# 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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Study Objective(s):Primary-To compare the overall survival (OS) of subjects with locally advanced or metastatic urothelialcancer treated with enfortumab vedotin (EV) to the OS of subjects treated with chemotherapySecondary-To compare progression-...

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Renal and urinary tract neoplasms malignant and unspecified |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON52767

**Source**
ToetsingOnline

**Brief title**
7465-CL-0301

### Condition

- Renal and urinary tract neoplasms malignant and unspecified

**Synonym**
Transitional cell carcinoma, Urothelial cancer

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Astellas Pharma
**Source(s) of monetary or material Support:** Farmaceutische Industrie

## Intervention

**Keyword:** Enfortumab Vedotin, Phase 3, Urothelial Cancer

## Outcome measures

### Primary outcome

Primary

-Overall Survival

### Secondary outcome

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 ECG 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

# Study description

**Background summary**

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) and gemcitabine with 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.

**Study objective**

Study Objective(s):
Primary

-To compare the overall survival (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
-To assess the incidence of antitherapeutic antibodies (ATA)
-To evaluate PFS in the next line of therapy (PFS2) of EV compared to chemotherapy
-Healthcare resources utilization (HRU)

**Study design**

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 550 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 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. 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 treatment discontinuation criteria are met. No on-study crossover will be allowed. This study will consist of three 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 antibodydrug
conjugate (ADC) and monomethyl auristatin 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 timepoints. 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 250 OS events (about 65% of the
total planned events) are observed. The primary analysis will occur at 384 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.

**Intervention**

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 reescalated
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] (please refer to the protocol synopsis for the tables).
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. Subjects may not receive other investigational
drugs, radiotherapy or systemic anti-neoplastic therapy during dose delays. If a subject is dose
reduced due to toxicity that subsequently resolves (returns to baseline or * Grade 1) the subject may
resume treatment at the original dose at the discretion of the site investigator. If there is a dose
interruption, the schedule for response assessments will not be adjusted.

Comparative Drug(s):
Docetaxel

Dose, Mode of Administration and Dose Modification:
Docetaxel will be administered intravenously on Day 1 of every21-day cycle. The starting dose of docetaxel 75 mg/m2 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 x ULN with concomitant alkaline phosphatase > 2.5 x 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/mm3 . Severe fluid retention has been reported following docetaxel therapy.

Subjects should be premedicated with oral 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.

Please refer to the Protocol Synopsis for the recommended dose modification guidelines.

Comparative Drug(s):
Vinflunine
Dose, Mode of Administration and Dose Modification:
Vinflunine will be administered intravenously on Day 1 of every 21-day cycle.

Vinflunine will beadministered intravenously over a 20-minute period. For subsequent administrations, vinflunine is
contraindicated in subjects with baseline ANC < 1,000/mm3 or platelets < 100,000/mm3 .
The starting dose of vinflunine 320 mg/m2 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.
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.

Comparative Drug(s):
Paclitaxel
Dose, Mode of Administration and Dose Modification:
Study treatment of paclitaxel should be administered on Day 1 of every 21 day cycle after all
procedures/assessments have been completed. The starting dose of paclitaxel 175 mg/m2 will be administered as an IV
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/mm3 . Subjects should not be re-treated with subsequent cycles of paclitaxel until
neutrophils recover to a level > 1500 cells/mm3 and platelets recover to a level > 100000/mm3. 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/m2 .
Recommended dose modification guidelines specific for subjects receiving paclitaxel are
detailed 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.

Please refer to the protocol synopsis for the recommended dose modifications for subjects receiving paclitaxel.

**Study burden and risks**

- Blood draws
- Study visits
- Questionnaires: Quality of Life and Healthcare Resource Utilization
- Scans: Chest, Abdomen and Pelvis scan at baseline and repeated every 56 days.
- Side effects (see question E9)
- Risks related to study procedures:

Blood Samples:
Blood draws may cause pain, bleeding, and/or bruising. You may faint and/or get an infection with redness and irritation at the place where the needle enters your vein.

Electrocardiogram (ECG):
The ECG test is a painless recording of the electrical activity of your heart. The sticky pads used may be cold when applied and sometimes cause some discomfort such as redness or itching. If the hair under the patches needs to be shaved, irritation from shaving also could occur.

CT Scan:
Computed tomography (CT) scans send x-rays through the body at different angles. You will be exposed to small doses of radiation. This dose of radiation could be potentially harmful, but the risks are so small that they are difficult to measure. The amount of radiation is the equivalent of about 3 extra years' worth of natural background radiation, which is radiation that naturally occurs in the atmosphere and rocks in the soil. All radiation adds up over a lifetime. Some people may feel *closed in* while lying in the scanner. However, the scanner is open at both ends and an intercom allows you to talk with the doctors and staff. If you feel anxious during the scan, medical staff may provide comfort or the scan may be stopped. If a CT scan is being done of the abdomen, you usually drink a liquid contrast agent to help define various abdominal organs. This liquid may cause hives, itching, or other allergic symptoms, nausea and/or vomiting and/or diarrhea. You may also receive an IV contrast to make the x-ray pictures more accurate. This IV solution may cause flushing, nausea, and/or very infrequent severe allergic reactions which rarely lead to death. Please inform the study doctor if you have a history of allergic reactions while getting ready for a CT scan.

Bone Scan:
A radioactive dye will be injected into your vein to see if any cancer has spread to your bones. A tiny amount of radiation is used in the dye, and nearly all of it is released from your body within two or three days.

Magnetic Resonance Imaging (MRI):
An MRI scan cannot be performed on certain individuals, such as those who have cardiac pacemakers or certain other metal implants. If you have any metallic objects in your body, the magnetic field can cause dangerous interactions. It is very important you tell the doctor or clinic staff about any previous surgery, implanted devices such as pacemakers, bullets or shrapnel wounds. You will have to lie flat within a relatively small space for as long as 1 hour. There may be some anxiety and claustrophobia (fear of closed spaces) associated with the scanner. If you think this might be a problem for you, please discuss it with the doctor before scheduling the test. Some sedation may be needed for participants who feel too anxious about the MRI. The risks with sedation are: irritation or inflammation of veins; drowsiness; a decrease in breathing, airway obstruction, high or low blood pressure, abnormal heart rhythms, nausea, vomiting and shivering.

Tumor Biopsy for Biomarker Studies:
If you do not have a tumor tissue sample available for central laboratory confirmation, this sample will be obtained by a biopsy.
Risks related to tumor biopsies include bleeding from the biopsy site, pain, local reaction to the anesthesia, infection, and scarring. Your study doctor will further discuss the risks involved with these biopsies if you are providing a sample of your tumor tissue.

Eye Exam:
An eye doctor will do an eye exam if you have had problems with your eyes and vision within the three months prior to the screening period or during the study. For this eye exam, the eye doctor will dilate your pupils, which will make your vision blurry for a short period of time. You may not be able to drive right after the exam.

# Contacts

**Public**
Astellas Pharma

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US
**Scientific**

Astellas Pharma

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written informed consent and privacy language as per national regulations 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. 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-PD1 or anti-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/mm3, * 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), * alanine aminotransferase (ALT) and aspartate aminotransferase (AST) * 2.5 × ULN or * 3 x ULN for subjects with liver metastases, 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)., * 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., 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 criteria

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. Subject with hypothyroidism or panhypopituitarism related to treatment with PD-1 and PD-L1 inhibitors may be enrolled. Subject on hormone replacement therapy may be enrolled if on a stable dose. Subjects with ongoing immunotherapy related colitis, uveitis, 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 monomethyl auristatin E (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-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 the following: docetaxel, Paclitaxel, vinflunine or to any of the other excipients listed in product label., 16. 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., 17. 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., 18. 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.

# Study design

## Design

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| Study phase: | 3 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 06-02-2019 |

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|---|---|
| Enrollment: | 18 |
| Type: | Actual |

### Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | Abraxane |
| Generic name: | paclitaxel |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | ASG-22ME |
| Generic name: | Enfortumab Vedotin |
| Product type: | Medicine |
| Brand name: | Javlor |
| Generic name: | vinflunine |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Taxotere |
| Generic name: | Docetaxel |
| Registration: | Yes - NL intended use |

## Ethics review

| | |
|---|---|
| Approved WMO Date: | 25-05-2018 |
| Application type: | First submission |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 26-11-2018 |
| Application type: | First submission |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 02-01-2019 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO | |

| | |
|---|---|
| Date: | 29-01-2019 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 20-02-2019 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 20-03-2019 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 17-06-2019 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 18-06-2019 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 22-07-2019 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 29-07-2019 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 11-02-2020 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 23-03-2020 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO | |

| | |
|---|---|
| Date: | 06-07-2020 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 08-07-2020 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 05-08-2020 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 30-10-2020 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 21-12-2020 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 28-05-2021 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 01-06-2021 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 02-07-2021 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 20-07-2021 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO | |

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|---|---|
| Date: | 15-04-2022 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 04-05-2022 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2017-003344-21-NL |
| ClinicalTrials.gov | NCT03474107 |
| CCMO | NL65968.091.18 |