An Open-Label, Randomized Phase 3 Study to Evaluate Enfortumab Vedotin vs Chemotherapy in Subjects with Previously Treated Locally Advanced or Metastatic Urothelial Cancer (EV-301)

ISN/Protocol 7465-CL-0301

Version 4.0

Incorporating Substantial Amendment 3 [See Section 13]

14 Sep 2020

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Sponsor:

Astellas Pharma Global Development, Inc. (APGD)

1 Astellas Way

Northbrook, IL 60062

Protocol History:
Version 1.0 Original [20Dec2017]
Version 2.0 Incorporating Substantial Amendment 1 [22Aug2018]
Version 3.0 Incorporating Substantial Amendment 2 [11Dec2019]

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I. SIGNATURES

1. AGREEMENT BETWEEN THE SPONSOR'S RESPONSIBLE PERSON AND THE INVESTIGATOR

This clinical study will be conducted in adherence to GCP, ICH Guidelines and applicable laws and regulatory requirements, as well as this study protocol. As the evidence of the agreement, the investigator (CHIKEN SEKININ ISHI) and responsible person of the Sponsor (CHIKEN IRAI SEKININSHA) inscribe in the bipartite agreement by signature or "printed name and seal".

2. SPONSOR'S SIGNATURES

Required signatures (e.g., Protocol authors and contributors, etc.) are located in [Section 15 Sponsor's Signatures], located at the end of this document.

3. COORDINATING INVESTIGATOR'S SIGNATURE

The Coordinating Investigator's signature can be found in [Section 14 Coordinating Investigator's Signature].

4. INVESTIGATOR'S SIGNATURE

An Open-Label, Randomized Phase 3 Study to Evaluate Enfortumab Vedotin vs Chemotherapy in Subjects with Previously Treated Locally Advanced or Metastatic Urothelial Cancer (EV-301)

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14 Sep 2020

I have read all pages of this clinical study protocol for which Astellas is the sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and applicable local regulations. I will also ensure that subinvestigator(s) and other relevant members of my staff have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

Principal Investigator:

Signature: ----------

Date (DD MMM YYYY)

Printed Name:----------
<Insert name and qualification of the Investigator>
Address: ----------

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

24h-Contact for Serious Adverse Events (SAEs) See [Section 5.6.5 Reporting of Serious Adverse Events] for SAE Fax Number and Email	**Please fax or email the SAE Worksheet to:** Astellas Pharma Global Development, Inc. Global Pharmacovigilance North America Fax: 1-888-396-3750 North America Alternate Fax: 1-847-317-1241 International Fax: +44-800-471-5263 Email: safety-us@astellas.com **For Japan:** PAREXEL International Clinical Development Fax number +81-(0)3-6888-1654 Astellas Pharma Inc. – Japan JP Clinical Development Fax number +81-(0)3-3243-5737
Parexel Medical Monitor:	PPD PAREXEL International PPD
Astellas Medical Expert:	PPD Medical Science Oncology, Astellas Pharma Global Development, Inc. 1 Astellas Way Northbrook, IL 60062 PPD
Clinical Research Contacts:	PPD Clinical Science Astellas Pharma Global Development, Inc. 1 Astellas Way Northbrook, IL 60062 PPD

III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
ADC	Antibody drug conjugate
AE	adverse event
Alb	albumin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APEBV	Astellas Pharma Europe B.V.
APGD	Astellas Pharma Global Development
AST	aspartate aminotransferase
AT	aminotransferases
ATA	antitherapeutic antibodies
AUST	Astellas US Technologies
BLOQ	below the lower limit of quantification
BUN	blood urea nitrogen
CA	competent authority
cfDNA	circulating free deoxyribonucleic acid
CFR	Code of Federal Regulations
CHO	Chinese Hamster Ovary
CIOMS	council for international organizations of medical sciences
CNS	central nervous system
CPI	checkpoint inhibitor
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
COE	crossover extension
CYP3A4	cytochrome P450 3A4
DCR	disease control rate
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EDC	electronic data capture
EEA	European Economic Area

Abbreviations	Description of abbreviations
EORTC	European Organisation for Research and Treatment of Cancer
EOT	end of treatment
ePRO	electronic patient reported outcome
EQ-5D-5L	EuroQOL 5-dimensions
EV	enfortumab vedotin
FAS	full analysis set
FDA	Food and Drug Administration
GCP	good clinical practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GMP	good manufacturing practice
HbA1c	Hemoglobin A1c
HBsAg	hepatitis B surface antigen
Hct	hematocrit
HCV	hepatitis C virus
Hgb	hemoglobin
HIPAA	health insurance portability and accountability act
HIV	human immunodeficiency virus
HRU	healthcare resource utilization
IARC	International Agency for Research on Cancer
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDAC	Independent data analysis center
IDMC	Independent data monitoring committee
IEC	independent ethics committee
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
IRR	infusion-related reaction
IRT	interactive response technology
ITT	Intent to treat
ISN	international study number
IUD	intrauterine device
IUS	intrauterine hormone releasing system
LA-CRF	liver abnormality case report form
LFT	liver function test
MMAE	monomethyl auristatin E
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mUC	metastatic urothelial cancer
MVAC	methotrexate, vinblastine, doxorubicin, and cisplatin

Abbreviations	Description of abbreviations
NCI-CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
NOAEL	no observed adverse effect level
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PDAS	pharmacodynamics analysis set
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PFS	progression free survival
P-gp	p-glycoprotein
PGx	pharmacogenomics analyses
PKAS	pharmacokinetic analysis set
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PRO	patient reported outcome
QLQ-C30	EORTC Quality of Life Questionnaire
QOL	quality of life
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RES	response evaluable set
ROW	rest of the world
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SD	stable disease
SmPC	Summary of product characteristics
SOP	standard operating Procedure
Tab	total antibody
TBL	total bilirubin
TEAE	treatment emergent adverse events
TMF	trial master file
TP	total protein
ULN	upper limit of normal
US	United States
WBC	white blood cell

Definition of Key Study Terms

Terms	Definition of terms
Baseline	Assessments of subjects as they enter a trial before they receive any treatment.
Endpoint	Variable that pertains to the efficacy or safety evaluations of a trial.
Enroll	To register or enter a subject into a clinical trial. NOTE: Once a subject has received the study drug or placebo, the clinical trial protocol applies to the subject.
Investigational period	Period of time where major interests of protocol objectives are observed, and where the test drug or comparative drug (sometimes without randomization) is usually given to a subject, and continues until the last assessment after completing administration of the test drug or comparative drug.
Randomization	The process of assigning trial subjects to treatment or control groups using an element of chance to determine assignments in order to reduce bias.
Screening	A process of active consideration of potential subjects for enrollment in a trial.
Screen failure	Potential subject who did not meet 1 or more criteria required for participation in a trial.
Screening period	Period of time before entering the investigational period, usually from the time when a subject signs the consent until just before the test drug or comparative drug (sometimes without randomization) is given to a subject.
Study period	Period of time from the first site initiation date to the last site completing the study.
Variable	Any entity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

IV. SYNOPSIS

Date and Version # of Protocol Synopsis:	14 Sep 2020, Version 4.0
Study Sponsor: Astellas Pharma Global Development Inc. (APGD) **Study Collaborator:** Seattle Genetics, Inc.	**Protocol Number:** 7465-CL-0301
Name of Study Drug: Enfortumab Vedotin (ASG-22CE)	**Phase of Development:** Phase 3
Title of Study: An Open-Label, Randomized Phase 3 Study to Evaluate Enfortumab Vedotin vs Chemotherapy in Subjects with Previously Treated Locally Advanced or Metastatic Urothelial Cancer (EV-301)	
Planned Study Period: 2Q2018 to 2Q2021. The planned study enrollment is approximately 24 months from first subject enrolled with an additional 12 months anticipated for overall survival (OS) follow-up after the last subject enrolled. The total study duration will be approximately 36 months.	
Study Objective(s): **Primary** • To compare the OS of subjects with locally advanced or metastatic urothelial cancer treated with enfortumab vedotin (EV) to the OS of subjects treated with chemotherapy **Secondary** • To compare progression-free survival on study therapy (PFS1) per Response Evaluation Criteria in Solid Tumors (RECIST) V1.1 of subjects treated with EV to subjects treated with chemotherapy • To compare the overall response rate (ORR) per RECIST V1.1 of EV to chemotherapy • To evaluate the duration of response (DOR) per RECIST V1.1 of EV and chemotherapy • To compare the disease control rate (DCR) per RECIST V1.1 of EV to chemotherapy • To assess the safety and tolerability of EV • To assess quality of life (QOL) and Patient Reported Outcomes (PRO) parameters **Exploratory** • Exploratory genomic and/or other biomarkers in tumor tissue and in peripheral blood that may correlate with treatment outcome, including Nectin-4 expression • To assess the pharmacokinetics of EV (total antibody [TAb], antibody-drug conjugate [ADC] and monomethyl auristatin E [MMAE]) • To assess the incidence of antitherapeutic antibodies (ATA) • To evaluate PFS as assessed by RECIST V1.1 by investigator review in the next line of therapy (PFS2) in subjects treated with EV compared to chemotherapy • Healthcare resources utilization (HRU)	
Planned Total Number of Study Centers and Locations: Approximately 185 study centers in North America, Europe, Asia Pacific and Latin America	
Study Population: Subjects with locally advanced or metastatic urothelial cancer previously treated with platinum-based chemotherapy and an immune checkpoint inhibitor (CPI)	

Number of Subjects to be Enrolled / Randomized:
Approximately 600 subjects

Study Design Overview:

This is a global, open-label, randomized Phase 3 study in adult subjects with locally advanced or metastatic urothelial cancer who have received a platinum-containing chemotherapy and have experienced disease progression or relapse during or following treatment with an immune checkpoint inhibitor. Approximately 600 subjects will be randomized to EV (Arm A) or chemotherapy (Arm B) in a 1:1 ratio. Subjects will be stratified according to the following: Eastern Cooperative Oncology Group Performance Status (ECOG PS), regions of the world and liver metastasis.

OS is the primary endpoint. OS is defined as the time from randomization to the date of death. Secondary endpoints include PFS1, ORR, DOR, DCR, safety and QOL/PRO.

Subjects in Arm A will receive EV on Days 1, 8 and 15 of each 28-day cycle. Subjects in arm B will receive docetaxel, paclitaxel or vinflunine (as decided by the investigator prior to randomization: vinflunine is a choice of comparator only in countries where it is approved for urothelial cancer) on Day 1 of every 21-day cycle. Within the control arm, the overall proportion of subjects receiving vinflunine will be capped at approximately 35%. Subjects will continue to receive study treatment until radiological disease progression as determined per investigator assessment or other discontinuation criteria are met or upon study termination, or study completion, whichever occurs first. No on-study crossover will be allowed other than as allowed in [Appendix 12.10]. This study will consist of 3 phases: screening, treatment and follow-up.

Screening will take place up to 28 days prior to randomization. Subjects will start with cycle 1 and continue on to subsequent 21-day or 28-day cycles until one of the discontinuation criteria are met. A treatment cycle is defined as 28 days for Arm A and 21 days for Arm B. Subjects randomized to Arm A (EV) will receive treatment and evaluation on Days 1, 8 and 15 of all treatment cycles. Subjects randomized to Arm B (docetaxel, paclitaxel or vinflunine) will receive treatment and evaluation on Day 1 of all treatment cycles.

Subjects will be evaluated for response according to the RECIST V1.1. Imaging for both arms will be performed at baseline and every 56 days (± 7 days) from the first dose of study treatment throughout the study until PFS1 is documented by radiological disease progression or the subject is lost to follow-up, death, withdraws study consent or starts a subsequent anti-cancer therapy. Baseline imaging performed prior to informed consent as standard of care may be used so long as it is performed within 28 days prior to randomization. All subjects will have a bone scan (scintigraphy) performed at screening/baseline. Subjects with positive bone scans at baseline will have a bone scan performed every 56 days (± 7 days) throughout the study or more frequently if clinically indicated. Subjects should have a follow-up bone scan performed if clinically indicated regardless of baseline status. Brain scans (computed tomography with contrast/magnetic resonance imaging [MRI]) will only be performed if clinically indicated at screening/baseline and repeated as clinically indicated or per standard of care throughout the study.

QOL assessments and PRO will be collected at protocol-specified time points from all randomized subjects. The following validated tools will be used: European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) and EuroQOL 5-dimensions (EQ-5D-5L). Healthcare Resource Utilization (HRU) information will be collected at protocol-specified time points with particular focus on the number of subjects who have an unplanned use of healthcare resources related to clinical or AEs from subjects assigned to treatment arms A and B.

Blood samples for pharmacokinetics and ATA will be collected throughout the study for subjects randomized into Arm A. Validated assays will be used to measure the concentrations of EV ADC and MMAE in serum or plasma and to assess ATA. Pharmacokinetic samples will not be collected from subjects randomized into Arm B. Samples for exploratory biomarkers will be collected at protocol-specified time points. Biomarker assessments will not be used for subject selection.

Following discontinuation from study drug, subjects will have a follow-up visit 30 days (+ 7 days) after their last dose of drug for safety assessments. If a subject discontinues study drug prior to radiographic disease progression (i.e., PFS1), the subject should enter the post treatment follow-up period and continue to undergo imaging assessments every 56 days (± 7 days) until PFS1 is documented or the subject starts another anticancer treatment, whichever occurs earlier.

Following PFS1, subjects will enter the long-term follow-up period and be followed per institutional guidelines, but not less than every 3 months from the date of the follow-up visit for survival status and progression status on subsequent therapy (i.e., PFS2).

Subjects will be followed until PFS2 is documented or the subject starts another anticancer treatment, whichever occurs earlier. All subsequent anticancer therapy including date and site of progression for PFS2 will be recorded on the case report form.

Following PFS2, subjects will enter the survival follow-up period and be followed every 3 months for survival status until death, lost to follow-up, withdrawal of study consent, or study termination by sponsor. This study is expected to end once final survival analysis is complete.

An Independent Data Monitoring Committee (IDMC) will be chartered to oversee safety and the planned interim efficacy analysis, which will occur after at least 285 OS events (about 65% of the total planned events) are observed. The primary analysis will occur at 439 OS events. The IDMC may recommend to the sponsor whether the trial should be terminated, modified or continue unchanged based on ongoing reviews of safety data and interim efficacy analysis. Further details will be outlined in the IDMC charter.

Inclusion/Exclusion Criteria:

Inclusion:

Subject is eligible for the study if all of the following apply:

1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written informed consent and privacy language as per national regulations (e.g., Health Insurance Portability and Accountability Act [HIPAA] Authorization for US sites) must be obtained from the subject prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Subject is legally an adult according to local regulation at the time of signing informed consent.
3. Subject has histologically or cytologically confirmed urothelial carcinoma (i.e., cancer of the bladder, renal pelvis, ureter or urethra). Subjects with urothelial carcinoma (transitional cell) with squamous differentiation or mixed cell types are eligible.
4. Subject must have experienced radiographic progression or relapse during or after a CPI (anti-programmed cell death-1 [PD-1] or anti-programmed cell death-ligand 1 [PD-L1]) for locally advanced or metastatic disease. Subjects who discontinued CPI treatment due to toxicity are eligible provided that they have evidence of disease progression following discontinuation. The CPI need not be the most recent therapy. Subjects for whom the most recent therapy has been a non-CPI based regimen are eligible if they have progressed/relapsed during or after their most recent therapy. Locally advanced disease must not be amenable to resection with curative intent per the treating physician.

Inclusion/Exclusion Criteria:

Inclusion continued:

5. Subject must have received a platinum containing regimen (cisplatin or carboplatin) in the metastatic/locally advanced, neoadjuvant or adjuvant setting. If platinum was administered in the adjuvant/neoadjuvant setting subject must have progressed within 12 months of completion.
6. Subject has radiologically documented metastatic or locally advanced disease at baseline.
7. An archival tumor tissue sample should be available for submission to central laboratory prior to study treatment. If an archival tumor tissue sample is not available, a fresh tissue sample should be provided. If a fresh tissue sample cannot be provided due to safety concerns, enrollment into the study must be discussed with the medical monitor.
8. Subject has ECOG PS of 0 or 1
9. The subject has the following baseline laboratory data:
   - absolute neutrophil count (ANC) $\geq 1500/mm^3$
   - platelet count $\geq 100 \times 10^9/L$
   - hemoglobin ≥ 9 g/dL
   - serum total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN)* or $\leq 3 \times$ ULN for subjects with Gilbert's disease
   - creatinine clearance (CrCl) ≥ 30 mL/min as estimated per institutional standards or as measured by 24 hour urine collection (glomerular filtration rate [GFR] can also be used instead of CrCl)
   - alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 2.5 \times$ ULN or $\leq 3 \times$ ULN for subjects with liver metastases*
     * Docetaxel should not be chosen as a comparator for subjects if total bilirubin > ULN, or if AST and/or ALT > 1.5 × ULN concomitant with alkaline phosphatase > 2.5 × ULN.
10. Female subject must either:
    - Be of nonchildbearing potential:
      - Postmenopausal (defined as at least 1 year without any menses for which there is no other obvious pathological or physiological cause) prior to screening, or
      - Documented surgically sterile (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy).

      Note: Those who are amenorrheic due to an alternative medical cause are not considered postmenopausal and must follow the criteria for childbearing potential subjects.
    - Or, if of childbearing potential:
      - Agree not to try to become pregnant during the study and for at least 6 months after the final study drug administration,
      - And have a negative urine or serum pregnancy test within 7 days prior to Day 1 (Females with false positive results and documented verification of negative pregnancy status are eligible for participation),
      - And if heterosexually active, agree to consistently use a condom plus 1 form of highly effective birth control * per locally accepted standards starting at screening and throughout the study period and for at least 6 months after the final study drug administration.
11. Female subject must agree not to breastfeed or donate ova starting at screening and throughout the study period, and for at least 6 months after the final study drug administration.

12. A sexually active male subject with female partner(s) who is of childbearing potential is eligible if:
    - Agrees to use a male condom starting at screening and continue throughout the study treatment and for at least 6 months after final study drug administration. If the male subject has not had a vasectomy or is not sterile as defined below their female partner(s) is utilizing 1 form of highly effective birth control* per locally accepted standards starting at screening and continue throughout study treatment and for at least 6 months after the male subject receives his final study drug administration.

    *Highly effective forms of birth control include:
    - Consistent and correct usage of established hormonal contraceptives that inhibit ovulation,
    - Established intrauterine device (IUD) or intrauterine hormone releasing system (IUS).
    - Bilateral tubal occlusion
    - Vasectomy (A vasectomy is a highly effective contraception method provided the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used)
    - Male is sterile due to a bilateral orchiectomy or radical cystoprostatectomy/removal of seminal vesicles
    - Sexual Abstinence is considered a highly effective method only if defined as refraining from heterosexual activity during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

      Please note: Sexual abstinence is not sufficient as contraception method in Switzerland.
13. Male subject must not donate sperm starting at screening and throughout the study period, and for at least 6 months after the final study drug administration.
14. Male subject with a pregnant or breastfeeding partner(s) must agree to abstinence or use a condom for the duration of the pregnancy or time partner is breastfeeding throughout the study period and for at least 6 months after the final study drug administration.
15. Subject agrees not to participate in another interventional study while on treatment in present study.

Waivers to the inclusion criteria will **NOT** be allowed.

Exclusion:

Subject will be excluded from participation if any of the following apply:

1. Subject has preexisting sensory or motor neuropathy Grade ≥ 2.
2. Subject has active central nervous system (CNS) metastases. Subjects with treated CNS metastases are permitted on study if all the following are true:
    - CNS metastases have been clinically stable for at least 6 weeks prior to screening
    - If requiring steroid treatment for CNS metastases, the subject is on a stable dose ≤ 20 mg/day of prednisone or equivalent for at least 2 weeks
    - Baseline scans show no evidence of new or enlarged brain metastasis
    - Subject does not have leptomeningeal disease

3. Subject has ongoing clinically significant toxicity (Grade 2 or higher with the exception of alopecia) associated with prior treatment (including systemic therapy, radiotherapy or surgery). Subject with ≤ Grade 2 immunotherapy-related hypothyroidism or panhypopituitarism may be enrolled when well-maintained/controlled on a stable dose of hormone replacement therapy (if indicated). Patients with ongoing ≥ Grade 3 immunotherapy-related hypothyroidism or panhypopituitarism are excluded. Subjects with ongoing immunotherapy related colitis, uveitis, myocarditis, or pneumonitis or subjects with other immunotherapy related AEs requiring high doses of steroids (> 20 mg/day of prednisone or equivalent) are excluded.
4. Subject has prior treatment with EV or other MMAE-based ADCs.
5. Subject has received prior chemotherapy for urothelial cancer with all available study therapies in the control arm (i.e., both prior paclitaxel and docetaxel in regions where vinflunine is not an approved therapy, or prior paclitaxel, docetaxel and vinflunine in regions where vinflunine is an approved therapy).

   Note: After vinflunine cap is reached subjects who have received both docetaxel and paclitaxel will be excluded.
6. Subject has received more than 1 prior chemotherapy regimen for locally advanced or metastatic urothelial cancer, including chemotherapy for adjuvant or neo-adjuvant disease if recurrence occurred within 12 months of completing therapy. The substitution of carboplatin for cisplatin does not constitute a new regimen provided no new chemotherapeutic agents were added to the regimen.
7. Subject has history of another malignancy within 3 years before the first dose of study drug, or any evidence of residual disease from a previously diagnosed malignancy. Subjects with nonmelanoma skin cancer, localized prostate cancer treated with curative intent with no evidence of progression, low-risk or very low-risk (per standard guidelines) localized prostate cancer under active surveillance/watchful waiting without intent to treat, or carcinoma in situ of any type (if complete resection was performed) are allowed.
8. Subject is currently receiving systemic antimicrobial treatment for viral, bacterial, or fungal infection at the time of first dose of EV. Routine antimicrobial prophylaxis is permitted.
9. Subject has known active Hepatitis B (e.g., HBsAg reactive) or active hepatitis C (e.g., HCV RNA [qualitative] is detected).
10. Subject has known history of human immunodeficiency virus (HIV) infection (HIV 1 or 2).
11. Subject has documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, myocardial infarction, or cardiac symptoms (including congestive heart failure) consistent with New York Heart Association Class III to IV within 6 months prior to the first dose of study drug.
12. Subject has radiotherapy or major surgery within 4 weeks prior to first dose of study drug.
13. Subject has had chemotherapy, biologics, investigational agents, and/or antitumor treatment with immunotherapy that is not completed 2 weeks prior to first dose of study drug.
14. Subject has known hypersensitivity to EV or to any excipient contained in the drug formulation of EV (including histidine, trehalose dihydrate, and polysorbate 20); OR subject has known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary (CHO) cells.

15. Subject has known hypersensitivity to:
    - docetaxel or to any of the other excipients listed in product label, including polysorbate 80;
    - paclitaxel or to any of the other excipients listed in product label, including macrogolglycerol ricinoleate 35 (Ph.Eur.); and
    - vinflunine or to any of the other excipients listed in product label, including other vinca alkaloids (vinblastine, vincristine, vindesine, vinorelbine).
16. [Criterion removed].
17. Subject has known active keratitis or corneal ulcerations. Subject with superficial punctate keratitis is allowed if the disorder is being adequately treated in the opinion of the investigator.
18. Subject has other 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.
19. History of uncontrolled diabetes mellitus within 3 months of the first dose of study drug. Uncontrolled diabetes is defined as hemoglobin A1C (HbA1c) ≥ 8% or HbA1c between 7 and < 8% with associated diabetes symptoms (polyuria or polydipsia) that are not otherwise explained.

Waivers to the exclusion criteria will **NOT** be allowed.

Investigational Product:

Enfortumab Vedotin

Dose, Mode of Administration and Dose Modification:

EV 1.25 mg/kg will be administered on Days 1, 8, and 15 of every 28-day cycle. The investigational product will be administered intravenously over a 30-minute period.

EV will be administered based on the subject's actual body weight on Day 1 of every cycle except for subjects weighing greater than 100 kg; in such cases, the dose will be calculated based on a maximum weight of 100 kg. The dose does not need to be re-calculated based on actual weight on Day 8 and 15 of each cycle for Arm A unless it is required by institutional standards.

Dose reduction to 1 mg/kg (dose level - 1) and to 0.75 mg/kg (dose level - 2) will be allowed depending on the type and severity of toxicity. Subjects requiring a dose reduction may be re-escalated by 1 dose level (i.e., 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. EV should not be administered to subjects with CrCl < 30 mL/min. Dose modification recommendations for EV associated toxicity are presented in [Table A] and [Table B].

Dose interruptions for other EV associated toxicity is permitted at the discretion of the site investigator. Dose interruptions may last up to 8 weeks (2 cycles). Dose interruptions for subjects who are deriving clinical benefit from treatment may be extended beyond 8 weeks, if the subject's toxicity does not otherwise require permanent discontinuation. If there is a dose interruption, the schedule for response assessments will not be adjusted.

Table A Recommended dose modifications for enfortumab vedotin associated hematologic toxicity*

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

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

Table B Recommended dose modifications for enfortumab vedotin associated nonhematologic toxicity

Grade 1	Grade 2	Grade 3	Grade 4
Continue at same dose level. If ocular symptoms and/or changes in vision are identified, the subject should be evaluated with an ophthalmologic exam.**	Continue at same dose level, except in the event of Grade 2 neuropathy or corneal AEs. For Grade 2 neuropathy or corneal AE's, withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, and then resume treatment at the same dose level. For the second occurrence of Grade 2 neuropathy or corneal AE's withhold dose until toxicity is ≤ Grade 1, and 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 with an ophthalmologic exam.**	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 3 neuropathy or corneal AEs, discontinue treatment For Grade 3 hyperglycemia/elevated blood glucose, withhold EV treatment. Resume treatment once hyperglycemia/elevated blood glucose has improved to ≤ Grade 2 and subject is clinically and metabolically stable. If ocular symptoms and/or changes in vision are identified, the subject should be evaluated with an ophthalmologic exam.**	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.

AE: adverse events; EV: enfortumab vedotin

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

**Ophthalmologic exam should be performed by an ophthalmologist. In countries where optometrists can perform exams and prescribe medications, an optometrist may be used instead.

Comparative Drug(s):

In general, treatment with the chemotherapy comparators (docetaxel, paclitaxel or vinflunine) should be withheld for drug related Grade 4 hematologic toxicities and for non-hematologic toxicities ≥ Grade 3, and subsequent doses modified as per Table 6. Recommended dose modification guidelines specific for subjects receiving docetaxel, paclitaxel or vinflunine are detailed below. Dose modifications should also be considered according to local product labels or summary of product characteristics (SmPC) and institutional guidelines. For docetaxel, paclitaxel or vinflunine associated hematologic toxicities ≥ Grade 3, transfusions or growth factors may be used as indicated per institutional guidelines.

Docetaxel

Dose, Mode of Administration and Dose Modification:

Docetaxel will be administered intravenously on Day 1 of every 21-day cycle. The starting dose of docetaxel 75 mg/m^2 will be administered over 60-minute period or per local requirement. Refer to local product label or SmPC and institution guidelines for docetaxel for further guidance on docetaxel dosing.

Docetaxel should not be given to subjects with total bilirubin > ULN, or to subjects with AST and/or ALT > 1.5 × ULN with concomitant alkaline phosphatase > 2.5 × ULN. Subjects with elevations of bilirubin or abnormalities of transaminase concurrent with alkaline phosphatase are at increased risk for the development of Grade 4 neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death. Docetaxel should also not be given to subjects with a neutrophil count of < 1500 cells/mm^3. Severe fluid retention has been reported following docetaxel therapy.

Subjects should be premedicated with corticosteroids per institutional guidelines prior to each docetaxel administration. Subjects with pre-existing effusions should be closely monitored from the first dose for the possible exacerbation of the effusions. Subjects developing peripheral edema may be treated with standard measures, e.g., salt restriction, oral diuretic(s). Dose interruptions may last up to 6 weeks (2 cycles). Dose interruptions 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.

Dose modifications not specified in Table C (e.g., severe or cumulative cutaneous reactions) should also be considered according to local product label or SmPC and institutional guidelines.

Table C Recommended dose modifications for subjects receiving docetaxel

Toxicity	Grade	Occurrence	Hold Treatment	Dose Modification	Discontinue Treatment
Peripheral Neuropathy	Grade 1, 2		No	60 mg/m^2	N/A
	Grade 3, 4		Yes	N/A	Discontinue upon onset
Neutropenic fever (defined as T ≥ 100.5°F (38.1°C) and ANC ≤ 1,000/L)		1	Hold treatment until ANC ≥ 1,500/L	60 mg/m^2	
		2	Hold treatment until ANC ≥ 1,500/L	50 mg/m^2	
		3	Yes	N/A	Yes

ANC: absolute neutrophil count; N/A: not applicable; T: temperature

Vinflunine

Dose, Mode of Administration and Dose Modification:

Vinflunine will be administered intravenously on Day 1 of every 21-day cycle. The starting dose of vinflunine 320 mg/m^2 will be administered over a 20-minute period (or per local requirement) unless otherwise specified below. In case of WHO/ECOG PS of ≥ 1 or ECOG PS of 0 and prior pelvic irradiation, vinflunine treatment should be started at the dose of 280 mg/m². In the absence of any hematological toxicity during the first cycle causing treatment delay or dose reduction, the dose may be increased to 320 mg/m² every 21-days for the subsequent cycles.

In subjects with moderate renal impairment (40 mL/min ≤ CrCl ≤ 60 mL/min), the recommended dose is 280 mg/m² given once every 21-day cycle. In subjects with renal impairment (30 mL/min ≤ CrCl < 40 mL/min), the recommended dose is 250 mg/m² given once every 21-day cycle. The recommended dose of vinflunine is 250 mg/m² given once every 21-day cycle in subjects with mild liver impairment (Child-Pugh grade A).

The doses recommended in subjects ≥ 75 years old are as follows:

- in subjects at least 75 years old but less than 80 years, the dose of vinflunine to be given is 280 mg/m² every 21-day cycle.
- in subjects 80 years old and beyond, the dose of vinflunine to be given is 250 mg/m² every 21-day cycle.

Refer to local product label or SmPC and institution guidelines for vinflunine for further guidance on vinflunine dosing.

Dose interruptions may last up to 6 weeks (2 cycles). Dose interruptions 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. Please refer to the approved product label for specific dose modifications for subjects receiving vinflunine.

Paclitaxel

Dose, Mode of Administration and Dose Modification:

Study treatment of paclitaxel should be administered intravenously on Day 1 of every 21-day cycle after all procedures/assessments have been completed. The starting dose of paclitaxel 175 mg/m^2 will be administered as an intravenous infusion administered over 3 hours or per local requirement See guidelines on adjustment of initial dose. Refer to local product label or SmPC and institution guidelines for paclitaxel for further guidance on paclitaxel dosing.

All subjects should be premedicated prior to paclitaxel administration per institutional guidelines in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg orally administered approximately 12 and 6 hours before paclitaxel, diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to paclitaxel, and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before paclitaxel. The appropriate premedication regimen may be determined by the investigator.

Paclitaxel should not be administered to subjects with baseline neutrophil counts of less than 1500 cells/mm^3. Subjects should not be re-treated with subsequent cycles of paclitaxel until neutrophils recover to a level > 1500 cells/mm^3 and platelets recover to a level > 100000/mm^3. Severe conduction abnormalities have been documented in < 1% of subjects during paclitaxel therapy and in some cases requiring pacemaker placement. If subjects develop significant conduction abnormalities during paclitaxel infusion, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with paclitaxel.

In case of mild hepatic impairment (total bilirubin ≥ 1.25 ULN), paclitaxel should be started at a dose of 135 mg/m^2.

Recommended dose modification guidelines specific for subjects receiving paclitaxel are detailed in Table D below. Dose modifications should also be considered according to local product label or SmPC and institutional guidelines.

Dose interruptions may last up to 6 weeks (2 cycles). Dose interruptions 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.

Table D Recommended dose modifications for subjects receiving paclitaxel

Toxicity	Grade	Occurrence	Hold Treatment	Dose Modification	Treatment Discontinuation
Peripheral Neuropathy	Grade 1, 2		No	135 mg/m^2	N/A
	Grade 3, 4		Yes	N/A	Discontinue upon onset
Neutropenic fever (defined as T ≥ 100.5°F (38.1°C) and ANC ≤ 1,000/L)		1	Hold until ANC ≥ 1,500/L	135 mg/m^2	
		2	Hold until ANC ≥ 1,500/L	100 mg/m^2	
		3	yes	N/A	Yes

N/A: not applicable; T: temperature

Discontinuation Criteria:

A discontinuation from treatment applies to a subject who enrolled in the study and for whom study treatment is permanently discontinued for any reason.

The subject is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to discontinue the subject from study treatment or to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it. If a subject is discontinued from the study with an ongoing adverse event (AE) or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until the condition stabilizes or no longer is clinically significant.

The following are discontinuation criteria from treatment for individual subjects:

- Subject develops radiological disease progression.
- Subject is required to receive another systemic anti-cancer treatment for underlying or new cancer.
- Subject develops unacceptable toxicity.
- Female subject becomes pregnant.
- Investigator decides it is in the subject's best interest to discontinue.
- Subject declines further treatment.
- Subject is noncompliant with the protocol based on the investigator or medical monitor assessment.

- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject.
- Death.

Subjects who discontinue treatment prior to radiological disease progression will enter the post treatment follow-up period and continue to undergo imaging assessments every 56 days (± 7 days) until PFS1 is documented by radiological disease progression or the subject starts another anticancer treatment, whichever occurs earlier.

Following PFS1, subjects will enter the long-term follow up period and be followed per institutional guidelines but not less than every 3 months from the date of the follow-up visit for survival status and progression on next line therapy until PFS2 is documented or the subject starts another anticancer treatment, whichever occurs earlier.

Subjects will then enter the survival follow-up period. Subjects will be followed every 3 months for survival status until any of the discontinuation criteria for OS are met. The subject will be discontinued from the OS post treatment follow-up period if any of the following occur:

- Subject declines further study participation (i.e., withdraws consent).
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject.
- Death.
- Study termination.

Concomitant Medication Restrictions or Requirements:

If the investigator determines that any of the following medications are deemed necessary to provide adequate medical support to the subject, the subject must be withdrawn from further administration of the study treatment:

- Other investigational drugs
- Chemotherapy or other medications intended for antitumor activity. This does not apply to subjects with a history of breast cancer on adjuvant endocrine therapy, or to subjects on agents intended for the treatment of bone metastasis (e.g., bisphosphonates, or RANK ligand inhibitors).
- Radiation therapy
- Note: Radiation therapy to a symptomatic solitary lesion or to the bone may be considered on an exceptional case-by-case basis after consultation with Sponsor. The radiated lesion must be a non-target lesion per RECIST V1.1 and the subject must have clear measurable disease outside the radiated field.

Arm A (Enfortumab vedotin)

- Subjects who are receiving strong cytochrome P450 (CYP)3A4 inhibitors or P-pg inhibitors concomitantly with EV should be closely monitored for adverse reactions.

Arm B (Docetaxel)

- Concomitant use of drugs that strongly inhibit or induce CYP3A4 may affect exposure to docetaxel and should be avoided.

Arm B (Vinflunine)

- Strong inhibitors or inducers of the CYP3A4 enzymes for subjects receiving vinflunine should be avoided.
- QT/QTc interval prolonging medicinal products should be avoided.

Arm B (Paclitaxel)

- Caution should be exercised when paclitaxel is administered with strong inhibitors or inducers of CYP3A4 and CYP2C8.

Please refer to the local package insert for concomitant medication restrictions or requirements for docetaxel, paclitaxel and vinflunine.

Duration of Treatment:

Subjects will be allowed to receive EV or comparator until discontinuation criteria are met or upon study termination, or study completion, whichever occurs first.

Endpoints for Evaluation:

Primary

- OS

Secondary

- PFS1 per RECIST V1.1
- ORR (complete response [CR] + PR) per RECIST V1.1
- DCR (CR + PR + stable disease [SD]) per RECIST V1.1
- DOR per RECIST V1.1
- Safety variables (e.g., AEs, laboratory tests, vital sign measurements, 12-lead electrocardiogram and ECOG PS)
- QOL and PRO parameters (QLQ-C30 and EQ-5D-5L)

Exploratory

- Exploratory genomic and/or other biomarkers in tumor tissue and in peripheral blood that may correlate with treatment outcome, including Nectin-4 expression
- Selected plasma or serum concentrations of TAb, ADC and MMAE
- Incidence of ATA to EV
- PFS2 per RECIST V1.1
- HRU

Statistical Methods:

Approximately 600 subjects will be randomized in a 1:1 ratio to 2 treatment arms: Arm A (EV) and Arm B (docetaxel, paclitaxel or vinflunine). Randomization will be stratified by:

- Liver Metastasis (yes/no)
- ECOG PS (0 vs 1)
- Regions of the world (US, Western Europe and Rest of World)

Sample Size Justification:

Approximately 600 subjects (with 10% dropout rate and 1 interim analysis) will be randomized in a 1:1 ratio to receive EV or chemotherapy.

- Primary endpoint: OS
- One-sided 2.5% Type I error; 85% Power
- OS Assumption: hazard ratio (HR) = 0.75 (median OS of 10.7m vs 8m, for EV vs Chemotherapy arm)
- A formal interim efficacy analysis will be done when approximately 65% of deaths have occurred.
- Primary analysis will occur at about 439 OS events

For planned interim efficacy analysis, a group sequential design using the O'Brien-Fleming boundaries as implemented by Lan-DeMets method will be used to control the overall 1-sided 0.025 type I error. If the interim analysis demonstrates a statistically significant outcome for EV in efficacy, the study may be stopped and concluded due to efficacy.

The Full Analysis Set (FAS) will be used for the efficacy analysis on OS and PFS1. All subjects who are randomized will be included in the FAS. For time to event endpoints including OS and PFS1 log-rank test stratified by randomization stratification factors including liver metastasis, baseline ECOG PS and regions of the world at baseline will be used to compare the 2 treatment arms. The hazard ratio and corresponding 95% confidence interval from the stratified Cox proportional hazards regression model will also be presented. The median OS, PFS1 and DOR will be estimated using the Kaplan-Meier method and will be reported along with the corresponding 95% confidence interval by treatment arm.

ORR and DCR will be compared between treatment arms using Cochran-Mantel-Haenszel test, stratified by the same stratification factors used in time to event analyses. The difference in response rates between the treatment arms will be estimated along with the corresponding 95% confidence interval.

Safety:

The Safety Analysis Set (SAF) will be used for the safety analysis. All subjects who are randomized and received study drug will be included in the SAF. The frequency of AEs and the serious AEs will be summarized by MedDRA system organ class and preferred term. In addition, summary statistics will be provided for the following safety parameters:

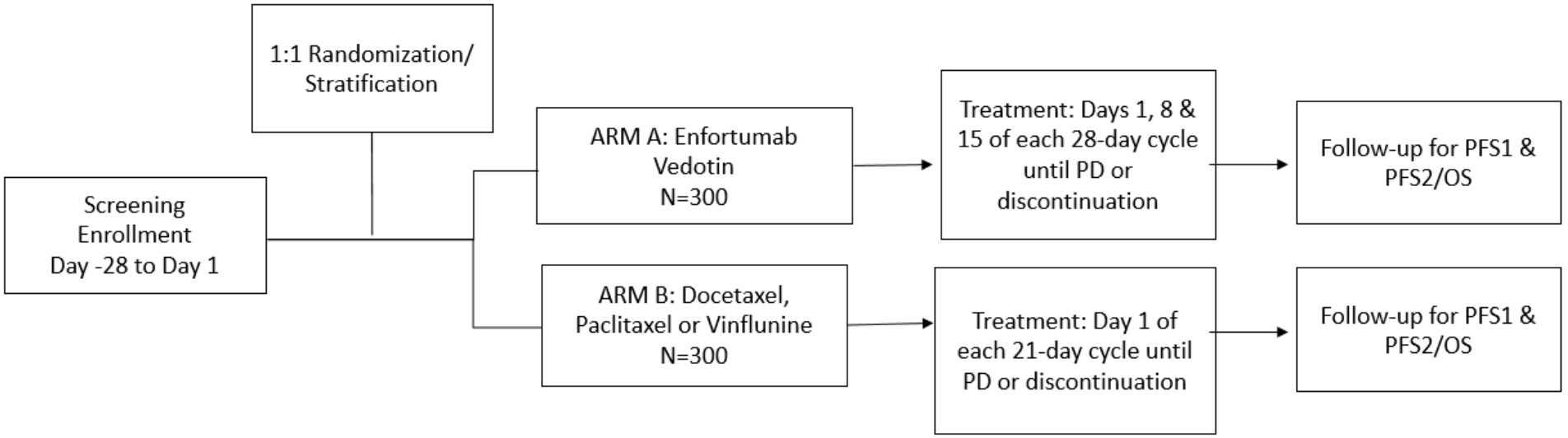
- Laboratory values
- Vital sign measurements
- ECOG PS

Pharmacokinetics:

Descriptive statistics (e.g., number, mean, standard deviation, minimum, median, maximum, coefficient of variation and geometric mean) will be provided for plasma or serum concentrations of TAb, ADC and MMAE. The incidence of ATA to EV will be summarized by cycle and overall, and possible relationship to pharmacokinetics explored. Additional model-based analyses and exposure response may be performed and reported separately.

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

Figure 1 Study Schema



OS: overall survival; PD: progressive disease; PFS: progression free survival; PFS1: progression free survival on study therapy; PFS2: progression free survival on subsequent therapy

*Imaging for both Arms will be performed at baseline and every 56 days (± 7 days) from the first dose of study treatment throughout the study until radiological disease progression, lost to follow-up, withdrawal of study consent, or start of a subsequent anti-cancer therapy. If a subject discontinues study drug prior to radiographic disease progression (i.e., PFS1), the subject should continue to undergo imaging assessment (including brain/bone imaging when indicated and collection of tumor measurements) every 56 days (± 7 days) in the post treatment follow-up period until PFS1 is documented per the investigator or the subject starts another cancer treatment, whichever occurs earlier. After PFS1, subjects will be followed in the long-term follow-up period per institutional guidelines, but not less frequently than every 3 months to confirm survival status and collect subsequent anticancer treatment details and progression status until PFS2 is documented or the subject starts another cancer treatment, whichever occurs earlier. Phone contact with subject is sufficient for follow-up. Additional follow-up contacts may be required per sponsor request for analysis purposes.

Table 1 Schedule of Assessments for Arms A and B

Visit	Screening/Baseline[1]		Every Cycle				End of Treatment[21]	Follow-up[18]	Post treatment Follow-Up	Long Term Treatment Follow-up	Survival Follow-up
Base Date	**Day -28 to -1**	**Day -7 to -1**	**Day 1**	**Day 8 Arm A (only)**	**Day 15 Arm A (only)**	**Every 56 Days**	**Date of Last Dose**	**Date of last Dose +30 days**	**Every 56 days**	**Every 3 months**	**Every 3 months**
Visit Window	NA	NA	± 3 days	± 3 day	± 3 days	± 7 days	+ 7 days	+ 7 days	± 7 days	± 7 days	± 7 days
Informed Consent	X										
Medical and Disease History	X										
Confirmation of Eligibility			X								
Tumor Tissue Sample[2]	X										
Brain Scan[3]	X					X			X		
Bone Scan[4]	X					X			X		
PGx blood sample (optional)		X									
Serum/Urine Pregnancy Test[5]		X	X				X	X	X[5]	X[5]	X[5]
Physical Examination[6]		X	X				X				
Weight		X	X	X[6]	X[6]		X				
Vital Signs		X	X	X[6]	X[6]		X	X			
Biochemistry[7]		X	X	X[7]	X[7]		X	X			
Hemoglobin A1C[8]		X					X				
Hematology[9]		X	X	X[9]	X[9]		X	X			
ECOG PS		X	X				X	X			
12-lead ECG[10]		X					X				
Ophthalmology Assessment[11]	X						X				
Randomization[12]		X									
Arm A: EV Administration – 28 Day Cycle[13]			X	X	X						
Arm B: Docetaxel/Paclitaxel/ Vinflunine Administration – 21 Day Cycle[14]			X								

Table continued on next page

Visit	Screening/Baseline [1]		Every Cycle				End of Treatment[21]	Follow-up[18]	Post treatment Follow-Up	Long Term Treatment Follow-up	Survival Follow-up
Base Date	Day -28 to -1	Day -7 to -1	Day 1	Day 8 Arm A (only)	Day 15 Arm A (only)	Every 56 Days	Date of Last Dose	Date of last Dose +30 days	Every 56 days	Every 3 months	Every 3 months
Visit Window	NA	NA	± 3 days	± 3 day	± 3 days	± 7 days	+ 7 days	+ 7 days	± 7 days	± 7 days	± 7 days
Image Assessment[15]	X					X[15]			X [19]		
Subsequent Therapy Assessment[20]							X	X	X	X	
Concomitant Medication	X	X	X	X	X	X	X	X			
AE	X	X	X	X	X	X	X	X			
QOL[16]		X	X				X	X			
HRU[22]			X [22]				X	X			
Overall Survival[17]								X	X	X	X

AE: adverse event; ALT: alanine transaminase; AST: aspartate transaminase; CR: complete response; CT: computed tomography; ECG: electrocardiogram; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EORTC-QLQ-C30: European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; EOT: end of treatment; EQ-5D-5L: EuroQOL 5-Dimension 5-Level Questionnaire; EV: enfortumab vedotin; HRU: health resource utilization; MRI: magnetic resonance imaging; NA: Not Applicable; PD: progressive disease; PFS1: progression free survival on study therapy; PFS2: progression free survival on subsequent therapy; PGx: Pharmacogenetic analyses; PR: partial response; QOL: quality of life; RECIST: Response Evaluation Criteria in Solid Tumors

1. Screening period is 28 days. Subjects may have screening assessments repeated once. If more than 1 assessment is taken during the screening, the assessment closest to enrollment date should be used for eligibility.
2. Archival tumor tissue (from primary or metastatic site) for biomarker studies should be available for submission to the Sponsor prior to study treatment. If an archival tumor tissue sample is not available, a fresh tissue sample should be provided. A tissue block or a minimum of 10 and up to 15 freshly sectioned, unstained charged slides should be provided.
3. Only if clinically indicated at baseline. Repeat as clinically indicated or per standard of care throughout the study.
4. All subjects will have a baseline bone scan (scintigraphy) performed at screening. Subjects with positive bone scans at baseline will have a bone scan performed every 56 days (± 7 days) throughout the study or more frequently if clinically indicated. Subjects should have a follow-up bone scan performed if clinically indicated regardless of baseline status.
5. For all female subjects of child bearing potential only, a urine or serum pregnancy test will be performed at baseline. A urine or serum pregnancy test will then be repeated on day 1 of each cycle prior to EV or chemotherapy administration, at EOT and Follow-up visits. After EOT, a monthly (± 7 days) pregnancy test will be maintained until 6 months after the last dose of study treatment.

Footnotes continued on next page

6. Full Physical examination and other evaluations including height (at screening only); weight, ECOG PS and vital signs (pulse, temperature and blood pressure) will be performed at screening. The physical examination will also be performed on day 1 of each cycle and EOT visit. Physical examination is only repeated on Cycle 1 Day 1 if clinically significant changes from Screening (in the opinion of the investigator) are observed. For subsequent and EOT visits physical examinations maybe more directed but should include examination of lungs, abdomen, skin and cardiovascular systems. Vital signs and weight will be completed on days 1, 8 and 15 of each cycle for Arm A and on day 1 of each cycle for Arm B, and at EOT visit. Vital signs will also be performed at follow up visit.
7. Biochemistry: See [Section 5.5.3 Laboratory Assessments]. Amylase and lipase will only be collected at screening and Day 1 of each Cycle. All biochemistry laboratory tests should be collected at the start of the following time points: Screening, Cycle 1 Day 1, Cycle 1 Day 8 (Arm A only), Cycle 1 Day 15 (Arm A only) and Day 1 of each subsequent cycle. If all biochemistry laboratory tests were performed within 7 days prior to the first day of dosing, they do not need to be repeated on Cycle 1 Day 1. Biochemistry tests will be sent to a central laboratory for analysis. Local laboratory results may be used to determine eligibility if the screening results from the central laboratory are not available in time for planned randomization. In the event that the central laboratory results received after randomization are not within eligibility parameters, the subject will still be considered eligible, if local labs met the eligibility criteria, and will not be considered a protocol deviation. Local laboratory results that support eligibility and dosing decisions must be entered into the clinical database. If local laboratory is to be used to support dosing decisions, local laboratory tests will include complete blood count (CBC) with differential, glucose, serum creatinine, ALT and AST. Additional assessments may be done centrally or locally to monitor AEs or as required by dose modification requirements.
8. If HbA1c is elevated (≥ 6.5%), refer subject to appropriate provider during Cycle 1 for glucose management.
9. Hematology: See [Section 5.5.3 Laboratory Assessments]. Hematology tests should be collected at the following time points: Screening, Cycle 1 Day 1, Cycle 1 Day 8 (Arm A only), Cycle 1 Day 15 (Arm A only) and Day 1 of each subsequent cycle. If hematology tests were performed within 7 days prior to the first day of dosing, they do not need to be repeated on Cycle 1 Day 1. Hematology tests will be sent to a central laboratory for analysis. Local laboratory results may be used to determine eligibility if the screening results from the central laboratory are not available in time for planned randomization. In the event that the central laboratory results received after randomization are not within eligibility parameters, the subject will still be considered eligible if local laboratory results met the eligibility criteria; such evens will not be considered protocol deviations. Local laboratory results that support eligibility and dosing decisions must be entered into the clinical database. If local laboratory is to be used to support dosing decisions, local laboratory tests will include CBC with differential, glucose, serum creatinine, ALT and AST. Additional assessments may be done centrally or locally to monitor AEs or as required by dose modification requirements.
10. ECGs will be read locally.
11. Ophthalmologic assessment for subjects with recent ocular complaints (within 3 months of screening) are required. Assessments should include the following: visual acuity, slit lamp, tonometry examination and dilated fundus examination. Prior ophthalmologic exam done within 3 months of screening is acceptable provided symptoms are not new since the exam. Ophthalmology assessments should be performed per standard of care or if clinically indicated (e.g., subject develops new or worsening ocular symptoms). EOT slit lamp examinations are required for subjects who experience corneal adverse events during the study. EOT slit lamp examinations must be performed ≥ 4 weeks from last dose. Additional eye examinations are to be conducted as clinically indicated.
12. Randomization will be allowed starting at Day -3 to allow for premedication in Arm B. Cycle 1 Day 1 treatment should occur within 3 days of randomization.
13. EV will be administered on Days 1, 8 and 15 of every 28-day cycle. Weight-based dosing is calculated using the subject's actual body weight on Day 1 of each cycle. The dose does not need to be recalculated based on actual weight on Day 8 and 15 of each cycle for Arm A unless it is required by institutional standards. At least 1 week must elapse between doses of EV. Subjects receiving EV should be observed during EV administration and for at least 60 minutes following the infusion for the first 3 cycles.
14. Docetaxel, paclitaxel or vinflunine will be administered on Day 1 of every 21-day cycle. Subjects receiving docetaxel, paclitaxel or vinflunine should be observed during study drug administration and for at least 30 minutes following the infusion during the first 3 cycles.

Footnotes continued on next page.

15. Imaging for Arms A & B will be evaluated at Baseline and every 56 days (± 7 days) throughout the study. CT scan with contrast (chest, abdomen and pelvis) is the preferred modality for tumor assessment. MRI is acceptable if local standard practice or if CT scans are contraindicated in a subject (e.g., subject is allergic to contrast media). All other RECIST approved scanning methods such as x-ray are optional. To ensure comparability, the screening and subsequent assessment of response should be performed using identical techniques. The same method should be employed and assessed by the same individual on each occasion if possible. Imaging assessments methods used at Baseline are to be used throughout the study.
16. QOL questionnaires (EORTC-QLQ-C30 and EQ-5D-5L) will be completed at Baseline (Day -7 to -1) and on Day 1 of each week (+7 days) for the first 12 weeks and then every 12 weeks afterward, EOT visit and at the follow-up visit. QOL questionnaire completion timing should be calculated based on Cycle 1 Day 1dosing. If a visit occurs out of the assessment window, QOL questionnaires should still be completed. QOL questionnaires will be completed by the subject at home on hand-held devices prior to coming to the clinic visit with the exception of Baseline Day 1 of the first week. The EOT and the follow-up visits at which the QOL questionnaires will be completed by the subject at the clinic.
17. Contact subjects in the survival follow-up period approximately every 3 months to collect survival status until subject death or study closure. Additional follow-up contacts may be required per sponsor request for analysis purposes.
18. Follow up assessments should be completed prior to the initiation of the next therapy.
19. If a subject discontinues study drug prior to radiographic disease progression (i.e., PFS1), the subject should continue to undergo imaging assessment (including brain/bone imaging when indicated and collection of tumor measurements) every 56 days (± 7 days) in the post-treatment follow-up period until PFS1 is documented per the investigator, or the subject starts another cancer treatment, whichever occurs earlier.
20. After PFS1, subjects will be followed in the long-term follow-up period per institutional guidelines, but not less frequently than every 3 months to confirm survival status and collect subsequent anticancer treatment details and progression status until PFS2 is documented or the subject starts another cancer treatment, whichever occurs earlier. Phone contact with subject is sufficient for follow-up. Additional follow-up contacts may be required per sponsor request for analysis purposes.
21. EOT visit will occur within 7 days after the last dose or when the decision is made by the investigator to discontinue subject from treatment.
22. HRU questionnaires will be completed monthly (Day 1 of every 4 weeks [+7 days]), starting on Week 5 Day 1 (timing calculated based on Cycle 1 Day 1dosing), and at the EOT and follow-up visit. HRU questionnaires will be completed by the subject at home on hand-held devices prior to coming to the clinic visit with the exception of the EOT and the follow-up visits at which the HRU questionnaires will be completed by the subject at the clinic.

Table 2 Pharmacokinetic, ATA and Biomarker Blood Sample Collection Time Points - Arm A

	Study Day	Time	Window	Relative Time	Blood				
							Biomarkers		
							Plasma		PBMC
					Pharmacokinetics	ATA	Cytokines	cf DNA	Immuno-phenotyping
Cycles 1	Day 1	Pre-dose	within 24 hr	START of infusion	X	X	X	X	X
		End of infusion	Within 15 min	END of infusion	X				
	Day 8	Pre-dose	Within 24 hrs	START of infusion	X		X		X
	Day 15	Pre-dose	Within 24 hrs	START of infusion	X		X		X
		End of infusion	Within 15 min	END of infusion	X				
Cycle 2	Day 1	Pre-dose	Within 24 hrs	START of infusion	X	X	X	X	X
Cycles 3, 4 , 6, 8 and 10	Day 1	Pre-dose	Within 24 hrs	START of infusion	X[A]	X[A]	X[B]	X[C]	X[B]
End of Treatment (Date of last dose + 7 days)					X	X	X	X	X
Follow-up (Date of last dose +30 days)					X	X			

ATA: antitherapeutic antibodies; PBMC: peripheral blood mononuclear cells; cfDNA: circulating free deoxyribonucleic acid

A. Pharmacokinetics and ATA: Pre-dose of cycle 3, 4, 6, 8 and 10
B. Cytokines and Immuno-phenotyping: Pre-dose cycles 3 and 4 only
C. cfDNA: Pre-dose every even numbered cycle up to 10 cycles (e.g., cycle 4, 6, 8, 10)

Table 3 Biomarker Blood Sample Collection Time Points - Arm B

	Study Day	Time	Window	Relative Time	Biomarkers		
					Plasma		PBMC
					Cytokines	cf DNA	Immuno-phenotyping
Cycle 1	Day 1	Pre-dose	Within 24 hr	START of infusion	X	X	X
Cycle 2	Day 1	Pre-dose	Within 24 hr	START of infusion	X	X	X
Subsequent Dosing Cycles	Day 1	Pre-dose	Within 24 hr	START of infusion	X[B]	X[A]	X[B]
End of Treatment (Date of last dose + 7 days)					X	X	X

cfDNA: circulating free deoxyribonucleic acid; PBMC: peripheral blood mononuclear cells

A. cfDNA: Pre-dose every even numbered cycle up to 10 cycles (e.g., cycle 4, 6, 8, 10)

B. Cytokines and immune-phenotyping: pre-dose cycles 3 and 4 only

1 INTRODUCTION

1.1 Urothelial Cancer

According to the International Agency for Research on Cancer (IARC), urothelial cancer kills more than 165000 patients annually and is the ninth most common cancer overall worldwide. Approximately 151000 new cases of urothelial cancer are diagnosed annually in Europe, with 52000 deaths per year. Over 22000 new cases are diagnosed annually in Japan, with 7600 deaths per year [Cancer Fact Sheets, 2017]. According to National Cancer Institute estimates, over 79000 new cases of urothelial cancer were diagnosed in 2017, and more than 16000 people died from the disease in the United States (US) [SEER Cancer Stat Facts, 2017].

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

For second line treatment, the small-molecule tubulin inhibitor vinflunine (Javlor®) is approved only in Europe. The median OS is 6.9 months compared to a median OS of 4.6 months for best supportive care [Bellmunt et al, 2009]. For decades, there were no major changes to the treatment landscape with only cytotoxic chemotherapies available, until the recent approvals of immune check point inhibitors (CPI) targeting the programmed death 1/programmed death-ligand 1 (PD-1/PD-L1). As of May 2016, starting with the PD-L1 inhibitor atezolizumab, several CPIs have received FDA approval for urothelial cancer for platinum-pretreated patients in the United States. Most approvals have been based on single arm phase II data [Tecentriq Prescribing Information, Genentech, Apr 2017], [Opdivo Prescribing Information, Bristol-Myers Squibb, September 2017], [Imfinzi Prescribing Information, AstraZeneca, May 2017] and [Bavencio Prescribing Information, EMD Serono, Mar 2017]. However, in 2017, results from the phase III trial KEYNOTE-045 demonstrated that patients treated with pembrolizumab had significantly longer survival when compared with the standard second-line chemotherapy [Bellmunt et al, 2017]. This led to the regular approval of pembrolizumab as second line treatment for patients with locally advanced or metastatic urothelial cancer (mUC; [Keytruda Prescribing Information, Merck, Sep 2017]). The approval was based on a median OS of 10.3 months for pembrolizumab compared with 7.4 months with taxane chemotherapy or vinflunine [Bellmunt et al, 2017]. Marketing approval of CPIs in Europe have followed and approvals in Asia are expected. Other PD-1 and PD-L1 inhibitors are currently being evaluated in clinical trials for urothelial cancer, as first and second line therapy [Mullane & Bellmunt, 2016].

Currently, no therapies are approved for patients with locally advanced or mUC previously treated with a CPI.

1.2 Nonclinical and Clinical Data

1.2.1 Enfortumab Vedotin Nonclinical Pharmacology

AGS-22M6E is an antibody drug conjugate (ADC) derived from a murine hybridoma cell line that was used in pharmacology and toxicology studies, as well as in a completed phase I study. The amino acid sequence of this antibody is identical to that of enfortumab vedotin (EV), the final product used for clinical development that is derived from a Chinese Hamster Ovary (CHO) cell line. In addition to having identical amino acid sequences, these 2 antibodies also have comparable pharmacological characteristics, such as binding affinity to Nectin-4, in vitro cytotoxicity, and in vivo antitumor activity [RD12-001, RD12-002, RD12-003, RD12-004]. Both AGS-22M6E and EV are ADCs comprised of a fully human IgG1κ antibody conjugated to the microtubule-disrupting agent MMAE, which targets human Nectin-4, a member of the Nectin family of adhesion molecules. Nectin-4 has been identified as one of the genes markedly upregulated in bladder cancer tissue [ES10-005, ES10-007].

AGS-22M6E specifically binds to human Nectin-4 with high affinity and cross-reacts with cynomolgus monkey and rat orthologs of Nectin-4 [RD10-013, RD10-018]. AGS-22M6E does not cross-react with other Nectin family members, such as Nectin-1, -2, and -3 [RD10-015].

In in vitro pharmacology studies, AGS-22M6E inhibited cell survival in a cell line engineered to express human Nectin-4. It was observed that AGS-22M6E was internalized after binding to Nectin-4 on the surface of cells [ES10-006]. Intracellular release of MMAE by proteolytic cleavage induced cell death. Antitumor activity of AGS-22M6E was evaluated in a panel of tumor xenograft models and significantly inhibited the tumor growth in a xenograft model of human bladder cancer [RD10-009].

1.2.2 Enfortumab Vedotin

Toxicokinetics, immunogenicity and comparability of AGS-22M6E and AGS-22C3E bulk drug substance were evaluated in a 4-week study comparing AGS-22M6E and AGS-22C3E administered by intravenous infusion in cynomolgus monkeys with a 6-week recovery period [CRL Study No. 20021751].

The toxicokinetics of the 2 materials, AGS-22M6E and AGS-22C3E were considered to be comparable. Please refer to the Investigator's Brochure for further details.

1.2.3 Enfortumab Vedotin Nonclinical Toxicology

In a 4-week GLP toxicity study in rats [CRL Study No. 20005662], AGS-22M6E (ADC: 2, 5 and 10 mg/kg) and AGS-22M6 (unconjugated antibody: 10 mg/kg) were intravenously administered once every week for a total of 4 doses. One animal administered AGS-22M6E at 10 mg/kg was noted with severe abrasions and had loss of bodyweight, and was found dead on Day 27. AGS-22M6E-related changes mainly included skin abrasion at 5 mg/kg and 10 mg/kg,

decreased body weight and food consumption at 10 mg/kg. Decreased indicators of red cell mass (red blood cell [RBC], hemoglobin concentration and hematocrit) and increased reticulocyte count at 5 and 10 mg/kg, were also observed. Increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) levels at 5 and 10 mg/kg, decreased testis weight with histopathological changes (tubular epithelial degeneration), and epididymides (hypospermia/abnormal spermatids in the ducts) were observed at all dose levels. Femur bone marrow hypocellularity, and skin ulceration and/or epidermal inflammation were seen at 5 and 10 mg/kg dosing. After the 6-week recovery period, the testicular and epididymal findings were more severe. Bone marrow hypocellularity and skin ulcers/inflammation resolved in the recovery animals. There were no adverse AGS-22M6-related findings. A no observed adverse effect level (NOAEL) following administration of AGS-22M6E for four weekly intravenous injections in rats was not established due to the findings noted in the testis.

In a 4-week GLP toxicity study in cynomolgus monkeys [CRL Study No. 200056640, AGS-22M6E (1, 3 and 6 mg/kg) and AGS-22M6 (6 mg/kg) were administered by intravenous infusion once weekly for a total of 4 doses. Administration of AGS-22M6E at 1 and 3 mg/kg was generally well tolerated, however doses of 6 mg/kg led to the unscheduled euthanasia of 3 animals on Day 11-13 due to severe dry skin/reddened skin and abrasions. These findings are considered a target-related effect based on the known expression of Nectin-4 in the epidermis of the skin. AGS-22M6E-related findings mainly included dry/reddened areas on the skin at all dose groups with ulceration, inflammation and hyperkeratosis in the skin at doses 3 mg/kg or more. Bone marrow suppression associated with MMAE toxicity included decreased reticulocyte count and red cell parameters, increased platelet counts, decreased neutrophils, eosinophils, and leukocyte counts at doses 3 mg/kg or more. All changes noted showed reversibility after a 6-week non-treatment period. There were no adverse AGS-22M6-related findings.

The NOAEL for once weekly administration of AGS-22M6E in cynomolgus monkeys was considered to be 3 mg/kg per day.

A 4-week GLP bridging study in cynomolgus monkeys [CRL Study No. 20021751] was conducted to evaluate comparability of the hybridoma cell line-derived product (AGS-22M6E) and the CHO cell line- derived product (AGS-22C3E) when given at the same dose of 3 mg/kg per week.

All test article-related effects identified in both AGS-22M6E and AGS-22C3E-dosed animals were at similar incidence and severity. After a 6-week non-treatment period, all test article-related effects returned to normal. The data support the conclusion that AGS-22M6E and AGS-22C3E demonstrate comparable toxicity profiles and toxicokinetic characteristics, when given at the same 3 mg/kg dose by intravenous infusion once weekly for 4 weeks to cynomolgus monkeys.

In genotoxic studies performed with other investigational compounds containing MMAE [ADCETRIS package insert] the MMAE was found to be genotoxic in the rat bone marrow micronucleus assay through an aneugenic mechanism. This effect is consistent with the

pharmacological effect of MMAE as a microtubule disrupting agent. MMAE was not mutagenic in the bacterial reverse mutation assay (Ames test) or mouse lymphoma assay [ADCETRIS package insert]. Maleimide, which is a component of the linker, is reported to be mutagenic in Ames test and mouse lymphoma assay.

1.2.4 Clinical Data

A phase 1 dose escalation and expansion study with EV monotherapy in patients with metastatic urothelial cancer and other malignant solid tumors is ongoing [Study ASG-22CE-13-2]. In this study, patients received doses of EV ranging from 0.5 to 1.25 mg/kg on Days 1, 8, and 15 of each 28-day cycle. As of the data cut-off date of 02 Oct 2017, 140 metastatic urothelial cancer patients had been enrolled in the phase 1 study. Interim data suggest that EV is generally well tolerated at doses up to 1.25 mg/kg.

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

Drug doses were reduced in 18 out of 140 metastatic urothelial cancer patients (13%) due to adverse events (AEs), including 16 out of 97 patients (17%) in the 1.25 mg/kg dose group.

Drug was withdrawn in 26 out of 140 (19%) metastatic urothelial cancer patients due to AEs, including 13 out of 97 (13%) from the 1.25 mg/kg dose group. Across all dose levels, drug was withdrawn from 12 out of 140 (8.6%) metastatic urothelial cancer patients due to AEs deemed possibly or probably related to EV. In the 1.25 mg/kg dose group, drug was withdrawn from 6 out of 97 (6%) metastatic urothelial cancer patients due to AEs deemed as possibly or probably related to EV. TEAEs leading to study drug discontinuation in more than 1 urothelial cancer patient included urosepsis, AST increased, blood creatinine increased, neuropathy peripheral and acute kidney injury (all events occurred in 2 subjects).

Fifty-five out of 140 (39%) metastatic urothelial cancer patients experienced at least one treatment emergent serious adverse event (SAE). Sixteen out of 140 (11%) patients had SAEs that were deemed by the investigator to be possibly or probably related to treatment. At the 1.25 mg/kg dose level, 31 out of 97 patients (32%) had at least one treatment emergent SAE. Nine patients (9%) at the 1.25 mg/kg dose level had SAEs that were deemed by the investigator to be possibly or probably related to treatment. As of the 02 Oct 2017 data cut-off date, there were 6 fatal TEAEs in 6 out of 140 (4%) metastatic urothelial cancer patients during this study, and 2 events were deemed to be drug-related (1 event of urinary tract obstruction and 1 event of respiratory failure). One patient experienced a serious adverse event of hyperglycemia in conjunction with a drug-related fatal event.

Following the data cut-off date, 2 additional treatment-related fatal events were reported in metastatic urothelial patients; 1 patient died of diabetic ketoacidosis and hyperglycemia and the other patient died of multi-organ failure in conjunction with a serious adverse event of

hyperglycemia. All active EV study protocols (including the current study) were amended to address this new safety information.

Preliminary EV data show encouraging antitumor activity in patients with metastatic urothelial cancer with either post-baseline imaging or who had discontinued treatment before imaging. As of the data cut-off date of 02 Oct 2017, there were 4 CRs and 29 partial responses (PRs) (ORR=27.3%, 33 of 121 patients) across dose levels. The ORR at 1.25 mg/kg (the dose level for the present study) was 32.1% (25 out of 78 patients).

EV also shows promising antitumor activity in metastatic urothelial cancer patients previously treated with CPIs who had either post-baseline imaging or had discontinued treatment before imaging. At the 1.25 mg/kg dose level, the ORR was 31% (17 of 55 patients).

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

1.3 Summary of Key Safety Information for Enfortumab Vedotin

Overall (data cutoff date 02 Oct 2017), 198 patients received at least 1 dose of EV across all studies (Study AGS-22M6E-11-1, Study ASG-22CE-13-2, Study 7465-CL-0101). AEs of interest for EV are based on current safety data from clinical studies and known risks with similar ADCs. Among them, the risks identified for EV are extravasation site reactions (important identified risk); rash, peripheral neuropathy, diarrhea, nausea and vomiting (identified risks); antitherapeutic antibodies (ATAs), infusion-related reactions (IRRs) other than extravasation, anemia and neutropenia, gastrointestinal disorders other than diarrhea, nausea and vomiting, ocular toxicity (corneal disorders), and hyperglycemia (potential risks). Please refer to the Investigator's Brochure for further details.

1.4 Risk Benefit Assessment

Subjects with locally advanced or metastatic urothelial cancer that has recurred or progressed following platinum-based chemotherapy present a challenge. While CPIs offer a new approach to treatment of metastatic urothelial cancer, tumor responses have occurred in a minority of patients and the improvement in long-term survival is only a few months. Most patients with locally advanced or metastatic urothelial cancer do not respond to CPIs and many who do respond ultimately develop disease progression [Rosenberg, 2016]. Currently, no therapies are approved for patients previously treated with a CPI. Although taxanes are not approved in this setting; they are a common choice for third line treatment (and were a standard second line treatment before atezolizumab was approved). Taxanes have response rates of approximately 10% as second line therapy, with progression-free survival (PFS) and OS of only 3.3 months and 7.4 months, respectively [Bellmunt et al, 2017]. Vinflunine is approved only in Europe and has an equally low response rate of 9% and a trend toward survival benefit when compared with best supportive care [Bellmunt et al, 2009]. No data are currently available regarding the clinical activity of taxanes or vinflunine in the third line setting after CPI therapy. The lack of approved therapies for patients with mUC after

treatment with a CPI and the limited activity observed with second line chemotherapy underscores the need for more treatment options in this patient population.

The potential risks associated with EV are outlined in [Sections 1.2.3, 1.2.4, and 1.3], and in the Investigator's Brochure. The potential risks associated with the chemotherapy comparators are well characterized and are outlined in [Section 5.1 Dosing and Administration of Study Drug(s) and Other Medication(s)], for more detailed information, please refer to their respective local product label.

Clinical data to date support a favorable benefit-risk ratio for EV in patients with locally advanced or metastatic urothelial carcinoma who previously received CPI therapy. Evidence of clinical activity has been observed in other single arm studies of EV (described in [Section 1.2.4 Clinical Data]) and this may translate into an improvement in effectiveness over the control arm. However, there may still be no direct benefit to subjects participating in the current clinical trial. To assure an ongoing favorable risk/benefit assessment for subjects enrolled into the study, an Independent Data Monitoring Committee (IDMC) will be utilized to monitor safety data and interim efficacy analysis.

2 STUDY OBJECTIVE(S), DESIGN AND ENDPOINTS

2.1 Study Objective(s)

2.1.1 Primary Objective

To compare the OS of subjects with locally advanced or metastatic urothelial cancer treated with EV to the OS of patients treated with chemotherapy.

2.1.2 Secondary Objectives

- To compare progression free survival on study therapy (PFS1) per Response Evaluation Criteria in Solid Tumors (RECIST) V1.1 of subjects treated with EV to patients treated with chemotherapy
- To compare the overall response rate (ORR) per RECIST V1.1 of EV to chemotherapy
- To evaluate the duration of response (DOR) per RECIST V1.1 of EV and chemotherapy
- To compare the disease control rate (DCR) per RECIST V1.1 of EV to chemotherapy
- To assess the safety and tolerability of EV
- To assess quality of life (QOL) and Patient Reported Outcomes (PRO) parameters

2.1.3 Exploratory Objectives

- Exploratory genomic and/or other biomarkers in tumor tissue and in peripheral blood that may correlate with treatment outcome, including Nectin-4 expression
- To assess the pharmacokinetics of EV (TAb, ADC and MMAE)
- To assess the incidence of ATA
- To evaluate PFS as assessed by RECIST V1.1 by investigator review in the next line of therapy (PFS2) in subjects treated with EV compared to docetaxel, paclitaxel or vinflunine.
- Healthcare resources utilization (HRU)

2.2 Study Design and Dose Rationale

2.2.1 Study Design

This is a global, open-label, randomized Phase 3 study in adult subjects with locally advanced or metastatic urothelial cancer who have received a platinum-containing chemotherapy and have experienced disease progression or relapse during or following treatment with an immune checkpoint inhibitor. Subjects who discontinued CPI treatment due to toxicity are eligible provided that they have evidence of disease progression following discontinuation. Approximately 600 subjects will be randomized to EV (Arm A) or chemotherapy (Arm B) in a 1:1 ratio. Subjects will be stratified according to the following: Eastern Cooperative Oncology Group Performance Status (ECOG PS), regions of the world and liver metastasis.

OS is the primary endpoint. OS is defined as the time from randomization to the date of death. Secondary endpoints include PFS1, ORR, DOR, DCR, safety and QOL/PRO.

Subjects in Arm A will receive EV on Days 1, 8 and 15 of each 28-day cycle. Subjects in arm B will receive docetaxel, paclitaxel or vinflunine as decided by the investigator prior to randomization, (vinflunine is a choice of comparator only in countries where it is approved for urothelial cancer) on Day 1 of every 21-day cycle. Within the control arm, the overall proportion of subjects receiving vinflunine will be capped at approximately 35%. Subjects will continue to receive study treatment until radiological disease progression as determined per investigator assessment or other discontinuation criteria are met or upon study termination, or study completion, whichever occurs first. No on-study crossover will be allowed other than as allowed in [Appendix 12.10]. Subjects assigned to the chemotherapy arm will not be allowed to switch to a different chemotherapy treatment during study treatment. This study will consist of three phases: screening, treatment and follow-up.

Screening will take place up to 28 days prior to randomization. Screening assessments may be repeated within the 28-day screening period.

Subjects do not need to be “screen failed” in IRT and re-entered in screening with a new subject ID as long as the subject is enrolled within the 28-day window from signing of the informed consent. If more than 28 days elapses from the date of signing the informed consent, the subject must be screen failed in IRT. A new consent must be signed and the subject entered into screening with a new subject ID. Subjects may only be rescreened once.

Subjects will start with cycle 1 and continue on to subsequent 21-day or 28-day cycles until one of the discontinuation criteria are met or upon study termination, or study completion, whichever occurs first. A treatment cycle is defined as 28 days for Arm A and 21 days for Arm B.

Subjects will be evaluated for response according to RECIST V1.1. Imaging for both arms will be performed at baseline and every 56 days (± 7 days) from the first dose of study treatment throughout the study until PFS1 is documented by radiological disease progression or the subject is lost to follow-up, death, withdraws study consent or starts a subsequent anti-cancer therapy. Baseline imaging performed prior to informed consent as standard of care

may be used so long as it is performed within 28 days prior to randomization. All subjects will have a bone scan (scintigraphy) performed at screening/baseline. Subjects with positive bone scans at baseline will have a bone scan performed every 56 days (± 7 days) throughout the study or more frequently if clinically indicated. Subjects should have a follow-up bone scan performed if clinically indicated regardless of baseline status. Brain scans (computed tomography [CT] with contrast/magnetic resonance imaging [MRI]) will only be performed if clinically indicated at screening/baseline and repeated as clinically indicated or per standard of care throughout the study.

QOL assessments and PRO will be collected at protocol-specified time points from all randomized subjects. The following validated tools will be used: European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) and EuroQOL 5-dimension 5-Level Questionnaire (EQ-5D-5L). HRU information will be collected at protocol-specified time points with particular focus on the number of subjects who have an unplanned use of healthcare resources related to clinical or AEs from subjects assigned to treatment arms A and B.

Blood samples for pharmacokinetics and ATA will be collected throughout the study for subjects randomized into Arm A. Validated assays will be used to measure the concentrations of EV ADC and monomethylauristatin E (MMAE) in serum or plasma and to assess ATA. Pharmacokinetic samples will not be collected from subjects randomized into Arm B. Samples for exploratory biomarkers will be collected at protocol-specified time points. Biomarker assessments will not be used for subject selection.

Following discontinuation from study drug, subjects will have a follow-up visit 30 days (+ 7 days) after their last dose of drug for safety assessments. If a subject discontinues study drug prior to radiographic disease progression (i.e., PFS1), the subject should enter the post-treatment follow-up period and continue to undergo imaging assessments every 56 days (± 7 days) until PFS1 is documented, or the subject starts another anticancer treatment, whichever occurs earlier.

Following PFS1, subjects will enter the long-term follow-up period and be followed per institutional guidelines but not less than every 3 months from the date of the follow-up visit for survival status and progression status on subsequent therapy (i.e., PFS2).

Subjects will be followed until PFS2 is documented or the subject starts another anticancer treatment, whichever occurs earlier. All subsequent anticancer therapy including date and site of progression for PFS2 will be recorded on the case report form.

Following PFS2, subjects will enter the survival follow-up period and be followed every 3 months for survival status until death, lost to follow-up, withdrawal of study consent, or study termination by sponsor. This study is expected to end once final survival analysis is complete. Subjects will be eligible to continue receiving treatment in this study until they meet a discontinuation criterion as outlined in [Section 6 Discontinuation] or upon study termination, or study completion, whichever occurs first.

An IDMC will be chartered to oversee safety and the planned interim efficacy analysis, which will occur after at least 285 OS events (about 65% of the total planned events) are observed. The primary analysis will occur at 439 OS events. The IDMC may recommend to the sponsor whether the trial should be terminated, modified or continue unchanged based on ongoing reviews of safety data and interim efficacy analysis. Further details will be outlined in the IDMC charter.

2.2.2 Dose Rationale

Enfortumab Vedotin

EV will be administered at a dose of 1.25 mg/kg as an intravenous infusion over approximately 30 minutes on Days 1, 8, and 15 of each 28-day cycle. This dose and regimen has demonstrated an acceptable safety profile and encouraging clinical activity in the phase 1 study [Study ASG-22CE-13-2], which evaluated escalating dose levels of 0.5, 0.75, 1 and 1.25 mg/kg, with expansion cohorts at the 0.75, 1, and 1.25 mg/kg dose levels. A maximum tolerated dose (MTD) was not reached in this study. At the 1 mg/kg dose level, 2 dose-limiting toxicities (DLTs) were observed: Grade 3 proctalgia (later changed to grade 2 by the investigator) thought related to radiation recall and Grade 4 hyperuricemia without clinical sequelae. No DLT was observed at 1.25 mg/kg and doses above 1.25 mg/kg were not tested.

Incidence of some of the most frequent drug-related AEs, such as diarrhea and rash, although primarily Grades 1–2 and clinically manageable, increased with increasing dose levels. Moreover, dose reductions due to AEs were more frequent for the 1.25 mg/kg vs lower dose levels. Safety assessments of both metastatic urothelial cancer patients and non-metastatic urothelial cancer patients showed that frequency of all TEAEs, AEs leading to withdrawal, and Grade 3–4 TEAEs were comparable across all dose levels.

While all doses of EV demonstrated activity, the 1.25 mg/kg dose was associated with the highest activity and had an acceptable safety profile.

Based on pharmacokinetic data from the phase 1 study [Study ASG-22CE-13-2], the half-life of EV is ~ 1 – 2 days. No notable (< 30%) intra-cycle accumulation of ADC was observed with the current dosing regimen (on Days 1, 8 and 15 of every 28-day cycle) at any dose level. Minimal (< 50%) intra-cycle accumulation of MMAE was observed. It is anticipated that the dosing schedule in the study will maintain ADC exposures over each 28-day cycle, contributing to a favorable balance of activity and safety, as observed in the phase 1 trial [Study ASG-22CE-13-2].

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

Comparators

There is no accepted standard of care following CPI treatment for locally advanced or mUC; however, prior to CPI approvals, taxanes were commonly used following platinum-based therapy as recommended in the treatment guidelines [NCCN, 2017; ESMO, 2017]. In

addition, vinflunine is approved in Europe for treatment of mUC after failure of a prior platinum-based regimen [Bellmunt et al, 2011].

KEYNOTE-045, a multicenter, randomized, active-controlled trial in patients with locally advanced or mUC with disease progression on or after platinum-containing chemotherapy, compared pembrolizumab to investigator's choice of paclitaxel, docetaxel, or vinflunine every 3 weeks [Bellmunt et al, 2017].

Although no labeled dosing guidelines for taxanes are available in this setting, this is the only large randomized trial that has reported combined survival data for these agents, as such the current phase 3 study of enfortumab vs chemotherapy will use the same choice of comparators and their corresponding doses. Patients randomized to the chemotherapy arm in the KEYNOTE-045 study were treated with paclitaxel (175 mg/m^2), docetaxel (75 mg/m^2) or vinflunine (320 mg/m^2), administered intravenously every 3 weeks. The overall proportion of subjects receiving vinflunine in the control arm was capped at approximately 35% (KEYNOTE protocol).

2.3 Endpoints

2.3.1 Primary Endpoints

- OS

2.3.2 Secondary Endpoints

- PFS1 by RECIST V1.1
- ORR (CR + PR) by RECIST V1.1
- DCR (CR + PR + SD) by RECIST V1.1
- DOR by RECIST V1.1
- Safety variables (e.g., AEs, laboratory tests, vital sign measurements, 12-lead ECG and ECOG PS)
- QOL and PRO parameters (QLQ-C30 and EQ-5D-5L)

2.3.3 Exploratory Endpoints

- Exploratory genomic and/or other biomarkers in tumor tissue and in peripheral blood that may correlate with treatment outcome, including Nectin-4 expression
- Plasma or serum concentrations of TAb, ADC and MMAE
- Incidence of ATA to EV
- PFS2
- HRU

3 STUDY POPULATION

3.1 Selection of Study Population

Patients with locally advanced or metastatic urothelial cancer previously treated with platinum-based chemotherapy and an immune checkpoint inhibitor (CPI).

3.2 Inclusion Criteria

Subject is eligible for the study if all of the following apply:

1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written informed consent and privacy language as per national regulations (e.g., Health Insurance Portability and Accountability Act [HIPAA] Authorization for US sites) must be obtained from the subject prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).

2. Subject is legally an adult according to local regulation at the time of signing informed consent.

3. Subject has histologically or cytologically confirmed urothelial carcinoma (i.e., cancer of the bladder, renal pelvis, ureter, or urethra). Subjects with urothelial carcinoma (transitional cell) with squamous differentiation or mixed cell types are eligible.

4. Subject must have experienced radiographic progression or relapse during or after a CPI (anti-programmed cell death protein-1 [PD-1] or anti-programmed cell death-ligand 1 [PD-L1]) for locally advanced or metastatic disease. Subjects who discontinued CPI treatment due to toxicity are eligible provided that they have evidence of disease progression following discontinuation. The CPI need not be the most recent therapy. Subjects for whom the most recent therapy has been a non-CPI based regimen are eligible if they have progressed/relapsed during or after their most recent therapy. Locally advanced disease must not be amenable to resection with curative intent per the treating physician.

5. Subject must have received a platinum containing regimen (cisplatin or carboplatin) in the metastatic/locally advanced, neoadjuvant or adjuvant setting. If platinum was administered in the adjuvant/neoadjuvant setting subject must have progressed within 12 months of completion.

6. Subject has radiologically documented metastatic or locally advanced disease at baseline.

7. An archival tumor tissue sample should be available for submission to central laboratory prior to study treatment. If an archival tumor tissue sample is not available, a fresh tissue sample should be provided. If a fresh tissue sample cannot be provided due to safety concerns, enrollment into the study must be discussed with the medical monitor.

8. Subject has ECOG PS of 0 or 1.

9. The subject has the following baseline laboratory data:

- absolute neutrophil count (ANC) ≥ 1500/mm^3
- platelet count ≥ 100 × 10^9/L
- hemoglobin ≥ 9 g/dL
- serum total bilirubin ≤ 1.5 × upper limit of normal (ULN)* or ≤ 3 × ULN for subjects with Gilbert's disease
- creatinine clearance (CrCl) ≥ 30 mL/min as estimated per institutional standards or as measured by 24 hour urine collection (glomerular filtration rate [GFR] can also be used instead of CrCl)
- ALT and AST ≤ 2.5 × ULN or ≤ 3 × ULN for subjects with liver metastases*

*Docetaxel should not be chosen as a comparator for subjects if total bilirubin > ULN, or if AST and/or ALT > 1.5 × ULN concomitant with alkaline phosphatase > 2.5 × ULN.

10. Female subject must either:

- Be of nonchildbearing potential:
  - Postmenopausal (defined as at least 1 year without any menses for which there is no other obvious pathological or physiological cause) prior to screening, or
  - Documented surgically sterile (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy).

  Note: Those who are amenorrheic due to an alternative medical cause are not considered postmenopausal and must follow the criteria for childbearing potential subjects.

- Or, if of childbearing potential:
  - Agree not to try to become pregnant during the study and for at least 6 months after the final study drug administration,
  - And have a negative urine or serum pregnancy test within 7 days prior to Day 1 (Females with false positive results and documented verification of negative pregnancy status are eligible for participation),
  - And if heterosexually active, agree to consistently use a condom plus 1 form of highly effective birth control * per locally accepted standards starting at screening and throughout the study period and for at least 6 months after the final study drug administration.

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

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

- Agrees to use a male condom starting at screening and continue throughout the study treatment and for at least 6 months after final study drug administration. If the male subject has not had a vasectomy or is not sterile as defined below his female partner(s) is utilizing 1 form of highly effective birth control* per locally accepted standards starting at screening and continue throughout study treatment and for at least 6 months after the male subject receives his final study drug administration.

*Highly effective forms of birth control include:

- Consistent and correct usage of established hormonal contraceptives that inhibit ovulation,
- Established intrauterine device (IUD) or intrauterine hormone releasing system (IUS).
- Bilateral tubal occlusion
- Vasectomy (A vasectomy is a highly effective contraception method provided the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used)
- Male is sterile due to a bilateral orchiectomy or radical cystoprostatectomy/removal of seminal vesicles
- Sexual Abstinence is considered a highly effective method only if defined as refraining from heterosexual activity during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant

Please note: Sexual abstinence is not sufficient as contraception method in Switzerland

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

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

15. Subject agrees not to participate in another interventional study while on treatment in present study.

Waivers to the inclusion criteria will **NOT** be allowed.

3.3 Exclusion Criteria

Subject will be excluded from participation if any of the following apply:

1. Subject has preexisting sensory or motor neuropathy Grade ≥ 2.

2. Subject has active central nervous system (CNS) metastases. Subjects with treated CNS metastases are permitted on study if all the following are true:
- CNS metastases have been clinically stable for at least 6 weeks prior to screening
- If requiring steroid treatment for CNS metastases, the subject is on a stable dose ≤ 20 mg/day of prednisone or equivalent for at least 2 weeks
- Baseline scans show no evidence of new or enlarged brain metastasis
- Subject does not have leptomeningeal disease

3. Subject has ongoing clinically significant toxicity (Grade 2 or higher with the exception of alopecia) associated with prior treatment (including systemic therapy, radiotherapy or surgery). Subject with ≤ Grade 2 immunotherapy-related hypothyroidism or panhypopituitarism may be enrolled when well-maintained/controlled on a stable dose of hormone replacement therapy (if indicated). Patients with ongoing ≥ Grade 3 immunotherapy-related hypothyroidism or panhypopituitarism are excluded. Subjects with ongoing immunotherapy related colitis, uveitis, myocarditis, or pneumonitis or subjects with other immunotherapy related AEs requiring high doses of steroids (> 20 mg/day of prednisone or equivalent) are excluded.

4. Subject has prior treatment with EV or other MMAE-based ADCs.

5. Subject has received prior chemotherapy for urothelial cancer with all available study therapies in the control arm (i.e., both prior paclitaxel and docetaxel in regions where vinflunine is not an approved therapy, or prior paclitaxel, docetaxel and vinflunine in regions where vinflunine is an approved therapy).

Note: After vinflunine cap is reached, subjects who have received both docetaxel and paclitaxel will be excluded.

6. Subject has received more than 1 prior chemotherapy regimen for locally advanced or metastatic urothelial cancer, including chemotherapy for adjuvant or neo-adjuvant disease if recurrence occurred within 12 months of completing therapy. The substitution of carboplatin for cisplatin does not constitute a new regimen provided no new chemotherapeutic agents were added to the regimen.

7. Subject has history of another malignancy within 3 years before the first dose of study drug, or any evidence of residual disease from a previously diagnosed malignancy. Subjects with nonmelanoma skin cancer, localized prostate cancer treated with curative intent with no evidence of progression, low-risk or very low-risk (per standard guidelines) localized prostate cancer under active surveillance/watchful waiting without intent to treat, or carcinoma in situ of any type (if complete resection was performed) are allowed.

8. Subject is currently receiving systemic antimicrobial treatment for viral, bacterial, or fungal infection at the time of first dose of EV. Routine antimicrobial prophylaxis is permitted.

9. Subject has known active Hepatitis B (e.g., HBsAg reactive) or active hepatitis C (e.g., HCV RNA [qualitative] is detected).

10. Subject has known history of human immunodeficiency virus (HIV) infection (HIV 1 or 2).

11. Subject has documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, myocardial infarction, or cardiac symptoms (including congestive heart failure) consistent with New York Heart Association Class III to IV within 6 months prior to the first dose of study drug.

12. Subject has radiotherapy or major surgery within 4 weeks prior to first dose of study drug.

13. Subject has had chemotherapy, biologics, investigational agents, and/or antitumor treatment with immunotherapy that is not completed 2 weeks prior to first dose of study drug.

14. Subject has known hypersensitivity to EV or to any excipient contained in the drug formulation of EV (including histidine, trehalose dihydrate, and polysorbate 20); OR subject has known hypersensitivity to biopharmaceuticals produced in CHO cells.

15. Subject has known hypersensitivity to the following:

- docetaxel or to any of the other excipients listed in product label, including polysorbate 80;
- paclitaxel or to any of the other excipients listed in product label, including macrogolglycerol ricinoleate 35 (Ph.Eur.); and
- vinflunine or to any of the other excipient listed in product label, including other vinca alkaloids (vinblastine, vincristine, vindesine, vinorelbine).

16. [Criterion removed].

17. Subject has known active keratitis or corneal ulcerations. Subject with superficial punctate keratitis is allowed if the disorder is being adequately treated in the opinion of the investigator.

18. Subject has other 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.

19. History of uncontrolled diabetes mellitus within 3 months of the first dose of study drug. Uncontrolled diabetes is defined as hemoglobin A1C (HbA1c) ≥ 8% or HbA1c between 7 and < 8% with associated diabetes symptoms (polyuria or polydipsia) that are not otherwise explained.

Waivers to the exclusion criteria will **NOT** be allowed.

4 TREATMENT(S)

4.1 Identification of Investigational Product(s)

4.1.1 Study Drug(s)

The investigational product, EV (ASG-22CE), is a sterile, preservative-free, white to off-white lyophilized powder to be reconstituted for intravenous administration. The investigational product is supplied by Astellas in single-use glass vials containing 30 mg EV (ASG-22CE) in each vial. The investigational product should be stored at 2-8°C. Details of investigational product receipt, labeling, storage and preparation are provided in a supplemental pharmacy guide.

4.1.2 Comparative Drug(s)

Comparative drugs will be supplied by the responsible site pharmacy of each investigational site. If the site is unable to procure or utilize local supplies for the comparative drug, supplies may be provided centrally by the sponsor as applicable. Sites are permitted to utilize generic docetaxel and paclitaxel that is approved by the respective regulatory authority. Refer to product labels for docetaxel, paclitaxel and vinflunine for storage & handling conditions and caution statements.

Please refer to [Section 5.1 Dosing and Administration of Study Drug(s) and Other Medication(s)] for specific dosing instructions.

For sponsor supplied comparative drug, details of product receipt, labeling, storage and preparation are provided in a supplemental pharmacy guide.

4.2 Packaging and Labeling

EV (ASG-22CE) used in this study will be prepared, packaged, and labeled under the responsibility of qualified staff at APGD-Astellas US Technologies (AUST) or sponsor's designee in accordance with APGD-AUST or sponsor's designee Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, ICH GCP guidelines, and applicable local laws/regulations.

Each carton and vial will bear a label conforming to regulatory guidelines, GMP and local laws and regulations that identifies the contents as investigational drug.

Where supplied by the Sponsor, the comparative drug(s) used in this study will be labeled under the responsibility of APGD-AUST or sponsor's designee in accordance with APGD-AUST or sponsor's designee SOPs, GMP guidelines, ICH GCP guidelines, and applicable local laws/regulations.

A qualified person of Astellas Pharma Europe B.V. (APEBV) or sponsor's designee will perform the final release of the medication according to the requirements of the EU Directive 2003/94/EC annex 13.

4.3 Study Drug Handling

Current ICH GCP Guidelines require the investigator to ensure that study drug deliveries from the sponsor are received by the investigator/or designee and that:

- such deliveries are recorded,
- study drug is handled and stored according to labeled storage conditions,
- study drug with appropriate expiry/retest and is only dispensed to study subjects in accordance with the protocol, and
- any unused study drug is returned to the sponsor or standard procedures (reviewed and approved by Astellas) for the alternative disposition of unused study drug are followed.

The head of the study site or the study drug storage manager should take accountability of the study drugs as follows:

- The study drug storage manager should store and take accountability of the study drugs in conforming to the procedures for handling the study drugs written by the sponsor.
- The study drug storage manager should prepare and retain records of the study drug's receipt, the inventory at the study site, the use by each subject, and the return to the sponsor or alternative disposal of unused study drugs. These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the study drugs and subjects.
- The study drug storage manager should prepare and retain records that document adequately that the subjects were provided the doses specified by the protocol, and reconcile all the study drugs supplied from the sponsor.

4.4 Blinding

This is an open label study.

Although the study is an open label study, to maintain trial integrity, analyses or summaries by randomized treatment assignment or actual treatment assignment will be limited and documented while the study is ongoing and before the primary hard lock. Interim analysis will be conducted externally by independent data analysis center (IDAC). Details will be included in SAP.

4.5 Assignment and Allocation

Subjects will be randomized in a 1:1 ratio to a treatment arm according to the randomization schedules through Interactive Response Technology (IRT). All subjects who meet the eligibility criteria will be randomized. The site personnel will dispense the treatment according to the IRT system’s assignment. Specific procedures for randomization through the IRT are contained in the study procedures manual. Investigators must select one treatment among the Arm B options before randomization occurs to be used in the event that the subject is randomized to the Arm B. Within the control arm, the overall proportion of subjects receiving vinflunine will be capped at approximately 35%.

5 TREATMENTS AND EVALUATION

5.1 Dosing and Administration of Study Drug(s) and Other Medication(s)

5.1.1 Dose/Dose Regimen and Administration Period

5.1.1.1 Enfortumab Vedotin

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

Weight-based dosing is calculated using the subject's actual body weight on Day 1 of each cycle. The dose does not need to be re-calculated based on actual weight on Day 8 and 15 of each cycle for Arm A unless it is required by institutional standards. An exception to weight-based dosing is made for subjects weighing greater than 100 kg; doses will be based on 100 kg for these individuals. The maximum dose permitted on this study is 125 mg. Subject weight must be measured during all relevant assessment time points as described in the schedule of events.

The subject should be observed during EV 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 injection 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.

5.1.1.2 Comparative Drug(s)

Local product labels or summary of product characteristics (SmPC) and institutional guidelines will be followed for the administration of chemotherapy agents and precautions taken to prevent extravasation per institutional standards and as described in "Chemotherapy and Biotherapy Guidelines and Recommendations for Practice" [Polovich et al, 2014] and "Management of Chemotherapy Extravasation: ESMO-EONS Clinical Practice Guidelines" [Fidalgo et al, 2012].

Male subjects randomized to receive docetaxel, vinflunine or paclitaxel should seek medical advice regarding cryopreservation of sperm prior to receiving treatment due to the possibility of infertility.

5.1.1.2.1 Docetaxel

Study treatment of docetaxel should be administered as an intravenous infusion on Day 1 of every 21-day cycle after all procedures/assessments have been completed, including the required premedication per local standard of care prior to Day 1. Docetaxel will be administered at 75 mg/m^2 unless specified otherwise in [Sections 5.1.2.2 and 5.1.2.3]. Refer to local product label or SmPC where supplied centrally and institution guidelines for docetaxel for further guidance on docetaxel dosing.

Docetaxel will be administered over 1 hour or per local guidelines. The subject should be observed during docetaxel administration and for at least 30 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.

All subjects should be premedicated per local standard of care with corticosteroids, such as dexamethasone 16 mg/day orally (e.g., 8 mg twice daily) for 3 days starting 1 day prior to docetaxel administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. The appropriate premedication regimen may be determined by the investigator.

5.1.1.2.2 Vinflunine

Study treatment of vinflunine should be administered as an intravenous infusion on Day 1 of every 21-day cycle after all procedures/assessments have been completed. Vinflunine will be administered at 320 mg/m^2 unless otherwise specified in [Section 5.1.2.4 Vinflunine Dose Modifications]. See [Section 5.1.2.4 Vinflunine Dose Modifications] for guidelines on adjustment of initial dose. The subject should be observed during vinflunine administration and for at least 30 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. Refer to local product label or SmPC and institution guidelines for vinflunine for further guidance on vinflunine dosing.

5.1.1.2.3 Paclitaxel

Study treatment of paclitaxel should be administered as an intravenous infusion on Day 1 of every 21-day cycle after all procedures/assessments have been completed. Paclitaxel will be administered at 175 mg/m^2 unless specified otherwise in [Section 5.1.2.5 Paclitaxel Dose Modifications]. See [Section 5.1.2.5 Paclitaxel Dose Modifications] for guidelines on adjustment of initial dose. Paclitaxel should be administered over 3 hours or per local guidelines. The subject should be observed during paclitaxel administration and for at least 30 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. Refer to local product label or SmPC and institution guidelines for paclitaxel for further guidance on paclitaxel dosing.

All subjects should be premedicated prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg

orally administered approximately 12 and 6 hours before paclitaxel, diphenhydramine (or its equivalent) 50 mg intravenous 30 to 60 minutes prior to paclitaxel, and cimetidine (300 mg) or ranitidine (50 mg) intravenous 30 to 60 minutes before paclitaxel. The appropriate premedication regimen may be determined by the investigator.

5.1.2 Increase or Reduction in Dose of the Study Drug(s)

5.1.2.1 Enfortumab Vedotin

Dose reduction to 1 mg/kg (dose level - 1) and to 0.75 mg/kg (dose level - 2) will be allowed depending on the type and severity of toxicity. Subjects requiring a dose reduction may be re-escalated by 1 dose level (i.e., 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.

EV should not be administered to subjects with CrCl < 30 mL/min. Dose modification recommendations for EV associated toxicity are presented in Table 4 and Table 5. Dose interruptions for other EV associated toxicity is permitted at the discretion of the site investigator. Dose interruptions may last up to 8 weeks (2 cycles). Dose interruptions for subjects who are deriving clinical benefit from treatment may be extended beyond 8 weeks, if the subject's toxicity does not otherwise require permanent discontinuation. If there is a dose interruption, the schedule for response assessments will not be adjusted.

Table 4 Recommended dose modifications for enfortumab vedotin associated hematologic toxicity*

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

Table 5 Recommended dose modifications for enfortumab vedotin associated nonhematologic toxicity

Grade 1	Grade 2	Grade 3	Grade 4
Continue at same dose level. If ocular symptoms and/or changes in vision are identified, the subject should be evaluated with an ophthalmologic exam.**	Continue at same dose level, except in the event of Grade 2 neuropathy or corneal AEs. For Grade 2 neuropathy or corneal AE's, withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, and then resume treatment at the same dose level. For the second occurrence of Grade 2 neuropathy or corneal AE's, withhold dose until toxicity is ≤ Grade 1, and 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 with an ophthalmologic exam.**	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 3 neuropathy or corneal AEs, discontinue treatment. For Grade 3 hyperglycemia/ elevated blood glucose, withhold EV treatment. Resume treatment once hyperglycemia/ elevated blood glucose has improved to ≤ Grade 2 and subject is clinically and metabolically stable. If ocular symptoms and/or changes in vision are identified, the subject should be evaluated with an ophthalmologic exam.**	For Grade 4 AEs, discontinue treatment.* Grade 4 vomiting and/or diarrhea that improves to ≤ Grade 2 or less within 72 hours with supportive management does not require discontinuation. .

AE: adverse event; EV: enfortumab vedotin

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

**Ophthalmologic exam should be performed by an ophthalmologist. In countries where optometrists can perform exams and prescribe medications, an optometrist may be used instead.

Enfortumab Vedotin Related Rash

In the phase 1 study [Study ASG-22CE-13-2], rash and similar dermatologic AE's were common among patients treated with EV, and were seen more frequently at the highest dose. Although the exact etiology of dermatologic toxicities associated with EV is unclear at this time, due to the expression of nectin-4 in the skin, rash maybe an on target toxicity. The most common type of dermatological AE reported in ASG-22CE-13-2 was maculo-papular rash, rash, skin exfoliation, and skin pigmentation disorder. Most occurred early on (during cycle 1), and some were associated with pruritus. Mild rash due to EV should be treated using local supportive care as needed. Topical corticosteroids have been used along with antihistamines for pruritus as needed. Grade 3 rash that is not limiting self-care activities of daily living or associated with infection requiring systemic antibiotics does not require treatment interruption, provided symptoms are not severe and can be managed with supportive treatment.

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 (13.9 mmol/L) (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. Blood glucose > 500 mg/dL (27.8 mmol/L) (Grade 4) considered related to EV requires treatment discontinuation. If a subject experiences new onset diabetes mellitus, evaluate subjects with a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide to assess for new onset type 1 diabetes in the setting of prior CPI.

Management of Enfortumab Vedotin Infusion Related Reactions (IRR)

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.

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

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

5.1.2.2 Dose Modification for treatment with Docetaxel, Paclitaxel or Vinflunine

In general, treatment with the chemotherapy comparators (docetaxel, paclitaxel or vinflunine) should be withheld for drug-related Grade 4 hematologic toxicities and for non-hematologic toxicity ≥ Grade 3, and subsequent doses modified as per Table 6 below. Dose modifications will be applied for all subsequent doses. Specific dose modification guidance for docetaxel, paclitaxel, and vinflunine is found below in [Sections 5.1.2.3, 5.1.2.4 and 5.1.2.5]. Dose modifications should also be considered according to local product labels or SmPC and institutional guidelines. For docetaxel, paclitaxel or vinflunine associated hematologic toxicities ≥ 3, transfusions or growth factors may be used as indicated per institutional guidelines.

Table 6 Dose Modification Guidelines for Drug-Related Adverse Events on the Active Comparator Arm

Toxicity*	Grade	Occurrence	Hold Treatment	Dose Modification	Treatment Discontinuation
Neutropenia	Grade 1, 2, 3 or Grade 4 lasting ≤ 7 days	All	Hold treatment until neutrophils recover to > 1500 cells/mm^3	NA	NA
	Grade 4 lasting > 7 days	1st	Hold treatment until neutrophils recover to > 1500 cells/mm^3	Restart treatment at: Paclitaxel: 135 mg/m^2 Docetaxel: 60 mg/m^2 Vinflunine: 280 mg/m^2	Treatment Discontinuation should be considered
		2nd	Hold treatment until neutrophils recover to > 1500 cells/mm^3	Restart treatment at: Paclitaxel: 100 mg/m^2 Docetaxel: 50 mg/m^2 Vinflunine: 250 mg/m^2	Treatment Discontinuation should be considered
		3rd	Yes	NA	Yes

Table continued on next page

Toxicity*	**Grade**	**Occurrence**	**Hold Treatment**	**Dose Modification**	**Treatment Discontinuation**
Thrombocytopenia	Grade 1,2, 3	All	Hold treatment until platelets recover to > 100000 cells/mm^3	NA	NA
	Grade 4	1st	Hold treatment until platelets recover to > 100000 cells/mm^3	Restart treatment at: Paclitaxel: 135 mg/m^2 Docetaxel: 60 mg/m^2 Vinflunine: 280 mg/m^2	Treatment discontinuation should be considered
		2nd	Hold treatment until platelets recover to > 100000 cells/mm^3	Restart treatment at: Paclitaxel: 100 mg/m^2 Docetaxel: 50 mg/m^2 Vinflunine: 250 mg/m^2	Treatment Discontinuation should be considered
		3rd	Yes	NA	Yes
Anemia	Grade 1,2, 3	All	Until anemia resolves to Grade 1 or baseline	NA	NA
	Grade 4	1st	Until anemia resolves to Grade 1 or baseline	Restart treatment at: Paclitaxel: 135 mg/m^2 Docetaxel: 60 mg/m^2 Vinflunine: 280 mg/m^2	Treatment discontinuation should be considered
		2nd	Until anemia resolves to Grade 1 or baseline	Restart treatment at: Paclitaxel: 100 mg/m^2 Docetaxel: 50 mg/m^2 Vinflunine: 250 mg/m^2	Treatment Discontinuation should be considered
		3rd	Yes	NA	Yes

Table continued on next page

Toxicity*	Grade	Occurrence	Hold Treatment	Dose Modification	Treatment Discontinuation
Nonhematological toxicity and other hematological toxicity not described above.**	Grade 1, 2	All	No	None	NA
	Grade 3, 4	1st	Yes, until toxicity resolves to Grade 0-1 or baseline	Restart treatment at: Paclitaxel: 135 mg/m^2 Docetaxel: 60 mg/m^2 Vinflunine: 280 mg/m^2	Treatment Discontinuation should be considered
		2nd	Yes, until toxicity resolves to Grade 0-1 or baseline	Restart treatment at: Paclitaxel: 100 mg/m^2 Docetaxel: 50 mg/m^2 Vinflunine: 250 mg/m^2	Treatment Discontinuation should be considered
		3rd	Yes	NA	Yes

*See Table 7, Table 8 and Table 9 for additional dose modifications for drug-related adverse events specific to docetaxel, vinflunine and paclitaxel, respectively.

**Subjects who experience suspected severe hypersensitivity reaction to paclitaxel or vinflunine (e.g., generalized rash/erythema, hypotension and/or bronchospasm, angioedema or anaphylaxis) should be discontinued from trial treatment.

*** For docetaxel, paclitaxel or vinflunine associated hematologic toxicities ≥ Grade 3, transfusions or growth factors may be used as indicated per institutional guidelines.

See Table 7 and Table 9 for guidelines on management of peripheral neuropathy specific to docetaxel and paclitaxel, respectively.

NA: not applicable

5.1.2.3 Docetaxel Dose Modifications

Docetaxel should not be given to subjects with total bilirubin > ULN, or to subjects with AST and/or ALT > 1.5 × ULN with concomitant alkaline phosphatase > 2.5 × ULN. Subjects with elevations of bilirubin or abnormalities of transaminase concurrent with alkaline phosphatase are at increased risk for the development of Grade 4 neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death. Docetaxel should also not be given to subjects with a neutrophil count of < 1500 cells/mm^3.

Severe fluid retention has been reported following docetaxel therapy. Subjects should be premedicated with corticosteroids prior to each docetaxel injection administration to reduce the incidence and severity of fluid retention. Subjects with pre-existing effusions should be closely monitored from the first dose for the possible exacerbation of the effusions. Subjects developing peripheral edema may be treated with standard measures, e.g., salt restriction, oral diuretic(s). Dose interruptions may last up to 6 weeks (2 cycles). Dose interruptions for subjects who are responding to treatment may be extended beyond 6 weeks, if the subject's toxicity does not otherwise require permanent discontinuation. Recommended dose modification guidelines for subjects receiving docetaxel are detailed below in Table 7. Dose

modifications not specified below (e.g., severe or cumulative cutaneous reactions) and starting doses should also consider local product label or SmPC and institutional guidelines.

Table 7 Recommended Docetaxel Dose Modification Guidelines

Toxicity	Grade	Occurrence	Hold Treatment	Dose Modification	Discontinue Treatment
Peripheral Neuropathy	Grade 1, 2		No	60 mg/m^2	N/A
	Grade 3, 4		Yes	N/A	Discontinue upon onset
Neutropenic fever (defined as T ≥ 100.5°F (38.1°C) and ANC ≤ 1000/L)		1	Hold treatment until ANC ≥ 1500/L	60 mg/m^2	
		2	Hold treatment until ANC ≥ 1500/L	50 mg/m^2	
		3	Yes	N/A	Yes

ANC: absolute neutrophil count; N/A: not applicable; T: temperature

5.1.2.4 Vinflunine Dose Modifications

In case of WHO/ECOG PS of 1 or ECOG PS of 0 and prior pelvic irradiation, vinflunine treatment should be started at the dose of 280 mg/m². In the absence of any hematological toxicity during the first cycle causing treatment delay or dose reduction, the dose may be increased to 320 mg/m² every 21 days for the subsequent cycles. In subjects with moderate renal impairment (40 mL/min ≤ CrCl ≤ 60 mL/min), the recommended dose is 280 mg/m² given once every 21 day cycle. In subjects with renal impairment (30 mL/min ≤ CrCl < 40 mL/min), the recommended dose is 250 mg/m² given once every 21 day cycle.

The recommended dose of vinflunine is 250 mg/m² given once every 21-day cycle in subjects with mild liver impairment (Child-Pugh grade A). Please refer to local product label or SmPC and institutional guidelines for further dose modifications.

The doses recommended in subjects ≥ 75 years old are as follows:

- in subjects at least 75 years old but less than 80 years, the dose of vinflunine to be given is 280 mg/m² every 21 day cycle.
- in subjects 80 years old and beyond, the dose of vinflunine to be given is 250 mg/m² every 21 day cycle.

In subjects who initiate vinflunine at 280 mg/m^2 and who experience an AE requiring dose modification, the dose should be reduced to 250 mg/m^2 following the 1st occurrence and resolution, and discontinued following a 2nd occurrence. In subjects who initiate vinflunine at 250 mg/m^2 and who experience an AE requiring dose modification, vinflunine should be discontinued.

Cases of Posterior Reversible Encephalopathy Syndrome (PRES) have been observed after administration of vinflunine. The typical clinical symptoms are, with various degrees: neurological (headache, confusion, seizure, visual disorders), systemic (hypertension), and

gastrointestinal (nausea, vomiting). Radiological signs are white matter abnormalities in the posterior regions of the brain. Vinflunine must be discontinued in subjects who develop neurological signs of PRES. Dose modifications for subjects receiving vinflunine are detailed below in Table 8. Dose interruptions may last up to 6 weeks (2 cycles). Dose interruptions 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. Please refer to the vineflunine (Javlor®) SmPC for additional information.

Table 8 Vinflunine Dose Modifications

Toxicity	**Dose Adjustments**				
	Initial Dose: Vinflunine 320 mg/m²			**Initial Dose: Vinflunine 280 mg/m²**	
	1st Event	**2nd Consecutive Event**	**3rd Consecutive Event**	**1st Event**	**2nd Consecutive Event**
Neutropenic fever (defined as T ≥ 100.5°F (38.1°C) and ANC ≤ 1000/L)	Vinflunine 280 mg/m²	Vinflunine 250 mg/m²	Discontinue treatment	Vinflunine 250 mg/m²	Discontinue treatment
Mucositis or Constipation Grade 2 ≥ 5 days or Grade 3 ≥ any duration[1]					
Cardiac ischemia in patients with prior history of myocardial infarction or angina pectoris	Discontinue treatment	N/A	N/A	Discontinue treatment	N/A

ANC: absolute neutrophil count; N/A: not applicable; T: temperature

[1] National Cancer Institute Common Terminology Criteria for Adverse Events Grade 2 constipation is defined as requiring laxatives, Grade 3 as an obstipation requiring manual evacuation or enema, Grade 4 as an obstruction or toxic megacolon. Mucositis Grade 2 is defined as "moderate," Grade 3 as "severe" and Grade 4 as "life-threatening."

5.1.2.5 Paclitaxel Dose Modifications

Paclitaxel should not be administered to subjects with baseline neutrophil counts of less than 1500 cells/mm^3. Subjects should not be re-treated with subsequent cycles of paclitaxel until neutrophils recover to a level > 1500 cells/mm^3 and platelets recover to a level > 100000/mm^3. Severe conduction abnormalities have been documented in < 1% of subjects during paclitaxel therapy and in some cases requiring pacemaker placement. If subjects develop significant conduction abnormalities during paclitaxel infusion, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with paclitaxel provided the subject does not require discontinuation.

In case of mild hepatic impairment (total bilirubin ≥ 1.25 ULN), paclitaxel should be started at a dose of 135 mg/m^2. Dose modifications for subjects receiving paclitaxel are detailed below. Dose interruptions may last up to 6 weeks (2 cycles). Dose interruptions for subjects who are responding to treatment may be extended beyond 6 weeks if the subject's toxicity does not otherwise require permanent discontinuation. Recommended dose modification guidelines for subjects receiving paclitaxel are detailed below in Table 9. Please refer to local product label or SmPC and institutional guidelines for further dose modifications.

Table 9 Recommended Dose Modification Guidelines Paclitaxel

Toxicity	Grade	Occurrence	Hold Treatment	Dose Modification	Treatment Discontinuation
Peripheral Neuropathy	Grade 1, 2		No	135 mg/m^2	N/A
	Grade 3, 4		Yes	N/A	Discontinue upon onset
Neutropenic fever (defined as T ≥ 100.5°F (38.1°C) and ANC ≤ 1,000/L)		1	Hold until ANC ≥ 1,500/L	135 mg/m^2	
		2	Hold until ANC ≥ 1,500/L	100 mg/m^2	
		3	yes	N/A	Yes

ANC: absolute neutrophil count; N/A: not applicable; T: temperature

5.1.3 Previous and Concomitant Treatment (Medication and Nonmedication Therapy)

If the investigator determines that any of the following medications are deemed necessary to provide adequate medical support to the subject, the subject must be withdrawn from further administration of the study treatment:

- Other investigational drugs
- Chemotherapy or other medications intended for antitumor activity. This does not apply to subjects with a history of breast cancer on adjuvant endocrine therapy, or for subjects on agents intended for the treatment of bone metastasis (e.g., bisphosphonates, or RANK ligand inhibitors).
- Radiation therapy

  Note: Radiation therapy to a symptomatic solitary lesion or to the bone may be considered on an exceptional case-by-case basis after consultation with Sponsor. The radiated lesion must be a non-target lesion per RECIST V1.1 and the subject must have clear measurable disease outside the radiated field.

Arm A (enfortumab vedotin)

- Subjects who are receiving strong cytochrome P450 (CYP)3A4 inhibitors or P-pg inhibitors concomitantly with EV should be closely monitored for adverse reactions.

Arm B (Docetaxel)

- Concomitant use of drugs that strongly inhibit or induce CYP3A4 may affect exposure to docetaxel and should be avoided.

Arm B (Vinflunine)

- Strong inhibitors of the CYP3A4 enzymes for subjects receiving vinflunine should be avoided.
- QT/QTc interval prolonging medicinal products should be avoided.

Arm B (Paclitaxel)

- Caution should be exercised when paclitaxel is administered with strong inhibitors or inducers of CYP3A4 and CYP2C8.

Please refer to the local package inserts for concomitant medication restrictions or requirements for docetaxel, paclitaxel and vinflunine. All concomitant treatments will be recorded in the eCRF or electronic data source unless otherwise specified.

5.1.4 Treatment Compliance

The dose and schedule of EV, paclitaxel, docetaxel and vinflunine administered to each subject will be recorded on the appropriate electronic case report form (eCRF) at every cycle. Reasons for dose delay, reduction or omission will also be recorded.

If toxicities or adverse events occur on Day 1 of any cycle and EV cannot be administered, then the start of the cycle may be delayed. If toxicities occur on Days 8 or 15 of any cycle and require the dose to be held > 3 days, then the dose(s) must be eliminated, rather than delayed. If a subject only receives day 1 and needs to skip days 8 and 15, the subject could resume the next cycle as early as day 22 (new day 1), if the toxicity has resolved by then.

5.2 Demographics and Baseline Characteristics

5.2.1 Demographics

Demographic information will be collected for all subjects as allowed per local regulation and will include date of birth, sex, race, ethnicity and tobacco use history (pack years).

5.2.2 Medical History

Medical history will include all significant medical conditions other than urothelial cancer that have resolved prior to informed consent or are ongoing at the time of consent. Details that will be collected include the onset date and recovery date and Common Terminology Criteria for Adverse Events (CTCAE) grade, if applicable for ongoing conditions.

5.2.3 Diagnosis of the Target Disease, Severity, and Duration of Disease

For urothelial carcinoma, the following information including but not limited to will be collected during the screening period, and be entered in the eCRF:

- Date of initial diagnosis of the primary carcinoma, histological type, date of histopathological or cytopathological diagnosis

- Date of diagnosis for the locally advanced or metastatic or recurrent disease
- TNM classification and disease stage at screening
- Sampling method and the type of the tumor tissues for Nectin-4 mutation analysis
- Previous treatment (including medication, radiotherapy and surgery) for underlying disease

5.2.4 Performance Status

The ECOG PS Scale [Oken et al, 1982] will be used to assess performance status. Refer to [Appendix 12.8].

5.3 Efficacy Assessments

Response and progression will be evaluated using RECIST v1.1 [Appendix 12.7].

Imaging for both Arms will be performed at screening/baseline and every 56 days (± 7 days) from the first dose of study treatment throughout the study. Baseline imaging performed prior to informed consent as standard of care may be used so long as it is performed within 28 days prior to randomization. All subjects will have a bone scan (scintigraphy) performed at screening/baseline. Subjects with positive bone scans at baseline will have a bone scan performed every 56 days (± 7 days) throughout the study or more frequently if clinically indicated. Subjects with negative bone scans at baseline should have a bone scan performed if clinically indicated throughout the study even if not positive at baseline. Brain scans (CT with contrast/MRI) will only be performed if clinically indicated at screening/baseline and repeated as clinically indicated or per standard of care throughout the study. If a subject discontinues study drug prior to radiological disease progression, the subject should continue to undergo imaging assessments every 56 days (± 7 days) until disease progression is documented, or the subject starts another anticancer treatment whichever occurs earlier.

A CT scan with contrast (chest and abdomen) is the preferred modality for tumor assessment. Magnetic resonance imaging is acceptable if local standard practice or if CT scans are contraindicated in a subject (e.g., subject is allergic to contrast media). All other RECIST-approved scanning methods such as x-ray are optional. Additional instructions for imaging assessments can be found in the study procedures manual.

The assessment will include tumor measurements for target lesions, nontarget lesions and any new lesions. An overall assessment will be characterized for a given time point evaluation. At the end of study for that subject, the best overall response to the study regimen will be characterized. To ensure comparability, the screening and subsequent assessment of response should be performed using identical techniques. The same individual should assess images for any 1 subject for the duration of the study if possible. For subjects with known brain metastases at study entry, it is recommended that repeat imaging also include the brain and the same methods used to detect brain lesions at Baseline are to be used to follow the lesions throughout the study.

The site of disease progression including target, non-target and/or new lesions should be documented in the eCRF. Additional imaging may be performed at any time to confirm suspected progression of disease.

This study will be analyzed based on the results of local (investigator site) radiologic assessments, including dates of progression and death. Since imaging scans may be needed for future regulatory purposes or an independent review of all or a representative sample of scans may be considered following the completion of PFS1 analysis, copies of all scans will be collected throughout the study and stored centrally by a coordinating vendor. Images from all randomized subjects will be sent to the imaging vendor according to the frequency of Table 1.

5.3.1 Evaluation of Target Lesions

5.3.1.1 Complete Response

CR is defined as disappearance of all target and nontarget lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm from baseline measurement.

5.3.1.2 Partial Response

PR is defined as at least a 30% decrease in the sum of diameters (longest for nonnodal lesions, short axis for nodal lesions) of target lesions taking as reference to the baseline sum of diameters.

5.3.1.3 Stable Disease

SD is defined as neither sufficient decrease to qualify for PR nor sufficient increase to qualify for progressive disease taking as reference the smallest sum of diameters while on study drug.

5.3.1.4 Progressive Disease

PD is defined as at least a 20% increase in the sum of diameters (longest for nonnodal lesions, short axis for nodal lesions) of the target lesions taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered progression.

5.3.2 Evaluation of Nontarget Lesions

To achieve unequivocal progression on the basis of nontarget lesions, there must be an overall level of substantial worsening in nontarget disease such that, even in presence of SD or PR of target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of 1 or more nontarget lesions is usually not sufficient to qualify for unequivocal progression.

5.3.2.1 Complete Response

For CR of nontarget lesions, subjects must have disappearance of all nontarget lesions and all lymph nodes must be nonpathological in size (< 10 mm short axis).

5.3.2.2 NonCR/NonPD

NonCR/NonPD of nontarget lesions is defined as persistence of 1 or more nontarget lesions.

5.3.2.3 Progressive Disease

PD of nontarget lesions is defined as unequivocal progression of existing nontarget lesions or the appearance of 1 or more new lesions.

5.3.3 Evaluation of Time Point Response

The overall response status at each time point for subjects with measurable disease at baseline will be reported according to the table in [Appendix 12.7].

5.4 Pharmacokinetic Assessment

PK samples will be collected during the treatment period and at the post-treatment follow-up visit for subjects who receive EV for determination of ADC and MMAE concentrations. If a subject presents to clinic but does not get dosed, a predose PK sample collection should be performed.

Blood samples (7 mL/sample) for pharmacokinetic analyses should be collected at the time points indicated in the Schedule of Assessments (Table 1). Blood samples should be collected via a peripherally placed intravenous cannula or by direct venipuncture.

Blood should not be drawn from the arm or port used for study drug infusion.

Bioanalysis of TAb, ADC and MMAE in serum or plasma will be performed using validated methods at bioanalytical laboratories specified by the sponsor.

5.5 Safety Assessment

5.5.1 Vital Signs

Vital signs, including systolic and diastolic blood pressures (mmHg), radial pulse rate (beats/minute) and temperature will be obtained according to the Schedule of Assessments (Table 1) and recorded. All vital sign measures will be obtained with the subject in the sitting or supine position.

If clinically significant vital sign changes from Baseline (pretreatment) are noted, the changes will be documented as AEs on the AE page of the eCRF. Clinical significance will be defined as a variation in vital signs that has medical relevance as deemed by the investigator that could result in an alteration in medical care. The investigator will continue to monitor the subject until the parameter returns to Grade ≤ 1, or to the Baseline (pretreatment) value, or until the investigator determines that follow up is no longer medically necessary.

5.5.2 Adverse Events

See [Section 5.6 Adverse Events and Other Safety Aspects] for information regarding AE collection and data handling.

5.5.2.1 Adverse Events of Possible Hepatic Origin

See [Appendix 12.2 Liver Safety Monitoring and Assessment] for detailed information on liver abnormalities, monitoring and assessment, if the AE for a subject enrolled in a study

and receiving study drug is accompanied by increases in Liver Function Tests value ([LFT], e.g., AST, ALT, bilirubin, etc.) or is suspected to be due to hepatic dysfunction.

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

5.5.3 Laboratory Assessments

Below is a table of the laboratory tests that will be performed during the conduct of the study. See Schedule of Assessments for study visit collection dates.

Biochemistry	Sodium (Na), Magnesium (Mg), Potassium (K), Calcium (Ca), Chloride (Cl), Phosphate (P), Serum Creatinine, Glucose (Gl), Blood Urea Nitrogen (BUN), ALP, AST, ALT, Lactate Dehydrogenase (LDH), Bilirubin (total and direct), Total Protein (TP), Albumin (Alb), Bicarbonate (HCO3), Amylase, Lipase, Uric Acid, Hemoglobin A1c (screening only), Serum HCG for female subjects of childbearing potential
Hematology	Red Blood Cell Count (RBC), Hematocrit (Hct), Hemoglobin (Hgb), Platelets, white blood cell count (WBC)/differential (Neutrophils, Eosinophils, Basophils, Lymphocytes, Monocytes),
Urinalysis	Pregnancy
HbA1c	

Laboratory tests will be performed predose according to the Schedule of Assessments and sent to a central laboratory for analysis. All screening labs must be sent to the central laboratory, but local laboratory results may be used to determine eligibility if the screening results from the central laboratory are not available in time for planned randomization. In the event that the central laboratory results received after randomization are not within eligibility parameters, the subject will still be considered eligible if local labs met the eligibility criteria and will not be considered a protocol deviation. Local laboratory results that support eligibility and dosing decisions must be entered into the clinical database. If local laboratory is to be used to support dosing decisions, local laboratory tests will include complete blood count with differential, glucose, serum creatinine, ALT and AST. In case of multiple laboratory data within this period, the most recent data should be used. Laboratory assessments collected outside of -7 days of randomization should be repeated. Additional assessments may be done centrally or locally to monitor AEs or as required by dose modification requirements.

Assessment of creatinine clearance or estimation of GFR per institutional guidelines should be performed prior to administration of vinflunine and EV as recommended in [Section 5.1.2 Increase or Reduction in Dose of the Study Drug(s)].

Additional laboratory tests should be performed according to institutional standard of care. Clinical significance of out-of-range laboratory findings is to be determined and documented by the investigator/sub-investigator who is a qualified physician.

5.5.4 Physical Examination

Standard, full physical examinations will be performed at screening to assess general appearance, skin, eyes, ears, nose, throat, neck, cardiovascular, chest and lungs, abdomen, musculoskeletal, neurologic status, mental status and lymphatic systems. For subsequent and end of treatment (EOT) visits, physical examinations maybe more directed but should include examination of lungs, abdomen, skin, and cardiovascular system. Physical examinations will be conducted at visits as outlined in the Schedule of Assessments (Table 1). Each physical examination will include weight; height is only required at Screening. If clinically significant worsening of findings from Baseline is noted at any study visit, the changes will be documented as AEs on the AE eCRF. Clinical significance is defined as any variation in physical findings that has medical relevance that could result in an alteration in medical care. The investigator will continue to monitor the subject until the parameter returns to Grade ≤ 1, or to the Baseline condition, or until the investigator determines that follow up is no longer medically necessary.

5.5.5 Ophthalmology Examination

Ophthalmologic assessment for subjects with recent ocular complaints (within 3 months of screening) are required. Assessments should include the following: visual acuity, slit lamp, tonometry examination, and dilated fundus examination. Prior ophthalmologic exam done within 3 months of screening is acceptable provided symptoms are not new since the exam. Ophthalmology assessments during treatment should be performed per standard of care or if clinically indicated (e.g., subject develops new or worsening ocular symptoms). EOT slit lamp examinations are required for subjects who experience corneal adverse events during the study. EOT slit lamp examinations must be performed ≥ 4 weeks from last dose. Additional eye examinations are to be conducted as clinically indicated.

5.5.6 Electrocardiogram

A standard 12-lead ECG will be performed and assessed using local standard procedures according to the schedule of assessments in Table 1. Clinically significant abnormal findings at screening should be recorded as medical history.

5.6 Adverse Events and Other Safety Aspects

5.6.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

In order to identify any events that may be associated with study procedures and could lead to a change in the conduct of the study, Astellas collects AEs even if the subject has not received study drug treatment. AE collection begins after the signing of the informed consent and will be collected until 30 days after the last dose of study drug.

5.6.1.1 Abnormal Laboratory Findings

Any abnormal laboratory test result (e.g., hematology, clinical chemistry, or urinalysis) or other safety assessment (e.g., ECGs, radiographic scans, vital signs measurements, physical examination), including those that worsen from baseline, that is considered to be clinically significant in the medical and scientific judgment of the investigator and not related to underlying disease, is to be reported as an (S)AE.

Any clinically significant abnormal laboratory finding or other abnormal safety assessment which is associated with the underlying disease does not require reporting as an (S)AE, unless judged by the investigator to be more severe than expected for the subject's condition.

Repeating an abnormal laboratory test or other safety assessment, in the absence of any of the above criteria, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

5.6.1.2 Potential Cases of Drug-Induced Liver Injury

Refer to **[Appendix 12.2 Liver Safety Monitoring and Assessment]** for detailed instructions on Drug Induced Liver Injury (DILI). Abnormal values in AST and/or ALT concurrent or with abnormal elevations in total bilirubin that meet the criteria outlined in **[Appendix 12.2 Liver Safety Monitoring and Assessment]**, in the absence of other causes of liver injury, are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and are always to be considered important medical events and reported per [Section 5.6.5 Reporting of Serious Adverse Events].

5.6.1.3 Disease Progression and Study Endpoints

Under this protocol, the following event(s) will not be considered as an(S)AE:

- Disease Progression: events including defined study endpoints that are clearly consistent with the expected pattern of progression of the underlying disease are not to be recorded as AEs unless resulting in death. These data will be captured as efficacy assessment data as outlined in [Section 5.3 Efficacy Assessments]. If there is any uncertainty as to whether an event is due to anticipated disease progression and/or if there is evidence suggesting a causal relationship between the study drug and the event, it should be reported as an (S)AE. All deaths within 30 days of the last dose of study drug must be reported as SAEs.
- Pre-planned and elective hospitalizations or procedures for diagnostic, therapeutic, or surgical procedures for a pre-existing condition that did not worsen during the course of the clinical trial. These procedures are collected per the eCRFs Completion Guidelines.

5.6.2 Definition of Serious Adverse Events (SAEs)

An AE is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Results in death
- Is life-threatening (an AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death)
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly, or birth defect
- Requires inpatient hospitalization (except for planned procedures as allowed per study) or leads to prolongation of hospitalization (except if prolongation of planned hospitalization is not caused by an AE). Hospitalization for treatment/observation/examination caused by AE is to be considered as serious.)
- Other medically important events (defined in paragraph below)

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, usually are considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

The sponsor has a list of events that they classify as "always serious" events. If an AE is reported that is considered to be an event per this classification as "always serious", additional information on the event may be requested.

5.6.3 Criteria for Causal Relationship to Study Drug

The investigator is obligated to assess the relationship between the study drug and each occurrence of each (S)AE. The investigator will use clinical judgment to determine the relationship. The investigator should also use the Investigator's Brochure (IB) and/or Product Information, for marketed products. The investigator is requested to provide an explanation for the causality assessment for each SAE and must document this on the SAE worksheet. The causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may revise his/her assessment of causality in light of new information regarding the SAE and shall send an SAE follow-up report and update the eCRF with the new information and updated causality assessment.

Following a review of the relevant data, the causal relationship between the study drug and each (S)AE will be assessed by answering '**yes**' or '**no**' to the question "**Do you consider**

that there is a reasonable possibility that the event may have been caused by the study drug".

When making an assessment of causality, the following factors are to be considered when deciding if there is evidence and/or arguments to suggest there is a 'reasonable possibility' that an (S)AE may have been caused by the study drug (rather than a relationship cannot be ruled out) or if there is evidence to reasonably deny a causal relationship:

- Plausible temporal relationship between exposure to the study drug and (S)AE onset and/or resolution. Has the subject actually received the study drug? Did the (S)AE occur in a reasonable temporal relationship to the administration of the study drug?
- Plausibility; i.e., could the event been caused by the study drug? Consider biologic and/or pharmacologic mechanism, half-life, literature evidence, drug class, preclinical and clinical study data, etc.
- Dechallenge/Dose reduction/Rechallenge:
    - Did the (S)AE resolve or improve after stopping or reducing the dose of the suspect drug? Also consider the impact of treatment for the event when evaluating a dechallenge experience.
    - Did the (S)AE reoccur if the suspected drug was reintroduced after having been stopped?
- Laboratory or other test results; a specific lab investigation supports the assessment of the relationship between the (S)AE and the study drug (e.g., based on values pre-, during and post-treatment)
- Available alternative explanations independent of study drug exposure; such as other concomitant drugs, past medical history, concurrent or underlying disease, risk factors including medical and family history, season, location, etc. and strength of the alternative explanation

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor. With limited or insufficient information about the event to make an informed judgment and in absence of any indication or evidence to establish a causal relationship, a causality assessment of 'no' is to be considered. In such instance, the investigator is expected to obtain additional information regarding the event as soon as possible and to re-evaluate the causality upon receipt of additional information.

5.6.4 Criteria for Defining the Severity of an Adverse Event

AEs, including abnormal clinical laboratory values, will be graded using the NCI-CTCAE guidelines (Version 4.03). The items that are not stipulated in the NCI-CTCAE Version 4.03 will be assessed according to the criteria below and entered into the eCRF.

Grade	Assessment Standard
1-Mild	Asymptomatic or mild symptoms, clinical or diagnostic observations noted; intervention not indicated.
2-Moderate	Local or noninvasive intervention indicated.
3-Severe	Medically significant but not immediately life threatening, hospitalization or prolonged hospitalization.
4-Life Threatening	Life threatening consequences, urgent intervention indicated
5-Death	Death related to AE

The investigator will use the following definitions to rate the severity of each adverse event

- Mild: No disruption of normal daily activities
- Moderate: Affect normal daily activities
- Severe: Inability to perform daily activities

5.6.5 Reporting of Serious Adverse Events

The collection of AEs and the expedited reporting of SAEs will start following receipt of the informed consent and will continue to 30 days after last administration of study drug.

In the case of a SAE, the investigator must contact the sponsor by fax or email immediately (within 24 hours of awareness).

The investigator must complete and submit a SAE worksheet containing all information that is required by local and/or regional regulations to the sponsor by email or fax immediately (within 24 hours of awareness). If the faxing of an SAE Worksheet is not possible or is not possible within 24 hours, the local drug safety contact should be informed by phone.

For sites located in Japan:

In the case of a serious adverse event (SAE), the investigator or sub-investigator must report to the head of the study site and must contact the sponsor (directly or via the delegated CRO) by telephone or fax immediately (within 24 hours of awareness).

The investigator should complete and submit JUTOKUNA YUUGAIJISHOU HOUKOKUSHO containing all information that is required by the Regulatory Authorities to the sponsor (directly or via the delegated CRO) by fax immediately (within 24 hours of awareness) and to the head of the hospital. If the faxing of JUTOKUNA YUUGAIJISHOU HOUKOKUSHO is not possible or is not possible within 24 hours, the sponsor should be informed by phone.

For contact details, see [Section II Contact Details of Key Sponsor's Personnel].

Please Fax or email the SAE Worksheet for Japan (JUTOKUNA YUUGAIJISHOU HOUKOKUSHO) to:

PAREXEL International
Clinical Development
Fax number +81-(0)3-6888-1654
or
Astellas Pharma Inc. – Japan
JP Clinical Development,
Fax number +81-(0)3-3243-5737

If there are any questions, or if clarification is needed regarding the SAE, please contact the sponsor's Medical Monitor/Study Physician or his/her designee [Section II Contact Details of Key Sponsor's Personnel].

Follow-up information for the event should be sent promptly (within 2 days of the initial notification.

For sites located in all other countries:

Please fax or email the SAE worksheet for all other country sites to:

Astellas Pharma Global Development, Inc.
Pharmacovigilance
North America Fax number 1-888-396-3750
Alternate North America Fax number 1-847-317-1241
International Fax number +44-800-471-5263
Email: safety-us@astellas.com

If there are any questions, or if clarification is needed regarding the SAE, please contact the sponsor's Medical Monitor/Study Physician or his/her designee [Section II Contact Details of Key Sponsor's Personnel].

Follow-up information for the event should be sent promptly (within 7 days of the initial notification.

Full details of the SAE should be recorded on the medical records, SAE/Special Situation Worksheet and on the (e)CRF.

The following minimum information is required:

- International Study Number (ISN)/Study number,
- Subject number, sex and age,
- The date of report,
- A description of the SAE (event, seriousness criteria),
- Causal relationship to the study drug (including reason), and
- The drug provided (if any)

The sponsor or sponsor's designee will submit expedited safety reports (e.g., Investigational New Drug [IND] Safety Reports, Council for International Organizations of Medical

Sciences [CIOMS-I]) to Competent Authorities (CA) and concerned Ethics Committee (cEC) per current local regulations, and will inform the investigators of such regulatory reports as required. Investigators must submit safety reports as required by their IRB/local IEC within timelines set by regional regulations (e.g., EU, (e)CTD, FDA) where required. Documentation of the submission to and receipt by the IRB/local IEC of expedited safety reports should be retained by the site.

The sponsor will notify all investigators responsible for ongoing clinical studies with the study drug of all Suspected Unexpected Serious Adverse Reactions, which require submission per local requirements of the IRB/IEC.

The investigators should provide written documentation of IRB/IEC notification for each report to the sponsor.

5.6.6 Follow-up of Adverse Events

All AEs occurring during or after the subject has discontinued the study are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized by the investigator.

If after the protocol defined AE collection period [see Section 5.6.1 Definition of Adverse Event], an AE progresses to a SAE, or the investigator learns of any (S)AE including death, where he/she considers there is reasonable possibility it is related to the study drug treatment or study participation, the investigator must promptly notify the sponsor.

5.6.7 Monitoring of Common Serious Adverse Events

Common SAEs are SAEs commonly anticipated to occur in the study population independent of drug exposure. SAEs classified as “common” are provided in [Appendix 12.3 Common Serious Adverse Events] for reference. The list does NOT change the investigator’s reporting obligations, nor his obligations to perform a causality assessment, or prevent the need to report an AE meeting the definition of an SAE as detailed above. The purpose of this list is to alert the investigator that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of “common SAEs” as specified in [Appendix 12.3 Common Serious Adverse Events]. The sponsor will monitor these events throughout the course of the study for any change in frequency. Any changes to this list will be communicated to the participating investigational sites. Investigators must report individual occurrences of these events as stated in [Section 5.6.5 Reporting of Serious Adverse Events].

5.6.8 Special Situations

Certain Special Situations observed in association with the study drug(s), such as incorrect administration (e.g., wrong dose of study drug, comparator, or background therapy) are collected in the eCRF, as Protocol Deviation per [Section 8.1.6 Protocol Deviations] or may require special reporting, as described below. These Special Situations are not considered AEs, but do require to be communicated to Astellas as per the timelines defined below.

If a Special Situation is associated with, or results in, an AE, the AE is to be assessed separately from the Special Situation and captured as an AE in the eCRF. If the AE meets the definition of a SAE, the SAE is to be reported as described in [Section 5.6.5 Reporting of Serious Adverse Events] and the details of the associated Special Situation are to be included in the clinical description on the SAE worksheet.

The Special Situations are:

- Pregnancy
- Medication Error and Overdose
- Misuse/abuse
- Occupational exposure
- Suspected Drug-Drug interaction

5.6.8.1 Pregnancy

If a female subject becomes pregnant during the study dosing period or within 6 months from the discontinuation of dosing, the investigator is to report the information to the sponsor according to the timelines in **[**Section 5.6.5 Reporting of Serious Adverse Events] using the Pregnancy Reporting Form and in the eCRF.

The investigator will attempt to collect pregnancy information on any female partner of a male subject who becomes pregnant during the study dosing period or within 6 months from the discontinuation of dosing and report the information to the sponsor according to the timelines in [Section 5.6.5 Reporting of Serious Adverse Event**s**] using the Pregnancy Reporting Form.

The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result and neonatal data etc., should be included in this information.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or termination (including elective termination) of a pregnancy is to be reported for a female study subject as an AE in the eCRF or SAE per [Section 5.6.5 Reporting of Serious Adverse Events]. For (S)AEs experienced by a female partner of a male subject, (S)AEs are to be reported via the Pregnancy Reporting Form.

Additional information regarding the outcome of a pregnancy when also categorized as an SAE is mentioned below:

- ″Spontaneous abortion″ includes miscarriage, abortion and missed abortion.
- Death of a newborn or infant within 1 month after birth is to be reported as an SAE regardless of its relationship with the study drug.
- If an infant dies more than 1 month after the birth, is to be reported if a relationship between the death and intrauterine exposure to the study drug is judged as ″possible″ by the investigator.
- Congenital anomaly (including anomaly in miscarried fetus)

Unless a congenital anomaly is identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination. (S)AEs experienced by the newborn/infant should be reported via the Pregnancy Reporting Form. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date.

5.6.8.2 Medication Error, Overdose and "Off-Label Use"

If a Medication Error, Overdose or "Off label Use" (i.e., use outside of what is stated in the protocol) is suspected, refer to [Section 8.1.6 Protocol Deviations]. Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of a SAE, the SAE is also to be reported as described in [Section 5.6.5 Reporting of Serious Adverse Events] together with the details of the medication error, overdose or "Off-Label Use".

In the event of suspected EV overdose or accidental infusion as a bolus, the subject should receive supportive care and monitoring. The Medical Monitor/Expert should be contacted as applicable.

No specific procedures are available to treat overdose of EV or accidental infusion as a bolus, and only supportive treatment can be given. If EV is accidentally overdosed or accidentally infused as a bolus, the investigator/sub-investigator will provide emergency procedures and/or general maintenance therapy according to the symptoms to assure the subject's safety.

In the event of suspected overdose of paclitaxel, docetaxel or vinflunine, refer to the approved Package Insert, SmPC, or local product information supplied by the manufacturer for each agent.

Events of overdose should be recorded in the eCRF with the dosages actually administered.

5.6.8.3 Misuse/Abuse

If misuse or abuse of the study drug(s) is suspected, the investigator must forward the Special Situation worksheet to the sponsor by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of a SAE, the SAE is also to be reported as described in [Section 5.6.5 Reporting of Serious Adverse Events] together with details of the misuse or abuse of the study drug(s).

5.6.8.4 Occupational Exposure

If occupational exposure (e.g., inadvertent exposure to the study drug(s) of site staff whilst preparing it for administration to the patient) to the study drug(s) occurs, the investigator must forward the Special Situation worksheet to the sponsor by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs occurring to the individual associated with or resulting from the Special Situation are to be reported on the Special Situations worksheet.

5.6.8.5 Suspected Drug-Drug Interaction

If a drug-drug interaction associated with the study drug(s) is suspected, the investigator must forward the Special Situation worksheet to the sponsor by fax or email immediately (within

24 hours of awareness). Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of a SAE, the SAE is also to be reported as described in [Section 5.6.5 Reporting of Serious Adverse Events] together with details of the suspected drug-drug interaction.

5.6.9 Supply of New Information Affecting the Conduct of the Study

When new information necessary for conducting the clinical study properly becomes available, the sponsor will inform all investigators involved in the clinical study as well as the regulatory authorities. Investigators should inform the IRB/IEC of such information when needed.

The investigator will also inform the subjects, who will be required to sign an updated informed consent form in order to continue in the clinical study.

For sites located in Japan:

1. When information is obtained regarding serious and unexpected adverse drug reactions (or other) that are specified in Article 273 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics, in compliance with Article 80-2 Paragraph 6 of the Pharmaceutical Affairs Law, the sponsor should inform all the investigators involved in the clinical study, the head of the study site, and the regulatory authorities of such information. The head of the study site who receives such information will decide whether the clinical study should be continued after hearing the opinions of the IRB. The investigator will supply the new information to the subjects, in compliance with [Section 8.2.3.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information.]
2. In addition to the above item (1), when the head of the study site receives the revisions of the Investigator's Brochure, protocol, or written information, information on the matters covering the quality of the study drug, efficacy and safety, information necessary for conducting the clinical study properly, or documents to be examined by the IRB these documents should be sent to the IRB.

5.6.10 Deviations from the Protocol and Other Actions Taken to Avoid Life-Threatening Risks to Subjects (Unique to Japan)

The investigator must not deviate from the protocol, excluding an emergency case for avoiding risks to the subjects. When the investigator does not follow the protocol in order to avoid urgent risks for subjects, the investigator should take the following actions.

1. Describe the contents of the deviation and the reasons for it in a written notice, and immediately send the document stating the deviation or amendment and the reasons to the sponsor and the head of the study site. Keep a copy of the notice.
2. Consult with the sponsor at the earliest possibility for cases in which it is necessary to amend the protocol. Obtain approval for a draft of the amended protocol from the IRB and the head of the study site as well as written approval from the sponsor.

5.7 Test Drug Concentration

Blood samples for PK and ATA will be collected throughout the study per the sample collection schedule provided in Table 2. Validated assays will be used to measure the concentrations of ADC, total antibody (TAb) and MMAE in serum or plasma. PK samples will be collected and archived for possible analysis of other EV-related species. A validated assay will also be used to determine the levels of ATA in serum.

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

5.8 Other Measurements, Assessments or Methods

5.8.1 Exploratory Biomarker

The procedures for the collection, handling, and shipping of samples will be specified in the laboratory manual.

The samples described in [Section 5.8.2 Biomarkers in Blood] and [Section 5.8.3 Biomarkers in Pre-Treatment Tumor Tissue] may be analyzed for other biomarkers including DNA, RNA and protein, to investigate possible associations with mechanisms of resistance or sensitivity to study treatment, dynamic changes associated with study treatment and method development or validation of diagnostic assays related to study treatment.

The samples may be stored at the study Sponsor's facility or a contract laboratory facility for up to 15 years after database closure, at which time the samples will be destroyed.

5.8.2 Biomarkers in Blood

The plasma and peripheral blood mononuclear cells (PBMC) samples collected at baseline and post-baseline time points may be analyzed for markers of immune function, immune cell subsets and cytokines. The plasma and PBMC sample may be used for additional exploratory analyses as described in [Section 5.8.1 Exploratory Biomarker].

5.8.3 Biomarkers in Pre-Treatment Tumor Tissue

Submission of a FFPE tumor block or freshly sectioned unstained charged slides (at least 10 and up to 15 slides) at screening should be provided (unless prior approval is obtained from the sponsor). Either archival tissue or pretreatment fresh tumor tissue (obtained from a fresh biopsy) is acceptable. See the Laboratory Manual for details. The tumor tissue samples may be analyzed for Nectin-4 expression, markers of disease subtype and markers related to the tumor immune microenvironment. The tumor tissue sample may be used for additional exploratory analyses as described in [Section 5.8.1 Exploratory Biomarker].

5.8.4 Blood Sample for Future Pharmacogenomic Analysis (Retrospective)

Pharmacogenomics (PGx) research may be conducted in the future to analyze or determine genes of relevance to clinical response, pharmacokinetics, and toxicity/safety issues. After randomization (see schedule of assessments), a 4 mL sample of whole blood for possible

retrospective PGx analysis will be collected. Samples will be shipped to a sponsor designated banking CRO.

Details on sample collection, labeling, storage and shipment procedures will be provided in a separate laboratory manual.

See [Appendix 12.4. Retrospective PGx Sub-study] for further details on the banking procedures.

5.8.5 EORTC Core Quality of Life Questionnaire, QLQ-C30

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

- functional domains (physical, role, cognitive, emotional, social);
- 3 symptom scales (fatigue, pain, nausea & vomiting);
- Single items for symptoms (shortness of breath, loss of appetite, sleep disturbance, constipation, diarrhea) and financial impact of the disease; and
- 2 global items (health, overall QOL).

5.8.6 EuroQOL-5 Dimensions

The EQ-5D-5L 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-5L 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 5 levels (no problems, slight problems, moderate problems, severe problems, extreme problems). A unique EQ-5D-5L health state is defined by combining 1 level from each of the 5 dimensions. This questionnaire also records the respondent's self-rated health status on a vertical graduated (0 to 100) visual analogue scale. Responses to the 5 items will also be converted to a weighted health state index (utility score) based on values derived from general population samples [Herdman, 2011].

5.8.7 Healthcare Resource Utilization (HRU)

HRU information will be collected with particular focus on the number of subjects who have an unplanned use of healthcare resources related to clinical events or AEs from all subjects [Appendix 12.7].

5.9 Total Amount of Blood

The total amount of blood collected for study assessments for each subject will vary depending on how long the subject stays on treatment.

At any time during the study, if any laboratory abnormalities are found for a subject or for disease assessment, additional blood may be drawn for monitoring.

Additional blood beyond standard monitoring that will be drawn for this study will include draws for eligibility assessment; hematology and chemistry evaluations at specific study defined time points; pharmacokinetics; and bioanalytical sampling.

The maximum amount of blood collected is approximately 130.0 mL in Cycle 1 for subjects randomized to Arm A and 37.0 mL in Cycle 1 for subjects randomized to Arm B. The maximum amount of blood collected for subjects that participate from Cycle 2 up to Cycle 6 and complete the EOT visit is 219.0 mL for subjects randomized to Arm A and 164.0 mL for subjects randomized to Arm B.

6 DISCONTINUATION

6.1 Discontinuation of Individual Subject(s)

A discontinuation from treatment is a subject who enrolled in the study and for whom study treatment is permanently discontinued for any reason.

The subject is free to discontinue from study treatment and/or withdraw from the study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to discontinue the subject from study treatment or to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

All subjects who discontinue study treatment will remain in the study and must continue to be followed for protocol specific follow up procedures as outlined in the Schedule of Assessments (Table 1) until the subject specifically withdraws consent for any further contact with him/her or persons previously authorized by the participant to provide this information.

If a subject is discontinued from the study with an ongoing AE or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until the condition stabilizes or no longer is clinically significant.

The following are discontinuation criteria from treatment for individual subjects:

- Subject develops radiological disease progression.
- Subject is required to receive another systemic anti-cancer treatment for underlying or new cancer.
- Subject develops unacceptable toxicity.
- Female subject becomes pregnant.
- Investigator decides it is in the subject’s best interest to discontinue.
- Subject declines further treatment.
- Subject is noncompliant with the protocol based on the investigator or medical monitor assessment.
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject.
- Death.

Subjects who discontinue study drug prior to reaching PFS1 and enter the post treatment follow-up period will be discontinued from the post treatment period if any of the following occur:

- Subject develops radiological progressive disease (i.e., PFS1) based on investigator assessment
- Subject initiates a new systemic anticancer treatment (first line of anticancer therapy after discontinuation of study drug)
- Death
- Subject declines further study participation (i.e., withdraws consent)
- Subject is lost to follow up despite reasonable efforts by the investigator to locate the subject

The subject will be discontinued from the long-term follow-up period (for PFS2) if any of the following occur:

- Subject initiates a new systemic anticancer treatment (second line of anticancer therapy after discontinuation of study drug)
- Subject exhibits evidence of PD based on investigator assessment
- Subject declines further study participation (i.e., withdraws consent)
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject
- Death
- Sponsor ends long-term follow-up collection period

The subject will be discontinued from the survival follow-up period if any of the following occur:

- Subject declines further study participation (i.e., withdraws consent)
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject
- Death
- Sponsor ends survival follow-up collection period

6.2 Discontinuation of the Site

If an investigator intends to discontinue participation in the study, the investigator must immediately inform the sponsor (**Japan only**) and the head of the Study site.

6.3 Discontinuation of the Study

The sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns. If the sponsor terminates the study for safety reasons, the sponsor will immediately notify the investigator and subsequently provide written instructions for study termination.

7 STATISTICAL METHODOLOGY

A Statistical Analysis Plan (SAP) will be written to provide details of the analysis, along with specifications for tables, listings and figures to be produced. The SAP will be finalized before the first subject is enrolled. Any changes from the analyses planned in SAP will be justified in the Clinical Study Report.

In general, continuous data will be summarized with descriptive statistics (number of subjects, mean, SD, minimum, median and maximum), and frequency and percentage for categorical data.

7.1 Sample Size

Approximately 600 subjects will be randomized in a 1:1 ratio to 2 treatment arms: EV (Arm A) and chemotherapy (Arm B). Randomization will be stratified by baseline ECOG PS (0 vs 1), regions of the world (Western EU, US or the rest of world) and liver metastasis (yes or no). Assuming HR = 0.75 (median OS in Arm A and Arm B are 10.7 months and 8 months, respectively) drop-out rate of 10%, the final analysis at the planned 439 death events and 1 interim analysis at 65% of the total planned events (285 death events), this sample size will provide 85% power to detect a statistically significant difference at overall type I error rate of 1-sided 0.025.

Sample size is determined by primary endpoint OS; the 600 subjects will provide more than 90% power to detect statistically significant differences on selected secondary endpoints: PFS1(assuming median PFS1 in Arm A and Arm B are 6 months and 4 months, respectively), ORR and DCR (assuming 15% treatment difference between Arm A and Arm B for both ORR and DCR).

7.2 Analysis Sets

Detailed criteria for analysis sets will be laid out in SAP or Classification Specifications and the allocation of subjects to analysis sets will be determined prior to database hard-lock.

7.2.1 Full Analysis Set

The full analysis set (FAS) will consist of all subjects who are randomized. This analysis set is in compliance with the intent to treat (ITT) principle that includes all randomized subjects, the FAS is equivalent to the ITT population. This will be the primary analysis set for efficacy analyses except for response related efficacy endpoints.

7.2.2 Safety Analysis Set

The safety analysis set (SAF), which consists of all subjects who received any amount of study drug, will be used for safety analyses.

7.2.3 Response Evaluable Set

The response evaluable set (RES) is defined as all subjects in FAS and with measurable disease (per RECIST V1.1) at baseline. RES will be used for primary efficacy analysis of response related endpoints, e.g., ORR and DCR.

7.2.4 Pharmacokinetic Analysis Set

Pharmacokinetics Analysis Set (PKAS) includes subjects who received active drug for whom at least one blood sample was collected and assayed for measurement of the TAb, ADC and MMAE serum/plasma concentrations and for whom the time of sampling and the time of dosing on the day of sampling is known.

7.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment group and overall. Ethnic origin will only be summarized in demographic table. Descriptive statistics will include number of subjects, mean, standard deviation, minimum, median and maximum for continuous endpoints, and frequency and percentage for categorical endpoints.

7.3.1 Subject Disposition

The number and percentage of subjects who completed and discontinued treatment and reasons for treatment discontinuation will be presented for all randomized subjects and for subjects in the SAF by treatment group and overall. Similar tables for screening disposition, investigational period disposition and follow-up disposition will also be presented for all randomized subjects by treatment group and overall. All disposition details and dates of first and last evaluations for each subject will be listed.

7.3.2 Previous and Concomitant Medications

All previous and concomitant medications will be presented in a listing. The frequency of concomitant medications (prescription, over-the-counter and nutritional supplements) will be summarized by treatment group and preferred term (PT) for SAF. Medications will be coded using the WHO drug dictionary. Medications will be counted by the number of subjects who took each medication. A subject taking the same medication multiple times will only be counted once for that medication. Medications will be presented in decreasing order of frequency based on the total number of subjects who took each medication.

7.3.3 Medical History

Medical history for each subject will be presented in a listing. A detailed medical history for each subject will be obtained during screening period and will be summarized by treatment group and overall.

7.4 Analysis of Efficacy

Efficacy analysis for OS and PFS will be conducted on the FAS. The interpretation of results from statistical tests will be based on the FAS. Efficacy analysis for response related endpoints, e.g., ORR and DCR will be conducted on RES.

The family-wise type I error rate for this study is strongly controlled at 2.5% (one-sided) that allows the study to declare positive on primary endpoint OS on the FAS population. OS will be formally tested at both interim analysis and final analysis. Formal hypothesis tests on the selected secondary endpoints including PFS1, ORR and DCR, will be performed hierarchically (per the order of PFS1-> ORR->DCR) only when the OS analysis is rejected.

PFS1 is planned to test at either the interim analysis or final analysis when OS is rejected. ORR and DCR will be tested only once after both OS and PFS1 are rejected (at either interim analysis or final analysis) and the test statistics will be computed from the interim data. DCR will be tested after ORR is rejected. The details about the significance levels at interim analysis and final analysis for each efficacy endpoints (OS, PFS1, ORR and DCR) are specified in SAP.

7.4.1 Analysis of Primary Endpoint

7.4.1.1 Primary Analysis

The primary efficacy endpoint of OS will be analyzed using the log-rank test stratified by ECOG PS (0 vs 1), regions of the world (Western EU, US or the rest of world) and liver metastasis (yes or no). Randomized treatment and the strata used for randomization will be used for the analysis. In addition, the stratified Cox proportional hazard model will be used to estimate the hazard ratio and the corresponding 95% confidence interval. The median OS will be estimated using the Kaplan-Meier method and will be reported along with the corresponding 95% confidence interval by treatment arm.

The primary analysis will be performed using the FAS.

7.4.1.2 Sensitivity Analysis

Additional analyses such as unstratified log-rank test and OS analyses adjusting the crossover effect may be conducted, if appropriate. Details will be specified in the SAP.

7.4.2 Analysis of Secondary Endpoints

7.4.2.1 Progression Free Survival

For each subject, PFS1 is defined as the time from the date of randomization until the date of radiological disease progression (per RECIST V1.1), or until death due to any cause. If a subject has neither progressed nor died, the subject will be censored at the date of last radiological assessment. Subjects who receive any further anticancer therapy for the disease before radiological progression will be censored at the date of the last radiological assessment before the anticancer therapy started. In addition, subjects who have PD or death after 2 or more missed disease assessments will be censored at the last disease assessment prior to the 2 or more missed disease assessments.

The efficacy endpoint of PFS1 will be analyzed using the log-rank test stratified by ECOG PS (0 vs 1), regions of the world (Western EU, US or the rest of world) and liver metastasis (yes or no). Randomized treatment and the strata used for randomization will be used for the analysis. In addition, stratified Cox proportional hazard model will be used to estimate the hazard ratio and the corresponding 95% confidence interval. The median PFS1 will be estimated using the Kaplan-Meier method and will be reported along with the corresponding 95% confidence interval by treatment arm.

The primary analysis will be performed using the FAS. Additional sensitivity analyses for PFS1 will also be performed. Details will in specified in the SAP.

7.4.2.2 Overall Response Rate

The overall response rate (ORR) is defined as the proportion of subjects with complete or partial objective response based on the RECIST V1.1. The comparison of ORR between Arm A and Arm B will be performed using a stratified CMH test. Same stratification factors used in time to event analyses will be used for the stratified CMH test. The difference in response rates between the treatment arms will be estimated along with the corresponding 95% confidence interval. In addition, ORR for each arm will be estimated and corresponding 95% confidence interval will be constructed. The primary analysis will be performed using the RES.

7.4.2.3 Duration of Response

Duration of Response (DOR) is defined as the time from the date of the first response CR/PR per RECIST V1.1 (whichever is first recorded) that is subsequently confirmed as assessed by investigator to the date of radiological progression or date of death for subjects who achieved CR or PR. If a subject has not progressed or died, the subject will be censored at the date of last radiological assessment or at the date of first CR/PR if no other post-baseline radiological assessment is available after the first CR/PR. Subjects who receive any further anti-cancer therapy for the disease before radiological progression will be censored at the date of the last radiological assessment before the anticancer therapy started. In addition, subjects who have PD or death after 2 or more missed disease assessments will be censored at the last disease assessment prior to the 2 or more missed disease assessments.

The median DOR will be estimated using the Kaplan-Meier method and will be reported along with the corresponding 95% confidence interval by treatment arm.

7.4.2.4 Disease Control Rate (DCR)

The DCR is defined as the proportion of subjects with a complete or partial objective response or a stable disease based on RECIST V1.1. The comparison of DCR between Arm A and Arm B will be performed using a stratified CMH test. Same stratification factors used in time to event analyses will be used for the stratified CMH test. The difference in response rates between the treatment arms will be estimated along with the corresponding 95% confidence interval. In addition, DCR for each arm will be estimated and corresponding 95% confidence interval will be constructed. The primary analysis will be performed using the RES.

7.4.2.5 QOL and PRO Parameters

Descriptive QOL and PRO analyses will be performed on the FAS. Completion rate for each questionnaire will be summarized. Additional analyses will be discussed in detail in the statistical analysis plan.

7.4.3 Subgroup Analysis

Using FAS, the analysis for OS, PFS1 and ORR will be repeated by ECOG PS (0 vs 1), regions of the world, and liver metastasis respectively.

In addition, subgroup analyses may be conducted for selected endpoints to determine whether the treatment effect is consistent. Subgroups may include but are not limited to the following:

- Age category (< 65 vs ≥ 65 years; < 75 vs ≥ 75 years)
- Sex (female vs male)
- Prior platinum (cisplatin vs carboplatin vs both)
- Prior lines of systemic therapy in locally advanced or metastatic setting (1 to 2 vs ≥ 3)
- Best response to most recent CPI (responder vs non-responder) CPI most recent treatment (yes vs no)
- Baseline hemoglobin (≥ 10 vs < 10 g/dL)
- Histology (Urothelial Carcinoma/transitional cell vs Urothelial Carcinoma mixed vs other)
- Primary site of tumor (upper tract vs bladder/other)
- Smoking status (never vs former vs current)
- Brain metastasis status (prior brain metastasis vs no prior brain metastasis)
- Investigators' choice of paclitaxel/docetaxel or vinflunine
- Baseline Nectin-4 IHC score (<150 vs 150 - 225 vs >225)
- Prior taxane (yes vs no)
- PD-L1 CPS (<10 vs ≥10)

7.4.4 Analysis of Exploratory Endpoints

Exploratory analysis for efficacy endpoints will be discussed in the statistical analysis plan.

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

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

7.5 Analysis of Safety

SAF will be used to perform all safety analysis. All treated subjects will be analyzed according to the treatment they received.

7.5.1 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

A TEAE is defined as an AE observed or worsened after starting administration of the study drug.

The number and percentage of subjects with treatment-emergent AEs, SAEs, AEs leading to withdrawal of treatment, and AEs related to study drug will be summarized by system organ class, preferred term and treatment group. The number and percentage of AEs by severity will also be summarized. All AEs will be listed.

A study drug-related TEAE is defined as any TEAE with a causal relationship of YES by the investigator. AEs of interest as classified by customized MedDRA queries and/or standard MedDRA queries will also be summarized.

7.5.2 Laboratory Assessments

For quantitative laboratory measurements descriptive statistics will be used to summarize results and change from baseline for subjects in the SAF by treatment group and time point.

Shifts relative to normal ranges from baseline to each time point during treatment period in lab tests will also be tabulated. Laboratory data will be displayed in listings.

7.5.3 Vital Signs

Vital sign results and changes from baseline at scheduled visits will be summarized with descriptive statistics for subjects in the SAF by treatment group. Vital signs data will be displayed in listings.

7.5.4 Routine 12-lead Electrocardiograms

The 12-lead ECG results will be summarized by treatment group and time point.

7.5.5 ECOG Performance Status

Summary statistics (number and percent of subjects) for each category of the ECOG PS at each assessment will be provided. The change from baseline to final visit or early termination will also be summarized. Negative change scores indicate an improvement. Positive scores indicate a decline in performance.

7.5.6 Exposure-Response Relationship Analysis

Relationships between TAb, ADC and MMAE concentrations and certain efficacy or safety endpoints may be analyzed in an exploratory manner. Further details of these analyses will be described in an exposure-response analysis plan.

7.6 Analysis of Pharmacokinetics

Individual and summary tables of serum TAb and ADC and plasma MMAE concentrations and a listing of blood collection times and concentrations will be provided.

Summary statistics will be provided including n, mean, SD, geometric mean, minimum, median, maximum, and %CV. Values below the lower limit of quantification (BLOQ) will be set to not be calculated if all values are BLOQ. In cases where more than half of the individual data in a group are BLOQ, the geometric mean will not be calculated. Additional model-based analyses may be performed and will be described in a separate population PK analysis plan.

7.7 Major Protocol Deviations and Other Analyses

Major protocol deviations as defined in [Section 8.1.6 Major Protocol Deviations] will be summarized for all randomized subjects by treatment group and total as well as by site. A data listing will be provided by site and subject.

The major protocol deviation criteria will be uniquely identified in the summary table and listing. The unique identifiers will be as follows:

PD1 - Entered into the study even though they did not satisfy entry criteria,

PD2 - Developed withdrawal criteria during the study and was not withdrawn,

PD3 - Received wrong treatment or incorrect dose,

PD4 - Received excluded concomitant treatment.

7.8 Interim Analysis (and Early Discontinuation of the Clinical Study)

An interim efficacy analysis is planned to occur after approximately 285 OS events (about 65% of the total planned events) are observed. OS will be tested at 1-sided 0.00541 significance level for efficacy according to the O'Brien-Fleming boundary as implemented by Lan-DeMets alpha spending function [Lan-DeMets, 1983]. The IDMC may recommend terminating the trial at the interim analysis based on statistically significant OS results favoring EV. When total deaths reach 439, the final OS analysis will be conducted at the 1-sided 0.02332 significance level. If the exact numbers of events at interim and final analyses are different than planned, the significance level will be adjusted accordingly, based on the O'Brien-Fleming method with a Lan-DeMets alpha spending function.

The interim analysis will be conducted by IDAC and reviewed by the IDMC. In addition, safety data reviews during the trial will be conducted by the IDMC on a periodic basis. For example, the IDMC will review safety data after the first 50 subjects have been randomized and on study drug for approximately 3 months. The full procedures for IDMC safety review and interim analysis will be described in a separate IDMC charter and Interim Analysis Plan.

7.9 Handling of Missing Data, Outliers, Visit Windows, and Other Information

Imputation methods for missing data, if applicable, and the definitions for windows to be used for analyses will be outlined in the SAP.

8 OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS

8.1 Procedure for Clinical Study Quality Control

8.1.1 Data Collection

The investigator or site designee will enter data collected using an Electronic Data Capture (EDC) system. In the interest of collecting data in the most efficient manner, the investigator or site designee should record data (including laboratory values, if applicable) in the eCRF within 5 days after the subject visit.

The investigator or site designee is responsible to ensure that all data in the eCRFs and queries are accurate and complete and that all entries are verifiable with source documents. These documents should be appropriately maintained by the site.

The monitor should verify the data in the eCRFs with source documents and confirm that there are no inconsistencies between them.

Laboratory tests are performed at the central laboratory. Central laboratory data will be transferred electronically to the sponsor or designee at predefined intervals during the study. The central laboratory will provide the sponsor or designee with a complete and clean copy of the data.

For screen failures the demographic data, reason for failing, informed consent, inclusion and exclusion criteria and AEs will be collected in the eCRF.

For sites located in Japan:

For screen failures, the minimum demographic data (sex, birth date or age, race and informed consent date), AEs and reason for screen failure will be collected in screen failure log (SFL), if applicable. This information will be entered into the study database.

Electronic Patient Reported Outcome (ePRO):

Questionnaires will be completed by the subject on an electronic device. Subjects will be provided with digital support (e.g., instruction) to fill in the questionnaires at home. The information completed by the subject on the electronic device will be automatically uploaded into a central website. The investigator or site designee should review the diaries and questionnaire data on the website for correct completion while the subject is at the site. The diary and questionnaire data will be transferred electronically to sponsor or designee at predefined intervals during the study. The vendor will provide sponsor or designee with a complete and clean copy of the data.

For subjects who are unable to read a language in a country for which ePRO translation is available or who is illiterate will not be required to complete the ePRO part of the study.

8.1.2 Specification of Source Documents

Source data must be available at the site to document the existence of the study subjects and to substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the subject.

The following information should be included in the source medical records:

- Demographic data (age, sex, race, ethnicity, height and body weight)
- Inclusion and exclusion criteria details
- Participation in study and original signed and dated informed consent forms
- Visit dates
- Medical history and physical examination details
- Key efficacy, pharmacokinetic and safety data, if applicable
- AEs and concomitant medication
- Results of relevant examinations (e.g., ECG charts, X-ray films etc.)
- Laboratory printouts (if applicable)

- Details of dispensing and return of study drug
- Reason for premature discontinuation (if applicable)
- Randomization number
- Pharmacokinetic sample processing and storage history, including date/time each sample is transferred to the freezer, freezer identification and the temperature log for the freezer

8.1.3 Clinical Study Monitoring

The sponsor is responsible for monitoring the clinical study to ensure that subject's human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol and GCP, and study data reported by the investigator/sub-investigator are accurate and complete and that they are verifiable with study-related records such as source documents. The sponsor is responsible for assigning study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

8.1.4 Direct Access to Source Data/Documents

The investigator and the study site must accept monitoring and auditing by the sponsor or delegated CRO as well as inspections from the IRB/IEC and relevant regulatory authorities. In these instances, they must provide all study-related records, such as source documents [refer to Section 8.1.2 Specification of Source Documents] when they are requested by the sponsor monitors and auditors, the IRB/IEC, or regulatory authorities. The confidentiality of the subject's identities shall be well protected consistent with local and national regulations when the source documents are subject to direct access.

8.1.5 Data Management

Data Management will be coordinated by the Data Science of the sponsor in accordance with the SOPs for data management. All study-specific processes and definitions will be documented by Data Management. eCRF completion will be described in the eCRF instructions. Coding of medical terms and medications will be performed using MedDRA and WHO Drug Dictionary, respectively.

8.1.6 Major Protocol Deviations

A major protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety, and welfare of subjects. The investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to study subjects.

A protocol waiver is a documented prospective approval of a request from an investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

The major protocol deviation criteria are as follows:

PD1 - Entered into the study even though they did not satisfy entry criteria,

PD2 - Developed withdrawal criteria during the study and was not withdrawn,

PD3 - Received wrong treatment or incorrect dose,

PD4 - Received excluded concomitant treatment.

When a major deviation from the protocol is identified for an individual subject, the investigator or designee must ensure the sponsor is notified. The sponsor will follow-up with the investigator, as applicable, to assess the deviation and the possible impact to the safety and/or efficacy of the subject to determine subject continuation in the study.

If a major deviation impacts the safety of a subject, the investigator must contact the sponsor immediately.

The investigator will also assure that deviations meeting IRB/IEC and applicable regulatory authorities' criteria are documented and communicated appropriately. All documentation and communications to the IRB/IEC and applicable regulatory authorities will be provided to the sponsor and maintained within the trial master file (TMF).

8.1.7 End of Trial in All Participating Countries

Study completion is defined as the conclusion of data collection for the defined study endpoints. The end of study in all participating countries is therefore defined as the last subject's last visit, or last contact. The study may be closed within a participating country per local regulations once the study has completed, if all subjects enrolled in the country are no longer receiving study treatment and once final survival analysis is completed.

8.2 Ethics and Protection of Subject Confidentiality

8.2.1 Institutional Review Board/Independent Ethics Committee/Competent Authorities

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any substantial amendments to the protocol will require IEC/IRB approval prior to implementation of the changes made to the study design at the site. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Any SAEs that meet reporting criteria, as dictated by local regulations, will be reported to both responsible ethics committees and regulatory agencies, as required. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to sponsor.

If required by local regulations, the investigator shall make accurate and adequate written progress reports to the IEC/IRB at appropriate intervals, not exceeding 1 year. The investigator shall make an accurate and adequate final report to the IRB/IEC within 90 days after the close-out visit or termination of the study.

8.2.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

8.2.3 Informed Consent of Subjects

8.2.3.1 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject or his/her guardian or legal representative, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed (place a personal seal, if applicable) and dated by the subject or his/her guardian or legal representative, the person who administered the informed consent and any other signatories according to local requirements. A copy of the signed or sealed informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

The signed consent forms will be retained by the investigator and made available (for review only) to the study monitor and auditor regulatory authorities and other applicable individuals upon request.

8.2.3.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information

1. The investigator or his/her representative will immediately inform the subject orally whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue to participate in the study (e.g., report of serious drug adverse drug reaction). The communication must be documented in the subject's medical records and whether the subject is willing to remain in the study or not must be confirmed and documented.
2. The investigator must update their ICF and submit it for approval to the IRB/IEC. The investigator or his/her representative must obtain written informed consent from the subject on all updated ICFs throughout their participation in the study. The investigator or his/her designee must reconsent subjects with the updated ICF even if relevant information was provided orally. The investigator or his/her representative who obtained the written informed consent and the subject should sign and date the informed consent form (place a personal seal, if applicable). A copy of the signed or sealed informed consent form will be given to the subject and the original will be

placed in the subject's medical record. An entry must be made in the subject's records documenting the re-consent process.

8.2.4 Subject Confidentiality and Privacy

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Such medical information may be given only after approval of the subject to the subject's physician or to other appropriate medical personnel responsible for the subject's well-being.

The sponsor shall not disclose any confidential information on subjects obtained during the performance of their duties in the clinical study without justifiable reasons.

Even though any individuals involved in the study, including the study monitors and auditors, may get to know matters related to subject's privacy due to direct access to source documents, or from other sources, they may not leak the content to third parties.

The sponsor affirms the subject's right to protection against invasion of privacy. Only a subject identification number and/or initials will identify subject data retrieved by the sponsor. However, the sponsor requires the investigator to permit the sponsor, sponsor's representative(s), the IRB/IEC and when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study.

The sponsor agrees to comply and process personal data in accordance with all applicable privacy laws and regulations, including, without limitation, the Personal Information Protection Law in Japan and Privacy laws in the US. If the services will involve the collection or processing of personal data (as defined by applicable data protection legislation) within the European Economic Area (EEA), then sponsor shall serve as the controller of such data, as defined by the EU Data Protection Directive, and Investigator and/or third party shall act only under the instructions of the sponsor in regard to personal data. If sponsor is not based in the EEA, sponsor must appoint a third party to act as its local data protection representative or arrange for a co-controller established in the EU for data protection purposes in order to comply with the Directive.

8.3 Administrative Matters

8.3.1 Arrangement for Use of Information and Publication of the Clinical Study

Information concerning the study drug, patent applications, processes, unpublished scientific data, the Investigator's Brochure and other pertinent information is confidential and remains the property of the sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The investigator may use this information for the purpose of the study only. It is understood by the investigator that the sponsor will use the information obtained during the clinical study in connection with the development of the drug and therefore may disclose it as required to other clinical investigators or to regulatory agencies. In order to allow for the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide the sponsor with all data obtained during the study.

Publication of the study results is discussed in the clinical study agreement.

After agreement between investigator(s) and sponsor, the manuscript can be submitted for publication.

8.3.2 Documents and Records Related to the Clinical Study

The sponsor will provide the investigator and/or institution with the following:

- Study protocol (and amendments, where applicable)
- Investigator's Brochure (and amendments, where applicable)
- eCRFs and JUTOKUNA YUUGAIJISHOU HOUKOKUSHO
- Study drug with all necessary documentation
- Study contract

In order to start the study, the investigator and/or study site is required to provide the following documentation to the sponsor:

- Financial disclosure in compliance with federal regulation 21 Code of Federal Regulations Part 54
- Signed and dated FDA form 1572
- Signed Investigator's Statement in this protocol and eCRF
- Current Curricula Vitae of all investigators
- List of sub-investigators and collaborators
- IRB approval of the protocol, protocol amendments (if applicable) including a membership list with names and qualification (COPY)
- Instruction and decision of the head of the study site
- Study contract
- Laboratory normal reference ranges (if applicable, signed and dated by the responsible laboratory employee)

The investigator will archive all study data (e.g., subject identification code list, source data, CRFs, and investigator's file) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation (for US sites, two years after approval of the NDA or discontinuation of the IND). The sponsor will notify the site/investigator if the NDA/MAA/J-NDA is approved or if the IND/IMPD/CHIKEN TODOKE is discontinued. The investigator agrees to obtain the sponsor's agreement prior to disposal, moving, or transferring of any study-related records. The sponsor will archive and retain all documents pertaining to the study according to local regulations.

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes.

Data will be collected for each subject for the clinical study database via electronic data source.

For sites located in Japan:

The following are the major documents to be retained at the study site.

1. Source documents (clinical data, documents, and records for preparing the CRF)*:* hospital records, medical records, test records, memoranda, subject diary or check lists for evaluation, administration records, data recorded by automatic measuring instruments, reproductions or transcripts verified as precise copies, microfiche, negative films, microfilms/magnetic media, X-ray films, subject files and study-related records kept at either a pharmacy, a laboratory, or medical technical office, as well as subject registration forms, laboratory test slips including central measurement, worksheets specified by the sponsor, records of clinical coordinators, and records related to the clinical study selected from those verified in other departments or hospitals.
2. Contracts, written informed consent forms, written information, and other documents or their copies prepared by the study personnel. A letter of request for clinical study (including a request for continuation/amendment), letter of request for review, notice of clinical study contract, clinical study contract, notification of discontinuation or completion of clinical study, written information for informed consent (including revisions), signed and dated written informed consent (including revisions), CVs of investigators, list of sub-investigators, list of signatures and print of seals (copy), and case report forms (copy), etc.
3. The protocol, documents obtained from the IRB related to the adequacy of conducting the clinical study by the head of the study sites (Article 32-1, MHW Ordinance No. 28), documents obtained from the IRB related to the adequacy of conducting a clinical study whose period exceeds 1 year or the adequacy of continuously conducting the clinical study from which information on adverse drug reactions is obtained, and other documents obtained. An agreed-upon protocol (including revisions), Investigator's Brochure (including revisions), operational procedures for the investigator, materials and information supplied by the sponsor (e.g., AE report), matters reported by the investigator (revisions of the protocol, AE reports, etc.), operational procedures for the IRB, the list of names of the IRB members, materials for IRB review (including continuous deliberation), IRB review records (including continuous deliberation), and the review result report of the IRB (including continuous deliberation), etc.
4. Records of control for study drugs and other duties related to the clinical study. Procedure for controlling the study drugs, drug inventory and accountability record, vouchers for the receipt and return of the study drugs, and the prescriptions for concomitant medications

8.3.3 Protocol Amendment and/or Revision

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments: substantial amendments and/or non-substantial amendments. Depending on the nature of the amendment, either IRB/IEC, Competent Authority approval or notification may be required. The changes will become effective only after the approval of the sponsor, the investigator, the regulatory authority, and the IRB/IEC (if applicable).

Amendments to this protocol must be signed by the sponsor and the investigator. Written verification of IRB/IEC approval will be obtained before any amendment is implemented which affects subject safety or the evaluation of safety, and/or efficacy. Modifications to the protocol that are administrative in nature do not require IRB/IEC approval, but will be submitted to the IRB/IEC for their information, if required by local regulations.

If there are changes to the informed consent, written verification of IRB/IEC approval must be forwarded to the sponsor. An approved copy of the new informed consent must also be forwarded to the sponsor.

8.3.4 Insurance of Subjects and Others

The sponsor has covered this study by means of an insurance of the study according to national requirements. The name and address of the relevant insurance company, the certificate of insurance, the policy number and the sum insured are provided in the investigator's file.

If a subject suffers any study-related injury, the sponsor will compensate appropriately according to the severity and duration of the damage. However, if it was caused intentionally or was due to gross negligence by the study site, the sponsor will consult with the study site about handling the injury, based on the agreed study contract. Compensation for the study-related injury is provided by the following procedures:

1. If a subject incurs an injury as a result of participation in the clinical study, the study site should provide medical treatment and other necessary measures. The sponsor should be notified of the injury.
2. When the subject claims compensation from the study site for the above study-related injury, or such compensation may be claimed, the study site should immediately communicate the fact to the sponsor. Both parties should work together towards compensation settlement.
3. The sponsor shall pay compensation or indemnification and bear expenses necessary for the settlement as provided in the clinical contract.
4. The sponsor shall make an arranging for insurance and take measures necessary to ensure the compensation or indemnification mentioned above.

8.3.5 Signatory Investigator for Clinical Study Report

ICH E3 guidelines recommend and EU Directive 2001/83/EC requires that a final study report which forms part of a marketing authorization application be signed by the representative for the coordinating investigator(s) or the principal investigator(s). The representative for the coordinating investigator (s) or the principal investigator(s) will have the responsibility to review the final study results to confirm to the best of his/her knowledge it accurately describes the conduct and results of the study. The representative for coordinating investigator(s) or the principal investigator(s) will be selected from the participating investigators by the sponsor prior to database lock.

9 QUALITY ASSURANCE

The sponsor is implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that studies are conducted and data are generated, documented, recorded, and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s). Where applicable, the quality assurance and quality control systems and written SOPs of the CRO will be applied.

The sponsor or sponsor's designee may arrange to audit the clinical study at any or all investigational sites and facilities. The audit may include on-site review of regulatory documents, case report forms, and source documents. Direct access to these documents will be required by the auditors.

10 STUDY ORGANIZATION

10.1 Independent Data-Monitoring Committee

An IDMC will be chartered to oversee safety and the planned interim efficacy analysis, which will occur after at least 285 events (about 65% of the total planned events) are observed. The primary analysis will occur at 439 OS events. The interim analysis will be conducted by the IDMC. In addition, safety data reviews during the trial will be conducted by the IDMC on a periodic basis. For example, the IDMC will review safety data after the first 50 subjects have been randomized and on study drug for approximately 3 months. The IDMC may recommend to the sponsor whether the trial should be terminated, modified or continue unchanged based on ongoing reviews of safety data and interim efficacy analysis. Further details will be outlined in the IDMC charter.

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12 APPENDICES

12.1 List of Cautionary Concomitant Medications

The following list describes medications and foods that are common strong inhibitors/inducers of CYP3A, CYP2C8 and p-glycoprotein (P-gp) inhibitors that should be avoided, used with caution, or closely monitored. This list should not be considered all inclusive; consult individual drug labels for specific information. If there are concerns or questions about concomitant use of any drugs listed below, discussion with the sponsor is encouraged.

P-gp Inhibitors	Strong CYP3A Inhibitors	Strong CYP3A4 Inducers	Strong CYP2C8 Inhibitors	Strong CYP2C8 Inducers
amiodarone carvedilol clarithromycin drenedarone itraconazole lapatinib lopinavir/ritonavir propafenone quinidine ranolazine saquinavir/ritonavir telaprevir tipranavir/ritonavir verapamil	boceprevir cobicistat conivaptan danoprevir/ ritonavir elvitegravir/ ritonavir grapefruit juice indinavir/ ritonavir itraconazole ketoconazole lopinavir/ritonavir paritaprevir/ ritonavir/ (ombitasvir and/or dasabuvir) posaconazole ritonavir saquinavir/ ritonavir telaprevir tipranavir/ritonavir troleandomycin voriconazole	carbamazepine enzalutamide mitotane phenytoin rifampin St John's wort	clopidogrel gemfibrozil	rifampin

Note: Any additional strong inhibitors/inducers of CYP3A, CYP2C8, and P-gp inhibitors that are identified or become commercially available while the clinical trial in ongoing are also applicable. P-gp: p-glycoprotein

Table 10 Summary of Potential Drug Reactions

	Arm A: EV	Arm B: Docetaxel	Arm B: Vinflunine	Arm B: Paclitaxel
Strong CYP3A4 inhibitor	Closely monitor	Should avoid	Should avoid	Exercise caution
Strong CYP3A4 inducer		Should avoid	Should avoid	Exercise caution
P-gp inhibitor	Closely monitor			
Strong CYP2C8 inhibitor/inducer				Exercise caution

EV: enfortumab vedotin; P-gp: p-glycoprotein

Additional information for inhibitors/inducers can be found in FDA's guidance (Drug Interaction and Labeling).

https://www fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664 htm#table5-2

12.2 Liver Safety Monitoring and Assessment

Any subject enrolled in a clinical study with active drug therapy and reveals an increase of serum aminotransferases (AT) to > 3 × ULN (to > 5 × ULN in subjects with liver metastases) or bilirubin > 2 × ULN should undergo detailed testing for liver enzymes (including at least ALT, AST, ALP, and TBL). Testing should be repeated within 72 hours of notification of the test results. For studies for which a central laboratory is used, alerts will be generated by the central laboratory regarding moderate and severe liver abnormality to inform the investigator, study monitor and study team. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

Confirmed abnormalities will be characterized as moderate and severe where ULN:

	ALT or AST		**Total Bilirubin**
Moderate	> 3 × ULN (in patients without liver metastases), > 5 × ULN (in patients with liver metastases)	or	> 2 × ULN
Severe	> 3 × ULN	and	> 2 × ULN

In addition, the subject should be considered to have severe hepatic abnormalities for any of the following:

- ALT or AST > 8 × ULN.
- ALT or AST > 5 × ULN for more than 2 weeks (in the absence of liver metastases).
- 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 fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash 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.

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. The site should complete the liver abnormality case report form (LA-CRF) that has been developed globally and can be activated for any study or appropriate document. Subjects with confirmed abnormal liver function testing should be followed as described below.

Confirmed moderately abnormal 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 findings, the investigator is expected to:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new-onset diseases is to be recorded as "AEs" in the (e)CRF. Illnesses and conditions such as hypotensive events, and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Nonalcoholic steatohepatitis is seen in obese hyperlipoproteinemic, and/or diabetic patients and may be associated with fluctuating AT levels. The investigator should ensure that the medical history form captures any illness that predates study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including nonprescription medication, complementary and alternative medications), alcohol use, recreational drug use and special diets. Medications, including dose, is to be entered in the (e)CRF. Information on alcohol, other substance use and diet should be entered on the LA-CRF or an appropriate document.
- 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.
- Submit results for any additional testing and possible etiology on the LA-CRF or an appropriate document.

Study Discontinuation

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

- ALT or AST > 8 × ULN.
- ALT or AST > 5 × ULN for more than 2 weeks (in subjects without liver metastases).
- ALT or AST > 3 × ULN and TBL > 2 × ULN or INR > 1.5 (If INR testing is applicable/evaluated).
- ALT or AST > 5 × ULN and (TBL > 2 × ULN in patients with liver metastases).
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

In addition, if close monitoring for a subject with moderate or severe hepatic laboratory tests is not possible, drug should be discontinued.

*Hy's Law Definition:

1. Evidence that a drug can cause hepatocellular-type injury, generally shown by a higher rate than control of people with 3 × and greater transaminase elevations over the upper limit of normal (2 × elevations are too common in treated and untreated patients to be discriminating).

2. Cases of increased bilirubin (to at least 2 × ULN) in people with concomitant transaminase elevation to at least 3 × ULN (but it is almost invariably higher) and no evidence of intra-or extra-hepatic bilirubin obstruction (elevated alkaline phosphatase) or Gilbert's syndrome. [Temple, 2006]

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo.

2. Among trial subjects showing such AT elevations, often with ATs much greater than 3 × ULN, one or more also show elevation of serum TBL to > 2 × ULN, without initial findings of cholestasis (elevated serum ALP).

3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury [Guidance for Industry, 2009].

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12.3 Common Serious Adverse Events

The following is a list of SAE that the sponsor considers to be associated with the disease state being studied. The list does NOT change your reporting obligations or prevent the need to report an AE meeting the definition of an SAE as detailed in [Section 5.6.2 Definition of Serious Adverse Events]. The purpose of this list is to alert the investigator that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of "common SAEs". The investigator is required to follow the requirements detailed in [Section 5.6.5 Reporting of Serious Adverse Events].

- Urinary tract pain
- Bladder disorder
- Dysuria
- Hemorrhage urinary tract (hematuria)
- Urinary tract obstruction

12.4 Retrospective PGx Sub-Study

INTRODUCTION

PGx research aims to provide information regarding how naturally occurring changes in a subject's gene and/or expression based on genetic variation may impact what treatment options are best suited for the subject. Through investigation of PGx by technologies such as genotyping, gene sequencing, statistical genetics and Genome-Wide Association Studies, the relationship between gene profiles and a drug's kinetics, efficacy or toxicity may be better understood. As many diseases may be influenced by 1 or more genetic variations, PGx research may identify which genes are involved in determining the way a subject may or may not respond to a drug.

OBJECTIVES

The PGx research that may be conducted in the future with acquired blood samples is exploratory. The objective of this research will be to analyze or determine genes of relevance to clinical response, pharmacokinetics and toxicity/safety issues.

By analyzing genetic variations, it may be possible to predict an individual subject's response to treatment in terms of efficacy and/or toxicity.

SUBJECT PARTICIPATION

Subjects who have consented to participate in this study may participate in this PGx sub-study. As part of this sub-study, subjects must provide written consent prior to providing any blood samples that may be used at a later time for genetic analysis.

SAMPLE COLLECTION AND STORAGE

Subjects who consent to participate in this sub-study will provide one approximately 4-6 mL tube of whole blood per Astellas' instructions. Each sample will be identified by the unique subject number (first code). Samples will be shipped frozen to a designated banking CRO either directly from site or via a central laboratory as directed by Astellas.

PGx ANALYSIS

Details on the potential PGx analysis cannot be established yet. Astellas may initiate the PGx analysis in case evidence suggests that genetic variants may be influencing the drug's kinetics, efficacy and/or safety.

DISPOSAL OF PGx SAMPLES / DATA

All PGx samples collected will be stored for a period of up to 15 years following study database hardlock. If there is no requirement for analysis, the whole blood sample will be destroyed after the planned storage period. The subject has the right to withdraw consent at any time. When a subject's withdraw notification is received, the PGx sample will be destroyed. The results of any PGx analysis conducted on a sample prior to its withdrawal will be retained at Astellas indefinitely.

INFORMATION DISCLOSURE TO THE SUBJECTS

Exploratory PGx analysis may be conducted following the conclusion of the clinical study, if applicable. The results of the genetic analysis will not be provided to any investigators or subjects, nor can the results be requested at a later date. Any information that is obtained from the PGx analysis will be the property of Astellas and its collaborator.

12.5 EORTC-QLQ-30

ENGLISH

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):

	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

ENGLISH

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

12.6 EQ-5D-5L

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

MOBILITY

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

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

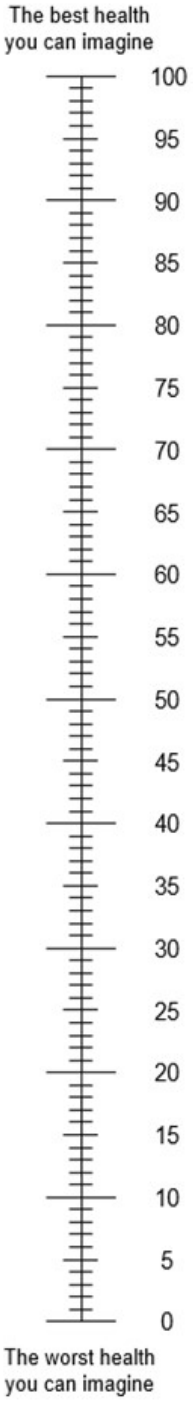
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

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 ❑

- 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 = ☐



2

12.7 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.)?

12.8 RECIST V1.1

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 EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-47.

12.9 ECOG Performance Status

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

ECOG: Eastern Cooperative Oncology Group

Reproduced from: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-55.

12.10 Crossover Extension

Note: The crossover extension study described below and outlined in the Crossover Extension (COE) schematic [Figure 2] will be conducted if the EV-301 Interim Analysis results in a positive outcome. With the exception of those procedures and processes indicated below, this extension study will be performed using the same general approach as described in the protocol. Refer to the main protocol for any study details not contained in the supplemental COE appendix.

12.10.1 Rationale

Upon decision to stop the study for efficacy based on statistically significant OS result favoring EV, all eligible Arm B subjects can be evaluated for eligibility for COE EV treatment at the discretion of the subject and investigator. Day 1 of the COE will occur after COE informed consent form is signed and eligibility is confirmed. Treatment with EV will be stopped upon disease progression and/or when discontinuation criteria are met [Section 12.10.5 Duration of Treatment and Criteria for Discontinuation]. Arm B Subjects who do not participate in the COE will continue to follow Arm B protocol procedures.

12.10.2 Inclusion Criteria

Subject is eligible for the COE if they continue to meet all inclusion criteria from the main protocol in addition to the following when the patient is evaluated for eligibility to participate in the COE portion of the study:

1. IRB/IEC approved written COE informed consent and privacy language as per national regulations (e.g., HIPAA Authorization for US sites) must be obtained from the subject prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Subject was randomized to Arm B and is either currently on study treatment or has discontinued study treatment due to intolerance, AE or progression of disease, has not started a new systemic anticancer treatment and is still participating in the follow up phase of the study.

Waivers to the COE inclusion criteria will NOT be provided.

12.10.3 Exclusion Criteria

Subject will be excluded from participation in the COE if they meet any of the exclusion criteria listed in the main protocol or if any of the following apply when the patient is evaluated for eligibility to participate in the COE portion of the study:

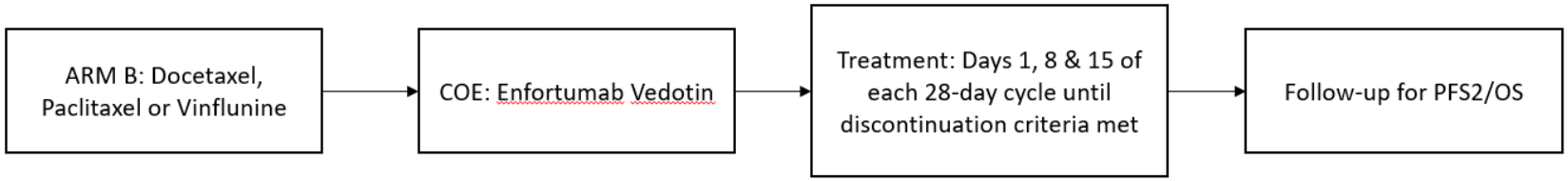
1. Subject has been diagnosed with a new malignancy while on Arm B in the EV-301 study. Subjects with nonmelanoma skin cancer, localized prostate cancer treated with curative intent with no evidence of progression, low-risk or very low-risk (per standard guidelines) localized prostate cancer under active surveillance/watchful waiting without intent to treat, or carcinoma in situ of any type (if complete resection was performed) are allowed.

Waivers to the COE exclusion criteria will **NOT** be allowed.

12.10.4 Schedule and Assessments

Arm B subjects meeting criteria as indicated in [Section 12.10.3] will sign informed consent prior to COE Day 1 dosing. The COE subjects will follow the COE Schematic and COE Schedule of Assessments [Table 11].

Figure 2 Crossover Extension Schema



COE: crossover extension; OS: overall survival; PFS2: progression free survival on subsequent therapy

Table 11 Schedule of Assessments for Crossover Extension

Visit	Every Cycle				End of Treatment[1]	Follow-up[2]	Long Term PFS2 Treatment Follow-up	Survival Follow-up
Base Date	**Day 1**	**Day 8**	**Day 15**	**Every 56 Days**	**Date of Last Dose**	**Date of last Dose + 30 days**	**Every 3 months**	**Every 3 months**
Visit Window	± 3 days	± 3 day	± 3 days	± 7 days	+ 7 days	+ 7 days	± 7 days	± 7 days
Informed Consent	X[3,4]							
Confirmation of Eligibility for COE	X[3,4]							
Brain Scan[5]	X[3,5]			X[5]				
Bone Scan[6]	X[6]			X[6]				
Serum/Urine Pregnancy Test[7]	X				X	X	X[7]	X[7]
Physical Examination[8]	X				X			
Weight[8]	X	X	X		X			
Vital Signs[8]	X	X	X		X	X		
Biochemistry[9]	X	X	X		X	X		
Hemoglobin A1C[10]	X				X			
Hematology[11]	X	X	X		X	X		
ECOG PS	X				X	X		
12-lead ECG[12]	X[3,12]				X[12]			
Ophthalmology Assessment[13]	X				X			
COE Enrollment via IRT	X[4]							
EV Administration	X	X	X					
Image Assessment[14]	X			X[14]				
Concomitant Medication	X	X	X	X	X	X		
Adverse Events	X	X	X	X	X	X		
QOL[15]	X				X	X		
HRU[16]	X[16]				X	X		
Table continued on next page								

Visit	**Every Cycle**				**End of Treatment[1]**	**Follow-up[2]**	**Long Term PFS2 Treatment Follow-up**	**Survival Follow-up**
Base Date	**Day 1**	**Day 8**	**Day 15**	**Every 56 Days**	**Date of Last Dose**	**Date of last Dose + 30 days**	**Every 3 months**	**Every 3 months**
Visit Window	± 3 days	± 3 day	± 3 days	± 7 days	+ 7 days	+ 7 days	± 7 days	± 7 days
ATA[19]	X				X	X		
Subsequent Therapy assessment[17]						X	X	
Overall Survival[18]						X	X	X

AE: adverse event; ALT: alanine transaminase; AST: aspartate transaminase; ATA: antitherapeutic antibody; C: cycle; COE: crossover extension; CR: complete response; CT: computed tomography; D: day; ECG: electrocardiogram; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EORTC-QLQ-C30: European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; EOT: end of treatment; EQ-5D-5L: EuroQOL 5-Dimension 5-Level Questionnaire; EV: enfortumab vedotin; HRU: health resource utilization; MRI: magnetic resonance imaging; NA: Not Applicable; PD: progressive disease; PFS1: progression free survival on study therapy; PFS2: progression free survival on subsequent therapy; PGx: Pharmacogenetic analyses; PR: partial response; QOL: quality of life; RECIST: Response Evaluation Criteria in Solid Tumors

1. EOT visit will occur within 7 days after the last dose or when the decision is made by the investigator to discontinue subject from treatment.
2. Follow up assessments should be completed prior to the initiation of the next therapy.
3. May be completed within 28 days prior to COE C1D1 visit.
4. COE Cycle 1 only.
5. Only if clinically indicated at time of COE eligibility assessment. Repeat as clinically indicated or per standard of care throughout the study.
6. All subjects will have a bone scan (scintigraphy) within 28 days prior to COE C1D1 dosing. Subjects with positive bone scans at time of COE eligibility assessment will have a bone scan performed every 56 days (± 7 days) throughout the study or more frequently if clinically indicated. Subjects should have a follow-up bone scan performed if clinically indicated regardless of status at time of COE eligibility assessment.
7. For all female subjects of child bearing potential only, a urine or serum pregnancy test will be performed within -7 days of COE C1D1 visit. A urine or serum pregnancy test will be performed at COE Day 1 prior to dosing, on day 1 of each cycle prior to EV administration, at EOT and Follow-up visits. After EOT, a monthly (± 7 days) pregnancy test will be maintained until 6 months after the last dose of study treatment.
8. Full Physical examination, weight, ECOG PS and vital signs (pulse, temperature and blood pressure) will be performed at COE C1D1 prior to dosing. The physical examination will also be performed on day 1 of each cycle and EOT visit. For subsequent and EOT visits, physical examinations maybe more directed but should include examination of lungs, abdomen, skin and cardiovascular systems. Vital signs and weight will be completed on days 1, 8 and 15 of each cycle and at EOT visit. Vital signs will also be performed at follow up visit.

Footnotes continued on next page

9. Biochemistry: See [Section 5.5.3 Laboratory Assessments]. Amylase and lipase will only be collected at COE Day 1 of each Cycle. All biochemistry laboratory tests should be collected at the start of the following COE time points: C1D1, C1D8, C1D15 and D1 of each subsequent cycle. If all biochemistry laboratory tests were performed within 7 days prior to the first day of dosing, they do not need to be repeated at C1D1. Biochemistry tests will be sent to a central laboratory for analysis. Local laboratory results may be used to determine eligibility if the C1D1 results from the central laboratory are not available in time for planned C1D1 dosing. In the event that the central laboratory results received after C1D1 dosing are not within eligibility parameters, the subject will still be considered eligible, if local labs met the eligibility criteria, and will not be considered a protocol deviation.

   Local laboratory results that support eligibility and dosing decisions must be entered into the clinical database. If local laboratory is to be used to support dosing decisions, local laboratory tests will include complete blood count (CBC) with differential, glucose, serum creatinine, ALT and AST. Additional assessments may be done centrally or locally to monitor AEs or as required by dose modification requirements.
10. If HbA1c was performed within 7 days prior to the first day of COE C1D1 dosing, it does not need to be repeated at COE C1D1. If HbA1c is elevated (≥ 6.5%), refer subject to appropriate provider during Cycle 1 for glucose management.
11. Hematology: See [Section 5.5.3 Laboratory Assessments]. Hematology tests should be collected at the following COE time points: C1D1, C1D8, C1D15 and Day 1 of each subsequent cycle. If hematology tests were performed within 7 days prior to the first day of dosing, they do not need to be repeated on C1D1. Hematology tests will be sent to a central laboratory for analysis. Local laboratory results may be used to determine eligibility if the C1D1 results from the central laboratory are not available in time for planned dosing. In the event that the central laboratory results received after C1D1 dosing are not within eligibility parameters, the subject will still be considered eligible if local laboratory results met the eligibility criteria; such events will not be considered protocol deviations. Local laboratory results that support eligibility and dosing decisions must be entered into the clinical database. If local laboratory is to be used to support dosing decisions, local laboratory tests will include CBC with differential, glucose, serum creatinine, ALT and AST. Additional assessments may be done centrally or locally to monitor AEs or as required by dose modification requirements.
12. ECGs will be read locally. If there is no reason to suspect cardiac issues, ECG will not be required.
13. Ophthalmologic assessments for subjects with recent ocular complaints (within 3 months of COE consent) are required. Assessments should include the following: visual acuity, slit lamp, tonometry examination and dilated fundus examination. Prior ophthalmologic exam done within 3 months of COE consent is acceptable provided symptoms are not new since the exam. Ophthalmology assessments should be performed per standard of care or if clinically indicated (e.g., subject develops new or worsening ocular symptoms). EOT slit lamp examinations are required for subjects who experience corneal adverse events during the study. EOT slit lamp examinations must be performed ≥ 4 weeks from last dose. Additional eye examinations are to be conducted as clinically indicated.
14. Imaging will be evaluated within 28 days prior to COE C1D1 dosing and every 56 days (± 7 days) throughout the study. CT scan with contrast (chest, abdomen and pelvis) is the preferred modality for tumor assessment. MRI is acceptable if local standard practice or if CT scans are contraindicated in a subject (e.g., subject is allergic to contrast media). All other RECIST approved scanning methods such as x-ray are optional. To ensure comparability, the COE eligibility scan and subsequent assessment of response should be performed using identical techniques as were performed during Arm B participation. The same method should be employed and assessed by the same individual on each occasion if possible. Imaging assessments methods used at Baseline of the main study are to continue to be used throughout the study.

Footnotes continued on next page

15. QOL will be collected pre-dose on COE C1D1, every 12 weeks during treatment period, EOT visit and at the 30-day follow-up visit. QOL questionnaire completion timing should be calculated based on COE C1D1 dosing. If a visit occurs out of the assessment window, QOL questionnaires should still be completed. QOL questionnaires will be completed by the subject at home on hand-held devices prior to coming to the clinic visit with the exception of COE Day 1 of the first week, the EOT and the follow-up visits at which the QOL questionnaires will be completed by the subject at the clinic.
16. HRU will be collected pre-dose on COE C1D1. Subsequent questionnaires will be completed monthly (COE Day 1 of every 4 weeks [+7 days]), starting on COE Week 5 Day 1 (timing calculated based on COE C1D1 dosing), and at the EOT and follow-up visit. HRU questionnaires will be completed by the subject at home on hand-held devices prior to coming to the clinic visit with the exception of the COE C1D1, EOT and the follow-up visits at which the HRU questionnaires will be completed by the subject at the clinic.
17. Subjects that discontinue EV for reasons other than progressive disease will be followed in the long term follow up period per institutional guidelines, but not less frequently than every 3 months to confirm survival status until PFS2 is documented or the subject starts another cancer treatment, whichever is earlier. Phone contact is sufficient for follow up. Additional follow up contacts may be required per sponsor request for analysis purposes.
18. Contact subjects in the survival follow-up period approximately every 3 months to collect survival status until subject death or study closure. Additional follow-up contacts may be required per sponsor request for analysis purposes.
19. ATA will be collected at COE Cycles 1, 2, 3, 4, 6, 8 and 10 predose within 24 hrs of the start of the infusion EOT (Date of last dose + 7 days) and follow-up (Date of last dose +30 days).

12.10.5 Duration of Treatment and Discontinuation Criteria

A discontinuation from treatment is a subject who enrolled in the COE and for whom study treatment is permanently discontinued for any reason.

The subject is free to discontinue from study treatment and/or withdraw from the COE study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to discontinue the subject from COE study treatment or to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

All subjects who discontinue COE study treatment will remain in the study and must continue to be followed for protocol specific follow up procedures as outlined in the COE Schedule of Assessments [Table 11] until the subject specifically withdraws consent for any further contact with him/her or persons previously authorized by the participant to provide this information.

If a subject is discontinued from the study with an ongoing AE or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until the condition stabilizes or no longer is clinically significant.

The following are discontinuation criteria from treatment for individual subjects:

- Subject develops radiological disease progression relative to scan performed within 28 days of COE C1D1 dose.
- Subject is required to receive another systemic anti-cancer treatment for underlying or new cancer
- Subject develops unacceptable toxicity
- Female subject becomes pregnant
- Investigator decides it is in the subject’s best interest to discontinue.
- Subject declines further treatment
- Subject is noncompliant with the protocol based on the investigator or medical monitor assessment.
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject.
- Death.

The subject will be discontinued from the long-term PFS2 follow-up period if any of the following occur:

- Subject initiates a new systemic anticancer treatment
- Subject exhibits evidence of PD based on investigator assessment
- Subject declines further study participation (i.e., withdraws consent)
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject
- Death
- Sponsor ends long-term follow-up collection period

The subject will be discontinued from the survival follow-up period if any of the following occur:

- Subject declines further study participation (i.e., withdraws consent)
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject
- Death
- Sponsor ends survival follow-up collection period

12.10.6 Statistical Methods

All eligible Arm B subjects who cross to COE EV treatment will be the analysis population, and analyzed in the same way as described in [Section 7 Statistical Methodology] for all applicable safety endpoints with data collected in COE period unless otherwise specified in SAP. The following analysis will be provided:

- Study population in COE period:
    - Disposition at EOT, 30-day follow-up, long-term follow-up and survival follow-up
    - Days in the study and previous study treatment outcomes at the time initiating the EV treatment
    - Major protocol deviations in COE period
    - Demographics and other characteristics at original study enrollment
    - Concomitant medications in COE period.
- Study drug exposure in COE period
- Analysis of safety in COE period:
    - Adverse events
    - Lab assessments
    - Vital signs
    - 12-lead ECG
    - ECOG performance status

Details will be specified in the SAP.

13 ATTACHMENT 1: SUBSTANTIAL AMENDMENT 3

I. The purpose of this amendment is:

Substantial Changes
1. Add a Crossover Extension (COE) to Study Design
DESCRIPTION OF CHANGE:
A COE is added to the study design. Details of this extension amendment are added as Appendix 12.10 and include a rationale, enrollment criteria, schedule of assessments, duration of treatment and discontinuation criteria.
RATIONALE:
A COE is added for when the enfortumab vedotin (EV)-301 interim analysis results in a positive outcome.

Nonsubstantial Changes
1. Update Clinical Research Contact
DESCRIPTION OF CHANGE:
Contact details for the clinical research contact are revised.
RATIONALE:
This change is made due to changes to study personnel.
2. Update Schedule of Assessments
DESCRIPTION OF CHANGE:
In Table 2, the row for Subsequent Dosing Cycles is revised to specify cycles 3, 4, 6, 8 and 10 and footnotes A and C are updated with cycle numbers. In Table 3, footnote A is updated to include cycles 8 and 10.
RATIONALE:
This change is made because the pharmacokinetics of EV (antibody drug conjugate, total antibody and monomethyl auristatin E) reaches steady-state by end of cycle 1 and immunogenicity of EV is low based on previous studies, sufficient pharmacokinetic and antitherapeutic antibodies data are collected by cycle 10 and most patients are off the study by cycle 10.
3. Update Response Evaluable Set (RES)
DESCRIPTION OF CHANGE:

The definition of the RES is updated to remove the requirement that subjects had at least 6 months of follow-up since randomization.
RATIONALE:
This revision is made based on regulatory agency feedback.
4. Add Clarification to Efficacy Analysis
DESCRIPTION OF CHANGE:
Additional text is added to clarify when progression-free survival on study therapy (PFS1), overall response rate (ORR) and disease control rate (DCR) can be tested.
RATIONALE:
This revision is made due to enrollment completion earlier. The multiplicity strategy was updated accordingly.
5. Update Duration of Response
DESCRIPTION OF CHANGE:
Additional text is added to clarify when radiological progression will be censored.
RATIONALE:
This revision is made to update the censor rules for PFS1 and duration of response (DOR) to also censor the progressive disease (PD) or death after 2 or more missed disease assessments based on regulatory agency feedback.
6. Clarify Progression Free Survival
DESCRIPTION OF CHANGE:
Additional text is added to clarify the requirements for progression free survival.
RATIONALE:
This revision is made to update the censor rules for PFS1 and DOR to also censor the PD or death after 2 or more missed disease assessments based on regulatory agency feedback.
7. Minor Administrative-type Changes
DESCRIPTION OF CHANGE:
Include minor administrative-type changes (e.g., typos, format, numbering and consistency throughout the protocol), add COE to the list of abbreviations and update an exploratory endpoint in the synopsis to match the same endpoint in the body of the protocol.
RATIONALE:
To provide clarifications to the protocol and to ensure complete understanding of study procedures.

II. Amendment Summary of Changes:

IIA. Substantial Changes

12 Appendices
ADDED:
12.10 Crossover Extension **Note: The crossover extension study described below and outlined in the Crossover Extension (COE) schematic [Figure 2] will be conducted if the EV-301 Interim Analysis results in a positive outcome. With the exception of those procedures and processes indicated below, this extension study will be performed using the same general approach as described in the protocol. Refer to the main protocol for any study details not contained in the supplemental COE appendix.** **12.10.1 Rationale** **Upon decision to stop the study for efficacy based on statistically significant OS result favoring EV, all eligible Arm B subjects can be evaluated for eligibility for COE EV treatment at the discretion of the subject and investigator. Day 1 of the COE will occur after COE informed consent form is signed and eligibility is confirmed. Treatment with EV will be stopped upon disease progression and/or when discontinuation criteria are met [Section 12.10.5 Duration of Treatment and Criteria for Discontinuation]. Arm B Subjects who do not participate in the COE will continue to follow Arm B protocol procedures.** **12.10.2 Inclusion Criteria** **Subject is eligible for the COE if they continue to meet all inclusion criteria from the main protocol in addition to the following when the patient is evaluated for eligibility to participate in the COE portion of the study:** **1. IRB/IEC approved written COE informed consent and privacy language as per national regulations (e.g., HIPAA Authorization for US sites) must be obtained from the subject prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).** **2. Subject was randomized to Arm B and is either currently on study treatment or has discontinued study treatment due to intolerance, AE or progression of disease, has not started a new systemic anticancer treatment and is still participating in the follow up phase of the study.** **Waivers to the COE inclusion criteria will NOT be provided.** **12.10.3 Exclusion Criteria** **Subject will be excluded from participation in the COE if they meet any of the exclusion criteria listed in the main protocol or if any of the following apply when the patient is evaluated for eligibility to participate in the COE portion of the study:** **1. Subject has been diagnosed with a new malignancy while on Arm B in the EV-301 study. Subjects with nonmelanoma skin cancer, localized prostate cancer treated with curative intent with no evidence of progression, low-risk or very low-risk (per standard guidelines) localized prostate cancer under active**

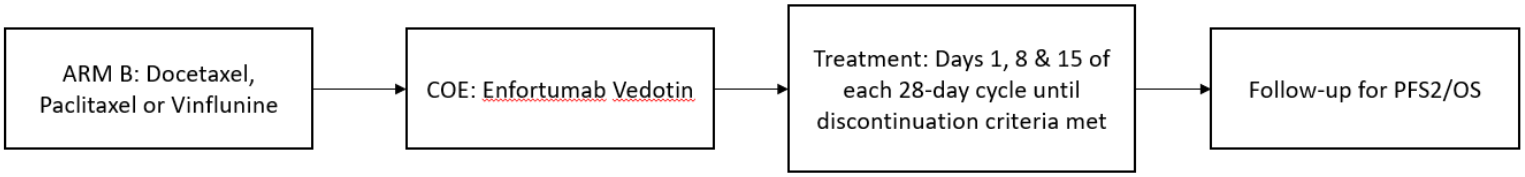
surveillance/watchful waiting without intent to treat, or carcinoma in situ of any type (if complete resection was performed) are allowed.

Waivers to the COE exclusion criteria will NOT be allowed.

12.10.4 Schedule and Assessments

Arm B subjects meeting criteria as indicated in [Section 12.10.3] will sign informed consent prior to COE Day 1 dosing. The COE subjects will follow the COE Schematic and COE Schedule of Assessments [Table 11].

Figure 2 Crossover Extension Schema



COE: crossover extension; OS: overall survival; PFS2: progression free survival on subsequent therapy

Table 11 Schedule of Assessments for Crossover Extension

Visit	Every Cycle				End of Treatment[1]	Follow-up[2]	Long Term PFS2 Treatment Follow-up	Survival Follow-up
Base Date	Day 1	Day 8	Day 15	Every 56 Days	Date of Last Dose	Date of last Dose + 30 days	Every 3 months	Every 3 months
Visit Window	± 3 days	± 3 day	± 3 days	± 7 days	+ 7 days	+ 7 days	± 7 days	± 7 days
Informed Consent	X[3,4]							
Confirmation of Eligibility for COE	X[3,4]							
Brain Scan[5]	X[3,5]			X[5]				
Bone Scan[6]	X[6]			X[6]				
Serum/Urine Pregnancy Test[7]	X				X	X	X[7]	X[7]
Physical Examination[8]	X				X			
Weight[8]	X	X	X		X			
Vital Signs[8]	X	X	X		X	X		
Biochemistry[9]	X	X	X		X	X		
Hemoglobin A1C[10]	X				X			
Hematology[11]	X	X	X		X	X		
ECOG PS	X				X	X		
12-lead ECG[12]	X[3,12]				X[12]			

Ophthalmology Assessment[13]	**X**				**X**			
COE Enrollment via IRT	**X[4]**							
EV Administration	**X**	**X**	**X**					
Image Assessment[14]	**X**			**X[14]**				
Concomitant Medication	**X**	**X**	**X**	**X**	**X**	**X**		
Adverse Events	**X**	**X**	**X**	**X**	**X**	**X**		
QOL[15]	**X**				**X**	**X**		
HRU[16]	**X[16]**				**X**	**X**		
ATA[19]	**X**				**X**	**X**		
Subsequent Therapy Assessment[17]						**X**	**X**	
Overall Survival[18]						**X**	**X**	**X**

AE: adverse event; ALT: alanine transaminase; AST: aspartate transaminase; ATA: antitherapeutic antibody; C: cycle; COE: crossover extension; CR: complete response; CT: computed tomography; D: day; ECG: electrocardiogram; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EORTC-QLQ-C30: European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; EOT: end of treatment; EQ-5D-5L: EuroQOL 5-Dimension 5-Level Questionnaire; EV: enfortumab vedotin; HRU: health resource utilization; MRI: magnetic resonance imaging; NA: Not Applicable; PD: progressive disease; PFS1: progression free survival on study therapy; PFS2: progression free survival on subsequent therapy; PGx: Pharmacogenetic analyses; PR: partial response; QOL: quality of life; RECIST: Response Evaluation Criteria in Solid Tumors

1. **EOT visit will occur within 7 days after the last dose or when the decision is made by the investigator to discontinue subject from treatment.**
2. **Follow up assessments should be completed prior to the initiation of the next therapy.**
3. **May be completed within 28 days prior to COE C1D1 visit.**
4. **COE Cycle 1 only.**
5. **Only if clinically indicated at time of COE eligibility assessment. Repeat as clinically indicated or per standard of care throughout the study.**
6. **All subjects will have a bone scan (scintigraphy) within 28 days prior to COE C1D1 dosing. Subjects with positive bone scans at time of COE eligibility assessment will have a bone scan performed every 56 days (± 7 days) throughout the study or more frequently if clinically indicated. Subjects should have a follow-up bone scan performed if clinically indicated regardless of status at time of COE eligibility assessment.**
7. **For all female subjects of child bearing potential only, a urine or serum pregnancy test will be performed within -7 days of COE C1D1 visit. A urine or serum pregnancy test will be performed at COE Day 1 prior to dosing, on day 1 of each cycle prior to EV administration, at EOT and Follow-up visits. After EOT, a monthly (± 7 days) pregnancy test will be maintained until 6 months after the last dose of study treatment.**
8. **Full Physical examination, weight, ECOG PS and vital signs (pulse, temperature and blood pressure) will be performed at COE C1D1 prior to dosing. The physical examination will also be performed on day 1 of each cycle and EOT visit. For subsequent and EOT visits, physical**

examinations maybe more directed but should include examination of lungs, abdomen, skin and cardiovascular systems. Vital signs and weight will be completed on days 1, 8 and 15 of each cycle and at EOT visit. Vital signs will also be performed at follow up visit.

9. **Biochemistry: See [Section 5.5.3 Laboratory Assessments]. Amylase and lipase will only be collected at COE Day 1 of each Cycle. All biochemistry laboratory tests should be collected at the start of the following COE time points: C1D1, C1D8, C1D15 and D1 of each subsequent cycle. If all biochemistry laboratory tests were performed within 7 days prior to the first day of dosing, they do not need to be repeated at C1D1. Biochemistry tests will be sent to a central laboratory for analysis. Local laboratory results may be used to determine eligibility if the C1D1 results from the central laboratory are not available in time for planned C1D1 dosing. In the event that the central laboratory results received after C1D1 dosing are not within eligibility parameters, the subject will still be considered eligible, if local labs met the eligibility criteria, and will not be considered a protocol deviation.**

   Local laboratory results that support eligibility and dosing decisions must be entered into the clinical database. If local laboratory is to be used to support dosing decisions, local laboratory tests will include complete blood count (CBC) with differential, glucose, serum creatinine, ALT and AST. Additional assessments may be done centrally or locally to monitor AEs or as required by dose modification requirements.
10. **If HbA1c was performed within 7 days prior to the first day of COE C1D1 dosing, it does not need to be repeated at COE C1D1. If HbA1c is elevated (≥ 6.5%), refer subject to appropriate provider during Cycle 1 for glucose management.**
11. **Hematology: See [Section 5.5.3 Laboratory Assessments]. Hematology tests should be collected at the following COE time points: C1D1, C1D8, C1D15 and Day 1 of each subsequent cycle. If hematology tests were performed within 7 days prior to the first day of dosing, they do not need to be repeated on C1D1. Hematology tests will be sent to a central laboratory for analysis. Local laboratory results may be used to determine eligibility if the C1D1 results from the central laboratory are not available in time for planned dosing. In the event that the central laboratory results received after C1D1 dosing are not within eligibility parameters, the subject will still be considered eligible if local laboratory results met the eligibility criteria; such events will not be considered protocol deviations. Local laboratory results that support eligibility and dosing decisions must be entered into the clinical database. If local laboratory is to be used to support dosing decisions, local laboratory tests will include CBC with differential, glucose, serum creatinine, ALT and AST. Additional assessments may be done centrally or locally to monitor AEs or as required by dose modification requirements.**
12. **ECGs will be read locally. If there is no reason to suspect cardiac issues, ECG will not be required.**
13. **Ophthalmologic assessments for subjects with recent ocular complaints (within 3 months of COE consent) are required. Assessments should include the following: visual acuity, slit lamp, tonometry examination and dilated fundus examination. Prior ophthalmologic exam done within 3 months of COE consent is acceptable provided symptoms are not new since the exam. Ophthalmology assessments should be performed per standard of care or if clinically indicated (e.g., subject develops new or worsening ocular symptoms). EOT slit lamp examinations are required for subjects who experience corneal adverse events during the study. EOT slit lamp examinations must be performed ≥ 4 weeks from last dose. Additional eye examinations are to be conducted as clinically indicated.**
14. **Imaging will be evaluated within 28 days prior to COE C1D1 dosing and every 56 days (± 7 days) throughout the study. CT scan with contrast (chest, abdomen and pelvis) is the preferred modality for tumor assessment. MRI is acceptable if local standard practice or if CT scans are contraindicated in a subject (e.g., subject is allergic to contrast media). All other RECIST approved scanning methods such as x-ray are optional. To ensure comparability, the COE eligibility scan and subsequent assessment of response should be performed using identical techniques as were performed during Arm B participation. The same method should be employed and assessed by the same individual on each occasion if possible. Imaging assessments methods used at Baseline of the main study are to continue to be used throughout the study.**

15. QOL will be collected pre-dose on COE C1D1, every 12 weeks during treatment period, EOT visit and at the 30-day follow-up visit. QOL questionnaire completion timing should be calculated based on COE C1D1 dosing. If a visit occurs out of the assessment window, QOL questionnaires should still be completed. QOL questionnaires will be completed by the subject at home on hand-held devices prior to coming to the clinic visit with the exception of COE Day 1 of the first week, the EOT and the follow-up visits at which the QOL questionnaires will be completed by the subject at the clinic.

16. HRU will be collected pre-dose on COE C1D1. Subsequent questionnaires will be completed monthly (COE Day 1 of every 4 weeks [+7 days]), starting on COE Week 5 Day 1 (timing calculated based on COE C1D1 dosing), and at the EOT and follow-up visit. HRU questionnaires will be completed by the subject at home on hand-held devices prior to coming to the clinic visit with the exception of the COE C1D1, EOT and the follow-up visits at which the HRU questionnaires will be completed by the subject at the clinic.

17. Subjects that discontinue EV for reasons other than progressive disease will be followed in the long term follow up period per institutional guidelines, but not less frequently than every 3 months to confirm survival status until PFS2 is documented or the subject starts another cancer treatment, whichever is earlier. Phone contact is sufficient for follow up. Additional follow up contacts may be required per sponsor request for analysis purposes.

18. Contact subjects in the survival follow-up period approximately every 3 months to collect survival status until subject death or study closure. Additional follow-up contacts may be required per sponsor request for analysis purposes.

19. ATA will be collected at COE Cycles 1, 2, 3, 4, 6, 8 and 10 predose within 24 hrs of the start of the infusion EOT (Date of last dose + 7 days) and follow-up (Date of last dose +30 days).

12.10.5 Duration of Treatment and Discontinuation Criteria

A discontinuation from treatment is a subject who enrolled in the COE and for whom study treatment is permanently discontinued for any reason.

The subject is free to discontinue from study treatment and/or withdraw from the COE study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to discontinue the subject from COE study treatment or to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

All subjects who discontinue COE study treatment will remain in the study and must continue to be followed for protocol specific follow up procedures as outlined in the COE Schedule of Assessments [Table 11] until the subject specifically withdraws consent for any further contact with him/her or persons previously authorized by the participant to provide this information.

If a subject is discontinued from the study with an ongoing AE or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until the condition stabilizes or no longer is clinically significant.

The following are discontinuation criteria from treatment for individual subjects:

- **Subject develops radiological disease progression relative to scan performed within 28 days of COE C1D1 dose.**
- **Subject is required to receive another systemic anti-cancer treatment for underlying or new cancer**
- **Subject develops unacceptable toxicity**
- **Female subject becomes pregnant**
- **Investigator decides it is in the subject's best interest to discontinue.**
- **Subject declines further treatment**
- **Subject is noncompliant with the protocol based on the investigator or medical monitor assessment.**
- **Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject.**
- **Death.**

The subject will be discontinued from the long-term PFS2 follow-up period if any of the following occur:

- **Subject initiates a new systemic anticancer treatment**
- **Subject exhibits evidence of PD based on investigator assessment**
- **Subject declines further study participation (i.e., withdraws consent)**
- **Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject**
- **Death**
- **Sponsor ends long-term follow-up collection period**

The subject will be discontinued from the survival follow-up period if any of the following occur:

- **Subject declines further study participation (i.e., withdraws consent)**

- **Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject**
- **Death**
- **Sponsor ends survival follow-up collection period**

12.10.6 Statistical Methods

All eligible Arm B subjects who cross to COE EV treatment will be the analysis population, and analyzed in the same way as described in [Section 7 Statistical Methodology] for all applicable safety endpoints with data collected in COE period unless otherwise specified in SAP. The following analysis will be provided:

- **Study population in COE period:**
  - **Disposition at EOT, 30-day follow-up, long-term follow-up and survival follow-up**
  - **Days in the study and previous study treatment outcomes at the time initiating the EV treatment**
  - **Major protocol deviations in COE period**
  - **Demographics and other characteristics at original study enrollment**
  - **Concomitant medications in COE period**
- **Study drug exposure in COE period**
- **Analysis of safety in COE period:**
  - **Adverse events**
  - **Lab assessments**
  - **Vital signs**
  - **12-lead ECG**
  - **ECOG performance status**

Details will be specified in the SAP.

IIB. Nonsubstantial Changes

II Contact Details of Key Sponsor's Personnel	
WAS:	
Clinical Research Contacts:	PPD , Clinical Science Astellas Pharma Global Development, Inc. 1 Astellas Way Northbrook, IL 60062 PPD

IS AMENDED TO:	
Clinical Research Contacts:	PPD, Clinical Science Astellas Pharma Global Development, Inc. 1 Astellas Way Northbrook, IL 60062 PPD

III List of Abbreviations and Definitions of Key Terms *List of Abbreviations*	
ADDED:	
COE	**Crossover Extension**

IV Synopsis, Study Objectives
WAS:
Exploratory • To evaluate PFS in the next line of therapy (PFS2) of EV compared to chemotherapy
IS AMENDED TO:
Exploratory • To evaluate PFS **as assessed by RECIST V1.1 by investigator review** in the next line of therapy (PFS2) **in subjects treated with~~of~~** EV compared to chemotherapy

V Flow Chart and Schedule of Assessments
Table 2 Pharmacokinetic, ATA, and biomarker blood sample collection timepoints - Arm A

WAS:

	Study Day	Time	Window	Relative Time	Blood				
					Pharma	ATA	Biomarkers		
Subsequent Dosing Cycles	Day 1	Pre-dose	Within 24 hrs	START of infusion	X[A]	X[A]	X[B]	X[C]	X[B]

A. Pharmacokinetics and ATA: Pre-dose of cycle 3, 4 and every even numbered cycle there after
B. Cytokines and Immuno-phenotyping: Pre-dose cycles 3 and 4 only
C. cfDNA: Pre-dose every even numbered cycle (e.g., cycle 4, 6, etc.) only

IS AMENDED TO:

Cycles 3, 4 , 6, 8 and 10 ~~Subsequent Dosing Cycles~~	Day 1	Pre-dose	Within 24 hrs	START of infusion	X[A]	X[A]	X[B]	X[C]	X[B]

A. Pharmacokinetics and ATA: Pre-dose of cycle 3, 4**, 6, 8 and 10** ~~and every even numbered cycle there after~~
B. Cytokines and Immuno-phenotyping: Pre-dose cycles 3 and 4 only
C. cfDNA: Pre-dose every even numbered cycle **up to 10 cycles** (e.g., cycle 4, 6, **8, 10**~~etc.~~) ~~only~~

V Flow Chart and Schedule of Assessments
Biomarker blood sample collection timepoints - Arm B

WAS:

A. cfDNA: Pre-dose every even numbered cycle (e.g., cycle 4, 6, etc.) only

IS AMENDED TO:

A. cfDNA: Pre-dose every even numbered cycle **up to 10 cycles** (e.g., cycle 4, 6, ~~etc~~ **8, 10**~~.~~) ~~only~~

IV Synopsis, Study Design Overview and 2 Study Objective(s), Design and Endpoints *2.2.1 Study Design*
WAS:
Subjects in Arm A will receive EV on Days 1, 8 and 15 of each 28-day cycle. Subjects in arm B will receive either docetaxel, paclitaxel or vinflunine (as decided by the investigator prior to randomization: vinflunine is a choice of comparator only in countries where it is approved for urothelial cancer) on Day 1 of every 21 day cycle. No on-study crossover will be allowed. This study will consist of 3 phases: screening, treatment and follow-up.
IS AMENDED TO:
Subjects in Arm A will receive EV on Days 1, 8 and 15 of each 28-day cycle. Subjects in arm B will receive ~~either~~ docetaxel, paclitaxel or vinflunine (as decided by the investigator prior to randomization: vinflunine is a choice of comparator only in countries where it is approved for urothelial cancer) on Day 1 of every 21 day cycle. No on-study crossover will be allowed **other than as allowed in Appendix 12.10**. This study will consist of 3 phases: screening, treatment and follow-up.

7 Statistical Methodology *7.2.3 Response Evaluable Set*
WAS:
The response evaluable set (RES) is defined as all subjects in FAS and with measurable disease at baseline and had at least 6 months follow up since randomization. RES will be used for primary efficacy analysis of response related endpoints, e.g., ORR and DCR.
IS AMENDED TO:
The response evaluable set (RES) is defined as all subjects in FAS and with measurable disease **(per RECIST V1.1)** at baseline ~~and had at least 6 months follow up since randomization~~. RES will be used for primary efficacy analysis of response related endpoints, e.g., ORR and DCR.

7 Statistical Methodology *7.4 Analysis of Efficacy*
WAS:
family-wise type I error rate for this study is strongly controlled at 2.5% (one-sided) that allows the study to declare positive on primary endpoint OS on the FAS population. OS will be formally tested at both interim analysis and final analysis. At either interim or final analysis, the formal hypothesis tests on the selected secondary endpoints including PFS1, ORR and DCR, will be performed hierarchically (per the order of PFS1-> ORR->DCR) only when the OS analysis is rejected. The details about the significance levels at interim analysis and final analysis for each efficacy endpoints (OS, PFS1, ORR and DCR) is specified in SAP.

IS AMENDED TO:
The family-wise type I error rate for this study is strongly controlled at 2.5% (one-sided) that allows the study to declare positive on primary endpoint OS on the FAS population. OS will be formally tested at both interim analysis and final analysis. ~~At either interim or final analysis, the f~~**F**ormal hypothesis tests on the selected secondary endpoints including PFS1, ORR and DCR, will be performed hierarchically (per the order of PFS1-> ORR->DCR) only when the OS analysis is rejected. **PFS1 is planned to test at either the interim analysis or final analysis when OS is rejected. ORR and DCR will be tested only once after both OS and PFS1 are rejected (at either interim analysis or final analysis) and the test statistics will be computed from the interim data. DCR will be tested after ORR is rejected.** The details about the significance levels at interim analysis and final analysis for each efficacy endpoints (OS, PFS1, ORR and DCR) ~~is~~ **are** specified in SAP.

7 Statistical Methodology *7.4.2.1 Progression Free Survival*
ADDED:
In addition, subjects who have PD or death after 2 or more missed disease assessments will be censored at the last disease assessment prior to the 2 or more missed disease assessments.

7 Statistical Methodology *7.4.2.3 Duration of Response*
ADDED:
Subjects who receive any further anti-cancer therapy for the disease before radiological progression will be censored at the date of the last radiological assessment before the anticancer therapy started. In addition, subjects who have PD or death after 2 or more missed disease assessments will be censored at the last disease assessment prior to the 2 or more missed disease assessments.

14 COORDINATING INVESTIGATOR'S SIGNATURE

An Open-Label, Randomized Phase 3 Study to Evaluate Enfortumab Vedotin vs Chemotherapy in Subjects with Previously Treated Locally Advanced or Metastatic Urothelial Cancer (EV-301)

ISN/Protocol 7465-CL-0301

Version 4.0 Incorporating Substantial Amendment 3

14 Sep 2020

I have read all pages of this clinical study protocol for which Astellas is the sponsor. I agree that it contains all the information required to conduct this study.

Coordinating Investigator:

Signature: _____ _____
Date (DD MMM YYYY)

<Insert name, department/affiliation, name of institution>

Printed Name: _____

Address: _____

_____

15 SPONSOR'S SIGNATURES