<7 days) use of systemic corticosteroids is allowed when use is considered standard of care.
    c. Subjects with vitiligo, psoriasis, type 1 diabetes mellitus, hypothyroidism, or resolved childhood asthma/atopy will not be excluded.
    d. Subjects requiring intermittent use of bronchodilators, inhaled steroids, or local steroid injections will not be excluded.
    e. Subjects with hypothyroidism that is stable with hormone replacement or Sjögren's syndrome will not be excluded.
21. Subjects with a history of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan.
22. Subjects who have received a prior allogeneic stem cell or solid organ transplant.

23. Subjects who have received a live attenuated vaccine within 30 days prior to randomization. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
24. Subjects with active tuberculosis
25. Subjects with another underlying medical condition that, in the opinion of the investigator, would impair the ability of the subject to receive or tolerate the planned treatment and follow-up; any known psychiatric or substance abuse disorders that would interfere with cooperating with the requirements of the study.

4.3. Removal of Subjects From Therapy or Assessment

4.3.1. Discontinuation of Study Treatment

A subject's study treatment will be discontinued for any of the following reasons:

- Progressive disease (BICR-confirmed or clinical progression [see Section 7.3])
    - Confirmed progressive disease per iRECIST (Appendix K) as assessed by investigator in subjects in study Arm A treated beyond BICR-confirmed disease progression (see criteria in Section 5.8)
- AE
- Pregnancy
- Investigator decision
- Start of a subsequent anticancer therapy
- Subject decision, non-AE
- Study termination by sponsor
- Completion of study treatment
- Other, non-AE

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

Pembrolizumab may be administered for up to a total of 35 cycles (approximately 2 years).

Cisplatin, carboplatin, and gemcitabine may be administered for up to a total of 6 cycles.

Maintenance therapy (eg, avelumab) may be used following completion and/or discontinuation of platinum-containing therapy, if locally available, and provided the subject is deemed appropriate by the investigator. Avelumab must be used in accordance with the latest version of the Summary of Product Characteristics (SmPC) currently available. The following conditions should also be met:

- Completion of end of treatment (EOT) visit

- All study-related procedures occurring post-EOT, including all disease assessments until BICR-confirmed disease progression occurs, should be continued per the Schedule of Assessments (see Appendix A).

4.3.2. Subject Discontinuation From Study

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

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

5. TREATMENTS

5.1. Treatments Administered

For subjects randomized to enfortumab vedotin + cisplatin or carboplatin + pembrolizumab (Arm C) in a previous protocol version, please follow cisplatin and carboplatin dosing and treatment administration guidelines below. See Appendix M for additional details specific to Arm C.

Enfortumab vedotin (Arm A)

Enfortumab vedotin 1.25 mg/kg, the investigational product under study, will be administered as an IV infusion over approximately 30 minutes on Days 1 and 8 of every 3-week cycle.

Pembrolizumab (Arm A)

Pembrolizumab 200 mg will be administered as an IV infusion approximately 30 minutes after completion of enfortumab vedotin (Arm A) on Cycle 1 Day 1. A delay of 15 minutes may be used for subsequent infusions if the previous infusion was well tolerated.

Gemcitabine (Arm B)

Gemcitabine 1000 mg/m^2 will be administered as an IV infusion on Days 1 and 8 of each 3-week cycle.

Cisplatin (Arm B)

On Day 1 (or Day 2 if required per institutional guidelines) of each 3-week cycle, cisplatin 70 mg/m^2 will be administered (with adequate pre- and post-hydration) as an IV infusion per institutional standards (Arm B). The body surface area used to calculate cisplatin dose may be capped per institutional standards.

Carboplatin (Arm B)

On Day 1 of each 3-week cycle, carboplatin at AUC 4.5, or AUC of 5 according to local guidelines, will be administered (with adequate pre- and post-hydration) as an IV infusion per institutional standards (Arm B). Body weight used to calculate carboplatin may be capped as per institutional standards.

Table 4: Interventions and treatment arms

Agent (IV)	Arm A (EV+Pembro)	Arm B[a] (Gemcitabine + Cisplatin/Carboplatin)
Enfortumab vedotin	1.25 mg/kg over 30 min on Days 1 and 8	
Pembrolizumab	200 mg over 30 min on Day 1	
Gemcitabine		1000 mg/m^2 on Days 1 and 8
Cisplatin[b]		70 mg/m^2 on Day 1 over 1 hour, or per local label or institutional standards
Carboplatin[c]		AUC 4.5 on Day 1 over 1 hour, or per local label or institutional standards

a Subjects will receive either cisplatin or carboplatin.
b Can be given on Day 2 if required per institutional standards.
c A starting dose of AUC 5 can be given according to local guidelines.

5.2. Investigational Product

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

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.

5.2.2. Method of Procurement

The investigational study drug (enfortumab vedotin) will be provided by the sponsor.

5.2.3. Dose and Administration

Enfortumab vedotin will be administered on Days 1 and 8 of every 3-week cycle by IV infusion given over approximately 30 minutes. In the absence of IRRs, the infusion rate for all subjects should be calculated in order to achieve a 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.

Enfortumab vedotin may be administered for an unlimited number of cycles until a protocol defined reason for treatment discontinuation occurs (see Section 5.8).

Weight-based dosing is based on the subject's actual body weight. Doses must be adjusted for subjects who experience a ≥10% change in weight from baseline or previous cycle. Subject weight must be measured during all relevant assessment windows as described in the schedule of

events as well as per institutional standards, if applicable. Other dose adjustments for changes in body weight <10% are permitted per institutional standard. **An exception to weight-based dosing of enfortumab vedotin is made for subjects weighing greater than 100 kg; doses will be based on 100 kg for these individuals. The maximum dose permitted on study is 125 mg.**

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

The infusion site should be monitored closely for redness, swelling, pain, and infection during and at any time after administration. Subjects should be advised to report redness or discomfort promptly at the time of administration or after infusion. For subjects with difficult peripheral venous access or who are at risk for extravasation (ie, limited vein selection, small or fragile veins, local neuropathies, or lymphedema), placement of a central venous port or catheter should be considered. Institutional guidelines will be followed for the administration of chemotherapy agents and precautions taken to prevent extravasation per institutional standards and as described in (Polovich 2014) and (Perez Fidalgo 2012). In case of enfortumab vedotin extravasation, the combination drug(s) should be held until consultation and further discussion with the medical monitor/sponsor.

5.2.4. Dose Modifications

Dose modification recommendations for enfortumab vedotin associated toxicity (hematologic and non-hematologic, by CTCAE v4.03 grade) are presented in Table 5 and Table 6.

Dose reduction or delay for other enfortumab vedotin-associated toxicity is permitted at the discretion of the site investigator. Dose reduction from 1.25 mg/kg to 1 mg/kg or to 0.75 mg/kg will be allowed depending on the type and severity of toxicity. Subjects requiring a dose reduction may be re-escalated by 1 dose level (ie, subjects 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. Subjects with ≥ Grade 2 corneal AEs will not be permitted to dose re-escalate.

The Day 8 dose of enfortumab vedotin must be given within 4 days of the planned dose (Day 8 + 4 days). If the Day 8 dose cannot be administered within this timeframe, the dose should be held until Day 1 of the next treatment cycle. Dose delay for other EV associated toxicity is permitted at the discretion of the site investigator. A dose delay may last up to 6 weeks (2 cycles). Dose delays for subjects who are deriving clinical benefit from treatment may be extended beyond 6 weeks, if the subject's toxicity does not otherwise require permanent discontinuation. If there is a dose delay, the schedule for response assessments will not be adjusted.

Enfortumab vedotin may be delayed for situations other than treatment-related AEs such as medical/surgical events or logistical reasons not related to study therapy. Subjects should resume study therapy as soon as clinically safe as assessed by the investigator. For delays longer than 6 weeks, the medical monitor should be consulted before resuming study therapy. The reason for delay should be documented in the subject's case report form (CRF).

For subjects in the enfortumab vedotin plus pembrolizumab treatment arm who develop a rash or a skin reaction that is determined by the investigator to be related to study treatment, initial

management actions (ie, to withhold or discontinue study treatment) should apply to both study treatments, and the investigator should follow the most conservative dose modification recommendations described below in Table 6 for enfortumab vedotin or in Section 5.3.4 (Table 7) for pembrolizumab. However, for Grade 2 skin reactions that are stable (not worsening and in the absence of fever) with supportive measures and not limiting the subject's activities of daily living, continued dosing of enfortumab vedotin may be considered following consultation with the sponsor. Neither enfortumab vedotin nor pembrolizumab should be administered in the setting of a Grade ≥3 skin reaction.

Table 5: Recommended dose modification 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.

Note: Hematologic toxicity refers to anemia, thrombocytopenia, neutropenia, and febrile neutropenia.

Table 6: Recommended dose modifications for enfortumab vedotin-associated nonhematologic toxicity

<table>
<tr><td>Toxicity</td><td colspan="4">Grade</td></tr>
<tr><td rowspan="4">Skin reactions</td><td colspan="4">Any Grade</td></tr>
<tr><td colspan="4">For suspected Stevens-Johnson syndrome (SJS), suspected toxic epidermal necrolysis (TEN), or bullous lesions, immediately withhold enfortumab vedotin and refer the subject to a dermatologist/specialist for diagnosis and specialized care.
For confirmed SJS or TEN, permanently discontinue treatment.
If SJS or TEN is ruled out, see recommendations provided below for skin reactions.</td></tr>
<tr><td>Grade 1</td><td>Grade 2</td><td>Grade 3</td><td>Grade 4</td></tr>
<tr><td>For Grade 1 rash or skin reactions, may continue at same dose level. See also Section 5.10.5 for recommended management of rash.</td><td>Continue at same dose level.
For worsening rash or skin reactions or skin reactions with concomitant fever, withhold enfortumab vedotin until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose level or consider dose reduction by 1 level. Consider referral of the subject to a dermatologist/ specialist for diagnosis and specialized care.</td><td>For Grade 3 rash or skin reactions withhold enfortumab vedotin until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose level or consider dose reduction by 1 level. Consider referral of the subject to a dermatologist/ specialist for diagnosis and specialized care.
Subjects who have confirmed SJS or recurrent Grade 3 rash events should have therapy permanently discontinued.</td><td>For confirmed SJS or TEN, or Grade 4 rash, permanently discontinue treatment.</td></tr>
</table>

Ocular	Grade 1	Grade 2	Grade 3	Grade 4
	Continue at same dose level. If ocular symptoms and/or changes in vision are identified, the subject should be evaluated by an optometrist or ophthalmologist.	For Grade 2 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 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 subject should be evaluated by an optometrist or ophthalmologist.	For Grade 3 corneal AEs, discontinue treatment at the discretion of the investigator. If ocular symptoms and/or changes in vision are identified, the subject should be evaluated by an optometrist or ophthalmologist.	For Grade 4 AEs, discontinue treatment.
Neuropathy	Grade 1	Grade 2	Grade 3	Grade 4
	Continue at same dose level.	For Grade 2 neuropathy 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 withhold dose until toxicity is ≤ Grade 1, then reduce the dose by 1 dose level and resume treatment.	For Grade 3 neuropathy AEs, discontinue treatment at the discretion of the investigator.	For Grade 4 AEs, discontinue treatment.

Gastrointestinal	Grade 1	Grade 2	Grade 3	Grade 4
	Continue at same dose level.	Continue at 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.	For Grade 4 AEs, discontinue treatment. Grade 4 vomiting and/or diarrhea that improves to ≤ Grade 2 within 72 hours with supportive management does not require discontinuation.
Hyperglycemia	Grade 1	Grade 2	Grade 3	Grade 4
	Continue at same dose level.	Continue at same dose level.	For Grade 3 hyperglycemia/elevated blood glucose, withhold enfortumab vedotin treatment. Resume treatment once hyperglycemia/elevated blood glucose has improved to ≤ Grade 2 and subject is clinically and metabolically stable. See also pembrolizumab dose modification recommendations for hyperglycemia in Table 7.	For Grade 4 hyperglycemia/elevated blood glucose withhold enfortumab vedotin treatment and undertake a full evaluation of the hyperglycemia to determine the underlying diagnosis. Once blood glucose returns to ≤ Grade 2, drug dosing may resume with close monitoring after consultation with the medical monitor. See also pembrolizumab dose modification recommendations for hyperglycemia in Table 7.
Pneumonitis/ILD	Grade 1	Grade 2	Grade 3	Grade 4
	Continue at same dose level.	Withhold dose until ≤ Grade 1, then resume at the same dose level or consider dose reduction by 1 dose level.	Permanently discontinue treatment.	Permanently discontinue treatment.
All Other (not previously mentioned)	Grade 1	Grade 2	Grade 3	Grade 4
	Continue at same dose level.	Continue at same dose level.	Withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same	For Grade 4 AEs, discontinue treatment.*

			dose level or consider dose reduction by 1 dose level.*	

* Grade 3/4 electrolyte imbalances/laboratory abnormalities, except hyperglycemia, that are not associated with clinical sequelae or are corrected with supplementation/appropriate management within 72 h of their onset do not require discontinuation (eg, Grade 4 hypouricemia). Grade 3 or 4 elevations of amylase or lipase, if asymptomatic do not require treatment delay.

5.2.5. 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.

Vials of enfortumab vedotin lyophilized powder, reconstituted drug product and/or dosing solutions should be protected from direct sunlight.

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. Drug accountability procedures are provided in the Pharmacy Binder.

5.2.6. Packaging and Labeling

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

5.2.7. 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. Pembrolizumab

5.3.1. Description

Pembrolizumab is a humanized mAb that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4 kappa Ig with an approximate molecular weight of 149 kDa.

Pembrolizumab injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for IV infusion. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, United States Pharmacopeia (USP).

5.3.2. Method of Procurement

Pembrolizumab will be provided to all study sites by the sponsor. In countries outside the US, pembrolizumab will also be relabeled by the sponsor, to meet country-specific regulatory requirements.

5.3.3. Dose and Administration

Pembrolizumab will be administered at a dose of 200 mg on Day 1 of every 3-week cycle by IV infusion given over approximately 30 minutes.

Pembrolizumab may be administered for a maximum of 35 cycles.

5.3.4. Dose Modifications

5.3.4.1. Dose Delays and Toxicity Management for Immune-related Adverse Events Associated with Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These imAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. The dose of pembrolizumab should not be reduced. Based on existing clinical study data, most imAEs were reversible and could be managed with a delay of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected imAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, and/or skin biopsy may be included as part of the evaluation. Based on the severity of imAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose delay and toxicity management guidelines for imAEs associated with pembrolizumab are provided in Table 7 and are also detailed in the pembrolizumab package insert.

Table 7: Guidelines for management of pembrolizumab immune-related adverse events

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening imAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if imAEs cannot be controlled by corticosteroids.

Immune-mediated AEs	Toxicity Grade or Conditions (CTCAE v4.03)	Action Taken to Pembrolizumab	imAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1–2 mg/kg prednisone or equivalent) followed by taper	Monitor subjects for signs and symptoms of pneumonitis Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1–2 mg/kg prednisone or equivalent) followed by taper	Monitor subjects for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) Subjects with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis Subjects with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Grade 4 or recurrent Grade 3	Permanently discontinue		

Immune-mediated AEs	Toxicity Grade or Conditions (CTCAE v4.03)	Action Taken to Pembrolizumab	imAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
AST/ALT elevation or Increased bilirubin	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5–1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	Administer corticosteroids (initial dose of 1–2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold[a]	Initiate insulin replacement therapy for subjects with T1DM Administer anti-hyperglycemic in subjects with hyperglycemia	Monitor subjects for hyperglycemia or other signs and symptoms of diabetes See also enfortumab vedotin dose modification recommendations and management for hyperglycemia in Table 6
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[a]		
Hyperthyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (eg, propranolol) or thioamides as appropriate	Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue[a]		
Hypothyroidism	Grade 2–4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders
Nephritis and Renal dysfunction	Grade 2	Withhold	Administer corticosteroids (prednisone 1–2 mg/kg or equivalent) followed by taper.	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		

Footnotes

Immune-mediated AEs	Toxicity Grade or Conditions (CTCAE v4.03)	Action Taken to Pembrolizumab	imAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
All other immune-mediated AEs	Persistent Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue[b].		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

Note: Non-immune related (ir)AE will be managed as appropriate, following clinical practice recommendations.
a The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.
b Events that require discontinuation include but are not limited to: Guillain-Barre Syndrome, encephalitis, Drug Rash with Eosinophilia and Systemic Symptom (DRESS), Stevens-Johnson Syndrome, toxic epidermal necrolysis, myelitis, and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

5.3.4.2. Dose Delays and Toxicity Management of Infusion-reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 h of completion of infusion. Dose delay and treatment guidelines on pembrolizumab associated infusion reaction are provided in Table 8.

Table 8: Pembrolizumab infusion reaction dose modifications and treatment guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Stop Infusion Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until	Subject may be premedicated 1.5 h (±30 minutes) prior to infusion of study intervention with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500–1000 mg PO (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
	symptoms resolve and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug intervention.	
Grade 3 or 4 **Grade 3** Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) **Grade 4** Life-threatening; pressor or ventilator support indicated	**Stop Infusion** Additional appropriate medical therapy may include but is not limited to: Epinephrine**, IV fluids, antihistamines, NSAIDs, acetaminophen, narcotics, oxygen, pressors, and corticosteroids. Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Subject is permanently discontinued from further pembrolizumab treatment.	No subsequent dosing

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the CTCAE v4.03.

5.3.5. Storage and Handling

Refer to the Pharmacy Binder for storage and handling instructions.

5.3.6. Packaging and Labeling

Drug product vials may be labeled as pembrolizumab, the United States Adopted Name and International Nonproprietary Name.

5.3.7. Preparation

The pharmacy manual contains specific instructions for the preparation of the pembrolizumab solution.

5.4. Other Allowed Dose Delays for Enfortumab Vedotin and Pembrolizumab

Enfortumab vedotin and/or pembrolizumab may be delayed for situations other than treatment-related AEs such as medical/surgical events or logistical reasons not related to study therapy. Subjects should resume study therapy as soon as clinically safe as assessed by the investigator. For delays longer than 6 weeks, the medical monitor should be consulted before resuming study therapy. The reason for delay should be documented in the subject's CRF.

5.5. Cisplatin

5.5.1. Description

Alone or in combination with other anticancer agents, cis-diamminedichloroplatinum (II) (cisplatin) is used in the management of many solid malignancies, including for advanced UC that is no longer amenable to local treatments, such as surgery and/or radiotherapy. Cisplatin is a platinum-containing anticancer agent classified as a direct DNA-interacting agent.

Cisplatin is a yellow to orange crystalline powder with the molecular formula PtCl2H6N2, and a molecular weight of 300.1. Cisplatin is a heavy metal complex containing a central atom of platinum surrounded by two chloride atoms and two ammonia molecules in the cis position. It is soluble in water or saline at 1 mg/mL.

Cisplatin injection infusion concentrate is a clear, colorless, sterile aqueous solution available in amber vials. Each 50, 100, or 200 mL amber vial of infusion concentrate contains 1 mg/mL cisplatin, 9 mg/mL sodium chloride, hydrochloric acid and sodium hydroxide to approximate pH of 4.0, and water for injection to a final volume of 50, 100, or 200 mL, respectively. Cisplatin Injection infusion concentrate must be further diluted prior to administration.

5.5.2. Method of Procurement

Cisplatin is commercially available and details regarding sourcing of cisplatin may vary by site and/or region as outlined in other documents such as Clinical Trial Agreements (CTA).

5.5.3. Dose and Administration

Subjects that are determined to be cisplatin-eligible per protocol should receive cisplatin.

Cisplatin will be administered with adequate pre- and post-hydration at a dose of 70 mg/m^2 on Day 1 (or Day 2 if required by institutional guidelines) of each 3-week cycle as an IV infusion per institutional standards (Arm B). Cisplatin may be administered for a maximum of 6 cycles.

Weight-based dosing of cisplatin is based on the subject's actual body weight. Doses must be adjusted for subjects who experience a ≥10% change in weight from baseline or previous cycle. Subject weight must be measured during all relevant assessment windows as described in the schedule of events as well as per institutional standards, if applicable. Other dose adjustments for changes in body weight <10% are permitted per institutional standard.

The body surface area used to calculate cisplatin dose may be capped per institutional standards. Split dosing of cisplatin is not allowed. See the cisplatin package insert for detailed instructions.

Cisplatin dose modifications are shown below in Table 9. Additional details can be found in the package insert.

Table 9: Dose modifications for cisplatin toxicity

Worst Toxicity in Previous Cycle	Cisplatin Dose for Next Cycle[a]
Grade 4 platelets ≥5 days, Grade 4 ANC ≥5 days[b], thrombocytopenic bleeding, or febrile neutropenia	Decrease dose by 25%
Grade 2 neurotoxicity or ototoxicity	Decrease dose by 25% or discontinue depending on risk-benefit
Grade 3 or 4 neurotoxicity or ototoxicity	Discontinue
Other Grade 3 non-hematologic/organ toxicity	Decrease dose by 25%
Other Grade 4 non-hematologic/organ toxicity	Discontinue

a Do not retreat until platelets ≥100,000/µL, ANC ≥1500/µL, and toxicity has recovered to ≤ Grade 2 (Grade 1 for neurotoxicity).
b Growth factor support is allowed per institutional standards.

5.5.3.1. Dosage with Renal Impairment

Renal function should return to baseline before subjects are retreated. Cisplatin dosing should be discontinued if creatinine clearance (CrCl) is <30 mL/min. The same method to determine CrCl should be used consistently for a subject over the course of the study with the exception of carboplatin dose calculation where Cockcroft-Gault method should be used in all subjects.

If a subject develops acute kidney injury that fails to resolve during treatment with cisplatin-containing therapy, a one-time switch from cisplatin to carboplatin for the remaining cycles will be permitted if deemed appropriate by the investigator. In the event that kidney function improves, switching back to cisplatin will not be permitted. Switching due to lack of response or disease progression is not permitted.

5.5.4. Storage and Handling

Refer to the cisplatin package insert in the Pharmacy Binder for storage and handling instructions.

5.5.5. Packaging and Labeling

Refer to the cisplatin package insert in the Pharmacy Binder for packaging and labeling information.

5.5.6. Preparation

Refer to the cisplatin package insert in the Pharmacy Binder for preparation instructions.

5.6. Carboplatin

5.6.1. Description

Alone or in combination with other anticancer agents, cis-Diammine (cyclobutane-1,1-dicarboxylato)platinum (carboplatin) is used in the management of many solid malignancies, including for advanced UC which is no longer amenable to local treatments, such as surgery and/or radiotherapy, and which is not eligible for treatment with cisplatin as defined

by a consensus working group (Galsky 2011). Carboplatin is a platinum-containing anticancer agent classified as a cisplatin analog, with similar actions and uses.

Carboplatin is a crystalline powder with the molecular formula C6H12N2O4Pt and a molecular weight of 371.25. It is soluble in water at a rate of approximately 14 mg/mL, and the pH of a 1% solution is 5 to 7.

Carboplatin injection is supplied as a sterile, pyrogen-free, aqueous solution of carboplatin, USP. Each 50, 150, 450, or 600 mg multidose vial of solution contains 10 mg/mL carboplatin.

5.6.2. Method of Procurement

Carboplatin is commercially available and details regarding sourcing of carboplatin may vary by site and/or region as outlined in other documents such as CTAs.

5.6.3. Dose and Administration

Subjects that are determined to be cisplatin-ineligible per protocol should receive carboplatin.

Carboplatin will be administered with adequate pre- and post-hydration at a dose of AUC 4.5, or AUC of 5 according to local guidelines, on Day 1 of each 3-week cycle as an IV infusion per institutional standards (Arm B).

Carboplatin may be administered for a maximum of 6 cycles.

The recommended dose of carboplatin is for a targeted AUC of 4.5 mg/mL per minute calculated based on the Calvert formula; carboplatin dose in mg=AUC × (CrCl + 25) administered (with adequate pre- and post-administration hydration) as an IV infusion. The IDMC and/or the sponsor may recommend using a targeted AUC of 5 mg/mL per minute based on the totality of the data available at that time (adjusted carboplatin dose in mg=AUC × [CrCl + 25]). Hydration may be administered during gemcitabine infusions (Arm B). CrCl (mL/min) is estimated by the Cockcroft-Gault formula (CrCl [mL/min] = [((140-age) × weight in kgs)/(72 × serum creatinine in mg/dL)] x 0.85 [if female]). The estimated CrCl for calculating carboplatin dose should not exceed 125 mL/min. Body weight may be capped per institutional standards. See the carboplatin package insert for detailed instructions.

Dosing of carboplatin is based on the subject's actual body weight and estimated CrCl on Day 1 of each treatment cycle.

If the performance status or renal function of a subject improves during treatment with carboplatin-containing therapy such that the subject is deemed eligible for cisplatin therapy, a one-time switch from carboplatin to cisplatin for the remaining cycles will be permitted if deemed appropriate by the investigator. If the subject experiences a subsequent AE to cisplatin that prevents further treatment, switching back to carboplatin will not be permitted and platinum-containing chemotherapy must be discontinued. Switching due to lack of response or disease progression is not permitted.

Carboplatin dose modifications are shown below in Table 10. Additional details can be found in the package insert.

Table 10: Dose modification for carboplatin toxicity

Worst Toxicity in Previous Cycle	Carboplatin Dose for Next Cycle*
Grade ≥3 platelets and/or thrombocytopenic bleeding, Grade 4 ANC ≥5 days and/or febrile neutropenia	Decrease dose by 25%
Grade 2 neurotoxicity	Hold dose until event resolves to Grade 0 or 1 or discontinue depending on risk-benefit
Grade 3 or 4 neurotoxicity	Discontinue
Other Grade 3 non-hematologic/organ toxicity	Decrease dose by 25%
Other Grade 4 non-hematologic/organ toxicity	Discontinue

* Do not retreat until platelets ≥100,000/µL, ANC ≥1500/µL, and toxicity has recovered to ≤Grade 2 (Grade 1 for neurotoxicity).

5.6.3.1. Dosage for Renal Impairment

Renal function should return to baseline before subjects are retreated. Carboplatin dosing should be discontinued if CrCl is <30 mL/min per the Cockcroft-Gault formula.

5.6.4. Storage and Handling

Refer to the carboplatin package insert in the Pharmacy Binder for storage and handling instructions.

5.6.5. Packaging and Labeling

Refer to the carboplatin package insert in the Pharmacy Binder for packaging and labeling instructions.

5.6.6. Preparation

Refer to the carboplatin package insert in the Pharmacy Binder for preparation information.

5.7. Gemcitabine

5.7.1. Description

Alone or in combination with other anticancer agents, 4-Amino-1-(2-deoxy-2,2-difluoro-β-D-ribofuranosyl)pyrimidin-2(1H)-one hydrochloride; 2'-Deoxy-2',2'-difluorocytidine hydrochloride (gemcitabine) is a pyrimidine antimetabolite that is structurally similar to cytarabine and has demonstrated antitumor activity in several malignancies. In advanced UC, it is commonly used as a combination product, or in patients that are not eligible for treatment with platinum-containing therapy.

Gemcitabine is a white or almost white powder with a molecular formula C9H11F2N3O4 • HCl and a molecular weight of 299.66. A 1% solution in water has a pH of 2.0 to 3.0.

Gemcitabine injection is a clear and colorless to light straw-colored solution available in sterile single-use vials containing gemcitabine: 200 mg, 1 g, and 2 g. Each mL contains equivalent of 38 mg of gemcitabine in water for injection, USP.

5.7.2. Method of Procurement

Gemcitabine is commercially available and details regarding sourcing of gemcitabine may vary by site and/or region as outlined in other documents such as CTAs.

5.7.3. Dose and Administration

Gemcitabine will be administered at a dose of 1000 mg/m^2 on Days 1 and 8 of every 3-week cycle as an IV infusion. BSA may be capped per institutional standards.

Weight-based dosing of gemcitabine is based on the subject's actual body weight. Doses must be adjusted for subjects who experience a ≥10% change in weight from baseline or previous cycle. Subject weight must be measured during all relevant assessment windows as described in the schedule of events as well as per institutional standards, if applicable. Other dose adjustments for changes in body weight <10% are permitted per institutional standard.

Gemcitabine may be administered for a maximum of 6 cycles.

5.7.4. Dose Modifications

Dose modifications of gemcitabine are allowed per the local label or institutional standards. See the local label for further information.

The Day 8 dose of gemcitabine must be given within 4 days of the planned dose (Day 8 [–1 to + 4 days]). If the Day 8 dose cannot be administered within this timeframe, the dose should be held until Day 1 of the next treatment cycle.

5.7.5. Storage and Handling

Refer to the gemcitabine package insert in the Pharmacy Binder for storage and handling instructions.

5.7.6. Packaging and Labeling

Refer to the gemcitabine package insert in the Pharmacy Binder for packaging and labeling information.

5.7.7. Preparation

Refer to the gemcitabine package insert in the Pharmacy Binder for preparation instructions.

5.8. Treatment Duration

Enfortumab vedotin may be administered for an unlimited number of cycles until a protocol-defined reason for treatment discontinuation occurs. Pembrolizumab may be administered for a maximum of 35 cycles or a protocol-defined reason for treatment discontinuation occurs, whichever is first. Cisplatin, carboplatin, and/or gemcitabine may be administered for a maximum of 6 cycles or a protocol-defined reason for treatment discontinuation occurs, whichever is first.

Subjects may continue on study treatment until one of the following protocol-defined reasons for treatment discontinuation occurs:

- Progressive disease (BICR-confirmed or clinical progression [see Section 7.3])

    - Confirmed progressive disease per iRECIST (Appendix K) as assessed by investigator in subjects in study Arm A treated beyond BICR-confirmed disease progression (see criteria below)
- AE
- Pregnancy
- Investigator decision
- Start of a subsequent anticancer therapy
- Subject decision, non-AE
- Study termination by the sponsor.
- Completion of study treatment
- Other, non-AE

In Arm A, subjects who experience an unacceptable AE that is attributable only to pembrolizumab may continue on enfortumab vedotin monotherapy until a protocol-defined reason for treatment discontinuation. Subjects who experience toxicity that is attributable only to enfortumab vedotin may continue on pembrolizumab monotherapy up to a maximum of 35 cycles.

In Arm B, subjects who experience an unacceptable AE that is attributable only to platinum-containing chemotherapy may continue on gemcitabine for up to 6 cycles. Subjects who experience an unacceptable AE that is attributable only to gemcitabine may continue on platinum-containing chemotherapy for up to 6 cycles.

Subjects in Arm A may be treated beyond disease progression per RECIST v1.1 provided they are deriving clinical benefit, as defined by all of the following:

- Improvement in clinical symptoms or functional status as assessed by the investigator
- No decline in WHO or ECOG performance status attributable to disease progression
- Absence of symptoms or signs (including worsening laboratory values) of unequivocal disease progression
- Absence of disease progression at critical anatomic sites (eg, CNS, spinal cord compression)

The subject should additionally be informed of other available treatment options. If, in the opinion of the investigator, all of the above criteria have been met, the subject may be treated beyond disease progression per RECIST v1.1. Protocol treatment must be discontinued upon confirmed disease progression by iRECIST per investigator (see Appendix K).

Study drug that is discontinued cannot be subsequently restarted.

5.9. Concomitant Therapy

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care except for those medications identified as prohibited (see Section 5.9.3).

All concomitant medications and blood products administered will be recorded from Day 1 (predose) through 30 days after the last study treatment, or 90 days after the last study treatment for SAEs related to pembrolizumab (see Section 7.8.1.3 and Section 7.8.1.6). Any concomitant medication given for a study protocol-related AE should be recorded from the time of informed consent.

5.9.1. Required Concomitant Therapy

There are no required concomitant therapies.

5.9.2. Allowed Concomitant Therapy

During study treatment, palliative radiotherapy on a stable (not growing), symptomatic nontarget bone lesion is allowed and will not be considered a subsequent anticancer therapy. Study treatment should be held for at least 7 days prior to and 14 days following administration of radiation.

Surgical resection for curative intent, including TUR for papillary lesions, during study treatment may be permitted in subjects with favorable tumor response after discussion with the medical monitor.

The use of anti-emetics is permitted. For subjects randomized to the platinum-containing treatment arm, substance P/neurokinin 1 inhibitors (eg, Aprepitant), 5-HT3 antagonists (eg, Ondansetron), and short courses (≤1 week) of corticosteroids (eg, Dexamethasone) may be administered per local label and/or institutional guidelines for platinum-related nausea prevention.

Granulocyte stimulating growth factors (eg, Filgrastim) may be administered on or after Day 9 of each treatment cycle for neutropenia prevention/treatment according to local guidelines.

The use of insulin is permitted as part of standard of care. Pre-medications for IRRs per Section 5.10.2 are permitted; however, prophylactic premedication prior to combination treatment on Cycle 1 Day 1 for prevention of IRRs may not be administered.

Therapy to manage enfortumab vedotin-associated toxicity as recommended in Section 5.2.4 is permitted, including hematopoietic growth factors and transfusions.

Subjects who are receiving strong CYP3A4 inhibitors or P-glycoprotein inhibitors concomitantly with enfortumab vedotin should be monitored for adverse reactions.

Routine prophylaxis with vaccines is permitted; however, subjects may not be treated with a live, attenuated vaccine during the study and for 90 days after the last dose of study treatment.

Antimicrobial prophylaxis or ongoing treatment of resolving and/or controlled infection is permitted during the study.

The following applies to subjects receiving pembrolizumab (Arm A):

With approval from the medical monitor, concomitant chronic prednisone (or equivalent) may be used at a dose of ≤10 mg/day to manage pre-existing conditions. Higher doses of prednisone (or equivalent) are permitted for limited duration to treat acute conditions that arise during the study as medically indicated. The medical monitor should be notified of subjects requiring systemic steroids (≥10 mg prednisone or equivalent) for longer than 24 hours for management of a

treatment-related AE. Chronic use of inhaled or topical steroids are permitted in the absence of active autoimmune disease.

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

5.9.3. Prohibited Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the course of study treatment. If there is a clinical indication for any medication or vaccination specifically prohibited during study treatment, discontinuation of study treatment may be required. The investigator should discuss any questions regarding this with the medical monitor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on study treatment requires the mutual agreement of the investigator, the sponsor, and the subject.

Listed below are specific restrictions for concomitant therapy or vaccination during the course of study treatment:

- Systemic antineoplastic therapy with the exception of adjuvant hormonal therapy for localized breast or prostate cancer that has undergone definitive treatment
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab or enfortumab vedotin
- Radiation therapy

Note: Radiation therapy to a stable (not growing) symptomatic nontarget bone lesion is permitted at the investigator's discretion (see Section 5.9.2).

- Live vaccines within 30 days prior to the first dose of study treatment, while participating in the study, and for 90 days after the last dose of study treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist) are live attenuated vaccines and are not allowed.

Subjects who, in the assessment of the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from study treatment.

5.10. Management of Adverse Reactions

5.10.1. Overlapping Adverse Reactions

The Investigator's Brochures for enfortumab vedotin and pembrolizumab and package inserts for cisplatin, carboplatin, and gemcitabine individually describe AEs commonly observed relative to individual study treatments, as well as less common serious findings. The respective

Investigator's Brochures and package inserts should be referenced when attributing causality; however, the final decision regarding causality is at the discretion of the investigator.

Some AEs, including rash or skin reactions or pneumonitis/interstitial lung disease (ILD), may represent overlapping toxicities for enfortumab vedotin and pembrolizumab, and attribution to an individual study treatment may be difficult. For overlapping AEs of skin reaction or pneumonitis/ILD, the management actions (ie, to withhold or discontinue study treatment) should apply to both enfortumab vedotin and pembrolizumab, and the investigator should follow the most conservative dose modification guidelines as described in Section 5.2.4 (Table 6) and Section 5.3.4 (Table 7). However, for Grade 2 skin reactions that are stable (not worsening and in the absence of fever) with supportive measures and not limiting the subject's activities of daily living, continued dosing of enfortumab vedotin may be considered following consultation with the sponsor.

5.10.2. Management of Infusion Reactions

5.10.2.1. Enfortumab Vedotin

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.

Pre-medications for IRRs are permitted as described below; however, prophylactic premedication prior to combination treatment on Cycle 1 Day 1 for prevention of IRRs may not be administered. Subjects who have experienced an IRR may be premedicated for subsequent infusions. Premedication may include pain medication (eg, acetaminophen or equivalent), an antihistamine (eg, diphenhydramine hydrochloride), and a corticosteroid administered approximately 30–60 minutes prior to each enfortumab vedotin infusion or according to institutional standards. Should a subject experience IRRs in the setting of premedication, continued treatment 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.

5.10.2.2. Pembrolizumab

Please refer to the recommendations in Table 8.

5.10.2.3. Infusion-related Reaction of Uncertain Cause

Anaphylactic-like reactions to carboplatin have been reported and may occur within minutes of administration. Epinephrine, corticosteroids, and antihistamines have been employed to alleviate symptoms.

Anaphylactic-like reactions to cisplatin have been reported. Facial edema, bronchoconstriction, tachycardia, and hypotension may occur within minutes of cisplatin administration. Epinephrine, corticosteroids, and antihistamines have been effectively employed to alleviate symptoms.

If anaphylaxis occurs, administration of the implicated drug should be immediately and permanently discontinued.

If a subject experiences an IRR after receiving study treatments and a single cause of the IRR cannot be determined, appropriate sets of guidelines for IRRs must be followed. For chemotherapy combinations, institutional guidelines should be followed.

5.10.3. Supportive Care Guidelines for Pembrolizumab

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.3.4, and Table 7. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Table 7 in Section 5.3.4 for guidelines regarding dose modification and supportive care.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

5.10.4. 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, subjects should be treated according to local standard of care and referral to endocrinology may be considered.

Subjects, 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.

Subjects 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). Dosing may continue once the subject's blood glucose has improved to ≤ Grade 2 and subject is clinically and metabolically stable. The use of insulin is permitted as part of standard of care. Blood glucose >500 mg/dL (Grade 4) considered related to enfortumab vedotin requires drug interruption and a full evaluation of the hyperglycemia to determine the underlying diagnosis. Once hyperglycemia/elevated blood glucose has improved to ≤ Grade 2, drug dosing may resume with close monitoring after consultation with medical monitor.

5.10.5. Management of Rash Related to Enfortumab Vedotin

Enfortumab vedotin is a Nectin-4 directed antibody drug conjugate. Nectin-4 is a cell adhesion molecule that is highly expressed in urothelial carcinoma. Low to moderate levels of Nectin-4 are also expressed on normal tissues, including skin keratinocytes, sweat glands and hair follicles; thus, skin reactions are anticipated events. As such, skin reactions are adverse events of interest in all clinical studies with enfortumab vedotin.

A cumulative review of post-marketing safety data from 18 Dec 2019 (the approval date of enfortumab vedotin in the US) through 22 Oct 2020 identified reports of severe cutaneous adverse reactions in 15 patients receiving enfortumab vedotin, some of whom had fatal outcomes. These reactions occurred predominantly during the first cycle of treatment. Adverse events reported in these cases included SJS (5 cases), blister (3 cases), dermatitis bullous (3 cases), symmetrical drug-related intertriginous and flexural exanthema (SDRIFE; 2 cases), and 1 case each of dermatitis exfoliative, exfoliative rash, epidermal necrosis, oropharyngeal blistering, stomatitis, and TEN.

In enfortumab vedotin monotherapy studies of urothelial carcinoma, SAEs of severe cutaneous adverse reactions were reported in 11 of 749 subjects (1.5%) and included dermatitis bullous (0.4%), drug eruption (0.4%), blister (0.1%), conjunctivitis (0.1%), SJS (0.1%), stomatitis (0.1%), and toxic skin eruption (0.1%).

Subjects should be informed that rash and severe skin reactions have occurred after administration of enfortumab vedotin and to contact the Investigator immediately if they have signs and symptoms of skin reactions, oral mucosal and ocular abnormalities including mucositis or conjunctivitis. Starting in the first cycle and throughout treatment, closely monitor subjects for skin reactions. For mild to moderate skin reactions, consider appropriate treatment, such as topical corticosteroids and antihistamines as clinically indicated. For recommendations regarding dose modifications for skin reactions due to enfortumab vedotin, refer to Section 5.2.4.

5.10.6. Management of Pneumonitis/ILD Related to Enfortumab Vedotin

Severe, life-threatening or fatal pneumonitis/ILD have occurred in subjects receiving enfortumab vedotin. Monitor subjects for signs and symptoms indicative of pneumonitis/ILD such as hypoxia, cough, dyspnea or interstitial infiltrates on radiologic exams. For all subjects, including subjects with asymptomatic/Grade 1 pneumonitis/ILD, clinical monitoring and supportive measures consistent with local medical guidelines should be followed as appropriate throughout the study. Medical intervention per standard of care should be considered for Grade ≥2 events (eg, corticosteroids initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper). For recommendations regarding dose modifications for pneumonitis/ILD due to enfortumab vedotin, refer to Section 5.2.4.

5.10.7. Management of Overdose

5.10.7.1. Enfortumab Vedotin

Weight-based dosing for enfortumab vedotin is based on the subject's actual body weight, with the exception of subjects weighing greater than 100 kg; doses will be based on 100 kg for these individuals. **The maximum dose calculated per cycle in this study is 125 mg.**

In the event of an overdose of enfortumab vedotin >10%, study personnel should:

- Care for and medically stabilize the subject until there is no immediate risk of complications or death, if applicable. There is currently no known antidote for an overdose of enfortumab vedotin.
- Notify the Medical Monitor as soon as they become aware of the overdose, to discuss details of the overdose (eg, exact amount of enfortumab vedotin administered, subject weight) and AEs, if any.

5.10.7.2. Pembrolizumab

For this study, an overdose of pembrolizumab will be defined as ≥1000 mg (5 times the dose) of pembrolizumab. No specific information is available on the treatment of overdose of pembrolizumab. In the event of an overdose, the site should notify the sponsor as soon as they are aware of the overdose. The subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

5.10.7.3. Cisplatin

For cisplatin, the maximum dose calculated per cycle in this study is 70 mg/m^2. In the event of an overdose (≥10% of the calculated dose) of cisplatin, the event should be managed according to the product label and/or institutional standard of care, and promptly reported to the sponsor.

5.10.7.4. Carboplatin

For carboplatin, the maximum dose calculated per cycle in this study is calculated using an AUC=5. In the event of an overdose (≥10% of the calculated dose) of carboplatin, the event should be managed according to the product label and/or institutional standard of care, and promptly reported to the sponsor.

5.10.7.5. Gemcitabine

For gemcitabine, the maximum dose calculated per cycle in this study is 1000 mg/m^2. In the event of an overdose (≥10% of the calculated dose) of gemcitabine, the event should be managed according to the product label and/or institutional standard of care, and promptly reported to the sponsor.

5.11. 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

AEs and concomitant medications (see Section 5.9) will be recorded from Day 1 (predose) through the safety reporting period (see Section 7.8.1.3). Any study protocol-related AE (defined

in Section 7.8.1.1) as well as any concomitant medications given for treatment of the AE, should be recorded from the time of informed consent.

Clinical laboratory assessments (serum chemistry panel, complete blood count [CBC] with differential [manual differential if clinically indicated, see Section 7.8.4], physical exam, weight, and performance status) may be performed within 1 day prior to administration of study drug. The results from all relevant clinical laboratory assessments must be reviewed prior to dosing by qualified site medical personnel.

Initial QOL, pain and health resource utilization (HRU) assessments will be completed within 24 hours of Cycle 1 Day 1 at the clinic using an electronic patient-reported outcome (ePRO) device. Subsequent assessments will be completed at home by the subject between clinic visits using the ePRO device (see Section 7.7 and Table 13).

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.

6.2. Screening and Baseline Visits

6.2.1. Days –42 to Randomization

- Informed consent
- Initiate collection of archival tumor tissue or a new tumor biopsy sample (see Section 7.5)
- Transthoracic echocardiogram or multiple-gated acquisition (MUGA) scan with left ventricular ejection fraction is required for subjects with NYHA Class III Heart Failure or a history of coronary heart disease, arrhythmia or other significant heart disease (see Section 7.8.6)

6.2.2. Days –28 to Randomization

- Study eligibility per inclusion/exclusion criteria
- Medical history (see Section 7.1)
- Complete ophthalmologic examination, (see Section 7.8.7)
- Brain scan (magnetic resonance imaging [MRI] with gadolinium preferred; if contraindicated, see Appendix C), will be conducted at screening/baseline in subjects with a history of CNS metastasis or signs/symptoms of CNS metastasis
- Bone scan will be conducted at screening/baseline in subjects with a history of skeletal metastasis or suspicion of skeletal metastasis based on imaging or symptoms
- CT scan with contrast (preferred; if contraindicated, see Appendix C), including chest, abdomen, and pelvis. Other regions should be scanned if the subject has known disease in that region (see Section 7.3)
- International normalized ration (INR)/prothrombin time (PT) and partial thromboplastin time (PTT)

- HbA1c. If HbA1c is elevated (≥6.5%), refer subject to appropriate provider during Cycle 1 for glucose management
- Urinalysis (with reflexive microscopy, if abnormal)
- Amylase
- Lipase
- Thyroid function tests (see Section 7.8.4)

6.2.3. Days –7 to Randomization

- Height and weight
- Vital signs (see Section 7.8.3)
- Electrocardiogram (ECG) (see Section 7.8.6)
- Pregnancy test for subjects of childbearing potential (see Section 7.8.8 and Appendix A)
- Physical exam (see Section 7.8.2)
- ECOG performance status (see Section 7.8.5)
- Serum chemistry panel (see Section 7.8.4)
- CBC with differential (see Section 7.8.4)
- CrCl (see Section 7.8.4)

6.2.4. Days –3 to Day 1

- Randomization

6.3. Treatment Period (Day 1 to Day 21)

6.3.1. Day 1 (±2 days beginning with Cycle 2)

- Results from clinical laboratory assessments must be reviewed and must confirm eligibility to receive study drug prior to administration
- The following activities will occur prior to study drug dosing:
    - Physical exam (including weight) (not required if performed within 1 day prior to administration of study drug; see Section 7.8.2 and Appendix A)
    - Vital signs
    - ECOG performance status (not required if performed within 1 day prior to administration of study drug; see Section 7.8.5 and Appendix A)
    - Serum chemistry panel (not required if performed within 1 day prior to administration of study drug; see Section 7.8.4 and Appendix A)
        - Verify blood glucose is <250 mg/dL prior to dosing (see Section 5.10.4). Subjects with diabetes must be tested in the clinic and

blood glucose must be <250 mg/dL prior to dosing. Use of insulin is permitted as part of the standard of care.

- CBC with differential (not required if performed within 1 day prior to administration of study drug; see Section 7.8.4 and Appendix A)
- Thyroid function test
  - Arm A: Cycle 2 and every even cycle thereafter
  - Arm B: If clinically indicated
- Pregnancy test for subjects of childbearing potential (not required if performed within 1 day prior to administration of study drug; see Section 7.8.8 and Appendix A)
- QOL, pain, and HRU assessments (administer before any study procedures within 24 hours of Cycle 1 Day 1; see Section 7.7)
- Blood samples for PK and biomarker assessments (see Section 7.4, Section 7.5, and Table 12)
- Urine sample for biomarker assessments (Cycles 1, 3 and 5 only; see Section 7.5, and Table 12)

- If Baseline Visit activities occur within 1 day prior to Cycle 1, Day 1, the following assessments do not need to be repeated: physical exam (including weight), ECOG performance status, serum chemistry panel, CBC with differential, thyroid function test, and pregnancy test.
- Arm A
  - Enfortumab vedotin administration (see Section 5.2.3)
  - Pembrolizumab administration (see Section 5.3.3)
- Arm B
  - Cisplatin (see Section 5.5.3) or carboplatin (see Section 5.6.3) administration
  - Gemcitabine administration (see Section 5.7.3)
- The following activities will occur postdose:
  - Blood samples for PK assessments (Cycles 1 and 2 only; see Section 7.4, and Table 12)

6.3.2. Day 8 (–1 to +4 days)

- The following activities will occur prior to study drug dosing:
  - Vital signs
  - Serum chemistry panel
    - Verify blood glucose is <250 mg/dL prior to dosing (see Section 5.10.4). Subjects with diabetes must be tested in the clinic and

blood glucose must be <250 mg/dL prior to dosing. Use of insulin is permitted as part of the standard of care

    - CBC with differential
    - Blood samples for PK assessments (Cycles 1 and 2 only; see Section 7.4, and Table 12)

- Arm A
    - Enfortumab vedotin administration (see Section 5.2.3)
- Arm B
    - Gemcitabine administration (see Section 5.7.3)
- The following activities will occur postdose:
    - Blood samples for PK assessment (Cycles 1 and 2 only; see Section 7.4, Section 7.5, and Table 12)

6.3.3. Day 15 (±1 day) Cycles 1 and 2 only

The following activities will occur:

- Serum chemistry panel (Cycles 1 and 2 only, unless clinically indicated)
- CBC with differential (Cycles 1 and 2 only, unless clinically indicated)

6.3.4. Response Assessments

Scans should be conducted on the following schedule until progressive disease (BICR-confirmed progressive disease), consent withdrawal, death, or study closure.

- CT scans with contrast (unless contraindicated; see Section 7.3 and Appendix C) every 9 weeks (±1 week) timed from randomization until 18 months after randomization, then every 12 weeks (±1 week) thereafter.

  Objective responses will be confirmed per RECIST v1.1 (Appendix J) with repeat scans done at the next scheduled response assessment per protocol after first documentation of response. Subsequent response assessments should be performed every 9 weeks (±1 week) until 18 months after randomization, regardless of dose interruptions, then every 12 weeks (±1 week) thereafter. Tumor imaging should also be performed, and BICR evaluation triggered, whenever disease progression is suspected.
- Brain scan (MRI with gadolinium preferred; if contraindicated, see Appendix C), will be conducted every 9 weeks (±1 week) timed from randomization until 18 months after randomization, then every 12 weeks (±1 week) thereafter, and as clinically indicated in subjects with a history of CNS metastasis or signs/symptoms of CNS metastasis
- Bone scan will be conducted 9 weeks (±1 week), timed from randomization until 18 months after randomization, then every 12 weeks (±1 week) thereafter, and as

clinically indicated in subjects with a history of skeletal metastasis or suspicion of skeletal metastasis based on imaging or symptoms.

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

End of treatment 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. If EOT evaluations are completed before 30 days after the last study treatment, the subject will be contacted 30 to 37 days following the last treatment to assess for AEs.

- Physical examination (including weight)
- ECOG performance status (Appendix B)
- Serum chemistry panel
- CBC with differential
- Serum or urine β-hCG pregnancy test (only subjects of childbearing potential)
- CT scan with contrast (unless contraindicated; see Section 7.3 and Appendix C). Not required if previous scan conducted <4 weeks prior to EOT
- Brain scan (in subjects with a history of CNS metastasis or signs/symptoms of CNS metastasis. MRI with gadolinium, unless contraindicated; see Appendix C)
- Bone imaging (in subjects with a history of skeletal metastasis or suspicion of skeletal metastasis based on imaging or symptoms)
- Blood samples for PK and immunogenicity anti-therapeutic antibodies (ATAs) assessments (see Section 7.4, and Table 12)
- Blood samples for biomarker assessments (see Section 7.5)
- Urine samples for biomarker assessments (see Section 7.5)

6.5. Follow-up (Every 9 Weeks [±1 week])

The assessments listed below will be done every 9 weeks (±1 week) from the date of randomization until 18 months after randomization, then every 12 weeks (±1 week) until BICR-confirmed progressive disease per RECIST v1.1 (Appendix J), subject death, study closure, or withdrawal of consent, whichever occurs first.

- Physical exam – may be discontinued at initiation of subsequent anticancer therapy
- ECOG performance status (Appendix B) – may be discontinued at initiation of subsequent anticancer therapy
- CT scan with contrast preferred (if contraindicated, see Section 7.3 and Appendix C). Repeat scans at the next scheduled response assessment per protocol after first documentation of response. For confirmation of disease progression, repeat scans at 4 to 9 weeks.

- Brain scans (MRI with gadolinium preferred; if contraindicated, see Appendix C) should be conducted in subjects with a history of CNS metastasis or signs/symptoms of CNS metastasis.
- Bone imaging should also be repeated at this time point in subjects with a history of skeletal metastasis or suspicion of skeletal metastasis based on imaging or symptoms.
- QOL, pain, and HRU assessments will be conducted according to the schedule in Table 13.

6.6. Survival Follow-up (Every 12 weeks [±1 week])

All randomized subjects will be contacted every 12 weeks (±1 week) after EOT or 12 weeks (±1 week) from last study visit, whichever is later, for survival status and collection of subsequent anticancer therapy information until death, study closure, lost to follow-up, or withdrawal of consent, whichever occurs first. QOL, pain, and HRU assessments will be conducted according to the schedule in Table 13

6.7. Subject End of Study/End of Follow-up

All randomized subjects will remain on study until death, study closure, lost to follow-up, or withdrawal of consent, whichever occurs first. The date the subject met criteria for study discontinuation and the reason for study discontinuation will be recorded. For subjects who are lost to follow-up or withdraw consent from study participation, data for OS will be collected from public records as allowed per local regulations.

7. STUDY ASSESSMENTS

7.1. Screening/Baseline Assessments

Only subjects who meet all inclusion and exclusion criteria specified in Section 4 will be enrolled in this study.

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

Acquisition of a new tumor biopsy tissue or collection of an archived tumor specimen, an ophthalmologic examination (see Appendix A), brain scan (MRI with gadolinium contrast preferred; see Appendix C for preferred imaging methods), bone scan, CT scan with contrast (preferred; see Appendix C for preferred imaging methods) for baseline tumor imaging, INR/PT/PTT, urinalysis (with reflexive microscopy, if abnormal), HbA1c, amylase, lipase, and thyroid function tests are required for all subjects at screening. A pregnancy test (either urine or serum, for females of childbearing potential), physical examination (including weight), collection of height, vital signs, CBC with differential, serum chemistry panel, CrCl (see Section 7.8.4), ECOG performance status assessment, and ECG are required at baseline.

7.2. Randomization

Randomization will occur at Day –3 to 1, prior to the first dose of study drug.

7.3. Response/Efficacy Assessments

CT scans with contrast (unless contraindicated), including chest, abdomen, and pelvis at the minimum, will be used to assess antitumor activity at protocol-specified time points. Subjects must receive the same imaging method throughout the study for response assessments. For subjects who cannot receive CT scans with contrast, MRI may be used as long as it will continue to be used for all disease assessments. Bone imaging and/or brain scans should be repeated at disease assessment time points, and as clinically indicated throughout the study, in subjects with a history of skeletal metastasis or suspicion of skeletal metastasis based on imaging or symptoms, or a history of CNS metastasis or signs/symptoms of CNS metastasis. Other regions should be scanned if the subject has known disease or new symptoms suggestive of disease in that region.

Objective responses will be assessed according to RECIST v1.1 (Eisenhauer 2009) (Appendix J) by BICR. Response assessments should be performed every 9 weeks (±1 week) timed from the randomization date until 18 months after randomization, then every 12 weeks (±1 week) thereafter. Tumor imaging should also be performed, and BICR evaluation triggered, whenever disease progression is suspected. Objective responses will also be assessed according to iRECIST per investigator assessment for all subjects in Arm A.

Treatment beyond disease progression per RECIST v1.1 may be considered for subjects in study Arm A who are deriving clinical benefit as defined in Section 5.8. Subjects treated beyond disease progression per RECIST v1.1 may continue until confirmed disease progression per iRECIST (Seymour 2017) (Appendix K) as assessed by the investigator. Confirmatory scans must be performed 4 to 9 weeks after disease progression per RECIST v1.1 by BICR (see Table 11).

Table 11: Imaging and treatment after first radiologic evidence of progressive disease

	Clinically Stable	
	Imaging	Treatment
First radiologic evidence of PD by RECIST v1.1 per BICR	Repeat imaging at 4 to 9 weeks to confirm PD.	May continue study intervention after the subject's consent and at the investigator's discretion while awaiting confirmed PD by iRECIST per investigator assessment.
Repeat tumor imaging confirms PD (iCPD) by iRECIST per investigator assessment.	No additional imaging required.	Discontinue treatment

Repeat tumor imaging shows iUPD by iRECIST per investigator assessment.	Repeat imaging at next regularly scheduled imaging visit. If this scan is within 4 weeks of the next scheduled timepoint, it can be used to satisfy both imaging timepoints.	Continue study intervention at the investigator's discretion.
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study intervention at the investigator's discretion.

iCPD=iRECIST confirmed progressive disease; iCR=iRECIST complete response; iPR=iRECIST partial response; iRECIST=modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD=iRECIST stable disease; iUPD=iRECIST unconfirmed progressive disease; PD=progressive disease
Note: If progression has been centrally verified, further management is by the site, based on iRECIST. Any further imaging should still be submitted to the CRO, but no expedited review will occur.

In the event disease progression is suspected by the investigator, the images must be transferred to the Imaging Contract Research Organization (CRO) for expedited BICR. The investigator seeking an expedited review should indicate this request to the Imaging CRO on a designated form. In all instances, the process at the Imaging CRO will ensure that the BICR remains blinded to the results of the local assessment and to the nature of the review. The result of the BICR will be communicated directly to the trial site.

Every effort should be made to continue the subject on study treatment during the BICR period, as long as it is clinically acceptable. If the BICR verifies disease progression, the subject must permanently discontinue study treatment unless they are eligible per the criteria in Section 5.8 for treatment beyond disease progression per iRECIST.

If the BICR does not verify disease progression, every effort must be made to continue study treatment, as long as it is clinically acceptable. Subjects should continue on-trial radiological evaluation.

Subjects who discontinue study treatment for reasons other than radiographically-confirmed disease progression per BICR or consent withdrawal will continue to receive CT scans with contrast (unless contraindicated) every 9 weeks (±1 week) for the first 18 months timed from the randomization date, then every 12 weeks (±1 week) until the subject has BICR-confirmed disease progression per RECIST v1.1, dies, the study closes, or the subject withdraws consent, whichever occurs first. For subjects that initiate subsequent anticancer therapy prior to disease progression per BICR, response assessment should be continued and submitted until BICR confirmed disease progression. Sites should contact the medical monitor prior to discontinuing study disease assessments and/or initiating subsequent anti-cancer therapy.

Survival status and information on subsequent anticancer therapy will be updated every 12 weeks (±1 week) until death, withdrawal of consent, lost to follow-up, or study closure, whichever occurs first.

Subjects' clinical data must be available for CRF source verification. Copies of tumor images must be made available for review by the sponsor (or its designee), upon request.

7.4. Pharmacokinetic and Immunogenicity Assessments

Blood samples for PK and ATA will be collected for Arm A only, per the sample collection schedule provided in Table 12. Validated or qualified assays will be used to measure the concentrations of enfortumab vedotin and MMAE in serum or plasma. A validated assay will be used to determine the levels of ATA for enfortumab vedotin in serum. PK and ATA samples for pembrolizumab will be collected. Determination of serum levels for pembrolizumab concentrations and pembrolizumab ATA will be performed only if required.

If at some point prospective PK blood sample collection is no longer required, sites will be notified. Refer to the Central Laboratory Manual for information on collection, processing, storage, and shipment of samples.

7.5. Biomarker Studies

To identify markers of sensitivity, resistance, and possible AEs, samples for biomarker analyses will be collected at protocol-specified time points (see Table 12). All subjects must provide pre-treatment tumor non-decalcified tissue collected by core needle biopsy or excision for biomarker analysis (fine needle aspirate is not acceptable). Archived tumor tissue, not previously irradiated, should be collected after completion of the most recent prior systemic therapy, ideally within 12 months prior to enrollment, if possible. If adequate archival tumor samples are not available, a fresh biopsy may be performed. A formalin-fixed, paraffin embedded (FFPE) tumor block is preferred.

To understand the relationship between the biological characteristics of tumors before treatment and subject outcomes, tumor tissue from pre-treatment biopsies will be examined. Subjects will be stratified prior to randomization according to PD-L1 status (PD-L1 high: CPS ≥10 and PD-L1 low: CPS <10 based on Dako/Agilent PD-L1 IHC 22C3 PharmDx). Exploratory biomarker assessments on pre-treatment tumor tissue may include, but are not limited to, Nectin-4 expression, assessment of tumor subtyping, tumor microenvironment, and mutations associated with response to enfortumab vedotin in metastatic UC. Biomarkers from serially collected peripheral blood and urine may include, but are not limited to, cell -free tumor DNA, cytokines, and T-cell clonality analyses as markers of tumor response or resistance. Methods of analysis may include, but are not limited to, IHC, next-generation sequencing of DNA and RNA, and immunoassays. These assessments will be compared to similar assessments conducted in enfortumab vedotin monotherapy trials and may provide insight into treatment-related changes.

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

Table 12: Pharmacokinetic, immunogenicity, and biomarker sample collection time points

	Study Day	Time	Window	Relative Time	Pharmacokinetics and Immunogenicity **(Arm A only)**				Blood Biomarkers (All arms)		Urine Biomarkers (All arms)	Tissue Biomarkers (All arms)
					EV PK	Pembro PK	ATA EV	ATA Pembro	Serum	Plasma	Urine	Tumor Tissue
Screening	Days –42 to RND	N/A	N/A	N/A								X
Cycles 1 and 2	Day 1	Predose	Within 4 h	Start of EV, gemcitabine or platinum infusion	X	X[A]	X	X	X	X	X[A]	
		End of EV IV infusion	Within 15 min	End of EV infusion	X							
		End of Pembro IV infusion	Within 15 min	End of Pembro infusion		X[A]						
	Day 8	Predose	Within 4 h	Start of EV infusion	X							
		End of EV IV infusion	Within 15 min	End of EV infusion	X							
Cycle 3 and every odd-numbered cycle thereafter	Day 1	Predose	Within 24 h	Start of EV, gemcitabine or platinum infusion	X[C]	X[C]	X[C]	X[C]	X[B]	X[B]	X[B]	
End of Treatment (within 30–37 days of last dose)				N/A	X	X	X	X	X	X	X	

RND=randomization.
A Cycle 1 only.
B Cycle 3 and 5.
C Up to Cycle 9 only.

7.6. Biospecimen Repository

In the US only, for subjects who provide additional consent, remaining de-identified unused blood and/or tissue and/or urine will be retained by Seagen 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 of ADCs. Blood, urine, 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 after the study has been completed and all applicable regulatory obligations have been met.

7.7. Electronic Patient-Reported Outcomes (ePRO)

Electronic PRO assessments will include the EuroQOL 5-dimensions (EQ-5D-5L), EORTC Quality of Life Core 30 (QLQ-C30), Brief Pain Inventory – Short Form (BPI-SF), and HRU questionnaires. Electronic PROs will be administered per the schedule outlined in Table 13.

Table 13: Electronic Patient-Reported Outcomes Schedule of Events

	ePRO Assessment Timepoints				
Questionnaires[a]	Week 0	Week 1	Weeks 2[b] to 12	Week 14	Week 17+
Time Interval	Day 1	+3 to 4 days from Week 0	Weekly	Once	Every 3 weeks[c]
EuroQOL 5-dimensions	X	X	X	X	X
Brief Pain Inventory – Short Form	X	X	X	X	X
EORTC Quality of Life Core 30	X	X	X	X	X
Healthcare Resource Utilization	X	X	X	X	X

EORTC=European Organisation for Research and Treatment of Cancer; ePRO=electronic patient-reported outcome; QOL=quality of life.
a If study procedures/assessments are performed on ePRO completion day, questionnaires should be done first.
b Week 2 questionnaires are completed on Days 11 to 12.
c Through disease progression and survival follow-up.

Questionnaires will be completed by the subject on an electronic device. On Cycle 1 Day 1, subjects will complete the questionnaires in the clinic up to 24 hours prior to the first dose of study treatment and before any study procedures/assessments are conducted. After Cycle 1 Day 1, questionnaires will be completed at home several days prior to a clinic visit. Subjects will be provided with digital support (eg, instruction) to fill in the questionnaires at home in between clinic visits, with the exception of Cycle 1 Day 1. The ePRO device will notify subjects to complete the questionnaires at the appropriate time points. This will ensure that data are collected in between study treatments.

The information completed by the subject on the electronic device will be automatically uploaded into a central website. The investigator or site designee will closely monitor the questionnaire data on the website for each subject during study treatment and the follow up

period and address any compliance issues that may arise. If a subject does not complete the questionnaires per protocol, the investigator or site designee should document the event as a protocol deviation.

The investigator or site designee, and site personnel will be trained on how to provide support to each subject on the use of the ePRO device. Refer to the ePRO site user guide for additional information on the questionnaire schedule and ePRO device operation.

7.7.1. EORTC Core Quality of Life (QLQ-C-30) Questionnaire

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 symptoms scales (fatigue, pain, nausea and 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)

Each domain is scored from 0 to 100. For the global health status/QOL and functional domain scores, higher scores represent better QOL and functioning, respectively. For symptom scales, higher scores represent greater symptomatology (see Appendix F).

7.7.2. EuroQOL-5 Dimensions (EQ-5D-5L)

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. Responses to the 5 items are then converted to a weighted health state index (utility score) based on values derived from general population samples (Herdman 2011). The health utility score is between 0 and 1, where 0 is death and 1 is perfect health. In addition to the utility score, this questionnaire also records the respondent's self-rated health status on a vertical graduated (0 to 100) visual analogue scale (VAS) (See Appendix G).

7.7.3. Brief Pain Inventory – Short Form (BPI-SF)

The BPI-SF is a validated PRO designed to assess the severity of pain and its impact on functioning specifically in the clinical trial setting (Cleeland 1994; Atkinson 2011). The BPI-SF measures worst, least, and average pain experienced in the last 24 hours, the location of the pain and the medications used for treatment of the pain. Additionally, it also asks questions about the interference due to pain in general activity, mood, walking, normal work, relationships, sleep and enjoyment of life. The pain severity and interference questions are answered on a 10-point Likert

scale and scoring is calculated using arithmetic mean of the four severity items to provide measurement of the pain severity and the arithmetic mean of the seven interference items to measure of pain interference. Individual scores for each severity item as well as each interference item can also be done. Higher scores are associated with higher pain levels (Cleeland 2009) (Appendix H).

7.7.4. Health Resource Utilization

HRU information will be collected using a questionnaire designed to collect data from the subject perspective summarizing unplanned use of health resources outside of the clinical trial (Appendix I).

7.8. 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, vital signs, protocol-specified laboratory tests, ECOG status, ECGs, ophthalmologic examination findings and pregnancy testing.

Safety will be monitored over the course of the study by an IDMC.

7.8.1. Adverse Events

7.8.1.1. 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 312.32, Investigational New Drug (IND) Safety Reporting, an AE is any untoward medical occurrence in a subject 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 (during and post-dose) through the end of the safety reporting period (see Section 7.8.1.3). Complications that occur in association with any procedure (eg, 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 (eg, 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 subject 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. Hospitalizations or prolonged hospitalizations for scheduled therapy of the underlying cancer or study target disease need not be captured as SAEs.
Disabling/ incapacitating:	An AE that resulted in a persistent or significant incapacity or substantial disruption of the subject's ability to conduct normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a subject 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 subject 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. Potential drug-induced liver injury (DILI) also is considered a medically significant event (see Section 7.8.1.2 for the definition of potential DILI.)

Adverse Event Severity

AE severity should be graded using the NCI CTCAE, version 4.03.

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, pembrolizumab, and/or cisplatin or carboplatin, and gemcitabine and cisplatin or carboplatin 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 (eg, 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 (eg, tendon rupture)
Unrelated:	Another cause of the AE is more plausible (eg, 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

7.8.1.2. Procedures for Eliciting and Recording Adverse Events

Investigator and study personnel will report all AEs and SAEs whether elicited during subject 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 AE.

Important exceptions for this study are adverse reactions associated with the infusion of study drug. For this study, adverse reactions associated with the infusion of study drugs must be recorded as a NCI CTCAE term, which includes IRR, or a more specific diagnosis if appropriate (ie, 'cytokine release syndrome,' 'acute infusion reaction,' or 'allergic or hypersensitivity reaction'). Each sign or symptom that occurs within a given infusion-related event (ie, chills, fever, rash) must also be recorded. Level of severity for both the overall IRR term and the individual signs and symptoms should be recorded.

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 Underlying Malignancy

Since progression of underlying malignancy is being assessed as an efficacy variable, it should not be reported as an AE or SAE. The terms "Disease Progression", "Progression of Disease", or "Malignant disease progression" and other similar terms should not be used to describe an AE or SAE. However, clinical symptoms of progression may be reported as AEs or SAEs if the symptom cannot be determined as exclusively due to progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study. In addition, complications from progression of the underlying malignancy should be reported as AEs or SAEs.

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 study subject who is able to father a child. Only report pregnancies that occur in a subject's partner if the estimated date of conception is after the subject's first study drug dose. Email or fax to the sponsor's Drug Safety Department within 48 hours of becoming aware of a pregnancy. As part of the study all pregnancies will be monitored for the full duration and 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 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 7.8.1.1) should be reported as SAEs.

Corneal Adverse Events

Corneal ulcer or keratitis AEs ≥ Grade 2 should be graded within their respective NCI CTCAE 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.

Diabetes and Hyperglycemia

Grading for diabetes should be based on the NCI CTCAE v4.03 event term of glucose intolerance. Grading for hyperglycemia should be based on the NCI CTCAE v4.03 event term of hyperglycemia.

Potential Drug-Induced Liver Injury

The observation of the critical importance of altered liver function has been referred to informally as Hy's Law (Reuben 2004). Hy's Law can be used to estimate severity and the likelihood that a study drug may cause an increased incidence of severe hepatotoxicity.

The absence of hepatotoxicity in clinical trials provides a limited predictive value for potential hepatotoxicity in the clinical setting(s) being studied. However, finding 1 Hy's Law case in clinical trials is ominous; finding 2 cases is highly predictive of a potential for severe DILI.

Definition

Briefly, potential Hy's Law cases include the following 3 components:

1. Aminotransferase (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) elevation >3x upper limit of normal (ULN)

AND

2. Total bilirubin >2x ULN, without initial findings of cholestasis (ie, elevated serum alkaline phosphatase),

AND

3. No other immediately apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Reporting Requirements

Any potential Hy's Law case should be handled as a serious adverse reaction associated with the use of the drug and reported promptly to the Sponsor on an SAE form.

Reporting should include all available information and should initiate close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

Follow-up for Abnormal Laboratory Results Suggesting Potential DILI

In general, an increase of serum ALT or AST to >3x ULN should be followed by repeat testing within 48 to 72 hours of serum ALT, AST, alkaline phosphatase, and total bilirubin, to confirm the abnormalities and to determine whether they are worsening.

Appropriate medical assessment should be initiated to investigate potential confounding factors and alternative causes of hepatotoxicity. During this investigation, consider withholding study drug.

7.8.1.3. Reporting Periods for Adverse Events and Serious Adverse Events

The safety reporting period for all AEs and SAEs (except SAEs related to pembrolizumab) 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. The reporting period for SAEs related to pembrolizumab is from study Day 1 (predose) through 90 days after the last study treatment, or 30 days following cessation of study treatment if the subject initiates a new anticancer therapy. 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 subject dies or withdraws consent. All non-serious AEs will be followed through the safety reporting period. Certain non-serious AEs of interest may be followed until resolution, return to baseline, or study closure (see Section 7.8.1.6).

7.8.1.4. 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:

- Subject number
- Date of event onset
- Description of the event
- Investigator's causality assessment
- Study treatment, if known

The completed SAE forms are to be emailed or faxed to the sponsor's Drug Safety Department within 24 hours (see email or fax number specified on the SAE report form), unless otherwise instructed on the Sponsor's SAE form.

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

7.8.1.5. Sponsor Reporting Requirements

The sponsor will handle and report suspected unexpected serious adverse reactions (SUSARs) according to relevant local legislation or regulation.

7.8.1.6. Adverse Events of Special Interest

Certain non-serious AESIs may be followed (including collection of relevant concomitant medications) until resolution, return to baseline, subject withdrawal, study closure, or the events become chronic to the extent that they are adequately characterized.

AESIs related to enfortumab vedotin or enfortumab vedotin in combination with pembrolizumab for this purpose include those events in the list below (*denotes that event must be Grade ≥2 or any grade resulting in a dose modification to be considered an AESI):

- Skin reactions
- Neuropathy (PN, Guillain-Barre)
- Corneal event or uveitis
- Hyperglycemia or Type 1 diabetes
- IRR
- Pneumonitis*
- Diarrhea* or colitis*
- Hepatitis* or AST/ALT increased* or bilirubin increased*
- Endocrinopathy* (defined as hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism)
- Nephritis or acute renal failure
- Myocarditis
- Pancreatitis
- Myasthenia gravis or syndrome
- Vasculitis
- Sclerosing cholangitis

AESIs should be promptly reported by electronic data capture (EDC). If an event is medically significant or meets serious criteria it should be reported as a serious event within 24 hours (see Section 7.8.1.4).

Adverse Events of Special Interest Requiring Immediate Reporting

For the time period beginning at Cycle 1, Day 1 through 30 days following the last study drug dose, any AESI listed below, or follow-up to an AESI, whether or not related to the sponsor's product, must be reported within 24 hours to the sponsor, either by electronic media or by paper. Electronic reporting procedures can be found in the EDC data entry guidelines.

AESIs for this purpose include:

- An overdose of sponsor's product, as defined in Section 5.10.7.1 (enfortumab vedotin) and Section 5.10.7.2 (pembrolizumab) that is not associated with clinical symptoms or abnormal laboratory results.

- Increased LFTs not otherwise explained by an underlying liver condition as defined in Appendix E. Additional recommendations for liver safety monitoring and assessment are also included in Appendix E.

7.8.2. Physical Examination

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

7.8.3. 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 AE or pre-existing condition.

7.8.4. Clinical Laboratory Tests

Samples will be drawn for local laboratory testing. Local lab results will be sent to a local laboratory data repository.

Local laboratory testing will include institutional standard tests for evaluating study eligibility, safety and making clinical decisions. If local laboratory testing for bicarbonate is not available, a central laboratory will perform the test. The following laboratory assessments will be performed by the local lab to evaluate safety at scheduled timepoints (see Appendix A) during the course of the study:

- The chemistry panel is to include the following tests: albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen, calcium, creatinine, chloride, lactate dehydrogenase, phosphorus, potassium, sodium, non-fasting glucose, and total bilirubin.
- Amylase and lipase
- 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.
- CrCl at baseline should be calculated via either Cockcroft-Gault, MDRD or 24-hour urine, per institutional standard. The same method to determine CrCl should be used consistently for a subject over the course of the study with the exception of carboplatin dose calculation where Cockcroft-Gault method should be used in all subjects.
- Thyroid function tests, including:
    - Triiodothyronine or free triiodothyronine
    - Free thyroxine

- Thyroid-stimulating hormone

- Standard urinalysis (with reflexive microscopy, if abnormal)
- INR/PT/PTT (at baseline and as clinically indicated thereafter)
- A serum or urine β-hCG pregnancy test for females of childbearing potential
- HbA1c. If HbA1c is elevated (≥6.5%), refer subject to appropriate provider during Cycle 1 for glucose management.

7.8.5. ECOG Status

ECOG performance status (Appendix B) will be evaluated at protocol-specified time points (see Appendix A).

7.8.6. Cardiac Monitoring

ECGs will be conducted at baseline. Routine 12-lead ECGs will be performed after the subject has been in a supine position for at least 5 minutes. For subjects with NYHA Class III Heart Failure (see Appendix D) or a history of coronary heart disease, arrhythmia or other significant heart disease, a transthoracic ECHO or MUGA scan with left ventricular ejection fraction is required.

7.8.7. Ophthalmologic Examination

Subjects will have a complete ophthalmologic examination at screening including, but not limited to, visual acuity, slit lamp, tonometry examination and dilated fundus examination. Subsequent ophthalmology assessments should be performed as clinically indicated throughout the study. EOT slit lamp examinations are required for subjects who experience corneal AEs during the study and must be performed ≥4 weeks from the last dose.

7.8.8. Pregnancy Testing

For subjects of childbearing potential, a serum or urine β-hCG pregnancy test with sensitivity of at least 25 mIU/mL will be performed at baseline, on Day 1 of every cycle, and at the EOT visit. A negative pregnancy result is required before the subject may receive study drug on Day 1 of each cycle. The pregnancy test may be performed within 1 day prior to administration of study drug. Pregnancy tests may also be repeated as requested per Institutional Review Board/Independent Ethics Committee (IRB/IEC) or if required by local regulations.

7.9. Post-treatment Assessments

7.9.1. Follow-up Assessments

Subjects who discontinue study treatment will receive physical exams and ECOG assessment. Physical exams and ECOG assessments may be discontinued for subjects that start a new anticancer therapy. Response assessments every 9 weeks (±1 week) for the first 18 months timed from the randomization date, and every 12 weeks (±1 week) thereafter. ePRO questionnaires (QLQ-C30, EQ-5D-5L, BPI-SF, HRU) will continue to be completed per the schedule outlined in Table 13 Scans are to be done until BICR confirmed progressive disease per RECIST v1.1 (Appendix J), subject death, study closure, or withdrawal of consent, whichever occurs first.

During study treatment, palliative radiotherapy on a nontarget bone lesion that is not progressing will not be considered a subsequent anticancer therapy; however, radiotherapy on any new or progressing lesion, per RECIST v1.1 as assessed by the investigator or after BICR-confirmed progression, will be considered a subsequent anticancer therapy and subjects will not be permitted to resume study treatment. Surgical resection for curative intent during study treatment may be permitted in subjects with favorable tumor response after discussion with the medical monitor.

7.9.2. Survival Follow-up Assessments

After discontinuation of study treatment, all randomized subjects will be contacted every 12 weeks (±1 week) to obtain information on subsequent anticancer therapy and survival status. ePRO questionnaires (QLQ-C30, EQ–5D-5L, BPI-SF, HRU) will continue to be completed per the schedule outlined in Table 13. Survival follow-up will continue until subject death, study closure, lost to follow-up, or withdrawal of consent, whichever occurs first.

7.10. 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 BICR-confirmed radiographically-confirmed objective response assessments as defined by RECIST v1.1 (Eisenhauer 2009) (Appendix J). Treatment decisions by the investigator will be based on investigator-assessed disease progression per RECIST v1.1 with BICR confirmation. RECIST 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. iRECIST guidelines are newly published criteria that will be applied as exploratory criteria for this study in cohorts that utilize pembrolizumab. These guidelines allow consideration that immunotherapeutics, such as pembrolizumab, may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. The guidelines are identical to those of RECIST v1.1 in many respects but have been adapted to account for instances where an increase in tumor burden, or the appearance of new lesions, does not reflect true tumor progression (Seymour 2017) (Appendix K).

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

PK 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 pre-treatment tumor tissue are similarly common. Peripheral blood, urine and tissue 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 subjects at the site, Seagen 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/package insert
- Recording and reporting AEs and SAEs
- Enrollment goals and study timelines
- The CRF completion process and source documentation requirements
- Use of the ePRO device
- Monitoring requirements
- 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
- Subject coding and randomization
- Study samples/specimen collection, handling and shipping
- Protocol compliance
- Clinical study 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 Seagen representative will typically 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 subjects 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 Seagen or its designated monitors and by quality assurance auditors, or representatives of regulatory authorities.

8.2. Data Management Procedures

Seagen 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 subject confidentiality are to be employed during monitoring. The CRFs and related source documents will typically 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 the 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 during monitoring visits to the study centers and/or by centralized monitoring. Any discrepancies will be resolved with the investigator or designees as appropriate.

8.5. Quality Assurance Procedures

The Research and Development Quality group or its designee may conduct audits at the clinical site or other study-related facilities and organizations. Audit reports will be retained by the Research and Development Quality group of Seagen 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 EDC 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 subject records) for the maximum period required by the country and institution in which the study will be conducted, or for the period specified by Seagen, whichever is longer. The investigator must contact Seagen 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 to Seagen.

9. DATA ANALYSIS METHODS

9.1. Determination of Sample Size

Approximately 860 subjects will be randomized in a 1:1 ratio to one of the study arms. Control arm assumptions are based on recent trials: EORTC 30987, which tested gemcitabine + cisplatin (Bellmunt 2012), EORTC 30986, which tested gemcitabine + carboplatin (De Santis 2012), CALGB 90601 which included gemcitabine + cisplatin + placebo (Rosenberg 2019a) and IMvigor130 which included gemcitabine + cisplatin or carboplatin + placebo (Galsky 2020). Median PFS for the EORTC trials gemcitabine + platinum-containing control arms was 7.6 and 5.8 months, respectively, and corresponding median OS was 12.7 months and 9.3 months. In the CALGB 90601 trial, the gemcitabine + cisplatin reference arm achieved a median PFS of 6.6 months and median OS of 14.3 months. In IMvigor130, median PFS for the control arm was 6.3 months and median OS was 13.4 months. Notably, the proportion of carboplatin-treated subjects approached 70% due to an initial study design which only enrolled cisplatin-ineligible subjects. In the JAVELIN Bladder 100 trial, median OS was 21.4 months for the avelumab arm and 14.3 months for the control arm (best supportive care alone) (BAVENCIO® US Prescribing Information, EMD Serono, Nov 2020).

PFS and OS assumptions for the control arm for the currently proposed trial were calculated utilizing a weighted average (anticipating 60% cisplatin-eligible/40% carboplatin-eligible enrollment). Thus, median OS and PFS assumptions for the control arm of the current trial were adjusted for expected improvement in survival outcomes in the contemporary era; the current trial assumes a control arm median PFS of 7 months and median OS of 15.3 months accounting for subjects receiving maintenance therapy.

This sample size of 430 subjects per arm is determined by providing a sufficient power in OS superiority test between Arms A and B. More specifically, with 430 subjects per arm, approximately 489 OS events are required to provide 93% power to demonstrate superiority at a two-sided alpha of 4.5% without alpha roll-over with 1 IA around 72.8% information fraction under the following assumptions:

1. OS curves follow piecewise exponential distribution with a reduced hazard rate (50% of the initial rate) starting from 24 months;

2. hazard ratio (HR) of OS is 0.73 between the experimental and control arms;
3. median OS for the control arm is 15.3 months;
4. an enrollment period of 30 months;
5. a yearly dropout rate of 5%.

[redacted]

With 430 subjects per arm, the number of PFS events in total is estimated to be 526 events, providing 90% power to demonstrate superiority at a two-sided alpha of 0.5% without alpha roll-over based on the following assumptions:

1. PFS curves follow piecewise exponential distribution with a reduced hazard rate (20% of the initial rate) starting from 15 months;
2. HR of PFS is 0.70 between the experimental and control arms;
3. median PFS for the control arm is 7 months;
4. an enrollment period of 30 months;
5. a yearly dropout rate of 5%.

9.1.1. China Portion of the Study

To evaluate the consistency of efficacy and safety in a China subpopulation compared with the global population, after completion of enrollment in the global portion, subjects in China may continue to be randomized in a 1:1 ratio to either the experimental arm or the control arm until the planned sample size of approximately 130 subjects in China is reached, including those randomized in the global portion and China portion. Subjects in China randomized after completion of enrollment in the global portion will not be included in the analysis of the global portion. Subjects enrolled in China will be analyzed separately for efficacy and safety (Section 9.3.1.7). Details of analysis of the China portion of the study will be provided in the statistical analysis plan (SAP).

9.2. Study Efficacy Endpoint Definitions

PFS per BICR and OS are the dual primary endpoints for the study. See Section 2 for a complete list of endpoints.

9.2.1. Progression-Free Survival Per BICR

PFS per BICR is defined as the time from randomization to first documentation of disease progression per RECIST v1.1 by BICR, or to death due to any cause, whichever comes first.

If a subject has neither progressed nor died, the subject will be censored at the date of last radiological assessment. Subjects who receive new anticancer therapy (excluding maintenance therapy [eg, avelumab] following first-line platinum-containing chemotherapy) for locally advanced or metastatic UC before disease progression will be censored at the date of the last radiological assessment before the anticancer therapy started. Subjects lacking radiological assessment data beyond the day of randomization will be censored at the day of randomization.

Details of the censoring scheme for the primary analysis of PFS are described in the SAP.

9.2.2. Overall Survival

OS is defined as the time from date of randomization to date of death due to any cause. In the absence of confirmation of death, survival time will be censored at the last date the subject is known to be alive.

9.2.3. Objective Response Rate

ORR is defined as the proportion of subjects with confirmed CR or PR according to RECIST v1.1 (Eisenhauer 2009) (Appendix J). Subjects who do not have at least 2 (initial response and confirmation scan) post-baseline response assessments will be counted as non-responders for the primary analysis of ORR. The definition of confirmed CR and PR will be specified in the SAP. ORR per investigator and per BICR will be analyzed.

9.2.4. Disease Control Rate

DCR is defined as the proportion of subjects with confirmed CR, PR, or SD according to RECIST v1.1 (Eisenhauer 2009) (Appendix J). The definition of confirmed CR and PR will be specified in the SAP. DCR per investigator and per BICR will be analyzed.

9.2.5. Duration of Response

DOR is defined as the time from first documented response of CR or PR (that is subsequently confirmed) to the first documented disease progression per RECIST v1.1 (Eisenhauer 2009) (Appendix J), or to death due to any cause, whichever comes first. DOR will only be calculated for the subjects achieving a confirmed CR or PR. DOR per investigator and per BICR will be analyzed.

9.2.6. Progression-Free Survival Per Investigator Assessment

PFS, per investigator assessment, is defined as the time from randomization to first documentation of disease progression per RECIST v1.1 (Eisenhauer 2009) (Appendix J), or to death due to any cause, whichever comes first.

The same censoring rules outlined in Section 9.2.1 for PFS per BICR will be applied to PFS per investigator.

9.3. Statistical and Analytical Plans

The statistical and analytical plans are presented below. Additional analysis details of the global portion and China population will be provided in the SAP. A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters site conduct (eg, adding baseline assessments to define a subgroup). Changes in the SAP related to primary or secondary endpoints after the study has begun, but prior to database lock for primary analysis will be documented in a SAP amendment and will be described and justified in the clinical study report.

9.3.1. General Considerations

Overall, descriptive statistics will be used to summarize continuous data (eg, number of subjects, mean, standard deviation, median, minimum and maximum). Categorical data will be summarized using frequency and percentage.

Tabular summaries will be presented by treatment arm unless otherwise specified.

9.3.1.1. Randomization and Blinding

Subjects will be randomized in a 1:1 ratio to one of the treatment arms based on the following stratification factors: cisplatin eligibility (eligible or ineligible), PD-L1 expression (high or low), and liver metastases (present or absent).

Although this is an open-label study, to maintain trial integrity, until database lock and study unblinding for the pre-planned analyses, analyses or summaries by treatment assignment are only planned for the purpose of the IDMC monitoring and will be conducted by an external vendor. In addition, the primary endpoint of PFS by BICR will be based on assessment of radiological scans by BICR without knowledge of treatment assignment. Additional details will be provided in a separate document.

9.3.1.2. Adjustments for Covariates

The randomization scheme will include the following stratification factors: Cisplatin eligibility (eligible or ineligible), PD-L1 expression (high or low), and Liver metastases (present or absent). These stratification factors used for randomization will be included in both the stratified log-rank test and the stratified Cox proportional hazards model for the analyses of the primary endpoints of PFS and OS.

9.3.1.3. Handling of Dropouts and Missing Data

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

9.3.1.4. Multicenter Studies

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

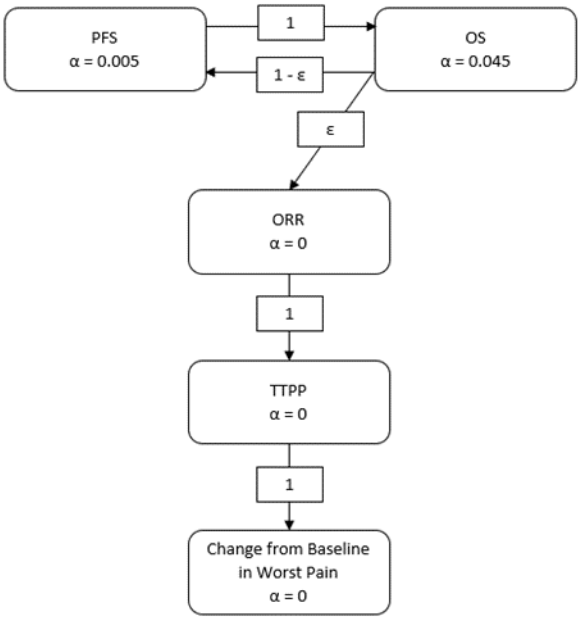
9.3.1.5. Multiple Comparisons and Multiplicity

The proposed 2-arm study will have dual primary endpoints of PFS and OS. The study can be considered positive if enfortumab vedotin plus pembrolizumab (Arm A) is superior to the control arm (Arm B) in either PFS or OS. A graphical approach with group sequential testing outlined in Maurer and Bretz (Maurer 2013) will be used to strongly control the family-wise type I error rate at a two-sided 5% level.

The initial alpha allocation for each test with lines connecting between hypotheses: 4.5% and 0.5% two-sided alpha for comparisons between Arm A and Arm B in OS and PFS, respectively, as shown in Figure 2. These are also the alpha values used for sample size and power planning. The updated graph and rejection boundaries will be derived using the algorithm outlined in Maurer and Bretz (Maurer 2013). O'Brien-Fleming boundaries will be used to calculate the

rejection boundaries based on the actual information fraction observed for OS data. As an example, if the null hypothesis for PFS is rejected, the 0.5% alpha of PFS will be passed to OS. Thus, OS can be re-tested using a 2-sided alpha of 5%. The rejection boundaries of OS IA and final analysis (FA) will be re-calculated based on 5% alpha and actual information fraction using the O'Brien-Fleming function.

Figure 2: Initial graph of multiplicity adjustment (2-sided FWER=5%)



ε is a positive number close to zero, indicating the potential to pass alpha to ORR only if both PFS and OS are statistically significant.
FWER=family-wise error rate

When the null hypotheses for PFS and OS are both rejected, selected secondary endpoints will be tested in the following order using a gatekeeping testing strategy:

1. ORR by BICR
2. Time to pain progression (TTPP)
3. Mean change from baseline in worst pain at Week 26

Each test will be at the 5% significance level (2-sided) as long as all preceding null hypotheses are rejected. These secondary endpoints will only be tested once at either the OS interim or final analysis after the null hypotheses for PFS and OS are both rejected, and the test statistics for inferential testing will be computed from the data at the time of OS IA. In the event that only the null hypothesis for PFS is rejected and the superiority boundary for OS has not been crossed at the time of OS IA, these secondary endpoints will not be tested and will only be analyzed descriptively.

9.3.1.6. Data Transformations and Derivations

Time variables based on 2 dates (eg, start date and end date) will be calculated as (end date – start date +1 [in days]) unless otherwise specified.

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

9.3.1.7. Analysis Sets

All subjects who are randomized will be included in the intent-to-treat (ITT) analysis set. Subjects will be included in the treatment group assigned at randomization regardless of the actual treatment received. The primary analysis of the efficacy endpoints of OS and PFS will be based on the ITT analysis set. Demographic and baseline characteristics will be summarized for the ITT analysis set.

The response evaluable set will include all randomized subjects who have measurable disease per RECIST v1.1 at baseline. Subjects will be analyzed according to the treatment arm assigned at randomization regardless of the actual treatment received. The response evaluable set will be used for primary analysis of response related endpoints, eg, ORR, DCR, and DOR.

The safety analysis set will include all randomized subjects who received at least 1 dose of investigational product (or any component of combination therapy). Subjects will be evaluated by the treatment actually received. Treatment exposure and AE will be summarized in the safety analysis set.

The PRO FAS will include all randomized subjects who have received at least 1 dose of investigational product (or any component of combination therapy) and have completed at least 1 PRO assessment at baseline. Subjects will be analyzed according to the treatment arm assigned at randomization. The PRO FAS will be used for PRO analyses, unless otherwise specified.

Subjects in China who are randomized in the China portion will not be included in the analysis population for the global portion. The China ITT population, including all subjects in China randomized in both the global portion and the China portion, will be analyzed in the China-specific efficacy analyses. The China safety analysis set, including all randomized subjects in China (from both the global portion and the China portion) who receive at least 1 dose of investigational product (or any component of combination therapy) will be analyzed in the China-specific safety analyses.

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

9.3.1.8. Examination of Subgroups

As exploratory analyses, subgroup analyses may be conducted for selected endpoints. Subgroup analyses will include an analysis of OS, PFS, and ORR by PD-L1 status at baseline (low or high). Detailed methodology for all subgroups analyses will be provided in the SAP.

9.3.1.9. Interim Analysis

A single planned analysis (FA) for PFS will take place when approximately 526 PFS events or 356 OS events (72.8% information fraction) in the ITT analysis set have occurred, whichever is later.

Two analyses are planned for OS. OS IA is planned at the time of the final PFS analysis. At IA, the OS events in total will be approximately 356 (about 72.8% of information). O'Brien-Fleming boundaries will be used to calculate the rejection boundaries based on the actual information fraction observed. [redacted]

Estimated analyses timing and the rejection boundaries at the planned PFS and OS analyses are presented in Table 14. The results are based on the initial alpha allocated to each hypothesis before any alpha recycling. O'Brien-Fleming boundaries will be used to calculate the rejection boundaries for the interim and final OS analyses based on the actual number of deaths observed in the study.

Table 14: Summary of timing of analyses and estimated rejection boundaries

Analysis		2-sided α^d	Est. Time after Enrollment Completion	Planned # of Events	p-value (2-sided) at Boundary	Approx. Obs. HR at Boundary	Planned Power
Analysis Time 1[a]	FA: PFS	0.5%	7 months	526	0.005	0.783	90%
	IA: OS	1.5%	7 months	356 (72.8% info.)	0.015	0.773	70%[b]
Analysis Time 2	FA: OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

a Analysis Time 1 is triggered by the planned number of PFS events in total (526 events) or 356 OS events (72.8% information fraction), whichever is later.
b Probability to cross the efficacy boundary at the interim analysis
c Overall power at the final OS analysis
d Cumulative alpha assigned for each test without alpha roll-over. For OS IA, 1.5% is the estimated alpha spent at IA.

9.3.2. Subject Disposition

Subject enrollment and disposition will be summarized by each treatment arm and also by total. The number and percentage of subjects who discontinue study treatment and subjects who withdraw from the study will be summarized with reason for discontinuation or withdrawal. The number of subjects who signed informed consent and the number of subjects in each analysis set will be summarized by treatment group and total.

9.3.3. Subject Characteristics

Demographics and other baseline characteristics will be summarized by treatment arm and by total with counts and percentages for categorical variables and with summary statistics for continuous variable. Details will be provided in the SAP.

9.3.4. Efficacy Analyses

The primary analysis of efficacy endpoints of OS and PFS will be analyzed using the ITT analysis set. ORR, DCR, and DOR will be analyzed using the response evaluable set.

For the primary endpoints of OS and PFS, a log-rank test stratified by randomization stratification factors will be used to compare the experimental arm to the control arm. The estimated HR and corresponding 95% CI from the stratified Cox proportional hazards regression model will also be presented. The median survival will be estimated using the Kaplan-Meier

(KM) method and will be reported along with estimated KM curves and the corresponding 95% CI by treatment arm. Similar estimation methods will be used for the other time-to-event endpoints. DOR will be summarized descriptively by Kaplan-Meier methods for subjects with a confirmed response (complete response or partial response per RECIST v1.1 [Appendix J]).

ORR and disease control rate will be estimated for each treatment arm based on the response evaluable set based on the response evaluable set. Additionally, p-value between treatment arms using the Cochran Mantel-Haenszel test, controlling for randomization stratification factors will be provided.

Due to the limited sample size of subjects receiving enfortumab vedotin + platinum + pembrolizumab, only a listing of efficacy data will be provided for subjects randomized to this treatment arm. Additional sensitivity analyses for the efficacy endpoints and the exploratory analysis per iRECIST (Appendix K) will be specified in the SAP.

9.3.5. Pharmacokinetic and Immunogenicity Analyses

Descriptive statistics will be provided for antibody drug-conjugate and unconjugated drug (MMAE) concentrations in the experimental arm at each PK sampling time point. Any additional PK and PK/pharmacodynamic analyses may be described in a separate analysis plan and presented in a separate report. The incidence of ATA will be summarized.

Pembrolizumab PK and immunogenicity analysis will be performed only if required. If pembrolizumab analysis are performed, the PK and immunogenicity results will be presented in a separate report.

9.3.6. Biomarker Analyses

Relationships of biomarker parameters (eg, baseline values, absolute and relative changes from baseline) to efficacy, safety, and PK may be explored. Relationships and associated data that are determined to be of interest will be summarized. Details will be described separately.

9.3.7. Patient-Reported Outcomes Analyses

Descriptive analyses for EORTC QLQ-C30, EQ-5D-5L, and BPI-SF will be performed on the PRO FAS. Compliance and completion rate will be summarized for each scheduled assessment by treatment arm using the ITT analysis set for Arm A and Arm B.

PRO-based secondary endpoints TTPP and mean change from baseline in worst pain at Week 26 will be hierarchically tested when OS, PFS, and ORR are all statistically significant. Additional PRO analyses of remaining BPI-SF, EORTC QLQ-C30, and EQ-5D-5L questionnaires will be described in the supplemental PRO SAP.

9.3.7.1. Time to Pain Progression

TTPP is defined as the time from randomization to the first date a subject experiences a pain progression. Pain progression is defined as either an increase of 2 or more points from baseline on question 3 of the BPI-SF or initiation of new opioid pain medication.

TTPP will be compared between the experimental and control arms using a stratified log-rank test. Kaplan-Meier curves and the median TTPP with 95% CI will be presented. Further details on the TTPP analysis, will be provided in the SAP.

9.3.7.2. Mean Change from Baseline in Worst Pain at Week 26

Using the BPI-SF question 3, mean change from baseline in worst pain will be calculated for each postbaseline assessment timepoint for Arm A and Arm B. A mixed model for repeated measures (MMRM) will be used to estimate marginal mean change scores and differences between Arm A and Arm B. The difference in mean change from baseline between treatment arms at Week 26 will be evaluated for statistical significance.

9.3.8. Safety Analyses

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

9.3.8.1. Extent of Exposure

Duration of treatment will be summarized and listed.

Duration of treatment, number of cycles, total dose and dose intensity will be summarized by treatment arm. Details will be provided in the SAP.

9.3.8.2. Adverse Events

An overview of TEAEs will provide a tabulation of the number and incidence of TEAEs, treatment-related TEAEs, Grade 3 and higher TEAEs, serious TEAEs, treatment-related serious TEAEs, TEAE leading to deaths, and TEAEs leading to study treatment discontinuation. AEs will be defined as treatment-emergent if they are newly occurring or worsen after the first dose of study treatment through 30 days after the last dose of the study drug or through 90 days after the last dose of study treatment for SAE in Arms A and C.

AEs will be listed and summarized by MedDRA, system organ class (SOC), preferred term, severity, and relationship to study drug. In the event of multiple occurrences of the same AE with the same preferred term in one subject, the AE will be counted once as the occurrence. The incidence of TEAEs will be tabulated by preferred term and treatment group. TEAEs leading to premature discontinuation of study drug will be summarized and listed in the same manner.

9.3.8.3. 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.

9.3.8.4. Clinical Laboratory Results

For laboratory values (eg, chemistry and hematology), summary statistics of actual values and change from baseline may be presented as appropriate by scheduled visit. Laboratory shift tables will also be provided by treatment group. Laboratory values will also be listed with grade per NCI CTCAE v4.03 and flagged when values are outside the normal reference range. Details will be provided in the SAP.

9.3.8.5. Other Safety Analyses

Vital Signs

Vital signs will be listed by subject and scheduled visit.

ECOG Status

Shifts from baseline to the best and worst post-baseline score may be tabulated.

ECG

A by-subject listing will be generated.

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 (R2); 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 presenting the risks and benefits of study participation to the subject in simple terms using the IRB/IEC approved informed consent document and for ensuring subjects 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 subject, 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.

For phase 1 studies, it is preferable for a subject to provide consent themselves. If informed consent is obtained from a legally acceptable representative for a subject who is unable to provide informed consent at study entry (if applicable), but the subject is later able to provide informed consent, the investigator must obtain written informed consent from the subject.

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 (eg, 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 sub investigators 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 subject) must be approved by the sponsor prior to seeking approval from the IRB/IEC, and prior to implementing. The investigator is responsible for enrolling subjects 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 subject medical records in the subject 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 subject medical information must be handled in accordance with local and national laws, rules, and regulations and consistent with the terms of the subject 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 subject 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 CTA.

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APPENDIX A. SCHEDULE OF EVENTS

		Screening/ Baseline			Every 3-week Cycle			EOT	Follow-up	Survival Follow-up
	Day	D –42 to RND	D –28 to RND	D –7 to RND	D1[A]	D8[A]	D15	Within 30 to 37 d of last dose[B]	Every 9 weeks[G]	Every 12 weeks
	Visit window[W]				±2 d[U]	–1 to +4 d	±1 d		±7 d	±7 d
Screening/Baseline Assessments	Inclusion/Exclusion, medical history		X							
	Informed consent	X								
	Acquire and submit archival or fresh tumor biopsy tissue[C]	X								
	Ophthalmologic examination[D]		X							
	Brain scan (if indicated)		X[E]		X[R]			X[R]	X[R]	
	Bone scan		X[E]		X[R]			X[R]	X[R]	
	INR/PT/PTT		X							
	HbA1c[N]		X							
	Urinalysis (with reflexive microscopy, if abnormal)		X							
	Pregnancy test (urine or serum; only for females of childbearing potential)			X[Q]	X			X		
	Randomization[Y]			X						
Safety Assessments	Physical exam (including weight)			X	X[F,T]			X	X[G]	
	Height			X						
	Vital signs			X	X[T]	X [T]		X		
	CBC with differential[O]			X	X[F,T]	X [T]	X[Z]	X		
	Serum chemistry panel[O]			X	X[F,S,T]	X[S,T]	X[Z]	X		
	Amylase		X							
	Lipase		X							
	CrCl[BB]			X						

Footnotes

		Screening/ Baseline			Every 3-week Cycle			EOT	Follow-up	Survival Follow-up
	Day	D –42 to RND	D –28 to RND	D –7 to RND	D1[A]	D8[A]	D15	Within 30 to 37 d of last dose[B]	Every 9 weeks[G]	Every 12 weeks
	Visit window[W]				±2 d[U]	–1 to +4 d	±1 d		±7 d	±7 d
	Thyroid function tests[X]		X		X[F]					
	ECOG performance status			X	X[F,T]			X	X[G]	
	ECG			X						
	Transthoracic ECHO or MUGA[AA]	X								
	Concomitant medications	Related to study procedures[H]			Collect from Day 1 (predose) through 30 days (AEs/SAEs) post last dose, or 90 days (SAEs related to pembrolizumab) post last dose (30 days post last dose if new anticancer therapy is started). For AESIs, AEs and concomitant medications may be followed until AE resolution, return to baseline, subject withdrawal, study closure, or the event becomes chronic.					
	Adverse event collection									
Patient-Reported Outcome Assessments	Quality of Life (QOL) and Pain Assessment				See Electronic Patient-Reported Outcomes Schedule of Events table for assessment details[V]					
	Healthcare Resource Utilization (HRU)									
Treatment	Enfortumab vedotin administration[P]				X	X				
	Pembrolizumab administration[I]				X					
	Gemcitabine administration[I]				X	X				
	Cisplatin administration[I]				X					
	Carboplatin administration[I]				X					
PK/Imunogenicity/ Biomarker	Blood, urine and tissue sample collection			See PK, Immunogenicity, and Biomarker table for sample collection details[A]						
Response Assessment	CT/MRI scan with contrast[J]		X		X[K]			X[L]	X[K]	
	Survival status									X[M]

RND=Randomization

A See Table 12 for PK, immunogenicity, and biomarker sampling.

B EOT evaluations should be obtained before the initiation of non-protocol therapy. If EOT evaluations are completed before 30 days following the last study treatment, conduct a phone screen 30–37 days following the subject's last study treatment to ensure that no changes in AE profile have occurred.

Footnotes

C Archival tumor tissue must be available for participation in the study. Archived tumor tissue, not previously irradiated, should be collected after completion of the most recent prior systemic therapy, ideally within 12 months prior to enrollment, if possible. If adequate archival tumor sample is not available, a new biopsy may be performed. Tumor FFPE block is preferred. Core needle biopsy or excision of non-decalcified tissue is required (fine needle aspirate is not acceptable).

D A complete ophthalmologic examination will include, but is not limited to, visual acuity, slit lamp, tonometry examination and dilated fundus examination. Subsequent ophthalmology assessments should be performed as clinically indicated. End of treatment slit lamp examinations are required for subjects who experience corneal AEs during the study and must be performed ≥4 weeks from last dose.

E Brain scans will be conducted at screening/baseline in subjects with a history of CNS metastasis or signs/symptoms of CNS metastasis. Bone scans will be conducted at screening/baseline in subjects with a history of skeletal metastasis or suspicion of skeletal metastasis based on imaging or symptoms. See Appendix C for preferred imaging methods.

F Clinical laboratory assessments, physical exam, weight, and ECOG performance status are not required if performed within 1 day prior to administration of study drug.

G Subjects who discontinue study treatment for reasons other than BICR-confirmed radiographically-confirmed disease progression by RECIST v1.1 guidelines or consent withdrawal will have physical exams, ECOG, and disease assessments every 9 weeks (±1 week) for the first 18 months timed from the randomization date, then every 12 weeks (±1 week) until the subject has BICR-confirmed radiologically-confirmed disease progression (per RECIST v1.1), subject death, study closure, or withdrawal of consent, whichever occurs first. ECOG status and physical exams may be discontinued at start of subsequent anticancer therapy. Palliative radiotherapy on a nontarget lesion that is not progressing will not be considered a subsequent anticancer therapy; however, radiotherapy on any new or progressing target lesion will be a subsequent anticancer therapy.

H From time of informed consent.

I On Day 1 of each cycle, pembrolizumab should be administered approximately 30 minutes after completion of enfortumab vedotin administration (Arm A). On Day 1, or Day 2 if required per institutional standards for cisplatin, of each cycle, cisplatin or carboplatin and gemcitabine should be administered per institutional standard (Arm B).

J Computed tomography (CT) scan with contrast, including chest, abdomen, and pelvis. Other regions should be scanned if the subject has known disease or new symptoms suggestive of disease in that region. Response assessment will be evaluated using RECIST v1.1.

K Response assessment will be performed every 9 weeks (±1 week) from the randomization date. Objective responses will be confirmed per RECIST v1.1 with repeat scans done at the next scheduled scan per protocol. Subsequent scans are to be performed every 9 weeks ((±1 week) until 18 months after randomization, then every 12 weeks (±1 week). Tumor imaging should also be performed whenever disease progression is suspected.

L Not required if conducted <4 weeks prior to EOT.

M Contact subject for survival status and collection of subsequent anticancer treatment information every 12 weeks (±1 week) after BICR-confirmed radiologically-confirmed progressive disease per RECIST v1.1 guidelines until death, study closure, lost to follow-up, or subject withdraws consent, whichever occurs first. Additional follow-up contacts may be required per sponsor request for analysis purposes.

N If HbA1c is elevated (≥6.5%), refer subject to appropriate provider during Cycle 1 for glucose management.

O Safety labs may be collected 1 day prior to dosing.

P At least 6 days must elapse between doses of enfortumab vedotin

Q Either serum or urine pregnancy test. May be performed within 1 day prior to administration of study drug.

R Brain scans should be repeated every 9 weeks (± 1 week) for the first 18 months timed from the randomization date, then every 12 weeks (±1 week) thereafter, and as clinically indicated in subjects with a history of CNS metastasis or signs/symptoms of CNS metastasis. Bone imaging should be repeated every 9 weeks (± 1 week) for the first 18 months timed from the randomization date, then every 12 weeks (±1 week) thereafter, and as clinically indicated in subjects with a history of skeletal metastasis or suspicion of skeletal metastasis based on imaging or symptoms. See Appendix C for preferred imaging methods.

S Verify blood glucose is <250 mg/dL prior to dosing. Subjects with diabetes must be tested in the clinic and blood glucose must be <250 mg/dL prior to dosing. Use of insulin is permitted as part of the standard of care.

T Procedures should be conducted pre-dose.

U Window applies to Cycle 2+

V The EQ-5D-5L, BPI-SF, EORTC QLQ-C30, and HRU questionnaires will be completed in clinic at Cycle 1 Day 1 before any study procedures/assessments. Questionnaires will be completed by the subject at home in between clinic visits on the ePRO device beginning with Cycle 1 Day 4 or 5, once weekly for the first 12 weeks, on Week 14 and once every 3 weeks for the remainder of the study through disease progression and survival follow-up. See Section 7.7; Table 13.

W Visit windows do not apply to QOL, Pain, or HRU assessments.

X Thyroid function tests (see Section 7.8.4) should be conducted for all subjects at screening/baseline. Subjects in Arm A should be tested at Cycle 2, and every even cycle thereafter. Subjects in Arm B should be tested as clinically indicated.

Y All screening/baseline procedures should occur prior to randomization. Randomization will be allowed at Day –3 to 1 and must occur prior to the first dose of study drug.

Z Cycles 1 and 2 only, unless clinically indicated.

AA A transthoracic echocardiogram or multiple-gated acquisition (MUGA) scan with left ventricular ejection fraction (LVEF) is required for subjects with NYHA Class III Heart Failure or a history of coronary heart disease, arrhythmia, or other significant heart disease.

BB The same method to determine CrCl should be used consistently for a subject over the course of the study with the exception of carboplatin dose calculation, where the Cockcroft-Gault method should be used in all subjects.

APPENDIX B. PERFORMANCE STATUS SCALES CONVERSION

Karnofsky		ECOG	
Percent	Description	Score	Description
100	Normal, no complaints, no evidence of disease.	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.		
80	Normal activity with effort; some signs or symptoms of disease.	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.		
60	Requires occasional assistance but is able to care for most of his/her needs.	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.		
40	Disabled, requires special care and assistance.	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.		
20	Very sick, hospitalization indicated. Death not imminent.	4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
10	Moribund, fatal processes progressing rapidly.		
0	Dead.	5	Dead.

APPENDIX C. SCANNING AND CONTRAST OPTIONS

In decreasing order of preference

Brain Scan

1. Brain magnetic resonance imaging (MRI) with gadolinium

If gadolinium is medically contraindicated:

2. Brain MRI without gadolinium
3. Brain computed tomography (CT) with intravenous (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

5. Radio opaque agents (eg, iodine and barium based agents)
6. 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 D. 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 E. LIVER SAFETY MONITORING AND ASSESSMENT*

In the absence of an explanation for increased LFTs, such as viral hepatitis, pre-existing or acute liver disease, or exposure to other agents associated with liver injury, the subject may be discontinued from the study treatment. The investigator may determine that it is not in the subject's best interest to continue study treatment. Discontinuation of treatment should be considered if any of the **severe** liver abnormalities listed below should occur.

Any subject with an increase of serum aminotransferases to >3× 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). 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 (eg, 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.

* 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.

** 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 subjects 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. Subjects 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 subject 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 subjects 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 subjects 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 subject'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.

APPENDIX F. EORTC QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

APPENDIX G. EQ-5D-5L

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

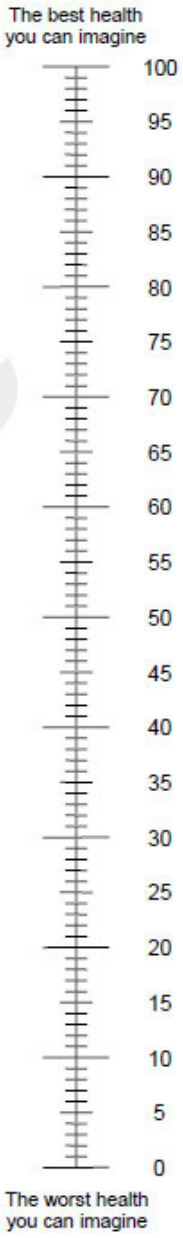
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



APPENDIX H. BPI-SF

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Brief Pain Inventory (Short Form)

Date: ____/____/____ Time: _____

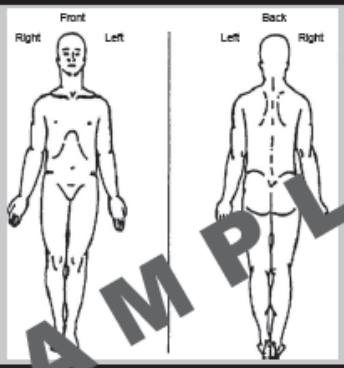
Name: _____ _____ _____

Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

Page 1 of 2

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Date:____/____/____ Time:_____

Name:_____ _____ _____

Last First Middle Initial

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

Page 2 of 2

APPENDIX I. HEALTH RESOURCE UTILIZATION

1. Since your last study visit, have you had any visits to the emergency room (ER)?

   ☐ No (if no, go to 4)

   ☐ Yes (if yes, go to 2)

2. Since your last visit, how many emergency room visits have you had? _____

3. For each emergency room visit please complete the following:

	Result in a Hospital Admission (more than a 24-hour stay)?	Length of stay in hospital (number of days)
ER Visit 1	Yes/No	
ER Visit 2	Yes/No	
ER Visit 3	Yes/No	

4. Since your last study visit, have you had any hospital admissions (more than a 24 hour stay) that occurred without first going to the emergency room (ER)?

   ☐ No (if no, go to 7)

   ☐ Yes (if yes, go to 5)

5. How many hospital admissions (more than 24-hour stay; without previous ER transferal)?

6. For each hospital admission (more than 24 hour stay; without previous ER transferal) visit please complete the following:

	Length of stay in hospital (number of days)
Hospital Visit 1	
Hospital Visit 2	
Hospital Visit 3	

7. Since your last study visit, have you had any visits to a general practitioner (primary care physician)?

   ☐ No (if no, go to 9)

   ☐ Yes (if yes, go to 8)

8. How many visits have you had to a general practitioner (primary care physician)?

9. Since your last study visit, did you have any visits to a specialist physician (e.g., oncologist, rheumatologist, endocrinologist, orthopedic surgeon, etc.)?

   ☐ No

   ☐ Yes (if yes, go to 10)

10. How many visits have you had to a specialist physician (e.g., oncologist, rheumatologist, endocrinologist, orthopedic surgeon, etc.)?

APPENDIX J. RECIST CRITERIA VERSION 1.1

Table 1 – Time point response: patients with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 2 – Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Table 3 – Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.
a If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Reproduced from (Eisenhauer 2009)

APPENDIX K. IRECIST: GUIDELINES FOR RESPONSE CRITERIA FOR USE IN TRIALS TESTING IMMUNOTHERAPEUTICS

Response will also be assessed using modified RECIST v1.1 for immune-based therapeutics (iRECIST) guidelines (Seymour 2017). Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. The criteria are identical to those of RECIST v1.1 in many respects but have been adapted to account for instances where an increase in tumor burden, or the appearance of new lesions, does not reflect true tumor progression.

Key differences are described below. All responses defined using iRECIST guidelines are designated with a prefix. iRECIST time point and best responses will be recorded separately.

Confirming Disease Progression

Unlike RECIST v1.1, the iRECIST guidelines require the confirmation of progression and uses the terms unconfirmed immune progressive disease (iUPD) and confirmed immune progressive disease (iCPD). Confirmatory scans should be performed at least 4 weeks, but no longer than 9 weeks after iUPD.

iCPD is confirmed if further increase in tumor burden, compared to the last assessment, is seen as evidenced by 1 or more of the following:

- Continued increase in tumor burden (from iUPD) where RECIST v1.1 definitions of progression had been met (from nadir) in target, nontarget disease or new lesions
    - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum
    - Continued unequivocal progression in nontarget disease with an increase in tumor burden
    - Increase in size of previously identified new lesion (s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions.
- RECIST v1.1 criteria are met in lesions types (target or nontarget or new lesions) where progression was not previously identified, including the appearance of additional new lesions.

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or immune stable disease [iSD], immune partial response [iPR] or immune complete response [iCR] if those criteria are met compared to baseline).

New Lesions

New lesions should be assessed and measured as they appear using RECIST v1.1 criteria (maximum of 5 lesions, no more than 2 per site, at least 10 mm in long axis (or 15 mm in short axis for nodal lesions), and recorded as New Lesions-Target (NLT) and New Lesion-Non-Target (NLNT) to allow clear differentiation from baseline target and nontarget lesions.

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of target lesions should NOT be included in the sum of measures of original target lesions identified at baseline. Rather, these measurements will be collected separately in the case report form.

APPENDIX L. GUIDANCE ON CONTRACEPTION

For the purposes of this guidance, complete abstinence, if consistent with the subject's preferred lifestyle, is an acceptable form of contraception. Complete abstinence is defined as abstinence starting from the time of informed consent and continuing throughout the study and until the end of systemic exposure (at least 6 months after the final dose of study drug; see Section 4.1).

Acceptable methods for highly effective birth control (preventing conception)

Subjects who are of childbearing potentiala or whose partners are of childbearing potential[a] and who are sexually active in a way that could lead to pregnancy may choose any TWO of the following methods (please see acceptable combinations below):

- Hormonal methods of contraception (excluding progestin-only pills; method must be associated with inhibition of ovulation), unless contraindicated
- Intrauterine device with failure rate <1%
- Tubal ligation
- Vasectomy (at least 90 days from the date of surgery with a semen analysis documenting azoospermia)
- Barrier method (male or female condom with or without spermicide, cervical cap with or without spermicide, diaphragm with or without spermicide)[b]

a A person of childbearing potential is defined as anyone born female who has experienced menarche and who has not undergone surgical sterilization (eg, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or has not completed menopause. Menopause is defined clinically as 12 months of amenorrhea in a person born female over age 45 in the absence of other biological, physiological, or pharmacological causes.

b A barrier method should only be used with a highly effective birth control method that is not a barrier method. Barrier methods alone, including a double-barrier method, are not considered highly effective contraceptive measures (see unacceptable methods of contraception).

Acceptable combinations of contraceptive methods:

- Hormonal method and vasectomy
- Hormonal method and barrier method
- Intrauterine device and vasectomy
- Intrauterine device and barrier method
- Tubal ligation and vasectomy
- Tubal ligation and barrier method

Acceptable methods for preventing secondary exposure to seminal fluid

Subjects born male and who are sexually active with a pregnant or breastfeeding person must use the contraceptives in Options 1 or 2:

- Option 1: Male condom (with or without spermicide) and cervical cap
- Option 2: Male condom (with or without spermicide) and diaphragm

Unacceptable methods of contraception

- Periodic abstinence
- No method
- Withdrawal
- Rhythm
- Spermicide only
- Progestin-only pills
- Concomitant use of female and male condoms
- Barrier methods alone, including double-barrier methods

APPENDIX M. MANAGEMENT OF EXISTING ARM C SUBJECTS (US ONLY)

For subjects randomized to enfortumab vedotin + pembrolizumab + cisplatin or carboplatin (Arm C) on the original protocol and Protocol Amendment 1, investigators should discuss the updated study design, removal of Arm C, and the subject should be re-consented to Protocol Amendment 2. Upon re-consenting, and after discussion with the principal or treating investigator, subjects may be given the option to continue and complete platinum chemotherapy per the previous protocol versions or discontinue platinum chemotherapy and continue with enfortumab vedotin and pembrolizumab therapy. Subjects that continue platinum chemotherapy should follow the chemotherapy dosing guidelines, including dose modifications and concomitant medications, as outlined in Section 5 of this protocol for cisplatin and carboplatin.

Arm C Treatments Administered

Enfortumab vedotin

Enfortumab vedotin 1.25 mg/kg, the investigational product under study, will be administered as an IV infusion over approximately 30 minutes on Days 1 and 8 of every 3-week cycle.

Pembrolizumab

Pembrolizumab 200 mg will be administered as an IV infusion approximately 30 minutes after completion of platinum-containing chemotherapy, on Day 1 of every 3-week cycle. Pembrolizumab may be administered during post chemotherapy hydration.

Cisplatin

On Day 1 (or Day 2 if required per institutional guidelines) of each 3-week cycle, cisplatin 70 mg/m^2 will be administered (with adequate pre- and post-hydration) as an IV infusion per institutional standards after completion of enfortumab vedotin administration. The body surface area used to calculate cisplatin dose may be capped per institutional standards.

Carboplatin

On Day 1 of each 3-week cycle, carboplatin at AUC 4.5, or AUC of 5 according to local guidelines, will be administered (with adequate pre- and post-hydration) as an IV infusion per institutional standards after completion of enfortumab vedotin administration. Body weight used to calculate carboplatin may be capped as per institutional standards.

APPENDIX N. INVESTIGATOR SIGNATURE PAGE

Investigator Statement and Signature

I have read the attached protocol entitled "An open-label, randomized, controlled phase 3 study of enfortumab vedotin in combination with pembrolizumab versus chemotherapy alone in previously untreated locally advanced or metastatic urothelial cancer"

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 O. DOCUMENT HISTORY

Version	Date
Original	03-Dec-2019
Amendment 1	25-Jun-2020
Amendment 2	12-Aug-2020
Amendment 3	10-Feb-2021
Amendment 4	11-Nov-2021
Amendment 5	29-Mar-2022
Amendment 6	12-Apr-2022
Amendment 7	30-Nov-2022
Amendment 8	15-Feb-2023
Amendment 9	29-Sep-2023

Summary of Changes in Amendment 01

Section(s)	Change	Rationale
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Section(s)	Change	Rationale
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Summary of Changes in Amendment 02

Section(s)	Change	Rationale
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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Section(s)	Change	Rationale
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Section(s)	Change	Rationale
		

Section(s)	Change	Rationale
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Section(s)	Change	Rationale
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Section(s)	Change	Rationale
		

Section(s)	Change	Rationale
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Section(s)	Change	Rationale
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[redacted]	[redacted]	[redacted]

Section(s)	Change	Rationale
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Section(s)	Change	Rationale
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Summary of Changes in Amendment 03

Section(s)	Change	Rationale
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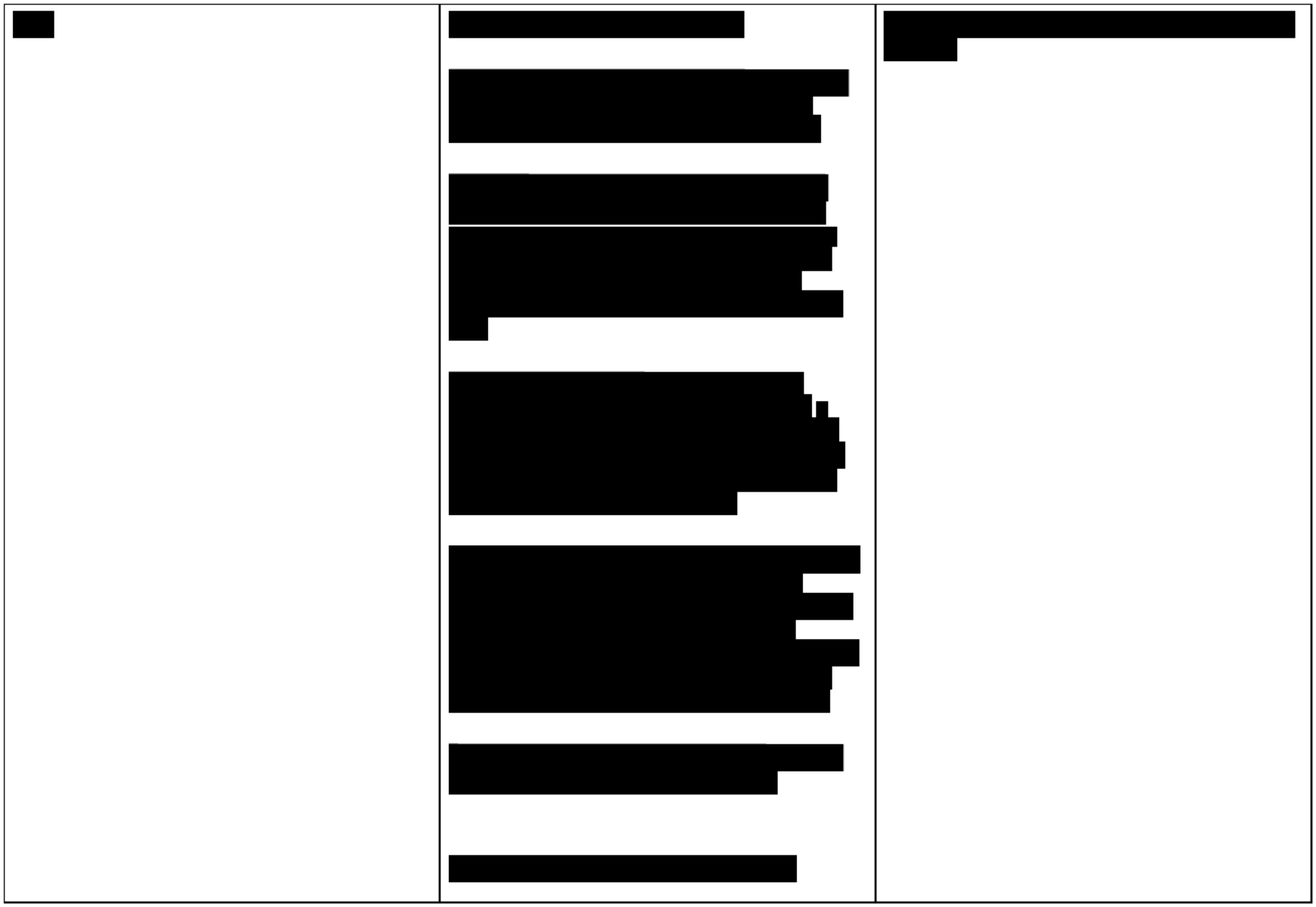

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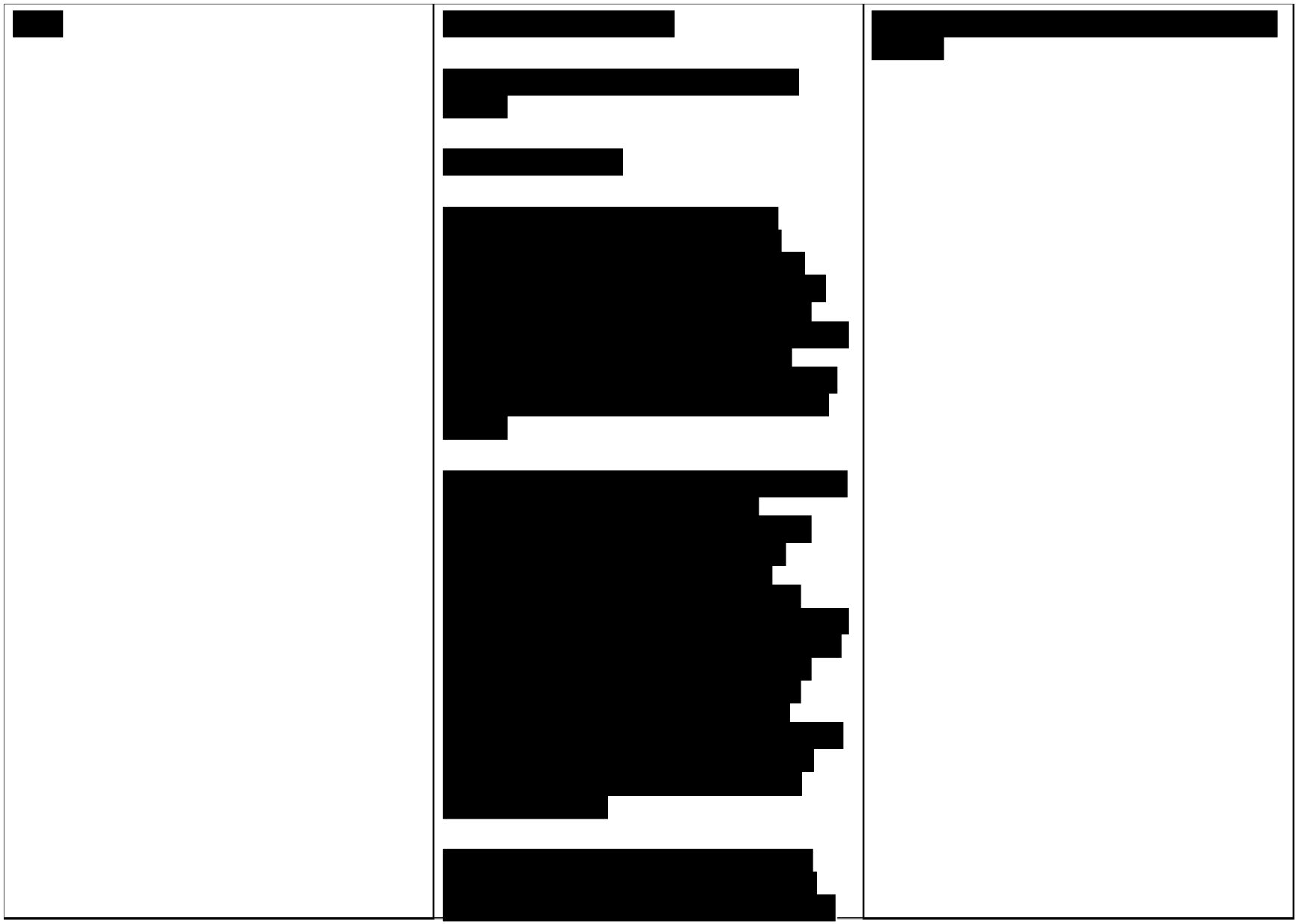

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Summary of Changes in Amendment 04

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Section(s)	Change	Rationale
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Section(s)	Change	Rationale
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Section(s)	Change	Rationale
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Section(s)	Change	Rationale
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Section(s)	Change	Rationale
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Section(s)	Change	Rationale
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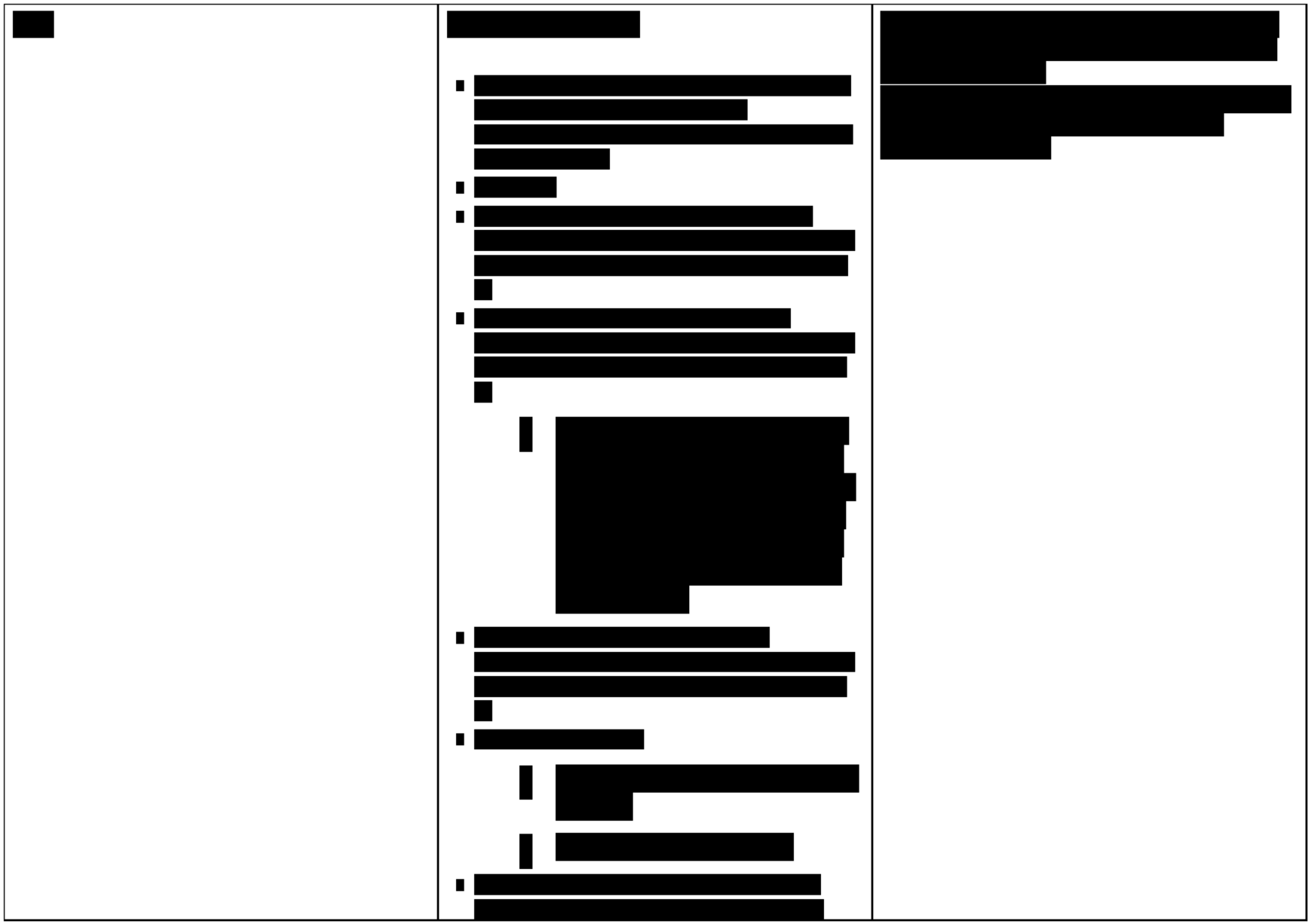

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Section(s)	Change	Rationale
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Section(s)	Change	Rationale
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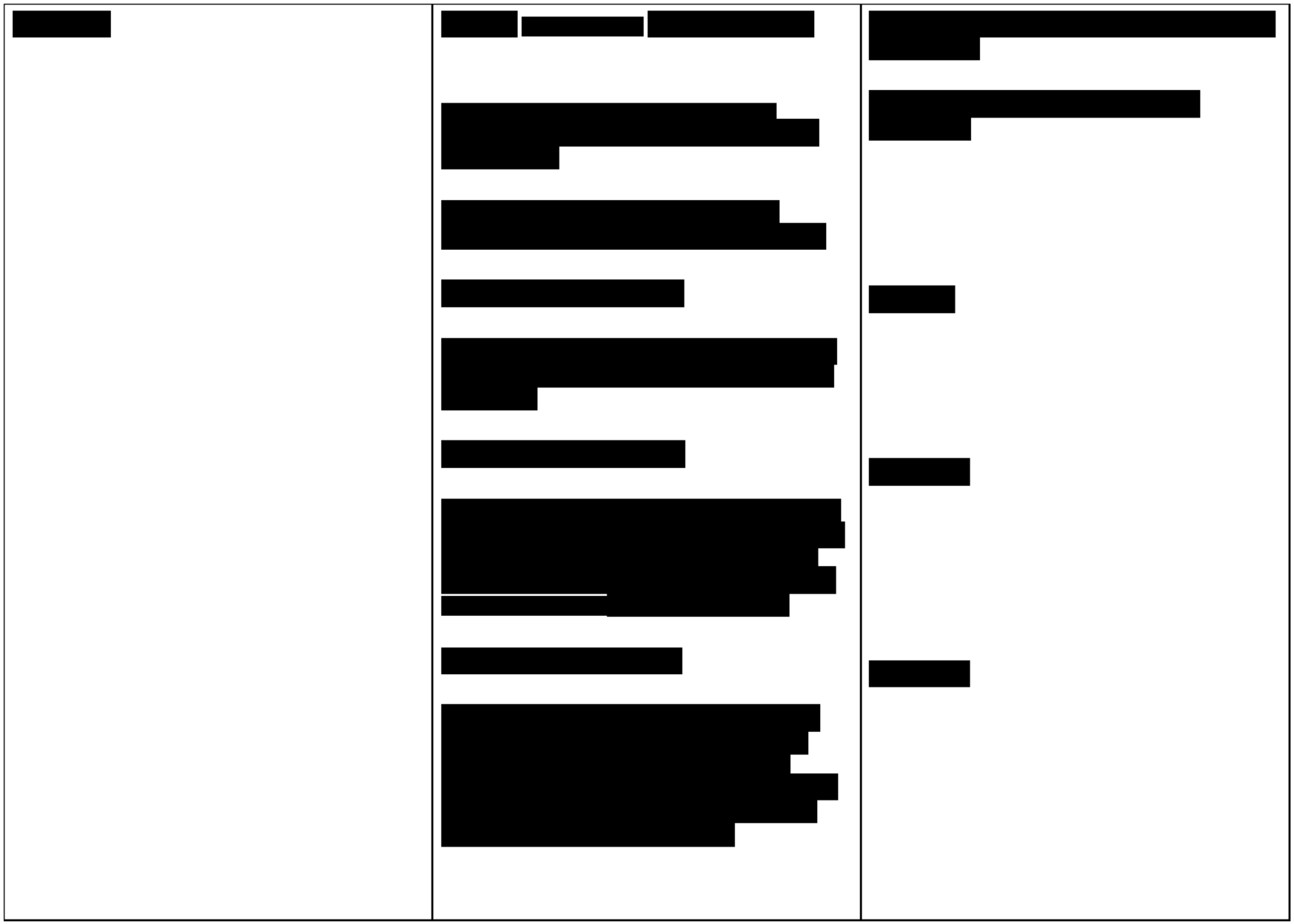

Section(s)	Change	Rationale
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Section(s)	Change	Rationale
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Summary of Changes in Amendment 05

Sections	Change	Rationale
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[redacted]	[redacted]	[redacted]

Summary of Changes in Amendment 06

Section(s)	Change	Rationale
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Section(s)	Change	Rationale
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Section(s)	Change	Rationale
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Section(s)	Change	Rationale
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Summary of Changes in Amendment 07

Section(s)	Change	Rationale
[redacted]	[redacted]	[redacted]

Section(s)	Change	Rationale
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Section(s)	Change	Rationale
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Section(s)	Change	Rationale
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Section(s)	Change	Rationale
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Section(s)	Change	Rationale
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[redacted]	[redacted]	[redacted]
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Summary of Changes in Amendment 08

Section(s)	Change	Rationale
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Section(s)	Change	Rationale
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Section(s)	Change	Rationale
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Summary of Changes in Amendment 09

Section(s)	Change	Rationale
Title Page	Updated medical monitor information. Updated address. Added EU CT number.	Administrative change
5.6.1	Each 50, 150, 450, or 600 m~~L~~g multidose vial of solution contains 10 mg/mL carboplatin.	Correction
5.10.6	**5.10.6. Management of Pneumonitis/ILD Related to Enfortumab Vedotin** Severe, life-threatening or fatal pneumonitis/ILD have occurred in subjects receiving enfortumab vedotin. Monitor subjects for signs and symptoms indicative of pneumonitis/ILD such as hypoxia, cough, dyspnea or interstitial infiltrates on radiologic exams. For all subjects, including subjects with asymptomatic/Grade 1 pneumonitis/ILD, clinical monitoring and supportive measures consistent with local medical guidelines should be followed as appropriate throughout the study. Medical intervention per standard of care should be considered for Grade ≥2 events (eg, corticosteroids initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper). For recommendations regarding dose modifications for pneumonitis/ILD due to enfortumab vedotin, refer to Section 5.2.4.	Additional instructions were added to the protocol to clarify recommended steps for management of subjects who develop pneumonitis/ILD due to enfortumab vedotin.
7.5	To understand the relationship between the biological characteristics of tumors before treatment and subject outcomes, tumor tissue from pre-treatment biopsies will be examined. ~~Tumor tissue from any standard of care biopsies may also be collected to assess the on-treatment effects of enfortumab vedotin.~~ Subjects will be stratified prior to randomization according to PD-L1 status (PD-L1 high: CPS ≥10 and PD-L1 low: CPS <10 based on Dako/Agilent PD-L1 IHC 22C3 PharmDx).	On-treatment biopsy samples are not collected as part of the study. The stricken text was included in the protocol inadvertently and is being removed for consistency with study procedures

Section(s)	Change	Rationale
7.8.1.1	AE severity should be graded using the NCI CTCAE, version 4.03. ~~These criteria are provided in the study manual.~~	Correction