25 July 2024
EMA/CHMP/310405/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Padcev

International non-proprietary name: Enfortumab vedotin

Procedure No. EMEA/H/C/005392/II/0013

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

2Q3W	2 doses every 3 weeks
3Q4W	3 doses every 4 weeks
ADC	antibody-drug conjugate
AE	adverse event
AEOSI	pembrolizumab adverse event(s) of special interest
AESI	enfortumab vedotin adverse event(s) of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATA	antitherapeutic antibody(ies)
AUC	area under the concentration curve
BICR	blinded independent central review
BMI	body mass index
BPI-SF	Brief Pain Inventory-Short Form
BSC	best supportive care
C_{avg}	model-predicted individual average exposures
$C_{avg,C3}$	average concentration up to 3 cycles
$C_{avg,hyperglycemia}$	average concentration to occurrence of hyperglycemia
$C_{avg,ORR}$	average concentration to time of event
C_{avgtoE}	average concentration up to time of event or end of treatment
CI	confidence interval
Combo	Combination
COVID-19	coronavirus disease 2019
CPS	combined positive score
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DOR	duration of response
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EOI	end of infusion
EORTC	European Organisation for Research and Treatment of Cancer
E/PY	events per patient-year
ER	exposure-response
EV	enfortumab vedotin
EV Mono	enfortumab vedotin monotherapy
HbA1c	hemoglobin A1c
HR	hazard ratio
H-score	histoscore
IARC	International Agency for Research on Cancer
IFNγ	interferon gamma
Ig	Immunoglobulin
IgG	immunoglobulin G
IHC	immunohistochemistry
IL	interleukin
ILD	interstitial lung disease

ISS	integrated summary of safety
ITT	intent-to-treat
IV	intravenous
LA/mUC	locally advanced or metastatic urothelial cancer
mAb	monoclonal antibody(ies)
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
MIBC	muscle invasive bladder cancer
MMAE	monomethyl auristatin E
NCI	National Cancer Institute
NE	not evaluable
Nectin-4	nectin cell adhesion molecule 4
ORR	objective response rate
OS	overall survival
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PFS	progression-free survival
PK	pharmacokinetic(s)
PN	peripheral neuropathy
PopPK	population pharmacokinetics
PRO	patient reported outcomes
PT	preferred term
PY	patient-year, the total duration of exposure in years
Q3W	every 3 weeks
Q6W	every 6 weeks
QOL	quality of life
RDI	relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
RSD	reference safety dataset
SAE	serious adverse event
SAP	statistical analysis plan
SAWP	Scientific Advice Working Party
SCAR	severe cutaneous adverse reaction
SmPC	Summary of Product Characteristics
SMQ	standard MedDRA query
TAb	total antibody (enfortumab vedotin)
TEAE	treatment-emergent adverse event
TNFα	tumor necrosis factor alpha
TTPP	time to pain progression
TTR	time to response
USPI	United States Prescribing Information

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Astellas Pharma Europe B.V. submitted to the European Medicines Agency on 9 January 2024 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include in combination with pembrolizumab, the first-line treatment of adult patients with locally advanced or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy for PADCEV, based on the final results from study KEYNOTE-A39/EV-302: "An open label, randomized, controlled phase 3 study of enfortumab vedotin in combination with pembrolizumab versus chemotherapy alone in previously untreated locally advanced (LA) or metastatic urothelial cancer (mUC)"; As a consequence, sections 4.1, 4.2, 4.4, 4.6, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.0 of the RMP has also been submitted. As part of the application the MAH is requesting a 1-year extension of the market protection.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision EMEA-002299-PIP01-17 (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 MAH 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.

Scientific advice

The MAH received Scientific advice from the CHMP on 17 October 2019 /EMEA/H/SA/4246/1/2019/II. The Scientific advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Aaron Sosa Mejia Co-Rapporteur: Alexandre Moreau

Timetable	Actual dates
Submission date	9 January 2024
Start of procedure:	27 January 2024
CHMP Rapporteur Assessment Report	22 March 2024
PRAC Rapporteur Assessment Report	27 March 2024
CHMP Co-Rapporteur Assessment	3 April 2024
PRAC Outcome	11 April 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	18 April 2024
Request for supplementary information (RSI)	25 April 2024
MAH's responses submitted to the CHMP on:	23 May 2024
CHMP Rapporteur Assessment Report	24 June 2024
PRAC Rapporteur Assessment Report	28 June 2024
Updated PRAC Rapporteur Assessment Report	28 June 2024
PRAC Outcome	11 July 2024
Updated CHMP Rapporteur Assessment Report	18 July 2024
Opinion	25 July 2024
The CHMP adopted a report significant clinical benefit for Padcev in comparison with existing therapies	25 July 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The Marketing Authorization Holder (MAH) applied for the therapeutic use of *Padcev, in combination with pembrolizumab for the first-line treatment of adult patients with locally advanced or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy.*

Epidemiology

Urothelial cancer (UC) encompasses carcinomas of both the lower urinary tract (bladder and urethra) and upper tract (ureter and renal pelvis), with disease that originates in the bladder accounting for 90% to 95% of all UC cases [Leow et al, 2020; Petros, 2020].

Based on yearly incidence rates, bladder cancer is currently the 10th most common cancer worldwide [Sung et al, 2021] and the fifth most common in Europe as of 2020 [Bladder cancer statistics | World Cancer Research Fund International (wcrf.org).

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.

Clinical presentation

Clinical presentation of UC ranges from superficial and localized to metastatic disease. Approximately 12% of patients have locally advanced or metastatic urothelial cancer (LA/mUC) at initial presentation [2020 Petros FG. Transl Androl Urol. 2020;9(4):1794-8]. Among patients whose disease is localized but muscle invasive at diagnosis, about half will ultimately progress to LA/mUC [Patel et al, 2020]. Unresectable LA/mUC is a serious and incurable condition with high mortality and poor long-term survival. Prognosis is especially poor for advanced stages, with less than 10% 5 years survival in Europe for metastatic disease [Ripoll et al, 2021; Andreassen et al, 2016; Marcos-Gragera et al, 2015] and 9.5% in Japan as of 2020 as described in the Cancer Information Service vital statistics. For patients who do not undergo treatment, median survival time rarely exceeds 3 to 6 months [Bellmunt et al, 2012].

Management

Established guidelines recommend the use of cisplatin or carboplatin in combination with gemcitabine or other anti-cancer agents for patients who receive first-line treatment for LA/mUC and can tolerate

these regimens [Koufopoulou et al, 2020]. Platinum-containing therapy may be followed by avelumab maintenance for a subset of patients who have not progressed following chemotherapy where approved [Jackson-Spence et al, 2022], including the US (as of Jun 2020) [BAVENCIO USPI], the EU (January 2021) [BAVENCIO EU SmPC] and Japan (February 2021). For patients who are not eligible for cisplatin-containing chemotherapy, checkpoint inhibitors such as pembrolizumab or atezolizumab can be considered, noting that in Europe, such indications are restricted based on tumoural PD-L1 expression (Keytruda | European Medicines Agency (europa.eu) Tecentriq | European Medicines Agency (europa.eu).

Chemotherapy and Chemotherapy Followed by Avelumab Maintenance

Of the available platinum-based regimens, cisplatin-containing therapy is the preferred option for those who can tolerate it and considered the established first-line standard of care for LA/mUC. When evaluated in clinical trials, cisplatin-containing therapy was associated with a median OS of 13 to 14 months [Bellmunt et al, 2012; von der Maase et al, 2005]. Although cisplatin-containing therapy yields longer median OS than what has been observed with carboplatin-based therapy in clinical trials (9 to 11 months) [Holmsten et al, 2020; De Santis et al, 2012] and the real-world setting (10.5 months) [Morgans et al, 2023], cisplatin is associated with cumulative toxicities leading to nephrotoxicity, neuropathy and ototoxicity, as well as acute gastrointestinal toxicity and myelosuppression [Kato et al, 2021; Chovanec et al, 2017; Barabas et al, 2008]. Consequently, since patients with LA/mUC are often of advanced age and have multiple comorbidities [Grivas et al, 2020; Kim et al, 2020; Galsky et al, 2018], approximately half are unable to tolerate cisplatin-containing therapy due to impaired renal function, poor performance status or other comorbidities such as heart failure, hearing loss or peripheral neuropathy [Bellmunt et al, 2016; Galsky et al, 2011; Dash et al, 2006]. In these patients, carboplatin plus gemcitabine is the standard of care first-line therapy, even though it is considered inferior to cisplatin. Importantly, carboplatin-based chemotherapy can still be challenging to tolerate in some patients [Kim et al, 2020; Galsky et al, 2011; Petrioli et al, 1996]. AEs reported with carboplatin-based regimens include thrombocytopenia with bleeding, anemia, leukopenia, neutropenia, febrile neutropenia, renal toxicity and mucositis [Holmsten et al, 2020; Park & Lee, 2020; Freshwater et al, 2019; Dogliotti et al, 2007; Linardou et al, 2004; Carles et al, 2000].

Maintenance therapy with avelumab is an option for a subset of patients who do not progress after first-line platinum-containing therapy where approved [Powles et al, 2020b]. A substantial proportion of patients comprising the broader LA/mUC population do not respond to treatment with platinum-containing therapy or have early progression and, therefore, do not meet criteria for receiving avelumab maintenance therapy [Galsky et al, 2022; Ozaki et al, 2022].

Frontline chemoimmunotherapy

Concurrent 1L immunotherapy plus chemotherapy combinations have demonstrated OS and PFS benefits compared with chemotherapy alone in several tumour types. For advanced urothelial cancer, results are mixed: at least two large phase III randomised trials have not met their predefined statistical boundaries for OS/PFS superiority over SOC cisplatin + gemcitabine (KEYNOTE-361, Powles et al, Lancet Oncol 2021; IMvigor130, Galsky et al, Lancet Oncol 2020), whereas CHECKMATE-901 did recently show statistically significant improvements in OS and PFS with the addition of nivolumab to SOC cisplatin + gemcitabine (van der Heijden N Engl J Med. 2023). However, nivolumab does not hold an indication in this setting yet (Opdivo SmPC).

Other Therapeutic Options

For patients who are not eligible for cisplatin-containing chemotherapy, monotherapy with an immune checkpoint inhibitor is used as first-line therapy. In the EU, where these agents are also used as first-line treatment [Puente et al, 2023], pembrolizumab is approved as monotherapy for the treatment of

LA/mUC for patients who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 with CPS ≥ 10 [KEYTRUDA EU SmPC], and atezolizumab is approved for patients who are considered cisplatin ineligible and whose tumors have a PD-L1 expression ≥ 5% [TECENTRIQ EU SmPC].

Unmet Medical Need

In Europe, the proportion of patients with LA/mUC who receive first-line therapy is 45% to 85%and many patients with advanced UC never receive first-line therapy [Morgans et al, 2023; Niegisch et al, 2023; Puente et al, 2023; Aly et al, 2019; Flannery et al, 2019; Galsky et al, 2018]. Overall median survival for patients who receive any type of first-line treatment is 10.8 to 14.5 months [Morgans et al, 2023; Geynisman et al, 2022; Flannery et al, 2019]. After receiving their initial therapy, < 50% of LA/mUC patients will receive second-line therapy, with mortality reported as a common reason that patients do not proceed to second-line therapy [Morgans et al, 2023].

The relatively short duration of survival associated with first-line therapy outlined above, combined with the finding that some patients never receive first-line therapy and many refuse or are unable to receive subsequent therapy, highlights the need for more effective and tolerable first-line treatment options. Very few recent advancements have improved outcomes for patients with LA/mUC. Furthermore, even with the currently available first line regimens, including avelumab maintenance, there remains a high unmet medical need for this disease.

2.1.2. About the product

Enfortumab Vedotin

Enfortumab vedotin (EV) is a Nectin-4 targeted antibody-drug conjugate (ADC) comprised of a fully human anti-Nectin 4 IgG1 kappa mAb conjugated to the small molecule microtubule disrupting agent, MMAE, via a protease cleavable maleimidocaproyl (MMAE) vc-linker. Enfortumab vedotin induces cytotoxicity in cancer cells by binding Nectin-4 target on the cell surface and forming an ADC-Nectin-4 complex. Nectin-4 is expressed in multiple cancers, particularly those of epithelial origin such as urothelial, breast, lung, pancreatic and ovarian cancers [Challita-Eid et al, 2016]. EV was approved in Europe (April 2022) for the treatment of locally advanced or metastatic urothelial cancer who had previously received a platinum-containing chemotherapy and a programmed death receptor 1 (PD-1) or programmed death ligand 1 (PD-L1) inhibitor.

Pembrolizumab

Pembrolizumab is a humanized monoclonal antibody (mAb) designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and, ultimately, immune rejection. In vitro and in vivo experiences have shown that PD-1 and PD-L1 blockade using an mAb can result in activation of antitumor T-cells and subsequent tumor regression. Pembrolizumab is approved in Europe (July 2015) for the treatment of multiple cancers.

2.1.3. The development programme

Rationale for the Enfortumab Vedotin and Pembrolizumab Combination

Preclinical data show enhanced antitumor activity when EV is combined with PD-1 inhibitors across multiple in vivo tumour models. EV has also demonstrated induction of immunogenic cell death of Nectin-4 positive tumours, an increase in inflammatory mediators and recruitment of innate

inflammatory cells to the tumour microenvironment consistent with the increased tumour immunogenicity demonstrated with other MMAE ADCs preclinically [Olson et al, 2022; Liu et al, 2020; Gardai et al, 2015].

In addition, preclinical studies demonstrated that EV-induced immunomodulatory effects may generate lasting antitumor immunity and enhanced antitumour activity when enfortumab vedotin is combined with a PD 1 inhibitor [Olson et al, 2022]. These findings suggest that for EV, and consistent with preclinical data with other ADCs that contain the same MMAE drug linker, enhanced antitumor activity may be achieved when used in combination with a PD-1 inhibitor due to complementary mechanisms of MMAE-induced cell cytotoxicity and induction of immunogenic cell death, plus the up-regulation of antitumor immune function by PD-1 inhibition [Olson et al, 2022; Diefenbach et al, 2016].

Based on the preclinical enhancement of antitumor activity and antitumor immunity, it was hypothesized that combining EV with pembrolizumab had the potential to improve clinical outcomes relative to either agent alone in patients with LA or mUC, providing support for clinical development of the combination.

EV is currently in clinical development globally for several solid tumour indications. Clinical development of pembrolizumab is likewise ongoing globally in numerous solid tumour indications.

The current submission seeks regulatory approvals for EV in combination with pembrolizumab for the first-line treatment of patients with LA/mUC based on data from the phase 3 Study EV-302. The clinical development program for the combination in LA/mUC includes the pivotal, phase 3, active-controlled study, EV 302, and a phase 1b/2 study, EV-103.

The EV 302 study is intended to support global regulatory approval of EV in combination with pembrolizumab for the treatment of patients with LA/mUC.

Ev is approved in Europe 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.

2.1.4. General comments on compliance with GCP

The Applicant claim that all clinical trials were conducted according to Good Clinical Practice as defined by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

2.2. Non-clinical aspects

2.2.1. Introduction

Enfortumab vedotin is already authorised as monotherapy for the treatment of patients with locally advanced or metastatic urothelial cancer (mUC), and a full package of pharmacology, pharmacokinetics and toxicology has already been assessed and accepted in support of the indication in the original MAA.

Five new pharmacology studies as well as an updated ERA were submitted in support of the new indication for the combined treatment with pembrolizumab. The studies submitted were: Study SGN-NC-000714, Study SGN-NC-000715, Study SGN-NC-000808 Study SGN-NC-000717 Study 7465-PH-0002 described below.

2.2.2. Pharmacology

Enfortumab vedotin (ASG-22CE, AGS-22C3E) is an ADC composed of a fully human IgG1 kappa antibody conjugated to the microtubule-disrupting agent MMAE via a protease-cleavable vc maleimidocaproyl linker [Challita-Eid et al, 2016].

In vitro and in vivo primary pharmacology studies were performed to evaluate the antitumor activity of enfortumab vedotin in combination with immune checkpoint inhibitors and the ability of enfortumab vedotin to elicit hallmarks of immunogenic cell death (ICD) and subsequent immunomodulatory effects that can enhance the antitumor activity of enfortumab vedotin when combined with immune checkpoint inhibitors.

Primary pharmacodynamic studies

In Vitro Primary Pharmacodynamics

Study SGN-NC-000714 ***Induction of Immunogenic Cell Death (ICD) by Enfortumab Vedotin***

In vitro experiments in human urothelial carcinoma models showed that enfortumab vedotin treatment of Nectin-4 expressing tumour cells elicited hallmarks of ICD, such as induction of the endoplasmic reticulum (ER) stress response, extracellular release of ATP and high mobility group protein B1 (HMGB1), and cell surface exposure of calreticulin. In addition, innate immune cells were activated when cocultured with enfortumab vedotin-treated dying cancer cells. These effects were mediated by the intracellular delivery of the MMAE payload by enfortumab vedotin since minimal immunomodulatory effects were observed after treatment with a nontargeting monoclonal antibody conjugated to MMAE or unconjugated Nectin-4-specific antibody.

In Vivo Primary Pharmacodynamics

Changes to Tumour Microenvironment Elicited by Enfortumab Vedotin

Study SGN-NC-000715: Enfortumab vedotin induced ICD and subsequent immune-related changes in the tumour microenvironment in a Nectin-4 expressing xenograft mouse model. Tumours treated with enfortumab vedotin showed upregulation of ICD-related gene signatures and increased levels of mouse proinflammatory mediators. Further IHC analysis indicated the recruitment of mouse innate immune cells, including macrophages and other APCs, to the tumour site (data not shown).

Study SGN-NC-000808***: Enfortumab Vedotin Treatment Results in Antitumor Immunity***

The ability of enfortumab vedotin-treated cells to drive antitumour immunity and protection against rechallenge, consistent with the induction of ICD, was tested in vivo. Mice were immunized with a single dose of human Nectin-4 expressing urothelial carcinoma cells induced to undergo cell death by pretreatment with enfortumab vedotin. Significantly decreased tumour volume and increased survival were observed after re-challenge with untreated human Nectin-4 expressing and parental tumour cells. The antitumour immunity to parental cells shows development of effective antitumour immunity against tumour-associated antigens consistent with the induction of ICD.

Study SGN-NC-000717 ***Enfortumab Vedotin Efficacy in Combination with anti-mPD-1 in Bladder Cancer Model***

Enfortumab vedotin showed enhanced antitumour activity when combined with the immune checkpoint inhibitor anti-mPD-1 in a syngeneic mouse bladder carcinoma model engineered to express human Nectin-4. Macrophage recruitment to the tumour site increased significantly with combination therapy compared to each monotherapy. The combination treatment also resulted in higher tumour growth inhibition and incidence of complete tumour regressions compared to either monotherapy. Finally, rechallenge of tumour-free survivors with parental tumour cells showed the development of durable antitumour immunity in animals dosed with enfortumab vedotin plus anti-mPD-1 (data not shown).

Study 7465-PH-0002 ***Enfortumab Vedotin Efficacy in Combination with anti-mPD-1 in Breast Cancer Model***

Enfortumab vedotin showed enhanced antitumour activity in combination with the immune checkpoint inhibitor anti-mPD-1 in a syngeneic mouse breast cancer model engineered to express human Nectin-4. The combination therapy resulted in higher tumour growth inhibition and incidence of complete tumour regressions compared to each monotherapy, consistent with the ability of enfortumab vedotin to induce immunomodulatory effects via ICD (data not shown).

2.2.3. Pharmacokinetics

No new PK studies were submitted, which is acceptable.

2.2.4. Toxicology

No new toxicology studies were submitted, which is acceptable.

2.2.5. Ecotoxicity/environmental risk assessment

The mode of action of enfortumab vedotin involves the internalization and subsequent breakdown of the antibody by the target cells and the release of the cytotoxic payload, monomethyl auristatin E (MMAE). Therefore, the primary substance available for excretion would be MMAE. The active ingredient is not amenable to the determination of log Kow according to standard guidelines. Instead a study investigating the partitioning behaviour of MMAE was performed. MMAE is an ionisable substance with a pKa of approximately 7.3 (estimated based on structure). The neutral form of MMAE will be the dominant species at pH 9, across the environmental relevant range of pH, ionized species of MMAE will be present. Therefore, the study technically determined log Dow values for MMAE.

PBT screening

The n-octanol/water distribution coefficient (log Dow) of MMAE was determined according to the OECD guideline number 107 "Shake-flask method" in accordance with the principals of GLP (Study number: 14171.6115).

Phase I $PEC_{surface\ water}$ calculation

The applicant conducted a phase I assessment estimating the PECsurfacewater for MMAE to 438 ng/L using the default values from the ERA guidance and a maximum dose of enfortumab vedotin of 1.25 mg·kg-1 bw and a bodyweight of 70 kg. This value is above the action limit of 10 ng/L. Therefore, the applicant refined the PEC by using prevalence data based on the highest prevalence for any EU Member State of 171.94 per 100,000 inhabitants (IARC GLOCOBAN 2020 database), correcting this

value for the assumption that 90% of these bladder cancer cases are urothelial cancer, thus estimating urothelial cancer prevalence is 154.7 per 100,000 inhabitants.

Table 1: 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 1.45 at pH 7 2.23 at pH 9	Potential PBT (N)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default	0.438	µg/L	> 0.01 threshold (Y)
PEC $_{surfacewater}$, refined (prevalence, treatment cycles)	0.00892	µg/L	> 0.01 threshold (N)

2.2.6. Discussion on non-clinical aspects

Five new in vitro and in vivo pharmacology studies were submitted in support of the new indication for combination therapy with an anti-PD-1 agent. The pharmacological mode of action of EV was confirmed as well as the effect of each component of the conjugated active substance containing the Nectin-4 targeting monoclonal antibody (mAb) component as well as the cytotoxic component, MMAE, which is the cytotoxic payload delivered to tumour cells by the targeting mAb. The antitumour effect of enfortumab vedotin in combination with an immune checkpoint inhibitor anti-mPD-1 showed enhanced effect in terms of higher tumour growth inhibition and incidence of complete tumour regressions compared to each monotherapy, consistent with the induction of immunogenic cell death.

In support of this variation, an updated ERA was submitted. Monomethyl auristatin E (MMAE) was identified as the compound of potential environmental concern, as the active substance enfortumab vedotin is expected to degrade due to being a monoclonal antibody. MMAE is an ionisable compound and the study data provided for determining logDow is acceptable. The determined log Dow values are below 4.5, thus a PBT assessment is not required. A refined PEC surfacewater value was determined as the default PEC surfacewater was above the trigger limit. Prevalence data in EU as well as treatment regime were used to refine the PEC surface water value. Using this refinement, PEC surface water is estimated at 8.92 ng/L, which is below the trigger limit of 10 ng/L. Therefore, a Phase II environmental risk assessment is not required.

The updated ERA submitted showed no risk for the environment in line with the assessment included in the original authorisation.

Section 5.3 of the SmPC was updated to reflect that no non-clinical testing has been performed with enfortumab vedotin in combination with pembrolizumab. This is accepted, and no further update of the non-clinical sections of the SmPC is considered warranted.

2.2.7. Conclusion on the non-clinical aspects

The submitted non-clinical data is considered sufficient to support the authorisation of enfortumab vedotin in combination with pembrolizumab for the treatment of patients with locally advanced or metastatic urothelial cancer (mUC).

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

- **Tabular overview of clinical studies**

Table 2: Population and Studies in the PopPK and Exposure-Response Analyses

Study Number (Phase)	Study Title	EV Treatments (e.g., dose groups, treatment)	Population and Number of Subjects	Pharmacokinetic Sampling Times	Bioanalytical Summary (ELISA for EV and LC/MS/MS for unconjugated MMAE)
EV-103 (Phase 1b/2)	A Phase 1b/2 Study of the Safety and Pharmacokinetics of Enfortumab Vedotin (ASG-22CE) as Monotherapy or in Combination with Other Anticancer Therapies for the Treatment of Urothelial Carcinoma	Dosed on days 1 and 8 of 21-day cycle at 1 to 1.25 mg/kg	199 subjects enrolled. 198 subjects had at least one detectable PK post-baseline; PK not available from 1 subject from Cohort K EV mono n = 10 (Escalation Cohorts, EV 1L cisplatin-ineligible or 2L) n = 40 (Cohort A: EV + Pembro 1L, cisplatin-ineligible) n = 148 (Cohort K: EV mono [n = 72] and EV + Pembro [n = 76] 1L, cisplatin-ineligible) Status: PK sample cut-off date: Nov 1, 2021 Efficacy data cut-off date: June 2022 Safety data cut-off date: March 2023	For EV: Cycles 1 and 2: Pre-dose, EOI and 2, 4, 24, 48, 72 hours post EOI for 1st dose; Pre-dose, EOI, 2, 4, 24, 48, 72 and 168 hours post EOI for the 2nd dose All other cycles: Pre-dose on Day 1 EOT: 30-37 days after last dose	Bioanalytical lab: PPD (for both EV and MMAE). LLOQ: 25 ng/mL for EV and 10 pg/mL for MMAE.
EV-302 (Phase 3)	An Open-Label, Randomized, Controlled Phase 3 Study of Enfortumab Vedotin in Combination with Pembrolizumab versus Chemotherapy Alone in Previously Untreated Locally Advanced or Metastatic Urothelial Cancer	Dosed on days 1 and 8 of 21-day cycle at 1.25 mg/kg	442 subjects randomized to receive EV + Pembro 1L (Arm A) 444 subjects randomized to receive gemcitabine + cisplatin or carboplatin (Arm B) 11 subjects randomized to EV+Pembro+Plat (Arm C) 3 subjects received EV + Pembro from Japan safety run-in cohort Status: PK sample cut-off date: Dec 2, 2022 Data cut-off date: Aug 8 2023	Cycles 1 and 2: Pre-dose and EOI Cycle 3 and every odd-numbered subsequent cycle: Pre-dose on day 1 EOT: 30-37 after last dose	Bioanalytical lab: PPD(for both EV and MMAE). LLOQ: 25 ng/mL for EV and 10 pg/mL for MMAE

2.3.2. Pharmacokinetics

Bioanalytical methods

Bioanalytical methods were not changed since the granting of the MA for Padcev. However, the three bioanalytical methods for ADC (Validation report Addendum 3), total antibody (Validation report

Addendum 3) and MMAE (Validation report Addendum 4) were successfully partially validated including long term stability in the presence of pembrolizumab.

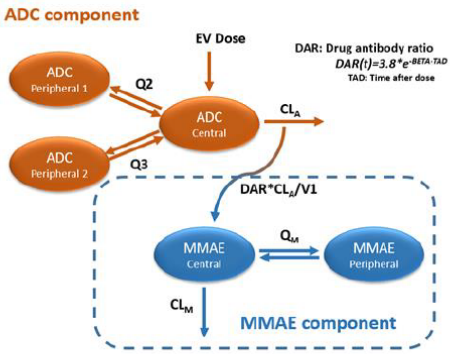
Pop PK modelling

Modeling was conducted using NONMEM 7.5.1 and FOCEI. R version 4.2.3 or later was used for pre- and post-processing. PsN version 5.3.0 or later was used to facilitate NONMEM runs and for pc-VPCs.

The PopPK analysis included data from studies EV-103 and EV-302 in subjects with urothelial cancer who received at least 1 dose of enfortumab vedotin and had at least 1 post-dose quantifiable sample. This population included 198 subjects in Study EV-103 (72 subjects received 1.25 mg/kg 2Q3W enfortumab vedotin monotherapy and 126 subjects received 1.0 or 1.25 mg/kg 2Q3W enfortumab vedotin in combination with pembrolizumab [EV + Pembro]) and 446 subjects in study EV-302 (432 subjects from Arm A and 3 subjects from Japan safety run-in cohort received 1.25 mg/kg 2Q3W EV + Pembro, and 11 subjects from Arm C received 1.25 mg/kg 2Q3W EV + Pembro + Plat). The final ADC model included 5400 PK samples from 642 subjects, and the final unconjugated MMAE model included 5447 PK samples from 639 subjects. Despite a weight-based dosing, increased ADC and unconjugated MMAE exposures were observed for subjects with higher body weight. For patients with body weight ≥ 100 kg, the dose was limited to 125 mg.

A previous Padcev PopPK model was developed on ADC and unconjugated MMAE concentrations from 748 subjects treated in 5 monotherapy clinical studies. In the Phase 2 and 3 studies EV-201 and EV-301, subjects received the approved 1.25 mg/kg 3Q4W dose regimen. The ADC concentration data was described by a linear 3-compartment model with first order elimination, while the unconjugated MMAE concentration data was described by a 2-compartment model with first-order elimination and a time varying conversion from enfortumab vedotin to unconjugated MMAE assumed to decay exponentially after each dose (Figure 1). Effect of bodyweight was incorporated by allometric scaling on disposition parameters.

Figure 1: PK Structural Models for ADC and Unconjugated MMAE

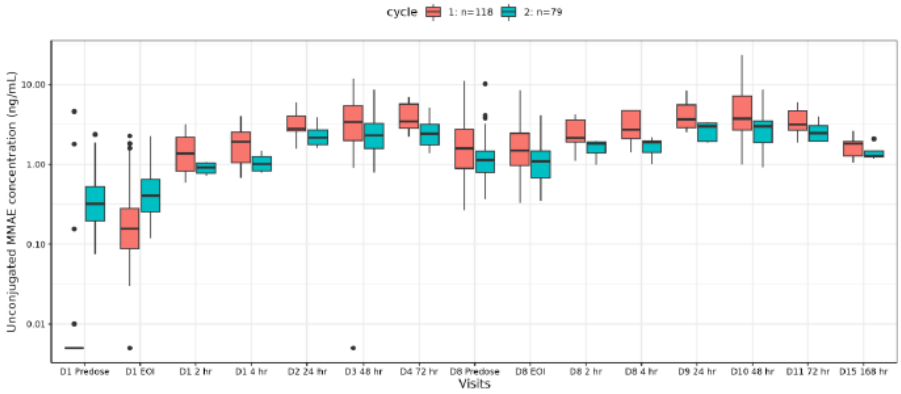


Abbreviations: ADC: antibody-drug conjugate; CL_A and CL_M: ADC and MMAE clearance; DAR: drug antibody ratio; EV: enfortumab vedotin; Q2, Q3, and Q_M: distribution clearances to compartments 2, 3, and the peripheral MMAE compartment; TAD time after dose; V1: ADC central volume of distribution.

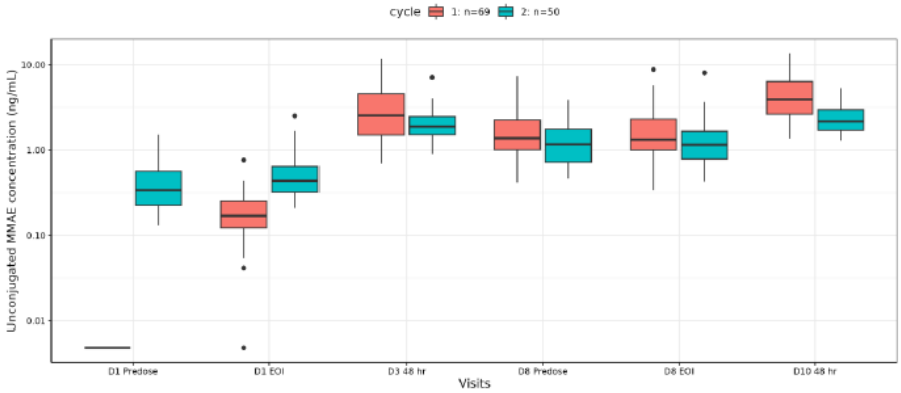
The concentration-time profiles of unconjugated MMAE, exhibited declining PK profiles over time despite continued dosing where the observed concentrations in Cycle 2 were lower than Cycle 1 from studies EV-103 and EV-302 (Figure 2). The estimated median decline in the formation rate of unconjugated MMAE was 31% at the end of Cycle 1 and 45% asymptotically.

Figure 2: Comparison of Observed Unconjugated MMAE Concentrations Between Cycle 1 and Cycle 2 for Subjects Receiving 1.25 mg/kg EV + Pembro (A) and Enfortumab Vedotin Monotherapy (B) in Study EV-103

A)



B)



Abbreviations: Dx: Day x; EOI: end of infusion; Pembro: pembrolizumab.
Notes: Boxes indicate the median (horizontal line) and interquartile range. Whiskers indicate the closest point within 1.5 times the interquartile range. Dots represent observations outside the whiskers. Samples post dose modifications were removed from analysis.
Source: exploratorypk_sbla.R

As a result, external validation using the previously developed PopPK model was performed only for ADC while the unconjugated MMAE model was further revised to characterize the time-varying trends. The time-dependent decrease in formation is described by the empirical term EMPIR:

$$\text{Formation} = k_{10} \times \text{DAR}(t) \times \exp(EMPIR(t)) \times A_1$$

$$\text{EMPIR(t)} = \text{TMAX} \cdot \text{t}/(\text{TC50} + \text{t})$$

EMPIR is characterized by T_{MAX} (maximal extent of reduction), TC50 (time to approximately 50% of the reduction), and t (time after first dose). At time t= 0, exp(EMPIR) equals 1. The estimated maximum extent of reduction is 45% (calculated as [1- exp(T_{MAX})]). Note that T_{MAX} includes intersubject variability. The final revised MMAE model included effects of weight, CrCL, ALB, and ECOG PS on CLM, and weight and ALB on VM. CrCL is a new covariate identified where unconjugated MMAE clearance was predicted to increase with increasing CrCL. Parameters of the final revised MMAE model is shown in Table 3 and GoF plots in Figure 3 and Figure 4.

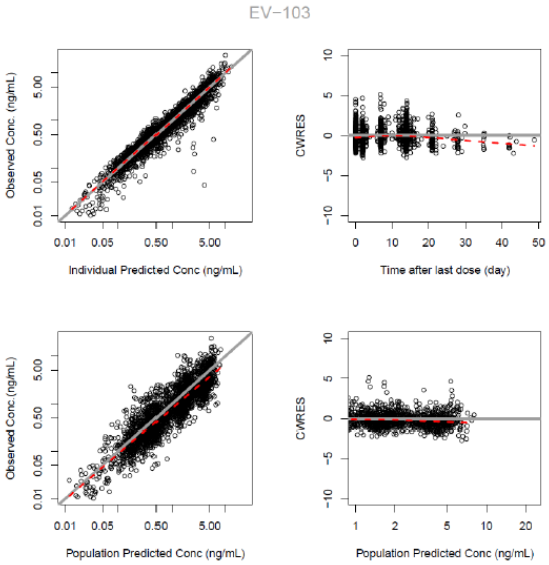
Table 3: Summary of Unconjugated MMAE Model Parameters

Parameter (Unit)	Base Model (run46.lst)		Final Model (run52.lst)		
	Estimate	RSE (%)	Estimate	RSE (%)	Shrinkage (%)
CL_M (L/hr)	2.01	5.46	2.24	3.85	-
V_M (L)	94.7	4.66	96.9	3.7	-
Q_M (L/hr)	6.5	50.2	6.78	15.1	-
V_{MP} (L)	43.3	17.4	44.1	12	-
DAR0 (unitless)	3.8 (fixed)	-	3.8 (fixed)	-	-
BETA (1/h)	0.000431	33.0	0.000432	21.7	-
TMAX (unitless)	-0.598	7.34	-0.6	6.94	-
TC50 (hr)	307	28.7	309	14.3	-
Covariate Effect					
$WTCL_M$	0.702	12.5	0.369	26.2	-
WTV_M	1 (fixed)	-	1 (fixed)	-	-
$CrCLCL_M$	-	-	0.228	25.3	-
$ALBCL_M$	-	-	1.16	15	-
ECOG PS CL_M	-	-	-0.143	27.7	-
$ALBV_M$	-	-	0.861	28.4	-
Inter-subject Variability					
ω^2 CL_M	0.249	7.42	0.205	7.65	8.6
ω^2 V_M	0.588	8.55	0.572	8.09	8.8
ω^2 TMAX	0.454	16.1	0.442	13.3	21.3
Residual					
σ^2 Proportional	0.312	2.68	0.313	2.54	12.0
σ^2 Additive	0.00914	30.9	0.00907	22.7	12.0

Abbreviations: ω: inter-subject variability standard deviation; σ: residual variability standard deviation; $ALBCL_M$: albumin effect on CL_M; $ALBV_M$: albumin effect on V_M; BETA: rate of decrease of DAR; CL_M: MMAE clearance; $CrCLCL_M$: creatinine clearance effect on CL_M; DAR0: drug-antibody-ratio at time 0; ECOG PS: Eastern Cooperative Oncology Group performance status; ECOG PS CL_M: ECOG effect on CL_M; Q_M: distribution clearance of MMAE; RSE: relative standard error; TC50: time to reach half-maximal decrease in MMAE formation over time; TMAX: maximum extent of decrease in MMAE formation over time; V_M: central volume of distribution of MMAE; V_{MP}: peripheral volume of distribution of MMAE; $WTCL_M$: weight effect on CL_M; WTV_M: weight effect on V_M.

Notes: Inter-subject variability is reported as variance (ω^2). RSE calculated as standard error/estimate x 100%. Shrinkage calculated as (1 – SD(ETA)/ω)×100% by NONMEM.

Figure 3: Goodness-of-Fit Plots of the Final Unconjugated MMAE Model for Study EV-103

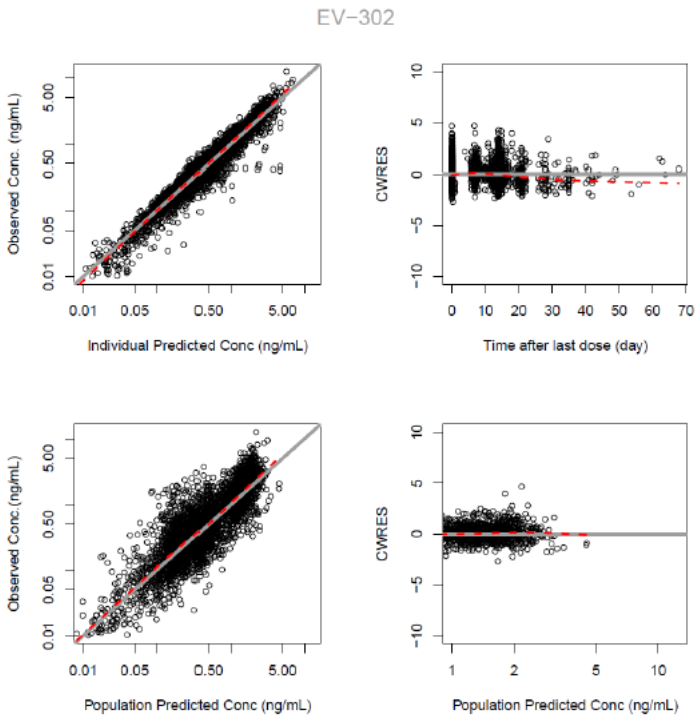


Abbreviations: conc: concentration; CWRES: conditional weighted residuals; PPK: population pharmacokinetics.

Notes: Solid gray line is line of unity. Red dashed line is a locally estimated scatterplot smoothing line.

Source: mmae.pk.model.r

Figure 4: Goodness-of-Fit Plots of the Final Unconjugated MMAE Model for Study EV-302

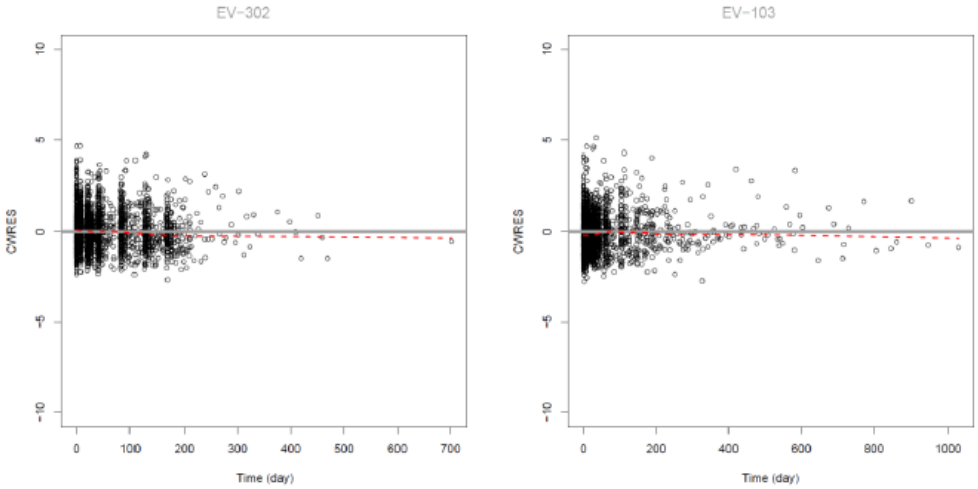


Abbreviations: conc: concentration; CWRES: conditional weighted residuals; PPK: population pharmacokinetics.

Notes: Solid gray line is line of unity. Red dashed line is a locally estimated scatterplot smoothing line.

Source: mmae.pk.model.r

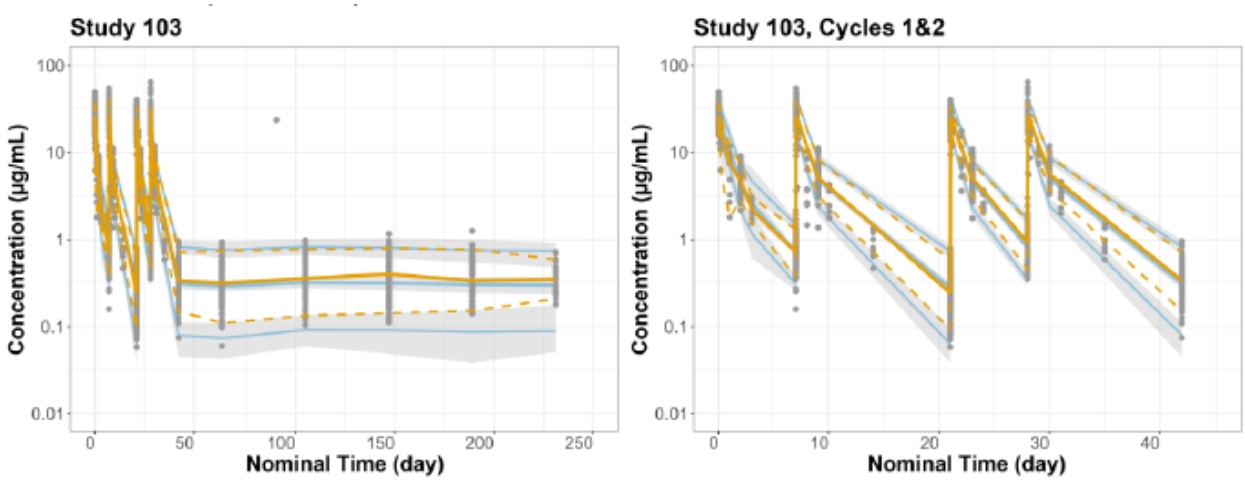
Figure 5: CWRES vs Time by Study for the Final Unconjugated MMAE Model



Abbreviations: CWRES: conditional weighted residuals.
Notes: Solid gray line is line of unity. Red dashed line is a locally estimated scatterplot smoothing line.
Source: mmae.pk.model.r

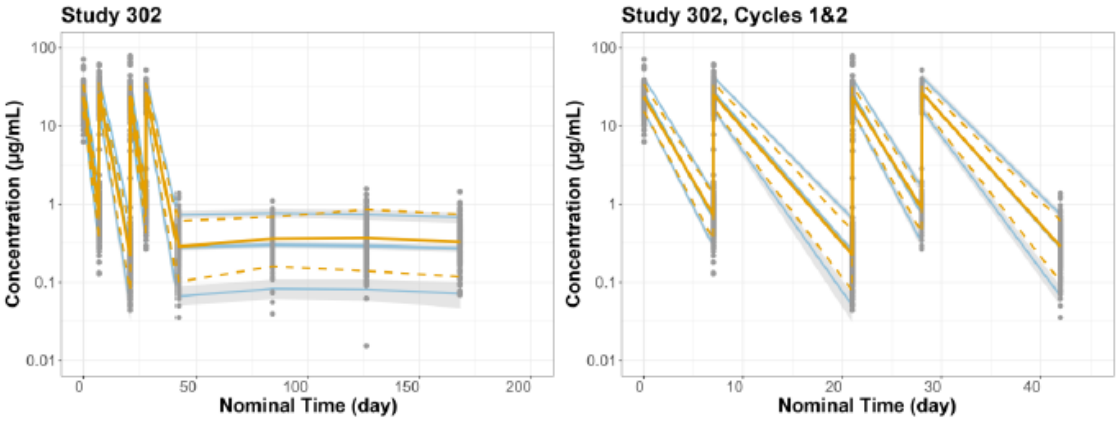
Precision corrected VPCs of ADC in study EV-103 and EV-302 fitted by external validation are shown in Figure 6 and Figure 7, while pc-VPCs of unconjugated MMAE fitted by the revised model are shown in Figure 8 and Figure 9.

Figure 6: pcVPC Plots of ADC in Study EV-103 Using the Previous PopPK Model (run21c.1st)



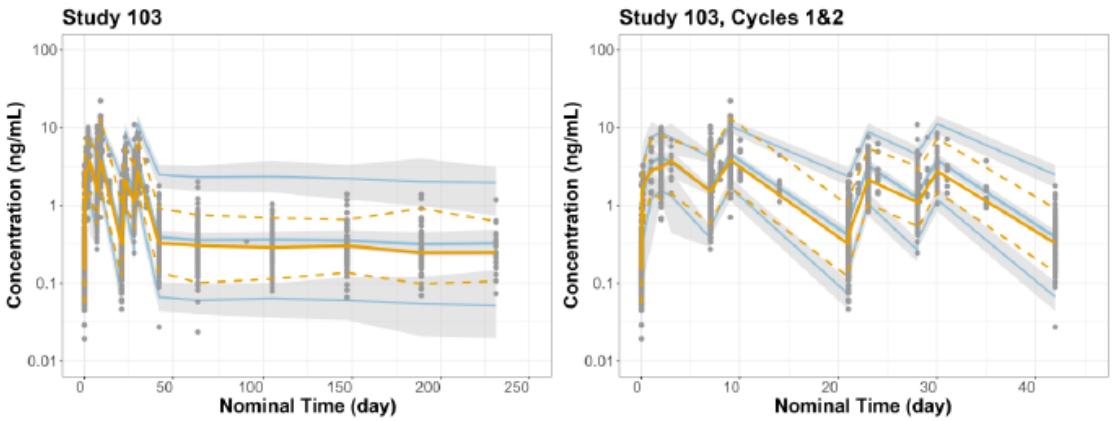
Abbreviations: pcVPC: prediction-corrected visual predictive check; PopPK: population pharmacokinetics.
Notes: Dots are prediction-corrected observed concentrations. Orange dashed lines are the 95th, 50th, and fifth percentiles of the observed data. Blue lines are the 95th, 50th and fifth percentiles of the simulations. The gray shaded region indicates the fifth to 95th percentile prediction interval.
Source: adc.pk.model.r

Figure 7: pcVPC Plots of ADC in Study EV-302 Using the Previous PopPK Model (run21c.1st)



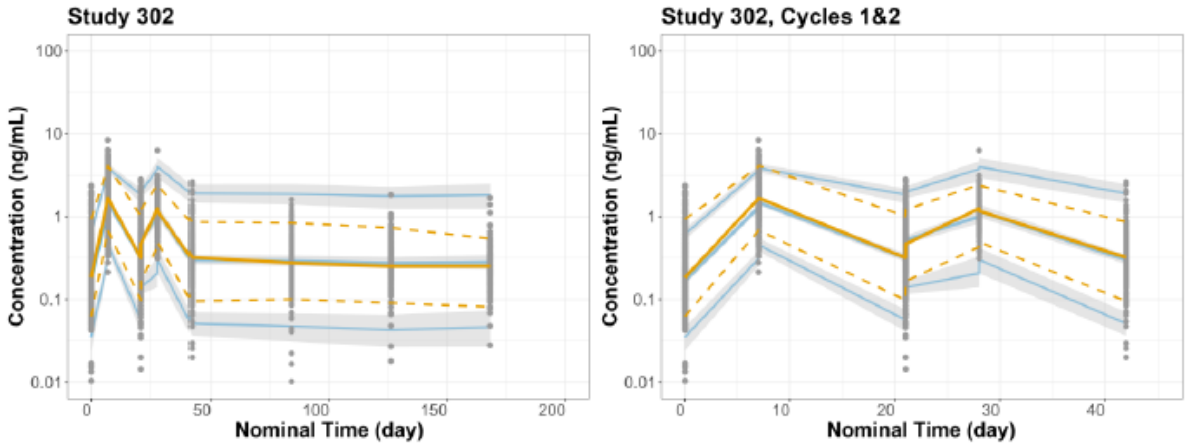
Abbreviations: pcVPC: prediction-corrected visual predictive check; PopPK: population pharmacokinetics.
Notes: Dots are prediction-corrected observed concentrations. Orange dashed lines are the 95th, 50th, and fifth percentiles of the observed data. Blue lines are the 95th, 50th and fifth percentiles of the simulations. The gray shaded region indicates the fifth to 95th percentile prediction interval.
Source: adc.pk.model.r

Figure 8: pcVPC Plots of of Unconjugated MMAE for Study EV-103



Abbreviations: pcVPC: prediction-corrected visual predictive check.
Notes: Dots are prediction-corrected observed concentrations. Orange dashed lines are the 95th, 50th, and fifth percentiles of the observed data. Blue lines are the 95th, 50th and fifth percentiles of the simulations. The gray shaded region indicates the fifth to 95th percentile prediction interval.
Source: mmae.pk.model.r

Figure 9: pcVPC Plots of Unconjugated MMAE for Study EV-302



Abbreviations: pcVPC: prediction-corrected visual predictive check.
Notes: Dots are prediction-corrected observed concentrations. Orange dashed lines are the 95th, 50th, and fifth percentiles of the observed data. Blue lines are the 95th, 50th and fifth percentiles of the simulations. The gray shaded region indicates the fifth to 95th percentile prediction interval.
Source: mmae.pk.model.r

An erratum was submitted to correct the population PK simulation results to include a dose cap of 125 mg for patients with body weight ≥100 kg (about 10%) in alignment with the dosing regimen utilized in studies EV-103 and EV-302. Table 4 and Table 5 shows the impact on simulated PK parameters and sensitivity analysis of other covariates.

Table 4: Comparisons of ADC and Unconjugated MMAE Cycle 1 PK Parameters for 1.25 mg/kg Enfortumab Vedotin from Original and Revised Simulation

Analyte	Parameter	Statistic	Study 103 (N=121) (Original)	Study 103 (N=121) (Revised)	Study 302 (N=427) (Original)	Study 302 (N=427) (Revised)
ADC	AUC (µg/mL×day)	Median [Min, Max]	73.4 [37.3, 123.8]	71.0 [37.3, 123.8]	70.5 [40.0, 202.7]	69.6 [40.0, 202.7]
		Mean (SD)	74.3 (16.1)	72.8 (15.6)	71.5 (14.6)	70.8 (14.1)
		GM (%GCV)	72.5 (22.7%)	71.1 (22.1%)	70.2 (19.5%)	69.6 (19.0%)
	C_{max} (µg/mL)	Median [Min, Max]	27.0 [16.1, 42.8]	26.9 [16.1, 42.8]	25.9 [16.1, 58.3]	25.6 [16.1, 57.7]
		Mean (SD)	27.5 (5.3)	27.0 (5.0)	26.5 (5.3)	26.2 (5.0)
		GM (%GCV)	27.0 (19.7%)	26.5 (19.0%)	26.0 (19.0%)	25.8 (18.3%)
	C_{trough} (µg/mL)	Median [Min, Max]	0.30 [0.07, 0.94]	0.30 [0.07, 0.89]	0.28 [0.04, 2.43]	0.28 [0.04, 2.43]
		Mean (SD)	0.33 (0.18)	0.32 (0.17)	0.31 (0.19)	0.31 (0.19)
		GM (%GCV)	0.3 (59.7%)	0.3 (60.2%)	0.3 (56.5%)	0.3 (56.1%)
	C_{avg} (µg/mL)	Median [Min, Max]	3.49 [1.78, 5.90]	3.38 [1.78, 5.90]	3.36 [1.91, 9.65]	3.31 [1.91, 9.65]
		Mean (SD)	3.54 (0.77)	3.47 (0.74)	3.41 (0.69)	3.37 (0.67)
		GM (%GCV)	3.5 (22.7%)	3.4 (22.1%)	3.3 (19.5%)	3.3 (19.0%)
	Half-life (day)	Median [Min, Max]	4.0 [2.7, 8.2]	4.0 [2.7, 8.2]	3.9 [2.5, 8.8]	3.9 [2.5, 8.8]
		Mean (SD)	4.1 (0.9)	4.1 (0.9)	4.1 (0.9)	4.1 (0.9)
		GM (%GCV)	4.0 (21.4%)	4.0 (21.4%)	4.0 (20.5%)	4.0 (20.5%)
MMAE	AUC (ng/mL×day)	Median [Min, Max]	52.6 [15.8, 148.3]	52.1 [15.8, 148.3]	53.7 [15.4, 197.3]	52.8 [15.4, 197.3]
		Mean (SD)	59.1 (30.3)	57.8 (29.4)	59.9 (26.1)	59.3 (25.6)
		GM (%GCV)	52.2 (53.9%)	51.1 (53.2%)	54.8 (44.1%)	54.3 (43.9%)
	C_{max} (ng/mL)	Median [Min, Max]	5.0 [1.5, 11.4]	4.9 [1.5, 11.4]	5.2 [1.7, 15.4]	5.1 [1.7, 14.7]
		Mean (SD)	5.3 (2.4)	5.2 (2.4)	5.7 (2.4)	5.6 (2.3)
		GM (%GCV)	4.8 (50.4%)	4.7 (49.8%)	5.2 (42.2%)	5.2 (42.0%)
	C_{trough} (ng/mL)	Median [Min, Max]	0.44 [0.09, 3.18]	0.44 [0.09, 3.18]	0.42 [0.06, 4.94]	0.42 [0.06, 4.94]
		Mean (SD)	0.64 (0.56)	0.63 (0.55)	0.57 (0.50)	0.57 (0.50)
		GM (%GCV)	0.5 (88.4%)	0.5 (87.4%)	0.4 (77.3%)	0.4 (77.0%)
	C_{avg} (ng/mL)	Median [Min, Max]	2.50 [0.75, 7.06]	2.48 [0.75, 7.06]	2.56 [0.74, 9.40]	2.51 [0.74, 9.40]
		Mean (SD)	2.81 (1.44)	2.75 (1.40)	2.85 (1.24)	2.82 (1.22)
		GM (%GCV)	2.5 (53.9%)	2.4 (53.2%)	2.6 (44.1%)	2.6 (43.9%)
	Half-life (day)	Median [Min, Max]	3.7 [2.5, 8.1]	3.7 [2.5, 8.1]	3.4 [2.2, 8.4]	3.4 [2.2, 8.4]
		Mean (SD)	3.7 (0.8)	3.7 (0.8)	3.6 (0.8)	3.6 (0.8)
		GM (%GCV)	3.7 (19.5%)	3.7 (19.5%)	3.5 (19.5%)	3.5 (19.5%)

Abbreviation: ADC: antibody drug conjugate; AUC: area under the curve; C_{avg}: average concentration; C_{max}: maximum concentration; C_{trough}: trough concentration; GCV: geometric coefficient of variation; GM: geometric mean; Max: maximum; Min: minimum; PK: pharmacokinetic; SD: standard deviation.

Notes: PK parameters computed using posthoc parameters of first-line subjects receiving combination therapy with the 1.25 mg/kg EV dose using 0-168 hour data in the first cycle.

Source: Original output corresponds to Table 8 in original report; revised output corresponds to Table 8 in erratum

Table 5: Comparisons of Summary of Clinical Implications of Covariates in the PopPK Model from Original and Revised Simulation

Covariate	Category	Reference Category	N	% Change in C1 ADC Exposure (Original)	% Change in C1 ADC Exposure (Revised)	% Change in C1 MMAE Exposure (Original)	% Change in C1 MMAE Exposure (Revised)
Age	<65 years	Overall	167	-3.4%	-3.5%	-7.2%	-7.3%
	65 to <75 years	Overall	242	0.1%	-0.2%	3.6%	3.3%
	>=75 years	Overall	139	4.0%	4.6%	2.8%	3.5%
Weight	<60 kg	Overall	94	-13.0%	-12.1%	-10.4%	-9.4%
	[60,80) kg	Overall	237	-3.5%	-2.4%	-3.0%	-1.9%
	[80,100) kg	Overall	162	8.4%	9.6%	6.8%	8.0%
	>=100 kg	Overall	55	16.8%	5.6%	13.2%	2.3%
Sex	Female	Male	127	2.9%	4.2%	-5.0%	-3.8%
Japan Country	Japan	Non-Japan	19	-8.8%	-7.7%	3.0%	4.2%
Korea Country	South Korea	Non-South Korea	30	-2.3%	-1.1%	-31.5%	-30.7%
Asian Race	Asian	Non-Asian	102	-5.1%	-3.8%	-13.5%	-12.3%
Tumor Size	[10,31]	Overall	141	5.0%	5.2%	-18.3%	-18.1%
	(31,49.5]	Overall	133	2.8%	2.5%	-2.1%	-2.3%
	(49.5,82.5]	Overall	136	-1.5%	-1.60	1.3%	1.2%
	(82.5,250]	Overall	137	-6.0%	-5.9%	24.1%	24.2%
ECOG PS	1	0	252	-4.9%	-4.6%	19.7%	20.2%
	2	0	31	-11.5%	-11.2%	32.6%	33.1%
Albumin	Hypoalbuminemia	Normal	87	-14.9%	-14.0%	31.8%	33.3%
	Severe Hypoalbuminemia	Normal	5	-22.4%	-21.4%	30.8%	32.5%
Cisplatin Eligible	Yes	No	230	0.8%	1.1%	-6.3%	-6.0%
Nectin-4 Expression	[0,280]	Below median	256	-0.3%	-0.2%	0.1%	0.2%

Exposure-response modelling

Exposure-response analysis was conducted using R version 4.2.2 or greater. Individual predicted ADC Cavg and MMAE Cavg were calculated using post-hoc PK parameter estimates from the final PopPK model as the average concentration up to the event or over the duration of exposure. Of note, the population PK derived exposures used for E-R was not corrected for the 125 mg dose cap for patients with body weight ≥100 kg. In the 1L EV + Pembro population, 55/548 subjects had body weight ≥100 kg (10.0%).

Efficacy models

The efficacy endpoints were ORR, OS and PFS. OS and PFS were only evaluated in the study population of EV-302 while ORR were evaluated in patients from both studies.

For EV-103, the primary analysis for ORR focused on the 1L subjects who received EV + pembro from dose escalation (N = 5), Cohort A (N = 40), and Cohort K (N = 76). In Cohort K (EV monotherapy), 72 subjects were analysed separately for comparison. In total, 6 subjects were excluded.

For EV-302, 442 subjects were enrolled in Arm A (EV + Pembro), while 10 subjects were excluded. For ORR additional 5 subjects were excluded. In Arm B (Plat + Gem), 444 subjects were enrolled while 11 subjects were excluded.

Table 6: Summary Statistics for Responses (Binary Endpoints and Time to Event Endpoints) and Exposures of Enfortumab Vedotin Evaluated in Exposure-response Analyses

Study	Endpoint	N	Event Rate Count (%)	Time to ORR (months) Median [Min, Max]	Selected ADC Exposure Metric	Exposure (µg/mL) Median [min, max] Mean (SD)
EV-103	Best Overall Response	121	82 (67.8%)	2.07 [1.15, 13.2]#	$C_{avg,ORR}$	3.23 [1.04, 5.69] 3.14 (0.97)
EV-302	Overall Survival	432	NE	NE	$C_{avg,C3}$	3.16 [0.945, 6.02] 3.10 (0.761)
	Progression Free Survival	432	NE	NE		
	Best Overall Response	427	294 (68.9%)	2.10 [1.31, 12.2]#	$C_{avg,ORR}$	3.05 [0.722, 5.96] 3.05 (0.79)

Abbreviations: ADC: antibody drug conjugate; $C_{avg,C3}$: average concentration up to end of Cycle 3; $C_{avg,ORR}$: average concentration to ORR; CI: confidence interval; max: maximum; min: minimum; N: number of subjects; NE: not evaluated; ORR: objective response rate; SD: standard deviation.

Notes: #Time to event for 82 subjects in Study EV-103 and 294 subjects in Study EV-302 who experienced ORR.

Source: SGN-075-EVP-PKER-103-302-datasum.r, SGN-075-EVP-PKER-103-302-EE.r.

For ORR, Cavg was evaluated to time of event. In previous monotherapy studies, an inverse relationship between average unconjugated MMAE exposure quartiles and ORR was statistically significant ($p < 0.05$). Improvement of disease may have resulted in slower proteolytical degradation of ADC resulting in slower formation of unconjugated MMAE. Exposure-ORR was evaluated by exploratory barplots and not further discussed here.

For PFS and OS, Cavg decreased with longer treatment duration due to dose modifications (lower dose intensity). Therefore, Cavg,C3 was adopted as the exposure metric for exposure-response analysis of PFS and OS. For time-to-event endpoints (OS, PFS), a Cox proportional hazards exposure-response model was tested if initial Kaplan-Meier curves indicated a positive correlation to exposure.

For PFS, the Kaplan-Meier plot of Cavg,C3 and PFS showed improved median PFS for all quartiles when compared to the chemotherapy arm, while univariate Cox regression analysis did not identify a significant effect of EV Cavg,C3 on PFS event times ($p > 0.05$).

For OS, exploratory graphical evaluation showed a trend between increasing enfortumab vedotin Cavg,C3 and OS event times in Study EV-302. Univariate Cox regression analysis identified a significant effect of EV Cavg,C3 on OS event times ($p = 0.004$). The hazard for OS was increased 30% with a unit increase in Cavg,C3 (Table 7).

Table 7: Final Parameter Estimates for Exposure-Efficacy Model for OS

Efficacy Endpoint	Parameter	Estimate	Standard Error	RSE (%)	p-value	Hazard Ratio
OS	$C_{avg,C3}$	-0.351	0.122	35	0.004	0.704 [0.554,0.894]

Abbreviations: $C_{avg,C3}$: average concentration up to end of Cycle 3; RSE = relative standard error.
Source: SGN-075-EVP-PKER-103-302-EE.r

Safety models

The exposure-safety analysis population included data from 121 subjects in study EV-103 and 432 subjects in study EV-302 who received EV + pembro in 1L. In Cohort K (EV monotherapy), the 72 subjects were analysed separately for comparison. A total of 13 subjects were excluded from the analyses.

The safety endpoints investigated were: drug-related TEAEs ≥Grade 3; TEAEs leading to dose adjustments; rash ≥Grade 3; severe cutaneous AR ≥Grade 3; hyperglycemia ≥Grade 3 and peripheral neuropathy ≥Grade 2.

The median ADC Cavg up to the safety events of interest were generally comparable across safety parameters and comparable to the median predicted Cycle 1 ADC Cavg, except for the ADC Cavg for peripheral neuropathy which had a later onset. Cycle 1 unconjugated MMAE average concentrations were consistent across studies.

Table 8: Summary Statistics for Responses and Exposures of Enfortumab Vedotin and Unconjugated MMAE Included in the Exposure-Safety Analysis Population

Analysis Population (N)	Endpoint	Event Rate Count (%)	Time to Event (months) Median [Min, Max]*	Model Predicted Exposures Median [Min, Max] Mean (SD)	
				ADC $C_{avg\ to\ Event}$ (µg/mL)	MMAE $C_{avg,C1}$ (MMAE $C_{avg,PN}$ for PN only) ng/mL)
Study EV-103 (N = 121)	Drug-related TEAEs ≥ Grade 3	78 (64.5%)	1.64 [0.164, 16.1]	3.23 [0.730, 9.86] 3.45 (1.53)	2.50 [0.759, 7.05] 2.69 (1.33)
	TEAEs leading to dose adjustments	93 (76.9%)	1.87 [0.0329, 12.9]	3.42 [1.19, 18.3] 3.75 (1.85)	
	Rash ≥ Grade 3	25 (20.7%)	2.63 [0.296, 16.1]	2.52 [0.731, 9.86] 2.74 (1.49)	
	Severe cutaneous AR ≥ Grade 3	6 (5.00%)	3.40 [0.558, 16.5]	2.36 [0.579, 5.48] 2.37 (1.01)	
	Hyperglycemia ≥ Grade 3	14 (11.6%)	1.00 [0.230, 11.1]	2.44 [0.579, 5.60] 2.52 (1.15)	
	Peripheral neuropathy ≥ Grade 2	60 (49.6%)	5.80 [0.328, 25.3]	2.83 [0.829, 7.77] 2.82 (1.03)	1.4 [0.225, 8.58] 1.74 (1.23)
Study EV-302 (N = 432)	Drug-related TEAEs ≥ Grade 3	244 (56.5%)	2.1 [0.0986, 20.3]	2.96 [0.314, 9.03] 3.06 (1.18)	2.45 [0.555, 8.75] 2.71 (1.21)
	TEAEs leading to dose adjustment	348 (80.6%)	2.1 [0.0329, 17.1]	3.40 [1.30, 10.3] 3.60 (1.20)	
	Rash ≥ Grade 3	69 (16.0%)	1.61 [0.131, 17.2]	2.57 [0.31, 8.44] 2.65 (1.06)	
	Severe cutaneous AR ≥ Grade 3	13 (3.00%)	2.69 [0.427, 17.2]	2.42 [0.173, 5.47] 2.42 (0.866)	
	Hyperglycemia ≥ Grade 3	38 (8.80%)	0.805 [0.263, 15.2]	2.46 [0.173, 6.17] 2.5 (0.958)	
	Peripheral neuropathy ≥ Grade 2	181 (41.9%)	5.75 [0.328, 20.3]	2.76 [0.173, 6.6] 2.81 (0.813)	1.62 [0.141, 9.13] 1.91 (1.2)
Studies EV-103 and EV-302 (N=553)	Drug-related TEAEs ≥ Grade 3	322 (58.2%)	2.02 [0.0986, 20.3]	3.02 [0.314, 9.86] 3.15 (1.27)	2.45 [0.555, 8.75] 2.70 (1.24)
	TEAEs leading to dose adjustment	441 (79.7%)	2.07 [0.0329, 17.1]	3.41 [1.19, 18.3] 3.63 (1.37)	
	Rash ≥ Grade 3	94 (17.0%)	1.69 [0.131, 17.2]	2.56 [0.31, 9.86] 2.67 (1.17)	
	Severe cutaneous AR ≥ Grade 3	19 (3.4%)	2.69 [0.427, 17.2]	2.41 [0.173, 5.48] 2.41 (0.900)	
	Hyperglycemia ≥ Grade 3	52 (9.4%)	0.805 [0.23, 15.2]	2.45 [0.173, 6.17] 2.51 (1.00)	
	Peripheral neuropathy ≥ Grade 2	241 (43.6%)	5.75 [0.328, 25.3]	2.78 [0.173, 7.77] 2.82 (1.17)	1.57 [0.141, 9.13] 1.87 (1.21)

Abbreviations: C_{avg}: average concentration; $C_{avg\ to\ Event}$ = average concentration to event or, if no event, end of treatment; CI: confidence interval; max: maximum; min: minimum; N: number of subjects; NE: not evaluated; PN = peripheral neuropathy; SD: standard deviation.

Notes: Median [Min,Max] treatment duration in Studies EV-103, EV-302 and combined studies was 9.00 [0.560, 34.4] months, 9.45 [0.260, 31.9] months and 9.43 [0.260, 34.4] months, respectively. *Subjects who experienced an event only.

Source: SGN-075-EVP-PKER-103-302-datasum.r, SGN-075-EVP-PKER-103-302-ES.r.

For every safety endpoint, safety incidences and exposure-safety relations were evaluated by exploratory plots and Kaplan-Meier curves. Logistic regression analysis was applied for every safety endpoint and final model parameters are shown in Table 9, Table 10, Table 11, Table 12, Table 13, Table 14.

Logistic regression found ADC Cavg,dose adj to be a significant covariate for TEAEs leading to enfortumab vedotin dose adjustments. Final parameters are shown in Table 9.

Table 9: Final Parameter Estimates for Exposure-Safety Model for TEAEs Leading to Dose Adjustment

Safety Endpoint	Parameter	Estimate	Standard Error	RSE (%)	Odds Ratio
TEAEs leading to Dose Adjustment	Intercept	-1.96	0.49	25	
	$C_{avg,dose\ adj}$	1.01	0.155	15	2.75 [2.03, 3.72]

Abbreviations: $C_{avg,TEAE}$: average concentration to time of TEAE or end of treatment; RSE = relative standard error; TEAE: treatment-emergent adverse event.

Source: SGN-075-EVP-PKER-103-302-ES.r

Logistic regression in pooled studies EV-103 and EV-302 found ADC Cavg,TEAE is a statistically significant covariate for ≥ Grade 3 TEAEs. Based on the model, the odds of a subject experiencing ≥ Grade 3 TEAEs was increased 3.13-fold for every 1 µg/mL increase in exposure. Final model parameters are shown in Table 10.

Table 10: Final Parameter Estimates for Exposure-Safety Model for ≥ Grade 3 TEAEs

Safety Endpoint	Parameter	Estimate	Standard Error	RSE (%)	Odds Ratio
≥ Grade 3 TEAEs	Intercept	-3.07	0.361	12	
	$C_{avg,TEAE}$	1.14	0.121	11	3.13 [2.47, 3.96]

Abbreviations: $C_{avg,TEAE}$: average concentration to time of TEAE or end of treatment; RSE = relative standard error; TEAE: treatment-emergent adverse event.

Source: SGN-075-EVP-PKER-103-302-ES.r

The linear logistic regression fit for ≥ Grade 3 hyperglycaemia showed a statistically significant ($p < 0.001$) relationship between increasing Cavg,hyperglycaemia and ≥ Grade 3 hyperglycemia. Based on the model, the odds of a subject experiencing ≥ Grade 3 hyperglycaemia was increased 3.49-fold for every 1 µg/mL increase in exposure (Table 11).

Table 11: Final Parameter Estimates for Exposure-Safety Model for ≥ Grade 3 Hyperglycemia

Safety Endpoint	Parameter	Estimate	Standard Error	RSE (%)	Odds Ratio
≥ Grade 3 Hyperglycemia	Intercept	-5.97	0.563	9	-
	$C_{avg,hyperglycemia}$	1.25	0.163	13	3.49 [2.54, 4.80]

Abbreviations: $C_{avg,hyperglycemia}$: average concentration to time of hyperglycemia event or end of treatment; RSE = relative standard error.

Source: SGN-075-EVP-PKER-103-302-ES.r

The linear logistic regression fit for ≥ Grade 3 rash showed increased incidence with increase in ADC Cavg,Rash, however, the trend was not evident for MMAE Cycle 1 Cavg. The ADC exposure-response trend was not observed for EV-103 EV monotherapy (N=72). There was a statistically significant ($p < 0.001$) relationship between increasing ADC Cavg,rash and probability of ≥ Grade 3 rash. Based on the model, the odds of a subject experiencing ≥ Grade 3 rash was increased 3.46-fold for every 1 µg/mL increase in exposure (Table 12).

Table 12: Final Parameter Estimates for Exposure-Safety Model for ≥ Grade 3 Rash

Safety Endpoint	Parameter	Estimate	Standard Error	RSE (%)	Odds Ratio
≥ Grade 3 rash	Intercept	-5.33	0.475	9	
	$C_{avg,rash}$	1.24	0.144	12	3.46 [2.61, 4.58]

Abbreviations: $C_{avg,rash}$: average concentration to time of SCAR event or end of treatment; RSE = relative standard error.

Source: SGN-075-EVP-PKER-103-302-ES.r

Logistic regression found ADC Cavg, SCAR to be a statistically significant predictor of ≥ Grade 3 SCAR. Based on the model, the odds of a subject experiencing ≥ Grade 3 SCAR was increased 3.13-fold for every 1 µg/mL increase in ADC exposure (Table 13).

Table 13: Final Parameter Estimates for Exposure-Safety Model for ≥ Grade 3 Severe Cutaneous Reactions

Safety Endpoint	Parameter	Estimate	Standard Error	RSE (%)	Odds Ratio
≥ Grade 3 severe cutaneous reactions	Intercept	-6.57	0.844	13	
	$C_{avg,SCAR}$	1.14	0.247	22	3.13 [1.93, 5.07]

Abbreviations: $C_{avg,SCAR}$: average concentration to time of SCAR event or end of treatment; RSE = relative standard error; SCAR = severe cutaneous adverse reaction.

Source: SGN-075-EVP-PKER-103-302-ES.r

Logistic regression found ADC Cavg,PN to be a statistically significant covariate for ≥ Grade 2 peripheral neuropathy. Based on the model, the odds of a subject experiencing ≥ Grade 2 peripheral neuropathy was increased 2.14-fold for every 1 µg/mL increase in exposure (Table 14).

Table 14: Final Parameter Estimates for Exposure-Safety Model for ≥ Grade 2 Peripheral Neuropathy

Safety Endpoint	Parameter	Estimate	Standard Error	RSE (%)	Odds Ratio
≥ Grade 2 peripheral neuropathy	Intercept	-2.42	0.350	14	
	$C_{avg,PN}$	0.763	0.119	16	2.14 [1.70, 2.71]

Abbreviations: $C_{avg,:PN}$: average concentration to time of peripheral neuropathy event or end of treatment; RSE = relative standard error.

Source: SGN-075-EVP-PKER-103-302-ES.r

Absorption

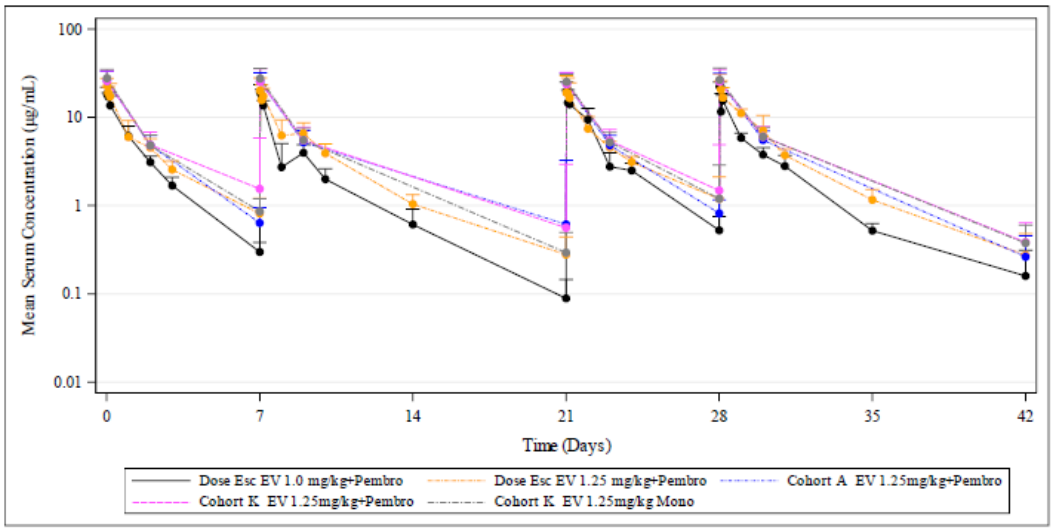
Clinical study EV-103 (Phase 1b/2) Enfortumab Vedotin in Combination with pembrolizumab (Dose Escalation and Cohorts A and K)

Enfortumab vedotin Pharmacokinetics

Serum EV

Concentration-time profiles indicate that mean (SD) serum EV concentrations peaked at the end of infusion, decreasing multi-exponentially following the end of infusion across cohorts Figure 10.

Figure 10: Mean (SD) Serum ADC Concentration-Time Profile (PKAS)



LLOQ: 0.0214 µg/mL

Table 15: PK Parameters for ADC in the Dose Escalation Cohort (PKAS)

Timepoint	Parameter, GM (%CV)	Dose Escalation	
		EV 1.0 mg/kg + Pembro (N = 3)	EV 1.25 mg/kg + Pembro (N = 7)
Cycle 1 Day 1/ Dose 1	n	3	7
	$AUC_{(d0-7)}$, day·µg/mL	19.8 (20.5)	26.4 (13.6)*
	C_{max}, µg/mL	19.1 (16.3)	22.6 (22.4)
	T_{max}, day†	0.020 (0.02, 0.10)	0.100 (0.02, 0.18)
Cycle 1 Day 8/ Dose 2	n	3	6
	$AUC_{(d0-7)}$, day·µg/mL	18.8 (19.5)	30.9 (17.8)
	$AUC_{(d0-14)}$, day·µg/mL	20.6 (20.9)	34.6 (19.7)
	C_{max}, µg/mL	19.4 (21.8)	23.0 (13.6)
	T_{max}, day†	0.030 (0.02, 0.10)	0.030 (0.02, 0.17)
	C_{trough}, µg/mL	0.291 (27.8)	0.737 (48.0)

Timepoint	Parameter, GM (%CV)	Dose Escalation	
		EV 1.0 mg/kg + Pembro (N = 3)	EV 1.25 mg/kg + Pembro (N = 7)
Cycle 2, Day 1/ Dose 1	n	3	5
	$AUC_{(d0-7)}$, day·µg/mL	24.0 (25.0)	31.0 (14.1)
	C_{max}, µg/mL	19.3 (27.4)	23.3 (22.5)
	T_{max}, day†	0.020 (0.02, 0.02)	0.090 (0.02, 0.10)
	C_{trough}, µg/mL	0.078 (64.6)	0.240 (58.5)*
Cycle 2, Day 8/ Dose 2	n	3	5
	$AUC_{(d0-7)}$, day·µg/mL	24.2 (12.5)	36.3 (14.7)
	$AUC_{(d0-14)}$, day·µg/mL	26.3 (13.8)	41.2 (16.1)
	C_{max}, µg/mL	22.2 (11.9)	26.2 (16.8)
	T_{max}, day†	0.020 (0.02, 0.03)	0.020 (0.02, 0.03)
	C_{trough} µg/mL	0.495 (43.6)	0.991 (77.5)*

LLOQ: 0.0214 µg/mL

%CV: coefficient of variation; EV: enfortumab vedotin; GM: geometric mean; Pembro: pembrolizumab.

† Median (min, max) shown for Tmax.

*n=6

Table 16: ADC Serum Concentrations in Cohorts A and K (PKAS)

Timepoint	Statistic, µg/mL	Cohort A	Cohort K	
		EV 1.25 mg/kg + Pembro (N = 40)	EV 1.25 mg/kg + Pembro (N = 76)	EV 1.25 mg/kg Monotherapy (N = 72)
Cycle 1 Day 1, End-of-Infusion [Peak] after 1st dose of Cycle 1	n/N	40/40	68/70	67/67
	Mean (SD)	26.1 (7.10)	26.0 (7.95)	27.8 (7.22)
	Median (min, max)	24.4 (14.6, 40.7)	25.9 (0.010, 48.3)	26.9 (16.4, 47.0)
Cycle 1 Day 8, Pre-dose [Trough] after 1st dose of Cycle 1	n/N	40/40	65/65	64/64
	Mean (SD)	0.637 (0.314)	1.55 (4.29)	0.860 (0.339)
	Median (min, max)	0.625 (0.13, 1.61)	0.718 (0.26, 27.8)	0.822 (0.190, 1.54)
Cycle 1, Day 8, End-of-Infusion [Peak] after 2nd dose of Cycle 1	n/N	39/39	63/63	62/62
	Mean (SD)	25.6 (6.33)	25.3 (10.3)	27.6 (8.31)
	Median (min, max)	24.1 (12.9, 40.5)	25.7 (0.40, 56.5)	27.2 (1.22, 54.6)
Cycle 2, Day 1, Pre-dose [Trough] after 2nd dose of Cycle 1	n/N	36/37	57/64	60/63
	Mean (SD)	0.614 (2.66)	0.561 (2.38)	0.293 (0.205)
	Median (min, max)	0.116 (0.01, 16.3)	0.219 (0.01, 19.2)	0.260 (0.01, 1.00)
Cycle 2 Day 1, End-of-Infusion [Peak] after 1st dose of Cycle 2	n/N	35/36	64/64	63/63
	Mean (SD)	24.1 (7.83)	23.9 (8.28)	25.2 (5.65)
	Median (min, max)	24.5 (0.01, 35.7)	24.8 (0.10, 40.5)	24.4 (12.3, 38.5)
Cycle 2, Day 8, Pre-dose [Trough] after 1st dose of Cycle 2	n/N	35/35	63/63	57/57
	Mean (SD)	0.818 (0.345)	1.48 (3.41)	1.20 (1.68)
	Median (min, max)	0.754 (0.23, 1.93)	1.00 (0.03, 27.8)	0.936 (0.32, 13.2)
Cycle 2, Day 8, End-of-Infusion [Peak] after 2nd dose of Cycle 2	n/N	34/34	64/64	56/56
	Mean (SD)	25.6 (6.08)	25.5 (9.31)	26.6 (9.69)
	Median (min, max)	25.2 (5.36, 37.3)	25.8 (0.59, 60.4)	25.1 (0.99, 66.3)
Cycle 3, Day 1, Predose [Trough] after 2nd dose of Cycle 2	n/N	36/39	56/58	48/50
	Mean (SD)	0.263 (0.194)	0.385 (0.250)	0.376 (0.224)
	Median (min, max)	0.244 (0.01, 0.83)	0.340 (0.01, 1.18)	0.362 (0.01, 1.08)

LLOQ: 0.0214 µg/mL

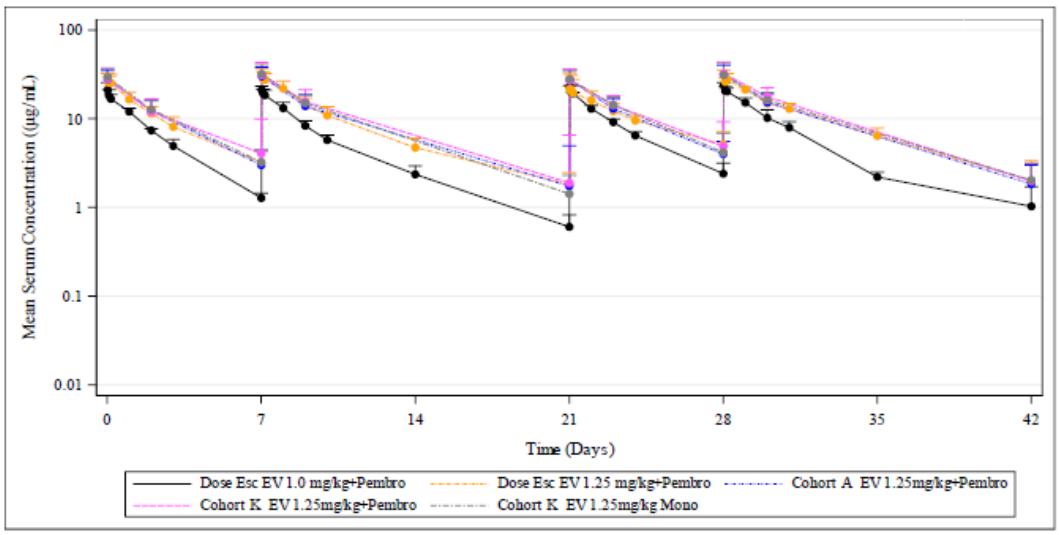
ADC: antibody-drug conjugate; EV: enfortumab vedotin; Pembro: pembrolizumab.

Source: Table 12.4.1.1.

Total Antibody (Tab)

Concentration-time profiles indicate that mean (SD) serum TAb concentrations peaked at the end of infusion, decreasing multi-exponentially following the end of infusion across cohorts Figure 11.

Figure 11: Mean (SD) Serum TAb Concentration-Time Profile (PKAS)



LLOQ: 0.0232 µg/mL

Table 17: PK Parameters for TAb in the Dose Escalation Cohort (PKAS)

Timepoint	Parameter, GM (%CV)	Dose Escalation	
		EV 1.0 mg/kg + Pembro (N = 3)	EV 1.25 mg/kg + Pembro (N = 7)
Cycle 1 Day 1/ Dose 1	n	3	7
	$AUC_{(d0-7)}$, day·µg/mL	40.6 (10.2)	66.2 (21.2)*
	C_{max}, µg/mL	20.9 (19.9)	27.7 (18.3)
	T_{max}, day†	0.020 (0.020, 0.020)	0.030 (0.020, 0.180)
Cycle 1 Day 8/ Dose 2	n	3	6
	$AUC_{(d0-7)}$, day·µg/mL	48.5 (14.1)	82.7 (21.3)
	$AUC_{(d0-14)}$, day·µg/mL	57.3 (16.4)	102.3 (23.3)
	C_{max}, µg/mL	20.9 (10.5)	31.3 (17.4)
	T_{max}, day†	0.020 (0.02, 0.03)	0.030 (0.02, 0.11)
	C_{trough}, µg/mL	1.27 (13.2)	3.03 (33.7)
Cycle 2, Day 1/ Dose 1	n	3	5
	$AUC_{(d0-7)}$, day·µg/mL	50.5 (10.1)	75.2 (8.4)
	C_{max}, µg/mL	22.8 (3.2)	26.7 (17.0)
	T_{max}, day†	0.020 (0.02, 0.02)	0.030 (0.02, 0.11)
	C_{trough}, µg/mL	0.577 (37.1)	1.72 (35.5)*
Cycle 2, Day 8/ Dose 2	n	3	5
	$AUC_{(d0-7)}$, day·µg/mL	57.9 (12.9)	91.6 (8.3)
	$AUC_{(d0-14)}$, day·µg/mL	68.6 (13.9)	123.1 (10.8)
	C_{max}, µg/mL	24.0 (6.5)	31.4 (12.2)
	T_{max}, day†	0.020 (0.02, 0.03)	0.020 (0.02, 0.03)
	C_{trough}, µg/mL	2.33 (31.0)	4.85 (39.5)*

LLOQ: 0.0232 µg/mL
%CV: coefficient of variation; EV: enfortumab vedotin; GM: geometric mean; Pembro: pembrolizumab.
† Median (min, max) shown for T_{max}.
*n=6

Table 18: TAb Serum Concentrations in Cohorts A and K (PKAS)

Timepoint	Statistic, µg/mL	Cohort A	Cohort K	
		EV 1.25 mg/kg + Pembro (N = 40)	EV 1.25 mg/kg + Pembro (N = 76)	EV 1.25 mg/kg Monotherapy (N = 72)
Cycle 1 Day 1, End-of-Infusion [Peak] after 1st dose of Cycle 1	n/N	40/40	68/70	67/67
	Mean (SD)	27.9 (6.67)	28.3 (8.60)	29.2 (7.49)
	Median (min, max)	28.4 (15.0, 43.3)	28.0 (0.01, 48.0)	29.1 (15.4, 49.1)
Cycle 1 Day 8, Pre-dose [Trough] after 1st dose of Cycle 1	n/N	40/40	66/66	64/64
	Mean (SD)	3.00 (1.43)	4.06 (5.84)	3.23 (1.20)
	Median (min, max)	2.92 (0.49, 5.6)	2.93 (0.90, 43.0)	3.21 (0.94, 6.36)
Cycle 1, Day 8, End-of Infusion [Peak] after 2nd dose of Cycle 1	n/N	39/39	64/64	62/62
	Mean (SD)	30.1 (7.79)	31.3 (11.5)	31.8 (8.54)
	Median (min, max)	30.6 (15, 44)	31.1 (1, 53)	31.7 (3.81, 53.4)
Cycle 2, Day 1, Pre-dose [Trough] after 2nd dose of Cycle 1	n/N	37/37	64/65	63/63
	Mean (SD)	1.74 (3.20)	1.89 (4.63)	1.42 (0.874)
	Median (min, max)	1.18 (0.11, 20.1)	1.18 (0.01, 37.9)	1.40 (0.04, 4.40)
Cycle 2 Day 1, End-of-Infusion [Peak] after 1st dose of Cycle 2	n/N	36/36	64/64	63/63
	Mean (SD)	27.3 (8.40)	27.1 (9.04)	27.8 (6.47)
	Median (min, max)	27.2 (0.06, 41.0)	27.8 (0.57, 42.9)	27.9 (14.4, 42.4)
Cycle 2, Day 8, Pre-dose [Trough] after 1st dose of Cycle 2	n/N	35/35	63/63	57/57
	Mean (SD)	3.99 (1.53)	4.86 (4.40)	4.17 (2.68)
	Median (min, max)	3.71 (1.34, 8.55)	4.28 (0.16, 35.6)	3.76 (1.16, 19.2)
Cycle 2, Day 8, End-of-Infusion [Peak] after 2nd dose of Cycle 2	n/N	34/34	64/64	55/55
	Mean (SD)	31.8 (8.38)	32.3 (11.28)	31.1 (10.9)
	Median (min, max)	31.4 (9.00, 55.5)	32.3 (2.44, 67.1)	30.9 (3.95, 81.4)
Cycle 3, Day 1, Predose [Trough] after 2nd dose of Cycle 2	n/N	39/39	58/58	50/50
	Mean (SD)	1.83 (1.17)	1.98 (1.16)	2.03 (1.14)
	Median (min, max)	1.73 (0.05, 5.55)	1.78 (0.11, 4.85)	1.82 (0.05, 5.30)

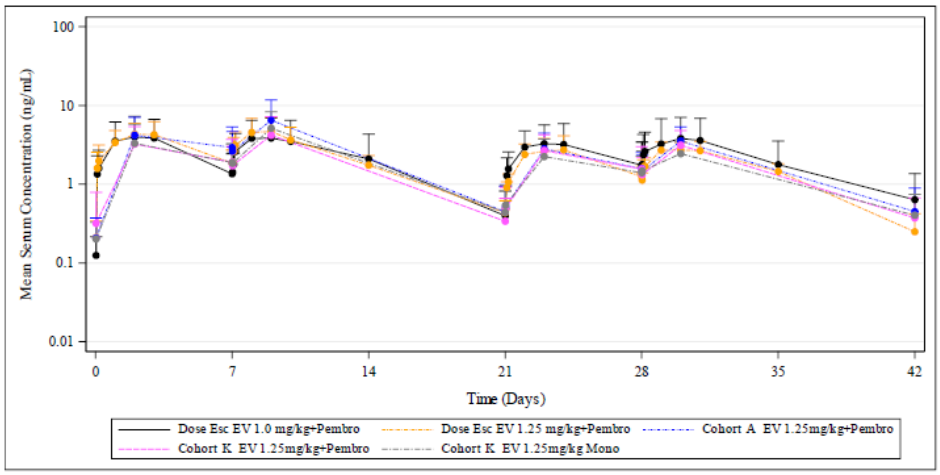
LLOQ: 0.0232 µg/mL

EV: enfortumab vedotin; Pembro: pembrolizumab.

MMAE

Concentration-time profiles indicate that mean (SD) unconjugated MMAE plasma concentrations peaked approximately two days after the end of infusion, decreasing multi-exponentially thereafter across cohorts [Figure 12]. PK parameters for unconjugated MMAE in Cycles 1 and 2 appear in Table 19 for the dose escalation cohort, and Table 20 for Cohorts A and K.

Figure 12: Mean (SD) Unconjugated MMAE Concentration-Time Profile (PKAS)



LLOQ: 0.010 ng/mL

Table 19: PK Parameters for Unconjugated MMAE in the Dose Escalation Cohort (PKAS)

Timepoint	Parameter, GM (%CV)	Dose Escalation	
		EV 1.0 mg/kg + Pembro (N = 3)	EV 1.25 mg/kg + Pembro (N = 7)
Cycle 1 Day 1 (Dose 1)	n	3	7
	$AUC_{(d0-7)}$, day·ng/mL	15.3 (75.9)	19.7 (45.3)*
	C_{max}, ng/mL	3.4 (74.4)	4.2 (41.1)
	T_{max}, day†	1.98 (0.910, 3.10)	1.94 (1.90, 3.12)
Cycle 1 Day 8 (Dose 2)	n	3	6
	$AUC_{(d0-7)}$, day·ng/mL	16.8 (85.8)	20.9 (43.2)
	$AUC_{(d0-14)}$, day·ng/mL	21.7 (90.9)	27.0 (39.6)
	C_{max}, ng/mL	3.3 (74.4)	4.4 (50.5)
	T_{max}, day†	1.13 (0.940, 2.05)	1.46 (0.980, 1.94)
	C_{trough}, ng/mL	1.03 (78.7)	1.67 (47.5)
Cycle 2, Day 1 (Dose 1)	n	3	5
	$AUC_{(d0-7)}$, day·ng/mL	13.9 (80.9)	12.2 (30.8)
	C_{max}, ng/mL	2.8 (72.3)	2.3 (41.0)
	T_{max}, day†	2.03 (0.910, 2.93)	1.96 (0.960, 3.14)
	C_{trough}, ng/mL	0.268 (105.8)	0.409 (42.4)*
Cycle 2, Day 8 (Dose 2)	n	3	5
	$AUC_{(d0-7)}$, day·ng/mL	14.7 (95.1)	14.9 (26.7)
	$AUC_{(d0-14)}$, day·ng/mL	19.8 (99.3)	20.4 (27.2)
	C_{max}, ng/mL	2.9 (85.0)	2.8 (29.4)
	T_{max}, day†	2.03 (0.98, 2.08)	2.00 (0.970, 2.98)
	C_{trough}, ng/mL	1.20 (96.7)	1.18 (36.8)*

LLOQ: 0.010 ng/mL

%CV: coefficient of variation; EV: enfortumab vedotin; GM: geometric mean; Pembro: pembrolizumab.

† Median (min, max) shown for T_{max}.

*n=6

Table 20: MMAE Serum Concentrations in Cohorts A and K (PKAS)

Timepoint	Statistic, ng/mL	Cohort A	Cohort K	
		EV 1.25 mg/kg + Pembro (N = 40)	EV 1.25 mg/kg + Pembro (N = 76)	EV 1.25 mg/kg Monotherapy (N = 72)
Cycle 1 Day 3, End-of-Infusion +48 hrs [Peak] after 1st dose of Cycle 1	n/N	39/39	23/24	23/23
	Mean (SD)	4.20 (2.85)	3.24 (2.17)	3.30 (2.50)
	Median (min, max)	2.88 (0.90, 11.9)	2.96 (0.01, 9.43)	2.54 (0.70, 11.7)
Cycle 1 Day 8, Pre-dose [Trough] after 1st dose of Cycle 1	n/N	40/40	64/64	64/64
	Mean (SD)	2.92 (2.42)	1.91 (1.81)	1.88 (1.37)
	Median (min, max)	2.07 (0.40, 9.92)	1.43 (0.27, 11.1)	1.38 (0.42, 7.40)
Cycle 1, Day 10, End-of Infusion +48 hrs [Peak] after 2nd dose of Cycle 1	n/N	34/34	20/20	21/21
	Mean (SD)	6.50 (5.22)	4.20 (2.97)	5.13 (3.15)
	Median (min, max)	4.61 (1.00, 23.3)	3.34 (1.01, 12.9)	3.93 (1.37, 13.5)
Cycle 2, Day 1, Pre-dose [Trough] after 2nd dose of Cycle 1	n/N	37/37	62/64	62/63
	Mean (SD)	0.448 (0.486)	0.338 (0.327)	0.441 (0.376)
	Median (min, max)	0.291 (0.05, 2.36)	0.222 (0.01, 1.73)	0.319 (0.01, 1.52)
Cycle 2 Day 3, End-of-Infusion +48 hrs [Peak] after 1st dose of Cycle 2	n/N	35/35	25/25	19/19
	Mean (SD)	2.81 (1.65)	2.67 (1.56)	2.24 (1.50)
	Median (min, max)	2.45 (0.79, 8.58)	1.96 (1.02, 5.86)	1.83 (0.90, 7.10)
Cycle 2, Day 8, Pre-dose [Trough] after 1st dose of Cycle 2	n/N	35/35	61/61	57/57
	Mean (SD)	1.58 (0.952)	1.56 (1.44)	1.40 (0.872)
	Median (min, max)	1.22 (0.37, 4.13)	1.19 (0.17, 10.20)	1.19 (0.39, 4.89)
Cycle 2, Day 10, End-of-Infusion +48 hrs [Peak] after 2nd dose of Cycle 2	n/N	32/32	24/24	18/18
	Mean (SD)	3.52 (1.8)	3.12 (1.7)	2.44 (1.0)
	Median (min, max)	3.11 (0.91, 8.60)	2.64 (1.31, 7.12)	2.20 (1.30, 5.27)
Cycle 3, Day 1, Predose [Trough] after 2nd dose of Cycle 2	n/N	39/39	59/59	46/47
	Mean (SD)	0.449 (0.447)	0.373 (0.297)	0.403 (0.338)
	Median (min, max)	0.301 (0.03, 2.40)	0.334 (0.01, 1.80)	0.260 (0.01, 1.67)

LLOQ: 0.010 ng/mL

EV: enfortumab vedotin; MMAE: monomethyl auristatin; Pembro: pembrolizumab.

Clinical study EV-302 (Phase 3) Enfortumab Vedotin in Combination with Pembrolizumab

Enfortumab vedotin Pharmacokinetic and Immunogenicity Results

All subjects treated with enfortumab vedotin received an IV infusion on days 1 and 8 of every 21-day cycle. Sparse samples were collected at specified timepoints pre- and post-infusion.

PK of enfortumab vedotin was evaluated in the EV PK analysis set, and enfortumab vedotin-related ATA incidence was summarized using the SAF.

Previous analyses have indicated that pembrolizumab PK and immunogenicity are not impacted by the coadministration of enfortumab vedotin and are consistent with pembrolizumab historical monotherapy data. Consequently, pembrolizumab PK and immunogenicity are not discussed in the context of study EV-302.

EV

At the end of infusion on Day 1 and 8 (Cycles 1 and 2), the mean (SD) concentrations of EV ranged from 22.4 (9.11) to 25.4 (15.4) µg/mL. The mean serum (SD) trough concentrations of EV at predose (Cycles 1-7) ranged from 0.378 (0.291) to 1.47 (4.16) µg/mL (Table 21).

Table 21: Concentrations of Enfortumab Vedotin ADC and Unconjugated MMAE (EV PK Analysis Set)

	Cycle 1 Day 1 EOI	Cycle 1 Day 8 Pre-dose	Cycle 1 Day 8 EOI	Cycle 2 Day 1 Pre-dose	Cycle 2 Day 1 EOI	Cycle 2 Day 8 Pre-dose	Cycle 2 Day 8 EOI	Cycle 3 Day 1 Pre-dose	Cycle 5 Day 1 Pre-dose	Cycle 7 Day 1 Pre-dose
ADC (µg/mL)										
n/N	391/397	370/373	367/368	341/364	353/354	115/115	112/112	333/349	267/281	211/223
Mean (SD)	23.6 (6.88)	1.08 (2.56)	25.4 (15.4)	0.436 (2.06)	22.4 (9.11)	1.47 (4.16)	25.1 (8.18)	0.763 (6.78)	0.444 (1.69)	0.378 (0.291)
%CV	29.2	236	60.4	473	40.7	284	32.6	889	380	76.9
Median	23.3	0.717	24.4	0.197	22.3	0.914	25.3	0.273	0.322	0.327
Min, max	0.0110, 55.2	0.0110, 26.5	0.0110, 281	0.0110, 22.9	0.0110, 115	0.0630, 33.9	0.562, 55.6	0.0110, 124	0.0110, 28.4	0.0110, 1.91
GM	20.6	0.700	22.4	0.200	18.7	0.900	22.4	0.200	0.300	0.300
MMAE (ng/mL)										
n/N	374/380	356/358	359/359	345/355	340/340	115/115	109/109	326/333	259/271	206/215
Mean (SD)	0.366 (0.476)	1.98 (1.38)	2.00 (1.29)	0.396 (0.404)	0.570 (0.424)	1.35 (0.773)	1.32 (0.736)	0.394 (0.386)	0.334 (0.290)	0.316 (0.269)
%CV	130	69.6	64.7	102	74.3	57.2	55.9	98.0	86.9	85.2
Median	0.185	1.67	1.70	0.296	0.454	1.16	1.19	0.305	0.256	0.262
Min, max	0.00500, 2.85	0.00500, 12.6	0.162, 9.48	0.00500, 3.73	0.0110, 2.72	0.0770, 4.07	0.110, 4.17	0.00500, 3.03	0.00500, 1.83	0.00500, 1.45
GM	0.200	1.60	1.70	0.200	0.400	1.10	1.10	0.200	0.200	0.200

%CV: Coefficient of variation expressed as a percentage; ADC: Antibody-drug conjugate; EOI: End of infusion; EV: Enfortumab vedotin; Max: Maximum; Min: Minimum; GM: Geometric mean; MMAE: Monomethyl auristatin E; PK: Pharmacokinetics; SD: Standard deviation

Source: Tables 12.4.1.1 and 12.4.2.1.

Dose proportionality and time dependencies

The updated POPPK model identified a time dependent decrease in the formation rate of MMAE. The estimated median decline in the formation rate of unconjugated MMAE was 31% at the end of Cycle 1 and 45% asymptotically. The time to 50% of maximal decline was 309 hours (12.9 days).

Special populations

Hepatic impairment

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% and 16% increase in unconjugated MMAE average concentrations in patients with previously treated and previously untreated locally advanced or metastatic urothelial cancer, respectively, with mild hepatic impairment (total bilirubin of 1 to 1.5 × ULN and AST any, or total bilirubin ≤ ULN and AST > ULN) compared to patients with normal hepatic function. Enfortumab vedotin has only been studied in a limited number of patients with moderate hepatic impairment (n=5) or severe hepatic impairment (n=1). 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.

2.3.3. Pharmacodynamics

Mechanism of action

(ADC) comprised of a fully human anti-Nectin 4 IgG1 kappa monoclonal antibody (mAb) conjugated to the small molecule microtubule disrupting agent, MMAE, via a protease cleavable maleimidocaproyl vc-linker. Conjugation takes place on cysteine residues that comprise the interchain disulfide bonds of the antibody to yield a product with a drug to antibody ratio of approximately 3.8. Enfortumab vedotin

binds to the V domain of Nectin-4 protein. Nectin-4 is expressed in multiple cancers, particularly those of epithelial origin such as urothelial, breast, lung, pancreatic and ovarian cancers [Challita-Eid et al, 2016].

Enfortumab vedotin induces cytotoxicity in cancer cells by binding Nectin-4 target on the cell surface and forming an ADC-Nectin-4 complex. This complex internalizes and traffics to lysosomal vesicles where MMAE is released by proteolytic cleavage of the vc-linker [Doronina et al, 2003]. Intracellularly released MMAE subsequently disrupts tubulin polymerization and leads to mitotic arrest and apoptosis of tumor cells through direct and bystander mediated cytotoxicity [Francisco et al, 2003]. Through these mechanisms, enfortumab vedotin has been shown to induce immunogenic cell death in Nectin-4 positive tumour cells [Olson et al, 2022].

Pembrolizumab is a highly selective humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. This blockade enhances functional activity of the target lymphocytes to facilitate tumour regression and, ultimately, immune rejection. In vitro and in vivo experiences have shown that PD-1 and PD-L1 blockade using an mAb can result in activation of antitumor T-cells and subsequent tumour regression. In T-cell activation assays using human donor blood cells, the half maximal effective concentration was in the range of 0.1 to 0.3 nM [Dulos et al, 2012]. Pembrolizumab also modulates the level of IL-2, TNFα, IFNγ and other cytokines. The antibody potentiates existing immune responses in the presence of antigen only; it does not non specifically activate T-cells.

Rationale for the Enfortumab Vedotin and Pembrolizumab Combination

Immune checkpoint inhibitors, such as the PD-1 inhibitor pembrolizumab, unleash the antitumor activity of T lymphocytes by targeting the T-cell inhibition pathway [Sonpavde, 2017]. Preclinical data show enhanced antitumour activity when enfortumab vedotin is combined with PD-1 inhibitors across multiple in vivo tumour models. Enfortumab vedotin has also demonstrated induction of immunogenic cell death of Nectin-4 positive tumours, an increase in inflammatory mediators and recruitment of innate inflammatory cells to the tumour microenvironment consistent with the increased tumour immunogenicity demonstrated with other MMAE ADCs preclinically [Olson et al, 2022; Liu et al, 2020; Gardai et al, 2015].

In addition, preclinical studies demonstrated that enfortumab vedotin-induced immunomodulatory effects may generate lasting antitumour immunity and enhanced antitumour activity when enfortumab vedotin is combined with a PD 1 inhibitor [Olson et al, 2022]. These findings demonstrate that for enfortumab vedotin, and consistent with preclinical data with other ADCs that contain the same MMAE drug linker, enhanced antitumor activity may be achieved when used in combination with a PD-1 inhibitor due to complementary mechanisms of MMAE-induced cell cytotoxicity and induction of immunogenic cell death, plus the up-regulation of antitumor immune function by PD-1 inhibition [Olson et al, 2022; Diefenbach et al, 2016].

Based on the preclinical enhancement of antitumour activity and antitumor immunity, it was hypothesized that combining enfortumab vedotin with pembrolizumab has the potential to improve clinical outcomes relative to either agent alone in patients with LA or mUC, providing support for clinical development of the combination.

Primary and secondary pharmacology

Immunogenicity Anti-treatment antibody (ATA)

Study EV-103

The dose escalation cohort, Cohort A, and Cohort K enrolled 199 subjects of which 179 were evaluable for ATA having both baseline and on-treatment samples. The following table summarises the incidence of ATA in the different cohorts from study EV-103.

Table 22: Summary of EV ATA incidence – Study EV-103

	Dose-Escalation		Cohort A	Cohort K		Dose Escal + Cohort A + Cohort K	Total
Subjects:	EV 1.0 mg/kg + Pembro (N = 3)	EV 1.25 mg/kg + Pembro (N = 7)	EV 1.25 mg/kg + Pembro (N = 40)	EV + Pembro (N = 76)	EV Mono (N = 73)	EV + Pembro (N = 126)	All Cohorts†† (N=199)
With a baseline and ≥1 postbaseline sample	3	6	39	67	64	115	179
Negative at baseline	3	6	36	65	64	110	174
Positive postbaseline†	0	0	2/36 (5.6%)	1/65 (1.5%)	2/64 (3.1%)	3/110 (2.7%)	5/174 (2.9%)
Positive at baseline	0	0	3	2	0	5	5
Positive postbaseline†	0	0	2/3 (66.7%)	1/2 (50%)	0	3/5 (60%)	3/5 (60%)

ATA: antitherapeutic antibody; Escal: escalation; EV: enfortumab vedotin; Mono: monotherapy; Pembro: pembrolizumab.
† Subjects who were positive for ATA at any time postbaseline.
†† Total of Dose-escalation Cohort, Cohort A and Cohort K, all doses.

Study EV-302

Enfortumab vedotin-related ATA incidence was summarized using the safety analysis set of EV-302, which included all subjects who received any study treatment. A total of 377 of 440 subjects who received enfortumab vedotin in combination with pembrolizumab were evaluable for ATA, having both baseline and on-treatment samples. The following table summarises the incidence of EV ATA in the EV+Pembro arm from study EV-302.

Table 23: Summary of Enfortumab Vedotin ATA Incidence (Safety Analysis Set)

	EV + Pembro EV-302 (N=440)	EV + Pembro Combo ISS (N=564)	EV Mono ISS (N=793)
Subjects with a baseline and at least one post-baseline sample	377	490	697
Baseline Negative	358	466	681
Negative post-baseline	347/358 (96.9%)	452/466 (97.0%)	657/681 (96.5%)
Positive post-baseline	11/358 (3.1%)	14/466 (3.0%)	24/681 (3.5%)
Baseline Positive	19	24	16
Negative post-baseline	11/19 (57.9%)	13/24 (54.2%)	12/16 (75.0%)
Positive post-baseline	8/19 (42.1%)	11/24 (45.8%)	4/16 (25.0%)
Treatment-boosted ATA [1]	0	0	3/16 (18.8%)

Table 24: Patients with Positive ATA to Enfortumab Vedotin at Baseline and Post-Baseline in EV-301 and EV-302

	EV-301	**EV-302**
Baseline Positive	12	19
Titer < 1 at Baseline	6/12 (50%)	10/19 (53%)
Titer > 1 at Baseline	4/12 (33%)	6/19 (32%)
Titer = 1 at Baseline	2/12 (17%)	3/19 (16%)
Positive Post-baseline	3/12 (25%)	8/19 (42%)

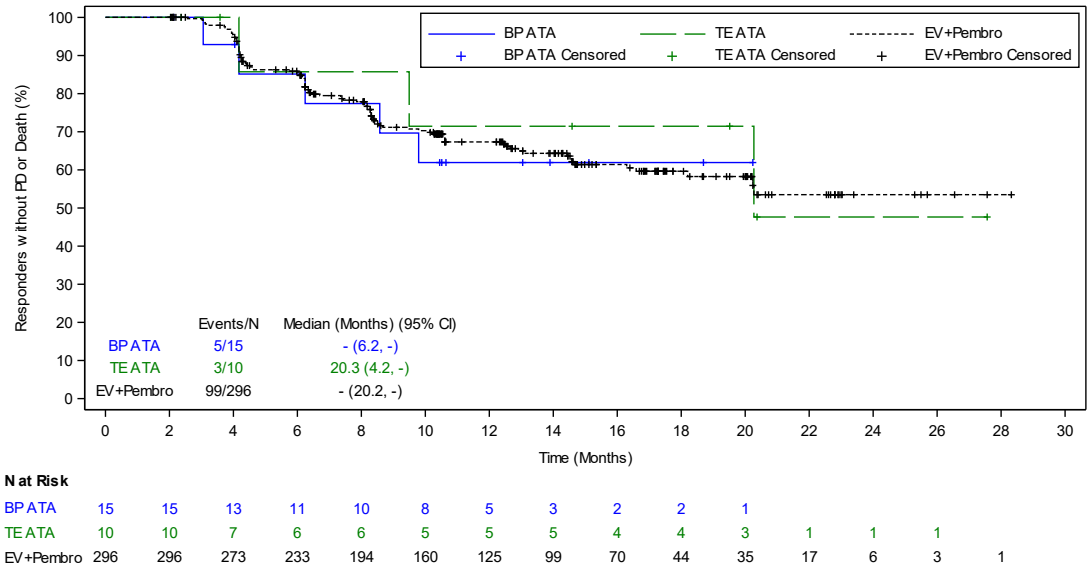
ATA: antitherapeutic antibodies. Source: EV-301 Bioanalytical Report and EV-302 Bioanalytical Report

Table 25: Summary of ORR per RECIST by BICR by Anti-EV ATA Positivity (EV + Pembro Arm, Response Evaluable Set)

	Baseline Positive Anti-EV ATA N = 19	**Treatment-Emergent Anti-EV ATA N = 11**	**Overall Population EV + Pembro N = 437**
ORR[†], n (%)	15 (78.9)	10 (90.9)	296 (67.7)
95% CI	54.4, 93.9	58.7, 99.8	63.1, 72.1

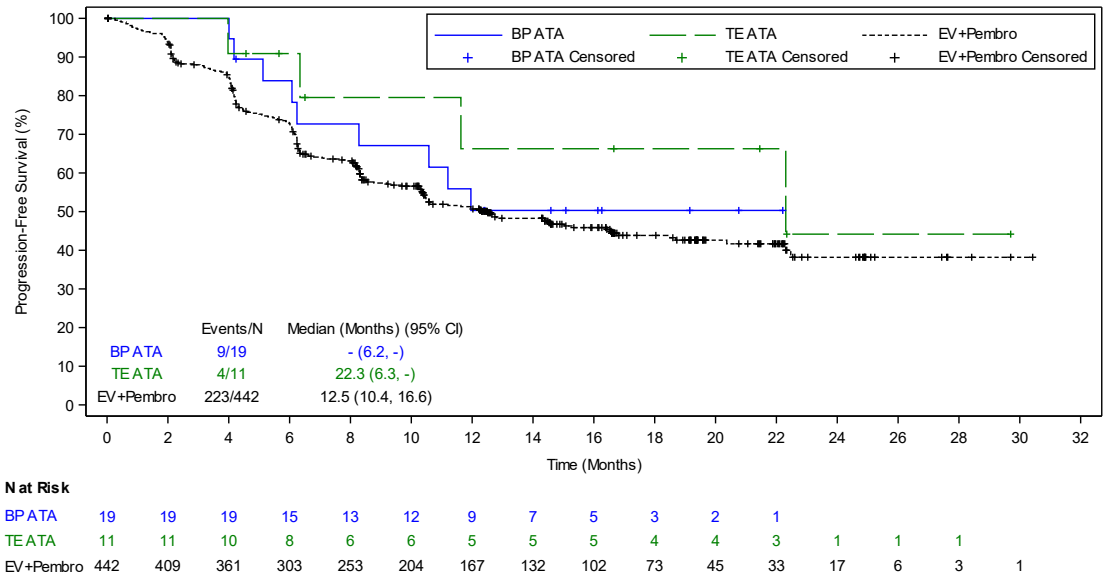
ATA: antitherapeutic antibody; BICR: blinded independent central review; ORR: objective response rate; RECIST: Response Evaluation Criteria in Solid Tumors. † Objective response (CR or PR) was confirmed with repeat scans ≥ 28 days after initial response according to RECIST v1.1.

Figure 13: Kaplan-Meier Plot of DOR per RECIST by BICR by Anti-EV ATA Positivity (EV + Pembro Arm, Response Evaluable Set)



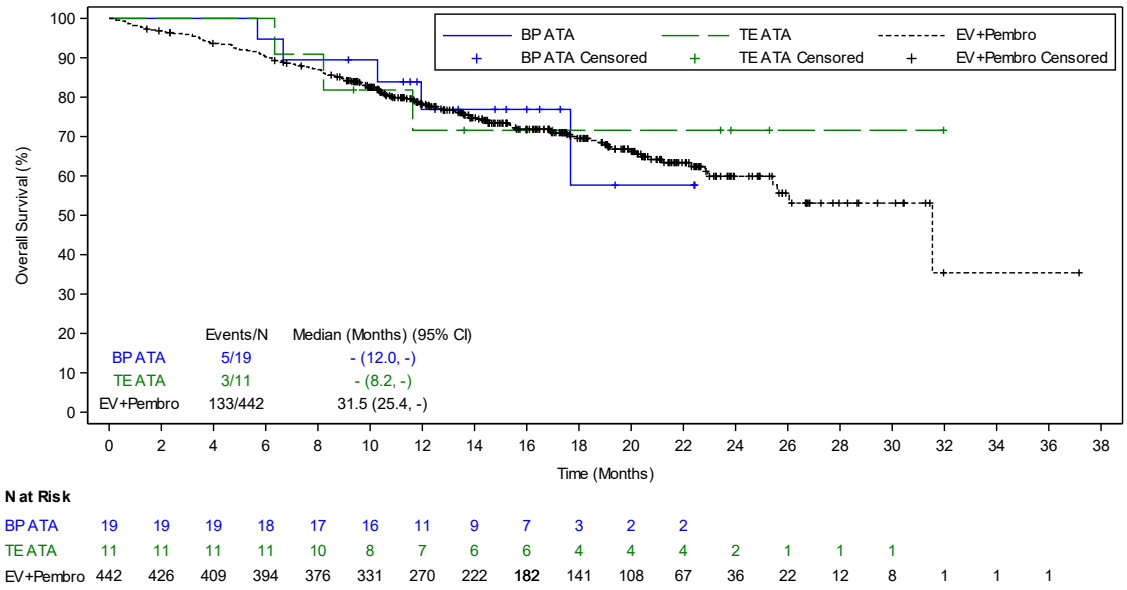
ATA: antitherapeutic antibody; BICR: blinded independent central review; BP ATA: baseline positive for anti-EV ATA; DOR: duration of response; RECIST: Response Evaluation Criteria in Solid Tumors; TE ATA: treatment-emergent positive for anti-EV ATA.

Figure 14: Kaplan-Meier Plot of PFS per RECIST by BICR for Subgroups Defined by Anti-EV ATA Positivity (EV + Pembro Arm, ITT Population)



ATA: antitherapeutic antibody; BICR: blinded independent central review; BP ATA: baseline positive for anti-EV ATA; ITT: intent-to-treat; PFS: progression-free survival; RECIST: Response Evaluation Criteria in Solid Tumors; TE ATA: treatment-emergent positive for anti-EV ATA.

Figure 15: Kaplan-Meier Plot of OS for Subgroups Defined by Anti-EV ATA Positivity (EV + Pembrolizumab Arm, ITT Population)



ATA: antitherapeutic antibody; BP ATA: baseline positive for anti-EV ATA; ITT: intent-to-treat; OS: overall survival; TE ATA: treatment-emergent positive for anti-EV ATA.

Relationship between plasma concentration and effect and safety

The exposure-response analysis was conducted to characterize the relationship between exposures of enfortumab vedotin with efficacy and safety endpoints for enfortumab vedotin administered as 1.25 mg/kg 2Q3W in combination with pembrolizumab from Studies EV-103 and EV-302 in subjects with LA/mUC in the 1L setting.

Exposure-Efficacy Analysis

Exposure-efficacy analysis was performed for the primary efficacy endpoint (ORR per RECIST v1.1 by BICR) in study EV-103 and the primary (PFS per RECIST by BICR and OS) and secondary (ORR per RECIST v1.1 by BICR) efficacy endpoints in study EV 302. Individual EV exposures calculated from the final PopPK model were adopted in the exposure-efficacy analysis. Exposure-efficacy analyses were conducted separately for studies EV-103 and EV-302.

For study EV-103, subjects receiving at least 1 dose of 1.25 mg/kg 2Q3W enfortumab vedotin plus pembrolizumab as 1L treatment and with quantifiable exposures (N = 121) were included in the analysis dataset.

For study EV-302, all subjects in Arm A (EV + Pembro) who received at least 1 dose of 1.25 mg/kg 2Q3W enfortumab vedotin plus pembrolizumab as 1L treatment and with quantifiable exposures (N = 432) were included in the OS and PFS analysis dataset. The study EV-302 exposure-efficacy analysis for ORR included data for 427 subjects in Arm A (EV + Pembro) who were in the response evaluable population, had received at least 1 dose of enfortumab vedotin at 1.25 mg/kg in combination with pembrolizumab and with quantifiable exposures. A summary of the efficacy endpoints, together with model-predicted exposures for enfortumab vedotin are shown in the following table:

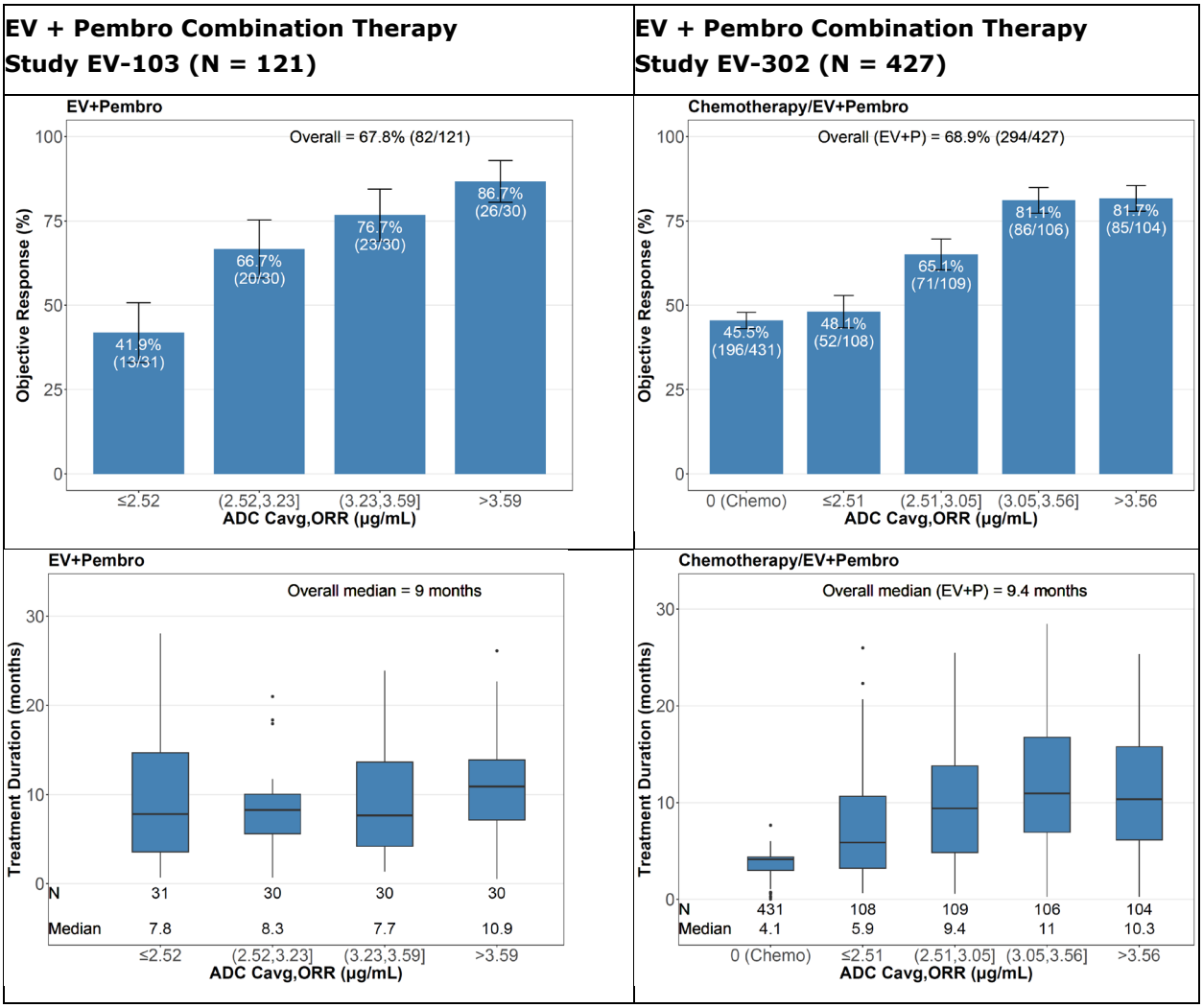
Table 26: Summary Statistics for Responses (Binary Endpoints and Time to Event Endpoints) and Exposures of Enfortumab Vedotin Evaluated in Exposure-response Analyses

Study	Endpoint	N	Event Rate Count (%)	Time to ORR (months) Median [Min, Max]	Selected ADC Exposure Metric	Exposure (µg/mL) Median [min, max] Mean (SD)
EV-103	Best Overall Response	121	82 (67.8%)	2.07 [1.15, 13.2]#	$C_{avg,ORR}$	3.23 [1.04, 5.69] 3.14 (0.97)
EV-302	Overall Survival	432	NE	NE	$C_{avg,C3}$	3.16 [0.945, 6.02] 3.10 (0.761)
	Progression Free Survival	432	NE	NE		
	Best Overall Response	427	294 (68.9%)	2.10 [1.31, 12.2] #	$C_{avg,ORR}$	3.05 [0.722, 5.96] 3.05 (0.79)

Abbreviations: ADC: antibody drug conjugate; $C_{avg,C3}$: average concentration up to end of Cycle 3; $C_{avg,ORR}$: average concentration to ORR; CI: confidence interval; max: maximum; min: minimum; N: number of subjects; NE: not evaluated; ORR: objective response rate; SD: standard deviation.

Notes: #Time to event for 82 subjects in Study EV-103 and 294 subjects in Study EV-302 who experienced ORR.

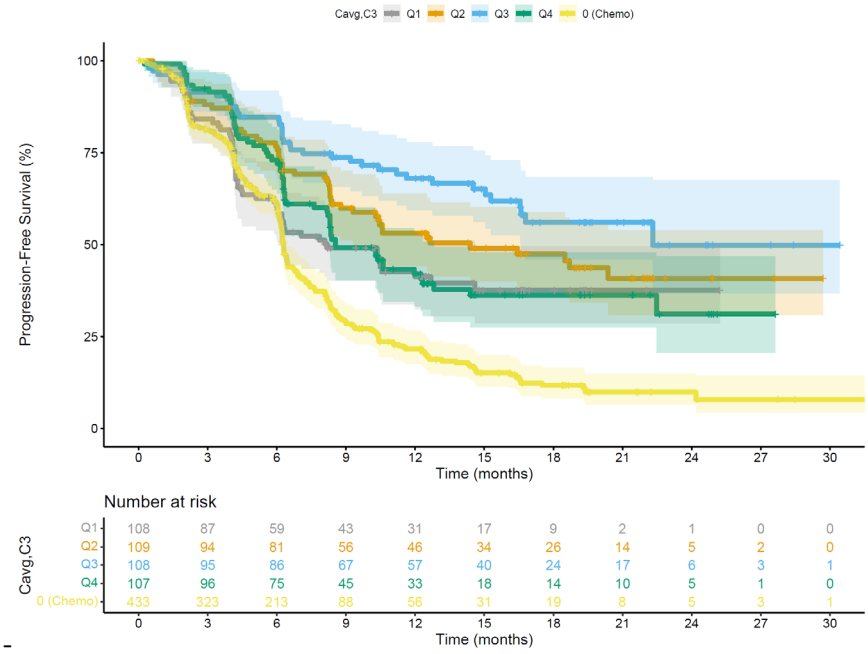
Figure 16: Exploratory Plots of Objective Response Rates in Studies EV-103 and EV-302



Abbreviations: C_{avg}: average concentration; ORR: objective response rate; N: number of subjects.

Notes: Barplots show event frequency. Labels are number of events (n)/number of subjects (N) per exposure quartile and also expressed as a percentage. The Study ORR in EV-302 included data for 427 subjects in Arm A who were in the response evaluable population, had received at least one dose of enfortumab vedotin at 1.25 mg/kg in combination with pembrolizumab and were PK evaluable.
Boxplots show distributions of times to event by exposure quartile; the thick horizontal line represents median, box ends show the upper and lower quartiles of the data, whiskers show the range of points within 1.5 times the interquartile range, and points are data that lie outside the whiskers.

Figure 17: Kaplan-Meier Curves for PFS Stratified by ADC Exposure Quartile in Study EV-302



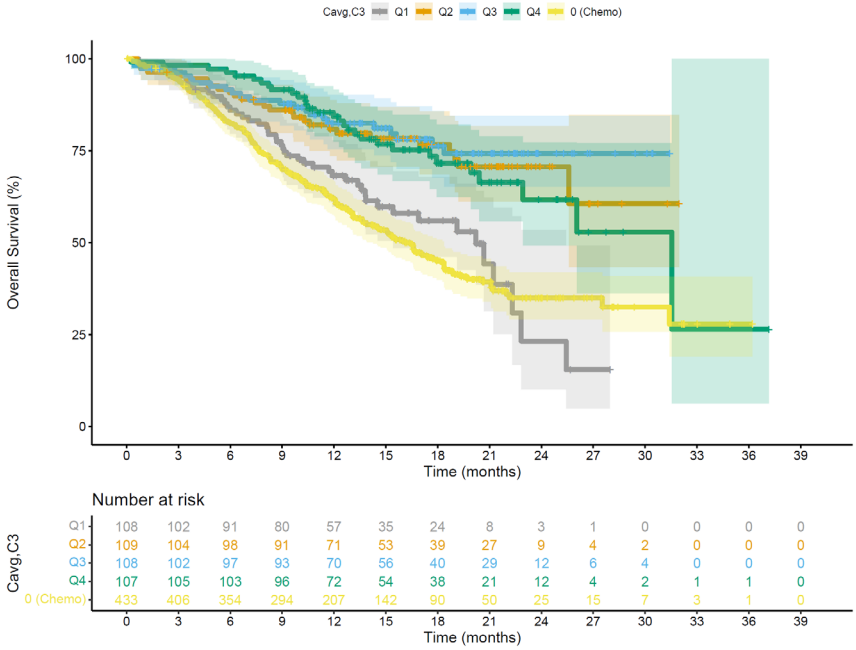
Abbreviations: C_{avg}: average concentration; PFS: progression-free survival.
Notes: Kaplan Meier curves are shown for the Chemotherapy (Chemo) arm and by exposure quartiles for the EV + Pembro arm in Study EV-302.

Table 27: Kaplan-Meier Survival Analysis of PFS by Enfortumab Vedotin Exposure Quartiles

Endpoint	$C_{avg,C3}$ Quartile (ug/mL)	N	Events	Time to 50% Survival (months)	95% CI of Time to 50% Survival (months)
PFS	Chemotherapy	433	306	6.28	6.21, 6.47
	EV Q1: [0.945,2.59]	108	60	8.18	6.05, 14.6
	EV Q2: (2.59,3.16]	109	55	14.39	9.30, NE
	EV Q3: (3.16,3.63]	108	40	22.31	16.6, NE
	EV Q4: (3.63,6.02]	107	62	8.54	8.21, 12.81

Abbreviations: $C_{avg,C3}$: average concentration from Cycles 1 to 3; CI: confidence interval; N: number of subjects; NE: not estimated; Q: quartile.
Notes: Time to 50% survival determined using the Greenwood formula for time-to-event endpoints.

Figure 18: Kaplan-Meier Curves for OS Stratified by ADC Exposure Quartile in Study EV-302



Abbreviations: C_{avg}: average concentration; OS = overall survival.
Notes: Kaplan Meier curves are shown for the chemotherapy (Chemo) arm and by exposure quartiles for the EV + Pembro arm in Study EV-302.
Source: PopPK-ER Report No. TRN-7428, Figure 38

Table 28: Kaplan-Meier Survival Analysis of OS by Enfortumab Vedotin Exposure Quartiles

Endpoint	$C_{avg,C3}$ Quartile (ug/mL)	N	Events	Median Survival (months)	95% CI of Time to 50% Survival (months)
OS	Chemotherapy	433	222	16.1	14.3, 18.4
	EV Q1: [0.945,2.59]	108	48	20.2	15.4, 25.4
	EV Q2: (2.59,3.16]	109	27	NE	25.6, NE
	EV Q3: (3.16,3.63]	108	23	NE	NE
	EV Q4: (3.63,6.02]	107	30	31.5	22.9, NE

Abbreviations: $C_{avg\ C3}$: average concentration from Cycles 1 to 3; CI: confidence interval; N: number of subjects; NE: not estimated; Q: quartile.
Notes: Time to 50% survival determined using the Greenwood formula for time-to-event endpoints.
Source: PopPK-ER Report No. TRN-7428, Table 14

Exposure-Safety Analysis

The exposure-safety analysis was performed for the following safety endpoints: TEAEs leading to dose adjustments (dose interruptions, dose reductions and discontinuations), ≥ Grade 3 drug-related TEAEs, ≥ Grade 3 hyperglycemia, ≥ Grade 3 rash, ≥ Grade 3 SCAR, and ≥ Grade 2 peripheral neuropathy. Exploratory (graphical) exposure-safety analysis was conducted for Studies EV-103 and EV-302 individually and pooled. Statistical exposure-safety analysis was conducted for only the pooled population of studies EV-103 and EV-302.

The Antibody drug-conjugates (ADC) exposure metric for the exposure-efficacy analysis was the average concentration up to the event or end of treatment duration. Due to the time-varying nature of unconjugated MMAE PK, Cycle 1 C_{avg} was adopted for early onset AEs while for late onset AE, ≥ Grade 2 peripheral neuropathy, unconjugated MMAE C_{avg} up to the time of event was adopted.

Graphical analysis was used to assess exposure-safety relationships. As all safety endpoints were binary, incidence was computed for each exposure quartile. Logistic regression models were used to describe the exposure-safety relationship. In addition, time to first event was examined using Kaplan-

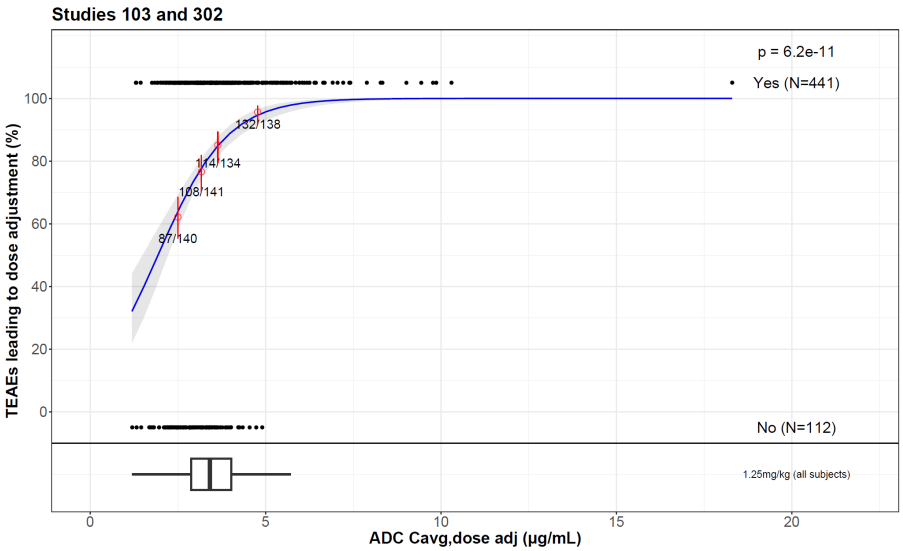
Meier curves, plotted by exposure quartile. Possible confounding variables, including treatment duration, dose modifications and covariates such as body weight, BMI, albumin, Nectin-4 expression (Nectin-4 IHC H-score), HbA1c, ECOG performance status score, prior peripheral neuropathy, prior hyperglycemia, and concomitant glucocorticoids, strong/moderate CYP3A4 inhibitors and P-gp inhibitors, were included in graphical evaluations.

Exposure-safety Analysis Population

The exposure-safety analysis population comprised data from 121 subjects in study EV-103 and 432 subjects in Arm A (EV + Pembro) of study EV-302 who received enfortumab vedotin at 1.25 mg/kg in combination with pembrolizumab in 1L and who were PK evaluable. From EV-103 study, in Cohort K (EV Mono arm), 72 subjects who received 1.25 mg/kg enfortumab vedotin monotherapy were analyzed separately for comparison with those who received enfortumab vedotin in combination with pembrolizumab. A total of 5 subjects in study EV-103 and 8 subjects in study EV-302 who received enfortumab vedotin in combination with pembrolizumab were excluded from the analysis because these subjects did not meet the exposure-safety population definition.

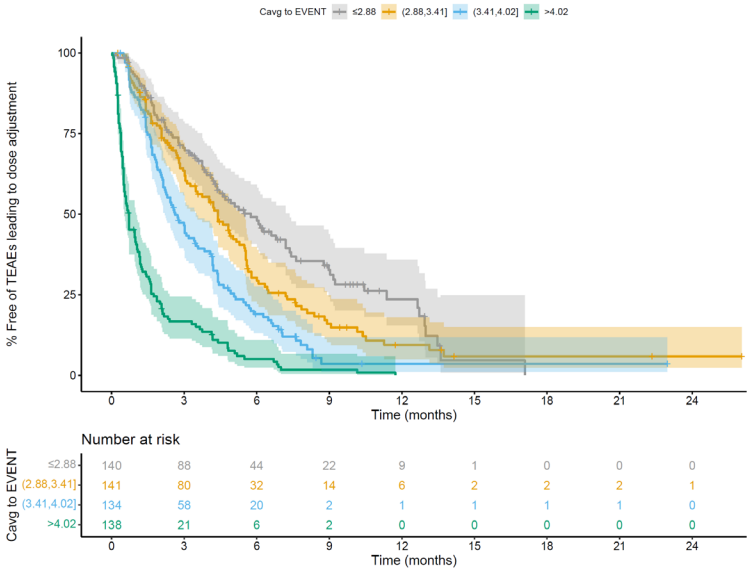
Key Findings from Exposure-Safety Modeling

Figure 19: Exposure Response Relationship for Treatment-emergent Adverse Events Leading to Enfortumab Vedotin Dose Adjustments (Interruptions, Reductions and Discontinuation) in the Exposure-Safety Population



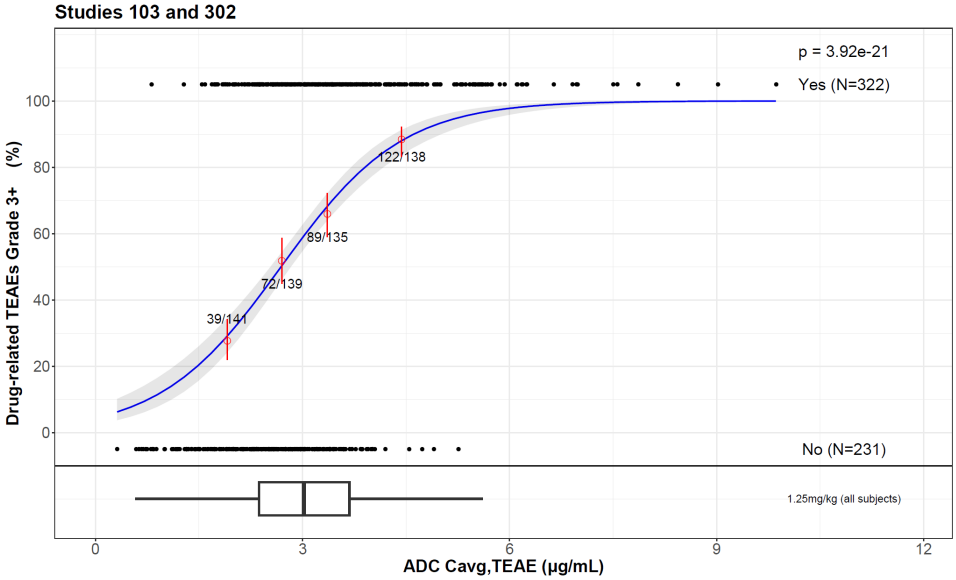
Plot shows probability of TEAEs leading to dose adjustment versus exposure. Yes and No refer to if subjects experienced or did not experience an event. Subjects are stratified into exposure quartiles. Red points are event rates per exposure quartile plotted at the median exposure of the quartile. Vertical red bars are 90% CIs of the AE rate. Blue line is the linear logistic regression fit. Gray band represents the 5th to 95th percentile CI of the fit. The P value is the significance level of the slope of the logistic regression fit using a z-test. Horizontal boxplot below shows the exposure distribution for all subjects (1.25-mg/kg dose); the box shows the interquartile range and whiskers show points within 1.5 times the interquartile range.
ADC: antibody-drug conjugate; AE: adverse event; C_{avg}: average concentration; CI: confidence interval; N: number of subjects; TEAE: treatment-emergent adverse event.

Figure 20: Kaplan-Meier Curves for TEAEs Leading to Enfortumab Vedotin Dose Adjustments (Interruptions, Reductions and Discontinuation) by Exposure Quartiles in the Exposure Safety Population



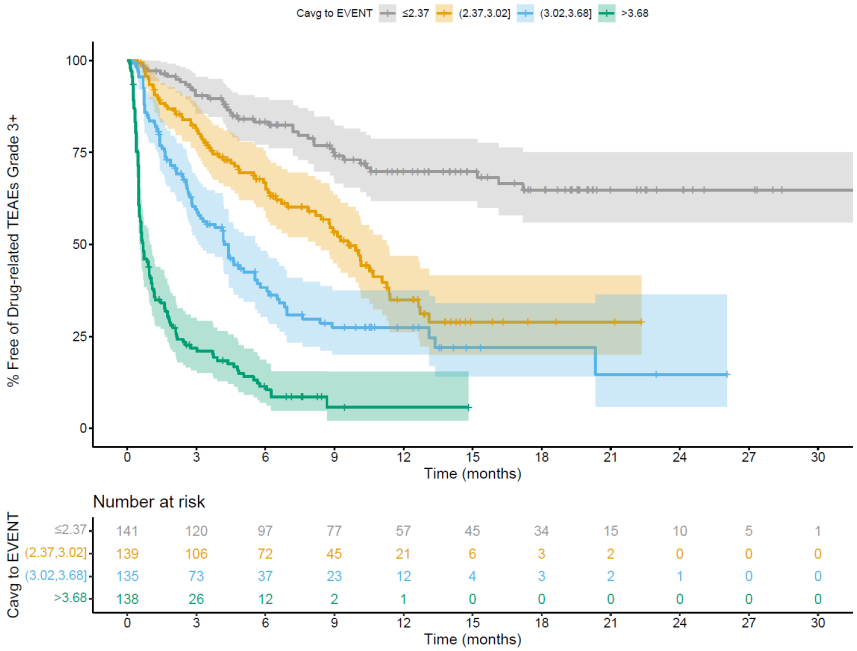
C_{avg}: average concentration; TEAE: treatment-emergent adverse event.

Figure 21: Exposure – Response Relationship for ≥ Grade 3 TEAEs



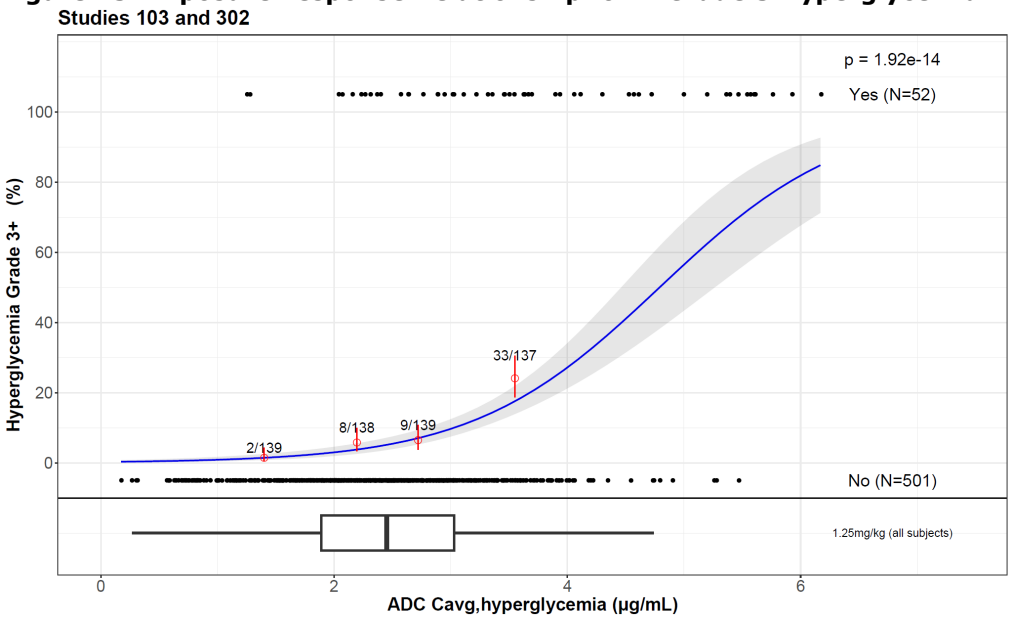
Plot shows probability of Grade ≥3 TEAEs versus exposure. Yes and No refer to if subjects experienced or did not experience an event. Subjects are stratified into exposure quartiles. Red points are AE rates per exposure quartile plotted at the median exposure of the quartile. Vertical red bars are 90% CIs of the AE rate. Blue line is the linear logistic regression fit. Gray band represents the 5^{th} to 95^{th} percentile CI of the fit. The P value is the significance level of the slope of the logistic regression fit using a z-test. Horizontal boxplot below shows the exposure distribution for all subjects (1.25-mg/kg dose); the box shows the interquartile range and whiskers show points within 1.5 times the interquartile range.
AE: adverse event; C_{avg}: average concentration; CI: confidence interval; N: number of subjects; TEAE: treatment-emergent adverse event.

Figure 22: Kaplan-Meier Curves for ≥ Grade 3 TEAEs by Exposure Quartiles in the Exposure-Safety population



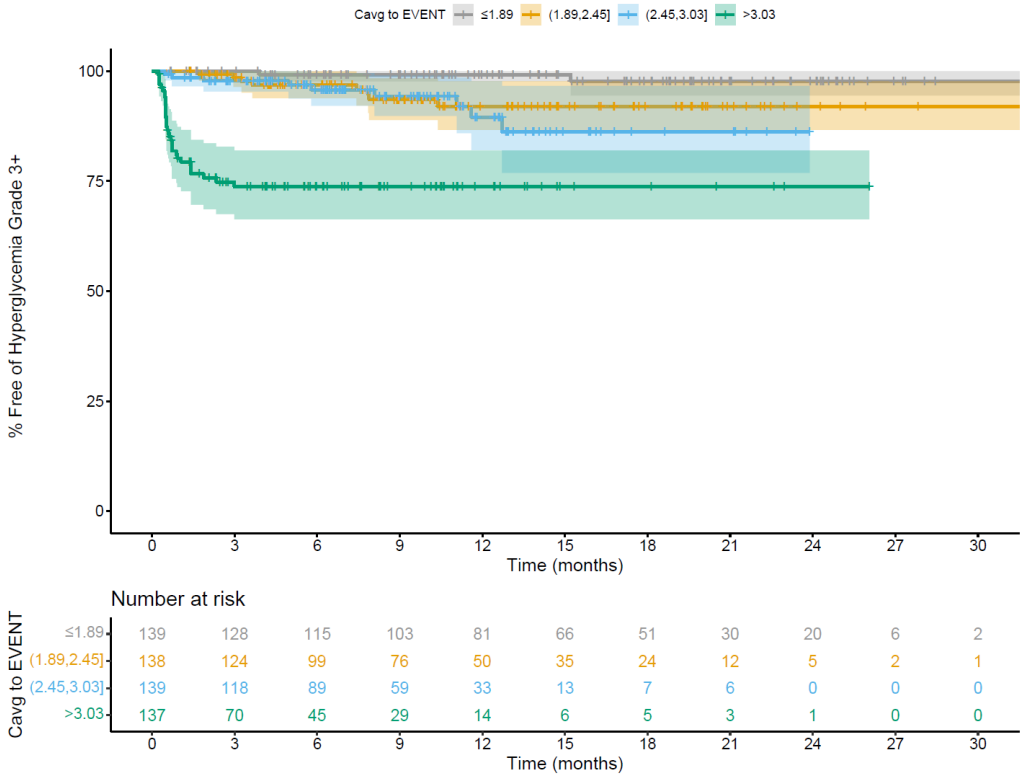
C_{avg}: average concentration; TEAE: treatment-emergent adverse event.

Figure 23: Exposure-response Relationship for ≥ Grade 3 Hyperglycemia



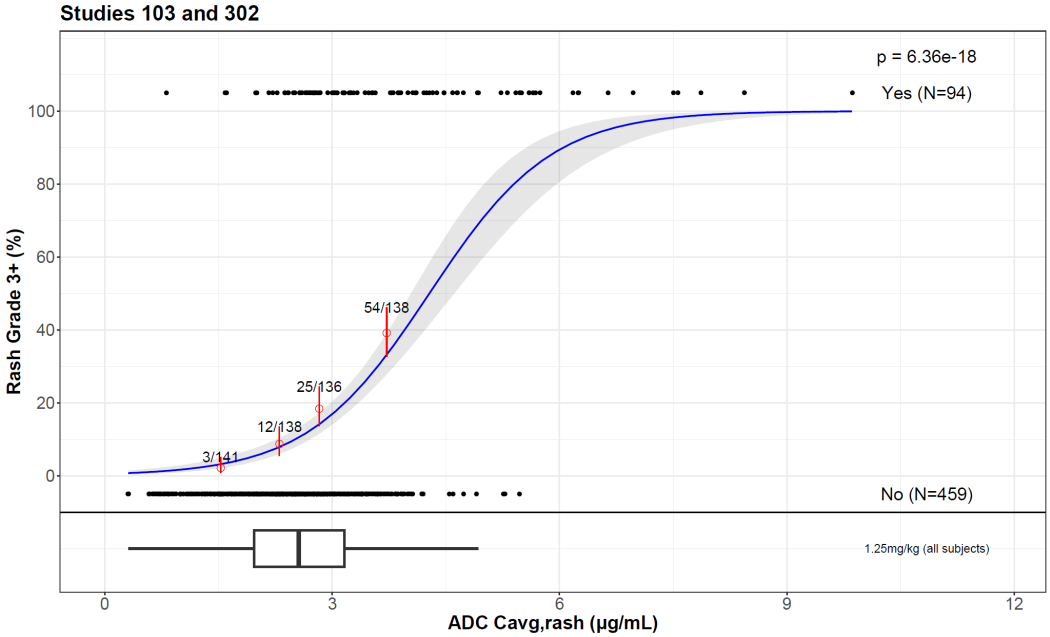
Plot shows probability of Grade ≥ 3 hyperglycemia versus exposure. Yes and No refer to if subjects experienced or did not experience an event. Subjects are stratified into exposure quartiles. Red points are AE rates per exposure quartile plotted at the median exposure of the quartile. Vertical red bars are 90% CIs of the AE rate. Blue line is the linear logistic regression fit. Gray band represents the 5th to 95th percentile CI of the fit. The P value is the significance level of the slope of the logistic regression fit using a z-test. Horizontal boxplot below shows the exposure distribution for all subjects (1.25-mg/kg dose); the box shows the interquartile range and whiskers show points within 1.5 times the interquartile range.
AE: adverse event; C_{avg}: average concentration; CI: confidence interval; EV: enfortumab vedotin; N: number of subjects; Pembro: pembrolizumab; TEAE: treatment-emergent adverse event.

Figure 24: Kaplan-Meier Curves for ≥ Grade 3 Hyperglycemia by Exposure Quartiles of Enfortumab Vedotin in the Exposure-Safety Population



C_{avg}: average concentration.

Figure 25: Exposure-response Relationship for Grade ≥ 3 Rash



Plot shows probability of Grade ≥ 3 rash versus exposure. Yes and No refer to if subjects experienced or did not experience an event. Subjects are stratified into exposure quartiles. Red points are AE rates per exposure quartile plotted at the median exposure of the quartile. Vertical red bars are 90% CIs of the AE rate. Blue line is the linear logistic regression fit. Gray band represents the 5th to 95th percentile CI of the fit. The P value is the significance level of the slope of the logistic regression fit using a z-test. Horizontal boxplot below shows the exposure distribution for all subjects (1.25-mg/kg dose); the box shows the interquartile range and whiskers show points within 1.5 times the interquartile range.
AE: adverse event; C_{avg}: average concentration; CI: confidence interval; N: number of subjects.

Figure 26: Exposure-response Relationship for Grade ≥ 3 Severe Cutaneous Adverse Reactions

Plot shows probability of Grade ≥ 3 severe cutaneous reactions versus exposure. Yes and No refer to if subjects experienced or did not experience an event. Subjects are stratified into exposure quartiles. Red points are AE rates per exposure quartile plotted at the median exposure of the quartile. Vertical red bars are 90% CIs of the AE rate. Blue line is the linear logistic regression fit. Gray band represents the 5th to 95th percentile CI of the fit. The P value is the significance level of the slope of the logistic regression fit using a z-test. Horizontal boxplot below shows the exposure distribution for all subjects (1.25-mg/kg dose); the box shows the interquartile range and whiskers show points within 1.5 times the interquartile range.
AE: adverse event; C_{avg}: average concentration; CI: confidence interval; N: number of subjects.

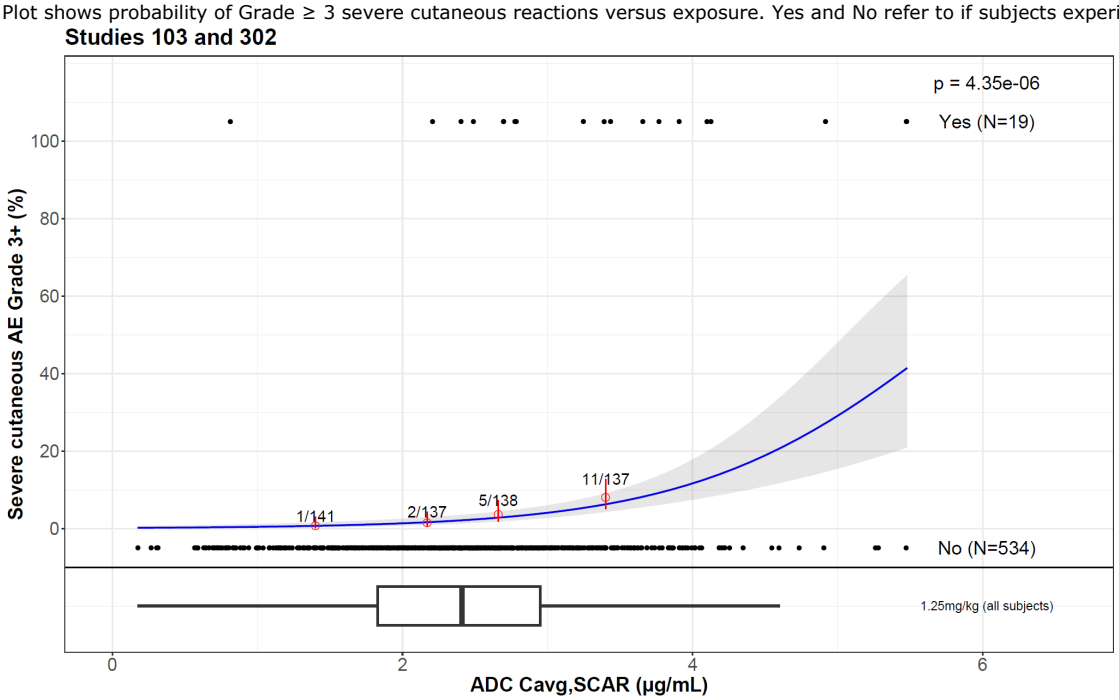
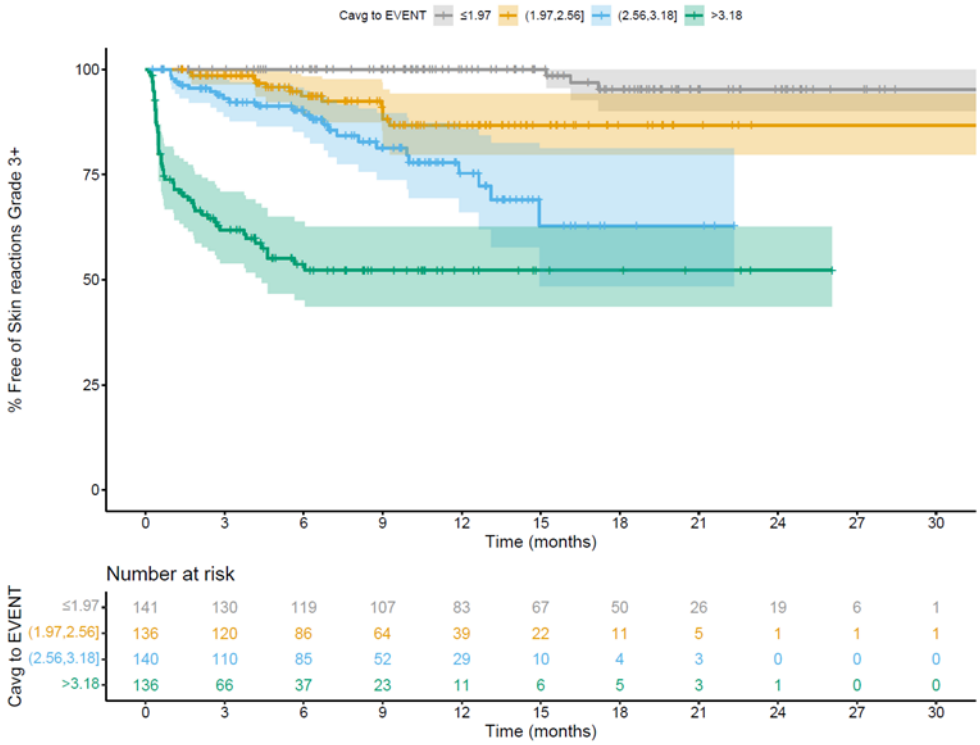
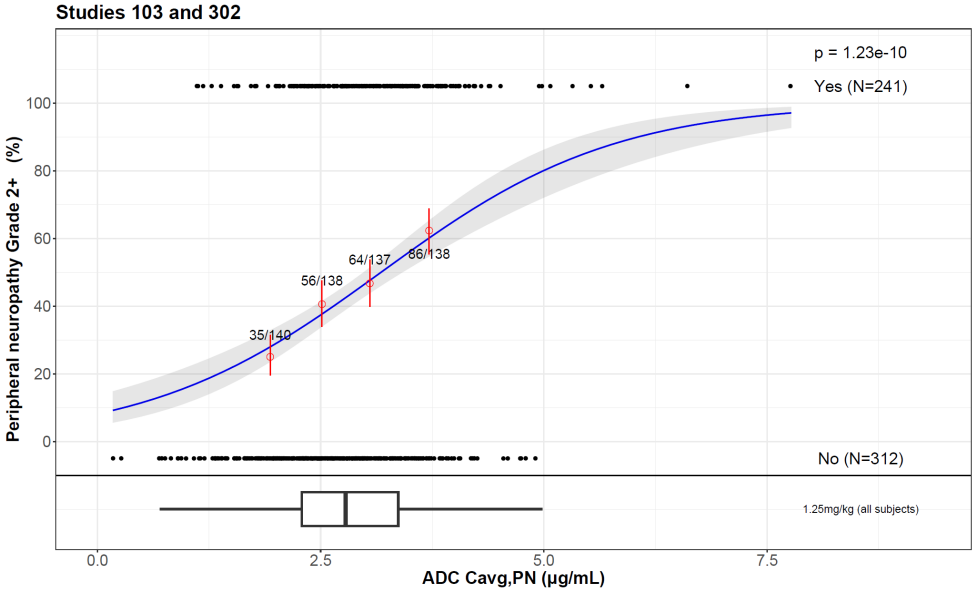


Figure 27: Kaplan-Meier Curves for ≥ Grade 3 Skin Reactions Free by ADC Exposure



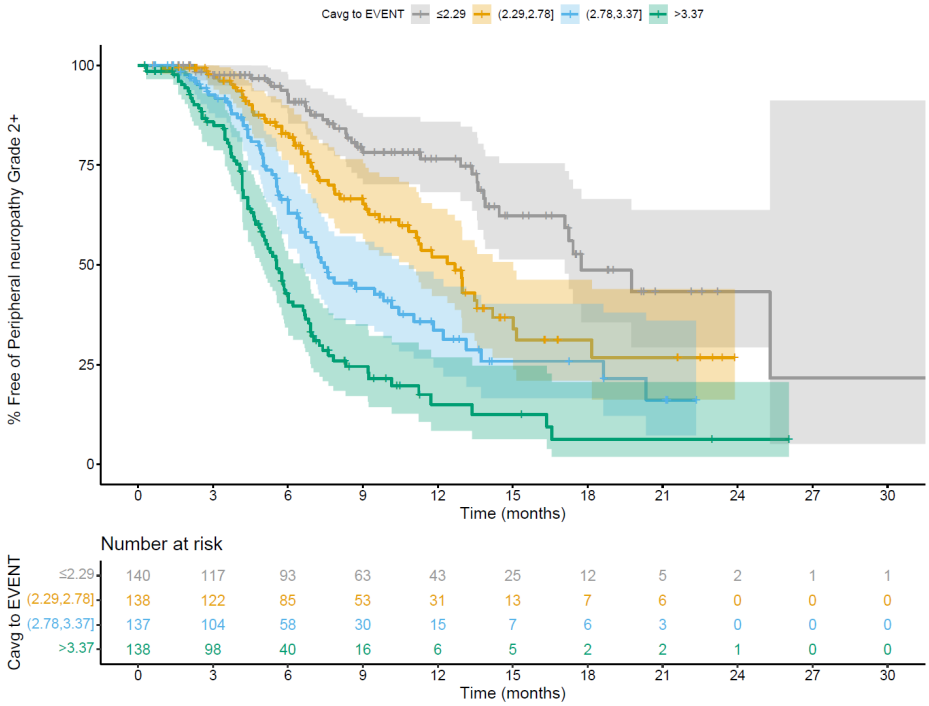
ADC: antibody-drug conjugate; C_{avg}: average concentration.

Figure 28: Exposure-response Relationship for Grade ≥ 2 Peripheral Neuropathy Quartiles



Plot shows probability of Grade ≥ 2 peripheral neuropathy versus exposure. Yes and No refer to if subjects experienced or did not experience an event. Subjects are stratified into exposure quartiles. Red points are AE rates per exposure quartile plotted at the median exposure of the quartile. Vertical red bars are 90% CIs of the AE rate. Blue line is the linear logistic regression fit. Gray band represents the 5th to 95th percentile CI of the fit. The P value is the significance level of the slope of the logistic regression fit using a z-test. Horizontal boxplot below shows the exposure distribution for all subjects (1.25-mg/kg dose); the box shows the interquartile range and whiskers show points within 1.5 times the interquartile range.
AE: adverse event; C_{avg}: average concentration; CI: confidence interval; N: number of subjects.

Figure 29: Kaplan-Meier Curves for Grade ≥2 Peripheral Neuropathy-free by ADC Exposure Quartiles



ADC: antibody-drug conjugate; C_{avg}: average concentration.

2.3.4. Discussion on clinical pharmacology

Bioanalytical methods and conduct of bioanalysis were demonstrated to be in control.

Antibody drug conjugated and unconjugated MMAE concentrations from studies EV-103 and EV-302 were described by Pop PK analysis in which enfortumab vedotin (EV) was dosed 1.25 mg/kg 2Q3W (Day 1 and Day 8 in a 21-day cycle) to subjects with urothelial cancer. Except for 72 subjects who received EV monotherapy, all subjects received EV in combination with pembrolizumab. The concentration-time profiles of unconjugated MMAE showed a decline over time following continued dosing. Therefore, a revised version of the previous free MMAE 2-compartment model was used to describe the time-dependent decrease in drug-antibody ratio. The previous 3-compartment model for ADC was used without modification for description of ADC data by external validation and showed a good fit of data. Of note, a dose cap of 125 mg for subjects with a BW ≥100 kg was not incorporated in the model by error, even this dose rule was applied in studies EV-103 and EV-302. Revised analyses, in which the correct dose regimens were applied, did not indicate clinically relevant impact on the model performance, covariate effects or predicted exposure for ADC or MMAE. The model is considered adequate for description of enfortumab vedotin PK and exposure metrics for exposure-response analyses.

PK evaluation on combo therapy of Enfortumab vedotin (EV)+Pembro was conducted mainly in the EV-103 study, whereas in study EV-302 samples were collected but not analysed.

Pembrolizumab was administered on day 1 of a 21-day cycle as 200 mg Q3W, which is the dosage and timing already approved for the monotherapy in the same population of patients, provided that they present a PD-L1 score of expression (CPS) ≥ 10. The observed PK parameters are similar between the combo- and mono-therapy arms meaning that Pembrolizumab doesn't impact the PK of EV. Furthermore, by a slight extrapolation when comparing to Pembro alone arm of supportive studies (KEYNOTE-001, -002, -006, -010, and -024), EV does not seem to impact the PK of Pembrolizumab either.

Study EV-103

PK profiles of enfortumab vedotin were obtained in patients in two subsequent cycles (42 days) for ADC, total antibody and MMAE for comparison of pharmacokinetics as monotherapy and in the presence of pembrolizumab. The number of patients in cohort K in which PK profiles were obtained for comparison of monotherapy and in combination were sufficient, i.e. N>70. No significant or systematic changes in PK parameters or serum concentrations were observed. Hence, from study EV-103, it can be concluded that pembrolizumab does not impact the pharmacokinetics of enfortumab vedotin (Padcev).

Study EV-302

In study EV-302, PK samples for enfortumab vedotin and MMAE were obtained at end of infusion (EOI) and/or pre-dose in cycle 1, 2, 3, 5 and 7. Mean serum concentrations of enfortumab vedotin and MMAE were similar to values observed in study EV-103. No accumulation was observed over the cause of the 7 cycles of treatment.

It should however be noted that the currently approved and the new dosing regimen are different. A comparison of exposure between the two dose regimen was not presented. The currently approved dosing regimen is intravenous infusion over 30 minutes on Days 1, 8 and 15 of a 28-day cycle and the new dosing regimen is infusion over 30 minutes on Days 1 and 8 of a 21-day cycle.

Simulations demonstrated a slight decrease in both ADC and MMAE for the dosing regimen designed for combination with pembrolizumab (2Q3W) as compared to the dosing regimen for mono-therapy (3Q4W).

The Cavg within the 12-week period is expected to be lower for the 2Q3W regimen, as it is one dose less than the 3Q4W regimen within a 12-week period. Nevertheless, the slight decrease in Cavg up to Week 4 and Week 12, which was observed between the two regimens for both ADC and unconjugated MMAE is considered to be within PK variability. As the dosing regimen for the combination results in slightly lower exposure to both ADC and MMAE, safety issues related to e.g. systemic exposure to MMAE is expected to be similar or lower than for the enfortumab vedotin dosing regimen as monotherapy.

When given in combination with pembrolizumab, 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 and 8 of every 3-week (21-day) cycle until disease progression or unacceptable toxicity. The recommended dose of pembrolizumab is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes. Patients should be administered pembrolizumab after enfortumab vedotin when given on the same day. Refer to the pembrolizumab SmPC for additional dosing information of pembrolizumab.

Time dependencies

The updated POPPK model identified a time dependent decrease in the formation rate of MMAE. The estimated median decline in the formation rate of unconjugated MMAE was 31% at the end of Cycle 1 and 45% asymptotically. The time to 50% of maximal decline was 309 hours (12.9 days).

The clinical implication for this time dependency was not discussed by the Applicant, however is not expected to be a safety concern or concern for lack of long-term efficacy.

Hepatic impairment

It is agreed that an increase of 16% MMAE (Cavg at C1) is estimated (2.49 ng/ml in normal and 2.92 ng/mL in subjects with mildly impaired liver function. The numbers are 3.44 (n=2) and 7.06 (n=1) for moderate and severe which is an increase of 37.1% and 180.9% respectively. Data from this one patient with severe hepatic impairment shows that treatment with enfortumab vedotin should be closely followed in patients with severe hepatic impairment. The wording on moderate and severe hepatic impairment was amended in sections 4.2 and 5.2 to inform physicians about the potential risk of AEs. However, no initial dose modification recommendations can be made based on the limited data.

Pharmacodynamics

Immunogenicity: Incidence of anti-EV antibodies in study EV-103 across the dose escalation cohort and cohorts A and K was overall low (≈3%), both at baseline and during treatment.

Exposure-efficacy analyses: Although a clear relationship between exposure to EV (in the EV+Pembro arm of EV-302) and response rates was observed, PFS and OS were consistently improved across quartiles of exposure and above chemotherapy performance. Of note, patients in the first quartile of exposure, likely impacted by dose reductions/interruptions, also obtained efficacy benefits from EV+Pembro in comparison to their chemotherapy counterparts.

Exposure-safety analyses: Overall, ADC exposure may be a better predictor of safety events given its more prominent exposure-response relationships. In general, an increase in incidence of all or most AEs was observed with an increase in body weight as the exposure trended higher in the higher body weight subjects under body weight-dosing; however high body weight may be also confounded by other risk factors.Combination of enfortumab vedotin with PD-1 inhibitors results in enhanced anti-

tumour activity, consistent with the complementary mechanisms of MMAE induced cell cytotoxicity and induction of immunogenic cell death, plus the up-regulation of immune function by PD-1 inhibition.

2.3.5. Conclusions on clinical pharmacology

Overall, the clinical pharmacology of enfortumab vedotin given in combination with pembrolizumab is considered well described and acceptable.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

Exposure-response models are described in the pharmacology sections.

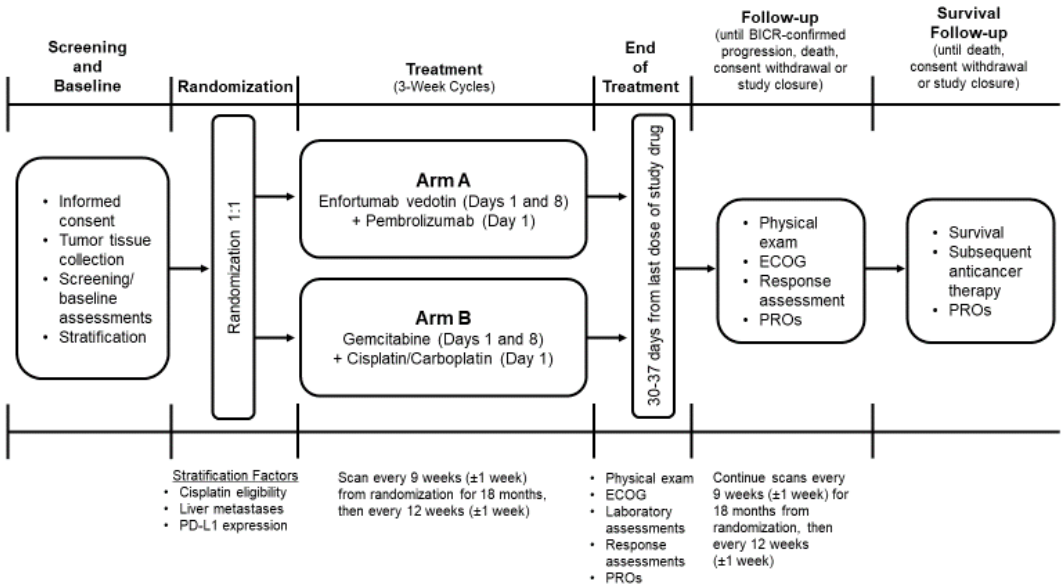
2.4.2. Main study

Title of Study EV-302 (KEYNOTE-A39)

Study EV-302 is an ongoing, global phase 3, open-label, 2-arm randomized multicenter study to evaluate the combination of EV+ Pembro (Arm A) versus standard of care Platinum + Gem (Arm B) in subjects with previously untreated LA/mUC.

The original protocol included a third arm (Arm C, enfortumab vedotin + pembrolizumab + cisplatin or carboplatin). Arm C was removed from the protocol in Amendment 2 based on data from external clinical trials. Prior to removal, 11 patients were enrolled in Arm C. The Clinical efficacy section will only focus on results from arm A (EV + Pembro) and arm B (Plat + Gem).

Figure 30: Design of Study EV-302 (KEYNOTE-A39)



After completion of enrollment in the global portion, subjects in China continued to be randomized in a 1:1 ratio to either the EV + Pembro arm or Plat + Gem arm until the planned sample size of approximately 130 subjects in China is reached. Subjects in China who are randomized after

completion of enrollment in the global portion of the study are not included in the analysis and CSR of the global portion.

Methods

Study participants

Main inclusion criteria:

1. Subjects must have had histologically documented, unresectable locally advanced or metastatic urothelial carcinoma (i.e. cancer of the bladder, renal pelvis, ureter, or urethra). Subjects with squamous or sarcomatoid differentiation or mixed cell types were eligible.
2. Subjects must have had measurable disease by investigator assessment according to RECIST v1.1.
    a. Subjects with prior definitive radiation therapy must have had measurable disease per RECIST v1.1 that is outside the radiation field or has demonstrated unequivocal progression since completion of radiation therapy
3. Subjects must not have received prior systemic therapy for locally advanced or metastatic urothelial carcinoma with the following exceptions:
    a. Subjects that received neoadjuvant chemotherapy with recurrence >12 months from completion of therapy were permitted
    b. Subjects that received adjuvant chemotherapy following cystectomy with recurrence >12 months from completion of therapy were permitted
4. Subjects must have been considered eligible to receive cisplatin- or carboplatin-containing chemotherapy, in the investigator's judgment.
    a. Subjects would have been considered cisplatin-ineligible, and would receive carboplatin, if they meet at least one of the following criteria:

        i. GFR <60 mL/min but ≥30 mL/min (measured by the Cockcroft-Gault formula, Modification of Diet in Renal Disease [MDRD] or 24-hour urine). Subjects with a GFR ≥ 50 mL/min and no other cisplatin ineligibility criteria may be considered cisplatin-eligible based on the investigator's clinical judgment

        ii. ECOG or WHO performance status of 2 (refer to inclusion criterion 6a for additional criteria for ECOG 2 subjects)

        iii. NCI CTCAE Grade ≥2 audiometric hearing loss

        iv. NYHA Class III heart failure

5. Archival tumor tissue comprising muscle-invasive urothelial carcinoma, or a biopsy of metastatic urothelial carcinoma were to be provided for PD-L1 testing (as determined by the Dako/Agilent PD-L1 IHC 22C3 PharmDx assay) prior to randomization. If adequate archival tumor sample was not available, or evaluable, a new biopsy sample may have been performed.
6. Subjects must have had an ECOG Performance Status score of 0, 1, or 2.
    a. Subjects with ECOG performance status of 2 must have additionally meet the following criteria:
7. Hemoglobin ≥10 g/dL
8. ii. GFR ≥50 mL/min
9. iii. May not have NYHA Class III heart failure

10. Subjects must have had adequate hematologic and organ function, including creatinine clearance ≥30 mL/min.

Main exclusion criteria:

1. Subjects who previously received enfortumab vedotin or other MMAE-based ADCs
2. Subjects who received prior treatment with a PD-(L)1 inhibitor for any malignancy, including earlier stage UC, defined as a PD-1 inhibitor or PD-L1 inhibitor
3. Subjects who previously received any prior treatment with an agent directed to another stimulatory or co-inhibitory T-cell receptor
4. Subjects who received anticancer treatment with chemotherapy, biologics, or investigational agents not otherwise prohibited by exclusion criteria above that were not completed 4 weeks prior to first dose of study treatment
5. Subjects with uncontrolled diabetes
6. Subjects with an estimated life expectancy < 12 weeks
7. Subjects with ongoing sensory or motor neuropathy Grade 2 or higher
8. Subjects with active CNS metastases
9. Subjects with ongoing clinically significant toxicity associated with prior treatment (including radiotherapy or surgery) that had not resolved to ≤ Grade 1 or returned to baseline
10. Subjects with conditions requiring high doses of steroids (> 10 mg/day of prednisone or equivalent) or other immunosuppressive medications were excluded. Inhaled or topical steroids were permitted in the absence of active autoimmune disease. Physiologic replacement doses of corticosteroids were permitted for subjects with adrenal insufficiency.
11. Subject with pneumonitis or other forms of interstitial lung disease
12. Subjects with a history of another invasive malignancy within 3 years before the first dose of study drug, or any evidence of residual disease from a previously diagnosed malignancy. Subjects with nonmelanoma skin cancer or carcinoma in situ of any type (if complete resection was performed) were allowed.

o A history of prostate cancer (T2NXMX or lower with Gleason score ≤ 7) treated with definitive intent (surgically or with radiation therapy) at least

Treatments

Table 29 summarises treatments in both arms of the pivotal trial.

Table 29: Treatments in Study EV-302 (KEYNOTE-A39)

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

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

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

Subjects in the Plat + Gem Arm (ArmB) received gemcitabine at 1000 mg/m2 as an IV infusion on days 1 and 8 of every 3 week cycle, and either cisplatin (70 mg/m2) or carboplatin (area under the curve [AUC] 4.5, or AUC 5 according to local guidelines) on day 1 of every 3 week cycle, with adequate pre and post-hydration, by IV infusion per institutional standards.

Maintenance therapy (e.g., avelumab) could be used following completion and/or discontinuation of platinum containing therapy, if locally available, and provided the subject was deemed eligible by the investigator. Avelumab must have been used in accordance with the latest version of the local labelling currently available.

Duration of treatment: Treatment with Plat + Gem may have been given up to 6 cycles. Treatment with pembrolizumab was discontinued once the subject had received a maximum of 35 administrations of pembrolizumab (approximately 2 years). There was no upper limit to the number of cycles of enfortumab vedotin permitted and enfortumab vedotin was administered until disease progression or an unacceptable AE occurred.

Crossover to the experimental arm of the trial (Arm A) was not permitted for subjects in the control arm (Arm B).

Dose modifications: Dose reduction or delay for other enfortumab vedotin-associated haematologic or non hematologic toxicity was permitted at the discretion of the site investigator. Dose reduction from 1.25 mg/kg to 1 mg/kg or to 0.75 mg/kg was allowed depending on the type and severity of toxicity. Dose reduction for pembrolizumab was not permitted, but it could be delayed in case of immune-related AEs (in which case administration of corticosteroids and other supportive treatment was permitted).

Other interventions: Palliative radiotherapy on a nontarget bone lesion that was not progressing was permitted and was not be considered a subsequent anticancer therapy; however, radiotherapy on any new or progressing lesion, per RECIST v1.1 as assessed by the investigator or after BICR-confirmed progression, was considered a subsequent anticancer therapy and subjects were not be permitted to

resume study treatment. Surgical resection for curative intent during study treatment may have been permitted in subjects with favourable tumour response after discussion with the medical monitor.

Objectives and corresponding endpoints

Specific objectives and corresponding endpoints for the study are summarized in Table 30.

Table 30: Objectives and corresponding endpoints in Study EV-302 (KEYNOTE-A39)

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

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

Sample size

The sample size of the study was determined to provide at least 90% power for each of the primary endpoints, at an initially allocated alpha of 0.005 (2-sided) for PFS and 0.045 (2-sided) for OS.

For the OS endpoint, 489 events were required to provide 93% power to detect a hazard ratio (HR) of 0.73 using a log-rank test at an alpha level of 0.045 (2-sided), taking into account one interim analysis at approximately 72.8% of the target number of events. Design assumptions for OS are the following: (1) OS curves follow piecewise exponential distribution with a reduced hazard rate (50% of the initial rate) starting from 24 months (Table 31); (2) hazard ratio of OS is 0.73 between Arm A and Arm B; (3) median OS for Arm B is 15.3 months; (4) an enrolment period of 30 months; (5) a yearly dropout rate of 5%.

Table 31: Hazard rates for OS curves

	Starting at Time	Hazard Rates	
Period #	(months)	Arm B	Arm A
1	0	0.045	0.033
2	24	0.023	0.017

Under the above assumptions, approximately 860 subjects were to be randomized in a 1:1 ratio to Arm A or Arm B. It was anticipated that 489 OS events were to be observed approximately 17 months after the last subject randomized. For the PFS endpoint, 526 events were required to provide 90% power to detect a hazard ratio of 0.7 at an alpha level of 0.005 (2-sided) under the following assumptions: (1) PFS curves follow piecewise exponential distribution with a reduced hazard rate (20% of the initial rate) starting from 15 months (Table 32); (2) HR of PFS is 0.70 between Arm A and Arm B; (3) median PFS for Arm B is 7 months; (4) an enrolment period of 30 months; (5) a yearly dropout rate of 5%.

Table 32: Hazard rates for PFS curves

Period #	Starting at Time (months)	Hazard Rates	
		Arm B	Arm A
1	0	0.099	0.069
2	15	0.02	0.014

Randomisation

Subjects were randomized in a 1:1:1 ratio to 1 of the following treatment arms:

- Arm A (enfortumab vedotin + pembrolizumab)
- Arm B (gemcitabine + cisplatin or carboplatin)
- Arm C (enfortumab vedotin + pembrolizumab + cisplatin or carboplatin)

Randomization was based on the following stratification factors: platinum eligibility (cisplatin versus carboplatin), PD-L1 expression (high or low), and liver metastases (present or absent).

Blinding (masking)

This is a randomized, open-label study.

To maintain trial integrity, until database lock and study unblinding for the pre-planned analyses, analyses or summaries by treatment assignment were only planned for the purpose of the IDMC monitoring and were to be conducted by an external vendor. The primary endpoint of PFS along with response-based secondary endpoints were to be assessed by BICR. All imaging for response assessment was centrally reviewed by the independent radiologists who did not have knowledge of treatment assignment.

Analysis sets

All Enrolled Subjects

All enrolled subjects included all subjects who signed the inform consent form, meet eligibility criteria, and were randomized in the study or enrolled for Japan-specific safety run in.

Intent-to-Treat (ITT) Analysis Set

The ITT analysis set included all randomized subjects. Subjects were to be analysed according to the treatment arm assigned at randomization regardless of the actual treatment received.

Response Evaluable Set

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

Safety Analysis Set

The safety analysis set included all enrolled subjects who received any amount of study treatment. Subjects were to be analysed according to the actual treatment received. If a subject receives incorrect study treatment for part of the treatment period, the subject were to be analysed under the treatment with the greater number of cycles.

Statistical methods

Unless otherwise specified, confidence intervals (CI) was calculated at 2-sided 95% level. The 2-sided 95% exact CI using Clopper-Pearson methodology was calculated for the response rates where applicable (e.g., ORR). For time-to-event endpoints, the median survival time was estimated using the Kaplan-Meier (KM) method; the associated 95% CI was calculated based on the complementary log-log transformation.

Any analysis that was not described in this plan was to be considered exploratory and documented as a post hoc analysis or a change to the planned analysis.

With the exception of the scenarios covered in this section, missing data were be imputed. Subjects who did not have at least two (initial response and confirmation scan) post-baseline response assessments were counted as non-responders for analysis of ORR.

Table 33: Efficacy Endpoints: Definitions and Key Summary Statistics

Endpoint	Definition/Key Summary Statistics
PFS‡	Time from date of randomization to first documentation of disease progression or to death due to any cause, whichever comes first • HR and 95% CIs • 2-sided p-value from stratified log-rank test • Kaplan-Meier plots • Median and 95% CIs • Graphical display (forest plot) of subgroup analysis
OS§	Time from date of randomization to date of death due to any cause • HR and 95% CIs • 2-sided p-value from stratified log-rank test • Kaplan-Meier plots • Median and 95% CIs • Graphical display (forest plot) of subgroup analysis
ORR†	Proportion of subjects with confirmed CR or PR • ORR and 95% CIs • 2-sided p-value from CMH test • Graphical display (forest plot) of subgroup analysis.
DOR‡	Time from first documentation of objective response (that is subsequently confirmed) to the first documentation of objective tumor progression or to death due to any cause, whichever comes first. • Kaplan-Meier plots • Median and 95% CIs
DCR	Proportion of subjects with confirmed response (CR or PR) or SD • DCR and 95% CIs

Table 34: Censoring scheme for primary analysis of PFS per RECIST v1.1 by BICR

Scenario	Progression/Censor Date	Outcome
PD or death before subsequent anticancer treatment and not after two or more consecutive missed assessments	Earliest date of PD or death	Event
PD or death immediately after two or more consecutive missed/NE tumor assessments	Date of last adequate tumor assessment prior to the missed visits or date of randomization if no post-baseline tumor assessment	Censored
No PD or death and no post-baseline tumor assessments	Date of randomization	Censored
No PD or death and no subsequent anticancer treatment	Date of last adequate tumor assessment	Censored
Subsequent anticancer treatment started before PD or death	Date of last adequate tumor assessment on or prior to start of subsequent anticancer treatment	Censored

Note: maintenance therapy (e.g., avelumab) that is received after discontinuation or completion of chemotherapy in Arm B and local therapy per medical adjudication will not be considered as subsequent anticancer therapy.

Overall Survival (OS)

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

Objective Response Rate (ORR)

ORR was defined as the proportion of subjects with confirmed CR or PR according to RECIST v1.1. Subjects who do not have at least 2 (initial response and confirmation scan) post-baseline response assessments would have been counted as non-responders for the primary analysis of ORR. For a response to be considered as confirmed, the subsequent response needed to be at least 4 weeks after the initial response. For subjects who do not have confirmed CR or PR, the best overall response was defined as SD if the subject has at least one response assessment of CR/PR/SD (or non-CR/non-PD) at least 6 weeks after the randomization date. ORR per investigator and per BICR would be analyzed.

Duration of Response

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

Progression-Free Survival Per Investigator Assessment

PFS, per investigator assessment, was defined as the time from randomization to first documentation of disease progression per RECIST v1.1, or to death due to any cause, whichever comes first. The same censoring rules for PFS per BICR would be applied to PFS per investigator.

Interim analysis

No interim analyses were planned for the primary endpoint of PFS. One interim analysis for superiority was conducted for the primary endpoint of OS at the time of the PFS final analysis. For the OS analysis, the Lan-DeMets spending function with O'Brien-Fleming boundaries was used to calculate the efficacy boundaries based on the actual number of events observed. If the treatment difference for OS was statistically significant at time of the interim analysis, it was to be considered the final OS analysis.

The PFS final analysis was to be triggered when approximately 526 PFS events or 356 OS events (72.8% information fraction) in the ITT analysis set have occurred, whichever was later. An OS IA was planned at the time of the PFS final analysis. At IA, the number of OS events would be approximately 356 (about 72.8% of information). The OS final analysis was triggered when approximately 489 OS events have occurred in the ITT analysis set. A summary of analyses timing at the planned PFS and OS analyses are presented in Table 35. The results are based on the initial alpha allocated to each endpoint before any alpha recycling: 0.005 to PFS and 0.045 to OS.

Table 35: Summary of timing of analyses

Analysis		2-sided alpha[d]	Est. Time after LPI	Planned # of Events	Power at Initial Alpha (0.005 to PFS, 0.045 to OS)	Power at Updated Alpha (0.05 to PFS and OS)
Analysis Time 1[a]	FA: PFS	0.005	7 months	526	90%	98%
	IA: OS	0.015	7 months	356 (72.8% info.)	70%[b]	72%[b]
Analysis Time 2	FA: OS	0.045	17 months	489	93%[c]	93%[c]

FA = Final Analysis; IA = Interim Analysis; LPI = Last Patient In

a Analysis Time 1 is triggered by the planned number of PFS events in total (526 events), or 356 OS events (72.8% information fraction), whichever is later.

b Probability to cross the efficacy boundary at the interim analysis

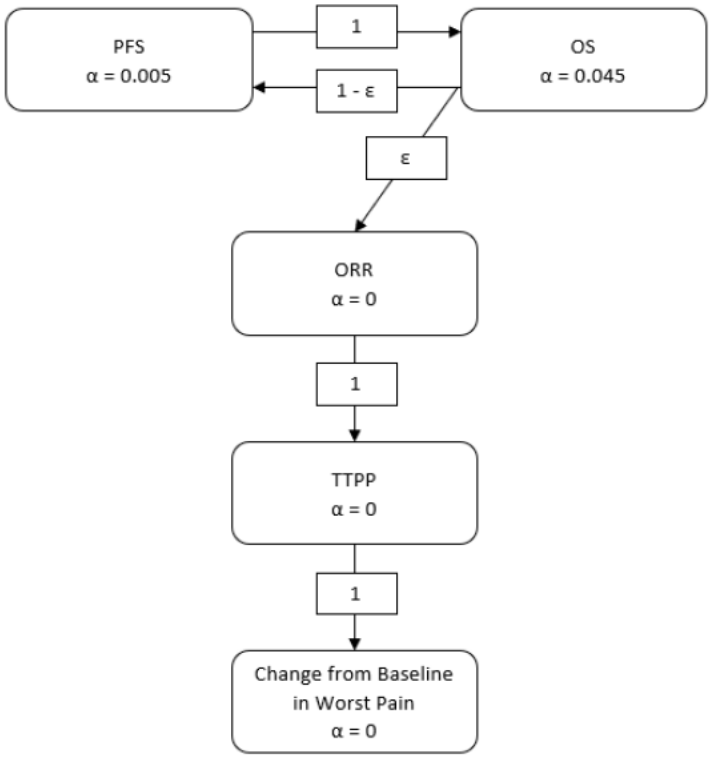
c Overall power at the final OS analysis

d Cumulative alpha assigned for each test without alpha roll-over. For OS IA, 0.015 is the estimated alpha spent at IA.

Multiplicity

The study was designed to assess the dual primary endpoints of PFS and OS. To maintain strong control of the family-wise type I error rate at 0.05 (2-sided), a graphical approach with group sequential testing outlined in Maurer and Bretz (Maurer 2013) was used. The initial alpha allocation was 0.005 to PFS and 0.045 to OS as shown in the figure below, in which ε is a positive number close to zero (i.e. a negligible amount), indicating the potential to pass alpha to ORR only if both PFS and OS are statistically significant. If one of the primary endpoints was statistically significant, the alpha initially assigned to that endpoint could be rolled over to the other endpoint.

Figure 31: Graphical Illustration of Multiplicity Adjustment



The study would test PFS only once at the time of PFS final analysis. The efficacy boundaries at the initially allocated alpha of 0.005 and the updated alpha of 0.05 (if OS is statistically significant) are shown in the following table.

Table 36: Efficacy boundaries for PFS analysis

	alpha=0.005		alpha=0.05	
Analysis	p-value	Approx. Obs. HR	p-value	Approx. Obs. HR
FA	0.005	0.783	0.05	0.843

The study was planned to have two OS analyses, one interim analysis at the time of PFS final analysis and one final analysis. The efficacy boundaries at the interim and final analyses would have been determined using the Lan-DeMets spending function to approximate O'Brien-Fleming boundaries. The following Table 37 shows the efficacy boundaries at the initially allocated alpha of 0.045 and the updated alpha of 0.05 (if PFS is statistically significant).

Table 37: Efficacy boundaries for OS analysis

	alpha=0.045		alpha=0.05	
Analysis	p-value	Approx. Obs. HR	p-value	Approx. Obs. HR
IA (Information Fraction: 72.8%)	0.015	0.773	0.017	0.777
FA	0.040	0.831	0.045	0.834

If both PFS and OS are statistically significant, selected secondary endpoints were to be tested in the following order using a gatekeeping testing strategy: 1. ORR by BICR

2. TTPP

3. Mean change from baseline in worst pain at Week 26.

Each test would be at the 0.05 significance level (2-sided) as long as all preceding null hypotheses were rejected. These secondary endpoints would only be tested once at either the OS interim or final analysis after the null hypotheses for PFS and OSwere both rejected, and the test statistics for inferential testing would be computed from the data at the time of OS interim analysis. In the event that only the null hypothesis for PFS was rejected and the superiority boundary for OS had not been crossed at the time of OS interim analysis, these secondary endpoints would have not be tested and only analyzed descriptively.

Changes from planned analyses

The current version of the SAP, version 4.0, was finalized on 22 Jun 2023, prior to the database lock. There were no changes to the planned analyses described in the final SAP.

Results

Participant flow

Results from Arm C are not presented within this report.

Figure 32: Subject disposition (ITT analysis set) in Study EV-302 (KEYNOTE-A39)

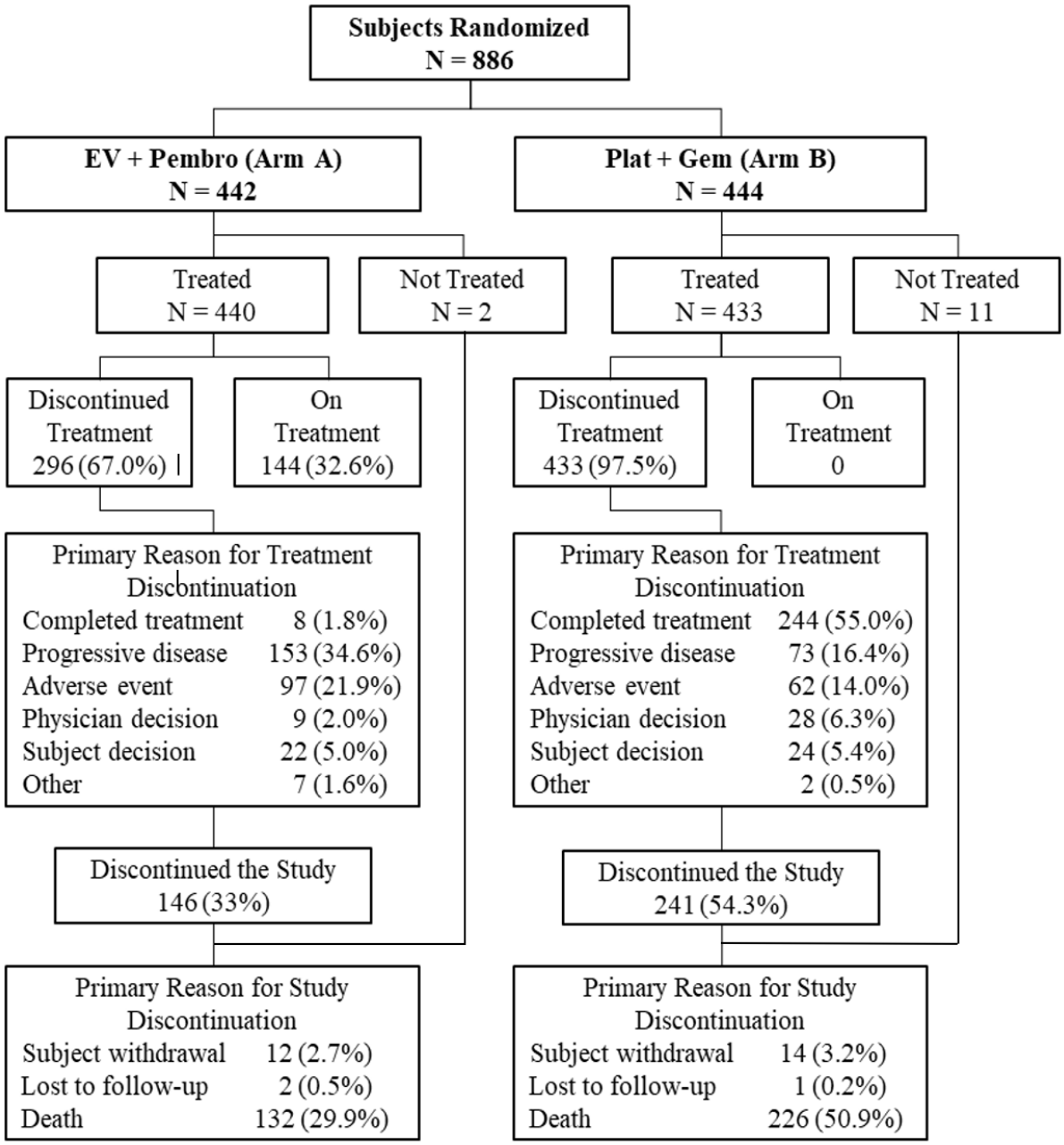


Table 38: Summary of screen failures in EV-302 (KEYNOTE-A39)

	Total (N=1297) n (%)
Subjects signed informed consent[a]	1297 (100)
Screen failures[b]	397 (30.6)
Reason for screening failures[c]	
Subject did not meet eligibility criteria	263/397 (66.2)
Subject withdrew consent	52/397 (13.1)
Death	19/397 (4.8)
Investigator decision	24/397 (6.0)
Other	39/397 (9.8)

Page 1 of 1

a. Subjects who were screened multiple times were only counted once.
b. Subjects who signed informed consent but not randomized or enrolled are considered screen failures. Subjects who failed screening initially and subsequently rescreened and randomized/enrolled to the study were not included.
c. For subjects who were rescreened, the last screen failure reason was summarized.
Snapshot date: 06Sep2023, data cutoff date: 08Aug2023

Recruitment

Beginning in 30 March 2020 (date of first signed informed consent), a total of 1,297 subjects were screened for participation in the study and 886 subjects were randomized to the EV + Pembro Arm (N = 442) or the Plat + Gem Arm (N = 444). There were over 180 study sites in the United States, Canada, the Netherlands, Belgium, France, Spain, Hungary, Italy, Switzerland, Czech Republic, the United Kingdom, Denmark, Poland, Germany, Argentina, Australia, Singapore, Thailand, Russia, Japan, South Korea, China, Taiwan, Turkey, and Israel that enrolled at least 1 subject into the EV + Pembro Arm or Plat + Gem Arm.

The last patient in the global portion of EV-302 was recruited on 05 October 2022.

As of the data cut-off date on 08 August 2023, median follow-up for both groups combined was 17.2 months (range 0-37 months).

Conduct of the study

Table 39: Summary of key protocol amendments in Study EV-302 (KEYNOTE-A39)

Amendment Number	Date	Key Changes	Rationale
Original	03 Dec 2019	Not applicable (original protocol)	Not applicable
Amendment 01	25 Jun 2020	• Amendments to inclusion and exclusion criteria relevant to birth control, hepatitis carrier status, and surgery prior to randomization.	• Update based on review comments received at the time of initial clinical trial application (VHP) to align the definition of highly effective birth control methods with the CTFG's recommendations with addition of the corresponding failure rate, to test for hepatitis B and C for those with

Amendment Number	Date	Key Changes	Rationale
			known active hepatitis B or C virus or according to the recommendations of the country-specific health authority, and to extend the window between major surgery and randomization from 3 to 4 weeks.
Amendment 02	12 Aug 2020	• Removed Arm C (EV + Pembro + Plat) and associated text throughout the protocol.	• Arm C removed due to results from Studies KEYNOTE-361 and IMvigor130 showing limited effect of combining immunotherapy with chemotherapy.
Amendment 03	10 Feb 2021	• Added guidance for management of rash or skin reactions by grade.	• Safety update addressing SCAR being identified as a new important risk for EV.
Amendment 04	11 Nov 2021	• Described the use of avelumab as maintenance therapy following study treatment and clarified censoring rules and the schedule of assessments for subjects who received avelumab maintenance. • Updated the median OS assumption for the control arm from 14 to 15.3 months. • Increased sample size from 760 to 860 subjects. • Modified the initial alpha allocation with a larger portion of the alpha (4.5%) assigned to OS and a more conservative alpha (0.5%) assigned to PFS. • Final PFS and OS analyses timing revised to be triggered by total number of PFS and OS events only, without requiring a minimum follow-up time after enrollment completion. • Updated guidelines for management of pembrolizumab immune-related AEs.	• After study initiation, avelumab was approved as a maintenance treatment following first-line platinum containing chemotherapy. Although avelumab was never prohibited as a subsequent therapy in Study EV-302, the protocol was amended to clarify that maintenance therapy may be used following completion of randomized treatment in the Plat + Gem Arm, if locally available, and provided the subject was deemed eligible by the investigator. Acknowledging avelumab being incorporated as a standard of care for maintenance following first-line treatment, censoring rules for PFS were updated to not censor subjects in the control arm for the use of maintenance therapy. The schedule of study assessments remained the same for patients receiving avelumab. • Median OS assumption for the control arm was updated to account for

Amendment Number	Date	Key Changes	Rationale
			use of maintenance therapy on the Plat + Gem Arm. • With the update to the median OS assumption, the estimated time to achieve target number of OS events was prolonged. To maintain the timing of OS final analysis, sample size was increased from 760 to 860. • With the change in standard of care in the 1L setting, a larger portion of the alpha (4.5%) was allocated to OS to emphasize the importance of OS endpoint, while still allowing testing of PFS with a more conservative alpha (0.5%). • The minimum follow-up time requirement was removed from the planning of PFS and OS analysis timing to keep them event-driven and prevent potential over-running. • Change in a medical monitoring procedure relevant to patient safety to align with Pembro IB v20.
Amendment 05	29 Mar 2022	• Dose modification recommendations updated for rashes and skin reactions by grade.	• Guidance was added to clarify dose modification recommendations for bullous lesions and certain Grade 2 skin reactions due to events in EV monotherapy expanded access program.
Amendment 06	12 Apr 2022	• Added China extension to study.	• China extension was designed to fulfill the HA requirement for the number of Chinese subjects in EV-302
Amendment 07	30 Nov 2022	• Added 2 PRO endpoints: TTPP and mean change from baseline in worst pain. • Added secondary endpoints of ORR by BICR, TTPP and mean change from baseline in worst pain to	• As informed by the EV-103 PRO data readout (Oct 2022) wherein EV + Pembro showed a clinically meaningful improvement from baseline in pain

Amendment Number	Date	Key Changes	Rationale
		statistical testing and updated multiplicity.	outcomes, PRO endpoints (TTPP and mean change from baseline in worst pain) were added to assess these outcomes robustly in a comparative setting. • With the high response rate and clinically meaningful improvement from baseline in pain outcomes observed in Study EV-103, secondary endpoints of ORR, TTPP, and mean change from baseline in worst pain were added to statistical testing. To control the overall type I error rate at a 5% level (2-sided), the multiplicity strategy was updated to allow testing of these secondary endpoints sequentially after the null hypotheses for both primary endpoints (PFS and OS) are rejected.
Amendment 08	15 Feb 2023	• Safety updates addressing pneumonitis/ILD related to enfortumab vedotin. • Mean change from baseline in worst pain time point corrected from week 24 to week 26.	• Pneumonitis/ILD was identified as a new important risk for EV. • Correction was made to the description of the secondary endpoint, mean change from baseline in worst pain at week 26, to align with the PRO assessment schedule as planned in the protocol.

Major protocol deviations

Table 40: Summary of important protocol deviations in Study EV-302 (KEYNOTE-A39)

Subjects, n (%)	Arm A EV+ Pembro N = 442	Arm B Plat + Gem N = 444	Total N = 886
Any important deviation†	16 (3.6)	34 (7.7)	50 (5.6)
Reason for important protocol deviation‡			
Inclusion criteria	2 (0.5)	7 (1.6)	9 (1.0)
Exclusion criteria	0	2 (0.5)	2 (0.2)
Patient withdrawal criteria	1 (0.2)	0	1 (0.1)
Drug administration	5 (1.1)	13 (2.9)	18 (2.0)
Study conduct	4 (0.9)	4 (0.9)	8 (0.9)
Informed consent	5 (1.1)	8 (1.8)	13 (1.5)

EV: Enfortumab vedotin; Gem: Gemcitabine; Pembro: Pembrolizumab; Plat: Platinum-based chemotherapy (cisplatin or carboplatin); ITT: Intent-to-treat

†Important deviations are Seagen protocol violations and inclusion/exclusion exemptions.

‡A subject may be counted in more than one category.

Table 41: Summary of COVID-19 impacts in Study EV-302 (KEYNOTE-A39)

Subjects, n (%)	Arm A EV + Pembro N = 442	Arm B Plat + Gem N =444	Total N = 886
Impacted visit, n (%)			
At least 1 visit impacted	50 (11.3)	23 (5.2)	73 (8.2)
Impacted assessment (missed, out of window, and/or modified), n (%)			
EV administration	41 (9.3)	-	41 (4.6)
Missed	25 (5.7)	-	25 (2.8)
Pembro administration	20 (4.5)	-	20 (2.3)
Missed	3 (0.7)	-	3 (0.3)
Gemcitabine administration	-	17 (3.8)	17 (1.9)
Missed	-	6 (1.4)	6 (0.7)
Cisplatin administration	-	3 (0.7)	3 (0.3)
Missed	-	0	0
Carboplatin administration	-	8 (1.8)	8 (0.9)
Missed	-	7 (1.6)	7 (0.8)
Imaging/scans	6 (1.4)	3 (0.7)	9 (1.0)
Missed	1 (0.2)	0	1 (0.1)
Safety laboratory sample	41 (9.3)	19 (4.3)	60 (6.8)
Missed	24 (5.4)	9 (2.0)	33 (3.7)
Vital signs	39 (8.8)	17 (3.8)	56 (6.3)
Missed	22 (5.0)	7 (1.6)	29 (3.3)
ECG	1 (0.2)	1 (0.2)	2 (0.2)
Missed	0	0	0
ECOG	21 (4.8)	11 (2.5)	32 (3.6)
Missed	3 (0.7)	2 (0.5)	5 (0.6)
Height	7 (1.6)	2 (0.5)	9 (1.0)
Missed	0	0	0
Ocular exam	2 (0.5)	0	2 (0.2)
Missed	0	0	0
Physical examination	23 (5.2)	12 (2.7)	35 (4.0)
Missed	2 (0.5)	4 (0.9)	6 (0.7)
PK/ATA sample collection	11 (2.5)	8 (1.8)	19 (2.1)
Missed	2 (0.5)	1 (0.2)	3 (0.3)
Urine sample collection	5 (1.1)	4 (0.9)	9 (1.0)
Missed	0	1 (0.2)	1 (0.1)
Tumor biopsy	1 (0.2)	0	1 (0.1)
Weight	21 (4.8)	12 (2.7)	33 (3.7)
Missed	4 (0.9)	2 (0.5)	6 (0.7)
Pregnancy test	1 (0.2)	0	1 (0.1)
Missed	1 (0.2)	0	1 (0.1)

ATA: Antitherapeutic antibody; ECG: Electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EV: Enfortumab vedotin; Gem: Gemcitabine; Pembro: Pembrolizumab; PK: Pharmacokinetics; Plat: Platinum-based chemotherapy (cisplatin or carboplatin); ITT: Intent-to-treat

Baseline data

Table 42: Demographics in the ITT analysis set of Study EV-302 (KEYNOTE-A39)

Parameter Statistic/Criteria	Arm A EV + Pembro (N=442)	Arm B Plat + Gem (N=444)	Total N = 886
Age (years)			
n	442	444	886
Mean (SD)	67.9 (9.1)	68.0 (9.4)	67.9 (9.2)
Median	69.0	69.0	69.0
Min, max	37, 87	22, 91	22, 91
Age group, n (%)			
< 65 years	144 (32.6)	135 (30.4)	279 (31.5)
65 to < 75 years	196 (44.3)	201 (45.3)	397 (44.8)
≥ 75 years	102 (23.1)	108 (24.3)	210 (23.7)
Sex, n (%)			
Male	344 (77.8)	336 (75.7)	680 (76.7)
Female	98 (22.2)	108 (24.3)	206 (23.3)
Ethnicity, n (%)			
Hispanic or Latino	52 (11.8)	52 (11.7)	104 (11.7)
Not Hispanic or Latino	359 (81.2)	343 (77.3)	702 (79.2)
Unknown	9 (2.0)	12 (2.7)	21 (2.4)
Not reportable	22 (5.0)	37 (8.3)	59 (6.7)
Race, n (%)			
American Indian or Alaska Native	2 (0.5)	2 (0.5)	4 (0.5)
Asian	99 (22.4)	92 (20.7)	191 (21.6)
Black or African American	3 (0.7)	7 (1.6)	10 (1.1)
Native Hawaiian or Other Pacific Islander	0	1 (0.2)	1 (0.1)
White	308 (69.7)	290 (65.3)	598 (67.5)
Other	3 (0.7)	1 (0.2)	4 (0.5)
Multiple	0	4 (0.9)	4 (0.5)
Unknown	5 (1.1)	10 (2.3)	15 (1.7)
Not reportable	22 (5.0)	37 (8.3)	59 (6.7)
Geographic region, n (%)			
North America	103 (23.3)	85 (19.1)	188 (21.2)
Europe	172 (38.9)	197 (44.4)	369 (41.6)
Rest of world	167 (37.8)	162 (36.5)	329 (37.1)

Table 43: Baseline characteristics in the ITT analysis set of Study EV-302 (KEYNOTE-A39)

Parameter Statistic/Criteria	Arm A EV + Pembro N=442	Arm B Plat + Gem N=444	Total N = 886
ECOG performance status, n (%)			
0	223 (50.5)	215 (48.4)	438 (49.4)
1	204 (46.2)	216 (48.6)	420 (47.4)
2	15 (3.4)	11 (2.5)	26 (2.9)
Missing	0	2(0.5)	2 (0.2)
Smoking status, n (%)			
Former or current smoker	301 (68.1)	279 (62.8)	580 (65.5)
Non-smoker	128 (29.0)	144 (32.4)	272 (30.7)
Unknown	13 (2.9)	21 (4.7)	34 (3.8)
Weight (kg)			
n	441	443	884
Mean (SD)	75.40 (17.29)	76.39 (18.37)	75.89 (17.84)
Median	75.00	74.10	74.80
Min, max	30.4, 136.0	35.0, 157.9	30.4, 157.9
Weight group, n (%)			
> 100 kg	31 (7.0)	40 (9.0)	71 (8.0)
≤ 100 kg	410 (92.8)	403 (90.8)	813 (91.8)
Body mass index (kg/m^2)			
n	439	441	880
Mean (SD)	26.08 (4.72)	26.66 (5.20)	26.37 (4.97)
Median	25.38	26.04	25.73
Min, max	15.1, 42.3	15.6, 49.3	15.1, 49.3
Body mass index, n (%)			
< 25 kg/m^2	206 (46.6)	185 (41.7)	391 (44.1)
25 to < 30 kg/m^2	144 (32.6)	155 (34.9)	299 (33.7)
≥ 30 kg/m^2	89 (20.1)	101 (22.7)	190 (21.4)
Missing	3 (0.7)	3 (0.7)	6 (0.7)
Body surface area (m^2)			
n	439	441	880
Mean (SD)	1.87 (0.26)	1.88 (0.26)	1.88 (0.26)
Median	1.88	1.87	1.87
Min, max	1.1, 2.7	1.2, 2.9	1.1, 2.9
Renal function based on CrCL†, n (%)			
Normal: ≥ 90 mL/min	84 (19.0)	95 (21.4)	179 (20.2)
Mild decrease: ≥ 60 and < 90 mL/min	165 (37.3)	162 (36.5)	327 (36.9)
Moderate decrease: ≥ 30 and < 60 mL/min	186 (42.1)	179 (40.3)	365 (41.2)
Severe decrease: ≥ 15 and < 30 mL/min	7 (1.6)	8 (1.8)	15 (1.7)
Hepatic function‡, n (%)			
Normal	394 (89.1)	392 (88.3)	786 (88.7)
Mild	44 (10.0)	48 (10.8)	92 (10.4)
Moderate	3 (0.7)	0	3 (0.3)
Severe	0	0	0
Unknown	1 (0.2)	4 (0.9)	5 (0.6)

Parameter Statistic/Criteria	Arm A EV + Pembro N=442	Arm B Plat + Gem N=444	Total N = 886
HbA1c (%)			
n	401	392	793
Mean (SD)	5.40 (1.08)	5.34 (1.12)	5.37 (1.10)
Median	5.60	5.60	5.60
Min, max	2.5, 9.7	0.5, 7.9	0.5, 9.7
HbA1c, n (%)			
< 5.7%	205 (46.4)	208 (46.8)	413 (46.6)
≥ 5.7 and < 6.5%	155 (35.1)	140 (31.5)	295 (33.3)
≥ 6.5%	41 (9.3)	44 (9.9)	85 (9.6)
Missing	41 (9.3)	52 (11.7)	93 (10.5)
Hemoglobin, n (%)			
< 10 g/dL	51 (11.5)	53 (11.9)	104 (11.7)
≥ 10 g/dL	391 (88.5)	391 (88.1)	782 (88.3)
Bajorin risk factors§, n (%)			
0	179 (40.5)	183 (41.2)	362 (40.9)
1	263 (59.5)	259 (58.3)	522 (58.9)
Missing	0	2 (0.5)	2 (0.2)

ALT: Alanine transaminase; AST: Aspartate transferase; CrCl: creatinine clearance; ECOG: Eastern Cooperative Oncology Group; EV: Enfortumab vedotin; Gem: Gemcitabine; Max: Maximum; Min: Minimum; HbA1c: Glycosylated hemoglobin; Pembro: Pembrolizumab; Plat: Platinum-based chemotherapy (cisplatin or carboplatin); PS: Performance status; SD: Standard deviation; ITT: Intent-to-treat; ULN: Upper limit of normal

†Creatinine clearance was estimated using Cockcroft-Gault formula based on the last non-missing serum creatinine measurement before the first dose of study treatment.

‡: Hepatic function was estimated based on the last non-missing AST and total bilirubin measurements before the first dose of study treatment. Normal: total bilirubin ≤ ULN and AST ≤ ULN; Mild: (total bilirubin > 1 - 1.5x ULN and any AST) or (total bilirubin ≤ ULN and AST > ULN); Moderate: total bilirubin > 1.5 - 3x ULN and any AST; Severe: total bilirubin > 3x ULN and any AST

§: Bajorin risk factors include visceral metastases (bone, lung, liver) and ECOG PS > 2. Subjects with ECOG PS > 2 were not eligible for the study.

Table 44: Baseline disease characteristics in the ITT analysis set of Study EV-302 (KEYNOTE-A39)

	Arm A EV + Pembro N=442	Arm B Plat + Gem N=444	Total N = 886
Disease status at randomization, n (%)			
Metastatic	421 (95.2)	420 (94.6)	841 (94.9)
Locally advanced	21 (4.8)	24 (5.4)	45 (5.1)
Time from diagnosis of locally advanced or metastatic disease to randomization† (months)			
n	442	444	886
Mean (SD)	2.72 (6.65)	2.59 (4.64)	2.65 (5.73)
Median	1.58	1.56	1.58
Q1, Q3	1.08, 2.50	1.02, 2.32	1.05, 2.37
Min, max	0.0, 125.2	0.0, 59.9	0.0, 125.2
Primary disease site of origin, n (%)			
Upper tract	135 (30.5)	104 (23.4)	239 (27.0)
Renal pelvis	88 (19.9)	66 (14.9)	154 (17.4)
Ureter	47 (10.6)	37 (8.3)	84 (9.5)
Kidney	0	1 (0.2)	1 (0.1)
Lower tract	305 (69.0)	339 (76.4)	644 (72.7)
Bladder	295 (66.7)	330 (74.3)	625 (70.5)
Urethra	9 (2.0)	8 (1.8)	17 (1.9)
Other	1 (0.2)	1 (0.2)	2 (0.2)
Unknown	2 (0.5)	1 (0.2)	3 (0.3)
Histology type, n (%)			
Urothelial carcinoma	379 (85.7)	373 (84.0)	752 (84.9)
Urothelial carcinoma mixed	50 (11.3)	53 (11.9)	103 (11.6)
Squamous differentiation	24 (5.4)	28 (6.3)	52 (5.9)
Glandular differentiation	3 (0.7)	3 (0.7)	6 (0.7)
Nested	4 (0.9)	6 (1.4)	10 (1.1)
Micropapillary	14 (3.2)	10 (2.3)	24 (2.7)
Plasmacytoid	2 (0.5)	3 (0.7)	5 (0.6)
Sarcomatoid	1 (0.2)	3 (0.7)	4 (0.5)
Other	7 (1.6)	7 (1.6)	14 (1.6)
Variant urothelial carcinoma only without typical UC	4 (0.9)	7 (1.6)	11 (1.2)
Unknown	9 (2.0)	11 (2.5)	20 (2.3)
Disease stage at randomization, n (%)			
III	1 (0.2)	0	1 (0.1)
IIIA	8 (1.8)	7 (1.6)	15 (1.7)
IIIB	8 (1.8)	13 (2.9)	21 (2.4)
IV	144 (32.6)	113 (25.5)	257 (29.0)
IVA	86 (19.5)	88 (19.8)	174 (19.6)
IVB	195 (44.1)	221 (49.8)	416 (47.0)
Other	0	1 (0.2)	1 (0.1)
Unknown	0	1 (0.2)	1 (0.1)

	Arm A EV + Pembro N=442	Arm B Plat + Gem N=444	Total N = 886
Metastatic disease site(s)‡, n (%)			
Adrenal Gland	22 (5.0)	23 (5.2)	45 (5.1)
Bladder	12 (2.7)	10 (2.3)	22 (2.5)
Bone	81 (18.3)	102 (23.0)	183 (20.7)
Intestine	1 (0.2)	2 (0.5)	3 (0.3)
Kidney	49 (11.1)	31 (7.0)	80 (9.0)
Liver	100 (22.6)	99 (22.3)	199 (22.5)
Lung	170 (38.5)	157 (35.4)	327 (36.9)
Lymph nodes	317 (71.7)	313 (70.5)	630 (71.1)
Pelvis	29 (6.6)	36 (8.1)	65 (7.3)
Soft tissue	32 (7.2)	43 (9.7)	75 (8.5)
Other visceral disease	31 (7.0)	26 (5.9)	57 (6.4)
Metastasis category, n (%)			
Visceral metastases	318 (71.9)	318 (71.6)	636 (71.8)
Lymph nodes only disease	103 (23.3)	104 (23.4)	207 (23.4)
Not applicable§	21 (4.8)	22 (5.0)	43 (4.9)

EV: Enfortumab vedotin; Gem: Gemcitabine; Max: Maximum; Min: Minimum; Pembro: Pembrolizumab; Plat: Platinum-based chemotherapy (cisplatin or carboplatin); Q: Quartile; SD: Standard deviation; ITT: Intent-to-treat; UC: Urothelial cancer

†Calculated from the date of locally advanced or metastatic disease, whichever is later, to the date of randomization.

‡A subject may have metastatic disease in more than one location.

§Subjects had locally advanced disease without metastasis to lymph nodes or distant organs.

Table 45: Reasons for cisplatin ineligibility in the ITT analysis set of Study EV-302 (KEYNOTE-A39)

	Arm A EV + Pembro N = 442	Arm B Plat + Gem N = 444	Total N = 886
Subjects who were cisplatin ineligible at randomization†	202	202	404
Subjects meeting at least one of the following criteria‡, n/N (%)	194/202 (96.0)	197/202 (97.5)	391/404 (96.8)
GFR < 60 mL/min	164/202 (81.2)	163/202 (80.7)	327/404 (80.9)
≥ Grade 2 hearing loss	29/202 (14.4)	29/202 (14.4)	58/404 (14.4)
ECOG PS of 2	9/202 (4.5)	8/202 (4.0)	17/404 (4.2)
NYHA Class III heart failure	4/202 (2.0)	7/202 (3.5)	11/404 (2.7)
Subjects meeting more than one criterion, n/N (%)	12/202 (5.9)	10/202 (5.0)	22/404 (5.4)

ECOG PS: Eastern Cooperative Oncology Group performance status; EV: Enfortumab vedotin; Gem: Gemcitabine; GFR: Glomerular filtration rate; NYHA: New York Heart Association; Pembro: Pembrolizumab; Plat: Platinum-based chemotherapy (cisplatin or carboplatin); ITT: Intent-to-treat

†As collected in RTSM (Randomization and Trial Supply Management).

‡A subject may be counted in more than one category.

Table 46: Biomarkers: expression of Nectin-4 and PD-L1 in tumour tissue by IHC in the ITT analysis set of Study EV-302 (KEYNOTE-A39)

Parameter Statistic/Criteria	Arm A EV + Pembro N = 442	Arm B Plat + Gem N = 444	Total N = 886
Nectin-4 expression†, H-score			
n‡	394	406	800
Mean (SD)	249.6 (70.3)	241.0 (75.3)	245.3 (73.0)
Median	280.0	270.0	275.0
Q1, Q3	230.0, 298.0	215.0, 297.0	225.0, 297.0
Min, max	0, 300	0, 300	0, 300
PD-L1 expression§, n/N (%)			
n‡	438	439	877
High (CPS ≥ 10)	254/438 (58.0)	254/439 (57.9)	508/877 (57.9)
Low (CPS < 10)	184/438 (42.0)	185/439 (42.1)	369/877 (42.1)

CPS: Combined positive score; EV: Enfortumab vedotin; Gem: Gemcitabine; IHC: Immunohistochemistry; Max: Maximum; Min: Minimum; PD-L1: Programmed death-ligand 1; Pembro: Pembrolizumab; Plat: Platinum-based chemotherapy (cisplatin or carboplatin). SD: Standard deviation

†Nectin-4 H-scores (range: 0-300) were determined using a validated Nectin-4 IHC assay run.

‡Reflects the number of subjects with evaluable data. Subjects whose tissue sample was found to be unsuitable per testing guidelines after randomization were excluded.

§ CPS was determined using the validated PD-L1 IHC 22C3 pharmDx assay.

Table 47: Nectin-4 H-Scores by Treatment Arm (ITT Analysis Set)

	Arm A EV + Pembro N = 442	Arm B Plat + Gem N = 444
Nectin-4 H-Score Quartiles (Subgroup 1)		
< 225 [< Q1], n (%)	88 (19.9)	106 (23.9)
≥ 225 to < 275 [≥ Q1 to < Q2], n (%)	89 (20.1)	106 (23.9)
≥ 275 to < 297 [≥ Q2 to < Q3], n (%)	110 (24.9)	92 (20.7)
≥ 297 [≥ Q3], n (%)	107 (24.2)	102 (23.0)
Nectin-4 H-score missing	48 (10.9)	38 (8.6)
Nectin-4 H-score (150 and 225; Subgroup 2)		
< 150, n (%)	38 (8.6)	50 (11.3)
≥ 150 to < 225, n (%)	50 (11.3)	56 (12.6)
≥ 225, n (%)	306 (69.2)	300 (67.6)
Nectin-4 H-score missing	48 (10.9)	38 (8.6)
Nectin-4 H-score (150; Subgroup 3)		
< 150, n (%)	38 (8.6)	50 (11.3)
≥ 150, n (%)	356 (80.5)	356 (80.2)
Nectin-4 H-score missing	48 (10.9)	38 (8.6)
Nectin-4 H-score (225; Subgroup 4)		
< 225, n (%)	88 (19.9)	106 (23.9)
≥ 225, n (%)	306 (69.2)	300 (67.6)
Nectin-4 H-score missing	48 (10.9)	38 (8.6)

EV: enfortumab vedotin; Gem: gemcitabine; Pembro: pembrolizumab; Plat: platinum-based chemotherapy (cisplatin or carboplatin); Q: quartile

‡ Reflects the number of subjects with evaluable data. Data was not available for some subjects due to inadequate tissue quality or quantity or unavailable for testing.

Prior therapies

Table 48: Prior therapies in the ITT analysis set of Study EV-302 (KEYNOTE-A39)

	Arm A EV + Pembro N = 442	Arm B Plat + Gem N = 444	Total N = 886
Prior systemic therapy in adjuvant or neoadjuvant setting, n (%)	40 (9.0)	39 (8.8)	79 (8.9)
Platinum-based therapy	40 (9.0)	36 (8.1)	76 (8.6)
Cisplatin-based therapy	35 (7.9)	33 (7.4)	68 (7.7)
Carboplatin-based therapy	5 (1.1)	3 (0.7)	8 (0.9)
Non-platinum-based therapy	1 (0.2)	4 (0.9)	5 (0.6)
Prior surgery, n (%)†	165 (37.3)	163 (36.7)	328 (37.0)
Cystectomy‡	92 (20.8)	106 (23.9)	198 (22.3)
Nephrectomy/ureterectomy §	85 (19.2)	68 (15.3)	153 (17.3)
Metastasectomy¶	8 (1.8)	14 (3.2)	22 (2.5)
Prior radiation therapy, n (%)	33 (7.5)	39 (8.8)	72 (8.1)

EV: Enfortumab vedotin; Gem: Gemcitabine; Pembro: Pembrolizumab; Plat: Platinum-based chemotherapy (cisplatin or carboplatin); ITT: Intent-to-treat

†Prior cystectomy, nephrectomy, metastasectomy, ureterectomy, or urethrectomy without including TURBT or biopsy. A subject may be counted in more than one category.

‡Includes partial and total cystectomy/cystoprostatectomy.

§Includes partial and total nephrectomy/nephroureterectomy/ureterectomy.

¶Includes surgical resection of one or more distant metastasis.

Numbers analysed

Efficacy, safety, PRO and PK analyses were performed using the analysis sets defined in Table 49, which shows the number of subjects included in each analysis set. The cut-off date for all data presented was 08 August 2023.

Table 49: Subjects enrolled and included in each analysis set, Study EV-302 (KEYNOTE-A39)

	Arm A EV + Pembro N = 442 n (%)	Arm B Plat + Gem N = 444 n (%)	Total N = 886 n (%)
ITT analysis set	442 (100)	444 (100)	886 (100)
SAF (safety analysis set)	440 (99.5)	433 (97.5)	873 (98.5)
Response evaluable set by BICR	437 (98.9)	441 (99.3)	878 (99.1)
Response evaluable set by investigator	441 (99.8)	442 (99.5)	883 (99.7)
EV PK analysis set	432 (97.7)	-	432 (48.8)
PRO full analysis set	376 (85.1)	355 (80.0)	731 (82.5)

Outcomes and estimation

Primary endpoint – PFS by BICR

Table 50: PFS by BICR in the ITT analysis set, Study EV-302 (KEYNOTE-A39), DCO 08-AUG-2023

	Arm A EV + Pembro N = 442	Arm B Plat + Gem N = 444
Subjects who progressed or died, n (%)	223 (50.5)	307 (69.1)
Stratified analysis†		
Hazard ratio‡ (95% CI)	0.450 (0.377, 0.538)	
Two-sided p-value§	<0.00001	
PFS¶, months		
Median (95% CI††)	12.5 (10.4, 16.6)	6.3 (6.2, 6.5)
Q1, Q3	5.1, -	4.1, 10.4
Observed min, max	0.03+, 30.42+	0.03+, 32.99+
PFS rate¶ (%) at:		
6 months (95% CI††)	72.8 (68.3, 76.8)	60.7 (55.7, 65.4)
12 months (95%, CI††)	50.7 (45.6, 55.5)	21.6 (17.2, 26.2)
18 months (95%, CI††)	43.9 (38.5, 49.1)	11.7 (8.0, 16.1)

BICR: Blinded independent central review; CI: Confidence interval; EV: Enfortumab vedotin; Gem: Gemcitabine; ITT: Intent-to-treat; Max: Maximum; Min: Minimum; PD-L1: Programmed cell death ligand 1; Pembro: Pembrolizumab; PFS: Progression free survival; Plat: Platinum-based chemotherapy (cisplatin or carboplatin); Q: Quartile; RECIST: Response Evaluation Criteria in Solid Tumors

†Stratification factors are cisplatin eligibility (eligible or ineligible), PD-L1 expression (high or low), and liver metastases (present or absent) at randomization.

‡Calculated using stratified Cox proportional hazards model. A hazard ratio < 1 favors the EV + Pembro Arm.

§Calculated using stratified log-rank test. The p-value threshold for statistical significance is 0.005.

¶As estimated using Kaplan-Meier method.

††Calculated using the complementary log-log transformation method (Collett, 1994).

+ indicates censoring.

Figure 33: Kaplan-Meier plot of PFS by BICR in the ITT analysis set, Study EV-302 (KEYNOTE-A39), DCO 08-AUG-2023

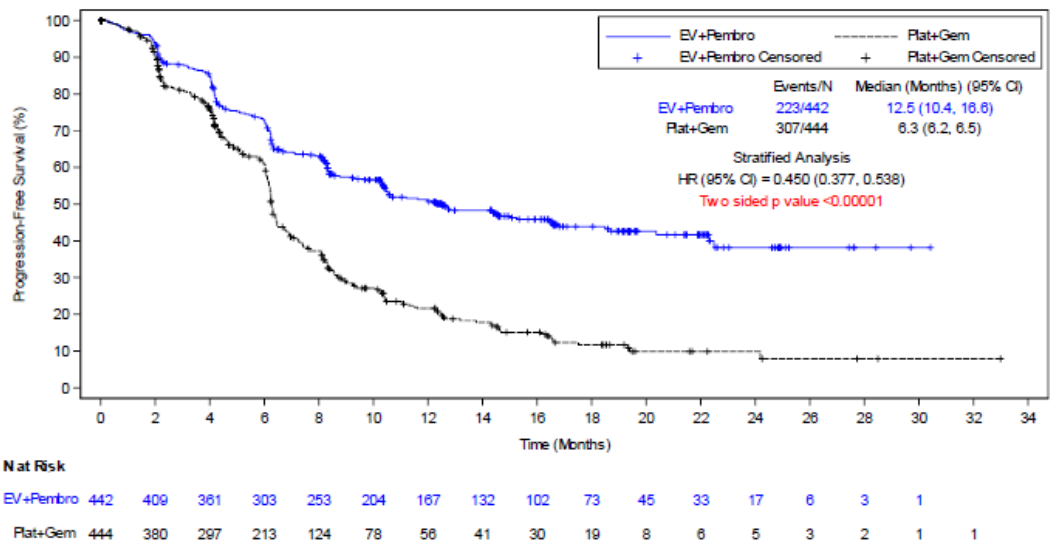


Table 51: Summary of censoring reasons for PFS by BICR, Study EV-302 (KEYNOTE-A39)

	EV+Pembro (N=442) n (%)	Plat+Gem (N=444) n (%)
Number of subjects censored	219 (49.5)	137 (30.9)
Censoring reason		
No adequate assessment post-baseline, on study	1 (0.2)	2 (0.5)
No adequate assessment post-baseline, off study	3 (0.7)	6 (1.4)
No PD or death, on study	184 (41.6)	70 (15.8)
No PD or death, off study	4 (0.9)	4 (0.9)
Started new anticancer therapy prior to PD or death	20 (4.5)	46 (10.4)
PD or death after >=2 missed visits	7 (1.6)	9 (2.0)

Primary endpoint – OS

Table 52: OS in the ITT analysis set, Study EV-302 (KEYNOTE-A39), DCO 08-AUG-2023

	Arm A EV + Pembro N = 442	**Arm B Plat + Gem N = 444**
Number of Deaths n (%)	133 (30.1)	226 (50.9)
Stratified analysis†		
Hazard ratio‡ (95% CI)	0.468 (0.376, 0.582)	
Two-sided p-value§	<0.00001	
OS¶, months		
Median (95% CI††)	31.5 (25.4, -)	16.1 (13.9, 18.3)
Q1, Q3	13.8, -	7.6, -
Min, max	0.26, 37.16+	0.07+, 36.21+
OS rate¶ (%) at:		
6 months (95% CI††)	90.2 (87.0, 92.6)	81.9 (77.9, 85.2)
12 months (95% CI††)	78.2 (73.9, 81.9)	61.4 (56.6, 65.9)
18 months (95% CI††)	69.5 (64.4, 74.1)	44.7 (39.2, 50.1)

CI: Confidence interval; EV: Enfortumab vedotin; Gem: Gemcitabine; ITT: Intent-to-treat; Max: Maximum; Min: Minimum; OS: Overall survival; Pembro: Pembrolizumab; Plat: Platinum-based chemotherapy (cisplatin or carboplatin); Q: Quartile.

†Stratification factors are cisplatin eligibility (eligible or ineligible), PD-L1 expression (high or low), and liver metastases (present or absent) at randomization

‡Calculated using stratified Cox proportional hazards model. A hazard ratio < 1 favors the EV + Pembro Arm.

§Calculated using stratified log-rank test. The threshold for statistical significance is 0.01548.

¶As estimated using Kaplan-Meier method.

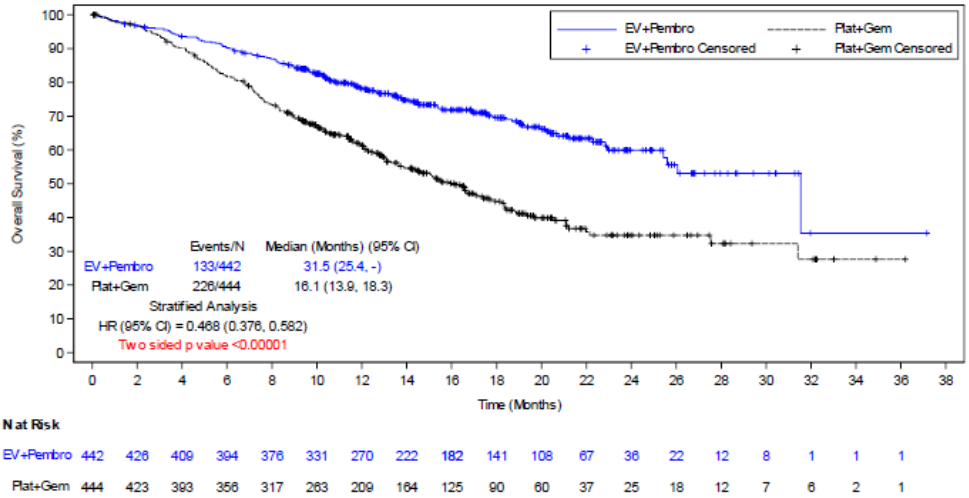
††Calculated using the complementary log-log transformation method (Collett, 1994).

+ indicates censoring.

Table 53: Summary of censoring reasons for OS, Study EV-302 (KEYNOTE-A39)

	EV+Pembro (N=442) n (%)	Plat+Gem (N=444) n (%)
Number of subjects censored, n (%)	309 (69.9)	218 (49.1)
Censoring reason		
No death, on study	296 (67.0)	203 (45.7)
No death, off study	13 (2.9)	15 (3.4)
No data post-baseline	0	0

Figure 34: Kaplan-Meier plot of OS in the ITT analysis set, Study EV-302 (KEYNOTE-A39), DCO 08-AUG-2023



Secondary endpoints

Objective response rate (ORR)

Table 54: ORR and best overall response per RECIST by BICR, Study EV-302 (KEYNOTE-A39)

	Arm A EV + Pembro	Arm B Plat + Gem
Response evaluable set per BICR	N = 437	N = 441
ORR, n (%)	296 (67.7)	196 (44.4)
95% CI†	(63.1, 72.1)	(39.7, 49.2)
2-sided p-value‡	<0.00001	
Best overall response§, n (%)		
CR	127 (29.1)	55 (12.5)
PR	169 (38.7)	141 (32.0)
SD	82 (18.8)	149 (33.8)
PD	38 (8.7)	60 (13.6)
NE¶	0	4 (0.9)
No assessment††	21 (4.8)	32 (7.3)

BICR: Blinded independent central review; CI: Confidence intervals; CR: Complete response; EV: Enfortumab vedotin; Gem: Gemcitabine; NE: Not evaluable; ORR: Objective response rate; PD: Progressive disease; PD-L1: Programmed death-ligand 1; Pembro: Pembrolizumab; Plat: Platinum-based chemotherapy (cisplatin or carboplatin); PR: Partial response; RECIST: Response Evaluation Criteria in Solid Tumors; SD: Stable disease.

† Computed using the Clopper-Pearson method (Clopper 1934).

‡ Cochran-Mantel-Haenszel test (CMH) controlling for stratification factors (liver metastases: present or absent; PD-L1 expression: high or low; cisplatin eligibility: eligible or ineligible) at randomization

§ Best overall response according to RECIST v1.1. CR or PR was confirmed with repeat scans ≥ 28 days after initial response.

¶ Subjects had post-baseline assessment and the best overall response was determined to be not evaluable per RECIST v1.1.

†† Subjects had no response assessment post -baseline.

Duration of response (DOR)

Table 55: DOR by BICR in the ITT analysis set, Study EV-302 (KEYNOTE-A39)

	Arm A EV + Pembro	Arm B Plat + Gem
Response evaluable set per BICR	N = 437	N = 441
Number of responders (confirmed CR or PR)	296	196
Responders who progressed or died, n/N (%)	99/296 (33.4)	119/196 (60.7)
Duration of response†, months		
Median (95% CI‡)	- (20.2, -)	7.0 (6.2, 10.2)
Q1, Q3	8.3, -	4.3, 14.7
Min, max	2.04+, 28.32+	1.48+, 30.92+
Responders (%) without PD or death† at:		
6 months (95% CI‡)	85.9 (81.3, 89.4)	60.6 (52.9, 67.5)
12 months (95%, CI‡)	67.3 (61.1, 72.7)	35.2 (27.6, 42.9)
18 months (95%, CI‡)	59.6 (52.6, 66.0)	19.3 (12.1, 27.7)

BICR: Blinded independent central review; CI: Confidence intervals; CR: Complete Response; DOR: Duration of response; EV: Enfortumab vedotin; Gem: Gemcitabine; Max: maximum; Min: Minimum; PD: Progressive disease; Pembro: Pembrolizumab; Plat: Platinum-based chemotherapy (cisplatin or carboplatin); PR: Partial response; RECIST: Response Evaluation Criteria in Solid Tumors

†As estimated using Kaplan-Meier methods.

‡Calculated using the complementary log-log transformation method (Collett, 1994).

Patient reported outcomes (PROs)

Overall, 84.8% of subjects in EV + Pembro Arm and 80.6% subjects in the Plat + Gem Arm completed at least one component of the BPI-SF questionnaire at baseline.

Table 56: Time to pain progression in the PRO full analysis set, Study EV-302 (KEYNOTE-A39)

	Arm A EV + Pembro N = 376	Arm B Plat + Gem N = 355
Number of subjects with baseline BPI-SF	374	355
Subjects with pain progression†, n (%)	162 (43.3)	144 (40.6)
Increase of 2 or more points on BPI-SF Question 3	132 (35.3)	119 (33.5)
Initiation of new opioid	30 (8.0)	25 (7.0)
Stratified analysis‡		
Hazard ratio§ (95% CI)	0.916 (0.720, 1.166)	
Two-sided p-value¶	0.48374	
Time to pain progression††, months		
Median (95% CI‡‡)	14.2 (6.6, -)	10.0 (5.9, -)
Q1, Q3	1.3, -	0.9, -
Min, max	0.03+, 31.47+	0.03+, 23.85+
% Subjects without pain progression at:		
6 months (95% CI‡‡)	55.7 (50.1, 60.9)	55.2 (49.2, 60.9)
12 months (95% CI‡‡)	51.0 (45.2, 56.5)	46.9 (39.5, 53.9)

BPI-SF: Brief Pain Inventory-Short Form; CI: Confidence interval; EV: Enfortumab vedotin; Gem: Gemcitabine; Max: Maximum; Min: Minimum; Pembro: Pembrolizumab; Plat: Platinum-based chemotherapy (cisplatin or carboplatin); PRO: Patient reported outcome; Q: Quartile.

† Including 2 or more points increase from baseline on BPI-SF Question 3 or initiation of new opioid medication from baseline for at least two consecutive assessments, whichever comes first.

‡ Controlling for age (< 65 or ≥ 65 years old), sex, region and stratification factors (cisplatin eligibility: eligible vs ineligible), PD-L1 expression: low vs high, liver metastases: present or absent) at randomization.

§ Calculated using stratified Cox proportional hazards model. A hazard ratio < 1 favors the EV + Pembro.

¶ Calculated using stratified log-rank test.

†† As estimated using Kaplan-Meier method.

‡‡ Calculated using the complementary log-log transformation method (Collett, 1994).

+ indicates censoring.

Figure 35: Kaplan-Meier Plot of Time to Pain Progression (PRO Full Analysis Set)

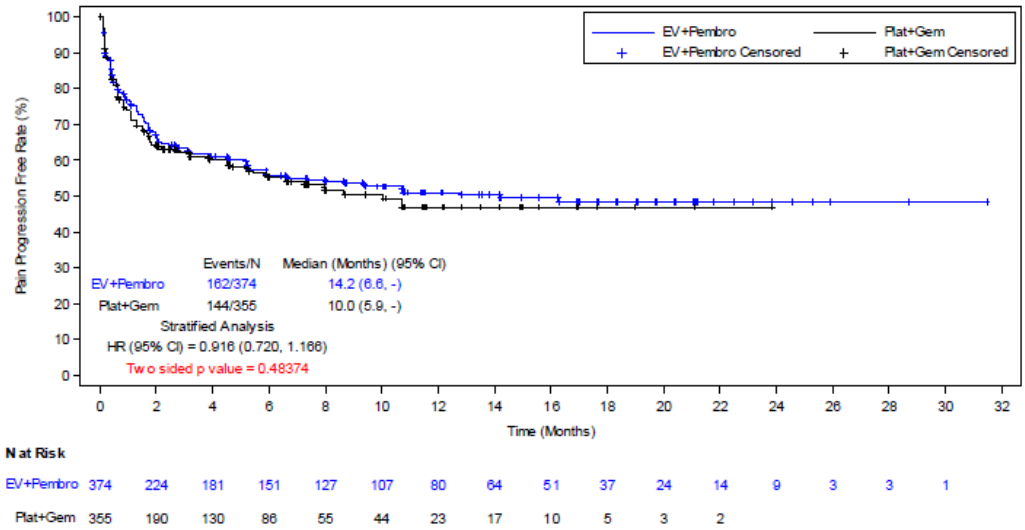
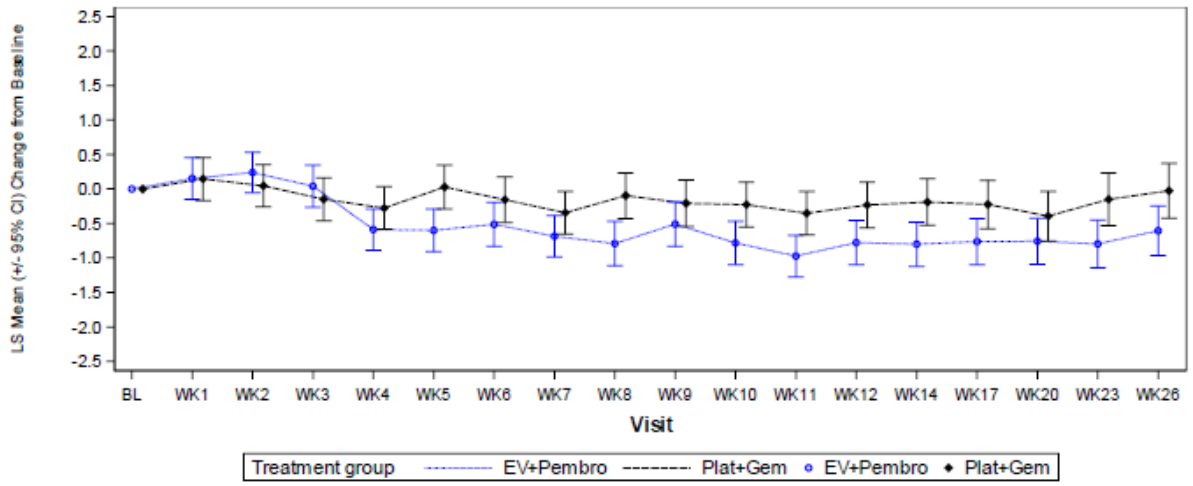


Figure 36: Least squares mean change from baseline in worst pain (±95% CI), BPI-SF Q3 in the PRO full analysis set, Study EV-302 (KEYNOTE-A39)



Number of Subjects

EV+Pembro	368	321	333	311	315	303	300	307	302	307	298	297	295	288	277	261	251	242
Plat+Gem	345	306	293	301	294	298	282	296	279	278	271	260	256	239	241	204	179	172

EORTC QLQ-C30

Overall, 82.8% subjects in the EV + Pembro Arm and 79.5% subjects in the Plat + Gem Arm completed at least 1 component of the EORTC QLQ-C30 questionnaire at baseline. At baseline, the mean global QoL score was 62.44 in the EV + Pembro Arm and 60.31 in the Plat + Gem Arm, and the mean functional domain scores were 70 or above in both treatment arms. There were no notable changes over time for any of the domain scores, inclusive of general quality of life, functioning, and symptom scores in either treatment arm. Individual domains remained stable throughout treatment based on mean score by cycle.

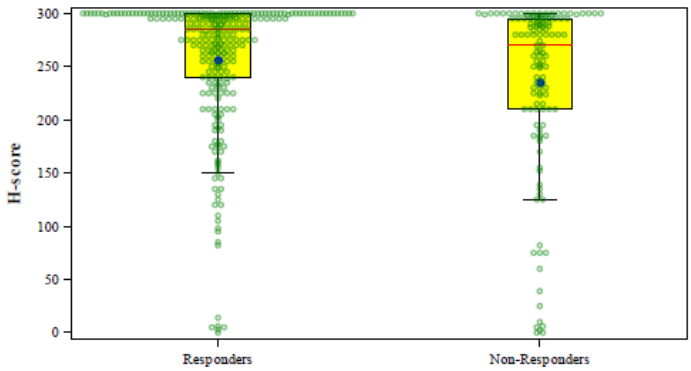
EQ-5D-5L

Overall, 85.3% of subjects in the EV + Pembro Arm and 80.6% of subjects in the Plat + Gem Arm completed at least 1 component of the EQ-5D-5L questionnaire at baseline. The mean baseline VAS scores were 72.8 in the EV + Pembro Arm and 69.7 in the Plat + Gem Arm; the Health State Index Scores (utility scores) were 0.844 and 0.818, respectively. During the treatment period, both VAS and utility scores remained stable with little to no change from baseline throughout the study period.

Exploratory endpoints

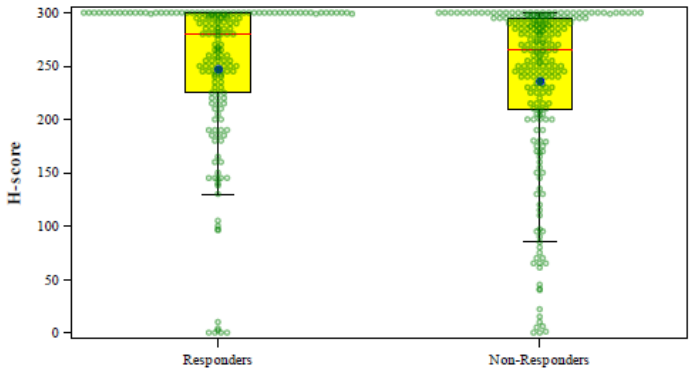
Response by Nectin-4

Figure 37: H-Score of Nectin-4 Expression at Baseline by Best Overall Response by BICR (ITT Analysis Set) – EV + Pembro Arm



The red dashed line indicates the median and the solid circle indicates the mean.
Responders are subjects whose best overall response is confirmed CR or PR. Non-Responders are subjects whose best overall response is a SD, Non-CR/Non-PD, PD, NE or no assessment.
Median H-Scores (Q1, Q3): 284.5 (240, 300) for responders and 270 (210, 295) for nonresponders.

Figure 38: H-Score of Nectin-4 Expression at Baseline by Best Overall Response by BICR (ITT Analysis Set) – Plat + Gem Arm



The red dashed line indicates the median and the solid circle indicates the mean.
Responders are subjects whose best overall response is confirmed CR or PR. Non-Responders are subjects whose best overall response is a SD, Non-CR/Non-PD, PD, NE or no assessment.
Median H-Scores (Q1, Q3): 280 (225, 300) for responders and 265 (210, 295) for nonresponders.

Ancillary analyses

Sensitivity analyses

PFS sensitivity analyses

Table 57: Progression-Free Survival per RECIST by BICR, Sensitivity 1 (Unstratified Analysis) SGN22E-003 ITT Analysis Set

	EV+Pembro (N=442)	Plat+Gem (N=444)
Subjects with progression or death, n (%)	223 (50.5)	307 (69.1)
Unstratified analysis		
Hazard ratio[a] (95% CI)	0.460 (0.386, 0.548)	
Two-sided p-value[b]	<0.00001	
Progression-free survival (PFS)[c] (months)		
Median (95% CI[d])	12.5 (10.4, 16.6)	6.3 (6.2, 6.5)
Q1, Q3	5.1, -	4.1, 10.4
Observed min, max	0.03+, 30.42+	0.03+, 32.99+

Page 1 of 1

a. Calculated using unstratified Cox proportional hazards model. A hazard ratio <1 favors the EV+Pembro arm.
b. Calculated using unstratified log-rank test
c. As estimated using Kaplan-Meier method
d. Calculated using the complementary log-log transformation method (Collett, 1994).
+ indicates censoring.

Table 58: Progression-Free Survival per RECIST by BICR, Sensitivity 2 (Ignore New Therapy before PD/Death) SGN22E-003 ITT Analysis Set

	EV+Pembro (N=442)	Plat+Gem (N=444)
Subjects with progression or death, n (%)	229 (51.8)	330 (74.3)
Stratified analysis[a]		
Hazard ratio[b] (95% CI)	0.446 (0.375, 0.530)	
Two-sided p-value[c]	<0.00001	
Progression-free survival (PFS)[d] (months)		
Median (95% CI[e])	12.3 (10.3, 16.6)	6.2 (6.2, 6.4)
Q1, Q3	5.1, -	4.0, 10.3
Observed min, max	0.03+, 30.49+	0.03+, 32.99+
PFS rate[d] (%) at		
6 months (95% CI[e])	72.6 (68.1, 76.6)	59.8 (54.8, 64.3)
12 months (95% CI[e])	50.2 (45.2, 54.9)	20.6 (16.5, 25.0)
18 months (95% CI[e])	43.0 (37.7, 48.2)	11.4 (7.9, 15.5)

Page 2 of 2

Sensitivity Analysis 2 (Ignore New Anticancer Therapy before PD/Death): starting new anticancer therapies is not a censoring reason.
a. Stratification factors are cisplatin eligibility (eligible or ineligible), PD-L1 expression (high or low), and liver metastases (present or absent) at randomization.
b. Calculated using stratified Cox proportional hazards model. A hazard ratio <1 favors the EV+Pembro arm.
c. Calculated using stratified log-rank test
d. As estimated using Kaplan-Meier method
e. Calculated using the complementary log-log transformation method (Collett, 1994).
+ indicates censoring

Table 59: Progression-Free Survival per RECIST by BICR, Sensitivity 3 (Ignore >=2 Missed Tumor Assessments) SGN22E-003 ITT Analysis Set

	EV+Pembro (N=442)	Plat+Gem (N=444)
Subjects with progression or death, n (%)	230 (52.0)	316 (71.2)
Stratified analysis[a]		
Hazard ratio[b] (95% CI)	0.453 (0.380, 0.540)	
Two-sided p-value[c]	<0.00001	
Progression-free survival (PFS)[d] (months)		
Median (95% CI[e])	12.5 (10.4, 16.6)	6.3 (6.2, 6.5)
Q1, Q3	5.1, -	4.1, 10.4
Observed min, max	0.03+, 30.42+	0.03+, 32.99+
PFS rate[d] (%) at		
6 months (95% CI[e])	73.0 (68.6, 77.0)	61.0 (56.0, 65.6)
12 months (95% CI[e])	50.7 (45.7, 55.5)	21.3 (17.0, 25.9)
18 months (95% CI[e])	42.7 (37.4, 48.0)	11.5 (7.9, 15.8)

Sensitivity Analysis 3 (Ignore Missing Tumor Assessments): missing 2 or more tumor assessments is not a censoring reason.
a. Stratification factors are cisplatin eligibility (eligible or ineligible), PD-L1 expression (high or low), and liver metastases (present or absent) at randomization.
b. Calculated using stratified Cox proportional hazards model. A hazard ratio <1 favors the EV+Pembro arm.
c. Calculated using stratified log-rank test
d. As estimated using Kaplan-Meier method
e. Calculated using the complementary log-log transformation method (Collett, 1994).
+ indicates censoring.

OS sensitivity analyses

Table 60: Overall Survival, Sensitivity 1 (Unstratified Analysis) SGN22E-003 ITT Analysis Set

	EV+Pembro (N=442)	Plat+Gem (N=444)
Number of deaths, n (%)	133 (30.1)	226 (50.9)
Unstratified analysis		
Hazard ratio[a] (95% CI)	0.486 (0.392, 0.602)	
Two-sided p-value[b]	<0.00001	
Overall survival (OS)[c] (months)		
Median (95% CI[d])	31.5 (25.4, -)	16.1 (13.9, 18.3)
Q1, Q3	13.8, -	7.6, -
Observed min, max	0.26, 37.16+	0.07+, 36.21+

a. Calculated using unstratified Cox proportional hazards model. A hazard ratio <1 favors the EV+Pembro arm.
b. Calculated using unstratified log-rank test
c. As estimated using Kaplan-Meier method
d. Calculated using the complementary log-log transformation method (Collett, 1994).
+ indicates censoring.

Table 61: Overall Survival, Sensitivity 3 (IPCW for Subsequent Anticancer Therapy) SGN22E-003 ITT Analysis Set

	EV+Pembro (N=442)	Plat+Gem (N=444)
Number of deaths, n (%)	133 (30.1)	226 (50.9)
IPCW method[a]		
Hazard ratio (95%CI)	0.482 (0.346, 0.672)	
Two-sided p-value	0.00002	

Sensitivity Analysis 3 (IPCW for Subsequent Anticancer Therapy): Apply inverse probability of censoring weights (IPCW) method [Robins and Finkelstein, 2000] to adjust OS for subsequent anticancer therapy. Maintenance therapy that was received after discontinuation or completion of chemotherapy in the Plat+Gem arm was not considered a subsequent anticancer therapy.

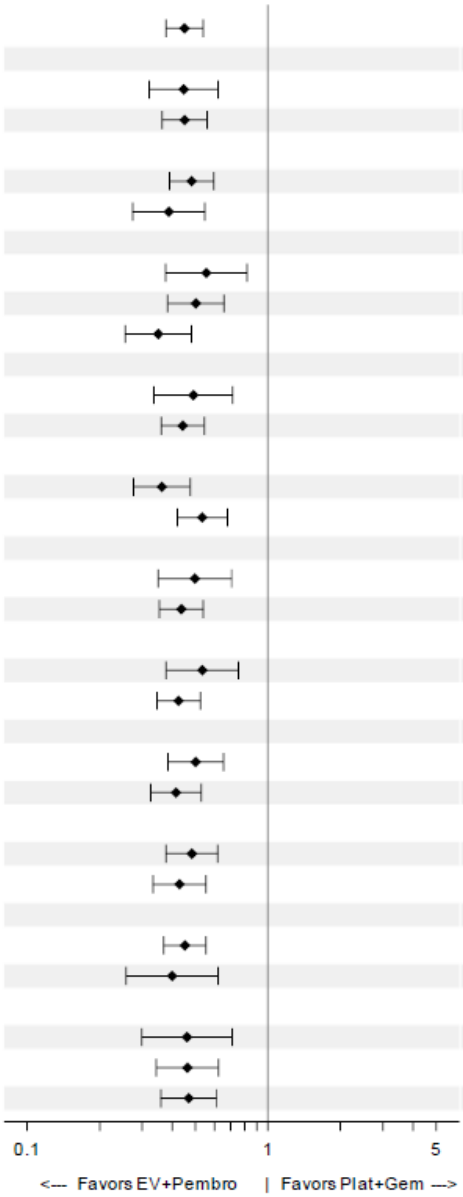
a. Based on a weighted stratified Cox proportional hazards model. A hazard ratio <1 favors the EV+Pembro arm. Stratification factors are cisplatin eligibility (eligible or ineligible), PD-L1 expression (high or low), and liver metastases (present or absent) at randomization. The weight was calculated as ratio of probabilities of receiving subsequent anticancer therapy estimated from two logistic regression models. One model included only baseline covariates (region, primary disease site and tumor sum of diameters by investigator). The other model included both baseline and time variant covariates (progressive disease as assessed by the investigator).

Subgroup Analysis

PFS

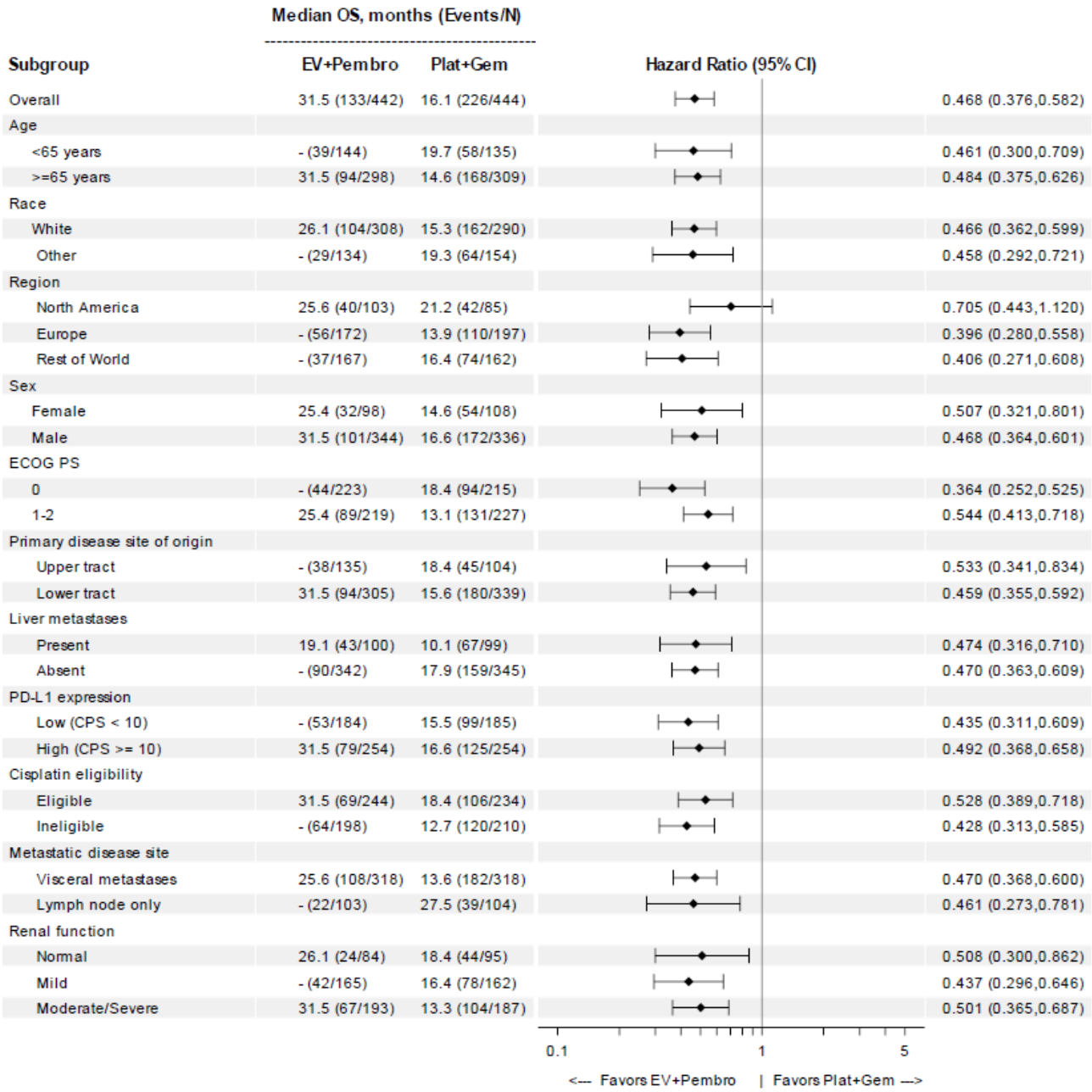
Figure 39: Subgroup analyses of PFS by BICR in the ITT analysis set, Study EV-302 (KEYNOTE-A39), DCO 08-AUG-2023

Subgroup	Median PFS, months (Events/N) EV+Pembro	Plat+Gem	Hazard Ratio (95% CI)
Overall	12.5 (223/442)	6.3 (307/444)	0.450 (0.377,0.538)
Age			
<65 years	12.7 (75/144)	6.4 (88/135)	0.446 (0.321,0.621)
>=65 years	12.0 (148/298)	6.2 (219/309)	0.451 (0.364,0.558)
Race			
White	10.4 (168/308)	6.2 (207/290)	0.482 (0.390,0.596)
Other	22.3 (55/134)	6.5 (100/154)	0.387 (0.274,0.547)
Region			
North America	12.0 (58/103)	6.3 (55/85)	0.555 (0.376,0.818)
Europe	10.4 (94/172)	6.3 (144/197)	0.502 (0.383,0.657)
Rest of World	- (71/167)	6.2 (108/162)	0.350 (0.255,0.481)
Sex			
Female	10.4 (55/98)	6.1 (74/108)	0.490 (0.336,0.714)
Male	14.6 (168/344)	6.3 (233/336)	0.442 (0.360,0.544)
ECOG PS			
0	22.3 (93/223)	6.7 (146/215)	0.362 (0.277,0.475)
1-2	9.3 (130/219)	6.1 (161/227)	0.534 (0.420,0.678)
Primary disease site of origin			
Upper tract	12.7 (69/135)	6.2 (70/104)	0.497 (0.350,0.706)
Lower tract	12.5 (152/305)	6.3 (236/339)	0.437 (0.354,0.539)
Liver metastases			
Present	8.2 (66/100)	6.0 (78/99)	0.534 (0.378,0.755)
Absent	16.4 (157/342)	6.4 (229/345)	0.425 (0.346,0.524)
PD-L1 expression			
Low (CPS < 10)	10.5 (105/184)	6.3 (127/185)	0.501 (0.384,0.653)
High (CPS >= 10)	18.5 (116/254)	6.2 (176/254)	0.415 (0.326,0.529)
Cisplatin eligibility			
Eligible	14.6 (117/244)	6.5 (149/234)	0.483 (0.377,0.619)
Ineligible	10.6 (106/198)	6.1 (158/210)	0.429 (0.333,0.553)
Metastatic disease site			
Visceral metastases	10.4 (176/318)	6.2 (238/318)	0.452 (0.369,0.552)
Lymph node only	- (38/103)	8.3 (55/104)	0.400 (0.258,0.621)
Renal function			
Normal	18.7 (38/84)	6.7 (61/95)	0.461 (0.299,0.709)
Mild	12.7 (79/165)	6.3 (114/162)	0.463 (0.344,0.623)
Moderate/Severe	10.5 (106/193)	6.2 (132/187)	0.469 (0.359,0.613)



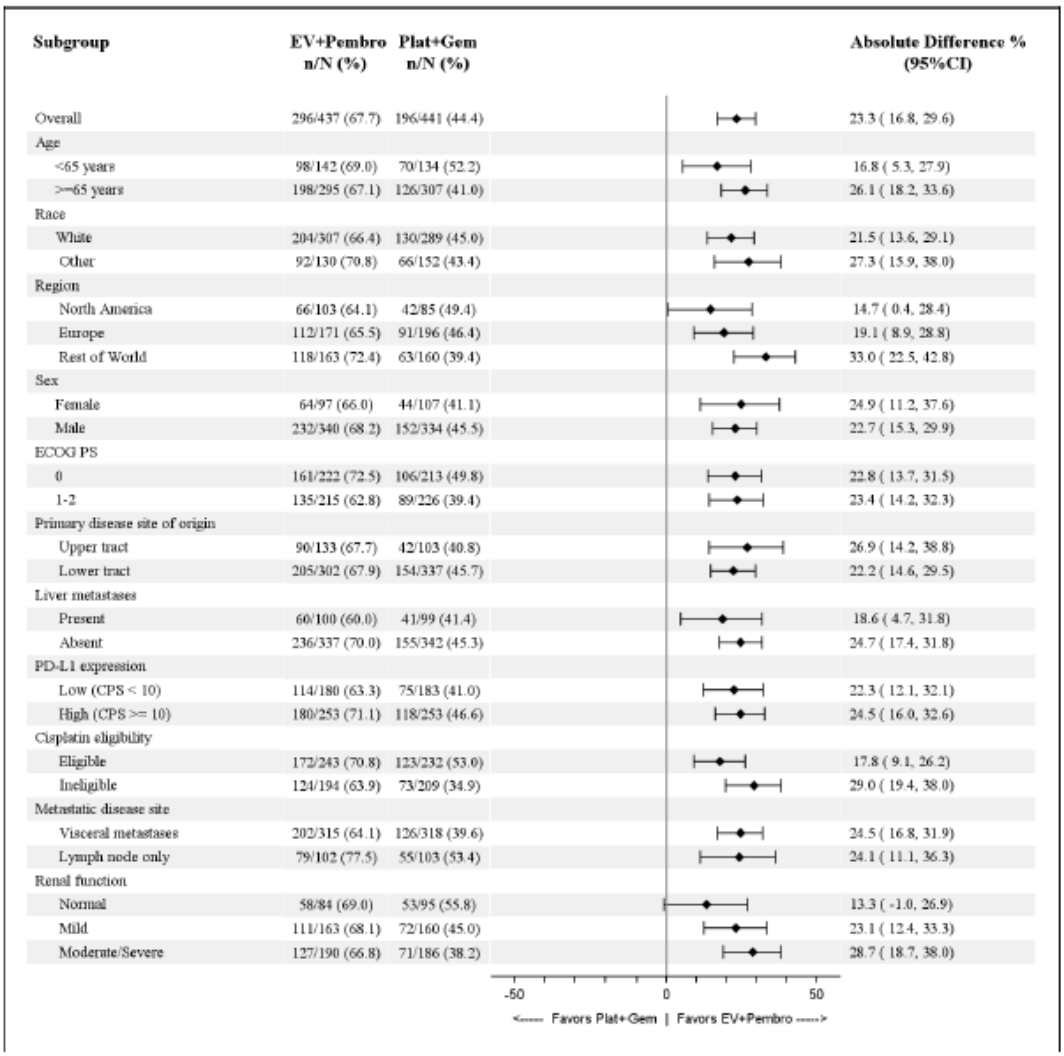
OS

Figure 40: Subgroup analyses of OS in the ITT analysis set, Study EV-302 (KEYNOTE-A39), DCO 08-AUG-2023



ORR

Figure 41: Subgroup Analysis of ORR by BICR (Response Evaluable Analysis Set)



Subgroup	EV+Pembro n/N (%)	Plat+Gem n/N (%)	Absolute Difference % (95%CI)
Overall	296/437 (67.7)	196/441 (44.4)	23.3 (16.8, 29.6)
Age			
<65 years	98/142 (69.0)	70/134 (52.2)	16.8 (5.3, 27.9)
>=65 years	198/295 (67.1)	126/307 (41.0)	26.1 (18.2, 33.6)
Race			
White	204/307 (66.4)	130/289 (45.0)	21.5 (13.6, 29.1)
Other	92/130 (70.8)	66/152 (43.4)	27.3 (15.9, 38.0)
Region			
North America	66/103 (64.1)	42/85 (49.4)	14.7 (0.4, 28.4)
Europe	112/171 (65.5)	91/196 (46.4)	19.1 (8.9, 28.8)
Rest of World	118/163 (72.4)	63/160 (39.4)	33.0 (22.5, 42.8)
Sex			
Female	64/97 (66.0)	44/107 (41.1)	24.9 (11.2, 37.6)
Male	232/340 (68.2)	152/334 (45.5)	22.7 (15.3, 29.9)
ECOG PS			
0	161/222 (72.5)	106/213 (49.8)	22.8 (13.7, 31.5)
1-2	135/215 (62.8)	89/226 (39.4)	23.4 (14.2, 32.3)
Primary disease site of origin			
Upper tract	90/133 (67.7)	42/103 (40.8)	26.9 (14.2, 38.8)
Lower tract	205/302 (67.9)	154/337 (45.7)	22.2 (14.6, 29.5)
Liver metastases			
Present	60/100 (60.0)	41/99 (41.4)	18.6 (4.7, 31.8)
Absent	236/337 (70.0)	155/342 (45.3)	24.7 (17.4, 31.8)
PD-L1 expression			
Low (CPS < 10)	114/180 (63.3)	75/183 (41.0)	22.3 (12.1, 32.1)
High (CPS >= 10)	180/253 (71.1)	118/253 (46.6)	24.5 (16.0, 32.6)
Cisplatin eligibility			
Eligible	172/243 (70.8)	123/232 (53.0)	17.8 (9.1, 26.2)
Ineligible	124/194 (63.9)	73/209 (34.9)	29.0 (19.4, 38.0)
Metastatic disease site			
Visceral metastases	202/315 (64.1)	126/318 (39.6)	24.5 (16.8, 31.9)
Lymph node only	79/102 (77.5)	55/103 (53.4)	24.1 (11.1, 36.3)
Renal function			
Normal	58/84 (69.0)	53/95 (55.8)	13.3 (-1.0, 26.9)
Mild	111/163 (68.1)	72/160 (45.0)	23.1 (12.4, 33.3)
Moderate/Severe	127/190 (66.8)	71/186 (38.2)	28.7 (18.7, 38.0)

Note: Liver metastases and cisplatin eligibility subgroups are based on post-randomization corrections CRF. Randomization was stratified by PD-L1 status (high or low) based on information available at screening. For subgroup analyses by PD-L1 status (low or high), subjects whose tissue sample was found to be unsuitable for PD-L1 22C3 per testing guidelines after randomization were not included in analyses by PD-L1 status.

Subgroup analysis by NECTIN-4 expression

Nectin-4

Figure 42: Subgroup Analysis of Progression-Free Survival per RECIST by BICR for H-Score of Nectin-4 Expression (EV-302 ITT Analysis Set)

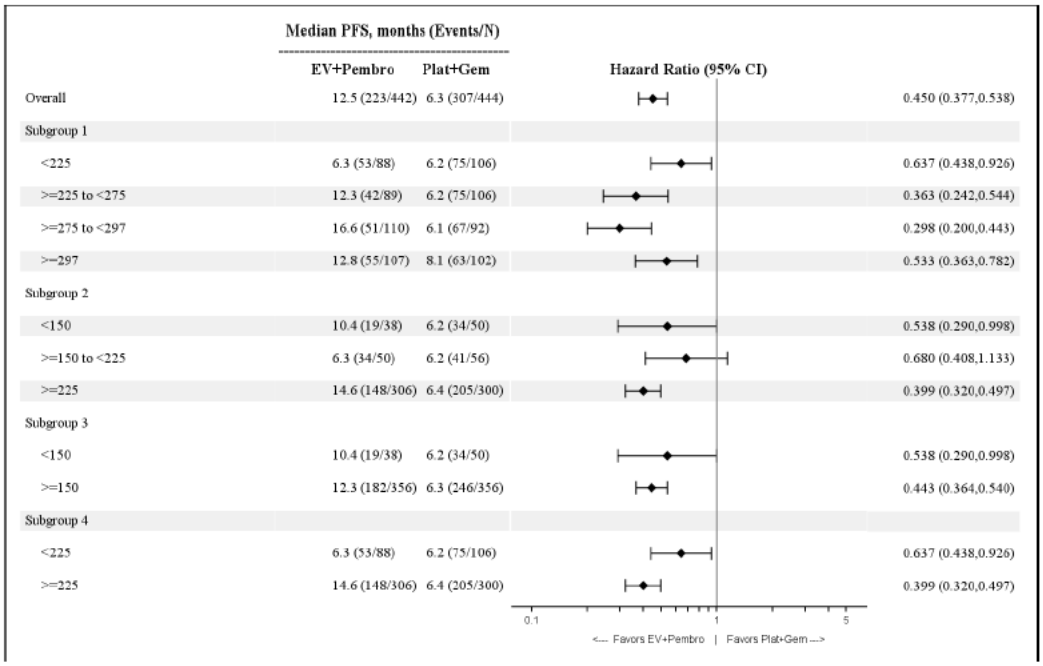


Figure 43: Subgroup Analysis of Overall Survival for H-Score of Nectin-4 Expression (EV-302 ITT Analysis Set)

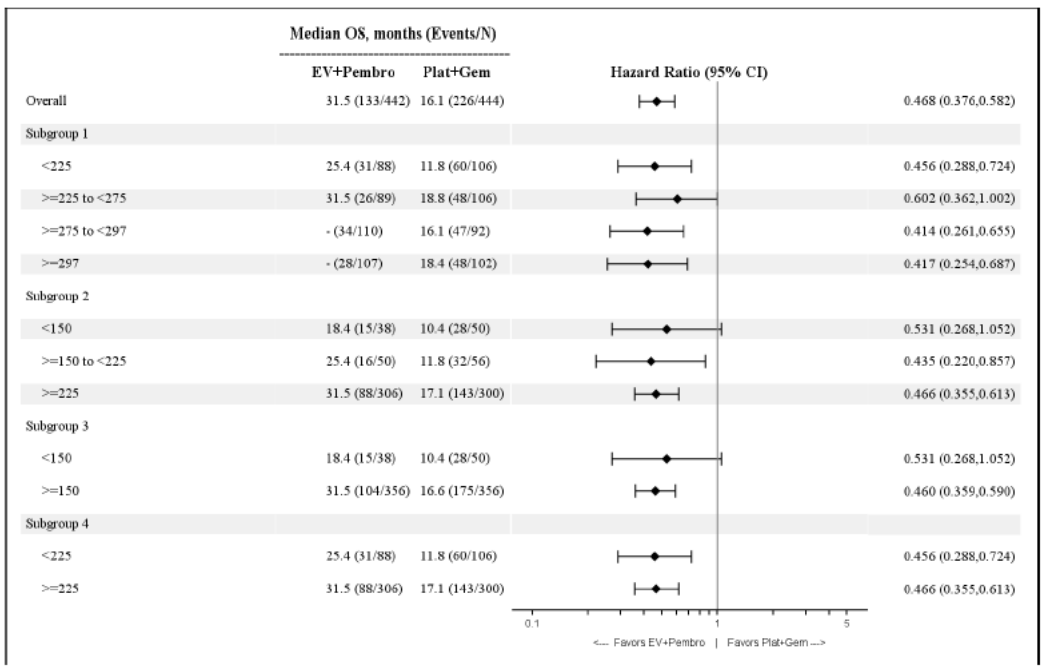
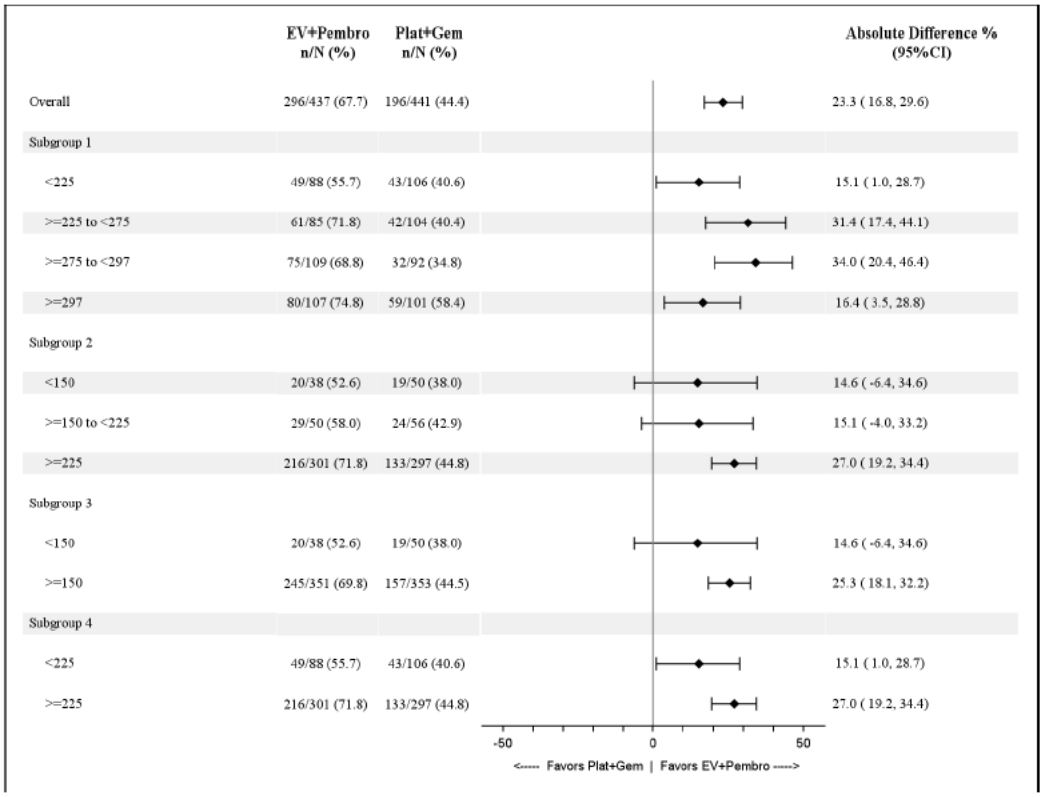


Figure 44: Subgroup Analysis of Objective Response Rate per RECIST by BICR for H-Score of Nectin-4 Expression (EV-302 Response Evaluable Set by BICR



PD-L1 by 22C3 assay

Table 62: Baseline Expression of PD-L1 in Tumor Tissue by IHC (ITT Analysis Set)

Parameter Statistic/Criteria	Arm A EV + Pembro N = 442	Arm B Plat + Gem N = 444	Total N = 886
PD-L1 expression, CPS§, n (%)			
n‡	438	439	877
High (CPS ≥ 10)	254 (58.0)	254 (57.9)	508 (57.9)
Low (CPS < 10)	184 (42.0)	185 (42.1)	369 (42.1)

Subgroup analysis by age

Table 63: PFS per RECIST v1.1 by BICR by Age Subgroup (EV-302 ITT Analysis Set)

	EV + Pembro N = 442	Plat + Gem N = 444
Age < 65 years, n	144	135
Number of events, n (%)	75/144 (52.1)	88/135 (65.2)
Median PFS (months)† (95% CI)	12.7 (10.3, 22.3)	6.4 (6.2, 7.3)
Hazard ratio‡ (95% CI)	0.446 (0.321, 0.621)	
Age 65 to < 75 years, n	196	201
Number of events, n (%)	100/196 (51.0)	139/201 (69.2)
Median PFS (months)† (95% CI)	12.0 (8.3, 18.5)	6.3 (6.2, 7.2)
Hazard ratio‡ (95% CI)	0.494 (0.379, 0.645)	
Age ≥ 75 years, n	102	108
Number of events, n (%)	48/102 (47.1)	80/108 (74.1)
Median PFS (months)† (95% CI)	12.3 (8.3, NE)	6.0 (4.4, 6.2)
Hazard ratio‡ (95% CI)	0.369 (0.251, 0.541)	

BICR: blinded independent central review; ITT: intent-to-treat; NE: not evaluable; PFS: progression-free survival; RECIST; Response Evaluation Criteria in Solid Tumors.
†As estimated using Kaplan-Meier method.
‡Calculated using stratified Cox proportional hazards model. A hazard ratio < 1 favors the EV + Pembro arm.

Table 64: OS by Age Subgroup (EV-302 ITT Analysis Set)

	EV + Pembro (N = 442)	Plat + Gem (N = 444)
Age < 65 years, n	144	135
Number of events, n (%)	39/144 (27.1)	58/135 (43.0)
Median OS (months)† (95% CI)	- (25.6, -)	19.7 (15.3, -)
Hazard ratio‡ (95% CI)	0.461 (0.300, 0.709)	
Age 65 to < 75 years, n	196	201
Number of events, n (%)	56/196 (28.6)	107/201 (53.2)
Median OS (months)† (95% CI)	NR (25.4, NE)	15.3 (13.1, 17.7)
Hazard ratio‡ (95% CI)	0.461 (0.333, 0.640)	
Age ≥ 75 years, n	102	108
Number of events, n (%)	38/102 (37.3)	61/108 (56.5)
Median OS (months)† (95% CI)	31.5 (17.7, NE)	12.1 (9.3, 18.3)
Hazard ratio‡ (95% CI)	0.497 (0.323, 0.764)	

ITT: intent-to-treat; NE: not evaluable; NR: not reached; OS: overall survival.
†As estimated using Kaplan-Meier method.
‡Calculated using stratified Cox proportional hazards model. A hazard ratio < 1 favors the EV + Pembro Arm.

Table 65: Summary of Overall Response per RECIST v1.1 by BICR by Age Subgroup (EV-302 Response Evaluable Set)

	EV + Pembro N = 437	Plat + Gem N = 441
Age < 65 years, n	142	134
Objective response†, n (%)	98/142 (69.0)	70/134 (52.2)
(95% CI)	(60.7, 76.5)	(43.4, 60.9)
Absolute difference in % (95% CI)	16.8 (5.3, 27.9)	
Age 65 to < 75 years, n	194	200
Objective response†, n (%)	131/194 (67.5)	85/200 (42.5)
(95% CI)	(60.4, 74.1)	(35.6, 49.7)
Absolute difference in % (95% CI)	25.0 (15.3, 34.3)	
Age ≥ 75 years, n	101	107
Objective response†, n (%)	67/101 (66.3)	41/107 (38.3)
(95% CI)	(56.2, 75.4)	(29.1, 48.2)
Absolute difference in % (95% CI)	28.0 (14.6, 40.5)	

BICR: blinded independent central review; RECIST: Response Evaluation Criteria in Solid Tumors.
† Objective response (complete or partial response) was confirmed with repeat scans ≥ 28 days after initial response according to RECIST v1.1.

Subsequent Therapies

Table 66: Subsequent Anticancer Therapy (ITT Analysis Set)

	Arm A EV + Pembro N = 442	Arm B Plat + Gem N = 444
Any subsequent therapy	140 (31.7)	313 (70.5)
Palliative radiotherapy	32 (7.2)	42 (9.5)
Non-palliative radiotherapy	6 (1.4)	6 (1.4)
Systemic therapy	128 (29.0)	294 (66.2)
Surgical procedure	8 (1.8)	14 (3.2)
Other	1 (0.2)	0
Number of lines of subsequent systemic therapy, n (%)		
1	94 (21.3)	196 (44.1)
2	22 (5.0)	75 (16.9)
≥ 3	12 (2.7)	23 (5.2)
First subsequent systemic therapy, n (%)		
Platinum-based therapy	110 (24.9)	17 (3.8)
Cisplatin based	53 (12.0)	8 (1.8)
Carboplatin based	56 (12.7)	8 (1.8)
Other	1 (0.2)	1 (0.2)
Maintenance PD-1/L1 inhibitor	0	143 (32.2)
Avelumab	0	135 (30.4)
Pembrolizumab	0	7 (1.6)
Other PD-1/L1 inhibitor-containing therapy	7 (1.6)	117 (26.4)
Other	11 (2.5)	17 (3.8)
Enfortumab vedotin	3 (0.7)	3 (0.7)
Second and beyond subsequent systemic therapy, n (%)		
Platinum-based therapy	8 (1.8)	10 (2.3)
Maintenance PD-1/L1 inhibitor	8 (1.8)	7 (1.6)
Other PD-1/L1 inhibitor containing therapy	7 (1.6)	12 (2.7)
Other	24 (5.4)	82 (18.5)
Enfortumab vedotin	0	54 (12.2)
Time from last dose to first subsequent systemic therapy for progressive disease (months)		
n	113	193
Mean (SD)	1.91 (2.32)	4.03 (3.81)
Median	1.02	3.02
Min, max	0.2, 17.7	0.3, 23.5

EV: Enfortumab vedotin; Gem: Gemcitabine; Max: Maximum; ITT: Intent-to-treat; Min: Minimum; Pembro: Pembrolizumab; Plat: platinum-based chemotherapy (cisplatin or carboplatin); SD: standard deviation

Summary of main study

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 67: Summary of Efficacy for trial EV-302 (KEYNOTE-A39)

Title: An Open-label, Randomized, Controlled Phase 3 Study of Enfortumab Vedotin in Combination with Pembrolizumab Versus Chemotherapy Alone in Previously Untreated Locally Advanced or Metastatic Urothelial Cancer		
Study identifier	SGN22E-003 (MK-3475-A39); IND 116360; NCT04223856; EudraCT 2019-004542-15	
Design	Open-label, randomised, controlled against platin-based chemotherapy	
	Duration of main phase: Duration of Run-in phase:	2 years not applicable

	Duration of Extension phase:		not applicable
Hypothesis	Superiority (PFS and OS) of EV+pembrolizumab vs. chemotherapy		
Treatments groups	Arm A, EV+Pembro		Enfortumab vedotin 1.25 mg/kg D1 and D8 Q3W + pembrolizumab 200 mg D1 Q3W N=442
	Arm B, Plat+Gem		Gemcitabine 1000 mg/m2 D1 and D8 Q3W and either cisplatin 70 mg/m2 or carboplatin AUC 4.5 D1 Q3W N=444
Endpoints and definitions	Co-Primary endpoint	PFS-BICR	Progression free survival by blinded independent central review
	Co-Primary endpoint	OS	Overall survival
	Secondary endpoint	ORR-BICR	Overall response rate by blinded independent central review
Database lock	08-AUG-2023		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat, data cut-off 08-AUG-2023		
Descriptive statistics and estimate variability	Treatment group	Arm A EV+Pembro	Arm B Plat+gem
	Number of subjects	N=442	N=444
	Median PFS-BICR (months)	12.5	6.3
	95% CI	10.4, 16.6	6.2, 6.5
	Median OS (months)	31.5	16.1
	95% CI	25.4, not reached	7.6, not reached
	ORR-BICR % (n/dataset*) 95% CI	67.7 (296/437) 63.1, 72.1	44.4 (196/4441) 39.7, 49.2
Effect estimate per comparison	Co-Primary endpoint PFS-BICR	Comparison groups	Arm A vs. Arm B
		Stratified HR‡	0.450
		95% CI	0.377, 0.538
		2-sided P-value§	<0.00001
	Co-Primary endpoint OS	Comparison groups	Arm A vs. Arm B
		Stratified HR‡	0.468
		95% CI	0.376, 0.582
		2-sided P-value§	<0.00001
Notes	*For response-related endpoints, response-evaluable dataset per BICR ‡Calculated using stratified Cox proportional hazards model §Calculated using stratified log-rank test		

Clinical Studies in special populations

Table 68. Clinical studies in special populations

	Controlled Trials	Non-controlled trials
Renal impairment* patients (Subjects number /total number)	171/886	38/121
Hepatic impairment patients (Subjects number /total number)**	3/886	1/121
Age 65-74 (Subjects number /total number)	397/886	52/121
Age 75-84 (Subjects number /total number)	194/886	30/121
Age 85+ (Subjects number /total number)	16/886	10/121
Other (Subjects number /total number)	279/886	29/121

* Renal impairment is defined as having creatinine clearance < 45 mL/min.
** Hepatic impairment is defined as having moderate or severe liver dysfunction, where moderate dysfunction = (total bilirubin > 1.5 - 3x ULN and any AST) and severe dysfunction = (total bilirubin > 3x ULN and any AST).
Note: Controlled trial includes only Study EV-302 and non-controlled trial includes only Study EV-103 (dose-escalation, Cohort A, and Cohort K [EV + Pembro arm]).

Supportive studies

Study EV-103 (KEYNOTE-859)

Study EV-103 provides both EV + Pembrolizumab data and EV monotherapy data in a population of 1L cisplatin-ineligible patients. The contribution of pembrolizumab is supported by comparing EV + Pembrolizumab data from EV-302 to EV monotherapy data from the Cohort K monotherapy arm of the EV-103 study. EV + Pembrolizumab data from Study EV-103 was included to demonstrate consistency of efficacy outcomes across studies.

Methods

Study Design

Study EV-103 is an ongoing phase 1b/2, global, multicenter study designed to evaluate the safety, antitumour activity, and PK of enfortumab vedotin as monotherapy or in combination with pembrolizumab and/or chemotherapy for the treatment of patients with LA/mUC. The LA/mUC component of study EV-103 includes a dose-escalation cohort, expansion cohorts (Cohorts A through G), as well as a randomized cohort (Cohort K) with 2 treatment arms (EV + Pembro arm and EV Mono arm). Efficacy results from the subjects treated in the 1L **cisplatin ineligible** setting with enfortumab vedotin 1.25 mg/kg as either a monotherapy or in combination with pembrolizumab in the dose-escalation cohort (n = 5), Cohort A (n = 40), and randomized Cohort K (N = 149) were presented.

Dose-escalation Cohort

Dose escalation was conducted using a standard 3 + 3 design. Enfortumab vedotin in combination with pembrolizumab was initially tested at 2 dose levels (1 and 1.25 mg/kg) in the dose-escalation cohort. The dose-escalation cohort included subjects with LA/mUC who were ineligible for 1L treatment with cisplatin-containing chemotherapy and subjects receiving treatment in the 2L setting. Subjects enrolled in the dose-escalation cohort were administered study treatment of IV enfortumab vedotin (starting dose of 1 mg/kg and escalated to 1.25 mg/kg) followed by IV pembrolizumab (200 mg) on day 1 and enfortumab vedotin alone on day 8 in 3-week cycles. Subjects were evaluated for DLTs to determine the recommended dose of enfortumab vedotin when given in combination with pembrolizumab.

Cohort A

In Cohort A, subjects ineligible for cisplatin-containing chemotherapy with no prior systemic treatment for LA/mUC received treatment with enfortumab vedotin 1.25 mg/kg in combination with pembrolizumab 200 mg.

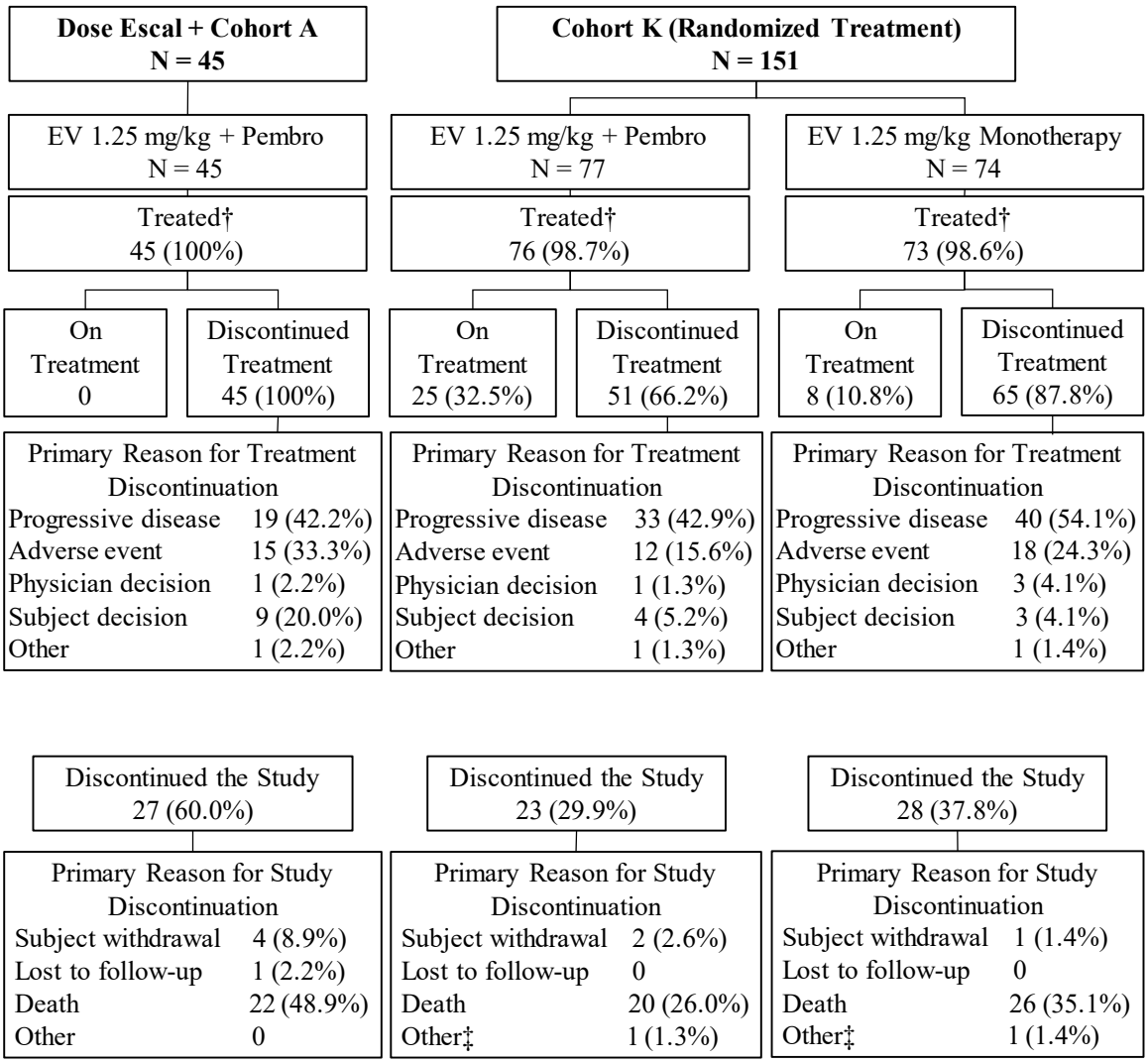
Randomized Cohort K

Cohort K, which was added to the study protocol in November 2019 (Amendment 6), enrolled a similar patient population as Cohort A. Subjects were randomized in a 1:1 manner to receive either enfortumab vedotin 1.25 mg/kg monotherapy (in the EV Mono arm) or enfortumab vedotin 1.25 mg/kg in combination with pembrolizumab 200 mg (in the EV + Pembro arm).

Results

Throughout this section, efficacy results for study EV-103 are displayed by treatment arm within randomized Cohort K, combined results from the dose-escalation cohort and Cohort A (dose escalation + Cohort A, N = 45).

Table 69: Study EV-103 Summary of Subject Disposition



Efficacy analyses were performed using the analysis sets defined in the following table.

Table 70: Study EV-103 Number of Subjects Enrolled and Included in Each Analysis Set

	Sample Size by Cohort						
	Dose Escalation		**Cohort A**	**Cohort K**		**Dose Escal + Cohort A†**	**Dose Escal + Cohorts A and K†**
	EV 1.0 mg/kg + Pembro	**EV 1.25 mg/kg + Pembro**	**EV 1.25 mg/kg + Pembro**	**EV 1.25 mg/kg + Pembro**	**EV 1.25 mg/kg Mono**	**EV 1.25 mg/kg + Pembro**	**EV 1.25 mg/kg + Pembro**
All enrolled subjects	3	5	40	77	74	45	122
Analysis sets							
FAS and Safety Analysis Set‡	3	7	40	76	73	45	121

Outcomes and Estimations

Primary Efficacy: ORR per RECIST v1.1 by BICR

Treatment with enfortumab vedotin in combination with pembrolizumab resulted in a high ORR with rapid responses for 1L cisplatin-ineligible patients with LA/mUC. In dose escalation + Cohorts A + K, ORR was 67.8% (95% CI: 58.7, 76.0), with 15 subjects (12.4%) achieving CR and 67 subjects (55.4%) achieving PR.

Cohort K (EV Mono) ORR was 45.2% (95% CI: 33.5, 57.3) including 3 subjects (4.1%) who achieved CR and 30 subjects (41.1%) who achieved PR. Cohort K (EV Mono) ORR was consistent with prior experience with enfortumab vedotin monotherapy in pretreated patients (studies EV-201 and EV-301) and demonstrated meaningful single-agent activity [Powles et al, 2021b; Yu et al, 2021]. Confirmed ORR as assessed by investigator is provided in the CSR. Confirmed ORR as assessed by BICR and by investigator were similar for dose escalation + Cohorts A + K, with a concordance rate of 89.8%, consistent with individual cohorts.

Study EV-103 ORR, DCR and BOR (per RECIST v1.1 by BICR) – Full Analysis Set, DCO 10-JUN-2022

Table 71: ORR, DCR, and Best Overall Response in Cohort A, Cohort K, and Combined Results (per RECIST v1.1, Full Analysis Set)

	Cohort A	Cohort K		Dose Escal + Cohort A†	Dose Escal + Cohorts A and K†
	EV + Pembro N = 40	EV + Pembro N = 76	EV Mono N = 73	EV + Pembro N = 45	EV + Pembro N = 121
BICR assessment					
ORR‡, n (%)	30 (75.0)	49 (64.5)	33 (45.2)	33 (73.3)	82 (67.8)
95% CI	(58.8, 87.3)	(52.7, 75.1)	(33.5, 57.3)	(58.1, 85.4)	(58.7, 76.0)
Best overall response, n (%)					
CR§	7 (17.5)	8 (10.5)	3 (4.1)	7 (15.6)	15 (12.4)
PR§	23 (57.5)	41 (53.9)	30 (41.1)	26 (57.8)	67 (55.4)
SD	4 (10.0)	17 (22.4)	25 (34.2)	5 (11.1)	22 (18.2)
PD	4 (10.0)	6 (7.9)	7 (9.6)	5 (11.1)	11 (9.1)
NE¶	0	3 (3.9)	5 (6.8)	0	3 (2.5)
No assessment††	2 (5.0)	1 (1.3)	3 (4.1)	2 (4.4)	3 (2.5)
DCR‡‡, n (%)	34 (85.0)	66 (86.8)	58 (79.5)	38 (84.4)	104 (86.0)
95% CI	(70.2, 94.3)	(77.1, 93.5)	(68.4, 88.0)	(70.5, 93.5)	(78.5, 91.6)
Investigator assessment					
ORR‡, n (%)	30 (75.0)	47 (61.8)	33 (45.2)	33 (73.3)	80 (66.1)
95% CI	(58.8, 87.3)	(50.0, 72.8)	(33.5, 57.3)	(58.1, 85.4)	(57.0, 74.5)
Best overall response, n (%)					
CR§	9 (22.5)	9 (11.8)	5 (6.8)	10 (22.2)	19 (15.7)
PR§	21 (52.5)	38 (50.0)	28 (38.4)	23 (51.1)	61 (50.4)
SD	7 (17.5)	19 (25.0)	24 (32.9)	9 (20.0)	28 (23.1)
PD	1 (2.5)	7 (9.2)	9 (12.3)	1 (2.2)	8 (6.6)
NE¶	0	2 (2.6)	3 (4.1)	0	2 (1.7)
No assessment††	2 (5.0)	1 (1.3)	4 (5.5)	2 (4.4)	3 (2.5)
DCR‡‡, n (%)	37 (92.5)	66 (86.8)	57 (78.1)	42 (93.3)	108 (89.3)
95% CI	(79.6, 98.4)	(77.1, 93.5)	(66.9, 86.9)	(81.7, 98.6)	(82.3, 94.2)
ORR concordance rate between BICR and investigator assessments§§	94.7%	86.7%	85.5%	95.3%	89.8%

BICR: blinded independent central review; CR: complete response; DCR: disease control rate; Escal: escalation; EV: enfortumab vedotin; NE: not evaluable; ORR: objective response rate; PD: progressive disease; Pembro: pembrolizumab; PR: partial response; RECIST: response evaluation criteria in solid tumours; SD: stable disease.

†Subjects assigned to EV 1.25 mg/kg + pembro and for whom study treatment was administered as first-line therapy (Dose Escal, n = 5; Cohort A, n = 40, Cohort K, n = 76).

‡Includes confirmed CR or PR.

§Confirmed with repeat scans ≥4 weeks after initial response.

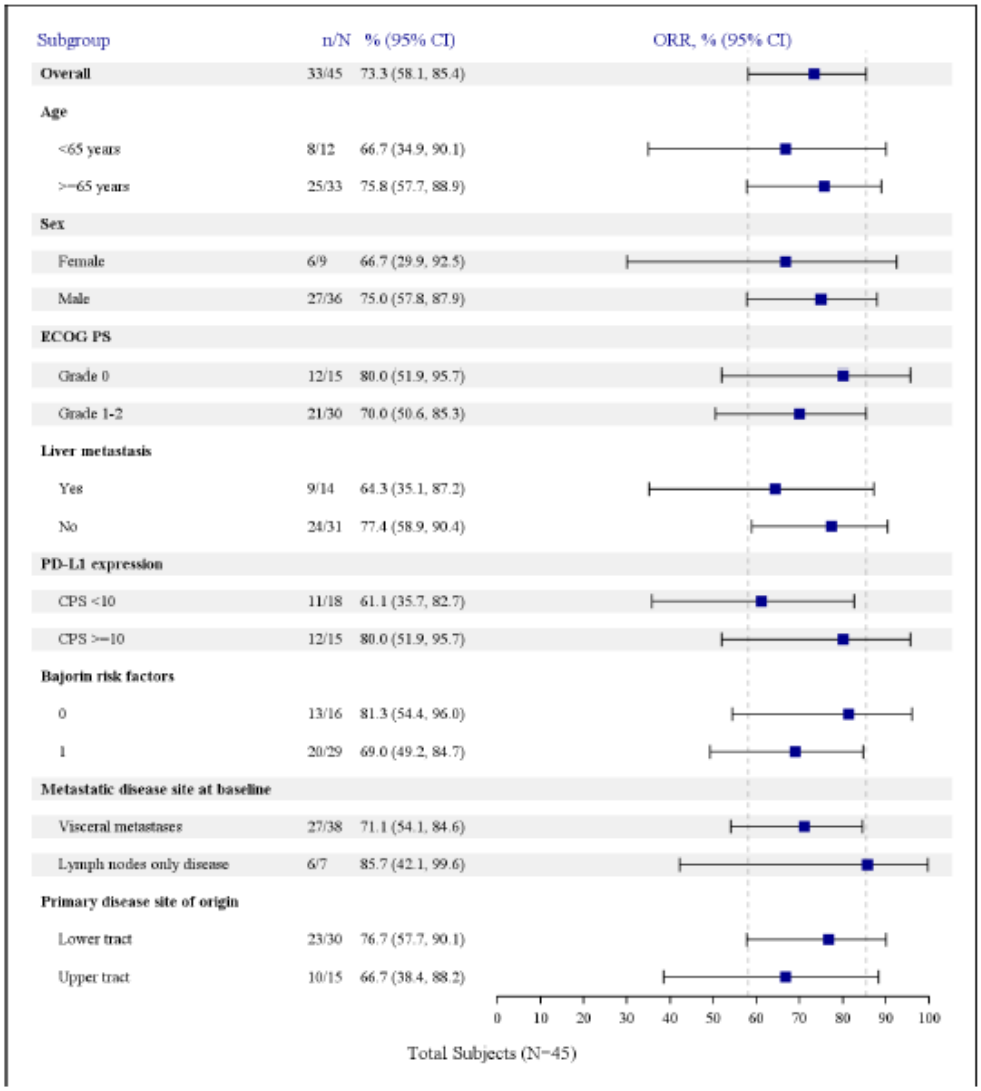
¶Subjects had post-baseline assessment and the best overall response was determined to be not evaluable per RECIST v1.1.

††Subjects had no response assessment post-baseline.

‡‡Includes CR, PR, or SD.

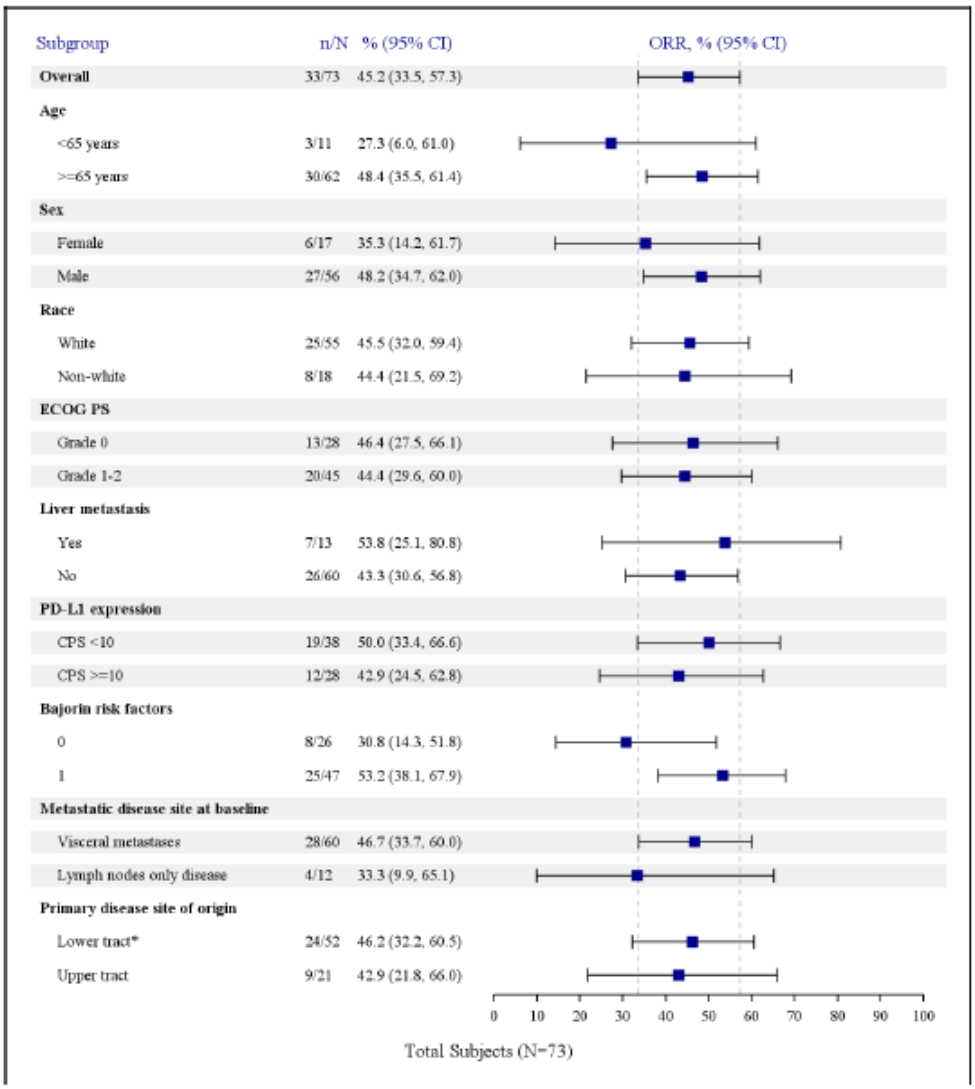
§§Concordance is the percent agreement between BICR and investigator reads, calculated as the (number of matched responders + number of matched non-responders)/total number of subjects assessed.

Figure 45: Subgroup Analyses of ORR pre RECIST v1.1 by BICR: Dose Escalation + Cohort A (EV + Pembrolizumab)



BICR: blinded independent central review; CPS: combined positive score; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EV: enfortumab vedotin; ORR: objective response rate; Pembro: pembrolizumab.

Figure 46: Subgroup Analyses of ORR pre RECIST v1.1 by BICR: Cohort K (EV Mono)



BICR: blinded independent central review; CPS: combined positive score; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EV: enfortumab vedotin; Mono: monotherapy; ORR: objective response rate.

Study KEYNOTE-361

Study KEYNOTE-361 provides pembrolizumab monotherapy data in a population of all-comer patients with LA/mUC. The contribution of enfortumab vedotin is supported by comparing EV + Pembro combination data from EV-302 to pembrolizumab monotherapy data from Study KEYNOTE-361.

Study KEYNOTE-361 was a phase 3, multi-site study designed to evaluate pembrolizumab with or without platinum-based combination chemotherapy versus chemotherapy alone in subjects with previously untreated LA/mUC. Subjects were enrolled regardless of PD-L1 status. Subjects enrolled in the pembrolizumab monotherapy and combination arm received pembrolizumab (200 mg) every 3 weeks (day 1 of each 3-week cycle) for a maximum of 35 doses. In the combination and chemotherapy only arms, subjects received 6 cycles of platinum-based combination chemotherapy as per investigator's choice of either cisplatin or carboplatin.

The results for study KEYNOTE-361 are based on published data[Powles et al, 2021a]. Between 19 October 2016 and 29 June 2018, 1010 subjects (ITT population) were enrolled and randomly allocated to receive pembrolizumab plus platinum-based chemotherapy (351 [35%]), pembrolizumab

monotherapy (307 [30%]), or platinum-based chemotherapy (352 [35%]). All 1010 subjects were assessed for the dual primary endpoints of the trial.

As of the 29 April 2020 data cut-off, the median OS was 15.6 months (95% CI: 12.1-17.9) in the pembrolizumab monotherapy group and 14.3 months (95% CI: 12.3–16.7) in the chemotherapy group (HR 0.92 [95% CI 0.77–1.11], p=0.0407). The confirmed ORR was 30.3% for pembrolizumab monotherapy and 44.9% for chemotherapy alone. Additionally, the median DOR was 28.2 months for the pembrolizumab monotherapy group and 6.2 months for chemotherapy alone [Powles et al, 2021a].

Study KEYNOTE-052

Study KEYNOTE-052 was a phase 2, multi-site study designed to evaluate pembrolizumab monotherapy in subjects with advanced/unresectable (inoperable) or metastatic urothelial cancer who had not received prior systemic chemotherapy (i.e. 1L) and who were not eligible to receive cisplatin. Study KEYNOTE-052 was an open-label study and subjects were enrolled into a single cohort.

The results for Study KEYNOTE-052 are based on published data[Vuky et al, 2020]. From 24 February 2015 (date of first signed informed consent) to 26 September 2018 (Study KEYNOTE-052 data cut-off date), 370 subjects were enrolled and treated with pembrolizumab as a monotherapy in study KEYNOTE-052. This study evaluated antitumor activity (ORR) of pembrolizumab as 1L therapy in LA/mUC subjects who were not eligible to receive cisplatin. Of the 370 subjects who were enrolled and received at least 1 dose of pembrolizumab, most subjects (90%) had no prior adjuvant or neoadjuvant platinum-containing chemotherapy. Study KEYNOTE-052 enrolled subjects across PD-L1 expression subgroups. The primary reason for cisplatin ineligibility was renal dysfunction (49.5%, defined as GFR of < 60 and > 30 mL/min), followed by ECOG PS of 2 (41.9%) [Vuky et al, 2020].

The confirmed ORR by BICR assessment was 28.6% (95% CI: 24.1%, 33.5%) and the median DOR was 30.1 months.

2.4.3. Discussion on clinical efficacy

This application is for the extension of indication of Keytruda in combination with enfortumab vedotin as first-line treatment for locally advanced or metastatic urothelial carcinoma (LA/mUC) based on the results of the pivotal study EV-302 (KEYNOTE-A39) supported by study EV-103.

Design and conduct of clinical studies

Study EV-302 (KEYNOTE-A39) is an ongoing, open-label, multicentre, randomized Phase III trial testing the superiority of enfortumab vedotin + pembrolizumab (Arm A, EV + Pembro) versus platinum-containing chemotherapy (i.e. cisplatin or carboplatin in combination with gemcitabine; Arm B, Plat + Gem) in subjects with previously untreated LA/mUC. The **comparator** arm can be deemed acceptable and in line with the current standard of care (SoC). However, avelumab as maintenance therapy following completion of randomized treatment in the Plat + Gem Arm became available during study enrollment, [Protocol Amendment 04; 11 November 2021], and was administrated if locally available provided the subject was deemed eligible by the investigator. Currently, approximately 30% of patients assigned to the control arm received avelumab. While acknowledging the demonstrated benefit of avelumab maintenance on overall survival, assignment to treatment was not randomised and the overall superiority of Keytruda/enfortumab vedotin vs chemotherapy in the ITT population appears unconfutable and of such a magnitude that a possible underperformance of the control arm is

not expected to significantly impact on the efficacy results. Therefore, no further data are deemed necessary.

In the original protocol, a third arm was contemplated (Arm C: EV + Pembro + Plat [cisplatin or carboplatin]). Arm C was removed with Amendment 2 based on the promising results of the EV-103 trial supporting the EV + Pembro combination, as well as other trials evaluating PD-(L)1 inhibitors in combination with platinum-containing chemotherapy that failed in achieving their primary goals. This change can be considered fully justified. Overall, the study design appears adequate for a B/R evaluation of the experimental arm vs a standard of care. Problematic from a methodological perspective is the lack, in study EV-302, of a monotherapy arm testing enfortumab vedotin or pembrolizumab alone, which makes the single component contribution to the efficacy results uncharacterised and partly derivable from external data. This aspect was already highlighted as a limiting factor in the Scientific Advice that the CHMP provided to the MAH (MEA/H/SA/4246/1/2019/II), particularly as regards the individual contributions of enfortumab vedotin and pembrolizumab, respectively, in nectin-4 and PD-L1 low-expressors. The consistency of response according to biomarkers as emerged in the subgroup analysis moderately attenuates this concern (see below).

The **study population** comprised a broad range of patients, including subjects eligible to receive either cisplatin- or carboplatin-containing chemotherapy. The cisplatin eligibility criteria were in line with standard practice. Inclusion criteria allowed the enrolment in the trial of a quite heterogeneous population in terms of ECOG PS score, although ECOG PS2 patients were considered eligible only in selected conditions (i.e. haemoglobin ≥10 g/dL, GFR ≥ 50 mL/min and no NYHA Class III heart failure).

Randomisation to treatment was in a 1:1 ratio to Arm A and Arm B and stratified by platinum eligibility (cisplatin versus carboplatin), PD-L1 expression (high or low), and liver metastases (present or absent). The combination of these categories resulted in 2x2x2=8 strata. The study was open label, so no blinding/unblinding procedures were planned. Some efforts to reduce the risk of bias due to the open label design were made.

The Intention-to-Treat (ITT) population served as the population for primary efficacy analyses. All randomized participants were included in this population. PFS per RECIST 1.1 based on BICR and OS were selected as **dual primary endpoints**, meaning that the study could be considered to have met its primary objective if a statistically significant difference between Arm A and Arm B was demonstrated for PFS or OS in the overall population. The analysis of hard endpoints mitigates the potential bias deriving from the open-label nature of the pivotal study. Secondary endpoints ORR per RECIST 1.1, duration response per RECIST 1.1 by BICR and QoL indicators were also evaluated.

The **sample size** was amended twice during the study course. The first updated was justified by the interruption of randomization in Arm C. Then, the sample size was re-calculated, the primary endpoints were powered as consequence and the multiplicity strategy was also updated.

At time of analysis (date of data cut-off: 08 August 2023), 1297 subjects were assessed for eligibility and 897 of them (69.1%) were randomized to the EV + Pembro (N = 442) and Plat + Gem arms (N = 444) and EV + Pembro + Plat Arm (N=11 were treated before this arm was closed to enrollment). The screen failure rate was 30.6%, mainly because patients did not meet eligibility criteria (66.2% of total screen failures). The majority was caused by participants not meeting inclusion criteria (43.8%), particularly due to lack of tumor sample availability (12.8%) or measurable disease (9.1%) or inadequate hematologic and organ function (9.3%), while among exclusion criteria (22.9% of total screen failures), uncontrolled diabetes as defined by hemoglobin A1c (HbA1c) ≥ 8% or HbA1c 7% to < 8%, was the prevailing reason (6%). Overall, the rate of screen failures is consistent with other clinical

trials conducted in the same clinical setting and is not considered compromising the target population representativeness of study EV-302.

In general, **eligibility criteria** enabled an adequate definition of a first-line LA/mUC patient population, (including subjects with failure of neoadjuvant/adjuvant treatment within 12 months). Both cisplatin eligible and non-eligible subjects were considered. However poor prognostic factors /baseline characteristics were not fully represented; specifically, only 26 patients (2.9% of study population) with an ECOG PS of 2 were included, which is quite debatable considering the expectedly high rate of reduced performance status in this patient population. Moreover, no patients with brain metastases were included.

Among the important **protocol deviations**, 13 subjects (3 in Arm A and 10 in Arm B) should have been considered screening failures due to violation of inclusion/exclusion criteria; additional 5 subjects (2 in Arm A and 3 in Arm B) did not perform the mandatory bone scan at baseline. These subjects were still randomized and the impact of these deviation was not investigated. However, it is not reasonable that it could affect the study results.

Statistical methods were well reported in the protocol section and in the final version of SAP (Version No. 4 dated 22 June 2023) and can be considered appropriate.

The protocol was subject to 8 general **amendments** of which Amendments 02 and 04 affected the sample size, the multiplicity adjustment strategy and the timing of efficacy analyses. The SAP was also subject to 4 amendments, to reflect the corresponding changes. An adequate rationale for protocol amendments was presented.

The ITT population served as the population for the primary efficacy analyses. All randomly assigned participants were included in this population. The median follow-up for OS was 17.3 (16.4, 18.2) for the pembrolizumab arm and 16.9 (16.1, 18.5) months for the control arm.

The efficacy analyses in this submission were based on IA1 (DCO 08 August 2023). At time of data cut-off, 530 PFS events (223 in the pembrolizumab arm and 307 in the control arm) and 359 OS events (133 in the pembrolizumab arm and 226 in the control arm, 73% information fraction) occurred. The number of both PFS and OS events was slightly higher than required as per protocol (526 PFS events and 356 OS events), suggesting that data were mature to perform the efficacy analyses. The pre-specified power of this planned IA1 is adequate.

To evaluate the robustness of the primary analysis results for PFS by BICR, additional pre-specified sensitivity analyses were performed, showing consistent results with the primary PFS analysis (HRs ranged from 0.446 to 0.460)

Part of the study was conducted during the coronavirus disease 2019 (COVID-19) pandemic. COVID-19 impacts were evaluated in the ITT Analysis Set and was summarized and listed. Only 73 subjects (50 in the pembrolizumab arm and 23 in the control arm) had at least 1 visit impacted. No sensitivy analysis of primary endpoint to assess the impact of COVID-19 was performed; however, the overall effect of treatment was unlikely impacted.

The graphical approach of Maurer and Bretz was applied to control the family-wise type I error rate at 0.05 (2-sided) among the dual primary hypotheses for PFS and OS and the key secondary hypothesis, while the efficacy boundaries at the interim and final analyses were determined using the Lan-DeMets spending function to approximate O'Brien-Fleming; these approaches are both endorsed.

The stratification factors used for randomization were applied to stratified efficacy analyses. The treatment effect of EV + Pembro on PFS by BICR was consistent across all pre-specified subgroups, with HRs ranging from 0.415 to 0.534 in favor of EV + Pembro across these subgroups.

Efficacy data and additional analyses

The current application is based on the first interim (and final) analysis of study KEYNOTE-A39. Of the total 356 planned OS events to be reached at the first interim analysis (72.8% of the total 489 events required for a powered analysis), 359 deaths were observed at the data cut-off date (DCO: 08 August 2023). Therefore, results can be considered sufficiently mature. As per protocol, given the statistical significance of OS reached at this stage, results are taken as final.

A total of 1297 subjects were consented with 897 being randomized across the three arms (442 in Arm A, EV + Pembro; 446 in Arm B (Plat + Gem); 11 in Arm C, EV + Pembro + Plat). Considering the limited sample size of Arm C, results from this group were separately presented in a descriptive manner for ORR and DoR. The comparison was formally conducted between Arm A and Arm B.

The ITT population comprised 886 patients (442 in the EV + Pembro and 444 in the Plat + Gem arm). Baseline characteristics were overall balanced between groups. The study population mainly included male subjects (76.7%) aged 69 years in median, with 23% of patients ≥75 years-old equally distributed in the two arms. The prevailing disease was urothelial carcinoma (89.4% vs 11.6% of urothelial carcinoma mixed), originating from the lower urinary tract (72.7%), metastatic (94.9%) and with visceral involvement (71.8% vs 23.4% lymph nodes only). The ICH H-score for Nectin-4 expression was quite homogenous (275 in median, [225.0, 297.0]), while high and low PD-L1 expressing tumours were well represented (CPS≥10 in 57.9% and CPS<10 42.1% of ITT). Prior therapies were given in the neoadjuvant/adjuvant setting in a limited subset of patients (8.9% of the ITT).

As of the data cut-off date, a higher percentage of subjects in the EV + Pembro Arm (67%) than the Plat + Gem Arm (45.7%) remained in the study. Treatment continued in 32.6% of subjects randomized to EV + Pembro, while no subjects remained on treatment in the Plat + Gem Arm. The most common reason for drug discontinuation in the EV + Pembro Arm was progressive disease (34.6%) and adverse event (21.9%); in the Plat + Gem Arm progressive disease (16.4%) and adverse event (14.0%) accounted for a minority of cases unable to complete the 6 cycles of treatment that, on the contrarily, were fully administrated to the 55% of patients. A lower portion of patients in the EV + Pembro Arm (33%) than the Plat + Gem Arm (54.3%) were off the study. The main reason for study discontinuation was death in both arms, although occurring at a remarkably lower rate in the EV + Pembro Arm (29.9%) than the Plat + Gem Arm (50.9%).

With a median follow-up of 17.2 months (range: 0.07 to 37.16) combining both treatment groups, the ITT analysis demonstrated a statistically significant superiority of EV + Pembro compared to Plat + Gem in both **primary endpoints**. Treatment Arm A provided a 53.2% reduction in the risk of death compared to treatment Arm B (HR = 0.468; 95% CI: 0.376, 0.582; 2-sided p-value <0.00001; threshold for statistical significance: 0.01548) and a gain of 15 months in median survival (31.5 months in EV + Pembro Arm and 16.1 months in the Plat + Gem Arm). A statistically significant advantage of EV + Pembro versus Plat + Gem was also demonstrated in PFS, with a 55% reduction in the risk of disease progression or death (HR = 0.450; 95% CI: 0.377, 0.538; 2-sided p-value <0.00001; threshold for statistical significance: 0.005).

Among **secondary endpoints,** response rate also met statistical significance with an improvement in ORR as assessed by BICR for EV + Pembro (67.7%; 95% CI: 63.1, 72.1) compared to Plat + Gem (44.4%; 95% CI: 39.7, 49.2) (2-sided p-value <0.00001), and a more durable response in Arm A (DoR not reached; 95% CI: 20.2, NE) compared to Arm B (7.0 months; 95% CI: 6.2, 10.2). Median TTR was 2.10 months in both treatment groups. Time to Pain Progression was not modified by the experimental arm compared to control (HR = 0.916; 2-sided p-value = 0.48). As per the hierarchical statistical analysis plan, the secondary endpoint of change from baseline in worst pain (BPI-SF Q3) at

week 26 was not formally tested. With regard to PRO, there were no changes over time for any of the domain scores, inclusive of general quality of life, functioning, and symptom scores in either treatment arm.

For the exploratory analysis of response by **biomarker**, data on Nectin-4 were of limited value. Indeed, the majority of tumors collected from subjects were high Nectin-4 expressors. A relationship between Nectin-4 level and clinical response was not identified in either arm. In any case, similarities in the distribution of Nectin-4 values between responders and non-responders were observed within each group of treatment. The analysis of response by PD-L1 was more explicative, with an efficacy valuation by CPS score (≥ or < 10) that revealed consistency of results for both primary (OS and PFS) and secondary (ORR) endpoints regardless of PD-L1 levels.

The **subgroup analyses** demonstrated a similar trend of response to treatment across all the main pre-specified subgroups. It is notable a lower performance of EV + Pembro compared to the effect observed in the ITT population in OS for the North America region (HR=0.705; 95% CI:0.443,1.20), which the MAH attributes to an imbalance in poor prognostic factors (i.e. ECOG score and liver metastases) favouring the control arm in this particular stratum.

Efficacy by **age** showed consistency of effect of EV + Pembro across subgroups in terms of gain in PFS and OS, and improvement in ORR, relatively to control.

Subsequent therapies were more frequently administrated in the Plat + Gem Arm (70.5%) than the EV + Pembro (31.7%). As expected, cytotoxic agents were more prevalent in Arm A (platinum-based therapies, 24.9%) while PD-L1 inhibitors were more often reported in Arm B (32.2%).

Supportive study

The Phase Ia/IIb **study EV-103** was submitted as supportive evidence for the claimed indication of enfortumab vedotin in combination with pembrolizumab in the first-line treatment of LA/mUC. The patient population of study EV-103 was restricted to cisplatin-ineligible patients. Otherwise, baseline and disease characteristics (including Nectin-4 and PD-L1 distribution) were similar to the pivotal trial, except from a predominance of North America (<90%) over Europe in recruitment sites.

The relevant data pertaining to the efficacy evaluation of enfortumab vedotin in combination with pembrolizumab in the intended indication are primarily those derived from Cohort K, which provides a controlled analysis of EV + Pembro (n=77) versus EV in monotherapy (n=74) on efficacy outcomes. Cohort A (expansion cohort) provides additional 39 patients who received combined treatment with EV + Pembro following the completion of the dose escalation part and selection of the dose for enfortumab vedotin (1.25 mg/kg) to be administrated in the combined regimen with pembrolizumab, and further data on drug combination come from the dose escalation cohort, accounting for a total number of 121 patients receiving EV + Pembro in study EV-103.

In Cohort K, randomisation to treatment was in 1:1 ratio and stratified by liver metastases (presence vs absence) and ECOG score (0 vs 1-2). Primary endpoints only included ORR by BICR. At the data cut-off date more patients were on treatment in the EV + Pembro (32.5%) than in the monotherapy arm (10.8%). Drug discontinuation was more often related to disease progression in the EV monotherapy group (54.1%) than in the drug combination group (42.9%). Unexpectedly, also drug discontinuation associated to adverse events was more frequently reported in the monotherapy than drug combination arm (24.3% vs 15.6%, respectively); a slight imbalance in the prevalence of patients aged ≥75 years and ECOG score distribution favouring the EV + Pembro arm might partially explain these results.

Overall response rate was more favourable in the combination arm EV + Pembro of Cohort K (64.5%) compared to EV monotherapy (45.2%); the result was confirmed when the totality of patients treated

with the combination (including dose escalation Cohort, Cohort A and Cohort K), was analysed (67.8%).

The subgroup analysis of Cohort K, however, showed a distinct advantage of EV + Pembro relative to EV monotherapy by PD-L1 score: ORR was 61.4% vs 50% in CPS<10 for the two treatment arms, respectively, while a wider between-treatment difference could be appreciated in the CPS≥10 group, with 67.7% vs 42.9% in ORR for the EV + Pembro and EV monotherapy arm, respectively. Unlike the pivotal study, PD-L1 was not a stratification factor in study EV-103. Therefore, it cannot be excluded that an imbalance between groups could have impacted results.

In conclusion, study EV-103 provides evidence for a more advantageous effect of the combination EV + Pembro relative to EV alone in terms of ORR in cisplatin-ineligible LA/mUC patients; however, the individual contribution of pembrolizumab to the combined treatment effect, particularly in patients harbouring a PD-L1 low-level tumour, is not clear.

In any case, the OS data derived from the Phase III study consistently showing superiority of EV +Pembro versus Plat + Gem regardless of PD-L1 score attenuates the concern around the individual contribution of pembrolizumab to the effect observed in PD-L1 low expressors.

Wording of the therapeutic indication (section 4.1 of the SmPC): The initially proposed therapeutic indication for Padcev clearly defined the essential inclusion criterion for the targeted –and recruited– population: eligibility to either a cisplatin or carboplatin-containing chemotherapy regimen. However, from a clinical point of view, platinum-eligibility does not seem to be an effect modifier in this setting. Upon this perspective, it had been considered to remove the platinum-eligibility clause from the indication, but the MAH for Padcev prefers that the indication reflects the eligibility criteria of pivotal study EV-302, which excluded platinum-ineligible patients. Considering that the supporting data for variations Padcev II-13 and Keytruda II-150 were identical, it was recommended to align indications for both products used in combination in order to avoid any risk of confusion regarding the approved indication for the combination treatment. However, since the wording of the indication is being discussed in the context of stand-alone procedures not part of a Work Sharing arrangement, a harmonised indication is not mandatory, as long as the B/R in both claimed indications is positive. Moreover, per inclusion criteria, locally advanced disease also had to be "unresectable", and this was not specified in the initially proposed wording. The therapeutic indication has therefore been amended to reflect this aspect. The final agreed indication is:

Padcev, in combination with pembrolizumab, is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy.

2.4.1. Conclusions on the clinical efficacy

Results from the primary analysis of study EV-302 showed statistically significant and clinically relevant improvements in survival from the combination of enfortumab vedotin and pembrolizumab (EV+Pembro) compared to standard-of-care platinum + gemcitabine (Plat+Gem) in the first line treatment of patients with locally advanced unresectable or metastatic urothelial cancer. Benefits from EV+Pembro over chemotherapy were also observed across PFS, ORR and DOR, and across prespecified subgroups (particularly Nectin-4 expression) and supported by sensitivity analyses.

2.5. Clinical safety

Introduction

Enfortumab vedotin (EV), an anti-nectin-4 antibody-drug conjugate, is currently indicated in monotherapy for the treatment of advanced urothelial cancer. The most common adverse reactions with EV are alopecia (48.8%), fatigue (46.8%), decreased appetite (44.9%), peripheral sensory neuropathy (38.7%), diarrhoea (37.6%), nausea (36%), pruritus (33.4%), dysgeusia (29.9%), anaemia (26.5%), weight decreased (23.4%), rash maculo-papular (22.9%), dry skin (21.6%), vomiting (18.4%), aspartate aminotransferase increased (15.3%), hyperglycaemia, (13.1%), dry eye (12.8%), alanine aminotransferase increased (12.1%) and rash (10.4%) (Padcev SmPC, section 4.8).

Pembrolizumab, an anti-PD-1 monoclonal antibody indicated as monotherapy and in combination with other products for a variety of early-stage and advanced cancers, is most commonly associated with immune-mediated adverse reactions (pneumonitis, colitis, hepatitis, nephritis, endocrinopathies and skin reactions, among others). The incidences of immune-mediated adverse reactions were 25% all Grades and 6% for Grades 3-5 in the metastatic setting (Keytruda SmPC, section 4.8).

Since the intended new therapeutic indication involves the combination of EV and pembrolizumab, the primary safety population is considered to be the EV + Pembro Combo ISS pool of 564 patients:

440 from Arm A of study EV-302 and 3 patients from the run-in of this study as well as 121 patients from study EV-103 (40 from Cohort A and 81 from Cohort K). All received EV and Pembro at the recommended dose. This is also the safety population presented in the SmPC.

Overview of the Safety Analysis Groups

The overall ISS evaluation is based on the following 6 ISS populations:

- **EV + Pembro EV-302 Population:** This population includes all subjects who received any amount of enfortumab vedotin at a starting dose of 1.25 mg/kg in combination with pembrolizumab in the global portion of the study EV-302 (SGN22E-003).
- **Chemotherapy EV-302 Population:** This population includes all subjects who received any amount of gemcitabine + cisplatin or carboplatin in the global portion of the study EV-302 (SGN22E-003). This analysis set is equivalent to the "Plat + Gem EV-302" analysis set used for presentation of efficacy results for study EV-302.
- **EV + Pembro Combo ISS (EV-103 DE/Coh A+Coh K+EV-302) Population (EV + Pembro Combo ISS):** This population includes all subjects who received any amount of enfortumab vedotin at a starting dose of 1.25 mg/kg in combination with pembrolizumab in Cohort K, Cohort A, and dose escalation cohort of the study EV-103 (SGN-22E-002), and in the global portion and Japan-specific safety run-in of the study EV-302 (SGN22E-003).
- **EV Monotherapy ISS Population (EV Mono ISS):** This population includes all subjects who received any amount of enfortumab vedotin monotherapy at a starting dose of 1.25 mg/kg in studies EV-101 (ASG-22CE-13-2), EV-102 (7465-CL-0101), EV-103 (SGN-22E-002) Cohort K EV monotherapy arm, EV-201 (SGN22E-001), EV-203 (7465-CL-1104), and EV-301 (7465-CL-0301).
- **Pembro Bladder Pool (KEYNOTE-045, KEYNOTE-052, and KEYNOTE-361) Population (Pembro Bladder Pool):** This population includes all subjects who received any amount of pembrolizumab as monotherapy in the KEYNOTE-045, KEYNOTE-052, and KEYNOTE-361 studies.

- **Pembro Reference Safety Data (RSD) Population (Pembro RSD):** This population includes subjects who received pembrolizumab as monotherapy, including subjects from 21 KEYNOTE studies (i.e., KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, KEYNOTE-010, KEYNOTE-012, KEYNOTE-013, KEYNOTE-024, KEYNOTE-040, KEYNOTE-042, KEYNOTE-045, KEYNOTE-048, KEYNOTE-052, KEYNOTE-054, KEYNOTE-055, KEYNOTE-087, KEYNOTE-158, KEYNOTE-164, KEYNOTE-177, KEYNOTE-204, KEYNOTE-564, and KEYNOTE-716).

The safety analysis set for each population consists of all subjects who received any amount of study drug.

Table 72 lists the studies and cohorts included in each population.

Table 72: ISS Analysis Populations and Rationale

Population	Included Studies†	Rationale
EV + Pembro EV-302 Population	EV-302 (SGN-22E-003) global portion	Evaluate the safety profile of EV-302 study, which is the phase 3 confirmatory study to support approval of enfortumab vedotin in combination with pembrolizumab for the proposed indication
Chemotherapy EV-302 Population	EV-302 (SGN-22E-003) global portion	
EV + Pembro Combo ISS Population	EV-103 (SGN-22E-002)-DE/Cohort A + Cohort K combo arm EV-302 (SGN-22E-003) (global portion and Japan-specific safety run-in)	Characterize the safety profile of enfortumab vedotin in combination with pembrolizumab in the pooled population from EV-103 and EV-302
EV Mono ISS Population	EV-101 (ASG-22CE-13-2) EV-102 (7465-CL-0101) EV-103 (SGN-22E-002)-Cohort K EV mono arm EV-201 (SGN22E-001) EV-203 (7465-CL-1104) EV-301 (7465-CL-0301)	Enables comparison with the safety profile of enfortumab vedotin monotherapy in advanced disease stage
Pembro Bladder Pool Population	KEYNOTE-045: 26OCT2017 KEYNOTE-052: 26SEP2018 KEYNOTE-361: 29APR2020	Enables comparison with safety profile of pembrolizumab monotherapy in advanced UC population
Pembro RSD Population	KEYNOTE-001-Melanoma: 18APR2014‡ KEYNOTE-001-NSCLC: 23JAN2015‡ KEYNOTE-002: 28FEB2015‡ KEYNOTE-006: 03MAR2015‡ KEYNOTE-010: 30SEP2015‡ KEYNOTE-012: 26APR2016 KEYNOTE-013: 28SEP2018 KEYNOTE-024: 10JUL2017 KEYNOTE-040: 15MAY2017 KEYNOTE-042: 04SEP2018 KEYNOTE-045: 26OCT2017 KEYNOTE-048: 25FEB2019 KEYNOTE-052: 26SEP2018 KEYNOTE-054: 03APR2020 KEYNOTE-055: 22APR2016 KEYNOTE-087: 15MAR2021 KEYNOTE-158: 05OCT2020 KEYNOTE-164: 09SEP2019 KEYNOTE-177: 19FEB2021 KEYNOTE-204: 16JAN2020 KEYNOTE-564: 14JUN2021 KEYNOTE-716: 21JUN2021	Enables comparison with established safety profile of pembrolizumab monotherapy

EV: enfortumab vedotin; ISS: Integrated Summary of Safety; Pembro: pembrolizumab; RSD: reference safety data; UC: urothelial cancer

Patient exposure

Dosing

Doses of enfortumab vedotin were administered based on subject weight, except for subjects weighing > 100 kg, for whom enfortumab vedotin doses were based on 100 kg (e.g., 125 mg for subjects receiving the 1.25 mg/kg dose level). There were 53 of 564 (9.4%) subjects in the EV + Pembro Combo ISS analysis group for whom this weight cap applied.

Pembrolizumab was administered at a dose of 200 mg.

Dose regimens

Extent of study drug exposure by safety analysis group is summarized in the following table.

Table 73: Overall Exposure to Study Drug (Safety Analysis Set)

Parameter Category/Statistic	**EV + Pembro EV-302 (N = 440)**	**Chemotherapy EV-302 (N = 433)**	**EV + Pembro Combo ISS (N = 564)**	**EV Mono ISS (N = 793)**	**Pembro Bladder Pool (N = 938)**	**Pembro RSD (N = 7631)**
Duration of exposure (months) †						
n	440	433	564	793	938	7631
Mean (SD)	10.22 (6.81)	3.62 (1.23)	10.36 (7.04)	6.66 (7.02)	7.29 (8.01)	7.85 (6.91)
Median	9.43	4.14	9.43	4.70	3.48	5.78
Min, Max	0.3, 31.9	0, 7.7	0.3, 34.4	0.3, 55.7	0, 28.1	0, 38.0
Duration of exposure (months), n (%)						
< 1	28 (6.4)	27 (6.2)	32 (5.7)	109 (13.7)	171 (18.2)	994 (13.0)
≥ 1 and < 6	115 (26.1)	405 (93.5)	151 (26.8)	382 (48.2)	416 (44.3)	2856 (37.4)
≥ 6 and < 12	141 (32.0)	1 (0.2)	182 (32.3)	190 (24.0)	150 (16.0)	2108 (27.6)
≥ 12	156 (35.5)	0	199 (35.3)	112 (14.1)	201 (21.4)	1673 (21.9)
Number of dosing cycles ‡						
n	440	433	564	NA	938	7631
Mean (SD)	13.7 (9.3)	4.9 (1.6)	13.6 (9.4)	NA	11.0 (11.2)	12.3 (10.1)
Median	12.0	6.0	12.0	NA	6.0	9.0
Min, Max	1, 46	1, 6	1, 46	NA	1, 36	1, 59

† Duration of exposure = (min [initial dose date of the last cycle + 20, cutoff date, death date] – first dose date + 1) / 30.4375 for any drug in studies EV-103 and EV-302 and (min [initial dose date of the last cycle + 27, cutoff date, death date] – first dose date + 1) / 30.4375 in other EV studies. Duration of exposure = (last dose date – first dose date + 1) / 30.4367 for pembrolizumab in Pembro studies.
‡ Total number of cycles with non-zero dosing in the cycle. Number of dosing cycles is not summarized for the EV Mono ISS due to different number of days per cycle (i.e., 21 days per cycle in EV-103/EV-302, 28 days per cycle in the other studies). In EV-302, Chemotherapy may be administered for up to a maximum of 6 cycles per protocol.

Subjects in the EV + Pembro EV-302 arm received enfortumab vedotin (1.25 mg/kg) followed by pembrolizumab (200 mg) on day 1 and enfortumab vedotin (1.25 mg/kg) alone on day 8 of each 21-day cycle. Treatment with pembrolizumab was to be discontinued once the subject received a maximum of 35 administrations.

Subjects in the Chemotherapy EV-302 arm received gemcitabine (1000 mg/m^2) on days 1 and 8 of every 21-day cycle and either cisplatin (70 mg/m^2) or carboplatin (AUC 4.5 or AUC 5 mg/mL/min, according to local guidelines) on day 1 of every 21-day cycle for a maximum of 6 cycles.

In the EV + Pembro Combo ISS analysis group, subjects in the dose escalation cohort, Cohort A and Cohort K (EV + Pembro) of EV-103, EV-302 global portion and Japan-specific safety run-in received enfortumab vedotin (1.25 mg/kg) followed by pembrolizumab (200 mg) on day 1 and enfortumab vedotin (1.25 mg/kg) alone on day 8 of each 21-day cycle. Treatment with pembrolizumab was to be discontinued once the subject received a maximum of 35 administrations.

Subjects in the EV Mono ISS analysis group, other than those from Cohort K (EV Mono) in Study EV-103, received enfortumab vedotin (1.25 mg/kg) on days 1, 8, and 15 of each 4-week cycle. Subjects in EV-103 Cohort K (EV Mono) received 1.25 mg/kg on days 1 and 8 of a 21-day cycle.

Subjects in the studies included in the Pembro Bladder Pool analysis group received pembrolizumab (200 mg) IV every 3 weeks. Subjects in the studies pooled in the Pembro RSD analysis group could have received any of the doses administered in the applicable studies.

Enfortumab vedotin exposure by treatment arm and analysis group is summarized in the following table.

Table 74: Study Drug Exposure – Enfortumab Vedotin (Safety Analysis Set)

Parameter Category/Statistic	**EV + Pembro EV-302 (N = 440)**	**EV + Pembro Combo ISS (N = 564)**	**EV Mono ISS (N = 793)**
Duration of exposure (months) †			
n	440	564	793
Mean (SD)	8.37 (5.73)	8.47 (5.94)	6.66 (7.02)
Median	7.01	6.97	4.70
Min, Max	0.3, 31.9	0.3, 34.4	0.3, 55.7
Duration of exposure (months), n (%)			
< 1	30 (6.8)	34 (6.0)	109 (13.7)
≥ 1 and < 6	152 (34.5)	196 (34.8)	382 (48.2)
≥ 6 and < 12	153 (34.8)	198 (35.1)	190 (24.0)
≥ 12	105 (23.9)	136 (24.1)	112 (14.1)
Relative dose intensity (%) ‡			
n	440	564	793
Mean (SD)	80.17 (15.98)	79.35 (16.52)	78.11 (18.81)
Median	82.61	81.40	79.70
Min, Max	22.4, 102.9	22.4, 102.9	23.0, 120.0

† Duration of exposure = (min [initial dose date of the last cycle + 20, cutoff date, death date] – first dose date + 1) / 30.4375 for EV in studies EV-103 and EV-302 and (min [initial dose date of the last cycle + 27, cutoff date, death date] – first dose date + 1) / 30.4375 in other EV studies.
‡ (Dose intensity/Planned dose intensity) x 100. RDI calculation uses subject weight capped at 100 kg for EV. At dose administration, some EV subjects were not weight capped at 100 kg and as a result, their RDI may be greater than 100%.

Pembrolizumab administration and exposure by treatment arm and analysis group is summarized in the following table.

Table 75: Study Drug Exposure – Pembrolizumab (Safety Analysis Set)

Parameter Category/Statistic	**EV + Pembro EV-302 (N = 440)**	**EV + Pembro Combo ISS (N = 564)**	**Pembro Bladder Pool (N = 938)**	**Pembro RSD (N = 7631)**
Duration of exposure (months) †				
n	440	564	938	7631
Mean (SD)	9.63 (6.87)	9.60 (7.02)	7.29 (8.01)	7.85 (6.91)
Median	8.51	8.26	3.48	5.78
Min, Max	0.3, 28.5	0.3, 32.3	0, 28.1	0, 38.0
Duration of exposure (months), n (%)				
< 1	39 (8.9)	43 (7.6)	171 (18.2)	994 (13.0)
≥ 1 and < 6	124 (28.2)	173 (30.7)	416 (44.3)	2856 (37.4)
≥ 6 and < 12	131 (29.8)	170 (30.1)	150 (16.0)	2108 (27.6)
≥ 12	146 (33.2)	178 (31.6)	201 (21.4)	1673 (21.9)
Number of dosing cycles ‡				
n	440	564	938	7631
Mean (SD)	12.9 (9.4)	12.6 (9.4)	11.0 (11.2)	12.3 (10.1)
Median	11.0	10.0	6.0	9.0
Min, Max	1, 35	1, 35	1, 36	1, 59

† Duration of exposure = (min [initial dose date of the last cycle + 20, cutoff date, death date] – first dose date + 1) / 30.4375 for Pembro in studies EV-103 and EV-302 and (last dose – first dose date + 1) / 30.4367 for Pembro in pembrolizumab studies.
‡ Total number of cycles with non-zero dosing in the cycle.

Table 76: Selected Baseline Characteristics (Safety Analysis Set)

Parameter Category/Statistic	EV + Pembro EV-302 (N = 440)	Chemotherapy EV-302 (N = 433)	EV + Pembro Combo ISS (N = 564)	EV Mono ISS (N = 793)	Pembro Bladder Pool (N = 938)	Pembro RSD ‡ (N = 7631)
ECOG performance status at baseline, n (%)						
0	223 (50.7)	209 (48.4)	273 (48.4)	284 (35.8)	329 (35.1)	4016 (52.7)
1	202 (45.9)	212 (49.1)	258 (45.7)	485 (61.2)	424 (45.2)	3440 (45.1)
2	15 (3.4)	11 (2.5)	33 (5.9)	24 (3.0)	184 (19.6)	167 (2.2)
3	0	0	0	0	1 (0.1)	2 (0.0)
Missing	0	1	0	0	0	6
Hemoglobin level (g/dL), n (%)						
< 10	50 (11.4)	53 (12.2)	62 (11.0)	169 (21.6)	118 (12.7)	NA
≥ 10	390 (88.6)	380 (87.8)	502 (89.0)	613 (78.4)	814 (87.3)	
Estimated creatinine clearance, † mL/min						
n	440	433	564	787	931	NA
Mean (SD)	68.92 (27.55)	71.13 (31.19)	66.96 (27.56)	65.71 (27.56)	62.83 (26.65)	
Median	64.65	64.12	61.79	60.36	57.59	
Min, Max	21.1, 219.8	24.0, 222.3	21.1, 219.8	11.9, 213.7	19.6, 216.2	
Renal function based on estimated creatinine clearance, † n (%)						
Normal	84 (19.1)	95 (21.9)	102 (18.1)	121 (15.4)	136 (14.6)	NA
Mild	164 (37.3)	157 (36.3)	190 (33.7)	276 (35.1)	277 (29.8)	
Moderate	187 (42.5)	175 (40.4)	263 (46.6)	365 (46.4)	474 (51.0)	
Severe	5 (1.1)	6 (1.4)	9 (1.6)	24 (3.0)	43 (4.6)	
ESRD	0	0	0	1 (0.1)	0	
Missing	0	0	0	6	8	

Missing row is not included in the denominator for the percentages.

Combo: combination; ECOG: Eastern Cooperative Oncology Group; ESRD: end-stage renal disease; EV: enfortumab vedotin; ISS: integrated summary of safety; Max: maximum; Min: minimum; Mono: monotherapy; NA: not available; Pembro: pembrolizumab; RSD: reference safety data; SD: standard deviation.

† Cockcroft-Gault formula is 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; ESRD: < 15 mL/min.

‡ Pembro RSD analysis group baseline variables were provided based on the availability.

Adverse events

Overview of AEs:

Table 77: Overview of TEAEs (Safety Analysis Set)

Parameter, n (%)	EV + Pembro EV-302 (N = 440)	Chemotherapy EV-302 (N = 433)	EV + Pembro Combo ISS (N = 564)	EV Mono ISS (N = 793)	Pembro Bladder Pool (N = 938)	Pembro RSD (N = 7631)
TEAE	439 (99.8)	427 (98.6)	563 (99.8)	786 (99.1)	900 (95.9)	7375 (96.6)
Drug-related† TEAE	427 (97.0)	414 (95.6)	549 (97.3)	747 (94.2)	613 (65.4)	5462 (71.6)
Serious TEAE‡	220 (50.0)	169 (39.0)	281 (49.8)	363 (45.8)	441 (47.0)	2742 (35.9)
Drug-related† serious TEAE‡	122 (27.7)	85 (19.6)	148 (26.2)	161 (20.3)	112 (11.9)	840 (11.0)
TEAE leading to death	19 (4.3)	14 (3.2)	26 (4.6)	56 (7.1)	65 (6.9)	346 (4.5)
Drug-related† TEAE leading to death	4 (0.9)	4 (0.9)	8 (1.4)	17 (2.1)	7 (0.7)	42 (0.6)

Parameter, n (%)	EV + Pembro EV-302 (N = 440)	Chemotherapy EV-302 (N = 433)	EV + Pembro Combo ISS (N = 564)	EV Mono ISS (N = 793)	Pembro Bladder Pool (N = 938)	Pembro RSD (N = 7631)
TEAE leading to death excluding disease progression	19 (4.3)	14 (3.2)	26 (4.6)	37 (4.7)	63 (6.7)	342 (4.5)
Drug-related† TEAE leading to death excluding disease progression	4 (0.9)	4 (0.9)	8 (1.4)	17 (2.1)	5 (0.5)	38 (0.5)
TEAE leading to permanent withdrawal of any treatment	175 (39.8)	93 (21.5)	238 (42.2)	166 (20.9)	137 (14.6)	1066 (14.0)
Drug-related † TEAE leading to permanent withdrawal of any treatment	154 (35.0)	80 (18.5)	214 (37.9)	118 (14.9)	77 (8.2)	639 (8.4)
TEAE leading to permanent withdrawal of enfortumab vedotin	153 (34.8)	NA	202 (35.8)	166 (20.9)	NA	NA
Drug-related † TEAE leading to permanent withdrawal of enfortumab vedotin	130 (29.5)	NA	176 (31.2)	118 (14.9)	NA	NA
TEAE leading to permanent withdrawal of pembrolizumab	117 (26.6)	NA	157 (27.8)	NA	137 (14.6)	1066 (14.0)
Drug-related † TEAE leading to permanent withdrawal of pembrolizumab	94 (21.4)	NA	131 (23.2)	NA	77 (8.2)	639 (8.4)
TEAE leading to dose reduction §	184 (41.8)	177 (40.9)	239 (42.4)	301 (38.0)	NA	NA
Drug-related† TEAE leading to dose reduction §	179 (40.7)	164 (37.9)	232 (41.1)	286 (36.1)	NA	NA
TEAE leading to dose interruption of any treatment	347 (78.9)	279 (64.4)	448 (79.4)	495 (62.4)	276 (29.4)	1993 (26.1)
Drug-related† TEAE leading to dose interruption of any treatment	299 (68.0)	229 (52.9)	385 (68.3)	404 (50.9)	146 (15.6)	1119 (14.7)
TEAE leading to dose interruption of enfortumab vedotin	319 (72.5)	NA	406 (72.0)	495 (62.4)	NA	NA
Drug-related † TEAE leading to dose interruption of enfortumab vedotin	266 (60.5)	NA	331 (58.7)	404 (50.9)	NA	NA
TEAE leading to dose interruption of pembrolizumab	268 (60.9)	NA	356 (63.1)	NA	276 (29.4)	1993 (26.1)
Drug-related † TEAE leading to dose interruption of pembrolizumab	218 (49.5)	NA	292 (51.8)	NA	146 (15.6)	1119 (14.7)
TEAE with NCI-CTCAE ≥ Grade 3	321 (73.0)	341 (78.8)	425 (75.4)	564 (71.1)	573 (61.1)	3514 (46.0)
Drug-related † TEAE with NCI-CTCAE ≥ Grade 3	246 (55.9)	301 (69.5)	324 (57.4)	403 (50.8)	172 (18.3)	1208 (15.8)

Number of subjects (n) and percentage of subjects (%) are shown.
†A reasonable possibility that the event may have been caused by the study drug (either EV, Chemotherapy or Pembro) as assessed by the investigator. If relationship is missing, then it is considered as drug-related for EV studies only.
‡ For EV-101, EV-102, EV-203 and EV-301, includes SAEs upgraded by the sponsor based on review of the sponsor's list of Always Serious terms, if any upgrade was done.
§ Dose reduction for EV or Chemotherapy.

Common AEs:

Table 78: Treatment-emergent Adverse Events by SOC and Preferred Term for TEAEs Occurring in ≥ 10% of Subjects in EV + Pembro Combo ISS (Safety Analysis Set)

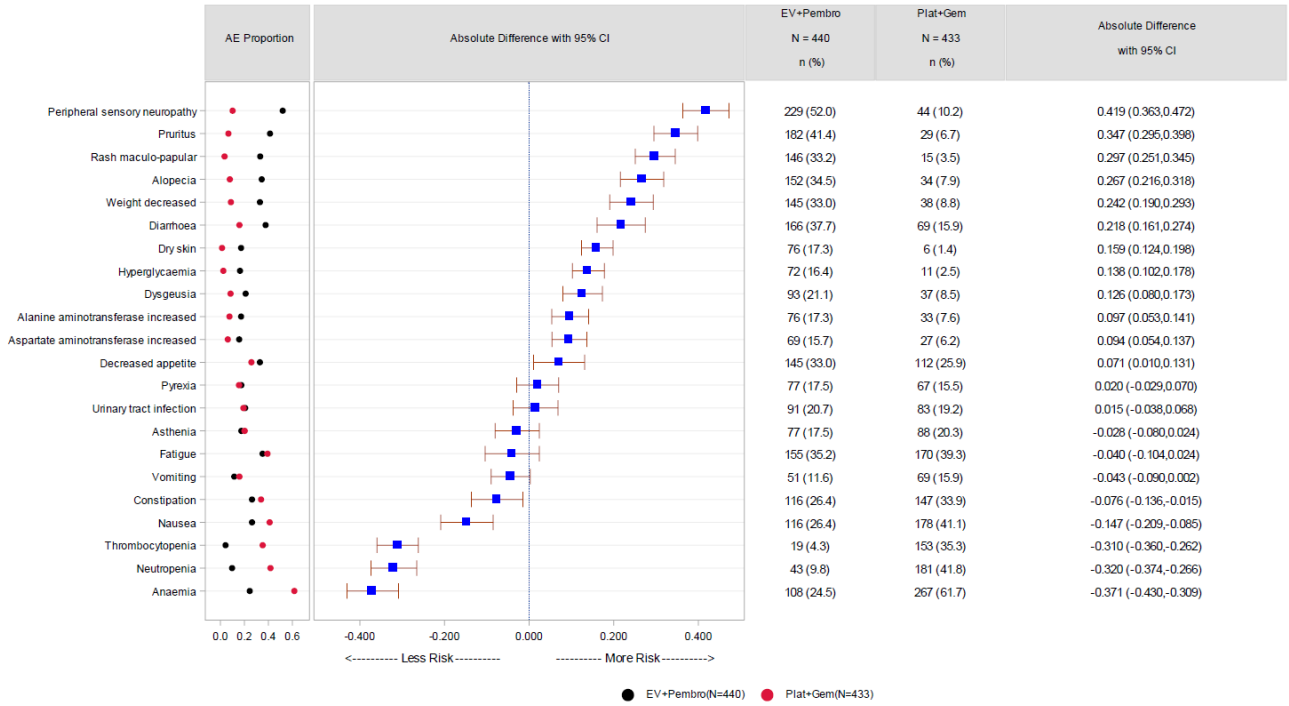
MedDRA (v26.0) SOC Preferred term, n (%)	**EV + Pembro EV-302 (N = 440)**	**Chemotherapy EV-302 (N = 433)**	**EV + Pembro Combo ISS (N = 564)**	**EV Mono ISS (N = 793)**	**Pembro Bladder Pool (N = 938)**	**Pembro RSD (N = 7631)**
Overall	**439 (99.8)**	**427 (98.6)**	**563 (99.8)**	**786 (99.1)**	**900 (95.9)**	**7375 (96.6)**
Blood and Lymphatic System Disorders	**157 (35.7)**	**340 (78.5)**	**206 (36.5)**	**298 (37.6)**	**236 (25.2)**	**1368 (17.9)**
Anaemia	108 (24.5)	267 (61.7)	145 (25.7)	231 (29.1)	201 (21.4)	982 (12.9)
Neutropenia	43 (9.8)	181 (41.8)	57 (10.1)	60 (7.6)	2 (0.2)	82 (1.1)
Endocrine Disorders	**70 (15.9)**	**6 (1.4)**	**89 (15.8)**	**14 (1.8)**	**131 (14.0)**	**1273 (16.7)**
Hypothyroidism	46 (10.5)	3 (0.7)	59 (10.5)	7 (0.9)	93 (9.9)	937 (12.3)
Eye Disorders	**152 (34.5)**	**26 (6.0)**	**205 (36.3)**	**301 (38.0)**	**71 (7.6)**	**798 (10.5)**
Dry eye	50 (11.4)	5 (1.2)	81 (14.4)	101 (12.7)	12 (1.3)	142 (1.9)
Gastrointestinal Disorders	**330 (75.0)**	**313 (72.3)**	**431 (76.4)**	**616 (77.7)**	**548 (58.4)**	**4406 (57.7)**
Diarrhea	166 (37.7)	69 (15.9)	221 (39.2)	310 (39.1)	191 (20.4)	1678 (22.0)
Nausea	116 (26.4)	178 (41.1)	160 (28.4)	300 (37.8)	179 (19.1)	1534 (20.1)
Constipation	116 (26.4)	147 (33.9)	151 (26.8)	229 (28.9)	200 (21.3)	1179 (15.5)
Vomiting	51 (11.6)	69 (15.9)	75 (13.3)	148 (18.7)	128 (13.6)	945 (12.4)
Abdominal pain	51 (11.6)	27 (6.2)	70 (12.4)	123 (15.5)	108 (11.5)	671 (8.8)
Dry mouth	41 (9.3)	7 (1.6)	59 (10.5)	65 (8.2)	42 (4.5)	388 (5.1)
General Disorders and Administration Site Conditions	**295 (67.0)**	**303 (70.0)**	**394 (69.9)**	**589 (74.3)**	**580 (61.8)**	**4519 (59.2)**
Fatigue	155 (35.2)	170 (39.3)	228 (40.4)	371 (46.8)	277 (29.5)	2368 (31.0)
Pyrexia	77 (17.5)	67 (15.5)	100 (17.7)	148 (18.7)	137 (14.6)	934 (12.2)
Asthenia	77 (17.5)	88 (20.3)	94 (16.7)	81 (10.2)	120 (12.8)	880 (11.5)
Oedema peripheral	60 (13.6)	48 (11.1)	92 (16.3)	138 (17.4)	122 (13.0)	630 (8.3)
Infections and Infestations	**265 (60.2)**	**160 (37.0)**	**347 (61.5)**	**423 (53.3)**	**457 (48.7)**	**3387 (44.4)**
Urinary tract infection	91 (20.7)	83 (19.2)	128 (22.7)	125 (15.8)	203 (21.6)	511 (6.7)
COVID-19	63 (14.3)	21 (4.8)	75 (13.3)	15 (1.9)	0	6 (0.1)
Investigations	**245 (55.7)**	**194 (44.8)**	**331 (58.7)**	**445 (56.1)**	**354 (37.7)**	**2574 (33.7)**
Weight decreased	145 (33.0)	38 (8.8)	203 (36.0)	200 (25.2)	107 (11.4)	628 (8.2)
Alanine aminotransferase increased	76 (17.3)	33 (7.6)	95 (16.8)	101 (12.7)	62 (6.6)	572 (7.5)
Aspartate aminotransferase increased	69 (15.7)	27 (6.2)	87 (15.4)	135 (17.0)	63 (6.7)	538 (7.1)
Metabolism and Nutrition Disorders	**254 (57.7)**	**195 (45.0)**	**341 (60.5)**	**554 (69.9)**	**439 (46.8)**	**2714 (35.6)**
Decreased appetite	145 (33.0)	112 (25.9)	191 (33.9)	374 (47.2)	233 (24.8)	1312 (17.2)
Hyperglycaemia	72 (16.4)	11 (2.5)	94 (16.7)	118 (14.9)	60 (6.4)	360 (4.7)
Musculoskeletal and Connective Tissue Disorders	**186 (42.3)**	**121 (27.9)**	**258 (45.7)**	**345 (43.5)**	**411 (43.8)**	**3360 (44.0)**

MedDRA (v26.0) SOC Preferred term, n (%)	**EV + Pembro EV-302 (N = 440)**	**Chemotherapy EV-302 (N = 433)**	**EV + Pembro Combo ISS (N = 564)**	**EV Mono ISS (N = 793)**	**Pembro Bladder Pool (N = 938)**	**Pembro RSD (N = 7631)**
Arthralgia	58 (13.2)	21 (4.8)	87 (15.4)	92 (11.6)	130 (13.9)	1436 (18.8)
Back pain	53 (12.0)	34 (7.9)	74 (13.1)	91 (11.5)	126 (13.4)	847 (11.1)
Nervous System Disorders	**329 (74.8)**	**144 (33.3)**	**431 (76.4)**	**547 (69.0)**	**249 (26.5)**	**2430 (31.8)**
Peripheral sensory neuropathy	229 (52.0)	44 (10.2)	301 (53.4)	305 (38.5)	9 (1.0)	83 (1.1)
Dysgeusia	93 (21.1)	37 (8.5)	137 (24.3)	241 (30.4)	30 (3.2)	150 (2.0)
Dizziness	36 (8.2)	43 (9.9)	64 (11.3)	92 (11.6)	72 (7.7)	564 (7.4)
Psychiatric Disorders	**76 (17.3)**	**44 (10.2)**	**109 (19.3)**	**176 (22.2)**	**155 (16.5)**	**1204 (15.8)**
Insomnia	45 (10.2)	24 (5.5)	60 (10.6)	101 (12.7)	65 (6.9)	528 (6.9)
Renal and Urinary Disorders	**143 (32.5)**	**125 (28.9)**	**201 (35.6)**	**244 (30.8)**	**321 (34.2)**	**909 (11.9)**
Haematuria	58 (13.2)	39 (9.0)	79 (14.0)	101 (12.7)	131 (14.0)	189 (2.5)
Respiratory, Thoracic and Mediastinal Disorders	**182 (41.4)**	**144 (33.3)**	**251 (44.5)**	**354 (44.6)**	**335 (35.7)**	**3310 (43.4)**
Dyspnoea	58 (13.2)	51 (11.8)	83 (14.7)	102 (12.9)	119 (12.7)	1130 (14.8)
Cough	54 (12.3)	23 (5.3)	72 (12.8)	104 (13.1)	145 (15.5)	1392 (18.2)
Skin and Subcutaneous Tissue Disorders	**366 (83.2)**	**112 (25.9)**	**481 (85.3)**	**642 (81.0)**	**400 (42.6)**	**3442 (45.1)**
Pruritus	182 (41.4)	29 (6.7)	232 (41.1)	265 (33.4)	219 (23.3)	1435 (18.8)
Alopecia	152 (34.5)	34 (7.9)	217 (38.5)	378 (47.7)	6 (0.6)	118 (1.5)
Rash maculo-papular	146 (33.2)	15 (3.5)	203 (36.0)	187 (23.6)	30 (3.2)	295 (3.9)
Dry skin	76 (17.3)	6 (1.4)	102 (18.1)	173 (21.8)	51 (5.4)	394 (5.2)
Rash macular	44 (10.0)	6 (1.4)	64 (11.3)	21 (2.6)	5 (0.5)	49 (0.6)

Number of subjects (n) and percentage of subjects (%) are shown.

Sorting order: alphabetical order by SOC and descending by the number of subjects in the EV + Pembro Combo ISS analysis group by PT. In case of ties, alphabetical order by preferred term is applied.
Combo: combination; COVID-19: coronavirus disease 2019; EV: enfortumab vedotin; ISS: integrated summary of safety; Mono: monotherapy; Pembro: pembrolizumab; PT: preferred term; RSD: reference safety data; TEAE: treatment-emergent adverse event.

Figure 47: Forest Plot for Most Common (>=15%) Treatment-Emergent Adverse Events by Preferred Term, Safety Analysis Set in Study EV-302 (KEYNOTE-A39)



Grade 3-4 AEs:

Table 79: Treatment-emergent Adverse Events of NCI-CTCAE Grade 3 or 4 by SOC and Preferred Term Occurring in ≥ 3% of Subjects in EV + Pembro Combo ISS (Safety Analysis Set)

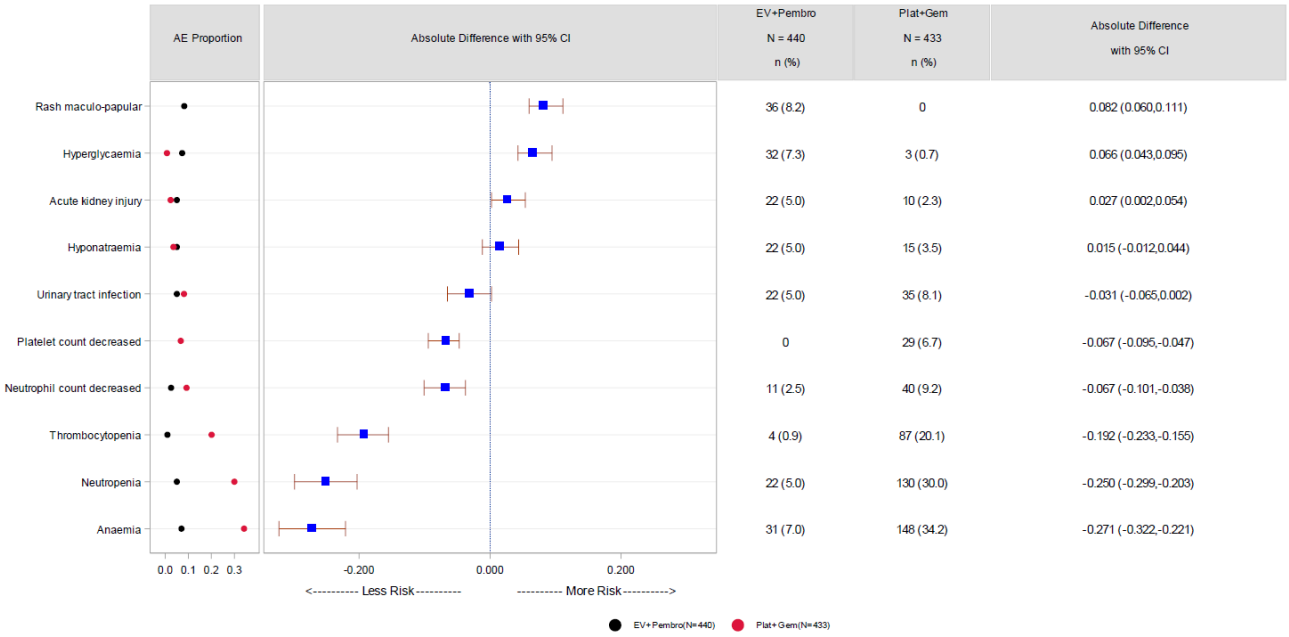
MedDRA (v26.0) SOC Preferred term, n (%)	**EV + Pembro EV-302 (N = 440)**	**Chemotherapy EV-302 (N = 433)**	**EV + Pembro Combo ISS (N = 564)**	**EV Mono ISS (N = 793)**	**Pembro Bladder Pool (N = 938)**	**Pembro RSD (N = 7631)**
Overall	**312 (70.9)**	**338 (78.1)**	**415 (73.6)**	**556 (70.1)**	**551 (58.7)**	**3373 (44.2)**
Blood and Lymphatic System Disorders	**60 (13.6)**	**245 (56.6)**	**88 (15.6)**	**129 (16.3)**	**91 (9.7)**	**364 (4.8)**
Anaemia	31 (7.0)	148 (34.2)	49 (8.7)	77 (9.7)	81 (8.6)	274 (3.6)
Neutropenia	22 (5.0)	130 (30.0)	33 (5.9)	46 (5.8)	0	21 (0.3)
Gastrointestinal Disorders	**55 (12.5)**	**33 (7.6)**	**71 (12.6)**	**104 (13.1)**	**89 (9.5)**	**579 (7.6)**
Diarrhoea	20 (4.5)	6 (1.4)	28 (5.0)	36 (4.5)	19 (2.0)	113 (1.5)
General Disorders and Administration Site Conditions	**33 (7.5)**	**45 (10.4)**	**50 (8.9)**	**102 (12.9)**	**75 (8.0)**	**421 (5.5)**
Fatigue	17 (3.9)	20 (4.6)	30 (5.3)	59 (7.4)	37 (3.9)	166 (2.2)
Infections and Infestations	**74 (16.8)**	**70 (16.2)**	**102 (18.1)**	**154 (19.4)**	**177 (18.9)**	**710 (9.3)**
Urinary tract infection	22 (5.0)	35 (8.1)	37 (6.6)	39 (4.9)	82 (8.7)	85 (1.1)
Investigations	**62 (14.1)**	**70 (16.2)**	**94 (16.7)**	**119 (15.0)**	**84 (9.0)**	**487 (6.4)**
Lipase increased	9 (2.0)	0	24 (4.3)	24 (3.0)	4 (0.4)	34 (0.4)
Weight decreased	16 (3.6)	1 (0.2)	22 (3.9)	7 (0.9)	5 (0.5)	35 (0.5)

MedDRA (v26.0) SOC Preferred term, n (%)	**EV + Pembro EV-302 (N = 440)**	**Chemotherapy EV-302 (N = 433)**	**EV + Pembro Combo ISS (N = 564)**	**EV Mono ISS (N = 793)**	**Pembro Bladder Pool (N = 938)**	**Pembro RSD (N = 7631)**
Metabolism and Nutrition Disorders	**86 (19.5)**	**46 (10.6)**	**123 (21.8)**	**188 (23.7)**	**136 (14.5)**	**656 (8.6)**
Hyperglycaemia	32 (7.3)	3 (0.7)	46 (8.2)	56 (7.1)	17 (1.8)	82 (1.1)
Hyponatraemia	22 (5.0)	15 (3.5)	30 (5.3)	47 (5.9)	32 (3.4)	169 (2.2)
Nervous System Disorders	**41 (9.3)**	**8 (1.8)**	**56 (9.9)**	**63 (7.9)**	**27 (2.9)**	**225 (2.9)**
Peripheral sensory neuropathy	17 (3.9)	0	20 (3.5)	25 (3.2)	0	2 (0.0)
Renal and Urinary Disorders	**40 (9.1)**	**31 (7.2)**	**68 (12.1)**	**69 (8.7)**	**113 (12.0)**	**164 (2.1)**
Acute kidney injury	22 (5.0)	10 (2.3)	32 (5.7)	34 (4.3)	36 (3.8)	62 (0.8)
Skin and Subcutaneous Tissue Disorders	**78 (17.7)**	**2 (0.5)**	**105 (18.6)**	**118 (14.9)**	**18 (1.9)**	**146 (1.9)**
Rash maculo-papular	36 (8.2)	0	54 (9.6)	43 (5.4)	1 (0.1)	23 (0.3)

Number of subjects (n) and percentage of subjects (%) are shown.

Sorting order: alphabetical order by SOC and descending by the number of subjects in the EV + Pembro Combo ISS analysis group by PT. In case of ties, alphabetical order by PT was applied.
Subjects will be counted only once by selecting maximum NCI CTCAE Grade within each SOC and PT.
Subjects with a maximum CTCAE grade of 3 or 4 in any preferred term were included in the "Overall" count.
Combo: combination; EV: enfortumab vedotin; ISS: integrated summary of safety; Mono: monotherapy; NCI-CTCAE: National Cancer Institute-Common Terminology Criteria for Adverse Events; Pembro: pembrolizumab; PT: preferred term; RSD: reference safety data; TEAE: treatment-emergent adverse event.

Figure 48: Forest Plot for Most Common (>=5%) Grade 3-5 Treatment-Emergent Adverse Events by Preferred Term Safety Analysis Set in Study EV-302 (KEYNOTE-A39)



Treatment-related Adverse Events

Table 80: Treatment-related TEAEs Reported in ≥10% † of Subjects in Either Arm (Safety Analysis Set)

Preferred Term	Arm A EV + Pembro N = 440 n (%)	Arm B Plat + Gem N = 433 n (%)
Overall	427 (97.0)	414 (95.6)
Peripheral sensory neuropathy	220 (50.0)	43 (9.9)
Pruritus	175 (39.8)	21 (4.8)
Alopecia	146 (33.2)	34 (7.9)
Rash maculo-papular	144 (32.7)	14 (3.2)
Fatigue	129 (29.3)	156 (36.0)
Diarrhoea	121 (27.5)	48 (11.1)
Decreased appetite	118 (26.8)	98 (22.6)
Nausea	89 (20.2)	168 (38.8)
Dysgeusia	83 (18.9)	36 (8.3)
Weight decreased	76 (17.3)	18 (4.2)
Alanine aminotransferase increased	68 (15.5)	29 (6.7)
Aspartate aminotransferase increased	64 (14.5)	24 (5.5)
Dry skin	64 (14.5)	4 (0.9)
Anaemia	61 (13.9)	245 (56.6)
Asthenia	61 (13.9)	74 (17.9)
Hyperglcaemia	48 (10.9)	3 (0.7)
Hypothyroidism	45 (10.2)	1 (0.2)
Neutropenia	40 (9.1)	180 (41.6)
Constipation	33 (7.5)	73 (16.9)
Vomiting	31 (7.0)	60 (13.9)
Neutrophil count decreased	16 (3.6)	54 (12.5)
Thrombocytopenia	15 (3.4)	148 (34.2)
Leukopenia	14 (3.2)	46 (10.6)
Platelet count decreased	3 (0.7)	63 (14.5)

EV: Enfortumab vedotin; Gem: Gemcitabine; Pembro: Pembrolizumab; Plat: Platinum-based chemotherapy (cisplatin or carboplatin); TEAE: Treatment-emergent adverse event

†Reported in either treatment arm. Preferred terms are sorted by descending order of incidence in the EV + Pembro Arm

ADVERSE DRUG REACTIONS (ADR)

TEAEs that have been determined by the sponsor to be associated with enfortumab vedotin, based on the totality of the data, are considered to be ADRs. The identified ADRs are detailed below.

The list of ADRs for enfortumab vedotin monotherapy are those listed below without an asterisk (*). The list of ADRs for enfortumab vedotin in combination with pembrolizumab include all the terms below (with and without asterisk (*)).

Table 81. List of adverse drug reactions

Anemia	Conjunctivitis
Nausea	Dermatitis

Diarrhea	Dermatitis allergic
Vomiting	Dermatitis bullous
Fatigue	Dermatitis contact
Infusion site extravasation	Dermatitis exfoliative generalized
Decreased appetite	Drug eruption
Hyperglycemia	Eczema
Dysgeusia	Epidermal necrosis
Burning sensation	Erythema
Demyelinating polyneuropathy	Erythema multiforme
Dysesthesia	Exfoliative rash
Febrile neutropenia	Hypothyroidism*
Gait disturbance	Intertrigo
Hypoesthesia	Lipase increased*
Interstitial lung disease	Myasthenia gravis*
Motor dysfunction	Myositis*
Muscle atrophy	Palmar-plantar erythrodysesthesia syndrome
Muscular weakness	Pemphigoid
Neuralgia	Pruritus
Neuropathy peripheral	Rash
Neurotoxicity	Rash erythematous
Neutropenia	Rash macular
Neutrophil count decreased	Rash maculovesicular
Paresthesia	Rash maculo-papular
Peripheral motor neuropathy	Rash papular
Peroneal nerve palsy	Rash pruritic
Peripheral sensorimotor neuropathy	Rash vesicular
Peripheral sensory neuropathy	Skin irritation
Pneumonitis	Stasis dermatitis
Polyneuropathy	Skin exfoliation
Skin burning sensation	Stevens-Johnson syndrome
Sensory loss	Stomatitis

Dry eye	Symmetrical drug-related intertriginous and flexural exanthema
Alopecia	Toxic epidermal necrolysis
Dry skin	Aspartate aminotransferase increased
Blister	Alanine aminotransferase increased
Blood blister	Weight decreased

Immunogenicity

See Summary of Enfortumab Vedotin ATA Incidence (Safety Analysis Set) in PK section

Serious adverse event/deaths/other significant events

SAEs:

Serious TEAEs occurring in ≥ 1% of subjects in the EV + Pembro Combo ISS analysis group are presented in Table 82.

Table 82: Serious Treatment-emergent Adverse Events in ≥ 1% of Subjects in EV + Pembro Combo ISS by SOC and Preferred Term (Safety Analysis Set)

MedDRA (v26.0) SOC Preferred term, n (%)	**EV + Pembro EV-302 (N = 440)**	**Chemotherapy EV-302 (N = 433)**	**EV + Pembro Combo ISS (N = 564)**	**EV Mono ISS (N = 793)**	**Pembro Bladder Pool (N = 938)**	**Pembro RSD (N = 7631)**
Overall	**220 (50.0)**	**169 (39.0)**	**281 (49.8)**	**363 (45.8)**	**441 (47.0)**	**2742 (35.9)**
Blood and Lymphatic System Disorders	**11 (2.5)**	**42 (9.7)**	**14 (2.5)**	**32 (4.0)**	**22 (2.3)**	**107 (1.4)**
Anaemia	3 (0.7)	17 (3.9)	6 (1.1)	7 (0.9)	18 (1.9)	65 (0.9)
Gastrointestinal Disorders	**47 (10.7)**	**17 (3.9)**	**57 (10.1)**	**74 (9.3)**	**70 (7.5)**	**453 (5.9)**
Diarrhoea	14 (3.2)	2 (0.5)	17 (3.0)	17 (2.1)	13 (1.4)	70 (0.9)
Abdominal pain	8 (1.8)	2 (0.5)	9 (1.6)	11 (1.4)	1 (0.1)	43 (0.6)
Vomiting	5 (1.1)	2 (0.5)	6 (1.1)	14 (1.8)	1 (0.1)	32 (0.4)
General Disorders and Administration Site Conditions	**21 (4.8)**	**26 (6.0)**	**25 (4.4)**	**53 (6.7)**	**35 (3.7)**	**274 (3.6)**
Pyrexia	9 (2.0)	10 (2.3)	9 (1.6)	13 (1.6)	13 (1.4)	79 (1.0)
Infections and Infestations	**70 (15.9)**	**73 (16.9)**	**94 (16.7)**	**138 (17.4)**	**175 (18.7)**	**749 (9.8)**
Urinary tract infection	16 (3.6)	31 (7.2)	24 (4.3)	32 (4.0)	58 (6.2)	67 (0.9)
Pneumonia	10 (2.3)	5 (1.2)	14 (2.5)	30 (3.8)	32 (3.4)	272 (3.6)
Sepsis	7 (1.6)	8 (1.8)	11 (2.0)	24 (3.0)	10 (1.1)	56 (0.7)
COVID-19	8 (1.8)	5 (1.2)	8 (1.4)	0	0	0
Urosepsis	2 (0.5)	5 (1.2)	8 (1.4)	4 (0.5)	25 (2.7)	27 (0.4)
COVID-19 pneumonia	5 (1.1)	3 (0.7)	6 (1.1)	0	0	2 (0.0)
Investigations	**12 (2.7)**	**6 (1.4)**	**14 (2.5)**	**16 (2.0)**	**8 (0.9)**	**59 (0.8)**
Aspartate aminotransferase increased	5 (1.1)	0	7 (1.2)	2 (0.3)	2 (0.2)	17 (0.2)
Alanine aminotransferase increased	5 (1.1)	0	6 (1.1)	2 (0.3)	2 (0.2)	16 (0.2)
Metabolism and Nutrition Disorders	**27 (6.1)**	**15 (3.5)**	**36 (6.4)**	**63 (7.9)**	**42 (4.5)**	**245 (3.2)**

MedDRA (v26.0) SOC Preferred term, n (%)	EV + Pembro EV-302 (N = 440)	Chemotherapy EV-302 (N = 433)	EV + Pembro Combo ISS (N = 564)	EV Mono ISS (N = 793)	Pembro Bladder Pool (N = 938)	Pembro RSD (N = 7631)
Decreased appetite	8 (1.8)	0	8 (1.4)	11 (1.4)	2 (0.2)	20 (0.3)
Hyperglycaemia	6 (1.4)	0	8 (1.4)	17 (2.1)	0	12 (0.2)
Hyponatraemia	5 (1.1)	5 (1.2)	7 (1.2)	9 (1.1)	3 (0.3)	43 (0.6)
Renal and Urinary Disorders	**39 (8.9)**	**28 (6.5)**	**56 (9.9)**	**73 (9.2)**	**94 (10.0)**	**168 (2.2)**
Acute kidney injury	23 (5.2)	11 (2.5)	32 (5.7)	50 (6.3)	31 (3.3)	65 (0.9)
Haematuria	7 (1.6)	10 (2.3)	11 (2.0)	15 (1.9)	31 (3.3)	17 (0.2)
Respiratory, Thoracic and Mediastinal Disorders	**38 (8.6)**	**15 (3.5)**	**47 (8.3)**	**42 (5.3)**	**44 (4.7)**	**559 (7.3)**
Pneumonitis	9 (2.0)	0	13 (2.3)	2 (0.3)	16 (1.7)	136 (1.8)
Pulmonary embolism	7 (1.6)	6 (1.4)	8 (1.4)	5 (0.6)	7 (0.7)	78 (1.0)
Skin and Subcutaneous Tissue Disorders	**26 (5.9)**	**1 (0.2)**	**29 (5.1)**	**33 (4.2)**	**4 (0.4)**	**56 (0.7)**
Rash maculo-papular	7 (1.6)	0	8 (1.4)	7 (0.9)	1 (0.1)	8 (0.1)

Number of subjects (n) and percentage of subjects (%) are shown.
Sorting order: alphabetical order by SOC and descending by the number of subjects in the EV + Pembro Combo ISS analysis group by PT. In case of ties, alphabetical order by PT was applied.
Combo: combination; COVID-19: coronavirus disease 2019; EV: enfortumab vedotin; ISS: integrated summary of safety; Mono: monotherapy; Pembro: pembrolizumab; PT: preferred term; RSD: reference safety data.

AEs leading to death:

Table 83: Summary of Treatment-emergent Adverse Events Leading to Death (Safety Analysis Set)

	EV + Pembro EV-302 (N=440) n (%)	Chemotherapy EV-302 (N=433) n (%)	EV + Pembro Combo ISS (N=564) n (%)	EV ISS Mono Pool (N=793) n (%)	Pembro Bladder Pool (N=938) n (%)	Pembro RSD (N=7631) n (%)
TEAEs Leading to Death	19 (4.3)	14 (3.2)	26 (4.6)	56 (7.1)	65 (6.9)	346 (4.5)
Drug-related TEAEs Leading to Death	4 (0.9)	4 (0.9)	8 (1.4)	17 (2.1)	7 (0.7)	42 (0.6)

Combo: combination; EV: enfortumab vedotin; ISS: integrated summary of safety; Mono: monotherapy; Pembro: pembrolizumab; RSD: reference safety data; TEAE: treatment-emergent adverse event.

Table 84: Treatment-emergent Adverse Events Leading to Death by Preferred Term (Safety Analysis Set)

MedDRA (v26.0) Preferred term, n (%)	EV + Pembro EV-302 (N = 440)		Chemotherapy EV-302 (N = 433)		EV + Pembro Combo ISS (N = 564)	
	Any	Drug Related	Any	Drug Related	Any	Drug Related
Overall	**19 (4.3)**	**4 (0.9)**	**14 (3.2)**	**4 (0.9)**	**26 (4.6)**	**8 (1.4)**
Acute respiratory failure	2 (0.5)	0	0	0	2 (0.4)	0
Cardiac arrest	1 (0.2)	0	1 (0.2)	0	2 (0.4)	0
Multiple organ dysfunction syndrome	1 (0.2)	1 (0.2)	0	0	2 (0.4)	2 (0.4)
Respiratory failure	1 (0.2)	0	0	0	2 (0.4)	1 (0.2)
Sepsis	1 (0.2)	0	2 (0.5)	1 (0.2)	2 (0.4)	1 (0.2)
Asthenia	1 (0.2)	1 (0.2)	0	0	1 (0.2)	1 (0.2)
Cardiac failure	1 (0.2)	0	0	0	1 (0.2)	0
Cardio-respiratory arrest	1 (0.2)	0	0	0	1 (0.2)	0
Cerebral haemorrhage	1 (0.2)	0	0	0	1 (0.2)	0
COVID -19	1 (0.2)	0	0	0	1 (0.2)	0
Death	1 (0.2)	0	0	0	1 (0.2)	0
Diarrhoea	1 (0.2)	1 (0.2)	0	0	1 (0.2)	1 (0.2)

MedDRA (v26.0) Preferred term, n (%)	EV + Pembro EV-302 (N = 440)		Chemotherapy EV-302 (N = 433)		EV + Pembro Combo ISS (N = 564)	
	Any	Drug Related	Any	Drug Related	Any	Drug Related
Hydrocephalus	0	0	0	0	1 (0.2)	0
Immune-mediated lung disease	1 (0.2)	1 (0.2)	0	0	1 (0.2)	1 (0.2)
Nervous system disorder	1 (0.2)	0	0	0	1 (0.2)	0
Pneumonia	1 (0.2)	0	0	0	1 (0.2)	0
Pneumonia aspiration	1 (0.2)	0	0	0	1 (0.2)	0
Pneumonitis	0	0	0	0	1 (0.2)	1 (0.2)
Renal failure	1 (0.2)	0	0	0	1 (0.2)	0
Sudden death	1 (0.2)	0	0	0	1 (0.2)	0
Septic shock	0	0	0	0	1 (0.2)	0
Acute right ventricular failure	0	0	1 (0.2)	0	0	0
Cerebrovascular accident	0	0	1 (0.2)	0	0	0
Chronic obstructive pulmonary disease	0	0	1 (0.2)	0	0	0
Febrile neutropenia	0	0	1 (0.2)	1 (0.2)	0	0
General physical health deterioration	0	0	2 (0.5)	0	0	0
Myocardial infarction	0	0	1 (0.2)	1 (0.2)	0	0
Neutropenic sepsis	0	0	1 (0.2)	1 (0.2)	0	0
Peritonitis	0	0	2 (0.5)	0	0	0
Shock	0	0	1 (0.2)	0	0	0

Number of subjects (n) and percentage of subjects (%) are shown.
TEAEs leading to death that were coded to disease progression SSQ/CMQ were excluded.
Sorting order: alphabetical order by the number of subjects in the EV + Pembro Combo ISS analysis group by PT. In case of ties, alphabetical order by PT is applied.
Combo: combination; COVID-19: coronavirus disease 2019; CMQ: customized medical query; EV: enfortumab vedotin; ISS: integrated summary of safety; Pembro: pembrolizumab; PT: preferred term; SSQ: sponsor-specific queries

Adverse events of special interest:

The following AESIs are defined for enfortumab vedotin:

- Skin reactions
- Pneumonitis/Interstitial lung disorder (ILD)
- Peripheral neuropathy
- Ocular disorders (including dry eye, corneal disorders, and blurred vision)
- Hyperglycaemia
- Infusion-related reactions (including site reactions)
- Anaemia
- Neutropenia (including neutropenic infections)
- GI Disorders: GI non-specific symptoms and therapeutic procedures SMQ (Narrow).

Skin Reactions

The target of enfortumab vedotin, Nectin-4, is expressed in epidermal keratinocytes and skin appendages (e.g., sweat glands and hair follicles); clinical AEs of skin reactions have been observed. A comprehensive SSQ/CMQ search strategy comprising rash (5 MedDRA HLTs of "Bullous conditions", "Dermatitis and eczema", "Rashes, eruptions and exanthemas NEC", "Erythemas", and "Dermatitis ascribed to specific agent") and SCAR (SMQ of SCAR) were used to capture events consistent with the medical concept of skin reactions. Rash consists of 114 MedDRA PTs and SCAR has 73 PTs, with 22 PTs included in both rash and SCAR search strategies.

Of the patients who experienced skin reactions and had data regarding resolution (N=366), 61% had complete resolution, 24% had partial improvement, and 15% had no improvement at the time of their last evaluation. Of the 39% of patients with residual skin reactions at last evaluation, 38% had Grade ≥2 events.

In clinical studies of enfortumab vedotin in combination with pembrolizumab, skin reactions occurred in 70% (392) of the 564 patients and a majority of these skin reactions included rash maculo-papular, rash macular and rash papular. Severe (Grade 3 or 4) skin reactions occurred in 17% (97) of patients (Grade 3: 16%, Grade 4: 1%). The median time to onset of severe skin reactions was 1.7 months (range: 0.1 to 17.2 months). Of the patients who experienced skin reactions and had data regarding resolution (N=391), 59% had complete resolution, 30% had partial improvement, and 10% had no improvement at the time of their last evaluation. Of the 41% of patients with residual skin reactions at last evaluation, 27% had Grade ≥2 events.

Table 85: Overview of Rash Treatment-emergent Adverse Events (Safety Analysis Set)

MedDRA (v26.0) Category, n (%)	**EV + Pembro EV-302 (N = 440)**	**Chemotherapy EV-302 (N = 433)**	**EV + Pembro Combo ISS (N = 564)**	**EV Mono ISS (N = 793)**
Subjects with any rash event †	**279 (63.4)**	**46 (10.6)**	**363 (64.4)**	**415 (52.3)**
Grade 1	86 (19.5)	31 (7.2)	113 (20.0)	169 (21.3)
Grade 2	124 (28.2)	15 (3.5)	156 (27.7)	146 (18.4)
Grade 3	66 (15.0)	0	89 (15.8)	97 (12.2)
Grade 4	3 (0.7)	0	5 (0.9)	3 (0.4)
Rash events by preferred term in ≥ 3% of subjects in EV + Pembro Combo ISS				
Rash maculo-papular	146 (33.2)	15 (3.5)	203 (36.0)	187 (23.6)
Grade 1	59 (13.4)	8 (1.8)	81 (14.4)	77 (9.7)
Grade 2	51 (11.6)	7 (1.6)	68 (12.1)	67 (8.4)
Grade 3	35 (8.0)	0	53 (9.4)	43 (5.4)
Grade 4	1 (0.2)	0	1 (0.2)	0
Rash macular	44 (10.0)	6 (1.4)	64 (11.3)	21 (2.6)
Grade 1	18 (4.1)	5 (1.2)	28 (5.0)	14 (1.8)
Grade 2	18 (4.1)	1 (0.2)	27 (4.8)	6 (0.8)
Grade 3	8 (1.8)	0	9 (1.6)	1 (0.1)
Rash papular	34 (7.7)	3 (0.7)	43 (7.6)	17 (2.1)
Grade 1	16 (3.6)	1 (0.2)	20 (3.5)	9 (1.1)
Grade 2	12 (2.7)	2 (0.5)	16 (2.8)	7 (0.9)
Grade 3	6 (1.4)	0	7 (1.2)	1 (0.1)
Eczema	29 (6.6)	4 (0.9)	29 (5.1)	12 (1.5)
Grade 1	12 (2.7)	4 (0.9)	12 (2.1)	5 (0.6)
Grade 2	13 (3.0)	0	13 (2.3)	6 (0.8)
Grade 3	4 (0.9)	0	4 (0.7)	1 (0.1)
Dermatitis	23 (5.2)	1 (0.2)	27 (4.8)	6 (0.8)
Grade 1	9 (2.0)	1 (0.2)	11 (2.0)	4 (0.5)
Grade 2	11 (2.5)	0	12 (2.1)	1 (0.1)
Grade 3	3 (0.7)	0	4 (0.7)	1 (0.1)
Dermatitis bullous	17 (3.9)	1 (0.2)	26 (4.6)	26 (3.3)
Grade 1	5 (1.1)	1 (0.2)	8 (1.4)	15 (1.9)
Grade 2	9 (2.0)	0	13 (2.3)	6 (0.8)
Grade 3	3 (0.7)	0	4 (0.7)	3 (0.4)
Grade 4	0	0	1 (0.2)	2 (0.3)
Erythema	17 (3.9)	5 (1.2)	21 (3.7)	32 (4.0)
Grade 1	10 (2.3)	3 (0.7)	13 (2.3)	24 (3.0)
Grade 2	6 (1.4)	2 (0.5)	7 (1.2)	6 (0.8)
Grade 3	1 (0.2)	0	1 (0.2)	2 (0.3)

MedDRA (v26.0) Category, n (%)	EV + Pembro EV-302 (N = 440)	Chemotherapy EV-302 (N = 433)	EV + Pembro Combo ISS (N = 564)	EV Mono ISS (N = 793)
Rash erythematous	15 (3.4)	4 (0.9)	21 (3.7)	37 (4.7)
Grade 1	5 (1.1)	3 (0.7)	8 (1.4)	17 (2.1)
Grade 2	8 (1.8)	1 (0.2)	10 (1.8)	7 (0.9)
Grade 3	2 (0.5)	0	3 (0.5)	13 (1.6)
Blister	13 (3.0)	0	18 (3.2)	28 (3.5)
Grade 1	5 (1.1)	0	9 (1.6)	21 (2.6)
Grade 2	7 (1.6)	0	8 (1.4)	5 (0.6)
Grade 3	1 (0.2)	0	1 (0.2)	2 (0.3)
Subjects with any drug-related rash events	**273 (62.0)**	**39 (9.0)**	**352 (62.4)**	**376 (47.4)**
Subjects with any serious rash events	**24 (5.5)**	**0**	**27 (4.8)**	**31 (3.9)**
Subjects with any drug-related serious rash events	**24 (5.5)**	**0**	**27 (4.8)**	**31 (3.9)**
Rash maculo-papular	7 (1.6)	0	8 (1.4)	7 (0.9)
Dermatitis bullous	3 (0.7)	0	4 (0.7)	4 (0.5)
Toxic epidermal necrolysis	3 (0.7)	0	3 (0.5)	0
Dermatitis	2 (0.5)	0	2 (0.4)	0
Rash erythematous	1 (0.2)	0	2 (0.4)	0
Rash macular	2 (0.5)	0	2 (0.4)	0
Rash morbilliform	2 (0.5)	0	2 (0.4)	0
Eczema	1 (0.2)	0	1 (0.2)	1 (0.1)
Erythema multiforme	0	0	1 (0.2)	0
Rash	1 (0.2)	0	1 (0.2)	7 (0.9)
SJS-TEN overlap	1 (0.2)	0	1 (0.2)	0
Toxic erythema of chemotherapy	1 (0.2)	0	1 (0.2)	0
Blister	0	0	0	1 (0.1)
Drug eruption	0	0	0	5 (0.6)
Rash vesicular	0	0	0	4 (0.5)
Stevens-Johnson syndrome	0	0	0	1 (0.1)
Toxic skin eruption	0	0	0	1 (0.1)
Subjects with any rash events leading to permanent withdrawal of treatment	**22 (5.0)**	**0**	**31 (5.5)**	**24 (3.0)**

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 were missing.

Sorting order: descending by the number of subjects in the EV + Pembro Combo ISS analysis group by PT. In case of ties, alphabetical order by PT was applied.

Adverse events related to study drug (either EV, Chemotherapy or Pembro) as assessed by investigator are shown. Missing relationship was considered as related in EV studies.

Treatment-emergent adverse events leading to withdrawal of any treatment (either EV, Chemotherapy or Pembro) are included.

Combo: combination; CMQ: customized medical query; EV: enfortumab vedotin; ISS: integrated summary of safety; Mono: monotherapy; NCI-CTCAE: National Cancer Institute - Common Terminology Criteria for Adverse Events; Pembro: pembrolizumab; PT: preferred term; SJS: Stevens-Johnson syndrome; SSQ: sponsor-specific queries; TEN: toxic epidermal necrolysis.

† Rash SSQ/CMQ

Table 86: Overview of Severe Cutaneous Adverse Reactions (Safety Analysis Set)

MedDRA (v26.0) Category, n (%)	EV + Pembro EV-302 (N = 440)	Chemotherapy EV-302 (N = 433)	EV + Pembro Combo ISS (N = 564)	EV Mono ISS (N = 793)
Subjects with any severe cutaneous adverse reactions †	**119 (27.0)**	**33 (7.6)**	**155 (27.5)**	**197 (24.8)**
Grade 1	56 (12.7)	26 (6.0)	73 (12.9)	105 (13.2)
Grade 2	50 (11.4)	6 (1.4)	63 (11.2)	59 (7.4)

MedDRA (v26.0) Category, n (%)	EV + Pembro EV-302 (N = 440)	Chemotherapy EV-302 (N = 433)	EV + Pembro Combo ISS (N = 564)	EV Mono ISS (N = 793)
Grade 3	10 (2.3)	1 (0.2)	14 (2.5)	31 (3.9)
Grade 4	3 (0.7)	0	5 (0.9)	2 (0.3)
Severe cutaneous adverse reactions by preferred term occurring in ≥ 3% of subjects in EV + Pembro Combo ISS				
Stomatitis	39 (8.9)	27 (6.2)	51 (9.0)	63 (7.9)
Grade 1	25 (5.7)	21 (4.8)	33 (5.9)	38 (4.8)
Grade 2	13 (3.0)	6 (1.4)	17 (3.0)	20 (2.5)
Grade 3	1 (0.2)	0	1 (0.2)	5 (0.6)
Conjunctivitis	27 (6.1)	0	34 (6.0)	37 (4.7)
Grade 1	20 (4.5)	0	22 (3.9)	19 (2.4)
Grade 2	7 (1.6)	0	12 (2.1)	17 (2.1)
Dermatitis bullous	17 (3.9)	1 (0.2)	26 (4.6)	26 (3.3)
Grade 1	5 (1.1)	1 (0.2)	8 (1.4)	15 (1.9)
Grade 2	9 (2.0)	0	13 (2.3)	6 (0.8)
Grade 3	3 (0.7)	0	4 (0.7)	3 (0.4)
Grade 4	0	0	1 (0.2)	2 (0.3)
Blister	13 (3.0)	0	18 (3.2)	28 (3.5)
Grade 1	5 (1.1)	0	9 (1.6)	21 (2.6)
Grade 2	7 (1.6)	0	8 (1.4)	5 (0.6)
Grade 3	1 (0.2)	0	1 (0.2)	2 (0.3)
Subjects with any drug-related severe cutaneous adverse reactions	**102 (23.2)**	**32 (7.4)**	**127 (22.5)**	**156 (19.7)**
Subjects with any serious severe cutaneous adverse reactions	**10 (2.3)**	**1 (0.2)**	**12 (2.1)**	**15 (1.9)**
Subjects with any drug-related serious severe cutaneous adverse reactions	**10 (2.3)**	**1 (0.2)**	**12 (2.1)**	**15 (1.9)**
Dermatitis bullous	3 (0.7)	0	4 (0.7)	4 (0.5)
Toxic epidermal necrolysis	3 (0.7)	0	3 (0.5)	0
Dermatitis exfoliative	1 (0.2)	0	1 (0.2)	1 (0.1)
Dermatitis exfoliative generalized	1 (0.2)	0	1 (0.2)	0
Erythema multiforme	0	0	1 (0.2)	0
Mouth ulceration	1 (0.2)	0	1 (0.2)	0
SJS-TEN overlap	1 (0.2)	0	1 (0.2)	0
Acute generalised exanthematous pustulosis	0	1 (0.2)	0	0
Blister	0	0	0	1 (0.1)
Conjunctivitis	0	0	0	1 (0.1)
Drug eruption	0	0	0	5 (0.6)
Stevens-Johnson syndrome	0	0	0	1 (0.1)
Stomatitis	0	0	0	1 (0.1)
Toxic skin eruption	0	0	0	1 (0.1)
Subjects with any severe cutaneous adverse reactions leading to permanent withdrawal of treatment	**8 (1.8)**	**1 (0.2)**	**13 (2.3)**	**11 (1.4)**

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 were missing.

Sorting order: descending by the number of subjects in the EV + Pembro Combo ISS analysis group by PT. In case of ties, alphabetical order by PT was applied.

Adverse events related to study drug (either EV, Chemotherapy or Pembro) as assessed by investigator are shown. Missing relationship was considered as related in EV studies.

Treatment-emergent adverse events leading to withdrawal of any treatment (either EV, Chemotherapy or Pembro) are included.

Combo: combination; EV: enfortumab vedotin; ISS: integrated summary of safety; Mono: monotherapy; NCI-CTCAE: National Cancer Institute - Common Terminology Criteria for Adverse Events; Pembro: pembrolizumab; PT: preferred term; SJS: Stevens-Johnson syndrome; SMQ: standardized MedDRA query; TEN: toxic epidermal necrolysis.

† Severe cutaneous adverse reaction SMQ (broad scope).

Pneumonitis/ILD

In clinical studies of enfortumab vedotin as monotherapy, pneumonitis/ILD occurred in 22 (2.8%) of the 793 patients treated with enfortumab vedotin 1.25 mg/kg. Less than 1% of patients experienced severe (Grade 3 or 4) pneumonitis/ILD (Grade 3: 0.3%, Grade 4: 0.3%). Pneumonitis/ILD led to discontinuation of enfortumab vedotin in 0.5% of patients. There were no deaths from pneumonitis/ILD. The median time to onset of any grade pneumonitis/ILD was 3.6 months (range: 0.8 to 6.0 months) and the median duration was 1.7 months (range: 0.2 to 43.0 months). Of the 19 patients who experienced pneumonitis/ILD, 6 (31.6%) had resolution of symptoms.

In clinical studies of enfortumab vedotin in combination with pembrolizumab, pneumonitis/ILD occurred in 58 (10.3%) of the 564 patients. Severe (Grade 3 or 4) pneumonitis/ILD occurred in 20 patients (Grade 3: 3.0%, Grade 4: 0.5%). Pneumonitis/ILD led to discontinuation of enfortumab vedotin in 4.8% of patients. Two patients experienced a fatal event of pneumonitis/ILD. The median time to onset of any grade pneumonitis/ILD was 4 months (range: 0.3 to 26.2 months).

Peripheral Neuropathy

The cytotoxic component of enfortumab vedotin, MMAE, is a microtubule-disrupting agent [Challita-Eid et al, 2016]. Peripheral neuropathy is part of the safety profile of drugs that affect microtubules including other MMAE ADCs [Donaghy, 2016]. A search strategy using the SMQ (broad scope) of peripheral neuropathy was used to capture events consistent with the medical concept of peripheral neuropathy. The frequency of TEAEs in the AESI of peripheral **neuropathy** observed in the EV + Pembro EV-302 arm was higher than that observed in the Chemotherapy EV-302 arm Table 87.

Table 87: Overview of Peripheral Neuropathy Treatment-emergent Adverse Events (Safety Analysis Set)

MedDRA (v26.0) Category, n (%)	EV + Pembro EV-302 (N = 440)	Chemotherapy EV-302 (N = 433)	EV + Pembro Combo ISS (N = 564)	EV Mono ISS (N = 793)
Subjects with any peripheral neuropathy event †	**293 (66.6)**	**60 (13.9)**	**376 (66.7)**	**422 (53.2)**
Subjects with any peripheral neuropathy sensory events ‡	**272 (61.8)**	**55 (12.7)**	**349 (61.9)**	**386 (48.7)**
Subjects with any peripheral neuropathy motor events §	**59 (13.4)**	**9 (2.1)**	**89 (15.8)**	**123 (15.5)**
Peripheral neuropathy events by preferred term occurring in ≥ 5% of subjects in EV + Pembro Combo ISS				
Peripheral sensory neuropathy	229 (52.0)	44 (10.2)	301 (53.4)	305 (38.5)
Grade 1	93 (21.1)	38 (8.8)	114 (20.2)	100 (12.6)
Grade 2	119 (27.0)	6 (1.4)	167 (29.6)	180 (22.7)
Grade 3	17 (3.9)	0	20 (3.5)	25 (3.2)
Muscular weakness	29 (6.6)	7 (1.6)	39 (6.9)	58 (7.3)
Grade 1	20 (4.5)	4 (0.9)	25 (4.4)	32 (4.0)
Grade 2	5 (1.1)	3 (0.7)	10 (1.8)	21 (2.6)
Grade 3	4 (0.9)	0	4 (0.7)	5 (0.6)
Peripheral motor neuropathy	21 (4.8)	1 (0.2)	38 (6.7)	53 (6.7)
Grade 1	5 (1.1)	1 (0.2)	8 (1.4)	18 (2.3)
Grade 2	12 (2.7)	0	25 (4.4)	27 (3.4)
Grade 3	4 (0.9)	0	5 (0.9)	8 (1.0)
Paraesthesia	36 (8.2)	8 (1.8)	37 (6.6)	35 (4.4)

MedDRA (v26.0) Category, n (%)	EV + Pembro EV-302 (N = 440)	Chemotherapy EV-302 (N = 433)	EV + Pembro Combo ISS (N = 564)	EV Mono ISS (N = 793)
Grade 1	26 (5.9)	7 (1.6)	27 (4.8)	20 (2.5)
Grade 2	10 (2.3)	1 (0.2)	10 (1.8)	14 (1.8)
Grade 3	0	0	0	1 (0.1)
Subjects with any drug-related peripheral neuropathy events	**278 (63.2)**	**53 (12.2)**	**358 (63.5)**	**381 (48.0)**
Subjects with any serious peripheral neuropathy events	**6 (1.4)**	**0**	**7 (1.2)**	**16 (2.0)**
Subjects with any serious drug-related peripheral neuropathy events	**4 (0.9)**	**0**	**5 (0.9)**	**10 (1.3)**
Subjects with any peripheral neuropathy events leading to permanent withdrawal of treatment	**65 (14.8)**	**1 (0.2)**	**93 (16.5)**	**53 (6.7)**

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 were missing.

Sorting order: descending by the number of subjects in the EV + Pembro Combo ISS analysis group by PT. In case of ties, alphabetical order by PT was applied.

Adverse events related to study drug (either EV, Chemotherapy or Pembro) as assessed by investigator are shown. Missing relationship was considered as related in EV studies.

Combo: combination; EV: enfortumab vedotin; ISS: integrated summary of safety; Mono: monotherapy; NCI-CTCAE: National Cancer Institute - Common Terminology Criteria for Adverse Events; Pembro: pembrolizumab; PT: preferred term.

† Peripheral neuropathy SMQ (broad scope).

‡ Including selected PTs from peripheral neuropathy SMQ (broad scope) classified as "motor" events.

§ Including selected PTs from peripheral neuropathy SMQ (broad scope) classified as "sensory" events.

Ocular Disorders

Ocular disorders in general have been commonly reported across the enfortumab vedotin program. Events of ocular disorders have been captured using an SSQ/CMQ comprising 3 subsets, each describing a different medical concept. These include the medical concept of dry eye the medical concept of corneal disorders and the medical concept of blurred vision. Combined, these 3 search strategies describe the medical concept of ocular disorders.

Table 88: Overview of Ocular Disorders Treatment-emergent Adverse Events (Safety Analysis Set)

MedDRA (v26.0) Category, n (%)	EV + Pembro EV-302 (N = 440)	Chemotherapy EV-302 (N = 433)	EV + Pembro Combo ISS (N = 564)	EV Mono ISS (N = 793)
Subjects with any ocular disorders events	**128 (29.1)**	**16 (3.7)**	**180 (31.9)**	**277 (34.9)**
Ocular disorders events by preferred term occurring in ≥ 5% of subjects in EV + Pembro Combo ISS				
Dry eye	50 (11.4)	5 (1.2)	81 (14.4)	101 (12.7)
Grade 1	45 (10.2)	5 (1.2)	69 (12.2)	86 (10.8)
Grade 2	5 (1.1)	0	12 (2.1)	15 (1.9)
Grade 3	0	0	0	0
Lacrimation increased	36 (8.2)	2 (0.5)	55 (9.8)	109 (13.7)
Grade 1	35 (8.0)	2 (0.5)	52 (9.2)	93 (11.7)
Grade 2	1 (0.2)	0	3 (0.5)	15 (1.9)
Grade 3	0	0	0	1 (0.1)
Conjunctivitis	27 (6.1)	0	34 (6.0)	37 (4.7)
Grade 1	20 (4.5)	0	22 (3.9)	19 (2.4)
Grade 2	7 (1.6)	0	12 (2.1)	17 (2.1)
Grade 3	0	0	0	1 (0.1)
Vision blurred	26 (5.9)	5 (1.2)	41 (7.3)	77 (9.7)
Grade 1	21 (4.8)	5 (1.2)	31 (5.5)	58 (7.3)
Grade 2	5 (1.1)	0	10 (1.8)	19 (2.4)
Grade 3	0	0	0	0
Drug-related ocular disorder events	**94 (21.4)**	**12 (2.8)**	**133 (23.6)**	**199 (25.1)**
Serious ocular disorder events	**1 (0.2)**	**0**	**1 (0.2)**	**2 (0.3)**
Serious drug-related ocular disorder events	**1 (0.2)**	**0**	**1 (0.2)**	**2 (0.3)**
Ocular disorder events leading to permanent withdrawal of treatment	**1 (0.2)**	**0**	**1 (0.2)**	**1 (0.1)**

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 were missing.

Sorting order: descending by the number of subjects in the EV + Pembro Combo ISS analysis group by PT. In case of ties, alphabetical order by PT was applied.

Details on the SSQ/CMQ category of any dry eye are now presented in this section as a composite of dry eye and corneal events

Adverse events related to study drug (either EV, Chemotherapy or Pembro) as assessed by investigator are shown. Missing relationship was considered as related in EV studies.

Combo: combination; CMQ: customized medical query; EV: enfortumab vedotin; ISS: integrated summary of safety; Mono: monotherapy; NCI-CTCAE: National Cancer Institute - Common Terminology Criteria for Adverse Events; Pembro: pembrolizumab; PT: preferred term; SSQ: sponsor-specific queries.

Hyperglycemia:

Hyperglycemia has been observed in subjects treated with enfortumab vedotin. A potential mechanism has not been established.

Table 89: Overview of Hyperglycemia Treatment-emergent Adverse Events (Safety Analysis Set)

MedDRA (v26.0) Category, n (%)	EV + Pembro EV-302 (N = 440)	Chemotherapy EV-302 (N = 433)	EV + Pembro Combo ISS (N = 564)	EV Mono ISS (N = 793)
Subjects with any hyperglycemia event †	**85 (19.3)**	**15 (3.5)**	**107 (19.0)**	**133 (16.8)**
Hyperglycemia event by preferred term occurring in ≥ 5% of subjects in EV + Pembro Combo ISS				
Hyperglycaemia	72 (16.4)	11 (2.5)	94 (16.7)	118 (14.9)

MedDRA (v26.0) Category, n (%)	EV + Pembro EV-302 (N = 440)	Chemotherapy EV-302 (N = 433)	EV + Pembro Combo ISS (N = 564)	EV Mono ISS (N = 793)
Grade 1	18 (4.1)	6 (1.4)	21 (3.7)	28 (3.5)
Grade 2	22 (5.0)	2 (0.5)	27 (4.8)	33 (4.2)
Grade 3	29 (6.6)	3 (0.7)	40 (7.1)	49 (6.2)
Grade 4	3 (0.7)	0	6 (1.1)	7 (0.9)
Grade 5	0	0	0	1 (0.1)
Subjects with any drug-related hyperglycemia events	**57 (13.0)**	**3 (0.7)**	**73 (12.9)**	**86 (10.8)**
Subjects with any serious hyperglycemia events	**9 (2.0)**	**1 (0.2)**	**11 (2.0)**	**20 (2.5)**
Subjects with any serious drug-related hyperglycemia events	**8 (1.8)**	**0**	**10 (1.8)**	**18 (2.3)**
Subjects with any hyperglycemia events leading to permanent withdrawal of treatment	**1 (0.2)**	**0**	**1 (0.2)**	**5 (0.6)**

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 were missing.

Sorting order: descending by the number of subjects in the EV + Pembro Combo ISS analysis group by PT. In case of ties, alphabetical order by PT was applied.

Adverse events related to study drug (either EV, Chemotherapy or Pembro) as assessed by investigator are shown. Missing relationship was considered as related in EV studies.

Combo: combination; CMQ: customized medical query; EV: enfortumab vedotin; ISS: integrated summary of safety; Mono: monotherapy; NCI-CTCAE: National Cancer Institute - Common Terminology Criteria for Adverse Events; Pembro: pembrolizumab; PT: preferred term; SSQ: sponsor-specific queries.

† SSQ/CMQ

A summary of hyperglycemia by history of hyperglycemia or diabetes, baseline BMI, and baseline HbA1c is provided in Table 90.

Table 90: Hyperglycemia by History of Hyperglycemia or Diabetes, Baseline Body Mass Index, and Baseline HbA1c (Safety Analysis Set)

MedDRA (v26.0) Category, n (%)	EV + Pembro EV-302 (N = 440)	Chemotherapy EV-302 (N = 433)	EV + Pembro Combo ISS (N = 564)	EV Mono ISS (N = 793)
Subjects without pre-existing hyperglycemia or diabetes				
n	369	347	463	607
Any hyperglycemia event †	56 (15.2)	10 (2.9)	64 (13.8)	64 (10.5)
Subjects with pre-existing hyperglycemia or diabetes				
n	71	86	101	186
Any hyperglycemia event †	29 (40.8)	5 (5.8)	43 (42.6)	69 (37.1)
Subjects with baseline BMI < 30 kg/m²				
n	348	332	441	662
Any hyperglycemia event †	59 (17.0)	11 (3.3)	68 (15.4)	93 (14.0)
Subjects with baseline BMI ≥ 30 kg/m²				
n	89	99	120	131
Any hyperglycemia event †	25 (28.1)	4 (4.0)	38 (31.7)	40 (30.5)
Subjects with baseline HbA1c < 5.7% (Normal)				
n	204	206	262	272
Any hyperglycemia event †	25 (12.3)	5 (2.4)	28 (10.7)	18 (6.6)
Subjects with baseline HbA1c ≥ 5.7% - < 6.5% (Prediabetes)				

MedDRA (v26.0) Category, n (%)	EV + Pembro EV-302 (N = 440)	Chemotherapy EV-302 (N = 433)	EV + Pembro Combo ISS (N = 564)	EV Mono ISS (N = 793)
n	155	134	210	264
Any hyperglycemia event †	31 (20.0)	3 (2.2)	42 (20.0)	54 (20.5)
Subjects with baseline HbA1c ≥ 6.5% (Diabetes)				
n	40	44	51	83
Any hyperglycemia event †	19 (47.5)	3 (6.8)	27 (52.9)	32 (38.6)

Baseline HbA1c was not collected in studies EV-102 and EV-101 prior to protocol amendment 5.

BMI: body mass index; Combo: combination; CMQ: customized medical query; Escal: escalation; EV: enfortumab vedotin; ISS: integrated summary of safety; Max: maximum; Min: minimum; Mono: monotherapy; Pembro: pembrolizumab; SSQ: sponsor-specific queries.

† SSQ/CMQ

Infusion-related Reactions

Table 91: Overview of Infusion-related Reactions Treatment-emergent Adverse Events other than Extravasation Site Reactions (Safety Analysis Set)

MedDRA (v26.0) Category, n (%)	EV + Pembro EV-302 (N = 440)	Chemotherapy EV-302 (N = 433)	EV + Pembro Combo ISS (N = 564)	EV Mono ISS (N = 793)
Subjects with: **Any infusion-related reaction**	**13 (3.0)**	**9 (2.1)**	**20 (3.5)**	**50 (6.3)**
Any systemic infusion-related reaction †	**4 (0.9)**	**5 (1.2)**	**8 (1.4)**	**35 (4.4)**
Any local infusion-related reaction	**9 (2.0)**	**5 (1.2)**	**13 (2.3)**	**16 (2.0)**
Any drug-related infusion-related reaction events	**9 (2.0)**	**9 (2.1)**	**15 (2.7)**	**49 (6.2)**
Any serious infusion-related reaction events	**0**	**0**	**1 (0.2)**	**4 (0.5)**
Any serious drug-related infusion-related reaction events	**0**	**0**	**1 (0.2)**	**4 (0.5)**
Any infusion-related reaction events leading to permanent withdrawal of treatment	**0**	**0**	**0**	**1 (0.1)**

Number of subjects (n) and percentage of subjects (%) are shown.

Adverse events related to study drug (either EV, Chemotherapy or Pembro) as assessed by investigator are shown. Missing relationship was considered as related in EV studies.

Combo: combination; CMQ: customized medical query; EV: enfortumab vedotin; ISS: integrated summary of safety; Mono: monotherapy; Pembro: pembrolizumab; SSQ: sponsor-specific queries.

† SSQ/CMQ

Anemia

Table 92: Overview of Anemia Treatment-emergent Adverse Events (Safety Analysis Set)

MedDRA (v26.0) Category, n (%)	EV + Pembro EV-302 (N = 440)	Chemotherapy EV-302 (N = 433)	EV + Pembro Combo ISS (N = 564)	EV Mono ISS (N = 793)
Subjects with any anemia event †	**108 (24.5)**	**267 (61.7)**	**145 (25.7)**	**231 (29.1)**
Anemia events by preferred term occurring in ≥ 5% of subjects in EV + Pembro Combo ISS				
Anaemia	108 (24.5)	267 (61.7)	145 (25.7)	231 (29.1)
Grade 1	39 (8.9)	21 (4.8)	50 (8.9)	54 (6.8)
Grade 2	38 (8.6)	98 (22.6)	46 (8.2)	100 (12.6)
Grade 3	29 (6.6)	147 (33.9)	47 (8.3)	77 (9.7)
Grade 4	2 (0.5)	1 (0.2)	2 (0.4)	0

MedDRA (v26.0) Category, n (%)	EV + Pembro EV-302 (N = 440)	Chemotherapy EV-302 (N = 433)	EV + Pembro Combo ISS (N = 564)	EV Mono ISS (N = 793)
Subjects with any drug-related anemia events †	**61 (13.9)**	**245 (56.6)**	**84 (14.9)**	**150 (18.9)**
Subjects with any serious anemia events †	**3 (0.7)**	**17 (3.9)**	**6 (1.1)**	**7 (0.9)**
Subjects with any serious drug-related anemia events †	**1 (0.2)**	**16 (3.7)**	**3 (0.5)**	**2 (0.3)**
Subjects with any anemia events leading to permanent withdrawal of treatment †	**2 (0.5)**	**12 (2.8)**	**2 (0.4)**	**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 were missing.

Adverse events related to study drug (either EV, Chemotherapy or Pembro) as assessed by investigator are shown. Missing relationship was considered as related in EV studies.

Combo: combination; EV: enfortumab vedotin; ISS: integrated summary of safety; Mono: monotherapy; NCI-CTCAE: National Cancer Institute - Common Terminology Criteria for Adverse Events; Pembro: pembrolizumab; SMQ: standardized MedDRA query.

† Haematopoietic erythropenia SMQ (broad scope).

Neutropenia

Table 93: Overview of Neutropenia Treatment-emergent Adverse Events (Safety Analysis Set)

MedDRA (v26.0) Category, n (%)	EV + Pembro EV-302 (N = 440)	Chemotherapy EV-302 (N = 433)	EV + Pembro Combo ISS (N = 564)	EV Mono ISS (N = 793)
Subjects with any neutropenia event †	60 (13.6)	238 (55.0)	78 (13.8)	134 (16.9)
Neutropenia events by preferred term occurring in ≥ 5% of subjects in EV + Pembro Combo ISS				
Neutropenia	43 (9.8)	181 (41.8)	57 (10.1)	60 (7.6)
Grade 1	5 (1.1)	15 (3.5)	7 (1.2)	7 (0.9)
Grade 2	16 (3.6)	36 (8.3)	17 (3.0)	7 (0.9)
Grade 3	19 (4.3)	93 (21.5)	27 (4.8)	32 (4.0)
Grade 4	3 (0.7)	37 (8.5)	6 (1.1)	14 (1.8)
Subjects with any drug-related neutropenia events †	**57 (13.0)**	**237 (54.7)**	**75 (13.3)**	**124 (15.6)**
Subjects with any serious neutropenia events †	**7 (1.6)**	**21 (4.8)**	**7 (1.2)**	**23 (2.9)**
Subjects with any serious drug-related neutropenia events †	**7 (1.6)**	**20 (4.6)**	**7 (1.2)**	**21 (2.6)**
Subjects with any neutropenia events leading to permanent withdrawal of treatment †	**0**	**12 (2.8)**	**0**	**1 (0.1)**

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 were missing.

Adverse events related to study drug (either EV, Chemotherapy or Pembro) as assessed by investigator are shown. Missing relationship was considered as related in EV studies.

Combo: combination; CMQ: customized medical query; EV: enfortumab vedotin; ISS: integrated summary of safety; Mono: monotherapy; NCI-CTCAE: National Cancer Institute - Common Terminology Criteria for Adverse Events; Pembro: pembrolizumab; SSQ: sponsor-specific queries.

† SSQ/CMQ

GI disorders: Nausea, Vomiting, and Diarrhea

Nectin-4 expression has been identified in the esophagus and the stomach (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.

The identified risks for enfortumab vedotin of nausea, vomiting, and diarrhea are reflected by the SMQ of gastrointestinal nonspecific symptoms and therapeutic procedures. Within this SMQ, the most commonly occurring events were diarrhea and nausea.

Table 94: Overview of Gastrointestinal Nonspecific Symptoms and Therapeutic Procedures SMQ Events (Safety Analysis Set)

MedDRA (v26.0) Category, n (%)	EV + Pembro EV-302 (N = 440)	Chemotherapy EV-302 (N = 433)	EV + Pembro Combo ISS (N = 564)	EV Mono ISS (N = 793)
Subjects with any gastrointestinal nonspecific symptoms and therapeutic procedures events †				
Grade 1	146 (33.2)	154 (35.6)	194 (34.4)	290 (36.6)
Grade 2	104 (23.6)	117 (27.0)	139 (24.6)	205 (25.9)
Grade 3	33 (7.5)	28 (6.5)	45 (8.0)	66 (8.3)
Grade 4	1 (0.2)	0	1 (0.2)	1 (0.1)
Grade 5	1 (0.2)	0	1 (0.2)	0
Total	285 (64.8)	299 (69.1)	380 (67.4)	562 (70.9)
Subjects with any gastrointestinal nonspecific symptoms and therapeutic procedure SMQ by preferred term in ≥ 20% of subjects in EV + Pembro Combo ISS				
Diarrhoea	166 (37.7)	69 (15.9)	221 (39.2)	310 (39.1)
Grade 1	92 (20.9)	51 (11.8)	124 (22.0)	202 (25.5)
Grade 2	53 (12.0)	12 (2.8)	68 (12.1)	72 (9.1)
Grade 3	19 (4.3)	6 (1.4)	27 (4.8)	35 (4.4)
Grade 4	1 (0.2)	0	1 (0.2)	1 (0.1)
Grade 5	1 (0.2)	0	1 (0.2)	0
Nausea	116 (26.4)	178 (41.1)	160 (28.4)	300 (37.8)
Grade 1	73 (16.6)	103 (23.8)	100 (17.7)	191 (24.1)
Grade 2	36 (8.2)	63 (14.5)	52 (9.2)	95 (12.0)
Grade 3	7 (1.6)	12 (2.8)	8 (1.4)	14 (1.8)
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Subjects with any drug-related gastrointestinal nonspecific symptoms and therapeutic procedure events †				
Gastrointestinal Nonspecific Symptoms and Therapeutic Procedure SMQ	199 (45.2)	235 (54.3)	271 (48.0)	418 (52.7)
Diarrhoea	121 (27.5)	48 (11.1)	164 (29.1)	228 (28.8)
Nausea	89 (20.2)	168 (38.8)	123 (21.8)	243 (30.6)
Subjects with any serious gastrointestinal nonspecific symptoms and therapeutic procedure events †				
Overall	22 (5.0)	10 (2.3)	28 (5.0)	39 (4.9)
Diarrhoea	14 (3.2)	2 (0.5)	17 (3.0)	17 (2.1)
Nausea	4 (0.9)	4 (0.9)	4 (0.7)	10 (1.3)
Subjects with any serious drug-related gastrointestinal nonspecific symptoms and therapeutic procedure events †				

MedDRA (v26.0) Category, n (%)	EV + Pembro EV-302 (N = 440)	Chemotherapy EV-302 (N = 433)	EV + Pembro Combo ISS (N = 564)	EV Mono ISS (N = 793)
Overall	12 (2.7)	6 (1.4)	14 (2.5)	20 (2.5)
Diarrhoea	10 (2.3)	1 (0.2)	12 (2.1)	12 (1.5)
Nausea	3 (0.7)	4 (0.9)	3 (0.5)	7 (0.9)
Subjects with any gastrointestinal nonspecific symptoms and therapeutic procedure events leading to permanent withdrawal of treatment †				
Overall	6 (1.4)	4 (0.9)	8 (1.4)	0
Diarrhoea	5 (1.1)	1 (0.2)	7 (1.2)	0
Nausea	1 (0.2)	3 (0.7)	1 (0.2)	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 were missing.

Sorting order: descending by the number of subjects in the EV + Pembro Combo ISS analysis group by PT. In case of ties, alphabetical order by preferred term was applied.

Adverse events related to study drug (either EV, Chemotherapy or Pembro) as assessed by investigator are shown. Missing relationship was considered as related in EV studies.

Combo: combination; EV: enfortumab vedotin; ISS: integrated summary of safety; Mono: monotherapy; NCI-CTCAE: National Cancer Institute - Common Terminology Criteria for Adverse Events; Pembro: pembrolizumab; PT: preferred term; SMQ: standardized MedDRA query.

† Nausea, vomiting and diarrhea is based on gastrointestinal nonspecific symptoms and therapeutic procedures SMQ (narrow scope).

Adverse Events of Special Interest (AEOSI) for Pembrolizumab

Pembrolizumab AEOSI are immune-mediated events and infusion-related reactions, which represent the known risks for and are considered causally associated with, pembrolizumab.(see Table 95):

Table 95: Pembrolizumab AEOSI (MedDRA v26.0) in ≥ 1 Subject in EV + Pembro Combo ISS by AEOSI Category and Preferred Term (Safety Analysis Set)

AEOSI Category Preferred Term, n (%)	EV + Pembro EV-302 (N = 440)	Chemotherapy EV-302 (N = 433)	EV + Pembro Combo ISS (N = 564)	Pembro Bladder Pool (N = 938)	Pembro RSD (N = 7631)
Subjects with ≥ 1 TEAE	193 (43.9)	21 (4.8)	256 (45.4)	220 (23.5)	2082 (27.3)
Subjects with No TEAEs	247 (56.1)	412 (95.2)	308 (54.6)	718 (76.5)	5549 (72.7)
Adrenal Insufficiency	7 (1.6)	0	11 (2.0)	11 (1.2)	74 (1.0)
Adrenal insufficiency	7 (1.6)	0	11 (2.0)	9 (1.0)	69 (0.9)
Arthritis	2 (0.5)	0	2 (0.4)	1 (0.1)	5 (0.1)
Immune-mediated arthritis	2 (0.5)	0	2 (0.4)	0	1 (0.0)
Cholangitis Sclerosing	1 (0.2)	0	1 (0.2)	0	0
Cholangitis sclerosing	1 (0.2)	0	1 (0.2)	0	0
Colitis	12 (2.7)	0	18 (3.2)	23 (2.5)	159 (2.1)
Colitis	9 (2.0)	0	15 (2.7)	20 (2.1)	134 (1.8)
Immune-mediated enterocolitis	3 (0.7)	0	3 (0.5)	0	6 (0.1)
Encephalitis	1 (0.2)	0	1 (0.2)	1 (0.1)	5 (0.1)
Immune-mediated encephalitis	1 (0.2)	0	1 (0.2)	0	0
Gastritis	9 (2.0)	3 (0.7)	9 (1.6)	4 (0.4)	57 (0.7)
Gastritis	7 (1.6)	3 (0.7)	7 (1.2)	4 (0.4)	52 (0.7)
Gastritis erosive	1 (0.2)	0	1 (0.2)	0	7 (0.1)
Haemorrhagic erosive gastritis	1 (0.2)	0	1 (0.2)	0	0
Hepatitis	14 (3.2)	2 (0.5)	16 (2.8)	10 (1.1)	80 (1.0)
Autoimmune hepatitis	5 (1.1)	0	5 (0.9)	2 (0.2)	35 (0.5)
Drug-induced liver injury	1 (0.2)	2 (0.5)	1 (0.2)	1 (0.1)	8 (0.1)

AEOSI Category Preferred Term, n (%)	EV + Pembro EV-302 (N = 440)	Chemotherapy EV-302 (N = 433)	EV + Pembro Combo ISS (N = 564)	Pembro Bladder Pool (N = 938)	Pembro RSD (N = 7631)
Hepatitis	5 (1.1)	0	5 (0.9)	7 (0.7)	34 (0.4)
Immune-mediated hepatitis	4 (0.9)	0	6 (1.1)	0	3 (0.0)
Hyperthyroidism	20 (4.5)	2 (0.5)	25 (4.4)	32 (3.4)	398 (5.2)
Hyperthyroidism	20 (4.5)	2 (0.5)	25 (4.4)	32 (3.4)	398 (5.2)
Hypophysitis	3 (0.7)	0	5 (0.9)	5 (0.5)	52 (0.7)
Hypophysitis	3 (0.7)	0	5 (0.9)	4 (0.4)	32 (0.4)
Hypothyroidism	47 (10.7)	3 (0.7)	60 (10.6)	93 (9.9)	939 (12.3)
Hypothyroidism	46 (10.5)	3 (0.7)	59 (10.5)	93 (9.9)	937 (12.3)
Immune-mediated hypothyroidism	1 (0.2)	0	1 (0.2)	0	0
Infusion Reactions	6 (1.4)	6 (1.4)	11 (2.0)	7 (0.7)	165 (2.2)
Drug hypersensitivity	2 (0.5)	0	3 (0.5)	1 (0.1)	24 (0.3)
Hypersensitivity	1 (0.2)	0	1 (0.2)	3 (0.3)	49 (0.6)
Infusion related reaction	3 (0.7)	6 (1.4)	7 (1.2)	3 (0.3)	75 (1.0)
Myasthenic Syndrome	0	0	3 (0.5)	0	8 (0.1)
Myasthenia gravis	0	0	3 (0.5)	0	5 (0.1)
Myocarditis	3 (0.7)	0	5 (0.9)	2 (0.2)	9 (0.1)
Immune-mediated myocarditis	1 (0.2)	0	1 (0.2)	0	0
Myocarditis	2 (0.5)	0	4 (0.7)	2 (0.2)	9 (0.1)
Myositis	4 (0.9)	2 (0.5)	8 (1.4)	3 (0.3)	34 (0.4)
Dermatomyositis	1 (0.2)	0	1 (0.2)	0	0
Myositis	2 (0.5)	1 (0.2)	6 (1.1)	3 (0.3)	22 (0.3)
Rhabdomyolysis	1 (0.2)	1 (0.2)	2 (0.4)	0	3 (0.0)
Nephritis	4 (0.9)	0	6 (1.1)	5 (0.5)	37 (0.5)
Immune-mediated nephritis	3 (0.7)	0	3 (0.5)	0	0
Tubulointerstitial nephritis	1 (0.2)	0	3 (0.5)	3 (0.3)	14 (0.2)
Optic Neuritis	2 (0.5)	0	2 (0.4)	0	2 (0.0)
Optic neuritis	2 (0.5)	0	2 (0.4)	0	2 (0.0)
Pancreatitis	5 (1.1)	1 (0.2)	7 (1.2)	4 (0.4)	28 (0.4)
Autoimmune pancreatitis	1 (0.2)	0	1 (0.2)	0	1 (0.0)
Pancreatitis	3 (0.7)	0	5 (0.9)	3 (0.3)	24 (0.3)
Pancreatitis acute	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.1)	4 (0.1)
Pneumonitis	42 (9.5)	1 (0.2)	54 (9.6)	45 (4.8)	324 (4.2)
Autoimmune lung disease	1 (0.2)	0	1 (0.2)	0	0
Immune-mediated lung disease	7 (1.6)	0	7 (1.2)	0	4 (0.1)
Interstitial lung disease	5 (1.1)	0	5 (0.9)	4 (0.4)	29 (0.4)
Organising pneumonia	1 (0.2)	0	1 (0.2)	0	3 (0.0)
Pneumonitis	29 (6.6)	1 (0.2)	41 (7.3)	41 (4.4)	291 (3.8)
Sarcoidosis	1 (0.2)	0	1 (0.2)	0	20 (0.3)
Sarcoidosis	1 (0.2)	0	1 (0.2)	0	18 (0.2)
Severe Skin Reactions	75 (17.0)	2 (0.5)	108 (19.1)	19 (2.0)	130 (1.7)
Dermatitis bullous	17 (3.9)	1 (0.2)	26 (4.6)	3 (0.3)	9 (0.1)
Dermatitis exfoliative	1 (0.2)	0	1 (0.2)	1 (0.1)	5 (0.1)
Dermatitis exfoliative generalised	3 (0.7)	0	4 (0.7)	0	2 (0.0)
Erythema multiforme	5 (1.1)	1 (0.2)	6 (1.1)	2 (0.2)	8 (0.1)
Exfoliative rash	0	0	1 (0.2)	0	2 (0.0)
Lichen planus pemphigoides	0	0	1 (0.2)	0	0
Pemphigoid	3 (0.7)	0	5 (0.9)	2 (0.2)	3 (0.0)
Pruritus	5 (1.1)	0	9 (1.6)	4 (0.4)	16 (0.2)
Rash	0	0	1 (0.2)	4 (0.4)	44 (0.6)
Rash erythematous	2 (0.5)	0	3 (0.5)	0	1 (0.0)
Rash maculo-papular	36 (8.2)	0	54 (9.6)	1 (0.1)	23 (0.3)
Rash pruritic	1 (0.2)	0	1 (0.2)	1 (0.1)	4 (0.1)
Rash pustular	1 (0.2)	0	1 (0.2)	0	2 (0.0)

AEOSI Category Preferred Term, n (%)	EV + Pembro EV-302 (N = 440)	Chemotherapy EV-302 (N = 433)	EV + Pembro Combo ISS (N = 564)	Pembro Bladder Pool (N = 938)	Pembro RSD (N = 7631)
SJS-TEN overlap	1 (0.2)	0	1 (0.2)	0	0
Toxic epidermal necrolysis	3 (0.7)	0	3 (0.5)	0	0
Toxic skin eruption	5 (1.1)	0	6 (1.1)	1 (0.1)	4 (0.1)
Thyroiditis	3 (0.7)	0	5 (0.9)	9 (1.0)	74 (1.0)
Autoimmune thyroiditis	1 (0.2)	0	1 (0.2)	2 (0.2)	22 (0.3)
Silent thyroiditis	0	0	1 (0.2)	0	0
Thyroiditis	2 (0.5)	0	3 (0.5)	6 (0.6)	50 (0.7)
Type 1 Diabetes Mellitus	1 (0.2)	0	1 (0.2)	6 (0.6)	34 (0.4)
Type 1 diabetes mellitus	1 (0.2)	0	1 (0.2)	4 (0.4)	25 (0.3)
Uveitis	1 (0.2)	0	1 (0.2)	0	25 (0.3)
Uveitis	1 (0.2)	0	1 (0.2)	0	16 (0.2)

Number of subjects (n) and percentage of subjects (%) are shown.

Sorting order: alphabetical order by AEOSI and PT.

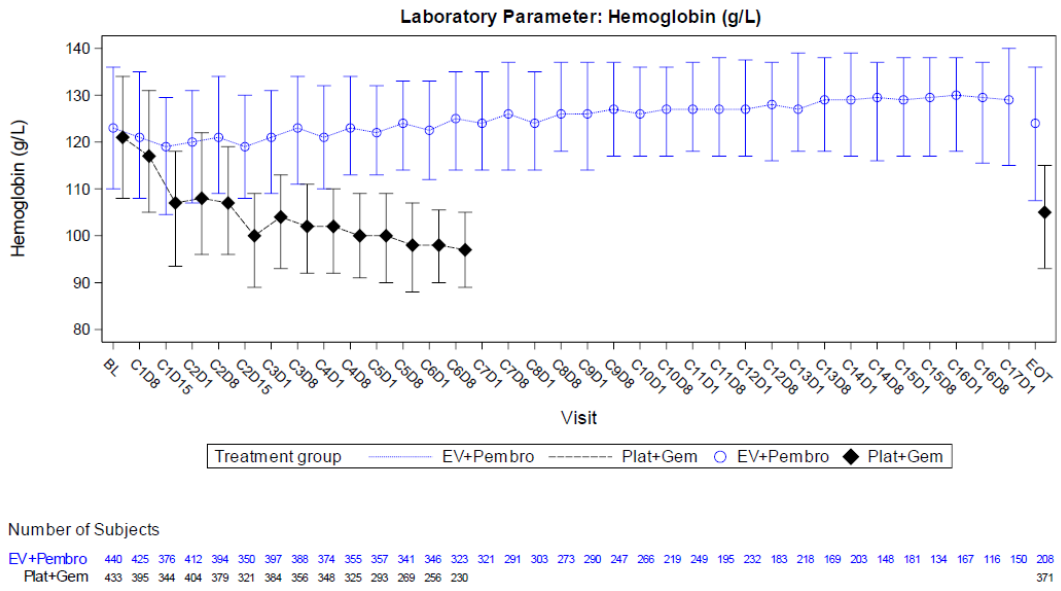
AEOSI: pembrolizumab adverse event(s) of special interest; Combo: combination; EV: enfortumab vedotin; ISS: integrated summary of safety; Pembro: pembrolizumab; PT: preferred term; RSD: reference safety data; SJS: Stevens-Johnson syndrome; TEAE: treatment-emergent adverse event; TEN: toxic epidermal necrolysis.

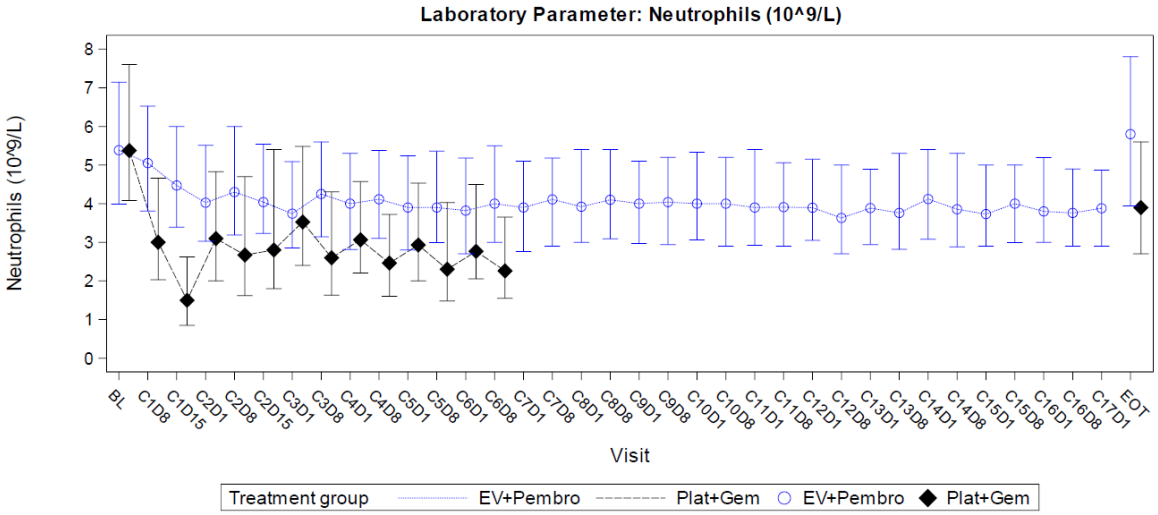
Laboratory findings

Hematology Laboratory Results

Anemia and neutropenia are identified risks for subjects treated with enfortumab vedotin and known toxicities for subjects treated with platinum + gemcitabine; these were described further in the AESIs section. Shifts in hematology parameters from baseline to worst postbaseline value in patients from **Study EV-302 (KEYNOTE-A39)** are presented for selected parameters:

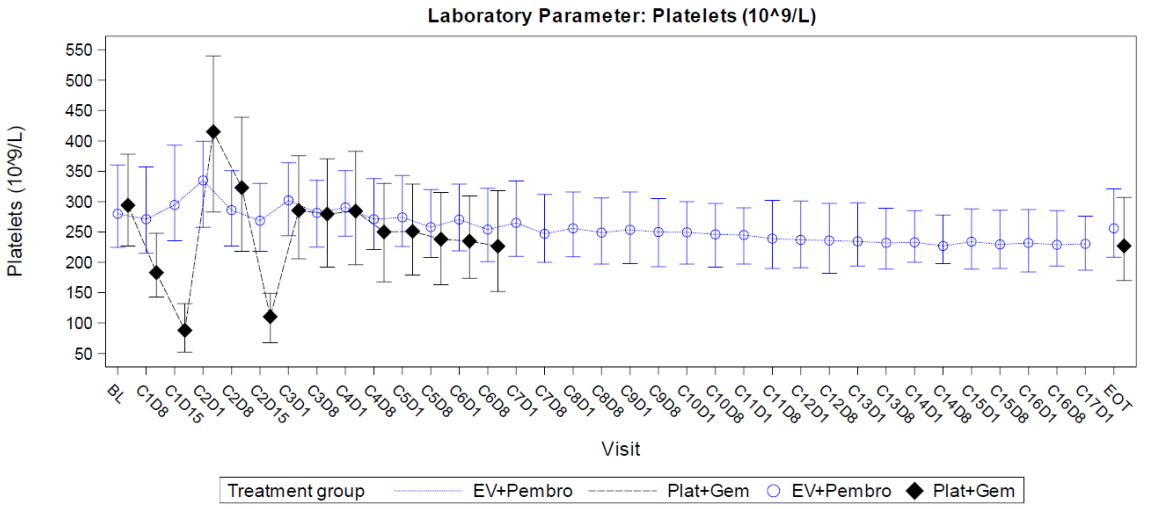
Figure 49: Median (Q1, Q3) Plot of Laboratory Test Results, Hematology SGN22E-003 Safety Analysis Set





Number of Subjects

	BL	C1D8	C1D15	C2D1	C2D8	C2D15	C3D1	C3D8	C4D1	C4D8	C5D1	C5D8	C6D1	C6D8	C7D1	C7D8	C8D1	C8D8	C9D1	C9D8	C10D1	C10D8	C11D1	C11D8	C12D1	C12D8	C13D1	C13D8	C14D1	C14D8	C15D1	C15D8	C16D1	C16D8	C17D1	EOT
EV+Pembro	440	424	376	410	393	347	397	387	373	354	357	341	346	323	321	291	303	273	290	247	265	219	249	195	232	183	218	169	203	148	181	134	167	115	150	208
Plat+Gem	432	395	341	402	377	319	384	356	348	325	293	269	256	228																						369



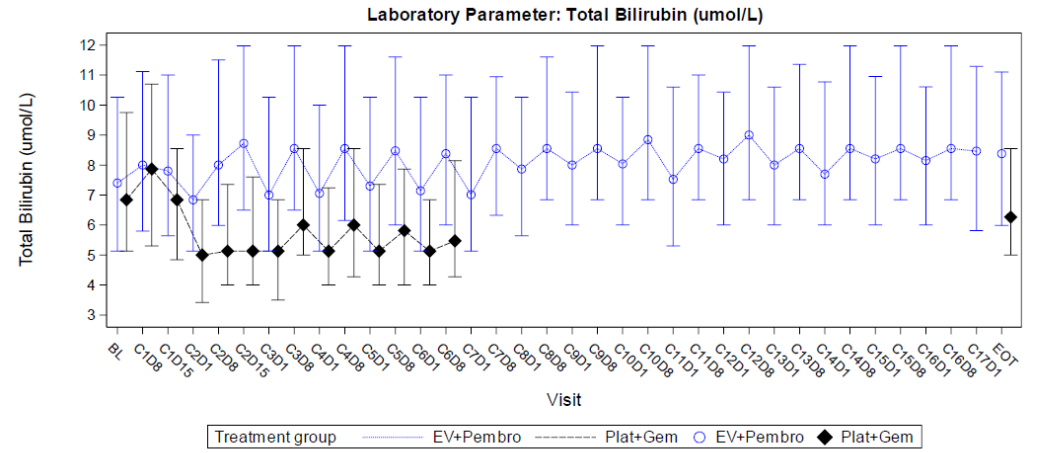
Number of Subjects

	BL	C1D8	C1D15	C2D1	C2D8	C2D15	C3D1	C3D8	C4D1	C4D8	C5D1	C5D8	C6D1	C6D8	C7D1	C7D8	C8D1	C8D8	C9D1	C9D8	C10D1	C10D8	C11D1	C11D8	C12D1	C12D8	C13D1	C13D8	C14D1	C14D8	C15D1	C15D8	C16D1	C16D8	C17D1	EOT
EV+Pembro	440	425	376	412	394	350	397	388	374	355	357	341	346	323	321	291	303	273	290	247	266	219	249	195	231	183	218	169	203	148	181	134	167	115	150	208
Plat+Gem	433	395	343	404	379	320	384	356	348	325	293	269	256	230																						371

Chemistry Laboratory Results

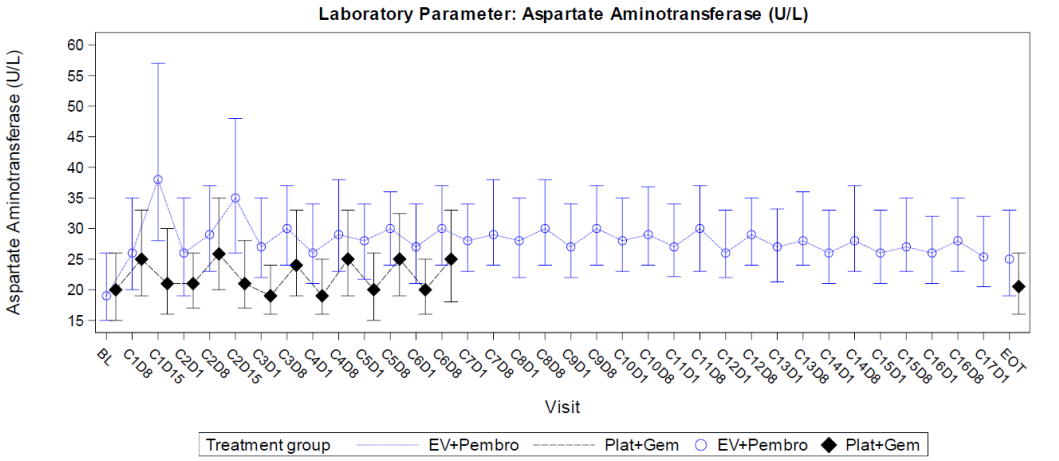
Shifts in hematology parameters from baseline to worst postbaseline value in patients from **Study EV-302 (KEYNOTE-A39)** are presented for selected parameters:

Figure 50: Median (Q1, Q3) Plot of Laboratory Test Results, Serum Chemistry SGN22E Safety Analysis Set



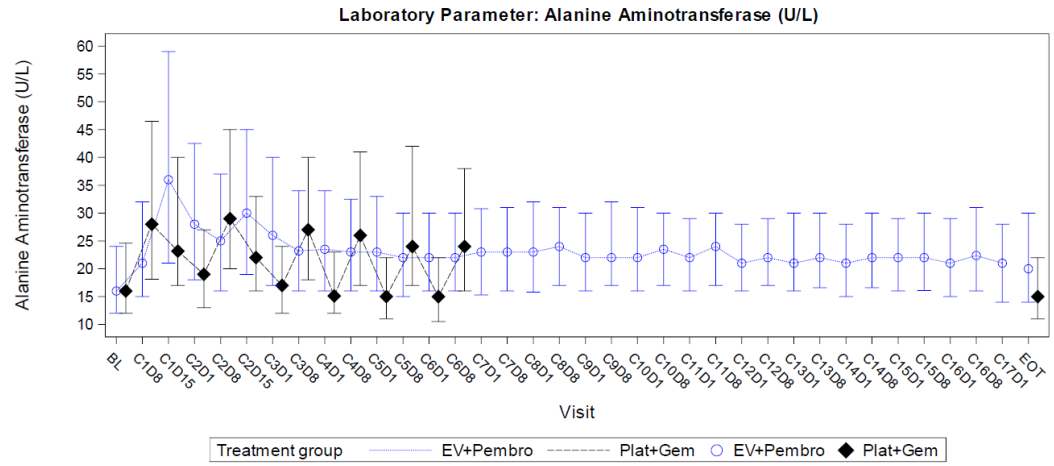
Number of Subjects

EV+Pembro	439	424	377	410	395	347	397	385	372	355	355	338	344	321	320	289	302	271	285	246	265	220	249	195	231	181	218	168	203	147	180	134	166	116	150	205
Plat+Gem	433	393	336	402	379	314	381	354	346	323	293	265	255	227																						366



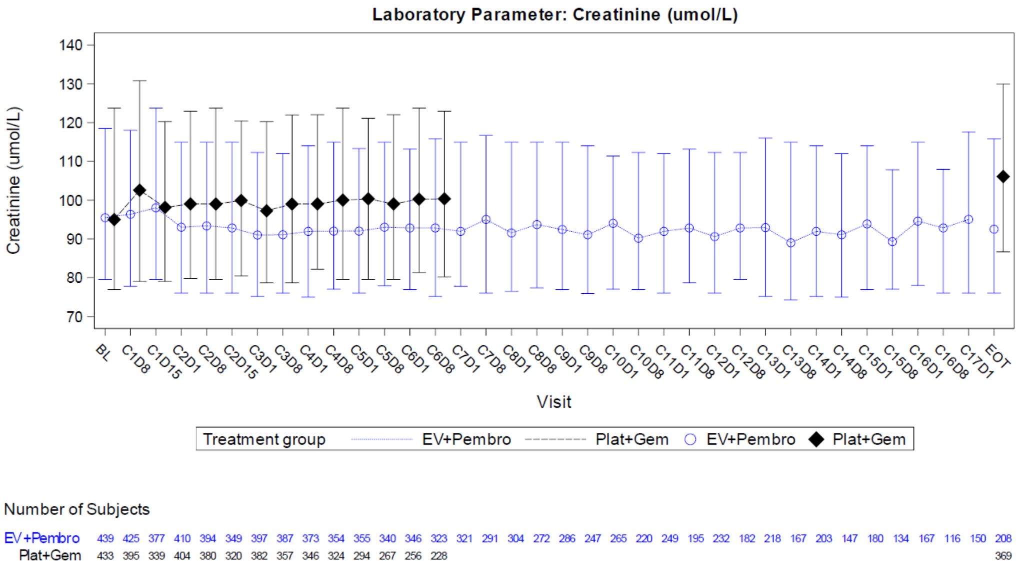
Number of Subjects

EV+Pembro	439	419	373	409	393	346	395	381	368	350	353	337	342	321	314	287	301	271	285	247	263	217	249	195	230	180	216	166	201	147	177	134	167	115	148	207
Plat+Gem	430	389	332	401	374	311	378	352	345	319	289	264	250	224																						364



Number of Subjects

EV+Pembro	439	422	377	410	393	347	397	385	373	355	353	339	345	322	321	290	303	271	286	247	265	220	249	196	232	183	217	167	203	147	180	134	167	116	150	205
Plat+Gem	433	392	336	403	379	313	380	355	348	323	291	265	256	228																						369



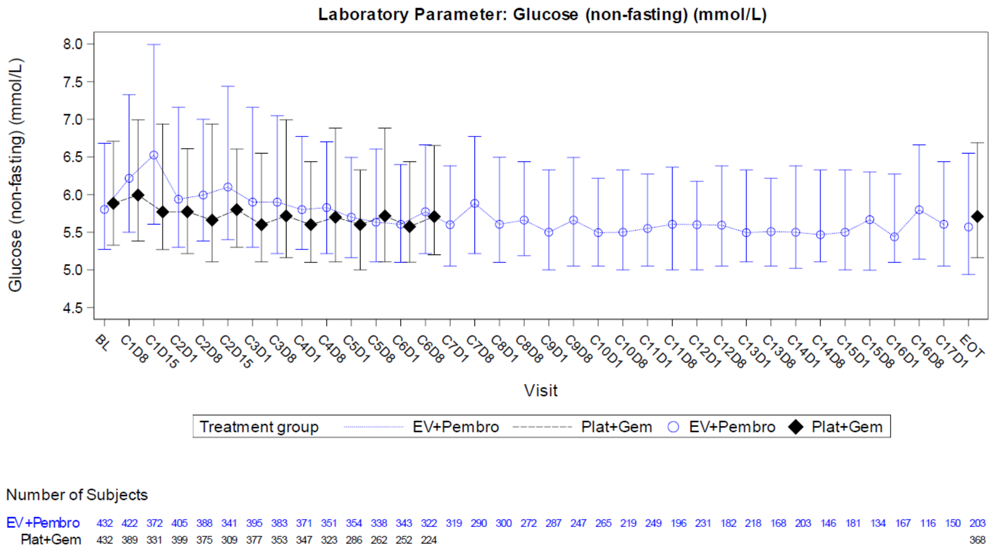


Table 96: Potentially Clinically Significant Values in Liver Enzymes and Total Bilirubin (Safety Analysis Set)

Parameter, n/N (%)	Criteria	EV + Pembro EV-302 (N = 440)	Chemotherapy EV-302 (N = 433)	EV + Pembro Combo ISS (N = 564)	EV Mono ISS (N = 793)	Pembro Bladder Pool (N = 938)
ALT	> 3 x ULN	56/439 (12.8)	37/425 (8.7)	78/563 (13.9)	29/785 (3.7)	62/903 (6.9)
	> 5 x ULN	21/439 (4.8)	14/425 (3.3)	30/563 (5.3)	8/785 (1.0)	30/903 (3.3)
	> 10 x ULN	5/439 (1.1)	7/425 (1.6)	6/563 (1.1)	2/785 (0.3)	12/903 (1.3)
	> 20 x ULN	4/439 (0.9)	2/425 (0.5)	4/563 (0.7)	0/785	5/903 (0.6)
AST	> 3 x ULN	55/438 (12.6)	26/425 (6.1)	81/562 (14.4)	56/784 (7.1)	66/904 (7.3)
	> 5 x ULN	20/438 (4.6)	14/425 (3.3)	31/562 (5.5)	16/784 (2.0)	38/904 (4.2)
	> 10 x ULN	8/438 (1.8)	7/425 (1.6)	9/562 (1.6)	2/784 (0.3)	19/904 (2.1)
	> 20 x ULN	4/438 (0.9)	2/425 (0.5)	4/562 (0.7)	0/784	4/904 (0.4)
ALT or AST	> 3 x ULN	70/439 (15.9)	46/426 (10.8)	98/563 (17.4)	65/785 (8.3)	86/905 (9.5)
	> 5 x ULN	28/439 (6.4)	19/426 (4.5)	42/563 (7.5)	18/785 (2.3)	46/905 (5.1)
	> 10 x ULN	8/439 (1.8)	8/426 (1.9)	10/563 (1.8)	3/785 (0.4)	24/905 (2.7)
	> 20 x ULN	4/439 (0.9)	2/426 (0.5)	4/563 (0.7)	0/785	6/905 (0.7)
Total bilirubin	> 2 x ULN	8/439 (1.8)	6/426 (1.4)	12/563 (2.1)	11/785 (1.4)	38/900 (4.2)
ALP	> 1.5 x ULN	106/439 (24.1)	114/425 (26.8)	140/563 (24.9)	149/785 (19.0)	264/902 (29.3)
ALT and/or AST AND total bilirubin†	ALT and/or AST > 3 x ULN Total bilirubin > 2 x ULN	2/439 (0.5)	2/425 (0.5)	6/563 (1.1)	6/785 (0.8)	18/900 (2.0)
ALT and/or AST AND ALP AND total bilirubin†	ALT and/or AST > 3 x ULN ALP < 2 x ULN Total bilirubin > 2 x ULN	1/439 (0.2)	1/423 (0.2)	2/563 (0.4)	3/785 (0.4)	1/897 (0.1)

Subject's highest post-baseline (including unscheduled visits) value of each parameter was used.

The denominator was the number of subjects who had at least one non-missing post-baseline value.

Combo: combination; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; EV: enfortumab vedotin; ISS: integrated summary of safety; Mono: monotherapy; Pembro: pembrolizumab; ULN: upper limit of normal.

† A combination of values measured within the same day or within 1 day apart.

Safety in special populations

5.1.1 Intrinsic Factors

The safety findings of enfortumab vedotin in combination with pembrolizumab based on intrinsic factors were generally consistent across the analysis groups.

5.1.1.1 Age

The effect of age on the safety of enfortumab vedotin in combination with pembrolizumab was assessed across the analysis groups Overall, there were no clinically meaningful differences observed between age subgroups. (Data not shown)

5.1.1.2 Sex

The effect of sex on the safety of enfortumab vedotin in combination with pembrolizumab was assessed across the analysis groups (Data not shown) Urothelial cancer is more prevalent in males, with approximately 75% of all new cases worldwide occurring in males and 25% in females [Antoni et al, 2017; Ferlay et al, 2015].

Overall, there were no clinically meaningful differences observed between the subgroups of males and females.

5.1.1.3 Race

The effect of race (white vs non-white) on the safety of enfortumab vedotin in combination with pembrolizumab was assessed across the analysis groups (Data not shown).

The majority of subjects in all of the analysis groups were white (>60%). Overall, there were no clinically meaningful differences observed between the subgroups of white and non-white subjects.

5.1.1.4 Ethnicity

The effect of ethnicity (non-Hispanic or Latino vs Hispanic or Latino) on the safety of enfortumab vedotin in combination with pembrolizumab was assessed across the analysis groups (Data not shown)

The number of Hispanic or Latino subjects available for this analysis was small, and there were no clinically meaningful differences observed between the subgroups of non-Hispanic or Latino and Hispanic or Latino.

5.1.1.5 Body Mass Index

The effect of BMI (< 30 kg/m2 or ≥ 30 kg/m2) on the safety of enfortumab vedotin in combination with pembrolizumab was assessed across the analysis groups (Data not shown).

There was a higher incidence of hyperglycemia events, serious TEAEs, drug related serious TEAEs and TEAEs leading to withdrawal by subjects with a BMI of ≥ 30 kg/m2 across the analysis populations compared with subjects with BMI < 30 kg/m2.

5.1.1.6 Renal Function Based on Estimated Creatinine Clearance

The effect of renal function based on estimated creatinine clearance (CrCl; normal, mild, moderate or severe insufficiency) on the safety of enfortumab vedotin in combination with pembrolizumab was assessed across the analysis groups (Data not shown) The assessment of renal impairment was based on estimated CrCl at baseline as determined using the Cockcroft-Gault Formula [Cockcroft and Gault, 1976].

Overall, there were no clinically meaningful differences observed between the renal function subgroups.

5.1.1.7 Hepatic Function

The effect of hepatic function (normal or mild hepatic insufficiency) on the safety of enfortumab vedotin in combination with pembrolizumab was assessed across the analysis groups(Data not shown)

The number of subjects with mild hepatic dysfunction was small (range: 8.9% to 10.9% across analysis groups and there were no clinically meaningful differences observed in the safety profile between the subgroups of hepatic function.

5.1.2 Baseline Characteristics

5.1.2.1 ECOG Performance Status

The effect of ECOG performance status at baseline on the safety of enfortumab vedotin in combination with pembrolizumab was assessed across the analysis groups (Data not shown)

Overall, there were no differences observed between the subgroups of ECOG performance status that were considered to be clinically meaningful.

5.1.2.2 Liver Metastases

The effect of the presence of a liver metastasis at baseline on the safety of enfortumab vedotin in combination with pembrolizumab was assessed across the analysis groups (Data not shown)

Overall, there were no differences observed that were considered clinically meaningful between the subgroups of subjects who had liver metastasis at baseline compared with subjects who did not have liver metastasis at baseline. **5.1.3 Extrinsic Factors**

5.1.3.1 Geographical Region

The effect of geographical region (Europe, North America, Rest of the World) on the safety of enfortumab vedotin in combination with pembrolizumab was assessed across the analysis groups (Data not shown).

Overall, there were no clinically meaningful differences observed between the geographical region subgroups.

5.1.4 Conclusion: Subgroup Analyses

Based on analyses to assess incidences of TEAEs for intrinsic and extrinsic factors and some additional prespecified demographic subgroups and disease characteristics, there was little impact of these factors on the safety of enfortumab vedotin in combination with pembrolizumab. Therefore, no specific safety precautions are warranted in the subgroups analyzed.

Safety related to drug-drug interactions and other interactions

Safety related to drug-drug interactions and other interactions

Enfortumab Vedotin

No new DDI studies were conducted for this submission. No effect of pembrolizumab on the PK and immunogenicity of enfortumab vedotin and unconjugated MMAE was observed.

Pembrolizumab

As pembrolizumab is an IgG antibody that is administered parenterally and cleared by catabolism, food and drug-drug interactions are not anticipated to influence exposure.

Use in Pregnancy and Lactation

Enfortumab Vedotin

No additional pregnancy and lactation data are available as of the safety data cutoff for EV-302. No pregnancies have been reported during clinical studies of enfortumab vedotin.

Pembrolizumab

No additional pregnancy and lactation data are available as of the safety data cutoff for EV-302.

Overdose

Enfortumab Vedotin

In Study EV-302, an important protocol deviation of enfortumab vedotin overdose occurred in 3 subjects in the EV + Pembro Arm; 2 due to the dose not being adjusted after the subject experienced a > 10% change in weight and 1 due to dose reduction information being overlooked by the pharmacist. In study EV-103, there were 3 important protocol deviations on overdose because the maximum weight of 100 kg was not used in the dose calculation. None of these overdoses resulted in a safety issue.

Neither the effects of overdose of enfortumab vedotin nor an antidote to overdose are known.

Pembrolizumab

An overdose of pembrolizumab (MK-3475) is defined as 1,000 mg or greater (≥ 5 x the indicated dose). No overdose of pembrolizumab occurred during study EV-103 or EV-302.

Discontinuation, dose reductions and interruptions due to adverse events

Table 97: Treatment-emergent Adverse Events Leading to Permanent Withdrawal of Treatment in > 1% of Subjects in EV + Pembro Combo ISS by SOC and Preferred Term (Safety Analysis Set)

Parameter, n (%)	EV + Pembro EV-302 (N = 440)		Chemotherapy EV-302 (N = 433)		EV + Pembro Combo ISS (N = 564)		EV Mono ISS (N = 793)		Pembro Bladder Pool (N = 938)		Pembro RSD (N = 7631)	
	All	Drug-related†	All	Drug-related†	All	Drug-related†	All	Drug-related†	All	Drug-related†	All	Drug-related†
Overall	**175 (39.8)**	**154 (35.0)**	**93 (21.5)**	**80 (18.5)**	**238 (42.2)**	**214 (37.9)**	**166 (20.9)**	**118 (14.9)**	**137 (14.6)**	**77 (8.2)**	**1066 (14.0)**	**639 (8.4)**
Gastrointestinal Disorders	**10 (2.3)**	**7 (1.6)**	**4 (0.9)**	**4 (0.9)**	**13 (2.3)**	**10 (1.8)**	**6 (0.8)**	**2 (0.3)**	**14 (1.5)**	**10 (1.1)**	**116 (1.5)**	**87 (1.1)**
Diarrhoea	5 (1.1)	4 (0.9)	1 (0.2)	1 (0.2)	7 (1.2)	6 (1.1)	0	0	3 (0.3)	3 (0.3)	19 (0.2)	17 (0.2)
General Disorders and Administration Site Conditions	**9 (2.0)**	**8 (1.8)**	**8 (1.8)**	**6 (1.4)**	**13 (2.3)**	**12 (2.1)**	**13 (1.6)**	**10 (1.3)**	**14 (1.5)**	**6 (0.6)**	**94 (1.2)**	**31 (0.4)**
Asthenia	4 (0.9)	4 (0.9)	0	0	6 (1.1)	6 (1.1)	1 (0.1)	1 (0.1)	0	0	5 (0.1)	1 (0.0)
Nervous System Disorders	**71 (16.1)**	**66 (15.0)**	**2 (0.5)**	**1 (0.2)**	**103 (18.3)**	**98 (17.4)**	**57 (7.2)**	**52 (6.6)**	**5 (0.5)**	**3 (0.3)**	**64 (0.8)**	**29 (0.4)**
Peripheral sensory neuropathy	49 (11.1)	47 (10.7)	1 (0.2)	1 (0.2)	69 (12.2)	67 (11.9)	38 (4.8)	36 (4.5)	0	0	2 (0.0)	2 (0.0)
Peripheral motor neuropathy	3 (0.7)	3 (0.7)	0	0	8 (1.4)	8 (1.4)	7 (0.9)	7 (0.9)	0	0	0	0
Paraesthesia	6 (1.4)	6 (1.4)	0	0	6 (1.1)	6 (1.1)	2 (0.3)	2 (0.3)	0	0	0	0
Peripheral sensorimotor neuropathy	4 (0.9)	4 (0.9)	0	0	6 (1.1)	6 (1.1)	2 (0.3)	2 (0.3)	0	0	0	0
Respiratory, Thoracic and Mediastinal Disorders	**22 (5.0)**	**20 (4.5)**	**2 (0.5)**	**0**	**28 (5.0)**	**26 (4.6)**	**13 (1.6)**	**6 (0.8)**	**20 (2.1)**	**17 (1.8)**	**216 (2.8)**	**144 (1.9)**
Pneumonitis	9 (2.0)	9 (2.0)	0	0	15 (2.7)	15 (2.7)	2 (0.3)	2 (0.3)	15 (1.6)	14 (1.5)	115 (1.5)	113 (1.5)
Immune-mediated lung disease	6 (1.4)	6 (1.4)	0	0	6 (1.1)	6 (1.1)	0	0	0	0	3 (0.0)	3 (0.0)
Skin and Subcutaneous Tissue Disorders	**30 (6.8)**	**30 (6.8)**	**1 (0.2)**	**1 (0.2)**	**42 (7.4)**	**42 (7.4)**	**25 (3.2)**	**25 (3.2)**	**7 (0.7)**	**7 (0.7)**	**44 (0.6)**	**40 (0.5)**
Rash maculo-papular	7 (1.6)	7 (1.6)	0	0	13 (2.3)	13 (2.3)	6 (0.8)	6 (0.8)	0	0	1 (0.0)	1 (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 in the EV + Pembro Combo ISS analysis group by PT. In case of ties, alphabetical order by PT was applied.
Combo: combination; EV: enfortumab vedotin; ISS: integrated summary of safety; Mono: monotherapy; Pembro: pembrolizumab; PT: preferred term; RSD: reference safety data.
† Adverse events related to study drug (either EV, Chemotherapy or Pembro related) as assessed by the investigator are shown. Missing relationship was considered as related in EV studies only

Table 98: Treatment-emergent Adverse Events Leading to Dose Reduction in > 1% of Subjects in EV + Pembro Combo ISS by SOC and Preferred Term (Safety Analysis Set)

Parameter, n (%)	EV + Pembro EV-302 (N = 440)		Chemotherapy EV-302 (N = 433)		EV + Pembro Combo ISS (N = 564)		EV Mono ISS (N = 793)	
	All	Drug-related†	All	Drug-related†	All	Drug-related†	All	Drug-related†
Overall	**184 (41.8)**	**179 (40.7)**	**177 (40.9)**	**164 (37.9)**	**239 (42.4)**	**232 (41.1)**	**301 (38.0)**	**286 (36.1)**
Blood and Lymphatic System Disorders	**10 (2.3)**	**10 (2.3)**	**100 (23.1)**	**98 (22.6)**	**17 (3.0)**	**17 (3.0)**	**22 (2.8)**	**20 (2.5)**
Neutropenia	6 (1.4)	6 (1.4)	39 (9.0)	39 (9.0)	12 (2.1)	12 (2.1)	12 (1.5)	12 (1.5)
Gastrointestinal Disorders	**21 (4.8)**	**21 (4.8)**	**7 (1.6)**	**7 (1.6)**	**27 (4.8)**	**27 (4.8)**	**24 (3.0)**	**24 (3.0)**
Diarrhoea	8 (1.8)	8 (1.8)	1 (0.2)	1 (0.2)	13 (2.3)	13 (2.3)	9 (1.1)	9 (1.1)
General Disorders and Administration Site Conditions	**18 (4.1)**	**17 (3.9)**	**23 (5.3)**	**20 (4.6)**	**25 (4.4)**	**24 (4.3)**	**53 (6.7)**	**50 (6.3)**
Fatigue	12 (2.7)	11 (2.5)	17 (3.9)	16 (3.7)	18 (3.2)	17 (3.0)	42 (5.3)	40 (5.0)
Asthenia	6 (1.4)	6 (1.4)	4 (0.9)	4 (0.9)	7 (1.2)	7 (1.2)	4 (0.5)	4 (0.5)
Nervous System Disorders	**60 (13.6)**	**60 (13.6)**	**3 (0.7)**	**3 (0.7)**	**81 (14.4)**	**81 (14.4)**	**114 (14.4)**	**112 (14.1)**
Peripheral sensory neuropathy	38 (8.6)	38 (8.6)	2 (0.5)	2 (0.5)	56 (9.9)	56 (9.9)	82 (10.3)	81 (10.2)
Skin and Subcutaneous Tissue Disorders	**80 (18.2)**	**77 (17.5)**	**1 (0.2)**	**1 (0.2)**	**96 (17.0)**	**93 (16.5)**	**87 (11.0)**	**86 (10.8)**
Rash maculo-papular	26 (5.9)	25 (5.7)	0	0	36 (6.4)	35 (6.2)	33 (4.2)	33 (4.2)
Rash macular	7 (1.6)	7 (1.6)	1 (0.2)	1 (0.2)	9 (1.6)	9 (1.6)	2 (0.3)	2 (0.3)
Eczema	8 (1.8)	8 (1.8)	0	0	8 (1.4)	8 (1.4)	4 (0.5)	4 (0.5)
Pruritis	6 (1.4)	6 (1.4)	0	0	8 (1.4)	8 (1.4)	10 (1.3)	10 (1.3)
Dermatitis	7 (1.6)	7 (1.6)	0	0	7 (1.2)	7 (1.2)	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 in the EV + Pembro Combo ISS analysis group by PT. In case of ties, alphabetical order by PT was applied.
Combo: combination; EV: enfortumab vedotin; ISS: integrated summary of safety; Mono: monotherapy; Pembro: pembrolizumab; PT: preferred term; RSD: reference safety data.
† Adverse events related to study drug (either EV, Chemotherapy or Pembro related) as assessed by the investigator are shown. Missing relationship was considered as related in EV studies only

Table 99: Treatment-emergent Adverse Events Leading to Dose Interruption in > 1% of Subjects in EV + Pembro Combo ISS by SOC and Preferred Term (Safety Analysis Set)

	EV + Pembro EV-302 (N = 440)		Chemotherapy EV-302 (N = 433)		EV + Pembro Combo ISS (N = 564)		EV Mono ISS (N = 793)		Pembro Bladder Pool (N = 938)		Pembro RSD (N = 7631)	
Parameter, n (%)	**All**	**Drug-related†**	**All**	**Drug-related†**	**All**	**Drug-related†**	**All**	**Drug-related†**	**All**	**Drug-related†**	**All**	**Drug-related†**
Overall	**347 (78.9)**	**299 (68.0)**	**279 (64.4)**	**229 (52.9)**	**448 (79.4)**	**385 (68.3)**	**495 (62.4)**	**404 (50.9)**	**276 (29.4)**	**146 (15.6)**	**1993 (26.1)**	**1119 (14.7)**
Blood and Lymphatic System Disorders	**35 (8.0)**	**29 (6.6)**	**162 (37.4)**	**158 (36.5)**	**48 (8.5)**	**39 (6.9)**	**48 (6.1)**	**39 (4.9)**	**12 (1.3)**	**5 (0.5)**	**82 (1.1)**	**30 (0.4)**
Neutropenia	18 (4.1)	18 (4.1)	96 (22.2)	95 (21.9)	26 (4.6)	26 (4.6)	15 (1.9)	14 (1.8)	1 (0.1)	1 (0.1)	6 (0.1)	5 (0.1)
Anaemia	10 (2.3)	4 (0.9)	59 (13.6)	55 (12.7)	14 (2.5)	6 (1.1)	25 (3.2)	19 (2.4)	9 (1.0)	2 (0.2)	60 (0.8)	19 (0.2)
Thrombocytopenia	5 (1.1)	5 (1.1)	39 (9.0)	38 (8.8)	6 (1.1)	5 (0.9)	8 (1.0)	7 (0.9)	1 (0.1)	1 (0.1)	9 (0.1)	4 (0.1)
Gastrointestinal Disorders	**54 (12.3)**	**44 (10.0)**	**22 (5.1)**	**16 (3.7)**	**66 (11.7)**	**53 (9.4)**	**62 (7.8)**	**38 (4.8)**	**52 (5.5)**	**29 (3.1)**	**358 (4.7)**	**222 (2.9)**
Diarrhoea	27 (6.1)	26 (5.9)	2 (0.5)	1 (0.2)	34 (6.0)	32 (5.7)	22 (2.8)	17 (2.1)	19 (2.0)	14 (1.5)	163 (2.1)	114 (1.5)
General Disorders and Administration Site Conditions	**43 (9.8)**	**30 (6.8)**	**45 (10.4)**	**23 (5.3)**	**57 (10.1)**	**42 (7.4)**	**109 (13.7)**	**85 (10.7)**	**25 (2.7)**	**12 (1.3)**	**238 (3.1)**	**116 (1.5)**
Fatigue	21 (4.8)	18 (4.1)	16 (3.7)	15 (3.5)	29 (5.1)	26 (4.6)	59 (7.4)	57 (7.2)	10 (1.1)	7 (0.7)	73 (1.0)	51 (0.7)
Pyrexia	10 (2.3)	0	13 (3.0)	3 (0.7)	11 (2.0)	1 (0.2)	14 (1.8)	2 (0.3)	2 (0.2)	0	53 (0.7)	8 (0.1)
Asthenia	8 (1.8)	7 (1.6)	8 (1.8)	4 (0.9)	9 (1.6)	8 (1.4)	11 (1.4)	7 (0.9)	2 (0.2)	1 (0.1)	29 (0.4)	15 (0.2)
Infections and Infestations	**109 (24.8)**	**9 (2.0)**	**66 (15.2)**	**15 (3.5)**	**132 (23.4)**	**12 (2.1)**	**112 (14.1)**	**27 (3.4)**	**72 (7.7)**	**10 (1.1)**	**471 (6.2)**	**66 (0.9)**
COVID-19	51 (11.6)	0	9 (2.1)	0	57 (10.1)	0	10 (1.3)	0	0	0	2 (0.0)	0
Pneumonia	14 (3.2)	2 (0.5)	4 (0.9)	1 (0.2)	16 (2.8)	2 (0.4)	15 (1.9)	5 (0.6)	9 (1.0)	1 (0.1)	110 (1.4)	14 (0.2)
Urinary tract infection	10 (2.3)	0	25 (5.8)	6 (1.4)	14 (2.5)	1 (0.2)	20 (2.5)	4 (0.5)	18 (1.9)	1 (0.1)	29 (0.4)	2 (0.0)
Upper respiratory tract infection	7 (1.6)	0	0	0	9 (1.6)	0	5 (0.6)	0	2 (0.2)	0	50 (0.7)	6 (0.1)
Cellulitis	3 (0.7)	2 (0.5)	0	0	6 (1.1)	3 (0.5)	8 (1.0)	5 (0.6)	2 (0.2)	1 (0.1)	7 (0.1)	2 (0.0)
Investigations	**44 (10.0)**	**40 (9.1)**	**59 (13.6)**	**54 (12.5)**	**64 (11.3)**	**58 (10.3)**	**105 (13.2)**	**87 (11.0)**	**42 (4.5)**	**26 (2.8)**	**290 (3.8)**	**179 (2.3)**
Alanine aminotransferase increased	18 (4.1)	18 (4.1)	6 (1.4)	5 (1.2)	23 (4.1)	23 (4.1)	25 (3.2)	23 (2.9)	12 (1.3)	11 (1.2)	106 (1.4)	69 (0.9)
Lipase increased	3 (0.7)	2 (0.5)	0	0	11 (2.0)	10 (1.8)	9 (1.1)	8 (1.0)	1 (0.1)	1 (0.1)	13 (0.2)	11 (0.1)
Neutrophil count decreased	7 (1.6)	7 (1.6)	34 (7.9)	33 (7.6)	9 (1.6)	9 (1.6)	24 (3.0)	24 (3.0)	1 (0.1)	1 (0.1)	2 (0.0)	2 (0.0)
Aspartate aminotransferase increased	6 (1.4)	6 (1.4)	1 (0.2)	1 (0.2)	7 (1.2)	7 (1.2)	27 (3.4)	24 (3.0)	7 (0.7)	7 (0.7)	98 (1.3)	62 (0.8)
Blood creatinine increased	6 (1.4)	5 (1.1)	8 (1.8)	5 (1.2)	6 (1.1)	5 (0.9)	12 (1.5)	5 (0.6)	6 (0.6)	3 (0.3)	27 (0.4)	13 (0.2)
Metabolism and Nutrition Disorders	**36 (8.2)**	**26 (5.9)**	**11 (2.5)**	**7 (1.6)**	**48 (8.5)**	**34 (6.0)**	**67 (8.4)**	**46 (5.8)**	**35 (3.7)**	**19 (2.0)**	**181 (2.4)**	**84 (1.1)**
Hyperglycaemia	17 (3.9)	14 (3.2)	0	0	21 (3.7)	17 (3.0)	25 (3.2)	16 (2.0)	2 (0.2)	2 (0.2)	14 (0.2)	9 (0.1)
Hyponatraemia	5 (1.1)	4 (0.9)	5 (1.2)	2 (0.5)	7 (1.2)	5 (0.9)	9 (1.1)	6 (0.8)	3 (0.3)	3 (0.3)	29 (0.4)	13 (0.2)
Hypokalaemia	4 (0.9)	1 (0.2)	0	0	6 (1.1)	3 (0.5)	2 (0.3)	2 (0.3)	3 (0.3)	1 (0.1)	10 (0.1)	5 (0.1)
Nervous System Disorders	**113 (25.7)**	**104 (23.6)**	**4 (0.9)**	**2 (0.5)**	**157 (27.8)**	**146 (25.9)**	**176 (22.2)**	**166 (20.9)**	**12 (1.3)**	**4 (0.4)**	**109 (1.4)**	**35 (0.5)**
Peripheral sensory neuropathy	79 (18.0)	78 (17.7)	1 (0.2)	1 (0.2)	112 (19.9)	111 (19.7)	117 (14.8)	115 (14.5)	0	0	1 (0.0)	1 (0.0)
Peripheral sensorimotor neuropathy	10 (2.3)	10 (2.3)	0	0	14 (2.5)	14 (2.5)	7 (0.9)	7 (0.9)	0	0	0	0
Peripheral motor neuropathy	8 (1.8)	8 (1.8)	0	0	11 (2.0)	11 (2.0)	17 (2.1)	16 (2.0)	0	0	0	0
Paraesthesia	6 (1.4)	6 (1.4)	0	0	6 (1.1)	6 (1.1)	5 (0.6)	5 (0.6)	2 (0.2)	0	5 (0.1)	1 (0.0)
Renal and Urinary Disorders	**16 (3.6)**	**7 (1.6)**	**22 (5.1)**	**13 (3.0)**	**26 (4.6)**	**9 (1.6)**	**43 (5.4)**	**11 (1.4)**	**43 (4.6)**	**5 (0.5)**	**81 (1.1)**	**26 (0.3)**
Acute kidney injury	9 (2.0)	4 (0.9)	11 (2.5)	10 (2.3)	14 (2.5)	4 (0.7)	23 (2.9)	7 (0.9)	13 (1.4)	0	21 (0.3)	4 (0.1)
Respiratory, Thoracic and Mediastinal Disorders	**42 (9.5)**	**30 (6.8)**	**9 (2.1)**	**3 (0.7)**	**52 (9.2)**	**37 (6.6)**	**28 (3.5)**	**15 (1.9)**	**37 (3.9)**	**19 (2.0)**	**305 (4.0)**	**160 (2.1)**
Pneumonitis	16 (3.6)	16 (3.6)	1 (0.2)	0	23 (4.1)	23 (4.1)	4 (0.5)	4 (0.5)	14 (1.5)	13 (1.4)	99 (1.3)	92 (1.2)
Skin and Subcutaneous Tissue Disorders	**119 (27.0)**	**119 (27.0)**	**1 (0.2)**	**1 (0.2)**	**148 (26.2)**	**144 (25.5)**	**105 (13.2)**	**102 (12.9)**	**26 (2.8)**	**24 (2.6)**	**166 (2.2)**	**145 (1.9)**
Rash maculo-papular	43 (9.8)	42 (9.5)	0	0	57 (10.1)	55 (9.8)	32 (4.0)	31 (3.9)	2 (0.2)	2 (0.2)	32 (0.4)	29 (0.4)
Pruritus	14 (3.2)	14 (3.2)	0	0	16 (2.8)	16 (2.8)	11 (1.4)	11 (1.4)	6 (0.6)	5 (0.5)	22 (0.3)	20 (0.3)
Dermatitis bullous	9 (2.0)	9 (2.0)	1 (0.2)	1 (0.2)	13 (2.3)	12 (2.1)	6 (0.8)	5 (0.6)	1 (0.1)	1 (0.1)	2 (0.0)	2 (0.0)
Rash macular	11 (2.5)	11 (2.5)	0	0	13 (2.3)	13 (2.3)	2 (0.3)	2 (0.3)	0	0	1 (0.0)	1 (0.0)
Dermatitis	8 (1.8)	8 (1.8)	0	0	9 (1.6)	8 (1.4)	2 (0.3)	2 (0.3)	1 (0.1)	1 (0.1)	5 (0.1)	3 (0.0)
Eczema	8 (1.8)	8 (1.8)	0	0	8 (1.4)	8 (1.4)	2 (0.3)	2 (0.3)	0	0	2 (0.0)	2 (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 in the EV + Pembro Combo ISS analysis group by PT. In case of ties, alphabetical order by PT was applied.
Combo: combination; EV: enfortumab vedotin; ISS: integrated summary of safety; Mono: monotherapy; Pembro: pembrolizumab; PT: preferred term; RSD: reference safety data.
† Adverse events related to study drug (either EV, Chemotherapy or Pembro related) as assessed by the investigator are shown. Missing relationship was considered as related in EV studies only.

Post marketing experience

Enfortumab Vedotin

Enfortumab vedotin was first approved for marketing in the US on 18 December 2019 under accelerated approval, and regular approval was granted on 09 July 2021. In Europe Enfortumab vedotin was approved in April 2022. The safety profile of enfortumab vedotin was most recently described in the Periodic Safety Update Report covering the period of 18 December 2022 through 17 June 2023. The cumulative number of patients receiving enfortumab vedotin since the launch of the product through 17 June 2023 is estimated as 29 778 patients.

There are no records of any enfortumab vedotin registration being revoked or withdrawn for safety reasons in any country. The overall safety profile remains favorable.

2.5.1. Discussion on clinical safety

The primary safety population for the evaluation of EV plus pembrolizumab in the intended clinical setting is considered to be the EV + Pembro Combo ISS pool of 564 patients: 440 from Arm A of study EV-302 and 3 patients from the run-in of this study as well as 121 patients from study EV-103 (40 from Cohort A and 81 from Cohort K). Despite mixing both platinum-eligible and cisplatin-ineligible patients with advanced urothelial cancer, all received EV and Pembro at the recommended dose and scheme. This is also the safety population presented in the SmPC and the size is considered sufficient for an evaluation of safety for the applied extension of indication.

The median exposure for the EV + Pembro EV-302 Arm and primary safety pool (both 9.43 months) was longer than that for the Chemotherapy EV-302 Arm (4.14 months), which is not unexpected, given that the recommended treatment for the Chemotherapy arm is 6 cycles given every 3 weeks, continuous until progression for EV, and up to 35 cycles for Pembro (given every 3 weeks).

As expected, differences in the safety profile of the EV + Pembro EV-302 Arm compared to the Chemotherapy EV-302 Arm were observed due to the different mechanisms of action of these agents, the distinct profile of known risks and the longer duration of exposure in the EV + Pembro EV-302 Arm. This longer treatment resulting in more AEs is only meaningful if there is a clear survival benefit and the AEs are considered tolerable by the patient. Baseline demographics were generally consistent across the analysis populations.

The safety profile for the EV+Pembro combination was generally consistent with that for enfortumab vedotin and pembrolizumab monotherapy:

The most common AEs reported at a higher frequency (> 10% difference) in the EV + Pembro EV-302 arm compared to the Chemotherapy EV-302 arm were peripheral sensory neuropathy (52.0% vs 10.2%), pruritus (41.4% vs 6.7%), maculo-papular rash (33.2% vs 3.5%) and diarrhea (37.7% vs 15.9%). These AEs are well-known for EV and/or Pembro, and the differences are clearly reflected in the corresponding SOCs with for instance Skin and Subcutaneous Tissue Disorders, having a frequency of 83.2% compared to 25.9% in the Chemotherapy arm and AEs in the SOC Blood and Lymphatic System Disorders being clearly higher in the Chemotherapy arm (35.7% vs 78.5%, respectively).

The frequencies of ≥Grade 3 AEs were comparable between the arms in study 302 and reflected the differences seen for common AEs with marked higher frequencies for the SOCs Skin and Subcutaneous Disorders, Nervous System Disorders, and Metabolism and Nutrition Disorders (mainly PT hyperglycaemia) for EV+Pembro, and Blood and Lymphatic Disorders for the chemotherapy arm. Although pneumonitis/ILD "only" had a frequency of 3.5% in the primary EV+Pembro safety pool this is markedly higher than in the chemotherapy arm (0.2%) of study EV-302.

The common AEs and ≥Grade 3 AEs by PT were generally similar between the EV + Pembro EV-302 arm and the primary safety population (EV + Pembro Combo ISS analysis pool).

The adverse reactions when combining EV with Pembro are presented in a separate column to the EV monotherapy adverse reactions in the SmPC, and a reference is made to the Pembro SmPC, as all known Pembro-related AEs cannot be expected to have been observed.

The incidences of SAEs and AEs leading to discontinuation were higher in the EV + Pembro EV-302 Arm, with the latter generally being consistent with the primary safety population. Generally, the serious adverse events observed were consistent with the known adverse events of special interest for

enfortumab vedotin, pembrolizumab or both drugs. Not unexpectedly, the AE leading to permanent withdrawal that occurred more frequently (> 10% difference) in the EV + Pembro Combo ISS analysis pool compared to the Pembro RSD analysis group was peripheral sensory neuropathy (12.2% vs 0%, respectively), which is a well-known AESI for EV. Generally, the incidence of AEs leading to discontinuation, was higher in the combination as compared with EV monotherapy or Pembro monotherapy.

Based on the inclusion and exclusion criteria, patients were expected to have a certain level of fitness nevertheless there was a marked difference in the SAE frequencies between the population <65 years of age and those above (35.3% compared to 56.3%, respectively in the primary safety population of n=564), which is reflected in the SmPC.

The frequency of AEs leading to death were similar between the two arms in study EV-302 and the primary safety population (EV + Pembro Combo pool). Given that exposure was longer in the EV+Pembro pool this is reassuring. No PTs were reported in more than 2 patients in the primary safety pool and no new PTs were identified.

The frequencies of the AESIs skin reactions and severe cutaneous adverse reactions were similar between the EV + Pembro Combo ISS and EV Mono ISS analysis groups implying that these are mainly EV-related. All of the serious severe cutaneous adverse reactions were considered drug-related by the investigator.

Pneumonitis/ILD, is a known risk for both EV and Pembro. In line with this, the frequency was higher in the EV + Pembro Combo ISS analysis pool compared to the EV monotherapy pool and the Pembro Bladder pool.

Peripheral neuropathy is a well-known high-frequency AE for EV and is also observed for Pembro to a lesser extent. The frequency of peripheral neuropathy observed in the EV + Pembro Combo ISS analysis pool was higher than that observed in the EV Mono ISS analysis pool, well explained by the addition of Pembro, for which this is listed as a Common ADR in the SmPC. The frequency of SAEs in any pool was low.

Patient information pack

The prescriber must discuss the risks of Padcev therapy, including combination therapy with pembrolizumab, with the patient. The patient should be provided with the patient information leaflet and patient card with each prescription.

2.5.2. Conclusions on clinical safety

The safety profile for enfortumab vedotin in combination with pembrolizumab remained generally consistent with the known safety profiles for enfortumab vedotin and pembrolizumab. No new safety signals were identified. As expected, classical chemotherapy-related AEs occurred less frequently with EV+Pembro, but a higher proportion of patients presented peripheral neuropathy, skin reactions (mostly maculo-papular rash), diarrhoea, and hyperglycemia. Regarding high-grade or serious events, ILD/pneumonitis seems to be the main risk from the novel combination, but this has been reflected in the SmPC.

2.5.3. PSUR cycle

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.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3.1 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 3.1 with the following content

Safety concerns

Summary of safety concerns	
Important identified risks	• Skin reactions • Hyperglycemia • Pneumonitis/Interstitial lung disease
Important potential risks	None
Missing information	None

Pharmacovigilance plan

Table 100: Table Part III.1: 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				
Category 3 - Required additional pharmacovigilance activities				
Protocol 7465-PV-0002 A non-interventional post authorization safety study (NI-PASS) to evaluate effectiveness of the patient card (Ongoing)	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	Submission of final report to EMA	Q4 2024

Risk minimisation measures

Table 101: Table Part V.3: Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Skin reactions	Routine risk communication: • EU-SmPC sections 4.2, 4.4 and 4.8; • PL sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • 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 first sign of a severe skin reaction, and patients should be observed, if this occurs. - 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. - 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. - Permanently discontinue enfortumab vedotin for confirmed SJS or TEN, Grade 4 or recurrent severe skin reactions. • Recommendations are provided in the EU-SmPC Section 4.2 for treatment interruption, dose reduction and treatment discontinuation of enfortumab vedotin. Additional risk minimization measures: • Patient card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • 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.
Hyperglycemia	Routine risk communication: • EU-SmPC sections 4.2, 4.4 and 4.8 • PL section 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • 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 hyperglycemia. If blood glucose is elevated >13.9 mmol/L (>250 mg/dL), enfortumab vedotin should be withheld until blood glucose is ≤13.9	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	mmol/L (≤250 mg/dL) and treat as appropriate. • Recommendations are provided in EU-SmPC Section 4.2 for treatment interruption and when to resume treatment of enfortumab vedotin. Additional risk minimization measures: • None	
Pneumonitis/Interstitial lung disease	Routine risk communication: • EU-SmPC sections 4.2, 4.4 and 4.8; • PL sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: - For Grade 2 pneumonitis/interstitial lung disease, withhold enfortumab vedotin until Grade ≤1, then resume at the same dose level or consider dose reduction by one dose level. -Permanently discontinue enfortumab vedotin for Grade ≥3 pneumonitis/interstitial lung disease Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

EU-SmPC: European Union-Summary of Product Characteristics; NI-PASS: Non-interventional Post-Authorization Safety Studies; PL: Package Leaflet; SJS: Stevens Johnson Syndrome; TEN: Toxic Epidermal Necrolysis.

2.7. Update of the Product information

As a consequence of this new indication, 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Padcev (initial submission). The bridging report submitted by the MAH has been found acceptable.

2.7.2. 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 is a biological product that is not covered by the previous category and authorised after 1 January 2011.

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 final agreed indication is:

Padcev, in combination with pembrolizumab, is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy.

3.1.2. Available therapies and unmet medical need

Established guidelines recommend the use of cisplatin or carboplatin in combination with gemcitabine or other anti-cancer agents for patients who receive first-line treatment for LA/mUC and can tolerate these regimens (Koufopoulou et al, 2020). Platinum-containing therapy may be followed by avelumab maintenance for a subset of patients who have not progressed following chemotherapy (Jackson-Spence et al, 2022). For patients who are not eligible for cisplatin-containing chemotherapy, checkpoint inhibitors such as pembrolizumab or atezolizumab in monotherapy can be considered, noting that in Europe, such indications are restricted based on tumoural PD-L1 expression.

The proportion of patients with LA/mUC who receive first-line therapy in Europe is 45% to 85% and many patients with advanced UC never receive first-line therapy [Morgans et al, 2023; Niegisch et al, 2023; Puente et al, 2023; Aly et al, 2019; Flannery et al, 2019; Galsky et al, 2018]. Overall median survival for patients who receive any type of first-line treatment is 10.8 to 14.5 months [Morgans et al, 2023; Geynisman et al, 2022; Flannery et al, 2019]. After receiving their initial therapy, < 50% of LA/mUC patients will receive second-line therapy, with mortality reported as a common reason that patients do not proceed to second-line therapy [Morgans et al, 2023].

The relatively short duration of survival associated with first-line therapy outlined above, combined with the finding that some patients never receive first-line therapy and many refuse or are unable to receive subsequent therapy, highlight the need for more effective and tolerable first-line treatment options. Very few recent advancements have improved outcomes for patients with LA/mUC. Furthermore, even with the currently available first line regimens, including avelumab maintenance, there remains a high unmet medical need for this disease.

3.1.3. Main clinical studies

EV-302 (KEYNOTE-A39) is an open-label, phase III trial that randomised 1:1 platinum-eligible patients with advanced urothelial cancer to EV+Pembro or standard-of-care platinum-based chemotherapy (either cisplatin or carboplatin + gemcitabine, i.e. Plat+Gem). Randomisation was stratified based on cisplatin eligibility, presence of liver metastases and PD-L1 status by 22C3 assay (CPS ≥10 or <10). Crossover was not allowed. The primary endpoints were OS and PFS assessed by blinded independent review in the ITT population. Key secondary endpoints were ORR and DOR.

As of March 2020, 886 patients were randomly assigned to receive EV+Pembro (n=442) or Plat+Gem (n=444). At data cut-off on 08 August 2023, median follow-up for survival was 17 months.

3.2. Favourable effects

- **BICR-PFS:** As per blinded evaluation of images, EV+Pembro was superior to Plat+Gem chemotherapy in preventing progression or death in patients with advanced UC. With 50% of PFS events in the EV+Pembro arm and 69% in the Plat+Gem arm, the HR for PFS was 0.45 (95% CI 0.38, 0.54; p<0.00001), with mPFS of 12.5 months in the EV+Pembro arm vs. 6.3 months in the Plat+Gem arm.
- **OS:** EV+Pembro also showed improved overall survival compared to Plat+Gem chemotherapy in the targeted population. With 30% of OS events in the EV+Pembro arm and 51% in the Plat+Gem arm, the HR for OS was 0.47 (95% CI 0.38, 0.58; p<0.00001), with almost doubled mOS of 31.5 months in the EV+Pembro arm vs. 16.1 months in the Plat+Gem arm.
- **BICR-ORR:** The proportion of confirmed responders in the subpopulation with measurable disease at baseline was considerably higher in the EV+Pembro (ORR 68%) than in the Plat+Gem arm (44%). This difference seemed to be driven by complete responses, which approached nearly one third of patients in the EV+Pembro arm (29% vs 12% in the Plat+Gem arm).
- **BICR-DOR:** Duration of responses was also significantly longer in the experimental arm. By the cut-off date, 61% of the responders in the Plat+Gem arm had progressed or died, vs. 33% in the EV+Pembro arm. mDOR had not been reached in the EV+Pembro arm (95% CI 20.2, -) and it was 7 months in the Plat+Gem arm.
- Efficacy analysis by CPS score (≥ or < 10) revealed consistency of results for both primary (OS and PFS) and secondary (ORR) endpoints regardless of PD-L1 level.

3.3. Uncertainties and limitations about favourable effects

None.

3.4. Unfavourable effects

- The common AEs and ≥Grade 3 AEs by PT were generally similar between the EV + Pembro EV-302 arm and the primary safety population (EV + Pembro Combo ISS analysis pool, n=564).
- Generally, the serious adverse events observed were consistent with the known adverse events of special interest for enfortumab vedotin, pembrolizumab or both drugs. The AE leading to permanent withdrawal that occurred more frequently (> 10% difference) in the EV + Pembro Combo ISS analysis pool compared to the Pembro RSD analysis group was peripheral sensory neuropathy (12.2% vs 0%, respectively), which is a well-known AESI for EV.
- There was a marked difference in the SAE frequencies between the population <65 years of age and those above (35.3% compared to 56.3%, respectively in the primary safety population of n=564), which is reflected in the SmPC. This was also apparent for ≥Grade 3 AEs by PT (64.2% and 80.3%, respectively).
- The frequencies of the AESIs skin reactions and severe cutaneous adverse reactions were similar between the EV + Pembro Combo ISS and EV Mono ISS analysis groups implying that these are mainly EV-related.
- Pneumonitis/ILD, is a known risk for both EV and Pembro. In line with this, the frequency was higher in the EV + Pembro Combo ISS analysis pool compared to the EV monotherapy pool and the Pembro Bladder pool.

3.5. Uncertainties and limitations about unfavourable effects

None

3.6. Effects Table

Table 102: Effects Table for Padcev in combination with pembrolizumab in the 1L treatment of patients with locally advanced or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy (data cut-off: 08-AUG-2023)

Effect	Short description	Unit	EV+Pembro n=442	Plat+Gem n=444	Uncertainties/ Strength of evidence	References
Favourable Effects						
Median BICR-PFS	Progression free survival by blinded independent central review	Months	12.5 95% CI 10.4, 16.6	6.3 95% CI 6.2, 6.5	HR 0.45 95% CI 0.38, 0.54	CSR
Median OS	Overall survival	Months	31.5 95% CI 25.4, NR	16.1 95% CI 7.6, NR	HR 0.47 95% CI 0.38, 0.58	CSR
ORR	Overall response rate	% n	68% 296/437	44% 196/441		CSR
DOR	Duration of response	Median in months (95% CI)[a]	NR (20.2, -)	7.0 (6.2, 10.2		
Unfavourable Effects:						
		%	**EV+Pembro ISS n=564**	**Plat+Gem n=433**	**Additional information**	
≥Grade 3 AEs	All: <65 yo: ≥65 yo:	%	75.4 64.2 80.3	78.8 69.2 82.8		Table 12/SCS ISS Table 12.6.1.7.1.1
SAEs	All: <65 yo: ≥65 yo:	%	49.8 35.3 56.3	39.0 30.8 42.6		Table 15/SCS ISS Table 12.6.1.7.1.1
Discontinuation due to AEs	 BMI <30 kg/m^2: ≥30 kg/m^2:	%	42.2 38.8 55.8	21.5 19.9 26.3		Table 16/SCS ISS Table 12.6.1.7.5
Severe cutaneous reactions	All: Grade 3-4	%	27.5 3.4	7.6 0.2		Table 21/SCS
Peripheral neuropathy	All: Grade 3-4	%	66.7 5.1	13.9 0		Table 22/SCS
Hyper-glycaemia	All: Grade 3-4	%	19.0 8.2	3.5 0.7		Table 25/SCS
Pneumonitis ILD	All: Grade 3-4	%	10.3 2.5	0.5 0	3 deaths in the EV+Pembro ISS	Table 33/SCS
Infections (SOC)	All: Grade 3-4	%	61.5 18.1	37.0 16.2		Table 11/SCS Table 12/SCS
Neutropenia*	All: Grade 3-4	%	13.8 5.9	55.0 30.0		Table 36/SCS

Notes: ORR was analysed in the subpopulation of patients with measurable disease at baseline (n=437 in the EV+pembro arm and n=441 in the Plat+Gem arm)

*† SSQ/CMQ

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The first line approach for patients with advanced urothelial cancer has remained unchanged for a few years. Patients who are deemed cisplatin eligible (if they do not fulfil any of the Galskly criteria) are often offered cisplatin plus gemcitabine in a standard regimen, and those who are cisplatin ineligible can receive carboplatin plus gemcitabine or an anti-PD-1/PD-L1 checkpoint inhibitor (as long as PD-L1 expression suffices according to the therapeutic indication or pembrolizumab or atezolizumab). Patients who receive chemotherapy and do not experience progression may also receive maintenance treatment with anti-PD-1 avelumab.

Patients' population eligible for platinum-based therapy in first line was the selected population for the pivotal trial supporting this application (Study EV302). The overall efficacy outcome of this pivotal trial is positive and showed efficacy benefits from EV+Pembro across all crucial endpoints (OS, PFS, ORR, DOR) over standard of care chemotherapy (Plat+Gem) followed by optional avelumab maintenance. This novel combination holds promise in the 1L approach to patients with advanced urothelial cancer.

The safety profile for enfortumab vedotin in combination with pembrolizumab remained generally consistent with the known safety profiles for enfortumab vedotin and pembrolizumab. No new safety signals were identified. As generally, adverse event frequencies were higher in patients ≥65 years of age compared to <65 years of age therefore caution is advised. (see SmPC)

As expected, differences in the safety profile of the EV + Pembro EV-302 Arm compared to chemotherapy were observed due to the different mechanisms of action of these agents, the distinct profile of known risks and the longer duration of exposure in the EV + Pembro EV-302 Arm. This expected longer treatment resulting in more AEs (albeit of a different nature than those seen with chemotherapy) is only meaningful since there is a clear survival benefit and the AEs are considered tolerable by the patient and overall manageable by the physician.

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+Pembrolizumab in first-line treatment of adult patients with unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy outweigh its risks.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Padcev in the intended therapeutic indication is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIB and IV

Extension of indication to include PADCEV in combination with pembrolizumab, the first-line treatment of adult patients with locally advanced or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy, based on the final results from study KEYNOTE-A39/EV-302. This was an open label, randomized, controlled phase 3 study of enfortumab vedotin in combination with pembrolizumab versus chemotherapy alone in previously untreated locally advanced (LA) or metastatic urothelial cancer (mUC)". As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.1 of the RMP has also been submitted. As part of the application the MAH is requesting a 1-year extension of the market protection.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, IIIB, IV and to the Risk Management Plan are recommended.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.