EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 February 2022
EMA/249357/2022
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Padcev

International non-proprietary name: enfortumab vedotin

Procedure No. EMEA/H/C/005392/0000

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# List of abbreviations

| Abbreviation | Definition |
|---|---|
| AUClast | area under the concentration-time curve from the time of dosing up to the time of the last measurable concentration |
| BCRP | breast cancer resistance protein |
| BICR | blinded independent central review |
| BSEP | bile salt export pump |
| Cavg | model predicted individual average exposure |
| CHO | Chinese hamster ovary |
| CI | confidence interval |
| Cmax | maximum concentration |
| CMQ | customized MedDRA query |
| CR | complete response |
| CrCl | creatinine clearance |
| CSR | clinical study report |
| CYP | cytochrome P450 |
| DDI | drug-drug interaction |
| DCR | disease control rate |
| $DCR_{16}$ | disease control rate at 16 weeks |
| DOR | duration of response |
| DL | drug-linker |
| DP | drug product |
| DS | drug substance |
| ECOG | Eastern Cooperative Oncology Group |
| EORTC | European Organisation for Research and Treatment of Cancer |
| EORIC QLQ-C30 | European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire |
| EQ-5D-5L | EuroQOL 5-Dimension 5-Level Questionnaire |
| ESMO | European Society for Medical Oncology |
| FAS | full analysis set |
| FGFR | fibroblast growth factor receptor |
| HLT | High Level Terms |
| HR | hazard ratio |
| IDMC | Independent Data Monitoring Committee |
| IHC | immunohistochemistry |
| ISS | integrated summary of safety |
| mAb | monoclonal antibody |
| MMAE | monomethyl auristatin E |
| MRP2 | multidrug resistance-associated protein 2 |
| MVAC | methotrexate, vinblastine, doxorubicin and cisplatin |
| NCCN | National Comprehensive Cancer Network |
| NCI | National Cancer Institute |
| NCI-CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| NSCLC | non-small cell lung cancer |
| OAT | organic anion transporter |
| OATP | organic anion transporting polypeptide |
| OCT2 | organic cation transporter 2 |
| ORR | overall response rate/objective response rate |
| OS | overall survival |
| PAER | periodic adverse experience report |

| | |
|---|---|
| PBPK | physiologically-based pharmacokinetic |
| PD-1 | programmed death receptor-1 |
| PD-L1 | programmed death-ligand 1 |
| PFS | progression-free survival |
| P-gp | P-glycoprotein |
| PR | partial response |
| PRO | patient-reported outcome |
| PT | preferred term |
| QTcF | corrected QT interval by Fridericia |
| RES | response evaluable set |
| SGD-1010 | (MMAE) monomethyl auristatin E, also MMAE |
| SGN-35 | brentuximab vedotin, fully human monoclonal antibody conjugated to cytotoxic agent monomethyl auristatin E targeting CD-30 |
| SMQ | standardized MedDRA query |
| SmPC | Summary of Product Characteristics |
| SSQ | sponsor-specific query |
| TAb | Total Antibody |
| $t_{1/2}$ | terminal elimination half-life |
| TEAE | treatment-emergent adverse event |
| UC | urothelial carcinoma |
| ULN | upper limit of normal |
| vc | valine-citrulline |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant Astellas Pharma Europe B.V. submitted on 5 March 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Padcev, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Padcev as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and a programmed death receptor-1 or programmed death-ligand 1 inhibitor (see SmPC section 5.1)

**The legal basis for this application refers to:**

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

## *Information on Paediatric requirements*

Pursuant to Regulation (EC) No 1901/2006, the application included an EMA Decision P/0114/2018 on the granting of a product-specific waiver.

## *Information relating to orphan market exclusivity*

## Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

## *Applicant's request(s) for consideration*

## Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

## New active Substance status

The applicant requested the active substance enfortumab vedotin contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

### *Scientific advice*

The applicant received Scientific Advice on the development relevant for the approved indication from the CHMP on 11 September 2017, and 28 June 2018. The Scientific Advice pertained to the following quality, non-clinical and clinical aspects of the dossier

- The proposed approach for drug product process validation, drug product stability,
- The overall design of a randomised open-label active comparator-controlled phase 3 study 7465-CL-0301, and specifically the proposed patient population, chemotherapy comparator, proposed statistical design and analysis plan, and primary endpoint.
- The clinical PK/pharmacology plan, and specifically the approach to characterize the potential for clinically significant drug-drug interactions, evaluate renal impairment, hepatic impairment and cardiac safety.

| **Date** | **Reference** | **SAWP co-ordinators** |
|---|---|---|
| 9 November 2017 | EMEA/H/SA/3684/1/2017/III | Prof. Dieter Deforce and Dr Jan Sjöberg |
| 28 June 2018 | EMEA/H/SA/3648/2/2018/II | Prof. Dieter Deforce and Dr Pierre Demolis |

## *1.2. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Sinan B. Sarac Co-Rapporteur: Alexandre Moreau

| | |
|---|---|
| The application was received by the EMA on | 5 March 2021 |
| Accelerated Assessment procedure was agreed-upon by CHMP on: | 25 February 2021 |
| The procedure started on | 25 March 2021 |
| The Rapporteur's first Assessment Report was circulated to all CHMP members on | 25 May 2021 |
| The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on | 26 May 2021 |
| The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on | 1 June 2021 |
| The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on | 22 June 2021 |
| The applicant submitted the responses to the CHMP consolidated List of Questions on | 12 August 2021 |
| The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on | 3 September 2021 |
| The CHMP agreed on a list of outstanding issues in writing to be sent to | 14 September 2021 |

| | |
|---|---|
| the applicant on | |
| The applicant submitted the responses to the CHMP List of Outstanding Issues on | 15 October 2021 |
| The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on | 22 November 2021 |
| The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Padcev on | 16 December 2021 |
| The EC requested the CHMP to assess the impact of new information related to the serious safety findings reported during the expanded access program and which lead to the suspension of the programme in France on | 24 January 2022 |
| The CHMP agreed on a list of question in writing to be sent to the applicant on | 27 January 2022 |
| The applicant submitted the responses to the CHMP List of question on | 7 February 2022 |
| The Rapporteurs circulated the Joint Assessment Report on the responses to the List Question to all CHMP members on | 14 February 2022 |
| The PRAC Rapporteur's circulated to all PRAC members on Assessment Report on the responses to the List Question to all PRAC members on | 22 February 2022 |
| The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, reconsidered the benefit-risk of Padcev and re-adopted the positive opinion which concluded that the application satisfied the criteria for authorisation and recommended the granting of the marketing authorisation on | 24 February 2022 |

# 2. Scientific discussion

## *2.1. Problem statement*

### 2.1.1. Disease or condition

The applicant applies for the therapeutic use of Padcev (enfortumab vedotin) for the treatment of adult patients with locally advanced (LA) or metastatic urothelial cancer (mUC) who have received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and who have received a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting.

### 2.1.2. Epidemiology and risk factors

Urothelial Cancer (UC) is an aggressive malignancy that kills more than 212000 patients annually (Bladder Globocan Factsheet, 2020). UC that originates in the bladder accounts for 90% of all UC cases, while the remaining originates in other parts of the urinary tract (Hepp et al, 2020; Miyazaki & Nishiyama, 2017). The UC is the 10th most common cancer worldwide, with more than 570000 new cases in 2020 (Bladder Globocan Factsheet, 2020; Hepp et al, 2020; Rouprêt et al, 2015). Approximately 203000 new cases of bladder cancer were diagnosed in 2020 in Europe, with approximately 67000 deaths (Bladder Globocan Factsheet, 2020).

Bladder Cancer epidemiology shows a clear male predominance, and incidence and mortality rates differ per European country, probably due to differences in risk factors, detection, and availability of treatments. Tobacco smoking intensity is the most well-established risk factor for and directly related to BC, causing 50–65% of male cases and 20–30% of female cases (EAU Guideline invasive metastatic bladder cancer, 2020).

### 2.1.3. Biologic features

Enfortumab vedotin targets Nectin-4,a type I transmembrane protein found to be highly expressed in a number of epithelial cancers, including, but not limited to, urothelial, lung, ovarian, head and neck, breast and pancreatic cancer specimens (Challita-Eid et al, 2016). In normal tissue, Nectin-4 expression goes from moderate to weak and is mainly found in the epithelium of the bladder, skin, salivary gland ducts, gastrointestinal tract and breast ducts.

### 2.1.4. Clinical presentation and diagnosis

UC is a progressive disease with a subset of patients presenting with, or progressing to, locally advanced or metastatic UC. Untreated metastatic UC is associated with a median survival time rarely exceeding 3 to 6 months (Bellmunt et al, 2012). Among patients treated with a cisplatin-containing regimen as the first-line treatment, the median OS is approximately 12 to 14 months and the 5-year mortality rate exceeds 85% (von der Maase et al, 2005). Locally advanced or metastatic UC is an incurable disease with poor long-term survival and represents a high unmet medical need.

UC presents the highest recurrence rate among solid tumours and is the second leading cause of death in genitourinary cancers. Despite recent advances in the understanding of the pathophysiology of the disease, the management of UC patients remains a clinically challenging problem (Siegel et al. 2014).

Approximately 10%-15% of patients present with metastatic UC at the time of diagnosis. Despite the low frequency of de novo disease, approximately half of the patients with locally advanced UC progress to metastatic disease within two years of cystectomy.

The most common presenting symptom is painless haematuria, seen in >80% of patients. Others may also present with irritative symptoms such as dysuria, frequency or urgency. Symptoms of metastases such as bone or flank pain are rare. (ESMO guideline for bladder cancer, 2014).

### 2.1.5. Management

Standard first-line treatment for fit patients with a good renal function is cisplatin-based combination chemotherapy. Most used regimens are GemCis or methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) or dose-dense MVAC demonstrating median OS of 12–14 months (EAU guideline for muscle-invasive and metastatic bladder cancer 2020). Cisplatin unfit is defined by at least one of the following criteria: PS > 1, glomerular filtration rate (GFR) ≤60 ml/min, grade ≥ 2 audiometric loss, peripheral neuropathy, and New York Heart Association (NYHA) class III heart failure, which comprises over 50% of patients with BC. Gemcitabine and carboplatin (GemCarbo) have long been the standard systemic treatment for cisplatin-unfit patients based on a phase 2/3 RCT by the EORTC where GemCarbo was more effective (overall response rate (ORR) 42% vs 30%) with less toxicity than methotrexate/ carboplatin/vinblastine. Pembrolizumab and atezolizumab are approved by the FDA and European Medicines Agency for first-line treatment in cisplatin-ineligible patients, but only for those whose tumours express PD-L1.

The only chemotherapy drug approved as second-line treatment in Europe was vinflunine. The approval was based on a phase 3 RCT, showing an ORR of 8.6% and a favourable safety profile. Statistically significant was found in the per-protocol patient population but not in the intention-to-treat (ITT) population). Another strategy is represented by the rechallenge of former cisplatin-sensitive patients if progression occurred at least 6–12 months after first-line cisplatin-based combination chemotherapy. Currently, vinflunine is reserved for patients with contraindications to immunotherapy or as third- or later-line treatment.

Most recently, second-line immunotherapy with PD-1/ PD-L1 checkpoint inhibitors has been established and is still being studied as standard second-line therapy. Pembrolizumab, nivolumab, atezolizumab, avelumab, and durvalumab have demonstrated similar efficacy and safety in second-line phase 1–3 trials. A phase 3 RCT with pembrolizumab, a PD-1 inhibitor, showed significant OS benefit over chemotherapy (paclitaxel, docetaxel, or vinflunine, 10.3 vs 7.4 mo, HR: 0.73; 95% CI: 0.59–0.91), leading to approval. The benefit was independent of PD-L1 expression levels, but consistent with longer follow-up.

There is no consensus for the treatment of patient relapsing or refractory to second-line therapy Options include chemotherapy, immunotherapy, clinical trial or best supportive care according to EAU guideline. ESMO eUpdate published in December 2019 recommends Enfortumab vedotin in patients with platinum- and CPI-refractory urothelial carcinoma (III, B) or after ChT in patients who are ineligible for CPIs.No treatment options are currently approved in the third-line setting for patients with metastatic urothelial cancer after failure of platinum-based and PD-1/PD-L1 therapies. While taxanes or vinflunine can be used, historically only approximately 10% of patients respond after platinum-based chemotherapy, irrespective of whether they have received prior PD-1/PD-L1 inhibitors, and the poor outcomes with taxane chemotherapy highlight the importance of developing more effective therapies for patients with advanced urothelial cancer (Keytruda SmPC, 2020; Drakaki et al, 2018; Powles et al, 2018). Thus, there is a significant unmet medical need, which is further underscored by

the limitations of current standard of care in frail or elderly patients who are not eligible for the currently available intervention strategies.

## *About the product*

Enfortumab vedotin, is a fully humanized anti-Nectin-4 immunoglobulin G1 kappa monoclonal antibody (mAb) conjugated to the small molecule microtubule-disrupting agent monomethyl auristatin E (MMAE), via a protease-cleavable maleimidocaproyl valine-cituline (vc) linker. Enfortumab vedotin targets the Nectin-4 adhesion protein expressed in multiple cancers including urothelial, breast, lung, pancreatic and ovarian cancers. Enfortumab vedotin induces cytotoxicity in cancer cells by binding to the Nectin-4 target on the cell surface and forming an ADC-Nectin-4 complex.

This complex is internalized and traffics to lysosomes where MMAE is released by proteolytic cleavage of the vc-linker. Intracellular release of MMAE subsequently disrupts tubulin polymerization resulting in G2/M phase cell cycle arrest and apoptosis. MMAE released from enfortumab vedotin targeted cells can diffuse into nearby Nectin-4 low-expressing cells resulting in cytotoxic cell death.

The applicant claimed the indication of treatment of adult patients with locally advanced (LA) or metastatic urothelial cancer (mUC) who have received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and who have received a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting.

The approved indication is as monotherapy for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and a programmed death receptor-1 or programmed death-ligand 1 inhibitor.

The SmPC specifies that treatment with Padcev should be initiated and supervised by a physician experienced in the use of anti-cancer therapies.

The recommended dose of enfortumab vedotin is 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) administered as an intravenous infusion over 30 minutes on Days 1, 8 and 15 of a 28-day cycle until disease progression or unacceptable toxicity.

The FDA has approved Padcev in the same indication as the current application in December 2019 under accelerated approval based on tumor response rate from the phase II study EV-201.

## *Type of Application and aspects on development*

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on positive results from a randomised phase III study (EV-301) and supportive evidence from a single arm trial (EV-201). Hence, it was considered that the product addresses a high unmet need and will most likely impact medical practice.

However, during assessment the CHMP concluded that it was no longer appropriate to pursue accelerated assessment, as further data and analysis were needed which was not compatible with the time frame of an accelerated timetable.

## *2.2. Quality aspects*

### 2.2.1. Introduction

The finished product is presented as a powder for concentrate for solution for infusion containing 20 mg or 30 mg of enfortumab vedotin as active substance.

Other ingredients are: histidine, histidine hydrochloride monohydrate, trehalose dihydrate and polysorbate 20.

The product (both strengths) is available in 10 mL Type I glass vial with a bromobutyl rubber stopper, aluminum seal and plastic flip-off cap. Each carton contains 1 vial.

### 2.2.2. Active Substance (AGS-22C3 monoclonal antibody intermediate

**General Information**

The active substance, enfortumab vedotin is an antibody-drug conjugate (ADC) targeting Nectin-4, an adhesion protein that is highly expressed in urothelial cancer, a common and aggressive malignancy. Enfortumab vedotin is comprised of a fully human anti-Nectin-4 immunoglobulin G1 kappa monoclonal antibody conjugated to the small molecule microtubule-disrupting agent monomethyl auristatin E (MMAE), via a protease-cleavable maleimidocaproyl valine-citrulline (vc) linker. The AGS-22C3 antibody (mAb) intermediate is a fully human IgG1, kappa subclass monoclonal antibody selectively binding to the nectin-4 extracellular domain on the surface of target cells.

**Manufacture, characterisation and process controls**

Satisfactory documentation of GMP has been provided by the mAb intermediate manufacturing and testing sites.

***Description of manufacturing process and process controls***

Description of manufacturing process and controls for the mAb intermediate is considered appropriately detailed and controlled by in-process tests with appropriate action limits or acceptance criteria. Batch and scale definition is provided.

The mAb intermediate is manufactured according to a fed batch mode culture. A subculture is initiated by thawing and inoculating cells from a working cell bank (WCB) vial into cell growth medium, and cell expansion is continued through several passages and used to inoculate the production bioreactor. The production culture is run in a fed-batch culture mode with nutrient feeds during the cultivation. The expressed antibody is separated from cells via filtration. The downstream purification process consists of three chromatography steps, two viral inactivation/removal steps and an ultrafiltration/diafiltration step before final conditioning.

***Control of materials***

Compendial and non-compendial raw materials are listed. For non-compendial materials, suitable test methods and specifications are provided. Filters and disposable containers used in cell culture process are listed. There are no raw materials directly derived from animals or humans used in the mAb intermediate manufacturing process other than the production cell line of Chinese hamster ovary origin. A two-tiered cell banking system including Master Cell Bank (MCB) and Working Cell Bank (WCB) is

established. Regarding the absence of adventitious agents, the testing panel is in accordance with ICHQ5A. In the event that generation of new WCBs is required in the future, relevant preparation and qualification procedures are described.

***Control of critical steps and intermediates***

Steps with CPPs and/or critical in-process controls (IPCs) are considered the critical steps. Critical steps with CPPs impacting critical quality attributes (CQAs) are defined. For these steps, CPPs with their proven acceptable ranges (PARs) and IPCs with acceptance criteria are provided. Exceeding acceptance criteria for critical in-process controls will lead to batch rejection.

***Process validation***

The applicant´s lifecycle of the process validation consists of three stages: Process Design, Process qualification and Continued process verification. The actual process validation data are obtained during process qualification. The performance parameter results obtained during process validation demonstrate that the cell culture and purification processes are under control and can be considered successfully validated. A qualification study was conducted to demonstrate the process-related impurity clearance. Overall the manufacturing process is capable to achieved sufficient impurity clearance. In-process manufacturing hold times were established during development of the commercial process. Resin lifetimes of chromatography steps were established by characterization studies. Resin reuse validation studies are on-going under a validation protocol. Batch uniformity was assessed and confirmed. A brief summary of shipment qualification is provided.

***Manufacturing process development***

Three manufacturing processes have been established for AGS-22C3 monoclonal antibody intermediate referred to as Hybridoma Process, Process A, and Process B (proposed commercial). Respective comparability exercises have been conducted. A comparability exercise was conducted to evaluate the similarity of mAb intermediate manufactured by Process A and Process B. The study includes release testing, extended characterisation and forced degradation. Overall the material manufactured by Process B is considered comparable with those manufactured by Process A.

A full process characterization was performed specifically for mAb intermediate. The overall control strategy of the mAb intermediate manufacturing is derived from current product and process understanding and is further addressed in subsequent sections.

The absence of extractable/leachable study performed with the material used for Material of Closure and Material of Closure liner should be completed as a future recommendation (REC).

***Characterisation***

The comprehensive characterisation studies provided for the mAb intermediate included analyses of the primary and higher order structures, glycoform structure, purity and impurities, binding properties, and biological activity. The materials used in characterisation studies are three mAb Intermediate batches manufactured by Process B. The batches 0316090/Z and 0416100/Z are two non-GMP batches manufactured at the beginning of the Process B from MCB. The mAb intermediate is a fully human IgG1 subclass monoclonal antibody directed against the extracellular V domain of Nectin-4. A single

consensus N-glycosylation site is located at heavy chain Asn297 and is occupied by glycans typical of those observed in CHO-derived IgG1 antibodies. Multiple, partially orthogonal methods were employed to investigate physico-chemical characteristics of the mAb intermediate. CE-SDS was used to assess the size distribution of mAb under denaturing conditions. Intact mAb is composed primarily of covalently associated monomer. The size distribution of mAb under native conditions was assessed by SEC and detected primarily antibody monomer. The pI of the most abundant form of mAb was established. mAb charge variants were characterized. Charge variants had similar binding activity as assessed by competitive binding ELISA. Fab-and Fc—mediated properties were investigated. Although the Mab intermediate is capable to mediate antibody dependent cellular cytotoxicity (ADCC) and antibody dependent cellular phagocytosis (ADCP) both activities are not considered to significantly contribute to the mechanism of action (MoA) of the ADC. The mAb intermediate did not promote cellular dependent cytotoxicity (CDC) activity.

Control of mAb intermediate

Specifications and acceptance criteria set for the AGS-22C3 monoclonal antibody intermediate are sufficient. The AGS-22C3 mAb intermediate specification include methods to evaluate appearance, pH, osmolality, identity, purity, protein concentration, potency, microbiology and glycosylation.

Sufficiently detailed descriptions of analytical methods are provided by the applicant. Methods are performed in compliance with the European Pharmacopoeia. Non-compendial analytical procedures have been validated according to ICHQ2A requirements. Compendial methods have been verified. Results indicate that the methods are suitable for release purposes.

All batch analysis data of AGS-22C3 monoclonal antibody intermediate are provided. All results are within the specification criteria at time of release and confirm that mAb intermediate can be manufactured consistently. Specifications for the AGS-22C3 monoclonal antibody intermediate have been established based on principles outlined in ICH Q6B. It is noted that at the current stage the mAb is an intermediate and therefore the specifications and acceptance criteria are sufficiently justified for forward processing.

Reference material

Product quality results for the commercial reference standard are provided and extended characterization of the material has been conducted. Comparability with historical reference standard material is established. Future reference standards will be prepared and fully qualified according to an established protocol. The acceptance criteria for stability (retest) and future reference standards establishment will be updated to reflect contemporary mAb intermediate and AS specifications.

Container closure system

AGS-22C3 monoclonal antibody intermediate (mAb intermediate) is stored in a 4 L bottle. Stability data support that the container closure system for the mAb intermediate is suitable for storage. The choice of the container closure system was justified and the container components are in line with current pharmaceutical standards for biopharmaceutical manufacturing. A recommendation is made to perform an extractables/leachable study for the product contact material.

***Stability***

The stability of AGS-22C3 mAb intermediate has been evaluated for multiple mAb intermediate batches. A shelf life of 42 months at the recommended storage condition (≤ –60°C) for mAb intermediate is acceptable based on the real time data obtained for the primary stability batches.

## 2.2.3. Active Substance

**General Information**

SGD-1006 is Maleimidolcaproyl-valine-citrulline-paminobenzyloxycarbonyl-monomethyl auristatin E (vcMMAE). SGD-1006 contains 12 stereogenic centers. SGD-1006 is a synthetic small molecule manufactured under GMP conditions for use as the drug-linker intermediate for further processing into vedotin-containing antibody drug conjugates (ADCs).

**Manufacture, characterisation and process controls**

Satisfactory GMP documentation from the druglinker manufacturing site has been provided.

The manufacturing process of SGD-1006 is organized into six stages and ten synthetic steps. Each stage results in an isolated intermediate that is in tested according to the specifications. The individual steps are described in sufficient detail including the used materials and their quantities

Control of materials: Six starting materials are identified for the synthesis of SGD-1006. Materials are tested according to approved specifications and are purchased from qualified suppliers. Information on fate and origin of impurities is provided. Appropriate controls and limits for such impurities are defined.

An appropriate control strategy is proposed for relevant critical process parameters.

Process validation: The SGD-1006 intermediate is manufactured under non-sterile conditions and the manufacturing process has been satisfactorily validated, including shipping validation results.

Identification of SGD-1006 critical quality attributes (CQAs) has included consideration of SGD-1006 input material variability and manufacturing process capability. The classification of CQA and non-critical attributes is appropriately justified and is further discussed in the subsequent sections. A risk-based approach was used to evaluate the performance of the SGD-1006 manufacturing process. Certain process parameters in each stage were identified as potentially critical (CPPs) and were subjected to further reaction characterization studies prior to process validation. This strategy used criticality assessments to inform process characterization studies, including both univariate and multifactorial studies such as Design of Experiments (DOE). The data were used to support the commercial SGD-1006 process control strategy and to identify critical process parameters whose variabilities have a significant impact on SGD-1006 CQAs. Just a few parameters were found to impact the critical quality attributes. Appropriate controls are in place at these stages.

Characterisation: Structural characterization of the SGD-1006 has been performed utilizing several analytical techniques. The identification, characterization, origin, and control strategy for potential impurities related to the manufacturing process are described. Impurity analysis data confirm that no or only very low quantities of related compounds may remain SGC-1006. Inorganic impurities are identified and listed. In general, the detected amounts are considered low and not posing a risk to patient safety. SGD-1006 is further processed by conjugation to form ADCs.

**Specification**

Control of AS (drug linker intermediate)

Specifications and limits set for SGD-1006 intermediate are considered acceptable and ensure sufficient purity. The acceptance criteria defined for residual solvents are in accordance with ICH Q3C, no class 1 solvents are used in the manufacture of SGD-1006. Non-compendial methods have been validated and the results indicate that the methods are fit for purpose. Pharmacopeial methods have been qualified/verified for their suitability and intended purpose.

The control strategy for SGD-1006 specifications include analytical specifications of starting materials, reagents, solvents, and intermediates, in-process analytical tests and acceptance criteria and also considers further SGD-1006 processing to the ADC active substance. Overall, the specifications and defined limits for SGD-1006 are considered adequately justified.

Reference material

Qualification results of the current reference material is provided. Upon completion of the initial qualification of a reference standard, to which a purity factor is assigned, subsequent re-qualification is performed at established regular intervals.

Container closure system

SGD-1006 is packaged in USP Type III soda-lime amber glass jars closed with a polytetrafluoroethylene (PTFE on product contact side) lined polypropylene screw cap.

**Stability**

Thirty-six months primary stability data are presented for six batches of SGD-1006 manufactured on a production-scale representing the commercial synthetic process throughout the manufacturing history. Data for more batches are available. The results of stability studies demonstrate the chemical stability of SGD-1006 when stored for up to 36 months at -20 °C/Ambient RH (recommended condition).

## 2.2.4. Active Substance (enfortumab vedotin)

***General Information***

The enfortumab vedotin active substance (AS) consists of fully human IgG1 mAb intermediate, AGS-22C3, conjugated to the drug-linker (DL) intermediate of SGD-1006 (microtubule-disrupting agent Monomethyl auristatin E (MMAE)) via thioether bonds, forming an ADC. The ADC has an average molar drug to antibody ratio (DAR) of approximately four drug molecules per antibody, resulting in a heterogeneous mixture of active conjugated isoforms. Binding of the ADC to Nectin-4-expressing tumor cells is followed by internalization of the ADC-Nectin-4 complex, and the release of MMAE via proteolytic cleavage. Release of MMAE disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptosis of the cells

***Manufacture, characterisation and process controls***

Satisfactory GMP documentation has been provided by the manufacturer of the Enfortumab vedotin active substance (AS).

Enfortumab vedotin active substance (AS) manufacturing is initiated by the thawing, pooling, filtering, and pH-adjusting of AGS-22C3 monoclonal antibody intermediate. Tris (2-carboxyethyl) phosphine (TCEP) is used to partially reduce the interchain disulfide bonds of the mAb intermediateSGD-1006 drug-linker intermediate (DL intermediate) is then added in excess to react with the mAb intermediate thiols and form the covalently-bonded antibody-drug conjugate.. This quenched conjugation reaction solution is concentrated and then purified and exchanged into the base buffer for formulation. The diafiltered solution is then formulated, filtered, filled into bottles, and frozen.

Process parameters and in-process controls were defined and respectively controlled within appropriate ranges and by action limits. Critical process parameters and in-process controls have been defined.

The microbial control strategy is deemed acceptable considering the limits set for enfortumab vedotin active substance.

***Control of materials***

Materials used in the manufacture of enfortumab vedotin AS are sourced from approved vendors, and are received and tested according to material specifications. The specifications for compendial materials are based on the relevant monographs. No animal-derived materials are directly used in the AS manufacturing process other than the mAb intermediate.

***Control of critical steps and intermediates***

Manufacturing steps having a significant impact on CQAs or have essential roles in controlling CQAs are controlled. Steps with CPPs and/or critical IPCs are considered the critical steps.

***Process validation***

The enfortumab vedotin AS process validation strategy was designed to demonstrate that the commercial process is capable of consistently delivering AS with the required product quality. The lifecycle of the process validation consists of three stages: Process design, process qualification, and continued process verification. This approach is acceptable and in line with the European "Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission". Process verification was executed with three consecutive manufacturing batches that were manufactured under process validation protocols and in the commercial manufacturing facility and at the commercial scale to demonstrate process consistency in commercial manufacturing. The process performance parameter results obtained during process qualification demonstrate that the AS manufacturing process consistently meets criteria for process performance and product quality specifications for AS.

***Manufacturing process development***

Three manufacturing processes have been established for enfortumab vedotin active substance manufacturing, referred to as Hybridoma Process, Process A, and Process B (proposed commercial). Overall the comparability exercise performed head-to-head between Hybridoma Process to Process A derived material indicates sufficient comparability and a better impurity profile. The comparability exercise between Process A and B derived material executed side-by-side using release and extended characterization assays show that Process B batches can be considered similar to Process A batches for all quality attributes assessed in the study. This is supported by forced degradation studies showing that degradation modes of Process B were similar to Process A.

Complete comparability studies were performed between Hybridoma Process/Process A and between Process A/Process B. The comparability study between Process B batches is considered sufficient The integrated strategy for control of product quality of SGD-1006 drug-linker intermediate (DL intermediate), AGS-22C3 Monoclonal antibody intermediate (mAb intermediate), enfortumab vedotin active substance and FP was developed by assessing the criticality of product quality attributes and evaluating manufacturing process impact to each CQA. The outcome of the enfortumab vedotin AS CQA risk assessment is considered adequate. Process characterization studies provided a comprehensive understanding of how the AS manufacturing process impacts on CQAs. The control strategy for the AS manufacturing process was established by determining the overall risk for each attribute. The presented overall control strategy is deemed acceptable.

***Characterisation***

Multiple mass spectrometric methods were employed to characterize the structure of AS. Analysis of free thiol and experimental extinction coefficient verification were also performed. The higher order structure of AS was evaluated using multiple biophysical techniques. The thermal denaturation profile was also characterized. The observed secondary and higher order structures were found to be typical for IgG1 monoclonal antibodies. the distribution of AS containing different amounts of conjugated drug-linker was described. The binding activity, cytotoxicity activity, and FcγRI, IIA, and IIIA activity of the drug load isoforms were assessed with appropriate binding and cell-based assays.

Process impurities for the AS process including FDRI are controlled in the active substance specification according to ICH Q3A(R2). Robust clearance was demonstrated for small molecular process related impurities in the impurity clearance studies.

Size variants, unconjugated antibody, acidic charge variants, and conjugated impurities have been classified as product-related impurities.

**Specification**

Specifications for enfortumab vedotin AS have been set based on principles outlined in ICH Q6A and ICH Q6B. Quality attributes controlled via specifications were identified by risk analysis which resulted in an appropriate control strategy. Tests are included for appearance and identity, strength and potency, purity and microbiological characteristics.

The specifications are adequate. Product-related impurities are controlled as well as the process-related impurities FDRI. Furthermore, other tests (appearance, pH, osmolality, identity, protein concentration, potency, microbiology and polysorbate 20 are also included in the specification). Two potency methods were proposed in the AS specification; Binding ELISA and cytotoxicity assay with also the determination of the DAR.

Compendial analytical procedures follow the current edition of the referenced pharmacopeia. Non-compendial analytical procedures are provided. Descriptions of analytical methods are sufficiently detailed including system suitability criteria and the calculation formulas. The compendial analytical procedures have been qualified for their intended use. The non-compendial analytical procedures have been validated according to ICH Q2 (R1) and found suitable for their intended purposes.

Batch analysis data for enfortumab vedotin active substance manufactured with the different processes are provided. These batches were tested by the methods at time of release and the acceptance criteria were met. The data further indicate the material derived from the different processes can be considered comparable.

Reference material

The reference standards were prepared from at scale Process B AS engineering batch without reprocessing or reformulation. Future reference standards will be prepared and fully qualified to ensure sufficient inventory for release and stability testing. These standards will originate from material representative of the commercial process and will be qualified against the primary reference standard according to predefined acceptance criteria.

Container Closure System

The container closure system is in line with current pharmaceutical containers used for biotech product manufacturing. The enfortumab vedotin active substance is stored in a 2 L sterile Polycarbonate (PC) container. No extractable/leachable study will be performed based on the risk analysis provided.

**Stability**

Batches that have been placed on stability are summarized and the acceptance criteria are provided. Stability studies were taken place under multiple storage conditions (≤ –60°C, –20±5°C and 5± 3°C). The proposed shelf life of 36 months for enfortumab vedotin AS when stored below -60°C is based on real time data of primary stability batches and deemed acceptable.

## 2.2.5. Finished Medicinal Product

**Description of the product and Pharmaceutical Development**

Enfortumab vedotin finished product (FP) is a sterile, preservative-free, white to off-white lyophilized powder, supplied in a single-dose vial. The FP is available in two strengths, 20 mg/vial and 30 mg/vial. Prior to administration, the FP is reconstituted with Sterile Water for Injection to obtain a colorless to light yellow, clear to slightly opalescent solution. The reconstituted solution is subsequently diluted in either sterile 5% (w/v) Dextrose Injection, sterile 0.9% Sodium Chloride Injection, or Lactated Ringer's Injection, in an intravenous infusion bag prior to administration. The composition of enfortumab vedotin FP is provided; the FP contains well known excipients of compendial degree. The composition is detailed in Table 1 below.

**Table 3**

| Component | Function | Quality Standard |
|---|---|---|
| Enfortumab vedotin | Active pharmaceutical ingredient | In-house |
| Histidine | Buffering agent | USP, Ph. Eur., JP |
| Histidine hydrochloride monohydrate | Buffering agent | Ph. Eur., JP |
| Trehalose dihydrate | Bulking agent | NF, Ph. Eur., JP |
| Polysorbate 20 | Stabilizing agent | NF, Ph. Eur., JPE |

A series of formulation screening studies for enfortumab vedotin was conducted with respect to the buffering agent, formulation pH, and bulking agent to establish the formulation composition with the sufficient levels of stability. There are no overages included in the manufacture of the finished product. An overfill volume was evaluated to meet the FP label claim for both 20 mg and 30 mg FP strengths according to USP <697> with a target concentration after reconstitution of 10 mg/mL EV. The overfill volume of 0.4 mL for both FP (20 mg) and FP (30 mg) was determined resulting in fill volumes of 2.4 mL and 3.4 mL, respectively.

Two manufacturing processes have been established for enfortumab vedotin finished product referred to as Process A and Process B (proposed commercial). Batch genealogy and a list of batches used in clinical studies are provided. Overall it can be concluded that the materials used in clinical studies can be considered comparable to material which is foreseen for commercialization.

The primary packaging components, 10 mL Type I glass vial and stopper, meet European Pharmacopoeia compendial requirements for glass containers for pharmaceutical use and elastomeric closures for injection. Given that the FP is lyophilized, the risk of leachables from the primary container closure system is low and the reconstituted FP is only in transient contact with the container closure.

**Manufacture of the product and process controls**

Satisfactory GMP documentation has been provided by the finished product manufacturing and testing sites.

There is no additional formulating process performed during FP manufacturing. The enfortumab vedotin finished product manufacturing process includes the following unit operations: AS Thawing, AS Pooling and Mixing, Sterile Filtration, Aseptic Filling, Lyophilization, Capping, Visual Inspection, and Bulk vial packaging AS bottles are thawed at ambient temperature. The description of the FP manufacturing process is in accordance with the process validation data. Steps with CPPs and/or critical IPCs are considered the critical steps. They are controlled through control of CPPs and critical IPCs.

Six batches comprised of three batches for 30 mg/vial strengths and three batches for 20 mg/vial strengths were successfully manufactured to the PPQ criteria.

Aseptic manufacture is further ensured by media fill validation. Maximum processing times are defined and are in line with the validation data. All excipients in enfortumab vedotin finished product are compendial and commonly used in the formulation of recombinant protein products.

**Product specification**

Specifications for enfortumab vedotin FP are set in accordance with the principles defined in ICH Q6B. Tests are included for appearance and identity, strength and potency, purity and microbiological characteristics.

Purity testing and limits are equivalent to those stated for the active substance, with the addition of a test for subvisible particles. Elemental impurities have been controlled at the level of the active substance and comply with ICH Q3D.

A multistep risk assessment was conducted by the applicant with regard to potential presence of nitrosamines and nitrosating agents. The assessment of AS indicated that enfortumab vedotin AS does not have any risk to contain nitrosamines and nitrosating agents. Also, in manufacturing process of FPs and primary packaging materials, risks on containing nitrosamines and nitrosating agents are considered very low.

**Specification**

Stability indicating methods are used for testing during stability studies. It is acceptable to use container closure integrity (CCI) instead of sterility during ongoing stability studies. The reconstitution time is added to the release specification. The proposed acceptance criteria are acceptable.

Compendial analytical procedures follow the current edition of the referenced pharmacopeia. Non-compendial analytical procedures descriptions include the preparation of samples for analysis, the conditions of analysis, and the calculation formulas. The majority of methods is already presented in the AS section. Only FP specific methods are provided in the FP section. Compendial analytical procedures have been qualified for their intended use. This includes endotoxin and sterility testing. For non-compendial analytical procedures validation results for the analytical procedures are summarized and mainly covered in the AS section. The dye penetration procedure can be considered suitable for used for Container Closure Integrity Testing. Enfortumab vedotin FP 20 mg and 30 mg batch analysis data are provided. All results are within specification criteria at time of release and confirm the FP can be manufactured consistently.

Reference standard

Reference standard used for finished product testing is the same as for the active substance.

Container Closure System

The primary packaging components, 10 mL Type I glass vial and stopper, meet European Pharmacopoeia compendial requirements for glass containers for pharmaceutical use and elastomeric closures for injection. Given that the FP is lyophilized, the risk of leachables from the primary container closure system is low and the reconstituted FP is only in transient contact with the container closure.

**Stability of the product**

Batches that have been placed on stability are summarized and the acceptance criteria are provided. Batches from both Process A and Process B at 20 mg and 30 mg were stored at 5± 3°C, 25°C/60% RH and 40°C/75% RH.

The applicant proposes a 36 months shelf-life for both 20 mg and 30 mg finished product. Considering that the fill volume is the only difference between the two strength it is acceptable to assign the same shelf life for both 20 mg and 30 mg finished product. The data support the claimed shelf-life of 36 months when stored at 2-8°C.

**Adventitious agents**

TSE compliance

All raw materials used in the manufacture process of enfortumab vedotin are sourced from qualified / approved vendors. The whole production process of enfortumab vedotin, including active substance and finished product manufacture, is free of animal or human derived materials. The product intermediates, AGS-22C3 mAb and its corresponding master and working cell bank as well as the SGD-1006 drug linker, are also produced without materials of direct animal or human origin with the exception of the AGS-22C3 expression cell line.

Virus safety

No direct animal or human derived reagents are used in the manufacture of enfortumab vedotin including the intermediates AGS-22C3 mAb and its corresponding master and working cell bank as well as SGD-1006 drug linker with the exception of the AGS-22C3 mAb expression cell line. None of the excipients are of human or animal origin. The AGS-22C3 master cell bank, working cell bank and an end-of-production cell bank have been tested sufficiently for adventitious viruses as well as retroviruses in accordance with ICH Q5A. No viruses except A-type retrovirus-like particles were detected which is acceptable as CHO-derived cells are known to produce such particles. The unprocessed bulk harvest is also tested routinely in compliance with ICH Q5A for adventitious viruses. No viruses may be found by these assays for further processing of the batch. Retrovirus-like particles have been found in several batches of the commercial process and the maximum number detected has been used for calculation of the retrovirus safety margin. The mAb purification process has been investigated for virus reduction in scale down models with representative viruses being appropriate to cover a wide range of physico-chemical behavior and resistance to inactivation/removal procedures. The studies were well conducted and in line with requirements of ICH Q5A and "Note for guidance on virus validation studies: the design, contribution and interpretation of studies validating the inactivation and removal or viruses" (CPMP/BWP/268/95). The scale down runs were performed either at expected worst case or target parameters. In summary, the virus safety of enfortumab vedotin has been sufficiently demonstrated.

## 2.2.6. Discussion on chemical, pharmaceutical and biological aspects

Enfortumab vedotin is an antibody-drug conjugate targeting Nectin-4, an adhesion protein that is highly expressed in urothelial cancer, a common and aggressive malignancy. Enfortumab vedotin is comprised of a fully human anti-Nectin-4 immunoglobulin G1 kappa monoclonal antibody conjugated to the small molecule microtubule-disrupting agent monomethyl auristatin E (MMAE), via a protease-cleavable

maleimidocaproyl valine-citrulline (vc) linker.

For the mAb intermediate the manufacturing process uses state-of-the-art methodologies frequently used for the manufacture of monoclonal antibodies. The process is well-described, characterized and validated. Also, the mAb intermediate is well characterized and controlled.

In the manufacturing process of the drug-linker intermediate SGD-1006, the isolated intermediates resulted in each stage are tested according to the specifications. Specifications and limits set for SGD-1006 intermediate are considered acceptable and ensure sufficient purity.

The enfortumab vedotin active substance consists of fully human IgG1 mAb intermediate, AGS-22C3, conjugated to the drug-linker (DL) intermediate of SGD-1006 (microtubule-disrupting agent monomethyl auristatin E (MMAE)) via thioether bonds, forming an antibody-drug conjugate (ADC). Specifications have been set based on principles outlined in ICH Q6A and ICH Q6B. They are covering the characteristics as identified by risk analysis which resulted in an appropriate control strategy and are considered acceptable.

Enfortumab vedotin finished product is a sterile, preservative-free, white to off-white lyophilized powder, supplied in a single-dose vial. The FP is available in two strengths, 20 mg/vial and 30 mg/vial. The quantitative and qualitative composition of enfortumab vedotin finished product is provided, the FP contains well known excipients of compendial degree. Specifications for enfortumab vedotin FP are set in accordance with the principles defined in ICH Q6B. Stability indicating methods are used for testing during stability studies.

One recommendation was requested, related to the extractable/leachable study for materials used in the Container closure system.

From the quality point of view, for enfortumab vedotin, the documentation provided for the manufacture, control and stability of the active substance and finished product are sufficiently detailed and the marketing authorisation application for Padcev (enfortumab vedotin) is approvable.

### 2.2.7. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

### 2.2.8. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- The extractable/leachable study for materials used in the Container closure system (Closure and Closure liner material) should be performed and the final report provided, due by Q2 2022.

## *2.3. Non-clinical aspects*

### 2.3.1. Introduction

During the clinical development, the production of the antibody component of the ADC was changed to improve product yield, quality and the manufacturing process from a hybridoma cell line-derived ADC,

AGS-22M6E, to a Chinese hamster ovary cell line-derived ADC, AGS-22C3E/enfortumab vedotin. Both ADCs were used in nonclinical studies to support this application. The ADCs are clinical grade material and share the same amino acid sequence, linker and cytotoxic drug. Equivalence of both products were studied in terms of quality, nonclinical and clinical aspects.

Table 7 summarizes the ADC and components used in the nonclinical pharmacology, pharmacokinetics and toxicology studies and Table 8 summarizes the batches used in nonclinical development and their manufacturing process.

**Table 2** Test articles used in the nonclinical program

| Investigational Product | Component | Component Code | Description |
|---|---|---|---|
| Enfortumab vedotin (ASG-22CE) | ADC | ASG-22CE (lyophilized drug product) | CHO cell-derived anti-Nectin-4 ADC comprised of antibody (AGS-22C3) conjugated to MMAE |
| | | AGS-22C3E (liquid drug substance) | |
| AGS-22M6E | ADC | AGS-22M6E | Initial clinical anti-Nectin-4 ADC (hybridoma-derived) comprised of antibody (AGS-22M6) conjugated to MMAE |
| | Antibody | AGS-22M6 | Antibody backbone of AGS-22M6E, referred to as "unconjugated antibody" |
| MMAE | Released drug | SGD-1010 | Released cytotoxic small molecule conjugated by the same protease cleavable linker (vc) on both enfortumab vedotin and AGS-22M6E |

ADC: antibody-drug conjugate; ASG-22CE: Chinese hamster ovary derived fully human monoclonal antibody conjugated to cytotoxic agent monomethyl auristatin E targeting Nectin-4; ASG-22M6: unconjugated hybridoma derived fully human monoclonal antibody targeting Nectin-4; ASG-22M6E: hybridoma derived fully human monoclonal antibody conjugated to cytotoxic agent monomethyl auristatin E targeting Nectin-4; CHO: Chinese hamster ovary; MMAE: monomethyl auristatin E; vc: valine-citrulline

**Table 3** Different batches used in nonclinical development and their manufacturing process

| Batch Number | Purity (% Main) | Total Quantifiable Impurities † (%w/w) | Study Number | Type of Study |
|---|---|---|---|---|
| **Proposed specification** | **≥ 90.0** | **ND** | | |
| AGS-22M6E (hybrioma-derived) | | | | |
| AGS-22M6-VCE-01 ‡ | 98.1 | < LOD | 8226169 | 4-week toxicity study of AGS-22M6E and AGS-22M6 in rats |
| FCG1001 TOX-01 § | 97.2 | 0.009 | 20005662 | 4-week toxicity study of AGS-22M6E and AGS-22M6 in rats |
| FCG1001 TOX-01 § | 97.2 | 0.009 | 20005664 | 4-week toxicity study of AGS-22M6E and AGS-22M6 in cynomolgus monkeys |
| 0K0001A ¶ | 97.8 | < LOQ | 20021751 | Bridging 4-week toxicity study of enfortumab vedotin and AGS-22M6E in monkeys |
| 1198-80 §§ | ND | ND | ES10-002 | Immunohistochemical evaluation of the tissue cross |

| | | | | |
|---|---|---|---|---|
| | | | | reactivity of AGS-22M6E with normal cynomolgus monkey tissues |
| 1198-80 §§ | ND | ND | 8236219 | Assessment of the potential tissue cross reactivity of AGS-22M6E with a selected panel of human tissues |
| Enfortumab vedotin/AGS-22C3E (CHO-derived) | | | | |
| 2C003AG †† (Process A) | 95.6 | < LOQ | 20021751 | Bridging 4-week toxicity study of enfortumab vedotin and AGS-22M6E in cynomolgus monkeys |
| ASY-012 ADC FB, Batch 1 ‡‡ (Process B) | 97.7 | < 0.15 | 20117437 | 3-month toxicity study of enfortumab vedotin in rats |
| ASY-012 ADC FB, Batch 1 ‡‡ (Process B) | 97.7 | < 0.15 | 20119695 | Embryo-fetal development of enfortumab vedotin |
| ASY-012 ADC FB, Batch 1 ‡‡ (Process B) | 97.7 | < 0.15 | 20135474 | 4-week testicular toxicity study of enfortumab vedotin in rats |

AGS-22M6: unconjugated hybridoma derived fully human monoclonal antibody targeting Nectin-4; AGS-22M6E: hybridoma derived fully human monoclonal antibody conjugated to
cytotoxic agent monomethyl auristatin E targeting Nectin-4; HCl: hydrochloric acid; LOD: limit of detection; LOQ: limit of quantitation; ND: not determined
† Total Quantifiable Impurities (includes SGD-1006 (MMAE) and unidentified impurities
‡ Lot AGS-22M6-VCE-01 was a research batch of AGS-22M6E formulated in 20 mM histidine, 10% sucrose, 0.02% polysorbate 20, pH 6.0. Purity defined as % nonaggregate.
§ Lot FCG1001 TOX-01 was formulated in 20 mM histidine-HCl, 10% sucrose, 0.02% polysorbate 20, pH 6.0.
¶ Lot 0K0001A was reconstituted to achieve 5% dextrose in sterile water for injection.
†† Lot 2C003AG was reconstituted to achieve 5% dextrose in sterile water for injection.
‡‡ ASY-012 ADC FB, Batch 1 was formulated in 20 mM Histidine-HCl pH 6.0, 5.5% Trehalose (w/v) with 0.02% Polysorbate-20 and diluted with 5% sterile dextrose solution.
§§ Lot 1198-80 was biotinylated AGS-22M6E from lot FCG1001 TOX-01 (97.2% purity) and was formulated in 20mM histidine, 5% sucrose, pH 6.0.

## 2.3.2. Pharmacology

### *Primary pharmacodynamic studies*

The pharmacodynamic activity of enfortumab vedotin was conducted in both *in vitro* and *in vivo* experimental systems.

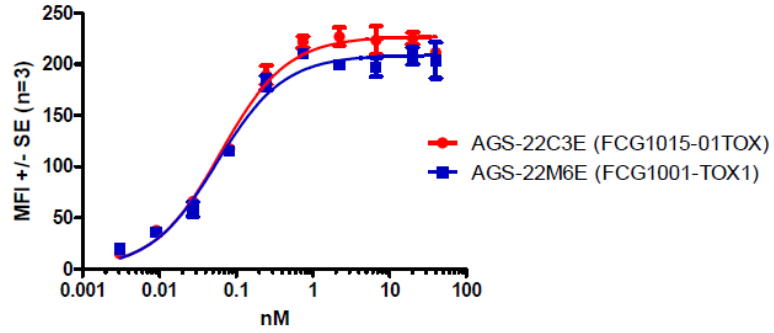
**In vitro**

**Binding to Nectin-4**

AGS-22M6E (hybridoma ADC)was characterized for binding specifically to human, cynomolgus monkey, rat and mouse Nectin-4 orthologs exogenously expressed on the surface of a human prostate cancer cell line (PC3 cells) and to human cancer cell lines that endogenously express Nectin-4 in vitro. The apparent binding affinity (dissociation constant, KD) value of AGS-22M6E (hybridoma ADC) was determined to be 0.387, 0.434, 0.463 and 3.79 nmol/L when tested against human, cynomolgus monkey, rat and mouse Nectin-4, respectively. Both enfortumab vedotin and AGS-22M6E bound specifically to the human Nectin-4-expressing PC3 cells with near identical binding constants showing

that both the hybridoma- and CHO-derived substances have similar binding affinities for the target antigen.

**Comparison of binding to Nectin-4 expressed on PC3-AGS22 cells**




| | AGS-22C3E (FCG1015-01TOX) | AGS-22M6E (FCG1001-TOX1) |
|---|---|---|
| Bmax | 227.1 | 209.0 |
| Kd | 0.06265 | 0.05693 |

**Figure 1** Representation Saturation Curve of AGS-22C3E and AGS-22M6E to Nectin-4 expressed on PC-3-AGS22 cells (Assay 1, Plate1)

**AGS-22M6E binds to recombinant human, cynomolgus monkey, rat and murine orthologs of Nectin-4**

The binding specificity and apparent affinity of AGS-22M6 and AGS-22M6E (HYBRIDOMA ADC) to various orthologs of Nectin-4 was determined by FACS based binding assay using the following recombinant PC3 cell lines: PC3-human-Nectin-4, PC3- cynomolgus monkey-Nectin-4, PC3-rat- Nectin-4 and PC3-murine-Nectin-4. The apparent KD values ranged from 0.279 nM to 70.3 nM for AGS-22M6 and 0.3869 nM to 3.787 nM for AGS-22M6E (HYBRIDOMA ADC) .

**Table 4** Affinity of AGS-22M6 and AGS-22M6E to variants orthologs of Nectin-4 expressed on recombinant PC3 cells.

| | PC3-human-Nectin-4 | | PC3-Cyno-Nectin-4 | | PC3-rat-Nectin-4 | | PC3-murine-Nectin-4 | |
|---|---|---|---|---|---|---|---|---|
| | **AGS-22M6** | **AGS-22M6E** | **AGS-22M6** | **AGS-22M6E** | **AGS-22M6** | **AGS-22M6E** | **AGS-22M6** | **AGS-22M6E** |
| **Bmax (MFI)** | 816.0 | 822.9 | 1146 | 1106 | 679.4 | 667.6 | 325.2 | 242.0 |
| **$K_D$ (nM)** | 0.2790 | 0.3869 | 0.3048 | 0.434 | 0.4401 | 0.4627 | 70.3 | 3.787 |
| **Std. Error** | | | | | | | | |
| Bmax (MFI) | 20.97 | 19.74 | 28.23 | 39.73 | 17.38 | 24.88 | 11.07 | 3.309 |
| $K_D$ (nM) | 0.03735 | 0.04659 | 0.03871 | 0.07719 | 0.05565 | 0.08472 | 6.972 | 0.2067 |
| **95% CI** | | | | | | | | |
| Bmax | 773.0 to 858.9 | 782.4 to 863.3 | 1089 to 1204 | 1025 to 1187 | 643.8 to 715.0 | 616.6 to 718.5 | 302.7 to 347.8 | 235.2 to 248.7 |
| $K_D$ | 0.2025 to 0.3555 | 0.2915 to 0.4823 | 0.2255 to 0.3841 | 0.2759 to 0.5921 | 0.3262 to 0.5541 | 0.2892 to 0.6362 | 56.12 to 84.47 | 3.363 to 4.210 |

**Specific binding of the ADC to Nectin-4**

Nectin-4 is one of four members of a family of cell surface single transmembrane cell-cell adhesion molecules, Nectins-1-4, that interact in homophilic and heterophilic fashion with protein on the surface of adjacent cells. FACS analysis showed that the monoclonal antibody AGS-22M6, and its antibody drug conjugate AGS-22M6E (HYBRIDOMA ADC), bind specifically to recombinant Rat1 (E) cells expressing Nectin-4, but not to recombinant Rat1(E) cells expressing Nectin-1, Nectin-2, or Nectin-3.

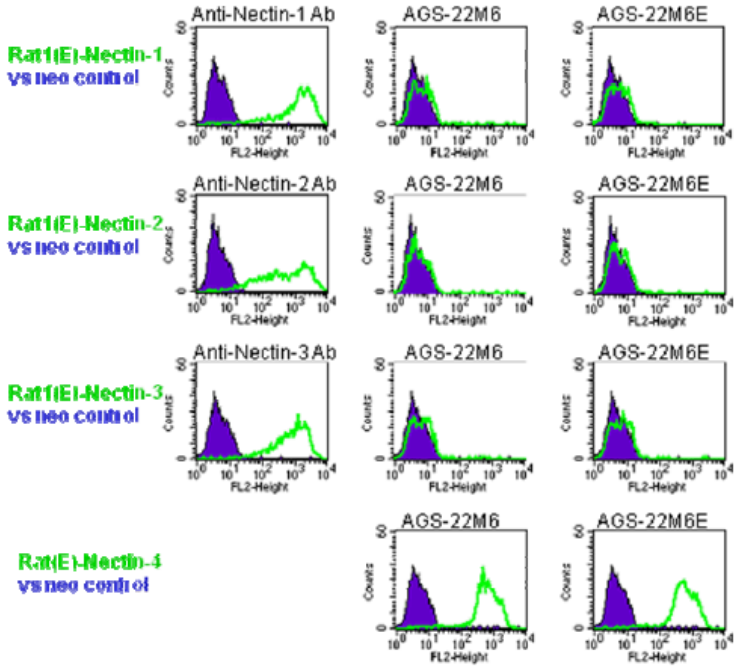
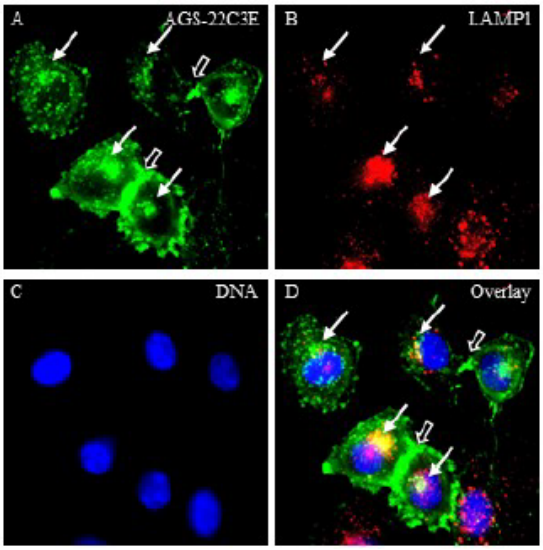



**Figure 2** FACS analysis histograms of AGS-22M6E and AGS-22M6 and Nectin-specific Abs to recombinant Rat1 € cells expressing Nectins 1,2,3, and 4

Enfortumab vedotin binds to Nectin-4 on the cell surface resulting in the internalization of the ADC-Nectin-4 complex, which then traffics to the lysosomal compartment where MMAE is released via proteolytic cleavage of the linker. Intracellular release of MMAE subsequently disrupts tubulin polymerization, resulting in G2/M phase cell cycle arrest and apoptosis of the tumor cells

**Fluorescence microscopy evaluation of AGS-22C3E internalization and lysosomal trafficking**

Nectin-4 bound AGS-22C3E ADC internalized to lysosomal vesicles in a bladder carcinoma cell line, T24 hNectin-4 (clone: 1A9), engineered to have high cell surface Nectin-4 expression. After 2 hours of incubation, most cells showed some AGS-22C3E internalization and colocalization to lysosomal vesicles, while a substantial portion of AGS-22C3E remained at the plasma membrane, particularly in the cell-cell junctions. The AGS-22C3E cell membrane staining signal continued to decrease after 4 hours and after 24 hours the overall signal was greatly reduced, suggesting most of the cell surface AGS-22C3E bound to Nectin-4 had been internalized and catabolized by the cells.




T24 hNectin-4 (clone: 1A9) cells were stained for AGS-22C3E binding (**A**, **D**; green), lysosomal marker LAMP1 (**B**, **D**; red) and Hoescht DNA stain (**C**, **D**; blue). White arrows show the areas where AGS-22C3E is colocalized with LAMP1 vesicles. Additionally, areas of strong membrane staining of AGS-22C3E at the junction between cells (open arrows) were detected. In the top right cell, an example of AGS-22C3E heavily localized between two cells in what appears to be an adherens junction in the process of breaking down or re-forming is visible.

**Figure 3** Co-localization of AGS-22C3E and LAMP1 in T24-Nectin-4 Cells after 2 HRS

**Intracellular release of MMAE by enfortumab vedotin**

The intracellular concentration of free MMAE drug delivered by AGS-22C3E ADC in Nectin-4 positive bladder carcinoma cells was measured using mass spectrometry.

A bladder carcinoma cell line T24, was transduced to overexpress cell surface human Nectin-4 protein. Figure 9

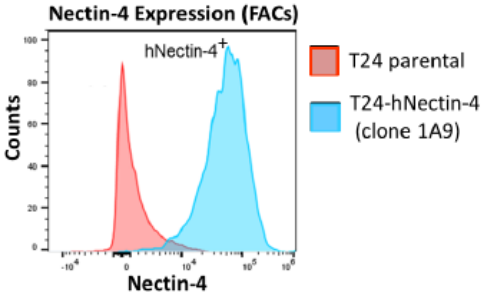



**Figure 4** Cell surface expression of Nectin-4 on the T24-hNectin-4 (clone:1A9) cell line

AGS-22C3E had cytotoxic activity (IC50 = 33 ng/mL) against the T24-hNectin-4 (clone: 1A9) cell line, but was not active against parental T24 cells. Figure 9

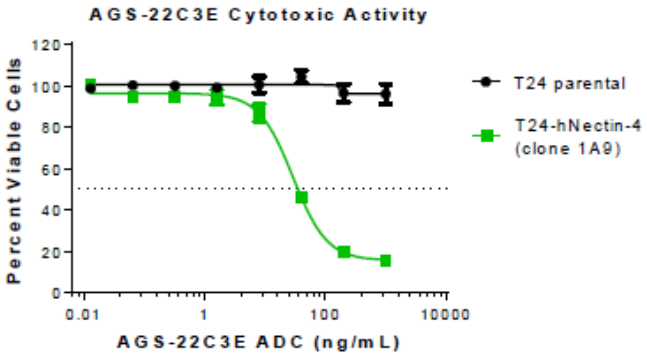



**Figure 5** AGS-22C3E antitumor activity against T24-Nectin-4 (clone:1A9) cells

To measure the intracellular concentration of MMAE delivered by AGS-22C3E, T24 parental and T24-hNectin-4 cells were treated for 24 hours with 100 and 1,000 ng/mL ADC andMass spectrometry was used to determine the intracellular concentration of MMAE for each experimental condition. AGS-22C3E delivered 95 nM and 249 nM intracellular MMAE to T24-hNectin-4 (clone: 1A9) cells at 100 ng/mL and 1,000 ng/mL ADC treatment concentrations, respectively. In contrast, intracellular MMAE drug delivered to T24 parental cells by AGS-22C3E was below the lower limit of quantitation (3.2 fmol) at 100 ng/mL and 0.6 nM at 1,000 ng/mL. demonstrating that AGS-22C3E delivers MMAE to tumor cells in a Nectin-4 dependent manner. Figure 11.

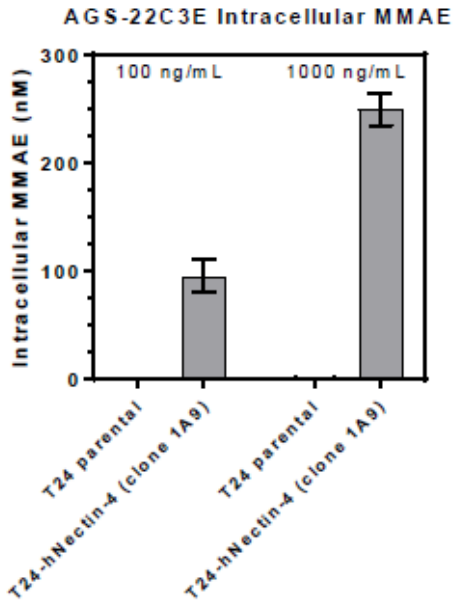



**Figure 6** Mass spectrometry measurement of intracellular MMAE in AGS-22C3E treated cells

**Table 5 Intracellular MMAE concentrations in AGS-22C3E treated cells**

| Cell Line | Drug | Nectin-4 Surface Expression (copies per cell) | Treatment Concentration | Intracellular MMAE (nM) |
|---|---|---|---|---|
| T24 parental | AGS-22C3E | <2000 | 100 ng/mL | BLLQ* |
| T24 parental | AGS-22C3E | <2000 | 1,000 ng/mL | 0.6 ± 0.25 |
| T24-Nectin-4 (clone: 1A9) | AGS-22C3E | 650,000 | 100 ng/mL | 94.9 ± 14.8 |
| T24-Nectin-4 (clone: 1A9) | AGS-22C3E | 650,000 | 1,000 ng/mL | 248.8 ± 15 |

*Below lower limit of quantification (3.2 fmol MMAE)

Fluorescence microscopy was used to demonstrate that AGS-22C3E treated T24-hNectin-4 cells are multi-nucleated and have disrupted microtubule networks. Figure 12.

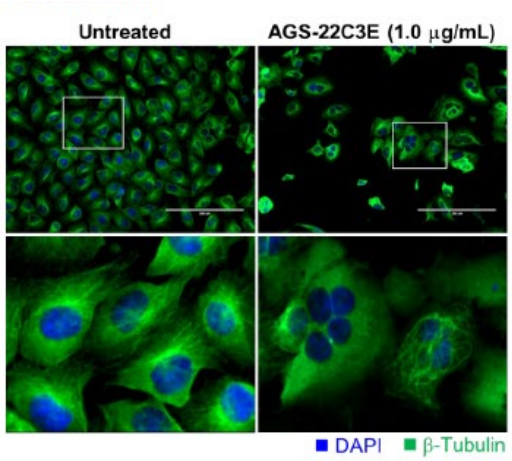



**Figure 7 AGS-22C3E treatment of Nectin-4 cells disrupts microtubules and produces multinucleated cells**

**Cytotoxicity**

Potency of AGS-22M6E (HYBRIDOMA ADC) and AGS-22M6 to induce cell death was evaluated first in a panel of PC3 cell lines engineered to express Nectin-4 antigen of human, cynomolgus monkey, rat and mouse origin. The data showed that AGS-22M6E (HYBRIDOMA ADC) specifically induces potent cytotoxic effect in the recombinant PC3 cells expressing the Nectin-4 orthologs with IC50 values ranging 0.008 -0.20 nM. The data also demonstrated potent cytotoxic activity of AGS-22M6E (HYBRIDOMA ADC) in T47D breast carcinoma cell line that endogenously expresses Nectin-4. IC50 value for inhibition of T47D cell survival was determined as 0.28 nM. Table 11.

**Table 6 Effect (IC50, nM) of AGS-22M6E and AGS-22M6 on survival of PC3-Neo, PC-3 human Nectin-4, PC3-rat-Nectin-4, PC3-cyno-Nectin-4 (A) and PC-3 murine-Nectin-4 cell (B) and by AGS-22M6E**

**A. (SET I)**

| Cell Line | $IC_{50}$, nM | |
|---|---|---|
| | AGS-22M6E | AGS-22M6 |
| PC3-neo | NA | NA |
| PC3-human-Nectin-4 | 0.008 | NA |
| PC3-rat-Nectin-4 | 0.03 | NA |
| PC3-cyno-Nectin-4 | 0.02 | NA |

**B. (SET II)**

| Cell Line | $IC_{50}$, nM | |
|---|---|---|
| | AGS-22M6E | AGS-22M6 |
| PC3-neo | NA | NA |
| PC3-murine-Nectin-4 | 0.20 | NA |

Comparison cytotoxicity activity of the monoclonal antibodies drug conjugates (ADCs) AGS-22C3E and AGS-22M6E (HYBRIDOMA ADC) was investigated using a PC3 cell line engineered to express human Nectin-4 antigen.Table 12.

**Table 7 Average % Relative Potency of AGS-22C3E when compared to AGS-22M6E**

| $EC_{50}$ Value Comparison using plates containing PC3-AGS22 Cells | | | | | | | |
|---|---|---|---|---|---|---|---|
| | *Assay 1* | *Assay 2* | *Assay 3* | | *Average* | *SD* | *% CV* |
| **AGS-22M6E** | *1.535* | 1.466 | 1.568 | | 1.523 | 0.052 | 3% |
| **AGS-22C3E** | *1.701* | *1.604* | *1.716* | | 1.674 | 0.061 | 4% |
| ***% Relative Potency*** | 90.2% | 91.4% | 91.4% | | ***91.0%*** | | |

- ***mAb Fc-mediated effector functions***

**Evaluation of Antibody Dependent Cell-Mediated Cytotoxicity (ADCC)**

The anti-Nectin-4 monoclonal antibody (mAb) AGS-22C3 and the antibody-drug conjugate (ADC) ASG-22CE were investigated for their ability to mediate antibody dependent cytotoxicity (ADCC) using target cell lines BT-483 (breast carcinoma) and PC3-AGS22 (human prostate carcinoma cell line expressing recombinant Nectin-4) in the presence of effector cells, normal human peripheral blood mononuclear cells (PBMCs), using the CytoTox 96® Non-Radioactive Cytotoxicity Assay (Promega). The release of lactate dehydrogenase (LDH) by the target cells was measured in the colorimetric enzymatic assay. The amount of LDH released is directly proportional to the amount of ADCC activity. Results obtained in the study indicate that neither the antibody AGS-22C3 nor the ADC ASG-22CE promote ADCC activity when tested using target cell lines BT-483 and PC3-AGS22 in the presence of effector cells, normal human PBMCs.

The positive control setup using Herceptin (anti-Her2 antibody) in the presence of the BT-483 target cells, demonstrated moderate ADCC activity (55%)

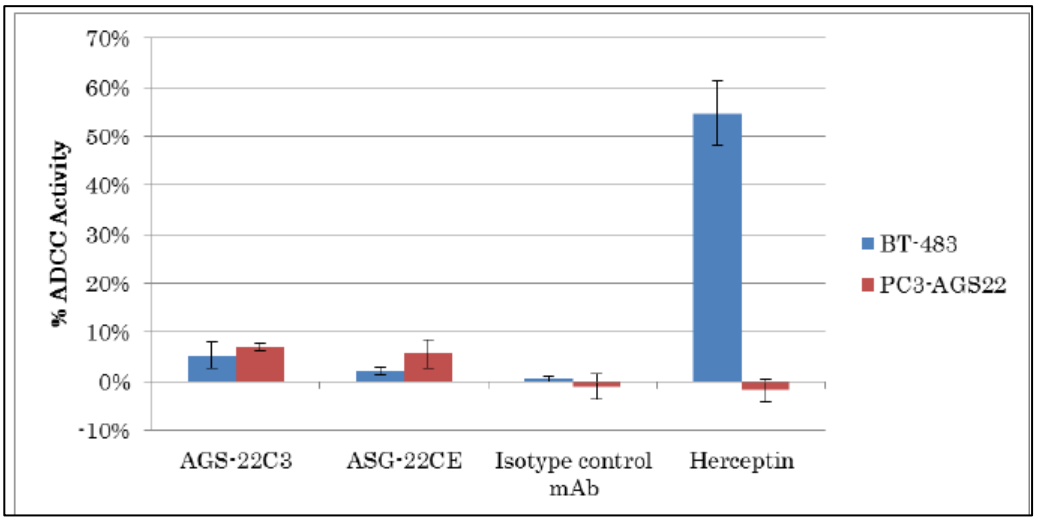



**Figure 8** Representative Graph of ADCC Activity of AGS-22C3 and ASG-22CE using BT-483 and PC3-AGS22 Target cells

**Evaluation of Complement-Dependent Cytotoxicity (CDC)**

The anti-Nectin-4 monoclonal antibody (mAb) AGS-22C3 and the antibody-drug conjugate (ADC) ASG-22CE were investigated for their ability to mediate complement-dependent cytotoxicity (CDC) using target cell lines BT-483 (breast carcinoma) and PC3-AGS22 (human prostate carcinoma cell line expressing recombinant Nectin-4) in the presence of baby rabbit complement. Cell death within the target cells was assessed by the addition of propidium iodide (PI) as a viability probe and analyzed by flow cytometry. Results obtained in the study indicate that neither the antibody AGS-22C3 nor the ADC ASG-22CE promote CDC activity when tested using target cell lines BT-483 and PC3-AGS22 in the presence of baby rabbit complement.

The human prostate carcinoma cell line engineered to express Nectin-4, PC3-AGS22, and breast carcinoma cell line BT-483 which endogenously expresses Nectin-4, were used as target cells in the study. Results obtained in the study indicate that neither antibody AGS-22C3 nor antibody-drug conjugate ASG-22CE promote CDC activity when tested against the target cell lines BT-483 and PC3-AGS22 in the presence of baby rabbit complement. The positive control setup using the antibody Rituximab and target cells Raji demonstrated strong CDC activity, ranging from 40% to 71% at various concentrations.

**Antibody-dependent cellular phagocytosis (ADCP)**

ADCP activity of AGS-22C3E ADC and AGS-22C3 mAb in PC-3-Nectin-4+ cells and MDA-MB-468 Nectin-4+ breast carcinoma cells, which natively express Nectin-4.

Phagocytic activity was determined by calculating the total macrophages that engulfed tumor cells as measured by flow cytometry and subtracting the background of the No Drug Control.

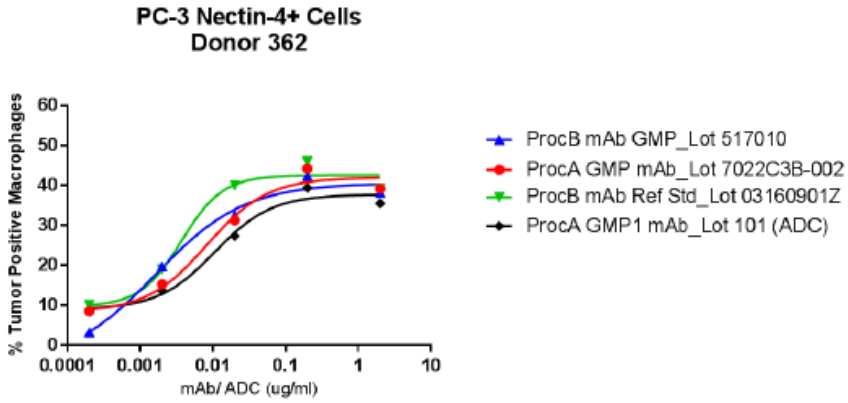


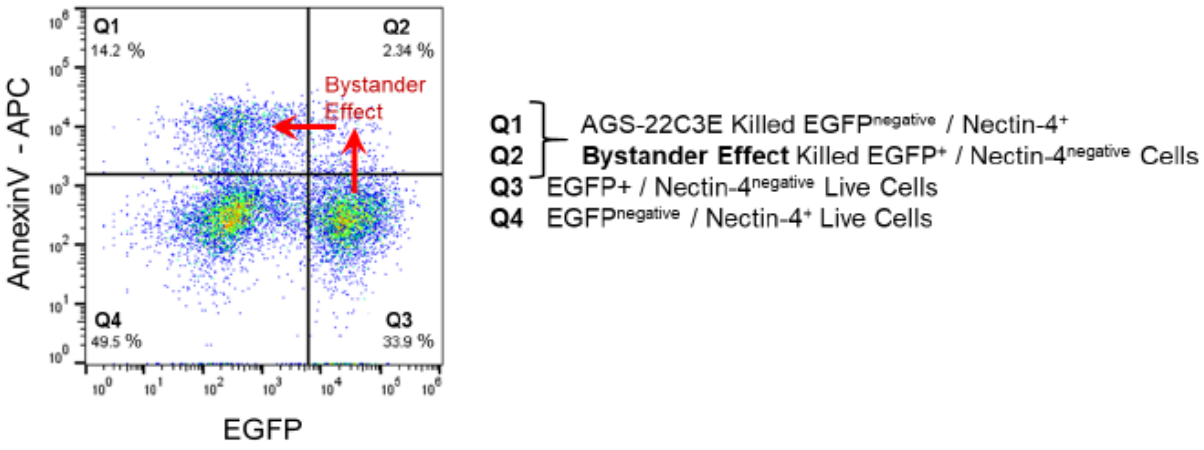

**Figure 9** ADCP assay using PC-3-Nectin-4 as target cells.PKH26-labeled target cells were treated with AGS-22C3 mAb lots and a control AGS-22C3 ADC, hIgG1-k or media only followd by incubation with macrophages from Donor 362 at 1 macrophage to 4 target cell (1:4 ratio). Phagocytic activity was determined by calculating the total macrophages that engulfed tumor cells as measured by flow cytometry and subtracting the background of the No Drug Control

• Cytotoxicity assays were developed using PC-3-Nectin-4+ and MDA-MB-468 target cells. Different AGS-22C3E ADC and AGS-22C3 antibody lots were tested to compare ADCP activity using two different human monocyte donors.

• AGS-22C3E and AGS-22C3 lots mediated ADCP activity in a range of 40 – 70% depending upon specific lot and human monocyte donor.

- ***Bystander effect secondary to release of MMAE from targeted tumor cells***

Two bladder carcinoma cell lines lacking endogenous Nectin-4, T24 and UM-UC-3, were transduced to overexpressing cell surface human Nectin-4 protein. The Nectin-4 targeting antibody drug conjugate AGS-22C3E had potent cytotoxic activity against the T24-hNectin-4 and UMUC3-hNectin4 cell lines, but was not active against T24 and UM-UC-3 cell lines engineered to overexpress green fluorescent protein (GFP). These cell lines were used to generate two co-culture model systems to measure AGS-22C3E *in vitro* bystander effect activity. Nectin-4 positive bladder carcinoma cells were mixed with Nectin-4 negative bladder carcinoma cells at a controlled 1:1 ratio, then treated for 72 or 168 hours with AGS-22C3E ADC. Bystander effect activity was determined using flow cytometry by measuring the percent cell viability decline of the Nectin-4 negative, GFP positive tumor cell population.




An admixed *in vitro* cell culture assay for measuring AGS-22C3E bystander effect activity on Nectin-4 negative bladder carcinoma cells. T24 EGFP+ / Nectin-4negative cells are co-cultured at a 1:1 ratio with T24-Nectin4+ / EGFPnegative cells. Cells are untreated in this figure. Bystander cell killing can be measured by the decrease in the percent viable T24 EGFP+ / Nectin-4negative cells in Q3 and their shift into Q2 and later Q1 (red arrows) with increased AnnexinV staining, a marker of apoptotic cell death. A second co-culture system to measure AGS-22C3E bystander effect activity was developed using UMUC3 EGFP+ / Nectin-4negative cells and UMUC3-Nectin4+ / EGFPnegative cells.

**Figure 10 Development of a Flow Cytometry Based Bystander Effect Assay**

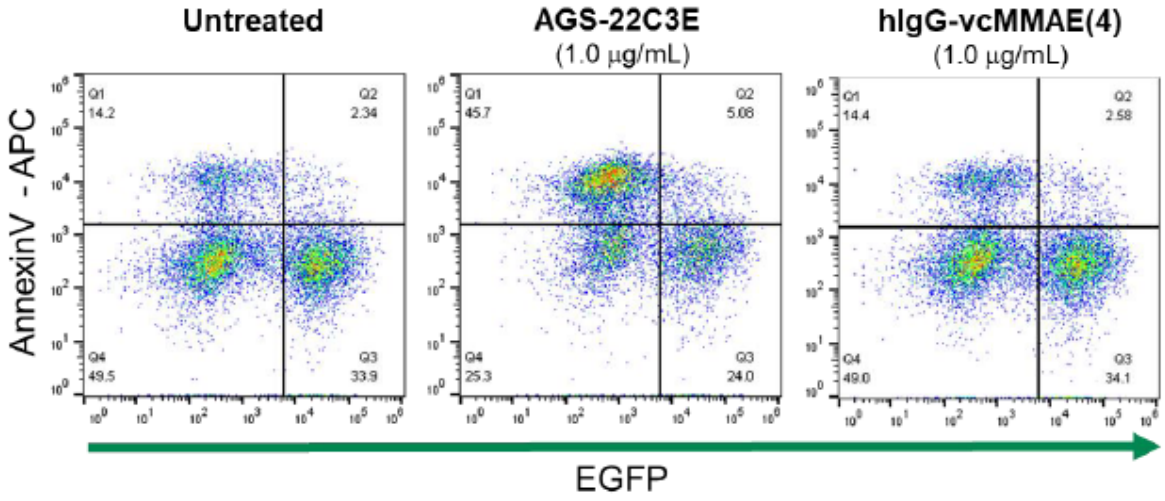



**Figure 11. AGS-22C3E Bystander Effect Activity in a T24 EGFP*/T24 Nectin-4 Co-culture Bladder Carcinoma Cell Line System**

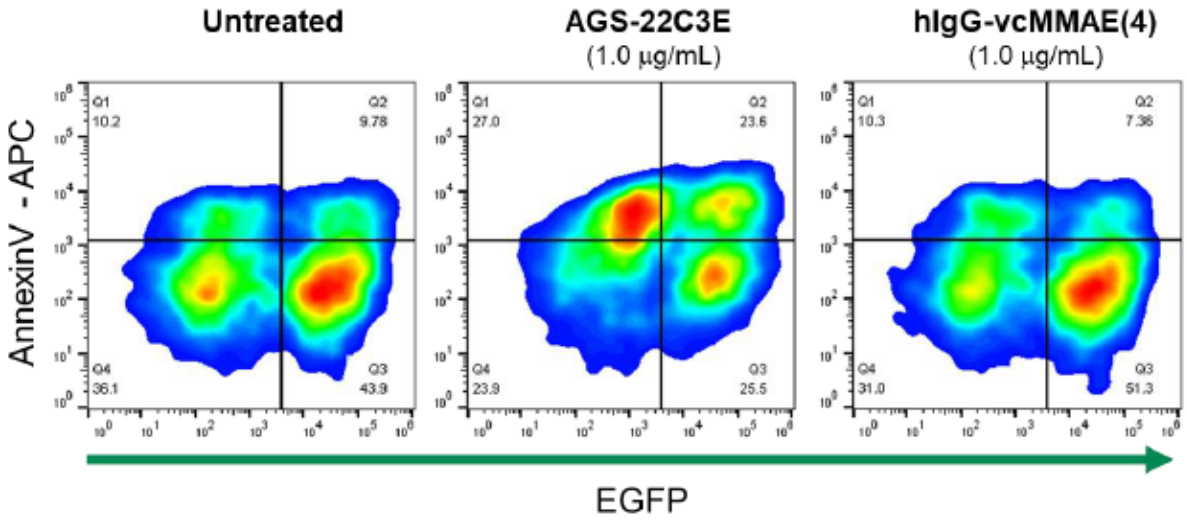
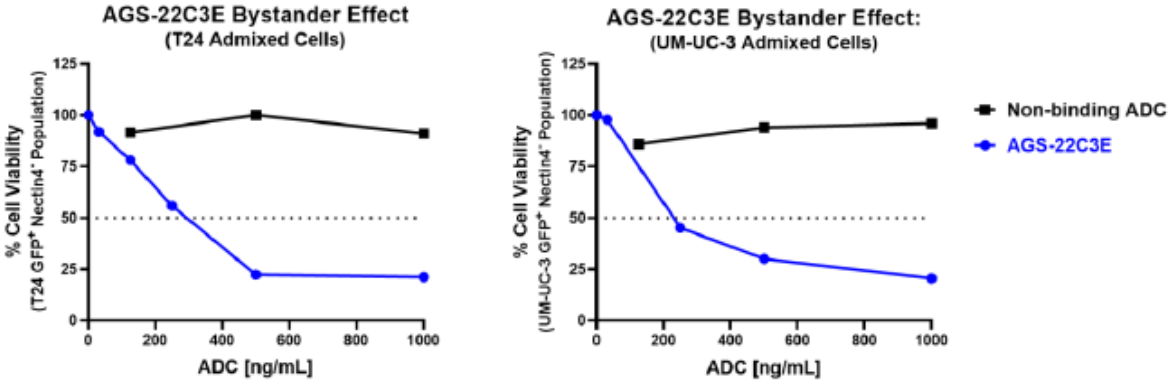



**Figure 12. AGS-22C3E Bystander Effect Activity in a UMUC3 EGFP*/UMUC3 Nectin-4 Co-culture Bladder Carcinoma Cell Line System**

AGS-22C3E treatment produced a maximum of 80% reduction in the cell viability of Nectin-4 negative, GFP positive bystander tumor cells at the highest tested ADC concentration of 1,000 ng/mL.

Furthermore, AGS-22C3E bystander effect activity was dose dependent. Figure 18.




AGS-22C3E bystander effect activity is dose-dependent. Admixed T24 EGFP+ / Nectin-4negative and T24-Nectin4+ / EGFPnegative bladder carcinoma cells (left panel) and admixed UMUC3 EGFP+ / Nectin-4negative and UMUC3-Nectin4+ / EGFPnegative bladder carcinoma cells (right panel) were co-cultured at a 1:1 ratio. Cells were treated with a dose titration of AGS-22C3E (1000, 500, 250, 125, 31.3, and 0.00 ng/mL) or non-binding MMAE ADC control (1000, 500, 125 ng/mL) for 168 hours. Flow cytometry was used to measure the percentage of viable

**Figure 13.** Dose-dependent AGS-22C3E Bystander Effect Activity in Admixed Nectin-4/Nectin-4 negative Bladder Carcinoma Cell Line Model

***In vivo* pharmacology**

The antitumor activity of AGS-22M6 (unconjugated antibody), AGS-22M6E (HYBRIDOMA ADC) and AGS-22C3E/enfortumab vedotin was evaluated in a panel of tumor xenograft models (bladder and breast cancer models in which expression of Nectin-4 was demonstrated.

**Efficacy Study of AGS-22M6E (HYBRIDOMA ADC) in a Xenograft Model of Human Bladder Cancer AG-B1 in SCID Mice**

AG-B1 xenograft tumors were implanted subcutaneously in SCID mice and treatment started when tumors reached approximately 200 mm3.

AGS-22M6E (HYBRIDOMA ADC) was tested at 0.4 mg/kg and 0.8 mg/kg every 4 days until study termination. A control ADC, H3-1.4.1.2-vcE (0.4 and 0.8 mg/kg), the unconjugated antibody AGS-22M6 (0.8 mg/kg) and the vehicle, 5% dextrose, were used as controls. The results showed that AGS-22M6E (HYBRIDOMA ADC) at 0.8 mg/kg statistically significantly inhibited tumor growth when compared to H3-1.4.1.2-vcE 0.8 mg/kg ($p$=0.0128), the antibody AGS-22M6 ($p$=0.0004) or 5% dextrose ($p$<0.0001), resulting in 70.9%, 75.3% and 75.7% tumor inhibition respectively. AGS-22M6E (HYBRIDOMA ADC) given at the lower dose of 0.4 mg/kg did not show significant antitumor activity when compared to any of the controls ($p$>0.05). Statistically significant difference ($p$=0.0063) was detected when the two doses of AGS-22M6E (HYBRIDOMA ADC) were compared, indicating the efficacy of AGS-22M6E (HYBRIDOMA ADC) was dose-dependent.

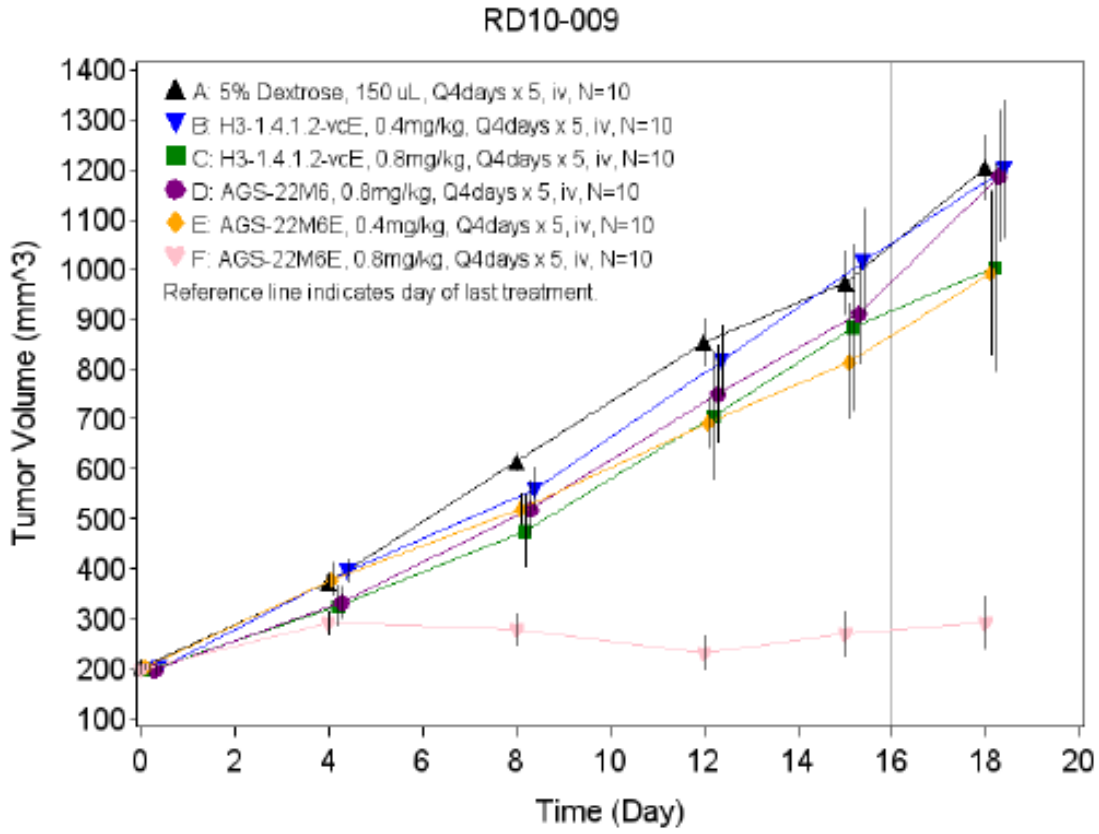



**Figure 14.** Tumor Volume Over time

**Efficacy Study of ASG-22CE in a Subcutaneously Established Xenograft Model of Human Bladder Cancer AG-B8 in CB17/SCID Mice**

Day 21 results showed statistically significant anti-tumor activity of ASG-22CE at all tested dosages, 0.5 mg/kg, 1.0 mg/kg, and 1.5 mg/kg, given intravenously twice a week for a total of three doses when compared to either the IgG1 isotype control ADC H3-1.4.1.2-vcE (p<0.0001) or the 5% Dextrose vehicle control (p<0.0001). Moreover, ASG-22CE at 0.5 mg/kg, 1.0 mg/kg, and 1.5 mg/kg, statistically significantly regressed the tumors by 12.0% (p=0.0044), 24.2% (p<0.0001), and 38.0%

(p<0.0001), respectively, when compared to the tumor size at the baseline.. Statistically significant difference in efficacy was observed between the 1.5 mg/kg and 0.5 mg/kg dose groups (p=0.0006) on day 21.

**Table 8** Design of Study SQ 15-059

| Group Code | Test Material | Dose, Route and Schedule | N |
|---|---|---|---|
| A (1) | Vehicle Control 5% Dextrose | 100 µL, IV, BIW x 3 doses | 10 |
| B (2) | H3-1.4.1.2-vcE | 1.5 mg/kg, IV, BIW x 3 doses | 10 |
| C (3) | ASG-22CE | 1.5 mg/kg, IV, BIW x 3 doses | 10 |
| D (4) | ASG-22CE | 1.0 mg/kg, IV, BIW x 3 doses | 10 |
| E (5) | ASG-22CE | 0.5 mg/kg, IV, BIW x 3 doses | 10 |

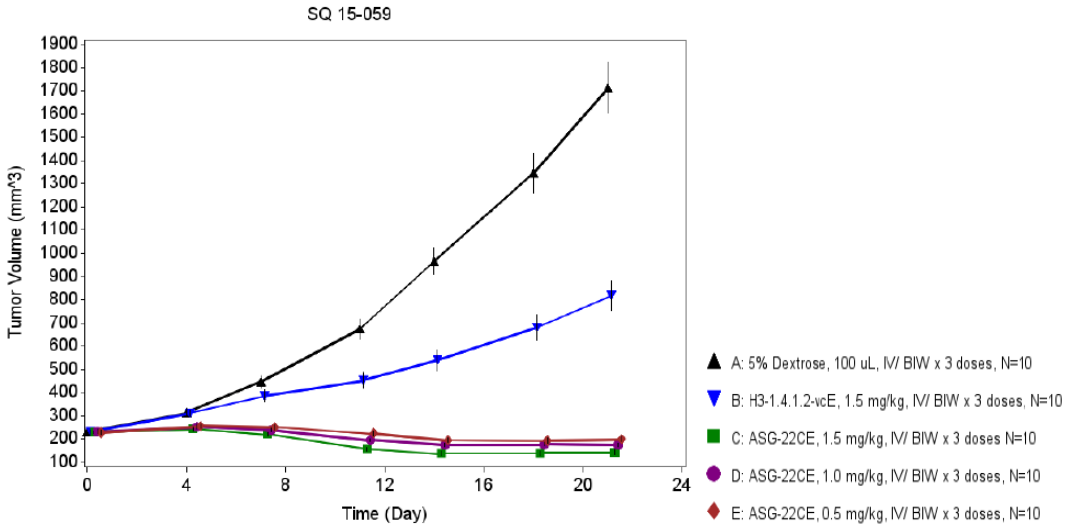



**Figure 15 Tumor Over time**

**Efficacy Study Comparing Hybridoma Cell Line-Derived AGS-22M6E and CHO Cell Line-Derived AGS-22C3E in a Subcutaneously Established Xenograft Model of Human Breast Cancer AG-Br7 in SCID Mice**

The antitumor efficacy of AGS-22M6E (HYBRIDOMA ADC) produced in hybridoma cells was compared to AGS-22C3E produced in CHO cells using the AG-Br7 patient-derived human breast cancer xenograft model. AG-Br7 xenograft tumors were implanted subcutaneously in SCID mice, and treatment was initiated when tumors reached approximately 200 mm3. AG-Br7 tumor-bearing mice were randomized into control and treatment groups. Animals in each of the treatment groups were administered either AGS-22M6E (HYBRIDOMA ADC) or AGS-22C3E, at 1.0 mg/kg or 2.0 mg/kg, twice per week until study termination. The control groups received the control ADC, H3-1.4.1.2-vcE, at 1.0 or 2.0 mg/kg, and also included a vehicle-treated arm (5% dextrose).

The tumor growth inhibition caused by both the hybridoma-derived and the CHO-derived ADCs was similar with no statistical difference between the AGS-22M6E and AGS-22C3E-treated groups ($p$>0.9999). Neither AGS-22M6E (HYBRIDOMA ADC) nor AGS-22C3E given at the lower dose of 1.0 mg/kg showed significant efficacy when compared to the vehicle or to the control ADC, H3-1.4.1.2-vcE, at identical dose ($p$=0.8879 and $p$=0.4154, respectively).

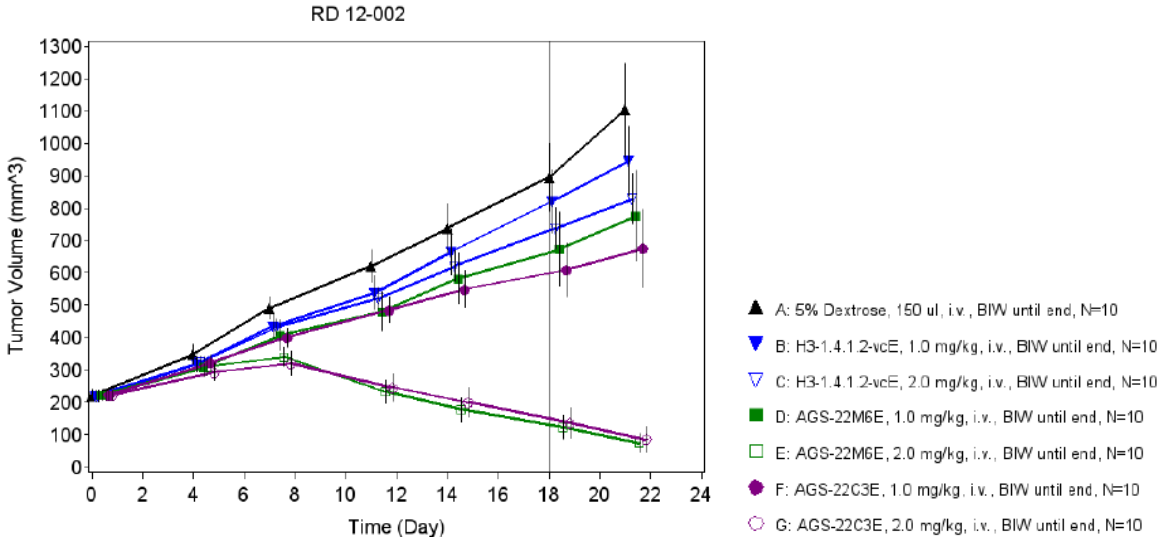



**Figure 16 Tumor Volume Over time**

## *Secondary pharmacodynamic studies*

No secondary pharmacodynamic studies of the ADCs were conducted; however, the hypothetical secondary effects of an ADC binding to Nectin-4 were discussed using a review of literature.

Skin toxicity observed with enfortumab vedotin in animals and patientsis are considered due entirely to target-dependent ADC uptake of MMAE in rapidly dividing epithelial cells.

The embryo-fetal toxicity observed is consistent with the pharmacology of MMAE on rapidly dividing cells.

Male animals from the repeat dose cynomolgus monkey toxicity study showed no indications of mammary gland effects at lethal doses (6 mg/kg per week).

In humans, Nectin-4 is involved as a mediator of measles virus entry into cells via Nectin-4-mediated micropinocytosis. There is a theoretical risk for coadministration of enfortumab vedotin with live measles vaccine. The attenuated live viruses used in measles vaccinations gain an adaption from growth in cell culture to enter cells also using CD46, a human membrane receptor expressed on all nucleated cells [Delpeut et al, 2014; Naniche et al, 1993]. Therefore, blockade of Nectin-4 is considered of minimal significance for vaccinations in the intended patient population.

The toxicity studies results show the ADC and the unconjugated antibody have no similar toxicological findings to those observed with antiangiogenic compounds and hence this is not considered a relevant pharmacology aspect.

## *Safety pharmacology programme*

Enfortumab vedotin safety pharmocolagy have been studied *in vitro* and *in vivo*. *In vitro* safety pharmacology was limited to the effects of MMAE on potassium conductance via the hERG channel.

*In vitro*

**Table 9** hERG studies with MMAE

| Type of study, GLP, Study no | Species, Gender and no/grp | Method of Admin, Duration of dosing | Concentrations | Safety pharmacology findings |
|---|---|---|---|---|
| **MMAE** | | | | |
| hERG assay<br><br>GLP<br><br>129-09-001 | *In vitro* | Human embryonic kidney cells (HEK293) | 10, 100 µM | MMAE resulted in concentration related inhibition of peak hERG tail current.<br>Control: 0.063<br>MMAE 10 µmol/L: 0.103<br>MMAE 100 µmol/L: 0.237*<br>Cisapride hydrate 25 nmol/L: 0.743<br>$IC_{50}$ value: > 100 µmol/L |

*In vivo* safety pharmacology (cardiovascular, respiratory and central nervous system [CNS]) of the hybridoma cell line-derived ADC, AGS-22M6E, and enfortumab vedotin were evaluated as part of the general toxicology studies.

- *In vivo*

**Table 10** *In vivo* toxicity studies with AGS-22M6E, AGS-22M6 and enfortumab vedotin

| Type of study, GLP, Study no | Species, Gender and no/grp | Method of Admin, Duration of dosing | Doses (mg/kg) | Safety pharmacology findings |
|---|---|---|---|---|
| **Cardiovascular system**<br>(blood pressure, heart rate, ECG)<br><br>GLP<br><br>20005664<br>(4-wk tox study) | Cynomolgus Monkey<br><br>5 males and 5 females | iv infusion/ (MMAE iv bolus) | 0 (vehicle control),<br>1, 3, 6 (AGS-22M6E),<br>6 (AGS-22M6), and<br>0.1093/0.0545 mg/kg (MMAE)<br>Dose reduction after 2 doses (weekly, 4 doses) | No changes in blood pressure, ECG or heart rate<br><br>(see TK parameters detailed in tox part) |
| **Central nervous system (behavior)**<br><br>GLP<br><br>20005662<br>(4-wk tox study) | Sprague-Dawley rat<br><br>15 males and 15 females | iv bolus | 0 (vehicle control),<br>2, 5, 10 (AGS-22M6E)<br>10 mg/kg (AGS-22M6)<br>(weekly, 4 doses) | No abnormal behavior<br><br>(see TK parameters detailed in tox part) |
| **Central nervous and respiratory system**<br>(behavior, body temperature, respiratory rate, heart rate)<br><br>GLP<br><br>20021751<br>(comparability 4-wk tox study) | Cynomolgus Monkey<br><br>5 males and 5 females<br>(2 males and 2 females in the control group) | iv infusion | 0 (vehicle control),<br>3 (AGS-22M6E) and<br>3 mg/kg (**enfortumab vedotin**)<br>(weekly, 4 doses) | no reports of abnormal behavior, body temperatures and no significant changes in respiratory rate or heart rate.<br><br>(see TK parameters detailed in tox part) |

The effect of SGD-1010 on hERG K+ channels, heterologously expressed in Human Embryonic Kidney (HEK293) cells, was evaluated using the conventional whole cell voltage clamp technique. The effects on hERG K+ currents were examined by measuring peak hERG tail current before and during test and

control article exposure at 35 ± 1oC. SGD-1010 effects at 10 and 100 μM were compared to the negative control (extracellular saline). Cisapride hydrate (25nM) was used as a positive control. MMAE, at concentrations 19405-fold higher than the clinically observed Cmax, had limited (less than 50%) inhibition of potassium conductance via the hERG channel and at 10 μmol/L there was no significant inhibition of hERG channel activity.

**Table 11** Mean Fractional block of peak hERG tail current and summary statistics

| Dose Perfusate | Mean | SD | SEM | Number of Cells |
|---|---|---|---|---|
| Negative Control | 0.063 | 0.046 | 0.023 | 4 |
| 10 μM | 0.103 | 0.059 | 0.030 | 4 |
| 100 μM* | 0.237 | 0.112 | 0.056 | 4 |
| Positive Control† | 0.743 | 0.007 | | 2 |

* Indicates statistically significant difference from the negative control ($p < 0.05$)
† Not tested for difference from the negative control

No effect was observed on the Fridericia corrected QT interval and RR-interval in cynomolgus monkeys at concentrations of AGS-22M6E up to approximately 6-fold the clinically observed Cmax. The ADC was not evaluated as the antibody component is too large to cross plasma membranes and therefore would be unable to access and block the promiscuous inner pore of the hERG channel.

No effect was observed on ECG, heart rate, blood pressure, respiratory or CNS safety pharmacology parameters evaluated as part of the general toxicology studies performed in cynomolgus monkeys with the ADC.

Enfortumab vedotin has no signals for safety pharmacology endpoints. In addition, there was no evidence of a clinical safety pharmacology signal.

### *Pharmacodynamic drug interactions*

Pharmacodynamic drug interactions of enfortumab vedotin have not been submitted in non-clinical studies.

## 2.3.3. Pharmacokinetics

Pharmacokinetics studies

The pharmacokinetics (toxicokinetics) of enfortumab vedotin, AGS-22M6E (HYBRIDOMA ADC), AGS-22M6 (unconjugated antibody) or MMAE were evaluated through 4-week intravenous dose toxicity studies in rats and/or cynomolgus monkeys after the first and the last dose. Immunogenicity of ADCs was also evaluated in these toxicity studies.

Since enfortumab vedotin and AGS-22M6E (HYBRIDOMA ADC) share the same linker-drug conjugation of brentuximab vedotin, historical plasma protein binding, metabolism, excretion and *in vitro* drug interaction potential of MMAE are discussed. No new studies were conducted to characterize the distribution, metabolism and excretion of enfortumab vedotin or AGS-22M6E (HYBRIDOMA ADC).

**Methods of analysis** Distinct methods of analysis were used to detect the antibody and small molecule components of enfortumab vedotin to support the toxicokinetic evaluations for each species and with each drug substance. Methods included immunoassays for antibody analytes in various biological matrices and liquid chromatography with tandem mass spectrometry (LC-MS/MS) for MMAE. All toxicokinetic assays were fully validated.

Immunoassays were developed to measure the antibody components as well as immunogenicity against the therapeutic. LC-MS/MS assays were employed to measure circulating amounts of the small cytotoxic molecule released from the ADC. The toxicokinetic analytes measured included ADC (AGS-22M6E (HYBRIDOMA ADC) [hybridoma derived] or enfortumab vedotin [CHO derived]), TAb (ADC plus unconjugated antibody), MMAE and Anti Therapeutics Antibody (ATA).

**Table 12** Analytical method- Test Article AGS-22M6, Enfortumab Vedotin, MMAE

| Type of Study | Species | Analytical Instrument and Detection Method | Study Number |
|---|---|---|---|
| **Analytical method (ADC)** | | | |
| AGS-22M6E ADC in serum | Rat | ELISA/Colorimetric | AR3587 |
| AGS-22M6E ADC in serum | Cynomolgus monkey | ELISA/Colorimetric | AR3590 |
| Enfortumab vedotin ADC in serum | Rat | ELISA/Colorimetric | AR161-C1128-17-0075 |
| Enfortumab vedotin ADC in serum | Cynomolgus monkey | ELISA/Colorimetric | AR4559 |
| **Analytical method (TAb)** | | | |
| AGS-22M6E or AGS-22M6 TAb in serum | Rat | ELISA/Colorimetric | AR3588 |
| AGS-22M6E or AGS-22M6 TAb in serum | Cynomolgus monkey | ELISA/Colorimetric | AR3591 |
| Enfortumab vedotin TAb in serum | Cynomolgus monkey | ELISA/Colorimetric | AR4560 |
| **Analytical method (ATA)** | | | |
| Anti-AGS22M6E antibody in serum | Rat | ELISA/Colorimetric | AR3589 |
| Anti-AGS22M6E antibody in serum | Cynomolgus monkey | ELISA/Colorimetric | AR3592 |
| Anti-enfortumab vedotin antibody in serum | Rat | ELISA/Colorimetric | AR161-C1128-17-0077 |
| Anti-enfortumab vedotin antibody in serum | Cynomolgus monkey | ELISA/Colorimetric | AR4562 |
| **Analytical method (MMAE)** | | | |
| MMAE in serum | Rat | LC-MS/MS | 8226174 |
| MMAE in serum | Cynomolgus monkey | LC-MS/MS | 8226175 |

**Table 13** Methods for antibody Drug Conjugate

**Test Article: AGS-22M6E, Enfortumab Vedotin**

| **Study number** | AR3587 | AR3590 | AR161-C1128-17-0075 | AR4559 |
|---|---|---|---|---|
| **Species** | Rat | Cynomolgus monkey | Rat | Cynomolgus monkey |
| **Sample (whole blood, plasma, serum etc.)** | Serum | Serum | Serum | Serum |
| **Analyte** | AGS-22M6E | AGS-22M6E | Enfortumab vedotin | Enfortumab vedotin |
| **Assay** | ELISA | ELISA | ELISA | ELISA |
| **Validation data** | | | | |
| **Lower limit of quantitation (ng/mL)** | 40 | 40 | 80 | 80 |
| **Concentration range (ng/mL)** | 40 to 1280 | 40 to 1280 | 80 to 1280 | 80 to 640 |
| **Selectivity (%)** | 100 ± 20 | 100 ± 20 | 100 ± 20 (100 ± 25 for LLQ) | 100 ± 20 (100 ± 25 for Low QC) |
| **Intraday precision (%)** | ≤ 20 (25 for LLQ) | ≤ 20 (25 for LLQ) | ≤ 20 (25 for LLQ) | ≤ 20 (25 for Low2 QC) |
| **Interday precision (%)** | ≤ 20 (25 for LLQ) | ≤ 20 (25 for LLQ) | ≤ 20 (25 for LLQ) | ≤ 20 (25 for Low2 QC) |
| **Intraday accuracy (%)** | 100 ± 20 (100 ± 25 for LLQ) | 100 ± 20 (100 ± 25 for LLQ) | 100 ± 20 (100 ± 25 for LLQ) | 100 ± 20 (100 ± 25 for Low2 QC) |
| **Interday accuracy (%)** | 100 ± 20 (100 ± 25 for LLQ) | 100 ± 20 (100 ± 25 for LLQ) | 100 ± 20 (100 ± 25 for LLQ) | 100 ± 20 (100 ± 25 for Low2 QC) |
| **LTS (months at -60°C to -80°C)** | 6 | 6 | 16 | 12 |
| **Additional information:** The values for precision and accuracy described above are not validation data, but acceptance criteria that the results must have met. | | | | |

AGS-22M6E: hybridoma derived fully human monoclonal antibody conjugated to cytotoxic agent monomethyl auristatin E targeting Nectin-4; ELISA: enzyme-linked immunosorbent assay; LLQ: lower limit of quantitation; LTS: long term stability; QC: quality control sample

**Table 14** Methods for total Antibody

**Test Article: AGS-22M6E, AGS-22M6, Enfortumab Vedotin**

| **Study number** | AR3588 | AR3591 | AR4560 |
|---|---|---|---|
| **Species** | Rat | Cynomolgus monkey | Cynomolgus monkey |
| **Sample (whole blood, plasma, serum etc.)** | Serum | Serum | Serum |
| **Analyte** | AGS-22M6E | AGS-22M6E | Enfortumab Vedotin |
| **Assay** | ELISA | ELISA | ELISA |
| **Validation data** | | | |
| **Lower limit of quantitation (ng/mL)** | 40 | 40 | 80 |
| **Concentration range (ng/mL)** | 40 to 1280 | 40 to 1280 | 80 to 640 |
| **Selectivity (%)** | 100 ± 20 | 100 ± 20 | 100 ± 20 (100 ± 25 for Low QC) |
| **Intraday precision (%)** | ≤ 20 (25 for LLQ) | ≤ 20 (25 for LLQ) | ≤ 20 (25 for Low2 QC) |
| **Interday precision (%)** | ≤ 20 (25 for LLQ) | ≤ 20 (25 for LLQ) | ≤ 20 (25 for Low2 QC) |
| **Intraday accuracy (%)** | 100 ± 20 (100 ± 25 for LLQ) | 100 ± 20 (100 ± 25 for LLQ) | 100 ± 20 (100 ± 25 for Low2 QC) |
| **Interday accuracy (%)** | 100 ± 20 (100 ± 25 for LLQ) | 100 ± 20 (100 ± 25 for LLQ) | 100 ± 20 (100 ± 25 for Low2 QC) |
| **LTS (months at -60°C to -80°C)** | 6 | 6 | 12 |
| **Additional information:** The values for precision and accuracy described above are not validation data, but acceptance criteria that the results must have met. | | | |

AGS-22M6: unconjugated hybridoma derived fully human monoclonal antibody targeting Nectin-4; AGS-22M6E: hybridoma derived fully human monoclonal antibody conjugated to cytotoxic agent monomethyl auristatin E targeting Nectin-4; ELISA: enzyme-linked immunosorbent assay; LLQ: lower limit of quantitation; LTS: long term stability; QC quality control sample

**Table 15** Methods for anti-therapeutic Antibodies

**Test Article: AGS-22M6E, AGS-22M6, Enfortumab Vedotin**

| Study number | AR3589 | AR161-C1128-17-0077 | AR3592 | AR4562 |
|---|---|---|---|---|
| Species | Rat | Rat | Cynomolgus monkey | Cynomolgus monkey |
| Sample (whole blood, plasma, serum etc.) | Serum | Serum | Serum | Serum |
| Positive control | M22-id6-1b40p | M22-id6-1a21.1#6 | M22-id6-1b40p | M22-id6-1b40p |
| Assay | ELISA | ELISA | ELISA | ELISA |
| Validation data | | | | |
| Sensitivity (ng/mL) | 0.5 | 63.94 | 1.0 | 1.96 |
| Drug tolerance † (ng/mL) at 30 ng/mL positive control | 100 | 250 ‡ | 100 | 1000 |
| Drug tolerance † (ng/mL) at 2.5 ng/mL positive control | 10 | ND | 10 | 1000 |
| Specificity confirmation | > 50% inhibition ADC | ≥ 43.8% inhibition ADC | > 50% inhibition ADC | > 50% inhibition ADC |
| Intraday precision of positive control (%) | ≤ 25 | ≤ 30 | ≤ 25 | ≤ 25 |
| Additional information: The values for precision described above are not validation data, but acceptance criteria that the results must have met. | | | | |

ADC: antibody-drug conjugate; AGS-22M6: unconjugated hybridoma derived fully human monoclonal antibody targeting Nectin-4; AGS-22M6E: hybridoma derived fully human monoclonal antibody conjugated to cytotoxic agent monomethyl auristatin E targeting Nectin-4; ELISA: enzyme-linked immunosorbent assay; ND: not determined

† Drug is enfortumab vedotin or AGS-22M6E.

‡ Drug tolerance was determined with 500 ng/mL rather than 30 ng/mL of M22-id6-1a21.1#6.

**Table 16** Methods for MMAE

**Test Article: AGS-22M6E, Enfortumab Vedotin, MMAE**

| Study number | 8226174 | 8226175 |
|---|---|---|
| Species | Rat | Cynomolgus monkey |
| Sample (whole blood, plasma, serum etc.) | Serum | Serum |
| Analyte | MMAE | MMAE |
| Assay | LC-MS/MS | LC-MS/MS |
| Validation data | | |
| Lower limit of quantitation (pg/mL) | 10.0 | 10.0 |
| Sample volume used (mL) | 0.05 | 0.05 |
| Concentration range (pg/mL) | 10 to 10000 | 10 to 10000 |
| Selectivity | < 20% of the response of MMAE from LLQ sample | < 20% of the response of MMAE from LLQ sample |
| Extraction recovery (%) | 82.5 | 87.2 |
| Intraday precision (%) | ≤ 15.0 (≤ 20.0 at LLQ) | ≤ 15.0 (≤ 20.0 at LLQ) |
| Interday precision (%) | ≤ 15.0 (≤ 20.0 at LLQ) | ≤ 15.0 (≤ 20.0 at LLQ) |
| Intraday accuracy (%) | 85.0 to 115.0 (80.0 to 120.0 at LLQ) | 85.0 to 115.0 (80.0 to 120.0 at LLQ) |
| Interday accuracy (%) | 85.0 to 115.0 (80.0 to 120.0 at LLQ) | 85.0 to 115.0 (80.0 to 120.0 at LLQ) |
| LTS (days at -60°C to -80°C) | 226 | 191 |
| Additional information: The values for precision and accuracy described above are not validation data, but acceptance criteria that the results must have met. | | |

AGS-22M6E: hybridoma derived fully human monoclonal antibody conjugated to cytotoxic agent monomethyl auristatin E targeting Nectin-4; LC-MS/MS: liquid chromatography with tandem mass spectrometry; LLQ: lower limit of quantitation; LTS: long term stability; MMAE: monomethyl auristatin E.

**Absorption**

The toxicokinetics of AGS-22M6E (HYBRIDOMA ADC) , AGS-22M6, enfortumab vedotin, MMAE and Total Antibody (TAb) following intravenous administration of AGS-22M6E (HYBRIDOMA ADC) , AGS-22M6 or enfortumab vedotin were evaluated in rats and cynomolgus monkeys. The toxicokinetics of MMAE following intravenous administration of unconjugated MMAE was also evaluated in cynomolgus monkeys.

**In Rat**

The toxicokinetics of AGS-22M6E (HYBRIDOMA ADC) and AGS-22M6 in rats were evaluated from GLP-compliant 4-week intravenous dose toxicity study after the first dose and the last dose (Study 20005662).

The PK parameters are presented below in the tables 12 and 13.

*Toxicokinetics of AGS-22M6E (HYBRIDOMA ADC) , TAb and MMAE after Repeated-dose Administration of AGS-22M6E (HYBRIDOMA ADC) or AGS-22M6 in Sprague-Dawley Rats*

**Table 17** ADC, TAb and MMAE Serum Toxicokinetic Parameters for Male and Female Rats on Study Days 1 and 22 Following 4 Weekly Intravenous Administration of AGS-22M6E (Study 20005662)

| AGS-22M6E Dose | 2 mg/kg | | | | 5 mg/kg | | | | 10 mg/kg | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day | 1 | | 22 | | 1 | | 22 | | 1 | | 22 | |
| Sex | F | M | F | M | F | M | F | M | F | M | F | M |
| TK Parameters† | ADC | | | | | | | | | | | |
| $AUC_{last}$‡ (µg·h/mL) | 1120 | 1180 | 549 | 1050 | 883 | 2250 | 1390 | 1960 | 5630 | 6570 | 3570 | 4170 |
| $C_{max}$ (µg/mL) | 55.0 | 59.7 | 52.8 | 55.3 | 24.6 | 137 | 96.9 | 124 | 280 | 271 | 153 | 209 |
| $t_{1/2}$ (day) | 0.887 | 1.13 | NR | NR | 1.21 | 1.09 | NR | NR | 1.20 | 1.29 | NR | NR |
| TK Parameters | TAb | | | | | | | | | | | |
| $AUC_{last}$‡ (µg·h/mL) | 1910 | 2190 | 832 | 2330 | 974 | 3940 | 1770 | 3370 | 9680 | 11600 | 6720 | 7700 |
| $C_{max}$ (µg/mL) | 69.6 | 74.8 | 63.2 | 69.6 | 27.5 | 160 | 121 | 147 | 332 | 324 | 194 | 260 |
| $t_{1/2}$ (day) | 1.33 | 1.50 | NR | NR | 1.68 | NR | NR | NR | 2.01 | 2.16 | NR | NR |
| TK Parameters | MMAE | | | | | | | | | | | |
| $AUC_{168h}$ (ng·h/mL) | 9.86 | 12.6 | 7.19 | 11.9 | 20.0 | 20.5 | 14.5 | 25.4 | 43.0 | 51.3 | 36.2 | 69.6 |
| $C_{max}$ (ng/mL) | 0.291 | 0.255 | 0.473 | 0.405 | 0.516 | 0.644 | 1.11 | 1.09 | 0.820 | 0.870 | 1.89 | 2.82 |
| $t_{max}$ (h) | 0.0167 | 0.0167 | 0.0167 | 0.0167 | 0.0167 | 0.0167 | 0.0167 | 0.0167 | 0.0167 | 0.0167 | 0.0167 | 0.0167 |
| $t_{1/2}$ (day) | 1.46 | 1.40 | NR | 1.93 | 1.30 | 0.940 | 1.61 | NR | 1.46 | 1.32 | 1.52 | 1.42 |

† TK parameters were characterized by non-compartmental analysis and derived using median concentration-time profiles obtained using sparse sampling (3 animals/sex/group).
‡ AUClast for ADC = AUC168h for Day 1 and Day 22; AUClast for TAb = AUC168h for Day 1 and AUC336h for Day 22

**Table 18** AGS-22M6 Unconjugated Antibody Serum Toxicokinetic Parameters for Male and Female Rats on Study Days 1 and 22 Following 4-Week Intravenous Administration

| AGS-22M6 Dose | 10 mg/kg | | | |
|---|---|---|---|---|
| Day | 1 | | 22 | |
| Sex | F | M | F | M |
| TK Parameters† | AGS-22M6 | | AGS-22M6 | |
| $AUC_{last}$‡ (µg·h/mL) | 16600 | 15700 | 36000 | 23100 |
| $AUC_{168h}$ (µg·h/mL) | 16600 | 15700 | 21800 | 18700 |
| $C_{max}$ (µg/mL) | 320 | 336 | 370 | 368 |
| tmax (h) | 0.0167 | 0.0167 | 0.0167 | 0.0167 |
| $t_{1/2}$ (day) | 4.66 | 4.62 | NR | NR |

**In monkeys**

The toxicokinetics of AGS-22M6E (HYBRIDOMA ADC) and AGS-22M6 in monkeys were evaluated from GLP-compliant 4-week intravenous dose toxicity study after the first dose and the last dose (Study 20005664).

PK parameters were analysed after administration of 1, 3 or 6 mg/kg AGS-22M6E (HYBRIDOMA ADC) or 6 mg/kg AGS-22M6 or 0.1093/0.0545 mg/kg MMAE (molar equivalent dose of the 6 mg/kg AGS-22M6E (HYBRIDOMA ADC) group) via intravenous infusion 30 min once weekly for 4 doses.

The PK parameters are presented below in the tables 24, 25 and 26.

**Table 19** ADC and TAb Toxicokinetic Parameters Obtained Following First and Last Dose of AGS-22M6E to Cynomolgus Monkeys

| Analyte | | ADC | | | | | | TAb | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AGS-22M6E Dose | | 1 mg/kg | | 3 mg/kg | | 6 mg/kg | | 1 mg/kg | | 3 mg/kg | | 6 mg/kg | |
| Dosing Day | | 1 | 22† | 1 | 22† | 1 | 8† | 1 | 22† | 1 | 22† | 1 | 8† |
| AUC168h (µg·h/mL) | Mean | 634 | 471 | 2450 | 903 | 5080 | 6150 | 1120 | 1070 | 4530 | 1610 | 10200 | 9210 |
| | SD | 73.1 | 264 | 319 | 732 | 573 | 858 | 122 | 689 | 625 | 1220 | 2100 | 2760 |
| | N‡ | 10 | 5 | 10 | 6 | 10 | 7 | 6 | 5 | 10 | 6 | 9 | 3 |
| $AUC_{last}$ (µg·h/mL) | Mean | 631 | 466 | 2430 | 856 | 5050 | 6310 | 1110 | 1060 | 4470 | 1850 | 10400 | 11900 |
| | SD | 72.5 | 266 | 315 | 689 | 567 | 850 | 104 | 687 | 611 | 1290 | 2360 | 3160 |
| | N‡ | 10 | 5 | 10 | 7 | 10 | 7 | 10 | 5 | 10 | 7 | 10 | 7 |
| Cmax (µg/mL) | Mean | 24.6 | 21.2 | 76.6 | 63.7 | 151 | 137 | 30.3 | 29.6 | 94.4 | 106 | 200 | 162 |
| | SD | 2.05 | 5.17 | 7.65 | 16.9 | 16.8 | 24.1 | 3.45 | 7.53 | 12.8 | 59.6 | 33.8 | 21.5 |
| | N‡ | 10 | 5 | 10 | 7 | 10 | 7 | 10 | 5 | 10 | 7 | 10 | 7 |
| t1/2 (day) | Mean | 1.37 | 1.20 | 1.43 | 0.700 | 1.72 | 1.53 | 2.14 | 1.66 | 2.46 | 1.02 | 2.75 | 1.82 |
| | SD | 0.0936 | 0.604 | 0.132 | 0.419 | 0.177 | ND | 0.173 | 1.08 | 0.332 | 0.649 | 0.888 | 0.596 |
| | N‡ | 10 | 5 | 10 | 6 | 10 | 2 | 6 | 5 | 10 | 6 | 9 | 3 |

† Day 8 and day 22 toxicokinetic parameters were from animals with no seroconversion on day of dosing.
‡ Differences in animal numbers between analytes were due to insufficient samples from individual animals for toxicokinetic curve fitting.

**Table 20** MMAE Serum Toxicokinetic Parameters Obtained from Cynomolgus Monkeys Following the First and Last Dose of AGS-22M6E

| AGS-22M6E Dose | | 1 mg/kg | | 3 mg/kg | | 6 mg/kg | |
|---|---|---|---|---|---|---|---|
| Day | | 1 | 22 | 1 | 22 | 1 | 8 |
| AUC168h (pg·h/mL) | Mean | 3710 | 4040 | 11700 | 15000 | 24400 | 24500 |
| | SD | 690 | 917 | 1040 | 2000 | 2990 | 2290 |
| | N | 8 | 7 | 4 | 8 | 4 | 7 |
| $AUC_{last}$ (pg·h/mL) | Mean | 3400 | 3370 | 12000 | 14100 | 23200 | 28900 |
| | SD | 790 | 1400 | 1400 | 3150 | 2600 | 2680 |
| | N | 10 | 10 | 10 | 10 | 10 | 7 |
| Cmax (pg/mL) | Mean | 34.3 | 42.9 | 105 | 226 | 202 | 215 |
| | SD | 5.96 | 6.69 | 12.2 | 142 | 34.2 | 40.0 |
| | N | 10 | 10 | 10 | 10 | 10 | 7 |
| $t_{1/2}$ (day) | Mean | 2.58 | 2.32 | 2.92 | 1.87 | 3.08 | 2.52 |
| | SD | 0.248 | 0.64 | 0.173 | 0.573 | 0.554 | ND |
| | N | 8 | 7 | 4 | 8 | 5 | 1 |

**Table 21** Toxicokinetic Comparison of AGS-22M6 and AGS-22M6E Following the First Intravenous Dose of 6 mg/kg in Cynomolgus Monkeys

| **Test Article** | **AGS-22M6** | **AGS-22M6E** | **AGS-22M6E** |
|---|---|---|---|
| **Analyte** | **Unconjugated Ab** | **ADC** | **TAb** |
| $AUC_{168h}$ (µg·h/mL) | 11800 (1240) | 5080 (573) | 10200 (2100) |
| $AUC_{last}$ (µg·h/mL) | 11500 (1210) | 5050 (567) | 10400 (2360) |
| $C_{max}$ (µg/mL) | 182 (16.7) | 151 (16.8) | 200 (33.8) |
| $t_{1/2}$ (day) | 4.74 (0.611) | 1.72 (0.177) | 2.75 (0.89) |

**Immunogenicity**

Anti-drug antibody (ADA) formation was evaluated in conjunction with the toxicokinetic assessment of exposure in nonclinical studies of AGS-22M6E, AGS-22M6 and enfortumab vedotin (**Table 27** ). In general, the incidence of ATA to AGS-22M6E (HYBRIDOMA ADC) appeared to be higher in cynomolgus monkeys than in rats, and the incidence of ATA to AGS-22M6E (HYBRIDOMA ADC) compared to enfortumab vedotin appeared to be similar in cynomolgus monkeys.

**Table 22** Incidence of ADA by test material, dosing regimen and species

| **Test Material** | **Species** | **Dose Schedule** | **Dose Level (mg/kg)** | **ATA Incidence N/N (%)†** | | | **Report Number** |
|---|---|---|---|---|---|---|---|
| | | | | **Male** | **Female** | **Pooled (M & F)** | |
| AGS-22M6E | Rat | q1wk x 4 | 2 | 5/14 (36) | 5/15 (33) | 10/29 (35) | 20005662 |
| | | q1wk x 4 | 5 | 4/15 (27) | 2/15 (13) | 6/30 (20) | |
| | | q1wk x 4 | 10 | 1/14 (7.1) | 1/15 (6.7) | 2/29 (6.9) | |
| | Cynomolgus monkey | q1wk x 4 | 1 | 3/5 (60) | 2/5 (40) | 5/10 (50) | 20005664 |
| | | q1wk x 4 | 3 | 2/5 (40) | 2/5 (40) | 4/10 (40) | |
| | | q1wk x 2 | 6 | 1/3 (33) | 2/4 (50) | 3/7 (43) | |
| AGS-22M6 | Rat | q1wk x 4 | 10 | 1/15 (6.7) | 2/15 (13) | 3/30 (10) | 20005662 |
| | Cynomolgus monkey | q1wk x 4 | 6 | 0/5 (0.0) | 1/5 (20) | 1/10 (10) | 20005664 |
| AGS-22M6E | Cynomolgus monkey | q1wk x 4 | 3 | 3/5 (60) | 1/5 (20) | 4/10 (40) | 20021751 |
| Enfortumab vedotin | Cynomolgus monkey | q1wk x 4 | 3 | 2/5 (40) | 2/5 (40) | 4/10 (40) | |

† Number of positive animals out of a total number of animals in the group (percent of animals with positive ATA results).
Source: Study 20005662, Table 13; Study 20005664, Table 25; Study 20021751, Table 4

**Distribution**

No distribution studies have been conducted with AGS-22M6E (HYBRIDOMA ADC) or enfortumab vedotin.

The distribution of MMAE was assessed by determination of in vitro plasma protein binding, blood cell partitioning and 3H-MMAE distribution in rats.

**Tissue Distribution via Quantitative Whole-Body Autoradiography in Male Long-Evans Rats Following a Single Intravenous Bolus Administration of 3H-MMAE**

3H-MMAE-derived radioactivity in Long-Evans rats was well distributed and most tissues had concentrations that were higher than blood from 0.17 hours through 24 hours postdose. The highest overall concentrations were observed in bile (1.476 μg eq./g at 0.17 hours), the contents of the alimentary canal (Cmax ranged from 0.019 μg eq./g in stomach contents at 24 hours to 0.975 μg eq./g in large intestine contents at 12 hours) and urinary bladder (0.369 μg eq./g at 4 hours).

Concentrations of > 0.20 μg eq./g at Cmax were found in anterior pituitary gland, lung, kidney cortex and kidney medulla. Elimination of radioactivity from most tissues was observed at 96 hours postdose, except for thymus, anterior and posterior pituitary glands and eye uveal tract, which were 0.013, 0.006, 0.005 and 0.009 μg eq./g, respectively.

The observed 3H-exchange in the plasma may have an effect on the interpretation of the tissue distribution data, especially after 4 hours postdose. There was approximately 10% in vivo 3H-exchange in plasma observed at 0.17 hours, and the extent of 3H-exchange increased to approximately 36% at 4 hours, 49% at 12 hours, 73% at 24 hours, and 96% at 96 hours.

**Plasma Protein Binding Assay of MMAE by Ultracentrifugation**

The plasma protein binding of MMAE in mouse, rat, monkey and human was assessed by evaluation of the *in vitro* plasma protein binding ratios. [3H]-MMAE was added to mouse, rat, monkey and human plasma at 3 concentrations (1 nmol/L, 10 nmol/L and 100 nmol/L), and the mixtures were ultracentrifuged. Radioactivity in plasma and supernatant was measured by liquid scintillation counting and the plasma protein binding ratio was calculated.

The protein binding ratios in mouse, rat, monkey and human plasma are tabulated below [3H]- MMAE, exhibits species dependent plasma protein binding and binding exhibits minimal dependence on [3H]-MMAE concentration over the range of 1 – 100 nmol/L.

| Species | 1 nmol/L | 10 nmol/L | 100 nmol/L |
|---|---|---|---|
| Mouse | 18.8% | 19.6% | 28.5% |
| Rat | 72.9% | 73.5% | 72.0% |
| Monkey | 17.1% | 17.8% | 18.9% |
| Human | 67.9% | 77.5% | 82.2% |

An in vitro study was conducted to evaluate the red blood cell (RBC) partitioning potential of MMAE in mice, rats, cynomolgus monkeys and humans. The blood to plasma concentration ratios of MMAE were 9.47 to 11.8 in mice, 1.86 to 2.36 in rats, 1.40 to 1.57 in cynomolgus monkeys and 0.926 to 0.976 in humans at 2 and 20 nmol/L (clinically relevant concentrations). The RBC partitioning was inversely concentration dependent at concentrations less than 1000 nmol/L in mouse, rat and cynomolgus monkey, whereas in human, no significant concentration dependency was observed.

## Metabolism

Traditional metabolism studies were not performed for the antibody component, AGS-22C3, which is expected to be catabolized into small peptides and amino acids, and to be excreted or recycled by the body.

Metabolism studies with 3H-MMAE were performed using both cultured hepatocytes and liver microsomes *in vitro* model systems. Hepatocytes were employed for metabolite identification study, while the microsomal systems were used for reaction phenotyping. Key findings from these studies

showed *in vitro* metabolism of MMAE in human hepatocytes generated the same metabolites observed in rat and cynomolgus monkey in vitro assays and MMAE is a CYP3A4 substrate.

***In vitro* metabolite profiling**

**MMAE (Study XT084007, non-GLP)** - **Cross-Species Metabolism**

A non-GLP study was conducted to determine *in vitro* metabolic profile of $^{3}$H-MMAE at 10 µmol/L following incubation with cryopreserved Sprague-Dawley rat, Cynomolgus monkey and human hepatocytes. The substrate loss data suggest that the initial rate and overall extent of $^{3}$H-MMAE metabolism by hepatocytes were comparable for all three species. A substrate loss of 32, 18 and 32% was observed over the 240-min incubation period with rat, monkey and human hepatocytes, respectively. Mass spectrometry analysis of the samples proposes formation of metabolites by hydroxylation, demethylation, dehydrogenation or hydrolysis. All metabolites detected in human hepatocytes were also detected in rat and/or cynomolgus monkey hepatocytes.

**Table 23** Metabolites detected *in vitro* in animal species and in human

| XT metabolite assignment | *m/z* | Change in mass (amu) from Parent | Proposed transformation from MMAE | Rat | Monkey | Human |
|---|---|---|---|---|---|---|
| C1 | 734 | +16 | Hydroxylation | + | + | ND |
| C2 | 734 | +16 | Hydroxylation | ND | + | ND |
| C3 | 734 | +16 | Hydroxylation | + | + | + |
| C4 | 704 | −14 | *O*-Demethylation | + | + | + |
| C5 | 605 | −113 | Amide hydrolysis | + | + | + |
| C6 | 734 | +16 | Hydroxylation | + | + | + |
| C7 | 704 | −14 | *N*-Demethylation | + | + | + |
| C8 | 716 | −2 | Oxidation of alcohol to form a ketone | + | + | + |
| C9 | 734 | +16 | Hydroxylation | + | + | + |
| C10 | 718 | +0 | *N*-demethylation + hydroxylation to form a nitroso compound | + | + | + |
| C11 | 734 | +16 | Hydroxylation | ND | + | ND |
| C12 | 716 | −2 | Oxidation of alcohol to form a carbonyl (following formation of the nitroso compound) | ND | + | + |
| Parent | 718 | +0 | - | + | + | + |

\+ Peak detected
ND Not detected

***Reaction Phenotyping - Human CYP Enzymes Involved in the In Vitro Metabolism***

**MMAE (Study XT084006, non-GLP)**

$^{3}$H-MMAE was converted to eight radioactive components by NADPH-fortified human liver microsomes, the major components being 7.0, 8.6 and 11.1. These components are proposed metabolites formed by O-demethylation (−14 amu), N-demethylation (−14 amu) and dehydrogenation (−2 amu), respectively. The formation of these major components by human liver microsomes was primarily mediated by CYP3A4 as determined by correlation analysis, experiments with recombinant human CYP enzymes and experiments with CYP-selective inhibitors. Additional CYP enzymes (e.g., CYP2D6) may be minor contributors to the formation of these components, and carbonyl reductases may conceivably contribute to the formation of component 11.1

***In vivo***

**MMAE in rats (study 420501, GLP) - Excretion, Mass Balance and Pharmacokinetics**

Metabolite profiling in urine and feces was conducted after intravenous administration of $^{3}$H-MMAE at 0.056 mg/kg (GLP). The radioactive species in urine and feces were determined using an HPLC radiometric/UV detection method and metabolites identified by LC-MS/MS. The primary molecular species excreted in feces and urine in animals dosed with $^{3}$H-MMAE was identified as unchanged 3H-MMAE. In feces, in addition to $^{3}$H-MMAE, a second radiolabeled molecular species was observed and identified by LC-MS/MS as dolaproline O-desmethyl-MMAE, a metabolite of the parent drug.

In urine, additional metabolites were observed, but no attempt was made to identify them by LC-MS/MS because of their low abundance.

**Comparison of MMAE metabolism between rat species and human (study CPH-SGN35-001)**

A clinical evaluation of the metabolism of MMAE in humans following a single intravenous dose of brentuximab vedotin (ADCETRIS, MAA in 2012) was performed with the excretion (urine and feces) samples collected. Patients with CD30-positive hematologic malignancies were treated with 1.8 mg/kg of brentuximab vedotin. Urine and feces were collected daily for 7 days post dose. Urine and feces were analyzed for MMAE metabolites by HPLC-MS/MS. Multiple minor metabolites were identified in urine and feces, presented in table 20.

**Table 24** *In vivo* MMAE metabolite profile in human following Brentuximab Vedotin dosing and rat following MMAE dosing

| Metabolite Designation | *m/z* | Change in Mass (amu) from Parent | Proposed Transformation from MMAE | Human Urine | Human Feces | Rat Feces |
|---|---|---|---|---|---|---|
| C1 | 734 | +16 | Hydroxylation | | | |
| C2 | 734 | +16 | Hydroxylation | | | |
| C3 | 734 | +16 | Hydroxylation | | | |
| C4 | 704 | −14 | *O*-Demethylation | | + | + |
| C5 | 605 | −113 | Amide hydrolysis | + | + | |
| C6 | 734 | +16 | Hydroxylation | + | | |
| C7 | 704 | −14 | *N*-Demethylation | + | | |
| C8 | 716 | −2 | Oxidation of alcohol to form a carbonyl | + | + | |
| C9 | 734 | +16 | Hydroxylation | | | |
| C10 | 718 | +0 | *N*-demethylation + hydroxylation to form a nitroso compound | + | | |
| C11 | 734 | +16 | Hydroxylation | | | |
| C12 | 716 | −2 | Oxidation of alcohol to form a carbonyl (following formation of the nitroso compound) | + | | |
| C13 | 702 | -16 | *O*-demethylation and oxidation of alcohol to form a carbonyl | + | + | |
| Parent | 718 | +0 | – | + | + | + |

**Excretion**

An excretion study was performed in rats following a single intravenous dose of 3H-MMAE. No other nonclinical excretion studies have been performed. The major route of elimination in rats dosed with $^{3}$H-MMAE was via feces.

**MMAE in rats (study 420501, GLP) - Excretion, Mass Balance and Pharmacokinetics**

Excretion was studied in urine and feces after intravenous administration of $^{3}$H-MMAE at 0.056 mg/kg in rats. The concentrations of radioactivity in blood, plasma, urine, feces and carcass were determined by liquid scintillation counting method. The major route of elimination in animals dosed with $^{3}$H-MMAE was via feces. For $^{3}$H-MMAE, mass balance was achieved with approximately 112% recovery of radioactivity in male and female rats. The majority of the radioactivity was recovered in feces for both male and female rats.

**Table 25** Excretion of radioactive material following single IV administration of [$^{3}$H]MMAE to rats

| Sex | Route | Percentage (SD) of Administered Dose†‡ | | | |
|---|---|---|---|---|---|
| | | Urine | Feces | Carcass | Total§ |
| Male | iv | 15.1 (1.2) | 96.7 (1.8) | 0 | 112.1 (1.2) |
| Female | iv | 9.4 (0.6) | 101.8 (1.9) | 0 | 111.5 (1.5) |

3H-MMAE: tritiated monomethyl auristatin E.
† Values represent mean percentage (SD) (n = 4 animals per timepoint).
‡ Excretion was determined over 672 hours in Sprague-Dawley rats.
§ Total includes radioactivity in cage washes.

**Excretion into milk**

Studies of enfortumab vedotin excretion in milk were not performed. Therefore, it is not known whether enfortumab vedotin or the active moiety SGD-1010 (MMAE)is excreted in human milk.

**Pharmacokinetic drug interactions**

The potential of MMAE to cause metabolic drug interactions has been assessed in vitro. In human hepatocytes, MMAE is not an inducer of CYP1A2, 2B6 and 3A4/5. MMAE was a moderate time-dependent inhibitor of CYP3A4/5 and a relatively weak reversible inhibitor of CYP3A4/5. In humans, the mean Cmax of MMAE following weekly administration of enfortumab vedotin at 1.25 mg/kg was approximately 5.2 nmol/L or 3.7 ng/mL [Study EV-201] (data cutoff date: 01 Mar 2019), which is approximately 3 orders of magnitude lower than the half maximal inhibitory concentration (IC50) for CYP3A4/5. MMAE is a substrate of P-gp but not a substrate of other transporters tested. MMAE is not an inhibitor of any of the transporters tested at clinically relevant concentrations.

Based on in vitro and in vivo metabolism studies, the predominant clearance pathway of MMAE in humans was likely via biliary/fecal excretion of intact parent molecule with limited CYP3A4/5-mediated metabolism. MMAE was identified as a CYP3A4 substrate.

**In Vitro Evaluation of MMAE as an Inducer of Cytochrome P450 Expression in Cultured Human Hepatocytes**

A non-GLP in vitro study was conducted to assess the potential of MMAE for CYP induction in cultured human hepatocytes from 3 donors. Hepatocytes were treated once daily for 3 consecutive days with MMAE at 4 concentrations (1, 10, 100 and 1000 nmol/L). Under the conditions of this study, treatment

of cultured human hepatocytes with up to 1000 nmol/L MMAE caused little or no increase in CYP1A2, 2B6 and 3A4/5 metabolic activity. In addition, MMAE did not cause any increase in CYP1A2, 2B6 and 3A4 messenger RNA levels or Western immunoblot protein levels. However, treatment of MMAE at the higher concentrations (100 and 1000 nmol/L) caused decreases in CYP1A2, 2B6 and 3A4/5 metabolic activity, messenger RNA levels or Western immunoblot protein levels from all three hepatocyte preparations tested.

***In Vitro* Evaluation of MMAE as an Inhibitor of Human Cytochrome P450 Enzymes**

To evaluate MMAE as a direct inhibitor of CYP activity, human liver microsomes from a pool of 16 individuals were incubated with marker substrates, at concentrations approximately equal to their apparent concentration of substrate that leads to half-maximal reaction velocity, in the presence or absence of MMAE at concentrations ranging from 0.1 to 100 $\mu$mol/L. MMAE caused little or no direct inhibition of CYP1A2, 2B6, 2C8, 2C9, 2C19 or 2D6. MMAE did exhibit direct inhibition of CYP3A4/5 as measured by midazolam 1´-hydroxylation with an IC50 value of 10 $\mu$mol/L, but did not inhibit CYP3A4/5 when measured by testosterone 6$\beta$-hydroxylation. MMAE also caused time-dependent inhibition of CYP3A4/5 as measured by both testosterone 6$\beta$-hydroxylation and midazolam 1´-hydroxylation.

***In vitro* Interaction Studies of MMAE with human BCRP, BSEP and MRP2 Efflux (ABC) Transporters, and with human OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2 Uptake Transporters**

A non-GLP in vitro assay was conducted to characterize the interaction of MMAE with the human efflux transporters BCRP, BSEP and MRP2 using vesicular transport system, and the human uptake transporters OAT1, OAT3,OATP1B1, OATP1B3, OCT1 and OCT2 using CHO or HEK293 cells. MMAE did not influence the transporter-mediated probe substrate accumulation in the tested concentration range (from 0.008 to 5 $\mu$mol/L) for BCRP, BSEP and MRP2 assays. MMAE inhibited the OCT1- and OCT2-mediated metformin transport at 5 $\mu$mol/L (the highest tested concentration) by 29% and 23%, respectively; however, MMAE did not influence the OAT1-, OAT3-, OATP1B1- or OATP1B3-mediated probe substrate accumulation up to the highest tested concentration of 5 $\mu$mol/L.

## 2.3.4. Toxicology

### *Single dose toxicity*

Rats and cynomolgus monkeys were selected as the nonclinical test species based on equivalent binding affinities of the ADC to rat, cynomolgus monkey and human Nectin-4.

Single dose toxicity studies were not performed.

### *Repeat dose toxicity*

Enfortumab vedotin and AGS-22M6E are cross-reactive in the rat and cynomolgus monkey with equivalent binding affinity to human Nectin-4. Repeat dose toxicity studies were performed in both species. In general, similar toxicity profiles were observed across species and therefore only the rat was studied in the chronic (13-week) repeat dose toxicity study (please refer to ICH S6, S9, S9 Q&A). The intravenous administration route and weekly dosing schedule were chosen to support the proposed clinical route and dose regimen.

The toxicity of MMAE and the unconjugated antibody, AGS-22M6, were studied in a 4-week repeat dose study in the cynomolgus monkey, with the unconjugated antibody also studied in a 4-week repeat dose study in the rat.

**A 4-Week Toxicity Study of AGS-22M6E (HYBRIDOMA ADC) and AGS-22M6 Administered by Intravenous Injection to Sprague-Dawley Rats, with a 6-Week Recovery Period (study 20005662)**

**Table 26** A 4-Week Toxicity Study of AGS-22M6E (HYBRIDOMA ADC) and AGS-22M6 Administered by Intravenous Injection to Sprague-Dawley Rats, with a 6-Week Recovery Period (study 20005662)

| Group No. | No. of Animals | | | | Test Material | Dose Level (mg/kg/dose) | Dose Concentration (mg/mL) | Dose Volume (mL/kg/dose) |
|---|---|---|---|---|---|---|---|---|
| | Main Study (Necropsy Day 29) | | Recovery (Necropsy Day 64) | | | | | |
| | Male | Female | Male | Female | | | | |
| 1 | 10 | 10 | 5 | 5 | Vehicle | 0 | 0 | 5 |
| 2 | 10 | 10 | 5 | 5 | AGS-22M6E | 2.0 | 0.4 | 5 |
| 3 | 10 | 10 | 5 | 5 | AGS-22M6E | 5 | 1.0 | 5 |
| 4 | 9[a] | 10 | 5 | 5 | AGS-22M6E | 10 | 2.0 | 5 |
| 5 | 10 | 10 | 5 | 5 | AGS-22M6 | 10 | 2.0 | 5 |
| Toxicokinetics | | | | | | | | |
| | Release from the Study Day 64 | | | | | | | |
| | Male | | Female | | | | | |
| 6 | 3 | | 3 | | Vehicle | 0 | 0 | 5 |
| 7 | 9 | | 8[a] | | AGS-22M6E | 2.0 | 0.4 | 5 |
| 8 | 9 | | 9 | | AGS-22M6E | 5 | 1.0 | 5 |
| 9 | 9 | | 9 | | AGS-22M6E | 10 | 2.0 | 5 |
| 10 | 9 | | 9 | | AGS-22M6 | 10 | 2.0 | 5 |

[a] Animal 4012 was found dead on Day 27; TK Animal 7504 was found dead on Day 3 immediately after blood collection.

AGS-22M6E at 10 mg/kg/dose resulted in one early death on Day 27.

AGS-22M6E-related changes in clinical observations included slight skin abrasions in the majority of 5 mg/kg-dosed animals, slight to moderate skin abrasion/sores in all 10 mg/kg-dosed animals and urine staining in individual 10 mg/kg dosed animals. Body weight gain was moderately decreased in 10-mg/kg-dosed males and the average food consumption was minimally lower in 10-mg/kg-dosed males between weeks 3-4. There were no AGS-22M6E-related clinical observations or changes in food consumption in recovery animals. AGS-22M6E-related changes in hematology parameters occurred in Groups 3 (5 mg/kg/dose) and 4 (10 mg/kg/dose) animals and included decreased indicators of red cell mass (RBC, hemoglobin concentration and hematocrit), and increased MCV, RDW, MCH and reticulocyte counts at Days 16 and 29. There was a higher incidence of abnormal red blood cell shape including slight spherocytes, schistocytes, and acanthocytes in 10 mg/kg-dosed animals.

AGS-22M6E-related changes in clinical chemistry parameters included increases in ALT, AST, ALP, and GGT levels in individual animals dosed at 5 and 10 mg/kg. In addition, albumin concentration (and total protein) was decreased in 10 mg/kg-dosed animals. At the end of the dose-free period (Day 64), all of the red blood cell parameters were substantially recovered (i.e., comparable to control) except RBC and MCV in males that had been dosed at 5 mg/kg and in males and females that had been dosed at 10 mg/kg. Also in Group 4, RDW (males only) and MCH were minimally increased. These residual

changes are biologically inconsequential. Other hematology parameters had completely recovered on Day 64.

**A 4-Week Toxicity Study of AGS-22M6E and AGS-22M6 Administered by Intravenous Infusion to Cynomolgus Monkeys, with a 6-Week Recovery Period (study 20005664)**

**Table 27** Study 20005664

| Group No. | No. of Animals | | | | Test Material | Dose Level (mg/kg/dose) | Dose Concentration (mg/mL) | Dose Volume (mL/kg/dose) |
|---|---|---|---|---|---|---|---|---|
| | Main Study (Necropsy Day 29) | | Recovery (Necropsy Day 63) | | | | | |
| | Male | Female | Male | Female | | | | |
| 1 | 3 | 3 | 2 | 2 | Vehicle | 0 | 0 | 5 |
| 2 | 3 | 3 | 2 | 2 | AGS-22M6E | 1 | 0.2 | 5 |
| 3 | 3 | 3 | 2 | 2 | AGS-22M6E | 3 | 0.6 | 5 |
| 4 | 3[a] | 3[a] | 2[a] | 2[a] | AGS-22M6E | 6 | 1.2 | 5 |
| 5 | 3 | 3 | 2 | 2 | AGS-22M6 | 6 | 1.2 | 5 |
| 6 | 3[b] | 3[b] | 2 | 2 | MMAE | 0.1093/0.0545[c] | 0.0218[c] | 5.0/2.5[c] |

Administration of 6 mg/kg/dose AGS-22M6E was associated with moribundity after the 2nd weekly dose resulting in the unscheduled euthanasia of 3 animals on study Days 11-13. Administration of 0.1093 mg/kg MMAE on Days 1 and 8 and 0.0545 mg/kg MMAE on Days 15 and 22 resulted in 1 unscheduled euthanasia (Animal No. 6503) on Day 19. One MMAE treated animal was found dead on Day 13.

Administration of **3 mg/kg/dose AGS-22M6E** did result in abrasions and dry/reddened skin, decreased reticulocyte count as compared to concurrent controls on Day 8 and on Day 15 (females only); decreased red cell parameters in females only on Days 15, 22, and 29; decreased neutrophils on Days 15 and 22; decreased eosinophils on Days 22 and 29; microscopic injection site lesions (mild mononuclear cell dermal inflammation and marked non-septic vascular thrombus) noted in 1 female, and mild thymic atrophy in 2 females.

Administration of **6 mg/kg/dose AGS-22M6E** on Days 1 and 8 resulted in the unscheduled euthanasia of 3 animals on Days 11-13 due to severe dry skin/reddened skin and abrasions occurring over the entire body and around the eyes.

Other test article-related findings included hematology changes (reduced reticulocyte and leukocyte counts) consistent with bone marrow toxicity. Reticulocyte counts were decreased on Days 8 and 15(males only) in spite of reduced red cell mass. Leukocyte counts were decreased on Day 8 (total leukocyte, neutrophil, lymphocyte, monocyte and eosinophil counts) but these changes showed partial recovery by Day 15 after dose discontinuation. In addition, these animals had clinical pathology changes consistent with an acute phase response (decreased albumin and increased globulin and fibrinogen) and increased potassium. Microscopic findings in the animals euthanized early included injection site lesions characterized by inflammation and/or hemorrhage in the dermis and perivascular area, mild subcutaneous degeneration of the veins and moderate erosion of the epidermis; ulceration, inflammation and hyperkeratosis of the skin; and thymic atrophy, possibly related to the general health condition of the animals

Administration of **0.1093 mg/kg MMAE** on Days 1 and 8 and 0.0545 mg/kg MMAE on Days 15 and 22 resulted in 1 unscheduled euthanasia due to a large patch of skin missing near the buttocks that could not be surgically repaired. Other test article-related effects from animals in this dose group were

similar to those noted for animals dosed with 6 mg/kg/dose AGS-22M6E with the exception that the dry/reddened skin and abrasions were largely not detected, but low food consumption and watery feces were. Clinical pathology changes from these animals were similar to those noted for AGS-22M6E-dosed animals and included changes consistent with bone marrow toxicity (decreased reticulocyte counts in spite of reduced red cell mass and reduction in leukocyte counts) on Day 8 with at least a partial recovery for most of these effects on Day 15, with a reduction in dose level beginning on this day

Based on these results, the AGS-22M6E NOAEL was 3 mg/kg/day (Cmax of 76.6 µg/mL, AUC(0-168h) of 2450 µg·h/mL on Day 1).

**A 4-Week Study of AGS-22M6E and AGS-22C3E by Intravenous Infusion Administration in Cynomolgus Monkeys with a 6-Week Recovery Period (study 20021751)**

The objectives of the study were to compare toxicologic and toxicokinetic properties of AGS-22M6E and AGS-22C3E, hybridoma and CHO-derived versions of the same product, when given at the same dose by weekly intravenous infusion for 4 weeks to cynomolgus monkeys.

**Table 28** Study 20021751

| Group No. | No. of Animals[a] | | | | Test Material | Dose Level (mg/kg/dose) | Dose Concentration (mg/mL) | Dose Volume (mL/kg/dose) |
|---|---|---|---|---|---|---|---|---|
| | Main Study | | Recovery | | | | | |
| | Male | Female | Male | Female | | | | |
| 1 | 2 | 2 | 0 | 0 | Control | 0 | 0 | 5 |
| 2 | 3 | 3 | 2 | 2 | AGS-22M6E | 3 | 0.6 | 5 |
| 3 | 3 | 3 | 2 | 2 | AGS-22C3E | 3 | 0.6 | 5 |

[a] Main study animals were euthanized Day 29. Recovery animals were euthanized Day 71.

All test article-related effects were noted in both AGS-22M6E and AGS-22C3E-dosed animals. Test article-related effects considered biologically significant included dry skin, reddened areas of skin, minimally decreased erythrocyte mass (red blood cell, hemoglobin, and hematocrit count), reticulocytes, neutrophils, and eosinophil counts, and microscopic findings in bone marrow, injection site, and skin.

The primary analysis for comparability was based on calculation of area under the concentration-time curve from time 0 to 7 days (AUC0-7) and Cmax after the first dose for AGS-22M6E and AGS-22C3EF. The 90% confidence intervals (CI) of the geometric mean ratios (GMR) for AUC0−7 and Cmax of ADC after the first dose were within the pre-specified comparability criteria (0.7−1.43) and therefore toxicokinetics of the two materials, AGS-22M6E and AGS-22C3E were considered to be comparable.(Table 34)

**Table 29** Point estimated and 90% confidence intervals of the geometric mean ratios for AUC0−7 and Cmax between AGS-22M6E and AGS-22C3E

| | No. of animals | $AUC_{\tau(0-7)}$ (day*µg/mL) | $C_{max}$ (µg/mL) |
|---|---|---|---|
| AGS-22M6E | 10 | 108 ± 8.11 | 77.9 ± 8.40 |
| AGS-22C3E | 10 | 125 ± 23.5 | 98.0 ± 8.96 |
| GMR [a] | - | 1.14 | 1.26 |
| 90% CI of the GMR | - | 1.02-1.28 | 1.17-1.36 |

$AUC_{0-7}$ = area under the concentration–time curve from zero to 7 days; $C_{max}$ = maximum serum concentration; CI = confidence interval; GMR = geometric mean ratio. $AUC_{\tau(0-7)}$ and $C_{max}$ are presented as Mean ± Standard deviation.
[a] Ratio of test material (AGS-22C3E) to reference material (AGS-22M6E).

Maximum serum AGS-22 concentrations for both antibody drug conjugates (ADC) were generally attained at the end of the IV infusion and showed a bi-exponential decline thereafter. Serum AGS-22 concentrations determined with the total antibody (TAb) ELISA were generally higher than the ADC concentrations. There were no sex-related differences observed in the toxicokinetic characteristics for ADC, TAb and small molecule metabolite for both ADC.

Maximum Monomethyl auristatin E (MMAE) metabolite concentration (Cmax) for both ADCs was attained between 24-72 hours post AGS-22 dose injection. The elimination half-life (T½ λz) for MMAE after administration of AGS-22M6E and AGS-22C3E was calculated as 4.31 days and 3.54 days, respectively.

**A GLP 3-Month Intravenous Toxicity Study of Enfortumab Vedotin in Sprague Dawley Rats**

Eighty main study (10/sex/Groups 1 through 4) and 54 toxicokinetic satellite Sprague Dawley rats (9/sex/Groups 5 through 7) were administered either control article (5% [w/v] sterile dextrose solution) or Enfortumab Vedotin as a once weekly IV bolus injection for 13 total doses (i.e., dosing on Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, and 85) at dose levels of 0.5, 2.0, and 5.0 mg/kg/dose. The dosing concentration was 1.0 mg/mL for all groups, and the dose volume was adjusted to achieve the intended dose levels. Animals were observed for 13 weeks following the first dose, with scheduled necropsy on Day 92 for all main study animals.

**Table 30** A GLP 3-Month Intravenous Toxicity Study of Enfortumab Vedotin in Sprague Dawley Rats

| Group No. | Test Material | Dose Level (mg/kg/dose) | Dose Volume (mL/kg) | Dose Concentration (mg/mL) | No. of Animals Main Study | |
|---|---|---|---|---|---|---|
| | | | | | Males | Females |
| 1 | Control | 0 | 5 | 0 | 10 | 10 |
| 2 | Enfortumab Vedotin | 0.5 | 0.5 | 1.0 | 10 | 10 |
| 3 | Enfortumab Vedotin | 2 | 2.0 | 1.0 | 10 | 10 |
| 4 | Enfortumab Vedotin | 5 | 5 | 1.0 | 10 | 10 |
| Toxicokinetics | | | | | | |
| 5 | Enfortumab Vedotin | 0.5 | 0.5 | 1.0 | 9 | 9 |
| 6 | Enfortumab Vedotin | 2 | 2.0 | 1.0 | 9 | 9 |
| 7 | Enfortumab Vedotin | 5 | 5 | 1.0 | 9 | 9 |

Study endpoints included morbidity and mortality assessment, clinical observations (including quantitative food consumption), body weights and body weight gain, ophthalmic exams, clinical pathology (hematology, clinical chemistry, coagulation, and urinalysis), blood collection for bioanalysis, toxicokinetic (TK), and anti-therapeutic antibody (ATA) evaluations, and pathology evaluation (gross necropsy findings, organ weights, and histopathologic examinations).

There were no Enfortumab Vedotin-related deaths. Definitive Enfortumab Vedotin-related clinical observations were limited to abrasions at 5 mg/kg/dose.

**Table 31** Enfortumab Vedotin-related Increased Incidence/Frequency of Abrasions

| Enfortumab Vedotin-related Increased Incidence/Frequency of Abrasions | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Male Dose (mg/kg/dose) | | | | Female Dose (mg/kg/dose) | | | |
| | 0 | 0.5 | 2.0 | 5.0 | 0 | 0.5 | 2.0 | 5.0 |
| Incidence of abrasions (n = 10) | 1 | 4 | 0 | 3 | 2 | 2 | 2 | 2 |
| Frequency of abrasions | 8 | 65 | 0 | 138 | 18 | 33 | 14 | 88 |

There were Enfortumab Vedotin-related changes in hematology and clinical chemistry parameters, most notably at 5 mg/kg/dose. Changes in hematology parameters consisted of decreased RBC mass (red blood cell count, hemoglobin, and hematocrit) for males at 5 mg/kg/dose and females at ≥ 0.5 mg/kg/dose, associated with minimally to mildly increased reticulocytes, mean corpuscular volume (males only), mean corpuscular hemoglobin (males only), and red cell distribution width at 5 mg/kg/dose, and minimally to mildly increased platelets at ≥ 2 mg/kg/dose. Changes in clinical chemistry parameters included minimally to mildly increased alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma glutamyltransferase (1 male), and bilirubin at 5 mg/kg/dose, in addition to minimally decreased albumin (females only) and albumin:globulin ratio and increased globulins at 5 mg/kg/dose. On Day 92, macroscopic changes included small and/or soft testes (microscopic degeneration/atrophy) at ≥ 2 mg/kg/dose that correlated with decreased absolute and relative testis weights. Secondary to Enfortumab Vedotin-related testicular degeneration/atrophy, cell debris, and reduced sperm were present in the epididymis at ≥ 2 mg/kg/dose. Other target organs of toxicity were identified including testis (≥ 2 mg/kg/dose), epididymis (≥ 2 mg/kg/dose), mammary gland (≥ 2 mg/kg/dose), eye (≥ 0.5 mg/kg/dose), harderian gland (5 mg/kg/dose), IV administration site (≥ 0.5 mg/kg/dose), and skin (5 mg/kg/dose). The primary histology findings in these tissues were abnormal mitotic indices, single cell necrosis, and/or degeneration/atrophy.

## *Genotoxicity*

Genotoxicity studies (table 37 below) were performed on the cytotoxic agent, MMAE. MMAE had no discernible *in vitro* genotoxic potential in a reverse mutation test in bacteria (Ames test) or in a L5178Y thymidine kinase+/- mouse lymphoma mutation assay. On the contrary, MMAE was aneugenic in the in vivo rat bone marrow micronucleus study, consistent with the pharmacological effect of MMAE on the mitotic apparatus (disruption of the microtubular network).

The linker portion of enfortumab vedotin is composed of maleimide, a caproyl spacer, vc dipeptide, and p-aminobenzyloxy carbonyl. The genotoxic potential of the linker molecule was assessed based on publically available data and by an in silico analysis. Maleimide is reported as being mutagenic in both the bacterial reverse mutation assay and the L5178Y thymidine kinase (TK)+/- mouse lymphoma forward mutation assay [TOXNET Toxicology Data Network; search term: maleimide] while caproic acid was negative in the bacterial reverse mutation assay [TOXNET Toxicology Data Network; search term: caproic acid]. In silico assessments of the valine, citrulline and the p-aminobenzyloxy carbonyl group by DEREK for Windows (version 12) indicated no structure alert for mutagenic potential with either moiety.

**Table 32** Overview of genotoxicity studies performed

| Type of test/study ID/GLP | Test system | Concentrations/ Concentration range/ Metabolising system | Results |
|---|---|---|---|
| **MMAE** | | | |
| Gene mutations in bacteria<br>GLP<br>AA66EH.503.BTL | S.typhinurium TA98, TA100, TA1535 and TA1537<br>E.coli WP2 uvrA | MMA<br>(batch n°RIL-B-114(8))<br>Solvent: DMSO<br>75, 200, 600,<br>1800, and 5000 µg<br>+/- S9 | NEGATIVE |
| *In Vitro* Mammalian Cell Gene Mutation Test (Mouse Lymphoma Assay)<br>GLP<br>8204-155 | L5178Y/TK+/- | MMAE<br>(batch n°2002E)<br>Solvent: 0.9% saline<br>Up to 15 ng/mL with S9<br>Up to 70 ng/mL with S9 | NEGATIVE |

| | | | |
|---|---|---|---|
| *in vivo* bone marrow micronucleus test<br>Rat<br>GLP<br>8204-151 | Rat, micronuclei in bone marrow<br><br>CD male rat (8 wk old) | MMAE<br>batch n°2002E)<br>single bolus iv injection<br>24h: 0.01, 0.1, 0.2 mg/kg<br>max tolerated dose<br><br>48h 0.2 mg/kg<br><br>Confirmatory assay (24h):<br>0.1 and 0.2 mg/kg<br>(kinetochore analysis) | **POSITIVE**<br><br>0.1 and 0.2 mg/kg (24 and 48h): increase in micronucleated PCE (first and confirmatory assay<br>0.2 mg/kg cytotoxicity<br><br>MoA: aneugenic mechanism (60-76% centromere +)<br><br>No TK analysis |

## *Carcinogenicity*

In accordance with ICH S9, carcinogenicity studies were not conducted as enfortumab vedotin is intended for the treatment of patients with late stage and advanced cancer

*Reproduction Toxicity*

In accordance with ICH S9, the embryo-fetal toxicity of enfortumab vedotin was assessed. Taking into account the intended patient population, studies of fertility and early embryonic development and of pre-/post-natal development were not conducted.

**Table 33** Overview of embryofetal-development studies

| Study type/ Study ID / GLP | Species; Number | Test article | Dose (mg/kg) | Dosing period | Major findings | NOAEL (mg/kg ) |
|---|---|---|---|---|---|---|
| EFD / 20119695<br>GLP | Rat<br>6 F / group | Enfortumab vedotin | 0,<br>2.0, 5.0 | q3d x5<br>GD6 – 13<br><br>q7d x 2<br>GD6, 13 | Total litter loss at 5.0mg/kg,<br>Increased post implantation loss at 2.0mg/kg | Not identified |
| EFD / 8204397 /GLP | Rat,<br>25 F main +<br>9 TK / group | SGN-35 | 0, 0.3, 1, 3, 10 | q7d x 2<br>GD6, 13 | Embryo-fetal lethality at > 1 mg/kg SGN-35 | F0 = 1 mg/kg<br>F1 = 1 mg/kg |
| | | SGD-1010 | 0.2 | | | ND |

ND = Not determined

**Fertility and early embryonic development**

Dedicated fertility and early embryonic development studies were not conducted in accordance with ICH S9.

Testicular toxicity of Enfortumab Vedotin was observed in rats on day 29 of the 4-week repeat dose study and on day 92 of the 13-week repeat dose study. Changes in the testes were noted at ≥2 mg/kg per dose in the 4-week study and the 13-week repeat dose rat study. Decreases in male reproductive organ (testes, epididymis, prostate, seminal vesicle) weights correlated with histological findings of tubular epithelial degenerations, abnormal spermatids and hypospermia. These findings were partially reversible at the end of a 24-week recovery period. These findings are consistent with the pharmacologic action of microtubule disrupting agents and have been reported with other MMAE containing ADCs.

**Embryo-foetal development**

The effect of enfortumab vedotin on embryo-foetal development was assessed in rats in 2 studies, a pivotal Study with SGN-35 and SGD-1010 (MMAE) and a Study of enfortumab vedotin by intravenous injection in rats.

**Repeat-dose IV embryo-foetal development study of SGN-35 and SGD-1010 (MMAE)in pregnant rats (8204937):**

Embryo-foetal development toxicity of SGN-35 and SGD-1010 (MMAE)was evaluated in a GLP-compliant study. Time-mated rats (25 + 9 TK/group) were treated IV on GD6 and 13 with vehicle, SGN-35 at 0.3, 1, 3 or 10 mg/kg or SGN-35 at 0.2 mg/kg. Main study dams were euthanized on GD21, TK dams on GD18.

In rats treated with SGN-35 at 0.3 and 1 mg/kg there were no adverse findings. However, treatment with SGN-35 at 3 and 10 mg/kg and SGD-1010 (MMAE)(0.2 mg/kg) resulted in embryo-foetal lethality and treatment-related effects in maternal clinical observations, body weight and food consumption, haematology, uterine weight, macroscopic and microscopic findings (Table 39).

In rats treated with SGN-35 at 3 and 10 mg/kg, body weights were decreased. This was partly attributed to decreases in mean gravid uterus weights in dams correlated with virtual absence (3 mg/kg) or absence (10 mg/kg) of viable foetuses. In these dams, the uterus demonstrated placentation resorption consistent with the reduction or absence of viable foetuses. Pregnancy rates ranged from 96 – 100 %, however, only 2 dams (3 mg/kg) had litters with viable foetuses. Thus, total resorptions/post-implantation loss was 99.4% and 100 %, and the incidence of dams without viable foetuses was 92 % and 100 %, respectively. Regarding foetal development, foetal weight was reduced at 3 mg/kg SGN-35. External malformation and foetal soft tissue variations/malformations were observed occasionally in SGN-35-treated groups. These findings were considered unrelated to treatment due to the low foetal and litter incidence of the findings.

Dams treated with 0.2 mg/kg SGD-1010 (MMAE)demonstrated an increase in uterine weights associated with viable foetuses, associated with normal placentation and pregnancy-associated vaginal modification indicating presence of viable foetuses. In this group, pregnancy rate was 96 %, and all but 1 dam had litters with viable foetuses. Thus, post-implantation loss was 27.4 %, and the incidence of dams with no viable foetus was 4.2 %. Following treatment with SGD-1010 (MMAE)external malformations, foetal soft tissue variations and foetal skeletal variations were observed. These findings were considered unrelated to treatment due to the low foetal and litter incidence of the findings.

**Table 34** Results for selected Parameters at the Mid and High doses of SGN-35 and the SGD-1010 dose in a GLP-Compliance Repeat-dose Intravenous Bolus Injection **Embryo-Fetal Development Study of SGN-35 and SGD-1010 in pregnant Sprague-Dawley Rats**

| | Mean Percent Change Versus Control[a] | | |
|---|---|---|---|
| **Parameter** | **SGN-35 3 mg/kg (n = 25 dams)** | **SGN-35 10 mg/kg (n = 25 dams)** | **SGD-1010 0.2 mg/kg (n = 25 dams)** |
| Body weight | –25% | –26% | –8% |
| Food consumption | –11% | –14% | 5% |
| Red blood cells | 18% | –4% | –35% |
| Hemoglobin | 20% | 2% | 31% |
| Hematocrit | 20% | 5% | –29% |
| Leukocytes | 13% | –15% | –19% |
| Neutrophils | –47% | –77% | –41% |
| Monocytes | –22% | –38% | 8% |
| Platelets | 759% | 691% | –8% |
| Reticulocytes | 13% | 119% | 218% |
| Mean corpuscular volume | 2% | 9% | 10% |
| Total resorptions | 13,200% | 13,500% | 3500% |
| Postimplantation loss | 9840% | 9900% | 2640% |
| Dams with viable fetuses | –92% | –100% | –8% |
| Uterine weight | –97% | –98% | –24% |
| Fetal weight | –43% | N/A[b] | –5% |

Source: Report 8204397.

GLP = Good Laboratory Practice; N/A = not applicable.

Note: No adverse embryo-fetal toxicity findings were observed in animals dosed with 0.3- and 1-mg/kg SGN-35.

a Values represent the mean percent change on Day 21 of gestation for body weights and Days 18 to 21 of gestation for food consumption as compared to the control group mean. Values represent the mean percent change on Day 20 of gestation for clinical pathology parameters as compared to the control group mean.

b No viable fetuses were present in dams dosed with 10-mg/kg SGN-35. n = 25 for control group.

TK analysis revealed that SGN-35, TAb, and SGD-1010 were transferred across the placenta. In dams treated with SGN-35, concentrations of SGN-35 were lower in foetal serum than in maternal serum; in amniotic fluid SGN-35 concentrations were below the limit of quantitation in the majority of animals. In contrast, SGD-1010 concentrations were higher in foetal serum and amniotic fluid than in maternal serum where SGD-1010 was generally blow the limit of quantitation.

In dams treated with SGD-1010, the toxin concentration (Cmax, AUC 0-1d) was higher than in dams treated with the antibody-drug conjugate while the residence time of SGD-1010 was shorter. Within 24 hours SGD-1010 concentrations decreased rapidly. Nevertheless, on GD18 SGD-1010 concentrations in amniotic fluid and foetal serum were higher than in maternal serum indicating that the toxin is transferred to the foetus.

The NOAEL of SGN-35 when administered to pregnant rats as 2 weekly IV injections was 1 mg/kg.

A Preliminary Embryo-Fetal Development Study of Enfortumab Vedotin by Intravenous Injection in Rats (study 20119695)

A GLP study was conducted to provide an evaluation of the effects of enfortumab vedotin on pregnant Sprague-Dawley rats and embryo and fetal development from implantation to close of the hard palate This study included assessment of fetal survival, body weight, and external and visceral examinations.

This study was designed to evaluate ICH Harmonised Tripartite Guideline stages C to D of the reproductive process.

Enfortumab vedotin was administered at dose levels of 0 (control article, 5% (w/v) sterile dextrose solution), 2.0, or 5.0 mg/kg per dose via intravenous (bolus) injection to 6 time-mated Sprague-Dawley female rats per group. Vehicle or enfortumab vedotin (2.0 or 5.0 mg/kg) was administered once on GD 6 and again on GD 13 at approximately the same time on each dosing day.

All animals survived until the day of scheduled euthanasia (GD 21); however, enfortumab vedotin administration resulted in maternal and embryo-fetal toxicity at both of the dose levels tested.

Enfortumab vedotin-related dose-dependent reductions in body weight or body weight gain occurred at the 2.0 and 5.0 mg/kg dose. Maternal toxicity at the 2.0 mg/kg per dose level was limited to reductions in body weight changes attributed, at least in part, to the embryo-fetal toxicity observed at this dose level. Maternal toxicity including reductions in body weight, body weight gain and food consumption that occurred at the 5.0 mg/kg dose level was also attributed to embryo/fetal toxicity (total resorption of all litters) that occurred in this dose group.

**Prenatal and postnatal development, including maternal function**

Since enfortumab vedotin is intended for the treatment of patients with late stage and advanced cancer, studies of fertility and early embryonic development and pre- and postnatal toxicity were not conducted.

**Studies in which the offspring (juvenile animals) are dosed and/or further evaluated**

No studies in juvenile animals have been conducted.

## Local Tolerance

Separate studies evaluating local tolerance of enfortumab vedotin were not performed. Histopathological examination of the injection sites occurred as part of the GLP repeat dose toxicology studies in both rats and cynomolgus monkeys. The treatment-related effects observed in rats and monkeys at or near the injection sites were considered related to the targeting of Nectin-4 which is expressed in the epidermis and epithelium of glands in the skin and were reversible at the end of the recovery period.

**Table 35** Histopathological findings observed in rat and monkey studies

| Species/ Strain/Study Number | Method of Administration | Doses (mg/kg) | Gender and Number Per Group | Noteworthy Findings |
|---|---|---|---|---|
| Sprague-Dawley rat<br><br>20117437 | iv bolus | 0, 0.5, 2, and 5 | M:10<br>F:10 | ≥ 0.5 mg/kg: minimal abnormal mitotic figures and single cell necrosis of the epidermis and/or adnexa including hair follicles and sebaceous glands<br>2 mg/kg, 1F: moderate necrosis of the subcutaneous tissue and regionally extensive area of epidermis, with ulceration, considered possibly associated with extravasated test material during injection due to the lack of similar findings at higher dose levels |
| Cynomolgus monkey<br><br>20021751 | iv infusion | 0, 3 | M:5 †<br>F:5 † | minimal or mild diffuse acanthosis, mild perivascular mononuclear inflammatory cell infiltrates and minimal fibrosis. These changes indicate a slightly increased inflammatory response at injection sites in animals dosed with AGS-22M6E (HYBRIDOMA ADC) and enfortumab vedotin, compared to the procedure-related inflammatory changes noted in controls. |

## *Other toxicity studies*

### Tissue Cross Reactivity

Two Tissue Cross Reactivity (TCR) studies were performed, one in human tissue and the second in monkeys. Results of these two studies are detailed below in Table 41. Immunohistochemical analysis for Nectin-4 expression in normal human tissues were also explored and results are reported in the same table.

**Table 36** Summary of TCR studies results

| Study | Method of Administration | Doses (mg/kg) | Gender and Number per Group | Noteworthy Findings |
|---|---|---|---|---|
| Tissue cross reactivity of<br>AGS-22M6E) with human<br>tissues<br><br>8236219<br><br>GLP | Tissue titration-Frozen tissue | AGS-22M6E-biotin at<br>2.5, 5, and 10 µg/ml | 3 donors | Positive staining:<br>eye (2 donors): Corneal epithelium<br>oesophagus (1 donor): Surface layers of epithelium<br>placenta (3 donors): Within the syncytiotrophoblast (epithial in origin)<br>skin (3 donors): Variable intensity in surface layers of<br>epithelium, epithelium cells of the luminal |

| | | | | |
|---|---|---|---|---|
| | | | | aspect of hair follicles and epithelium of<br>occasional glands<br>tonsil (3 donors): Squamous epithelium<br>uterus - cervix (2 donors): Surface layers of squamous epithelium<br>Non-specific staining: majority of tissues examined |
| Tissue Cross Reactivity of AGS-22M6E with Normal Cynomolgus Monkey Tissues<br><br>Study ES10-002<br><br>Non-GLP | Tissue titration-Frozen tissue | AGS-22M6E-biotin at 3, 10, or 30 µg/ml | 5 donors<br><br>31 organs tested | Positive staining:<br>skin (epidermis, hair follicles and sweat glands)<br>esophagus<br>tonsil<br>Negative staining: cerebellum, cerebrum, colon, heart, larynx, lymph node (mesenteric), mammary gland, ovary,<br>skeletal muscle, spinal cord, testis, thyroid, parathyroid, urinary bladder, and uterine cervix and<br>endometrium<br>Non-specific staining:<br>Adrenal gland, Jejunum, Kidney, Liver, Lung, pancreas, pituitary gland, spleen, and thymus |
| Immunohistochemical evaluation of Nectin-4 expression in normal human tissues<br><br>ES10-001 | Formalin-fixed and paraffinembedded tissue | Mouse anti-human<br>Nectin-4<br>M22-244b3.1.1.1 7.5 µg/ml | Tissue microarray<br><br>(33 types of human<br>Organs) | low level of expression in adult normal human tissues (physiological role in maintaining cell-cell adhesion) |

**Antigenicity**

No dedicated studies performed. Regarding ADA assessment in repeated-dose studies, please refer to PK section.

**Dependence**

Dedicated non-clinical studies to evaluate the dependence potential of enfortumab vedotin have not been conducted. Such studies are not warranted because a) the target is not expressed in central nervous system tissues, b) no CNS effects were noted in repeat-dose toxicology studies and c) of the anti-microtubule mechanism of action of SGD-1010.

**Metabolites**

The cytotoxic activity of the 3 major metabolites of SGD-1010 (MMAE), C4: O-demethyl-Dap-SGD-1010; C7: N-demethyl-Val-SGD-1010; C8: Keto-Nor-SGD-1010, was evaluated in vitro (study TRN-1201-A). CD30-positive tumour cells lines and primary human bone marrow CD34-positive cells were used as target cells. Of the 3 metabolites, C8 was as cytotoxic as SGD-1010, while C4 and C7 were less cytotoxic against these targets than the parent drug.

## Studies on impurities

The test material used in pivotal GLP-compliant non-clinical studies was comparable or identical to material used in clinical studies and to the intended marketed product. Thus, all impurities were adequately assessed and no additional studies are necessary.

**Phototoxicity**

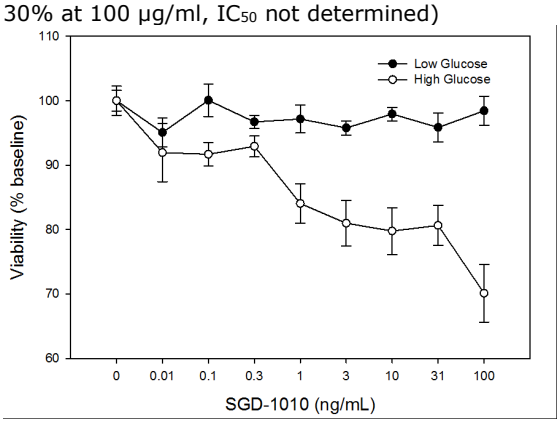
A non-GLP study was performed to evaluate the need for a photosafety assessment of SGD-1006 (vc-MMAE), SGD-1427 (N-acetylcysteine-vcMMAE), and SGD-1010 (MMAE) (Study TRN-2926-A). According to guidance ICH S10, photoreactive potential should be considered if a compound has a molar extinction coefficient (MEC) greater than 1000 L mol-1 cm-1 (M-1cm-1) at any wavelength between 290 and 700 nm. Absorption spectra were collected for both SGD-1006 and SGD-1427 in methanol. For both compounds, the wavelength of maximum absorption over the range of 290 to 700 nm was determined to be 290 nm. The MEC at this wavelength was calculated from triplicate sample preparations. The MEC of SGD-1006 was determined to be 770 M-1cm-1 at 290 nm while the MEC of SGD-1427 was determined to be 425 M-1cm-1. Thus, neither SGD-1006 nor SGD-1427 met the criteria for phototoxicity testing as defined in ICH S10. A subsequent study conducted on MMAE at SAFC (MilliporeSigma) confirmed that the compound has no absorption in the range of 290 to 700 nm and, as such, is not considered to pose a direct risk for phototoxicity.

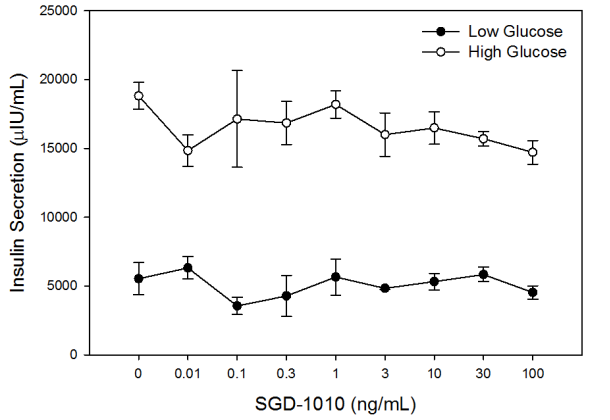
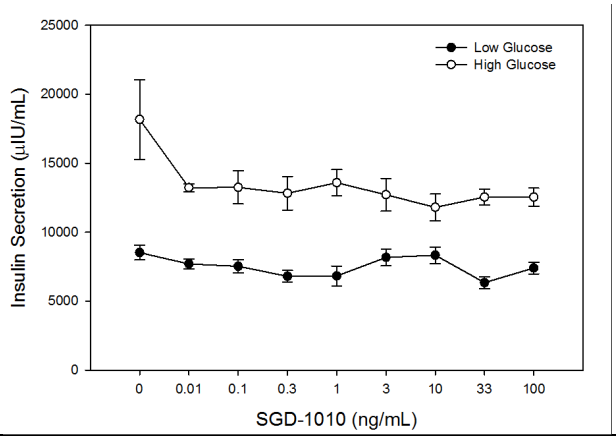
**Other Studies**

Additional mechanistic toxicity studies were performed to better characterize the testicular toxicity observed in repeat-dose toxicity studies and to determine if the payload presented any specific effects relating to hyperglycaemia.

**Table 37** Summary of investigative studies

| **Study ID/ GLP** | **Species/ Sex/Number/Group** | **Dose (mg/kg) /Route** | **Noteworthy findings** |
|---|---|---|---|
| Recovery of testicular toxicity<br><br>20135474<br><br>GLP | Rat (SD)<br><br>20M/group: 5/group/recovery time points (D29, D64, D127, D190) | Enfortumab Vedotin:<br>0, 2 mg/kg/dose<br><br>Once weekly (total of 4 dose)<br><br>24-week recovery (two complete cycles of spermatogenesis)<br><br>IV (bolus) | Objective: investigate toxicity observed in previous 4-wk rat study (20005662)<br><br>Results:<br>No mortality, no significant clinical observations, no body weights or food consumption<br><br>2 mg/kg<br>*Organ weights:*<br>D29, D64, D127: ↓ testes<br>D127: ↓ epididymides<br>D190: no differences in group mean testes or epididymides weights, 1/5 ↓ testes and ↓ epididymides<br>*microscopic findings:*<br>TESTES<br>D29: mild spermatocyte depletion in 2/5 rats |

| | | | |
|---|---|---|---|
| | | Batch: ASY-012 ADC FB, Batch 1 (CHO Process B) | D64: mild to moderate spermatocyte depletion in 2/5 rats and minimal vacuolation of the seminiferous tubules observed in 1/5 rats<br>D127: depletion of spermatids (moderate) and spermatocytes (minimal) and minimal vacuolation of the seminiferous tubules in 1/5 rats,<br>D190: mild spermatocyte depletion in 1/5 rats<br>EPIDIDYMES<br>D29 minimal-mild cell debris 1/5 rats<br>D64 minimal-mild cell debris 1/5 rats<br>D127 minimal-mild cell debris 2/5 rats<br>D190 minimal-mild cell debris 1/5 rats<br><br>PARTIAL RECOVERY (D190 lower incidence) |
| Peripheral Glucose Uptake and Islet Viability and Insulin Secretion<br><br>18022-076622 | 2 donors (human islets) and human skeletal muscle cells | *In vitro*<br><br>4 and 12 hour incubation periods<br><br>MMAE (SGD-1010): 0.01 – 100 ng/mL<br><br>MMAE ADC (h00-1006(4): 0.01 – 100 µg/mL | Objective: investigate mechanism potentially associated with hyperglycemia in human patients (impairment of glucose uptake into peripheral tissues (human skeletal muscle), impaired function of human islets after test article exposure)<br><br>Results:<br>*Skeletal Muscle Glucose Uptake*:<br>No effect except SGD-1010 at 100 ng/mL, which had a 1.5 times higher glucose uptake ($p<0.05$)<br><br>*Islet Viability*<br>After 4 hours:<br>no effect on cell viability for either test article<br><br>After 12 hours:<br>no concentration dependent effect in viability in response to h00-1006(4)<br>a concentration-dependent decline in cell viability in response to SGD-1010 (starting from 0.1 ng/mL to max 30% at 100 µg/ml, $IC_{50}$ not determined)<br>  <br><br><br>*Islet Insulin Secretion*<br>- no significant change in the amount of insulin secreted from islets after 4 hour exposure to various concentrations of h00-1006(4)<br>- small decline in insulin secretion from human islets incubated in high glucose media when exposed to SGD-1010 (22% and 31% for Donor 1 and 2 at max 100 µg/ml) |

| | | | |
|---|---|---|---|
| | | |  <br>  |

## 2.3.5. Ecotoxicity/environmental risk assessment

The procedure for Padcev included an CHMP environmental risk assessment (ERA) file. The risk assessment has been carried out according to the EMEA guideline CHMP/SWP/4447/00 corr.2 and its Q & A document.

**Summary of main study results**

| **Substance (INN/Invented Name): Enfortumab vedotin** | | | |
|---|---|---|---|
| **CAS-number (if available):** 1346452-25-2 | | | |
| PBT-screening: The active ingredient is composed of an antibody linked to MMAE via a maleimidocaproyl valine-citrulline linker. The complete active ingredient is due to its mostly protein nature not amenable to determination of log Kow. Log Kow for the MMAE part of the molecule which is likely one of the excreted moieties, has been determined to be 2.23 at pH 9 and thus below the 4.5 threshold (see below). | | | |
| ***PBT screening*** | | Result | **Conclusion** |
| *Bioaccumulation potential*- log $K_{ow}$ /$D_{ow}$ for monomethylauristatin E | OECD107 | -0.01 at pH 5<br>1.45 at pH 7<br>2.23 at pH 9 | Potential PBT (N) |
| ***Phase I*** | | | |
| ***Calculation*** | **Value** | **Unit** | **Conclusion** |
| PEC $_{surfacewater}$ , default | 0.4375 | µg/L | > 0.01 threshold (Y) |
| PEC $_{surfacewater}$ , refined (prevalence, treatment cycles) | 0.00776 | µg/L | > 0.01 threshold (N) |

## 2.3.6. Discussion on non-clinical aspects

**Pharmacology**

Initially, the nonclinical development program of enfortumab vedotin was conducted with the hybridoma cell line-derived ADC, AGS-22M6E (HYBRIDOMA ADC). The comparability between enfortumab vedotin and AGS-22M6E (HYBRIDOMA ADC) was confirmed also with similar binding to the human Nectin-4-expressing PC3 cells KD values of 0.062 and 0.057 respectively. Both AGS-22M6 and AGS-22M6E (HYBRIDOMA ADC) bound to the human, cynomolgus and rat Nectin-4 orthologs with similar affinity.

Enfortumab vedotin binds to Nectin-4 on the cell surface resulting in the internalization of the ADC-Nectin-4 complex, which then traffics to the lysosomal compartment where MMAE is released via proteolytic cleavage of the linker. ADC internalisation and co-localization with the lysosomal marker LAMP1 was demonstrated by confocal and fluorescence microscopy. The intracellular concentration of MMAE delivered by AGS-22C3E was investigated and it was shown that AGS-22C3E delivers MMAE to tumor cells in a Nectin-4 dependent manner and leads to disruption of microtubules. AGS-22M6E (HYBRIDOMA ADC) induced potent cytotoxic effect in PC3 cell lines engineered to express different orthologs of Nectin-4 (human, cynomolgus monkey, rat and mouse), while AGS-22M6 parent antibody did not show any cytotoxic effect on these cells in the same assay. The cytotoxic effect against murine Nectin-4 expressing cells was lower which may reflect the lower binding affinity.

The average % relative potency of AGS-22C3E when compared to AGS-22M6E (HYBRIDOMA ADC) was calculated to be 91.4% when tested on PC3-AGS22 cells demonstrating similar potency of the hybridoma cell line-derived ADC, AGS-22M6E (HYBRIDOMA ADC) and Enfortumab vedotin (AGS-22C3E). A newly Nectin 4 (AGS-22) variant 7 was discovered. qPCR data indicated that this Nectin-4 variant was expressed in normal and tumour tissues at levels comparable to that in the wild type. It was demonstrated that variant-expressing cells were killed in a similar manner as the wild type Nectin 4-expressing cells.

Data indicated that Enfortumab vedotin exhibits no ADCC or CDC. It was further shown that enfortumab vedotin has some variable antibody-dependent cellular phagocytosis (ADCP) activity in vitro which depends on the donors of macrophages but also on the mAb/ADC lot used in the assay. It is agreed that the effect might be neglected, as the unconjugated antibody shows no efficacy in the tumor xenograft models.

It was demonstrated that AGS-22C3E has in vitro bystander effect activity against Nectin-4 negative bladder carcinoma cells when in co-culture with Nectin-4 expressing bladder carcinoma cells.

The antitumor efficacy of AGS-22M6E (HYBRIDOMA ADC) was evaluated in a human bladder cancer xenograft model at different dosage levels. The primary mechanism is targeted delivery of a cytotoxic payload to tumour cells via cancer-associated membrane receptors. However, the tumour microenvironment likely plays a role in ADC penetration, distribution, and processing and thus impacts the overall antitumor activity. The potential contribution of Fc–FcgR interactions between ADCs and tumour-associated macrophages (TAM) to the preclinical antitumor activities of ADCs was reported and demonstrated in xenograft models. The antitumor efficacy of AGS-22M6E (HYBRIDOMA ADC) produced in hybridoma cells was compared to AGS-22C3E produced in CHO cells using the AG-Br7 patient-derived human breast cancer xenograft model. The tumour growth inhibition caused by both the hybridoma-derived and the CHO-derived ADCs was similar.

No secondary pharmacodynamic studies of the ADCs were conducted but hypothetical secondary effects of an ADC binding to Nectin-4 were discussed using a review of literature. This is considered sufficient when considered in connection with the results of the toxicity studies.

The potential effect of ADC on hERG K+ channels was not evaluated as the antibody component is too large to cross plasma membranes. The effect of SGD-1010 (MMAE) on hERG K+ channels, heterologous expressed in Human Embryonic Kidney (HEK293) cells, was evaluated using the conventional whole cell voltage clamp technique. In this assay a block of hERG channel was observed in cells treated with MMAE. This block was significantly different from control values at high concentration (100 µM) but was not large enough to define an IC50. At 100 µM, the MMAE concentration was > 19.000x higher than the Cmax in patients, which is considered a sufficient safety margin. At 10 µM, the block was not statistically different from the controls. No effect was observed on ECG, heart rate, blood pressure, respiratory or CNS safety pharmacology parameters evaluated as part of the general toxicology studies performed in cynomolgus monkeys with the ADC.

Pharmacodynamic drug interactions of enfortumab vedotin have not been evaluated in non-clinical studies. The available human data are considered sufficient to evaluate drug-drug-interactions.

**Pharmacokinetics**

The pharmacokinetics of enfortumab vedotin, AGS-22M6E (HYBRIDOMA ADC) , AGS-22M6 (unconjugated antibody) or MMAE were not evaluated, but toxicokinetics were evaluated from 4-week intravenous dose toxicity studies in rats and/or cynomolgus monkeys after the first and the last dose.

Immunoassays were developed to measure the antibody components as well as immunogenicity.

ADC, Tab and ADA concentrations in rat and cynomolgus monkey serum were determined by ELISA. LC-MS/MS assays were employed to measure circulating amounts of MMAE released from the ADC.

The analysis for the pharmacokinetic studies appears to be specific, sensitive and linear within the range of the specified concentrations. Methods of analysis and validations are sufficiently discussed. Units of measurement are clearly defined. Toxicokinetic studies were conducted in compliance with GLP. The toxicokinetics of AGS-22M6E (HYBRIDOMA ADC), AGS-22M6, enfortumab vedotin, MMAE and Tab following intravenous administration of AGS-22M6E (HYBRIDOMA ADC) , AGS-22M6 or enfortumab vedotin were evaluated in rats and cynomolgus monkeys. In cynomolgus monkeys, toxicokinetic profiles of enfortumab vedotin and AGS-22M6E (HYBRIDOMA ADC) were comparable. The toxicokinetics of MMAE following intravenous administration of unconjugated MMAE was also evaluated in cynomolgus monkeys. Exposure to AGS-22M6E (HYBRIDOMA ADC) was dose-proportional. No sex differences were observed.

Tissue distribution studies were not performed for AGS-22M6E (HYBRIDOMA ADC) or enfortumab vedotin. A high volume of distribution was determined for 3H-MMAE after single dose administration to rats. MMAE was well distributed and most tissues had concentrations that were higher than blood from 0.17 hours through 24 hours post-dose. The plasma protein binding of MMAE was species-dependent, with higher levels of binding in rats and humans than in mice and monkeys. MMAE showed species-dependent RBC partitioning with positive RBC partitioning in mouse, rat, and cynomolgus monkey blood, and negative RBC partitioning in human blood.

AGS-22C3 is an antibody and is therefore catabolized into small peptides and amino acids. 12 metabolites were identified in in vitro metabolism studies of MMAE in rat, monkey and human hepatocytes. Metabolites formed in human hepatocytes were similar to those formed in rat and monkey hepatocytes. The major metabolites C4, C7, and C8 were found to be approximately as cytotoxic (C8) or less cytotoxic than MMAE (C4, C7). Incubations with a panel of recombinant human CYP enzymes revealed that CYP3A4 converted 3H-MMAE to components C4, C7 and C8. CYP2D6 also converted 3H-MMAE to component C7. MMAE was metabolized in human liver microsomes primarily by CYP3A4, with minor contribution from CYP2D6. Additional information was obtained from clinical evaluation of the metabolism of MMAE in humans following a single intravenous dose of brentuximab vedotin. All detected metabolites, except an

additional C13 metabolite were previously observed in vitro. C13 was produced via a combination of the metabolic pathways of C4 and C8. Altogether, metabolism of MMAE was sufficiently investigated.

A GLP-compliant mass balance study of MMAE was conducted in rats with another MMAE containing ADC (SGN-35) and 3H-MMAE (SGD-1010). The major route of excretion in rats was via feces with urinary excretion accounting for less than 15%. SGD-1010 (MMAE) was the predominant metabolite excreted. Intact SGD-1010 (MMAE) was also the primary metabolite excreted in humans dosed with SGN-35 with higher excretion in feces than in urine, however, mass balance was not achieved in human studies.

Pharmacokinetic drug interactions were studied in vitro for different drug transporters and CYP isozymes. SGD-1010 (MMAE) was shown to be a substrate for P-gp, but not a potent inhibitor. SGD-1010 (MMAE) was identified as a CYP3A4 substrate. Therefore, potent CYP3A4 inducers or inhibitors may alter the pharmacokinetics of SGD-1010. SGD-1010 was also shown to be a time-dependent irreversible inhibitor of CYP3A4/5, but the inhibition constant is much higher than clinical exposures at Cmax and CYP3A4 enzyme turnover suggests complete regeneration within the dosing interval. Therefore, no clinical interactions should be expected from this irreversible inhibition. Apart from a potential involvement of OATPs, pharmacokinetic drug interactions were sufficiently addressed.

The Cmax values of MMAE following AGS-22M6E (HYBRIDOMA ADC) administration to rats and cynomolgus monkeys were approximately 0.2% and 0.04% of peak AGS-22M6E (HYBRIDOMA ADC) concentrations respectively, based on molar ratios, which indicates that AGS-22M6E (HYBRIDOMA ADC) is stable in plasma in vivo. Regarding the stability of the ADC (AGS-22M6E (HYBRIDOMA ADC) and enfortumab vedotin), stability studies were conducted with the ADC in serum in the ELISA validation [Study AR3905, Study AR4854 and Study 7465-ME-0002]. These quantitation methods capture the ADC with the mouse anti-MMAE antibody immobilized on a plate. Study results also confirmed the stability of the ADC in human serum. The ADC was stable in human serum for approximately 24 hours at room temperature.

**Toxicology**

Repeat dose toxicity studies were performed in rat and cynomolgus monkey. Similar toxicity profiles were observed across species. Skin and bone marrow seem to be the predominant target tissues with repeat dosing of both enfortumab vedotin and AGS-22M6E (HYBRIDOMA ADC) in both rats and cynomolgus monkeys. Skin toxicity such as abrasions and/or dry reddened skin was observed in both species. Skin lesions were noted in repeat dose studies in rats (4- and 13-weeks) and in monkeys (4-weeks). The skin changes were fully reversible by the end of a 6 week recovery period (see SmPC 5.3). The skin toxicity seen in both rats and cynomolgus monkeys was considered related to expression of Nectin-4 in the skin. Bone marrow toxicity was dose limiting in cynomolgus monkeys dosed with MMAE alone and seems to be a nontarget-dependent toxicity. There were similar hematologic findings between-species consistent with bone marrow toxicity. These included changes in parameters in red blood cells (RBCs) indicating reduced erythropoiesis. As the toxicity profiles seem to be comparable between rat and cynomolgus, and considering that cross-reactivity in the rat and cynomolgus monkey have equivalent binding affinity to human Nectin-4, it is acceptable to conduct the chronic (13-week) repeat dose toxicity study only in the rat.

In addition to the skin and bone marrow toxicities, testicular toxicity was observed in the pivotal study performed in rats. Additional target organs include epididymis, spleen, eye (cornea), lymphoid tissue, adrenal gland, Harderian gland, intestine, prostate, mammary gland, and liver. AGS-22M6E (HYBRIDOMA ADC) AGS-22M6E (HYBRIDOMA ADC).

The genotoxic potential of SGD-1010 (MMAE) was adequately evaluated in a standard *in vitro* and *in vivo* test battery. The toxin moiety of the ADC was found to be non-genotoxic in bacterial and mammalian cell mutation assays. However, in vivo SGD-1010 (MMAE) induced micronucleus formation in rat bone

marrow at a single dose of 0.1 and 0.2 mg/kg. Micronuclei were predominantly centromere-positive, which is consistent with the mode of action of SGD-1010 (MMAE) (see SmPC 5.3). Information on the genotoxic activity of the linker was provided based on publicly available data (www.toxnet.org) and in silico analysis using the DEREK software. Considering the indication and the expected negligibly low free plasma concentrations for the linker and its potential fragments, further qualification was not considered necessary.

As enfortumab vedotin is intended for the treatment of patients with late stage and advanced cancer the omission of carcinogenicity studies is accepted. Dedicated fertility and early embryonic development studies were not conducted in accordance with ICH S9.

Embryo-fetal development toxicity of SGN-35 and SGD-1010 was evaluated in a GLP-compliant repeat-dose IV embryo-fetal development study in pregnant rats. Treatment with SGN-35 was associated with embryo-fetal lethality. Administration of SGN-35 at 10 mg/kg resulted in greater embryo-fetal toxicity than administration of the toxin SGD-1010 at an equivalent molar dose of 0.2 mg/kg. This is likely due to the rapid elimination of SGD-1010 from the maternal circulation.

The embryo-fetal toxicity was appropriately evaluated and the observed findings are correctly reported in the SmPC. Enfortumab vedotin associated foetal skeletal variations were considered developmental delays. A dose of 2 mg/kg (approximately similar to the exposure at the recommended human dose) resulted in maternal toxicity, embryo-foetal lethality and structural malformations that included gastroschisis, malrotated hindlimb, absent forepaw, malpositioned internal organs and fused cervical arch. Additionally, skeletal anomalies (asymmetric, fused, incompletely ossified, and misshapen sternebrae, misshapen cervical arch, and unilateral ossification of the thoracic centra) and decreased foetal weight were observed (see SmPC 5.3). Since enfortumab vedotin is intended for the treatment of patients with late stage and advanced cancer, studies of fertility and early embryonic development and pre- and postnatal toxicity were not conducted.

Separate studies evaluating local tolerance of enfortumab vedotin were not performed. In accordance with ICH S6, the omission of dedicated local tolerance studies is acceptable. Histopathological examination of the injection sites was performed as part of the GLP repeat dose toxicology studies in both rats and cynomolgus monkeys. Increased inflammatory response at injection sites were found and are considered treatment-related effects. Injection site reactions were reversible at the end of the recovery period.

Additional mechanistic toxicity studies were performed to better characterize the testicular toxicity observed in repeat-dose toxicity studies and to determine if the payload presented any specific effects relating to hyperglycemia and phototoxicity. A GLP 4-week study with a 24-week recovery period was conducted to determine the recovery of testicular toxicity of enfortumab vedotin in rat. Repeat dose resulted in testicular toxicity and may alter male fertility. MMAE has been shown to have aneugenic properties. Testicular toxicity associated with enfortumab vedotin was partially reversible by the end of a 24 week recovery period (see SmPC 5.3).

Tissue Cross Reactivity studies with of AGS-22M6E-biotin reveal that the ADC cross reacts with a panel of normal cynomolgus monkey tissues indicating unspecific cell killing. Positive staining was seen with AGS-22M6E-biotin in tissue structures and cell types of epithelial origin within a number of human tissues examined. In addition, it was found that Nectin-4 is expressed in a variety of normal human tissues during adulthood. It is argued that Nectin-4 is mostly expressed at a low level and the over expression of Nectin-4 in human cancers may thus provide a therapeutic window for development of AGS-22M6E as a treatment of Nectin-4-expressing cancers.

SGD-1006 and SGD-1427 were evaluated for potential phototoxicity risks according to the principles outlined in ICH S10. Neither compound had absorbance in the range of natural sunlight that exceeded the defined threshold for potential phototoxic concern.

### 2.3.7. Conclusion on the non-clinical aspects

An adequate program of *in vitro* and *in vivo* pharmacology was conducted in disease models for enfortumab vedotin, supporting the intended clinical use.

Pharmacokinetics of enfortumab vedotin are well described, and no deficiencies were identified.

An abbreviated toxicology program was performed, in line with the ICH S6 and ICH S9 guidelines.

The SmPC reflects the findings of the toxicity studies, as well as the testicular toxicity observed. Enfortumab vedotin can cause foetal harm when administered to pregnant women based upon findings from animal studies. Embryo foetal development studies in female rats have shown that intravenous administration of enfortumab vedotin resulted in reduced numbers of viable foetuses, reduced litter size, and increased early resorptions. It is not recommended during pregnancy and in women of childbearing potential not using effective contraception. It is unknown whether enfortumab vedotin is excreted in human milk. A risk to breast fed children cannot be excluded. Breastfeeding should be discontinued during Padcev treatment and for at least 6 months after the last dose. In rats, repeat dose administration of enfortumab vedotin, resulted in testicular toxicity and may alter male fertility. MMAE has been shown to have aneugenic properties. Therefore, men being treated with this medicinal product are advised to have sperm samples frozen and stored before treatment. There are no data on the effect of Padcev on human fertility (see SmPC 4.6).

## *2.4. Clinical aspects*

### 2.4.1. Introduction

### *GCP*

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

**Table 38:** Tabular overview of clinical studies

| Study No. | Phase/ Description | Population/ Planned Enrollment | Dosage and Frequency | Study Status / Enfortumab Vedotin Subjects Dosed | Data Cutoff Date |
|---|---|---|---|---|---|
| AGS-22M6E-11-1 | Phase 1<br>Dose-escalation and bridging study to assess safety and pharmacokinetics of AGS-22M6E and enfortumab vedotin/single-arm | Nectin-4-expressing malignant solid tumors<br>n = 9† | 0.6 or 1.2 mg/kg every 3 weeks | Completed<br>Apr 2015/<br>9 subjects | NA |
| EV-101 (ASG-22CE-13-2) | Phase 1<br>Dose-escalation to evaluate safety, determine RP2D, pharmacokinetics and efficacy/single-arm | Metastatic UC and other Nectin-4-expressing malignant solid tumors<br>n = approx. 215 (including 18 in renal insufficiency cohort) | 0.5 to 1.25 mg/kg on days 1, 8 and 15 of a 28-day cycle | Ongoing<br>201 subjects | Data cut for primary analyses<br>25 Oct 2018<br><br>Data cut for renal insufficiency analyses<br>17 Feb 2020 |
| EV-102 (7465-CL-0101) | Phase 1<br>Safety and pharmacokinetics of enfortumab vedotin in Japanese subjects/randomized 2-arm | Japanese subjects with locally advanced or metastatic UC<br>n = approx. 12 to 16 | 1.0 or 1.25 mg/kg on days 1, 8 and 15 of a 28-day cycle | Completed<br>25 Feb 2019<br>17 subjects | NA |
| EV-201 (SGN22E-001) | Phase 2<br>Open-label, multicenter study of efficacy and safety as monotherapy/ single-arm | Locally advanced metastatic UC; previously treated with PD-1/PD-L1<br>n = approx. 200 | 1.25 mg/kg on days 1, 8 and 15 of a 28-day cycle | Ongoing<br>219 subjects‡ | Data cut for primary analyses:<br>Cohort 1<br>01 Mar 2019<br>Cohort 2<br>08 Sep 2020 |

*Table continued on next page*

| Study No. | Phase/ Description | Population/ Planned Enrollment | Dosage and Frequency | Study Status / Enfortumab Vedotin Subjects Dosed | Data Cutoff Date |
|---|---|---|---|---|---|
| EV-301 | Phase 3 Open-label, randomized Phase 3 study to evaluate enfortumab vedotin vs chemotherapy in subjects with previously treated locally advanced or metastatic urothelial cancer | Locally advanced or metastatic UC previously treated with CPI with disease progression or relapse n = approx. 600 | 1.25 mg/kg on days 1, 8 and 15 of a 28-day cycle | Ongoing 587 subjects§ | Data cut for primary analyses 15 Jul 2020 |

CHO: Chinese hamster ovary; CPI: checkpoint inhibitor (defined as a PD-1 or PD-L1 inhibitor); CSR: clinical study report; NA: not applicable; RP2D: recommended phase 2 dose; UC: urothelial cancer.

† This bridging study included subjects treated with both AGS-22M6E (hybridoma antibody intermediate) and enfortumab vedotin (CHO antibody intermediate). This table includes only subjects treated with enfortumab vedotin.

‡ Enrolled subjects: Cohort 1 - 128 enrolled subjects (125 treated), Cohort 2 - 91 enrolled (89 treated).

§ Of the 608 randomized subjects, 587 subjects (296 subjects in the enfortumab vedotin arm and 291 subjects in the chemotherapy arm) received study drug.

In addition, a population pharmacokinetic analysis and a physiologically based pharmacokinetic (PBPK) evaluation is included in this application.

## Pharmacokinetics

### Rationale for the Recommended dose selection

Selection of the recommended dose of enfortumab vedotin was based on results from the phase 1 clinical studies, Study AGS-22M6E-11-1 and Study EV-101. Based on the overall benefit/risk in Study EV-101, enfortumab vedotin at 1.25 mg/kg on days 1, 8 and 15 of a 28-day cycle was selected as the recommended phase 2 dose. This dose of 1.25 mg/kg was evaluated in subsequent cohorts of Study EV-101, Study EV-102, Study EV-201 and Study EV-301, the pivotal phase 3 study.

The clinical pharmacology programme assessed the PK, PD, and immunogenicity of enfortumab vedotin, in the above listed studies, Table 43.

### Analytical methods

Serum ADC or enfortumab vedotin (the conjugated monoclonal antibody) was determined with validated ELISA assays while free MMAE plasma concentrations (the unconjugated small molecule part of the drug) were determined using LC-MS/MS. Serum total antibody (TAb) and nAbs were determined using ELISA assays. Immunogenicity was assessed using ELISA or ECLIA assays. The bioanalysis conducted in support of enfortumab vedotin is considered well-documented.

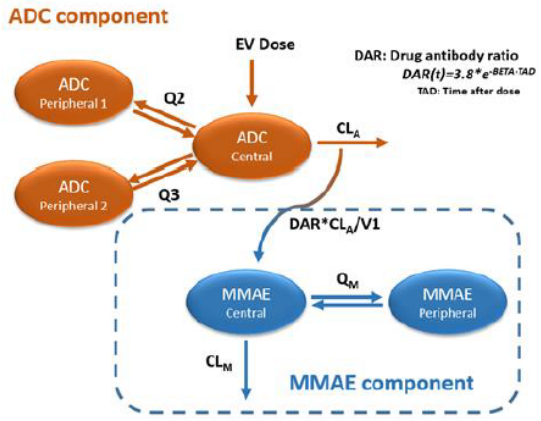
### Pharmacokinetic data analysis

Population pharmacokinetic analysis was used to assess the impact of covariates on the pharmacokinetics of enfortumab vedotin (ADC) and free MMAE. The relationship between enfortumab vedotin and free MMAE exposure and efficacy/safety endpoints were explored using model-based analysis. A linear mixed effects model was used to assess the relationship between enfortumab vedotin

or MMAE concentration and dQTcF intervals. Physiologically-based pharmacokinetic (PBPK) models were used for evaluation of the DDI potential of enfortumab vedotin and of free MMAE.

**Pop PK models**

A 3-compartment model with first-order elimination and a 2-compartment model with first-order elimination and time-varying conversion rate from enfortumab vedotin was used to characterise the concentration-time data of enfortumab vedotin and free MMAE, respectively.

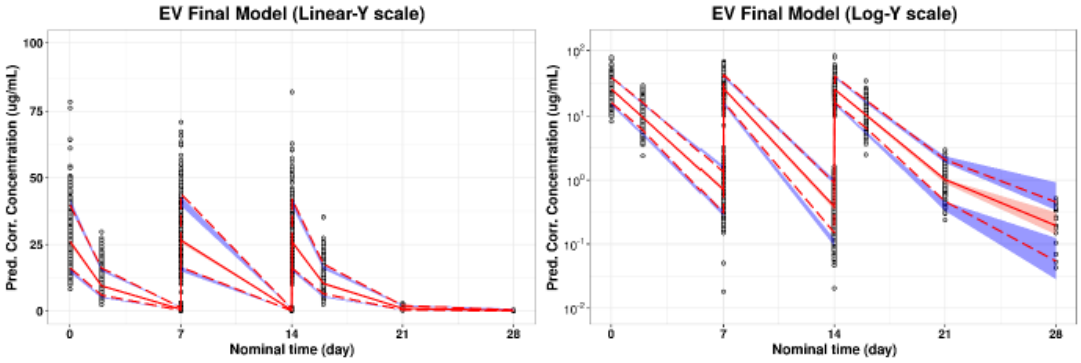



ADC, enfortumab vedotin; DAR, drug antibody ratio; $CL_A$, clearance of enfortumab vedotin by proteolytic degradation; Q2 and Q3, enfortumab vedotin inter-compartmental clearance; $CL_M$, free MMAE clearance; MMAE, monomethyl auristatin E; $Q_M$, free MMAE inter-compartmental clearance. BETA: conversion rate of free MMAE from conjugated ADC. TAD: time after previous dose.
Source: Figure 1 in Population PK report of Enfortumab Vedotin [7465-pk-0003]

**Figure 17** PopPK Model Structure for enfortumab vedotin (ADC) and Free MMAE

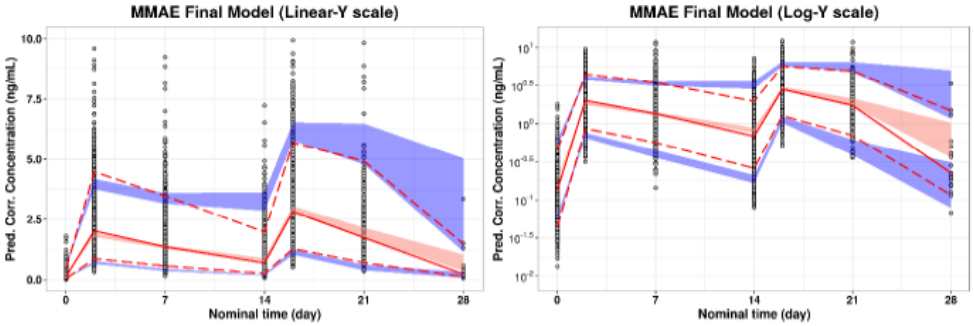
The parameters of the final models were estimated with adequate precision. None of the 95% CIs contained the null and a high percentage of bootstrap simulations converged successfully indicating the models were stable.

The provided Visual predictive checks (VPCs) for the final population and stratified for different influential covariates indicated that both models could describe the observed data. The Goodness of fit (GoF) plots did not indicate any major misspecifications.




Note: Black circles are observations. Red solid and dashed lines represent the median (solid line), 5th and 95th percentiles (dashed lines) of the observations. The shaded areas are the 95% prediction interval (2.5-97.5th percentiles) around the median (pink) and 5th and 95th percentiles (blue) based on model simulations. To avoid bias in the evaluation of model prediction, approximately 6% of overall concentration records were excluded from the plots as these exclusions were associated with sparse samples at trough with measurement times far out of the sampling window.
Source: ~/MSTask04/script_FINAL/Pred_Perf_Eval.R → ~/MSTask04/outputs_FINAL/VPC/pcVPC_ADC_final_scm1_500.png

**Figure 18** Prediction-corrected Visual Predictive Check Plots for the Final Model (model ADC-final-scm1) of enfortumab vedotin in the combined population




Note: Black circles are observations. Red solid and dashed lines represent the median (solid line), 5th and 95th percentiles (dashed lines) of the observations. The shaded areas are the 95% prediction interval (2.5-97.5th percentiles) around the median (pink) and 5th and 95th percentiles (blue) based on model simulations. To avoid bias in the evaluation of model prediction, approximately 6% of overall concentration records were excluded from the plots as these exclusions were associated with sparse samples at trough with measurement times far out of the sampling window.
Source: ~/MSTask04/script_FINAL/Pred_Perf_Eval.R
→ ~/MSTask04/outputs_FINAL/VPC/pcVPC_MMAE_final_scm3_500.png

**Figure 19** Prediction-corrected visual Predictive Check plots for the Final Model (MMAE-final-scm3) of free MMAE in the combined population

Sex, baseline albumin, haemoglobin, sum of tumor diameters, analytical lab and manufacturing process were identified to be statistically significant covariates for enfortumab vedotin, while sex, baseline albumin, haemoglobin, bilirubin, sum of tumor diameters, ECOG performance status, and manufacturing process were identified as statistically significant covariates for free MMAE. Effect of ADAs and concomitant medication on exposure could not be evaluated due to low sample size. Lower albumin levels were associated with higher MMAE exposure. Haemoglobin and to a lesser extent bilirubin and ECOG had impact on Ctrough MMAE, which increased with decreasing haemoglobin and increasing bilirubin. None of the identified significant covariates had clinically relevant effect on exposure.

Model-based MMAE CLM was estimated to be 2.11 L/h and total volume of distribution at steady state to be 183.5 L. The elimination half-life was calculated to be 61.2 h (2.6 d). IIV were 43.5 %CV (CLM), 55 %CV (VM) and 62.8% (VMP), and the corresponding η-shrinkage values ranged from 5% to 31%. Clearance (CLM) and volume of distributions (VM and VMP) of free MMAE increased with increasing body weight. Free MMAE were predicted to have 23% higher CLM, 26% lower VM and 104% higher VMP for manufacturing process A.

The final models of enfortumab vedotin and free MMAE were used to simulate enfortumab vedotin 1.25 mg/kg exposure (Table 44).

**Table 39** Model-predicted exposures for enfortumab vedotin and free MMAE

| Exposure Metrics | ADC<br>Mean (SD) | Free MMAE<br>Mean (SD) |
|---|---|---|
| Cycle 1 $C_{max}$ | 28 (6.1) µg/mL | 5.5 (3.0) ng/mL |
| Cycle 1 $AUC_{0\text{-}28d}$ | 110 (26) day*µg/mL | 85 (50) day*ng/mL |
| Cycle 1 $C_{trough}$ | 0.31 (0.18) µg/mL | 0.81 (0.88) ng/mL |

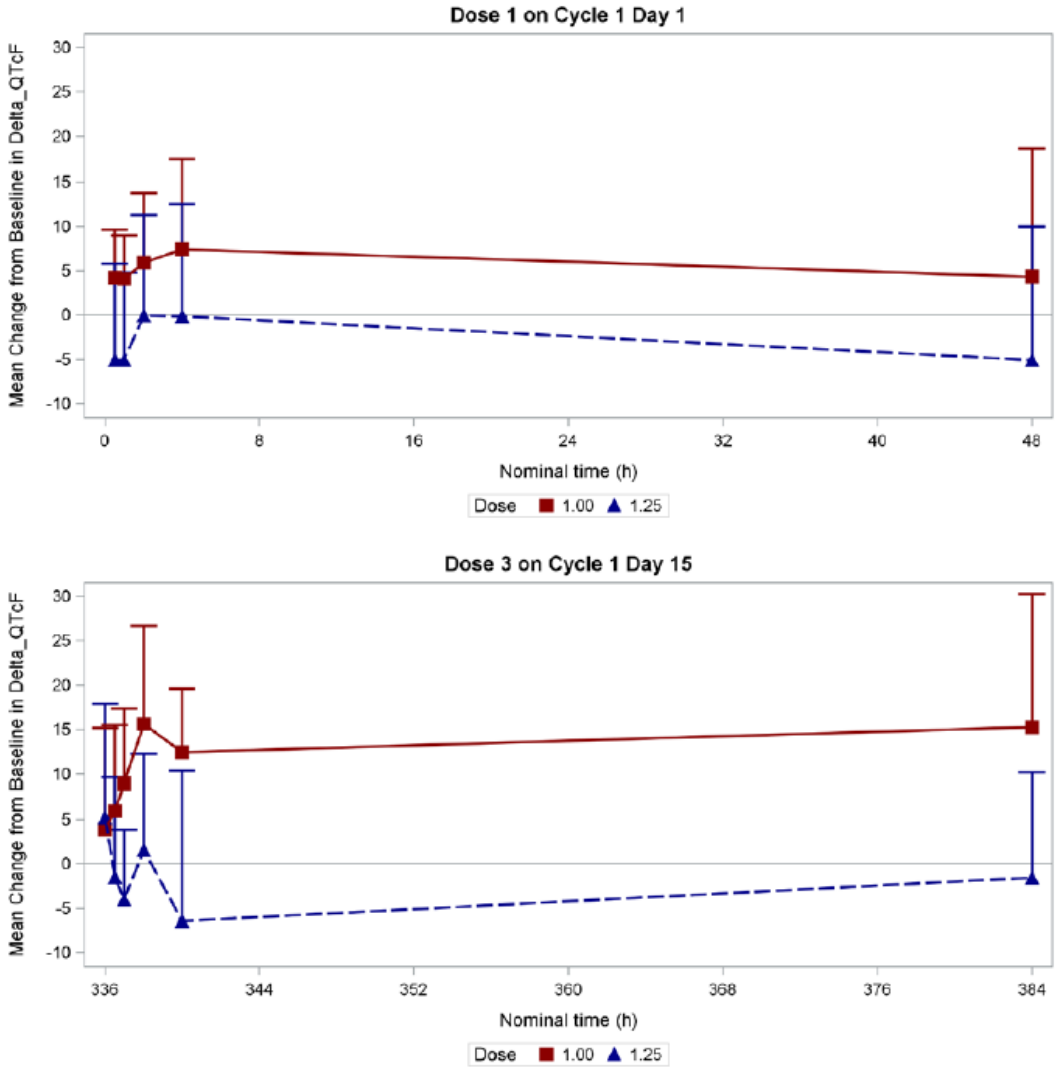
$C_{max}$: maximum concentration; $AUC_{0\text{-}28d}$ : area under the concentration-time curve from time zero to 28 days; $C_{trough}$ : pre-dose concentration on day 28 (Cycle 1 day 1).

**Exposure-response models**

For evaluation of exposure-response relations, cox proportional hazards modeling was used for overall survival (OS) data, while logistic regression models were used to model best overall response (BOR) and for modelling of selected safety measures. There was no adjustment of prognostic factors. Some safety endpoints with low occurrence were also included. Therefore, results should be interpreted with caution.

The relationship between enfortumab vedotin or MMAE concentration and dQTcF intervals was assessed using independent linear mixed effects models with time-matched concentration and ECG data from study EV-102. ADC showed slight delayed response in ΔQTcF after 3 dosing events (counter clock wise hysteresis) with persistent effect even 48 hours post-dose. This is not seen after first dose nor for free MMAE. There was also a trend of ΔQTcF increasing with increasing ADC concentration with several occurrences of ΔQTcF >20 ms. However, the most pronounced ΔQTcF effect occurred at the lower dose 1.0 mg/kg which is unexpected. Antibody drugs are usually not expected to cause QT prolongation due to their big size however examples have been published (Oncotarget, 2018, Vol. 9, (No. 39), pp: 25738-25749). Only 2 subjects were female.

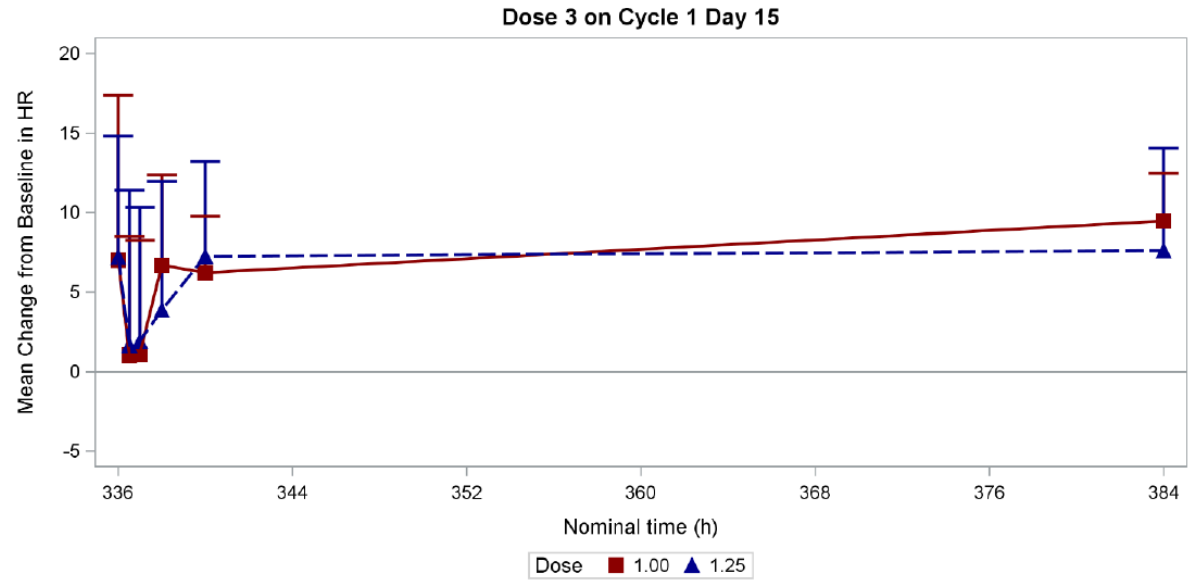
(a) **Time-dQTcF plot for each dose 1 and dose 3**

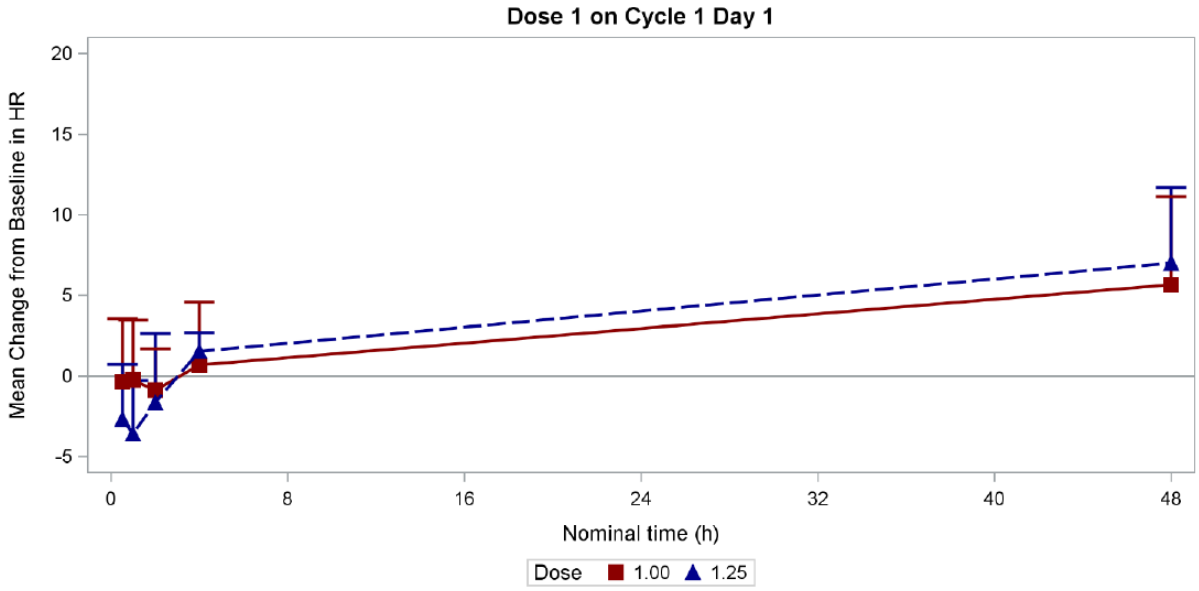



ADC: antibody-drug conjugate; dQTcF: change from baseline in QTcF; MMAE: monomethyl auristatin E.
Source: FigureA4_mean_hysterisys.sas

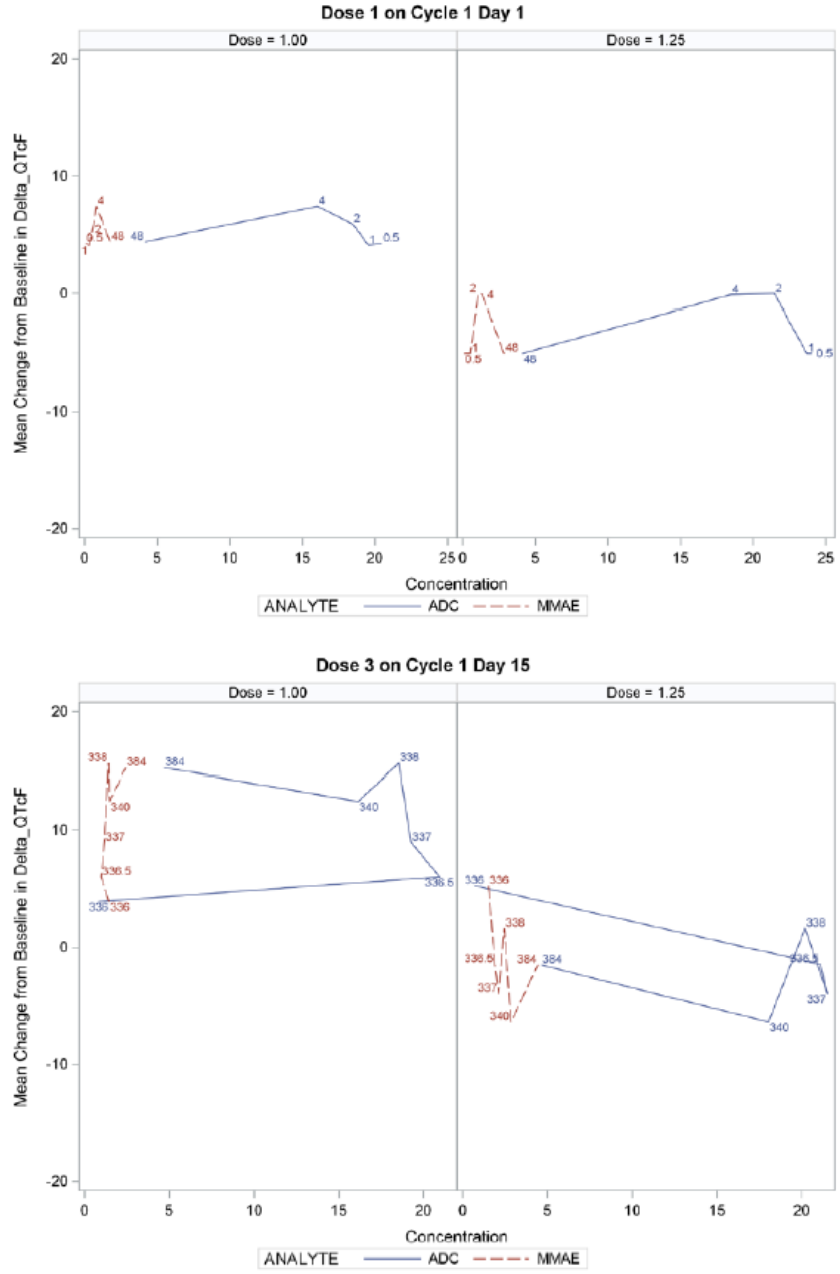
**Figure 20** dQtcF-Time Profiles and Exploratory Plots of Effects of Mean ADC and MMAE concentration on Mean dQTcF intervals by treatment dose

Figure 26 shows the change from baseline in QTcF (dQTcF) over time 0 to 48 hours after enfortumab vedotin intravenous administration for each dose 1 and dose 3 grouped by treatment dose, and a plot showing the change from baseline in heart rate (dHR) over time 0 to 48 hours after enfortumab vedotin intravenous administration for each dose 1 and dose 3 grouped by treatment dose are presented. Mean change from baseline in heart rate at dose 3 on cycle 1 day 15 was about up to 15 bpm and 17 bpm for doses of 1.25 mg/kg and 1 mg/kg, respectively (nominal time about 336 h). At 384 h, mean change from baseline was about up to 12 bpm to 14 bpm for doses of 1.25 mg/kg and 1 mg/kg, respectively.


Dose 3 on Cycle 1 Day 15
Mean Change from Baseline in HR
20
15
10
5
0
-5
336
344
352
360
368
376
384
Nominal time (h)
Dose 1.00 1.25


Dose 1 on Cycle 1 Day 1
Mean Change from Baseline in HR
20
15
10
5
0
-5
0
8
16
24
32
40
48
Nominal time (h)
Dose 1.00 1.25

(b) **Overlay Hysteresis Plot (Dose 1 vs Dose 3)**

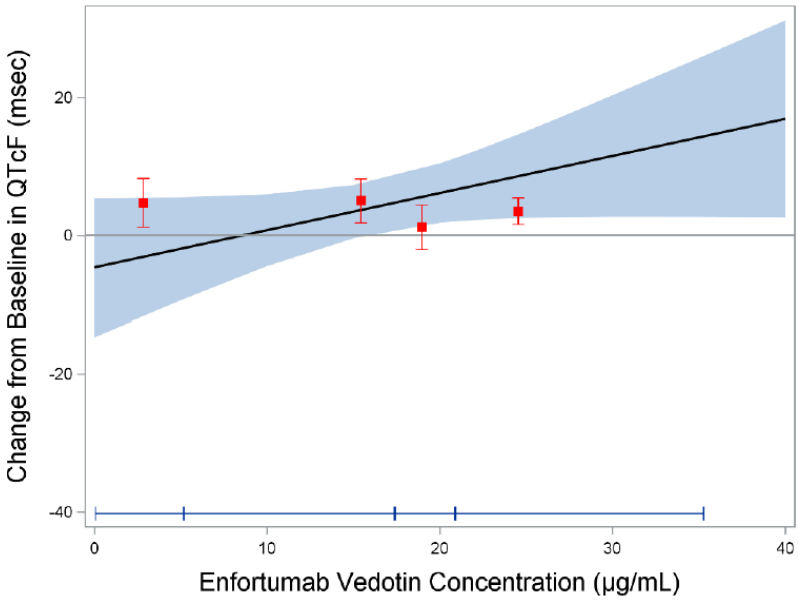



ADC: antibody-drug conjugate; dQTcF: change from baseline in QTcF; MMAE: monomethyl auristatin E.
Unit of concentration: ADC (µg/mL); MMAE (ng/mL)
Nominal time at 0.5 hour is $T_{max}$ of ADC, whereas nominal time at 2 hours is $T_{max}$ of MMAE.

**Figure 21** Change from baseline in HR Over Time Plot for Each Dose 1 and 3 by Treatment Dose

The results shown in Figure 27, suggest that dQTcF values were similar across concentration quartiles of both enfortumab vedotin and free MMAE.

**Figure 22** dQTcF versus Enfortumab Vedotin Concentration Quartile Plot




Model parameter estimates for ADC and MMAE including the 95% CI are presented in Table 45 and Table 46 respectively.

**Table 40** Linear mixed effects model parameter estimates for enfortumab vedotin concentration and QTcF Interval Change from Baseline

| Parameter | Estimate | SE | 95% CI | p-value |
|---|---|---|---|---|
| Intercept (msec) | -12.3 | 7.99 | (-28.3, 3.61) | 0.127 |
| Slope (msec/(µg/mL)) | 0.539 | 0.344 | (-0.156, 1.23) | 0.125 |

CI: confidence interval; QTcF: QT interval corrected for heart rate according to Fridericia's formula; SE: standard error. Source: [7465-PK-0012, Table 2]

**Table 41** Linear mixed effects model parameter estimates for MMAE

**Concentration and QTcF Interval Change from Baseline**

| Parameter | Estimate | SE | 95% CI | p-value |
|---|---|---|---|---|
| Intercept (msec) | 0.0923 | 2.38 | (-4.78, 4.97) | 0.969 |
| Slope (msec/(ng/mL)) | -2.40 | 2.21 | (-7.11, 2.31) | 0.295 |

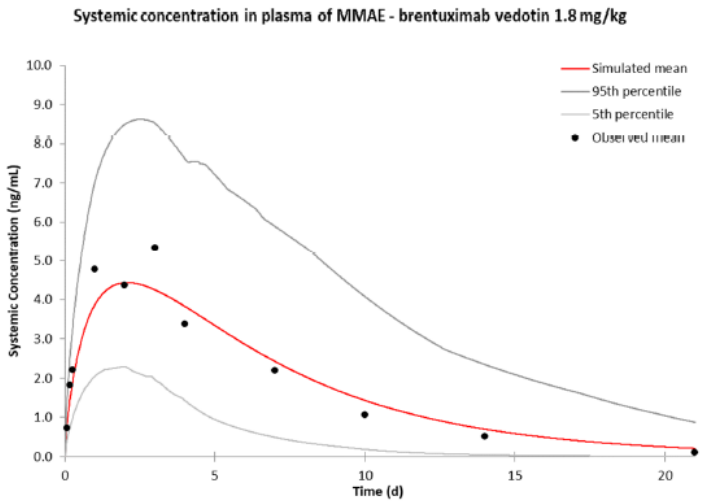
CI: confidence interval; MMAE: monomethyl auristatin E; QTcF: QT interval corrected for heart rate according to Fridericia's formula; SE: standard error. Source: [7465-PK-0012, Table 3]

## PBPK models

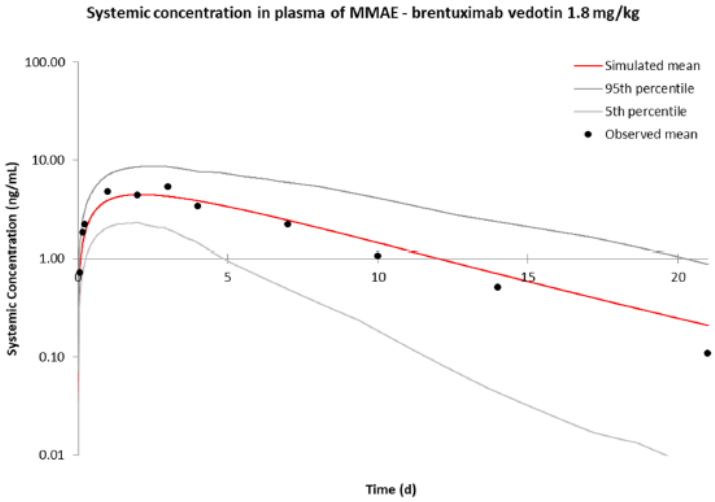
Brentuximab vedotin is an ADC conjugated to MMAE with a similar linker as enfortumab vedotin. The impact of ADC on midazolam (CYP3A4 substrate) and the impact of rifampin (CYP3A4 and P-gp inducer) and ketoconazole (CYP3A4 and P-gp inhibitor) on ADC and MMAE have been investigated in a published clinical DDI study with brentuximab vedotin [Han TH et al, 2013].

PBPK models were built for brentuximab vedotin and for enfortumab vedotin and verified against independent clinical PK data. Both models could reasonably well simulate observed concentration-time profiles after single dose and also after multiple dose administrations for enfortumab vedotin.

**a) Linear Plot**




**b) Semi-log Plot**

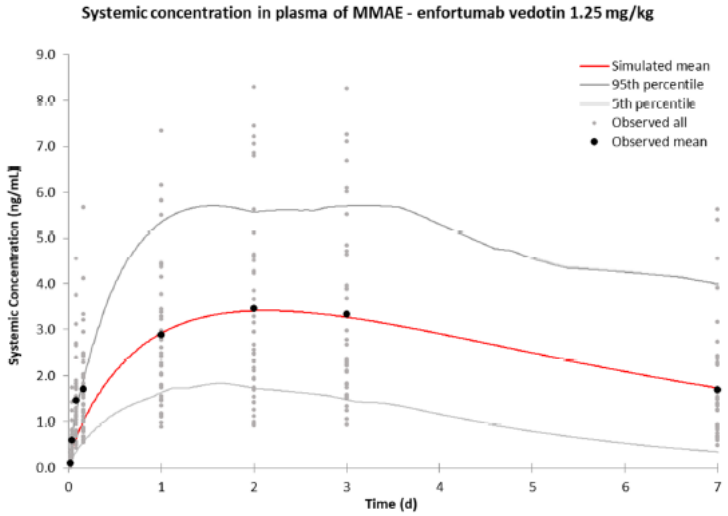



Simulated average (red line), simulated 95th and 5th percentiles (grey lines), observed mean (black filled circles)

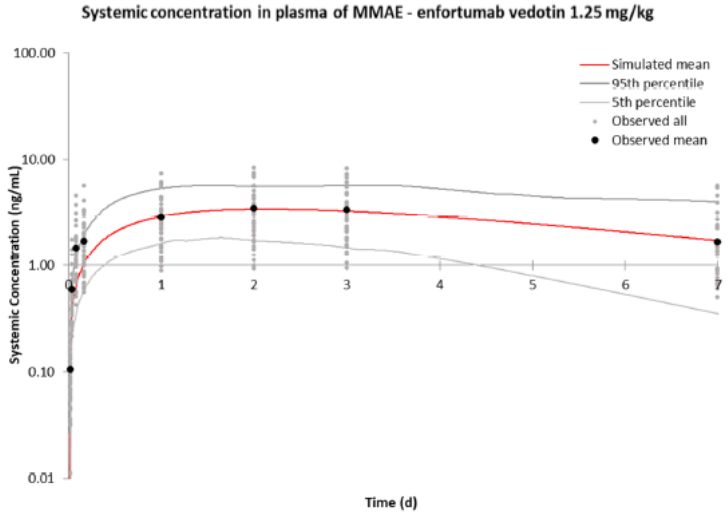
**Figure 23** Simulated and Observed Plasma Concentration-time Profile of MMAE following a single IV dose of Brentuximab Vedotin 1.8mg/kg

Both models could reasonably well simulate observed concentration-time profiles after single dose and also after multiple dose administrations for enfortumab vedotin.

**a) Linear Plot**




**b) Semi-log Plot**

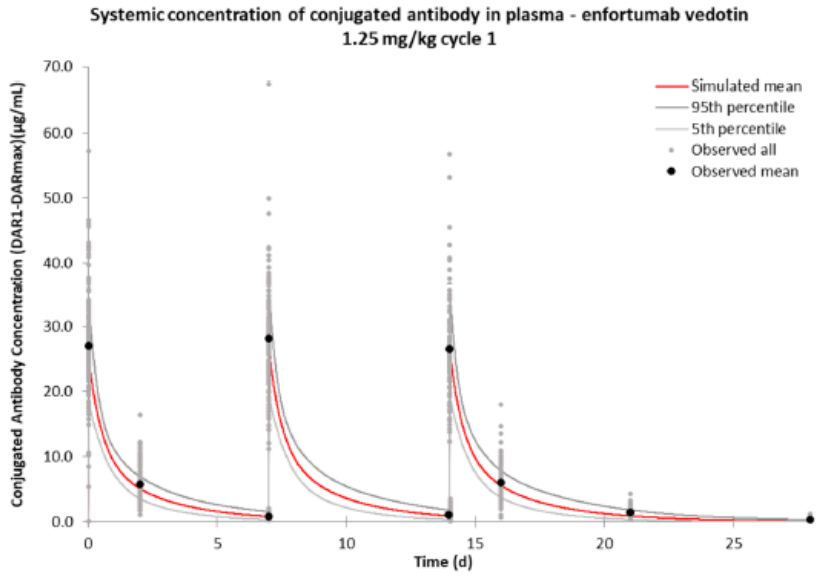



Simulated average (red line), simulated 95th and 5th percentiles (grey lines), observed mean (black filled circles), observed population (grey filled circles)

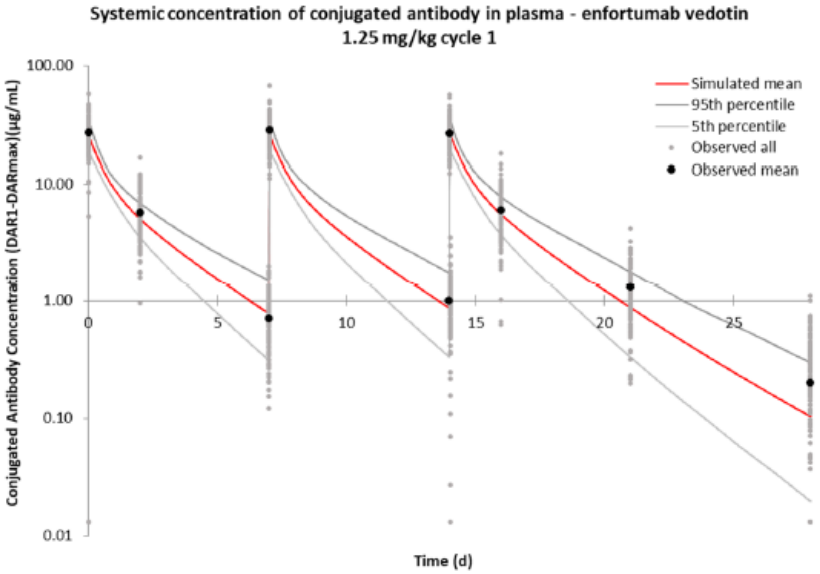
**Figure 24** Simulated and Observed Plasma Concentration-time Profile of MMAE following a single IV dose of 1.25 mg/kg Enfortumab Vedotin

Both models could reasonably well simulate observed concentration-time profiles after single dose and also after multiple dose administrations for enfortumab vedotin.

**a) Linear Plot**



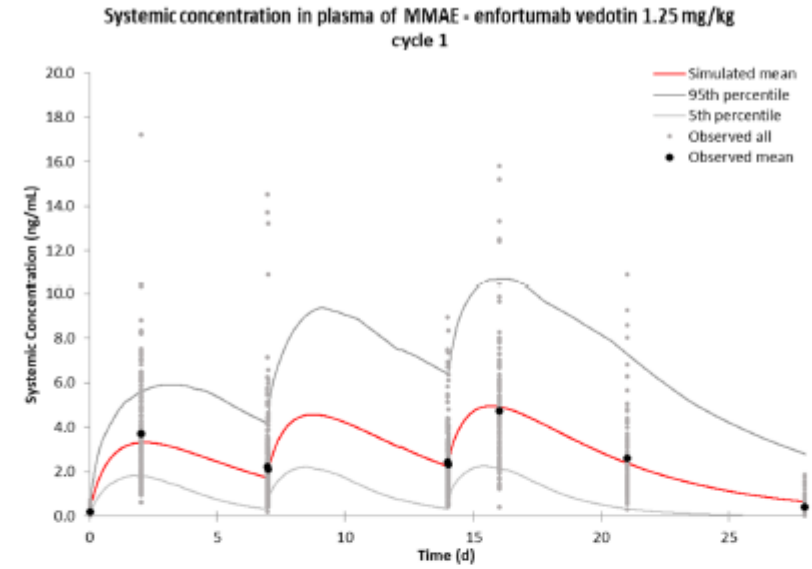

**b) Semi-log Plot**



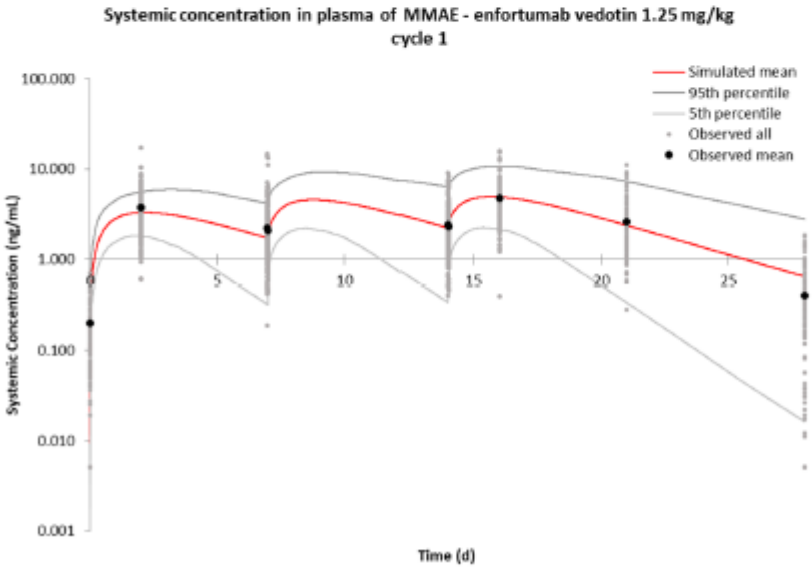

Simulated average (red line), simulated 95$^{th}$ and 5$^{th}$ percentiles (grey lines), observed mean (black filled circles), observed population (grey filled circles)

**Figure 25** Simulated and Observed Plasma Concentration-time Profile of enfortumab vedotin following multiple IV dose of 1.25 mg/kg on days 1, 8 and 15 of 28 day cycle

**a) Linear Plot**




**b) Semi-log Plot**




Simulated average (red line), simulated 95th and 5th percentiles (grey lines), observed mean (black filled circles), observed population (grey filled circles)

**Figure 26** Simulated and Observed Plasma Concentration-time Profile of MMAE following multiple IV dose of enfortumab vedotin 1.25 mg/kg on days 1, 8 and 15 of 28 day cycle

Predicted effects of brentuximab vedotin on midazolam, rifampin on ADC and MMAE in addition to ketoconazole on ADC and MMAE, were comparable to the published observed in terms of mean exposure ratios of Cmax and AUC. The brentuximab vedotin model utilized the same MMAE parameters as the enfortumab vedotin model.

**Table 42** The observed and predicted effects of ketoconazole or rifampin on enfortumab vedotin or brentuximab vedotin PK parameters and the effects of enfortumab vedotin or brentuximab vedotin on midazolam or digoxin PK parameters

| | | Observed† | | Simulated | | P/O Ratio | |
|---|---|---|---|---|---|---|---|
| | | $AUC_{inf}$ Ratio | $C_{max}$ Ratio | $AUC_{last}$ Ratio | $C_{max}$ Ratio | AUC Ratio | $C_{max}$ Ratio |
| **Ketoconazole (combined P-gp and strong CYP3A inhibitor)** | | | | | | | |
| **brentuximab vedotin 1.2 mg/kg** | GM | 1.34 | 1.25 | 1.37 | 1.15 | 1.02 | 0.92 |
| | 90% CI | 0.98 – 1.84 | 0.90 – 1.72 | 1.35 – 1.39 | 1.14 – 1.16 | | |
| **enfortumab vedotin 1.25 mg/kg** | GM | - | - | 1.38 | 1.15 | | |
| | 90% CI | - | - | 1.35 – 1.41 | 1.14 – 1.16 | | |
| **Rifampin (combined P-gp and strong CYP3A inducer)** | | | | | | | |
| **brentuximab vedotin 1.8 mg/kg** | GM | 0.54 | 0.56 | 0.47 | 0.70 | 0.89 | 1.25 |
| | 90% CI | 0.43 – 0.68 | 0.42 – 0.76 | 0.46 – 0.49 | 0.69 – 0.70 | | |
| **enfortumab vedotin 1.25 mg/kg** | GM | - | - | 0.47 | 0.72 | | |
| | 90% CI | - | - | 0.46 – 0.49 | 0.71 – 0.73 | | |
| **Midazolam (CYP3A4 substrate)** | | | | | | | |
| **brentuximab vedotin 1.8 mg/kg** | GM | 0.94 | 1.15 | 1.20 | 1.00 | 1.28 | 0.87 |
| | 90% CI | 0.81 – 1.10 | 0.76 – 1.74 | 1.18 – 1.21 | 1.00 – 1.00 | | |
| **enfortumab vedotin 1.25 mg/kg** | GM | - | - | 1.14 | 1.00 | | |
| | 90% CI | - | - | 1.13 – 1.16 | 1.00 – 1.00 | | |
| **Digoxin (P-gp substrate)** | | | | | | | |
| brentuximab vedotin 1.8 mg/kg | GM | - | - | 1.00 | 1.00 | | |
| | 90% CI | - | - | 1.00 – 1.00 | 1.00 – 1.00 | | |
| enfortumab vedotin 1.25 mg/kg | GM | - | - | 1.00 | 1.00 | | |
| | 90% CI | - | - | 1.00 – 1.00 | 1.00 – 1.00 | | |

GM: geometric mean

P/O: predicted/observed

90% CI: 90% confidence interval

†Cited from [Han TH et al., 2013], Table 2

## Absorption

The product is intended for intravenous administration, bio availability is therefore 100%, and the Cmax occurred at the end of infusion. The pharmacokinetic investigations included assessments of concentrations of both ADC, MMAE and Total Antibody (TAb).

**Study EV-101** investigated Cmax and AUC in subjects from the target population, (i.e. Part C which include subjects with mUC who had been previously treated with a check point inhibitor (CPI) in the metastatic setting) (Table 48**,** Table 49**,** Table 50)

**Table 43** Summary of Pharmacokinetic Parameters of ADC, Dose-escalation Phase (Part A) and Part C; Study EV-101

| **Cycle** Parameter | **Dose (mg/kg); GeoMean (%CV)** | | | | |
|---|---|---|---|---|---|
| | **Part A** | | | | **Part C** |
| | **0.5** | **0.75** | **1.0** | **1.25** | **1.25** |
| **Cycle 1, Dose 1/ Day 1** | | | | | |
| **n**† | 2 | 14 | 27 | 38 | 72 |
| Cmax; µg/mL | NA | 18.4 | 22.3 | 28.2 | 30.6 |

| | | | | | |
|---|---|---|---|---|---|
| AUC(d0-7); day·µg/mL | NA | 19.7 | 27.9 | 33.7 | 36.7 |
| **Cycle 1, Dose 3/ Day 15** | | | | | |
| **n**† | 2 | 12 | 23 | 25 | 25 |
| Cmax; µg/mL | NA | 18.9 | 22.5 | 29.4 | 33.6 |
| AUC(d0-7); day·µg/mL | NA | 24.4 | 37.1 | 41.6 | 44.3 |
| Rac (Cmax) | NA | 1.14 | 1.05 | 1.10 | 1.13 |
| Rac (AUC) | NA | 1.13 | 1.25 | 1.20 | 1.23 |
| **Cycle 2, Predose 1/ Day 1** | | | | | |
| **n** | NA | | | | 51 |
| Serum trough concentration; | | | | | 140 (132)‡ |

† Indicates the maximum n number across all pharmacokinetic parameters
‡ The GeoMean (%CV) are NA, therefore the mean (SD) are presented in this table.
ADC: antibody-drug conjugate; CV: coefficient of variation; Geo: geometric; NA: not applicable; Rac: accumulation ratio (day 15 to day 1).
Source: [EV-101 CSR, Table 12.4.2.1 and Table 12.4.1.4]

**Table 44** Summary of Pharmacokinetic Parameters of MMAE, Dose-escalation Phase (Part A) and Part C; Study EV-101

| **Cycle** Parameter | **Dose (mg/kg); GeoMean (%CV)** | | | | |
|---|---|---|---|---|---|
| | **Part A** | | | | **Part C** |
| | **0.5** | **0.75** | **1.0** | **1.25** | **1.25** |
| **Cycle 1, Dose 1/ Day 1** | | | | | |
| **n**† | 2 | 15 | 29 | 37 | 72 |
| Cmax; ng/mL | NA | 1.59 | 2.58 | 3.03 (65.5) | 3.35 |
| AUC(d0-7); day·ng/mL | NA | 5.25 | 13.3 | 16.0 (72.4) | 18.3 |
| **Cycle 1, Dose 3/ Day 15** | | | | | |
| **n**† | 2 | 12 | 23 | 26 | 56 |
| Cmax; ng/mL | NA | 2.01 | 2.89 | 3.69 (56.2) | 4.43 |
| AUC(d0-7); day·ng/mL | NA | 9.29 | 14.0 | 17.4 (52.8) | 20.5 |
| Rac (Cmax) | NA | 1.32 | 1.14 | 1.52 (64.9) | 1.21 |
| Rac (AUC) | NA | 1.28 | 1.00 | 1.63 (91.9) | 1.34 |
| **Cycle 2, Predose 1/ Day 1** | | | | | |
| **n** | NA | | | | 49 |
| Serum trough concentration; | | | | | 274 |

CV: coefficient of variation; Geo: geometric; MMAE: monomethyl auristatin E; NA: not applicable; PKAS: pharmacokinetic analysis set; Rac: accumulation ratio (day 15 to day 1).
† Indicates the maximum number across all pharmacokinetic parameters Source: [EV-101 CSR, Table 12.4.2.2 and Table 12.4.1.5]

**Table 45** Summary of Pharmacokinetic Parameters of TAb, Dose-escalation Phase (Part A) and Part C; Study EV-101

| **Cycle** Parameter | **Dose (mg/kg); GeoMean (%CV)** | | | | |
|---|---|---|---|---|---|
| | **Part A** | | | | **Part C** |
| | **0.5** | **0.75** | **1.0** | **1.25** | **1.25** |
| **Cycle 1, Dose 1/ Day 1** | | | | | |
| **n**† | 2 | 14 | 27 | 34 | 71 |
| Cmax; µg/mL | NA | 19.1 | 26.1 | 35.2 | 40.5 (45.1) |
| AUC(d0-7); day·µg/mL | NA | 40.4 | 55.5 | 75.9 | 89.3 (38.2) |
| **Cycle 1, Dose 3/ Day 15** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| **n**† | 2 | 12 | 24 | 26 | 57 |
| Cmax; µg/mL | NA | 21.6 | 28.1 | 41.4 | 45.3 (40.4) |
| AUC(d0-7); day·µg/mL | NA | 52.2 (17.9) | 73.6 (34.4) | 101.0 (22.4) | 116.0 (41.1) |
| Rac (Cmax) | NA | 1.14 | 1.17 | 1.26 | 1.17 (37.7) |
| Rac (AUC) | NA | 1.32 | 1.41 | 1.42 | 1.39 (17.9) |
| **Cycle 2, Predose 1/ Day 1** | | | | | |
| **n** | NA | | | | 51 |
| Serum trough concentration; | | | | | 2.56 |

ADC: antibody-drug conjugate; CV: coefficient of variation; Geo: geometric NA: not applicable; Rac: accumulation ratio (day 15 to day 1); TAb: total antibody.
† Indicates the maximum number across all pharmacokinetic parameters.
‡ The GeoMean (%CV) are NA, therefore the mean (SD) are presented in this table. Source: [EV-101 CSR, Table 12.4.2.3 and Table 12.4.1.6]

**Distribution**

Based on the population pharmacokinetic analysis, following a 1.25 mg/kg enfortumab vedotin intravenous dose, population mean total volume of distribution at steady state (sum of volume distribution to central and peripheral compartments) was estimated to be 12.8 L.

**Metabolism**

As enfortumab vedotin is a monoclonal antibody, no dedicated drug metabolism studies were performed. However, in vitro studies showed that MMAE was metabolized in human liver microsomes primarily by CYP3A4, with minor contribution from CYP2D6.

**Elimination**

According to the population PK analysis, the mean clearance of enfortumab vedotin and free MMAE in patients was estimated to be 0.110 L/h and 2.11 L/h, respectively.

Enfortumab vedotin and free MMAE exhibited multi-exponential declines with an elimination half-life of 3.6 days (87.2 h) and 2.6 days (61.2 h), respectively.

Based on Non-Compartmental Analysis (NCA) and across the clinical studies estimated half-life ranged from 3.04 to 5.19 d.

**Dose proportionality and time dependency**

**Study EV-101** investigated pharmacokinetics of escalating doses of enfortumab vedotin given as monotherapy in subjects with metastatic UC and other malignant solid tumours that express Nectin-4 (part A). Dose-proportionality was demonstrated for ADC, MMAE and Tab, within a dose range of 0,5 mg/kg – 1.25 mg/kg. Dose proportionality was assessed both after 1st dose, and after 3rd dose. See Table 51, Table 52, Table 53.

**Table 46** Statistical Assessment of Dose Proportionality for ADC (Power Model) Part A Cohort (PKAS); Study EV-101

| Dose Range | Dosing | Parameter | Slope Estimat | 90% CI of Slope |
|---|---|---|---|---|
| 0.5 mg/kg – 1.25 mg/kg | Cycle 1 1st dose | AUC(d0-7) (day·µg/mL) | 0.891 (0.139) | (0.660, 1.12) |
| | | Cmax (µg/mL) | 0.637 (0.152) | (0.384, 0.890) |
| | Cycle 1 3rd dose | AUC(d0-7) (day·µg/mL) | 1.01 (0.158) | (0.740, 1.27) |
| | | Cmax (µg/mL) | 0.529 (0.169) | (0.246, 0.812) |

ADC: antibody-drug conjugate; PKAS: pharmacokinetic analysis set. Source: [EV-101 CSR, Table 12.4.3.1]

**Table 47** Statistical Assessment of Dose Proportionality for MMAE (Power Model) Part A Cohort (PKAS); Study EV-101

| Dose Range | Dosing | Parameter | Slope Estimat | 90% CI of Slope |
|---|---|---|---|---|
| 0.5 mg/kg – 1.25 mg/kg | Cycle 1 1st dose | AUC(d0-7) (day·ng/mL) | 1.74 (0.459) | (0.964, 2.51) |
| | | Cmax (ng/mL) | 0.996 (0.283) | (0.525, 1.47) |
| | Cycle 1 3rd dose | AUC(d0-7) (day·ng/mL) | 0.946 (0.313) | (0.422, 1.47) |
| | | Cmax (ng/mL) | 0.952 (0.295) | (0.458, 1.45) |

MMAE: monomethyl auristatin E. Source: [EV-101 CSR, Table 12.4.3.2]

**Table 48** Statistical Assessment of Dose Proportionality for TAb (Power Model) Part A Cohort (PKAS); Study EV-101

| Dose Range | Dosing | Parameter | Slope Estimat | 90% CI of Slope |
|---|---|---|---|---|
| 0.5 mg/kg – 1.25 mg/kg | Cycle 1 1st dose | AUC(d0-7) (day·µg/mL) | 1.23 (0.160) | (0.966, 1.50) |
| | | Cmax (µg/mL) | 1.05 (0.165) | (0.772, 1.32) |
| | Cycle 1 3rd dose | AUC(d0-7) (day·µg/mL) | 1.39 (0.149) | (1.14, 1.64) |
| | | Cmax (µg/mL) | 1.23 (0.175) | (0.938, 1.52) |

PKAS: pharmacokinetic analysis set; TAb: total antibody. Source: [EV-101 CSR, Table 12.4.3.3]

**Intra- and inter- individual variability**

Based on the population pharmacokinetic analysis, the model predicted Cycle 1 AUC(0-28d) and Cmax, and evaluated for the covariates following: 1.25 mg/kg enfortumab vedotin (capped at 125 mg for body weights ≥100 kg) were within 0.85 to 1.27-fold of enfortumab vedotin exposures and 0.79 to 1.49-fold of free MMAE exposures for the reference population. The model-predicted Cycle 1 Ctrough were within 0.65 to 1.29-fold of enfortumab vedotin exposures and 0.68 to 1.53-fold of free MMAE exposures for the reference population. The range of effects for all the covariates relative to the reference population was within the observed variability in the modelling dataset for both analytes.

**Special populations**

**Impaired renal function**

Based on population pharmacokinetic analysis, the pharmacokinetics of enfortumab vedotin and MMAE were not affected by baseline renal function in subjects with mild, moderate or severe renal function.

**Impaired hepatic function**

Based on population pharmacokinetic analysis, the pharmacokinetics of enfortumab vedotin were not affected by baseline hepatic function in subjects with mild hepatic impairment and there was a 37% AUC increase in free MMAE exposure in patients with mild hepatic impairment compared to normal hepatic function, while exposure to enfortumab vedotin was not changed.

The TEAEs observed in patients with mild hepatic impairment in **study EV-301** were consistent with the TEAEs observed in patients with normal hepatic function. Thus, no dose adjustments are warranted for subjects with mild hepatic impairment.

**Age, gender and race**

The population pharmacokinetic model of enfortumab vedotin included various intrinsic covariates (i.e., age, race, sex and organ impairment). Though some covariates showed a difference in exposure, the magnitude of changes in exposure are not considered clinically meaningful.

**Weight**

Weight-based dosing with a dose cap of 125 mg for patients ≥100 kg for enfortumab vedotin was supported by population pharmacokinetic modelling and simulation analyses. Although a maximum tolerated dose (MTD) for enfortumab vedotin was not identified, a maximum absolute dose limit of 125 mg (dose cap) was implemented following the potential treatment related adverse events observed in obese subjects in the Phase 1 Study EV-101.

**Interactions**

**Coadministration of CYP3A4 substrates**

Formal drug-drug interaction studies with enfortumab vedotin have not been conducted, PBPK modeling was conducted to predict the drug-drug interaction potential of free MMAE. Based on PBPK analysis, concomitant use of enfortumab vedotin is predicted not to affect exposure to midazolam (a sensitive in vivo probe of CYP3A4 activity).

**Coadministration of CYP3A4 Inhibitors**

Based on PBPK analysis, when 1.25 mg/kg of enfortumab vedotin is co-administered with ketoconazole, a combined P-gp and strong CYP3A inhibitor, the geometric mean of $C_{max}$ and $AUC_{inf}$ for free MMAE is predicted to increase by 15% and 38%, respectively, with no change in ADC exposure.

**Coadministration of CYP3A4 inducers**

Based on PBPK modeling, when 1.25 mg/kg of enfortumab vedotin was administered with rifampin, a combined P-gp and strong CYP3A inducer, the $C_{max}$ and $AUC_{last}$ for free MMAE were predicted to decrease by 28% and 53%, respectively, with no change in ADC exposure.

**Immunogenicity**

A total of 590 patients were tested for immunogenicity to enfortumab vedotin 1.25 mg/kg; 15 patients were confirmed to be positive at baseline for antitherapeutic antibody (ATA), and in patients who were negative at baseline (N = 575), a total of 16 (2.8%) were positive postbaseline (13 transiently and 3 persistently).

## Pharmacodynamics

### Mechanism of action

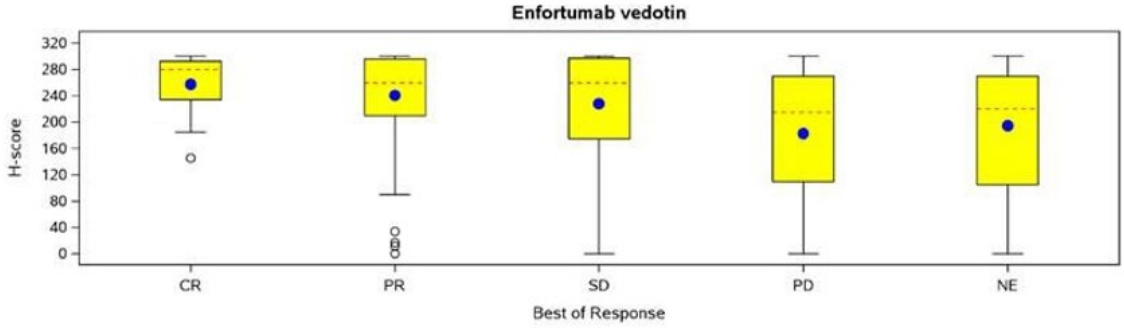
Enfortumab vedotin is an Antibody Drug conjugated (ADC) comprised of a fully human anti-Nectin-4 IgG1 kappa monoclonal antibody conjugated to the small molecule microtubule disrupting agent, MMAE via a protease-cleavable maleimidocaproyl valine-citrulline (vc) linker. The drug-linker is conjugated to the antibody via cysteine residues. The conjugation process results in an ADC product with a drug-to-antibody ratio of approximately 3.8.

Enfortumab vedotin is thought to induce cytotoxicity by ADC binding to Nectin-4 on the surface of cells, leading to internalization, proteolytic cleavage of the vc linker and release of MMAE that subsequently disrupts tubulin polymerization and leads to mitotic arrest and apoptotic cell death.

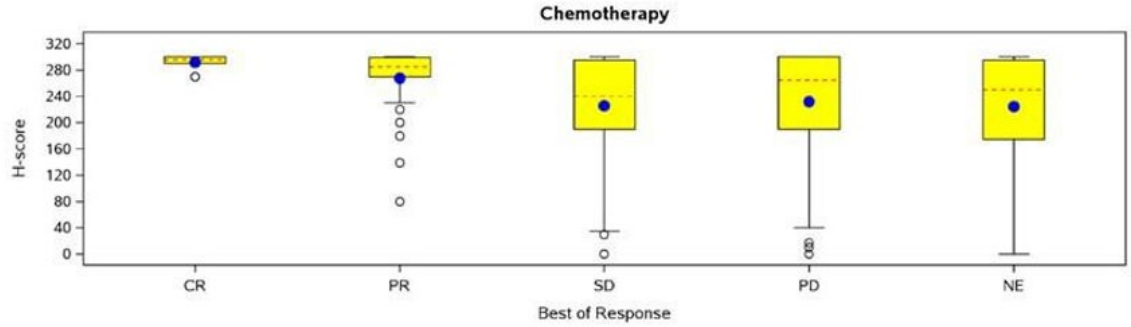
### Primary pharmacology

In the ongoing pivotal EV-301 study, 98% of subjects with evaluable Nectin-4 results had detectable (H-score > 0) Nectin-4 by immunohistochemistry (IHC). In both study arms, Nectin-4 was expressed at high levels, as evidenced by high median H-scores of 250 in the enfortumab vedotin arm and 270 in the chemotherapy arm, respectively (H-score range: 0 – 300).

A relationship between Nectin-4 expression and clinical response was assessed via box plots of baseline Nectin-4 IHC H-scores by best overall response (BOR) category Figure 32




| BOR | N | Mean | Std | Min | Max | Median | Q1 | Q3 |
|---|---|---|---|---|---|---|---|---|
| CR | 12 | 257.8 | 50.9 | 145.0 | 300.0 | 280.0 | 234.0 | 292.5 |
| PR | 95 | 240.5 | 68.9 | 0.0 | 300.0 | 260.0 | 210.0 | 296.0 |
| SD | 90 | 228.0 | 82.8 | 0.0 | 300.0 | 260.0 | 175.0 | 297.0 |
| PD | 40 | 183.0 | 103.5 | 0.0 | 300.0 | 215.0 | 110.0 | 270.0 |
| NE | 34 | 194.6 | 94.2 | 0.0 | 300.0 | 220.0 | 105.0 | 270.0 |




| BOR | N | Mean | Std | Min | Max | Median | Q1 | Q3 |
|---|---|---|---|---|---|---|---|---|
| CR | 6 | 291.8 | 11.7 | 270.0 | 300.0 | 295.5 | 290.0 | 300.0 |
| PR | 37 | 267.8 | 48.9 | 80.0 | 300.0 | 285.0 | 270.0 | 299.0 |
| SD | 96 | 225.7 | 74.9 | 0.0 | 300.0 | 240.0 | 190.0 | 295.0 |
| PD | 72 | 231.8 | 80.5 | 0.0 | 300.0 | 265.0 | 190.0 | 300.0 |
| NE | 45 | 224.2 | 81.1 | 0.0 | 300.0 | 250.0 | 175.0 | 295.0 |

BOR: best overall response; CR: complete response; FAS: Full Analysis Set; H-score: histoscore; Max: maximum; Min: minimum; NE: not evaluable; PD: progressive disease; PR: partial response; Q: quartile SD: stable disease; Std: standard deviation.

**Figure 27** Box plot of baseline H-score by Response (FAS), study EV-301

**Secondary pharmacology**

**Relationship between PK and QTcF data**

To assess the potential for QTcF interval prolongation, the effect of enfortumab vedotin on the duration of cardiac ventricular repolarization was evaluated. Enfortumab vedotin and MMAE concentration-time data and ECG data from cycle 1 of phase 1 in study EV-102 were analysed. In this study 17 Japanese patients with urothelial cancer were treated with 1.0 mg/kg (n=7) or 1.25 mg/kg (n=8) enfortumab vedotin. Blood samples and ECG data were drawn in Cycle 1,Day 1 pre-dose, End of infusion (EOI) , 0.5, 2, 4 (Day 1), and48 h post EOI (Day 3) and Cycle 1 Day 15 pre-dose, EOI, 0.5, 2, 4 (Day 15), and 48 h post EOI (Day 17).

QTc interval was corrected using Fridericia's formula ($QTcF = QT/(RR)^{1/3}$). Triplicate QTcF intervals were averaged and rounded to the nearest integer prior to analysis. Baseline was defined as the pre-dose on Cycle 1 Day 1 (C1D1) in triplicate. dQTcF intervals were calculated. The relationship between enfortumab vedotin or MMAE concentration and dQTcF intervals was assessed using the linear mixed effects model with the SAS MIXED procedure. A treatment effect was not included in the model since there was no placebo arm in the study.

Of the 17 patients, 15 were male, and 2 were female. The median age was 67.0 (57 - 82) years, weight at baseline was 64.20 (50.3 - 77.6) kg. A total of 157 observations in 17 patients were used for this analysis. One patient had a QTcF change from baseline > 30 ms at 2 h and 48 h post EOI during cycle 1 day 15 and the safety follow-up visit, respectively. No patients had a QTcF interval > 450 ms or a change from baseline > 60 ms. Clinically significant ECG abnormalities were noted in five patients as assessed by the investigators; two patients at the screening visit prior to dosing of enfortumab vedotin and three patients after enfortumab vedotin administration.

The dQTcF intervals predicted at the geometric mean $C_{max}$ for the dose of 1.25 mg/kg of enfortumab vedotin was 20.1 µg/mL and of MMAE 3.94 ng/mL. The $t_{max}$ of MMAE ranged from 1 to 3 days. Intra-cycle accumulation for $C_{max}$ in cycle 1 was 0.946 for enfortumab vedotin and 1.60 for MMAE at the 1.25 mg/kg dose. At the 1.0 mg/kg and 1.25 mg/kg, the observed concentrations for enfortumab vedotin were 0.0354 - 35.3 µg/mL and for MMAE and 0.0182 - 10.7 ng/mL, respectively.

A concentration-QTc interval model of dQTcF interval and enfortumab vedotin exposure using the linear mixed effects model provided a slope estimate of 0.539 ms/(µg/mL) with 90% CI (-0.0401, 1.12 ms/(µg/mL) Figure 33. For free MMAE a negative slope of -2.40 ms/(ng/mL) with 90% CI (-6.28, 1.48 ms/(ng/mL) was estimated. The slope estimates were not statistically significant.

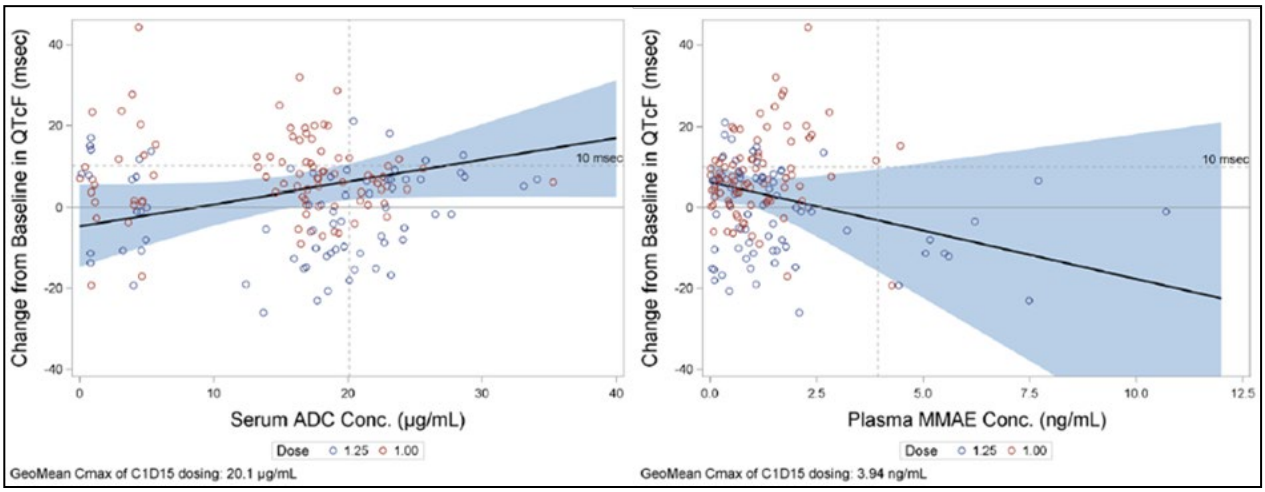



**Figure 28** Effect of the enfortumab vedotin (left) and MMAE (right) concentration on QTcF

The dQTcF intervals at a maximum dose of 1.25 mg/kg was estimated to occur at a geometric mean $C_{max}$ of 20.1 µg/mL for enfortumab vedotin and 3.94 ng/mL for MMAE after the 3rd dose during cycle 1 day 15 (Table 54). The estimated population mean (upper 1-sided 95% CI) for dQTcF intervals at 1.25 mg/kg was 6.17 (10.5) ms and - 3.14 (9.52) ms.

**Table 49** Predicted effects of enfortumab vedotin and MMAE on dQTcF intervals at the geometric mean $C_{max}$ at 1.25 mg/kg

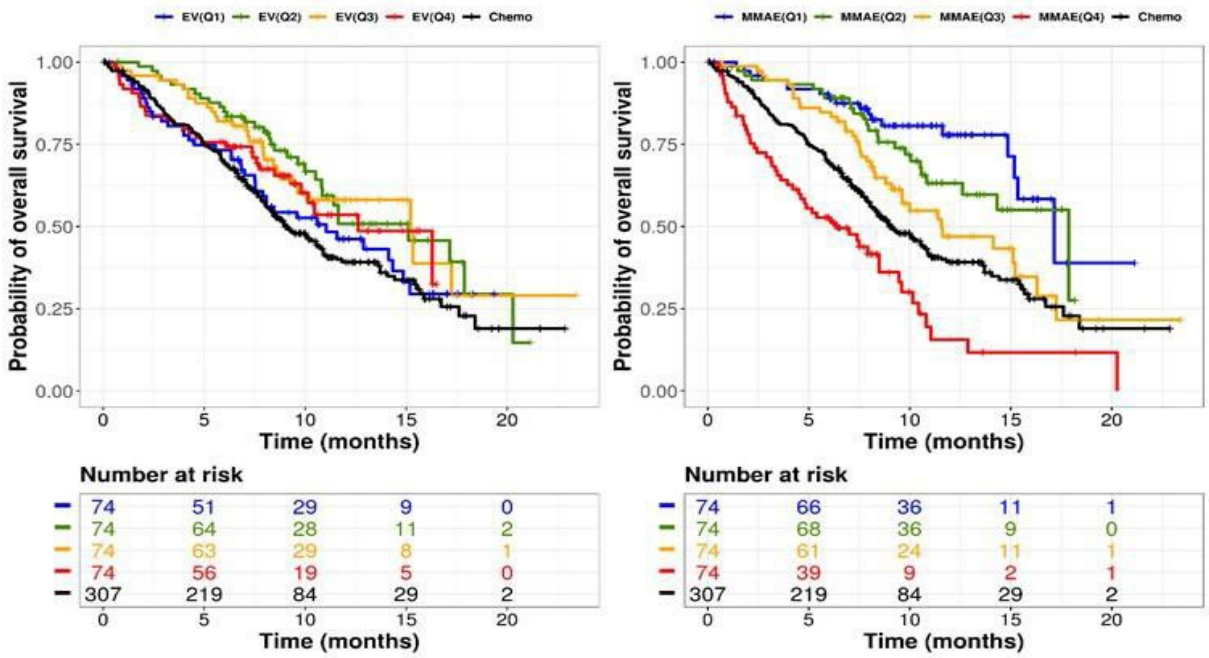
| Analyte | $C_{max}$ | Predicted dQTcF Interval (msec) | |
|---|---|---|---|
| | Geometric Mean | Mean ± SE | 90% CI for Mean |
| Enfortumab Vedotin | 20.1 (µg/mL) | 6.17 ± 2.53 | (1.83, 10.5) |
| MMAE | 3.94 (ng/mL) | -3.14 ± 7.22 | (-15.8, 9.52) |

CI: confidence interval; dQTcF: Change from baseline in QTcF; MMAE: monomethyl auristatin E; SE: standard error.

**Relationship between plasma concentration and effect**

**Exposure-response for efficacy**

Cox proportional hazard analysis of exposure-OS relationship in study EV-301 enfortumab vedotin (EV) arm and suggested that enfortumab vedotin Cavg was not a statistically significant predictor of OS. However, when compared to chemotherapy, all the 4 quartiles of enfortumab vedotin Cavg (median OS: 11.0 to 15.2 months) were associated with longer median OS than that of chemotherapy (8.96 months). Figure 34




Chemo: chemotherapy arm of study EV-301; OS: overall survival; Q1: Minimum to 25$^{th}$ percentile of Cavg; Q2: 25$^{th}$ to 50$^{th}$ percentile of Cavg; Q3: 50$^{th}$ – 75$^{th}$ percentile of Cavg; Q4: 75$^{th}$ percentile to maximum of Cavg.
Source: [7465-PK-0010, Figure 3]

**Figure 29** Kaplan-Meier Curves of OS by Enfortumab Vedotin (Left) and Free MMAE (Right) Exposure Quartiles in Study EV-301

**Exposure- safety**

The exposure-response analyses established that enfortumab vedotin Cavg was a statistically significant positive predictor for the probability of drug-related TEAEs Grade ≥ 3, TEAEs leading to dose adjustment, rash or severe cutaneous adverse reaction Grade ≥ 3, peripheral neuropathy Grade ≥ 2, and any hyperglycaemia Grade ≥ 3. The increase in enfortumab vedotin Cavg was associated with increase in the probability of these adverse events.

Free MMAE exposure was also identified as a statistically significant predictor for all the adverse events in the exposure-safety modeling except for any hyperglycaemia Grade ≥ 3. Increase in free MMAE $C_{avg}$ was associated with increase of probability of drug-related TEAEs Grade ≥ 3, TEAEs leading to dose adjustment and rash or severe cutaneous adverse reaction Grade ≥ 3, while with decreased probability of peripheral neuropathy Grade ≥ 2.

Overall, despite these relationships between enfortumab vedotin exposure and reported safety outcomes, treatment with 1.25 mg/kg enfortumab vedotin was generally well tolerated with a manageable safety profile in patients with advanced urothelial cancer.

## Discussion on clinical pharmacology

Serum of enfortumab vedotin (the conjugated monoclonal antibody)(ADC) was determined with validated ELISA assays. Free MMAE plasma concentrations (the unconjugated small molecule part of the drug) were determined using LC-MS/MS. Serum total antibody (TAb) and nAbs were determined using ELISA assays and Immunogenicity was tested by ELISA or ECLIA assays.

A 3-compartment model with first-order elimination and a 2-compartment model with first-order elimination and time-varying conversion rate from enfortumab vedotin was used to characterize the

concentration-time data of enfortumab vedotin and free MMAE, respectively. No target-mediated drug disposition model (TMDD) was tested during the model development procedure. Enfortumab vedotin and MMAE were not modelled in a combined model. Overall, the model for enfortumab vedotin seem able to describe the general trend of the concentration-time profiles. For MMAE, an under-prediction of the highly variable concentrations can be observed, in particular after the first dose, while this trend is reduced after the third dose. As the high variability of MMAE concentrations seems not to be captured very good by the model, the model-based assumptions for pharmacokinetics and dose/exposure-response, in particularly for MMAE, should be interpreted with caution. While different manufacturing processes lead to minor differences in exposure for enfortumab vedotin and free MMAE, the potential reasons for the observed differences remain unclear. Lower albumin levels were associated with higher MMAE exposure. Exposure-Response relations used cox proportional hazards modeling for overall survival (OS) data, and logistic regression models for best overall response (BOR) and for selected safety measures.

The effect of enfortumab vedotin and MMAE on QTc was best described by a linear model, indicating no general trend for an increased ΔQTcF with concentration.

No clinical DDI studies have been conducted. Physiologically-based pharmacokinetic (PBPK) models for both enfortumab vedotin and MMAE were used to assess potential DDI. A PBPK model was developed for brentuximab vedotin which is an ADC with MMAE and similar linker. Clinical DDI data for this compound were used to verify the brentuximab vedotin DDI model and to bridge to enfortumab vedotin. The PBPK model showed some limitations in the quantitative predictions which were considered minor in view of the overall weight of evidence supporting limited clinical impact in the population indicated for treatment. Concomitant use of enfortumab vedotin with ketoconazole (a combined P gp and strong CYP3A inhibitor) is predicted to increase unconjugated MMAE Cmax and AUCexposure to a minor extent, with no change in ADC exposure. Concomitant use of enfortumab vedotin with rifampin (a combined P gp and strong CYP3A inducer) is predicted to decrease unconjugated MMAE Cmax and AUC exposure with moderate effect, with no change in ADC exposure. The full impact of rifampin on the Cmax of MMAE may be underestimated in the PBPK model. Concomitant use of enfortumab vedotin is predicted not to affect exposure to midazolam (a sensitive CYP3A substrate) (see SmPC 5.2).

Five clinical studies form the basis of the pharmacokinetic profile of enfortumab vedotin: 3 phase 1 studies (Study AGS-22M6E-11-1, Study EV-101, and Study EV-102) one phase 2 study (Study EV-201, Cohorts 1 and 2) and a pivotal phase 3 study (EV-301).

Overall, the submitted pharmacology package describes the pharmacokinetic of enfortumab vedotin in details.

Based on these studies, a recommended dose selection of 1.25 mg/kg on days 1, 8 and 15 of a 28-day cycle was determined.

The effect of renal impairment has been appropriately investigated. The pharmacokinetics of ADC and unconjugated MMAE were evaluated after the administration of 1.25 mg/kg of enfortumab vedotin to patients with mild (CrCL >60–90 mL/min; n=272), moderate (CrCL 30–60 mL/min; n=315) and severe (CrCL 15–<30 mL/min; n=25) renal impairment. No significant differences in AUC exposure of ADC or unconjugated MMAE were observed in patients with mild, moderate or severe renal impairment compared to patients with normal renal function. Enfortumab vedotin has not been evaluated in patients with end stage renal disease (CrCL <15 mL/min) (see SmPC 5.2).

As for hepatic impairment, only data from patients with mild impairment are available. Based on population pharmacokinetics analysis using data from clinical studies in patients with metastatic UC, there was no significant differences in ADC exposure and a 37% increase in unconjugated MMAE AUC were observed in patients with mild hepatic impairment (total bilirubin of 1 to 1.5 × ULN and AST any, or total bilirubin ≤ ULN and AST > ULN, n=65) compared to patients with normal hepatic function. Weight

over 125 kg included in the pop PK analysis, and in one clinical study, was shown to increase the risk of adverse events. Enfortumab vedotin has only been studied in a limited number of patients with moderate hepatic impairment (n=3). The effect of moderate or severe hepatic impairment (total bilirubin >1.5 x ULN and AST any) or liver transplantation on the pharmacokinetics of ADC or unconjugated MMAE is unknown.

Concomitant administration of enfortumab vedotin and a CYP3A4 metabolised drug, did not show clinically relevant risk of inducing pharmacokinetic interactions.

No standalone pharmacodynamic studies have been performed which is in accordance with the EMA guideline on therapeutic proteins (CHMP/EWP/89249/2004) and thus acceptable. However, one clinical study has investigated whether use of enfortumab vedotin increases the risk of QTc prolongation (**Study EV-102**).

Study EV-102, investigating the relationship between antibody-drug conjugate (ADC) and MMAE concentrations and the QT interval corrected for heart rate according to Fridericia's formula (QTcF) and assessing the potential for QT prolongation, indicated that, at the recommended dose of 1.25 mg/kg, enfortumab vedotin had no large effect on QTc prolongation (>20 msec).

A relationship between Nectin-4 expression and clinical response has been investigated in Study EV-301 and is presented and discussed in the Efficacy section below.

Exposure-response relationship between clinically relevant concentrations of enfortumab vedotin, and free MMAE and the risk of adverse events were investigated in Study EV-301. The results showed that the increase in enfortumab vedotin Cavg, and free MMAE was associated with increase in the probability of adverse events. In general, these adverse events were well tolerated, and the safety was manageable.

Relationship between exposure and efficacy was investigated in Study EV-301. Kaplan-Meier Curves showing overall survival (OS) of Enfortumab Vedotin and free MMAE exposure quartiles in Study EV-301 were presented. Compared to chemotherapy, all 4 quartiles of enfortumab vedotin Cavg (median OS: 11.0 to 15.2 months) were associated with longer median OS than that of chemotherapy (8.96 months). This is considered to be of clinically relevance, and it shows a relationship between exposure and efficacy. However,free MMAE $C_{avg}$ was identified as a statistically significant negative predictor for OS in Study EV-301 and for best overall response (BOR) in Study EV-201 Cohort 2.

The reason for this relationship with MMAE seems unknown. Multiple confounding disease factors may have negatively impacted both exposure and response, as reported for other biologics [Wang et al, 2017; Kagedal et al, 2017; Li et al, 2017; Turner et al, 2018].

## Conclusions on clinical pharmacology

The clinical pharmacology programme consists of five clinical studies, a pop PK analysis, and a PBPK analysis

The mean estimate of steady state volume of distribution of ADC was 12.8 L following 1.25 mg/kg of enfortumab vedotin. In vitro, the binding of MMAE to human plasma proteins ranged from 68% to 82%. MMAE is not likely to displace or to be displaced by highly protein bound medicinal products. In vitro studies indicate that MMAE is a substrate of P glycoprotein. A small fraction of MMAE released from enfortumab vedotin is metabolised. In vitro data indicate that the metabolism of MMAE occurs primarily via oxidation by CYP3A4. The mean clearance of ADC and unconjugated MMAE in patients was 0.11 L/h and 2.11 L/h, respectively. ADC elimination exhibited a multi exponential decline with a half life of 3.6 days. Elimination of MMAE appeared to be limited by its rate of release from enfortumab vedotin. MMAE elimination exhibited a multi exponential decline with a half-life of 2.6 days. The excretion of MMAE occurs mainly in faeces with a smaller proportion in urine. After a single dose of another ADC that contained MMAE, approximately 24% of the total MMAE administered was recovered

in faeces and urine as unchanged MMAE over a 1 week period. The majority of recovered MMAE was excreted in faeces (72%). A similar excretion profile is expected for MMAE after enfortumab vedotin administration. Population pharmacokinetic analysis indicates that age [range: 24 to 90 years; 60% (450/748) >65 years, 19% (143/748) >75 years, race [69% (519/748) White, 21% (158/748) Asian, 1% (10/748) Black and 8% (61/748) others or unknown] and gender [73% (544/748) male] do not have a clinically meaningful effect on the pharmacokinetics of enfortumab vedotin (see SmPC 5.2).In conclusion, the pharmacology package is considered adequate and the proposed dosing of enfortumab vedotin is considered appropriate.

## *2.5. Clinical efficacy*

**Table 50:** Tabular overview of the relevant clinical studies**.**

| Study Identifier | Study Design and Type of Control | Population | Test Product(s); Dosage Regimen; Route of Administration | Duration of Treatment | Endpoints of the Study | Number of Subjects Enrolled (treated) | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|
| EV-301 (7465-CL-0301)† | Phase 3 global, open-label, randomized trial of enfortumab vedotin vs chemotherapy | Subjects with locally advanced or metastatic UC who have received a platinum-containing chemotherapy and have experienced disease progression or relapse during or following treatment with a PD-1 or PD-L1 inhibitor | Enfortumab vedotin: 1.25 mg/kg 30-min iv infusion on days 1, 8 and 15 of a 28-day cycle or Docetaxel 75 mg/m$^2$, paclitaxel 175 mg/m$^2$ or vinflunine 320 mg/m$^2$ on day 1 of a 21-day cycle | Until radiological disease progression as assessed by the investigator, or other discontinuation criteria are met | Primary: OS Secondary: PFS, ORR, DOR, DCR, safety and tolerability, quality of life and subject-reported outcome parameters | Enrolled: 608 (587) Arm A, enfortumab vedotin = 301 (296); Arm B, chemotherapy = 307 (291) | Ongoing (enrollment closed); Primary Analysis CSR |
| EV-201 (SGN22E-001)‡ | Phase 2, open-label, multicenter, multi-cohort study of enfortumab vedotin in subjects who have previously received a PD-1 or PD-L1 inhibitor | Cohort 1: Subjects with locally advanced or metastatic UC who have previously received a PD-1/ PD-L1 inhibitor and a platinum-containing chemotherapy Cohort 2: Subjects who have received a PD-1/PD-L1 inhibitor and are not eligible for cisplatin containing chemotherapy. | Enfortumab vedotin: 1.25 mg/kg 30-min iv infusion on days 1, 8 and 15 of a 28-day cycle | Until disease progression, unacceptable toxicity, investigator decision, consent withdrawal, start of subsequent anticancer therapy, pregnancy or study termination by the sponsor. | Primary: ORR Secondary: DOR, DCR$_{16}$, PFS, OS, PK, immunogenicity, safety and tolerability | Enrolled: 219 (214) Cohort 1 = 128 (125); Cohort 2 = 91 (89) | Ongoing (enrollment closed); Cohort 1 Primary Analysis CSR* and Cohort 2 primary analysis CSR |
| EV-101 (ASG-22CE-13-2)§ | Phase 1, open-label, nonrandomized, multicenter study of the safety and PK of escalating doses of enfortumab vedotin as monotherapy followed by expansion | Subjects with metastatic UC and other Nectin-4-expressing malignant solid tumors | Enfortumab vedotin: 0.5, 0.75, 1.0, 1.25 mg/kg 30-min iv infusion on days 1, 8 and 15 of a 28-day cycle | Until disease progression, intolerability of enfortumab vedotin, investigator decision or consent withdrawal | Primary: safety and PK Secondary: immunogenicity and antitumor activity | Enrolled: 213 (213) Part A: 87 Part B: 52 (NSCLC: 18 Ovarian: 16 Renal insufficiency: 18) Part C: 74 | Ongoing; Primary analysis CSR* and CSR Addendum for Renal Insufficiency Cohort |

† EV-301 data cutoff date is 15 Jul 2020

‡ EV-201 data cutoff is 01 Mar 2019 for cohort 1 primary analysis and 08 Sep 202 for cohort 2 primary analysis

§ EV-101 data cutoff date is 25 Oct 2018 for the primary analysis and 17 Feb 2020 for addendum to primary CSR that includes the renal insufficiency cohort

## 2.5.1. Dose response study(ies)

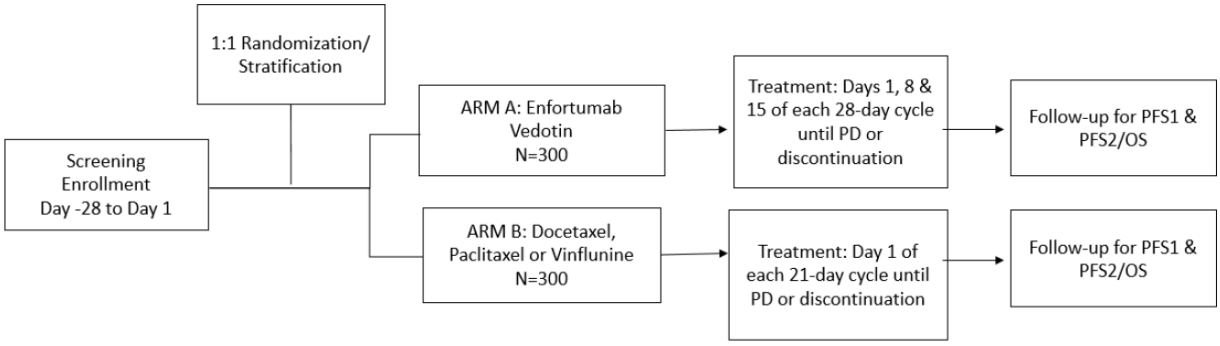
**Rationale for the Recommended dose selection**

Selection of the recommended dose of enfortumab vedotin was based on results from phase 1 clinical studies, Study AGS-22M6E-11-1 and Study EV-101. Based on the overall benefit/risk in Study EV-101, enfortumab vedotin at 1.25 mg/kg on days 1, 8 and 15 of a 28-day cycle was selected as the recommended for subsequent studies: Study EV-102, Study EV-201 and the pivotal study (Study EV-301).

## 2.5.2. Main study

**Study EV-301 (7465-CL-0301)** is a global, open-label, randomised phase III study in adult subjects with locally advanced or mUC who had received a platinum-containing chemotherapy and had experienced disease progression or relapse during or following treatment with PD-1 or PD-L1 inhibitors.

**Figure 30:** EV-301 study scheme




Approximately 600 subjects were to be randomized to enfortumab vedotin (Arm A) or chemotherapy (Arm B) in a 1:1 ratio.

Subjects started with cycle 1 and continued on to subsequent 21-day (Arm B) or 28-day (Arm A) cycles until one of the discontinuation criteria were met or upon study termination, or study completion, whichever occurred first.

Subjects were evaluated for response based on investigator assessment according to RECIST v1.1. Imaging for both arms was performed at baseline and every 56 days (± 7 days) from the first dose of study treatment throughout the study until PFS1 was documented by radiological disease progression or the subject was lost to follow-up, died, withdrew study consent or started a subsequent anticancer therapy.

Following PFS1, subjects entered the long-term follow-up period and were 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).

Vinflunine cap: Within the control arm, the overall proportion of subjects receiving vinflunine was to be capped at approximately 35%. After vinflunine cap was reached, subjects who had received both docetaxel and paclitaxel were to be excluded.

## *Methods*

## *Study Participants*

Key inclusion criteria:

1. Subject had 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 were eligible.
2. Subject must have experienced radiographic progression or relapse during or after a CPI (anti-PD-1 or anti-PD-L1) for locally advanced or metastatic disease. Subjects who discontinued CPI treatment because of toxicity were eligible provided that they had evidence of disease progression following discontinuation. The CPI need not have been the most recent therapy. Subjects for whom the most recent therapy had been a non-CPI based regimen were eligible if they had progressed/relapsed during or after their most recent therapy. Locally advanced disease must not have been amenable to resection with curative intent per the treating physician.
3. 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, the subject must have progressed within 12 months of completion.
4. Subject had radiologically documented metastatic or locally advanced disease at baseline.
5. An archival tumour tissue sample was to have been available for submission to central laboratory prior to study treatment. If an archival tumour tissue sample was not available, a fresh tissue sample was to have been provided. If a fresh tissue sample could not be provided because of safety concerns, enrolment into the study was to have been discussed with the medical monitor.
6. Subject had ECOG PS of 0 or 1.
7. Adequate hematologic and end-organ function, as defined by laboratory results.

Key exclusion criteria:

1. Subject had pre-existing sensory or motor neuropathy Grade ≥ 2.
2. Subject had active central nervous system (CNS) metastases. Subjects with treated CNS metastases were permitted on study if the metastases had been clinically stable for at least 6 weeks prior to screening;.
3. Subject had ongoing clinically significant toxicity (≥ Grade 2 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 have been enrolled when well-maintained/controlled on a stable dose of hormone replacement therapy (if indicated). Subjects with ongoing ≥ Grade 3 immunotherapy-related hypothyroidism or panhypopituitarism were 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) were excluded.
4. Subject had received prior chemotherapy for UC 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).

6. Subject had received more than 1 prior chemotherapy regimen for locally advanced or mUC, including chemotherapy for adjuvant or neo-adjuvant disease if recurrence had occurred within 12 months of completing therapy. The substitution of carboplatin for cisplatin was not to constitute a new regimen provided no new chemotherapeutic agents had been added to the regimen.
7. Subject had 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) were allowed.
8. Subject had known active hepatitis B, active hepatitis C or known history of HIV infection.
9. Subject had 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.
10. Subject has radiotherapy or major surgery within 4 weeks prior to first dose of study drug or chemotherapy, biologics, investigational agents, and/or antitumor treatment with immunotherapy that is not completed 2 weeks prior to first dose of study drug.
11. 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.
12. 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.
13. History of uncontrolled diabetes mellitus within 3 months of the first dose of study drug. Uncontrolled diabetes is defined as haemoglobin A1C (HbA1c) $\geq$ 8% or HbA1c between 7 and < 8% with associated diabetes symptoms (polyuria or polydipsia) that are not otherwise explained.

## *Treatments*

Enfortumab vedotin (EV) was 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.

Dose reduction to 1 mg/kg (a reduction of 1 dose level [to dose level – 1]) and to 0.75 mg/kg (a reduction of 2 dose levels [to dose level – 2]) was allowed depending on the type and severity of toxicity. Subjects requiring a dose reduction could be re-escalated by 1 dose level (i.e., subjects reduced to 0.75 mg/kg may only have been re-escalated to 1 mg/kg) provided the toxicity did not require study drug discontinuation and had returned to baseline or ≤ Grade 1. If the toxicity recurred, re-escalation was not permitted. Subjects with ≥ Grade 2 corneal AEs were not permitted to dose re-escalate.

Docetaxel was administered at 75 mg/m2 as an intravenous infusion on day 1 of every 21-day cycle. All subjects were to have been premedicated per local standard of care with corticosteroids.

Paclitaxel was administered at 175 mg/m2 as an intravenous infusion on day 1 of every 21-day cycle. All subjects were to have been premedicated prior to paclitaxel administration in order to prevent severe hypersensitivity reactions.

Vinflunine was administered at 320 mg/m2 as an intravenous infusion on day 1 of every 21-day cycle.

In general, treatment with the chemotherapy comparators (docetaxel, paclitaxel or vinflunine) was to have been withheld for drug-related Grade 4 hematologic toxicities and for nonhematologic toxicity ≥ Grade 3, and subsequent doses modified as per the protocol. Dose modifications were applied for all subsequent doses. Specific dose modification guidance for docetaxel, vinflunine and paclitaxel can be found in the protocol.

Crossover: No on-study crossover was allowed in the first three versions of the protocol. However, as of Amendment 3 (protocol version 4.0, 14-SEP-2020), a crossover extension study was implemented since the interim analysis resulted in a positive outcome: eligible Arm B subjects could be evaluated for eligibility for cross-over to EV treatment at the discretion of the subject and investigator.

Subjects assigned to the chemotherapy arm were not allowed to switch to a different chemotherapy treatment during study treatment.

## *Objectives*

The Primary objective was:

To compare the OS of subjects with locally advanced or mUC treated with enfortumab vedotin to the OS of subjects treated with chemotherapy.

Secondary objectives

- To compare progression-free survival (PFS) on study therapy (PFS1) per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 of subjects treated with enfortumab vedotin to subjects treated with chemotherapy
- To compare the overall response rate (ORR) per RECIST v1.1 of enfortumab vedotin to chemotherapy
- To evaluate the duration of response (DOR) per RECIST v1.1 of enfortumab vedotin and chemotherapy
- To compare the disease control rate (DCR) per RECIST v1.1 of enfortumab vedotin to chemotherapy
- To assess the safety and tolerability of enfortumab vedotin
- To assess quality of life (QOL) and patient-reported outcomes (PRO) parameters

Exploratory Objectives

- Exploratory genomic and/or other biomarkers in tumour tissue and in peripheral blood that may correlate with treatment outcome, including Nectin-4 expression
- To assess the pharmacokinetics of enfortumab vedotin (total antibody [TAb], ADC and MMAE)
- To assess the incidence of antitherapeutic antibodies (ATAs)
- To evaluate PFS in the next line of therapy (PFS2) in subjects treated with enfortumab vedotin compared to docetaxel, paclitaxel or vinflunine
- Healthcare resources utilization (HRU)

## *Outcomes/endpoints*

The primary endpoint was:

OS, defined as the time from the date of randomisation until the documented date of death from any cause. All events of death on or prior to analysis cut-off date will be included, regardless of whether the event occurred while the subject is still taking study drug or after the subject discontinue study drug.

Secondary endpoints were:

PFS1, defined as the time from the date of randomization until the date of documented radiological disease progression per investigator based on RECIST V1.1, or until death due to any cause, whichever occurs first.

Overall response rate (ORR), defined as the proportion of subjects with best overall response (BOR) as confirmed complete response (CR) or partial response (PR), per RECIST v1.1 as assessed by investigator.

DOR, defined as the time from the date of the first CR/PR (whichever is first recorded) that is subsequently confirmed as assessed by investigator to the date of documented disease progression or death due to any cause whichever occurs first.

Disease control rate (DCR), defined as the proportion of subjects with BOR of confirmed CR or confirmed PR or SD, per RECIST v1.1 as assessed by investigator.

Exploratory efficacy endpoints

Biomarkers: Nectin-4 and PD-L1 expression in tissue were tested using screening/baseline tumour tissue sample. Nectin-4 expression in tissue were assessed by IHC H-score. PD-L1 expression in tissue were assessed by IHC combined positive score (CPS) with validated IHC assay with monoclonal mouse anti-PD-L1, clone 22C3. Subjects may have also been tested for PD-L1 expression prior to enrolment and these PD-L1 test results (i.e., prior PD-L1 testing) were collected when available.

PFS in the next line of therapy (PFS2),defined as the time from randomization to subsequent disease progression after initiation of new anti-cancer therapy, or death from any cause, whichever occurs first.

## *Sample size*

Sample size was determined by primary endpoint OS. Assuming HR = 0.75 (median OS in Arm A and Arm B were 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.

The planned sample size 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).

Following these calculations, approximately 600 subjects were randomized in a 1:1 ratio to 2 treatment arms: EV (Arm A) and chemotherapy (Arm B).

## *Randomisation and blinding (masking)*

Subjects randomisation l occurred centrally through Interactive Response Technology (IRT). There were two treatment arms. Subjects were assigned randomly in a 1:1 ratio to Arm A (EV) OR Arm B (investigator's choice of paclitaxel, docetaxel or vinflunine). Investigators must have selected one treatment among the Arm B options before randomization occurred, to use in the event that the subject is randomized to the Arm B. Within the control arm (Arm B), the overall proportion of subjects receiving vinflunine was capped at approximately 35%.

Randomisation was stratified according to the following factors:

(1) ECOG PS: 0 vs. 1

(2) Region of the world: Western EU vs. US vs. Rest of World

(3) Liver metastasis status: Yes vs. No

## *Statistical methods*

Study population: The full analysis set (FAS) consists of all subjects who were randomized. This analysis set was in compliance with the ITT principle that includes all randomized subjects, the FAS was equivalent to the ITT population. The FAS was the primary analysis set for efficacy analyses except for response related efficacy endpoints. Demographic and baseline characteristics were summarized for the FAS. The response evaluable set (RES) was defined as all subjects in FAS who have measurable disease (per RECIST V1.1) per investigator at baseline. RES was used for primary efficacy analysis of response related endpoints, e.g., ORR and DCR.

Primary endpoint – OS: The distribution of OS was estimated for each treatment arm using Kaplan-Meier methodology and the primary analysis on comparing Arm A and Arm B was conducted using the log-rank test stratified by ECOG PS (0 vs. 1), region (US, EU and the Rest of world) and liver metastasis status (Yes vs. No) per IRT. In addition, stratified Cox proportional hazard model (same stratification factors as used for stratified log-rank test) was used to estimate the hazard ratio and the corresponding 95% confidence interval. Comparison of Arm A (EV) and Arm B (Chemotherapies) was tested at a planned interim analysis and the final (primary) analysis.

Censoring rules for OS: All events of death on or prior to analysis cutoff date were to be included, regardless of whether the event occurred while the subject was still taking study drug or after the subject discontinue study drug. Subjects who were still alive at the time of data cutoff date were censored at the last known alive date or at the analysis cutoff date, whichever was earlier. Subjects with death or last known alive date after the analysis cutoff date were censored at the analysis cutoff date.

Sensitivity analyses for OS: OS analyses based on unstratified log-rank test were performed to assess imbalance in the use of subsequent anti-cancer therapy (including subsequent use of EV) and to assess potential COVID-19 impact.

Secondary endpoint – investigator-based PFS1:

The distribution of PFS1 was estimated for each treatment arm using Kaplan-Meier methodology and compared between Arm A and Arm B using log-rank test stratified by ECOG PS (0 and 1), region (US, EU and the Rest of world) and liver metastasis status (Yes vs. No) per IRT. In addition, stratified Cox

proportional hazard model was used to estimate the hazard ratio and the corresponding 95% confidence interval.

Censoring rules for investigator-based PFS1

**Table 51** Censoring rules

**Censoring Rules for Primary and Sensitivity Analysis of PFS1**

| Situation | Primary Analysis | Sensitivity Analysis |
|---|---|---|
| No PD and no death; new anticancer treatment is not initiated | Censored at last disease assessment or randomization date if no post-baseline tumor assessment | Censored at last disease assessment or randomization date if no post-baseline tumor assessment |
| No PD and no death; new anticancer treatment is initiated | Censored at last disease assessment before new anticancer treatment or randomization date if no post-baseline tumor assessment before new anticancer treatment | Censored at last disease assessment before new anticancer treatment or randomization date if no post-baseline tumor assessment before new anticancer treatment |
| PD or death documented after ≤ 1 missed disease assessment | Progressed at date of documented PD or death | Progressed at date of documented PD or death |
| PD or death documented after ≥ 2 missed disease assessments | Censored at last disease assessment prior to the ≥ 2 missed disease assessment | Progressed at date of documented PD or death |

Sensitivity analysis for investigator-based PFS1

- PFS1 analysis based on unstratified log-rank test
- Sensitivity analysis on FAS when removing the censoring of PD or death events occurred after missing 2 consecutive tumour assessments.
- To assess potential COVID-19 impact, below sensitivity analyses maybe conducted:
    - Same as OS primary analysis, except that subjects died due to COVID-19 infection will be censored at the death date.
    - Same as OS primary analysis, but exclude the subjects died due to COVID-19 infection from the analysis.

Secondary endpoint – ORR: The comparison of ORR between Arm A and Arm B was performed using stratified CMH test. The primary analysis was performed on RES. In addition, ORR for each arm was estimated and corresponding 95% confidence interval was constructed.

Secondary endpoint – DCR: The comparison of DCR between Arm A and Arm B was performed using stratified CMH test. In addition, DCR for each arm was estimated and corresponding 95% confidence interval was constructed.

Subgroup analyses: In order to determine whether the treatment effect was consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for OS, PFS1 and ORR were estimated and plotted within each category of the following classification variables: age, sex, region, ECOG PS, liver metastases, pre-selected control therapy by INV, primary site of tumour, prior lines of systemic therapy, and best response to CPI.

Changes to study design and planned analyses

Several changes to the design and statistical methods were done while the study was ongoing, as part

of protocol amendments and SAP revisions. Details and justification regarding the main update to EV-301 study design, represented by the increase in sample size and targeted number of deaths, were provided. This increase was related to an increase in power (from 80 to 85%), and interim and multiplicity decision rules were adapted accordingly. These updates were introduced as part of protocol amendment 2 which was finalized on 11-DEC-2019. An OS analysis according to the original protocol plan for the interim analysis, i.e. based on the first 250 death events was also provided.

Multiplicity Adjustment:

The family-wise type I error rate for this study was strongly controlled at 2.5% (one -sided) that allows the study to declare positive on primary endpoint OS on the FAS population. OS was formally tested at both the interim analysis and final analysis according to the O'Brien-Fleming boundary per Lan and DeMets method.

Formal hypothesis testings on the selected secondary endpoints including PFS1, ORR and DCR, were performed hierarchically (per the order of PFS1-> ORR->DCR) only when the OS testing result was rejected. PFS1was planned to test at either the interim analysis or final analysis when OS was rejected. The significance level of PFS1 at the interim and final analysis was based on Pocock boundary per Lan and DeMets method. ORR and DCR were tested only once after both OS and PFS1 were rejected (at either IA or FA) and the test statistics was computed from the interim data. The significance level of both ORR and DCR were 0.025. DCR was to be tested after ORR was rejected.

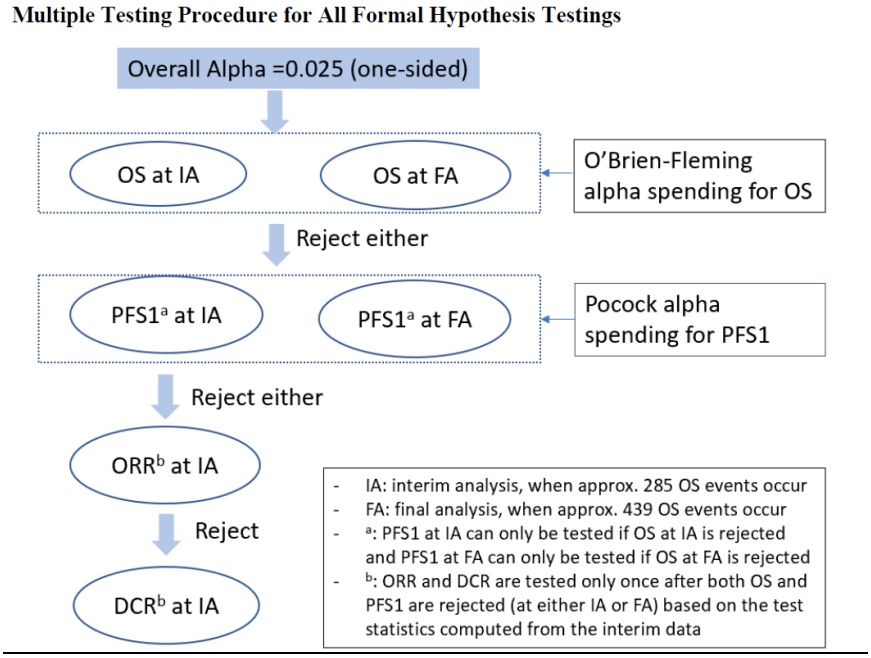



**Figure 31** Multiple testing Procedure

## *Results*

## Participant flow

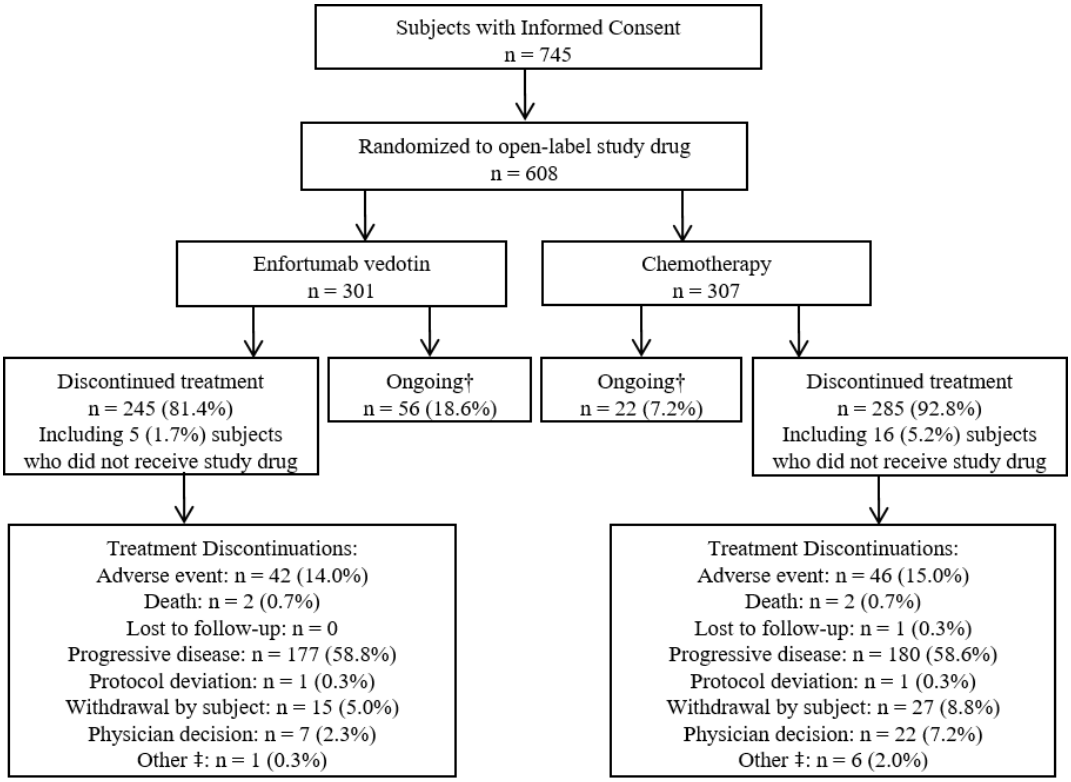
From 27-JUN- 2018 to 15-JUL-2020 (the study data cutoff date), a total of 745 subjects gave informed consent to be enrolled in the study. A total of 608 subjects were randomized from 02-JUL-2018 to 17-JAN-2020. Of the 608 randomized subjects, 587 subjects (296 subjects in the enfortumab vedotin arm and 291 subjects in the chemotherapy arm) received study drug.

Out of the 291 subjects that received treatment in the chemotherapy arm, 109 (37%) received docetaxel, 107 (37%) paclitaxel and 75 (26%) vinflunine.

Median follow-up of OS at data cutoff was 11.10 months across arms (11.10 in the EV arm and 11.07 in the chemotherapy arm).

One hundred and fifty-eighth study sites in 19 countries in North and South America, Europe, and the Asia-Pacific region randomized subjects in this study. Enrolment by region was 255 subjects (41.9%) in Western Europe, 87 subjects (14.3%) in the US and 266 subjects (43.8%) in Rest of the World.

**Figure 32** Subject Disposition: EV-301 (FAS)




Data cutoff date: 15 Jul 2020.

All subjects who were randomized (FAS).

† Subjects were still on-treatment by the data cutoff date (or no documentation of treatment discontinuation was received).

‡ Reasons for Other – enfortumab vedotin arm: because of COVID-19 travel restrictions; chemotherapy arm: hospitalization; 2 subjects received standard number of cycles of chemotherapy consistent with standard of care; chose weekly paclitaxel; subject had known sensitivity to alcohol confirmed after randomization; surgery.

**Table 52** Screening Failure (all subjects with informed consent)

Screening Failure
All Subjects With Informed Consent

| Parameter | Category | Total (N=745) |
|---|---|---|
| Screen Failure [1] | No | 608 ( 81.6%) |
| | Yes | 137 ( 18.4%) |
| Primary Screen Failure Reason [2] | Inclusion/Exclusion Criteria | 117 ( 15.7%) |
| | Withdrawal by Subject | 16 ( 2.1%) |
| | Study Terminated by Sponsor | 0 |
| | Other | 4 ( 0.5%) |

## Conduct of the study

The original protocol for EV-301 was dated 20-DEC-2017. There were 3 substantial amendments to the protocol.

Substantial amendment 1 (Protocol V2.0, 22-AUG-2018)

Whiting the 17 substantial amendments the following are considered clinically relevant:

- Update of the exclusion criteria
- Revision of the criteria detailing when imaging assessments every 56 days (± 7 days) were to end in the post-treatment follow-up period. Revision was done to be consistent with on treatment follow-up for PFS1. To evaluate the impact on missing visits, additional sensitivity analysis on PFS1 was to be conducted.
- Inclusion and definition of a new analysis set (response evaluable set [RES]) to use for efficacy analysis on ORR and DCR. Efficacy analysis on OS and PFS was to be conducted on the full analysis set. The pharmacodynamics analysis set was removed. The efficacy variables to be tested (only OS, PFS1, ORR and DCR) were stated formally and the multiplicity adjustment rule was included.
- Text was added to indicate that additional sensitivity analyses was to be performed for PFS1 for subjects censored when missing 2 consecutive tumour visits

For the subgroup analyses, 1 subgroup (burden of disease at baseline) was removed and existing subgroups (prior platinum, setting of most recent prior chemotherapy, histology, time from completion/discontinuation of most recent platinum-based prior therapy and the primary site of tumour) were clarified. Substantial amendment 2 (Protocol version 3.0, 11-DEC-2019)

- The number of death events at the final analysis was increased from 384 to 439 to rise the power of the study from 80% to 85%, and to ensure sufficient statistical power for final analysis and increased the total number of subjects to be randomized from 550 to 600; this was associated with the aforementioned increase in the number of death events and to maintain the analysis timeline. It also increased the number of death events for the planned interim efficacy analysis from at least 250 to 285 OS events (about 65% of the total planned events).
- Duration of treatment was amended and the text in **bold was** added: 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.

Substantial amendment 3 (Protocol version 4.0, 14-SEP-2020)

- A crossover extension (COE) was added to the study design. Upon decision to stop the study for efficacy based on statistically significant OS result favouring EV, all eligible Arm B subjects could be evaluated for eligibility for COE EV treatment at the discretion of the subject and investigator. Treatment with EV would be stopped upon disease progression and/or when discontinuation criteria were met. Arm B Subjects who did not participate in the COE would continue to follow Arm B protocol procedures.

**Protocol deviations**

**Table 53** Summary of major protocol deviations (FAS)

| Deviation Category | Enfortumab Vedotin (n = 301) | Chemotherapy (n = 307) |
|---|---|---|
| Any Major Deviation, n (%) | 21 (7.0) | 12 (3.9) |
| Protocol Deviation 1: Entered into the study even though they did not satisfy entry criteria, n (%) | 8 (2.7) | 9 (2.9) |
| Protocol Deviation 2: Developed withdrawal criteria during the study and was not withdrawn, n (%) | 8 (2.7) | 2 (0.7) |
| Protocol Deviation 3: Received wrong treatment or incorrect dose, n (%) | 4 (1.3) | 0 |
| Protocol Deviation 4: Received excluded concomitant treatment, n (%) | 1 (0.3) | 1 (0.3) |

All subjects who were randomized (FAS).
FAS: full analysis set.
Subjects deviating from a criterion more than once were counted once for the corresponding criterion. Any subjects who had more than one protocol deviation were counted once in the overall summary.

## Baseline data

The demographics and selected baseline characteristics for patients included in Full Analysis Set FAS) are summarized in the tables below.

**Table 54** Demographics and selected baseline characteristics (FAS)

| Parameter Statistics/Criteria | Enfortumab Vedotin (n = 301) | Chemotherapy (n = 307) | Total (n = 608) |
|---|---|---|---|
| Sex, n (%) | | | |
| Male | 238 (79.1) | 232 (75.6) | 470 (77.3) |
| Female | 63 (20.9) | 75 (24.4) | 138 (22.7) |
| Age (years) | | | |
| Mean (SD) | 66.52 (9.11) | 66.81 (9.93) | 66.67 (9.53) |
| Median (min, max) | 68.0 (34.0, 85.0) | 68.0 (30.0, 88.0) | 68.0 (30.0, 88.0) |

| | | | |
|---|---|---|---|
| **Age Category (years), n (%)** | | | |
| < 65 | 108 (35.9) | 111 (36.2) | 219 (36.0) |
| 65 to < 75 | 141 (46.8) | 128 (41.7) | 269 (44.2) |
| ≥ 75 | 52 (17.3) | 68 (22.1) | 120 (19.7) |
| **Race, n (%)** | | | |
| White | 159 (52.8) | 155 (50.5) | 314 (51.6) |
| Black or African American | 2 (0.7) | 2 (0.7) | 4 (0.7) |
| Asian | 97 (32.2) | 103 (33.6) | 200 (32.9) |
| Native Hawaiian or Other Pacific Islander | 0 | 1 (0.3) | 1 (0.2) |
| Not Reported | 43 (14.3) | 46 (15.0) | 89 (14.6) |
| **Ethnicity, n (%)** | | | |
| Hispanic or Latino | 29 (9.6) | 24 (7.8) | 53 (8.7) |
| Not Hispanic or Latino | 230 (76.4) | 238 (77.5) | 468 (77.0) |
| Not Reported | 42 (14.0) | 45 (14.7) | 87 (14.3) |
| **Weight (kg), n (%)** | | | |
| N | 301 | 307 | 608 |
| Mean (SD) | 74.51 (16.75) | 73.25 (15.90) | 73.87 (16.33) |
| Median (min, max) | 74.20 (40.0, 146.5) | 72.20 (37.3, 148.3) | 73.10 (37.3, 148.3) |
| **Body Mass Index ($kg/m^2$), n (%)** | | | |
| N | 301 | 306 | 607 |
| Mean (SD) | 25.68 (4.49) | 25.56 (4.86) | 25.62 (4.68) |
| Median (min, max) | 25.41 (15.9, 43.0) | 25.05 (14.5, 47.9) | 25.14 (14.5, 47.9) |
| **Body Mass Index Category ($kg/m^2$), n (%)** | | | |
| < 18.5 | 12 (4.0) | 15 (4.9) | 27 (4.4) |
| ≥ 18.5 to < 25 | 123 (40.9) | 136 (44.3) | 259 (42.6) |
| ≥ 25 to < 30 | 123 (40.9) | 107 (34.9) | 230 (37.8) |
| ≥ 30 | 43 (14.3) | 48 (15.6) | 91 (15.0) |
| Not Reported | 0 | 1 (0.3) | 1 (0.2) |
| **Renal Function †, n (%)** | | | |
| Normal | 48 (15.9) | 53 (17.3) | 101 (16.6) |
| Mild | 107 (35.5) | 110 (35.8) | 217 (35.7) |
| Moderate | 136 (45.2) | 139 (45.3) | 275 (45.2) |
| Severe | 4 (1.3) | 5 (1.6) | 9 (1.5) |
| Not reported | 6 (2.0) | 0 | 6 (1.0) |

All subjects who were randomized (FAS).
FAS: full analysis set; max: maximum; min: minimum.
† Cockcroft-Gault formula was used to estimate creatinine clearance. Normal: ≥ 90 mL/min; Mild: ≥ 60 and < 90 mL/min; Moderate: ≥ 30 and < 60 mL/min; Severe: ≥ 15 and < 30 mL/min.

**Table 55** Disease history and baseline characteristics (FAS)

| Parameter<br>Statistics/Criteria | Enfortumab Vedotin<br>(n = 301) | Chemotherapy<br>(n = 307) | Total<br>(n = 608) |
|---|---|---|---|
| **ECOG PS at Study Entry, n (%)** | | | |
| 0 | 120 (39.9) | 124 (40.4) | 244 (40.1) |
| 1 | 181 (60.1) | 183 (59.6) | 364 (59.9) |
| **Region, n (%)** | | | |
| Western Europe | 126 (41.9) | 129 (42.0) | 255 (41.9) |
| US | 43 (14.3) | 44 (14.3) | 87 (14.3) |
| Rest of the World | 132 (43.9) | 134 (43.6) | 266 (43.8) |
| **Liver Metastasis, n (%)** | | | |
| Yes | 93 (30.9) | 95 (30.9) | 188 (30.9) |
| No | 208 (69.1) | 212 (69.1) | 420 (69.1) |
| **Primary Disease Site of Origin†, n (%)** | | | |
| Upper Tract | 98 (32.6) | 107 (34.9) | 205 (33.7) |
| Bladder/Other | 203 (67.4) | 200 (65.1) | 403 (66.3) |
| **Current Extent of Disease, n (%)** | | | |
| Metastatic | 290 (96.3) | 289 (94.1) | 579 (95.2) |
| Locally Advanced | 11 (3.7) | 18 (5.9) | 29 (4.8) |
| **Histology Type at Initial Diagnosis, n (%)** | | | |
| Urothelial Carcinoma/Transitional Cell | 229 (76.1) | 230 (75.4) | 459 (75.7) |
| Urothelial Carcinoma Mixed | 45 (15.0) | 42 (13.8) | 87 (14.4) |
| Other ‡ | 27 (9.0) | 33 (10.8) | 60 (9.9) |
| Unknown | 0 | 2 (0.7) | 2 (0.3) |
| **Visceral Metastasis§, n (%)** | | | |
| Yes | 234 (77.7) | 250 (81.7) | 484 (79.7) |
| No | 67 (22.3) | 56 (18.3) | 123 (20.3) |
| Missing | 0 | 1 (0.3) | 1 (0.2) |
| **Lymph Node Only Metastasis, n (%)** | | | |
| Yes | 34 (11.3) | 28 (9.2) | 62 (10.2) |
| No | 267 (88.7) | 278 (90.8) | 545 (89.8) |
| Missing | 0 | 1 (0.3) | 1 (0.2) |

ECOG PS: Eastern Cooperative Oncology Group Performance Status; FAS: Full Analysis Set.
† Upper tract included renal pelvis and ureter. Bladder/other included urethra, bladder and other.
‡ Other histologies include adenocarcinoma, squamous cell carcinoma and pseudosarcomatic differentiation.
§ Subjects had baseline tumor results at the locations of lung, liver, spleen, adrenal gland, kidney, heart, colon, bone or prostate gland.

**Table 56** Baseline biomarker results (FAS)

| | Enfortumab Vedotin (n = 301) | Chemotherapy (n = 307) | Total (n = 608) |
|---|---|---|---|
| **Nectin-4 IHC H Score (tissue)** | | | |
| N † | 271 | 256 | 527 |
| Mean (SD) | 222.8 (84.61) | 234.8 (75.22) | 228.6 (80.34) |
| Median (min, max) | 250.0 (0, 300) | 270.0 (0, 300) | 258.0 (0, 300) |
| **Nectin-4 IHC H Score Category (tissue)** | | | |
| < 150 | 47 (17.3) | 36 (14.1) | 83 (15.7) |
| ≥ 150 to ≤ 225 | 66 (24.4) | 57 (22.3) | 123 (23.3) |
| > 225 | 158 (58.3) | 163 (63.7) | 321 (60.9) |
| Missing | 30 ⁋ | 51 ⁋ | 81 |
| **PD-L1 IHC ‡ Combined Positive Score (tissue), N (%) †** | | | |
| N † | 254 | 243 | 497 |
| CPS < 10 | 180 (70.9) | 170 (70.0) | 350 (70.4) |
| CPS ≥ 10 | 74 (29.1) | 73 (30.0) | 147 (29.6) |
| Missing | 47 ⁋ | 64 ⁋ | 111 |

CPS: combined positive score; FAS: Full Analysis Set; IHC: immunohistochemistry; max: maximum; min: minimum; N: number of subjects with evaluable data; PD-L1: programmed cell death-ligand 1.

† Number of subjects with evaluable data. Data was not available for some subjects because of inadequate tissue quality or quantity, or unavailable tissue.

‡ A validated IHC assay with monoclonal mouse anti-PD-L1, clone 22C3 was used. A CPS ≥ 10 is interpreted as PD-L1 high.

⁋ Data was not available for some subjects because of inadequate tissue quality or quantity, or unavailable tissue.

Baseline tumor tissue biomarker results were obtained from validated ICH assay

**Table 57** Prior procedures and radiation therapy for primary cancer (FAS)

| | Enfortumab Vedotin (n = 301) | Chemotherapy (n = 307) | Total (n = 608) |
|---|---|---|---|
| **Prior Procedures for Primary Cancer, n (%)** | | | |
| Yes | 277 (92.0) | 284 (92.5) | 561 (92.3) |
| No | 24 (8.0) | 23 (7.5) | 47 (7.7) |
| **Procedure, n (%)** | | | |
| Radical Cystectomy | 74 (24.6) | 75 (24.4) | 149 (24.5) |
| Partial Cystectomy | 15 (5.0) | 11 (3.6) | 26 (4.3) |
| Transurethral Resection of the Bladder Tumor | 155 (51.5) | 163 (53.1) | 318 (52.3) |
| Nephroureterectomy | 65 (21.6) | 73 (23.8) | 138 (22.7) |
| Other | 131 (43.5) | 135 (44.0) | 266 (43.8) |
| **Prior Radiation Therapy, n (%)** | | | |
| Yes | 96 (31.9) | 103 (33.6) | 199 (32.7) |
| No | 205 (68.1) | 204 (66.4) | 409 (67.3) |

**Table 58** Prior systemic anticancer therapy (FAS)

| Parameter | Enfortumab Vedotin (n = 301) | Chemotherapy (n = 307) | Total (n = 608) |
|---|---|---|---|
| **Prior Lines of Systemic Therapy under Locally Advanced or Metastatic Setting †, n (%)** | | | |
| 1 | 39 (13.0) | 32 (10.4) | 71 (11.7) |
| 2 | 223 (74.1) | 238 (77.5) | 461 (75.8) |
| ≥ 3 | 39 (13.0) | 37 (12.1) | 76 (12.5) |
| **Type of Prior CPI received ‡, n (%)** | | | |
| Nivolumab | 21 (7.0) | 13 (4.2) | 34 (5.6) |
| Pembrolizumab | 146 (48.5) | 144 (46.9) | 290 (47.7) |
| Atezolizumab | 86 (28.6) | 89 (29.0) | 175 (28.8) |
| Avelumab | 16 (5.3) | 13 (4.2) | 29 (4.8) |
| Durvalumab | 35 (11.6) | 56 (18.2) | 91 (15.0) |
| Other | 11 (3.7) | 11 (3.6) | 22 (3.6) |
| **PD-1/PD-L1 use, n (%)** | | | |
| PD-1 inhibitors only | 164 (54.5) | 150 (48.9) | 314 (51.6) |
| PD-L1 inhibitors only | 133 (44.2) | 151 (49.2) | 284 (46.7) |
| PD-1 and PD-L1 inhibitors | 3 (1.0) | 6 (2.0) | 9 (1.5) |
| **Type of Prior Platinum-based Treatment Received, n (%)** | | | |
| Cisplatin-based only | 193 (64.1) | 190 (61.9) | 383 (63.0) |
| Carboplatin-based Only | 74 (24.6) | 85 (27.7) | 159 (26.2) |
| Both Cisplatin-based and Carboplatin-based | 34 (11.3) | 31 (10.1) | 65 (10.7) |
| **CPI as Most Recent Therapy, n (%)** | | | |
| No | 40 (13.3) | 37 (12.1) | 77 (12.7) |
| Yes | 261 (86.7) | 270 (87.9) | 531 (87.3) |
| **Best Overall Response on Prior CPI Therapy, n (%)** | | | |
| Complete Response | 16 (5.3) | 9 (2.9) | 25 (4.1) |
| Partial Response | 45 (15.0) | 41 (13.4) | 86 (14.1) |
| Stable Disease | 51 (16.9) | 63 (20.5) | 114 (18.8) |
| Progressive Disease | 156 (51.8) | 152 (49.5) | 308 (50.7) |
| Nonevaluable | 6 (2.0) | 4 (1.3) | 10 (1.6) |
| Unknown | 20 (6.6) | 36 (11.7) | 56 (9.2) |
| Not Applicable | 6 (2.0) | 2 (0.7) | 8 (1.3) |

All subjects who were randomized (FAS). Subjects can be counted in more than one row.
CPI: checkpoint inhibitor; FAS: full analysis set; PD-I: programmed cell death 1; PD-L1: programmed cell death-ligand 1.
† Including platinum-based therapy in the neoadjuvant/adjuvant setting and the subject progressed within 12 months of therapy completion.
‡ One subject did not receive prior CPI therapy.

**Table 59** Study drug exposure and treatment compliance (SAF)

| Parameter Statistics/Criteria | Enfortumab Vedotin (n = 296) | Chemotherapy | | | |
|---|---|---|---|---|---|
| | | Combined (n = 291) | Docetaxel (n = 109) | Paclitaxel (n = 107) | Vinflunine (n = 75) |
| **Duration of Exposure † (months)** | | | | | |
| Mean (SD) | 5.36 (3.72) | 3.96 (2.95) | 3.62 (2.85) | 3.90 (2.61) | 4.55 (3.45) |
| Median (min, max) | 4.99 (0.5, 19.4) | 3.45 (0.2, 15.0) | 2.23 (0.3, 15.0) | 3.68 (0.3, 12.3) | 3.91 (0.2, 13.9) |
| **Relative Dose Intensity ‡ (%)** | | | | | |
| Mean (SD) | 79.35 (17.52) | 91.76 (11.61) | 91.78 (12.29) | 92.25 (10.25) | 91.01 (12.53) |
| Median (min, max) | 80.73 (30.6, 104.9) | 97.36 (32.5, 114.2) | 98.17 (32.5, 105.0) | 96.71 (57.9, 107.2) | 92.54 (37.6, 114.2) |

All subjects who received any amount of study drug (SAF).
max: maximum; min: minimum; SAF: safety analysis set.
† Last date of exposure – first dose date + 1. Enfortumab vedotin cycle length is 28 days, chemotherapy cycle length is 21 days.
‡ (dose intensity/planned dose intensity)*100

**Numbers analysed**

**Table 60** Analysis sets (All randomised subjects)

| Analysis Sets | Enfortumab Vedotin (n = 301) | Chemotherapy (n = 307) |
|---|---|---|
| Full Analysis Set †, n (%) | 301 (100) | 307 (100) |
| Safety Analysis Set ‡, n (%) | 296 (98.3) | 291 (94.8) |
| Response Evaluable Set §, n (%) | 288 (95.7) | 296 (96.4) |
| Pharmacokinetics Analysis Set ¶, n (%) | 296 (98.3) | N/A |

N/A: not applicable.
All randomized subjects. The denominator for percentages is the number of subjects randomized for each treatment arm and overall.
† The full analysis set (FAS) consists of all randomized subjects.
‡ The safety analysis set (SAF) consists of all subjects who took any amount of study drug.
§ The response evaluable set (RES) is defined as all subjects in the FAS who had measurable disease (per RECIST v1.1) per investigator at baseline.
¶ The pharmacokinetics analysis set (PKAS) includes subjects who received active drug and for whom at least one blood sample was collected and assayed for measurement of enfortumab vedotin (ASG-22CE) serum/plasma concentrations and for whom the time of sampling and the time of dosing on the day of sampling was known.

An additional dataset with data cut-off 30-JUL-2020, composed of subjects with available tissue samples for nectin-4 analysis, was provided during the procedure. This dataset included 15 additional tissue samples which increased the number of biomarker-available subjects for the final OS analysis to 542 (n=274 in EV arm and n=268 in chemotherapy arm).

## Outcomes and estimation

Primary efficacy endpoint –

OS in ITT population defined as the time from the date of randomisation until the documented date of death from any cause is summarized in the table below.

**Table 61** Primary efficacy analysis based on OS: EV-301 (FAS)

| Category<br>Parameter/Statistic | Enfortumab Vedotin (n = 301) | Chemotherapy (n = 307) |
|---|---|---|
| **OS** | | |
| Deaths, n (%) | 134 (44.5) | 167 (54.4) |
| Duration of OS (months) † | | |
| Median (95% CI) | 12.88 (10.58, 15.21) | 8.97 (8.05, 10.74) |
| Range ‡ | 0.30, 23.39+ | 0.03+, 22.87+ |
| **Stratified Analysis §** | | |
| 1-sided P value ¶ | 0.00142 * | |
| Hazard ratio (95% CI) †† | 0.702 (0.556, 0.886) | |
| **OS Rate, % (95% CI) ‡‡** | | |
| At 6 months | 77.9 (72.74, 82.25) | 69.5 (63.85, 74.38) |
| At 12 months | 51.5 (44.63, 58.03) | 39.2 (32.60, 45.64) |

All subjects who were randomized (FAS) Data cutoff date was 15 Jul 2020. † Based on Kaplan-Meier estimate. ‡ + indicates censoring § Stratification factors were ECOG performance status, geographic region and liver metastasis per interactive response technology. ¶ Based on log-rank test. Note: * indicates that the P value of OS is ≤ the predetermined 1-sided significance level of 0.00679 based on the number of observed deaths. †† Based on Cox proportional hazards model with treatment, ECOG performance status, geographic region and liver metastasis as the explanatory variables. Assuming proportional hazards, a hazard ratio < 1

indicates a reduction in hazard rate in favor of the treatment arm. ‡‡ Survival rate and 95% CI were estimated using Kaplan-Meier method and Greenwood formula.

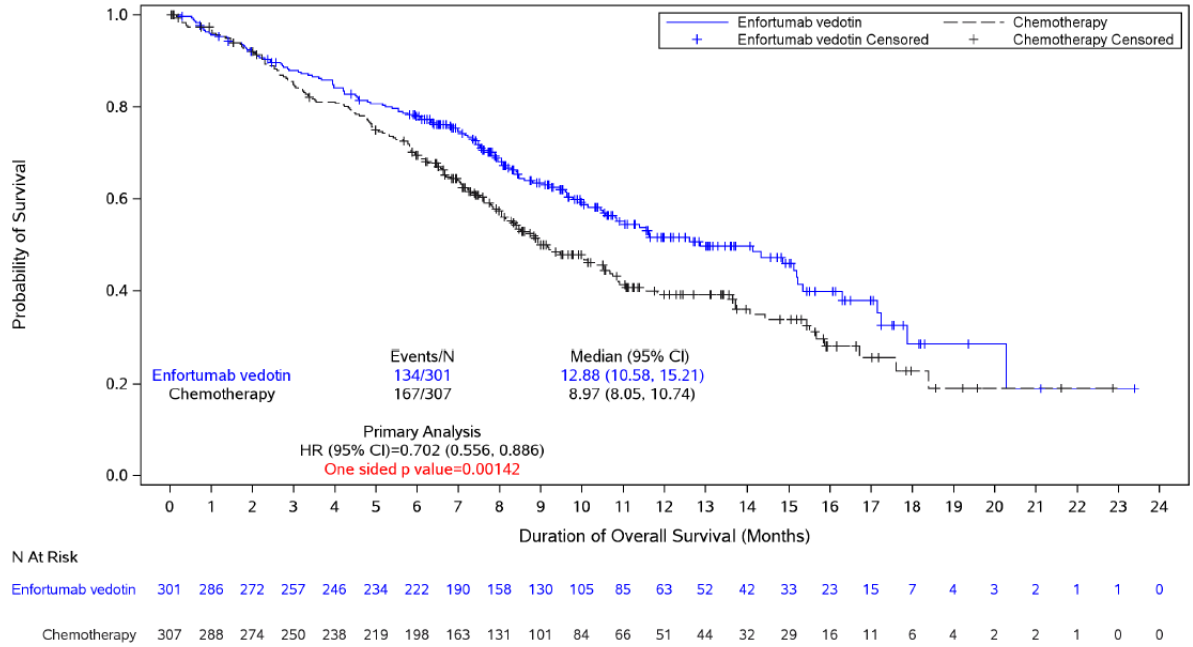



**Figure 33** Kaplan-Meier plot of OS: EV-301 (FAS)

### Table 62 Final analysis of OS as per SAP, data cutoff 30-JUL-2021

Summary of Overall Survival
Full Analysis Set

| Measure | Enfortumab vedotin (N=301) | Chemotherapy (N=307) |
|---|---|---|
| Deaths, n (%) | 207 ( 68.8%) | 237 ( 77.2%) |
| Censored, n (%) | 94 ( 31.2%) | 70 ( 22.8%) |
| Censored within 14 days of Cutoff Date | 76 (25.2%) | 53 (17.3%) |
| Censored More Than 14 days before Cutoff Date | 18 (6.0%) | 17 (5.5%) |
| Duration of Overall Survival, Months [1] | | |
| Median (95% CI) | 12.91 (11.01, 14.92) | 8.94 (8.25, 10.25) |
| 1st Quartile (95% CI) | 7.00 (5.22, 7.92) | 4.96 (4.34, 5.95) |
| 3rd Quartile (95% CI) | 27.17 (21.75, NE) | 18.66 (15.87, 23.92) |
| Range [2] | 0.30, 35.81+ | 0.03+, 32.13+ |
| Stratified Analysis [3] | | |
| 1-sided P-value [4] | 0.00015 | |
| Hazard Ratio (95% CI) [5] | 0.704 (0.581, 0.852) | |
| Unstratified Analysis (Sensitivity) | | |
| 1-sided P-value [4] | 0.001 | |
| Hazard Ratio (95% CI) [5] | 0.738 (0.612, 0.889) | |
| Median (95% CI) Follow-up of OS, Months [6] | 23.52 (22.11, 24.51) | 24.18 (23.49, 25.82) |
| Overall | 23.75 (23.10, 24.51) | |
| Overall Survival Rate, % (95% CI) [7] | | |
| At 6 Months | 77.9 (72.74, 82.25) | 69.5 (63.88, 74.40) |
| At 12 Months | 53.0 (47.05, 58.56) | 38.7 (33.12, 44.28) |
| At 24 Months | 29.3 (23.92, 34.89) | 19.8 (15.28, 24.84) |

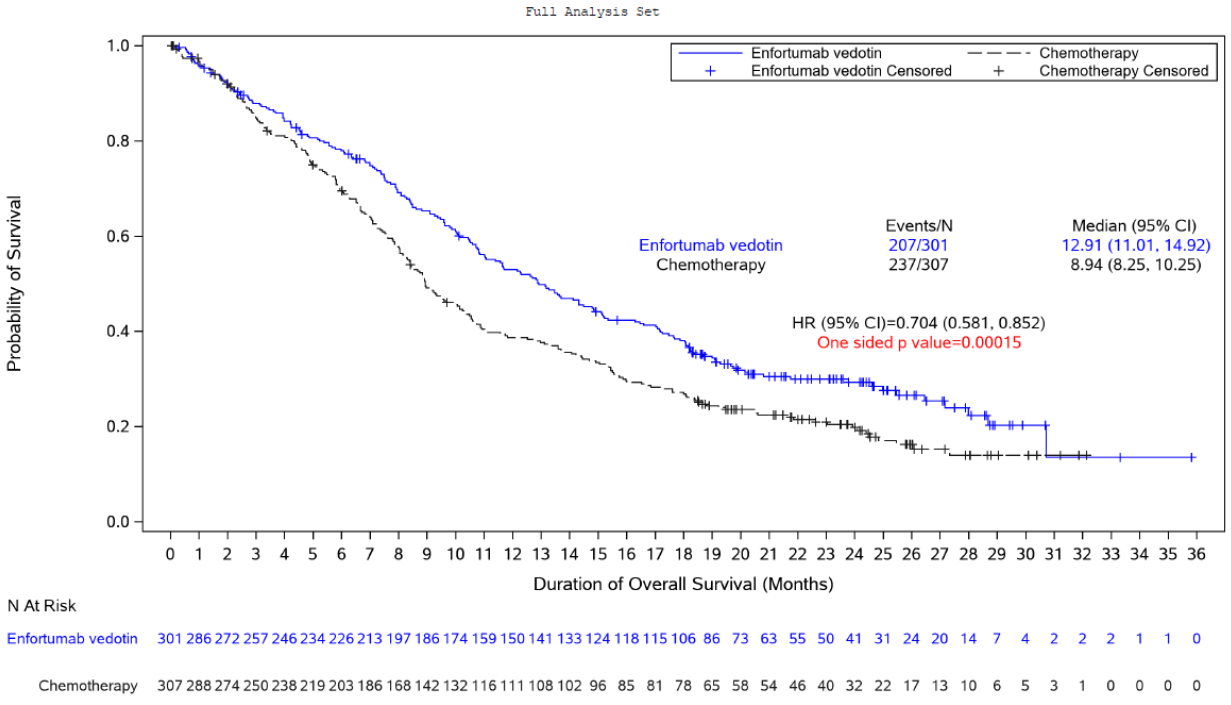



**Figure 34** Kaplan-Meier plot of OS, final analysis: EV-301 (FAS) data cutoff 30-JUL-2021

## Secondary efficacy endpoint

### Progression Free Survival by Investigator in ITT population

**Table 63** PFS1, Investigator Assessment: EV-301 (FAS)

| Category<br>Parameter/Statistics | Enfortumab Vedotin<br>(n = 301) | Chemotherapy<br>(n = 307) |
|---|---|---|
| **PFS events, n (%)** | 201 (66.8) | 231 (75.2) |
| Radiographic progression | 172 (57.1) | 195 (63.5) |
| Death without documented progression | 29 (9.6) | 36 (11.7) |
| Censored | 100 (33.2) | 76 (24.8) |
| No PFS event | 89 (29.6) | 64 (20.8) |
| PFS event after new anticancer therapy | 8 (2.7) | 9 (2.9) |
| PFS event after missing ≥ 2 consecutive assessments | 3 (1.0) | 3 (1.0) |
| **Duration of PFS (months)** † | | |
| Median (95% CI) | 5.55 (5.32, 5.82) | 3.71 (3.52, 3.94) |
| Range ‡ | 0.03+, 20.27+ | 0.03+, 18.69+ |
| **Stratified analysis** § | | |
| 1-sided P value ¶ | < 0.00001* | |
| Hazard ratio (95% CI) †† | 0.615 (0.505, 0.748) | |
| **PFS rate, % (95% CI)** ‡‡ | | |
| At 6 months | 44.0 (37.96, 49.84) | 28.2 (22.85, 33.76) |
| At 12 months | 21.7 (16.26, 27.71) | 8.3 (4.61, 13.36) |

All subjects who were randomized (FAS).

Data cutoff date was 15 Jul 2020.

PFS is defined as the time from randomization until death from any cause or radiographic disease progression assessed according to RECIST 1.1, whichever occurs first. For a subject with none of these events, PFS was censored based on rules defined in the SAP.

CI: confidence interval; CSR: clinical study report; ECOG: Eastern Cooperative Oncology Group Performance Status; FAS: full analysis set; IRT: interactive response technology; PFS: progression-free survival; RECIST: Response Evaluation Criteria in Solid Tumors; SAP: statistical analysis plan.

† Based on Kaplan-Meier estimate.

‡ + indicates censoring.

§ Stratification factors were ECOG, region and liver metastasis per IRT.

¶ Based on log-rank test. For stratified analysis, * indicates that the P value of PFS is ≤ the predetermined 1-sided significance level of 0.02189 based on the number of observed PFS events.

†† Based on Cox proportional hazards model with treatment, ECOG PS, region and liver metastasis as the explanatory variables. Assuming proportional hazards, a hazard ratio < 1 indicates a reduction in hazard rate in favor of treatment arm.

‡‡ PFS rate and 95% CI were estimated using Kaplan-Meier method and Greenwood formula.

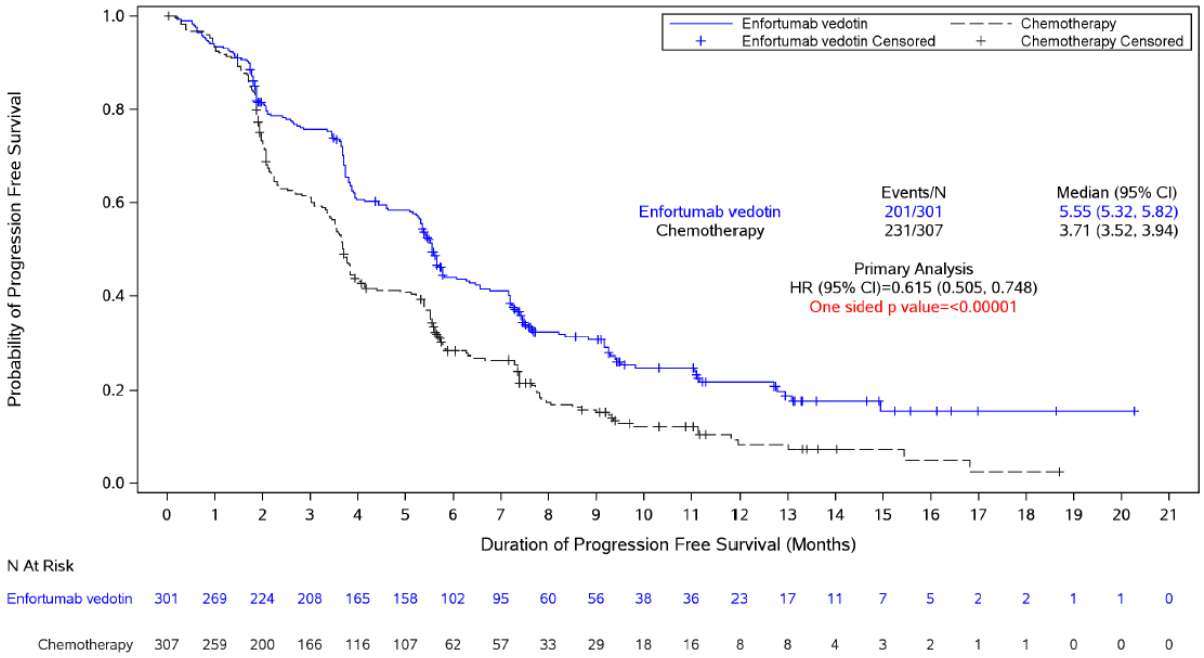



**Figure 35** Kaplan-Meier plot of PFS1: EV-301 (FAS)

Overall Response Rate and Disease Control Rate by investigators in the Response Evaluable SET

**Table 64** Summary of best overall response per Investigator: EV-301 (RES)

| Category<br>Parameter/Statistics | Enfortumab Vedotin<br>(n = 288) | Chemotherapy<br>(n = 296) |
|---|---|---|
| **Best overall response, confirmed, n (%) †** | | |
| Confirmed CR | 14 (4.9) | 8 (2.7) |
| Confirmed PR | 103 (35.8) | 45 (15.2) |
| Stable disease | 90 (31.3) | 105 (35.5) |
| Progressive disease | 44 (15.3) | 83 (28.0) |
| Not evaluable | 37 (12.8) | 55 (18.6) |
| **ORR, confirmed, n (%)** | 117 (40.6) | 53 (17.9) |
| 95% CI for overall response rate (%) ‡ | (34.90, 46.54) | (13.71, 22.76) |
| Stratified 1-sided P value § | < 0.001* | |
| **Disease control rate, confirmed, n (%) ¶** | 207 (71.9) | 158 (53.4) |
| 95% CI for disease control rate (%) ‡ | (66.30, 76.99) | (47.52, 59.17) |
| Stratified 1-sided P value § | < 0.001* | |

All subjects in the FAS (all subjects who were randomized) who had measurable disease per investigator at baseline (RES).

Data cutoff date was 15 Jul 2020.

CI: confidence interval; CR: complete response; CSR: clinical study report; DCR: disease control rate; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FAS: full analysis set; IRT: interactive response technology; ORR: overall response rate; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumors; RES: response evaluable set.

† The definition of best overall response followed RECIST 1.1. CR/PR must have been confirmed by 2 scans a minimum of 4 weeks apart. The minimum duration for stable disease was 7 weeks.

‡ Using exact method based on binomial distribution [Clopper & Pearson, 1934].

§ Based on Cochran-Mantel-Haenszel test. Stratification factors were ECOG PS, Region and Liver Metastasis per IRT. For the P values of ORR and DCR, * indicates that the P values of endpoints are ≤ the predetermined efficacy boundary of 0.025, 1-sided (adjusted by 100% information fraction).

¶ Disease control rate was defined as the proportion of subjects who had a best overall response of confirmed CR, confirmed PR or stable disease (≥ 7 weeks).

Duration of Response per Investigator assessment in All Responders

**Table 65** DOR per Investigator Assessment: EV-301 (All Responders)

| **Category**<br>Parameter/Statistics | **Enfortumab Vedotin (n = 117)** | **Chemotherapy (n = 53)** |
|---|---|---|
| **Events, n (%)** | 63 (53.8) | 29 (54.7) |
| Radiographical progression | 62 (53.0) | 28 (52.8) |
| Death without documented progression | 1 (0.9) | 1 (1.9) |
| **Censored, n (%)** | 54 (46.2) | 24 (45.3) |
| No event | 52 (44.4) | 23 (43.4) |
| Event after new anticancer therapy | 2 (1.7) | 1 (1.9) |
| **Duration of response, months †** | | |
| Median (95% CI) | 7.39 (5.59, 9.46) | 8.11 (5.65, 9.56) |
| Range ‡ | 1.84+, 18.23+ | 3.48, 16.89+ |
| **Rate of subjects with neither PD nor died, % (95% CI) §** | | |
| At 6 months | 53.8 (43.67, 62.97) | 56.0 (40.13, 69.24) |
| At 12 months | 27.7 (17.00, 39.53) | 19.8 (7.04, 37.18) |

All subjects in the FAS (all subjects who were randomized) who had measurable disease per investigator at baseline (RES).

Data cutoff date was 15 Jul 2020.

CI: confidence interval; CR: complete response; CSR: clinical study report; DOR: duration of response; FAS: full analysis set; PD: progressive disease; PR: partial response; RES: response evaluable set.

† Based on Kaplan-Meier estimate.

‡ + indicates censoring.

§ Rate of subjects who were neither PD nor death since they achieved the first confirmed CR or PR. Rates at other time points and the 95% CIs are estimated based on DOR using Kaplan-Meier method and Greenwood formula.

Exploratory endpoint – Subsequent therapies and PFS2 in ITT

**Table 66** Subsequent systemic anti-cancer therapies (FAS)

| | | | |
|---|---|---|---|
| CISPLATIN W/PACLITAXEL | 1 ( 0.3%) | 0 | 1 ( 0.2%) |
| DEBIO 1347 | 1 ( 0.3%) | 0 | 1 ( 0.2%) |
| DOXORUBICIN | 0 | 1 ( 0.3%) | 1 ( 0.2%) |
| DURVALUMAB | 1 ( 0.3%) | 0 | 1 ( 0.2%) |
| LENVATINIB | 0 | 1 ( 0.3%) | 1 ( 0.2%) |
| MONOCLONAL ANTIBODIES | 0 | 1 ( 0.3%) | 1 ( 0.2%) |
| RIBOCICLIB | 1 ( 0.3%) | 0 | 1 ( 0.2%) |
| RUCAPARIB | 0 | 1 ( 0.3%) | 1 ( 0.2%) |
| SUNITINIB | 0 | 1 ( 0.3%) | 1 ( 0.2%) |
| TEMSIROLIMUS | 0 | 1 ( 0.3%) | 1 ( 0.2%) |
| TUBERCULIN | 0 | 1 ( 0.3%) | 1 ( 0.2%) |

Subsequent Systemic Anti-Cancer Therapies by Preferred WHO Name
Full Analysis Set

| Preferred WHO Name | Enfortumab Vedotin (N=301) n (%) | Chemotherapy (N=307) n (%) | Total (N=608) n (%) |
|---|---|---|---|
| Overall | 95 ( 31.6%) | 102 ( 33.2%) | 197 ( 32.4%) |
| PACLITAXEL | 19 ( 6.3%) | 18 ( 5.9%) | 37 ( 6.1%) |
| COMBINATIONS OF ANTINEOPLASTIC AGENTS | 13 ( 4.3%) | 12 ( 3.9%) | 25 ( 4.1%) |
| PEMBROLIZUMAB | 8 ( 2.7%) | 17 ( 5.5%) | 25 ( 4.1%) |
| CARBOPLATIN W/GEMCITABINE | 7 ( 2.3%) | 4 ( 1.3%) | 11 ( 1.8%) |
| DOCETAXEL | 9 ( 3.0%) | 2 ( 0.7%) | 11 ( 1.8%) |
| SACITUZUMAB GOVITECAN | 1 ( 0.3%) | 8 ( 2.6%) | 9 ( 1.5%) |
| VINFLUNINE | 9 ( 3.0%) | 0 | 9 ( 1.5%) |
| CISPLATIN W/GEMCITABINE | 4 ( 1.3%) | 4 ( 1.3%) | 8 ( 1.3%) |
| ERDAFITINIB | 4 ( 1.3%) | 4 ( 1.3%) | 8 ( 1.3%) |
| ENFORTUMAB VEDOTIN | 3 ( 1.0%) | 4 ( 1.3%) | 7 ( 1.2%) |
| PEMETREXED | 4 ( 1.3%) | 3 ( 1.0%) | 7 ( 1.2%) |
| CISPLATIN W/DOXORUBICIN/METHOTREXATE/ VINBLAST | 2 ( 0.7%) | 4 ( 1.3%) | 6 ( 1.0%) |
| CARBOPLATIN | 0 | 4 ( 1.3%) | 4 ( 0.7%) |
| CARBOPLATIN W/PACLITAXEL | 2 ( 0.7%) | 2 ( 0.7%) | 4 ( 0.7%) |
| CISPLATIN;GEMCITABINE;PACLITAXEL | 0 | 4 ( 1.3%) | 4 ( 0.7%) |
| GEMCITABINE W/PACLITAXEL | 3 ( 1.0%) | 1 ( 0.3%) | 4 ( 0.7%) |
| ATEZOLIZUMAB | 1 ( 0.3%) | 2 ( 0.7%) | 3 ( 0.5%) |
| CISPLATIN | 1 ( 0.3%) | 2 ( 0.7%) | 3 ( 0.5%) |
| CISPLATIN W/GEMCITABINE HYDROCHLORIDE | 1 ( 0.3%) | 2 ( 0.7%) | 3 ( 0.5%) |
| ABEMACICLIB | 1 ( 0.3%) | 1 ( 0.3%) | 2 ( 0.3%) |
| AFATINIB | 2 ( 0.7%) | 0 | 2 ( 0.3%) |
| CARBOPLATIN W/GEMCITABINE HYDROCHLORIDE | 0 | 2 ( 0.7%) | 2 ( 0.3%) |
| CISPLATIN;METHOTREXATE;VINBLASTINE | 1 ( 0.3%) | 1 ( 0.3%) | 2 ( 0.3%) |
| DERAZANTINIB | 1 ( 0.3%) | 1 ( 0.3%) | 2 ( 0.3%) |
| GEMCITABINE | 1 ( 0.3%) | 1 ( 0.3%) | 2 ( 0.3%) |
| IBRUTINIB | 1 ( 0.3%) | 1 ( 0.3%) | 2 ( 0.3%) |
| INVESTIGATIONAL ANTINEOPLASTIC DRUGS | 1 ( 0.3%) | 1 ( 0.3%) | 2 ( 0.3%) |
| IPILIMUMAB W/NIVOLUMAB | 0 | 2 ( 0.7%) | 2 ( 0.3%) |
| PERTUZUMAB W/TRASTUZUMAB | 2 ( 0.7%) | 0 | 2 ( 0.3%) |
| AZD 1775 | 0 | 1 ( 0.3%) | 1 ( 0.2%) |
| CANCER VACCINES, THERAPEUTIC | 1 ( 0.3%) | 0 | 1 ( 0.2%) |
| CASODEX W/ZOLADEX | 0 | 1 ( 0.3%) | 1 ( 0.2%) |

**Table 67.** Summary of PFS after next-line therapy by investigator (PFS2)

| | Enfortumab Vedotin (n = 301) | Chemotherapy (n = 307) |
|---|---|---|
| PFS2 Events, n (%) | 152 (50.5%) | 195 (63.5%) |
| Progression of Disease | 36 (12.0%) | 54 (17.6%) |
| Death from any Cause | 104 (34.6%) | 125 (40.7%) |
| Other PFS2 Events † | 12 (4.0%) | 16 (5.2%) |
| Censored, n (%) | 149 (49.5%) | 112 (36.5%) |
| Duration of PFS2 (months) ‡ | | |
| Median (95% CI) | 9.63 (8.21, 10.58) | 7.00 (6.54, 8.05) |
| Range § | 0.03+, 23.39+ | 0.03+, 20.27 |
| Stratified Analysis ¶ | | |
| 1-sided P-value †† | < 0.001 | |
| Hazard Ratio (95% CI) ‡‡ | 0.619 (0.497, 0.771) | |

All subjects who were randomized (FAS).
ECOG PS: Eastern Cooperative Oncology Group Performance Status; FAS: full analysis set; PFS2: progression-free survival after next-line therapy; SAP: statistical analysis plan.
PFS2 was defined as the time from the date of randomization to subsequent progression after initiation of new anticancer therapy, or death from any cause, whichever occurred first. If progression after next-line therapy could not be reliably determined, a PFS2 event was defined as start of a different treatment or death from any cause, whichever occurred first. For a subject with none of these events, PFS2 was censored based on rules defined in SAP.
† Includes start of a different treatment after the subsequent new anti-cancer therapy after end of study drug treatment.
‡ Based on Kaplan-Meier estimate.
§ + indicates censoring
¶ Stratification factors were ECOG PS, geographic region and liver metastasis from the electronic Case Report Form.
†† Based on log-rank test.
‡‡ Based on Cox proportional hazards model with treatment, ECOG PS, geographic region and liver metastasis as the explanatory variables. Assuming proportional hazards, a hazard ratio < 1 indicates a reduction in hazard rate in favor of treatment arm

Exploratory endpoint – Efficacy by Nectin-4 expression

**Table 68** Summary of Nectin-4 expression (FAS)

| Parameter | Enfortumab Vedotin (n = 301) | Chemotherapy (n = 307) |
|---|---|---|
| **Nectin-4 IHC H-score (tissue)** | | |
| n † | 271 | 256 |
| Mean (standard deviation) | 222.8 (84.61) | 234.8 (75.22) |
| Median (min, max) | 250.0 (0, 300) | 270.0 (0, 300) |
| **Nectin-4 IHC H-score category (tissue), n (%)** | | |
| < 150 | 47 (17.3) | 36 (14.1) |
| ≥ 150 to ≤ 225 | 66 (24.4) | 57 (22.3) |
| > 225 | 158 (58.3) | 163 (63.7) |
| Missing | 30 | 51 |

All subjects who were randomized (FAS).

Data cutoff date was 15 Jul 2020.

Baseline tumor tissue biomarker results were obtained from validated IHC assays run at Quest Diagnostics/Q2 Solutions.

CPS: combined positive score; CSR: clinical study report; FAS: full analysis set; H-score: histoscore; IHC: immunohistochemistry; max: maximum; min: minimum;

† Number of subjects with evaluable data. Data was not available for some subjects due to unavailable tissue, or inadequate tissue quality or quantity.

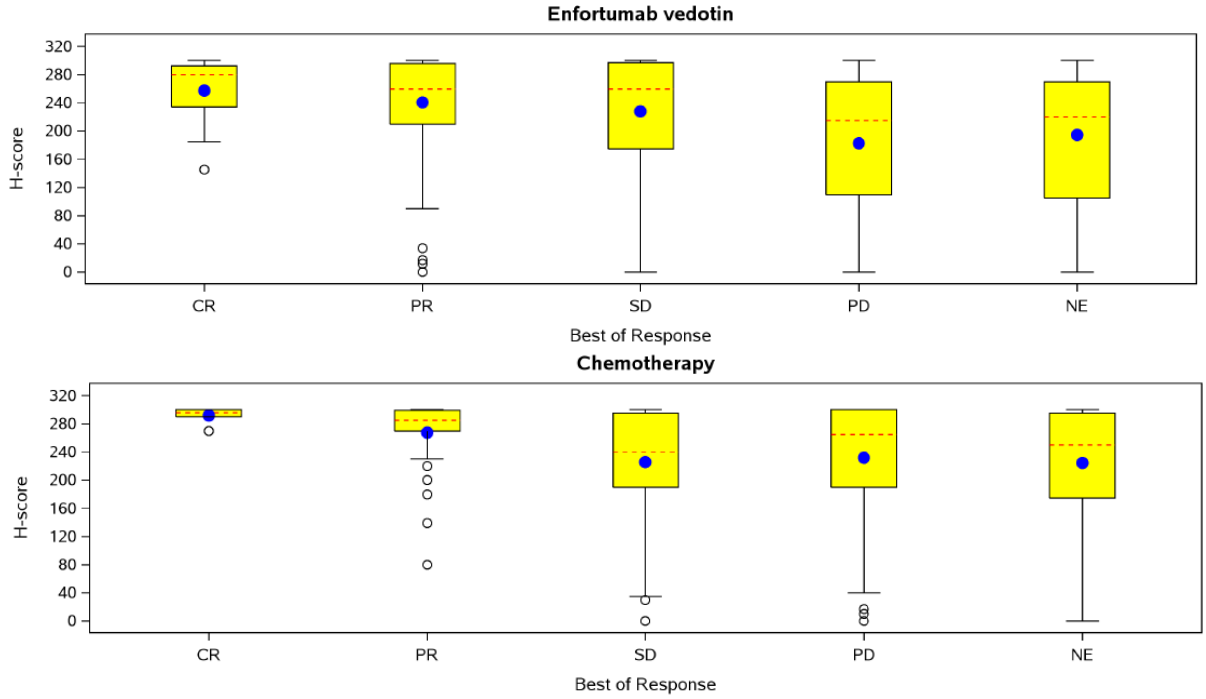
‡ A validated IHC assay with monoclonal mouse anti-PD-L1, clone 22C3 was used. A CPS ≥ 10 is interpreted as PD-L1 high.

**Table 69.** Summary of confirmed ORR by Nectin-4 expression

Subgroup Analysis of Confirmed Overall Response Rate (ORR), Investigator Assessment
By Nectin-4 IHC H Score of 150 and 225
Response Evaluable Set

| | | Enfortumab vedotin | | | Chemotherapy | | | Absolute Difference [1] | 2-sided Interaction |
|---|---|---|---|---|---|---|---|---|---|
| Parameter | Value | N | ORR, n (%) | 95% CI | N | ORR, n (%) | 95% CI | 95% CI | P-value [2] |
| Nectin-4 IHC H Score (tissue) | < 150 | 45 | 9 (20.0%) | (9.58%, 34.60%) | 35 | 2 (5.7%) | (0.70%, 19.16%) | 14.3% (-1.61%, 29.85%) | 0.858 |
| | >= 150 | 214 | 98 (45.8%) | (38.99%, 52.72%) | 213 | 41 (19.2%) | (14.18%, 25.19%) | 26.5% (17.45%, 35.08%) | |
| Nectin-4 IHC H Score (tissue) | < 150 | 45 | 9 (20.0%) | (9.58%, 34.60%) | 35 | 2 (5.7%) | (0.70%, 19.16%) | 14.3% (-1.61%, 29.85%) | 0.046 |
| | >= 150 to <= 225 | 64 | 29 (45.3%) | (32.82%, 58.25%) | 56 | 3 (5.4%) | (1.12%, 14.87%) | 40.0% (24.92%, 53.74%) | |
| | > 225 | 150 | 69 (46.0%) | (37.84%, 54.32%) | 157 | 38 (24.2%) | (17.73%, 31.67%) | 21.8% (10.53%, 32.22%) | |

Data cutoff date is 15 Jul 2020




All subjects who were randomized (FAS).Data cutoff date was 15 Jul 2020.Subjects without any post-baseline images are also included in NE.

**Figure 36** Box plot of baseline H-score by response (FAS)

## Ancillary analyses

### In vitro biomarker test for patient selection for efficacy

Nectin-4 expression in tumour specimens was measured retrospectively by immunohistochemistry (IHC) using an analytically validated assay. Nectin-4 expression was reported using the IHC H-score ranging from 0 to 300, which combined percentage of positive tumour cells and intensity of expression of Nectin-4. Across enfortumab vedotin clinical studies, IHC assay results have confirmed Nectin-4 is highly prevalent in urothelial carcinoma (i.e., expressed in over 96% of urothelial carcinoma patients).

Nectin-4 assay analytical method

The Nectin-4 assay was developed as a semiquantitative IHC assay of Nectin-4 in formalin-fixed paraffin-embedded (FFPE) human tissue using the Leica Microsystems BOND autostainer and Bond Polymer Refine Detection. Analytical assay validation was performed on formalin-fixed specimens only.

To summarize the IHC staining method, after routine deparaffinization and rehydration of the tissue samples, an epitope retrieval procedure is performed. FFPE specimens are then incubated with the primary monoclonal antibody to Nectin-4 (mouse clone M22-321b41.1) or the negative control (mouse IgG2a antibody). Next, a horseradish peroxidase enzyme-labeled anti-mouse IgG secondary antibody is applied, which is directed against the IgG of the animal species in which the primary antibody has been raised. Finally, peroxidase is added, which reacts with the chromagen 3,3`-diaminobenzidine (DAB), producing brown precipitate at the reaction site. The specimens are counterstained to identify cellular and subcellular elements.

The read-out method to evaluate Nectin-4 IHC staining was performed by a trained pathologist using microscopy visual evaluation. Nectin-4 expression was reported using the H-score that considers both staining intensity and the percentage of cells stained at a specific range of intensities. The H-score is calculated by summing the products of the percentages of cells stained at a given intensity (0 - 100) and the staining intensity (0 - 3; 0 = no stain, 1 = low intensity, 2 = medium intensity, 3 = high intensity):

H-score = [1 x (% cells with intensity of 1)] + [2 x (% cells with intensity of 2)] + [3 x (% cells with intensity of 3)]

The IHC H-score range is 0 to 300. The H-score value of 150 was selected as it represents the mid-point of the H-score range (0 - 300). Likewise, an H-score value of 225 represents the mid-point between 150 and 300 (i.e., 75% of the maximum Nectin-4 expression).

Nectin-4 assay analytical validation

- The Nectin-4 IHC assay was used retrospectively. Validation was performed per College of American Pathologists (CAP) Principles of Analytical Validation of Immunohistochemistry Assays and Clinical Laboratory Improvement Amendments (CLIA) standards for assay validations for research use only. Assay validation included the following parameters:
- Sensitivity: defined as positive staining in the tissues expected to express the antigen based on the literature.
- Specificity: differential staining observed across various tissue types, both expected and not expected to express the antigen using human specimens, each assayed in triplicate.
- Precision (intra-run): assessment of quantitative agreement of H-score values across replicates using FFPE specimens representing the full range of Nectin-4 expression.
- Precision (inter-run / reproducibility): assessment of quantitative agreement of H-score values using3 FFPE specimens representing the full range of Nectin-4 expression.
- Concordance (inter-laboratory / inter-pathologist): concordance (agreement) was assessed using FFPE specimens. For each specimen, FFPE slides from the same block were stained and scored by different pathologists.

A stability study demonstrated a minimum of 3 months cut-slide stability for the Nectin-4 IHC assayFor each validation parameter, the prespecified acceptance criteria were met. In addition, upon a technology transfer, assay parameters were evaluated using analytical sensitivity, inter-laboratory/inter-pathologist concordance and precision on FFPE tumor tissue samples and again all acceptance criteria were met. In

accordance with the CAP common checklist COM.40000 on method validation/verification approval, the method is considered acceptable for human tissue sample testing.

Nectin-4 assay clinical validity

Clinical validation has not been performed for the Nectin-4 IHC assay.

Nectin-4 cut-point selection and validation

The Nectin-4 IHC assay was validated for exploratory purposes and has been used to assess Nectin-4 expression retrospectively in patients' tumors for enfortumab vedotin clinical studies in urothelial carcinoma. Cut-points have not been validated.

**Sensitivity analyses**

**Table 70** Primary efficacy sensitivity analysis: Rank preserving structural failure time (RPSFT) Method - based on OS (FAS)

| | **Enfortumab Vedotin (n = 301)** | **Chemotherapy (n = 307)** |
|---|---|---|
| **Overall Survival** | | |
| Deaths, n (%) | 134 (44.5%) | 167 (54.4%) |
| Censored, n (%) | 167 (55.5%) | 140 (45.6%) |
| **Adjusting in Chemotherapy Arm Based on the RPSFT Method** | | |
| Duration of Overall Survival (months) † | | |
| Median (95% CI) | 12.88 (10.58, 15.21) | 8.94 (8.05, NE) |
| Range ‡ | 0.30, 23.39+ | 0.03+, 12.55+ |
| Hazard Ratio (95% CI) § | 0.705 (0.516, 0.853) | |
| 1-sided P value ¶ | 0.001 | |

All subjects who were randomized (FAS). Data cutoff date was 15 Jul 2020.

CI: confidence interval; CSR: clinical study report; FAS: full analysis set; NE: not evaluable; RPSFT: Rank Preserving Structural Failure Time.† Based on Kaplan-Meier estimate.‡ + indicates censoring.§ Stratified Cox proportional hazards model was analyzed on 1000 bootstrapping simulated datasets. The CI was from 2.5 percentile and 97.5 percentile of 1000 simulations. ¶ The P value was calculated from 1000 simulations.

**Table 71** Primary efficacy sensitivity analysis: Inverse probability of censoring weighting (IPCW) Method - based on OS (FAS)

| | **Enfortumab Vedotin (n = 301)** | **Chemotherapy (n = 307)** |
|---|---|---|
| Overall Survival | | |
| Deaths, n (%) | 134 (44.5) | 167 (54.4) |
| Censored, n (%) | 167 (55.5) | 140 (45.6) |
| **Adjusting in Chemotherapy Arm Based on the IPCW Method** | | |
| Duration of Overall Survival (months) † | | |
| Median (95% CI) | 17.87 (11.63, NE) | 10.32 (8.31, 15.67) |
| Range ‡ | 0.30, 21.13+ | 0.03+, 19.58+ |
| Hazard Ratio (95% CI) § | 0.630 (0.435, 0.912) | |
| 1-sided P value ¶ | 0.001 | |

All subjects who were randomized (FAS). Data cutoff date was 15 Jul 2020. CI: confidence interval; CSR: clinical study report; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FAS: full analysis set; IPCW: inverse probability of censoring weights; IRT: interactive response technology; NE: not estimable. † Based on weighted Kaplan-Meier estimate. ‡ + indicates censoring.§ Based on weighted stratified Cox proportional hazards model with treatment as the explanatory variables. Stratification factors were ECOG PS, geographic region and liver metastasis per IRT. The weight was calculated from 2 logistic models. One model included only baseline covariates (age group, primary site of tumor and prior lines of therapy in locally advanced or metastatic setting. The other model included both baseline covariates and time dependent variables (sum of diameter and ECOG assessments).

¶ Based on weighted stratified log-rank test.

**Table 72** Summary of PFS1, Investigator assessment: sensitivity analysis (FAS)

| | **Enfortumab Vedotin (n = 301)** | **Chemotherapy (n = 307)** |
|---|---|---|
| PFS Events, n (%) | 204 (67.8) | 234 (76.2) |
| Radiographical Progression | 172 (57.1) | 195 (63.5) |
| Death without Documented Progression | 32 (10.6) | 39 (12.7) |
| Censored, n (%) | 97 (32.2) | 73 (23.8) |
| No PFS Event | 89 (29.6) | 64 (20.8) |
| PFS Event After New Anticancer Therapy | 8 (2.7) | 9 (2.9) |
| Duration of PFS (months) † | | |
| Median (95% CI) | 5.55 (5.32, 6.08) | 3.71 (3.52, 3.98) |
| Range ‡ | 0.03+, 20.27+ | 0.03+, 18.69+ |
| Stratified Analysis § | | |
| 1-sided P-value ¶ | < 0.001 | |
| Hazard Ratio (95% CI) †† | 0.616 (0.507, 0.749) | |
| PFS Rate, % (95% CI) ‡‡ | | |
| At 6 Months | 44.2 (38.21, 50.03) | 28.6 (23.28, 34.18) |
| At 12 Months | 21.3 (15.92, 27.23) | 8.2 (4.52, 13.14) |

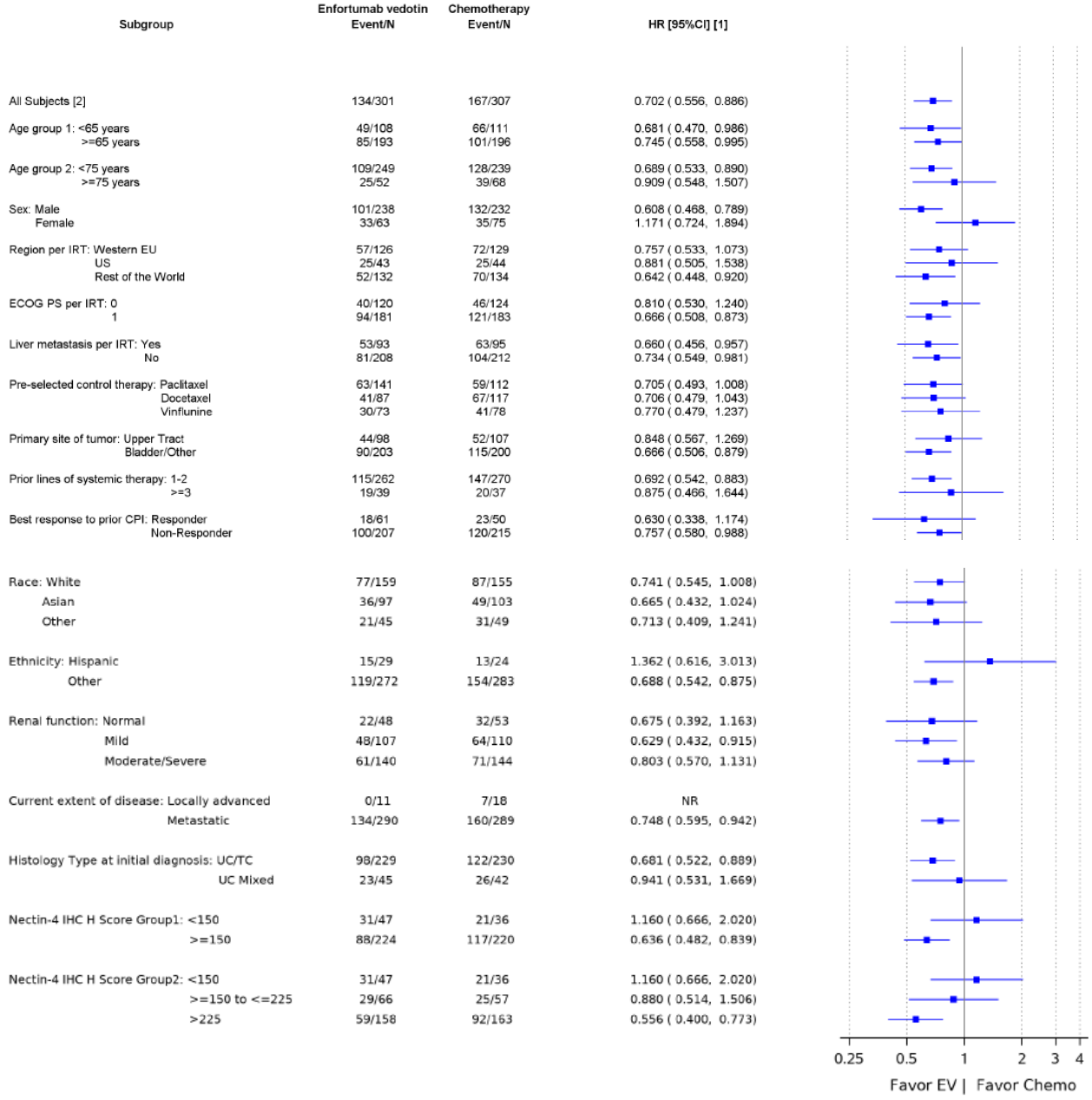
All subjects who were randomized (FAS).
ECOG PS: Eastern Cooperative Oncology Group Performance Status; FAS: full analysis set; IRT: interactive response technology; PFS: progression-free survival; RECIST: Response Evaluation Criteria in Solid Tumours.
PFS is defined as the time from randomization until death from any cause or radiographic disease progression assessed according to RECIST 1.1, whichever occurred first. For a subject with none of these events, progression free survival was censored based on rules defined in SAP.

† Based on Kaplan-Meier estimate.
‡ + indicates censoring
§ Stratification factors were ECOG PS, geographic region and liver metastasis per IRT.
¶ Based on log-rank test.
†† Based on Cox proportional hazards model with treatment, ECOG PS, geographic region and liver metastasis as the explanatory variables. Assuming proportional hazards, a hazard ratio < 1 indicates a reduction in hazard rate in favor of treatment arm.
‡‡ PFS rate and 95% CI were estimated using Kaplan-Meier method and Greenwood formula.

**Subgroup analyses**

OS by demographic and disease characteristics

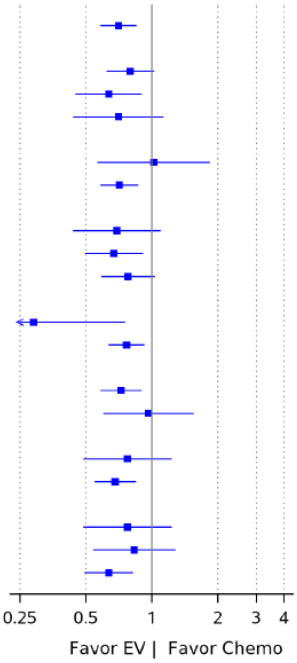
**Figure 37** Forest plot for subgroup analysis for OS: EV-301 (FAS)




Data cutoff date is 15 Jul 2020

**Figure 38** Forest plot for subgroup analysis of OS, based on final analysis (30-JUL-2021)

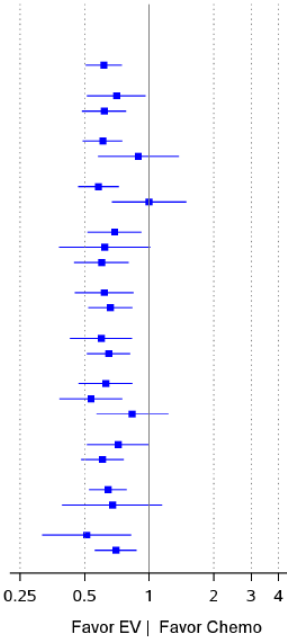
| Subgroup | EV Event/N | Chemotherapy Event/N | HR [95%CI] [1] |
|---|---|---|---|
| All Subjects [2] | 207/301 | 237/307 | 0.704 ( 0.581, 0.852) |
| Race: White | 120/159 | 122/155 | 0.798 ( 0.620, 1.027) |
| Asian | 57/97 | 75/103 | 0.635 ( 0.449, 0.899) |
| Other | 30/45 | 40/49 | 0.702 ( 0.437, 1.129) |
| Ethnicity: Hispanic | 25/29 | 20/24 | 1.019 ( 0.565, 1.838) |
| Other | 182/272 | 217/283 | 0.710 ( 0.583, 0.865) |
| Renal function: Normal | 33/48 | 41/53 | 0.690 ( 0.434, 1.096) |
| Mild | 79/107 | 88/110 | 0.669 ( 0.493, 0.908) |
| Moderate/Severe | 90/140 | 108/144 | 0.777 ( 0.587, 1.028) |
| Current extent of disease: Locally advanced | 6/11 | 15/18 | 0.288 ( 0.110, 0.755) |
| Metastatic | 201/290 | 222/289 | 0.766 ( 0.633, 0.927) |
| Histology Type at initial diagnosis: UC/TC | 152/229 | 173/230 | 0.723 ( 0.581, 0.899) |
| UC Mixed | 34/45 | 35/42 | 0.966 ( 0.600, 1.555) |
| Nectin-4 IHC H Score Group1: <150 | 38/47 | 36/38 | 0.774 ( 0.485, 1.234) |
| >=150 | 148/227 | 176/230 | 0.680 ( 0.546, 0.847) |
| Nectin-4 IHC H Score Group2: <150 | 38/47 | 36/38 | 0.774 ( 0.485, 1.234) |
| >=150 to <=225 | 43/66 | 40/59 | 0.830 ( 0.539, 1.278) |
| >225 | 105/161 | 136/171 | 0.636 ( 0.493, 0.821) |



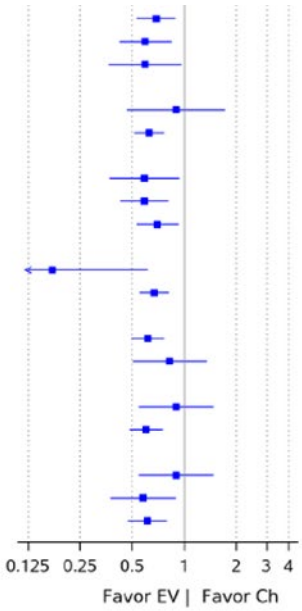

PFS by demographic and disease characteristics

**Figure 39** Forest plot for subgroup analysis of PFS by Investigator: EV-301 (FAS)

| Subgroup | Enfortumab vedotin Event/N | Chemotherapy Event/N | HR [95%CI] [1] |
|---|---|---|---|
| All Subjects [2] | 201/301 | 231/307 | 0.615 ( 0.505, 0.748) |
| Age group 1: <65 years | 75/108 | 80/111 | 0.702 ( 0.512, 0.965) |
| >=65 years | 126/193 | 151/196 | 0.616 ( 0.485, 0.781) |
| Age group 2: <75 years | 166/249 | 180/239 | 0.607 ( 0.491, 0.751) |
| >=75 years | 35/52 | 51/68 | 0.889 ( 0.577, 1.370) |
| Sex: Male | 153/238 | 180/232 | 0.579 ( 0.466, 0.720) |
| Female | 48/63 | 51/75 | 0.997 ( 0.667, 1.490) |
| Region per IRT: Western EU | 86/126 | 95/129 | 0.688 ( 0.514, 0.922) |
| US | 30/43 | 35/44 | 0.619 ( 0.378, 1.013) |
| Rest of the World | 85/132 | 101/134 | 0.599 ( 0.446, 0.804) |
| ECOG PS per IRT: 0 | 71/120 | 86/124 | 0.617 ( 0.450, 0.846) |
| 1 | 130/181 | 145/183 | 0.659 ( 0.519, 0.837) |
| Liver metastasis per IRT: Yes | 71/93 | 75/95 | 0.597 ( 0.428, 0.833) |
| No | 130/208 | 156/212 | 0.648 ( 0.512, 0.818) |
| Pre-selected control therapy: Paclitaxel | 96/141 | 90/112 | 0.627 ( 0.469, 0.837) |
| Docetaxel | 56/87 | 87/117 | 0.535 ( 0.380, 0.753) |
| Vinflunine | 49/73 | 54/78 | 0.834 ( 0.566, 1.228) |
| Primary site of tumor: Upper Tract | 63/98 | 74/107 | 0.716 ( 0.511, 1.003) |
| Bladder/Other | 138/203 | 157/200 | 0.606 ( 0.481, 0.763) |
| Prior lines of systemic therapy: 1-2 | 175/262 | 203/270 | 0.640 ( 0.523, 0.785) |
| >=3 | 26/39 | 28/37 | 0.672 ( 0.393, 1.150) |
| Best response to prior CPI: Responder | 32/61 | 36/50 | 0.511 ( 0.317, 0.826) |
| Non-Responder | 146/207 | 160/215 | 0.697 ( 0.556, 0.873) |



| | | | |
|---|---|---|---|
| Race: White | 112/159 | 117/155 | 0.686 ( 0.529, 0.890) |
| Asian | 60/97 | 76/103 | 0.595 ( 0.422, 0.840) |
| Other | 29/45 | 38/49 | 0.592 ( 0.363, 0.966) |
| Ethnicity: Hispanic | 18/29 | 18/24 | 0.896 ( 0.465, 1.725) |
| Other | 183/272 | 213/283 | 0.625 ( 0.513, 0.763) |
| Renal function: Normal | 34/48 | 41/53 | 0.587 ( 0.369, 0.935) |
| Mild | 72/107 | 83/110 | 0.587 ( 0.427, 0.807) |
| Moderate/Severe | 90/140 | 107/144 | 0.699 ( 0.528, 0.927) |
| Current extent of disease: Locally advanced | 4/11 | 13/18 | 0.172 ( 0.048, 0.614) |
| Metastatic | 197/290 | 218/289 | 0.669 ( 0.551, 0.812) |
| Histology Type at initial diagnosis: UC/TC | 149/229 | 173/230 | 0.614 ( 0.492, 0.765) |
| UC Mixed | 33/45 | 33/42 | 0.825 ( 0.505, 1.349) |
| Nectin-4 IHC H Score Group1: <150 | 37/47 | 28/36 | 0.896 ( 0.545, 1.474) |
| >=150 | 145/224 | 165/220 | 0.602 ( 0.481, 0.754) |
| Nectin-4 IHC H Score Group2: <150 | 37/47 | 28/36 | 0.896 ( 0.545, 1.474) |
| >=150 to <=225 | 39/66 | 44/57 | 0.577 ( 0.372, 0.894) |
| >225 | 106/158 | 121/163 | 0.613 ( 0.471, 0.796) |




Data cutoff date is 15 Jul 2020

**Patient Report Outcomes (PROs)**

Baseline compliance rates were comparable for enfortumab vedotin and chemotherapy treatment groups in both EORTC QLQ-C30 (90.7% and 88.6%, respectively) and EQ-5D-5L (91.0% and 89.9%, respectively). Baseline completion rates were similar for enfortumab vedotin and chemotherapy treatment groups in both the EORTC QLQ-C30 questionnaire (90.7% and 88.6%, respectively) and EQ-5D-5L (91.0% and 89.9%, respectively). There was a commensurate drop off in the number of subjects available for each visit in both instruments, with both compliance and completion rates between treatment groups comparable throughout the study, and a decrease post week 12.

EORTC QLQ-C30: The change in the Global Health Status (QL2, 2-item QOL subscale of the EORTC QLQ-C30) score from baseline assessment to week 12 assessment was prespecified as a secondary endpoint in the study protocol and SAP. Mean baseline (SD) scores were 63.83 (19.89) in the enfortumab vedotin arm and 64.58 (19.19) in the chemotherapy arm. Results from the Model Repeated Measures Approach (MMRM) analysis of QL2 indicated that QOL was maintained from baseline to week 12, with a smaller decrease in estimate values for the enfortumab vedotin arm (-2.825 [1.348]) compared to subjects in the chemotherapy arm (-4.996 [1.479]), and no significant differences noted (P = 0.2429).

Mean (SD) scores from the EORTC QLQ-C30 showed there was little deterioration in self-rated functional health from baseline to week 12 in the enfortumab vedotin arm, with reductions ranging from -0.92 (15.76) in cognitive functioning to -5.12 (23.80) in social functioning. For subjects in the chemotherapy arm, worsening in mean scores was overall numerically larger, ranging from -0.49 (16.66) in cognitive functioning to -9.15 (26.29) in role functioning. For subjects in the enfortumab vedotin arm, a decrease in symptom burden from baseline to week 12 was observed for several subscales, including numerical improvements in insomnia (-3.67 [30.06]) and constipation (-6.04 [27.99]). The largest numerical improvement was seen in change from baseline to week 12 in reduction of self-reported pain (-6.96 [26.26]). Little change in nausea and vomiting (-0.39 [16.73]) was reported, with small numerical increases in fatigue (3.94 [23.32]), dyspnoea (4.20 [20.14]), appetite loss (5.77 [32.56]) and diarrhoea (3.94 [24.35]). For subjects in the chemotherapy arm, increases in symptoms from baseline to week 12 were reported in pain (1.96 [24.07]), diarrhoea (3.27

[19.63]), appetite loss (3.92 [27.87]), dyspnoea (4.90 [20.66]) and fatigue (6.64 [22.56]). Little change was seen in mean scores of nausea and vomiting (0.16 [14.55]) and constipation (-0.98 [24.13]), with a small improvement in insomnia (-1.63 [27.90]).

EQ-5D-5L: A total of 13 subjects from 4 sites were removed from the Visual Analog Scale (VAS) analysis because of device display error on the VAS and their data were not included in the VAS analysis. Descriptive results from the EQ-5D-5L were largely consistent with EORTC QLQ-C30 QOL findings. Mean (SD) VAS scores at baseline were 68.2 (18.1) (median 70.0 [range 0 to 100]) for subjects in the enfortumab vedotin arm and 68.3 (18.8) (median 71 [range 0 to 100]) for subjects in the chemotherapy arm. Little deterioration was reported in mean (SD) VAS score from baseline to week 12 in the enfortumab vedotin arm (-1.8 [16.6]), with a larger decrease during the same time period in the chemotherapy arm (-5.3 [14.5]). Frequencies of problems in mobility, self-care, usual activities, pain and anxiety/depression largely mirrored QLQ-C30 findings.

## Summary of main study(ies)

The following table summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections)

**Table 73** Summary of efficacy for trial EV-301

| **EV-301: an open-label, randomised phase 3 study to evaluate Enfortumab vedotin vs chemotherapy in subjects with previously treated locally advanced or metastatic urothelial Cancer** | | | |
|---|---|---|---|
| Study identifier | EudraCT 2017-003344-21; NCT03474107 | | |
| Design | Phase III, multicentre, global, randomised, open-label, two-arm | | |
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase: | | Not applicable, event-driven<br>Not applicable<br>Not applicable |
| Hypothesis | Superiority | | |
| Treatments groups | Arm A (Enfortumab vedotin) | | Enfortumab vedotin D1, D8 and D15 Q4W until PD or discontinuation<br>n=301 |
| | Arm B (Chemotherapy) | | Docetaxel or paclitaxel or vinflunine (as decided by INV) Q3W until PD or discontinuation<br>n=307 |
| Endpoints and definitions | Primary endpoint | OS | Overall survival: time from randomisation to date of death from any cause |
| | Secondary endpoint | PFS1-INV | Progression free survival 1: time from the date of randomisation until the date of radiological disease progression (per RECIST v1.1) per the investigator, or until death from any cause. |
| | Secondary endpoint | ORR-INV | Overall response rate: proportion of subjects with confirmed complete or partial objective response based on the RECIST v.1.1 per the investigator |
| | Secondary endpoint | DOR-INV | Duration of response: 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 the investigator to the date of radiological progression or date of death for subjects who achieved CR or PR. |

| | | | |
|---|---|---|---|
| | Exploratory endpoint | PFS2-INV | Progression free survival 2: time from the date of randomisation until the date of radiological disease progression (per RECIST v1.1) per the investigator on next-line therapy, or until death from any cause. |
| Data cutoff | 15-JUL-2020 | | |
| Database lock | 15-SEP-2020 | | |

**Results and Analysis**

| **Analysis description** | **Primary Analysis (interim analysis results crossed the efficacy stopping boundary)** | | |
|---|---|---|---|
| Analysis population and time point description | Intent to treat=608, interim analysis planned to occur after ~285 OS events | | |
| | Treatment group | Enfortumab vedotin | Chemotherapy |
| | Number of subjects | 301 | 308 |
| | OS, patients with event (%) | 134 (44.5) | 167 (54.4) |
| | Median OS, months[a] | 12.88 | 8.97 |
| | 95% CI | 10.58, 15.21 | 8.05, 10.74 |
| | PFS1-INV, patients with event (%) | 201 (66.8) | 231 (75.2) |
| | Median PFS1, months[a] | 5.55 | 3.71 |
| | 95% CI | 5.32, 5.82 | 3.52, 3.94 |
| | ORR-INV (%) | 117 (40.6) | 53 (17.9) |
| | 95% CI | 34.90, 46.54 | 13.71, 22.76 |
| | DOR-INV, patients with event (%) | 63 (53.8) | 29 (54.8) |
| | Median DOR, months[a] | 7.39 | 8.11 |
| | 95% CI | 5.59, 9.46 | 5.65, 9.56 |
| | PFS2-INV, patients with event (%) | 152 (50.5) | 195 (63.5) |
| | Median PFS2, months[a] | 9.63 | 7.00 |
| | 95% CI | 8.21, 10.58 | 6.54, 8.05 |

| | | | |
|---|---|---|---|
| Effect estimate per comparison | Primary endpoint, OS | Comparison groups | Enfortumab vedotin vs. Chemotherapy |
| | | Stratified Hazard Ratio[b] | 0.702 |
| | | 95% CI | 0.556, 0.886 |
| | | P-value[c] | 0.00142 |
| | Secondary endpoint, PFS1-INV | Comparison groups | Enfortumab vedotin vs. Chemotherapy |
| | | Stratified Hazard Ratio[b] | 0.615 |
| | | 95% CI | 0.505, 0.748 |
| | | P-value[c] | <0.00001 |
| | Secondary endpoint, ORR-INV | Comparison groups | Enfortumab vedotin vs. Chemotherapy |
| | | P-value[d] | <0.001 |
| | Exploratory endpoint, PFS2-INV | Comparison groups | Enfortumab vedotin vs. Chemotherapy |
| | | Stratified Hazard Ratio[b] | 0.619 |
| | | 95% CI | 0.497, 0.771 |
| | | P-value[c] | <0.001 |
| Notes | [a]Based on Kaplan-Meier estimate<br>[b]Based on Cox proportional hazards model<br>[c]Based on log-rank test<br>[d]Based on Cochran-Mantel-Haenzel test | | |

## Analysis performed across trials (pooled analyses and meta-analysis)

Not performed for efficacy.

## Clinical studies in special populations

**Table 74**

| | **Age 65-74 (Older subjects number /total number)** | **Age 75-84 (Older subjects number /total number)** | **Age 85+ (Older subjects number /total number)** |
|---|---|---|---|
| Controlled Trials | 269 | 115 | 5 |
| Non Controlled trials | 73 | 70 | 10 |

## *Supportive studies*

**Study EV-201**

EV-201 was a phase 2, open-label, multicentre, multi-cohort study of EV in subjects who have previously received a PD-1 or PD-L1 inhibitor.

Cohort 1 enrolled patients similar to those enrolled in EV-301 with locally advanced or metastatic UC previously treated with a PD-1/PD-L1 inhibitor and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting.

Cohort 2 was constituted by patients with locally advanced or metastatic UC who had received a PD-1/PD-L1 inhibitor and were platinum-naïve in the locally advanced/metastatic setting and were not eligible for cisplatin-containing chemotherapy.

**Study EV-101**

EV-101 was a phase 1, open-label, nonrandomized, multicentre study of the safety and PK of escalating doses of enfortumab vedotin as monotherapy followed by expansion.

Part A of EV-101 consisted of the initial dose escalation and expansion cohort. Part B consisted of 3 expansion cohorts for subjects with metastatic NSCLC, metastatic ovarian cancer or metastatic UC with renal insufficiency (CrCl ≥ 15 ml/min and < 30 ml/min). Part C consisted of subjects with metastatic UC who were previously treated with a PD-1/PD-L1 inhibitor in the metastatic setting.

**Table 75** Summary of comparative efficacy analysis across pivotal EV-301 and supportive studies

| Parameter Statistics/Criteria | EV-301† | | EV-201‡ | | EV-101 |
|---|---|---|---|---|---|
| | Enfortumab Vedotin (n = 301) | Chemotherapy (n = 307) | Cohort 1 Enfortumab Vedotin (n = 125) | Cohort 2 Enfortumab Vedotin (n = 89) | Part C§ Enfortumab Vedotin (n = 74) |
| **EV-301 primary endpoint - OS¶** | | | | | |
| Median (95% CI), months | 12.88 (10.58, 15.21) | 8.97 (8.05, 10.74) | 12.4 (9.46, 15.57) | 14.7 (10.51, 18.20) | 12.2 (8.15, 16.85) |
| **EV-301 secondary endpoints** | | | | | |
| **PFS††** | | | | | |
| Median (95% CI), months | 5.55 (5.32, 5.82) | 3.71 (3.52, 3.94) | 5.8 (4.93, 7.46) | 5.8 (5.03, 8.28) | 6.6 (5.32, 8.15) |
| **ORR††** | | | | | |
| Confirmed ORR (CR or PR), n (%) | 117 (40.6) | 53 (17.9) | 55 (44) | 46 (52) | 33 (44.6) |
| 95% CI for ORR | (34.90, 46.54) | (13.71, 22.76) | (35.1, 53.2) | (40.8, 62.4) | (33.02, 56.61) |
| **DOR††** | | | | | |
| Median (95% CI), months | 7.39 (5.59, 9.46) | 8.11 (5.65, 9.56) | 7.6 (6.34, NE) | 10.9 (5.78, NE) | 7.5 (5.78, NE) |

In EV-301, FAS was defined as all subjects who were randomized; in EV-201 and EV-101, FAS was defined as all subjects enrolled in a study who received any amount of enfortumab vedotin. In EV-301, RES was defined as all subjects in the FAS with measurable disease per investigator at baseline.
*Footnotes continued on next page*
Data cutoff dates: 15 Jul 2020 (EV-301); 08 Sep 2020 (EV-201 Cohort 1 [OS only] and Cohort 2); 01 Mar 2019 (EV-201 Cohort 1 [PFS, ORR, DOR]); 25 Oct 2018 (EV-101).
BICR: blinded independent central review; CI: confidence interval; CSR: clinical study report; DOR: duration of response; FAS: full analysis set; NE: not estimable; ORR: overall response rate; OS: overall survival; PD-1 programmed death receptor-1; PD-L1: programmed death-ligand 1; PFS: progression-free survival; RES: response evaluable set.
† EV-301 subjects were previously treated with platinum-containing chemotherapy and a PD-1/PD-L1 inhibitor.
‡ EV-201 subjects were previously treated with a PD-1/PD-L1 inhibitor. Subjects in Cohort 1 had also received platinum-containing chemotherapy; subjects in Cohort 2 were platinum-naïve and cisplatin-ineligible.
§ EV-101 subjects in Part C were previously treated with a PD-1/PD-L1 inhibitor.
¶ OS was a secondary efficacy endpoint in EV-201 and EV-101. The OS analysis was conducted on FAS in all studies.
†† PFS, ORR and DOR were based on investigator assessment in EV-301 and BICR assessment in EV-201 and EV-101. PFS analysis was conducted on the FAS in all studies. ORR and DOR analysis were conducted on the RES in EV-301 and on the FAS in EV-201 and EV-101.

## 2.5.3. Discussion on clinical efficacy

***Design and conduct of clinical studies***

The application for a marketing authorisation for EV is based on results from phase III trial EV-301, phase I EV-101 and phase II EV-201.

Based on favourable efficacy and safety results from phase I EV-101 and phase II EV-201 trials, the applicant designed EV-301 as an open-label phase III randomised controlled trial to evaluate enfortumab vedotin (EV) in comparison to one of three chemotherapy choices (paclitaxel, docetaxel or vinflunine) in the post-platinum and post-immunotherapy setting of advanced urothelial cancer.

The design of the pivotal EV-301 trial had been discussed with the CHMP before starting recruitment (SA dated November 2017, original protocol dated December 2017). The targeted population, primary and secondary endpoints, chemotherapy comparators in the control arm and statistical analysis plan were all deemed appropriate.

Cross over from chemotherapy to EV was not allowed until after results from the interim analysis were considered final (protocol V4).

Inclusion and exclusion criteria did not suffer major changes along protocol amendments during the recruitment period. The proposed therapeutic indication for EV reflects the population included in EV-301.

The primary endpoint of EV-301 was OS, which is considered appropriate and in accordance with relevant European guidelines (EMA/CHMP/205/95). Secondary endpoints (PFS, ORR, DCR, DOR) used RECIST criteria for response evaluation, and although an independent review of the imaging was not

set up, the risk of investigator-bias in this open label trial is considered mitigated by OS being the primary endpoint.

Statistical methods: Sample size was increased while recruitment was ongoing, which is not expected to affect integrity of the trial. The randomisation procedure is appropriate and the stratification factors (ECOG PS, Region of the World and liver metastases) are clinically relevant. ITT was used for OS and PFS1 analyses, while patients without measurable disease at baseline were excluded from the denominator in response-dependent endpoints ORR and DCR. The statistical methods for the analysis of OS and PFS1 are endorsed and the strategies implemented to control type I error along hierarchical testing are appropriate. SAP amendments on censoring rules and sensitivity analyses do not affect the interpretation of the results. An independent data analysis centre (IDAC) was used to produce unblinded summaries for the IDMC session, and aggregate safety summaries combined treatment groups for medical monitoring.

Major protocol violations were rare and balanced between arms. The main criticism to the conduct of the trial was removing prespecified subgroup analyses of efficacy according to nectin-4 expression in protocol V2, but this was addressed by submitting the required data (see below).

Results: 608 patients were randomised in the recruitment period: 301 to the EV arm and the remainder 307 to chemotherapy. The subject disposition tree can be followed, noticing a slightly higher proportion of patients who were randomised and withdrew consent before treatment in the control arm, an expectable situation in open-label trials.

The overall demographic and disease characteristics of the population were balanced between arms and fairly represent clinical practice in the post-platinum post-immunotherapy setting of Urothelial Cancer, except for the proportion of upper (34%) vs. lower tract disease (66%) in EV-301. The applicant explains this difference on better opportunity for trial participation for this subgroup with worse prognosis.

## *Efficacy data and additional analyses*

At data cutoff 15-JUL-2020 and with a median follow-up of 11.1 months, 301 deaths had occurred (49.5% of OS maturity) in the ITT population of EV-301. The study met its primary endpoint, as HR for OS showed superiority of EV over chemotherapy: 0.70 (95% CI 0.56, 0.89), p-value 0.00142. K-M estimates of median OS are 12.9 months in the EV arm and 9.0 in the chemotherapy arm. Sensitivity analyses that account for the effect of cross-over (RPSFT and IPCW methods, using the number of OS events specified in the original protocol) produced consistent HRs. Updated data from the final analysis of OS (data cutoff 30-JUL-2021) with 73% of event maturity provided consistent results, with an HR of 0.70 (95% CI 0.58, 0.85).

At 71% of PFS events, HR for PFS1 was 0.62 (95% CI 0.51, 0.75), p-value <0.00001. K-M estimates of median PFS1 were 5.6 months in the EV arm and 3.7 in the chemotherapy arm. Sensitivity analyses with less conservative censoring rules produced similar results.

Confirmed ORR rate was 41% in the EV arm and 18% in the chemo arm, noticing consistent results in requested sensitivity analyses that used ITT as denominator. K-M estimates of median DOR were numerically longer in the chemo arm (8.1 months) than the EV arm (7.4 months), but the 12-month landmark analyses of DOR suggest improved performance of EV (28% still on response) vs. chemo (20%). In support of the survival advantage, median PFS2 is numerically longer in the EV arm (9.6 months) as compared to the chemo arm (7.0 months).

Superiority of EV over chemo is observed across most of the predefined subgroup analyses of OS and PFS1, albeit noticing diminished survival in the female subgroup (HR 1.171, 95% CI 0.724, 1.894). The

subgroup comprises 23% of the ITT, paralleling gender distribution of the global incidence of urothelial cancers. Since the pattern of worse survival for female patients with bladder cancer seems established and attributable to a multiplicity of factors (Donsky et al, 2013; Liu et al, 2015), clinical plausibility of the findings from EV-301 appears unlikely.

As supportive data, the applicant submitted efficacy results from advanced urothelial cancer cohorts of phase I and II trials along the clinical development of EV. ORR is consistently above 40% across prior-platinum and platinum-naïve cohorts, noticing overall similar median PFS (range 5.55-6.60 months) and median OS (range 12.12-14.7 months).

Efficacy according to nectin-4 expression:

The mechanism of action of EV relies on cytotoxicity by specifically binding to nectin-4 protein, markedly upregulated on the surface of bladder cancer cells, and implicated in crucial tumoural biology mechanisms (proliferation, invasion, migration, metastasis, angiogenesis and anchorage independence). Since nectin-4 can be objectively measured (analytical validation of nectin-4 IHC is presented in the Ancillary analysis section), the potential relationship between this biomarker and efficacy was explored in patients from EV-301 with available tissue.

Even if nectin-4 expression evaluability was not an inclusion criterion, IHC H-score results were retrospectively analysed for ~87% (n=527) of the ITT (N=608). Efficacy parameters and their confidence intervals in the biomarker-available population are overall comparable to those in the ITT population: HR for OS is 0.69 (0.70 in ITT); HR for PFS is 0.61 in both populations; ORR for EV is 39% (nectin-4) and 41% (ITT); and ORR for chemotherapy is 17% (nectin-4) and 18% (ITT).

Albeit results from the initial analyses suggested that a survival advantage was not apparent in low-expressors, data from the final analysis of OS indicate that there is insufficient evidence to conclude that efficacy is affected by nectin-4 expression in the biomarker-available population.

### 2.5.4. Conclusions on the clinical efficacy

Pivotal study EV-301 had a positive outcome, showing a statistically significant and clinically relevant survival advantage of enfortumab vedotin over chemotherapy in the post-platinum post-immunotherapy setting of advanced urothelial cancer. The benefit was observed across most subgroups, was consistent over diverse sensitivity analyses and updated results, and is further supported by superiority across PFS1, PFS2 and response-related endpoints.

## *2.6. Clinical safety*

The safety profile of enfortumab vedotin was established from 5 ongoing or completed clinical studies and includes 680 unique subjects dosed with enfortumab vedotin 1.25 mg/kg. The overall safety evaluation is based on the EV-301 enfortumab vedotin population; the EV-301 chemotherapy population; Cohort 1 of EV-201; Cohort 2 of EV-201; and all subjects who received a starting dose of enfortumab vedotin of 1.25 mg/kg in EV-301, EV-201, EV-101 and EV-102 (enfortumab vedotin 1.25 mg/kg safety analysis group). (Table 81).

**Table 76** Clinical Studies Included in the Integrated Safety Analysis

| Type of Study | Study Identifier | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects Enrolled (treated) | Diagnosis of Subjects | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| **Monotherapy Studies** | | | | | | | | |
| Efficacy, Safety | EV-301 (7465-CL-0301)† | Primary: OS<br>Secondary: PFS, ORR, DOR, DCR, safety and tolerability, quality of life and subject-reported outcome parameters | Phase 3 global, open-label, randomized trial of enfortumab vedotin vs chemotherapy | Enfortumab vedotin: 1.25 mg/kg 30-min iv infusion on days 1, 8 and 15 of a 28-day cycle<br>or<br>Docetaxel 75 mg/m$^2$, paclitaxel 175 mg/m$^2$ or vinflunine 320 mg/m$^2$ on day 1 of a 21-day cycle | Enrolled: 608 (587)<br>Arm A, enfortumab vedotin = 301 (296);<br>Arm B, chemotherapy = 307 (291) | Subjects with locally advanced or metastatic UC who have received a platinum-containing chemotherapy and have experienced disease progression or relapse during or following treatment with a PD-1 or PD-L1 inhibitor | Until radiological disease progression as assessed by the investigator, or other discontinuation criteria are met | Ongoing (enrollment closed);<br>Primary Analysis CSR |
| Efficacy, Safety | EV-201 (SGN22E-001)‡ | Primary: ORR<br>Secondary: DOR, DCR$_{16}$, PFS, OS, PK, immunogenicity, safety and tolerability | Phase 2, open-label, multicenter, multi-cohort study of enfortumab vedotin in subjects who have previously received a PD-1 or PD-L1 inhibitor | Enfortumab vedotin:<br>1.25 mg/kg 30-min iv infusion on days 1, 8 and 15 of a 28-day cycle | Enrolled: 219<br>(214)<br>Cohort 1 = 128 (125);<br>Cohort 2 = 91 (89) | Cohort 1: Subjects with locally advanced or metastatic UC who have previously received a PD-1/ PD-L1 inhibitor and a platinum-containing chemotherapy<br>Cohort 2: Subjects who have received a PD-1/PD-L1 inhibitor and are not eligible for cisplatin containing chemotherapy. | Until disease progression, unacceptable toxicity, investigator decision, consent withdrawal, start of subsequent anticancer therapy, pregnancy or study termination by the sponsor. | Ongoing (enrollment closed); Cohort 1 Primary Analysis CSR* and Cohort 2 primary analysis CSR |

*Table continued on next page*

| Type of Study | Study Identifier | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects Enrolled (treated) | Diagnosis of Subjects | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Safety, PK | EV-101 (ASG-22CE-13-2)§ | Primary: safety and PK<br>Secondary: immunogenicity and antitumor activity | Phase 1, open-label, nonrandomized, multicenter study of the safety and PK of escalating doses of enfortumab vedotin as monotherapy followed by expansion | Enfortumab vedotin:<br>0.5, 0.75, 1.0, 1.25 mg/kg<br>30-min iv infusion on days 1, 8 and 15 of a 28-day cycle | Enrolled: 213 (213)<br>Part A: 87<br>Part B: 52<br>(NSCLC: 18<br>Ovarian: 16<br>Renal insufficiency: 18)<br>Part C: 74 | Subjects with metastatic UC and other Nectin-4-expressing malignant solid tumors | Until disease progression, intolerability of enfortumab vedotin, investigator decision or consent withdrawal | Ongoing;<br>Primary analysis CSR* and CSR Addendum for Renal Insufficiency Cohort |
| Safety, PK | EV-102 (7465-CL-0101)¶ | Primary: safety, tolerability and PK<br>Secondary: immunogenicity and antitumor activity | Phase 1, open-label, randomized, multicenter study of the safety, tolerability and PK of 2 doses of enfortumab vedotin in Japanese subjects | Enfortumab vedotin:<br>1.0 or 1.25 mg/kg 30-min iv infusion on days 1, 8 and 15 of a 28-day cycle | Enrolled 19 (17)<br>Arm A: 10 (9)<br>Arm B: 9 (8) | Japanese subjects with locally advanced or metastatic UC | Until disease progression, clinically significant toxicity of enfortumab vedotin, investigator decision or informed consent withdrawal | Complete;<br>Final CSR |
| Safety, PK | AGS-22M6E-11-1†† | Primary: safety and PK<br>Secondary: immunogenicity and effectiveness | Phase 1, open-label, nonrandomized, multicenter study of the safety and PK of escalating doses of AGS-22M6E and bridging with enfortumab vedotin as monotherapy | Enfortumab vedotin:<br>0.6 and 1.2 mg/kg 30-min iv infusion once every 3 weeks | Enfortumab vedotin: 9‡‡ | Subjects with malignant solid tumors that express Nectin-4 | Until disease progression, intolerability of enfortumab vedotin, investigator decision or consent withdrawal | Complete; Final CSR* |

CHO: Chinese hamster ovary; CSR: clinical study report; $DCR_{16}$: disease control rate at 16 weeks; DOR: duration of response; iv: intravenous; NSCLC: non-small cell lung carcinoma; ORR: objective response rate; OS: overall survival; PD-1: programmed cell death protein-1; PD-L1: programmed death-ligand 1; PFS: progression-free survival; PK: pharmacokinetics; UC: urothelial carcinoma

† EV-301 data cutoff date is 15 Jul 2020.

‡ EV-201 data cutoff date is 01 Mar 2019 for Cohort 1 primary analysis and 08 Sep 2020 for Cohort 2 primary analysis.

§ EV-101 data cutoff date is 25 Oct 2018 for the primary analysis and 17 Feb 2020 for addendum to primary CSR that includes the renal insufficiency cohort.

¶ EV-102 date last evaluation is 25 Feb 2019.

†† AGS-22M6E-11-1 date last evaluation is 27 Apr 2015.

‡‡ This bridging study included 25 other subjects treated with AGS-22M6E (hybridoma antibody intermediate) in addition to the 9 subjects who received enfortumab vedotin (CHO antibody intermediate).

*CSR previously submitted to FDA in BLA 761137

## *Patient exposure*

A total of 4 clinical studies are included in the safety data sets for the current application (pivotal Study EV-301, Study EV-201, Study -101 and Study EV-102). There were 680 subjects treated with enfortumab vedotin at the intended posology 1.25 mg/kg and 291 subjects treated with chemotherapy. All the studies included in the ISS are ongoing except Study EV-102; 60-day updated safety data from the ongoing studies has been provided.

**Table 77** Integrated Safety Analysis Groups

| **Population** | **Included Studies**† |
|---|---|
| EV-301 Enfortumab Vedotin Population (n = 296) | EV-301 (7465-CL-0301) |
| EV-301 Chemotherapy Population (n = 291) | EV-301 (7465-CL-0301) |
| EV-201 Cohort 1 Population (n = 125) | EV-201 (SGN22E-001) |
| EV-201 Cohort 2 Population (n = 89) | EV-201 (SGN22E-001) |
| Enfortumab Vedotin 1.25 mg/kg Population (n = 680) | EV-101 (ASG-22CE-13-2)<br>EV-102 (7465-CL-0101)<br>EV-201 (SGN22E-001)<br>EV-301 (7465-CL-0301) |

ISS: integrated summary of safety; SAP: statistical analytical plan † Included studies does not mean all subjects in those studies belong to that population. Source: ISS SAP

The safety evaluation is mainly focus on the phase 3 study EV-301 and the additional data from study EV-201/ Cohort 1 (201/C1), where the patient population was similar to patients in study EV-301 (prior PD1/PD-L1 inhibitor and cisplatin-containing therapy).

Study EV-201, Cohort 2, had prior PD-1/PD-L1 inhibitor therapy but were deemed ineligible for cisplatin-containing therapy (cut-off 8 Sep 2020).

In addition, 170 patients having received 1.25 mg/kg enfortumab vedotin in the two phase 1 studies EV-101 and EV-102 were included in the entire 680 patients ISS (integrated summary of safety). Thirty-five of these did not have urothelial cancer but NSCLC or ovarian cancer.

The median exposure to enfortumab vedotin in study EV-301 was 4.99 months and 4.60 months in study 201/ Cohort 1. Exposure to chemotherapy in study EV-301 was 3.45 months (Table 83).

**Table 78 Study drug exposure (Safety Analysis Set)**

| Parameter Category/Statistic | Study EV-301 | | Study EV-201 | | Enfortumab Vedotin† 1.25 mg/kg (n =680) |
|---|---|---|---|---|---|
| | Enfortumab Vedotin (n = 296) | Chemotherapy (n = 291) | Cohort 1 Enfortumab Vedotin (n = 125) | Cohort 2 Enfortumab Vedotin (n = 89) | |
| **Duration of exposure (months) ‡** | | | | | |
| N | 296 | 291 | 125 | 89 | 680 |
| Mean (SD) | 5.36 (3.72) | 3.96 (2.95) | 6.00 (5.73) | 6.38 (4.62) | 5.77 (5.06) |
| Min, max | 0.5, 19.4 | 0.2, 15.0 | 0.5, 29.4 | 0.3, 24.6 | 0.3, 34.8 |
| Median | 4.99 | 3.45 | 4.60 | 5.98 | 4.67 |
| **Duration of exposure (months), n (%)** | | | | | |
| < 1 | 43 (14.5) | 38 (13.1) | 14 (11.2) | 13 (14.6) | 99 (14.6) |
| ≥ 1 and < 6 | 143 (48.3) | 189 (64.9) | 71 (56.8) | 32 (36.0) | 333 (49.0) |
| ≥ 6 and < 12 | 92 (31.1) | 59 (20.3) | 27 (21.6) | 32 (36.0) | 184 (27.1) |
| ≥ 12 | 18 (6.1) | 5 (1.7) | 13 (10.4) | 12 (13.5) | 64 (9.4) |
| **Planned dose intensity ¶** | | | | | |
| N | 296 | N/A* | 125 | 89 | 680 |
| Mean (SD) | 3.750 (0) | N/A | 3.750 (0) | 3.750 (0) | 3.750 (0) |
| Min, max | 3.75, 3.75 | N/A | 3.75, 3.75 | 3.75, 3.75 | 3.75, 3.75 |
| Median | 3.750 | N/A | 3.750 | 3.750 | 3.750 |
| **Dose intensity ††** | | | | | |
| N | 296 | N/A* | 125 | 89 | 680 |
| Mean (SD) | 2.98 (0.66) | N/A | 2.92 (0.66) | 2.90 (0.67) | 2.94 (0.70) |
| Min, max | 1.1, 3.9 | N/A | 1.0, 3.8 | 1.3, 3.8 | 1.0, 4.5 |
| Median | 3.03 | N/A | 2.95 | 2.96 | 3.02 |
| **Relative dose intensity (%) ‡‡** | | | | | |
| n | 296 | 290 | 125 | 89 | 680 |
| Mean (SD) | 79.35 (17.52) | 91.76 (11.61) | 77.81 (17.60) | 77.24 (18.00) | 78.46 (18.55) |
| Min, max | 30.6, 104.9 | 32.5, 114.2 | 26.2, 101.8 | 33.3, 102.2 | 26.2, 120.0 |
| Median | 80.73 | 97.36 | 78.67 | 78.95 | 80.40 |

ISS: integrated summary of safety; Max: maximum; Min: minimum; RDI: relative dose intensity; SD: standard deviation

† Enfortumab vedotin 1.25 mg/kg column includes all subjects in the following studies who received a 1.25 mg/kg dose of enfortumab vedotin: EV-101, EV-102, EV-201, and EV-301.

‡ Duration of exposure = (min (initial dose date of the last cycle + 27, cutoff date, death date) - first dose date + 1) / 30.4375 for enfortumab vedotin and duration of exposure = (min (initial dose date of the last cycle + 20, cutoff date, death date)- first dose date + 1) / 30.4375 for chemotherapy.

¶ Initial dose multiplied by planned number of dosing days per cycle. Unit for enfortumab vedotin is mg/kg/cycle.

†† Actual weight adjusted total dose per cycle. For derivation details see [SAP Section 5.3]. Unit for enfortumab vedotin is mg/kg/cycle.

‡‡ (Dose intensity/Planned dose intensity) x 100%. RDI calculation uses subject weight capped at 100 kg for enfortumab vedotin. At dose administration, some enfortumab vedotin subjects were not weight capped at 100 kg and as a result, their RDI may be greater than 100%.

* Due to differences between docetaxel, vinflunine and paclitaxel, dose intensity for the chemotherapy arm was not summarized.

ISS: integrated summary of safety; Max: maximum; Min: minimum; RDI: relative dose intensity; SD: standard deviation

Demographics and baseline disease characteristics:

Demographic characteristics for the Safety data set are presented for studies EV 301 and EV 201/Cohort 1.

The median age was comparable between the arms in EV-301 and compared to EV-201/C1, but there were more patients ≥75 years in the chemotherapy arm (22.3 %) compared to EV-301 (17.2%), although less than in EV- 201/C1 (27.2%) (see also the subgroup section).

**Table 79** Demographic Characteristics (Safety Analysis Set)

| Parameter Category/Statistic | Study EV-301 | | Study EV-201 | | Enfortumab Vedotin 1.25 mg/kg† |
|---|---|---|---|---|---|
| | Enfortumab Vedotin (n = 296) | Chemotherapy (n = 291) | Cohort 1 Enfortumab Vedotin (n = 125) | Cohort 2 Enfortumab Vedotin (n = 89) | (n = 680) |
| Sex, n (%) | | | | | |
| Male | 234 (79.1) | 219 (75.3) | 88 (70.4) | 66 (74.2) | 497 (73.1) |
| Female | 62 (20.9) | 72 (24.7) | 37 (29.6) | 23 (25.8) | 183 (26.9) |
| Ethnicity, n (%) | | | | | |
| Not Hispanic or Latino | 229 (77.4) | 224 (77.0) | 118 (94.4) | 83 (93.3) | 593 (87.2) |
| Hispanic or Latino | 28 (9.5) | 24 (8.2) | 5 (4.0) | 1 (1.1) | 40 (5.9) |
| Not reportable | 39 (13.2) | 43 (14.8) | 2 (1.6) | 5 (5.6) | 46 (6.8) |
| Unknown | 0 | 0 | 0 | 0 | 1 (0.1) |
| Race, n (%) | | | | | |
| White | 157 (53.0) | 145 (49.8) | 106 (84.8) | 62 (69.7) | 472 (69.5) |
| Black or African American | 2 (0.7) | 2 (0.7) | 2 (1.6) | 0 | 7 (1.0) |
| Asian | 97 (32.8) | 98 (33.7) | 11 (8.8) | 20 (22.5) | 145 (21.4) |
| Other | 40 (13.5) | 46 (15.8) | 6 (4.8) | 7 (7.9) | 55 (8.1) |
| Missing | 0 | 0 | 0 | 0 | 1 |
| Region, n (%) | | | | | |
| North America | 70 (23.6) | 63 (21.6) | 117 (93.6) | 57 (64.0) | 406 (59.7) |
| Europe | 125 (42.2) | 125 (43.0) | 0 | 14 (15.7) | 139 (20.4) |
| Rest of world | 101 (34.1) | 103 (35.4) | 8 (6.4) | 18 (20.2) | 135 (19.9) |
| Age, years | | | | | |
| n | 296 | 291 | 125 | 89 | 680 |
| Mean (SD) | 66.5 (9.1) | 66.9 (10.0) | 67.4 (10.0) | 73.2 (8.8) | 67.5 (9.8) |
| Min, max | 34, 85 | 30, 88 | 40, 84 | 49, 90 | 24, 90 |
| Median | 68.0 | 68.0 | 69.0 | 75.0 | 69.0 |
| Age group (years), n (%) | | | | | |
| < 65 | 106 (35.8) | 103 (35.4) | 45 (36.0) | 16 (18.0) | 240 (35.3) |
| ≥ 65 to < 75 | 139 (47.0) | 123 (42.3) | 46 (36.8) | 27 (30.3) | 272 (40.0) |
| ≥ 75 | 51 (17.2) | 65 (22.3) | 34 (27.2) | 46 (51.7) | 168 (24.7) |
| EudraCT age group (years), n (%) | | | | | |
| ≥ 18 to ≤ 64 | 106 (35.8) | 103 (35.4) | 45 (36.0) | 16 (18.0) | 240 (35.3) |
| ≥ 65 to ≤ 84 | 189 (63.9) | 184 (63.2) | 80 (64.0) | 63 (70.8) | 425 (62.5) |
| ≥ 85 | 1 (0.3) | 4 (1.4) | 0 | 10 (11.2) | 15 (2.2) |
| Weight (kg) | | | | | |
| n | 296 | 291 | 125 | 89 | 680 |
| Mean (SD) | 74.36 (16.75) | 73.21 (15.79) | 76.53 (14.00) | 75.88 (18.40) | 76.01 (16.89) |
| Min, max | 40.0, 146.5 | 37.3, 148.3 | 45.3, 114.5 | 40.0, 128.8 | 36.9, 146.5 |
| Median | 74.00 | 72.20 | 76.10 | 73.80 | 75.00 |
| Weight group (kg), n (%) | | | | | |
| ≤ 100 | 275 (92.9) | 278 (95.5) | 121 (96.8) | 81 (91.0) | 632 (92.9) |
| > 100 to ≤ 120 | 20 (6.8) | 12 (4.1) | 4 (3.2) | 6 (6.7) | 40 (5.9) |
| > 120 | 1 (0.3) | 1 (0.3) | 0 | 2 (2.2) | 8 (1.2) |
| BMI ($kg/m^2$) | | | | | |
| n | 296 | 290 | 125 | 89 | 680 |

| Parameter Category/Statistic | Study EV-301 | | Study EV-201 | | Enfortumab Vedotin 1.25 mg/kg† |
|---|---|---|---|---|---|
| | Enfortumab Vedotin (n = 296) | Chemotherapy (n = 291) | Cohort 1 Enfortumab Vedotin (n = 125) | Cohort 2 Enfortumab Vedotin (n = 89) | (n = 680) |
| Mean (SD) | 25.66 (4.49) | 25.59 (4.88) | 25.97 (4.25) | 25.93 (4.58) | 26.11 (4.65) |
| Min, max | 15.9, 43.0 | 14.5, 47.9 | 17.3, 39.8 | 17.8, 39.1 | 15.9, 43.0 |
| Median | 25.37 | 25.05 | 25.25 | 25.26 | 25.56 |
| BMI category (kg/m$^2$), n (%) | | | | | |
| < 25 | 134 (45.3) | 143 (49.3) | 58 (46.4) | 43 (48.3) | 295 (43.4) |
| ≥ 25 to < 30 | 121 (40.9) | 101 (34.8) | 46 (36.8) | 33 (37.1) | 272 (40.0) |
| ≥ 30 | 41 (13.9) | 46 (15.9) | 21 (16.8) | 13 (14.6) | 113 (16.6) |
| Missing‡ | 0 | 1 | 0 | 0 | 0 |

Number of subjects (n) and percentage of subjects (%) are shown.
Missing row is not included in the denominator for the percentages.
Race category 'Other' included subjects with multiracial, other race(s), or race 'Unknown' or 'Not Reported'.
BMI: body mass index (weight [kg]/height [m$^2$]); ISS: integrated summary of safety; max: maximum; min: minimum; SD: standard deviation.
† Enfortumab vedotin 1.25 mg/kg column includes all subjects in the following studies who received a 1.25 mg/kg dose of enfortumab vedotin: EV-101, EV-102, EV-201, and EV-301.
‡ Missing values are not presented in EV-201 ISS Table 12.1.2.1, so zeros were added for Study EV-201 as all the numbers in each category add up to the total n.
Source: EV-201 and EV-301 ISS Table 12.1.2.1

Baseline disease characteristics were generally comparable between the arms in study EV-301. When comparing to 201/C1 fewer patients with renal impairment and more patients peripheral neuropathy and higher Bellmunt Risk Score were seen.

**Table 80** Selected Baseline Characteristics (Safety Analysis Set)

| Parameter Category/Statistic | Study EV-301 | | Study EV-201 | | Enfortumab Vedotin 1.25 mg/kg† |
|---|---|---|---|---|---|
| | Enfortumab Vedotin (n = 296) | Chemotherapy (n = 291) | Cohort 1 Enfortumab Vedotin (n = 125) | Cohort 2 Enfortumab Vedotin (n = 89) | (n = 680) |
| ECOG performance status at baseline ‡, n (%) | | | | | |
| 0 | 112 (37.8) | 109 (37.5) | 40 (32.0) | 37 (41.6) | 246 (36.2) |
| 1 | 182 (61.5) | 182 (62.5) | 85 (68.0) | 41 (46.1) | 420 (61.8) |
| 2 | 2 (0.7) | 0 | 0 | 11 (12.4) | 14 (2.1) |
| Hemoglobin, g/dL | | | | | |
| n | 286 | 289 | 124 | 89 | 669 |
| Mean (SD) | 11.33 (1.62) | 11.29 (1.60) | 10.85 (1.39) | 11.37, 1.72 | 11.28 (1.61) |
| Min, max | 7.9, 17.2 | 7.7, 16.2 | 8.1, 13.9 | 8.1, 16.4 | 7.9, 17.2 |
| Median | 11.20 | 11.10 | 10.75 | 11.40 | 11.20 |
| Hemoglobin level (g/dL), § n (%) | | | | | |
| < 10 | 67 (23.4) | 61 (21.1) | 35 (28.2) | 18 (20.2) | 157 (23.5) |
| ≥ 10 | 219 (76.6) | 228 (78.9) | 89 (71.8) | 71 (79.8) | 512 (76.5) |
| Missing | 10 | 2 | 1 | 0 | 11 |
| Estimated creatinine clearance, mL/min | | | | | |
| n | 290 | 291 | 125 | 89 | 674 |
| Mean (SD) | 67.84 (27.44) | 67.24 (29.70) | 70.33 (25.74) | 55.63 (21.20) | 66.87 (27.26) |
| Min, max | 25.6, 213.7 | 23.9, 277.5 | 22.8, 161.5 | 25.2, 132.5 | 11.9, 213.7 |
| Median | 61.83 | 61.03 | 66.40 | 50.64 | 61.74 |
| Renal function based on estimated creatinine clearance, n (%) | | | | | |
| Normal | 48 (16.6) | 50 (17.2) | 26 (20.8) | 5 (5.6) | 112 (16.6) |
| Mild | 105 (36.2) | 101 (34.7) | 51 (40.8) | 22 (24.7) | 245 (36.4) |
| Moderate | 133 (45.9) | 135 (46.4) | 47 (37.6) | 60 (67.4) | 295 (43.8) |
| Severe | 4 (1.4) | 5 (1.7) | 1 (0.8) | 2 (2.2) | 21 (3.1) |

| Parameter Category/Statistic | Study EV-301 Enfortumab Vedotin (n = 296) | Study EV-301 Chemotherapy (n = 291) | Study EV-201 Cohort 1 Enfortumab Vedotin (n = 125) | Study EV-201 Cohort 2 Enfortumab Vedotin (n = 89) | Enfortumab Vedotin 1.25 mg/kg† (n = 680) |
|---|---|---|---|---|---|
| ESRD | 0 | 0 | 0 | 0 | 1 (0.1) |
| Missing | 6 | 0 | 0 | 0 | 6 |
| Hepatic dysfunction group, ††, n (%) | | | | | |
| Normal | 256 (86.5) | 253 (86.9%) | 110 (88.0) | 80 (89.9) | 603 (88.7) |
| Mild | 28 (9.5) | 33 (11.3) | 14 (11.2) | 8 (9.0) | 63 (9.3) |
| Moderate | 2 (0.7) | 2 (0.7) | 0 | 1 (1.1) | 3 (0.4) |
| Severe* | 0 | 1 (0.3) | 0 | 0 | 0 |
| Unknown‡‡ | 10 (3.4) | 2 (0.7) | 1 (0.8) | 0 | 11 (1.6) |
| Tobacco history, n (%) | | | | | |
| Never | 89 (30.4) | 99 (34.4) | 43 (34.4) | 36 (40.4) | 220 (32.5) |
| Former | 164 (56.0) | 153 (53.1) | 71 (56.8) | 50 (56.2) | 389 (57.5) |
| Current | 29 (9.9) | 30 (10.4) | 11 (8.8) | 3 (3.4) | 57 (8.4) |
| Unknown | 11 (3.8) | 6 (2.1) | 0 | 0 | 11 (1.6) |
| Missing | 3 | 3 | 0 | 0 | 3 |
| Medical history of diabetes / hyperglycemia ‡‡, n (%) | | | | | |
| Yes | 55 (18.6) | 56 (19.2) | 21 (16.8) | 20 (22.5) | 153 (22.5) |
| No | 241 (81.4) | 235 (80.8) | 104 (83.2) | 69 (77.5) | 527 (77.5) |
| Medical history of peripheral neuropathy, §§, n (%) | | | | | |
| Yes | 55 (18.6) | 58 (19.9) | 49 (39.2) | 15 (16.9) | 210 (30.9) |
| No | 241 (81.4) | 233 (80.1) | 76 (60.8) | 74 (83.1) | 470 (69.1) |
| Bellmunt Risk Score, ¶¶, n (%) | | | | | |
| 0 to 1 | 194 (67.8) | 198 (68.5) | 72 (58.1) | - | 438 (65.5) |
| ≥ 2 | 92 (32.2) | 91 (31.5) | 52 (41.9) | - | 231 (34.5) |
| Missing | 10 | 2 | 1 | - | 11 |
| HbA1c at baseline, †††, n (%) | | | | | |
| Normal | 116 (41.1) | 125 (44.2) | 65 (54.6) | 40 (46.0) | 231 (45.7) |
| Prediabetes | 129 (45.7) | 125 (44.2) | 45 (37.8) | 34 (39.1) | 213 (42.1) |
| Diabetes | 37 (13.1) | 33 (11.7) | 9 (7.6) | 13 (14.9) | 62 (12.3) |
| Missing | 14 | 8 | 6 | 2 | 174 |

Number of subjects (n) and percentage of subjects (%) are shown.
AST: aspartate aminotransferase; CMQ: customized MedDRA query; ECOG: Eastern Cooperative Oncology Group; ESRD: end-stage renal disease; ISS: integrated summary of safety; max: maximum; min: minimum; NCI: National Cancer Institute; SD: standard deviation; SMQ: standardized MedDRA query; SSQ sponsor-specific queries; ULN: upper limit of normal.
† Enfortumab vedotin 1.25 mg/kg column includes all subjects in the following studies who received a 1.25 mg/kg dose of enfortumab vedotin: EV-101, EV-102, EV-201, and EV-301.
‡ One EV-101 and 2 EV-301 subjects have ECOG=0, 1 at screening but ECOG=2 just before the first dosing. Other subjects with ECOG=2 are from EV-201 Cohort 2.
§ Central lab hemoglobin value was not available for 1 subject from EV-201; 10 enfortumab vedotin subjects and 2 chemotherapy subjects from EV-301.

The number of patients with time ≥12 months since diagnosis was higher in 301/EV and 201/C1 compared to 301/Ch (62.3% and 62.1% vs 53.8%).

**Table 81** Disease History (Safety Analysis Set)

| Parameter Category, n (%) | Study EV-301 Enfortumab Vedotin (n = 296) | Study EV-301 Chemotherapy (n = 291) | Study EV-201 Cohort 1 Enfortumab Vedotin (n = 125) | Study EV-201 Cohort 2 Enfortumab Vedotin (n = 89) | Enfortumab Vedotin 1.25 mg/kg† (n =680) |
|---|---|---|---|---|---|
| Time since locally advanced or metastatic disease diagnosis categories‡ | | | | | |
| < 12 months | 110 (37.7) | 133 (46.2) | 47 (37.9) | 56 (62.9) | 264 (39.1) |
| ≥ 12 months | 182 (62.3) | 155 (53.8) | 77 (62.1) | 33 (37.1) | 411 (60.9) |

| Parameter Category, n (%) | Study EV-301 | | Study EV-201 | | Enfortumab Vedotin 1.25 mg/kg† |
|---|---|---|---|---|---|
| | Enfortumab Vedotin (n = 296) | Chemotherapy (n = 291) | Cohort 1 Enfortumab Vedotin (n = 125) | Cohort 2 Enfortumab Vedotin (n = 89) | (n =680) |
| Missing | 4 | 3 | 1 | 0 | 5 |
| Type of solid tumor cancer | | | | | |
| Urothelial | 296 (100) | 290 (99.7) | 125 (100) | 89 (100) | 645 (94.9) |
| Other | 0 | 1 (0.3) | 0 | 0 | 35 (5.1) |
| Location of primary urothelial cancer | | | | | |
| Upper tract§ | 96 (32.4) | 102 (35.1) | 44 (35.2) | 38 (42.7) | 210 (30.9) |
| Bladder/other | 200 (67.6) | 188 (64.6) | 81 (64.8) | 51 (57.3) | 435 (64.0) |
| Not applicable | 0 | 1 (0.3) | 0 | 0 | 35 (5.1) |
| Liver metastasis at baseline | | | | | |
| Yes | 90 (30.4) | 92 (31.6) | 50 (40.0) | 21 (23.6) | 221 (32.5) |
| No | 206 (69.6) | 199 (68.4) | 75 (60.0) | 68 (76.4) | 459 (67.5) |

Number of subjects (n) and percentage of subjects (%) are shown.
ISS: integrated summary of safety.
† Enfortumab vedotin 1.25 mg/kg column includes all subjects in the following studies who received a 1.25 mg/kg dose of enfortumab vedotin: EV-101, EV-102, EV-201, and EV-301.
‡ Time from metastatic disease for all subjects except subjects who have only locally advanced diagnosis at enrollment to first dose day.
§ Upper tract includes renal pelvis, ureter, and kidney.
Source: EV-201 and EV-301 ISS Table 12.1.2.3

Prior cystectomy and nephrectomy were comparable in study 301 and 201/C1. The numbers of prior systemic therapies were comparable between the arms in study 301, but markedly higher in study 201/C1 (Table 87).

**Table 82** Prior Cancer Treatment History (Safety Analysis Set)

| Parameter Category, n (%) | Study EV-301 | | Study EV-201 | | Enfortumab Vedotin 1.25 mg/kg† |
|---|---|---|---|---|---|
| | Enfortumab Vedotin (n = 296) | Chemotherapy (n = 291) | Cohort 1 Enfortumab Vedotin (n = 125) | Cohort 2 Enfortumab Vedotin (n = 89) | (n = 680) |
| Prior cystectomy ‡ | | | | | |
| Yes | 109 (36.8) | 99 (34.0) | 43 (34.4) | 25 (28.1) | 229 (33.7) |
| Prior nephrectomy‡ | | | | | |
| Yes | 67 (22.6) | 78 (26.8) | 36 (28.8) | 35 (39.3) | 171 (25.1) |
| Prior radiation therapy | | | | | |
| Yes | 93 (31.4) | 98 (33.7) | 44 (35.2) | 18 (20.2) | 211 (31.0) |
| Prior systemic therapy | | | | | |
| Yes | 296 (100) | 291 (100) | 125 (100) | 89 (100) | 676 (99.4) |
| Number of prior systemic therapies under all settings | | | | | |
| 0 | 0 | 0 | 0 | 0 | 4 (0.6) |
| 1 | 32 (10.8) | 28 (9.6) | 3 (2.4) | 56 (62.9) | 109 (16.0) |
| 2 | 212 (71.6) | 206 (70.8) | 58 (46.4) | 26 (29.2) | 358 (52.6) |
| ≥ 3 | 52 (17.6) | 57 (19.6) | 64 (51.2) | 7 (7.9) | 209 (30.7) |
| Undetermined§ | 0 | 0 | 0 | 0 | 0 |
| Number of prior systemic therapies under metastatic settings | | | | | |
| 0 | 0 | 0 | 3 (2.4) | 8 (9.0) | 15 (2.2) |
| 1 | 31 (10.5) | 27 (9.3) | 30 (24.0) | 69 (77.5) | 174 (25.6) |
| 2 | 200 (67.6) | 187 (64.3) | 49 (39.2) | 11 (12.4) | 311 (45.7) |
| ≥ 3 | 50 (16.9) | 56 (19.2) | 43 (34.4) | 1 (1.1) | 153 (22.5) |
| Undetermined§ | 15 (5.1) | 21 (7.2) | 0 | 0 | 27 (4.0) |

| Parameter Category, n (%) | Study EV-301 | | Study EV-201 | | Enfortumab Vedotin 1.25 mg/kg† (n = 680) |
|---|---|---|---|---|---|
| | Enfortumab Vedotin (n = 296) | Chemotherapy (n = 291) | Cohort 1 Enfortumab Vedotin (n = 125) | Cohort 2 Enfortumab Vedotin (n = 89) | |
| Prior platinum treatment received | | | | | |
| Yes | 296 (100) | 291 (100) | 125 (100) | 1 (1.1) | 580 (85.3) |
| Type of prior platinum-containing therapy | | | | | |
| Cisplatin-containing therapy only | 192 (64.9) | 181 (62.2) | 82 (65.6) | 1 (1.1) | 356 (52.4) |
| Carboplatin- containing therapy only | 71 (24.0) | 81 (27.8) | 33 (26.4) | 0 | 151 (22.2) |
| Cisplatin and carboplatin-containing therapy | 33 (11.1) | 29 (10.0) | 10 (8.0) | 0 | 73 (10.7) |
| Prior CPI treatment received (at any time) ¶ | | | | | |
| Yes | 295 (99.7) | 291 (100) | 125 (100) | 89 (100) | 627 (92.2) |
| CPI most recent treatment received ¶ | | | | | |
| Yes | 257 (86.8) | 257 (88.3) | 86 (68.8) | 84 (94.4) | 508 (74.7) |

Number of subjects (n) and percentage of subjects (%) are shown.
CPI: immune checkpoint inhibitor; ISS: integrated summary of safety; PD-1: programmed cell death protein-1; PD-L1: programmed death-ligand 1.
† Enfortumab vedotin 1.25 mg/kg column includes all subjects in the following studies who received a 1.25 mg/kg dose of enfortumab vedotin: EV-101, EV-102, EV-201, and EV-301.
‡ Including partial and full procedures.
§ Includes subjects who have 'Yes' for 'prior systemic therapy' but number of prior systemic therapies not collected.
¶ CPI is defined as a PD-1 or PD-L1 inhibitor as monotherapy or part of a combination therapy.
Source: EV-201 and EV-301 ISS Table 12.1.4

## *Adverse events*

An overview of TEAEs across the safety analysis groups is presented in Table 88

Given the difference between the 2 treatment arms in terms of time on treatment (median duration of treatment was 4.99 months for the enfortumab vedotin arm and 3.45 months for the chemotherapy arm), AE data are also represented in terms of events per patient-year (P-Y).

**Table 83** Overview of TEAEs Adjusted by Patient-Year (Safety Analysis Set)

| Parameter, n (%) | Study EV-301 | | | | Study EV-201 | | Enfortumab Vedotin 1.25 mg/kg† (n = 680) |
|---|---|---|---|---|---|---|---|
| | Enfortumab Vedotin | | Chemotherapy | | Cohort 1 Enfortumab Vedotin (n = 125) | Cohort 2 Enfortumab Vedotin (n = 89) | |
| | (n = 296) n (%) | P-Y = 132.3 E (E/P-Y) | (n = 291) n (%) | P-Y = 96.1 E (E/P-Y) | | | |
| TEAE | 290 (98.0) | 5051 (38.2) | 288 (99.0) | 3173 (33.0) | 125 (100) | 89 (100) | 673 (99.0) |
| Drug-related‡ TEAE | 278 (93.9) | 3033 (22.9) | 267 (91.8) | 1982 (20.6) | 117 (93.6) | 86 (96.6) | 639 (94.0) |
| Serious TEAE§ | 138 (46.6) | 314 (2.4) | 128 (44.0) | 269 (2.8) | 59 (47.2) | 35 (39.3) | 306 (45.0) |
| Drug-related‡ serious TEAE§ | 67 (22.6) | 114 (0.9) | 68 (23.4) | 120 (1.2) | 24 (19.2) | 15 (16.9) | 132 (19.4) |
| TEAE leading to death | 21 (7.1) | 21 (0.2) | 16 (5.5) | 18 (0.2) | 7 (5.6) | 8 (9.0) | 47 (6.9) |
| Drug-related‡ TEAE leading to death | 7 (2.4) | 7 (0.1) | 3 (1.0) | 3 (0.0) | 0 | 3 (3.4) | 14 (2.1) |
| TEAE leading to permanent withdrawal of study drug | 51 (17.2) | 66 (0.5) | 51 (17.5) | 60 (0.6) | 21 (16.8) | 18 (20.2) | 126 (18.5) |
| Drug-related‡ TEAE leading to permanent withdrawal of study drug | 40 (13.5) | 51 (0.4) | 33 (11.3) | 38 (0.4) | 15 (12.0) | 14 (15.7) | 84 (12.4) |
| TEAE leading to dose reduction | 101 (34.1) | 170 (1.3) | 81 (27.8) | 119 (1.2) | 42 (33.6) | 44 (49.4) | 238 (35.0) |
| Drug-related‡ TEAE leading to dose reduction | 96 (32.4) | 165 (1.2) | 80 (27.5) | 112 (1.2) | 39 (31.2) | 41 (46.1) | 225 (33.1) |
| TEAE leading to dose interruption | 180 (60.8) | 536 (4.1) | 85 (29.2) | 140 (1.5) | 82 (65.6) | 53 (59.6) | 424 (62.4) |
| Drug-related‡ TEAE leading to dose interruption | 151 (51.0) | 384 (2.9) | 55 (18.9) | 90 (0.9) | 62 (49.6) | 45 (50.6) | 344 (50.6) |
| TEAE with NCI-CTCAE ≥ Grade 3 | 210 (70.9) | 617 (4.7) | 193 (66.3) | 594 (6.2) | 93 (74.4) | 62 (69.7) | 468 (68.8) |
| Drug-related‡ TEAE with NCI-CTCAE ≥ Grade 3 | 152 (51.4) | 320 (2.4) | 145 (49.8) | 416 (4.3) | 70 (56.0) | 49 (55.1) | 332 (48.8) |

Number of subjects (n) and percentage of subjects (%) are shown.

One subject from EV-301 study and 2 subjects from EV-201 study (1 each from Cohort 1 and Cohort 2) who had drug-related (assessed as related per investigator) deaths that occurred outside of the treatment-emergent window are not included in any TEAE summary. E: number of events; ISS: integrated summary of safety; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; P-Y: patient-year = Min((Date of initial dose of last cycle + 21 -1), death date) - first dose date +1 in years for AGS-22M6E-11-1 study, and the total duration of exposure in years for other studies; TEAE: treatment-emergent adverse event. †Enfortumab vedotin 1.25 mg/kg column includes all subjects in the following studies who received a 1.25 mg/kg dose of enfortumab vedotin: EV-101, EV-102, EV-201 and EV-301.‡A reasonable possibility that the event could have been caused by the study drug as assessed by the investigator. If relationship is missing then it is considered as drug related. §Includes Serious TEAEs upgraded by the sponsor based on their review, if any upgrade was done. This upgrade was not applicable for EV-201 study.

Common treatment emergent adverse events by SOC and preferred term (PT)

*Study EV-301:*

In the enfortumab vedotin arm, the most common TEAEs occurring in ≥ 20% of subjects by PT were alopecia, decreased appetite, fatigue, diarrhea, peripheral sensory neuropathy, pruritus, nausea, constipation, dysgeusia, and pyrexia.

In the chemotherapy arm, the most common TEAEs occurring in ≥ 20% of subjects by PT were alopecia, anemia, decreased appetite, fatigue, nausea, constipation, diarrhea, and peripheral sensory neuropathy.

**Table 84** Treatment-emergent Adverse Events (≥ 10% of Subjects in the Enfortumab Vedotin 1.25 mg/kg Group†) by SOC and Preferred Term (Safety Analysis Set)

| MedDRA (v23.0)<br>SOC<br>Preferred term, n (%) | Study EV-301 | | Study EV-201 | | Enfortumab Vedotin 1.25 mg/kg†<br>(n = 680) |
|---|---|---|---|---|---|
| | Enfortumab Vedotin<br>(n = 296) | Chemotherapy<br>(n = 291) | Cohort 1<br>Enfortumab Vedotin<br>(n = 125) | Cohort 2<br>Enfortumab Vedotin<br>(n = 89) | |
| **Overall** | **290 (98.0)** | **288 (99.0)** | **125 (100)** | **89 (100)** | **673 (99.0)** |
| **Blood and Lymphatic System Disorders** | 84 (28.4) | 123 (42.3) | 58 (46.4) | 41 (46.1) | 238 (35.0) |
| Anaemia | 59 (19.9) | 87 (29.9) | 44 (35.2) | 34 (38.2) | 180 (26.5) |
| **Cardiac Disorders** | 22 (7.4) | 14 (4.8) | 15 (12.0) | 14 (15.7) | 77 (11.3) |
| **Eye Disorders** | 80 (27.0) | 26 (8.9) | 64 (51.2) | 35 (39.3) | 253 (37.2) |
| Lacrimation increased | 30 (10.1) | 12 (4.1) | 21 (16.8) | 12 (13.5) | 89 (13.1) |
| Dry eye | 19 (6.4) | 3 (1.0) | 30 (24.0) | 17 (19.1) | 87 (12.8) |
| **Gastrointestinal Disorders** | 206 (69.6) | 182 (62.5) | 109 (87.2) | 63 (70.8) | 516 (75.9) |
| Diarrhea | 103 (34.8) | 66 (22.7) | 53 (42.4) | 31 (34.8) | 256 (37.6) |
| Nausea | 89 (30.1) | 74 (25.4) | 57 (45.6) | 27 (30.3) | 245 (36.0) |
| Constipation | 82 (27.7) | 73 (25.1) | 35 (28.0) | 18 (20.2) | 179 (26.3) |
| Vomiting | 42 (14.2) | 44 (15.1) | 25 (20.0) | 12 (13.5) | 125 (18.4) |
| Abdominal pain | 39 (13.2) | 27 (9.3) | 26 (20.8) | 6 (6.7) | 106 (15.6) |
| **General Disorders and Administration Site Conditions** | 209 (70.6) | 186 (63.9) | 92 (73.6) | 63 (70.8) | 494 (72.6) |
| Fatigue | 107 (36.1) | 78 (26.8) | 69 (55.2) | 40 (44.9) | 318 (46.8) |
| Pyrexia | 65 (22.0) | 41 (14.1) | 17 (13.6) | 15 (16.9) | 121 (17.8) |
| Oedema peripheral | 27 (9.1) | 39 (13.4) | 31 (24.8) | 20 (22.5) | 105 (15.4) |
| **Infections and Infestations** | 152 (51.4) | 102 (35.1) | 66 (52.8) | 38 (42.7) | 350 (51.5) |
| Urinary tract infection | 26 (8.8) | 18 (6.2) | 24 (19.2) | 13 (14.6) | 101 (14.9) |
| **Injury, Poisoning and Procedural Complications** | 38 (12.8) | 32 (11.0) | 32 (25.6) | 20 (22.5) | 128 (18.8) |
| **Investigations** | 133 (44.9) | 119 (40.9) | 69 (55.2) | 56 (62.9) | 367 (54.0) |
| Weight decreased | 47 (15.9) | 20 (6.9) | 40 (32.0) | 31 (34.8) | 159 (23.4) |
| Aspartate aminotransferase increased | 36 (12.2) | 5 (1.7) | 19 (15.2%) | 11 (12.4) | 104 (15.3) |
| Alanine aminotransferase increased | 27 (9.1) | 4 (1.4) | 15 (12.0) | 9 (10.1) | 82 (12.1) |
| Blood creatinine increased | 26 (8.8) | 7 (2.4) | 10 (8.0) | 5 (5.6) | 68 (10) |

| MedDRA (v23.0) SOC<br>Preferred term, n (%) | Study EV-301 | | Study EV-201 | | Enfortumab Vedotin 1.25 mg/kg† (n = 680) |
|---|---|---|---|---|---|
| | Enfortumab Vedotin (n = 296) | Chemotherapy (n = 291) | Cohort 1 Enfortumab Vedotin (n = 125) | Cohort 2 Enfortumab Vedotin (n = 89) | |
| **Metabolism and Nutrition Disorders** | 174 (58.8) | 124 (42.6) | 94 (75.2) | 58 (65.2) | 455 (66.9) |
| Decreased appetite | 121 (40.9) | 78 (26.8) | 65 (52.0) | 36 (40.4) | 305 (44.9) |
| Hyperglycaemia | 31 (10.5) | 6 (2.1) | 19 (15.2) | 14 (15.7) | 89 (13.1) |
| Hyponatraemia | 19 (6.4) | 13 (4.5) | 18 (14.4) | 9 (10.1) | 69 (10.1) |
| **Musculoskeletal and Connective Tissue Disorders** | 99 (33.4) | 119 (40.9) | 62 (49.6) | 35 (39.3) | 285 (41.9) |
| Back pain | 26 (8.8) | 26 (8.9) | 20 (16.0) | 4 (4.5) | 72 (10.6) |
| **Nervous System Disorders** | 189 (63.9) | 137 (47.1) | 88 (70.4) | 64 (71.9) | 464 (68.2) |
| Peripheral sensory neuropathy | 102 (34.5) | 66 (22.7) | 54 (43.2) | 44 (49.4) | 263 (38.7) |
| Dysgeusia | 74 (25.0) | 23 (7.9) | 49 (39.2) | 26 (29.2) | 203 (29.9) |
| Dizziness | 26 (8.8) | 16 (5.5) | 20 (16.0) | 10 (11.2) | 78 (11.5) |
| **Psychiatric Disorders** | 54 (18.2) | 46 (15.8) | 32 (25.6) | 22 (24.7) | 147 (21.6) |
| Insomnia | 31 (10.5) | 23 (7.9) | 18 (14.4) | 13 (14.6) | 84 (12.4) |
| **Renal and Urinary Disorders** | 75 (25.3) | 50 (17.2) | 32 (25.6) | 33 (37.1) | 194 (28.5) |
| Haematuria | 33 (11.1) | 25 (8.6) | 12 (9.6) | 10 (11.2) | 77 (11.3) |
| **Respiratory, Thoracic and Mediastinal Disorders** | 101 (34.1) | 67 (23.0) | 60 (48.0) | 41 (46.1) | 295 (43.4) |
| Dyspnoea | 28 (9.5) | 28 (9.6) | 20 (16.0) | 14 (15.7) | 93 (13.7) |
| Cough | 24 (8.1) | 18 (6.2) | 22 (17.6) | 12 (13.5) | 84 (12.4) |
| **Skin and Subcutaneous Tissue Disorders** | 237 (80.1) | 149 (51.2) | 101 (80.8) | 75 (84.3) | 547 (80.4) |
| Alopecia | 139 (47.0) | 110 (37.8) | 64 (51.2) | 47 (52.8) | 332 (48.8) |
| Pruritus | 102 (34.5) | 20 (6.9) | 34 (27.2) | 31 (34.8) | 227 (33.4) |
| Rash maculo-papular | 50 (16.9) | 6 (2.1) | 29 (23.2) | 29 (32.6) | 156 (22.9) |
| Dry skin | 50 (16.9) | 11 (3.8) | 35 (28.0) | 17 (19.1) | 147 (21.6) |
| Rash | 50 (16.9) | 16 (5.5) | 2 (1.6) | 3 (3.4) | 71 (10.4) |
| **Vascular Disorders** | 43 (14.5) | 37 (12.7) | 26 (20.8) | 12 (13.5) | 124 (18.2) |

Number of subjects (n) and percentage of subjects (%) are shown.

Sorting order: alphabetical order by SOC and descending by the number of subjects of 'enfortumab vedotin 1.25 mg/kg' by preferred term. In case of ties, alphabetical order by preferred term is applied.

ISS: integrated summary of safety.

† Enfortumab vedotin 1.25 mg/kg column includes all subjects in the following studies who received a 1.25 mg/kg dose of enfortumab vedotin: EV-101, EV-102, EV-201 and EV-301.

Of the adverse events considered drug-related that occurred in ≥ 10% of subjects in either arm in study 301, the incidence of peripheral sensory neuropathy, dysgeusia, pruritis, rash, dry skin and rash maculo-papular was higher in the enfortumab vedotin arm (Table 90).

**Table 85** Drug-related Treatment-emergent Adverse Events (≥ 5% of Subjects in the Enfortumab Vedotin 1.25 mg/kg Group†) by SOC and Preferred Term (Safety Analysis Set)

| MedDRA (v23.0) SOC<br>Preferred term, n (%) | Study EV-301 | | Study EV-201 | | Enfortumab Vedotin 1.25 mg/kg† (n = 680) |
|---|---|---|---|---|---|
| | Enfortumab Vedotin (n =296) | Chemotherapy (n =291) | Cohort 1 Enfortumab Vedotin (n =125) | Cohort 2 Enfortumab Vedotin (n =89) | |
| **Overall** | **278 (93.9)** | **267 (91.8)** | **117 (93.6)** | **86 (96.6)** | **639 (94.0)** |
| **Blood and Lymphatic System Disorders** | 58 (19.6) | 95 (32.6) | 41 (32.8) | 29 (32.6) | 165 (24.3) |
| Anaemia | 34 (11.5) | 59 (20.3) | 27 (21.6) | 22 (24.7) | 110 (16.2) |
| Neutropenia | 20 (6.8) | 24 (8.2) | 13 (10.4) | 11 (12.4) | 51 (7.5) |
| **Eye Disorders** | 58 (19.6) | 16 (5.5) | 48 (38.4) | 23 (25.8) | 180 (26.5) |
| Lacrimation increased | 23 (7.8) | 8 (2.7) | 21 (16.8) | 9 (10.1) | 73 (10.7) |
| Dry eye | 15 (5.1) | 0 | 25 (20.0) | 11 (12.4) | 66 (9.7) |
| Vision blurred | 12 (4.1) | 4 (1.4) | 16 (12.8) | 5 (5.6) | 45 (6.6) |
| **Gastrointestinal Disorders** | 156 (52.7) | 148 (50.9) | 88 (70.4) | 42 (47.2) | 392 (57.6) |
| Nausea | 67 (22.6) | 63 (21.6) | 50 (40.0) | 20 (22.5) | 193 (28.4) |
| Diarrhoea | 72 (24.3) | 48 (16.5) | 41 (32.8) | 20 (22.5) | 186 (27.4) |
| Vomiting | 26 (8.8) | 31 (10.7) | 19 (15.2) | 7 (7.9) | 84 (12.4) |
| Constipation | 37 (12.5) | 48 (16.5) | 15 (12.0) | 4 (4.5) | 76 (11.2) |
| Stomatitis | 21 (7.1) | 19 (6.5) | 10 (8.0) | 5 (5.6) | 45 (6.6) |
| Dry mouth | 19 (6.4) | 5 (1.7) | 6 (4.8) | 5 (5.6) | 40 (5.9) |
| Abdominal pain | 18 (6.1) | 16 (5.5) | 4 (3.2) | 4 (4.5) | 38 (5.6) |
| **General Disorders and Administration site Conditions** | 156 (52.7) | 134 (46.0) | 77 (61.6) | 44 (49.4) | 375 (55.1) |
| Fatigue | 92 (31.1) | 66 (22.7) | 62 (49.6) | 30 (33.7) | 271 (39.9) |
| Asthenia | 31 (10.5) | 32 (11.0) | 5 (4.0) | 6 (6.7) | 45 (6.6) |
| Oedema peripheral | 7 (2.4) | 16 (5.5) | 15 (12.0) | 10 (11.2) | 43 (6.3) |
| **Infections and Infestations** | 43 (14.5) | 29 (10.0) | 14 (11.2) | 9 (10.1) | 91 (13.4) |
| **Injury, Poisoning and Procedural Complications** | 11 (3.7) | 11 (3.8) | 10 (8.0) | 7 (7.9) | 35 (5.1) |
| **Investigations** | 95 (32.1) | 87 (29.9) | 59 (47.2) | 42 (47.2) | 275 (40.4) |
| Weight decreased | 35 (11.8) | 11 (3.8) | 29 (23.2) | 23 (25.8) | 109 (16.0) |
| Aspartate aminotransferase increased | 26 (8.8) | 3 (1.0) | 17 (13.6) | 7 (7.9) | 85 (12.5) |
| Alanine aminotransferase increased | 20 (6.8) | 4 (1.4) | 14 (11.2) | 6 (6.7) | 68 (10.0) |
| Neutrophil count decreased | 30 (10.1) | 49 (16.8) | 3 (2.4) | 3 (3.4) | 42 (6.2) |
| White blood cell count decreased | 16 (5.4) | 31 (10.7) | 5 (4.0) | 4 (4.5) | 36 (5.3) |
| **Metabolism and Nutrition Disorders** | 118 (39.9) | 85 (29.2) | 72 (57.6) | 39 (43.8) | 322 (47.4) |
| Decreased appetite | 91 (30.7) | 68 (23.4) | 55 (44.0) | 29 (32.6) | 238 (35.0) |
| Hyperglycaemia | 15 (5.1) | 1 (0.3) | 12 (9.6) | 8 (9.0) | 46 (6.8) |
| **Musculoskeletal and Connective Tissue Disorders** | 32 (10.8) | 59 (20.3) | 30 (24.0) | 12 (13.5) | 109 (16.0) |
| **Nervous System** | 169 (57.1) | 113 (38.8) | 77 (61.6) | 56 (62.9) | 408 (60.0) |

| MedDRA (v23.0) SOC<br>Preferred term, n (%) | Study EV-301 | | Study EV-201 | | Enfortumab Vedotin 1.25 mg/kg† (n = 680) |
|---|---|---|---|---|---|
| | Enfortumab Vedotin (n =296) | Chemotherapy (n =291) | Cohort 1 Enfortumab Vedotin (n =125) | Cohort 2 Enfortumab Vedotin (n =89) | |
| **Disorders** | | | | | |
| Peripheral sensory neuropathy | 100 (33.8) | 62 (21.3) | 50 (40.0) | 42 (47.2) | 249 (36.6) |
| Dysgeusia | 72 (24.3) | 21 (7.2) | 47 (37.6) | 24 (27.0) | 196 (28.8) |
| Peripheral motor neuropathy | 10 (3.4) | 0 | 12 (9.6) | 8 (9.0) | 38 (5.6) |
| **Renal and Urinary Disorders** | 13 (4.4) | 8 (2.7) | 5 (4.0) | 7 (7.9) | 37 (5.4) |
| **Respiratory, Thoracic and Mediastinal Disorders** | 40 (13.5) | 23 (7.9) | 22 (17.6) | 17 (19.1) | 111 (16.3) |
| **Skin and Subcutaneous Tissue Disorders** | 228 (77.0) | 135 (46.4) | 96 (76.8) | 72 (80.9) | 520 (76.5) |
| Alopecia | 134 (45.3) | 106 (36.4) | 62 (49.6) | 45 (50.6) | 321 (47.2) |
| Pruritus | 95 (32.1) | 13 (4.5) | 32 (25.6) | 27 (30.3) | 209 (30.7) |
| Rash maculo-papular | 48 (16.2) | 5 (1.7) | 28 (22.4) | 27 (30.3) | 147 (21.6) |
| Dry skin | 42 (14.2) | 2 (0.7) | 30 (24.0) | 16 (18.0) | 120 (17.6) |
| Rash | 45 (15.2) | 11 (3.8) | 2 (1.6) | 3 (3.4) | 64 (9.4) |
| Skin hyperpigmentation | 18 (6.1) | 1 (0.3) | 10 (8.0) | 2 (2.2) | 41 (6.0) |
| **Vascular Disorders** | 16 (5.4) | 15 (5.2) | 9 (7.2) | 5 (5.6) | 45 (6.6) |

Number of subjects (n) and percentage of subjects (%) are shown.
Sorting order: alphabetical order by SOC and descending by the number of subjects of 'enfortumab vedotin 1.25 mg/kg' group by preferred term. In case of ties, alphabetical order by preferred term is applied.
Adverse events related to study drug as assessed by the investigator, or missing relationship were shown.
ISS: integrated summary of safety.
† Enfortumab vedotin 1.25 mg/kg column includes all subjects in the following studies who received a 1.25 mg/kg dose of enfortumab vedotin: EV-101, EV-102, EV-201 and EV-301.
Source: EV-201 and EV-301 ISS Table 12.6.1.4.1

***Grade 3 and higher adverse events***

Grade ≥3 TEAEs reported in ≥5% of participants on the safety analysis set are summarised in Table 91

In the enfortumab vedotin arm, TEAEs with NCI-CTCAE Grade 3 or 4 occurring in ≥ 5% of subjects by PT were anaemia, fatigue, neutrophil count decreased, hyperglycaemia, decreased appetite, and rash maculo-papular. In the chemotherapy arm, the most common TEAEs Grade 3 or 4 occurring in ≥ 5% of subjects by PT were neutrophil count decreased, anaemia, neutropenia, white blood cell count decreased, and febrile neutropenia. Although diarrhoea is a frequent AE for EV (34.8%), Grade 3-4 was only observed in 3.7% [chemotherapy arm; 22.7% (all AEs) and 1.7% (Grade 3-4)].

The incidence of Grade 3-4 Infections (SOC) in study EV-301 was higher in the EV-arm despite neutropenia (laboratory and AE) occurring more frequently in the chemotherapy arm. The exposure was +1.5 months longer in the EV arm.

In study EV-301 Grade 3-4 hyperglycaemia occurred in 21 patients (7.1%;) in EV arm and in 2 patients (0.7%) in the chemotherapy arm.

The proportion of subjects who experienced TEAEs with Grade 3 or 4 in Cohort 1 EV-201 (74.4%) was numerically higher compared with Cohort 2 (68.5%).

The incidence of Grade 3 or 4 acute kidney injury was numerically higher in Cohort 2-EV-201 (10.1%) than in Cohort 1 -EV-201 (3.2%) (Table 91)

Acute kidney injury occurred in 8 patients (2.7%) in the EV-301 EV arm compared to 2 patients (0.7%) in the chemotherapy arm

**Table 86** Treatment-emergent Adverse Events NCI-CTCAE Grade 3 or 4 (≥ 3% of Subjects in the Enfortumab Vedotin 1.25 mg/kg Group†) by SOC and Preferred Term (Safety Analysis Set)

| MedDRA (v23.0) SOC<br>Preferred term, n (%) | Study EV-301 | | Study EV-201 | | Enfortumab Vedotin 1.25 mg/kg† (n = 680) |
|---|---|---|---|---|---|
| | Enfortumab Vedotin (n = 296) | Chemotherapy (n = 291) | Cohort 1 Enfortumab Vedotin (n = 125) | Cohort 2 Enfortumab Vedotin (n = 89) | |
| **Overall** | **204 (68.9)** | **184 (63.2)** | **93 (74.4)** | **61 (68.5)** | **460 (67.6)** |
| **Blood and Lymphatic System Disorders** | 32 (10.8) | 68 (23.4) | 31 (24.8) | 18 (20.2) | 103 (15.1) |
| Anaemia | 19 (6.4) | 34 (11.7) | 17 (13.6) | 10 (11.2) | 61 (9.0) |
| Neutropenia | 14 (4.7) | 22 (7.6) | 11 (8.8) | 9 (10.1) | 40 (5.9) |
| **Gastrointestinal Disorders** | 26 (8.8) | 34 (11.7) | 20 (16.0) | 13 (14.6) | 88 (12.9) |
| Diarrhoea | 11 (3.7) | 5 (1.7) | 5 (4.0) | 6 (6.7) | 26 (3.8) |
| **General Disorders and Administration Site Conditions** | 38 (12.8) | 28 (9.6) | 15 (12.0) | 13 (14.6) | 84 (12.4) |
| Fatigue | 20 (6.8) | 14 (4.8) | 8 (6.4) | 7 (7.9) | 47 (6.9) |
| **Infections and Infestations** | 50 (16.9) | 28 (9.6) | 23 (18.4) | 16 (18.0) | 120 (17.6) |
| Urinary tract infection | 6 (2.0) | 5 (1.7) | 6 (4.8) | 7 (7.9) | 28 (4.1) |
| Pneumonia | 11 (3.7) | 5 (1.7) | 3 (2.4) | 3 (3.4) | 26 (3.8) |
| **Investigations** | 45 (15.2) | 58 (19.9) | 20 (16.0) | 20 (22.5) | 100 (14.7) |
| Neutrophil count decreased | 21 (7.1) | 43 (14.8) | 4 (3.2) | 3 (3.4) | 30 (4.4) |
| Lipase increased | 8 (2.7) | 5 (1.7) | 6 (4.8) | 8 (9.0) | 22 (3.2) |
| **Metabolism and Nutrition Disorders** | 66 (22.3) | 32 (11.0) | 30 (24.0) | 25 (28.1) | 153 (22.5) |
| Hyperglycaemia | 20 (6.8) | 2 (0.7) | 9 (7.2) | 8 (9.0) | 46 (6.8) |
| Hyponatraemia | 12 (4.1) | 7 (2.4) | 7 (5.6) | 6 (6.7) | 37 (5.4) |
| Decreased appetite | 16 (5.4) | 7 (2.4) | 3 (2.4) | 5 (5.6) | 29 (4.3) |
| **Musculoskeletal and Connective Tissue Disorders** | 10 (3.4) | 15 (5.2) | 6 (4.8) | 4 (4.5) | 27 (4.0) |
| **Nervous System Disorders** | 21 (7.1) | 12 (4.1) | 8 (6.4) | 8 (9.0) | 47 (6.9) |
| **Renal and Urinary Disorders** | 20 (6.8) | 12 (4.1) | 11 (8.8) | 13 (14.6) | 53 (7.8) |
| Acute kidney injury | 8 (2.7) | 2 (0.7) | 4 (3.2) | 9 (10.1) | 26 (3.8) |
| **Respiratory, Thoracic and Mediastinal Disorders** | 14 (4.7) | 10 (3.4) | 11 (8.8) | 5 (5.6) | 43 (6.3) |
| **Skin and Subcutaneous Tissue Disorders** | 51 (17.2) | 1 (0.3) | 16 (12.8) | 14 (15.7) | 93 (13.7) |
| Rash maculo-papular | 22 (7.4) | 0 | 5 (4.0) | 7 (7.9) | 38 (5.6) |
| **Vascular Disorders** | 9 (3.0) | 7 (2.4) | 8 (6.4) | 8 (9.0) | 36 (5.3) |

Number of subjects (n) and percentage of subjects (%) are shown.
Sorting order: alphabetical order by SOC and descending by the number of subjects of 'enfortumab vedotin 1.25 mg/kg' by preferred term. In case of ties, alphabetical order by preferred term is applied.
ISS: integrated summary of safety; NCI-CTCAE: National Cancer Institute-Common Terminology Criteria for Adverse Events.
† Enfortumab vedotin 1.25 mg/kg column includes all subjects in the following studies who received a 1.25 mg/kg dose of enfortumab vedotin: EV-101, EV-102, EV-201, and EV-301.
Source: EV-201 and EV-301 ISS Table 12.6.1.2.4.1

In study 301, enfortumab vedotin arm, the Grade 3 or 4 adverse events considered drug-related occurring in ≥ 5% of subjects by PT were fatigue, neutrophil count decreased and rash maculo-papular. In the chemotherapy arm, the most common drug-related Grade 3 or 4 TEAEs occurring in ≥ 5% of subjects by PT were neutropenia, anaemia, febrile neutropenia, neutrophil count decreased, and white blood cell count decreased (Table 92).

**Table 87** Drug-related Treatment-emergent Adverse Events with NCI-CTCAE (V4.03) Grade 3 or 4 (≥ 1% of Subjects in the Enfortumab Vedotin 1.25 mg/kg Group†) by SOC and Preferred Term (Safety Analysis Set)

| MedDRA (v23.0) SOC<br>Preferred term, n (%) | Study EV-301 | | Study EV-201 | | Enfortumab Vedotin 1.25 mg/kg† (n = 680) |
|---|---|---|---|---|---|
| | Enfortumab Vedotin (n = 296) | Chemotherapy (n = 291) | Cohort 1 Enfortumab Vedotin (n =125) | Cohort 2 Enfortumab Vedotin (n =89) | |
| **Overall** | **147 (49.7)** | **142 (48.8)** | **70 (56.0)** | **49 (55.1)** | **327 (48.1)** |
| **Blood and Lymphatic System Disorders** | 22 (7.4) | 54 (18.6) | 24 (19.2) | 13 (14.6) | 72 (10.6) |
| Neutropenia | 14 (4.7) | 18 (6.2) | 10 (8.0) | 8 (9.0) | 38 (5.6) |
| Anaemia | 8 (2.7) | 21 (7.2) | 9 (7.2) | 4 (4.5) | 27 (4.0) |
| Febrile neutropenia | 2 (0.7) | 16 (5.5) | 5 (4.0) | 1 (1.1) | 8 (1.2) |
| **Gastrointestinal Disorders** | 15 (5.1) | 24 (8.2) | 13 (10.4) | 7 (7.9) | 42 (6.2) |
| Diarrhoea | 9 (3.0) | 5 (1.7) | 3 (2.4) | 5 (5.6) | 18 (2.6) |
| Nausea | 3 (1.0) | 4 (1.4) | 3 (2.4) | 1 (1.1) | 10 (1.5) |
| Vomiting | 2 (0.7) | 2 (0.7) | 3 (2.4) | 1 (1.1) | 8 (1.2) |
| **General Disorders and Administration Site Conditions** | 25 (8.4) | 23 (7.9) | 11 (8.8) | 10 (11.2) | 55 (8.1) |
| Fatigue | 19 (6.4) | 13 (4.5) | 8 (6.4) | 4 (4.5) | 40 (5.9) |
| Asthenia | 4 (1.4) | 7 (2.4) | 2 (1.6) | 2 (2.2) | 8 (1.2) |
| **Infections and Infestations** | 15 (5.1) | 9 (3.1) | 4 (3.2) | 2 (2.2) | 30 (4.4) |
| **Investigations** | 33 (11.1) | 53 (18.2) | 15 (12.0) | 15 (16.9) | 71 (10.4) |
| Neutrophil count decreased | 17 (5.7) | 39 (13.4) | 3 (2.4) | 3 (3.4) | 25 (3.7) |
| Lipase increased | 6 (2.0) | 3 (1.0) | 5 (4.0) | 5 (5.6) | 16 (2.4) |
| Aspartate aminotransferase increased | 2 (0.7) | 0 | 4 (3.2) | 2 (2.2) | 9 (1.3) |
| Amylase increased | 2 (0.7) | 1 (0.3) | 3 (2.4) | 3 (3.4) | 8 (1.2) |
| White blood cell count decreased | 4 (1.4) | 20 (6.9) | 1 (0.8) | 2 (2.2) | 7 (1.0) |
| **Metabolism and Nutrition Disorders** | 34 (11.5) | 14 (4.8) | 15 (12.0) | 13 (14.6) | 81 (11.9) |
| Hyperglycaemia | 10 (3.4) | 0 | 5 (4.0) | 5 (5.6) | 28 (4.1) |
| Decreased appetite | 9 (3.0) | 5 (1.7) | 1 (0.8) | 5 (5.6) | 19 (2.8) |
| Hyponatraemia | 4 (1.4) | 3 (1.0) | 3 (2.4) | 3 (3.4) | 15 (2.2) |
| Dehydration | 5 (1.7) | 4 (1.4) | 3 (2.4) | 0 | 9 (1.3) |
| **Musculoskeletal and Connective Tissue Disorders** | 4 (1.4) | 6 (2.1) | 1 (0.8) | 2 (2.2) | 7 (1.0) |
| **Nervous system Disorders** | 17 (5.7) | 9 (3.1) | 4 (3.2) | 6 (6.7) | 31 (4.6) |
| Peripheral sensory neuropathy | 9 (3.0) | 6 (2.1) | 2 (1.6) | 3 (3.4) | 16 (2.4) |
| **Renal and Urinary Disorders** | 3 (1.0) | 2 (0.7) | 2 (1.6) | 3 (3.4) | 11 (1.6) |
| Acute kidney injury | 2 (0.7) | 0 | 1 (0.8) | 3 (3.4) | 8 (1.2) |

| MedDRA (v23.0) SOC<br>Preferred term, n (%) | Study EV-301 | | Study EV-201 | | Enfortumab Vedotin 1.25 mg/kg† (n = 680) |
|---|---|---|---|---|---|
| | Enfortumab Vedotin (n = 296) | Chemotherapy (n = 291) | Cohort 1 Enfortumab Vedotin (n =125) | Cohort 2 Enfortumab Vedotin (n =89) | |
| **Respiratory, Thoracic and Mediastinal Disorders** | 5 (1.7) | 2 (0.7) | 2 (1.6) | 2 (2.2) | 13 (1.9) |
| **Skin and Subcutaneous Tissue Disorders** | 50 (16.9) | 1 (0.3) | 16 (12.8) | 14 (15.7) | 92 (13.5) |
| Rash maculo-papular | 22 (7.4) | 0 | 5 (4.0) | 7 (7.9) | 38 (5.6) |
| Rash erythematous | 4 (1.4) | 0 | 4 (3.2) | 2 (2.2) | 13 (1.9) |
| Pruritus | 4 (1.4) | 0 | 2 (1.6) | 3 (3.4) | 10 (1.5) |
| Drug eruption | 8 (2.7) | 1 (0.3) | 1 (0.8) | 0 | 9 (1.3) |
| Rash | 5 (1.7) | 0 | 0 | 2 (2.2) | 7 (1.0) |
| **Vascular Disorders** | 2 (0.7) | 1 (0.3) | 2 (1.6) | 4 (4.5) | 11 (1.6) |
| Hypertension | 1 (0.3) | 0 | 2 (1.6) | 1 (1.1) | 7 (1.0) |

Number of subjects (n) and percentage of subjects (%) are shown.
Sorting order: alphabetical order by SOC and descending by the number of subjects of 'enfortumab vedotin 1.25 mg/kg' group by preferred term. In case of ties, alphabetical order by preferred term is applied.
Adverse events related to study drug as assessed by the investigator, or missing relationship were shown.
Subjects are counted once under the maximum CTCAE grade.
ISS: integrated summary of safety; NCI-CTCAE: National Cancer Institute-Common Terminology Criteria for Adverse Events.
† Enfortumab vedotin 1.25 mg/kg column includes all subjects in the following studies who received a 1.25 mg/kg dose of enfortumab vedotin: EV-101, EV-102, EV-201, and EV-301.
Source: EV-201 and EV-301 ISS Table 12.6.1.4.3.1

## Adverse events of special interest (AEOI)

The AEOI categories were generated based on the following criteria:

- Potential or theoretical risk based on the nonclinical pharmacology and/or toxicology of enfortumab vedotin; and
- Observed findings in the clinical and laboratory data.

AEOIs for enfortumab vedotin include skin reactions (severe cutaneous adverse reactions and rash), hyperglycemia, peripheral neuropathy, diarrhea, nausea, vomiting, dry eye, anemia, extravasation events, neutropenia, infusion-related reactions (other than extravasation events), corneal disorders, blurred vision, and ATAs.

Overview of findings in study 301 (CSR):

**Table 88** Treatment-emergent Adverse Events of Special Interest (SAF)

| Preferred Term (MedDRA v23.0) | Overall Incidence, n (%) | |
|---|---|---|
| | Enfortumab Vedotin (n = 296) | Chemotherapy (n = 291) |
| Any infusion-related reactions (SSQ/CMQ) | | |
| Overall | 27 (9.1) | 17 (5.8) |
| ≥ Grade 3 | 4 (1.4) | 0 |
| Any ocular disorders | | |
| Overall | 83 (28.0) | 23 (7.9) |
| ≥ Grade 3 | 2 (0.7) | 1 (0.3) |
| Any skin reactions | | |
| Overall | 159 (53.7) | 58 (19.9) |
| ≥ Grade 3 | 43 (14.5) | 2 (0.7) |
| Any hyperglycemia (SSQ/CMQ) | | |
| Overall | 35 (11.8) | 8 (2.7) |
| ≥ Grade 3 | 21 (7.1) | 3 (1.0) |
| Any peripheral neuropathy (SMQ) | | |
| Overall | 149 (50.3) | 100 (34.4) |
| ≥ Grade 3 | 15 (5.1) | 8 (2.7) |

All randomized subjects who received any amount of study drug (SAF).
SAF: safety analysis set; SMQ: Standard MedDRA Query; SSQ/CMQ: Sponsor Specific Query/Customized Medical Query.

**Skin Reactions**

The incidence of all skin reactions and severe cutaneous adverse reactions in the EV arm of study EV-301 was high compared to the chemotherapy arm (53.7% / 26.0% vs 19.9% / 9.3%).

In Study 201/C1 53.6% of subjects experienced skin reactions. The median time to first onset of any grade skin reaction was 0.49 months (range 0.1 to 13.1). Both the incidence and time to onset were similar to study EV-301/EV-arm (0.46 months). The median time to resolution was 0.72 months (range 0.03 to 14.65) and the median time to improvement was 0.82 months (range 0.16 to 2.20). One patient experienced Stevens-Johnson syndrome (SJS) as assessed by two dermatologists but not confirmed by a third dermatologist.

**Table 89** Onset of Skin Reaction Treatment-emergent Adverse Events - Global Search (Safety Analysis Set)

| Parameter<br>Category/Statistic | Study EV-301 | | Study EV-201 | | Enfortumab Vedotin 1.25 mg/kg† (n = 680) |
|---|---|---|---|---|---|
| | Enfortumab Vedotin (n = 296) | Chemotherapy (n = 291) | Cohort 1 Enfortumab Vedotin (n = 125) | Cohort 2 Enfortumab Vedotin (n = 89) | |
| **Time to first onset of first event (any grade) (months)** | | | | | |
| n | 159 | 58 | 67 | 59 | 375 |
| Median | 0.46 | 0.66 | 0.49 | 0.49 | 0.49 |
| Min, Max | 0, 12.7 | 0.1, 9.6 | 0, 13.1 | 0.1, 5.8 | 0, 13.1 |
| **Time to first onset of any ≥ Grade 3 event (months)** | | | | | |
| n | 43 | 2 | 15 | 15 | 85 |
| Median | 0.53 | 0.21 | 1.18 | 0.59 | 0.62 |
| Min, Max | 0.1, 6.0 | 0.2, 0.2 | 0.2, 5.3 | 0.2, 5.8 | 0.1, 6.4 |

Note: This table includes rash and severe cutaneous adverse reactions events.max: maximum; min: minimum†Enfortumab vedotin 1.25 mg/kg column includes all subjects in the following studies who received a 1.25 mg/kg dose of enfortumab vedotin: EV-101, EV-102, EV-201, and EV-301.

**Table 90 Resolution of Skin Reaction Treatment-emergent Adverse Events (Safety Analysis Set)**

| Parameter<br>Category/Statistic | Study EV-201 | | |
|---|---|---|---|
| | Cohort 1 Enfortumab Vedotin (n = 125) | Cohort 2 Enfortumab Vedotin (n = 89) | Total (n = 214) |
| **Time to resolution (months)** | | | |
| Number of events with resolution † | 126 | 76 | 202 |
| Median | 0.723 | 0.920 | 0.821 |
| Min, Max | 0.03, 14.65 | 0.07, 19.58 | 0.03, 19.58 |
| **Time to improvement (months)** | | | |
| Number of events with improvement‡ | 3 | 3 | 6 |
| Median | 0.821 | 0.559 | 0.690 |
| Min, Max | 0.16, 2.20 | 0.53, 1.64 | 0.16, 2.20 |

max: maximum; min: minimum†Resolution is defined as events outcome of 'Recovered/Resolved' or 'Recovered/Resolved with Sequelae', or returning to baseline grade as of the last assessment for conditions that are ongoing at baseline. ‡For events that are not resolved, improvement is defined as at least 1 grade improvement from the worst grade at the last assessment.

Time to resolution/improvement was not available for Study EV-301.

The majority of skin reaction events did not require dose modifications. No TEAE of skin reaction leading to death was noted in the safety population of the current application.

Based on the enfortumab vedotin 1.25 mg/kg group a summary of the outcomes and management of the 23 subjects treated with enfortumab vedotin who had serious and Grade ≥ 3 TEAEs of skin reactions was provided. The outcomes for the majority (17/23 [73.9%]) of subjects with serious and Grade ≥ 3 TEAEs of skin reactions were recovered/resolved, recovered/resolved with sequelae, or recovering/resolving. Four (17.4%) subjects were not/recovered/not resolved, and the outcome for 2 (8.7%) subjects was unknown. There were no fatal outcomes.

**Peripheral Neuropathy**

The cytotoxic component of enfortumab vedotin, MMAE, is a microtubule-disrupting agent [Challita-Eid et al, 2016]. Peripheral neuropathy is often associated with drugs that affect microtubules and is associated with other MMAE ADCs [Donaghy, 2016].

Overall, peripheral neuropathy occurred commonly in the enfortumab vedotin-treated subjects, mainly at low grades; few subjects experienced Grade 3 events and 1 subject experienced a Grade 4 event.

Peripheral neuropathy events were predominantly sensory in nature. Peripheral neuropathy was the most common adverse event overall leading to treatment discontinuation in the enfortumab vedotin safety population (4.8 % in study 301 EV arm compared to 2.1% in the chemo-arm and 7.2 % in study EV-201/C1, see Table 110 /SCS in the Discontinuation section below).

**Table 91** Overview of Peripheral Neuropathy Treatment-emergent Adverse Events (Safety Analysis Set)

| | **Study EV-301** | | **Study EV-201** | | |
|---|---|---|---|---|---|
| **MedDRA (v23.0) Category, n (%)** | **Enfortumab Vedotin (n = 296)** | **Chemotherapy (n = 291)** | **Cohort 1 Enfortumab Vedotin (n = 125)** | **Cohort 2 Enfortumab Vedotin (n = 89)** | **Enfortumab Vedotin 1.25 mg/kg† (n = 680)** |
| **Subjects with any peripheral neuropathy event** | **149 (50.3)** | **100 (34.4)** | **70 (56.0)** | **52 (58.4)** | **352 (51.8)** |
| **Subjects with any peripheral neuropathy sensory events** | **139 (47.0)** | **97 (33.3)** | **60 (48.0)** | **49 (55.1)** | **322 (47.4)** |
| **Subjects with any peripheral neuropathy motor events** | **33 (11.1)** | **9 (3.1)** | **24 (19.2)** | **16 (18.0)** | **99 (14.6)** |
| **Peripheral neuropathy events by PT occurring in ≥ 5% of enfortumab vedotin 1.25 mg/kg group** | | | | | |
| Peripheral sensory neuropathy | 102 (34.5) | 66 (22.7) | 54 (43.2) | 44 (49.4) | 263 (38.7) |
| Grade 1 | 36 (12.2) | 34 (11.7) | 18 (14.4) | 12 (13.5) | 89 (13.1) |
| Grade 2 | 57 (19.3) | 26 (8.9) | 34 (27.2) | 29 (32.6) | 158 (23.2) |
| Grade 3 | 9 (3.0) | 6 (2.1) | 2 (1.6) | 3 (3.4) | 16 (2.4) |
| Grade 4 | 0 | 0 | 0 | 1 (1.1) | 0 |
| Muscular weakness | 16 (5.4) | 7 (2.4) | 10 (8.0) | 8 (9.0) | 50 (7.4) |
| Grade 1 | 7 (2.4) | 5 (1.7) | 5 (4.0) | 2 (2.2) | 27 (4.0) |
| Grade 2 | 7 (2.4) | 2 (0.7) | 4 (3.2) | 5 (5.6) | 19 (2.8) |
| Grade 3 | 2 (0.7) | 0 | 1 (0.8) | 1 (1.1) | 4 (0.6) |
| Grade 4 | 0 | 0 | 0 | 0 | 0 |
| Peripheral motor neuropathy | 11 (3.7) | 0 | 13 (10.4) | 8 (9.0) | 41 (6.0) |
| Grade 1 | 4 (1.4) | 0 | 4 (3.2) | 2 (2.2) | 14 (2.1) |
| Grade 2 | 4 (1.4) | 0 | 8 (6.4) | 4 (4.5) | 21 (3.1) |
| Grade 3 | 3 (1.0) | 0 | 1 (0.8) | 2 (2.2) | 6 (0.9) |
| Grade 4 | 0 | 0 | 0 | 0 | 0 |
| Gait disturbance | 8 (2.7) | 0 | 7 (5.6) | 9 (10.1) | 35 (5.1) |
| Grade 1 | 4 (1.4) | 0 | 4 (3.2) | 6 (6.7) | 22 (3.2) |
| Grade 2 | 4 (1.4) | 0 | 3 (2.4) | 1 (1.1) | 11 (1.6) |
| Grade 3 | 0 | 0 | 0 | 2 (2.2) | 2 (0.3) |
| Grade 4 | 0 | 0 | 0 | 0 | 0 |
| **Subjects with any drug-related TEAE** | 137 (46.3) | 89 (30.6) | 63 (50.4) | 48 (53.9) | 318 (46.8) |
| **Subjects with any serious TEAE** | 6 (2.0) | 2 (0.7) | 1 (0.8) | 2 (2.2) | 10 (1.5) |

| MedDRA (v23.0) Category, n (%) | Study EV-301 | | Study EV-201 | | Enfortumab Vedotin 1.25 mg/kg† (n = 680) |
|---|---|---|---|---|---|
| | Enfortumab Vedotin (n = 296) | Chemotherapy (n = 291) | Cohort 1 Enfortumab Vedotin (n = 125) | Cohort 2 Enfortumab Vedotin (n = 89) | |
| **Subjects with any serious drug-related TEAE** | 4 (1.4) | 1 (0.3) | 0 | 2 (2.2) | 6 (0.9) |
| Peripheral motor neuropathy | 0 | 0 | 0 | 1 (1.1) | 1 (0.1) |
| **Subjects with any TEAE leading to permanent withdrawal of study drug** | 14 (4.7) | 8 (2.7) | 9 (7.2) | 6 (6.7) | 34 (5.0) |

Number of subjects (n) and percentage of subjects (%) are shown.

Subjects were counted once under maximum NCI-CTCAE grade. Highest nonmissing grade was considered as the maximum NCI-CTCAE grade. A missing NCI-CTCAE grade was considered the maximum NCI-CTCAE grade when all grades for the subject are missing.

Events are sorted by descending number of subjects in the enfortumab vedotin 1.25 mg/kg group.

Drug-related treatment-emergent adverse events have a reasonable possibility that the event may have been caused by the study drug as assessed by the investigator. If relationship was missing, then it was considered drug related.

ISS: integrated summary of safety; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; PT: preferred term; TEAE: treatment-emergent adverse event.

† Enfortumab vedotin 1.25 mg/kg column includes all subjects in the following studies who received a 1.25 mg/kg dose of enfortumab vedotin: EV-101, EV-102, EV-201, and EV-301.

As of last follow-up, 15/70 subjects (21%) in study EV-201 had resolution of all events and an additional 24 subjects (34%) had resolution or improvement in at least some events meaning that 55/125 patients still had some degree of neuropathy. The majority of subjects with ongoing PN at last follow-up had either Grade 1 (36/55 subjects; 66%) or Grade 2 (17/55 subjects; 31%) events.

Recommendations regarding dose interruption, reduction, and discontinuation in case of peripheral neuropathy are included in the SmPC, section 4.2.

**Hyperglycaemia**

Overall, hyperglycemia has been reported in approximately 15% of subjects treated with enfortumab vedotin. Hyperglycemia events were most frequently Grade 3 in severity. In Study EV 301 11.8% in the EV arm and 2.7% in the Chemo-arm had any hyperglycaemic event, and one subject in the enfortumab vedotin arm died due to hyperglycemia. In Study EV-201 for subjects with treatment-emergent hyperglycemia, the median time to first onset of any grade hyperglycemia in Cohort 1 was 0.64 months (range 0.26 to 9.23) and the median time to first onset of ≥ Grade 3 hyperglycemia was 1.13 months (range 0.3 to 2.3). Most cases resolved (18/20) and the median time to resolution was 0.85 months (range 0.10 to 13.67).

Study EV-301 data suggest that hyperglycemia events were more common in subjects with a baseline BMI ≥ 30 kg/m2 (Table 98) and in patients with a prior medical history of hyperglycemia who were treated with enfortumab vedotin.

Recommendations regarding dose interruption in case of hyperglycaemia are included in SmPC section 4.2 while in section 4.4 information regarding a higher risk of hyperglycaemia in patients with BMI ≥ 30 kg/m$^2$ is also stated.

**Table 92** Overview of Hyperglycemia Treatment-emergent Adverse Events (Safety Analysis Set)

| MedDRA (v23.0) Category, n (%) | Study EV-301 | | Study EV-201 | | Enfortumab Vedotin 1.25 mg/kg† |
|---|---|---|---|---|---|
| | Enfortumab Vedotin (n = 296) | Chemotherapy (n = 291) | Cohort 1 Enfortumab Vedotin (n = 125) | Cohort 2 Enfortumab Vedotin (n = 89) | (n = 680) |
| **Subjects with any hyperglycemia event** | **35 (11.8)** | **8 (2.7)** | **20 (16.0)** | **16 (18.0)** | **98 (14.4)** |
| **Hyperglycemia event by PT occurring in ≥ 5% of enfortumab vedotin 1.25 mg/kg group** | | | | | |
| Hyperglycaemia | 31 (10.5) | 6 (2.1) | 19 (15.2) | 14 (15.7) | 89 (13.1) |
| Grade 1 | 5 (1.7) | 2 (0.7) | 4 (3.2) | 2 (2.2) | 20 (2.9) |
| Grade 2 | 5 (1.7) | 2 (0.7) | 6 (4.8) | 4 (4.5) | 22 (3.2) |
| Grade 3 | 19 (6.4) | 1 (0.3) | 8 (6.4) | 7 (7.9) | 42 (6.2) |
| Grade 4 | 1 (0.3) | 1 (0.3) | 1 (0.8) | 1 (1.1) | 4 (0.6) |
| Grade 5 | 1 (0.3) | 0 | 0 | 0 | 1 (0.1) |
| **Subjects with any drug-related TEAE** | 19 (6.4) | 1 (0.3) | 14 (11.2) | 9 (10.1) | 55 (8.1) |
| **Subjects with any serious TEAE** | 5 (1.7) | 1 (0.3) | 2 (1.6) | 2 (2.2) | 15 (2.2) |
| **Subjects with any serious drug-related TEAE** | 4 (1.4) | 0 | 1 (0.8) | 2 (2.2) | 13 (1.9) |
| Hyperglycaemia | 3 (1.0) | 0 | 1 (0.8) | 2 (2.2) | 12 (1.8) |
| Diabetic ketoacidosis | 0 | 0 | 0 | 0 | 1 (0.1) |
| Type 2 diabetes mellitus | 1 (0.3) | 0 | 0 | 0 | 1 (0.1) |
| **Subjects with any TEAE leading to permanent withdrawal of study drug** | 2 (0.7) | 0 | 1 (0.8) | 0 | 4 (0.6) |

Number of subjects (n) and percentage of subjects (%) are shown.

Subjects were counted once under maximum NCI-CTCAE grade. Highest non-missing grade was considered as the maximum NCI-CTCAE grade. A missing NCI-CTCAE grade was considered the maximum NCI-CTCAE grade when all grades for the subject are missing.

Events are sorted by descending number of subjects in the enfortumab vedotin 1.25 mg/kg group.

Drug-related treatment-emergent adverse events have a reasonable possibility that the event may have been caused by the study drug as assessed by the investigator. If relationship was missing, then it was considered drug related.

ISS: integrated summary of safety; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; PT: preferred term; TEAE: treatment-emergent adverse event.

† Enfortumab vedotin 1.25 mg/kg column includes all subjects in the following studies who received a 1.25 mg/kg dose of enfortumab vedotin: EV-101, EV-102, EV-201 and EV-301.

**Table 93** Study EV-301 Hyperglycemia by Baseline Body Mass Index (Safety Analysis Set)

| Parameter Category/Statistic | Study EV-301 | | |
|---|---|---|---|
| | Enfortumab Vedotin (n = 296) | Chemotherapy (n = 291) | Total (n = 499) |
| **Baseline BMI < 30 kg/m$^2$** | | | |
| Any hyperglycemia | 23/255 (9.0) | 7/244 (2.9) | 30/499 (6.0) |
| **Baseline BMI ≥ 30 kg/m$^2$** | | | |
| Any hyperglycemia | 12/41 (29.3) | 1/46 (2.2) | 13/87 (14.9) |

BMI: body mass index. Source: EV-301 CSR, Ad hoc Table 12.6.1.20.4.5

**Table 94** Treatment-emergent Adverse Event with Special Safety Interest: hyperclycemia (MedDRA v.23.o) by Pre-existing Condition of Hyperglycemia Ad hoc table Cut-off date 15 July 2020

Pre-existing Condition of Hyperglycemia yes

| Preferred Term | Enfortumab Vedotin (N=55) n (%) | Chemotherapy (N=56) n (%) | Total (N=111) n (%) |
|---|---|---|---|
| Any hyperglycemia (SSQ/CMQ) | 21 ( 38.2%) | 4 ( 7.1%) | 25 ( 22.5%) |
| Hyperglycaemia | 20 ( 36.4%) | 4 ( 7.1%) | 24 ( 21.6%) |
| Blood glucose increased | 1 ( 1.8%) | 0 | 1 ( 0.9%) |
| Diabetes mellitus inadequate control | 1 ( 1.8%) | 0 | 1 ( 0.9%) |
| Type 2 diabetes mellitus | 1 ( 1.8%) | 0 | 1 ( 0.9%) |

Pre-existing Condition of Hyperglycemia no

| Preferred Term | Enfortumab Vedotin (N=241) n (%) | Chemotherapy (N=235) n (%) | Total (N=476) n (%) |
|---|---|---|---|
| Any hyperglycemia (SSQ/CMQ) | 14 ( 5.8%) | 4 ( 1.7%) | 18 ( 3.8%) |
| Hyperglycaemia | 11 ( 4.6%) | 2 ( 0.9%) | 13 ( 2.7%) |
| Glucose tolerance impaired | 2 ( 0.8%) | 2 ( 0.9%) | 4 ( 0.8%) |
| Type 2 diabetes mellitus | 2 ( 0.8%) | 0 | 2 ( 0.4%) |

**Extravasation Events**

As enfortumab vedotin is administered intravenously extravasation may occur. In Study EV-301, 3 subjects (1.0%) in the enfortumab vedotin arm and 7 subjects (2.4%) in the chemotherapy arm experienced any extravasation events. These events were Grade 1 or Grade 2. None of subjects in either the enfortumab vedotin or chemotherapy arms reported extravasation events that resulted in treatment withdrawal, and only 1 event in the chemotherapy arm was considered serious. The incidence and severity of extravasation events was consistent across the safety analysis groups.

**Infusion-related Reactions (IRRs)**

As enfortumab vedotin is an ADC, there is a potential risk of a hypersensitivity reaction and/or systemic infusion-related reactions. The incidence and severity of infusion-related reactions was similar across safety analysis groups. In the enfortumab vedotin 1.25 mg/kg group, 6.3% of subjects had any infusion-related reaction and 1.0% of subjects experienced a Grade 3 infusion-related reaction. In Study EV-301, 9.1% of subjects in the enfortumab vedotin arm and 5.8% of subjects in the chemotherapy arm experienced any infusion-related reactions.

**Anaemia and Neutropenia**

Anaemia:

In Study EV-301, the proportion of subjects who experienced any anaemia event was higher in the chemotherapy arm (30.2%) compared with the enfortumab vedotin arm (19.9%) (Table 100).

In study 201 the incidence of anaemia was higher than in study 301 (35.2% for Cohort 1 and 19.9%, respectively).

**Table 95** Overview of Anemia Treatment-emergent Adverse Events (Safety Analysis Set)

| MedDRA (v23.0) Category, n (%) | Study EV-301 | | Study EV-201 | | Enfortumab Vedotin 1.25 mg/kg† (n = 680) |
|---|---|---|---|---|---|
| | Enfortumab Vedotin (n = 296) | Chemotherapy (n = 291) | Cohort 1 Enfortumab Vedotin (n = 125) | Cohort 2 Enfortumab Vedotin (n = 89) | |
| Subjects with any anaemia event | 59 (19.9) | 88 (30.2) | 44 (35.2) | 34 (38.2) | 180 (26.5) |
| Anaemia events by PT occurring in ≥ 5% of enfortumab vedotin 1.25 mg/kg group | | | | | |
| Anaemia | 59 (19.9) | 87 (29.9) | 44 (35.2) | 34 (38.2) | 180 (26.5) |
| Grade 1 | 12 (4.1) | 12 (4.1) | 11 (8.8) | 6 (6.7) | 34 (5.0) |
| Grade 2 | 28 (9.5) | 42 (14.4) | 16 (12.8) | 18 (20.2) | 85 (12.5) |
| Grade 3 | 19 (6.4) | 34 (11.7) | 17 (13.6) | 10 (11.2) | 61 (9.0) |
| Subjects with any drug-related TEAE | 34 (11.5) | 59 (20.3) | 27 (21.6) | 22 (24.7) | 110 (16.2) |
| Subjects with any serious TEAE | 4 (1.4) | 6 (2.1) | 0 | 0 | 5 (0.7) |
| Subjects with any serious drug-related TEAE | 2 (0.7) | 2 (0.7) | 0 | 0 | 2 (0.3) |
| Anaemia | 2 (0.7) | 2 (0.7) | 0 | 0 | 2 (0.3) |
| Subjects with any TEAE leading to permanent withdrawal of study drug | 0 | 2 (0.7) | 0 | 0 | 0 |

Number of subjects (n) and percentage of subjects (%) are shown.

Subjects were counted once under maximum NCI-CTCAE grade. Highest nonmissing grade was considered as the maximum NCI-CTCAE grade. A missing NCI-CTCAE grade was considered the maximum NCI-CTCAE grade when all grades for the subject are missing.

Events are sorted by descending number of subjects in the enfortumab vedotin 1.25 mg/kg group.

Drug-related treatment-emergent adverse events have a reasonable possibility that the event may have been caused by the study drug as assessed by the investigator. If relationship was missing, then it was considered drug related.

ISS: integrated summary of safety; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; PT: preferred term; TEAE: treatment-emergent adverse event.

† Enfortumab vedotin 1.25 mg/kg column includes all subjects in the following studies who received a 1.25 mg/kg dose of enfortumab vedotin: EV-101, EV-102, EV-201 and EV-301.

Neutropenia:

In Study EV-301, the proportion of subjects who experienced any neutropenia event was higher in the chemotherapy arm (29.6%) compared with the enfortumab vedotin arm (18.2%). The corresponding Grade 3-4 neutropenia events were 8.5% vs 4.7% (Table 101).

In Study EV-301 the incidence of subjects receiving colony stimulating factors was 7.1% in the enfortumab vedotin arm compared with 30.6% in the chemotherapy arm, which also has to be considered when assessing the incidence of neutropenia.

Despite neutropenia being less frequent in the EV arm compared to the chemotherapy arm in study 301 (4.7% vs 7.6%), the incidence of infections (by SOC) was higher in the EV arm (16.9% vs 9.6%) underlining the added risk of infection in the EV-arm despite the higher incidence of neutropenia in the chemotherapy arm.

In study EV-301, based on an *ad hoc* analysis, the incidence of Grade 3 or 4 infections within 14 days after an AE of neutropenia or neutrophil laboratory value of grade 3 or 4 was comparable between the EV and chemo arm (2.4% vs 1.7%).

**Table 96** Overview of Neutropenia Treatment-emergent Adverse Events (Safety Analysis Set)

| MedDRA (v23.0) Category, n (%) | Study EV-301 | | Study EV-201 | | Enfortumab Vedotin 1.25 mg/kg† (n = 680) |
|---|---|---|---|---|---|
| | Enfortumab Vedotin (n = 296) | Chemotherapy (n = 291) | Cohort 1 Enfortumab Vedotin (n = 125) | Cohort 2 Enfortumab Vedotin (n = 89) | |
| **Subjects with any any neutropenia event** | 54 (18.2) | 86 (29.6) | 21 (16.8) | 16 (18.0) | 104 (15.3) |
| **Neutropenia event by PT occurring in ≥ 5% of enfortumab vedotin 1.25 mg/kg group** | | | | | |
| Neutropenia | 20 (6.8) | 28 (9.6) | 14 (11.2) | 12 (13.5) | 53 (7.8) |
| Grade 1 | 2 (0.7) | 1 (0.3) | 2 (1.6) | 1 (1.1) | 6 (0.9) |
| Grade 2 | 4 (1.4) | 5 (1.7) | 1 (0.8) | 2 (2.2) | 7 (1.0) |
| Grade 3 | 11 (3.7) | 12 (4.1) | 8 (6.4) | 5 (5.6) | 29 (4.3) |
| Grade 4 | 3 (1.0) | 10 (3.4) | 3 (2.4) | 4 (4.5) | 11 (1.6) |
| Neutrophil count decreased | 33 (11.1) | 54 (18.6) | 5 (4.0) | 3 (3.4) | 47 (6.9) |
| Grade 1 | 4 (1.4) | 1 (0.3) | 1 (0.8) | 0 | 8 (1.2) |
| Grade 2 | 8 (2.7) | 10 (3.4) | 0 | 0 | 9 (1.3) |
| Grade 3 | 16 (5.4) | 18 (6.2) | 2 (1.6) | 2 (2.2) | 22 (3.2) |
| Grade 4 | 5 (1.7) | 25 (8.6) | 2 (1.6) | 1 (1.1) | 8 (1.2) |
| **Subjects with any drug-related TEAE** | 49 (16.6) | 80 (27.5) | 19 (15.2) | 15 (16.9) | 96 (14.1) |
| **Subjects with any serious TEAE** | 9 (3.0) | 29 (10.0) | 7 (5.6) | 3 (3.4) | 20 (2.9) |
| **Subjects with any serious drug-related TEAE** | 7 (2.4) | 29 (10.0) | 7 (5.6) | 3 (3.4) | 18 (2.6) |
| Neutropenia | 4 (1.4) | 8 (2.7) | 2 (1.6) | 2 (2.2) | 9 (1.3) |
| Febrile neutropenia | 2 (0.7) | 16 (5.5) | 5 (4.0) | 1 (1.1) | 8 (1.2) |
| Neutrophil count decreased | 2 (0.7) | 5 (1.7) | 1 (0.8) | 0 | 3 (0.4) |
| **Subjects with any TEAE leading to permanent withdrawal of study drug** | 1 (0.3) | 6 (2.1) | 0 | 0 | 1 (0.1) |

Number of subjects (n) and percentage of subjects (%) are shown.

Subjects were counted once under maximum NCI-CTCAE grade. Highest non-missing grade was considered as the maximum NCI-CTCAE grade. A missing NCI-CTCAE grade was considered the maximum NCI-CTCAE grade when all grades for the subject are missing.

Events are sorted by descending number of subjects in the enfortumab vedotin 1.25 mg/kg group.

Drug-related treatment-emergent adverse events have a reasonable possibility that the event may have been caused by the study drug as assessed by the investigator. If relationship was missing, then it was considered drug related.

ISS: integrated summary of safety; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; PT: preferred term; TEAE: treatment-emergent adverse event.

† Enfortumab vedotin 1.25 mg/kg column includes all subjects in the following studies who received a 1.25 mg/kg dose of enfortumab vedotin: EV-101, EV-102, EV-201 and EV-301.

### Gastrointestinal symptoms

Nectin-4 expression has been identified in the esophagus and the stomach in Study ES10-001 [Study ES10-001] and weak staining was observed in the mucosal glands of other gastrointestinal tract organs including the small intestine, colon, and rectum. The gastrointestinal toxicities of diarrhea, nausea and vomiting, are common events reported with the use of MMAE-ADCs, including enfortumab vedotin.

In Study EV-301, the incidence of diarrhoea was higher in the enfortumab vedotin arm (34.8%; 3.4% Grade 3, none Grade 4) compared with the chemotherapy arm (22.7%; 1.7% Grade 3, none Grade 4).

The incidence of vomiting was similar in both the treatment groups (14.2% in the enfortumab vedotin arm and 15.1% in the chemotherapy arm). In study EV-201/C1 the incidence of diarrhoea was 42.4% of which 4% were Grade 3 and none Grade 4.

No enfortumab vedotin subject reported gastrointestinal nonspecific symptoms and therapeutic procedure SMQs that resulted in treatment withdrawal, whereas three patients in the chemotherapy arm withdrew (1 due to vomiting, 2 due to constipation).

**Table 97** Overview of Gastrointestinal Nonspecific Symptoms and Therapeutic Procedures SMQ Events (Safety Analysis Set)

| | Study EV-301 | | Study EV-201 | | |
|---|---|---|---|---|---|
| **MedDRA (v23.0) Category, n (%)** | **Enfortumab Vedotin (n = 296)** | **Chemotherapy (n = 291)** | **Cohort 1 Enfortumab Vedotin (n = 125)** | **Cohort 2 Enfortumab Vedotin (n = 89)** | **Enfortumab Vedotin 1.25 mg/kg† (n = 680)** |
| **Subjects with any gastrointestinal nonspecific symptoms and therapeutic procedure SMQ** | 186 (62.8) | 167 (57.4) | 103 (82.4) | 56 (62.9) | 472 (69.4) |
| Grade 1 | 93 (31.4) | 82 (28.2) | 58 (46.4) | 28 (31.5) | 246 (36.2) |
| Grade 2 | 73 (24.7) | 61 (21.0) | 34 (27.2) | 19 (21.3) | 173 (25.4) |
| Grade 3 | 19 (6.4) | 24 (8.2) | 11 (8.8) | 9 (10.1) | 52 (7.6) |
| Grade 4 | 1 (0.3) | 0 | 0 | 0 | 1 (0.1) |
| **Subjects with any gastrointestinal nonspecific symptoms and therapeutic procedure SMQ by PT in ≥ 20% of subjects in the enfortumab vedotin 1.25 mg/kg†** | | | | | |
| Diarrhoea | 103 (34.8) | 66 (22.7) | 53 (42.4) | 31 (34.8) | 256 (37.6) |
| Grade 1 | 62 (20.9) | 45 (15.5) | 37 (29.6) | 19 (21.3) | 169 (24.9) |
| Grade 2 | 30 (10.1) | 16 (5.5) | 11 (8.8) | 6 (6.7) | 61 (9.0) |
| Grade 3 | 10 (3.4) | 5 (1.7) | 5 (4.0) | 6 (6.7) | 25 (3.7) |
| Nausea | 89 (30.1) | 74 (25.4) | 57 (45.6) | 27 (30.3) | 245 (36.0) |
| Grade 1 | 56 (18.9) | 52 (17.9) | 40 (32.0) | 19 (21.3) | 161 (23.7) |
| Grade 2 | 30 (10.1) | 17 (5.8) | 13 (10.4) | 7 (7.9) | 72 (10.6) |
| Grade 3 | 3 (1.0) | 5 (1.7) | 4 (3.2) | 1 (1.1) | 12 (1.8) |
| **Subjects with any drug-related TEAE** | | | | | |
| Gastrointestinal Nonspecific Symptoms and Therapeutic Procedure SMQ | 131 (44.3) | 134 (46.0) | 81 (64.0) | 37 (41.6) | 345 (50.7) |
| Nausea | 67 (22.6) | 63 (21.6) | 50 (40.0) | 20 (22.5) | 193 (28.4) |
| Diarrhoea | 72 (24.3) | 48 (16.5) | 41 (32.8) | 20 (22.5) | 186 (27.4) |
| Vomiting | 26 (8.8) | 31 (10.7) | 19 (15.2) | 7 (7.9) | 84 (12.4) |
| **Subjects with any serious TEAE** | | | | | |
| Gastrointestinal Nonspecific Symptoms and Therapeutic Procedure SMQ | 16 (5.4) | 18 (6.2) | 8 (6.4) | 4 (4.5) | 36 (5.3) |
| Nausea | 2 (0.7) | 2 (0.7) | 3 (2.4) | 2 (2.2) | 10 (1.5) |
| Diarrhoea | 7 (2.4) | 4 (1.4) | 3 (2.4) | 3 (3.4) | 15 (2.2) |
| Vomiting | 5 (1.7) | 1 (0.3) | 3 (2.4) | 1 (1.1) | 13 (1.9) |
| *Table continued on next page* | | | | | |
| **Subjects with any serious drug-related TEAE** | | | | | |
| Gastrointestinal Nonspecific Symptoms and Therapeutic Procedure SMQ | 9 (3.0) | 13 (4.5) | 4 (3.2) | 2 (2.2) | 19 (2.8) |
| Nausea | 2 (0.7) | 2 (0.7) | 3 (2.4) | 1 (1.1) | 7 (1.0) |

| MedDRA (v23.0) Category, n (%) | Study EV-301 | | Study EV-201 | | Enfortumab Vedotin 1.25 mg/kg† (n = 680) |
|---|---|---|---|---|---|
| | Enfortumab Vedotin (n = 296) | Chemotherapy (n = 291) | Cohort 1 Enfortumab Vedotin (n = 125) | Cohort 2 Enfortumab Vedotin (n = 89) | |
| Diarrhoea | 7 (2.4) | 4 (1.4) | 1 (0.8) | 2 (2.2) | 11 (1.6) |
| Vomiting | 3 (1.0) | 1 (0.3) | 3 (2.4) | 1 (1.1) | 10 (1.5) |
| **TEAEs leading to permanent withdrawal of study drug** | | | | | |
| Gastrointestinal Nonspecific Symptoms and Therapeutic Procedure SMQ | 0 | 3 (1.0) | 0 | 0 | 0 |
| Nausea | 0 | 0 | 0 | 0 | 0 |
| Diarrhoea | 0 | 0 | 0 | 0 | 0 |
| Vomiting | 0 | 1 (0.3) | 0 | 0 | 0 |

Number of subjects (n) and percentage of subjects (%) are shown.

Subjects were counted once under maximum NCI-CTCAE grade. Highest nonmissing grade was considered as the maximum NCI-CTCAE grade. A missing NCI-CTCAE grade was considered the maximum NCI-CTCAE grade when all grades for the subject are missing.

Events are sorted by descending number of subjects in the enfortumab vedotin 1.25 mg/kg group.

Drug-related treatment-emergent adverse events have a reasonable possibility that the event may have been caused by the study drug as assessed by the investigator. If relationship was missing, then it was considered drug related.

ISS: integrated summary of safety; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; PT: preferred term; SMQ: standardized MedDRA query; TEAE: treatment-emergent adverse event.

† Enfortumab vedotin 1.25 mg/kg column includes all subjects in the following studies who received a 1.25 mg/kg dose of enfortumab vedotin: EV-101, EV-102, EV-201 and EV-301.

### Ocular Disorders

In Study EV-301, the proportion of subjects who experienced any ocular disorder event was higher in the enfortumab vedotin arm (28%) compared with the chemotherapy arm (7.9%) (Table 103 3/SCS). The majority of the ocular events were of Grade 1 or 2, with 2 subjects reporting Grade 3 events in the enfortumab vedotin arm, and 1 in the chemotherapy arm. One subject in the enfortumab vedotin arm and none in the chemotherapy arm reported ocular events that resulted in treatment withdrawal. Two subjects in the enfortumab vedotin arm and none in the chemotherapy arm experienced ocular event that was considered serious. In the enfortumab vedotin arm, the most common ocular disorder events occurring in ≥ 5% of subjects by PT were lacrimation increased, dry eye, vision blurred and conjunctivitis. In the chemotherapy arm, there were no ocular disorder events occurring in ≥ 5% of subjects.

In Study EV-201, the proportion of subjects who experienced any ocular disorder event was higher in Cohort 1 (47.2%) compared with Cohort 2 (34.8%) and markedly higher than in study EV-301 (28%).

**Table 98** Overview of Ocular Disorders Treatment-emergent Adverse Events (Safety Analysis Set)

| MedDRA (v23.0) Category, n (%) | Study EV-301 | | Study EV-201 | | Enfortumab Vedotin 1.25 mg/kg† (n = 680) |
|---|---|---|---|---|---|
| | Enfortumab Vedotin (n = 296) | Chemotherapy (n = 291) | Cohort 1 Enfortumab Vedotin (n = 125) | Cohort 2 Enfortumab Vedotin (n = 89) | |
| **Subjects with any ocular disorders** | **83 (28.0)** | **23 (7.9)** | **59 (47.2)** | **31 (34.8)** | **238 (35.0)** |
| **Ocular disorders event by PT occurring in ≥ 5% of subjects in the enfortumab vedotin 1.25 mg/kg group** | | | | | |
| Lacrimation increased | 30 (10.1) | 12 (4.1) | 21 (16.8) | 12 (13.5) | 89 (13.1) |
| Grade 1 | 24 (8.1) | 10 (3.4) | 19 (15.2) | 11 (12.4) | 77 (11.3) |
| Grade 2 | 6 (2.0) | 1 (0.3) | 2 (1.6) | 1 (1.1) | 11 (1.6) |
| Grade 3 | 0 | 1 (0.3) | 0 | 0 | 1 (0.1) |

| MedDRA (v23.0) Category, n (%) | Study EV-301 | | Study EV-201 | | Enfortumab Vedotin 1.25 mg/kg† (n = 680) |
|---|---|---|---|---|---|
| | Enfortumab Vedotin (n = 296) | Chemotherapy (n = 291) | Cohort 1 Enfortumab Vedotin (n = 125) | Cohort 2 Enfortumab Vedotin (n = 89) | |
| Dry eye | 19 (6.4) | 3 (1.0) | 30 (24.0) | 17 (19.1) | 87 (12.8) |
| Grade 1 | 15 (5.1) | 0 | 26 (20.8) | 14 (15.7) | 75 (11.0) |
| Grade 2 | 4 (1.4) | 0 | 4 (3.2) | 3 (3.4) | 12 (1.8) |
| Grade 3 | 0 | 0 | 0 | 0 | 0 |
| Vision blurred | 16 (5.4) | 5 (1.7) | 20 (16.0) | 9 (10.1) | 63 (9.3) |
| Grade 1 | 13 (4.4) | 5 (1.7) | 15 (12.0) | 6 (6.7) | 49 (7.2) |
| Grade 2 | 3 (1.0) | 0 | 5 (4.0) | 3 (3.4) | 14 (2.1) |
| Grade 3 | 0 | 0 | 0 | 0 | 0 |
| **Drug-related ocular TEAEs** | 55 (18.6) | 14 (4.8) | 46 (36.8) | 20 (22.5) | 168 (24.7) |
| **Serious ocular TEAEs** | 2 (0.7) | 0 | 0 | 0 | 2 (0.3) |
| **Serious drug-related ocular TEAE** | 2 (0.7) | 0 | 0 | 0 | 2 (0.3) |
| **Ocular TEAE leading to permanent withdrawal of study drug** | 1 (0.3) | 0 | 0 | 0 | 1 (0.1) |

Number of subjects (n) and percentage of subjects (%) are shown.

Subjects were counted once under maximum NCI-CTCAE grade. Highest non-missing grade was considered as the maximum NCI-CTCAE grade. A missing NCI-CTCAE grade was considered the maximum NCI-CTCAE grade when all grades for the subject are missing.

Events are sorted by descending number of subjects in the enfortumab vedotin 1.25 mg/kg group.

Drug-related treatment-emergent adverse events have a reasonable possibility that the event may have been caused by the study drug as assessed by the investigator. If relationship was missing, then it was considered drug related.

ISS: integrated summary of safety; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; PT: preferred term; TEAE: treatment-emergent adverse event.

† Enfortumab vedotin 1.25 mg/kg column includes all subjects in the following studies who received a 1.25 mg/kg dose of enfortumab vedotin: EV-101, EV-102, EV-201 and EV-301.

### Anti-drug Antibodies (ADA)

Serum samples from subjects administered enfortumab vedotin were evaluated for ADA. None of the subjects who were confirmed positive for ADA post-baseline experienced systemic infusion-reactions.

**Table 99** Summary of Anti-drug Antibodies (Safety Analysis Set)

| Category/Statistic | Study EV-301 | Study EV-201 | | Enfortumab Vedotin 1.25 mg/kg† (n = 680) |
|---|---|---|---|---|
| | Enfortumab Vedotin (n = 296) | Cohort 1 Enfortumab Vedotin (n = 125) | Cohort 2 Enfortumab Vedotin (n = 89) | |
| **Subjects with a baseline and at least 1 postbaseline sample** | **258** | **114** | **81** | **590** |
| **Baseline negative** | 246 | 112 | 80 | 575 |
| Negative post-baseline, n/N (%) | 238/246 (96.7) | 109/112 (97.3) | 76/80 (95.0) | 559/575 (97.2) |
| Positive post-baseline, n/N (%) | 8/246 (3.3) | 3/112 (2.7) | 4/80 (5.0) | 16/575 (2.8) |
| Transiently positive, n/N (%) | 7/246 (2.8) | 2/112 (1.8) | 3/80 (3.8) | 13/575 (2.3) |
| Persistently positive, n/N (%) | 1/246 (0.4) | 1/112 (0.9) | 1/80 (1.3) | 3/575 (0.5) |

| Category/Statistic | Study EV-301 Enfortumab Vedotin (n = 296) | Study EV-201 Cohort 1 Enfortumab Vedotin (n = 125) | Study EV-201 Cohort 2 Enfortumab Vedotin (n = 89) | Enfortumab Vedotin 1.25 mg/kg† (n = 680) |
|---|---|---|---|---|
| **Baseline positive** | 12 | 2 | 1 | 15 |
| Negative post-baseline, n/N (%) | 9/12 (75.0) | 1/2 (50.0) | 1/1 (100) | 11/15 (73.3) |
| Positive post-baseline, n/N (%) | 3/12 (25.0) | 1/2 (50.0) | 0 | 4/15 (26.7) |
| Transiently positive, n/N (%) | 2/12 (16.7) | 1/2 (50.0) | 0 | 3/15 (20.0) |
| Persistently positive, n/N (%) | 1/12 (8.3) | 0 | 0 | 1/15 (6.7) |

ISS: integrated summary of safety

† Enfortumab vedotin 1.25 mg/kg column includes all subjects in the following studies who received a 1.25 mg/kg dose of enfortumab vedotin: EV-101, EV-102, EV-201 and EV-301.

## *Serious adverse event/deaths/other significant events*

**Deaths:**

Deaths reported for participants treated with Enfortumab Vedotin at the RTD are summarised in Table 105. The causes of death were mainly related to infections, organ dysfunction (including liver and kidney related AEs), and the AESI hyperglycaemia (including ketoacidosis).

**Table 100** Treatment-emergent Adverse Events Leading to Death by SOC and Preferred Term (Safety Analysis Set)

| MedDRA (v23.0) SOC Preferred term, n (%) | Study EV-301 Enfortumab Vedotin (n = 296) | Study EV-301 Chemotherapy (n = 291) | Study EV-201 Cohort 1 Enfortumab Vedotin (n = 125) | Study EV-201 Cohort 2 Enfortumab Vedotin (n = 89) | Enfortumab Vedotin 1.25 mg/kg† (n = 680) |
|---|---|---|---|---|---|
| **Overall** | **21 (7.1)** | **16 (5.5)** | **7 (5.6)** | **8 (9.0)** | **47 (6.9)** |
| **Blood and Lymphatic System Disorders** | 0 | 1 (0.3) | 0 | 0 | 0 |
| Pancytopenia | 0 | 1 (0.3) | 0 | 0 | 0 |
| **Cardiac Disorders** | 0 | 2 (0.7) | 1 (0.8) | 0 | 3 (0.4) |
| Cardiac arrest | 0 | 1 (0.3) | 0 | 0 | 2 (0.3) |
| Cardiac disorder | 0 | 0 | 1 (0.8) | 0 | 1 (0.1) |
| Cardiogenic shock | 0 | 1 (0.3) | 0 | 0 | 0 |
| **Gastrointestinal Disorders** | 0 | 0 | 0 | 0 | 1 (0.1) |
| Malignant gastrointestinal obstruction | 0 | 0 | 0 | 0 | 1 (0.1) |
| **General Disorders and Administration Site Conditions** | 3 (1.0) | 2 (0.7) | 0 | 1 (1.1) | 6 (0.9) |
| Multiple organ dysfunction syndrome | 3 (1.0) | 0 | 0 | 1 (1.1) | 5 (0.7) |
| Disease progression | 0 | 0 | 0 | 0 | 1 (0.1) |
| Death | 0 | 1 (0.3) | 0 | 0 | 0 |
| General physical health deterioration | 0 | 1 (0.3) | 0 | 0 | 0 |
| **Hepatobiliary Disorders** | 1 (0.3) | 0 | 0 | 0 | 1 (0.1) |
| Hepatic function abnormal | 1 (0.3) | 0 | 0 | 0 | 1 (0.1) |

| MedDRA (v23.0) SOC<br>Preferred term, n (%) | Study EV-301 | | Study EV-201 | | Enfortumab Vedotin 1.25 mg/kg† (n = 680) |
|---|---|---|---|---|---|
| | Enfortumab Vedotin (n = 296) | Chemotherapy (n = 291) | Cohort 1 Enfortumab Vedotin (n = 125) | Cohort 2 Enfortumab Vedotin (n = 89) | |
| **Infections and Infestations** | 4 (1.4) | 5 (1.7) | 1 (0.8) | 1 (1.1) | 7 (1.0) |
| Sepsis | 0 | 2 (0.7) | 1 (0.8) | 1 (1.1) | 3 (0.4) |
| Pneumonia | 2 (0.7) | 1 (0.3) | 0 | 0 | 2 (0.3) |
| Pelvic abscess | 1 (0.3) | 0 | 0 | 0 | 1 (0.1) |
| Septic shock | 1 (0.3) | 1 (0.3) | 0 | 0 | 1 (0.1) |
| Neutropenic sepsis | 0 | 1 (0.3) | 0 | 0 | 0 |
| Pneumocystis jirovecii pneumonia | 0 | 1 (0.3) | 0 | 0 | 0 |
| **Metabolism and Nutrition Disorders** | 1 (0.3) | 0 | 0 | 1 (1.1) | 3 (0.4) |
| Diabetic ketoacidosis | 0 | 0 | 0 | 0 | 1 (0.1) |
| Hyperglycaemia | 1 (0.3) | 0 | 0 | 0 | 1 (0.1) |
| Metabolic acidosis | 0 | 0 | 0 | 1 (1.1) | 1 (0.1) |
| **Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)** | 10 (3.4) | 6 (2.1) | 3 (2.4) | 3 (3.4) | 16 (2.4) |
| Malignant neoplasm progression | 10 (3.4) | 6 (2.1) | 0 | 0 | 10 (1.5) |
| Transitional cell carcinoma metastatic | 0 | 0 | 2 (1.6) | 3 (3.4) | 5 (0.7) |
| Transitional cell carcinoma | 0 | 0 | 1 (0.8) | 0 | 1 (0.1) |
| **Nervous System Disorders** | 1 (0.3) | 0 | 0 | 0 | 1 (0.1) |
| Brain oedema | 1 (0.3) | 0 | 0 | 0 | 1 (0.1) |
| **Renal and Urinary Disorders** | 0 | 0 | 0 | 2 (2.2) | 3 (0.4) |
| Acute kidney injury | 0 | 0 | 0 | 2 (2.2) | 2 (0.3) |
| Urinary tract obstruction | 0 | 0 | 0 | 0 | 1 (0.1) |
| **Respiratory, Thoracic and Mediastinal Disorders** | 1 (0.3) | 1 (0.3) | 2 (1.6) | 0 | 6 (0.9) |
| Acute respiratory failure | 0 | 0 | 1 (0.8) | 0 | 2 (0.3) |
| Dyspnoea | 1 (0.3) | 0 | 0 | 0 | 2 (0.3) |
| Pneumonia aspiration | 0 | 0 | 1 (0.8) | 0 | 1 (0.1) |
| Respiratory failure | 0 | 0 | 0 | 0 | 1 (0.1) |
| Respiratory distress | 0 | 1 (0.3) | 0 | 0 | 0 |

Number of subjects (n) and percentage of subjects (%) are shown.

Sorting order: alphabetical order by SOC and descending by the number of subjects of 'enfortumab vedotin 1.25 mg/kg' group by preferred term. In case of ties, alphabetical order by preferred term is applied.

One subject from EV-301 study and 2 subjects from EV-201 study (1 each from Cohort 1 and Cohort 2) who had drug-related deaths that occurred outside of the treatment-emergent window are not included in any TEAE summary.

ISS: integrated summary of safety.

†Enfortumab vedotin 1.25 mg/kg column includes all subjects in the following studies who received a 1.25 mg/kg dose of enfortumab vedotin: EV-101, EV-102, EV-201, and EV-301.

**Serious adverse events**

Serious adverse events for subjects treated with Enfortumab Vedotin at the RTD are summarized below

**Table 101** Serious Treatment-emergent Adverse Events (≥ 1% of Subjects in the Enfortumab Vedotin 1.25 mg/kg Group†) by SOC and Preferred Term (Safety Analysis Set)

| | Study EV-301 | | Study EV-201 | | |
|---|---|---|---|---|---|
| **MedDRA (v23.0) SOC** Preferred term, n (%) | **Enfortumab Vedotin (n = 296)** | **Chemotherapy (n = 291)** | **Cohort 1 Enfortumab Vedotin (n = 125)** | **Cohort 2 Enfortumab Vedotin (n = 89)** | **Enfortumab Vedotin 1.25 mg/kg† (n = 680)** |
| **Overall** | **138 (46.6)** | **128 (44.0)** | **59 (47.2)** | **35 (39.3)** | **306 (45.0)** |
| **Blood and Lymphatic System Disorders** | 12 (4.1) | 32 (11.0) | 7 (5.6) | 3 (3.4) | 25 (3.7) |
| Febrile neutropenia | 4 (1.4) | 16 (5.5) | 5 (4.0) | 1 (1.1) | 10 (1.5) |
| Neutropenia | 4 (1.4) | 8 (2.7) | 2 (1.6) | 2 (2.2) | 9 (1.3) |
| **Cardiac Disorders** | 7 (2.4) | 9 (3.1) | 1 (0.8) | 6 (6.7) | 22 (3.2) |
| Atrial fibrillation | 5 (1.7) | 1 (0.3) | 0 | 2 (2.2) | 10 (1.5) |
| **Gastrointestinal Disorders** | 21 (7.1) | 27 (9.3) | 14 (11.2) | 7 (7.9) | 65 (9.6) |
| Diarrhoea | 7 (2.4) | 4 (1.4) | 3 (2.4) | 3 (3.4) | 15 (2.2) |
| Vomiting | 5 (1.7) | 1 (0.3) | 3 (2.4) | 1 (1.1) | 13 (1.9) |
| Abdominal pain | 3 (1.0) | 6 (2.1) | 3 (2.4) | 1 (1.1) | 11 (1.6) |
| Nausea | 2 (0.7) | 2 (0.7) | 3 (2.4) | 2 (2.2) | 10 (1.5) |
| **General Disorders and Administration Site Conditions** | 24 (8.1) | 24 (8.2) | 8 (6.4) | 3 (3.4) | 44 (6.5) |
| Pyrexia | 6 (2.0) | 9 (3.1) | 2 (1.6) | 1 (1.1) | 11 (1.6) |
| Fatigue | 3 (1.0) | 2 (0.7) | 3 (2.4) | 0 | 7 (1.0) |
| **Infections and Infestations** | 52 (17.6) | 34 (11.7) | 19 (15.2) | 13 (14.6) | 109 (16.0) |
| Pneumonia | 12 (4.1) | 7 (2.4) | 3 (2.4) | 3 (3.4) | 24 (3.5) |
| Urinary tract infection | 7 (2.4) | 6 (2.1) | 6 (4.8) | 3 (3.4) | 23 (3.4) |
| Sepsis | 5 (1.7) | 3 (1.0) | 4 (3.2) | 4 (4.5) | 21 (3.1) |
| Cellulitis | 3 (1.0) | 2 (0.7) | 6 (4.8) | 0 | 10 (1.5) |
| Urinary tract infection bacterial | 9 (3.0) | 3 (1.0) | 0 | 0 | 10 (1.5) |
| **Injury, Poisoning and Procedural Complications** | 3 (1.0) | 5 (1.7) | 3 (2.4) | 0 | 10 (1.5) |
| **Investigations** | 5 (1.7) | 7 (2.4) | 1 (0.8) | 3 (3.4) | 12 (1.8) |
| **Metabolism and Nutrition Disorders** | 18 (6.1) | 15 (5.2) | 10 (8.0) | 8 (9.0) | 51 (7.5) |
| Hyperglycaemia | 4 (1.4) | 1 (0.3) | 2 (1.6) | 2 (2.2) | 14 (2.1) |
| Decreased appetite | 5 (1.7) | 1 (0.3) | 1 (0.8) | 2 (2.2) | 10 (1.5) |
| Dehydration | 2 (0.7) | 4 (1.4) | 1 (0.8) | 2 (2.2) | 9 (1.3) |
| Hyponatraemia | 2 (0.7) | 3 (1.0) | 3 (2.4) | 1 (1.1) | 8 (1.2) |
| **Musculoskeletal and Connective Tissue Disorders** | 6 (2.0) | 6 (2.1) | 2 (1.6) | 2 (2.2) | 15 (2.2) |

| MedDRA (v23.0) SOC<br>Preferred term, n (%) | Study EV-301 | | Study EV-201 | | Enfortumab Vedotin 1.25 mg/kg† (n = 680) |
|---|---|---|---|---|---|
| | Enfortumab Vedotin (n = 296) | Chemotherapy (n = 291) | Cohort 1 Enfortumab Vedotin (n = 125) | Cohort 2 Enfortumab Vedotin (n = 89) | |
| **Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)** | 17 (5.7) | 9 (3.1) | 5 (4.0) | 4 (4.5) | 29 (4.3) |
| Malignant neoplasm progression | 12 (4.1) | 7 (2.4) | 0 | 0 | 12 (1.8) |
| **Nervous System Disorders** | 10 (3.4) | 4 (1.4) | 3 (2.4) | 3 (3.4) | 22 (3.2) |
| **Renal and Urinary Disorders** | 28 (9.5) | 15 (5.2) | 9 (7.2) | 11 (12.4) | 63 (9.3) |
| Acute kidney injury | 19 (6.4) | 7 (2.4) | 4 (3.2) | 9 (10.1) | 43 (6.3) |
| Haematuria | 5 (1.7) | 3 (1.0) | 3 (2.4) | 1 (1.1) | 13 (1.9) |
| **Respiratory, Thoracic and Mediastinal Disorders** | 10 (3.4) | 10 (3.4) | 9 (7.2) | 3 (3.4) | 36 (5.3) |
| Dyspnoea | 4 (1.4) | 3 (1.0) | 4 (3.2) | 0 | 13 (1.9) |
| Hypoxia | 0 | 0 | 3 (2.4) | 0 | 7 (1.0) |
| **Skin and Subcutaneous Tissue Disorders** | 14 (4.7) | 1 (0.3) | 4 (3.2) | 3 (3.4) | 25 (3.7) |
| **Vascular Disorders** | 2 (0.7) | 6 (2.1) | 5 (4.0) | 3 (3.4) | 14 (2.1) |

Number of subjects (n) and percentage of subjects (%) are shown.

Sorting order: alphabetical order by SOC and descending by the number of subjects of ' enfortumab vedotin 1.25 mg/kg' group by preferred term. In case of ties, alphabetical order by preferred term is applied.

ISS: integrated summary of safety.

† Enfortumab vedotin 1.25 mg/kg column includes all subjects in the following studies who received a 1.25 mg/kg dose of enfortumab vedotin: EV-101, EV-102, EV-201, and EV-301.

## *Laboratory findings*

### Haematology

See also section on Adverse events of interest/ anaemia and neutropenia.

The incidence of Low lymphocytes, Grade 3-4, was higher in the chemotherapy arm in study EV-301 (12.7%) compared to the enfortumab vedotin arm (9.3%) despite the target of the latter being the B-lymphocytes. In study EV-201/ Cohort 1 the corresponding incidence was comparable (9.8%) and for the entire 1.25 mg/kg group it was 12.3%.

**Table 102** Summary of Treatment-emergent Haematology Laboratory Abnormalities Reported for ≥ 10% (all grades) or ≥5% (grade 3 to 4) of patients (SAF)

| Preferred Term (MedDRA v23.0) | Overall Incidence, n (%) | |
|---|---|---|
| | Enfortumab Vedotin (N = 296) | Chemotherapy (N = 291) |
| Hemoglobin decreased | | |
| All Grades | 116/281 (41.3) | 137/268 (51.1) |
| Grades 3 to 4 | 5/281 (1.8) | 26/268 (9.7) |
| Lymphocytes decreased | | |
| All Grades | 130/281 (46.3) | 124/268 (46.3) |
| Grades 3 to 4 | 26/281 (9.3) | 34/268 (12.7) |
| Neutrophils decreased | | |
| All Grades | 68/281 (24.2) | 31/268 (11.6) |
| Grades 3 to 4 | 11/281 (3.9) | 4/268 (1.5) |
| Platelets decreased | | |
| All Grades | 61/279 (21.9) | 26/268 (9.7) |
| Grades 3 to 4 | 0 | 4/268 (1.5) |
| Leukocytes decreased | | |
| All Grades | 77/281 (27.4) | 43/268 (16.0) |
| Grades 3 to 4 | 10/281 (3.6) | 4/268 (1.5) |

*Table continued on next page*

NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; SAF: safety analysis set.
Laboratory abnormality results are defined based on subject's worst/highest post-baseline NCI-CTCAE grade for a laboratory parameter and that grade is higher than the subject's baseline grade.
For each laboratory parameter, the denominator is the number of subjects with a baseline and at least one post-baseline value.

### Clinical chemistry

For Hyperglycaemia see the Adverse events/ AESI section.

## *Safety in special populations*

### Intrinsic factors

### Age

**Table 103** Total TEAEs in different age groups

| MedDRA Version 23.0 Terms | Age < 65 y (n = 240) n (%) | Age ≥ 65 to < 75 y (n = 272) n (%) | Age ≥ 75 to < 85 y (n = 153) n (%) | Age ≥ 85 y (n = 15) n (%) |
|---|---|---|---|---|
| Total TEAEs | 239 (99.6) | 269 (98.9) | 150 (98.0) | 15 (100.0) |
| Serious TEAEs† – Total | 98 (40.8) | 123 (45.2) | 76 (49.7) | 9 (60.0) |
| Fatal | 10 (4.2) | 18 (6.6) | 16 (10.5) | 3 (20.0) |

*Table continued on next page*

| MedDRA Version 23.0 Terms | Age < 65 y (n = 240) n (%) | Age ≥ 65 to < 75 y (n = 272) n (%) | Age ≥ 75 to < 85 y (n = 153) n (%) | Age ≥ 85 y (n = 15) n (%) |
|---|---|---|---|---|
| Hospitalization/prolong existing hospitalization | 75 (31.3) | 83 (30.5) | 40 (26.1) | 2 (13.3) |
| Life-threatening | 6 (2.5) | 4 (1.5) | 4 (2.6) | 0 |
| Disability/incapacity | 1 (0.4) | 1 (0.4) | 1 (0.7) | 0 |
| Congenital anomaly | 0 | 0 | 0 | 0 |
| Other (medically significant) | 3 (1.3) | 9 (3.3) | 5 (3.3) | 0 |
| TEAE leading to permanent withdrawal of study drug | 38 (15.8) | 47 (17.3) | 36 (23.5) | 5 (33.3) |
| Psychiatric disorders | 54 (22.5) | 52 (19.1) | 38 (24.8) | 3 (20.0) |
| Nervous system disorders | 169 (70.4) | 191 (70.2) | 94 (61.4) | 10 (66.7) |
| Accidents and injuries‡ | 29 (12.1) | 31 (11.4) | 24 (15.7) | 1 (6.7) |
| Cardiac disorders | 21 (8.8) | 28 (10.3) | 24 (15.7) | 4 (26.7) |
| Vascular disorders | 38 (15.8) | 49 (18.0) | 36 (23.5) | 1 (6.7) |
| Cerebrovascular disorders§ | 0 | 1 (0.4) | 3 (2.0) | 0 |
| Infections and infestations | 116 (48.3) | 144 (52.9) | 79 (51.6) | 11 (73.3) |
| Anticholinergic syndrome¶ | 0 | 0 | 0 | 0 |
| Quality of life decreased¶ | 0 | 0 | 0 | 0 |
| Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures†† | 39 (16.3) | 45 (16.5) | 43 (28.1) | 3 (20.0) |
| Other TEAEs appearing more frequently in older subjects‡‡ | | | | |
| Decreased appetite | 100 (41.7) | 126 (46.3) | 68 (44.4) | 11 (73.3) |
| Alopecia | 124 (51.7) | 135 (49.6) | 64 (41.8) | 9 (60.0) |
| Fatigue | 107 (44.6) | 119 (43.8) | 83 (54.2) | 9 (60.0) |
| Diarrhoea | 89 (37.1) | 97 (35.7) | 62 (40.5) | 8 (53.3) |
| Pruritus | 78 (32.5) | 100 (36.8) | 41 (26.8) | 8 (53.3) |
| Anaemia | 54 (22.5) | 72 (26.5) | 47 (30.7) | 7 (46.7) |
| Peripheral sensory neuropathy | 91 (37.9) | 116 (42.6) | 50 (32.7) | 6 (40.0) |
| Weight decreased | 53 (22.1) | 64 (23.5) | 36 (23.5) | 6 (40.0) |
| Dysgeusia | 71 (29.6) | 88 (32.4) | 39 (25.5) | 5 (33.3) |
| Dyspnoea | 28 (11.7) | 32 (11.8) | 28 (18.3) | 5 (33.3) |
| Cough | 22 (9.2) | 42 (15.4) | 15 (9.8) | 5 (33.3) |
| Lacrimation increased | 29 (12.1) | 40 (14.7) | 15 (9.8) | 5 (33.3) |
| Nausea | 95 (39.6) | 96 (35.3) | 49 (32.0) | 5 (33.3) |
| Abdominal pain | 41 (17.1) | 45 (16.5) | 16 (10.5) | 4 (26.7) |
| Chills | 17 (7.1) | 18 (6.6) | 8 (5.2) | 4 (26.7) |
| Dehydration | 12 (5.0) | 16 (5.9) | 17 (11.1) | 4 (26.7) |
| Haematuria | 28 (11.7) | 32 (11.8) | 13 (8.5) | 4 (26.7) |
| Hyperglycaemia | 23 (9.6) | 40 (14.7) | 22 (14.4) | 4 (26.7) |
| Oedema peripheral | 32 (13.3) | 42 (15.4) | 27 (17.6) | 4 (26.7) |
| Vomiting | 59 (24.6) | 45 (16.5) | 17 (11.1) | 4 (26.7) |
| Acute kidney injury | 14 (5.8) | 17 (6.3) | 19 (12.4) | 3 (20.0) |
| Anxiety | 8 (3.3) | 6 (2.2) | 5 (3.3) | 3 (20.0) |
| Dizziness | 25 (10.4) | 23 (8.5) | 27 (17.6) | 3 (20.0) |

*Table continued on next page*

| MedDRA Version 23.0 Terms | Age < 65 y (n = 240) n (%) | Age ≥ 65 to < 75 y (n = 272) n (%) | Age ≥ 75 to < 85 y (n = 153) n (%) | Age ≥ 85 y (n = 15) n (%) |
|---|---|---|---|---|
| Pneumonia | 15 (6.3) | 19 (7.0) | 11 (7.2) | 3 (20.0) |
| Rhinorrhoea | 17 (7.1) | 20 (7.4) | 8 (5.2) | 3 (20.0) |
| Vision blurred | 16 (6.7) | 24 (8.8) | 20 (13.1) | 3 (20.0) |
| Abdominal distension | 4 (1.7) | 11 (4.0) | 9 (5.9) | 2 (13.3) |
| Abdominal pain upper | 8 (3.3) | 13 (4.8) | 2 (1.3) | 2 (13.3) |
| Angina pectoris | 0 | 0 | 1 (0.7) | 2 (13.3) |
| Aspartate aminotransferase increased | 37 (15.4) | 45 (16.5) | 20 (13.1) | 2 (13.3) |
| Asthenia | 20 (8.3) | 25 (9.2) | 19 (12.4) | 2 (13.3) |
| Atrial fibrillation | 1 (0.4) | 6 (2.2) | 7 (4.6) | 2 (13.3) |
| Back pain | 27 (11.3) | 28 (10.3) | 15 (9.8) | 2 (13.3) |
| Confusional state | 3 (1.3) | 6 (2.2) | 6 (3.9) | 2 (13.3) |
| Conjunctivitis allergic | 0 | 0 | 1 (0.7) | 2 (13.3) |
| Constipation | 52 (21.7) | 89 (32.7) | 36 (23.5) | 2 (13.3) |
| Dry eye | 31 (12.9) | 31 (11.4) | 23 (15.0) | 2 (13.3) |
| Dry mouth | 20 (8.3) | 27 (9.9) | 10 (6.5) | 2 (13.3) |
| Dry skin | 56 (23.3) | 58 (21.3) | 31 (20.3) | 2 (13.3) |
| Dysphonia | 9 (3.8) | 20 (7.4) | 8 (5.2) | 2 (13.3) |
| Erythema | 8 (3.3) | 13 (4.8) | 3 (2.0) | 2 (13.3) |
| Generalised oedema | 0 | 2 (0.7) | 2 (1.3) | 2 (13.3) |
| Hypocalcaemia | 5 (2.1) | 18 (6.6) | 6 (3.9) | 2 (13.3) |
| Hyponatraemia | 20 (8.3) | 24 (8.8) | 23 (15.0) | 2 (13.3) |
| Hypoxia | 5 (2.1) | 2 (0.7) | 4 (2.6) | 2 (13.3) |
| Myalgia | 23 (9.6) | 12 (4.4) | 9 (5.9) | 2 (13.3) |
| Nasal congestion | 12 (5.0) | 9 (3.3) | 6 (3.9) | 2 (13.3) |
| Neuropathy peripheral | 8 (3.3) | 11 (4.0) | 1 (0.7) | 2 (13.3) |
| Oral candidiasis | 8 (3.3) | 12 (4.4) | 8 (5.2) | 2 (13.3) |
| Pain | 5 (2.1) | 7 (2.6) | 3 (2.0) | 2 (13.3) |
| Pain in extremity | 20 (8.3) | 23 (8.5) | 16 (10.5) | 2 (13.3) |
| Peripheral motor neuropathy | 16 (6.7) | 15 (5.5) | 8 (5.2) | 2 (13.3) |
| Punctate keratitis | 5 (2.1) | 5 (1.8) | 5 (3.3) | 2 (13.3) |
| Pyrexia | 47 (19.6) | 51 (18.8) | 21 (13.7) | 2 (13.3) |
| Rash | 27 (11.3) | 33 (12.1) | 9 (5.9) | 2 (13.3) |
| Rash maculo-papular | 57 (23.8) | 61 (22.4) | 36 (23.5) | 2 (13.3) |
| Thrombocytopenia | 3 (1.3) | 9 (3.3) | 6 (3.9) | 2 (13.3) |
| Urinary incontinence | 4 (1.7) | 3 (1.1) | 4 (2.6) | 2 (13.3) |
| Urinary tract infection | 41 (17.1) | 36 (13.2) | 22 (14.4) | 2 (13.3) |

EV 1.25 mg/kg population: All subjects who received any amount of enfortumab vedotin at a starting dose of 1.25mg/kg in Studies ASG-22CE-13-2 (EV-101), 7465-CL-0101 (EV-102), SGN22E-001 (EV-201) and 7465-CL-0301 (EV-301), regardless of tumor type.

AE: adverse event; SAE: serious adverse event.

† Includes SAEs upgraded by the sponsor based on review of the Sponsor's list of Always Serious terms, if any upgrade was done. This upgrade was not applicable for Study EV-201; SAE type was not collected in Study EV-201.

Footnotes continue in the next page

‡ Accidents and injuries SMQ (narrow)

§ Haemorrhagic central nervous system vascular conditions SMQ (narrow) and Ischaemic central nervous system vascular conditions SMQ (narrow)

¶ No subject in EV 1.25 mg/kg population had TEAEs of anticholinergic syndrome (preferred term), quality of life decreased (preferred term) or impaired quality of life (preferred term).

†† Fractures high level grouped term and preferred terms of orthostatic hypotension, fall, loss of consciousness, syncope, dizziness, and ataxia.

‡‡ Shown are TEAEs occurring in ≥ 2 subjects in the 'age ≥ 85' group. Sorting order: descending by the number of subjects of 'age ≥ 85' by preferred term. In case of ties, alphabetical order by preferred term is applied.

Generally various AEs (by SOC and PT) were slightly higher in patients age 75-85 years compared to the younger cohorts. There were too few patients in the age group > 85 years to conclude anything meaningful.

**Gender**

The effect of **sex** on the safety of enfortumab vedotin was assessed across the safety analysis groups. Urothelial cancer is more prevalent in males, with approximately 75% of all new cases worldwide occurring in males and 25% in females.

**Ethnicity**

The two major **ethnicities** in the safety studies were White and Asian. Only seven patients in the safety population were Black or African American. No marked difference in safety was seen with regards to **race** (White vs non-White).

**BMI**

The incidences of various AEs (SAEs, death, ≥ grade 3 AEs, discontinuation) were higher in patients with a **BMI** ≥ 30 kg/m$^2$ in the enfortumab vedotin arm compared to the patients in the chemotherapy arm where the incidences were generally the same or lower in the ≥ 30 kg/m$^2$ population. A table comparing the overview of TEAEs and the TEAEs by SOC and PT between subjects with BMI ≥ 30 kg/m$^2$ and < 30 kg/m$^2$ treated by enfortumab vedotin using the 60 day updated safety data has been provided.

**Table 104** Overview of treatment-emergent Adverse events by baseline BMI category

| Safety Endpoint n (%) | All EV † (n = 749) | | EV 1.25 mg/kg ‡ (n = 680) | |
|---|---|---|---|---|
| | BMI ≥ 30 n = 129 | BMI < 30 n = 620 | BMI ≥ 30 n = 113 | BMI < 30 n = 567 |
| TEAE | 128 (99.2) | 612 (98.7) | 113 (100.0) | 560 (98.8) |
| Drug-related§ TEAE | 121 (93.8) | 580 (93.5) | 108 (95.6) | 531 (93.7) |
| Serious TEAE¶ | 73 (56.6) | 266 (42.9) | 66 (58.4) | 243 (42.9) |
| Drug-related§ serious TEAE¶ | 42 (32.6) | 100 (16.1) | 39 (34.5) | 93 (16.4) |
| TEAE leading to death | 16 (12.4) | 34 (5.5) | 15 (13.3) | 32 (5.6) |
| Drug-related§ TEAE leading to death | 9 (7) | 5 (0.8) | 9 (8) | 5 (0.9) |
| TEAE leading to permanent withdrawal of study drug | 40 (31.0) | 107 (17.3) | 34 (30.1) | 94 (16.6) |
| Drug-related§ TEAE leading to permanent withdrawal of study drug | 28 (21.7) | 67 (10.8) | 25 (22.1) | 61 (10.8) |
| TEAE leading to dose reduction | 45 (34.9) | 204 (32.9) | 45 (39.8) | 196 (34.6) |

*Table continued on next page*

| Safety Endpoint n (%) | All EV † (n = 749) | | EV 1.25 mg/kg ‡ (n = 680) | |
|---|---|---|---|---|
| | BMI ≥ 30 n = 129 | BMI < 30 n = 620 | BMI ≥ 30 n = 113 | BMI < 30 n = 567 |
| Drug-related§ TEAE leading to dose reduction | 43 (33.3) | 192 (31.0) | 43 (38.1) | 185 (32.6) |
| TEAE leading to dose interruption | 84 (65.1) | 371 (59.8) | 80 (70.8) | 350 (61.7) |
| Drug-related§ TEAE leading to dose interruption | 75 (58.1) | 288 (46.5) | 72 (63.7) | 277 (48.9) |
| TEAE with NCI-CTCAE ≥ Grade 3 | 101 (78.3) | 409 (66.0) | 89 (78.8) | 382 (67.4) |
| Drug-related§ TEAE with NCI-CTCAE ≥ Grade 3 | 74 (57.4) | 282 (45.5) | 67 (59.3) | 267 (47.1) |

BMI: body mass index (kg/m$^2$); EV: enfortumab vedotin; NCI-CTCAE: National Cancer Institute – Common Terminology Criteria for Adverse Events; TEAE: treatment-emergent adverse event.

† All EV population: all subjects who received any amount of enfortumab vedotin at any dose level in studies EV-101, EV-102, EV-201, AGS-22M6E-11-1, and EV-301, regardless of tumor type.

‡ EV 1.25 mg/kg population: All subjects who received any amount of enfortumab vedotin at a starting dose of 1.25 mg/kg in studies EV-101, EV-102, EV-201, and EV-301, regardless of tumor type.

§ A reasonable possibility that the event may have been caused by the study drug as assessed by the investigator. If relationship was missing, then it was considered as drug-related.

¶ Included serious TEAEs upgraded by the Sponsor based on review of the Sponsor's list of Always Serious terms, if any upgrade was done. This upgrade was not applicable for the EV-201 study.

BMI ≥ 30 kg/m$^2$ was identified as a risk factor for hyperglycemia events. Additional TEAEs by SOCs and PT occurred more frequently in enfortumab vedotin–treated subjects with BMI ≥ 30 kg/m$^2$ compared to < 30 kg/m2 in the EV 1.25 mg/kg population: Gastrointestinal disorders (+13.7%) of which nausea (+21.2%) and diarrhoea (+15.7%), Metabolism and nutrition disorders (+10.7%) of which hyperglycemia (+18.2%), hypokalaemia (+7.4%) and hyperuricaemia (+ 7.6%), Renal and urinary disorders (+10.4%) including acute kidney injury (+10.6%). However, the limited number of patients in the BMI ≥ 30 kg/m$^2$ group prevents any clear conclusion.

The higher incidence of hyperglycaemia in patients with a BMI ≥ 30 kg/m$^2$ in the EV-arm is described in the Adverse events/ AESI section.

**Hepatic and Renal function**

No difference in adverse events (SAEs, death, discontinuation) were observed between normal and mild hepatic function in the EV arm of study EV-301 compared to the chemotherapy arm.

In study EV-301, 45.9% of subjects in EV arm and 46.4% in the chemotherapy arm had a moderate **renal function** at baseline. The overall incidence of TEAEs (related, serious, discontinued, dose reduced, etc.) were comparable between arms.

In study EV-301, 30.4% of subjects in EV arm and 31.6% in the chemotherapy arm had a **liver metastasis** at baseline . Subjects with or without a liver metastasis at baseline had a similar overall incidence of TEAEs (related, serious, discontinued, dose reduced).

**ECOG status**

In Study EV-301, 61.5% of subjects in the enfortumab vedotin arm and 62.5% of subjects in the chemotherapy arm had an **ECOG performance status** of 1 at baseline; only 2 subjects (0.7%) in the enfortumab vedotin arm and no subjects in the chemotherapy had an ECOG performance status of 2 at baseline. The incidences of serious, discontinued, and dose reduced AEs were comparable between the two ECOG performance status' in each arm, which is not unexpected given they are both low ECOGs.

**Extrinsic factors**

TEAEs by Geographic Region: The incidence of the most common TEAEs occurring in ≥ 10% of subjects was similar across all geographical regions. Subjects in Study EV-301 had a similar overall incidence of TEAEs (serious, deaths, discontinued, dose reduced) regardless of the prior lines of therapy they received.

**Immunological events**
See section on Adverse events of Special Interest/ Antitherapeutic Antibodies.

**Safety related to drug-drug interactions and other interactions**
See pharmacokinetic section.

## *Discontinuation due to AES*

**Treatment discontinuation**
In the enfortumab vedotin arm of study EV-301 the most common TEAEs leading to treatment discontinuation in ≥ 1% of subjects by PT were peripheral sensory neuropathy, peripheral motor neuropathy, malignant neoplasm progression, rash maculo-papular, and acute kidney injury. All these events were considered drug related, except for malignant neoplasm progression and for acute kidney injury.

In the chemotherapy arm, the most common TEAE that led to treatment discontinuation occurring in ≥ 1% of subjects by PT were febrile neutropenia, general physical health deterioration, sepsis, malignant neoplasm progression, and peripheral sensory neuropathy All events were considered drug related, except for malignant neoplasm progression. The incidence of discontinuation was comparable between the arms in study 301 and to study 201/C1 (Table 110).

In Study EV-301, in the enfortumab vedotin arm, the most common adverse events that led to treatment discontinuation occurring in ≥ 1% of subjects by PT were peripheral neuropathy, rash maculo-papular, and acute kidney injury (Table 24/ SCS). All these events were considered drug related, except for acute kidney injury, where only 1 subject out of 3 had an event that was considered drug related. In the chemotherapy arm, the most common TEAE that led to treatment discontinuation occurring in ≥ 1% of subjects by PT were febrile neutropenia, general physical health deterioration, sepsis, and peripheral (sensory) neuropathy. All events were considered drug related.

**Table 105** Treatment-emergent Adverse Events Leading to Treatment Discontinuation (> 1 Subject in the Enfortumab Vedotin 1.25 mg/kg Group†) by SOC and Preferred Term (Safety Analysis Set)

| MedDRA (v23.0) SOC Preferred term, n (%) | Study EV-301 | | | | Study EV-201 | | | | Enfortumab Vedotin 1.25 mg/kg† (n = 680) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Enfortumab Vedotin (n = 296) | | Chemotherapy (n = 291) | | Cohort 1 Enfortumab Vedotin (n = 125) | | Cohort 2 Enfortumab Vedotin (n = 89) | | | |
| | All | Drug-related‡ | All | Drug-related‡ | All | Drug-related‡ | All | Drug-related‡ | All | Drug-related‡ |
| **Overall** | **51 (17.2)** | **40 (13.5)** | **51 (17.5)** | **33 (11.3)** | **21 (16.8)** | **15 (12.0)** | **18 (20.2)** | **14 (15.7)** | **126 (18.5)** | **84 (12.4)** |
| **Blood and Lymphatic System Disorders** | 2 (0.7) | 2 (0.7) | 8 (2.7) | 6 (2.1) | 0 | 0 | 0 | 0 | 2 (0.3) | 2 (0.3) |
| **Gastrointestinal Disorders** | 0 | 0 | 4 (1.4) | 4 (1.4) | 1 (0.8) | 1 (0.8) | 0 | 0 | 5 (0.7) | 1 (0.1) |
| **General Disorders and Administration Site Conditions** | 2 (0.7) | 2 (0.7) | 7 (2.4) | 4 (1.4) | 2 (1.6) | 2 (1.6) | 1 (1.1) | 1 (1.1) | 10 (1.5) | 7 (1.0) |
| Fatigue | 1 (0.3) | 1 (0.3) | 0 | 0 | 1 (0.8) | 1 (0.8) | 0 | 0 | 4 (0.6) | 3 (0.4) |
| Multiple organ dysfunction syndrome | 1 (0.3) | 1 (0.3) | 0 | 0 | 0 | 0 | 1 (1.1) | 1 (1.1) | 3 (0.4) | 3 (0.4) |
| **Hepatobiliary Disorders** | 2 (0.7) | 1 (0.3) | 1 (0.3) | 1 (0.3) | 0 | 0 | 0 | 0 | 2 (0.3) | 1 (0.1) |
| Hepatic function abnormal | 2 (0.7) | 1 (0.3) | 1 (0.3) | 1 (0.3) | 0 | 0 | 0 | 0 | 2 (0.3) | 1 (0.1) |
| **Infections and Infestations** | 6 (2.0) | 4 (1.4) | 7 (2.4) | 2 (0.7) | 1 (0.8) | 0 | 2 (2.2) | 0 | 11 (1.6) | 5 (0.7) |
| Pneumonia | 2 (0.7) | 1 (0.3) | 2 (0.7) | 1 (0.3) | 0 | 0 | 1 (1.1) | 0 | 3 (0.4) | 1 (0.1) |
| Sepsis | 0 | 0 | 3 (1.0) | 1 (0.3) | 1 (0.8) | 0 | 1 (1.1) | 0 | 3 (0.4) | 0 |
| **Investigations** | 1 (0.3) | 1 (0.3) | 2 (0.7) | 2 (0.7) | 0 | 0 | 3 (3.4) | 2 (2.2) | 8 (1.2) | 5 (0.7) |
| Aspartate aminotransferase increased | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 (0.3) | 1 (0.1) |
| Lipase increased | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.2) | 2 (2.2) | 2 (0.3) | 2 (0.3) |
| **Metabolism and Nutrition Disorders** | 6 (2.0) | 4 (1.4) | 3 (1.0) | 2 (0.7) | 1 (0.8) | 1 (0.8) | 1 (1.1) | 1 (1.1) | 11 (1.6) | 7 (1.0) |
| Hypercalcaemia | 1 (0.3) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 (0.4) | 0 |
| Hyperglycaemia | 2 (0.7) | 2 (0.7) | 0 | 0 | 1 (0.8) | 1 (0.8) | 0 | 0 | 3 (0.4) | 3 (0.4) |
| Metabolic acidosis | 1 (0.3) | 1 (0.3) | 0 | 0 | 0 | 0 | 1 (1.1) | 1 (1.1) | 2 (0.3) | 2 (0.3) |

| MedDRA (v23.0) SOC<br>Preferred term, n (%) | Study EV-301 | | | | Study EV-201 | | | | Enfortumab Vedotin 1.25 mg/kg† (n = 680) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Enfortumab Vedotin (n = 296) | | Chemotherapy (n = 291) | | Cohort 1 Enfortumab Vedotin (n = 125) | | Cohort 2 Enfortumab Vedotin (n = 89) | | | |
| | All | Drug-related‡ | All | Drug-related‡ | All | Drug-related‡ | All | Drug-related‡ | All | Drug-related‡ |
| **Musculoskeletal and Connective Tissue Disorders** | 1 (0.3) | 1 (0.3) | 2 (0.7) | 1 (0.3) | 0 | 0 | 1 (1.1) | 1 (1.1) | 2 (0.3) | 2 (0.3) |
| Muscular weakness | 1 (0.3) | 1 (0.3) | 0 | 0 | 0 | 0 | 1 (1.1) | 1 (1.1) | 2 (0.3) | 2 (0.3) |
| **Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)** | 5 (1.7) | 0 | 5 (1.7) | 1 (0.3) | 1 (0.8) | 0 | 0 | 0 | 6 (0.9) | 0 |
| Malignant neoplasm progression | 5 (1.7) | 0 | 3 (1.0) | 0 | 0 | 0 | 0 | 0 | 5 (0.7) | 0 |
| **Nervous System Disorders** | 17 (5.7) | 16 (5.4) | 8 (2.7) | 8 (2.7) | 9 (7.2) | 8 (6.4) | 5 (5.6) | 5 (5.6) | 37 (5.4) | 33 (4.9) |
| Peripheral sensory neuropathy | 7 (2.4) | 7 (2.4) | 6 (2.1) | 6 (2.1) | 9 (7.2) | 8 (6.4) | 4 (4.5) | 4 (4.5) | 25 (3.7) | 23 (3.4) |
| Peripheral motor neuropathy | 5 (1.7) | 5 (1.7) | 0 | 0 | 0 | 0 | 1 (1.1) | 1 (1.1) | 6 (0.9) | 6 (0.9) |
| Neuropathy peripheral | 2 (0.7) | 2 (0.7) | 0 | 0 | 0 | 0 | 0 | 0 | 2 (0.3) | 2 (0.3) |
| **Renal and Urinary Disorders** | 4 (1.4) | 2 (0.7) | 0 | 0 | 0 | 0 | 3 (3.4) | 2 (2.2) | 8 (1.2) | 5 (0.7) |
| Acute kidney injury | 3 (1.0) | 1 (0.3) | 0 | 0 | 0 | 0 | 3 (3.4) | 2 (2.2) | 6 (0.9) | 3 (0.4) |
| **Respiratory, Thoracic and Mediastinal Disorders** | 0 | 0 | 3 (1.0) | 2 (0.7) | 3 (2.4) | 1 (0.8) | 1 (1.1) | 1 (1.1) | 12 (1.8) | 4 (0.6) |
| Acute respiratory failure | 0 | 0 | 0 | 0 | 1 (0.8) | 0 | 0 | 0 | 2 (0.3) | 0 |
| Dyspnoea | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 (0.3) | 1 (0.1) |
| Interstitial lung disease | 0 | 0 | 1 (0.3) | 1 (0.3) | 1 (0.8) | 1 (0.8) | 0 | 0 | 2 (0.3) | 1 (0.1) |
| **Skin and Subcutaneous Tissue Disorders** | 12 (4.1) | 12 (4.1) | 1 (0.3) | 1 (0.3) | 2 (1.6) | 2 (1.6) | 1 (1.1) | 1 (1.1) | 18 (2.6) | 18 (2.6) |
| Rash maculo-papular | 4 (1.4) | 4 (1.4) | 0 | 0 | 0 | 0 | 0 | 0 | 5 (0.7) | 5 (0.7) |
| Dermatitis bullous | 2 (0.7) | 2 (0.7) | 0 | 0 | 0 | 0 | 1 (1.1) | 1 (1.1) | 4 (0.6) | 4 (0.6) |
| Drug eruption | 2 (0.7) | 2 (0.7) | 1 (0.3) | 1 (0.3) | 1 (0.8) | 1 (0.8) | 0 | 0 | 3 (0.4) | 3 (0.4) |
| Rash erythematous | 1 (0.3) | 1 (0.3) | 0 | 0 | 0 | 0 | 0 | 0 | 2 (0.3) | 2 (0.3) |

Number of subjects (n) and percentage of subjects (%) are shown. Events are sorted in alphabetical order by SOC and descending order by the number of subjects in the enfortumab vedotin 1.25 mg/kg group by preferred term. In case of ties, alphabetical order by preferred term is applied. ISS: integrated summary of safety.

† Enfortumab vedotin 1.25 mg/kg column includes all subjects in the following studies who received a 1.25 mg/kg dose of enfortumab vedotin: EV-101, EV-102, EV-201 and EV-301. ‡ Adverse events related to study drug as assessed by the investigator, or missing relationship were shown.

**Dose reduction due to TEAEs**

In the enfortumab vedotin arm of study EV-301the most common TEAEs that led to a **dose reduction** occurring in ≥ 2% of subjects by PT were peripheral neuropathy, rash maculo-papular, decreased appetite, fatigue, and neutrophil count decreased (Table 111) The majority of these events were considered drug related. In the chemotherapy arm, the most common TEAEs leading to a dose reduction occurring in ≥ 2% of subjects by PT were peripheral neuropathy, fatigue, neutrophil count decreased, neutropenia, constipation, and febrile neutropenia. The majority of these events were considered drug related.

**Table 106** Treatment-emergent Adverse Events Leading to Dose Reduction (> 1 Subject in the Enfortumab Vedotin 1.25 mg/kg Group†) by SOC and Preferred Term (Safety Analysis Set)

| MedDRA (v23.0) SOC Preferred term, n (%) | Study EV-301 | | | | Study EV-201 | | | | Enfortumab Vedotin 1.25 mg/kg† (n = 680) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Enfortumab Vedotin (n = 296) | | Chemotherapy (n = 291) | | Cohort 1 Enfortumab Vedotin (n = 125) | | Cohort 2 Enfortumab Vedotin (n = 89) | | | |
| | All | Drug-related‡ | All | Drug-related‡ | All | Drug-related‡ | All | Drug-related‡ | All | Drug-related‡ |
| **Overall** | **101 (34.1)** | **96 (32.4)** | **81 (27.8)** | **80 (27.5)** | **42 (33.6)** | **39 (31.2)** | **44 (49.4)** | **41 (46.1)** | **238 (35.0)** | **225 (33.1)** |
| **Blood and Lymphatic System Disorders** | 6 (2.0) | 6 (2.0) | 19 (6.5) | 18 (6.2) | 6 (4.8) | 6 (4.8) | 2 (2.2) | 1 (1.1) | 15 (2.2) | 14 (2.1) |
| Neutropenia | 5 (1.7) | 5 (1.7) | 7 (2.4) | 6 (2.1) | 4 (3.2) | 4 (3.2) | 0 | 0 | 9 (1.3) | 9 (1.3) |
| Anaemia | 0 | 0 | 2 (0.7) | 2 (0.7) | 1 (0.8) | 1 (0.8) | 2 (2.2) | 1 (1.1) | 4 (0.6) | 3 (0.4) |
| Thrombocytopenia | 1 (0.3) | 1 (0.3) | 2 (0.7) | 1 (0.3) | 1 (0.8) | 1 (0.8) | 0 | 0 | 2 (0.3) | 2 (0.3) |
| **Eye Disorders** | 1 (0.3) | 1 (0.3) | 1 (0.3) | 1 (0.3) | 0 | 0 | 1 (1.1) | 1 (1.1) | 3 (0.4) | 3 (0.4) |
| **Gastrointestinal Disorders** | 11 (3.7) | 11 (3.7) | 15 (5.2) | 14 (4.8) | 1 (0.8) | 1 (0.8) | 3 (3.4) | 3 (3.4) | 19 (2.8) | 19 (2.8) |
| Diarrhoea | 4 (1.4) | 4 (1.4) | 2 (0.7) | 2 (0.7) | 1 (0.8) | 1 (0.8) | 1 (1.1) | 1 (1.1) | 6 (0.9) | 6 (0.9) |
| Nausea | 2 (0.7) | 2 (0.7) | 2 (0.7) | 2 (0.7) | 0 | 0 | 2 (2.2) | 2 (2.2) | 6 (0.9) | 6 (0.9) |
| Abdominal pain | 2 (0.7) | 2 (0.7) | 1 (0.3) | 1 (0.3) | 0 | 0 | 0 | 0 | 3 (0.4) | 3 (0.4) |
| Vomiting | 3 (1.0) | 3 (1.0) | 1 (0.3) | 1 (0.3) | 0 | 0 | 0 | 0 | 3 (0.4) | 3 (0.4) |
| **General Disorders and Administration Site Conditions** | 12 (4.1) | 12 (4.1) | 22 (7.6) | 21 (7.2) | 7 (5.6) | 6 (4.8) | 6 (6.7) | 5 (5.6) | 39 (5.7) | 36 (5.3) |
| Fatigue | 8 (2.7) | 8 (2.7) | 12 (4.1) | 11 (3.8) | 6 (4.8) | 6 (4.8) | 5 (5.6) | 4 (4.5) | 31 (4.6) | 29 (4.3) |
| Mucosal inflammation | 2 (0.7) | 2 (0.7) | 1 (0.3) | 1 (0.3) | 0 | 0 | 0 | 0 | 3 (0.4) | 3 (0.4) |
| Asthenia | 1 (0.3) | 1 (0.3) | 5 (1.7) | 5 (1.7) | 0 | 0 | 1 (1.1) | 1 (1.1) | 2 (0.3) | 2 (0.3) |
| Oedema peripheral | 0 | 0 | 0 | 0 | 1 (0.8) | 0 | 0 | 0 | 2 (0.3) | 1 (0.1) |
| **Hepatobiliary Disorders** | 3 (1.0) | 3 (1.0) | 0 | 0 | 0 | 0 | 0 | 0 | 3 (0.4) | 3 (0.4) |
| **Infections and Infestations** | 2 (0.7) | 2 (0.7) | 2 (0.7) | 2 (0.7) | 1 (0.8) | 0 | 0 | 0 | 3 (0.4) | 2 (0.3) |

| MedDRA (v23.0) SOC<br>Preferred term, n (%) | Study EV-301 | | | | Study EV-201 | | | | Enfortumab Vedotin 1.25 mg/kg† (n = 680) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Enfortumab Vedotin (n = 296) | | Chemotherapy (n = 291) | | Cohort 1 Enfortumab Vedotin (n = 125) | | Cohort 2 Enfortumab Vedotin (n = 89) | | | |
| | All | Drug-related‡ | All | Drug-related‡ | All | Drug-related‡ | All | Drug-related‡ | All | Drug-related‡ |
| *Table continued on next page* | | | | | | | | | | |
| **Injury, Poisoning and Procedural Complications** | 3 (1.0) | 3 (1.0) | 0 | 0 | 0 | 0 | 0 | 0 | 4 (0.6) | 4 (0.6) |
| **Investigations** | 14 (4.7) | 13 (4.4) | 9 (3.1) | 9 (3.1) | 2 (1.6) | 2 (1.6) | 10 (11.2) | 10 (11.2) | 34 (5.0) | 32 (4.7) |
| Neutrophil count decreased | 6 (2.0) | 6 (2.0) | 8 (2.7) | 8 (2.7) | 0 | 0 | 2 (2.2) | 2 (2.2) | 8 (1.2) | 8 (1.2) |
| Weight decreased | 1 (0.3) | 1 (0.3) | 1 (0.3) | 1 (0.3)) | 0 | 0 | 2 (2.2) | 2 (2.2) | 6 (0.9) | 5 (0.7) |
| Alanine aminotransferase increased | 1 (0.3) | 1 (0.3) | 0 | 0 | 0 | 0 | 2 (2.2) | 2 (2.2) | 5 (0.7) | 5 (0.7) |
| Aspartate aminotransferase increased | 2 (0.7) | 2 (0.7) | 0 | 0 | 1 (0.8) | 1 (0.8) | 0 | 0 | 5 (0.7) | 5 (0.7) |
| Lipase increased | 3 (1.0) | 2 (0.7) | 0 | 0 | 1 (0.8) | 1 (0.8) | 1 (1.1) | 1 (1.1) | 5 (0.7) | 4 (0.6) |
| Gamma-glutamyltransferase increased | 1 (0.3) | 1 (0.3) | 0 | 0 | 0 | 0 | 0 | 0 | 2 (0.3) | 2 (0.3) |
| **Metabolism and Nutrition Disorders** | 14 (4.7) | 14 (4.7) | 3 (1.0) | 3 (1.0) | 3 (2.4) | 2 (1.6) | 3 (3.4) | 2 (2.2) | 21 (3.1) | 19 (2.8) |
| Decreased appetite | 10 (3.4) | 10 (3.4) | 3 (1.0) | 3 (1.0) | 1 (0.8) | 1 (0.8) | 2 (2.2) | 1 (1.1) | 14 (2.1) | 13 (1.9) |
| Hyperglycaemia | 2 (0.7) | 2 (0.7) | 0 | 0 | 0 | 0 | 1 (1.1) | 1 (1.1) | 3 (0.4) | 3 (0.4) |
| Hyperuricaemia | 0 | 0 | 0 | 0 | 2 (1.6) | 1 (0.8) | 0 | 0 | 2 (0.3) | 1 (0.1) |
| **Nervous System Disorders** | 32 (10.8) | 30 (10.1) | 24 (8.2) | 23 (7.9) | 17 (13.6) | 17 (13.6) | 17 (19.1) | 17 (19.1) | 89 (13.1) | 87 (12.8) |
| Peripheral sensory neuropathy | 22 (7.4) | 21 (7.1) | 18 (6.2) | 18 (6.2) | 13 (10.4) | 13 (10.4) | 15 (16.9) | 15 (16.9) | 68 (10.0) | 67 (9.9) |
| Peripheral motor neuropathy | 0 | 0 | 0 | 0 | 2 (1.6) | 2 (1.6) | 2 (2.2) | 2 (2.2) | 6 (0.9) | 6 (0.9) |
| *Table continued on next page* | | | | | | | | | | |
| Neuropathy peripheral | 6 (2.0) | 5 (1.7) | 2 (0.7) | 2 (0.7) | 0 | 0 | 0 | 0 | 6 (0.9) | 5 (0.7) |
| Dizziness | 1 (0.3) | 1 (0.3) | 0 | 0 | 0 | 0 | 0 | 0 | 2 (0.3) | 2 (0.3) |
| Hypoaesthesia | 0 | 0 | 1 (0.3) | 1 (0.3) | 1 (0.8) | 1 (0.8) | 0 | 0 | 2 (0.3) | 2 (0.3) |
| **Psychiatric Disorders** | 2 (0.7) | 2 (0.7) | 0 | 0 | 0 | 0 | 0 | 0 | 2 (0.3) | 2 (0.3) |
| **Renal and Urinary Disorders** | 2 (0.7) | 2 (0.7) | 0 | 0 | 0 | 0 | 2 (2.2) | 1 (1.1) | 4 (0.6) | 3 (0.4) |
| Acute kidney injury | 1 (0.3) | 1 (0.3) | 0 | 0 | 0 | 0 | 1 (1.1) | 1 (1.1) | 2 (0.3) | 2 (0.3) |
| **Skin and Subcutaneous Tissue Disorders** | 28 (9.5) | 27 (9.1) | 1 (0.3) | 0 | 9 (7.2) | 9 (7.2) | 10 (11.2) | 10 (11.2) | 56 (8.2) | 55 (8.1) |
| Rash maculo-papular | 13 (4.4) | 13 (4.4) | 0 | 0 | 2 (1.6) | 2 (1.6) | 6 (6.7) | 6 (6.7) | 24 (3.5) | 24 (3.5) |

| MedDRA (v23.0) SOC | Study EV-301 | | | | Study EV-201 | | | | Enfortumab Vedotin 1.25 mg/kg† (n = 680) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Enfortumab Vedotin (n = 296) | | Chemotherapy (n = 291) | | Cohort 1 Enfortumab Vedotin (n = 125) | | Cohort 2 Enfortumab Vedotin (n = 89) | | | |
| Preferred term, n (%) | All | Drug-related‡ | All | Drug-related‡ | All | Drug-related‡ | All | Drug-related‡ | All | Drug-related‡ |
| Rash erythematous | 1 (0.3) | 1 (0.3) | 0 | 0 | 2 (1.6) | 2 (1.6) | 2 (2.2) | 2 (2.2) | 7 (1.0) | 7 (1.0) |
| Pruritus | 4 (1.4) | 4 (1.4) | 0 | 0 | 1 (0.8) | 1 (0.8) | 0 | 0 | 5 (0.7) | 5 (0.7) |
| Drug eruption | 4 (1.4) | 4 (1.4) | 0 | 0 | 0 | 0 | 0 | 0 | 4 (0.6) | 4 (0.6) |
| Rash | 3 (1.0) | 2 (0.7) | 0 | 0 | 0 | 0 | 1 (1.1) | 1 (1.1) | 4 (0.6) | 3 (0.4) |
| Eczema | 1 (0.3) | 1 (0.3) | 0 | 0 | 0 | 0 | 0 | 0 | 3 (0.4) | 3 (0.4) |
| Rash vesicular | 1 (0.3) | 1 (0.3) | 0 | 0 | 1 (0.8) | 1 (0.8) | 0 | 0 | 2 (0.3) | 2 (0.3) |
| **Vascular Disorders** | 0 | 0 | 0 | 0 | 1 (0.8) | 1 (0.8) | 0 | 0 | 2 (0.3) | 2 (0.3) |
| Hypertension | 0 | 0 | 0 | 0 | 1 (0.8) | 1 (0.8) | 0 | 0 | 2 (0.3) | 2 (0.3) |

Number of subjects (n) and percentage of subjects (%) are shown.

Events are sorted in alphabetical order by SOC and descending order by the number of subjects in the enfortumab vedotin 1.25 mg/kg group by preferred term. In case of ties, alphabetical order by preferred term is applied.

ISS: integrated summary of safety.

† Enfortumab vedotin 1.25 mg/kg column includes all subjects in the following studies who received a 1.25 mg/kg dose of enfortumab vedotin: EV-101, EV-102, EV-201 and EV-301.

‡ Adverse events related to study drug as assessed by the investigator, or missing relationship

## *Post marketing experience*

Padcev has been approved on 18 Dec 2019 in the United States of America for the treatment of adult subjects with locally advanced or metastatic UC who have previously received a PD-1 or PD-L1 inhibitor, and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting.

From 18 Dec 2019 to 17 Mar 2020, 55 cases were revealed. A total of 147 AEs was contained in the 55 case reports received during the reporting period. Of these, 64 were serious and unexpected, 18 were serious and expected, 26 were nonserious and unexpected and 39 were nonserious and expected (Periodic Adverse Drug Experience Report Date, 07 Apr 2020). The unexpected postmarketing AEs and all postmarketing serious AEs including deaths have been provided and discussed by the applicant.

Events related to disease progression were the most frequently reported events in the postmarketing setting. Skin reactions including skin toxicity, SJS and TEN are listed in the most frequently reported unexpected postmarketing adverse events. Of the 8 cases of SJS, one recovered, 2 were fatal and the outcomes of the other cases were not reported. Of the 5 TEN, one was not recovered as of 15 June 2021, 2 cases were fatal and the other cases had a non-reported outcome.

There was a total of 11 cases of neutropenia reported in postmarketing setting. Based on an evaluation report, it is concluded that there is sufficient evidence that supports a causal association between the occurrence of Neutropenia events and enfortumab vedotin.

Based on the last quarterly periodic adverse experience report (PAER) an update of the United States Prescribing Information has been updated with a warning regarding skin reactions.

**Additional safety information:**

The CHMP had initially adopted an opinion on 16 December 2021 but during the decision-making process further safety information was brought to the attention of the CHMP. In view of the seriousness of the safety findings, on 24 January 2022 the European Commission returned the pending decision Opinion to the CHMP in order to allow the CHMP to assess the possible impact of the findings on the marketing authorisation application.

Ten serious cases of SCAR (severe cutaneous adverse reaction) among the 231 subjects from the EV-902 expanded access program have been reported to the sponsor drug safety database as of 10 Jan 2022. Five cases occurred in France, four of which were fatal. Of the remaining 5 serious cases, 3 occurred in Austria, 1 in Japan, and 1 in Switzerland. The case in Switzerland also reported a fatal outcome, bringing the total number of fatal cases of SCAR events from the EV-902 program to five**.**

The most frequent PTs reported amongst all the 10 cases were dermatitis bullous (4 events) and SJS (3 events), TEN (2 events), SDRIFE (symmetrical drug-related intertriginous and flexural exanthema; 1 event) and drug eruption (1 event). Three events of dermatitis bullous, 1 event of SDRIFE and 1 event of SJS were reported with fatal outcome. The cause of death in the remaining 1 subject was MODS (multiple organ dysfunction syndrome).

The MAH provided a Comprehensive Assessment Report (CAR) including available narrative for the fatal cases, possible correlation between the skin AE, systemic reactions and death and predisposition factors.

Based on the assessment of these serious and fatal events the followings changes to the SmPC, section 4.2 and 4.4 were recommended:

*Dose modifications*

**Table 2. Dose interruption, reduction and discontinuation in patients with locally advanced or metastatic urothelial cancer**

| Adverse reaction | Severity* | Dose modification* |
|---|---|---|
| **Skin reactions** | Suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) or Bbullous lesions | Immediately wWithhold and referral for to specialised care should be considered. |
| | Confirmed SJS or TEN; Grade 4 or recurrent Grade 3 | Permanently discontinue. |
| | Grade 2 worsening<br>Grade 2 with fever<br>Grade 3 | • Withhold until Grade ≤1<br>• ReferReferral to specialised care should be considered<br>• Resume at the same dose level or consider dose reduction by one dose level (see Table 1) |

Skin reactions

Skin reactions are associated with enfortumab vedotin as a result of enfortumab vedotin binding to Nectin-4 expressed in the skin. Fever or flu-like symptoms may be the first sign of a severe skin reaction, and patients should be observed, if this occurs.

Mild to moderate skin reactions, predominantly maculopapular rash, have been reported (see section 4.8). Severe cutaneous adverse reactions, including SJS and TEN, with fatal outcome have also occurred in patients treated with enfortumab vedotin, predominantly during the first cycle of treatment. In clinical trials, the median time to onset of severe skin reactions was 0.6 months (range: 0.1 to 6.4).

Patients should be monitored starting with the first cycle and throughout treatment for skin reactions. Appropriate treatment such as topical corticosteroids and antihistamines can be considered for mild to moderate skin reactions. For suspected SJS or TEN, or in case of bullous lesions onset, withhold treatment immediately and ~~consider~~ referr~~al for~~ to specialised care; histologic confirmation, including consideration of multiple biopsies, is critical to early recognition, as diagnosis and intervention can improve prognosis. Permanently discontinue Padcev for confirmed SJS or TEN, Grade 4 or recurrent severe skin reactions. For Grade -2 worsening, Grade -2 with ~~F~~fever or Grade -3 skin reactions, treatment should be withheld until Grade ≤1 and referral for specialised care should be considered. Treatment should be resumed at the same dose level or consider dose reduction by one dose level (see section 4.2).

Furthermore, the CHMP and PRAC consider appropriate the implementation of a Patient Card for each patient treated with Padcev – see the RMP section.

## 2.6.1. Discussion on clinical safety

The evaluation of the safety profile of enfortumab vedotin in the intended population, i.e. locally advanced or metastatic UC that had previously received therapy with a PD-1/PD-L1 inhibitor and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting, is based on a total of 680 subjects treated with enfortumab vedotin at the intended posology of 1.25 mg/kg and 291 subjects treated with chemotherapy. A total of 4 clinical studies are included in the safety data sets for the current application (pivotal Study EV-301, Study EV-201, Study -101 and Study EV-102). The safety evaluation mainly focussed on the phase 3 study EV-301 and the additional data from study 201/ Cohort 1, where the patient population was similar (prior PD-1/PD-L1 inhibitor and cisplatin-containing therapy). The number of patients in the phase 3 study (n=296 in the EV arm and n=291 in the chemo arm) supported by safety data from four SATs in patients (n=384) who received an EV dose of 1.25 mg/kg are considered sufficient to address all relatively frequent adverse events.

The median exposure to enfortumab vedotin in study EV-301 was 4.99 months and 4.60 months in study EV-201/ Cohort 1. Exposure to chemotherapy in study EV-301 was 3.45 months.

In the main safety population (Study 301 and 201/C1) only 31 patients received enfortumab vedotin for ≥ 1 year. With the requested safety update the number of patients increased to 54; no new patients were included. Long-term safety data are scarce and are thus considered as Missing information in the Summary of safety concerns. (See RMP)

In study EV-301 in the enfortumab vedotin arm, the most common TEAEs occurring in ≥ 20% of subjects by PT were alopecia, decreased appetite, fatigue, diarrhea, peripheral sensory neuropathy, pruritus, nausea, constipation, dysgeusia, and pyrexia.

In the chemotherapy arm, the most common TEAEs occurring in ≥ 20% of subjects by PT were alopecia, anemia, decreased appetite, fatigue, nausea, constipation, diarrhea, and peripheral sensory neuropathy.

Generally, the adverse events occurring with a higher incidence in the EV arm of study EV-301 (compared to the chemotherapy arm) seemed to occur with an even higher incidence in study EV-201/C1. This could be reasonably explained by the difference between the populations in the two studies, 17.6% patients with ≥ 3 prior systemic therapies in study Ev-301 vs 51.2% in the EV-201 study.

In the enfortumab vedotin arm, TEAEs with Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade 3 or 4 occurring in ≥ 5% of subjects by PT were anemia, fatigue, neutrophil count decreased, hyperglycemia, decreased appetite, and rash maculo-papular. In the chemotherapy arm, the most common TEAEs Grade 3 or 4 occurring in ≥ 5% of subjects by PT were neutrophil count decreased, anemia, neutropenia, white blood cell count decreased, and febrile neutropenia.

Of the drug-related TEAEs that occurred in ≥ 10% of subjects in either arm, the incidence of peripheral sensory neuropathy, dysgeusia, pruritis, rash, dry skin and rash maculo-papular was higher in the enfortumab vedotin arm.

**AEOIs** for enfortumab vedotin include skin reactions (severe cutaneous adverse reactions and rash), peripheral neuropathy, hyperglycemia, diarrhea, nausea, vomiting, dry eye, anemia, extravasation events, neutropenia, infusion-related reactions (other than extravasation events), corneal disorders, blurred vision, and ATAs.

Skin reactions are considered as on-target toxicity of enfortumab vedotin due to Nectin-4 expression in the skin. The incidence of all skin reactions and severe cutaneous adverse reactions in the EV arm in study EV-301 compared to the chemotherapy arm (53.7% / 26.0% vs 19.9% / 9.3%) was high. For resolution data references were made to data from study EV-201where 53.6% of subjects experienced skin reactions. The median time to resolution was 0.72 months (range 0.03 to 14.65) and the median time to improvement was 0.82 months (range 0.16 to 2.20). One patient experienced Stevens-Johnson syndrome (SJS) as assessed by two dermatologists but not according to one other dermatologist. On February 2021, the studies' sponsors informed of an important safety concern within enfortumab vedotin regarding severe cutaneous adverse reactions, including fatal cases of Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) that have occurred in patients treated with enfortumab vedotin in the post-marketing setting and during clinical trials. These cutaneous adverse reactions have occurred predominantly during the first cycle of treatment with enfortumab vedotin but may occur later. Recommendations regarding dose interruption, reduction, and discontinuation in case of skin reactions including suspected SJS and toxic epidermal necrolysis are included in the SmPC, section 4.2. A review of all serious cases of skin reactions in the post-marketing setting and during clinical trials was performed by the applicant. At this stage, no additional minimization measure than those planned in the RMP is requested for the risk of skin reactions. SmPC section 4.4 reflects that skin reactions are associated with enfortumab vedotin as a result of

enfortumab vedotin binding to Nectin 4 expressed in the skin. Mild to moderate skin reactions, predominantly maculopapular rash, have been reported. Severe cutaneous adverse reactions, including SJS and TEN, with fatal outcome have also occurred in patients treated with enfortumab vedotin, predominantly during the first cycle of treatment. In clinical trials, the median time to onset of severe skin reactions was 0.6 months (range: 0.1 to 6.4). Patients should be monitored starting with the first cycle and throughout treatment for skin reactions. Appropriate treatment such as topical corticosteroids and antihistamines can be considered for mild to moderate skin reactions. For suspected SJS or TEN, withhold treatment and consider referral for specialised care. As discussed above (section 2.6) several fatal cases were observed in compassionate use programs. This information was assessed by the CHMP after the initial opinion and the SmPC and RMP were updated before the re-adoption of the opinion in order to properly mitigate these ADRs in the clinical setting.

Overall, peripheral neuropathy occurred commonly in the enfortumab vedotin-treated subjects, mainly at low grades; few subjects experienced Grade 3 events and 1 subject experienced a Grade 4 event. Peripheral neuropathy (PN) has been identified as adverse event of interest since it is often associated with drugs that affect microtubules such as enfortumab vedotin and is associated with other MMAE ADCs. Peripheral neuropathy, event that was predominantly sensory in nature, was the most common adverse event overall leading to treatment discontinuation in the enfortumab vedotin safety population (4.8 % in study EV-301 EV arm compared to 2.1% in the chemo-arm and 7.2 % in study EV- 201/C1). Peripheral neuropathy can be quite debilitating. For study EV-201/C1, as of last follow-up, 15/70 subjects (21%) had resolution of all events and an additional 24 subjects (34%) had resolution or improvement in at least some events meaning that 55/125 patients still had some degree of neuropathy. The majority of subjects with ongoing PN at last follow-up had either Grade 1 (36/55 subjects; 66%) or Grade 2 (17/55 subjects; 31%) events. Recommendations regarding dose interruption, reduction, and discontinuation in case of peripheral neuropathy are included in the SmPC, section 4.2. The SmPC reflects that peripheral neuropathy, predominantly peripheral sensory neuropathy, has occurred with enfortumab vedotin, including Grade ≥3 reactions. Patients with pre-existing peripheral neuropathy Grade ≥2 were excluded from clinical trials. Patients should be monitored for symptoms of new or worsening peripheral neuropathy as these patients may require a delay, dose reduction or discontinuation of enfortumab vedotin.

Hyperglycaemia is a key adverse event of interest. The causal mechanism is unknown. In Study EV-301, 11.8% of subjects in the EV arm and 2.7% in the Chemo-arm had any hyperglycaemic event, with Grade 3-4 hyperglycaemia occurring in 21 patients (7.1%;) in the EV arm and in 2 patients (0.7%) in the chemotherapy arm. A fatal case due to hyperglycaemia occurred in the enfortumab vedotin arm. Data in particular from the randomised study EV-301 suggest that hyperglycaemia events were more common in subjects with a baseline BMI ≥ 30 kg/m$^2$(Table 98) and in patients with a prior medical history of hyperglycaemia (Ad-hoc Table 99), who were treated with enfortumab vedotin.

Hyperglycaemia events generally occurred approximately 15 days after initiation of enfortumab vedotin treatment based on the median time to onset of 0.57 months (range 0.1 to 20.3) based on 98 events in EV 1.25mg/kg group. In Study EV-201, the median time to resolution of hyperglycaemia was 0.95 months based on 27 events and the median time to improvement was 0.48 months based on 6 events. Most events resolved and subjects without preexisting hyperglycaemia or diabetes requiring treatment did not require ongoing anti-diabetic medications. Serious hyperglycaemia events occurred in 15/680 (2.2%) patients from enfortumab vedotin 1.25 mg/kg group and represents 15.3% (15/98) of the hyperglycaemia events reported. Recommendations on dose interruption in case of hyperglycaemia are listed in the SmPC section 4.2. In section 4.4 information regarding a higher risk of hyperglycaemia in patients with BMI ≥ 30 kg/m$^2$ is also stated.

In Study EV-301, 9.1% of subjects in the enfortumab vedotin arm and 5.8% of subjects in the chemotherapy arm experienced any infusion-related reactions. Information regarding the use of antihistamines, acetaminophen, and corticosteroids is given in section 4.4 in the SmPC.

In Study EV-301, the proportion of subjects who experienced any anemia and neutropenia event was higher in the chemotherapy arm (30.2%; 29.6%) compared with the enfortumab vedotin arm (19.9%; 18.2). Grade 3-4 neutropenia events were 8.5% in the chemotherapy arm vs 4.7% for the enfortumab vedotin arm. The incidence of subjects receiving colony stimulating factors was 7.1% in the enfortumab vedotin arm compared with 30.6% in the chemotherapy arm, which has to be considered when assessing the risk of neutropenia. Despite neutropenia being less frequent in the EV arm compared to the chemotherapy arm in study 301 (4.7% vs 7.6%), the incidence of infections (by SOC) was higher in the EV arm (16.9% vs 9.6%) underlining the added risk of infection in the EV-arm despite the higher incidence of neutropenia in the chemotherapy arm. Neutropenia, febrile neutropenia and neutrophil count decreased are listed as adverse reactions in section 4.8 of the SmPC.

The gastrointestinal toxicities of diarrhea, nausea and vomiting, are common events reported with the use of MMAE-ADCs, including enfortumab vedotin. In Study EV-301, the incidence of diarrhoea was higher in the enfortumab vedotin arm (34.8%; 3.4% Grade 3, none Grade 4) compared with the chemotherapy arm (22.7%; 1.7% Grade 3, none Grade 4). The incidence of vomiting was similar in both the treatment groups (14.2% in the enfortumab vedotin arm and 15.1% in the chemotherapy arm). In study 201/C1 the incidence of diarrhoea was 42.4% of which 4% were Grade 3 and none Grade 4.

In Study EV-301, the proportion of subjects who experienced any ocular disorder event was higher in the enfortumab vedotin arm (28%) compared with the chemotherapy arm (7.9%) and the majority of events were of Grade 1 or 2. Section 4.4 of the SmPC reflects that ocular disorders, predominantly dry eye, have occurred in patients treated with enfortumab vedotin and that patients should be monitored for ocular disorders.

During the SA in 2018 the CHMP advised that cardiac toxicity should be monitored carefully in EV-301 trial. The applicant monitored cardiac events with standard methods; ECG, AEs and vital signs monitoring and cardiac events as part of routine pharmacovigilance. Two patients with documented abnormal clinically significant ECGs had other more likely causes for this than EV.

The causes of death were mainly related to infections, organ dysfunction (including liver and kidney related AEs), and the AESI hyperglycaemia (including ketoacidosis). Going through the narratives of study 301/EV-arm all deaths not considered by the applicant as drug-related (except one) were in the setting of progressive disease.

Although the incidence of febrile neutropenia was higher in the chemotherapy arm, the SAE incidence of Infections and Infestations (SOC) was higher in the EV arm (17.6%) compared to the chemotherapy arm (11.7%).

The incidence of discontinuation was comparable between the arms in study 301 and to study 201/C1.

A safety summary for drug interactions is not available due to the low number of subjects taking CYP3A4 inhibitors (see SmPC 4.5). Patients receiving concomitant strong CYP3A4 inhibitors should be monitored more closely for signs of toxicities.

Safety in patients with moderate or severe hepatic impairment is unknown, which has been stated in the SPC.

Given the mechanism of action (microtubule-disrupting agent) a potential for carcinogenicity could be expected. As enfortumab vedotin is intended for the treatment of patients with late stage and advanced cancer the omission of carcinogenicity studies has been accepted.

## 2.6.2. Conclusions on the clinical safety

Several adverse events specifically related to enfortumab vedotin have been identified. The most concerning events are severe skin reactions including fatal cases, hyperglycaemia, and polyneuropathy. Gastrointestinal adverse events affecting QoL are also of importance. In conclusion, the safety profile of enfortumab vedotin is clinically manageable and do not give rise to major objections.

## *2.7. Risk Management Plan*

The MAH submitted an updated RMP version 0.5 with this application.

The PRAC considered that the risk management plan version 0.5 is acceptable.

The CHMP endorsed the Risk Management Plan version 0.5 with the following content:

### *Safety concerns*

**Table 107** Summary of the Safety Concerns

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | ● Skin reactions<br>● Hyperglycemia |
| Important potential risks | None |
| Missing information | ● Long-term safety |

### *Pharmacovigilance plan*

**Table 108 Ongoing and planned additional pharmacovigilance activities**

| **Study Status** | **Summary of objectives** | **Safety concerns addressed** | **Milestones** | **Due dates** |
|---|---|---|---|---|
| **Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization** | | | | |
| Not applicable | | | | |
| **Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances** | | | | |
| Not applicable | | | | |

| Study Status | Summary of objectives | Safety concerns addressed | Milestones | Due dates |
|---|---|---|---|---|
| **Category 3 - Required additional pharmacovigilance activities** | | | | |
| Final overall survival report based on the prespecified final number of events for the clinical trial EV-301, titled "An Open-label, Randomized Phase 3 Study to Evaluate Enfortumab Vedotin vs Chemotherapy in Subjects with Previously Treated Locally Advanced or Metastatic Urothelial Cancer." (Ongoing) | Updated exploratory overall survival analysis to provide additional data on the efficacy and safety of treatment with enfortumab vedotin in patients enrolled in EV-301. Analysis will also include data for patients who have received treatment with enfortumab for 1 year or more. | Long-term safety | Final report submission | 2Q2022 |
| A non-interventional post authorization safety study (NI-PASS) to evaluate effectiveness of the patient card (Planned) | To evaluate patients' understanding and awareness of the content of the patient card related to risks of skin reactions and patient behaviours to minimize the risk | Skin reactions | Protocol submission | 9 months after EU approval |

## *Risk minimisation measures*

**Table 109** Summary table of pharmacovigilance activities and risk minimization activities by safety concern.

| Safety concern | Risk minimization measures | Pharmacovigilance activities |
|---|---|---|
| Skin reactions | Routine risk communication:<br>• EU-SmPC sections 4.2, 4.4 and 4.8;<br>• PL sections 2 and 4<br><br>Routine risk minimization activities recommending specific clinical measures to address the risk:<br>• Recommendations are provided in the EU-SmPC Section 4.4 to monitor for severe skin reactions starting with the first cycle and throughout enfortumab vedotin treatment. Fever or flu-like symptoms may be the | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None<br><br>Additional pharmacovigilance activities:<br>• NI-PASS category 3 study to assess evaluation of patients' understanding and awareness of the content of the patient card related to risks of skin reactions and patient behaviours to minimize the risk. |

| | | |
|---|---|---|
| | first sign of a severe skin reaction, and patients should be observed, if this occurs.<br>- For Grade 2 worsening, Grade 2 with Fever or Grade 3 skin reactions, treatment should be withheld until Grade ≤1 and referral for specialized care should be considered. Treatment should be resumed at the same dose level or consider dose reduction by one dose level.<br>- For suspected SJS or TEN, or in case of bullous lesions onset, withhold treatment immediately and refer to specialised care; histologic confirmation, including consideration of multiple biopsies, is critical to early recognition, as diagnosis and intervention can improve prognosis.<br>- Permanently discontinue enfortumab vedotin for confirmed SJS or TEN, Grade 4 or recurrent severe skin reactions.<br>• Recommendations are provided in the EU-SmPC Section 4.2 for treatment interruption, dose reduction and treatment discontinuation of enfortumab vedotin.<br>Additional risk minimization measures:<br>• Patient card | |
| Hyperglycemia | Routine risk communication:<br>• EU-SmPC sections 4.2, 4.4 and 4.8<br>• PL section 2<br><br>Routine risk minimization activities recommending specific clinical measures to address the risk:<br>• Recommendations are provided in the EU-SmPC Section 4.4 to monitor blood glucose levels prior to dosing and periodically throughout the course of treatment as clinically indicated in patients with or at risk for diabetes mellitus or hyperglycaemia. If blood glucose is elevated >13.9 mmol/L (>250 mg/dL), enfortumab vedotin should be withheld until blood glucose is | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None<br><br>Additional pharmacovigilance activities:<br>• None |

| | | |
|---|---|---|
| | ≤13.9 mmol/L (≤250 mg/dL) and treat as appropriate.<br>• Recommendations are provided in EU-SmPC Section 4.2 for treatment interruption and when to resume treatment of enfortumab vedotin.<br><br>Additional risk minimization measures:<br>• None | |
| Long-term safety | Routine risk communication:<br>• EU-SmPC section 5.1<br><br>Routine risk minimization activities recommending specific clinical measures to address the risk:<br>• None<br><br>Additional risk minimization measures:<br>• None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None<br><br>Additional pharmacovigilance activities:<br>• Final overall survival report based on the prespecified final number of events for the clinical trial EV-301, a PASS category 3 study, titled "An Open-label, Randomized Phase 3 Study to Evaluate Enfortumab Vedotin vs Chemotherapy in Subjects with Previously Treated Locally Advanced or Metastatic Urothelial Cancer". |

PL: Package Leaflet; EU-SmPC: European Union-Summary of Product Characteristics; SJS: Stevens Johnson Syndrome; TEN: Toxic Epidermal Necrolysis.

### *Pharmacovigilance system*

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

### *Periodic Safety Update Reports submission requirements*

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 18.12.2019. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

## *2.8. New Active Substance*

The applicant declared that enfortumab vedotin has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers enfortumab vedotin to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

## *2.9. Product information*

### 2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

### 2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Padcev (enfortumab vedotin) is included in the additional monitoring list as it contains a new active substance.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

The approved indication for enfortumab vedotin is as monotherapy for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and a programmed death receptor 1 or programmed death ligand 1 inhibitor.

### 3.1.2. Available therapies and unmet medical need

There is not an established standard of care in the post-platinum post-immunotherapy (anti PD-1/PD-L1 immune checkpoint inhibitor) setting for patients with advanced urothelial cancer. Chemotherapy choices include taxanes and vinflunine, but historically only approximately 10% of patients respond after platinum-based chemotherapy, irrespective of whether they have received prior PD-1/PD-L1 inhibitors, creating a significant unmet medical need for these patients.

### 3.1.3. Main clinical studies

The main evidence of efficacy of enfortumab vedotin submitted comes from Study EV-301 (7465-CL-0301) a global, open-label, randomised phase III study in adult subjects with locally advanced or metastatic UC who had received a platinum-containing chemotherapy and had experienced disease progression or relapse during or following treatment with PD-1 or PD-L1 inhibitors. The primary endpoint was OS. Secondary endpoints include PFS, ORR, disease control rate (DCR), DOR, safety, tolerability, quality of life and patient-reported outcome parameters. The primary analysis of PFS, ORR, DCR and DOR was based on RECIST v1.1 as assessed by the investigator. Cross-over from chemotherapy to Enfortumab Vedotin was allowed after the results from the interim analysis were considered final (protocol V4).

## 3.2. Favourable effects

At data cutoff, after 49.5% of OS events, pivotal study EV-301 met its primary endpoint: OS in the EV arm shows statistical superiority over chemotherapy [HR for OS 0.70 (95% CI 0.56, 0.89), p-value 0.00142]. K-M estimates of median OS are 12.9 months in the EV arm and 9.0 in the chemotherapy arm. The OS benefit from EV vs. chemo remains across diverse sensitivity analyses –also accounting for the effect of cross-over– and most of the predefined subgroups. Updated data from the final analysis of OS (data cutoff 30-JUL-2021) with 73% of event maturity provided consistent results with HR remaining 0.70 (95% CI 0.58, 0.85).

The PFS benefit in the EV arm is consistent with OS results: At 71% of PFS events, HR for PFS1 was 0.62 (95% CI 0.51, 0.75), p-value <0.00001. K-M estimates of median PFS1 were 5.6 months in the EV arm and 3.7 in the chemotherapy arm.

Confirmed ORR rate was 41% in the EV arm and 18% in the chemo arm. K-M estimates of median DOR were numerically longer in the chemo arm (8.1 months) than the EV arm (7.4 months), but the 12-month landmark analyses of DOR suggest improved performance of EV (28% still on response) vs. chemo (20%).

Median PFS2 was numerically longer in the EV arm (9.6 months) as compared to the chemo arm (7.0 months).

## 3.3. Uncertainties and limitations about favourable effects

A survival advantage is not unequivocally established in the female subgroup (23% of ITT, HR for OS 1.17, 95% CI 0.72, 1.89), but since the pattern of worse survival for female patients with bladder cancer seems established and attributable to a multiplicity of factors (Donsky et al, 2013; Liu et al, 2015), clinical plausibility of the findings from EV-301 appears unlikely.

## 3.4. Unfavourable effects

The most common TEAEs occurring in ≥ 20% of subjects in the enfortumab vedotin arm were alopecia, decreased appetite, fatigue, diarrhea, peripheral sensory neuropathy, pruritus, nausea, constipation, dysgeusia, and pyrexia.

The incidence of all skin reactions and severe cutaneous adverse reactions in the EV arm in study EV-301 compared to the chemotherapy arm (53.7% / 26.0% vs 19.9% / 9.3%) was high.

Peripheral neuropathy occurred commonly in the enfortumab vedotin-treated subjects (50.3% in the EV-arm and 34.4% in the chemo-arm in study 301), mainly at low grades; few subjects experienced Grade 3 events and 1 subject experienced a Grade 4 event. Peripheral neuropathy events were predominantly sensory in nature. Peripheral neuropathy was the most common adverse event overall leading to treatment discontinuation in the enfortumab vedotin safety population (4.8 % in study 301 EV arm compared to 2.1% in the chemo-arm and 7.2 % in study 201/C1).

Hyperglycaemia is a key adverse event of interest. In Study EV-301, 11.8% of subjects in the EV arm and 2.7% in the Chemo-arm had any hyperglycaemic event, with Grade 3-4 hyperglycaemia occurring in 21 patients (7.1%;) in the EV arm and in 2 patients (0.7%) in the chemotherapy arm. A fatal case due to hyperglycaemia occurred in the enfortumab vedotin arm. Data in particular from the randomised study 301 suggested that hyperglycaemia events were more common in subjects with a baseline BMI ≥

30 kg/m2 and in patients with a prior medical history of hyperglycaemia who were treated with enfortumab vedotin.

## 3.5. Uncertainties and limitations about unfavourable effects

- Long-term safety data is scarce. In the updated main safety population (Study EV-301 and 201/C1) only 54 patients received enfortumab vedotin for ≥ 1 year. Long-term safety has been added to the Summary of Safety concerns as Missing information (see RMP).
- A safety summary for drug interactions is not available due to the low number of subjects taking CYP3A4 inhibitors (see SmPC 4.5). Patients receiving concomitant strong CYP3A4 inhibitors should be monitored more closely for signs of toxicities.
- Safety in patients with moderate or severe hepatic impairment is unknown, which has been stated in the SPC
- Given the mechanism of action (microtubule-disrupting agent) a potential for carcinogenicity could be expected. As enfortumab vedotin is intended for the treatment of patients with late stage and advanced cancer the omission of carcinogenicity studies has been accepted.

## 3.6. Effects Table

**Table 110** Effects Table for Padcev, urothelial cancer after two prior treatments including a PD-L1 / PD-1 inhibitor and a cisplatin-containing regimen (Study EV-301, data cut-off: 15-JUL-2020)

| Effect | Short Description | Unit | Treatment Padcev N=301 | Control Chemo[1] N=307 | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| OS | Median overall survival | Months (95% CI) | 12.9 (0.3, 23.4) | 9.0 (8.0, 10.7) | Stratified HR 0.702 (95% CI 0.56, 0.89), p-value 0.00142 | |
| PFS-INV | Median progression free survival by investigator | Months (95% CI) | 5.6 (5.3, 5.8) | 3.7 (3.5, 3.9) | Stratified HR 0.615 (95% CI 0.51, 0.75), p-value <0.00001 | |
| ORR-INV | Overall response rate by investigator | % (n) | 40.6 (117) | 17.9 (53) | Evaluated in response evaluable population (n=584), i.e. excluding patients without measurable disease | |
| **Unfavourable Effects:** | | **n (%)** | **Padcev N=296** | **Chemo[1] N=291** | | |
| Severe cutaneous reactions | All grades:<br>Grade 3-4: | | 77 (26.0)<br>16 (5.4) | 27 (9.3)<br>2 (0.7) | | |
| Hyper-glycaemia | All grades:<br>Grade 3:<br>Grade 4:<br>Grade 5: | | 35 (11.8)<br>19 (6.4)<br>1 (0.3)<br>1 (0.3) | 8 (2.7)<br>1 (0.3)<br>1 (0.3)<br>0 | BMI < 30 kg/m$^2$: 9.0% vs 2.9% (all grades)<br>BMI ≥ 30 kg/m$^2$: 29.3% vs 2.2% (all grades) | |

| Effect | Short Description | Unit | Treatment Padcev N=301 | Control Chemo[1] N=307 | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| Peripheral neuropathy[2] | All grades:<br>Grade 3* (sensory):<br>Grade 3* (motor[3]):<br>SAE:<br>Discont.: | | 149 (50.3)<br>9 (3.0)<br>5 (1.7)<br>6 (2.0)<br>14 (4.7) | 100 (34.4)<br>6 (2.1)<br>0<br>2 (0.7)<br>8 (2.7) | | |
| GI disorders:<br>Diarrhoea<br><br>Nausea | <br>All grades:<br>Grade 3*:<br>All grades:<br>Grade 3*: | | <br>103 (34.8)<br>10 (3.4)<br>89 (30.1)<br>3 (1.0) | <br>66 (22.7)<br>5 (1.7)<br>74 (25.4)<br>5 (1.7) | | |
| Ocular disorders (any) | All grades:<br>SAEs: | | 83 (28.0)<br>2 (0.7) | 23 (7.9)<br>0 | | |
| Neutropenia (AE) | Grade 3-4 | | 14 (4.7) | 22 (7.6) | G-csf use:<br>EV arm: 7.1%<br>Chemo arm: 30.6% | |
| Infections (SOC) | Grade 3-4: | | 50 (16.9) | 28 (9.6) | | |

Abbreviations: SCS: summary of clinical safety, Discont.: discontinuation, GI: gastrointestinal. INV:investigator
Notes: *No Grade 4
[1] Docetaxel 75 mg/m$^2$ or paclitaxel 175 mg/m$^2$ or vinflunine 320 mg/m2 on day 1 of a 21-day cycle.
[2] Mainly sensory.
[3] Muscular weakness and peripheral motor neuropathy.

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

Untreated locally advanced or metastatic urothelial cancer is associated with median survival time rarely exceeding 4-6 months. Once patients are beyond platinum and immunotherapy, treatment choices are scarce. Taxanes and vinflunine evoke modest response rates and are often used in the few patients who maintain an appropriate clinical status to consider further treatment. As such, this population was enrolled in the comparator arm of the phase III trial EV-301, designed after promising response rates from enfortumab vedotin (EV) in preceding phase I and II studies on akin patient populations. The open-label nature of the trial is understandable in view of the multiple treatment choices in the control arm, and hence the importance of prioritising survival as the primary endpoint, with all other investigator-assessed endpoints as secondary.

Results of the interim analysis –now considered final– outline a statistically significant and clinically relevant survival advantage of the experimental EV arm over the chemotherapy arm. This benefit is seen across the majority of secondary endpoints and remains consistent in diverse sensitivity analysis of OS and PFS. Importantly, median PFS2 is also numerically longer in the experimental arm, supporting the notion that the survival advantage is specifically increased with EV. Upon these results, as the last amendment to the protocol states, crossover to EV upon progression will be offered to the few patients still ongoing treatment in the chemotherapy arm.

Subgroup analysis of survival showed benefit from EV over chemotherapy across most subgroups, except for the female subpopulation, but since clinical plausibility for this effect is not evident, this issue was not further pursued. Albeit results from the initial analyses suggested that a survival advantage was not

apparent in low nectin-4 expressors, data from the final analysis of OS does not allow to conclude that efficacy is affected by nectin-4 expression in the biomarker-available population.

The overall toxicity profile of EV appears similar to chemotherapy, with the most common AEs being alopecia, decreased appetite, fatigue, diarrhoea, peripheral sensory neuropathy, pruritus, nausea, constipation, dysgeusia, and pyrexia. The main AEs of special interest were skin reactions, neuropathy, and hyperglycaemia.

### 3.7.2. Balance of benefits and risks

Considering the clinically relevant improvement in overall survival and the acceptable safety profile, it can be concluded that the benefits of treatment with EV outweigh its risks in the post-platinum post-immunotherapy treatment setting of advanced Urothelial Cancer.

### 3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

## Conclusions

The overall benefit/risk balance of Padcev (enfortumab vedotin) is positive subject to the conditions stated in section 'Recommendations'.

# 4. Recommendations

### *Outcome*

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Padcev is favourable in the following indication:

Padcev as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and a programmed death receptor-1 or programmed death-ligand 1 inhibitor.

### *Conditions or restrictions regarding supply and use*

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

### *Other conditions and requirements of the marketing authorisation*

**Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

## *Conditions or restrictions with regard to the safe and effective use of the medicinal product*

**Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**Additional risk minimization measures:**

Prior to use of Padcev in each Member State the MAH should agree the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH should ensure that in each Member State where Padcev is marketed, all healthcare professionals who are expected to prescribe Padcev are provided with the following materials:

<u>The patient information pack:</u>

- Patient information leaflet
- Patient card
    - Patient card:
        - Information for patients that Padcev treatment may cause skin reactions including severe skin reactions such as SJS, TEN or other severe rashes.
        - Description of the symptoms of skin reactions and to immediately seek medical care as these may be signs of a severe skin reaction.
        - A warning message for healthcare professionals treating the patient at any time, including in conditions of emergency, that the patient is using Padcev.
        - Contact details of the treating physician who has prescribed Padcev.
        - Needs to be carried all the time and presented to any healthcare professional.

The MAH should also provide a patient card in each pack of the medicinal product, the text of which is included in Annex III.

## *New Active Substance Status*

Based on the CHMP review of the available data, the CHMP considers that enfortumab vedotin is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.