EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 July 2024
EMA/CHMP/310416/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Keytruda

International non-proprietary name: Pembrolizumab

Procedure No. EMEA/H/C/003820/II/0150

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
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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
DLT	dose-limited toxicity
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
PDL1	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, Merck Sharp & Dohme 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 enfortumab vedotin, the first-line treatment of locally advanced or metastatic urothelial carcinoma in adults, based on the final results from 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, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 43.0 of the RMP has also been submitted.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0043/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0043/2018 was completed.

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

MAH for Padcev 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: Paolo Gasparini

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
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	2 July 2024
PRAC Rapporteur Assessment Report	4 July 2024
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	11 July 2024
Updated CHMP Rapporteur Assessment Report	18 July 2024
Opinion	25 July 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The applicant applied for the therapeutic use of KEYTRUDA, in combination with enfortumab vedotin, is indicated for the first-line treatment of locally advanced or metastatic urothelial carcinoma in adults.

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).

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 as of 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% 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 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 June 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 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-901did 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 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

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.

In the setting of urothelial carcinoma, pembrolizumab as monotherapy has been approved in the 2L setting for the treatment of locally advanced or metastatic disease in adults who have received prior

platinum-containing chemotherapy, and in the 1L setting for adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10.

Pembrolizumab is approved in Europe since July 2015 for the treatment of multiple cancers (Keytruda | European Medicines Agency (europa.eu)).

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.

2.1.3. The development programme

Rationale for the Pembrolizumab and Enfortumab Vedotin (EV) Combination

Preclinical data show enhanced antitumor activity when EV is combined with PD-1 inhibitors across multiple in vivo tumor models. EV has also demonstrated induction of immunogenic cell death of Nectin-4 positive tumors, an increase in inflammatory mediators and recruitment of innate inflammatory cells to the tumor microenvironment consistent with the increased tumor 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 antitumor 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 pembrolizumab with EV 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.

The current submission seeks regulatory approval for pembrolizumab in combination with EV for the first-line treatment of patients with LA/mUC based on data from the phase 3 study EV-302 (KEYNOTE-A39). The clinical development program for the combination in LA/mUC includes along with the pivotal phase 3, active-controlled study, EV 302, and a phase 1b/2 study, EV-103.

2.1.4. General comments on compliance with GCP

The Applicants 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

No new non-clinical data have been submitted in this application, which is considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Pembrolizumab is a protein, which is expected to biodegrade in the environment and not be a significant risk to the environment. Thus, according to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00), pembrolizumab is exempt from preparation of an Environmental Risk Assessment as the product and excipients do not pose a significant risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- **Tabular overview of clinical studies**

Study ID	Phase	Country/ Region	Study Title	Study Design	Dosing Regimen	Study Population	Participant Exposure
SGN22E-003 (MK-3475-A39) [Ref. 5.3.5.1: PA39V01MK3475]	3	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.	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.	Randomized, parallel-group, active-controlled study.	Enfortumab vedotin with pembrolizumab (Arm A): enfortumab vedotin at 1.25 mg/kg, administered as an intravenous infusion on days 1 and 8 of every 21-day cycle, and pembrolizumab 200 mg as an intravenous infusion on day 1 of every 21-day cycle, after completion of the enfortumab vedotin infusion. Standard of care chemotherapy (cisplatin or carboplatin + gemcitabine) (Arm B): gemcitabine at 1000 mg/m^2 as an intravenous infusion on days 1 and 8 of every 21-day cycle, and either cisplatin (70 mg/m^2) or carboplatin (area under the curve [AUC]) 4.5, or AUC 5 according to local guidelines) on day 1 of every 21-day cycle, with adequate pre- and post-hydration, by intravenous infusion per institutional standards.	Previously untreated, unresectable, locally advanced, or metastatic urothelial cancer with measurable disease according to Response Evaluation Criteria in Solid Tumors v1.1.	Numbers of treated participants are the following: Enfortumab vedotin with pembrolizumab (Arm A): n=440. Standard of care chemotherapy (cisplatin or carboplatin + gemcitabine) (Arm B): n=433
SGN22E-002 (MK-3475-869) [Ref. 5.3.5.1: P869MK3475-mow]	1b/2	USA, Canada, France, Spain, and Italy	A Study of Enfortumab Vedotin (ASG-22CE) as Monotherapy or in Combination with Other Anticancer Therapies for the Treatment of Urothelial Cancer	Dose-escalation and expansion to determine recommended dose of enfortumab vedotin when given in combination with pembrolizumab, and randomized, parallel-group, active-controlled study.	Enfortumab vedotin: 1.25 mg/kg by intravenous infusion on Days 1 and 8 of each 21-day cycle. Pembrolizumab: 200 mg by intravenous infusion on Day 1 of each 21-day cycle.	Cisplatin-ineligible male/female participants with locally advanced or metastatic urothelial cancer.	Dose escalation and expansion Cohort A (enfortumab vedotin + pembrolizumab): n=45; Randomized treatment Cohort K: enfortumab vedotin + pembrolizumab: n=77; enfortumab vedotin monotherapy: n=74

2.3.2. Pharmacokinetics

The recommended dose of KEYTRUDA in adults is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes.

PK data from study EV103/KEYNOTE-869/SGN22E-002/MK-3475-869 (hereafter EV-103) was used in support of 200 mg Q3W as the recommended dose of pembrolizumab in combination with enfortumab vedotin in subjects with locally advanced or metastatic urothelial cancer.

Substantial characterization of the PK and immunogenicity of pembrolizumab have been provided in previous submissions. In particular, pembrolizumab PK disposition has been characterized via pooled population PK analyses using serum concentration-time data contributed from subjects across various clinical studies using a time-dependent PK (TDPK) model. The PK reference dataset for monotherapy includes all available PK data from subjects enrolled in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, KEYNOTE-010, and KEYNOTE-024, with an overall sample size of 2993. This serves as the PK reference analysis to support descriptions of pembrolizumab pharmacokinetics in the EU SmPC.

In addition to the dosing regimens of 200 mg Q3W or 2 mg/kg Q3W, the 400 mg Q6W dosing regimen was approved in the EU for all adult monotherapy indications (procedure number EMEA/H/C/003820/II/0062) and for all adult indications in combination with other anticancer agents (procedure number EMEA/H/C/003820/II/0102).

The dosing regimen of 400 mg Q6W is applicable across all adult indications regardless of the combination treatment type, thus, the 400 mg Q6W dosing regimen would have a similar benefit-risk profile as the 200 mg Q3W dosing regimen in the clinical use of pembrolizumab in subjects with locally advanced or metastatic urothelial cancer.

Absorption

Pembrolizumab is dosed via the intravenous route and therefore is immediately and completely bioavailable.

Distribution

Consistent with a limited extravascular distribution, the volume of distribution of pembrolizumab at steady state is small (6.0 L; coefficient of variation [CV]: 20%). Being an antibody, pembrolizumab does not bind to plasma proteins in a specific manner.

Elimination

Pembrolizumab CL is approximately 23% lower (geometric mean, 195 mL/day [CV%: 40%]) after achieving maximal change at steady state compared with the first dose (252 mL/day [CV%: 37%]); this decrease in CL with time is not considered clinically meaningful. The geometric mean value (CV%) for the terminal half-life is 22 days (32%) at steady-state.

Pharmacokinetic in target population

Considering that an extensive characterization of the PK and immunogenicity profile of pembrolizumab has been provided in previous submissions, the focus in this submission is on the data related to the characterization of the pharmacology for patients with locally advanced or metastatic urothelial cancer treated with pembrolizumab in combination with enfortumab vedotin.

PK Data EV103/KEYNOTE-869/SGN22E-002/MK-3475-869

The PK and ATA of pembrolizumab was evaluated in study EV103/KEYNOTE-869/SGN22E-002/MK-3475-869 (hereafter EV-103) in which enfortumab vedotin was studied in combination with pembrolizumab in subjects with locally advanced or metastatic urothelial cancer. This study includes a dose escalation cohort, Cohort A (expansion cohort) and Cohort K (randomized treatment cohort). All subjects in the dose escalation cohort and Cohort A received enfortumab vedotin in combination with pembrolizumab, whereas subjects in Cohort K were randomized to receive the combination or enfortumab vedotin monotherapy. Dose escalation was conducted using a standard 3 + 3 design to assess DLTs and determine the recommended dose of enfortumab vedotin when given in combination with pembrolizumab. All subjects received enfortumab vedotin as an IV infusion (1.00 mg/kg or 1.25 mg/kg) on days 1 and 8 and pembrolizumab (200 mg) on day 1 of each 21-day cycle (Q3W).

The expansion cohort (Cohort A) provided additional safety and efficacy data on the combination of enfortumab vedotin and pembrolizumab, while evaluating efficacy as a secondary objective. The dose of enfortumab vedotin carried forward to Cohort A was 1.25 mg/kg, which was given in combination with pembrolizumab according to the same dose (200 mg) and cycle used during dose escalation. Subjects who participated in Cohort K were randomly assigned in a 1:1 ratio to receive enfortumab vedotin 1.25 mg/kg in combination with pembrolizumab (200 mg) or enfortumab vedotin 1.25 mg/kg monotherapy.

Ten subjects were enrolled in the dose escalation cohort. The first 3 subjects received the 1.0 mg/kg dose of enfortumab vedotin in combination with pembrolizumab, while the final 7 subjects received enfortumab vedotin 1.25 mg/kg with pembrolizumab. As of the data cut-off date (10 June 2022), 2 subjects were continuing to receive treatment, 1 at each dose level.

In Cohort A (dose expansion) 40 subjects were enrolled and treated; in Cohort K (enfortumab vedotin 1.25 mg/kg+ pembro) 77 subjects were enrolled, whereas 74 subjects were enrolled in Cohort K enfortumab vedotin 1.25 mg/kg monotherapy.

Table 1: Overview of pembrolizumab Cohort included in Study EV-103 PK analysis

Cohort	Treatment	Cancer Type	Number of subjects providing PK [a]	Total number of subjects	PK cut-off date
Dose-Escalation. Cohort	EV 1.0 mg/kg EV + Pembro 200 mg Q3W	UC	2	124	01-Nov-2021
	EV 1.25 mg/kg + Pembro 200 mg Q3W		6		
Cohort A	Expansion Cohort: EV 1.25 mg/kg + Pembro 200 mg Q3W	UC	40		
Cohort K	Randomized Cohort: EV 1.25 mg/kg + Pembro 200 mg Q3W	UC	76		

[a] unique subjects providing PK samples, not all subjects have Cycle 1 day 1 samples.

UC: Urothelial Cancer; Q3W: every 3 weeks, EV: enfortumab vedotin; Pembro: pembrolizumab

PK and immunogenicity results are based on the data cut-off date of 01 November 2021.

PK schedule in study EV-103 for pembrolizumab 200 mg Q3W: Predose pembrolizumab serum concentrations (Ctrough) were obtained within 24 hours prior to dosing at day 1 of cycles 1, 2, 3, 4, 6 and every 2 cycles (6 weeks) thereafter. Postdose PK samples were drawn within approximately 30 minutes after the end of infusion in Cycle 1 and Cycle 2, and an end of treatment PK sample were collected at 30-37 days after the last administration.

Blood sample for pembrolizumab ATA determination were collected in Cycle 1 and Cycle 2 on day 1 predose and at day 1 predose in all other cycles and at the end of treatment.

For enfortumab vedotin an intensive PK sampling was foreseen; during the dose escalation phase, samples were collected at Cycle 1 and 2 on day 1 pre-dose, EoI, 2h, 4h, 24 h, 48 h, 72h; on day 8 pre-dose, EoI, 2h, 4 h, 24 h, 48 h, 72 h, 168 h; in the subsequent cycles samples were collected on Day 1 pre-dose and then at the EoT. In the expansion cohort, samples were collected at Cycle 1 and 2 at day 1 pre-dose and at the EoI, at Day 3 EoI, Day 8 pre-dose and EoI, day 10 EoI and for all other cycles samples were collected pre-dose and then at the EoT.

Pembrolizumab samples were analysed at PPD Laboratory Services facility in Richmond, Virginia. Sample analysis was performed according to the Method ICD 573 V 1.05, entitled "An ECL Method for the Quantitation of MK-3475 in Human Serum," which was validated under project code RCVB2 (issued in November 2014).

The nominal pembrolizumab concentration range of 25.0 to 800 ng/mL in 100% human serum was chosen to quantitate samples. The calibration standards ranged from 1.00 to 125 ng/mL, with anchor calibrators at 1.00 and 125 ng/mL after correction for the 1:10 MRD.

Samples were stored for a maximum of 1217 days between sample collection and analysis. All samples were analyzed within the 1218 days demonstrated long-term storage stability in human serum at -80 °C.

9.86% of the project samples were reassayed and incurred sample repeats met the acceptance criteria with an overall pass rate of 97.8%.

In total 930 PK samples with a 01 November 2021 data cut-off date were measured for 124 subjects in study EV- 103. General rules were applied to identify samples that should be excluded for summary PK calculation. These included: samples taken after discontinuation (end of treatment); unscheduled samples; PK samples drawn later than 42 days after last pembrolizumab administration; predose Cycle 1 samples with a pembrolizumab serum concentration > 0; 30- minute post infusion samples ("Postdose") with a serum concentration extremely low or below LOQ; Pre- and postdose samples in the same cycle with (almost) the same concentration value; Pre- and postdose samples in the same cycle that were obviously swapped: predose value is higher and associated postdose sample is lower; values identified as outliers, duplicate samples. After exclusion of these samples, 828 samples from 123 subjects are available to be included in the PK analysis.

Phoenix™ WinNonlin® (Version 8.1.1.279) software was used for pharmacokinetic analysis.

The MAH provided pembolizumab PK report aiming to summarize serum concentrations of pembrolizumab (MK-3475) obtained from subjects in study EV-103 with urothelial cancer and to compare observed pembrolizumab PK data from study EV-103 with reference model (TDPK model based) predicted exposure of pembrolizumab 200 mg Q3W dosing regimen.

Summary descriptive statistics of the pembrolizumab concentration after treatment with 200 mg pembrolizumab Q3W in combination with enfortumab vedotin for the dose escalation cohort, cohort A and cohort K combined, are presented in Table 2.

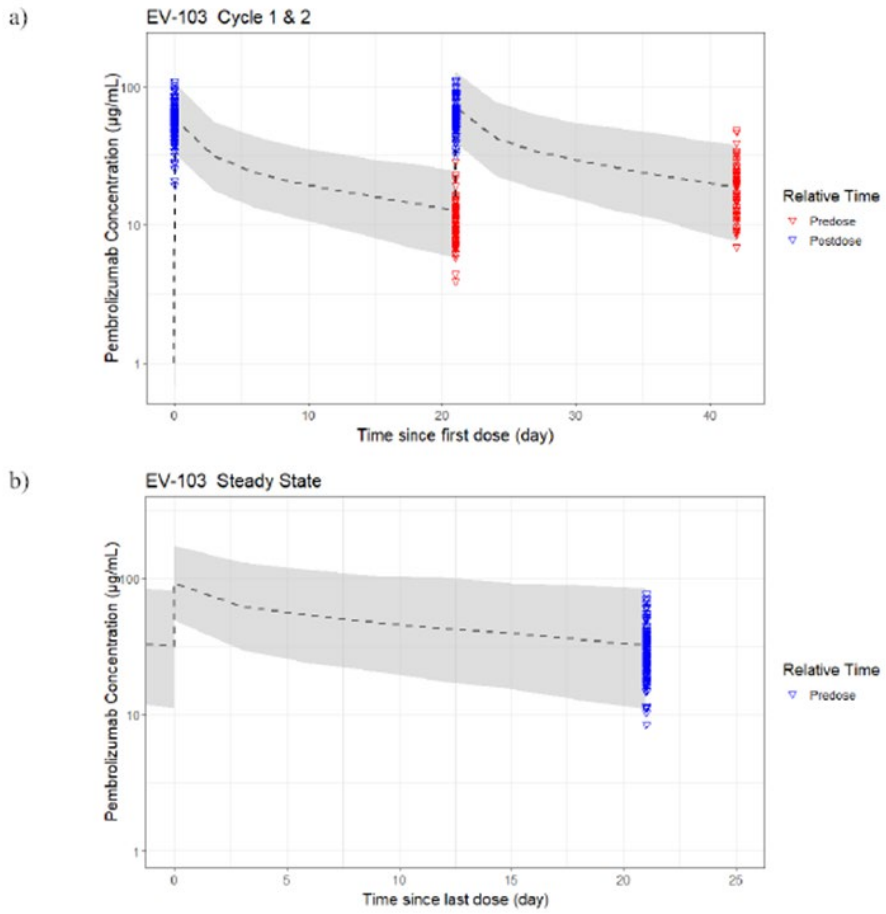
Table 2: Summary statistics of the pembrolizumab predose and postdose serum concentration after treatment with 200 mg pembrolizumab Q3W in combination with enfortumab vedotin

Dose (mg)	Time Point	Visit	Nominal Time (days)	N	AM(SD) (µg/mL)	GM(%CV) (µg/mL)	GM(SD) (µg/mL)	Min (µg/mL)	Median (µg/mL)	Max (µg/mL)
200	Postdose	Cycle 1 (Week0)	0.021	100	56.1 (17.0)	53.6 (32.3)	53.6 (17.0)	19.3	54.3	109
		Cycle 2 (Week3)	21.021	91	63.3 (16.6)	61.3 (26.2)	61.3 (16.6)	32.1	60.7	112
200	Predose	Cycle 1 (Week 0)	0.00	109	0.00 (0)	N/A	N/A	0.00	0.00	0.00
		Cycle 2 (Week 3)	21.0	95	10.8 (4.6)	9.86 (45.9)	9.86 (4.6)	2.63	10.3	28.8
		Cycle 3 (Week 6)	42.0	99	18.9 (8.2)	17.3 (44.3)	17.3 (8.2)	6.57	18.3	48.3
		Cycle 4 (Week 9)	63.0	90	21.5 (9.4)	19.6 (45.7)	19.6 (9.4)	8.08	20.4	54.4
		Cycle 6 (Week 15)	105	71	25.7 (10.9)	23.4 (49.4)	23.4 (10.9)	3.51	25.5	62.8
		Cycle 8 (Week 21)	147	53	29.7 (13.3)	26.8 (50.1)	26.8 (13.3)	8.44	27.4	67.1
		Cycle 10 (Week 27)	189	34	29.2 (11.9)	27.0 (42.9)	27.0 (11.9)	11.1	27.3	69.6
		Cycle 12 (Week 33)	231	25	37.8 (19.8)	34.0 (46.8)	34.0 (19.8)	19.3	33.0	98.2
		Cycle 14 (Week 39)	273	12	28.8 (10.0)	27.3 (36.6)	27.3 (10.0)	12.9	28.4	52.0
		Cycle 16 (Week 45)	315	9	34.1 (12.2)	32.4 (33.9)	32.4 (12.2)	19.9	33.5	60.9
		Cycle 18 (Week 51)	357	8	37.5 (15.1)	35.1 (40.6)	35.1 (15.1)	20.3	35.9	65.4
		Cycle 20 (Week 57)	399	9	29.1 (13.1)	26.7 (46.5)	26.7 (13.1)	15.6	27.0	53.0
		Cycle 22 (Week 63)	441	7	27.1 (12.3)	25.0 (44.1)	25.0 (12.3)	14.8	24.4	51.7
		Cycle 24 (Week 69)	483	4	29.5 (14.0)	27.3 (44.9)	27.3 (14.0)	18.5	24.8	49.8
		Cycle 26 (Week 75)	525	4	30.3 (12.2)	28.7 (37.9)	28.7 (12.2)	20.6	26.4	47.9

QW = Weekly dosing schedule (Q3W, every 3 weeks); N = number of subjects, N/A = Not Applicable;
GM = Geometric Mean; CV% = Geometric Coefficient of Variation; SD = Standard Deviation; AM = Arithmetic Mean;
Results reported for time points with N ≥ 3

Using a dataset with a sample size of 2993 participants, a time-dependent PK model was created to describe the PK profile as indicated in the EU SmPC. This model is used as the reference PK model to support the approval of the dosing regimen of 200 mg Q3W. Observed pembrolizumab concentration data in study EV-103, where pembrolizumab was administered in combination with enfortumab vedotin in subjects with urothelial cancer, are overlaid on the simulated profile using the reference model as shown in the figure below.

Figure 1: Observed concentrations in Study EV-103, where pembrolizumab was administered in combination with enfortumab vedotin reference model-predcited Pharmacogenetic profile for 200mg Q3W dose, a)Cycle 1 and Cycle2, b) Steady state



Note: Pembrolizumab model predictions and observed concentration data after 1st and 2nd dose (upper panel) and at steady state (at and after cycle 8, lower panel). Symbols are individual observed data (nominal time) from all cohorts combined; black line is median predicted concentrations from the model for a regimen of 200 mg Q3W and the gray shaded area represents the 90% prediction interval. Plots are displayed on log scale.

Data Source – 07Z6MT: adpcpem

In study EV302, PK and ATA samples for pembrolizumab were collected, but not analyzed.

Summary statistics of the observed pembrolizumab trough (pre-dose) and post-dose concentrations in UC subjects from KN052 and KN045 (in which pembrolizumab was used at the same dose of EV-103 study) are presented in the tables below:

Table 3: Summary statistics of pembrolizumab (pre-dose) and post-dose concentrations,post Cycle 1 serum concentration values following administration of multiple 200 mg I.V. Doses with a 3 week dosing interval in KN052

Cycle	NOMTAFD (day)	N	GM (%CV)	AM (SD)	Min	Median	Max
			(µg/mL)				
Predose (C_{trough})							
Cycle 2 (Week 3)	21	286	11.1 (42)	11.9 (4)	2.07	11.5	26.2
Cycle 4 (Week 9)	63	170	20.6 (51)	22.8 (9)	4.41	22.4	56.1
Cycle 8 (Week 21)	147	59	28.0 (38)	29.9 (10)	8.15	27.9	59.8
Cycle 12 (Week 33)	231	22	29.4 (53)	32.5 (14)	6.60	29.5	61.4
Cycle 16 (Week 45)	315	10	33.4 (38)	35.4 (12)	18.6	36.2	54.7
Postdose (within 30 min post end of infusion)							
Cycle 1 (Week 0)	0	298	58.0 (28)	60.2 (17)	22.8	57.4	148
Cycle 8 (Week 21)	147	53	83.1 (29)	86.4 (24)	37.2	81.1	149
Post C1 (additional samples drawn after Cycle 1 dosing)							
Cycle 1 (72-168 hr)	5	299	23.4 (31)	24.5 (8)	8.52	23.5	61.3
Cycle 1 (336 hr)	14	287	14.4 (36)	15.2 (5)	4.39	14.7	35.5

NOMTAFD = Nominal time after first dose;
GM = Geometric Mean;
%CV = Geometric Coefficient of Variation;
SD = Standard Deviation;
AM = Arithmetic Mean;
Results for time points with N > 3.

Table 4: Summary statistics of pembrolizumab (pre-dose) and post-dose concentrations, post Cycle 1 serum concentration values following administration of multiple 200 mg I.V. Doses with a 3 weeks dosing interval in KN045

Cycle	NOMTAFD day	N	GM (%CV)	AM (SD)	Min	Median	Max
			(µg/mL)				
Predose (C_{trough})							
Cycle 2 (Week 3)	21	233	13.1 (47)	14.2 (5)	0.475	13.9	29.3
Cycle 4 (Week 9)	63	169	25.3 (52)	27.7 (11)	0.677	26.6	62.1
Cycle 8 (Week 21)	147	104	33.4 (64)	37.8 (17)	1.13	37.5	95.6
Cycle 12 (Week 33)	231	73	39.2 (40)	42.0 (15)	14.5	39.4	83.1
Cycle 16 (Week 45)	315	44	39.0 (39)	41.7 (15)	12.2	42.2	90.9
Cycle 20 (Week 57)	399	22	38.7 (36)	41.0 (15)	19.3	37.3	82.8
Cycle 24 (Week 69)	483	8	36.7 (33)	38.5 (12)	25.3	37.8	54.5
Postdose (C_{max}) (within 30 min post end of infusion)							
Cycle 1 (Week 0)	0	247	65.7 (26)	67.9 (18)	33.9	65.9	144
Cycle 8 (Week 21)	147	97	103 (31)	107 (32)	44.8	103	219
Post Cycle 1 (72-168 hours post cycle 1)							
Cycle 1 (Week 0)	5	245	29.0 (29)	30.2 (9)	15.2	29.2	57.5

GM = Geometric Mean;
CV% = Geometric Coefficient of Variation;
SD = Standard Deviation;
AM = Arithmetic Mean;
Results reported for time points with N > 3.

2.3.3. Pharmacodynamics

Immunogenicity

Pembrolizumab ADA samples were available from 126 subjects. A subset of the subjects was not assessable for drug-induced immunogenicity analysis, because only a pre-treatment ADA sample was available (N=7). The remaining 119 subjects were assessable for drug-induced immunogenicity analysis.

Table 5: Overview of subjects included in the immunogenicity analysis for pembrolizumab after treatment with enfortumab vedotin in combination with pembrolizumab (200mgMK-3475Q3W) in subjects with urothelial cancer (EV-103)

Study	Enfortumab Vedotin Treatment	Subjects		
		Subjects Providing ADA Samples	Subjects Dosed with Pembrolizumab	Assessable Subjects Subjects Dosed with Pembrolizumab and Post Treatment Samples
Pembrolizumab (200 mg Q3W) Combination Therapy with Enfortumab Vedotin				
EV-103	Cohort A 1.25 mg/kg	40	40	39
	Cohort K 1.25 mg/kg	76	76	71
	Dose Escalation Cohort 1.00 mg/kg	3	3	3
	Dose Escalation Cohort 1.25 mg/kg	7	7	6
	Total	126	126	119

Data source: 07Z6QD: analysis-adada

Out of the 119 subjects included in the immunogenicity assessment, 2 subjects were inconclusive, resulting in 117 evaluable subjects. The observed incidence of treatment emergent ADA in evaluable subjects based on a pooled analysis (pembrolizumab combination therapy) in subjects with urothelial cancer is 3.4% (4 out of 117), based on 4 subjects with treatment emergent positive status, 2 subjects with non-treatment emergent positive status and 111 with negative immunogenicity status. From the 4 treatment-emergent positive subjects, 3 subjects had antibodies with neutralizing capacity, resulting in an incidence of treatment emergent neutralizing positive subjects of 2.6% (3 out of 117).

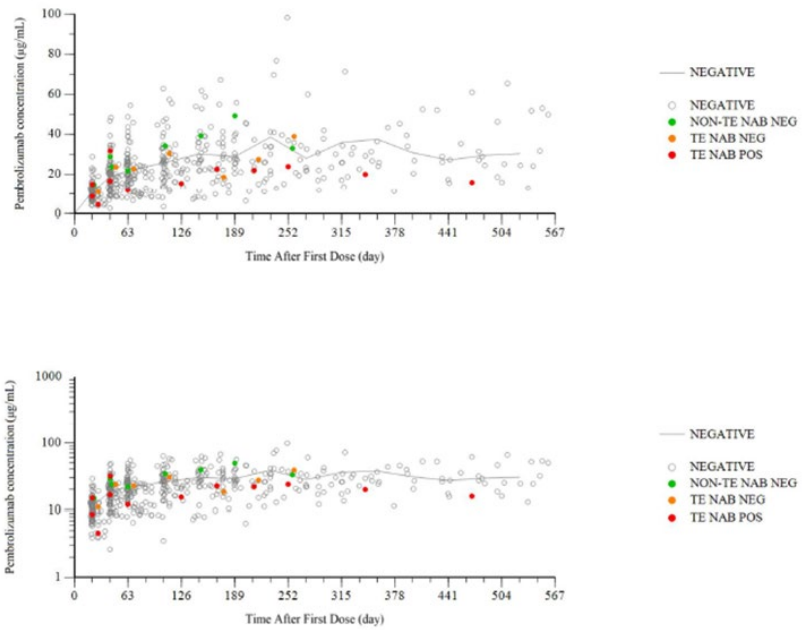
Table 6: Summary of subjects immunogenicity results for pembrolizumab in subjects with urothelial cancer treated with enfortumab vedotin in combination with pembrolizumab (200mgMK-3475Q3W) (EV-103)

Pembrolizumab (200 mg Q3W) Combination Therapy with Enfortumab Vedotin					
Immunogenicity status	**Total**	**Cohort A** 1.25 mg/kg	**Cohort K** 1.25 mg/kg	**Dose Escalation Cohort**	
				1.0 mg/kg	1.25 mg/kg
Assessable subjects[a]	119	39	71	3	6
Inconclusive subjects[b]	2	1	0	1	0
Evaluable subjects[c]	**117**	**38**	**71**	**2**	**6**
Negative[d]	111 (94.9%)	36	67	2	6
Non-Treatment emergent positive[d]	2 (1.7%)	0	2	0	0
Neutralizing negative	2 (1.7%)	0	2	0	0
Neutralizing positive	0	0	0	0	0
Treatment emergent positive[d]	4 (3.4%)	2	2	0	0
Neutralizing negative	1 (0.9%)	0	1	0	0
Neutralizing positive	3 (2.6%)	2	1	0	0

a: Included are subjects with at least one ADA sample available after treatment with pembrolizumab
b: Inconclusive subjects are the number of subjects with no positive ADA samples present and the drug concentration in the last sample above the drug tolerance level.
c: Evaluable subjects are the total number of negative and positive subjects (non-treatment emergent and treatment emergent.
d: Denominator was total number of evaluable subjects.

The effect of pembrolizumab ADA on drug levels, for the subjects with ADA positive samples, is compared with the subjects treated with the same regimen that only have ADA negative samples. For the ADA positive subjects, the pembrolizumab exposure was comparable with the exposures observed for the negative subjects treated with the same regimen.

Figure 2: Effect of pembrolizumab ADA on drug exposure in subjects with Urothelial Cancer treated with enfortumab vedotin in combination with pembolizumab (200mg MK-3475 Q3W), 9EV-103) linear Scale (top) and log scale (bottom)



Footnote: Figure includes ADA samples with corresponding PK concentrations. Samples taken > 42 days after last dose (> 2 times the scheduled time) are excluded. Pembrolizumab concentrations for samples with Cycle 1 predose PK concentrations >0 were set to missing as their results are unreliable.

If a subject is determined to be ADA positive (non-TE or TE, based on one or more positive samples), all datapoints belonging to that subject are shown in the color of the corresponding ADA status group.

2.3.4. Discussion on clinical pharmacology

Pembrolizumab PK has been evaluated in study EV103 in which it was administered as 200 mg Q3W, a posology already authorised for other indications. Pembrolizumab was administered in dose escalation cohort in combination with enfortumab vedotin dosed at 1.0 mg/kg or 1.25 mg/kg, in expansion cohort A and randomized cohort K with enfortumab vedotin 1.25 mg/kg.

The bioanalytical method used to determine pembrolizumab has already been validated and used during the lifecycle of the product. Samples from study EV103 have been analysed within the validated LTS (1218 days), albeit to the limit (1217 days). 828 samples out of 930 were considered for the PK analysis, therefore about 11% were excluded and this is considered acceptable.

A summary descriptive statistic has been provided for cohort A and K for pre-dose concentrations at Cycle 1 and Cycle 2 as well as the Ctrough concentration until cycle 26 (week 75). It is of note that pembrolizumab has been already approved as monotherapy in patients with locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum containing chemotherapy and in adults who are not eligible for cisplatin containing chemotherapy and whose tumours express PD L1 with a combined positive score (CPS) ≥ 10. These indications were approved in 2017 (II/23 variation) and data derived from KEYNOTE-012 cohort C (10 mg/kg Q2W), KEYNOTE-052 (200 mg Q3W) and KEYNOTE-045 (200 mg Q3W).

Observed pembrolizumab trough (pre-dose) and post-dose concentrations in UC subjects from KN052 and KN045 (in which pembrolizumab was used at the same dose of EV-103 study) with observed exposures in EV103, appear to be similar although in KN045 are slightly higher. Moreover, the MAH provided a comparison between the observed exposure in EV103 and the simulated exposures deriving from the PopPK model that includes 2993 participants, also demonstrating that pembrolizumab exposure is not influenced by the enfortumab vedotin administration.

One thousand eighty-six (1086) human serum samples were analysed for ADA with a validated method at the PPD Laboratory Services facility in Richmond Virginia. Samples were stored at -80 °C. The dose-limited toxicity (DTL) for the ADA assay, executed at the vendor PPD, is 124 µg/mL and all samples showed pembrolizumab concentrations below the DTL. 117 out of 119 subjects were evaluable for the immunogenicity. There were 4 treatment emergent positive subjects (incidence 3.4%) and 3 were Nab positive (incidence 2.6%).

Two subjects (one subject in Cohort A and one subject in Cohort K) were ADA positive Nab positive at the end of treatment; 3 subjects were ADA positive at one or more Cycles, but became negative in the subsequent cycles (one subject in Cohort A that was also Nab positive; one subject in Cohort K; one subject in Cohort K); one subject was ADA positive at last three cycles.

The incidence of ADA (3.4%) in subjects with urothelial cancer treated with enfortumab vedotin in combination with pembrolizumab in EV-103 is numerically higher when compared to the range observed for historical ADA data following pembrolizumab monotherapy across indications (0.6% to 2.9%) and currently reported in the SmPC (1.8%).

The MAH submitted data comparing the exposure of pembrolizumab in subjects with and without ADA(Data not shown).. A trend of a lower exposure in TE Nab positive samples is observed and it is

expected. However, due to the low number of ADA as well as Nab positive subjects no conclusion can be drawn on the relevance of this finding and no update to the SmPC is warranted.

2.3.5. Conclusions on clinical pharmacology

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

2.4. Clinical efficacy

2.4.1. Dose response study

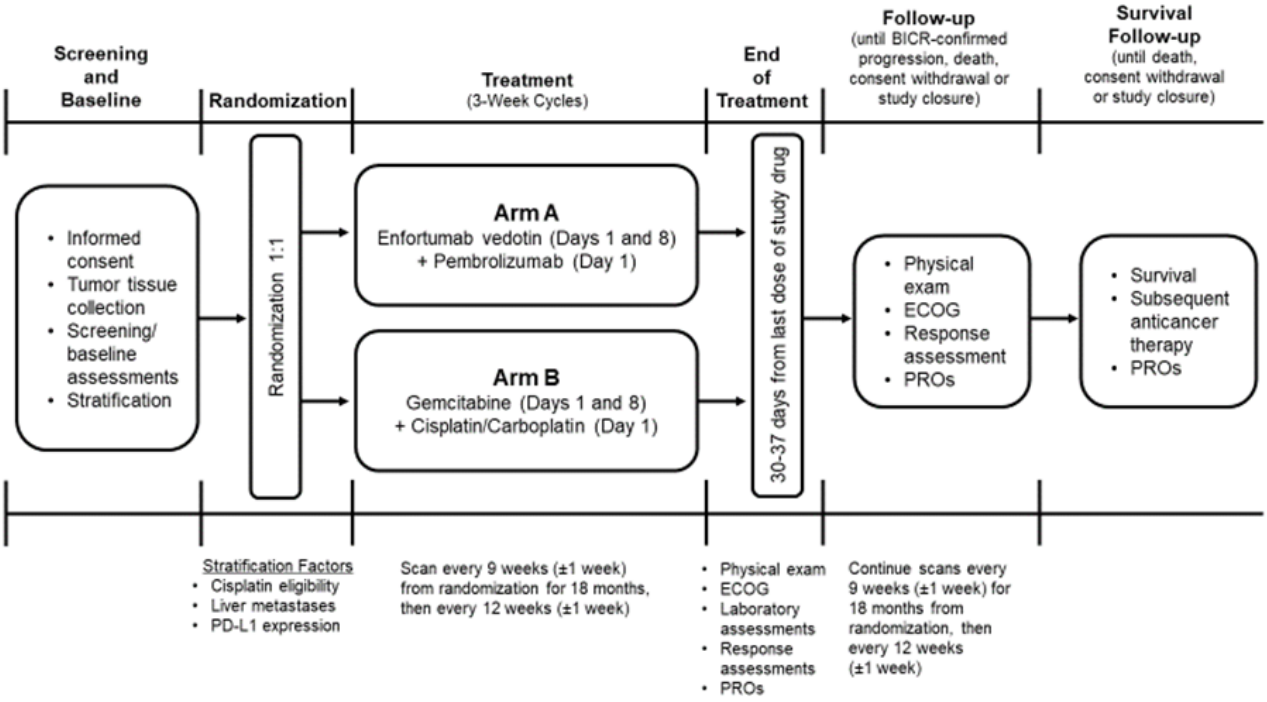
No dose-response studies were conducted to select the dose of pembrolizumab that was administrated at 200 mg Q3W in all clinical studies.

2.4.2. Main study

Title of Study: EV-302 (KEYNOTE-A39)

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. 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). EV-302 is an ongoing, global, phase 3, open-label, 2-arm randomized multicenter study to evaluate the combination of enfortumab vedotin + pembrolizumab vs standard of care gemcitabine + platinum-containing chemotherapy in subjects with previously untreated LA/mUC.

Figure 3: Trial Design



Arm C

The original protocol included a third arm (Arm C, EV + Pembro + Plat [cisplatin or carboplatin]). This arm was removed from the protocol in Amendment 2 based on encouraging efficacy data from EV-103 with the enfortumab vedotin and pembrolizumab combination, as well as emerging evidence from other clinical trials designed to evaluate use of PD-(L)1 inhibitors in combination with platinum-containing chemotherapy, which did not achieve their primary endpoints.

Methods

Study participants

Inclusion Criteria

Subjects with previously untreated, unresectable LA or mUC were enrolled in this study.

Key inclusion criteria were:

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:

i. Hemoglobin ≥10 g/dL

ii. GFR ≥50 mL/min

iii. May not have NYHA Class III heart failure

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

<u>Exclusion Criteria</u>

Key exclusion criteria were:

1. Subjects who previously received enfortumab vedotin or other MMAE-based ADCs ● 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
2. ●Subjects who previously received any prior treatment with an agent directed to another stimulatory or co-inhibitory T-cell receptor
3. ●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
4. ●Subjects with uncontrolled diabetes
5. ●Subjects with an estimated life expectancy < 12 weeks
6. ●Subjects with ongoing sensory or motor neuropathy Grade 2 or higher
7. ●Subjects with active CNS metastases

8. 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

9. 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.

10. 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 7 summarises treatments in both arms of the pivotal trial.

Table 7: Study treatment

Agent (IV)	Arm A EV + Pembro	Arm B* Gem + Plat	Arm C‡ EV + Pembro + Plat	Japan Safety Run-in
Enfortumab vedotin	1.25 mg/kg over 30 minutes on days 1 and 8	--	1.25 mg/kg over 30 minutes on days 1 and 8	1.25 mg/kg over 30 minutes on days 1 and 8
Pembrolizumab	200 mg over 30 minutes on day 1 (30 minutes after EV)	--	200 mg over 30 minutes on day 1 (30 minutes after EV)	200 mg over 30 minutes on day 1 (30 minutes after EV)
Gemcitabine	--	1000 mg/m^2 on days 1 and 8	--	--
Cisplatin§	--	70 mg/m^2 on day 1 over 1 hour or per local label or institutional standards	70 mg/m^2 on day 1 over 1 hour or per local label or institutional standards	--
Carboplatin¶	--	AUC 4.5 on day 1 over 1 hour or per local label or institutional standards	AUC 4.5 on day 1 over 1 hour or per local label or institutional standards	--

AUC: Area under the curve; EV: Enfortumab vedotin; Gem: Gemcitabine; Pembro: Pembrolizumab; Plat: platinum-based chemotherapy (cisplatin or carboplatin)

† All treatments were administered in 21-day cycles.

* Subjects received cisplatin or carboplatin.

‡Arm C was removed from the protocol in Amendment 2 based on data from external clinical trials (Section 5.1.1).

§ Given on day 2 if required by institutional standards.

¶ Starting dose of AUC 5 permitted according to local guidelines.

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.

Objectives

The study was designed to assess the dual primary endpoints of PFS and OS and was considered positive if either PFS by BICR or OS comparison was statistically significant between the experimental arm (Arm A; the EV + Pembro Arm) and the control arm (Arm B; cisplatin or carboplatin + gemcitabine; the Plat + Gem Arm).

Outcomes/endpoints

Table 8: Primary Objectives and Endpoints

Objectives	Endpoints
To compare PFS between the experimental arm (Arm A) and the control arm (Arm B) by BICR	PFS per RECIST v1.1 by BICR
To compare OS between the experimental arm (Arm A) and the control arm (Arm B)	OS

BICR: Blinded independent central review; OS: Overall survival; PFS: Progression free survival; RECIST: Response Evaluation Criteria in Solid Tumors

Table 9: Secondary Objectives and Endpoints

Objectives	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 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 between the experimental arm (Arm A) and the control arm (Arm B)	DOR per RECIST v1.1 by BICR DOR per RECIST v1.1 by investigator assessment
To evaluate 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 QoL, functioning, and symptoms from the subject perspective	Mean scores and change from baseline of the EORTC QLQ-C30, and EQ-5D-5L, 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

AE: Adverse event; BICR: Blinded independent central review; DCR: Disease control rate; DOR: Duration of response; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Core 30; EQ-5D-5L: EuroQoL 5-dimension 5-level Questionnaire; ORR: Objective response rate; PFS: Progression free survival; QoL: Quality of life; RECIST: Response Evaluation Criteria in Solid Tumors; TTPP: Time to pain progression; VAS: Visual analogue scale

Table 10: Exploratory Objectives and Endpoints

Objectives	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 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

ATA: Antitherapeutic antibody; DOR: Duration of response; HRU: Healthcare resources utilization; iRECIST: Modified RECIST v1.1 for immune-based therapeutics; MMAE: Monomethyl auristatin E; ORR: Objective response rate; PFS: Progression free survival; RECIST: Response Evaluation Criteria in Solid Tumors.

Sample size

Based on the last version of the protocol (Amendment 8 dated 15 February 2023), approximately 860 subjects (approximately 430 subjects per arm) were planned to be randomized in the global portion of the study. 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 of one interim analysis at approximately 72.8% of the target number of events. Design assumptions for OS were the following: (1) OS curves follow piecewise exponential distribution with a reduced hazard rate (50% of the initial rate) starting from 24 months; (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 enrollment period of 30 months; (5) a yearly dropout rate of 5%. It was anticipated that 489 OS events would have been 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; (2) HR of PFS is 0.70 between Arm A and Arm B; (3) median PFS for Arm B is 7 months; (4) an enrollment period of 30 months; (5) a yearly dropout rate of 5%.

The planned sample size was amended twice during the study period. Based on the initial protocol (version 1; 03 December 2019), approximately 1095 subjects (365 subjects per arm) were planned to be randomized in a 1:1:1 ratio to one of the three study arms. After Amendment 2 (12 August 2020), the Arm C was removed, and the sample size was recalculated as a consequence and 760 subjects (380 subjects per arm) were planned to be randomized in a 1:1 ratio to one of the two remaining study arms. The sample size was also updated after amendment 4 (11 November 2021) and was increased up to 860 (430 subjects per arm); a total of 489 OS events and 526 PFS events should have provided 93% and 90% power, respectively, to demonstrate superiority at a two-sided alpha of 4.5% for OS and 0.5% for PFS.

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.

Statistical methods

Protocol Amendments involving statistical methods

The protocol was subject to 8 general amendments, of which Amendment No. 02 (12 August 2020) and Amendment No. 04 (11 November 2021) modified the SAP language as follows.

Amendment No. 02 (12 August 2020): the Arm C was closed. The sample size was reduced from 1095 to 760 subjects (380 per Arm A and B). The multiplicity strategy was amended, the alpha was splitted only considering the comparison of Arm A and Arm B. Timing of analyses was also updated: the first IA was planned after 438 PFS events (~11 months) and was considerd as FA for PFS and IA for OS; the FA for OS was planned after 489 OS events (~21 months).

Amendment No. 04 (11 November 2021): The sample size was increased from 760 to 860 subjects (430 per arm), the timing of analyses was updated as follows: the first IA was planned after 526 PFS events (~11 months) and was considerd as FA for PFS and IA for OS; the FA for OS was planned after 489 OS events (~21 months). The alpha splitting strategy was also amended.

The SAP was also subject to 4 amendments, to reflect changes implemented in the protocol amendments. The final SAP is dated 22 June 2023 (version No. 04).

Statistical Methods for Efficacy Analyses

The Intention-to-Treat (ITT) population served as the population for primary efficacy analyses. All randomized participants were included in this population. Participants were included in the treatment group to which they are randomized. Efficacy endpoints were summarized using the ITT analysis set (including all randomized subjects) or response evaluable set (scans with the overall response not evaluable were not considered an adequate response assessment for the purpose of PFS and DOR censoring). The primary endpoints were PFS per RECIST v1.1 by BICR and OS. The study was considered positive if either PFS by BICR or OS comparison was statistically significant between Arm A and Arm B. For patients randomized in Arm C (dropped from the study under protocol Amendment 2) only limited summary were provided (sample size =11). Censoring scheme for the primary analysis of PFS are described below.

Table 11: 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.

For primary endpoints of OS and PFS, a log-rank test stratified by randomization stratification factors was used to compare the experimental arms to the control arm. The estimated HR and corresponding 95% CI from the stratified Cox proportional hazards regression model were also presented. The median survival time were estimated using the Kaplan-Meier method and were reported along with the corresponding 95% CI by treatment arm. Similar estimation methods were used for the other time-to-event endpoints. Duration of response (DOR) was summarized descriptively by Kaplan-Meier methods for subjects with a confirmed response (complete response or partial response per RECIST v1.1). Overall response rate and disease control rate were estimated for each arm. P-value comparing between the experimental arms and the control arm using the Cochran Mantel-Haenszel test stratified by randomization stratification factors was also reported. The difference in response rates between the experimental arms and the control arm was estimated along with the corresponding 95% CI.

To evaluate the robustness of efficacy results, the following sensitivity analyses were also performed:

1) Unstratified Analysis: PFS and OS analysis by unstratified log-rank test and an unstratified Cox regression model was used to estimate the hazard ratio and the corresponding 95% CI for the treatment effect. The primary censoring method was used.

2) Initiation of Subsequent Anticancer Therapy: For subjects who received subsequent anticancer therapy before PD or death, a sensitivity analysis of PFS without considering subsequent anticancer therapies as a censoring reason was performed. In addition, since the use of subsequent anticancer therapy was likely to bias the analyses of OS, more specifically, might underestimate OS comparison when the distribution of subsequent therapies was imbalanced between 2 arms. To reduce such bias, sensitivity analysis of OS using inverse probability of censoring weights (IPCW) method was performed. Subjects who start subsequent therapy were censored at the time of subsequent anticancer therapy, and subjects were weighted according to their probability to take subsequent therapy. This analysis was performed at OS interim analysis if the OS primary analysis was statistically significant or at OS final analysis.

3) Missing Tumour Assessments: To explore the potential impact of missing tumour assessments on PFS, subjects who miss two or more consecutive scheduled assessments before death or PD were considered to have an event on the date of death or progression.

4) Mis-stratification: In the case of >5% inconsistency in stratification factors between RTSM and eCRF, the stratification factors collected in eCRF were used as strata in both stratified log-rank test and stratified Cox proportional hazards regression model.

5) Non-proportional hazard: In the case that the PH assumption was violated, PFS/OS might be analyzed based on a restricted mean survival time (RMST) up to τ, defined as the minimum of (largest observed PFS/OS event time for Arm A, largest observed PFS/OS event time for Arm B). The difference in RMST between the treatment arms was analyzed adjusting for the randomization stratification factors.

The Response Evaluable Analysis Set was used to calculate the Objective Response Rate (ORR) and its 2-sided 95% exact CI for each treatment arm using the Clopper-Pearson method. The statistical comparison of ORR by BICR between 2 arms was performed only if both PFS and OS were statistically significant and the comparison will be evaluated at the 0.05 significance level (2-sided) by a Cochran-Mantel-Haenszel (CMH) test controlling for the stratification factors. The ORR by investigator assessment was not tested statistically. The nominal p-value from the stratified CMH test was reported. In addition, the concordance between BICR and investigator assessed responders and non-responders was summarized.

Duration of Response (DOR) is defined as the time from the first objective response (CR or PR that is subsequently confirmed) to the first documented PD per RECIST v1.1 or death from any cause, whichever occurred first. DOR only included subjects with a confirmed response (Responders only). The same censoring rules as described for primary PFS analysis were applied for DOR. DOR per the assessment by BICR and by investigator were analyzed as separate endpoints. DOR was displayed by KM plots. KM estimates of median DOR with corresponding 95% CIs for each treatment arm were provided. In addition, KM estimates of the 25^{th} and 75^{th} percentiles of DOR and the observed minimum and maximum DOR were reported.

Disease Control Rate (DCR) was defined as the proportion of patients with confirmed response (CR or PR) or SD per RECIST v1.1. Subjects who had no post-baseline response assessments were considered as non-responders for calculating the DCR. Only response assessments before the first documented PD or subsequent anticancer therapies were considered. DCR per the assessment by BICR and by investigator were analyzed as separate endpoints. The DCR and its 95% CIs were provided using Clopper-Pearson methodology for each treatment arm. Comparison of DCR between 2 arms were evaluated by a 2-sided CMH test controlling for the stratification factors. The nominal p-value from the stratified CMH test were reported.

PFS by investigator assessment was defined as the time from the date of randomization to the first documented disease progression per RECIST v1.1 by investigator assessment or death from any cause, whichever occurs first. The same censoring rules as described for primary PFS analysis were applied for PFS by investigator assessment. The same method as described for the primary analysis of PFS by BICR were used. Subgroup analyses and sensitivity analyses were not conducted for PFS by investigator assessment. In addition, the concordance between BICR and investigator assessed PFS events were summarized.

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

COVID-19 Impacts were evaluated in the ITT Analysis Set and was summarized and listed. Subjects with suspected or confirmed case of COVID-19 were listed.

Planned subgroup analyses:

As supportive analyses, treatment effect for PFS, OS and ORR was estimated and presented in forest plots for the following subgroup variables:

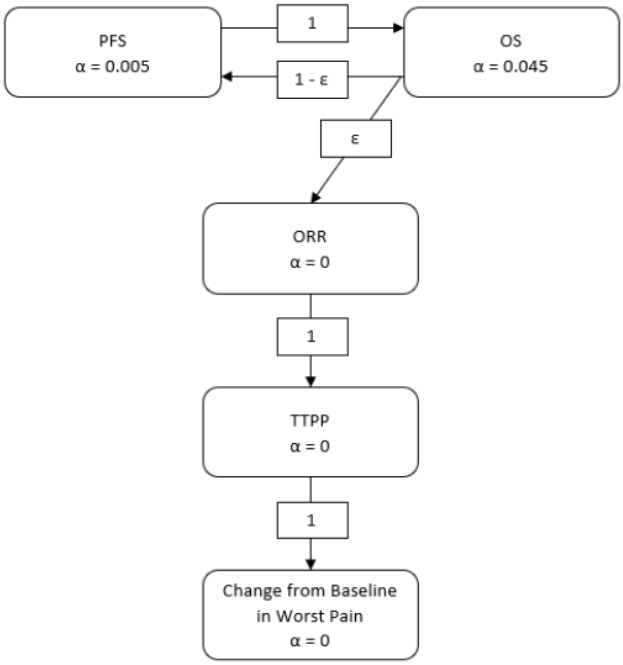
- Stratification factors: Cisplatin eligibility (eligible, ineligible); PD-L1 expression (low [CPS < 10], high [CPS ≥ 10]); Liver metastases status (present, absent).
- Age (<65, ≥65 years old)
- Region (North America, Europe, Rest of World)
- Sex (female, male)
- Race (white, non-white)
- ECOG performance status (PS) at baseline (0, 1-2)
- Visceral metastases vs. lymph nodes only metastases
- Primary disease site of origin (upper tract, lower tract)
- Renal function (normal, mild, moderate, severe).

Estimated treatment effect (with a nominal 95% CI) for PFS and OS was provided for each subgroup using a stratified Cox proportional hazards regression model controlling stratification factors. If the subgroup was a stratification factor, then the stratified models controlled for the rest of stratification factors. For ORR, the difference between treatment arms (with a nominal 95% CI) will be calculated for each subgroup. In addition, KM curves were generated by arm for selected subgroups (e.g. cisplatin eligibility and PD-L1 expression). A subgroup analysis was not performed if the total number of subjects in a subgroup was too small (e.g. < 10% of the total sample size). For subgroup variables with more than two levels, pooling might be considered when there was no sufficient sample size within one level.

Error probabilities, adjustment for multiplicity and interim analyses:

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 was used. The initial alpha allocation is 0.005 to PFS and 0.045 to OS as shown in the figure below. 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 4: **Graphical illustration of Multiplicity Adjustment**



The study was planned to have only one PFS analysis (at time of PFS final analysis) and two OS analyses, one interim analysis at the time of PFS final analysis and one final analysis. The Lan-DeMets spending function was used to approximate O'Brien-Fleming boundaries. The efficacy boundaries for PFS at the initially allocated alpha of 0.005 and the updated alpha of 0.05 (if OS is statistically significant) are shown in the table below.

Table 12: 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

Table below shows the efficacy boundaries for OS at the initially allocated alpha of 0.045 and the updated alpha of 0.05 (if PFS is statistically significant).

Table 13: 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 were statistically significant, selected secondary endpoints were 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 will be at the 0.05 significance level (2-sided) as long as

all preceding null hypotheses are rejected. 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 were analyzed only descriptively.

Two efficacy analyses were planned for this study. The PFS final analysis was planned when approximately 526 PFS events or 356 OS events (72.8% information fraction) in the ITT analysis set had occurred, whichever was later. An OS IA was planned at the time of the PFS final analysis. The OS final analysis was planned when approximately 489 OS events had occurred in the ITT analysis set. If OS was statistically significant at IA, this interim OS analysis became the final OS analysis. A summary of analyses timing at the planned PFS and OS analyses are presented in the table below.

Table 14: 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.

Changes from protocol-specified analyses

No changes from the planned analyses were reported. The SAP was updated through the study course in order to reflect changes in Protocol Amendments.

Results

Participant flow

Results from Arm C are not presented within this report.

Figure 5: **Subject disposition (ITT analysis set) in Study EV-302 (KEYNOTE-A39)**

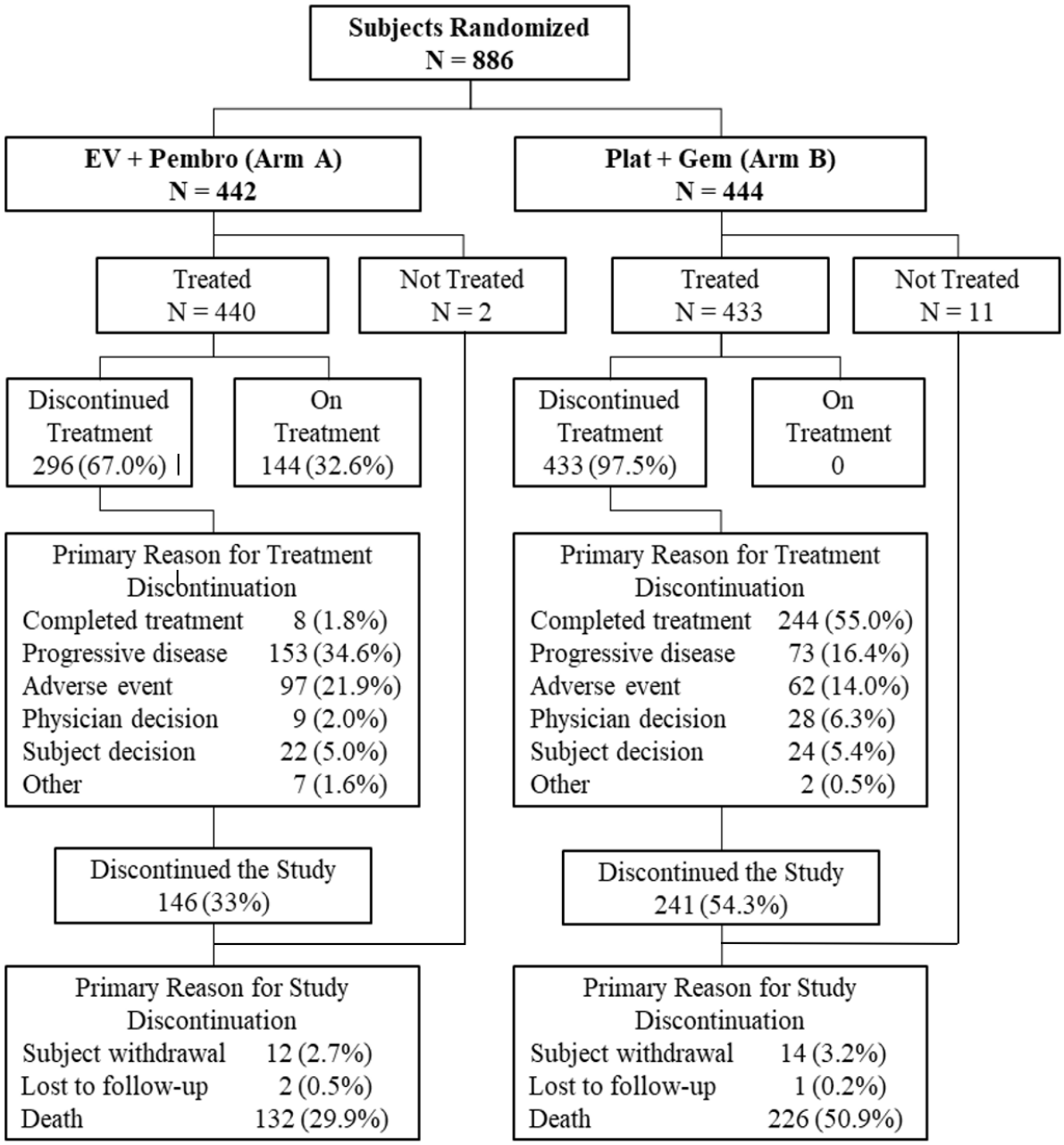


Table 15: Sumamry of screening failures

	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)

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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
Source: O:\Projects\ASG-22ME\SGN22E-003\csr_1552\v01\outputs\tlfs\pgms\t-disp-scm.sas Output: t12-01-01-02-disp-scm.rtf (28SEP23:08:50) Data: adsl

Recruitment

Beginning March 2020 (date of first signed informed consent), 1,297 subjects with previously untreated LA or mUC gave informed consent to participate in the study, and 886 were randomized to the EV + Pembro and Plat + Gem arms. 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.

Enrollment started in March 2020. The last subject was recruited to the global portion of study EV-302 on 05 October 2022.

As of the data cut-off date on 08 August 2023, median follow-up for both groups combined was 17.3 months (range 0-37.2 months).

Conduct of the study

Table 16: 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 known active hepatitis B

Amendment Number	Date	Key Changes	Rationale
			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 use of maintenance

Amendment Number	Date	Key Changes	Rationale
			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 statistical testing and updated multiplicity.	• As informed by the EV-103 PRO data readout (Oct 2022) wherein EV + Pembro showed a clinically meaningful improvement from baseline in pain outcomes, PRO

Amendment Number	Date	Key Changes	Rationale
			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 17: Summary of important protocol deviations (ITT Analysis set)

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 18: 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

Demographics

Table 19: 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)

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

Table 20: 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 21: Baseline 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.

Cisplatin Ineligibility

Table 22: reasons for cisplatin ineligibility (ITT analysis set)

	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 23: Biomarkers: Expression of Nectin-4 and 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
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 at CCI

‡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 at CCI

Prior therapies

Table 24: 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)

Numbers analysed

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

Table 25: Subjetcs enrolled and included in each analysis set

	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)

ITT analysis set includes all randomized subjects.

Safety analysis set includes all randomized subjects who received any amount of study treatment.

Response evaluable set by BICR includes all subjects in ITT analysis set who had measurable disease at baseline per RECIST v1.1 by BICR.

Response evaluable set by investigator includes all subjects in ITT analysis set who had measurable disease at baseline per RECIST v1.1 by investigator.

EV PK analysis set includes all randomized subjects who received any amount of enfortumab vedotin and had at least one PK sample.

PRO full analysis set includes all randomized subjects who received any amount of study treatment and completed at least one PRO assessment at baseline.

BICR: Blinded independent central review; EV: Enfortumab vedotin; Gem: Gemcitabine; ITT: Intent-to-treat; Pembro: Pembrolizumab; PFS: Progression free survival; PK: Pharmacokinetic; PRO: Patient reported outcome; Plat: Platinum-based chemotherapy (cisplatin or carboplatin); RECIST: Response Evaluation Criteria in Solid Tumors

Outcomes and estimation

Primary Endpoints

PFS by BICR

Table 26: 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.

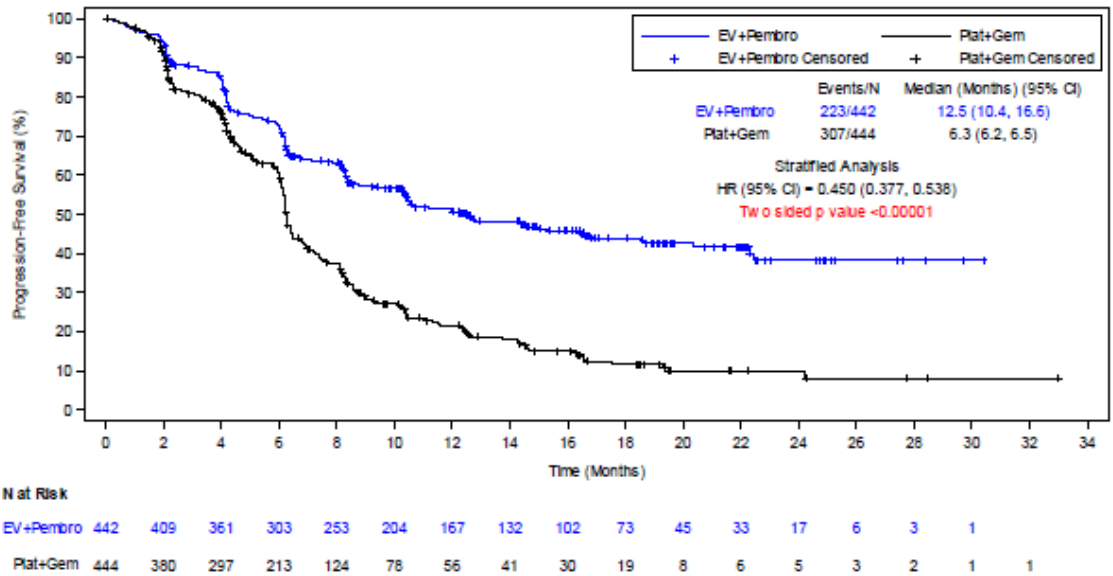
§Calculated using stratified log-rank test. The p-value threshold for statistical significance is 0.005.

¶As estimated using Kaplan-Meier method.

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

+ indicates censoring.

Figure 6: Kaplan-Meier plot of PFS by BICR in the ITT analysis set, Study EV-302 (KEYNOTE-A39), DCO 08-AUG-2023



Overall Survival

Table 27: 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.

Figure 7: Kaplan-Meier plot of OS in the ITT analysis set, Study EV-302 (KEYNOTE-A39), DCO 08-AUG-2023

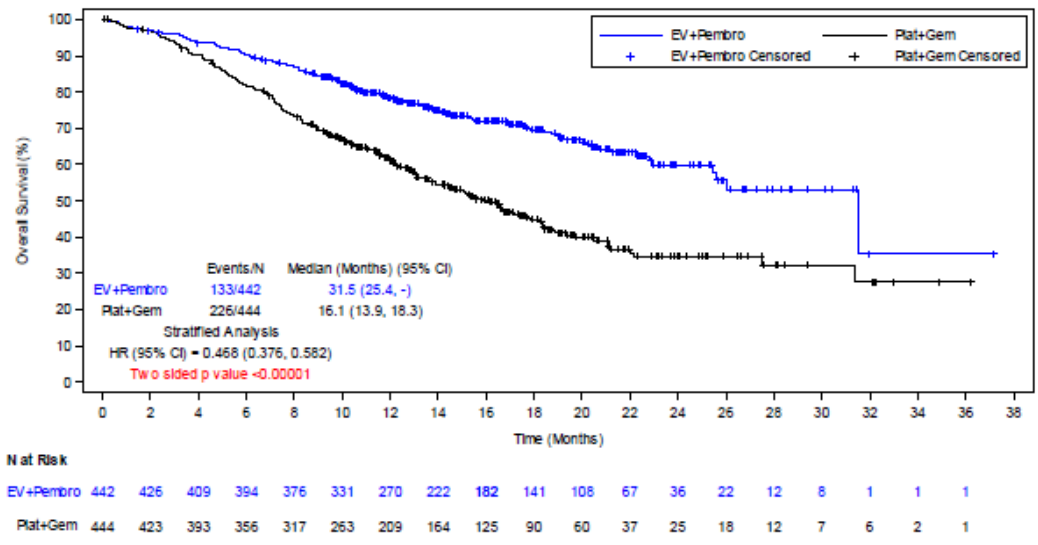


Table 28: Summary of censoring reasons for OS, Study EV-302 (KEYNOTE-A39)

	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

Secondary Endpoints

ORR by BICR

Table 29: ORR and Best Overall Resposnce per RECIST by BICR

	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.

DoR by BICR

Table 30: DOR per RECIST by BICR (Response Evaluable Analysis Set)

	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 (PRO)

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.

Time to Pain Progression (TTPP) (BPI-SF Q3 and Q7)

Table 31: Time to Pain Progression (PRO Full Analysis Set)

	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 8: Kaplan-Meier Plot of Time Progression (PRO full analysis set)

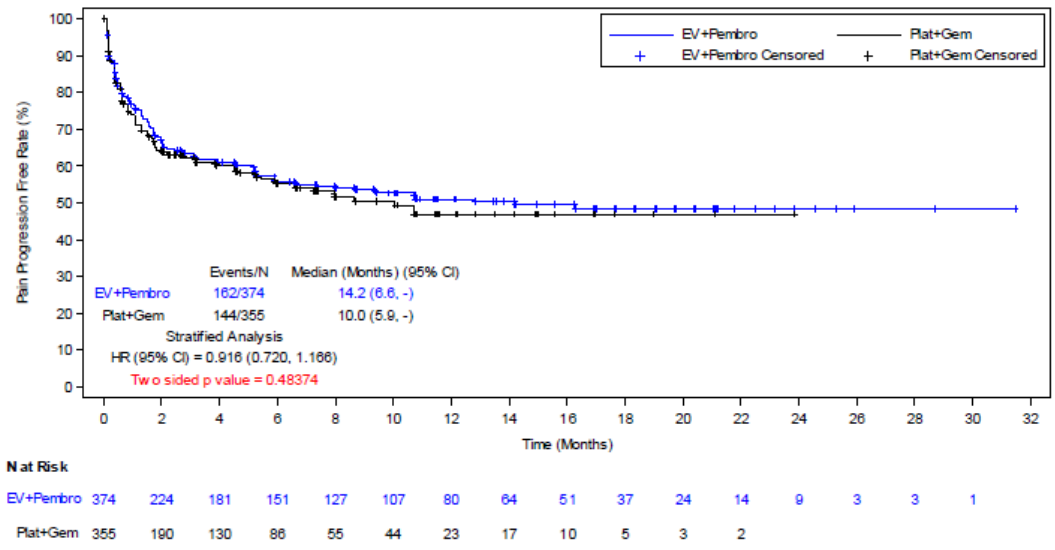
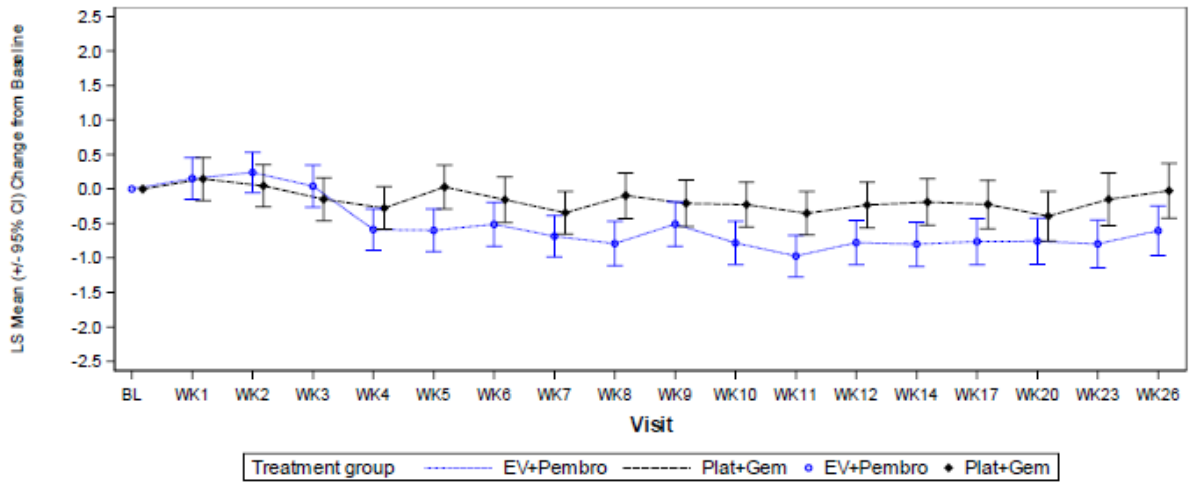


Figure 9: Least squares mean change from baseline in worst pain (±95% CI), BPI-SF Q3 in the PRO full analysis set, Study EV-302 (KEYNOTE-A39)



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

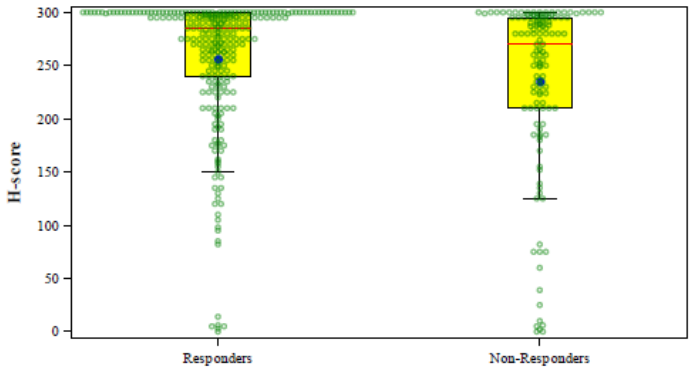
Overall, 85.3% of subjects in the EV + Pembro Arm and 80.6% of subjects in the Plat + Gem Arm completed at least 1 component of the EQ-5D-5L questionnaire at baseline. The mean baseline VAS scores were 72.8 in the EV + Pembro Arm and 69.7 in the Plat + Gem Arm; the Health State Index

Scores (utility scores) were 0.844 and 0.818, respectively. During the treatment period, both VAS and utility scoes remained stable with little to no change from baseline throughout the study period.

Exploratory endpoints

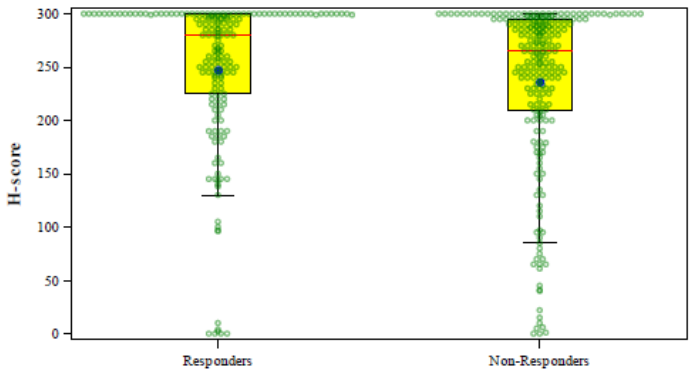
Response by Nectin-4

Figure 10: **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 11: **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 32: PFS per RECIST by BICR, Sensitivity1 (unstratified analysis).

	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+

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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 33: PFS per RECIST by BICR, Sensitivity 2 (Ignore New Therapy before PD/Death).

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)

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Sensitivity Analysis 2 (Ignore New Anticancer Therapy before PD/Death): starting new anticancer therapies is not a cenoring 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 34: PFS per RECIST by BICR, Sensitivity 3 (Ignore >= missing tumour assessment)

	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 35: OS per RECIST by BICR, Sensitivity1 (unstratified analysis).

	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 36: OS per RECIST by BICR, 3 (IPCW for subsequent Anticancer Therapy)

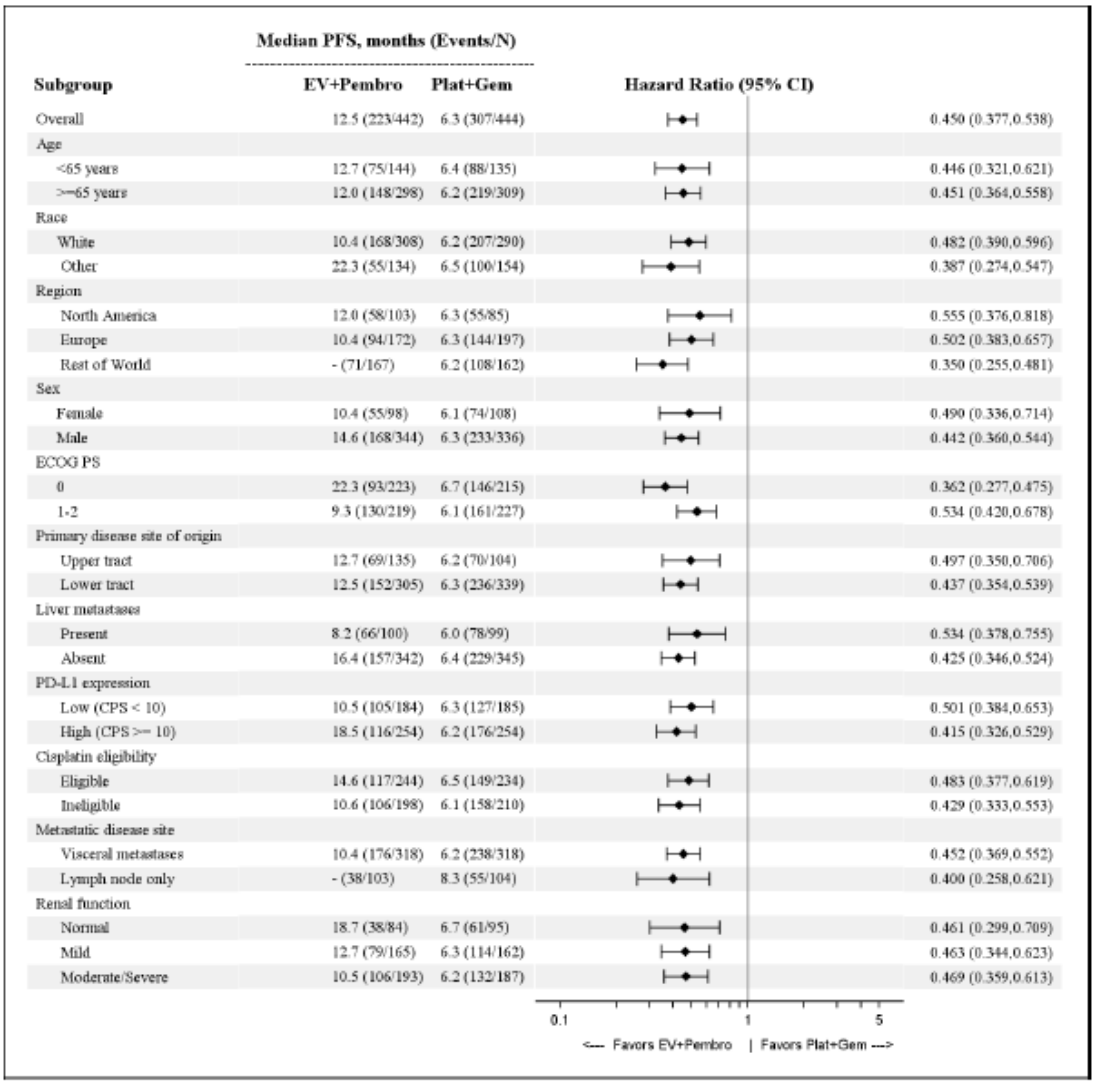
	EV+Pembro (N=442)	Plat+Gem (N=444)
Number of deaths, n (%)	133 (30.1)	226 (50.9)
IPCW method[a]		
Hazard ratio (95%CI)	0.482 (0.346, 0.672)	
Two-sided p-value	0.00002	

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

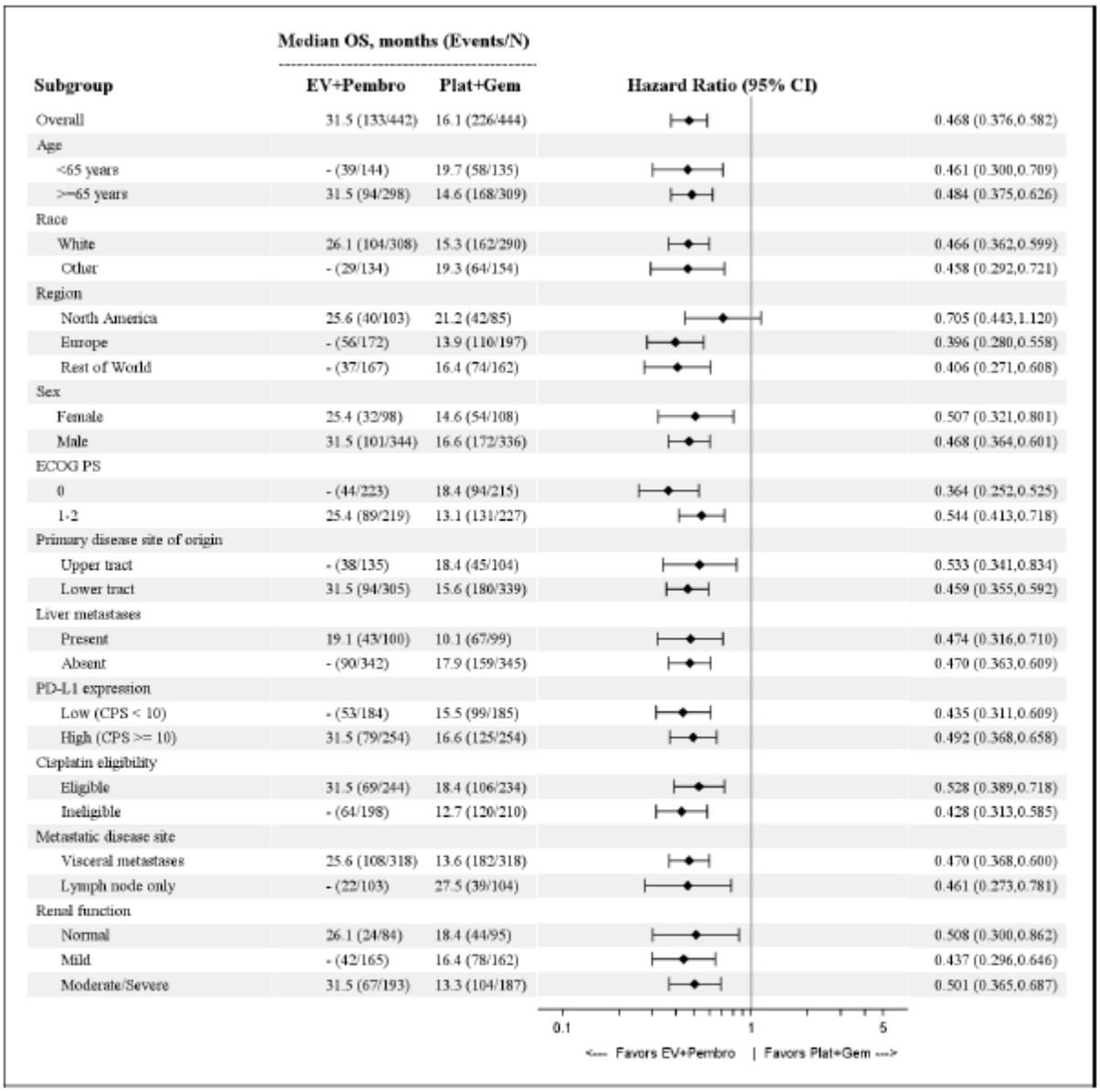


Note: Liver metastases and cisplatin eligibility subgroups are based on post-randomization corrections CRF. Randomization was stratified by PD-L1 status (high or low) based on information available at screening. For subgroup analyses by PD-L1 status (low or high), subjects whose tissue sample was found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

- indicates not reached; BICR: Blinded independent central review; CPS: combined positive score; CRF: Case Report Form; ECOG PS: Eastern Cooperative Oncology Group performance status; EV: Enfortumab vedotin; Gem: Gemcitabine; ITT: Intent to treat; Pembro: Pembrolizumab; Plat: Platinum-based chemotherapy; PFS: Progression free survival; Response Evaluation Criteria in Solid Tumors

OS

Figure 13: **Subgroup analyses of OS in the ITT analysis set, Study EV-302 (KEYNOTE-A39), DCO 08-AUG-2023**



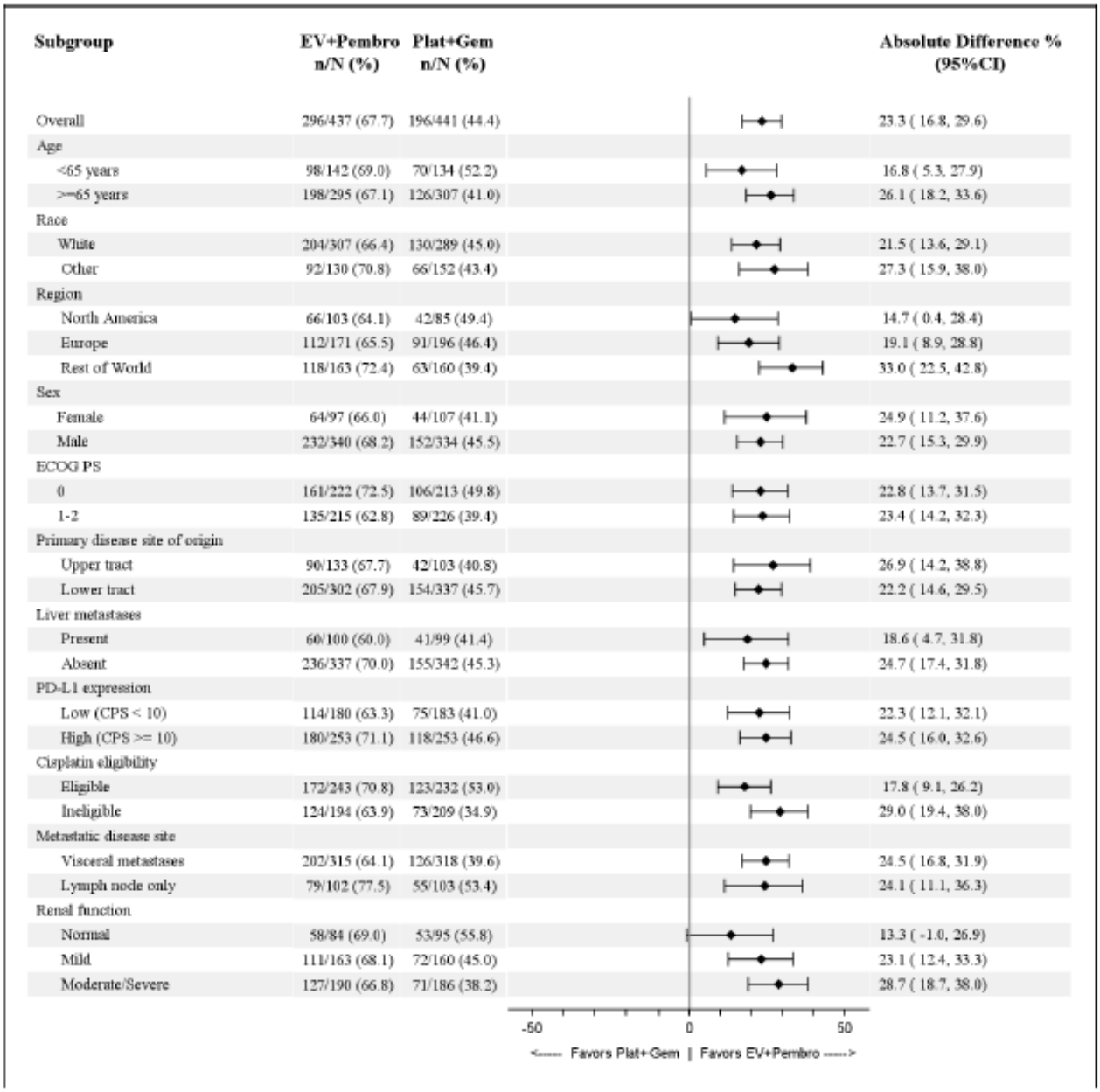
Note: Liver metastases and cisplatin eligibility subgroups are based on post-randomization corrections CRF.

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.

- indicates not reached; CPS: Combined positive score; CRF: Case report form; ECOG PS: Eastern Cooperative Oncology Group performance status; EV: Enfortumab vedotin; Gem: Gemcitabine; ITT: Intent to treat; Pembro: Pembrolizumab; Plat: Platinum-based chemotherapy; OS: Overall survival

ORR

Figure 14 : 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

Figure 15: **Subgroup Analysis of Progression-Free Survival per RECIST by BICR for H-Score of Nectin-4 Expression (EV-302 ITT Analysis Set)**

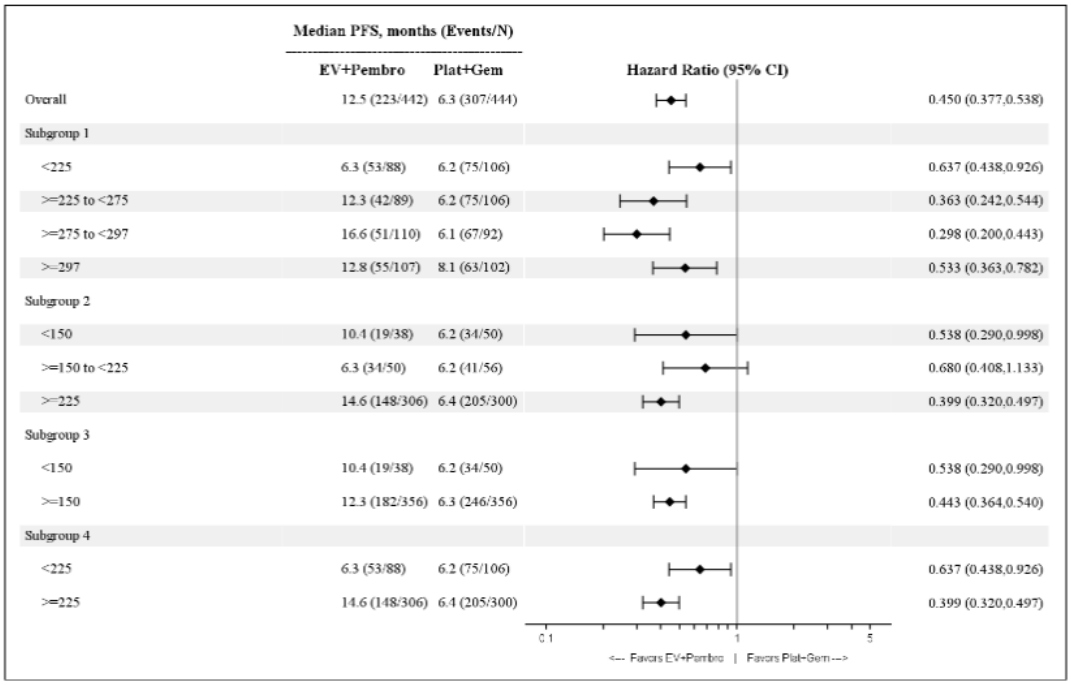
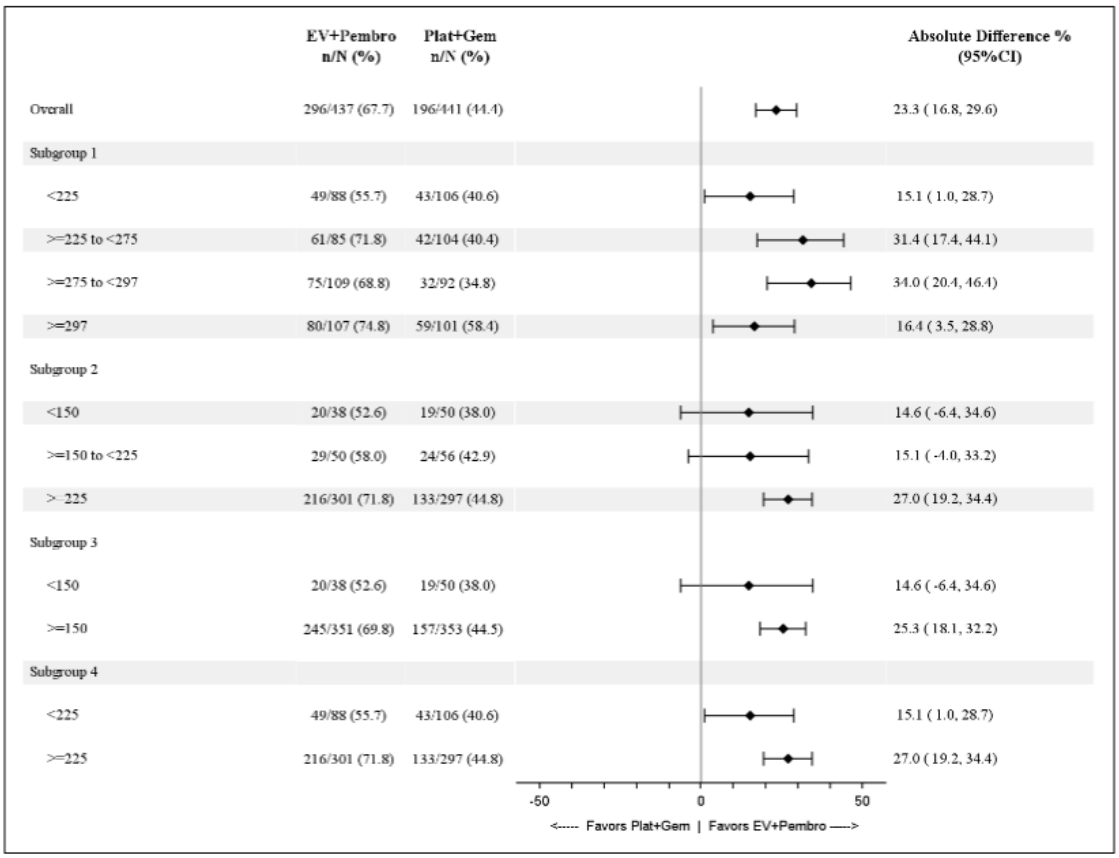


Figure 16: **Subgroup Analysis of Overall Survival for H-Score of Nectin-4 Expression (EV-302 ITT Analysis Set)**

Figure 17: **Subgroup Analysis of Objective Response Rate per RECIST by BICR for H-Score of Nectin-4 Expression (EV-302 Response Evaluable Set by BICR**



Subgroup analysis by age

Table 37: 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 38: 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 39: 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 40: Subsequent Anticancer Therapy (ITT analysis)

	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 tables summarise 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)

Summary of Efficacy for trial 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: Duration of Extension phase:	2 years not applicable 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 41: **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-869)

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.

Study Design

Study EV-103 is an ongoing phase 1b/2, global, multicenter study designed to evaluate the safety, antitumor 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.

Methods

Study Participants

Inclusion Criteria

Subjects enrolled in the dose escalation cohort were either (a) cisplatin ineligible (by investigator determination) and had not received prior systemic therapy for locally advanced or metastatic disease or (b) had previously experienced disease progression during or following treatment with at least 1 platinum-containing regimen. To be eligible for Cohort A or Cohort K, subjects must have satisfied all of the following criteria: been cisplatin ineligible, had not received prior systemic treatment for locally advanced or metastatic disease, and had not received adjuvant/neoadjuvant treatment with platinum-containing chemotherapies within 12 months. Cisplatin ineligibility was defined as at least 1 of the following criteria:

• Cohort A: CrCL ≥ 30, < 60 mL/min, ECOG PS of 2, hearing loss/dysfunction, age, and/or allergy to cisplatin.

• Cohort K: GFR ≥ 30, < 60 mL/min, ECOG PS of 2, Grade ≥ 2 hearing loss, or NYHA Class III heart failure (Subjects with ECOG PS of 2 must additionally have had hemoglobin ≥10 g/dL, GFR ≥50 mL/min, and been without NYHA Class III heart failure).

All subjects must have been eligible to receive a PD-1/PD-L1 inhibitor but may not have been treated previously with a drug in this class. Prior treatment with enfortumab vedotin or another MMAE-based ADC for urothelial cancer was not allowed, nor was known hypersensitivity to enfortumab vedotin or pembrolizumab (including excipients of either).

Exclusion criteria

Key exclusionary medical conditions included Grade ≥ 2 sensory or motor neuropathy; active keratitis or corneal ulcerations, uncontrolled diabetes, idiopathic pulmonary fibrosis, organizing pneumonia, or pneumonitis. Conditions that required high-dose steroids or other immunosuppressive agents, history of autoimmune disease (dose escalation and Cohort A), or active autoimmune disease that required systemic treatment within 2 years (Cohort K) were not permitted. Subjects were ineligible if they had a recent (< 6 months) cardiovascular event (i.e. stroke, cerebral vascular event, unstable angina, myocardial infarction). Subjects with NYHA Class III-IV heart failure were excluded from the dose escalation cohort and Cohort A, and those with NYHA Class IV were excluded from Cohort K.

Treatments

Table 42: Investigational Product

Cohort	Enfortumab vedotin IV	Pembrolizumab IV
Dose Escalation	1 mg/kg or 1.25 mg/kg over 30 min on days 1 and 8	200 mg over 30 min on day 1
Expansion Cohort A	1.25 mg/kg over 30 min on days 1 and 8	200 mg over 30 min on day 1
Randomized Cohort K		
Monotherapy arm	1.25 mg/kg over 30 min on days 1 and 8	--
Combination arm	1.25 mg/kg over 30 min on days 1 and 8	200 mg over 30 min on day 1

--: not applicable; IV: intravenous.

Objectives (outcomes/endpoints)

Dose Escalation

The primary objective of the dose escalation cohort was to assess safety and tolerability of enfortumab vedotin in combination with pembrolizumab. Determining the recommended dose of enfortumab vedotin for the combination based on assessment of DLTs was an important secondary objective.

Expansion Cohort A

The primary objective of Cohort A was to further assess the safety and tolerability of combination treatment that incorporated the recommended dose of enfortumab vedotin (i.e., 1.25 mg/kg); assessing antitumor activity of the combination was an important secondary objective of Cohort A.

Randomized Cohort K

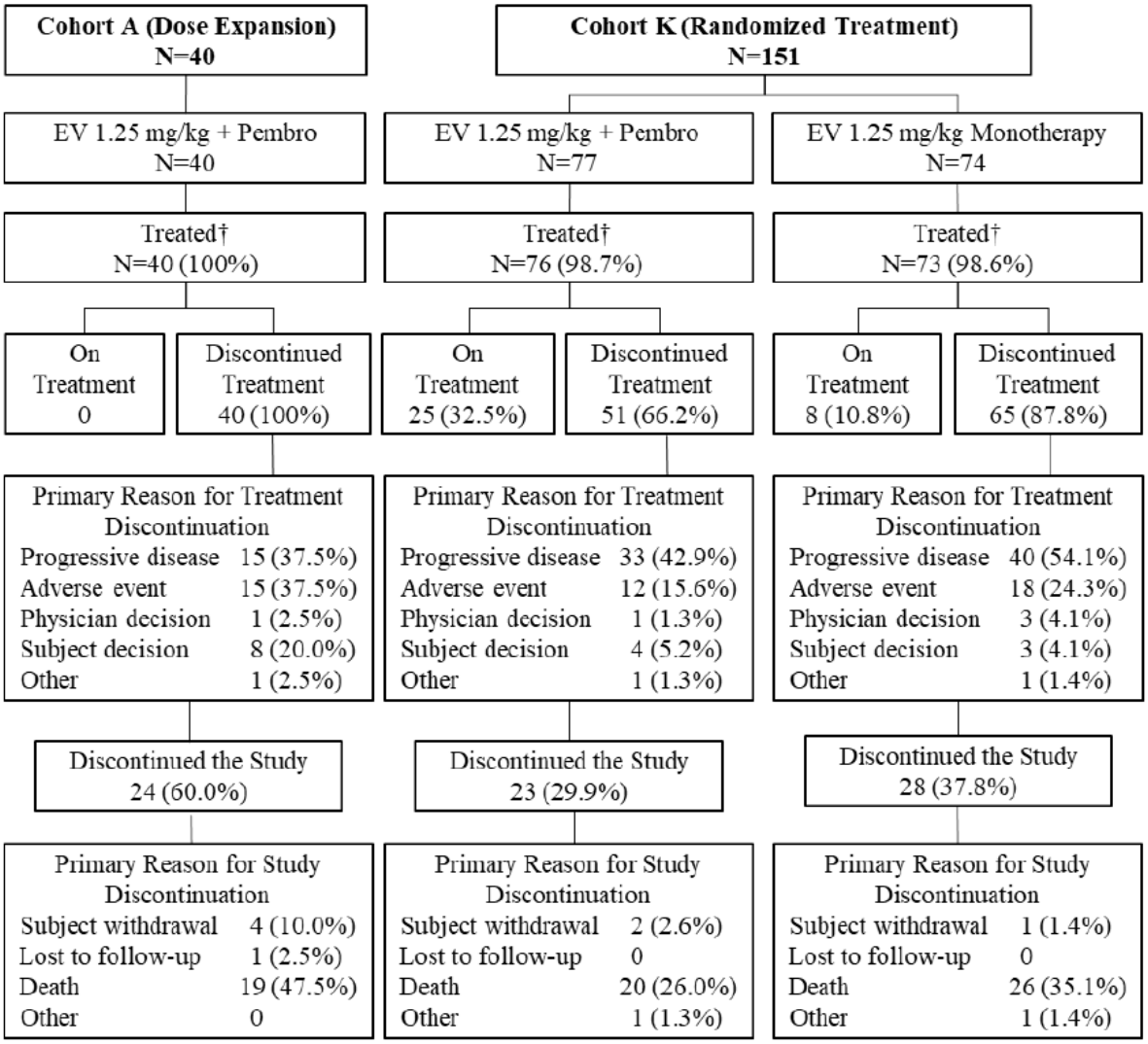
For Cohort K, the primary objective was to assess the antitumor activity of enfortumab vedotin in combination with pembrolizumab, as measured by ORR, defined as the proportion of subjects with confirmed CR and PR according to RECIST v1.1 by BICR assessment.

Subjects who did not have at least 2 post baseline response assessments (initial response and confirmation scan) were counted as non-responders. Confirmed ORR per RECIST v1.1 by investigator assessment was a secondary endpoint.

Results

Disposition

Figure 18: Subject disposition (ITT analysis set) in Study EV-302 (KEYNOTE-A39)



Baseline data

Table 43: Demographic (Full analysis set)

Parameter Statistic/Criteria	Cohort A EV + Pembro N = 40	Cohort K EV + Pembro N = 76	Cohort K EV Mono N = 73	Dose Escal + Cohort A† EV + Pembro N = 45	Dose Escal + Cohorts A and K† EV + Pembro N = 121
Age (years)					
Mean (SD)	70.0 (8.3)	71.7 (9.1)	73.2 (8.3)	70.1 (8.4)	71.1 (8.9)
Median (min, max)	69.0 (51, 90)	71.0 (51, 91)	74.0 (56, 89)	69.0 (51, 90)	71.0 (51, 91)
Age group (years), n (%)					
< 65	11 (27.5)	17 (22.4)	11 (15.1)	12 (26.7)	29 (24.0)
≥ 65	29 (72.5)	59 (77.6)	62 (84.9)	33 (73.3)	92 (76.0)
< 75	26 (65.0)	52 (68.4)	39 (53.4)	29 (64.4)	81 (66.9)
≥ 75	14 (35.0)	24 (31.6)	34 (46.6)	16 (35.6)	40 (33.1)
Sex, n (%)					
Female	9 (22.5)	22 (28.9)	17 (23.3)	9 (20.0)	31 (25.6)
Male	31 (77.5)	54 (71.1)	56 (76.7)	36 (80.0)	90 (74.4)
Ethnicity					
Hispanic or Latino	4 (10.0)	8 (10.5)	2 (2.7)	4 (8.9)	12 (9.9)
Not Hispanic or Latino	35 (87.5)	66 (86.8)	64 (87.7)	40 (88.9)	106 (87.6)
Not Reported	0	1 (1.3)	6 (8.2)	0	1 (0.8)
Unknown	1 (2.5)	1 (1.3)	1 (1.4)	1 (2.2)	2 (1.7)
Race					
Asian	0	5 (6.6)	6 (8.2)	0	5 (4.1)
Black or African American	0	5 (6.6)	5 (6.8)	1 (2.2)	6 (5.0)
White	38 (95.0)	61 (80.3)	55 (75.3)	42 (93.3)	103 (85.1)
Other	1 (2.5)	1 (1.3)	0	1 (2.2)	2 (1.7)
Unknown	1 (2.5)	3 (3.9)	1 (1.4)	1 (2.2)	4 (3.3)
Not Reported	0	1 (1.3)	6 (8.2)	0	1 (0.8)
Geographic Region					
North America	40 (100.0)	73 (96.1)	66 (90.4)	45 (100.0)	118 (97.5)
Europe	0	3 (3.9)	7 (9.6)	0	3 (2.5)

Escal: escalation; EV: enfortumab vedotin; Pembro: pembrolizumab.
†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).

Table 44: Baseline caractheristic (Full analysis set)

Parameter Statistic/Criteria	Cohort A EV + Pembro N = 40	Cohort K EV + Pembro N = 76	Cohort K EV Mono N = 73	Dose Escal + Cohort A† EV + Pembro N = 45	Dose Escal + Cohorts A and K† EV + Pembro N = 121
ECOG PS, n (%)					
0	14 (35.0)	33 (43.4)	28 (38.4)	15 (33.3)	48 (39.7)
1	19 (47.5)	33 (43.4)	35 (47.9)	22 (48.9)	55 (45.5)
2	7 (17.5)	10 (13.2)	10 (13.7)	8 (17.8)	18 (14.9)
Smoking status, n (%)					
Current or former	27 (67.5)	48 (63.2)	55 (75.3)	32 (71.1)	80 (66.1)
Non-smoker	13 (32.5)	28 (36.8)	18 (24.7)	13 (28.9)	41 (33.9)
Height, cm					
Mean (SD)	171.5 (9.2)	171.4 (10.7)	171.1 (9.9)	171.8 (8.9)	171.5 (10.0)
Median (min, max)	173.5 (150, 185)	170.8 (150, 203)	170.1 (152, 193)	173.0 (150, 185)	172.2 (150, 203)
Weight, kg					
Mean (SD)	83.7 (23.6)	79.2 (18.8)	77.7 (18.0)	83.5 (22.4)	80.8 (20.3)
Median (min, max)	79.9 (51, 172)	79.0 (42, 133)	76.5 (42, 116)	79.7 (51, 172)	79.2 (42, 172)
Weight (kg) category, n (%)					
≥100 kg	9 (22.5)	13 (17.1)	10 (13.7)	9 (20.0)	22 (18.2)
<100 kg	31 (77.5)	63 (82.9)	63 (86.3)	36 (80.0)	99 (81.8)
BMI, kg/m²					
Mean (SD)	28.3 (6.8)	26.8 (5.5)	26.3 (4.9)	28.1 (6.5)	27.3 (5.9)
Median (min, max)	27.9 (20, 55)	25.8 (14, 43)	26.4 (16, 42)	27.9 (20, 55)	26.4 (14, 55)
BMI (kg/m²) category, n (%)					
<25	15 (37.5)	34 (44.7)	30 (41.1)	16 (35.6)	50 (41.3)
25 to <30	14 (35.0)	22 (28.9)	27 (37.0)	18 (40.0)	40 (33.1)
≥30	11 (27.5)	20 (26.3)	16 (21.9)	11 (24.4)	31 (25.6)
Renal function‡, n (%)					
Normal	8 (20.0)	9 (11.8)	4 (5.5)	9 (20.0)	18 (14.9)
Mild decrease	12 (30.0)	14 (18.4)	13 (17.8)	12 (26.7)	26 (21.5)
Moderate decrease	19 (47.5)	50 (65.8)	53 (72.6)	23 (51.1)	73 (60.3)
Severe decrease	1 (2.5)	3 (3.9)	3 (4.1)	1 (2.2)	4 (3.3)
Hepatic function¶, n (%)					
Normal	36 (90.0)	73 (96.1)	65 (89.0)	41 (91.1)	114 (94.2)
Mild decrease	4 (10.0)	2 (2.6)	5 (6.8)	4 (8.9)	6 (5.0)
Moderate decrease	0	0	3 (4.1)	0	0
Severe decrease	0	1 (1.3)	0	0	1 (0.8)
Hemoglobin, n (%)					
<10 g/dL	2 (5.0)	9 (11.8)	9 (12.3)	3 (6.7)	12 (9.9)
≥ 10 g/dL	38 (95.0)	67 (88.2)	64 (87.7)	42 (93.3)	109 (90.1)
HbA1c (%) category, n (%)					
<5.7	21 (52.5)	35 (46.1)	25 (34.2)	22 (48.9)	57 (47.1)
≥5.7 to <6.5	16 (40.0)	34 (44.7)	34 (46.6)	20 (44.4)	54 (44.6)
≥6.5	3 (7.5)	7 (9.2)	14 (19.2)	3 (6.7)	10 (8.3)

AST: aspartate aminotransferase; CrCL: creatinine clearance; ECOG PS: Eastern Cooperative Oncology Group Performance Status; Escal: escalation; EV: enfortumab vedotin; Pembro: pembrolizumab; TB: total bilirubin; ULN: upper limit of normal.

†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).

‡CrCL estimated using Cockcroft-Gault formula based on last non-missing serum creatinine measurement before the first dose. Normal: ≥ 90 mL/min; Mild: ≥ 60 and < 90 mL/min; Moderate: ≥ 30 and < 60 mL/min; Severe: ≥ 15 and < 30 mL/min.

¶Based on the last non-missing AST and TB measurements before the first dose. Normal: TB ≤ ULN and AST ≤ ULN; Mild: (TB > 1 – 1.5 x ULN and any AST) or (TB ≤ ULN and AST > ULN); Moderate: TB > 1.5 – 3 x ULN and any AST; Severe: TB > 3 x ULN and any AST.

Table 45: Reasons for Cisplatin Ineligibility (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
Subjects meeting the following Galsky criteria, n (%)‡	39 (97.5)	76 (100.0)	72 (98.6)	44 (97.8)	120 (99.2)
(1) CrCL <60 and ≥30 mL/min§	23 (57.5)	48 (63.2)	44 (60.3)	25 (55.6)	73 (60.3)
(2) ECOG PS of 2	5 (12.5)	6 (7.9)	9 (12.3)	6 (13.3)	12 (9.9)
(3) ≥ Grade 2 hearing loss	4 (10.0)	11 (14.5)	11 (15.1)	5 (11.1)	16 (13.2)
Criteria (1) and (2)	2 (5.0)	4 (5.3)	1 (1.4)	2 (4.4)	6 (5.0)
Criteria (1) and (3)	5 (12.5)	7 (9.2)	7 (9.6)	5 (11.1)	12 (9.9)
Criteria (2) and (3)	0	0	0	1 (2.2)	1 (0.8)
Subjects considered cisplatin ineligible without meeting Galsky criteria, n (%)††	1 (2.5)	0	1 (1.4)	1 (2.2)	1 (0.8)

CrCL: creatinine clearance; ECOG PS: Eastern Cooperative Oncology Group Performance Status; Escal: escalation; EV: enfortumab vedotin; MDRD: Modification of Diet in Renal Disease; Pembro: pembrolizumab.

†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).

‡ Each subject can be in only 1 category. Assessments were done at the screening/baseline visit.

§ Estimated creatinine clearance per Cockcroft-Gault Criteria or 24-hr urine collection or MDRD equation.

††One subject in Cohort A was considered cisplatin ineligible by the investigator due to solitary kidney, and 1 subject in Cohort K was considered cisplatin ineligible by the investigator due to age and Grade 1 hearing loss.

Table 46: Biomarkers: Expression of Nectin-4 and PD-L1 in Tumor Tissue by IHC (Full Analysis Set)

Parameter Statistic/Criteria	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
Nectin-4 expression, H-score					
n‡	33	74	66	38	112
Mean (SD)	276.7 (45.4)	233.3 (83.8)	258.7 (55.2)	271.8 (53.0)	246.4 (76.7)
Median	300.0	262.5	284.0	300.0	286.0
Q1, Q3	290.0, 300.0	200.0, 297.0	240.0, 298.0	270.0, 300.0	220.0, 300.0
Min, max	110, 300	0, 300	90, 300	100, 300	0, 300
PD-L1 expression, CPS, n (%)					
n‡	28	75	66	33	108
PD-L1 high (CPS ≥ 10)	14 (50.0)	31 (41.3)	28 (42.4)	15 (45.5)	46 (42.6)
PD-L1 low (CPS < 10)	14 (50.0)	44 (58.7)	38 (57.6)	18 (54.5)	62 (57.4)

CPS: combined positive score; Escal: escalation; EV: enfortumab vedotin; IHC: immunohistochemistry; PD-L1: programmed cell death ligand 1; Pembro: pembrolizumab.

†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).

‡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.

Table 47: Baseline disease characteristics in the ITT analysis set of Study EV-302 (KEYNOTE-A39)

Parameter Statistic/Criteria	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
Bajorin risk factors‡, n (%)					
0	14 (35.0)	25 (32.9)	26 (35.6)	16 (35.6)	41 (33.9)
1	26 (65.0)	51 (67.1)	47 (64.4)	29 (64.4)	80 (66.1)
Extent of disease, n (%)					
Locally advanced	0	3 (3.9)	1 (1.4)	0	3 (2.5)
Metastatic	40 (100.0)	73 (96.1)	72 (98.6)	45 (100.0)	118 (97.5)
Time since diagnosis (months)§					
Mean (SD)	2.62 (2.58)	2.51 (4.68)	3.60 (10.32)	2.46 (2.48)	2.49 (3.99)
Median (min, max)	1.95 (0.3, 15.2)	1.38 (0.4, 34.8)	1.58 (0.5, 86.3)	1.84 (0.3, 15.2)	1.48 (0.3, 34.8)
Histology type, n (%)					
TCC only	12 (30.0)	32 (42.1)	19 (26.0)	15 (33.3)	47 (38.8)
TCC with squamous differentiation	7 (17.5)	8 (10.5)	7 (9.6)	8 (17.8)	16 (13.2)
TCC with other variants	21 (52.5)	36 (47.4)	47 (64.4)	22 (48.9)	58 (47.9)
Disease stage at baseline, n (%)					
IIIA	0	2 (2.6)	1 (1.4)	0	2 (1.7)
IV	14 (35.0)	30 (39.5)	23 (31.5)	15 (33.3)	45 (37.2)
IVA	6 (15.0)	12 (15.8)	11 (15.1)	7 (15.6)	19 (15.7)
IVB	20 (50.0)	32 (42.1)	38 (52.1)	23 (51.1)	55 (45.5)
Primary site of origin, n (%)					
Lower tract	26 (65.0)	46 (60.5)	51 (69.9)	30 (66.7)	76 (62.8)
Bladder	26 (65.0)	46 (60.5)	50 (68.5)	30 (66.7)	76 (62.8)
Urethra	0	0	1 (1.4)	0	0
Upper tract	14 (35.0)	30 (39.5)	21 (28.8)	15 (33.3)	45 (37.2)
Renal Pelvis	6 (15.0)	16 (21.1)	9 (12.3)	6 (13.3)	22 (18.2)
Ureter	8 (20.0)	14 (18.4)	12 (16.4)	9 (20.0)	23 (19.0)
Both¶	0	0	1 (1.4)	0	0
Metastatic site, n (%)					
Bone	7 (17.5)	19 (25.0)	21 (28.8)	8 (17.8)	27 (22.3)
Lymph nodes	29 (72.5)	51 (67.1)	56 (76.7)	34 (75.6)	85 (70.2)
Lung	18 (45.0)	37 (48.7)	30 (41.1)	19 (42.2)	56 (46.3)
Liver	12 (30.0)	13 (17.1)	13 (17.8)	14 (31.1)	27 (22.3)
Intra-thoracic/abdominal soft tissue (non-lymph node)	16 (40.0)	25 (32.9)	27 (37.0)	17 (37.8)	42 (34.7)
Other visceral disease	5 (12.5)	10 (13.2)	3 (4.1)	7 (15.6)	17 (14.0)
Metastasis category, n (%)					
Visceral	35 (87.5)	64 (84.2)	60 (82.2)	38 (84.4)	102 (84.3)
Lymph node only disease	5 (12.5)	10 (13.2)	12 (16.4)	7 (15.6)	17 (14.0)
Not applicable	0	2 (2.6)	1 (1.4)	0	2 (1.7)
CNS metastasis, n (%)	0	0	0	0	0

CNS: central nervous system; ECOG PS: Eastern Cooperative Oncology Group Performance Status; Escal: escalation; EV: enfortumab vedotin; Pembro: pembrolizumab; TCC: transitional cell carcinoma.

†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 visceral metastases (bone, lung, liver) or ECOG PS > 2 (subjects with ECOG PS > 2 not eligible for the study).

§Diagnosis of locally advanced or metastatic disease.

¶Includes primary disease in both bladder and ureter.

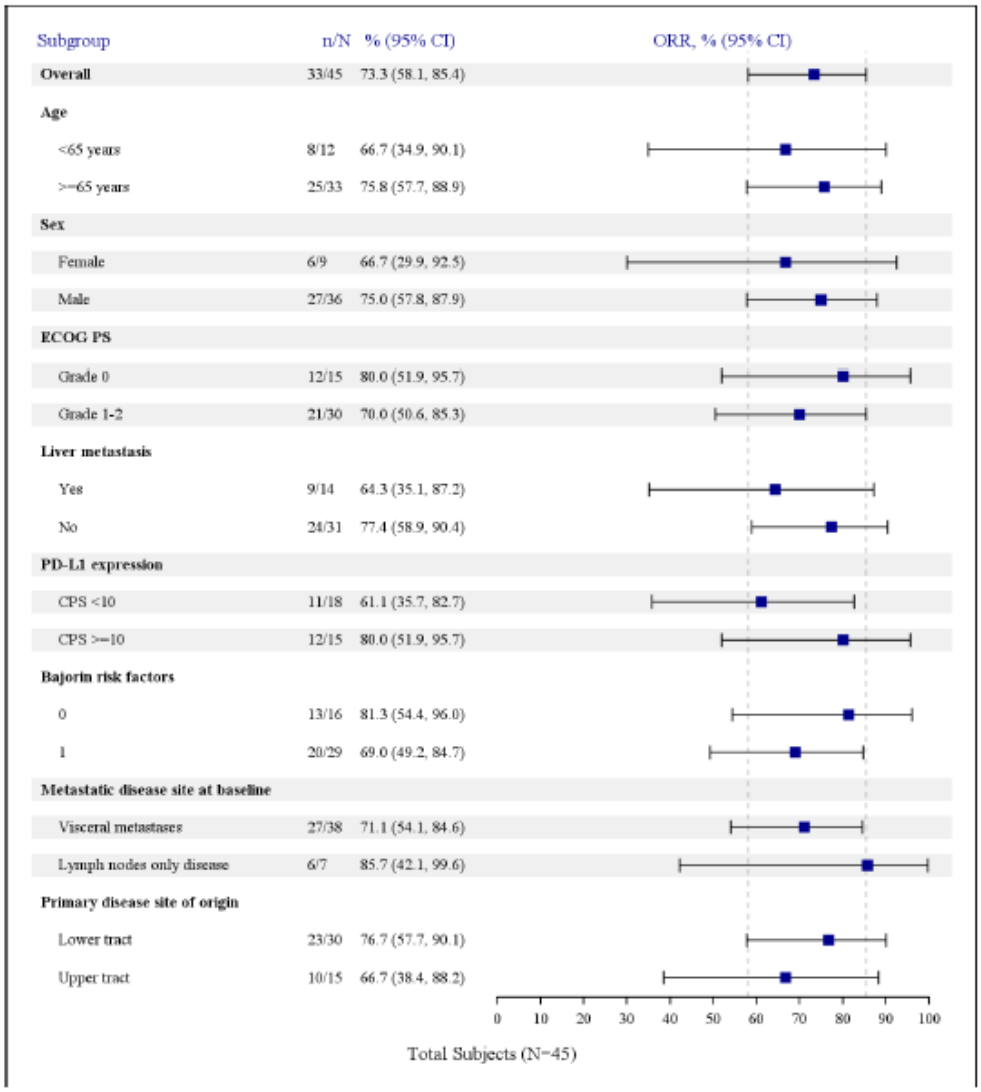
Outcomes and Estimations

Table 48: ORR, DCR and Best Overall Response in Cohort A, Cohort K and Combined Results (per RECIST v1.1, Full analys 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%

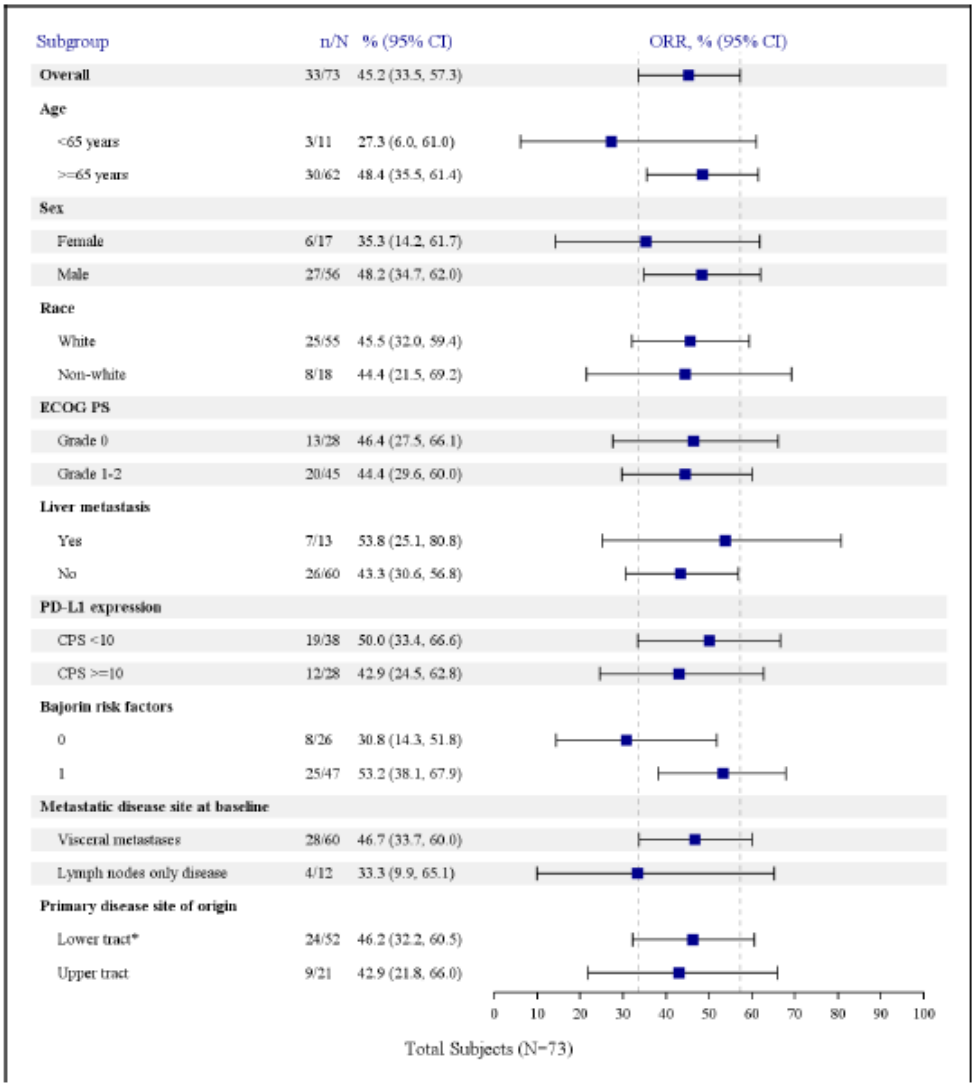
BICR: blinded independent central review; CR: complete response; DCR: disease control rate; Escal: escalation; EV: enfortumab vedotin; NE: not evaluable; ORR: objective response rate; PD: progressive disease; Pembro: pembrolizumab; PR: partial response; RECIST: response evaluation criteria in solid tumours; 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 19: Subgroup Analyses of ORR pre RECIST v1.1 by BICR: Dose Escalation + Cohort A (EV + Pembro)



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 20: **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 popultion 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. The MAH's sought wording of the indication (i.e. not specifying platinum eligibility) is deemed acceptable by the CHMP, as platinum-eligibility is not considered an effect modifier for pembrolizumab+EV combination. This criterion was used to select the study population fit for the control treatment. This would strictly constitute extrapolation to an extremely rare population of patients who are not candidate to even carboplatin-based treatment in 1L.

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 sensitivity 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 Ausgut 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 IHC 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.

2.4.4. Conclusions on the clinical efficacy

The efficacy evaluation of study EV-302 supports a statistically significant and clinically relevant advantage of the combined regimen enfortumab vedotin + pembrolizumab relative to platinum-based chemotherapy in the first-line treatment of LA/mUC patients. Benefits were observed across endpoints and across prespecified subgroups and supported by sensitivity analyses.

2.5. Clinical safety

Introduction

EV-302/KEYNOTE-A39 (hereafter study EV-302) is a global phase 3, open-label, 2-arm randomized multicenter study to evaluate the combination of enfortumab vedotin + pembrolizumab vs standard of care gemcitabine + platinum-containing chemotherapy in subjects with previously untreated LA/mUC. All-comer first-line subjects without preselection based on a tissue biomarker and regardless of PD-L1 expression status or cisplatin eligibility were enrolled.

In EV-302, a total of 886 subjects were randomized in a 1:1 to receive enfortumab vedotin + pembrolizumab in Arm A and gemcitabine + cisplatin or carboplatin in Arm B.

The integrated summary of safety (ISS/SCS) evaluates safety data pooled from 7 enfortumab vedotin studies (1 EV + Pembro combination study, 1 EV monotherapy or EV + Pembro combination study and 5 EV monotherapy studies) and pembrolizumab monotherapy reference safety data from 21 studies and pembrolizumab bladder pool from 3 studies (KEYNOTE-052, KEYNOTE-045 and KEYNOTE-361).

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

1. **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).

2. **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.

3. **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).

4. **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).

5. **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.

6. **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 table below lists the studies and cohorts included in each population.

Table 49: 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	Enables comparison with established safety profile of pembrolizumab monotherapy

	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	

EV: enfortumab vedotin; ISS: Integrated Summary of Safety; Pembro: pembrolizumab; RSD: reference safety data; UC: urothelial cancer
† Included studies does not mean all subjects in those studies belong to that population. The date for each Pembro monotherapy study refers to the specific cutoff date of datasets.
‡ Studies are included in the Pembro US RSD, which is a subset of Pembro RSD.
Source: EV-302 ISS SAP Table 2

The SAF for each population consists of all subjects who received any amount of study drug. This definition is consistent with the analysis of safety data conducted in the CSRs for each individual clinical study included in the integrated analyses. Severity of TEAEs in study EV-302 was graded according to the NCI CTCAE version 4.03. The coding dictionary for this safety analysis was MedDRA, which was used to summarize AEs by SOC and PT. The MedDRA version used for this SCS/ISS was 26.0. The MedDRA versions used for individual studies can be found in Section 6.1 of the EV-302 ISS/SCS SAP. The incidence or frequency of TEAEs reported in this document are subject incidence rates, unless otherwise specified. Subject incidence rates were calculated as the number of subjects experiencing an event divided by the number of subjects in the analysis population.

Patient exposure

Table 50: 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

EV: enfortumab vedotin; Combo: combination; ISS: integrated summary of safety; Max: maximum; Min: minimum; Mono: monotherapy; NA: not applicable; Pembro: pembrolizumab; RSD: reference safety data; SD: standard deviation.

† 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.

Table 51: 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

EV: enfortumab vedotin; Combo: combination; ISS: integrated summary of safety; Max: maximum; Min: minimum; Mono: monotherapy; Pembro: pembrolizumab; RSD: reference safety data; SD: standard deviation.
† 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 52: 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

EV: enfortumab vedotin; Combo: combination; ISS: integrated summary of safety; Max: maximum; Min: minimum; Mono: monotherapy; Pembro: pembrolizumab; RDI: relative dose intensity; SD: standard deviation.

† 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%.

Selected Demographic and Other Characteristics of the Study Populations

Table 53: 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	

Adverse events

Table 54: 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)

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.
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; RSD: reference safety data; TEAE: treatment-emergent adverse event.

† 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.

Table 55: Overview of TEAEs in Episodes Adjusted by Patient-Year (Safety Analysis Set)

Parameter	**EV + Pembro EV-302 (N = 440) PY = 385.6** E (E/PY)	Chemotherapy EV-302 (N = 433) PY = 147.8 E (E/PY)	EV + Pembro Combo ISS (N = 564) PY = 501.9 **E (E/PY)**	EV Mono ISS (N = 793) PY = 443.0 **E (E/PY)**	Pembro Bladder Pool (N = 938) PY = 647.0 E (E/PY)	Pembro RSD (N = 7631) PY = 5570.1 E (E/PY)
TEAE	7442 (19.302)	5034 (34.054)	10340 (20.601)	14414 (32.536)	9983 (15.430)	76878 (13.802)
Drug-related† TEAE	4274 (11.085)	3356 (22.703)	5788 (11.532)	8045 (18.159)	2624 (4.056)	24542 (4.406)
Serious TEAE ‡	440 (1.141)	328 (2.219)	590 (1.175)	844 (1.905)	827 (1.278)	4801 (0.862)
Drug-related† serious TEAE ‡	205 (0.532)	139 (0.940)	260 (0.518)	295 (0.666)	142 (0.219)	1093 (0.196)
TEAE leading to death	19 (0.049)	14 (0.095)	26 (0.052)	56 (0.126)	68 (0.105)	353 (0.063)
Drug-related† TEAE leading to death	4 (0.010)	4 (0.027)	8 (0.016)	17 (0.038)	7 (0.011)	42 (0.008)
TEAE leading to death excluding disease progression	19 (0.049)	14 (0.095)	26 (0.052)	37 (0.084)	66 (0.102)	349 (0.063)
Drug-related† TEAE leading to death excluding disease progression	4 (0.010)	4 (0.027)	8 (0.016)	17 (0.038)	5 (0.008)	38 (0.007)
TEAE leading to permanent withdrawal of any treatment	196 (0.508)	98 (0.663)	269 (0.536)	182 (0.411)	143 (0.221)	1165 (0.209)
Drug-related † TEAE leading to permanent withdrawal of any treatment	169 (0.438)	84 (0.568)	239 (0.476)	130 (0.293)	80 (0.124)	703 (0.126)
TEAE leading to permanent withdrawal of enfortumab vedotin	153 (0.397)	NA	202 (0.402)	182 (0.411)	NA	NA
Drug-related † TEAE leading to permanent withdrawal of enfortumab vedotin	130 (0.337)	NA	176 (0.351)	130 (0.293)	NA	NA
TEAE leading to permanent withdrawal of pembrolizumab	117 (0.303)	NA	157 (0.313)	NA	143 (0.221)	1165 (0.209)
Drug-related † TEAE leading to permanent withdrawal of pembrolizumab	94 (0.244)	NA	131 (0.261)	NA	80 (0.124)	703 (0.126)
TEAE leading to dose reduction §	224 (0.581)	235 (1.590)	292 (0.582)	431 (0.973)	NA	NA
Drug-related† TEAE leading to dose reduction §	217 (0.563)	215 (1.454)	283 (0.564)	410 (0.925)	NA	NA
TEAE leading to dose interruption of any treatment	785 (2.036)	561 (3.795)	1038 (2.068)	1245 (2.810)	515 (0.796)	3605 (0.647)
Drug-related † TEAE leading to dose interruption of any treatment	538 (1.395)	413 (2.794)	708 (1.411)	836 (1.887)	235 (0.363)	1755 (0.315)
TEAE leading to dose interruption of enfortumab vedotin	638 (1.655)	NA	833 (1.660)	1245 (2.810)	NA	NA
Drug-related † TEAE leading to dose interruption of enfortumab vedotin	426 (1.105)	NA	549 (1.094)	836 (1.887)	NA	NA
TEAE leading to dose interruption of pembrolizumab	467 (1.211)	NA	631 (1.257)	NA	515 (0.796)	3605 (0.647)
Drug-related † TEAE leading to dose interruption of pembrolizumab	320 (0.830)	NA	430 (0.857)	NA	235 (0.363)	1755 (0.315)
TEAE with NCI-CTCAE ≥ Grade 3	854 (2.215)	1069 (7.232)	1252 (2.494)	1759 (3.970)	1505 (2.326)	7463 (1.340)

Drug-related † TEAE with NCI-CTCAE ≥ Grade 3	491 (1.273)	792 (5.358)	697 (1.389)	878 (1.982)	297 (0.459)	1770 (0.318)

For Pembro studies, MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
E: number of events counted in episodes (which counts once for multiple records reported under the same adverse event identifier); EV: enfortumab vedotin; Mono: monotherapy; NCI-CTCAE: National Cancer Institute - Common Terminology Criteria for Adverse Events; Pembro: pembrolizumab; PY: patient-year, the total duration of exposure in years; RSD: reference safety data; TEAE: treatment-emergent adverse event.

† 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 Treatment-emergent Adverse Events

Table 56: 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)
Hyperglycemia	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)**
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.

Serious adverse event/deaths/other significant events

Table 57: Treatment-emergent Adverse Events of NCI-CTCAE Grade 3 or 4 by SOC and Preferred Term for TEAEs 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)
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.

Drug-related Treatment-emergent Adverse Events

In the EV + Pembro EV-302 arm, the most common drug-related TEAEs were peripheral sensory **neuropathy** (50.0%), **pruritus** (39.8%) and **alopecia** (33.2%).

In the Chemotherapy EV-302 arm, the most common drug-related TEAEs were anemia (56.6%), neutropenia (41.6%), and nausea (38.8%).

The most common drug-related TEAEs 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 (50.0% vs 9.9%), pruritus (39.8% vs 4.8%) and **rash** maculo-papular (32.7% vs 3.2%). The most common drug-related reported TEAEs reported at a higher frequency in the Chemotherapy EV-302 arm compared to the EV + Pembro EV-302 arm were anemia (56.6% vs 13.9%), neutropenia (41.6% vs 9.1%) and thrombocytopenia (34.2% vs 3.4%). The drug-related TEAEs by PT were generally similar between the EV + Pembro EV-302 arm and the EV + Pembro Combo ISS analysis group. The drug-related TEAEs reported at a higher frequency (> 10% difference) in the EV + Pembro Combo ISS analysis group compared to the EV Mono ISS analysis group were peripheral sensory neuropathy (51.4% vs 36.7%) and rash maculo-papular (34.8% vs 22.2%). The most common drug-related TEAEs reported at a higher frequency (> 10% difference) in the EV + Pembro Combo ISS analysis group compared to the Pembro Bladder Pool analysis group or the Pembro RSD analysis group were peripheral sensory neuropathy (51.4% vs 0.2% and 0.5%, respectively), alopecia (36.2% vs 0.2% and 0.7%, respectively) and rash maculo-papular (34.8% vs 3.0% and 3.1%, respectively).

Drug-related NCI-CTCAE Grade 3 or 4 Treatment-emergent Adverse Events

In the EV + Pembro EV-302 arm, the drug-related TEAEs of Grade 3 or 4 occurring in ≥ 5% of subjects by PT were **rash** maculo-papular (7.7%) and **hyperglycemia** (5.0%). In the Chemotherapy EV-302 arm, the most common drug-related TEAEs of Grade 3 or 4 occurring in ≥ 5% of subjects by PT were anemia (31.4%), neutropenia (30.0%) and thrombocytopenia (19.4%). The drug-related TEAEs of Grade 3 or 4 reported at a higher frequency (> 5% difference) in the EV + Pembro EV-302 arm compared to the Chemotherapy EV-302 arm were rash maculo-papular (7.7% vs 0%) and hyperglycemia (5.0% vs 0%). The drug-related TEAEs of Grade 3 or 4 reported at a higher frequency in the Chemotherapy EV-302 arm compared to the EV + Pembro EV-302 arm were anemia (31.4% vs 3.4%), neutropenia (30.0% vs 4.8%) and thrombocytopenia (19.4% vs 0.5%). The drug-related TEAEs of Grade 3 or 4 by PT were generally similar between the EV + Pembro EV-302 arm and the EV + Pembro Combo ISS analysis group.

The drug-related TEAEs of Grade 3 or 4 by PT were generally similar between the EV + Pembro Combo ISS analysis group and the EV Mono ISS analysis group. There were no TEAEs reported at a higher frequency (> 5% difference) in the EV + Pembro Combo ISS analysis group compared to the EV Mono ISS analysis group. The drug-related TEAEs of Grade 3 or 4 reported at a higher frequency (> 5% difference) in the EV + Pembro Combo ISS analysis group compared to the Pembro Bladder Pool analysis group or the Pembro RSD analysis group were rash maculo-papular (9.2% vs 0.1% and 0.3%, respectively), neutropenia (5.7% vs 0% and 0.2%, respectively) and hyperglycemia (5.5% vs 0.3% and 0.3%, respectively).

TEAEs Leading to Death

TEAEs leading to death across the safety analysis groups are presented in [**Table 58**, **Table 59**].

Table 58: 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 59: 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)
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

Drug-related TEAEs Leading to Death

The frequency of drug-related TEAEs leading to death in the EV + Pembro EV-302 arm (0.9%) was similar to the Chemotherapy EV-302 arm (0.9%) and to the EV + Pembro Combo ISS analysis group (1.4%). In the EV + Pembro EV-302 and the Chemotherapy EV-302 arms, no drug-related deaths by PT were reported in more than one subject. When adjusted for PY of exposure, drug-related TEAEs leading to death occurred at a rate of 0.010 E/PY in the EV + Pembro EV-302 arm and 0.027 E/PY in the Chemotherapy EV-302 arm (**Table 55**). The frequency of drug-related TEAEs leading to death in the EV + Pembro Combo ISS analysis group (1.4%) was similar to that observed in the EV Mono ISS analysis group (2.1%), in the Pembro Bladder Pool analysis group (0.7%) and in the Pembro RSD analysis group (0.6%). In the EV + Pembro Combo ISS analysis group, 2 subjects had a drug-related TEAE leading to death by PT of multiple organ dysfunction syndrome. No other drug-related TEAE leading to death was observed in more than 1 subject by PT in the EV + Pembro Combo ISS analysis group. In the EV Mono ISS analysis group, drug-related TEAEs leading to death in more than 1 subject by PT included multiple organ dysfunction syndrome (5 [0.6%] subjects) and respiratory failure (2 [0.3%] subjects). In the Pembro RSD analysis group, drug-related TEAEs leading to death in more than 1

subject by PT included pneumonitis (8 [0.1%] subjects), respiratory failure (2 [0.0%] subjects), pneumonia (4 [0.1%] subjects), death (3 [0.0%] subjects) and sudden death (2 [0.0%] subjects).

Other Serious Adverse Events

Serious TEAEs occurring in ≥ 1% of subjects in the EV + Pembro Combo ISS analysis group are presented in Table 60.

Table 60: 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)**
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.

Drug-related Serious Adverse Events

Overall, 27.7% of subjects in the EV + Pembro EV-302 arm and 19.6% of subjects in the Chemotherapy EV-302 arm experienced a drug-related serious TEAE (**Table 54**). When adjusted for patient-year of exposure, treatment-related serious TEAEs occurred at a rate of 0.532 E/PY and 0.940 E/PY, respectively (**Table 55**). In the EV + Pembro EV-302 arm, there were no drug-related serious TEAEs occurring in ≥ 3% of subjects by PT. In the Chemotherapy EV-302 arm, the drug-related serious TEAEs occurring in ≥ 3% of subjects by PT were anemia (3.7%) and thrombocytopenia (3.0%). There were no drug-related serious TEAEs reported at a higher frequency (> 5% difference) in the EV + Pembro EV-302 arm compared to the Chemotherapy EV-302 arm. The drug-related serious TEAEs by PT were generally similar between the EV + Pembro EV-302 arm and the EV + Pembro Combo ISS analysis group. There were no drug-related serious TEAEs reported at a higher frequency (> 5% difference) in the EV + Pembro Combo ISS analysis group compared to the EV Mono ISS analysis group. There were no drug-related serious TEAEs reported at a higher frequency (> 5% difference) in the EV + Pembro Combo ISS analysis group compared to the Pembro Bladder Pool analysis group or in the Pembro RSD analysis group.

Adverse Events Leading to Dose Modifications

Adverse Events Leading to Permanent Withdrawal of Treatment

TEAEs and drug-related TEAEs that led to permanent withdrawal of either treatment in > 1% of subjects in the EV + Pembro Combo ISS analysis group are presented in **Table 61**.

Table 61: 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.

Adverse Events Leading to Dose Reduction

TEAEs and drug-related TEAEs that led to an enfortumab vedotin dose reduction in > 1% of subjects in the EV + Pembro Combo ISS analysis group are presented in **Table 62**.

Table 62: 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.

Adverse Events Leading to Dose Interruption

TEAEs and drug-related TEAEs that led to dose interruption (doses skipped or delayed) in > 1% of subjects in the EV + Pembro Combo ISS analysis group are presented in **Table 63**.

Table 63: 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.

Adverse Events of Special Interest – Pembrolizumab

Pembrolizumab AEOSI include immune-mediated events and infusion related reactions that are causally associated with pembrolizumab Table 64.

Table 64: 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)
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)
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.

Severe Skin Reactions

Table 65: Severe Skin Reactions AEOSI (MedDRA v26.0) in ≥ 1 Subject in EV + Pembro Combo ISS by Preferred Term (Safety Analysis Set) for ≥ Grade 3

Preferred Term Grade 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 severe skin reactions	**75 (17.0)**	**2 (0.5)**	**108 (19.1)**	**19 (2.0)**	**130 (1.7)**
Grade 3	48 (10.9)	0	71 (12.6)	12 (1.3)	103 (1.3)
Grade 4	4 (0.9)	0	6 (1.1)	0	1 (0.0)
Grade 5	0	0	0	0	1 (0.0)
Severe skin reactions events by preferred term in ≥ 1 participant in EV + Pembro Combo ISS analysis group					
Dermatitis bullous					
Grade 3	3 (0.7)	0	4 (0.7)	0	0
Grade 4	0	0	1 (0.2)	0	1 (0.0)
Dermatitis exfoliative					
Grade 3	1 (0.2)	0	1 (0.2)	0	1 (0.0)
Dermatitis exfoliative generalised					
Grade 3	0	0	1 (0.2)	0	0
Grade 4	1 (0.2)	0	1 (0.2)	0	0
Erythema multiforme					
Grade 3	0	0	0	0	5 (0.1)
Grade 4	0	0	1 (0.2)	0	0
Lichen planus pemphigoides					
Grade 3	0	0	1 (0.2)	0	0
Pemphigoid					
Grade 3	2 (0.5)	0	3 (0.5)	1 (0.1)	3 (0.0)
Pruritus					
Grade 3	5 (1.1)	0	9 (1.6)	4 (0.4)	16 (0.2)
Rash					
Grade 3	0	0	1 (0.2)	4 (0.4)	44 (0.6)
Rash erythematous					
Grade 3	2 (0.5)	0	3 (0.5)	0	1 (0.0)
Rash maculo-papular					
Grade 3	35 (8.0)	0	53 (9.4)	1 (0.1)	23 (0.3)
Grade 4	1 (0.2)	0	1 (0.2)	0	0

Rash pruritic					
Grade 3	1 (0.2)	0	1 (0.2)	1 (0.1)	4 (0.1)
Rash pustular					
Grade 3	1 (0.2)	0	1 (0.2)	0	2 (0.0)
SJS-TEN overlap					
Grade 3	1 (0.2)	0	1 (0.2)	0	0
Toxic epidermal necrolysis					
Grade 3	1 (0.2)	0	1 (0.2)	0	0
Grade 4	2 (0.5)	0	2 (0.4)	0	0

Number of subjects (n) and percentage of subjects (%) are shown.
Subjects were counted once under maximum NCI-CTCAE grade. Highest nonmissing grade was considered as the maximum NCI-CTCAE grade. A missing NCI-CTCAE grade was considered the maximum NCI-CTCAE grade when all grades for the subject were missing.
Table includes PTs pertaining to the Severe Skin Reactions SSQ/CMQ
AEOSI: pembrolizumab adverse events of special interest; Combo: combination; CMQ: customized medical query; EV: enfortumab vedotin; ISS: integrated summary of safety; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; Pembro: pembrolizumab; PT: preferred term; RSD: reference safety data; SJS: Stevens-Johnson syndrome; SSQ: sponsor-specific queries; TEN: toxic epidermal necrolysis.

Pneumonitis

The AEOSI category of pneumonitis consists of 7 PTs, which are considered medically equivalent to pneumonitis. The proportion of subjects experiencing an AEOSI in the category of pneumonitis in the EV + Pembro EV-302 arm was higher than that in the Chemotherapy EV-302 arm (9.5% vs 0.2%) Table 66.

Table 66: Pneumonitis AEOSI (MedDRA v26.0) in ≥ 1 Subject in EV + Pembro Combo ISS by Preferred Term (Safety Analysis Set) for ≥ Grade 3

Preferred Term Grade 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 pneumonitis event	42 (9.5)	1 (0.2)	54 (9.6)	45 (4.8)	324 (4.2)
Grade 3	13 (3.0)	1 (0.2)	17 (3.0)	14 (1.5)	81 (1.1)
Grade 4	2 (0.5)	0	2 (0.4)	1 (0.1)	19 (0.2)
Grade 5	1 (0.2)	0	2 (0.4)	1 (0.1)	9 (0.1)
Pneumonitis events by preferred term in ≥ 1 participant in EV + Pembro Combo ISS analysis group					
Immune-mediated lung disease					
Grade 3	4 (0.9)	0	4 (0.7)	0	0
Grade 4	0	0	0	0	1 (0.0)
Grade 5	1 (0.2)	0	1 (0.2)	0	0
Interstitial lung disease					
Grade 3	4 (0.9)	0	4 (0.7)	2 (0.2)	9 (0.1)
Grade 4	0	0	0	1 (0.1)	1 (0.0)
Grade 5	0	0	0	0	1 (0.0)
Organising pneumonia					
Grade 3	1 (0.2)	0	1 (0.2)	0	0
Pneumonitis					
Grade 3	5 (1.1)	1 (0.2)	9 (1.6)	12 (1.3)	72 (0.9)

Grade 4	2 (0.5)	0	2 (0.4)	0	17 (0.2)
Grade 5	0	0	1 (0.2)	1 (0.1)	8 (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.
Table includes PTs pertaining to the Severe Skin Reactions SSQ/CMQ
AEOSI: pembrolizumab adverse events of special interest; Combo: combination; CMQ: customized medical query; EV: enfortumab vedotin; ISS: integrated summary of safety; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; Pembro: pembrolizumab; PT: preferred term; RSD: reference safety data; SSQ: sponsor-specific queries.

Adverse Events of Special Interest – Enfortumab Vedotin

Skin reactions, pneumonitis/ILD, and peripheral neuropathy were reported for a greater proportion of subjects during combination therapy than in previous experience with enfortumab vedotin monotherapy. The increase in **skin reactions and pneumonitis** were likely due to a contribution from both components of treatment and longer duration of exposure. The increase in **peripheral neuropathy** was likely due to longer duration of treatment with enfortumab vedotin during combination therapy than in previous experience with enfortumab vedotin monotherapy.

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.

Table 67: Onset of Skin Reactions Treatment-emergent Adverse Events (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)
Time to onset of first skin reactions event † (any grade) (months)				
n	304	68	392	452
Median	0.49	0.48	0.49	0.49
Min, Max	0, 12.4	0.0, 4.8	0.0, 18.5	0.0, 23.4
Time to onset of first ≥ Grade 3 skin reactions event † (months)				
n	71	1	97	108
Median	1.61	0.43	1.74	0.67
Min, Max	0.1, 17.2	0.4, 0.4	0.1, 17.2	0.1, 8.2

Combo: combination; CMQ: customized medical query; EV: enfortumab vedotin; ISS: integrated summary of safety; Mono: monotherapy; Max: maximum; Min: minimum; Pembro: pembrolizumab; SMQ: standardized MedDRA query; SSQ sponsor-specific queries.
† Rash SSQ/CMQ or cutaneous adverse events SMQ (broad scope).

Rash

Rash, a subset of skin reactions, includes events from the SSQ/CMQ for dermatologic events (5 HLTs under the HLGT of Epidermal and Dermal Conditions) and consists of 114 PTs. he frequency of TEAEs in the AESI of rash observed in the EV + Pembro EV-302 arm was higher than that observed the Chemotherapy EV-302 arm Table 68.

Table 68: 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)
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

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reaction is a subset of skin reactions and is composed of the MedDRA SMQ comprising 73 PTs. The frequency of TEAEs in the AESI of any severe cutaneous adverse reactions observed in the EV + Pembro EV-302 arm was higher than that observed in the Chemotherapy EV-302 arm. The frequency of TEAEs in the AESI of any severe cutaneous adverse reactions observed in the EV + Pembro EV-302 arm was generally similar to that observed in the EV + Pembro Combo ISS analysis group (**27.0%** vs 27.5%) **Table 69**.

Table 69: 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)
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).

Peripheral Neuropathy

The cytotoxic component of enfortumab vedotin, MMAE, is a microtubule-disrupting agent. Peripheral neuropathy is part of the safety profile of drugs that affect microtubules including other MMAE ADCs. 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 70**).

Table 70: 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)
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.

Table 71: Onset and Resolution of Peripheral Neuropathy Treatment-emergent Adverse Events (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)
Time to onset of first peripheral neuropathy event † (any grade) (months)				
n	293	60	376	422
Median	3.29	2.14	3.10	2.33
Min, Max	0.1, 17.7	0.0, 5.1	0.1, 17.7	0.0, 13.8
Time to first onset of any ≥ Grade 2 peripheral neuropathy event † (months)				
n	182	11	242	279
Median	5.75	2.14	5.75	4.96
Min, Max	0.3, 20.3	0.0, 4.0	0.3, 25.3	0.1, 20.2
Resolution status by subject, n/N (%)				
Subjects evaluable for resolution †	290	59	373	340
No improvement	**145/290 (50.0)**	**39/ 59 (66.1)**	170/373 (45.6)	138/340 (40.6)

Partial improvement	110/290 (37.9)	3/ 59 (5.1)	156/373 (41.8)	155/340 (45.6)
Resolved	35/290 (12.1)	17/ 59 (28.8)	47/373 (12.6)	47/340 (13.8)
Last evaluation for subjects with partial or no improvement n/N (%)				
n	255	42	326	293
Grade 1	145/255 (56.9)	34/42 (81.0)	180/326 (55.2)	143/293 (48.8)
Grade 2	89/255 (34.9)	8/42 (19.0)	121/326 (37.1)	127/293 (43.3)
Grade 3	**21/255 (8.2)**	0	25/326 (7.7)	22/293 (7.5)
Grade 4	0	0	0	1/293 (0.3)
≥ Grade 2	110/255 (43.1)	8/42 (19.0)	146/326 (44.8)	150/293 (51.2)
≥ Grade 3	21/255 (8.2)	0	25/326 (7.7)	23/293 (7.8)

Combo: combination; EV: enfortumab vedotin; ISS: integrated summary of safety; Max: maximum; Min: minimum; Mono: monotherapy; NA: not applicable; Pembro: pembrolizumab.
† Peripheral neuropathy SMQ (broad scope).

Hyperglycemia

Hyperglycemia has been observed in subjects treated with enfortumab vedotin. Despite a comprehensive literature review of the biology and potential risks of targeting Nectin-4, studies examining Nectin-4 expression and ADC tissue cross-reactivity, a thorough review of the in vivo toxicology studies, and data from in vitro assays examining the impact of ADC and free MMAE on human tissues relevant to glucose homeostasis, a potential mechanism of enfortumab vedotin-induced hyperglycemia has not been established.

Table 72: 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)
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 73.

Table 73: 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)				
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

Table 74: Onset of Hyperglycemia Treatment-emergent Adverse Events (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)
Time to onset of first hyperglycemia event (any grade) (months) †				
n	85	15	107	133
Median	0.72	1.64	0.72	0.53
Min, Max	0.0, 16.8	0.2, 3.5	0.0, 16.8	0.0, 20.3
Time to onset of first ≥ Grade 3 hyperglycemia event (months) †				
n	38	4	52	60
Median	0.80	1.30	0.80	0.56
Min, Max	0.3, 15.2	0.4, 3.4	0.2, 15.2	0.0, 3.3

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.

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.

EV-302 arm experienced an ocular disorders event that resulted in treatment withdrawal.

Table 75: 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.

Infusion-related Reactions

Table 76: 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

Pneumonitis/ILD

TEAEs of pneumonitis/ILD observed in the Study EV-302 are presented **Table 77**.

Table 77: Overview of Pneumonitis/ILD 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 pneumonitis/ILD event †	**45 (10.2)**	**2 (0.5)**	**58 (10.3)**	**26 (3.3)**
Grade 1	8 (1.8)	0	12 (2.1)	9 (1.1)
Grade 2	20 (4.5)	0	24 (4.3)	11 (1.4)
Grade 3	**13 (3.0)**	2 (0.5)	17 (3.0)	4 (0.5)
Grade 4	**3 (0.7)**	0	3 (0.5)	2 (0.3)
Grade 5	**1 (0.2)**	0	2 (0.4)	0
Subjects with any pneumonitis/ILD event by preferred term in ≥ 5% of subjects in EV + Pembro Combo ISS				
Pneumonitis	29 (6.6)	1 (0.2)	41 (7.3)	17 (2.1)
Grade 1	7 (1.6)	0	10 (1.8)	7 (0.9)
Grade 2	15 (3.4)	0	19 (3.4)	7 (0.9)
Grade 3	5 (1.1)	1 (0.2)	9 (1.6)	2 (0.3)
Grade 4	2 (0.5)	0	2 (0.4)	1 (0.1)
Grade 5	0	0	1 (0.2)	0
Subjects with any drug-related pneumonitis/ILD events †	**45 (10.2)**	**1 (0.2)**	**57 (10.1)**	**21 (2.6)**
Subjects with any serious pneumonitis/ILD events †	**20 (4.5)**	**0**	**24 (4.3)**	**6 (0.8)**
Subjects with any serious drug-related pneumonitis/ILD events †	**20 (4.5)**	**0**	**24 (4.3)**	**5 (0.6)**
Subjects with any pneumonitis/ILD events leading to permanent withdrawal of treatment †	**21 (4.8)**	**0**	**27 (4.8)**	**4 (0.5)**

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; ILD: interstitial lung disease; ISS: integrated summary of safety; Mono: monotherapy; NCI-CTCAE: National Cancer Institute - Common Terminology Criteria for Adverse Events; Pembro: pembrolizumab; SMQ: standardized MedDRA query.
† ILD SMQ (broad scope).

Table 78: Onset of Pneumonitis/ILD Treatment-emergent Adverse Events (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)
Time to onset of first pneumonitis/ILD event † (any grade) (months) †				
n	45	2	58	26
Median	3.94	2.05	3.98	2.71
Min, Max	0.3, 14.5	2.0, 2.1	0.3, 26.2	0.6, 6.0
Time to onset of first ≥ Grade 2 pneumonitis/ILD event (months) †				
n	37	2	46	17
Median	4.11	2.05	4.25	2.79
Min, Max	0.3, 16.6	2.0, 2.1	0.3, 28.2	0.6, 5.3
Time to onset of first ≥ Grade 3 pneumonitis/ILD event (months) †				
n	17	2	22	6
Median	4.83	2.05	4.37	3.25
Min, Max	0.3, 9.6	2.0, 2.1	0.3, 12.9	1.0, 4.3

Combo: combination; EV: enfortumab vedotin; ILD: interstitial lung disease; ISS: integrated summary of safety; Max: maximum; Min: minimum; Mono: monotherapy; Pembro: pembrolizumab; SMQ: standardized MedDRA query.

† ILD SMQ (broad scope).

Anemia

Table 79: 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
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 80: 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

Nausea, Vomiting, and Diarrhea

Table 81: 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 †				
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).

Laboratory findings

Hematology

Anemia and neutropenia are identified risks for subjects treated with enfortumab vedotin and known toxicities for subjects treated with platinum + gemcitabine. Hematology lab abnormalities, including Grade 3 or higher abnormalities, were generally higher in the Chemotherapy EV-302 arm than the other analysis groups including decreased hemoglobin, leukocytes, neutrophils, and platelets. Across the analysis groups, treatment-emergent shifts in hematology parameters were consistent with the known safety profile of the respective agents.

Chemistry

Increases in creatinine were common and occurred in a similar percentage of subjects in the EV + Pembro EV-302 arm and the Chemotherapy EV-302 arm, both overall (70.5% and 67.6%, respectively) and for Grade 3 to 4 increases (3.2% and 2.6%). Increases in glucose were more common in the EV + Pembro Combo EV-302 arm (65.7%) than in the Chemotherapy EV-302 arm (53.5%). Glucose increases were also the most common Grade 3 to 4 abnormality that occurred in the EV + Pembro EV-302 arm (13.7%) and occurred in more subjects than in the Chemotherapy EV-302 arm (4.7%). Other common Grade 3 to 4 laboratory abnormalities included sodium decreased (13.2% and 12.9%, respectively) and phosphate decreased (9.3% and 9.2%), which were similar in both arms. Across the analysis groups, treatment-emergent shifts in chemistry parameters were consistent with the known safety profile of the respective agents.

Liver Enzymes and Total Bilirubin

Table 82: 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

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)

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.

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.

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.

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.

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.

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.

Baseline Characteristics

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.

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.

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. Overall, there were no clinically meaningful differences observed between the geographical region subgroups (data not shown).

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

Antitherapeutic Antibodies

Pembrolizumab

The characterization of immunogenicity for pembrolizumab following coadministration with enfortumab vedotin was investigated in study EV-103. ATA rates for pembrolizumab in combination with enfortumab vedotin were low (3.4%) and comparable with the ATA rates reported for pembrolizumab in the monotherapy setting.

Enfortumab Vedotin

Serum samples from subjects administered enfortumab vedotin and/or pembrolizumab were evaluated for ATA. In EV-103 199 subjects received study treatment of which 179 were evaluable for ATA to enfortumab vedotin, having both baseline and on-treatment samples across the dose-escalation cohort, Cohort A and Cohort K. Of these 179 evaluable subjects, 174 were baseline-negative and among those 5 (2.9%; 5/174) were positive on treatment. In addition, the treatment-emergent ATA rate between enfortumab vedotin as monotherapy (3.1%, 2/64, Cohort K [EV Mono]) and in combination with pembrolizumab (2.7%, 3/110, combined dose-escalation cohort, Cohort A and Cohort K [EV + Pembro arm]) was approximately equivalent. A total of 377 of 440 subjects in the EV+ Pembro EV-302 arm were evaluable for ATA, having both baseline and on-treatment samples. Of these 377 evaluable subjects, 358 were baseline negative and among those 11 (3.1%; 11/358) were positive on treatment. A total of 490 of 564 subjects in the EV+ Pembro Combo ISS analysis group were evaluable for ATA, having both baseline and on-treatment samples. Of these 490 evaluable subjects, 466 were baseline negative and among those 14 (3.0%; 14/466) were positive on treatment. A total of 697 of 793 subjects in the EV Mono ISS analysis group were evaluable for ATA, having both baseline and on-treatment samples. Of these 697 evaluable subjects, 681 were baseline negative and among those 24 (3.5%; 24/681) were positive on treatment. The incidence of treatment-emergent ATA against enfortumab vedotin in subjects negative at baseline remains low and comparable to monotherapy studies. Pembrolizumab does not impact the immunogenicity of enfortumab vedotin in combination therapy.

Drug 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 cut-off 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 cut-off 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 83: 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)

	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	**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.
Source: EV-302 ISS Tables 12.6.1.2.6 and 12.6.1.4.4

Table 84: 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
Source: EV-302 ISS Tables 12.6.1.2.7 and 12.6.1.4.5

Table 85: 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)

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	**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.
Source: EV-302 ISS Tables 12.6.1.2.8 and 12.6.1.4.6

Post marketing experience

Pembrolizumab

Pembrolizumab was first approved in the US on 04 September 2014. And in Europe on 17 July 2015. The safety profile of pembrolizumab was most recently described in the Periodic Safety Update Report covering the period 04 September 2022 through 03 September 2023. There are no records of any pembrolizumab registration being revoked or withdrawn for safety reasons in any country.

2.5.1. Discussion on clinical safety

The safety analysis presented in support of this extension of indication for Keytruda in combination with enfortumab vedotin was conducted on a database comprising 7 enfortumab vedotin studies (1 EV + Pembro combination study, 1 EV monotherapy or EV + Pembro combination study and 5 EV monotherapy studies) and 21 pembrolizumab studies (Pembro Reference Safety Data (RSD) in addition to 3 pembrolizumab studies in the setting of urinary cancer disease (KEYNOTE-052, KEYNOTE-045 and KEYNOTE-361) (Pembro Bladder Pool), that served as reference for pembrolizumab. In total, 6 different populations were compared, including group EV + Pembro (n=440) and Chemotherapy (n=443) from the pivotal study EV-302; a global population receiving EV + Pembro including patients from EV-302, EV-103 studies (n=564); a reference group for enfortumab vedotin in monotherapy (n=793); a reference for pembrolizumab monotherapy (RSD; n=7631) and a disease-specific reference dataset for pembrolizumab monotherapy (Pembro Bladder Pool, n=938).

In study EV-302, exposure to EV + Pembro (9.43 months in median) was longer than chemotherapy (4.14 month in median); exposure in this group was also more protracted relatively to pembrolizumab reference datasets (5.78 and 3.48 months in median for RSD and Pembro Bladder pool, respectively).

The proportion of AEs in the two arms of study EV-302 was comparable. However, serious TEAE (50% vs 39%), TEAE leading to death excluding disease progression (4.3% vs 3.2%), TEAE leading to permanent withdrawal of any treatment (39.8% vs 21.5%) and TEAE leading to dose interruption of any treatment (78.9% vs 64.4%) were more frequent in the group EV + Pembro compared with chemotherapy. Similar differences were observed for their respective drug-related AE categories.

The most common TEAEs 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%), **rash maculo-papular** (33.2% vs 3.5%) and **diarrhea** (37.7% vs 15.9%).

In the EV + Pembro EV-302 arm, the most common **Grade 3 or 4** TEAEs were **rash maculo-papular** (8.2%), **hyperglycemia** (7.3%) and **anemia** (7.0%). In the Chemotherapy EV-302 arm, the most common Grade 3 or 4 TEAEs were anemia (34.2%), neutropenia (30.0%) and thrombocytopenia (20.1%).

In the EV + Pembro EV-302 arm, other serious TEAEs occurring in ≥ 3% of subjects by PT were **acute kidney** injury (**5.2%**), **urinary tract infection** (3.6%) and **diarrhea** (3.2%). In the Chemotherapy EV-302 arm, the serious TEAEs occurring in ≥ 3% of subjects by PT were urinary tract infection (7.2%), anemia (3.9%) and thrombocytopenia (3.0%).

In the EV + Pembro EV-302 arm, the TEAEs occurring in ≥ 2% of subjects by PT that led to permanent withdrawal of any treatment were **peripheral sensory neuropathy** (11.1%) and **pneumonitis** (2.0%).

Overall, **41.8%** of subjects in the EV + Pembro EV-302 arm and 40.9% in the Chemotherapy EV-302 arm experienced a **TEAE that led to dose reduction** of any treatment. In the EV + Pembro EV-302 arm, the TEAEs that led to an enfortumab vedotin dose reduction in ≥ 2% of subjects by PT included **peripheral sensory neuropathy** (8.6%), **rash maculo-papular** (5.9%) and **fatigue** (2.7%).

Overall, 78.9% of subjects in the EV + Pembro EV-302 arm and 64.4% of subjects in the Chemotherapy EV-302 arm experienced a TEAE that led to dose interruption. In the EV + Pembro EV-302 arm, the most common reported TEAEs that led to a dose interruption of any treatment in ≥ 2% of subjects by PT were **peripheral sensory neuropathy** (18.0%), COVID-19 (11.6%) and **rash maculo-papular** (9.8%).

Severe skin reactions (17.0%), hypothyroidism (10.7%), and pneumonitis (9.5%) were the most commonly reported **AEOSI** in the EV + Pembro EV-302 arm. Other AEOSI categories reported for ≥ 2% of subjects in the EV + Pembro EV-302 arm included **hyperthyroidism (4.5%), hepatitis (3.2%), colitis (2.7%), and gastritis (2.0%).**

Compared with the RSD, the safety profile of EV + Pembro arm of Study EV-302 was worse across all Medra SOC categories, with the exception of Musculoskeletal and Connective Tissue (42.3% vs 44%) and Respiratory, Thoracic and Mediastinal Disorders (41.4% vs 43.4%) that occurred with similar frequency between the two groups.

Compared with the Pembro Bladder Pool, toxicity was worse in the EV + Pembro population of study EV-302 in all Medra SOCs but Renal and Urinary Disorders, that were registered in similar proportion in the two populations (32.5% vs 34.2%).

Overall, the incidence of adverse reactions for pembrolizumab in combination with enfortumab vedotin was observed to be higher than for pembrolizumab monotherapy reflecting the contribution of enfortumab vedotin and the longer duration of treatment of the combination therapy.

Adverse reactions were generally similar to those observed in patients receiving pembrolizumab or enfortumab vedotin as monotherapy. The incidence of rash maculo-papular was 36% all Grades (10% Grades 3-4), which is higher than observed in pembrolizumab monotherapy.

Disease-specific considerations are likely to explain these results; moreover, the longer drug exposure and combined nature of treatment in the experimental arm are expectedly major contributors to the

increased toxicity observed in the EV + Pembro group relative to chemotherapy or the individual monotherapies.

As expected, tolerability decreased by increasing **age** in both treatment arms of study EV-302. Toxicity of EV + Pembro was worse than Chemotherapy in both patients aged < 75 and ≥ 75 years, and more AEs were registered in the combined regimen compared to pembrolizumab monotherapy datasets for both age categories. This is an expected effect of pembrolizumab when administrated in combination with other chemotherapeutic agents that is currently adequately addressed in the SmPC. However, it was also noted that adverse event in response to EV + Pembro were higher in patients ≥65 years of age compared to <65 years of age, particularly for serious adverse events (56.3% and 35.3%, respectively) and ≥Grade 3 events (80.3% and 64.2%, respectively). While probably recapitulated by the status of multi-comorbidity, such a difference in safety is clinically meaningful and is highlighted in the SmPC.

2.5.2. Conclusions on clinical safety

The safety profile for pembrolizumab in combination with enfortumab vedotin 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 MAH submitted an updated RMP version (43.0 date of final sign off July 2024) 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 43.0 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 43.0 with the following content:

Safety concerns

Table 86 Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Immune-mediated adverse reactions

Summary of safety concerns	
Important potential risks	For hematologic malignancies: increased risk of severe complications of allogeneic stem cell transplantation (SCT) in patients who have previously received pembrolizumab Graft versus host disease (GVHD) after pembrolizumab administration in patients with a history of allogeneic stem cell transplant (SCT)
Missing information	None

Pharmacovigilance plan

There are no ongoing or planned additional pharmacovigilance studies that are required for pembrolizumab.

Risk minimisation measures

Table 87 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Important Identified Risks: Immune-Mediated Adverse Reactions		
Immune-mediated adverse reactions	Routine risk minimisation measures: ▪ The risk of the immune-mediated adverse reactions associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Routine pharmacovigilance activities
	Additional risk minimisation measures: ▪ Patient card	Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types
Important Potential Risks		
For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab	Routine risk minimisation measures: ▪ For Hematologic malignancies: the increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab is described in the SmPC, Section 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Routine pharmacovigilance activities
	No additional risk minimisation measures warranted	Additional pharmacovigilance including: ▪ Safety monitoring in the ongoing HL trial (KN204).
	Routine risk minimisation measures:	Routine pharmacovigilance activities

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
GVHD after pembrolizumab administration in patients with a history of allogeneic SCT	▪ GVHD after pembrolizumab administration in patients with a history of allogeneic SCT is described in the SmPC, Section 4.4 and appropriate advice is provided to the prescriber to minimize the risk. No additional risk minimisation measures warranted	Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types

2.7. Update of the Product information

As a result of this variation, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: the proposed revision does not contain significant changes that would require the need to conduct a new user consultation.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The final indication is as follows:

KEYTRUDA, in combination with enfortumab vedotin, is indicated for the first-line treatment of unresectable or metastatic urothelial carcinoma in adults.

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 where approved [Jackson-Spence et al, 2022], including the US (as of June2020) [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.

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

The current application is supported by data from study EV-302. 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

- Serious TEAE (50% vs 39%), TEAE leading to death excluding disease progression (4.3% vs 3.2%), TEAE leading to permanent withdrawal of any treatment (39.8% vs 21.5%) and TEAE leading to dose interruption of any treatment (78.9% vs 64.4%) were more frequent in the group EV + Pembro compared with chemotherapy. Similar differences were observed for their respective drug-related AE categories.
- Severe skin reactions (17.0%), hypothyroidism (10.7%), and pneumonitis (9.5%) were the most commonly reported AEOSI in the EV + Pembro EV-302 arm. Other AEOSI categories reported for ≥ 2% of subjects in the EV + Pembro EV-302 arm included hyperthyroidism (4.5%), hepatitis (3.2%), colitis (2.7%), and gastritis (2.0%).
- Compared with the Pembro Bladder Pool, toxicity was worse in the EV + Pembro group in all Medra categories but Renal and Urinary Disorders, that were registered in similar proportion in the two populations (32.5% vs 34.2%).
- Compared with the RSD, the safety profile of EV + Pembro was worse across all Medra categories, with the exception of Musculoskeletal and Connective Tissue (42.3% vs 44%) and Respiratory, Thoracic and Mediastinal Disorders (41.4% vs 43.4%) that occurred with similar frequency between the two groups.
- Severe skin reactions (17.0%), hypothyroidism (10.7%), and pneumonitis (9.5%) were the most commonly reported AEOSI in the EV + Pembro EV-302 arm
- 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). Generally higher adverse event frequencies in patients ≥ 65 compared to < 65 years of age was observed also with the chemotherapy comparator.

3.5. Uncertainties and limitations about unfavourable effects

None.

3.6. Effects Table

Table 88: Effects Table for [KEYTRUDA in combination with PADCEV in 1st line LA/mUC] (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						
PFS	duration of survival without progression from randomization to PD or	months (95% CI)	12.5 (10.4, 16.6)	6.3 (6.2, 6.5)	HR 0.45 95% CI 0.38, 0.54	CSR

Effect	Short description	Unit	EV+Pembro n=442	Plat+Gem n=444	Uncertainties / Strength of evidence	References
	death whichever occurred first					
OS	duration of survival from randomization to death regardless of cause	months (95% CI)	31.5 (25.4, -)	16.1 (13.9, 18.3)	HR 0.47 95% CI 0.38, 0.58	
ORR	Confirmed CR + PR	%	67.7	44.4		
DoR	Duration of CR/PR until documented PD	months (95% CI)	- (20.2, -)	7.0 (6.2, 10.2)		
Unfavourable Effects						
		%	**EV+Pembro n=442**	**Plat+Gem n=444**	**Additional information**	
≥Grade 3 AEs		%	73	78.8		
SAEs		%	49.8	39.0		
Discontinuation due to AEs		%	39.8	21.5		
AEOSI Hyperthyroidism Hypothyroidism Pneumonitis		%	 4.5 10.7 9.5	 0.5 0.7 0.2		

Abbreviations: AE= adverse event; SAE=serious adverse event; AEOSI= adverse event of special interest

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).

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The pivotal trial KEYNOTE-A39 demonstrated a statistically significant and clinically relevant superiority of EV + Pembro compared to Plat + Gem as first-line treatment of LA/mUC patients. The combined treatment provided a 53.2% reduction in the risk of death compared to control (OS 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). 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 the experimental arm (DoR not reached; 95% CI: 20.2, NE) compared to control (7.0 months; 95% CI: 6.2, 10.2). Of note, only 30.4% of patients assigned to chemotherapy had received maintenance avelumab, that is an approved treatment having demonstrated to improve patient outcomes and survival, and part of the current practice in those patients receiving frontline chemotherapy and displaying no disease progression. Although recognising the demonstrated benefit of avelumab maintenance on overall survival, assignment to treatment was not randomised and the overall superiority of Keytruda/Padcev vs

chemotherapy in the ITT population appears inconfutable and of such a magnitude that a possible underperformance of the control arm is not expected to significantly impact on the efficacy results.

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 evaluation 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 safety profile of EV + pembro appears unfavourable with respect to platinum-containing chemotherapy, with an expected reduced tolerance to treatment by increasing age (which however also applies to the control arm). Toxicities are consistent with the known profile of the single agents, with no new safety signals reported for the combined regimen.

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 outweigh its risks.

3.7.3. Additional considerations on the benefit-risk balance

Platinum-eligibility was an inclusion criterion of the pivotal study KEYNOTE-A39 used to select the study population fit for the control treatment. The final indication includes patients regardless of their platinum-eligibility and strictly constitutes an extrapolation to an extremely rare population of patients who are not even candidate to carboplatin-based treatment in 1L. As platinum-eligibility is not considered an effect modifier for pembrolizumab+EV combination, the CHMP considers the B/R to be positive regardless of platinum-eligibility.

3.8. Conclusions

The overall B/R of KEYTRUDA 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 and IIIB

Extension of indication to include Keytruda in combination with enfortumab vedotin for the first-line treatment of unresectable or metastatic urothelial carcinoma in adults, based on the final results from 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, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 45.1 of the RMP has also been submitted.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.