21 May 2026
EMADOC-1700519818-3005526
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Padcev

International non-proprietary name: Enfortumab vedotin

Procedure No. EMA/VR/0000312495

Note

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

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List of abbreviations

Abbreviation	Definition
1L	first line
2L	second line
ADC	antibody-drug conjugate
AE	adverse event
AEOSI	adverse event of special interest (for pembrolizumab)
AESI	adverse event of special interest (for enfortumab vedotin)
ALT	alanine aminotransferase
APrS2	all participants receiving surgery 2
AST	aspartate aminotransferase
AUC	area under the curve
BCG	Bacillus Calmette-Guérin
BICR	blinded independent central review
CI	confidence interval
CIS	carcinoma in situ
CMV	cisplatin, methotrexate, and vinblastine
COVID-19	coronavirus disease 2019
CrCl	creatinine clearance
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough concentration
DCO	data cutoff
DFS	disease-free survival
DOR	duration of response
EAU	European Association of Urology
EC_{50}	half-maximal effective concentration
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EU	European Union
EV	enfortumab vedotin

FDA	Food and Drug Administration
GOR	grade of recommendation
HNSCC	head and neck squamous cell carcinoma
HR	hazard ratio
IA1	interim analysis 1
IFNγ	interferon gamma
IgG	immunoglobulin G
IL-2	interleukin-2
ISD	integrated safety dataset
ITT2	intent-to-treat 2
IV	intravenous
KM	Kaplan-Meier
LA-HNSCC	locally advanced head and neck squamous cell carcinoma
la/mUC	locally advanced/metastatic urothelial carcinoma
LOE	level of evidence
mAb	monoclonal antibody
MIBC	muscle-invasive bladder cancer
MIUC	muscle-invasive urothelial carcinoma
MMAE	monomethyl auristatin E
mUC	metastatic urothelial carcinoma
MVAC	methotrexate, vinblastine, doxorubicin, cisplatin
NCCN	National Comprehensive Cancer Network
NE	not evaluated
NMIBC	non-muscle invasive bladder cancer
NR	not reached
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
pCR	pathological complete response
PD-1	programmed cell death-1

PD-L1	programmed cell death ligand-1
PD-L2	programmed cell death ligand-2
pDS	pathologic downstaging
PFS	progression-free survival
PK	pharmacokinetic(s)
PLND	pelvic lymph node dissection
PS	performance status
PT	preferred term
qxw	every X weeks
RC	radical cystectomy
RCC	renal cell carcinoma
RSD	Reference Safety Dataset
RT	radiotherapy
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SMQ	Standardised MedDRA Query
SOC	standard of care
TNBC	triple-negative breast cancer
TNFα	tumor necrosis factor alpha
UC	urothelial carcinoma
US	United States
USPI	United States prescribing information
wks	weeks

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1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Astellas Pharma Europe B.V. submitted to the European Medicines Agency on 10 November 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include PADCEV, in combination with pembrolizumab, for use as neoadjuvant treatment and continued as adjuvant treatment following radical cystectomy, is indicated for the treatment of adult patients with muscle-invasive bladder cancer (MIBC) who are ineligible for cisplatin-containing chemotherapy, based on interim results from study EV-303/KN-905, an open label, randomised, interventional phase 3 study. 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 5.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet, and to bring the PI in line with the latest QRD template version 10.4.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

The new indication, which is the subject of this application, does not fall within any orphan designation.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0114/2018 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Thalia Marie Estrup Blicher

Timetable	Actual dates
Submission date	10 November 2025
Start of procedure:	29 November 2025
CHMP Rapporteur's preliminary assessment report circulated on:	23 January 2026
PRAC Rapporteur's preliminary assessment report circulated on:	30 January 2026
Joint Rapporteur's updated assessment report circulated on:	20 February 2026
Request for supplementary information and extension of timetable adopted by the CHMP on:	26 February 2026
MAH's responses submitted to the CHMP on:	23 March 2026
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	20 April 2026
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	24 April 2026
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	13 May 2026
CHMP opinion:	21 May 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The indication sought is:

PADCEV, in combination with pembrolizumab, as neoadjuvant treatment and then continued after radical cystectomy as adjuvant treatment, is indicated for the treatment of patients with muscle invasive bladder cancer (MIBC) who are ineligible for cisplatin-containing chemotherapy.

Epidemiology

Bladder cancer is the ninth most common cancer globally. Incidence varies across regions, with highest crude rates in Europe and North America[1]. The disease is most common in male. The most important risk factor for bladder cancer is tobacco smoking, followed by occupational exposure to aromatic amines and ionising radiation[2]. Lynch syndrome may also predispose to urothelial cancer.

Biologic features

More than 90% of urothelial tumors have origins in the bladder, the rest from the renal pelvis (8%) and from ureter and urethra (2%). Urothelial (transitional cell) carcinoma is the most common histologic subtype of bladder cancer. The majority of muscle invasive tumors are high-grade urothelial carcinomas[3].

Clinical presentation

Approximately 70% of patients with bladder cancer are initially diagnosed with non-muscular invasive bladder cancer (NMIBC), which can generally be treated with local procedures and carries overall good prognosis. Approximately 25% are diagnosed with muscular invasive bladder cancer (MIBC) at presentation and another 10% will progress from non-muscle-invasive tumors. Approximately 5% of patients have metastatic disease at the time of diagnosis[4].

Resectable MIBC is a heterogeneous disease, which ranges from cT2 (invasion of the muscularis propria) to cT4a tumors (invasion beyond the bladder/into adjacent organs) and N0 (no lymph node metastasis) to N1 (unilateral pelvic lymph node metastasis). Higher T stage and lymph node positivity are independent indicators of poor prognosis[5]. The current staging system is AJCC TNM 8th edition, 2017.

Staging after neoadjuvant chemotherapy (NAC) and radical cystectomy (RC) can be done (ypTNM); ypT0N0 after NAC and cystectomy is associated with better prognosis[6].

Management

Radical cystectomy (RC) with pelvic lymph node dissection (PLND) with its associated urinary diversion is the standard treatment of resectable MIBC with curative intent[7]. According to ESMO guidelines, 3 to 4 cycles of cisplatin-based neoadjuvant ChT should be given for MIBC, being cisplatin-gemcitabine (CG) or accelerated methotrexate, vinblastine, adriamycin and cisplatin (MVAC) the most widely used neoadjuvant chemotherapy regimens[8]. The NIAGARA phase III trial demonstrated significantly improved EFS and OS by adding peri-operative durvalumab to neoadjuvant CG chemotherapy, leading to the approval of this regimen by FDA[9]. However,

[1] Global Cancer Observatory (GCO): Cancer Today [Internet]. Lyon (France): International Agency for Research on Cancer (IARC); c1965-2025. Incidence, both sexes, in 2022: bladder; [cited 2025 Jan 6]; [about 2 screens]. Available from: https://gco.iarc.fr/today/home.
[2] Burger M, Catto JW, Dalbagni G, et al. Epidemiology and risk factors of urothelial bladder cancer. Eur Urol. 2013;63(2):234-241.
[3] NCCN guidelines Bladder Cancer v 2.2025
[4] Kamat AM, Hahn NM, Efstathiou JA, et al. Bladder cancer. Lancet. 2016 Dec 3;388:2796-810.
[5] Shariat SF, Karakiewicz PI, Palapattu GS, et al. Outcomes of radical cystectomy for transitional cell carcinoma of the bladder: a contemporary series from the Bladder Cancer Research Consortium. J Urol. 2006 Dec;176:2414-22.
[6] EAU Guidelines. Edn. presented at the EAU Annual Congress Madrid 2025. ISBN 978-94-92671-29-5. http://uroweb.org/guidelines/compilations-of-all-guidelines/
[7] NCCN guidelines Bladder Cancer v 2.2025
[8] Powles T, Bellmunt J, Comperat E, et al; ESMO Guidelines Committee. Bladder cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022 Mar;33(3):244-258.
[9] Powles T, Catto JWF, Galsky MD, et al; NIAGARA Investigators. Perioperative Durvalumab with Neoadjuvant Chemotherapy in Operable Bladder Cancer. N Engl J Med. 2024 Nov 14;391(19):1773-1786.

neoadjuvant cisplatin-based chemotherapy should only be used in patients eligible for cisplatin-combination chemotherapy[10].

Up to 50% of patients with MIBC are however considered unable to receive cisplatin-based chemotherapy due to comorbidities[11]. Cisplatin ineligibility is defined as meeting at least one of the following globally accepted criteria: GFR ≤ 60 mL/min; ECOG ≥ 2; CTCAE v4 Grade ≥2 for audiometric hearing loss or peripheral neuropathy; or NYHA Class III heart failure[12]. Among these factors, renal dysfunction and poor ECOG PS are the most common clinical factors for considering patients ineligible for cisplatin therapy[13]. Carboplatin-based neoadjuvant regimens for cisplatin-ineligible patients with MIBC have demonstrated limited clinical response[14], and it is not recognized as standard neoadjuvant regimen[15].

Regarding post-operative therapy, adjuvant cisplatin-based ChT in patients who did not receive neoadjuvant therapy remains an area of debate[16], although still only in patients who are cisplatin-eligible. Adjuvant nivolumab for 1 year versus placebo showed DFS improvement vs placebo in CHECKMATE-274[17], leading to FDA approval of this indication. OS was immature. Due to the inconsistency across trials (adjuvant atezolizumab did not improve DFS nor OS[18]) and uncertainty of the relationship between DFS and OS with immunotherapy, OS results are awaited before this treatment can be recommended by ESMO; nivolumab is currently approved in the EU in the adjuvant UC setting only for PD-L1 positive tumors (≥1%). In China, adjuvant immunotherapy is not recommended outside the context of clinical trials[19]. Postoperative RT may be an option for the subset of patients with high-risk pathology or presence of positive surgical margins after RC + PLND, and it is not considered standard treatment of patients with MIBC[20].

Up to 50% of patients with MIBC who undergo RC + PLND alone experience local or distant recurrence within 2 to 3 years[21], with five-year survival in about 50% of patients[22]. The literature on outcomes in cisplatin-ineligible MIBC is limited, and the available evidence is primarily from small, single-arm Phase 2 studies, or subset analyses. Effective treatment options for this frailer population are needed.

[10] EAU Guidelines. Edn. presented at the EAU Annual Congress Madrid 2025. ISBN 978-94-92671-29-5. http://uroweb.org/guidelines/compilations-of-all-guidelines/
[11] Thompson RH, Boorjian SA, Kim SP et al. Eligibility for neoadjuvant/adjuvant cisplatin-based chemotherapy among radical cystectomy patients. BJU Int 2014;113(5b):E17-21.
[12] Galsky MD, Hahn NM, Rosenberg J et al. Treatment of patients with metastatic urothelial cancer "unfit" for cisplatin-based chemotherapy. J Clin Oncol 2011;29:2432-8.
[13] Galsky MD, Ma E, Shah-Manek B, et al. Cisplatin ineligibility for patients with metastatic urothelial carcinoma: a survey of clinical practice perspectives among US oncologists. Bladder Cancer. 2019;5:281-8
[14] Fazili A, Jazayeri SB, Rose KM, et al. Cisplatin-ineligible patients with muscle-invasive bladder cancer demonstrate poor long-term survival following immediate radical cystectomy. BJU Int. 2026 Jan;137(1):181-188.
[15] Holzbeierlein J, Bixler BR, Buckley DI, et al. Treatment of non-metastatic muscle- invasive bladder cancer: AUA/ASCO/SUO guideline (2017; amended 2020, 2024). J Urol. 2024 Jul;212:3-10.
[16] Powles T, Bellmunt J, Comperat E, et al; ESMO Guidelines Committee. Bladder cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022 Mar;33(3):244-258.
[17] Bajorin DF, Witjes JA, Gschwend JE, et al. Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma. N Engl J Med. 2021 Jun 3;384(22):2102-2114. Erratum in: N Engl J Med. 2021 Aug 26;385(9):864.
[18] Bellmunt J, Hussain M, Gschwend JE, et al. Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma (IMvigor010): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2021;22(4):525-537.
[19] Dong X, Song G, Guan K, et al. Clinical practice guideline on bladder cancer (part III). Uro Precision. 2023;1:141–61.
[20] Powles T, Bellmunt J, Comperat E, et al; ESMO Guidelines Committee. Bladder cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022 Mar;33(3):244-258.
[21] Mari A, Campi R, Tellini R, et al. Patterns and predictors of recurrence after open radical cystectomy for bladder cancer: a comprehensive review of the literature. World J Urol. 2018;36:157-70.
[22] Stein, J.P., et al. Radical cystectomy for invasive bladder cancer: long-term results of a standard procedure. World J Urol, 2006. 24: 296.

Table 1 Phase 2 Key Efficacy Results in Participants with Cisplatin-ineligible MIBC

Clinical Study	Treatment	Population	Pathologic CR (pT0)	EFS / OS
ABACUS	Atezolizumab	Cisplatin-ineligible MIBC	31%	1-year RFS: 79%
GU14-188 Cohort 2	Pembrolizumab + gemcitabine	Cisplatin-ineligible MIBC	41%	3-year OS: 66%
EV-103 Cohort H	Neoadjuvant EV	Cisplatin-ineligible MIBC	36%	3-year EFS: 57%; 3-yr OS: 68%
EV-103 Cohort L	Perioperative EV	Cisplatin-ineligible MIBC	34%	NR

CR=complete response; EFS=event-free survival; gem-carbo=gemcitabine-carboplatin; IO=immuno-oncology; MIBC= muscle-invasive bladder cancer; NR=not reported; OS=overall survival; RFS=relapse-free survival.
Source: [Ref. 5.4: 08RHSX, 08W754, 08XJDT, 08RY7P]

2.1.2. About the product

Pharmacotherapeutic action

Enfortumab vedotin, also referred to as ASG-22CE and Padcev, is a Nectin-4 directed ADC comprised of a fully humanized anti-Nectin-4 IgG1 kappa mAb conjugated to the small molecule microtubule disrupting agent, MMAE, via a protease-cleavable maleimidocaproyl vc-linker. Conjugation takes place on cysteine residues that comprise the interchain disulfide bonds of the antibody to yield a product with a drug to antibody ratio of approximately 3.8.

Enfortumab vedotin binds to the V domain of Nectin-4 protein. Nectin-4 is expressed in multiple cancers, particularly those of epithelial origin such as urothelial cancers.

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

Previously approved indications

Padcev is approved for the following indications:

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

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

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Table 2 Overview of the Key Pembrolizumab and Enfortumab Vedotin Studies in the Clinical Development Program in Urothelial Carcinoma

Study No.	Phase	Description/Design	Enrolled	Dosage Regimen	Study Status
Pembrolizumab Monotherapy Studies					
KEYNOTE-052	Phase 2	Multicenter, open-label, nonrandomized; endpoints included ORR in all comers, CPS >1, CPS ≥10	374 participants with urothelial cancer who are cisplatin-ineligible	Pembrolizumab 200 mg q3w	Complete
KEYNOTE-361	Phase 3	Randomized, controlled, open label; endpoints included PFS in all comers and OS in all comers, CPS ≥10	1010 participants with la/mUC; 3 treatment regimens in the 1L setting; (1) pembrolizumab only, (2) pembrolizumab plus combination chemotherapy, (3) combination chemotherapy only	Treatment Arm 1 (Monotherapy): Pembrolizumab 200 mg q3w Treatment Arm 2 (Combination): Pembrolizumab + cisplatin/carboplatin + gemcitabine Treatment Arm 3 (Chemotherapy only): Cisplatin/carboplatin + gemcitabine	Complete
Enfortumab Vedotin Monotherapy Studies					
EV-201 (SGN22E-001)	Phase 2	Open-label, multicenter, multi-cohort study of enfortumab vedotin in participants who have previously received a PD-1/PD-L1 inhibitor	219 Cohort 1: Subjects with la/mUC who have previously received a PD-1/ PD-L1 inhibitor and a platinum-containing chemotherapy Cohort 2: Subjects who have received a PD-1/PD-L1 inhibitor and are not eligible for cisplatin-containing chemotherapy	Enfortumab vedotin: 1.25 mg/kg 30-min IV infusion on Days 1, 8, and 15 of a 28-day cycle	Complete

Study No.	Phase	Description/Design	Enrolled	Dosage Regimen	Study Status
EV-301 (7465-CL-0301)	Phase 3	Phase 3, global, openlabel, randomized study of enfortumab vedotin vs chemotherapy	608 Participants with la/mUC who have received a platinum-containing chemotherapy and have experienced disease progression or relapse during or following treatment with a PD-1 or PDL1 inhibitor	Enfortumab vedotin: 1.25 mg/kg 30min IV infusion on Days 1, 8, and 15 of a 28-day cycle or Docetaxel 75 mg/m^2, paclitaxel 175 mg/m2 or vinflunine 320 mg/m^2 (all IV) on Day 1 of a 21-day cycle	Ongoing
EV-103 (KEYNOTE-896/SGN22E-002/MK-3475-869) Cohorts H and L: See Enfortumab Vedotin + Pembrolizumab Studies for further details					
Enfortumab vedotin + Pembrolizumab Studies					

Study No.	Phase	Description/Design	Enrolled	Dosage Regimen	Study Status
EV-103 (EV-103/SGN22E-002/MK-3475-869)	Phase 1b/2	Enfortumab vedotin as monotherapy or in combination with other anticancer therapies for the treatment of UC LA/mUC Dose-escalation: 1L/2L cisplatin-ineligible EV+pembro Cohort A: 1L cisplatin-ineligible EV+Pembro Cohort K (randomized): 1L cisplatin-ineligible EV monotherapy or EV+pembro MIBC Cohort H: neoadjuvant in cisplatin-ineligible EV monotherapy Cohort L: perioperative cisplatin-ineligible EV monotherapy	LA/mUC Dose-escalation: 10 Cohort A: 40 Cohort K: 151 MIBC 58/60 Cohort H: 22 Cohort L: 41 Participants with la/mUC or MIBC. Cohort specific requirements for cisplatin eligibility and PD-1/PD-L1/PD-L2 inhibitor naïve.	Enfortumab vedotin: 1 to 1.25 mg/kg 30-min IV infusion on Days 1 and 8 of a 3-week cycle as monotherapy or in combination with pembrolizumab and/or chemotherapy	LA/mUC Ongoing; enrollment closed MIBC Ongoing; enrollment closed

Study No.	Phase	Description/Design	Enrolled	Dosage Regimen	Study Status
EV-302 (EV-302/ SGN22E-003/MK-3475-A39)	Phase 3	Randomized, openlabel, global study to evaluate EV in combination with pembrolizumab versus chemotherapy alone in previously untreated LA/mUC	886 Participants with previously untreated la/mUC who were eligible for platinum as 1L treatment	Arm A: Enfortumab vedotin at 1.25 mg/kg IV on days 1 and 8 of a 21day cycle; pembrolizumab 200 mg IV on Day 1 of each 21-day cycle Arm B: Gemcitabine 1000 mg/m^2 IV on Days 1 and 8 of a 21-day cycle; either cisplatin (70 mg/m^2) or carboplatin (AUC 5 or 4.5 mg/mL/min) (both IV) on Day 1 of each cycle.	Ongoing; enrollment closed
KEYNOTE-905	Phase 3	Randomized, controlled, parallel-group, multisite, open-label study of perioperative pembrolizumab plus RC+PLND and perioperative enfortumab vedotin in combination with pembrolizumab plus RC+PLND versus RC+PLND alone in participants with MIBC who are ineligible for or decline cisplatin-based chemotherapy; primary endpoint is EFS	595 participants with previously untreated MIBC who are either cisplatin-ineligible or decline cisplatin	Treatment Arm A Preoperative pembrolizumab 200 mg IV q3w for 3 cycles + cystectomy + postoperative pembrolizumab 200mg IV q3w for 14 cycles Treatment Arm B Cystectomy + postoperative observation Treatment Arm C Preoperative enfortumab vedotin 1.25 mg/kg on Days 1 and 8 q3w for 3 cycles + pembrolizumab 200mg IV q3w for 3 cycles + cystectomy + postoperative enfortumab vedotin 1.25 mg/kg on Days 1 and 8 q3w for 6 cycles + pembrolizumab 200 mg IV q3w for 14 cycles	Ongoing; enrollment closed

Study No.	Phase	Description/Design	Enrolled	Dosage Regimen	Study Status
KEYNOTE-B15	Phase 3	Randomized, controlled, parallel-group, multisite, open-label study of perioperative enfortumab vedotin + pembrolizumab plus RC+PLND versus neoadjuvant chemotherapy plus RC+PLND in cisplatin-eligible participants with MIBC; primary endpoint is EFS	808 participants with previously untreated MIBC that are cisplatin eligible	Treatment Arm 1 Preoperative enfortumab vedotin 1.25 mg/kg on Days 1 and 8 q3w for 4 cycles + pembrolizumab 200 mg IV q3w for 4 cycles + cystectomy + postoperative enfortumab vedotin 1.25 mg/kg on Days 1 and 8 q3w for 5 cycles + pembrolizumab 200 mg IV q3w for 13 cycles Treatment Arm 2 Preoperative gemcitabine 1000 mg/m^2 on Days 1 and 8 + cisplatin 70 mg/m^2 on Day 1 q3w for 4 cycles + cystectomy + postoperative observation	Ongoing; enrollment closed

1L=first-line; 2L=second-line; AUC=area under the curve; CPS=combined positive score; EFS=event-free survival; IV=intravenous; la/mUC=locally advanced or metastatic urothelial carcinoma; MIBC=muscle-invasive bladder cancer; NMIBC=non-muscle-invasive bladder cancer; ORR=objective response rate; OS=overall survival; PD-1= programmed cell death protein 1; PD-L1= programmed cell death ligand 1; PFS=progression-free survival; PLND=pelvic lymph node dissection; q3w=every 3 weeks; RC=radical cystectomy; UC=urothelial carcinoma.

2.1.4. General comments on compliance with GCP

The clinical studies were conducted in accordance with current standard research approaches with regard to the design, conduct, and analysis of such studies including the archiving of essential documents. All studies were conducted following appropriate Good Clinical Practice standards and considerations for the ethical treatment of human participants that were in place at the time the studies were performed.

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

Enfortumab vedotin is a Nectin-4 directed ADC comprised of a fully humanized anti-Nectin-4 IgG1 kappa mAb conjugated to the small molecule microtubule disrupting agent monomethyl auristatin E (MMAE), via a protease-cleavable maleimidocaproyl vc-linker. The mode of action of enfortumab vedotin involves the internalization and subsequent breakdown of the antibody-drug-conjugate by the target cells and the release of the cytotoxic payload (MMAE). Therefore, the primary substance available for excretion would be MMAE.

The Ab part of the drug is exempt from ERA studies according to the guideline as proteins are expected to biodegrade in the environment and not be a significant risk for the environment (Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use"; EMEA/CHMP/S/4447/00 Rev. 1- Corr).

An updated ERA was submitted in accordance with the revised Guideline on the environmental risk assessment of medicinal products for human use (2024) comprising a re-calculated PEC_{SW} for enfortumab vedotin, PBT/vPvB screening and the assessment of potential endocrine activity.

$PEC_{surface\ water}$ re-calculation

Based on default market penetration factor (F_{PEN}=1%)

PEC_{SW} is calculated based on the maximum dose of enfortumab vedotin of 1.25 mg·kg-1 bw and an average bodyweight in Europe of 70 kg.

The PEC_{SW} of enfortumab vedotin based on the default F_{PEN} value of 0.01 (1%) is greater than the action limit of 0.01 µg/L (PEC_{SW} = 0.4375 µg/L) proposed in EMA 2024, therefore further evaluation was required.

The refined F_{PEN} value can be determined based on the highest prevalence of bladder cancer within the EU, which is 186.9 per 100,000, and two possible treatment regimens of 1.25 mg·kg-1 bw on Day 1, 8 and 15 of a 28- day cycle (monotherapy) or 1.25 mg·kg-1 bw on Day 1 and 8 on a 21-day cycle (combo).

Using the refined Fpen value, calculated above, a refined PEC_{SW} value has been estimated as PEC_{SW} = 0.00875 µg/L.

The PEC_{SW} is below the trigger value of 0.01 µg/L therefore further testing at Phase II is not required.

PBT/vPvB Screening

Review of Physico-Chemical Properties

The determination of the partition coefficient has been focused on the cytotoxic payload (MMAE).

The n-octanol/water distribution coefficient (Log D_{OW}) of MMAE was determined according to the OECD guideline number 107 "Shake-flask method" and in accordance with the principles of GLP.

As the experimentally derived Log D_{OW} values are < 4.5 across the environmentally relevant pH range an assessment of the persistence, bioaccumulation, and toxicity (PBT assessment) is not required.

Screening Endocrine Assessment

Based on the mode of action, enfortumab vedotin would not be classed as an endocrine disruptor, therefore a tailored Phase II environmental risk assessment is not required.

Table 3 Summary of revised study results

Substance (INN/Invented Name):	Monomethyl auristatin E (MMAE)
CAS-number (if available):	474645-27-7

Phase I			
Parameter	**Value**	**Unit**	**Conclusion**
$PEC_{sw,refined}$ *(prevalence / treatment regime)*	0.00024	µg/L	≥ 0.01 threshold: N
PBT screening		**Result**	**Conclusion**
Bioaccumulation potential- log K_{ow} /D_{ow} for monomethylauristatin E	OECD107	< 4.5 for all relevant PH	Potential PBT (N)
Other concerns (e.g. chemical class)			N

$PEC_{surfacewater}$ for monomethyl auristatin E is below the action limit of 0.01 µg/L. Consequently, a Phase II_risk assessment is not required.

Conclusion on the non-clinical aspects

The updated ERA submitted showed that the conclusions drawn on the PBT screening in the initial marketing authorisation application comply with the ERA 2024 Guideline and remain applicable. The Phase I Exposure Assessment was made based on the most conservative maximum daily dose of 125 mg enfortumab vedotin and solely the fraction of monomethyl auristatin E (MMAE) was considered. Prevalence and treatment-based refinement comply with data requirements set out by the ERA 2024 Guideline. Considering the above data, enfortumab vedotin is not expected to pose 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
3475-905 [Ref. 5.3.5.1: P905V01MK3475]	3	Argentina, Belgium, Canada, Colombia, Denmark, France, Germany, Hungary, Ireland, Israel, Italy, Japan, Malaysia, Poland, Russia, Singapore, South Korea, Spain, Sweden, Thailand, Turkiye, UK, Ukraine, USA	A Randomized Phase 3 Study Evaluating Cystectomy with Perioperative Pembrolizumab and Cystectomy with Perioperative Enfortumab Vedotin and Pembrolizumab versus Cystectomy Alone in Participants who are Cisplatin-Ineligible or Decline Cisplatin with Muscle-Invasive Bladder Cancer (KEYNOTE-905/EV-303)	Multicenter, efficacy, safety, parallel assignment, open-label, active comparator intervention	Arm A: pembrolizumab 200 mg IV infusion q3w: 3 cycles neoadjuvant phase; 14 cycles adjuvant phase Arm B: standard of care RC + PLND Arm C: - pembrolizumab 200 mg IV infusion q3w; 3 cycles neoadjuvant phase; 14 cycles adjuvant phase - enfortumab vedotin 1.25 mg/kg IV infusion on Days 1 and 8 q3w; 3 cycles in the neoadjuvant phase and for 6 cycles in the adjuvant phase	Male or female participants at least 18 years of age with histologically confirmed MIBC clinical stage T2-T4aN0M0 or T1-T4aN1M0 who are ineligible for or decline cisplatin-based chemotherapy	Arm A: 166 participants were enrolled and 163 participants were treated Arm B: 259 participants were enrolled and 242 participants were treated Arm C: 170 participants were enrolled and 167 participants were treated

2.3.2. Clinical Pharmacology

Characterization of the clinical pharmacology of enfortumab vedotin, including mechanism of action, exposure-response analysis, and the impact of intrinsic and extrinsic factors on the PK of the ADC and the payload have been presented in multiple prior submissions (EMEA/H/C/005392; (EMEA/H/C/005392-II-0013).

This section will focus on the new data related to the characterization of PK and ADA of enfortumab vedotin (EV) and pembrolizumab in KEYNOTE-905 study population and its comparison against historical enfortumab vedotin and pembrolizumab data.

KEYNOTE-905 is an ongoing Phase 3, randomized, controlled, parallel-group, multisite, open-label study of perioperative pembrolizumab plus RC + PLND and perioperative EV in combination with pembrolizumab plus RC + PLND versus RC + PLND alone. Clinical pharmacology results specific to this submission include:

• PK and ADA results of enfortumab vedotin 1.25 mg/kg on Days 1 and 8 of a q3w cycle administered in combination with pembrolizumab 200 mg q3w to KEYNOTE-905 participants

• PK and ADA results of pembrolizumab 200 mg q3w administered in combination with enfortumab vedotin 1.25 mg/kg on Days 1 and 8 of a q3w cycle to KEYNOTE-905 participants

Table 4 Study design of 3475-905 (KEYNOTE-905/EV-303)

Study ID	Phase	Country/ Region	Study Title	Study Design	Dosing Regimen	Study Population	Participant Exposure
3475-905 [Ref. 5.3.5.1: P905V01MK3475]	3	Argentina, Belgium, Canada, Colombia, Denmark, France, Germany, Hungary, Ireland, Israel, Italy, Japan, Malaysia, Poland, Russia, Singapore, South Korea, Spain, Sweden, Thailand, Turkiye, UK, Ukraine, USA	A Randomized Phase 3 Study Evaluating Cystectomy with Perioperative Pembrolizumab and Cystectomy with Perioperative Enfortumab Vedotin and Pembrolizumab versus Cystectomy Alone in Participants who are Cisplatin-Ineligible or Decline Cisplatin with Muscle-Invasive Bladder Cancer (KEYNOTE-905/EV-303)	Multicenter, efficacy, safety, parallel assignment, open-label, active comparator intervention	Arm A: pembrolizumab 200 mg IV infusion q3w: 3 cycles neoadjuvant phase; 14 cycles adjuvant phase Arm B: standard of care RC + PLND Arm C: - pembrolizumab 200 mg IV infusion q3w; 3 cycles neoadjuvant phase; 14 cycles adjuvant phase - enfortumab vedotin 1.25 mg/kg IV infusion on Days 1 and 8 q3w; 3 cycles in the neoadjuvant phase and for 6 cycles in the adjuvant phase	Male or female participants at least 18 years of age with histologically confirmed MIBC clinical stage T2-T4aN0M0 or T1-T4aN1M0 who are ineligible for or decline cisplatin-based chemotherapy	Arm A: 166 participants were enrolled and 163 participants were treated Arm B: 259 participants were enrolled and 242 participants were treated Arm C: 170 participants were enrolled and 167 participants were treated

Bioanalytical methods

A new validated method (BTM-3778-R0) for measuring serum concentrations of unconjugated MMAE was used and is described in Table 5. Unconjugated MMAE concentrations in serum were measured using a validated LC-MS/MS with internal standard (D8-MMAE) method. The LLOQ was 10 pg/mL. This method met the acceptance criteria specified in the validation method plans for selectivity, within-run and between-run accuracy, and precision for the measurement of MMAE in clinical study samples.

Table 5 Method for measuring MMAE concentration

Validation Method No.	BTM-3778-R0
Matrix	Serum
Analyte	MMAE
Analytical instrument and detection method	LC-MS/MS
Sample preparation technique	SPE
Lower limit of quantitation (pg/mL)	10.0
Amount of matrix used (mL)	0.050
Concentration range (pg/mL)	10.0 to 30000
Within-run accuracy (%RE)	-2.0 to 17.0
Between-run accuracy (%RE)	-0.4 to 7.0
Within-run precision (%CV)	1.7 to 8.1
Between-run precision (%CV)	2.6 to 8.6
Dilution Integrity Accuracy (%RE) Precision (%CV)	10-fold 3.6 1.4
Short-term stability	6 hours in ice/water bath
Long-term stability	742 days at -70ºC 742 days at -20ºC
Freeze-thaw stability	5 cycles freeze (-70ºC)/thaw (ice/water bath)
Processed stability	236.0 hours at 4ºC
Test facility	Frontage Laboratories, Inc.

CV: coefficient of variation; LC-MS/MS: liquid chromatography tandem mass spectrometry; MMAE: monomethyl auristatin E; RE: relative error; SPE: solid-phase extraction

An alternative method (BTM-3778-R0) for measuring MMAE concentrations in serum has been utilized to analyze PK samples from Study KEYNOTE-905/EV-303, instead of the method which measured MMAE in plasma (LCMSX 869). A partial validation was conducted to assess the specific impact of the presence on enfortumab vedotin (ADC) on MMAE method performance and the potential interference from pembrolizumab. The partial validation is detailed in Report 1083-R14383 and the addendum report 1083-R14383A1. The partial validation results are summarized in Table 6.

Similar to the previous method for measuring MMAE is plasma (LCMSX 869) , the partial validation for measuring MMAE in serum in the presence of enfortumab vedotin met the acceptance criteria for accuracy, precision, short-term stability, freeze/thaw stability, and whole blood stability, and there was no interference from pembrolizumab, Table 6.

Table 6 Partial validation results of method BTM-3778-ROM for measuring MMAE concentration

Validation Method No.	BTM-3778-R0
Matrix	Serum
Analyte	MMAE
Analytical instrument and detection method	LC-MS/MS
Sample preparation technique	SPE
Lower limit of quantitation (pg/mL)	10.0
Amount of matrix used (mL)	0.050
Concentration range (pg/mL)	10.0 to 30000
Calibration standards precision (%CV)	≤ 5.7
Calibration standards bias (%RE)	-2.1 to 2.5
QC precision (%CV)	≤ 4.6
QC bias (%CV)	1.8 to 3.6
Pembrolizumab interference QC precision (CV%) QC bias (%RE)	 ≤ 1.6 -4.7 and 2.2
Short-term stability	MMAE stable in the presence of EV (50 µg/mL) up to 15.0 hours at room temperature
Freeze-thaw stability	MMAE stable in the presence of EV (50 µg/mL) for 7 freeze (-70 °C)/thaw (room temperature) cycles
Whole blood stability	MMAE stable for up to 60 minutes at room temperature and in iced water bath in presence of EV (50 µg/mL)
Test facility	Frontage Laboratories, Inc.

There have been no changes to the antitherapeutic antibodies (ATA) method since the initial PADCEV Marketing Application.

2.3.3. Pharmacokinetics

Pharmacokinetic modelling

The PK of the ADC and MMAE have been evaluated as monotherapy in clinical studies and in a PopPK analysis based on data from 748 participants from 5 clinical studies. Additionally, PopPK modelling was conducted for the ADC and MMAE in the combination setting (with pembrolizumab) in first-line treatment of LA/mUC based on data from Studies EV-103 (n = 198, of whom 72 received EV monotherapy in Cohort K) and EV-302 (n = 446).

The original population PK model developed on data from EV monotherapy studies was previously used to characterize the PK profile of the ADC and unconjugated MMAE in la/mUC (Locally Advanced/Metastatic Urothelial Carcinoma) participants who received EV in combination with pembrolizumab (Study EV-103 and EV-302) by external validation. The original model was used without modification for characterisation of ADC, while the MMAE model was modified. The ADC model was a linear 3-compartment model with zero-order input and first-order elimination, while the modified MMAE model was a 2-compartment model with first-order elimination and time-varying conversion rate from ADC using an empirical sigmoidal function. This modified EV model denoted "previous" was used to fit data from Phase 3 Study EV-303 (KEYNOTE-905), where EV therapy was combined with pembrolizumab in participants with MIBC (Muscle Invasive Bladder Cancer), by an external validation approach.

Study EV-303 included 2 phases of treatment surrounding RC/PLND surgery, where EV was administered as 1.25 mg/kg 2Q3W on days 1 and 8 of every 21-day treatment cycle for 3 cycles in the neoadjuvant phase and 6 cycles in the adjuvant phase. As of the data cut-off date of 06 Jun

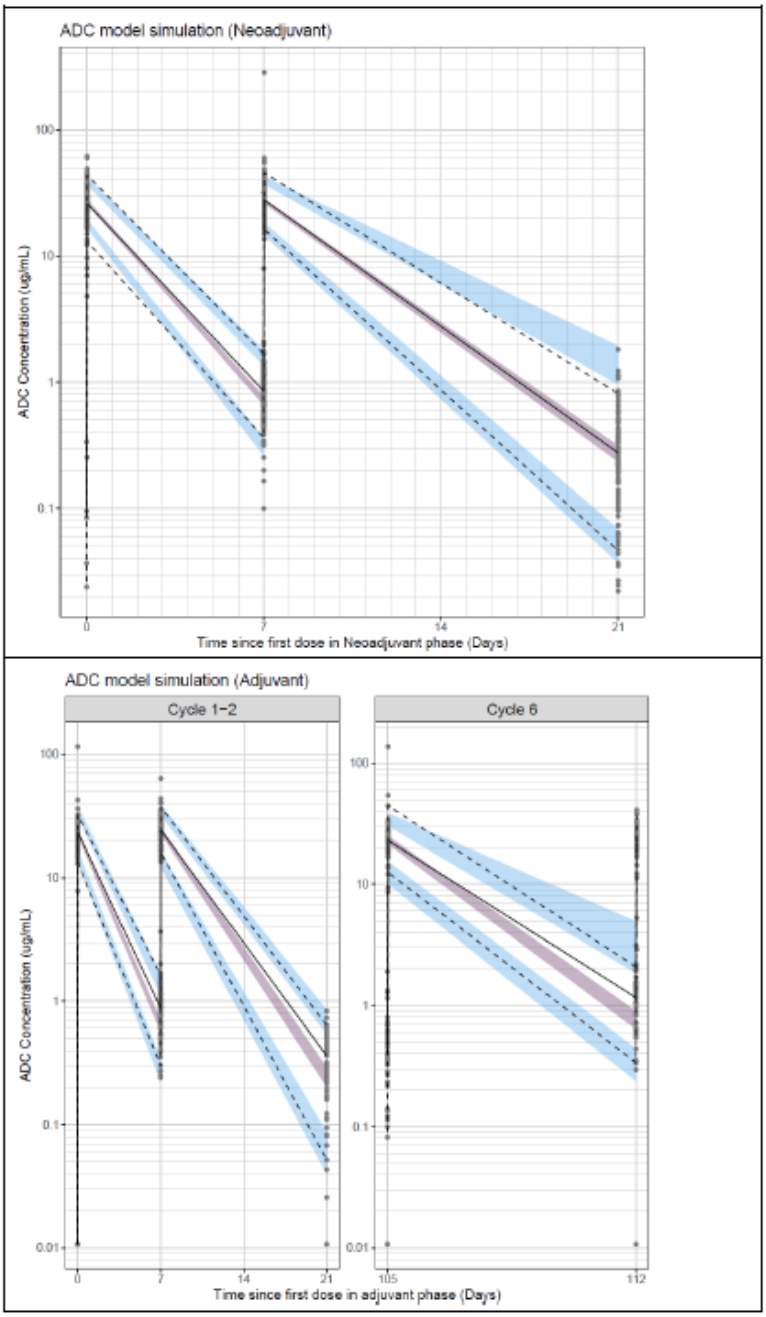
2025, a total of 2808 ADC and MMAE sparse samples (pre-dose and EOI) were available from 167 participants in the neoadjuvant phase and 91 participants in the adjuvant phase of Study EV-303. Pre-first dose PK samples (n= 332) were excluded. BLQ concentrations (n=218) were imputed to 0.5 times the LLOQ for the first BLQ record and 0 for the subsequent BLQs within a dosing interval. Ten samples with extreme low concentration values were considered as outliers and excluded. Missing data were imputed or excluded.

The datasets (1 for ADC and 1 for MMAE) from the previous modelling exercise (EV-102 and EV-302) were appended with the new PK data from participants in Study EV-303.

The first-order conditional estimation with interaction option (FOCEI) method in NONMEM was employed for all model runs. For Bayesian forecasting, MAXEVAL=0 option in the $ESTIMATION record was used to allow the previously developed ADC model to predict PK parameters for each individual to be included in the simulation of MMAE model, based on the individual dosing history, the baseline covariate values of the participants, and PK sampling times in Study EV-303.

For simulation, $SIM ONLYSIM was used with SUBPROBLEMS=1000 to simulate 1000 profiles with uncertainty (bootstrapped from for each participant in Study EV-303. VPC plots were generated by obtaining the 95% prediction intervals of the 5th, 50th and 95th percentile of the simulated data. VPCs of ADC and MMAE from Study EV-303 are presented in Figures 3 and 4. The VPCs indicated the PK of ADC and MMAE in EV-303 were comparable to earlier studies.

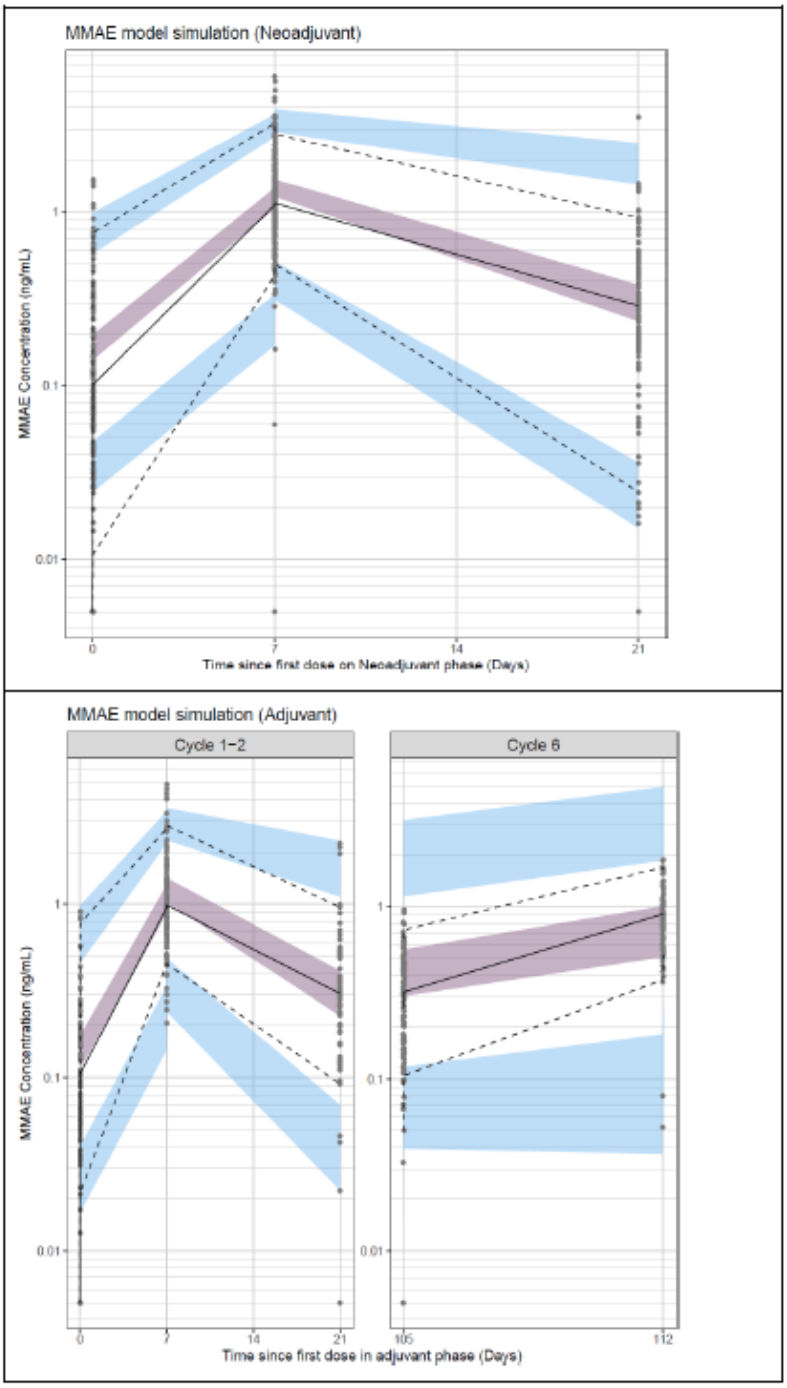
Figure 1 External Validation plot of ADC in EV-303



ADC: antibody drug conjugate

Grey circles are observations. Black solid line represents the median and the dashed lines represents the 5th and 95th percentiles of the observations. The shaded areas are the 95% prediction intervals (2.5-97.5th percentiles) around the median (plum) and 5th and 95th percentiles (blue) based on model simulations.

Figure 2 External validation Plots of MMAE in EV-303



MMAE: monomethyl auristatin E

Grey circles are observations. Black solid line represents the median of the observations and the dashed lines represents the 5th and 95th percentiles of the observations. The shaded areas are the 95% prediction intervals (2.5-97.5th percentiles) around the median (plum) and 5th and 95th percentiles (blue) based on model simulations.

Enfortumab Vedotin

This section summarizes the PK of enfortumab vedotin in combination with pembrolizumab in Study KEYNOTE-905 in participants receiving enfortumab vedotin 1.25 mg/kg (up to a maximum of 125 mg for participants with body weight ≥ 100 kg) on Day 1 and 8 of a q3w treatment cycle. The PK of enfortumab vedotin was evaluated in the enfortumab vedotin PK analysis set, which included all participants who received at least one enfortumab vedotin administration with a recorded dosing

time, and for whom at least one ADC or MMAE measurement with a corresponding sampling time is available.

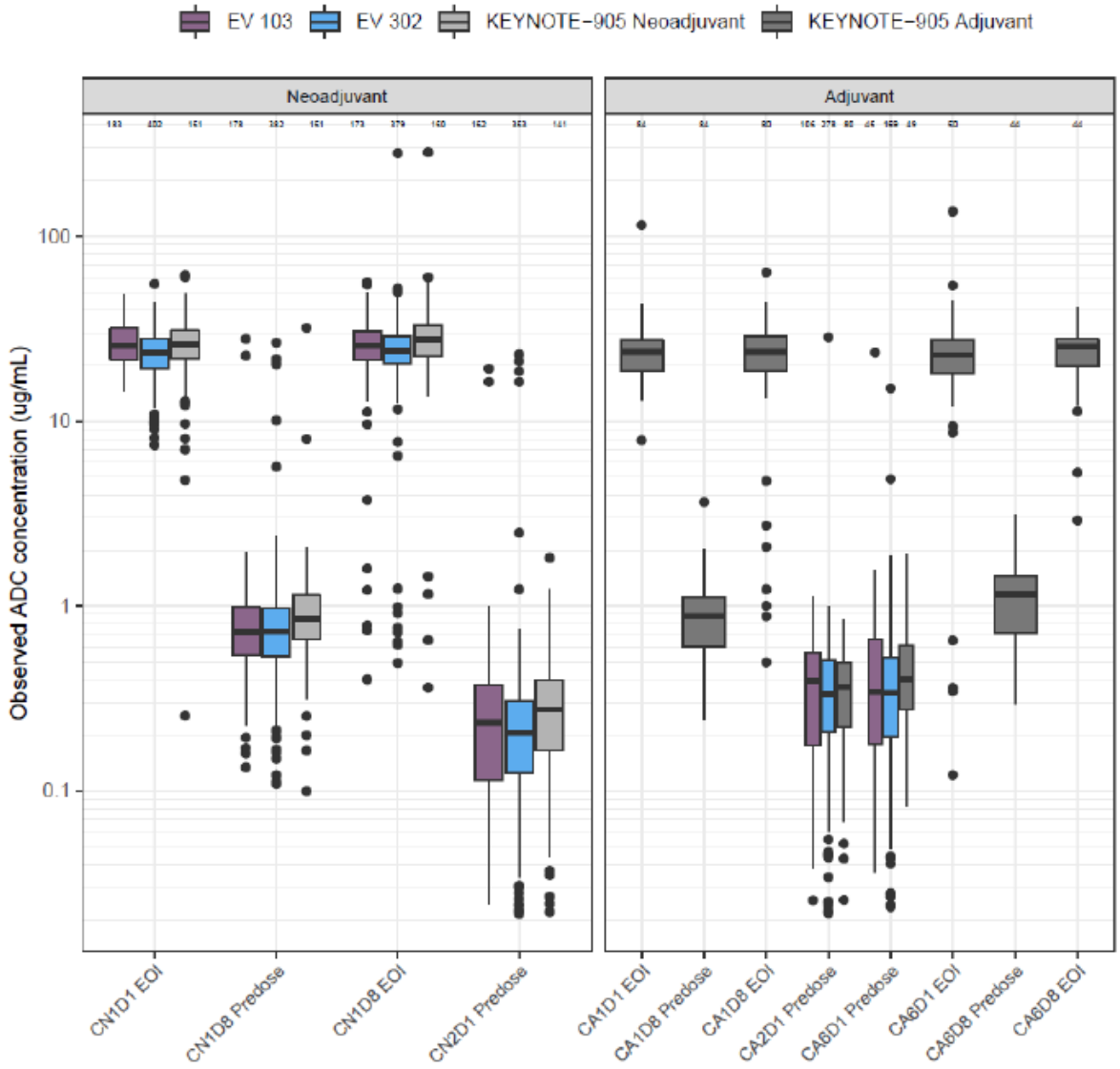
Enfortumab vedotin PK (ADC and unconjugated MMAE) profiles in the KEYNOTE-905 study population were comparable to the historical PK data obtained from studies EV-103 and EV-302 in participants with la/mUC. (Table 7, *Figure 3*, Figure 4)

Table 7 Summary of serum pharmacokinetics concentrations

Visit	Time Point	Summary Statistics	ADC (µg/mL)	MMAE (ng/mL)
Cycle 1 Day 1 Neoadjuvant	Predose	n Mean (SD) Median (min, max)	5 0.115 (0.127) 0.0844 (0.0239, 0.336)	0 NA NA
	EOI	n Mean (SD) Median (min, max)	151 26.9 (9.23) 26.0 (0.254, 61.6)	150 0.212 (0.280) 0.113 (0.0146, 1.54)
Cycle 1 Day 8 Neoadjuvant	Predose	n Mean (SD) Median (min, max)	151 1.14 (2.61) 0.853 (0.0995, 31.9)	151 1.35 (0.898) 1.10 (0.0598, 6.03)
	EOI	n Mean (SD) Median (min, max)	150 29.8 (23.1) 27.7 (0.362, 284)	151 1.32 (0.835) 1.13 (0.133, 5.66)
Cycle 2 Day 1 Neoadjuvant	Predose	n Mean (SD) Median (min, max)	141 0.328 (0.264) 0.275 (0.0221, 1.82)	145 0.381 (0.389) 0.293 (0.0161, 3.52)
Cycle 1 Day 1 Adjuvant	Predose	n Mean (SD) Median (min, max)	4 0.132 (0.187) 0.0446 (0.0262, 0.412)	0 NA NA
	EOI	n Mean (SD) Median (min, max)	84 24.3 (11.6) 23.7 (7.86, 115)	85 0.189 (0.208) 0.127 (0.0127, 0.909)
Cycle 1 Day 8 Adjuvant	Predose	n Mean (SD) Median (min, max)	84 0.914 (0.482) 0.875 (0.240, 3.65)	84 1.20 (0.828) 0.971 (0.247, 4.37)
	EOI	n Mean (SD) Median (min, max)	80 23.5 (10.2) 23.7 (0.495, 63.8)	80 1.22 (0.876) 0.994 (0.206, 4.95)
Cycle 2 Day 1 Adjuvant	Predose	n Mean (SD) Median (min, max)	80 0.353 (0.185) 0.365 (0.0256, 0.833)	82 0.399 (0.393) 0.305 (0.0222, 2.24)
Cycle 6 Day 1 Adjuvant	Predose	n Mean (SD) Median (min, max)	49 0.484 (0.346) 0.398 (0.0818, 1.90)	49 0.307 (0.193) 0.280 (0.0328, 0.814)
	EOI	n Mean (SD) Median (min, max)	50 24.4 (19.2) 22.8 (0.122, 136)	50 0.365 (0.213) 0.321 (0.0502, 0.960)
Cycle 6 Day 8 Adjuvant	Predose	n Mean (SD) Median (min, max)	44 1.20 (0.593) 1.16 (0.295, 3.12)	45 0.890 (0.403) 0.906 (0.0524, 1.86)
	EOI	n Mean (SD) Median (min, max)	44 23.8 (7.66) 25.1 (2.90, 41.0)	44 0.965 (0.364) 0.914 (0.393, 1.88)

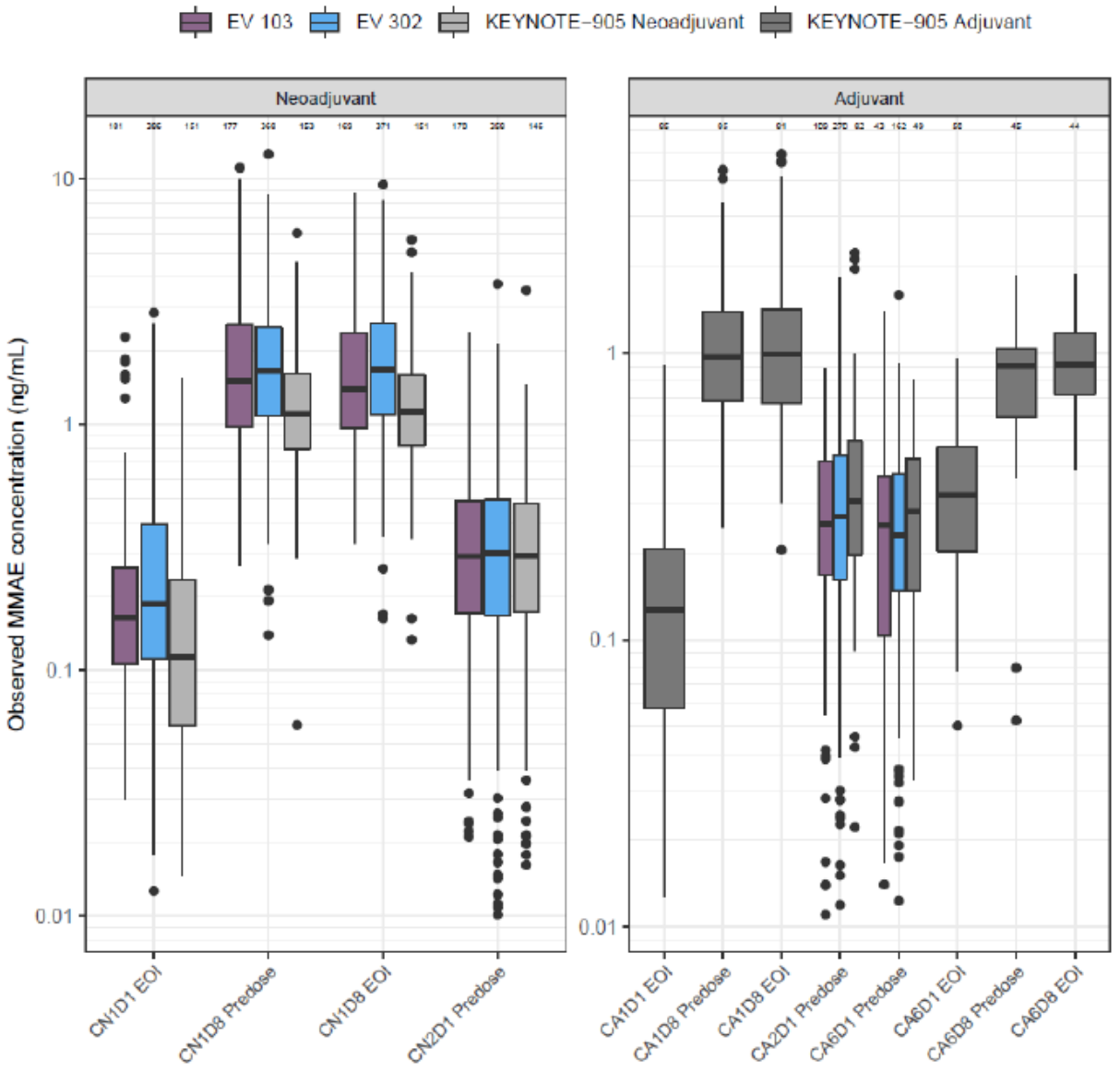
Note: concentrations below the limit of quantification were excluded from the calculation of summary statistics.
ADC: antibody drug conjugate; EOI: end of infusion; max: maximum; min: minimum; MMAE: monomethyl auristatin E; n: number of participants with PK data available at given time point; NA: not applicable
Source: Attachment 1 {08XZVZ}

Figure 3 Observed PK concentrations of ADC in Keynote-905 compared to EV-103/EV-302



ADC: antibody drug conjugate; C: cycle; CA: cycle adjuvant; CN: cycle neoajduvant; D: day; EOI: end of infusion; EV: enfortumab vedotin; CN1 in KEYNOTE-905 corresponds to C1 in EV-302, CN2 to C2, CA2 to C5, and CA6 to C9 (predose only). CN1 in KEYNOTE-905 corresponds to C1 in EV-103, CN2 to C2, CA2 to C6, and CA6 to C10 (predose only).
Source: Figure 1 {08XZVZ}

Figure 4 Observed PK concentrations of unconjugated MMAE in KEYNOTE-905 compared to EV-103/EV-302



MMAE: monomethyl auristatin E; C: cycle; CA: cycle adjuvant; CN: cycle neoadjuvant; D: day; EOI: end of infusion; EV: enfortumab vedotin. CN1 in KEYNOTE-905 corresponds to C1 in EV-302, CN2 to C2, CA2 to C5, and CA6 to C9 (predose only). CN1 in KEYNOTE-905 corresponds to C1 in EV-103, CN2 to C2, CA2 to C6, and CA6 to C10 (predose only).

2.3.4. Discussion on clinical pharmacology

Bioanalysis

The bioanalytical program for study KEYNOTE-905/EV-303 is acceptable.

Modelling

Previous Pop PK models based on data from EV-103 and EV-302 (la/mUC), where EV was combined with pembrolizumab, were used to describe the sparse concentration data for ADC and MMAE from 167 participants with MIBC in Study EV-303 by external validation. In EV-303, EV was also combined with pembrolizumab. These models for ADC and MMAE have been evaluated in previous submissions (EMEA/H/C/005392; (EMEA/H/C/005392-II-0013).

The previous models seem to fit the sparse data from Study EV-303, and the PK of the la/mUC and MICB patient populations are considered comparable.

Pharmacokinetics

Padcev is already marketed for two indications, one indication as monotherapy for locally advanced or metastatic urothelial cancer in patients who have previously received a platinum-containing chemotherapy and a programmed death receptor-1 or programmed death-ligand 1 inhibitor and one indication in combination with pembrolizumab for unresectable or metastatic urothelial cancer in patients who are eligible for platinum-containing chemotherapy. The new indication is Padcev with pembrolizumab, as neoadjuvant treatment and then continued after radical cystectomy as adjuvant treatment in patients with muscle invasive bladder cancer (MIBC) who are ineligible for cisplatin-containing chemotherapy. The two indications in combination with pembrolizumab share the same posology of 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) administered as an intravenous infusion over 30 minutes on Days 1 and 8 of every 3-week (21-day) cycle. The dosing regimen for the monotherapy indication is 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) administered as an intravenous infusion over 30 minutes on Days 1, 8 and 15 of a 28-day cycle until disease progression or unacceptable toxicity, i.e. similar but with one extra infusion within the cycle and a longer cycle (28 days instead of 21 days).

The observed exposure data of ADC and MMAE from the KEYNOTE-905 was compared to exposure obtained in clinical studies EV-103 and EV-302, in which Padcev was co-administered with pembrolizumab using the same posology as in the KEYNOTE-905 study. Hence, the exposure is expected to be similar. No tabular comparison was provided, only a logarithmic box-plot. By manual comparison with tabulated PK data provided for procedure Padcev II-0013, similar mean values are observed for e.g. Cmax/end of infusion concentrations for ADC for the three studies. The boxplot indicates slightly higher MMAE concentrations observed in EV-103 and EV-302 in the neoadjuvant phase than in KEYNOTE-905, whereas this seem to be the other way around in the adjuvant phase. Direct comparison to PK data for MMAE submitted in the Padcev II-0013 procedure appear not be shown for the same time points, hence no direct comparison could be made.

Overall, the logarithmic boxplot shows similar means and overlapping range of outliers and variability for both ADC and MMAE. MMAE show higher variability than ADC. However, this is expected from previous experience. As no correlation between MMAE plasma concentrations and safety or efficacy is observed, it is agreed that the observed minor differences in MME concentrations between the EV-103 and EV-302 versus the KEYNOTE-905 study is not likely to be of any clinical relevance.

2.3.5. Conclusions on clinical pharmacology

The clinical pharmacology is considered well-established for Padcev. The PK and immunogenicity of enfortumab vedotin appears consistent with previous assessments. The administration in combination with pembrolizumab had no impact on PK. The previously established population PK models for enfortumab vedotin were able to adequately characterise the PK of the combination.

2.4. Clinical efficacy

2.4.1. Dose response study

No new dose response study was submitted. The chosen dose is the same as in the EV-302 (Keynote-A39), which led to approval of enfortumab vedotin and pembrolizumab for the first-line treatment of adult patients with unresectable or metastatic urothelial cancer.

2.4.2. Main study

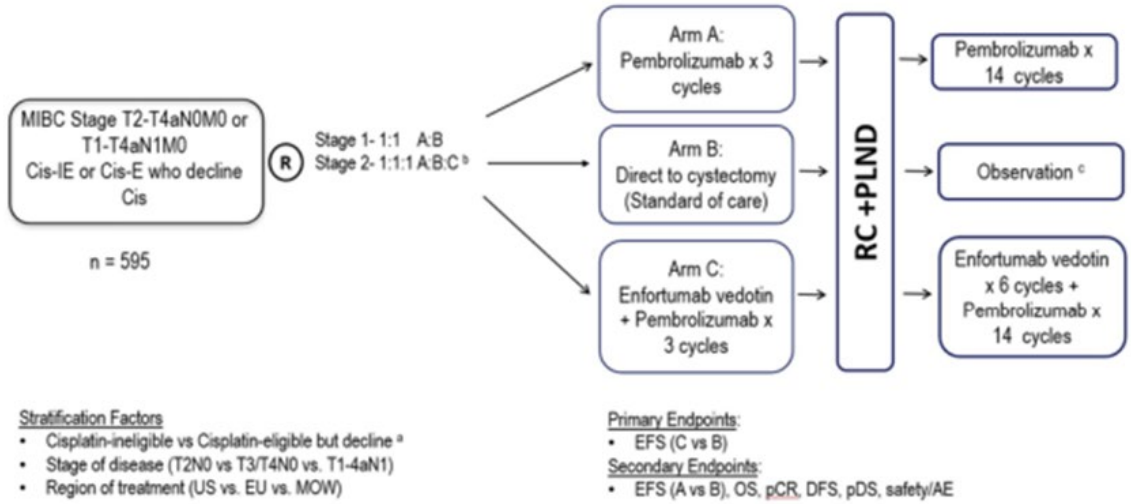
A Phase 3 Randomized Study of Cystectomy plus Perioperative Pembrolizumab versus Cystectomy Alone in Cisplatin-ineligible Participants with Muscle-invasive Bladder Cancer (KEYNOTE-905)

KEYNOTE-905 is a Phase 3, randomized, controlled, parallel-group, multisite, open-label study of perioperative pembrolizumab plus RC + PLND and perioperative EV in combination with pembrolizumab plus RC + PLND versus RC + PLND alone.

Participants with previously untreated MIBC who are **ineligible for or decline cisplatin-based chemotherapy** were randomized into Arm A (perioperative pembrolizumab group) and Arm B (RC + PLND alone) in a 1:1 ratio in Stage 1. With the subsequent addition of Arm C (perioperative EV + pembrolizumab group) with Protocol Amendment 01 (22-JUN-2020), participants were enrolled into each group in a 1:1:1 ratio, creating 2 stages (Stage 1; Arms A and B enrolling in a 1:1 ratio and Stage 2; Arms A, B, and C enrolling in a 1:1:1 ratio). Enfortumab vedotin + pembrolizumab group (Arm C) was added to the study after preliminary data from EV-103 dose escalation/Cohort A in 1L cisplatin-ineligible la/mUC were released, indicating promising antitumor activity and the potential of enfortumab vedotin + pembrolizumab to eradicate micrometastases that may be present at diagnosis in the KEYNOTE-905 study population, and consolidate the antitumor immune response to micrometastases and prevent disease recurrence by adding treatment also in the post-operative setting.

Due to positive results for enfortumab vedotin + pembrolizumab in Study EV-103 Cohort K, with Protocol Amendment 08 (01-NOV-2022) enrollment was stopped to the Arm A perioperative pembrolizumab group (except in France due to a request from the French Ethics Committee) and Stage 2 randomization proceeded into the perioperative EV + pembrolizumab (Arm C) and RC + PLND alone (Arm B) groups only. Also, as of Protocol Amendment 08, participants in the RC + PLND alone group (Arm B) at high risk of recurrence could receive adjuvant nivolumab per the approved product label, if locally available, and provided nivolumab was deemed appropriate for the participant by the investigator.

Figure 5 KEYNOTE-905 study design



[a] Stratification by Cisplatin eligibility applies to Stage 2. Prior to amendment 05, participants were stratified by PD-L1 status.
[b] Following Amendment 8 implementation, Stage 2 randomization will be under Arm B & Arm C only in a 1:1 ratio (randomization under Arm A will stop).
[c] For participants in Arm B at high risk of recurrence following RC+PLND, adjuvant nivolumab may be used per the approved product label, if locally available, and provided participants is deemed appropriate by the investigator. Note: Imaging must continue per protocol after starting adjuvant nivolumab.

AE = adverse event; Cis-IE = cisplatin-ineligible; Cis-E = cisplatin-eligible; DFS = disease-free survival; EFS = event-free survival; EU = European Union; MIBC = muscle-invasive bladder cancer; MOW = Most of World; OS = overall survival; pCR = pathological complete response; pDS = pathologic downstaging; R = randomization; RC + PLND = radical cystectomy + pelvic lymph node dissection; US = United States.
Note: Given the ± 3 days treatment window per neoadjuvant cycle and treatment-related AEs that may occur, it is possible that in Arm A and Arm C, RC + PLND may not be performed within 12 weeks of randomization.

Participants were enrolled in KEYNOTE-905 study arms in the following **stages**:

- Stage 1: Participants were enrolled in a 1:1 ratio in Arms A and B
- Stage 2 (Before Amendment 08): Participants were enrolled in a 1:1:1 ratio in Arms A, B, and C
- Stage 2 (after Amendment 08): Participants were enrolled in a 1:1 ratio in Arms B and C

Methods

Study participants

Key inclusion criteria

Male and female participants of at least 18 years with MIBC clinical stage T2-T4aN0M0.

To be eligible for inclusion in this study, the participant must:

1. Have a histologically confirmed diagnosis of muscle invasive bladder cancer (T2-T4aN0M0) with predominant (≥50%) urothelial histology (histology and presence of muscle invasion to be confirmed by BICR).

    Participants with mixed histology were eligible provided the urothelial component was ≥50%.

Urothelial carcinomas not originating from the bladder (eg, upper tract [ureters, renal pelvis], urethra) were not eligible.

Participants whose tumors contain any neuroendocrine component were not eligible.

2. Have clinically non-metastatic bladder cancer (N0M0) determined by imaging (CT chest and CT or MRI of the abdomen/pelvis), confirmed by BICR.

3. Be deemed eligible for RC + PLND by his/her urologist and/or oncologist and agree to undergo curative intent standard RC + PLND (including prostatectomy if applicable) as per AUA/ASTRO/ASCO/SUO guidelines.

4. Be ineligible for treatment with cisplatin, as defined by meeting at least one of the following criteria:

-Impaired renal function with measured or calculated CrCl 30 to 59 mL/min (calculated by Cockcroft-Gault method or measured by 24-hour urine collection).

-ECOG Performance Status 2

-CTCAE v.4 Grade ≥2 audiometric hearing loss (25 dB in two consecutive wave ranges))

-CTCAE v.4 Grade ≥2 peripheral neuropathy

-NYHA Class III heart failure

5. Have a transurethral resection (TUR) of a bladder tumor (obtained within 60 days prior to study enrollment [ICF signed]) which was submitted and adequate for evaluation of histology, muscle invasion and PD-L1 status. In the event the sample was not evaluable for PD-L1, the participant would have been assigned to the CPS <10 group for stratification. Formalin-fixed, paraffin embedded (FFPE) tissue blocks were preferred to slides.

6. Must have an ECOG performance status of 0, 1, or 2.

7. Demonstrate adequate organ function (based on protocol-specified criteria).

Exclusion Criteria

Key Exclusion Criteria

1. Had a known additional non-urothelial malignancy progressing or has required active treatment ≤3 years of study randomization.

2. Had received any prior systemic anti-neoplastic treatment for MIBC.

Note: Prior treatment for non-muscle invasive bladder cancer (NMIBC) with intravescical instillation therapy such as BCG or intravesical chemotherapy is permitted.

3. Had an abdomino-pelvic lymph node ≥15 mm in the short axis.

4. Had received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).

5. Had received prior systemic anti-cancer therapy including investigational agents within 3 years prior to randomization.

6. Had received any prior radiotherapy to the bladder.

7. Had a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study drug.

8. Had a known history of human immunodeficiency virus (HIV) infection. No HIV testing is required unless mandated by local health authority. Had a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as detectable HCV RNA via qualitative nucleic acid testing) infection. Note: No testing for Hepatitis B and Hepatitis C was required unless mandated by local health authority

Treatments

Treatment arm details for the study arms pertinent to this application:

Arm A: 3 cycles prior to surgery of pembrolizumab (IV 200 mg) every three weeks (Q3W), followed by radical cystectomy + pelvic lymph node dissection (RC + PLND)), followed by pembrolizumab 14 cycles.

Arm B: standard of care RC + PLND (hereafter referred to as "RC + PLND alone")

Arm C: 3 cycles of preoperative EV + pembrolizumab, followed by RC + PLND, followed by 6 cycles of postoperative EV + 14 cycles of postoperative pembrolizumab (hereafter referred to as "perioperative EV + pembrolizumab").

Table 8 Study Intervention Groups and Duration

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/Treatment Period/Vaccination Regimen	Use
Arm A	Pembrolizumab	100 mg/4 mL (25 mg/mL) solution in a single-dose vial	200 mg	IV Infusion	q3w – 3 cycles neoadjuvant phase; 14 cycles adjuvant phase	Test Product
Arm C	Pembrolizumab	100 mg/4 mL (25 mg/mL) solution in a single-dose vial	200 mg	IV Infusion	q3w – 3 cycles neoadjuvant phase; 14 cycles adjuvant phase	Test Product
Arm C	Enfortumab vedotin	30 mg single dose vial	1.25 mg/kg	IV Infusion	Days 1 and 8 q3w- 3 cycles neoadjuvant phase; 6 cycles adjuvant phase	Test Product

IV=intravenous; q3w=every 3 weeks.

Objectives

Outcomes/endpoints

Primary Objective	Primary Endpoint
Objective: To compare EFS between Arm C (perioperative enfortumab vedotin in combination with pembrolizumab and RC + PLND) and Arm B (RC + PLND). **Hypothesis (H1):** Perioperative enfortumab vedotin in combination with pembrolizumab plus RC + PLND will achieve superior EFS compared with RC + PLND alone.	EFS (defined as the time from randomization to the first of any of the following events): -Radiographic disease progression precluding a curative intent surgery as assessed by BICR prior to RC + PLND -Failure to undergo surgery for participants with residual muscle-invasive disease and any radiographic disease present, biopsy-proven MIBC will be considered an event regardless of radiographic findings -Gross residual disease left behind at time of surgery (surgeon unable to complete curative intent surgery due to unresectable tumor or newly discovered metastatic disease) -Local or distant recurrence post-RC + PLND as assessed by CT or MRI (BICR) and/or biopsy. If biopsy is not feasible due to participant safety, CT/MRI alone will be sufficient -Death from any cause
Secondary Objectives	**Secondary Endpoints**
Objective: To compare EFS between Arm A (perioperative pembrolizumab and RC + PLND) and Arm B (RC + PLND). **Hypothesis (H4):** Perioperative pembrolizumab plus RC + PLND will achieve superior EFS compared with RC + PLND alone.	EFS

Secondary Objectives	Secondary Endpoints
Objective: To compare OS between Arm C (perioperative enfortumab vedotin in combination with pembrolizumab and RC + PLND) and Arm B (RC + PLND) and between Arm A (perioperative pembrolizumab and RC + PLND) and Arm B. **Hypothesis (H2):** Perioperative enfortumab vedotin in combination with pembrolizumab plus RC + PLND will achieve superior OS compared with RC + PLND alone. **Hypothesis (H5):** Perioperative pembrolizumab plus RC + PLND will achieve superior OS compared with RC + PLND alone.	OS is defined as the time from randomization to death due to any cause
Objective: To compare pCR rates between Arm C (preoperative enfortumab vedotin in combination with pembrolizumab and RC + PLND) and Arm B (RC + PLND) and between Arm A (preoperative pembrolizumab and RC + PLND) and Arm B, based on central pathologic review. **Hypothesis (H3):** Preoperative enfortumab vedotin in combination with pembrolizumab plus RC + PLND will achieve superior pCR rates based on central pathologic review, compared with RC + PLND alone. **Hypothesis (H6):** Preoperative pembrolizumab plus RC + PLND will achieve superior pCR rates based on central pathologic review, compared with RC + PLND alone.	pCR, defined as absence of viable tumor (pT0N0) in examined tissue from RC + PLND
Objective: To assess DFS in participants from Arm A (perioperative pembrolizumab and RC + PLND), Arm B (RC + PLND), and Arm C (perioperative enfortumab vedotin in combination with pembrolizumab and RC + PLND) who are disease-free after surgery.	DFS (defined as the time from post-surgery baseline scan until the first occurrence of either): -Local or distant recurrence as assessed by CT or MRI (BICR) and/or biopsy -Death from any cause

Secondary Objectives	Secondary Endpoints
Objective: To compare the rates of pDS between Arm A (perioperative pembrolizumab and RC + PLND) and Arm B (RC + PLND) and between Arm C (perioperative enfortumab vedotin in combination with pembrolizumab and RC + PLND) and Arm B.	pDS is defined as participants with <pT2 (includes pT0, pTis, pTa, pT1) and N0 in examined tissue from RC + PLND
Objective: To evaluate the safety and tolerability of perioperative pembrolizumab with RC + PLND and perioperative enfortumab vedotin in combination with pembrolizumab with RC + PLND.	Participants experiencing AEs Participants discontinuing study drug due to AEs Participants experiencing perioperative complications

Exploratory objectives	Exploratory endpoints
To evaluate the mean change from baseline in Functional Assessment of Cancer Therapy – Bladder Cystectomy (FACT-Bl-Cys), Bladder Cancer Index (BCI), and EuroQol 5-dimension questionnaire (EQ-5 D-5 L) instruments.	PROs, quality of life scales.

Tumor assessments

Screening imaging of the chest, abdomen, and pelvis were performed within ≤28 days prior to randomization, and, for Arm B ≤35 days prior to cystectomy. Imaging were performed ≤5 weeks prior to cystectomy and 6 weeks post-cystectomy. Then, scans were performed every 12 weeks up to 96 weeks from the post-cystectomy baseline scan, and at discontinuation; then, every 24 weeks in Year 3 and beyond. Imaging was to be performed until BICR-verified disease progression/recurrence, pregnancy, death, or withdrawal of consent, whichever occurs first. For participants who discontinue study intervention, including for those who have started new anticancer treatment after RC + PLND, without documented BICR-verified disease progression/recurrence, every effort were to be made to continue monitoring disease status using the same imaging schedule until BICR-verified disease progression/recurrence, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

All imaging were submitted to the iCRO. When the investigator declared disease progression/recurrence, the iCRO performed expedited BICR verification of progression/recurrence. BICR verification of progression/recurrence process was removed from Protocol Amendments 02 through 09 but reinstated for Amendment 10.

Participants in Arm A and Arm C who did not undergo surgery must repeated a full disease assessment with cross-sectional imaging, cystoscopy (± biopsy), and urine cytology within 12 weeks after last dose of neoadjuvant treatment. Participants who did not undergo surgery and have achieved a cCR were censored for EFS and followed with serial disease assessments for efficacy analyses. Participants with persistent MIBC (≥T2 and/or N+) and radiographic evidence of disease by investigator assessment who refused or were unable to undergo surgery had to be counted as an EFS event and transitioned to Survival Follow-up. Participants with residual non-muscle-invasive disease (<T2), nodal downstaging (<N1 disease), or indeterminate disease status (ie, missing cross-sectional imaging, cystoscopy, cytology) who refused or were unable to undergo

surgery had to be censored for EFS and to be followed with serial disease assessments for efficacy analyses

Sample size

The study was event-driven and the final sample size was expected to be ~595. The participants have been randomized in 2 stages as follows:

1. Stage 1, ~168 participants are randomized in a 1:1 ratio under Arm A and Arm B, followed by
2. 2. Stage 2, participants are randomized in a 1:1:1 ratio under Arm A, Arm B and Arm C until Amendment 8 is implemented and Arm A enrollment is stopped (except France), followed by enrollment in a 1:1 ratio under Arm B and Arm C. A total of ~344 participants are randomized in this stage under Arm B and Arm C.

Approximately 427 participants were randomized in Stage 2 under Arm A, Arm B and Arm C. This accumulated to ~85 participants in each arm until implementation of Amendment 8 (except France), at which point Arm A enrolment was discontinued. After enrolment in Arm A stopped, Stage 2 continued in a 1:1 ratio under Arm B and Arm C with ~86 participants added in each arm. Stage 2 enrollment was halted once approximately 344 participants had been randomized across Arms B and C. This stopping point was independent of when enrollment in Arm A ended and was not influenced by the number of participants in Arm A. The study was designed with two sequential, seamless stages. For the comparison of Arm A versus Arm B, the analysis set includes all participants randomized prior to discontinuation of Arm A (~168 in Stage 1 and 170 in Stage 2; total 338). For the comparison of Arm C versus Arm B, all participants randomized in Stage 2 are included (344).

For the comparison of Arm C versus Arm B on the EFS endpoint, based on 344 participants, a target of 173 events, and 1st IA analysis at approximately 77% maturity, the study had about 93% power to detect a hazard ratio (HR)of 0.59 at a one-sided overall alpha level of 2.5% (1 sided) within a group-sequential design.

For the comparison of Arm C versus Arm B on the OS endpoint, based on 344 participants, a target of 174 events and 2 IAs at ~ 63% at 84% of maturity, the study had ~93% power to detect a HR of 0.59 at an overall α level of 2.475% (1 sided) within a group sequential setting.

The above sample size and power calculations for EFS and OS assume the following:

• EFS follows an exponential distribution with a median of 27 months for the control group.

• OS follows an exponential distribution with a median of 37 months for the control group.

• Enrollment period of 20 months with constant enrollment rate of ~9 participants per month for Stage 1, 27 months with constant enrollment rate of ~9 participants per month for Stage 2 before the implementation of Amendment 8, and 15 months with constant enrollment rate of ~12 participants per month for Stage 2 after the implementation of Amendment 8.

• A yearly dropout rate of 5.0% for EFS and 1% for OS.

These assumptions were derived from published randomized trials and real-world data in the target MIBC population. [Grossman, H. B., et al 2003] [Pfister, C., et al 2024] [Li, R., et al 2024] [Fischer-Valuck, B. W., et al 2018].

The sample size and design were revised across protocol amendments, notably with the addition of Arm C (Amendment 01), expansion to a three-stage design (Amendment 05), and discontinuation of Arm A (Amendment 8), resulting in a final enrolled population of approximately 595 participants and a focused Arm C versus Arm B comparison with maintained statistical power.

Randomisation

Approximately 608 participants with previously untreated MIBC were planned to be randomized in 2 stages. The study originally had 2 arms, and participants were enrolled into Arm A and Arm B in a 1:1 ratio. With the subsequent addition of Arm C, participants began to enroll into Arms A, B, and C in a 1:1:1 ratio. After implementation of Amendment 8, Stage 2 randomization was under Arms B and C only (randomization under Arm A was stopped except in France). At the time of the Amendment 10, the enrollment was completed, and ~595 participants are randomized in 2 stages: Stage 1, includes ~ 84 participants randomized to each arm (Arm A and Arm B in a 1:1 ratio); Stage 2, includes ~ 85 participants randomized to each arm (Arms A, B, and C in a 1:1:1 ratio) until implementation of Amendment 8. After implementation of Amendment 8, the study no longer randomized participants to Arm A (except France), and randomized ~86 additional participants to each arm (Arms B and C in a 1:1 ratio).

The randomization was stratified by:

1) Cisplatin eligibility (cisplatin-ineligible vs cisplatin-eligible but decline)

2) Tumor Stage (T2N0 vs T3/T4aN0 vs T1-4aN1)

3) Geographic regions (United States [US] vs European Union [EU] vs Most of World [MOW])

Blinding (masking)

The study was open-label. The primary endpoint, EFS, was assessed by BICR

Statistical methods

Analysis sets and statistical methods

Efficacy analyses of EFS, OS, pCR, and pDS were based on the **ITT2 population**, which comprised all participants randomized to Arm B and Arm C in Stage 2 regardless of whether treatment was administered. The hypotheses were evaluated by comparing the treatment groups with respect to EFS and OS using a stratified log-rank test, and with respect to pCR rates using the stratified Miettinen and Nurminen method. For EFS and OS, HRs and corresponding 95% CIs were estimated using a stratified Cox regression model. Event rates over time were estimated within each treatment group using the Kaplan-Meier method. The treatment difference and its 95% CI for pCR rate and pDS rate were estimated using the stratified Miettinen and Nurminen method with strata weighted by sample size. Efficacy analysis of DFS included participants who were disease free at the initial post-surgery scan. Participants in efficacy analysis populations were included in the treatment group to which they were randomized.

The stratification factors used for randomization (i.e., tumor clinical stage (T2N0 vs T3/T4aN0 vs T1-T4aN1), cisplatin eligibility (cisplatin-ineligible vs cisplatin-eligible but declined) and geographic regions (US vs EU vs MOW)) will be applied to all stratified analyses, in particular, the stratified log-rank test, stratified Cox model, and stratified Miettinen and Nurminen method.

Table 9 Censoring rules for primary and sensitivity analysis for EFS

Situation	Primary Analysis[a]	Sensitivity Analysis 1[a]	Sensitivity Analysis 2[b]
In participants who undergo surgery:			
PD, recurrence or death documented after ≤1 missed disease assessment and before new anticancer therapy, if any	Event at earliest date of documented PD, recurrence or death	Event at earliest date of documented PD, recurrence or death	Event at earliest date of documented PD, recurrence or death
PD, recurrence or death documented immediately after ≥2 consecutive missed disease assessments or after new anticancer therapy, if any	Event at earliest date of documented PD, recurrence or death	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessments and new anticancer therapy excluding the use of adjuvant nivolumab in Arm B, if any	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessments and new anticancer therapy including the use of adjuvant nivolumab in Arm B, if any
No PD, no recurrence and no death; and new anticancer therapy is not initiated	Censored at last disease assessment	Censored at last disease assessment	Censored at last disease assessment
No PD, no recurrence and no death; and new anticancer treatment is initiated[c]	Censored at last disease assessment	Censored at last disease assessment before new anticancer treatment excluding the use of adjuvant nivolumab in Arm B	Censored at last disease assessment before new anticancer treatment including the use of adjuvant nivolumab in Arm B
In participants who refuse or are unable to undergo surgery:			
MIBC[d,e], locally advanced disease[f], distant PD or death documented after ≤1 missed disease assessment and before new anticancer therapy, if any	Event at earliest date of documented MIBC, locally advanced disease, distant PD, or death	Event at earliest date of documented MIBC, locally advanced disease, distant PD, or death	Event at earliest date of documented MIBC, locally advanced disease, distant PD, or death
MIBC[d,e], locally advanced disease[f], distant PD, or death documented immediately after ≥2 consecutive missed disease assessments or after new anticancer therapy, if any	Event at earliest date of documented MIBC, locally advanced disease, distant PD, or death	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anticancer therapy excluding the use of adjuvant nivolumab in Arm B, if any	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anticancer therapy including the use of adjuvant nivolumab in Arm B, if any
No MIBC[d,e], no locally advanced disease[f], no distant PD, and no death whether or not new anticancer therapy is initiated	Censored at last disease assessment within 16 weeks of last dose of neoadjuvant treatment (or within 16 weeks of randomization for participants who do not receive any treatment)	Censored at last disease assessment	Censored at last disease assessment

Situation	Primary Analysis[a]	Sensitivity Analysis 1[a]	Sensitivity Analysis 2[b]
No post-screening scans available	Censored at Day 1 from randomization	Censored at Day 1 from randomization	Censored at Day 1 from randomization

EFS=event-free survival; PD=progressive disease; MIBC=muscle-invasive bladder cancer; NMIBC=nonmuscle-invasive bladder cancer.

[a] In the primary analysis and sensitivity analysis 1, the new anticancer therapy excludes the use of adjuvant nivolumab in Arm B.

[b] In sensitivity analysis 2, the new anticancer therapy includes the use of adjuvant nivolumab in Arm B.

[c] Includes cases with high-risk prostate cancer found at surgery who require subsequent anticancer treatment and for new anticancer therapy in bladder cancer initiated off-study without evidence of EFS event.

[d] Includes high risk NMIBC of the upper tracts.

[e] Presence of MIBC needs to be confirmed with imaging demonstrating radiographic disease present and a positive post-baseline cystoscopy with biopsy.

[f] Participants with T4b, N2/N3 disease as identified by imaging and confirmed by BICR.

Additional sensitivity analyses:

To assess the impact of PD-L1 expression on the analysis of the EFS endpoint, a sensitivity analysis was to be performed with PD-L1 expression (CPS ≥10 versus CPS<10) being added as a covariate to the stratified Cox proportional hazard model.

Unstratified log-rank test and unstratified Cox proportional hazard model will also be performed.

Subgroups

To determine whether the treatment effect was consistent across various subgroups, the between-group treatment effect (with a nominal 95% CI) for EFS, pCR and OS was to be estimated and plotted within each category of the following subgroup variables. For stratification factors, the strata derived based on eCRF was to be used.

- Cisplatin eligibility (cisplatin-ineligible vs cisplatin-eligible but declined)
- Tumor Stage (T2N0 vs T3/T4aN0 vs T1-4aN1)
- Geographical regions (US vs EU vs MOW)
- PD-L1 (CPS ≥10 vs CPS <10; PD-L1 not evaluable participants will be excluded from the subgroup analysis)
- Age category (<65 vs ≥65 years)
- Sex (female vs male)
- Race (white vs all others)
- Smoking status (never vs former vs current)

Interim analyses

Two efficacy IAs were planned in addition to the final analysis for this study. Results of the IAs was to be reviewed by an eDMC. If the EFS null hypotheses were rejected prior to the final analysis, the eDMC may recommended stopping the study early for EFS follow-up; however, in this case OS follow-up would have continued. This study was not planned to be stopped for futility.

At the time of an interim analysis, the observed number of events could differ substantially from the expected. To avoid overspending at an interim analysis and leave reasonable alpha for the final analysis, the minimum α spending strategy was adopted. At the IA, the information fraction used in Hwang-Shih-DeCani (HSD) spending function to determine the alpha spending at the IA was based on the minimum of the expected information fraction and the actual information fraction at each analysis. Specifically, In the scenario that the events accrue slower than expected and the observed number of events was less than the expected number of events at a given analysis, the information fraction was to be calculated as the observed number of events at the interim analysis over the target number of events at FA.

- In the scenario that the events accrue faster than expected and the observed number of events exceeds the expected number of events at a given analysis, then the information fraction was to be calculated as the expected number of events at the interim analysis over the target number of events at FA.
- The final analysis would use the remaining Type I error that had not been spent at the earlier analyses. The event counts for all analyses were to be used to compute correlations. The planned analyses, endpoints evaluated, and drivers of the timing are summarized in Table 10.

Table 10 Analysis planned, endpoint evaluated, and drivers of timing

Analysis	Endpoint	Criteria for Conduct of Analysis	Estimated Time After First Participant Randomized	Primary Purpose of Analysis
IA 1:	pCR, EFS, OS	All ITT2 participants have had the opportunity for RC + PLND with pCR evaluation, and ~133 EFS events have been observed in ITT2, and ~ 12 months follow-up after last participant randomized	~69 months	Final pCR analysis; interim EFS analysis; interim OS analysis
IA 2:	EFS, OS	~173 EFS events have been observed in ITT2.	~81 months	Final EFS analysis; interim OS analysis
FA:	OS	~174 OS events have been observed in ITT2	~92 months	Final OS analysis

Abbreviations: EFS = event-free survival; FA = final analysis; IA = interim analysis; OS = overall survival; pCR = pathological complete response; PLND = pelvic lymph node dissection; RC = radical cystectomy.

Note that for IA2, if the EFS event accrual in ITT2 is slower than expected, the Sponsor may conduct the analysis with up to 18 months of follow-up after IA1, or the specified number of EFS events is observed, whichever occurs first.

Note that if EFS hits in ITT2 at IA1, then IA2 may be triggered by OS events (i.e., ~145 OS events) in ITT2. If the OS event accrual in ITT2 is slower than expected, the Sponsor may conduct the analysis with up to an additional 18 months of follow-up after IA1, or the specified number of OS events is observed, whichever occurs first.

Note that for FA, if the OS event accrual in ITT2 is slower than expected, the Sponsor may conduct the analysis at the end of year 4 after last participant randomized at the latest.

This application is based on IA1. The actual number of EFS events was 143.

Table 11 Boundary properties for planned analyses of EFS based on potential alpha-levels to be used for testing (H1, Arm C vs Arm B)

Analysis	Value	α=2.5%
IA1: 77%[a]	Z	2.3385
N: 344	p (1-sided) [c]	0.0097
Events: 133	HR at bound [d]	0.6665
Month: 69[b]	P(Cross) if HR=1[e]	0.0097
	P(Cross) if HR=0.59[f]	0.7574
IA2: 100%[a]	Z	2.0070
N: 344	p (1-sided) [c]	0.0224
Events: 173	HR at bound [d]	0.7367
Month: 81[b]	P(Cross) if HR=1[e]	0.0250
	P(Cross) if HR=0. 59[f]	0.9300

Abbreviations: EFS=event-free survival; H=hypothesis; HR=hazard ratio; IA=interim analysis; ITT=intention-to-treat.

[b] Percentage of target number of events at final analysis needed at interim analysis

[c] Including 16 months of Stage 1 enrollment before Stage 2 enrollment started. The expected analysis time from first participant randomized for ITT2 is the listed analysis time minus 16 months.

[d] p (1-sided) is the α for testing

[e] HR at bound is the approximate HR required to reach an efficacy bound

[f] P(Cross if HR=1) is the probability of crossing a bound under the null hypothesis

[g] P(Cross if HR=0.59) is the probability of crossing a bound under the alternative hypothesis

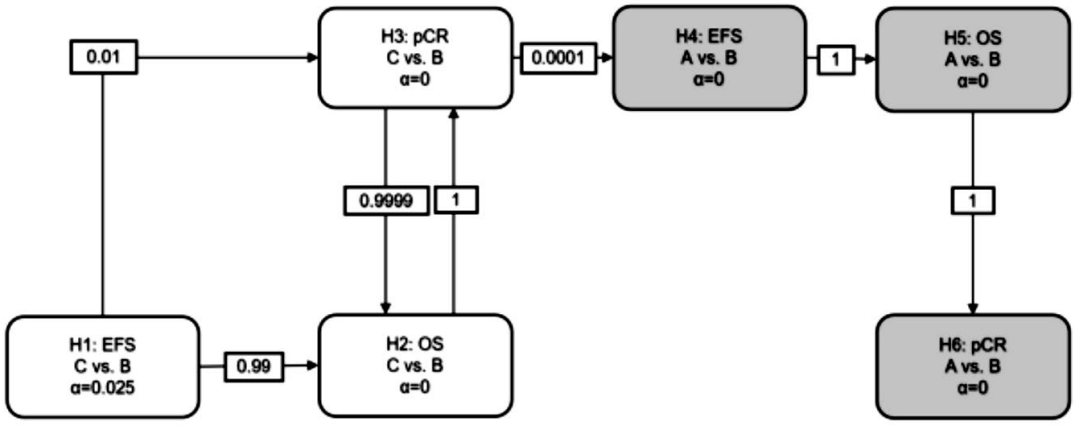
Multiplicity

The study uses the method of Maurer and Bretz [Maurer, W. and Bretz, F. 2013] to provide strong multiplicity control for multiple hypotheses as well as IAs. According to this approach, study hypotheses may be tested more than once, and when a particular null hypothesis is rejected, the α allocated to that hypothesis can be reallocated to other hypothesis tests.

Figure 6 shows the initial 1-sided α allocation and transition strategy for each hypothesis.

The weights for reallocation from each hypothesis to the others are represented in the small boxes on the arrows connecting hypotheses, and the directions of reallocation are represented by the arrows.

Figure 6 Multiplicity Graph for Type I error control of study endpoints



Abbreviations: EFS=event-free survival; H=hypothesis; OS=overall survival; pCR=pathologic complete response.

For Arm C versus Arm B, the study initially allocates all α=2.5% to H1. For Arm A versus Arm B, the study initially allocates α=0 to H4. If the null hypotheses for H1, H2 and H3 are all rejected, α=2.5% is reallocated to H4. Table 6 and Table 7 show the boundary properties for the planned interim and final analyses of EFS, derived using a HSD α-spending function with γ=-4. Note that the final row indicates the total power to reject the null hypothesis for EFS at the α level. If the actual number of EFS events at the IAs differ from those specified in the tables, the bounds will be adjusted using the HSD α-spending function.

Note that for IA2, if the EFS event accrual in ITT2 is slower than expected, the Sponsor may conduct the analysis with up to an additional 18 months of follow-up after IA1, or the specified number of EFS events is observed, whichever occurs first. In this situation, all of the remaining available alpha by will be used for the final EFS analysis in the ITT2.

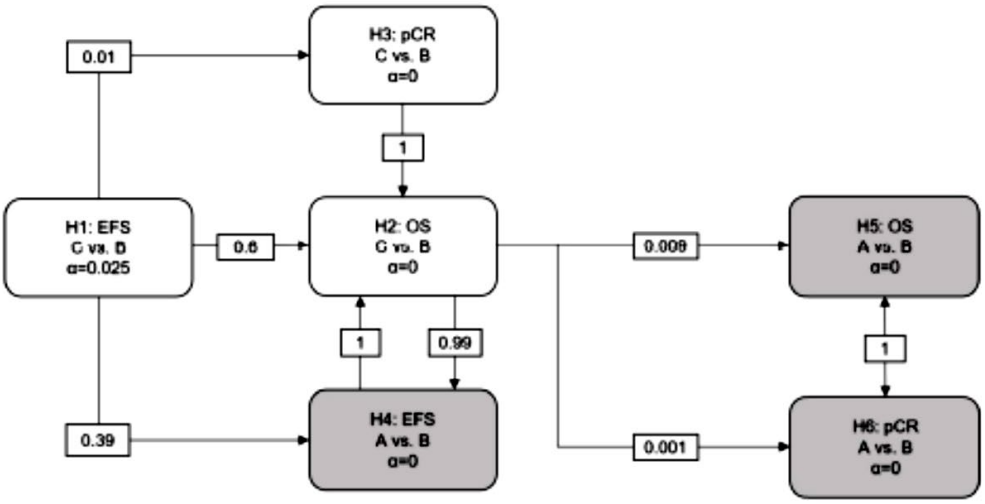
Changes to protocol pertinent to statistics

Amendment 08	01-NOV-2022	To stop randomization in Arm A, change Stage 2 randomization to Arm B and Arm C only in a 1:1 ratio, and remove Stage 3 randomization[a]. To reduce the sample size due to ceasing enrollment in Arm A, updating the multiplicity strategy, and by changing the assumption of hazard ratio of EFS and OS between Arm C versus Arm B from 0.65 to 0.59. To change pCR from a primary to a key secondary objective, update the hypothesis testing to prioritize the Arm C versus Arm B comparison for EFS, and update the analysis timing and multiplicity strategy in the SAP accordingly. In addition, adjuvant nivolumab will be permitted in Arm B when clinically indicated, changes were made to align with the EU CTR, and other minor updates and clarifications were made.
Amendment 05	25-JAN-2022	To broaden eligibility criteria and potentially enhance enrollment, changes were made to randomization, sample size, statistical analyses, stratification factors, and the study population to include cisplatin-eligible participants who decline cisplatin-based chemotherapy.
Amendment 01	22-JUN-2020	To add perioperative EV in combination with pembrolizumab plus RC + PLND (Arm C)[b]

Table 12 Analyses planned, endpoint evaluated and drivers of timing

Analysis	Endpoint	Criteria for Conduct of Analysis	Estimated Time After First Participant Randomized	Primary Purpose of Analysis
IA 1:	pCR, EFS, OS	Enrollment is completed in Stage 2. All ITT2 participants have had the opportunity for RC + PLND with pCR evaluation; at least 107 EFS events have been observed in ITT2	~67 months	Final pCR analysis; interim EFS analysis; interim OS analysis
IA 2:	EFS, OS	At least 135 EFS events have been observed in ITT2.	~79 months	Interim EFS analysis; interim OS analysis
IA 3:	EFS, OS	At least 155 EFS events have been observed in ITT2.	~90 months	Final EFS analysis; interim OS analysis
FA:	OS	At least 145 OS events have been observed in ITT2	~100 months	Final OS analysis
Abbreviations: EFS = event-free survival; FA = final analysis; IA = interim analysis; OS = overall survival; pCR = pathological complete response; PLND = pelvic lymph node dissection; RC = radical cystectomy.				

Figure 7 Multiplicity Graph for type I error control of study hypotheses



Abbreviations: EFS=event-free survival; H=hypothesis; OS=overall survival; pCR=pathologic complete response.

Table 13 Boundary properties for planned analyses of EFS based on potential alpha-levels to be used for testing (H1, Arm C vs Arm B)

Analysis	Value	α=2.5% [a]
IA1: 69%*	Z	2.4623
N: 308	p (1-sided) [§]	0.0069
Events: 107	HR at bound [%]	0.6208
Month: 67 [‡]	P(Cross) if HR=1 [†]	0.0069
	P(Cross) if HR=0.59 [#]	0.6030
IA2: 87%*	Z	2.2451
N: 308	p (1-sided) [§]	0.0124
Events: 135	HR at bound [%]	0.6790
Month: 79 [‡]	P(Cross) if HR=1 [†]	0.0147
	P(Cross) if HR=0. 59 [#]	0.8014
Final: 100%*	Z	2.0370
N: 308	p (1-sided) [§]	0.0208
Events: 155	HR at bound [%]	0.7207
Month: 90 [‡]	P(Cross) if HR=1 [†]	0.0250
	P(Cross) if HR=0. 59 [#]	0.9000

Abbreviations: EFS=event-free survival; H=hypothesis; HR=hazard ratio; IA=interim analysis; ITT=intention-to-treat.

*Percentage of target number of events at final analysis needed at interim analysis

‡ Including 18 months of Stage 1 enrollment. The actual analysis time from first participant randomized for ITT2 is the listed analysis time minus 18 months.

§ p (1-sided) is the α for testing

% HR at bound is the approximate HR required to reach an efficacy bound

† P(Cross if HR=1) is the probability of crossing a bound under the null hypothesis

P(Cross if HR=0.59) is the probability of crossing a bound under the alternative hypothesis

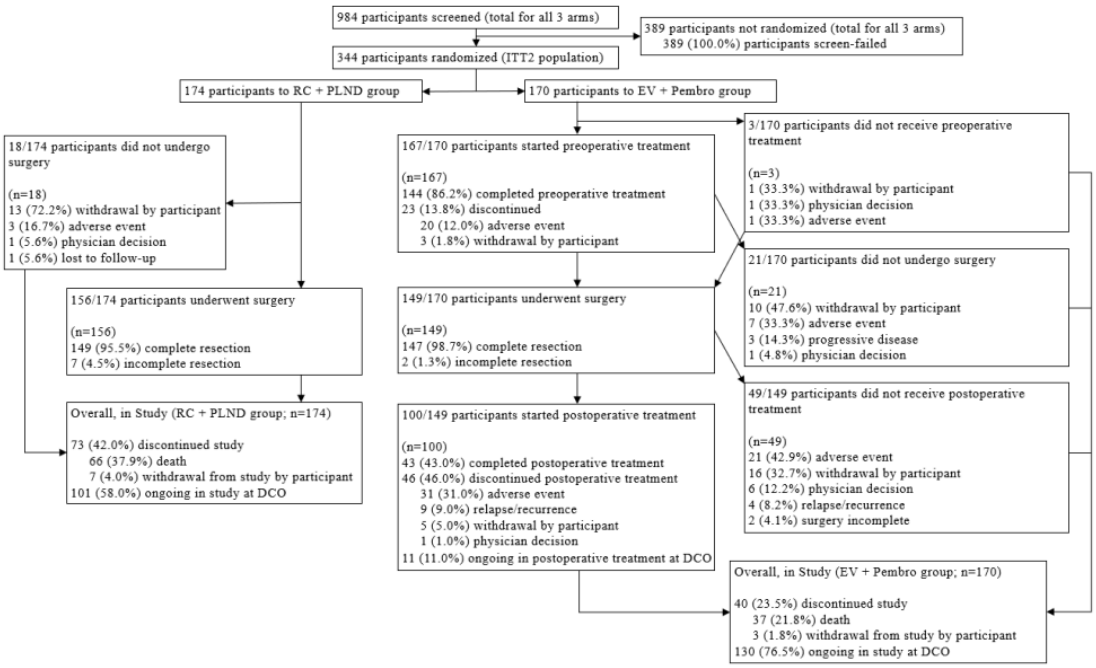
[a] Initial α allocated to H1

Results

Participant flow

A total of **984 participants** were screened and **595 were randomized** in the KEYNOTE-905 study. The ITT2 population consisted of 344 patients, 170 in arm C and 174 in arm B.

Figure 8 Consort diagram for KEYNOTE-905 (ITT2 population)



DCO=data cutoff; EV=enfortumab vedotin; ITT2=intent-to-treat2; Pembro=pembrolizumab; RC + PLND=radical cystectomy + pelvic lymph node dissection.
The ITT2 population comprised all participants that were randomized to Arm B and Arm C in Stage 2.
Participants randomized to the RC + PLND alone group proceeded straight to surgery and received no preoperative study medication.

Table 14 Disposition of Participants (ITT2 Population)

	EV + Pembro		RC + PLND	
	n	(%)	n	(%)
Participants in population	170		174	
Status for Trial				
Started	170		174	
Discontinued	40	(23.5)	73	(42.0)
Death	37	(21.8)	66	(37.9)
Withdrawal By Subject	3	(1.8)	7	(4.0)
Subsequently Died	1	(0.6)	2	(1.1)
Ongoing	130	(76.5)	101	(58.0)
Status for All Study Treatment (Preoperative/Surgical + Postoperative)				
Started	170		156	
Completed	43	(25.3)	149	(95.5)
Discontinued	116	(68.2)	7	(4.5)
Adverse Event	59	(34.7)	0	(0.0)
Physician Decision	9	(5.3)	0	(0.0)
Progressive Disease	3	(1.8)	0	(0.0)
Relapse/Recurrence	12	(7.1)	0	(0.0)
Surgery Incomplete	2	(1.2)	7	(4.5)
Withdrawal By Subject	31	(18.2)	0	(0.0)
Ongoing	11	(6.5)	0	(0.0)
Status for Participants Who Did Not Receive Preoperative Study Medications				
Did Not Receive Preoperative Study Medications	3		0	
Adverse Event	1	(33.3)	0	(0.0)
Physician Decision	1	(33.3)	0	(0.0)
Withdrawal By Subject	1	(33.3)	0	(0.0)
Status for Participants Who Received Preoperative Study Medications				
Started	167		0	
Completed	144	(86.2)	0	(0.0)
Discontinued	23	(13.8)	0	(0.0)
Adverse Event	20	(12.0)	0	(0.0)
Withdrawal By Subject	3	(1.8)	0	(0.0)
Status for Participants Who Did Not Undergo Surgery				
Did Not Undergo Surgery	21		18	
Adverse Event	7	(33.3)	3	(16.7)
Lost To Follow-Up	0	(0.0)	1	(5.6)
Physician Decision	1	(4.8)	1	(5.6)
Progressive Disease	3	(14.3)	0	(0.0)
Withdrawal By Subject	10	(47.6)	13	(72.2)
Status for Participants Who Underwent Surgery				
Started	149		156	
Complete Resection	147	(98.7)	149	(95.5)
Incomplete Resection	2	(1.3)	7	(4.5)
Newly Discovered Metastatic Disease	1	(0.7)	2	(1.3)
Unresectable Tumor	1	(0.7)	4	(2.6)
Other	0	(0.0)	1	(0.6)
Status for Participants Underwent Surgery Who Did Not Receive Postoperative Study Medications				
Underwent Surgery Who Did Not Receive	49		0	

Table 15 Summary of follow-up duration (ITT2 population)

Follow-up duration (months)[a]	EV + Pembro (N=170)	RC + PLND (N=174)	Total (N=344)
Median (Range)	20.4 (1.4, 52.6)	17.1 (0.6, 53.7)	18.5 (0.6, 53.7)
Mean (SD)	24.7 (13.9)	21.0 (13.6)	22.9 (13.9)

[a] Follow-up duration is defined as the time from randomization to the date of death or the database cutoff date if the participant is still alive.
Database Cutoff Date: 06JUN2025

Recruitment

Data cut-off for interim analysis 1 (IA1): 06 June 2025.

First participant first visit: 24 July 2019.

Last patient enrolled: Not reported.

Clinical investigator study sites were located in 24 countries: Argentina, Belgium, Canada, Colombia, Denmark, France, Germany, Hungary, Ireland, Israel, Italy, Japan, Malaysia, Poland, Russia, Singapore, South Korea, Spain, Sweden, Thailand, Turkey, UK, Ukraine, and USA.

Table 16 Summary of Follow-up Duration (ITT2 Population)

Follow-up duration (months)[a]	EV + Pembro (N=170)	RC + PLND (N=174)	Total (N=344)
Median (Range)	20.4 (1.4, 52.6)	17.1 (0.6, 53.7)	18.5 (0.6, 53.7)
Mean (SD)	24.7 (13.9)	21.0 (13.6)	22.9 (13.9)

[a] Follow-up duration is defined as the time from randomization to the date of death or the database cutoff date if the participant is still alive.
Database Cutoff Date: 06JUN2025

Conduct of the study

Amendments

The study has been amended multiple times. Four of these amendments can be considered substantial: Amendment 01, Amendment 05, Amendment 08 and Amendment 10

All of these amendments were stated to be "driven by external data and issued prior to the IA1 DCO (06-Jun-2025) to ensure maintenance of clinical study integrity".

A list of all protocol amendments is presented in the table below:

Table 17 Protocol Amendments for KEYNOTE-905

Document	Date of Issue	Overall Rationale
Amendment 11	16-JAN-2025	To clarify the EFS endpoint to indicate that any biopsy-proven residual MIBC will be considered an event and change pCR primary analysis to intention-to-treat.
Amendment 10	06-SEP-2024	To align the definition of the EFS endpoint and the statistical analysis plan with the clinical criteria required for evaluating residual MIBC and to revise the statistical analysis plan with updated protocol assumptions based on emerging literature in the target population.
Amendment 09	29-JUN-2023	To implement collection of late-onset peripheral neuropathy AEs and to maintain Arm A open in France. Recommendations regarding management and dose modifications for pneumonitis/ILD in participants receiving enfortumab vedotin were also added.
Amendment 08	01-NOV-2022	To stop randomization in Arm A, change Stage 2 randomization to Arm B and Arm C only in a 1:1 ratio, and remove Stage 3 randomization[a]. To reduce the sample size due to ceasing enrollment in Arm A, updating the multiplicity strategy, and by changing the assumption of hazard ratio of EFS and OS between Arm C versus Arm B from 0.65 to 0.59. To change pCR from a primary to a key secondary objective, update the hypothesis testing to prioritize the Arm C versus Arm B comparison for EFS, and update the analysis timing and multiplicity strategy in the SAP accordingly. In addition, adjuvant nivolumab will be permitted in Arm B when clinically indicated, changes were made to align with the EU CTR, and other minor updates and clarifications were made.
Amendment 07	14-JUN-2022	Ireland-specific amendment: Agency request (HPRA) for Ireland to ensure investigators are aware that fever or flu-like symptoms may be the first sign of a severe skin reaction.
Amendment 06	04-APR-2022	Added additional guidance on management of certain Grade 2 skin reactions and any grade bullous lesions.

Document	Date of Issue	Overall Rationale
Amendment 05	25-JAN-2022	To broaden eligibility criteria and potentially enhance enrollment, changes were made to randomization, sample size, statistical analyses, stratification factors, and the study population to include cisplatin-eligible participants who decline cisplatin-based chemotherapy.
Amendment 04	14-APR-2021	Updated dose modification and supportive care guidelines for rash related to enfortumab vedotin. Updated pembrolizumab dose modification table per FDA request to align with the USPI.
Amendment 03	24-MAR-2021	UK-specific amendment to update enfortumab vedotin dose modification and management guidelines for rash
Amendment 02	05-AUG-2020	Corrected errors in Amendment 01 and updated details on glucose monitoring and contraception while using EV
Amendment 01	22-JUN-2020	To add perioperative EV in combination with pembrolizumab plus RC + PLND (Arm C)[b]
Original Protocol	28-FEB-2019	Not applicable

AE=adverse event; EFS=event-free survival; EU CTR=European Union Clinical Trial Regulation; EV=enfortumab vedotin; FDA=Food and Drug Administration; HPRA=Health Products Regulatory Authority; ILD=interstitial lung disease; MIBC=muscle-invasive bladder cancer; OS=overall survival; pCR=pathological complete response; PLND=pelvic lymph node dissection; RC=radical cystectomy; SAP=statistical analysis plan; UK=United Kingdom; USPI=United States Prescribing Information.

[a] Stage 3 (which planned to randomize approximately 104 additional participants to Arms B and C in a 1:1 ratio once Stage 2 was completed) was included in Protocol Amendment 5 but was never implemented. After implementation of Protocol Amendment 8, Stage 2 no longer randomized participants in Arm A (except in France) and only randomized participants in Arm B and C in a 1:1 ratio; therefore, Stage 3 was no longer required and was removed.

[b] Amendment 01 was not released to the sites, but was further amended, and Amendment 02 was finalized on 05-AUG-2020 and released to the sites.

Protocol deviations

Protocol deviations were classified as per the ICH E3 classification of protocol deviations as important (those that may significantly impact the quality or integrity of key study data or that may significantly affect a participant's rights, safety, or well-being) or not important. Important protocol deviations were further classified as either clinically important (deviations that may compromise critical data analyses pertaining to primary efficacy and/or safety endpoints or the participant's safety) or not clinically important. Important protocol deviations were reported for 18 (10.6%) participants in the EV + pembrolizumab group and for 11 (6.3%) participants in the RC + PLND group. No participants had important protocol deviations that were considered to be clinically important. No protocol-defined overdose protocol deviations were reported in the ITT2 population. No participants' data were excluded from analysis due to a protocol deviation. No protocol deviations were classified as a serious GCP compliance issue. Part of this study was conducted during the COVID-19 pandemic. Protocol deviations associated with the pandemic were reported for 6 participants in the ITT2 population (3 in the EV + pembrolizumab group and 3 in the RC + PLND group).

Table 18 Summary of Important Protocol Deviations (ITT2 Population)

	EV + Pembro		RC + PLND	
	n	(%)	n	(%)
Participants in population	170		174	
with one or more important protocol deviations	18	(10.6)	11	(6.3)
with no important protocol deviations	152	(89.4)	163	(93.7)
Safety Reporting	**18**	**(10.6)**	**11**	**(6.3)**
Participant had a reportable Safety Event and/or follow up Safety Event information that was not reported per the timelines outlined in the protocol.	18	(10.6)	11	(6.3)
Every participant is counted a single time for each applicable row and column. Database Cutoff Date: 06JUN2025.				

Source: [P905V01MK3475: adam-adsl] [P905V01MK3475: sdtm-dv; suppdv]

Table 19 Summary of Important Protocol Deviations Considered to be Clinically Important (ITT2 Population

	EV + Pembro		RC + PLND	
	n	(%)	n	(%)
Participants in population	170		174	
with one or more clinically important protocol deviations	0	(0.0)	0	(0.0)
with no clinically important protocol deviations	170	(100.0)	174	(100.0)
Every participant is counted a single time for each applicable row and column. Database Cutoff Date: 06JUN2025.				

Source: [P905V01MK3475: adam-adsl] [P905V01MK3475: sdtm-dv; suppdv]

Table 20 Summary of Protocol Deviations Associated With COVID-19 (ITT2)

	EV + Pembro		RC + PLND	
	n	(%)	n	(%)
Participants in population	170		174	
with one or more protocol deviations associated with COVID-19	3	(1.8)	3	(1.7)
with no protocol deviations associated with COVID-19	167	(98.2)	171	(98.3)
Informed Consent	**1**	**(0.6)**	**0**	**(0.0)**
Not Important Informed Consent deviation	1	(0.6)	0	(0.0)
Trial Procedures	**2**	**(1.2)**	**3**	**(1.7)**
Not Important Trial Procedures deviation	2	(1.2)	3	(1.7)
Every participant is counted a single time for each applicable row and column. Database Cutoff Date: 06JUN2025.				

Baseline data

Table 21 Participant Characteristics (ITT2 Population)

	EV + Pembro		RC + PLND		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	170		174		344	
Sex						
Male	137	(80.6)	131	(75.3)	268	(77.9)
Female	33	(19.4)	43	(24.7)	76	(22.1)
Age (Years)						
< 65	29	(17.1)	29	(16.7)	58	(16.9)
≥ 65	141	(82.9)	145	(83.3)	286	(83.1)
Mean	72.1		71.6		71.8	
SD	7.9		7.8		7.8	
Median	74.0		72.5		73.0	
Range	47 to 87		46 to 87		46 to 87	
Race						
American Indian Or Alaska	0	(0.0)	1	(0.6)	1	(0.3)

Native						
Asian	31	(18.2)	25	(14.4)	56	(16.3)
Black Or African American	2	(1.2)	2	(1.1)	4	(1.2)
Multiple	4	(2.4)	7	(4.0)	11	(3.2)
White	132	(77.6)	136	(78.2)	268	(77.9)
Missing	1	(0.6)	3	(1.7)	4	(1.2)
Ethnicity						
Hispanic Or Latino	8	(4.7)	13	(7.5)	21	(6.1)
Not Hispanic Or Latino	160	(94.1)	153	(87.9)	313	(91.0)
Not Reported	2	(1.2)	8	(4.6)	10	(2.9)
Age (Years)						
< 65	29	(17.1)	29	(16.7)	58	(16.9)
≥65 and <75	63	(37.1)	77	(44.3)	140	(40.7)
≥75 and <85	74	(43.5)	63	(36.2)	137	(39.8)
≥85	4	(2.4)	5	(2.9)	9	(2.6)
Region						
US	21	(12.4)	23	(13.2)	44	(12.8)
EU	78	(45.9)	77	(44.3)	155	(45.1)
MOW	71	(41.8)	74	(42.5)	145	(42.2)
ECOG[a]						
0	102	(60.0)	95	(54.6)	197	(57.3)
1	47	(27.6)	53	(30.5)	100	(29.1)
2	21	(12.4)	26	(14.9)	47	(13.7)
PD-L1 Status (Actual)						
CPS ≥ 10	80	(47.1)	83	(47.7)	163	(47.4)
CPS < 10	87	(51.2)	90	(51.7)	177	(51.5)
Missing	3	(1.8)	1	(0.6)	4	(1.2)
Cisplatin Status (Actual)						
Cisplatin-Ineligible	142	(83.5)	139	(79.9)	281	(81.7)
Cisplatin-Eligible but Declined	28	(16.5)	35	(20.1)	63	(18.3)
Tumor Stage at Baseline (Actual)						
T2N0	30	(17.6)	32	(18.4)	62	(18.0)
T3/T4aN0	133	(78.2)	132	(75.9)	265	(77.0)
T1-4aN1	7	(4.1)	10	(5.7)	17	(4.9)
Histology of Tumor						
Urothelial Carcinoma	152	(89.4)	161	(92.5)	313	(91.0)
Urothelial Carcinoma with Glandular Differentiation	6	(3.5)	3	(1.7)	9	(2.6)
Urothelial Carcinoma with Squamous Differentiation	9	(5.3)	6	(3.4)	15	(4.4)
Urothelial Carcinoma with	3	(1.8)	4	(2.3)	7	(2.0)

Variant Histology						
Smoking Status						
Never Smoker	55	(32.4)	44	(25.3)	99	(28.8)
Former Smoker	82	(48.2)	86	(49.4)	168	(48.8)
Current Smoker	33	(19.4)	44	(25.3)	77	(22.4)
Weight (kg)						
≤ 100 kg	152	(89.4)	168	(96.6)	320	(93.0)
> 100 kg	18	(10.6)	6	(3.4)	24	(7.0)
Participants with data	170		174		344	
Mean	76.5		73.8		75.1	
SD	18.1		15.6		16.9	
Median	75.0		72.0		73.7	
Range	38.0 to 140.0		36.0 to 142.2		36.0 to 142.2	
Body Mass Index (kg/m2)						
< 25 kg/m2	68	(40.0)	79	(45.4)	147	(42.7)
25 to < 30 kg/m2	70	(41.2)	62	(35.6)	132	(38.4)
≥ 30 kg/m2	32	(18.8)	33	(19.0)	65	(18.9)
Participants with data	170		174		344	
Mean	25.9		25.7		25.8	
SD	5.0		4.9		4.9	
Median	26.0		25.0		25.0	
Range	14.0 to 47.0		15.0 to 46.0		14.0 to 47.0	
Renal function based on CrCL (mL/min)						
CrCL: ≥ 60 mL/min	68	(40.0)	72	(41.4)	140	(40.7)
CrCL: ≥ 30 and < 60 mL/min	102	(60.0)	101	(58.0)	203	(59.0)
CrCL: < 30 mL/min	0	(0.0)	1	(0.6)	1	(0.3)
HbA1c (%)						
< 5.7%	70	(41.2)	79	(45.4)	149	(43.3)
≥ 5.7% and < 6.5%	68	(40.0)	69	(39.7)	137	(39.8)
≥ 6.5%	28	(16.5)	21	(12.1)	49	(14.2)
Missing	4	(2.4)	5	(2.9)	9	(2.6)
Participants with data	166		169		335	
Mean	5.9		5.8		5.8	
SD	0.7		0.6		0.7	
Median	5.8		5.7		5.7	
Range	4.4 to 9.1		4.1 to 7.8		4.1 to 9.1	
Time from Current Diagnosis to Randomization (days)						

Participants with data	170	174	344
Mean	61.4	58.9	60.1
SD	34.9	24.6	30.1
Median	57.0	57.5	57.0
Range	12.0 to 407.0	1.0 to 203.0	1.0 to 407.0

SD=Standard deviation.

[a] ECOG performance status assessed during screening.

CPS=combined positive score, CrCl=creatinine clearance, ECOG=eastern cooperative oncology group, HbA1c=hemoglobin A1c, PD-L1=programmed cell death-ligand 1, US=United States, EU=European Union, MOW=most of world

kg=kilogram, mL/min=milliliters per minute, m2=square meter.

Database Cutoff Date: 06JUN2025.

Table 22 Participants with Subsequent Oncologic Therapies by Surgery Status (Incidence > 0% in One or More Treatment Groups) (ITT2 Population)

	EV + Pembro		RC + PLND	
	n	(%)	n	(%)
Participants in population	170		174	
with one or more subsequent oncologic therapies	24	(14.1)	85	(48.9)
with no subsequent oncologic therapies	146	(85.9)	89	(51.1)
Participants Who Did Not Undergo Surgery	**9**	**(5.3)**	**7**	**(4.0)**
Anti-PD-1 plus chemo	0	(0.0)	1	(0.6)
Anti-PD-1/PD-L1	2	(1.2)	0	(0.0)
Chemotherapy	5	(2.9)	5	(2.9)
Other	1	(0.6)	1	(0.6)
Radiation Therapy	6	(3.5)	4	(2.3)
Participants Who Underwent Surgery	**15**	**(8.8)**	**78**	**(44.8)**
Adjuvant	**7**	**(4.1)**	**34**	**(19.5)**
Anti-PD-1 plus chemo	1	(0.6)	0	(0.0)
Anti-PD-1/PD-L1	1	(0.6)	29	(16.7)
Avelumab	1	(0.6)	0	(0.0)
Nivolumab	0	(0.0)	29	(16.7)
Pembrolizumab	0	(0.0)	1	(0.6)
Chemotherapy	6	(3.5)	3	(1.7)
Other	0	(0.0)	2	(1.1)
Radiation Therapy	2	(1.2)	0	(0.0)
Recurrence/Metastatic	**8**	**(4.7)**	**46**	**(26.4)**
Anti-PD-1/PD-L1	1	(0.6)	21	(12.1)
Chemotherapy	5	(2.9)	34	(19.5)
EV	0	(0.0)	9	(5.2)
EV plus pembro	0	(0.0)	1	(0.6)
Other	0	(0.0)	3	(1.7)
Radiation Therapy	2	(1.2)	11	(6.3)
Other	**0**	**(0.0)**	**15**	**(8.6)**
Chemotherapy	0	(0.0)	15	(8.6)

Every participant is counted a single time for each applicable subsequent oncologic therapy. A participant with multiple subsequent oncologic therapies within a category is counted a single time for that category.

Participants who did not undergo surgery: report subsequent oncologic therapies received during the study for participants who did not undergo surgery.

Participants who underwent surgery - adjuvant: report subsequent oncologic therapies received after surgery for

participants who underwent surgery to reduce the risk of disease recurrence.
Participants who underwent surgery - recurrent/metastatic: report subsequent oncologic therapies received after surgery to treat recurrent/metastatic disease.
Participants who underwent surgery - other: report subsequent oncologic therapies received prior to surgery.
Database Cutoff Date: 06JUN2025.

Numbers analysed

The planned enrollment total was 608 participants. As of the data cutoff date for IA1, enrollment is complete, and 595 participants have been enrolled and randomized.

Analysis populations for efficacy are defined as follows:

ITT2: all participants who were randomized to the perioperative EV + pembrolizumab group and the RC + PLND alone group [Arm B and Arm C] in Stage 2 → **344** participants (**170 vs 174**)

The pivotal analyses are based on the ITT2 population.

ITT1: all participants randomized to the perioperative pembrolizumab versus RC + PLND alone [Arm A and Arm B] in Stages 1 and 2 from the beginning of the study until Arm A enrollment stopped → 338 participants (166 vs 172).

Outcomes and estimation

Primary endpoint: EFS

Table 23 Analysis of Event-Free Survival (Primary Censoring Rule) Based on BICR Assessment (ITT2 Population) Database Cutoff Date: 06JUN2025

	EV + Pembro (N=170)	RC + PLND (N=174)
Number of Events (%)	48 (28.2)	95 (54.6)
Number of Censored (%)	122 (71.8)	79 (45.4)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (37.3, NR)	15.7 (10.3, 20.5)
[Q1, Q3]	[17.4, NR]	[4.9, NR]
Person-months	3347.1	2453.4
Event Rate / 100 Person-months	1.4	3.9
vs RC + PLND		
Hazard Ratio (95% CI)[b]	0.40 (0.28, 0.57)	
p-value[c]	<0.0001	
EFS Rate at month 6 (%) (95% CI)	90.0 (84.2, 93.8)	70.6 (63.1, 76.9)
EFS Rate at month 12 (%) (95% CI)	77.8 (70.4, 83.5)	55.1 (47.2, 62.4)
EFS Rate at month 18 (%) (95% CI)	74.7 (66.9, 80.8)	47.0 (38.8, 54.8)
EFS Rate at month 24 (%) (95% CI)	74.7 (66.9, 80.8)	39.4 (31.0, 47.8)

[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by cisplatin status (cisplatin-ineligible vs cisplatin-eligible but declined), tumor stage (T2N0 vs T3/T4aN0 vs T1-4aN1), and geographic regions (US vs EU vs MOW) with small strata collapsed as pre-specified in the sSAP.

[c] One-sided p-value based on log-rank test stratified by cisplatin status (cisplatin-ineligible vs cisplatin-eligible but declined), tumor stage (T2N0 vs T3/T4aN0 vs T1-4aN1), and geographic regions (US vs EU vs MOW) with small strata collapsed as pre-specified in the sSAP.

NR = Not reached.

Database Cutoff Date: 06JUN2025.

Figure 9 Kaplan-Meier Plot of Event-Free Survival (Primary Censoring Rule) Based on BICR Assessment (ITT2 Population) Database Cutoff Date: 06JUN2025

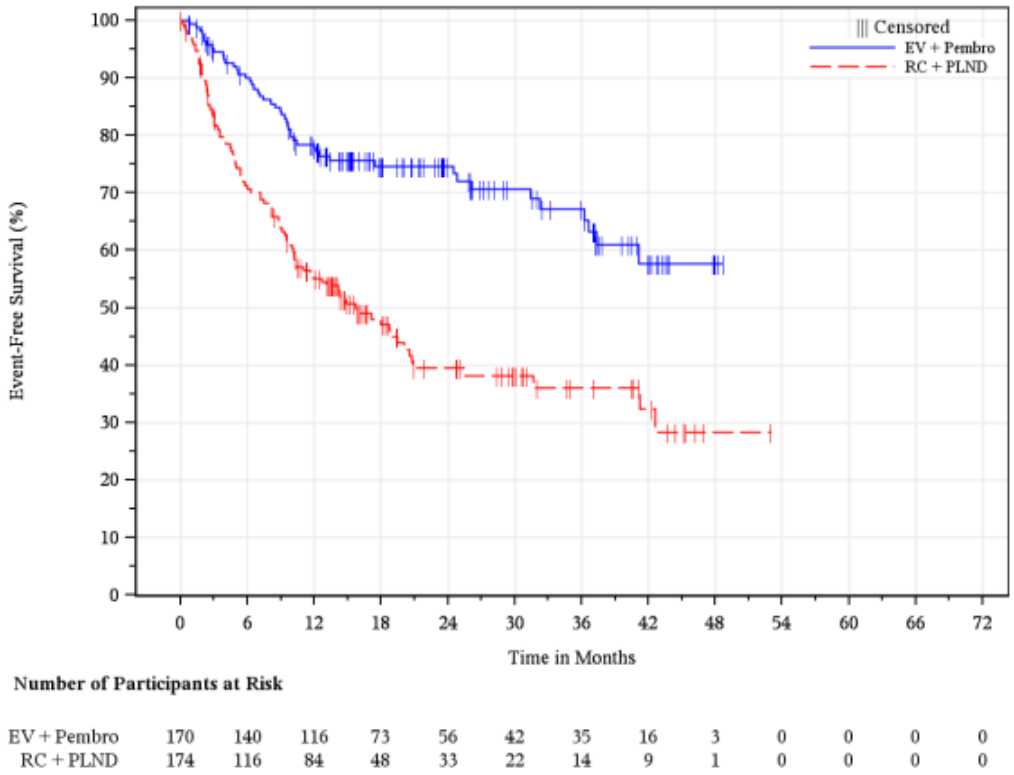


Table 24 Summary of First EFS Event Types Based on BICR Assessment (ITT2 Population) Database Cutoff Date: 06JUN2025

	EV + Pembro n (%)	RC + PLND n (%)
Participants in Population	170	174
No EFS event	122 (71.8)	79 (45.4)
With EFS event	48 (28.2)	95 (54.6)
Distant PD	4 (2.4)	3 (1.7)
Locally advanced disease	1 (0.6)	0 (0.0)
MIBC*	2 (1.2)	0 (0.0)
Incomplete resection	2 (1.2)	6 (3.4)
Disease recurrence*	16 (9.4)	51 (29.3)
Death	23 (13.5)	35 (20.1)

*Includes high-risk NMIBC (in addition to muscle-invasive cancer) of the upper-tract/remaining urothelium.
Database Cutoff Date: 06JUN2025

Source: [P905V01MK3475: adam-adsl; adtte]

"Death" was reported as the cause of death in situations where limited information was available, or where the investigator could not assign a specific cause of death in a participant with comorbidities and confounding factors that led to death.

Secondary endpoints

Overall survival

Since the EFS null hypothesis in the ITT2 population was rejected, OS was formally tested with the multiplicity-adjusted, 1-sided p-value boundary of 0.00488.

Table 25 Analysis of Overall Survival (ITT2 Population)

	EV + Pembro (N=170)	*RC + PLND (N=174)*
Number of Events (%)	*38 (22.4)*	*68 (39.1)*
Number of Censored (%)	*132 (77.6)*	*106 (60.9)*
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	*NR (NR, NR)*	*41.7 (31.8, NR)*
[Q1, Q3]	*[31.4, NR]*	*[12.7, NR]*
Person-months	*4103.2*	*3548.9*
Event Rate / 100 Person-months	*0.9*	*1.9*
vs RC + PLND		
Hazard Ratio (95% CI)[b]	*0.50 (0.33, 0.74)*	
p-value[c]	*0.0002*	
OS Rate at month 6 (%) (95% CI)	*94.6 (90.0, 97.2)*	*86.7 (80.7, 91.0)*
OS Rate at month 12 (%) (95% CI)	*86.3 (80.1, 90.7)*	*75.7 (68.5, 81.4)*
OS Rate at month 18 (%) (95% CI)	*80.7 (73.7, 86.1)*	*68.3 (60.5, 74.8)*
OS Rate at month 24 (%) (95% CI)	*79.7 (72.5, 85.3)*	*63.1 (54.7, 70.4)*

[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by cisplatin status (cisplatin-ineligible vs cisplatin-eligible but declined),

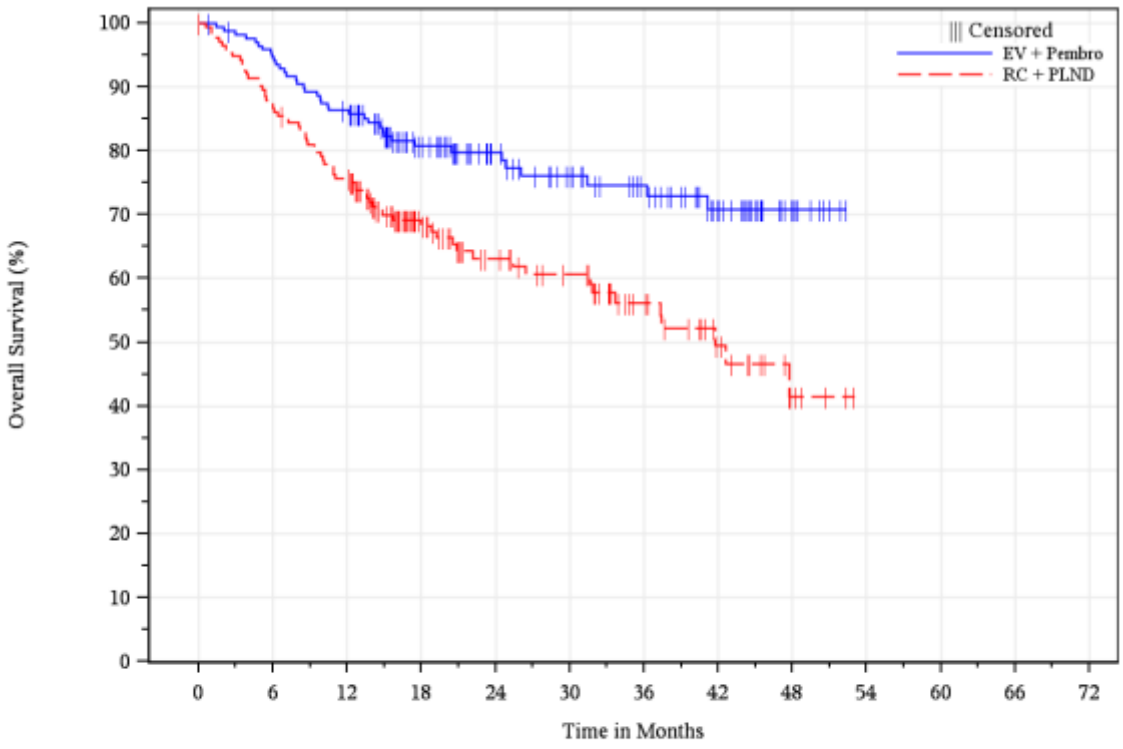
tumor stage (T2N0 vs T3/T4aN0 vs T1-4aN1), and geographic regions (US vs EU vs MOW) with small strata collapsed as pre-specified in the sSAP.

[c] One-sided p-value based on log-rank test stratified by cisplatin status (cisplatin-ineligible vs cisplatin-eligible but declined), tumor stage (T2N0 vs T3/T4aN0 vs T1-4aN1), and geographic regions (US vs EU vs MOW) with small strata collapsed as pre-specified in the sSAP.

NR = Not reached.

Database Cutoff Date: 06JUN2025.

Figure 10 Kaplan-Meier Plot of Overall Survival (ITT2 Population) Database Cutoff Date: 06JUN2025.



Pathological complete response

Since the EFS null hypothesis in the ITT2 population was rejected, pCR was formally tested with the multiplicity-adjusted, 1-sided p value boundary of 0.00025. A statistically significant improvement in pCR was shown.

Table 26 Analysis of Pathological Complete Response Based on BICR Assessment (ITT2 Population) Database Cutoff Date: 06JUN2025.

Treatment	N	Number of Pathological Complete Response	Pathological Complete Response Rate (%) (95% CI)	Difference in % vs. RC + PLND	
				Estimate % (95% CI)[a]	p-Value[b]
EV + Pembro	170	97	57.1 (49.3, 64.6)	48.3 (39.5, 56.5)	<0.000001
RC + PLND	174	15	8.6 (4.9, 13.8)		

[a] Based on Miettinen & Nurminen method stratified by cisplatin status (cisplatin-ineligible vs cisplatin-eligible but declined), tumor stage (T2N0 vs T3/T4aN0 vs T1-4aN1), and geographic regions (US vs EU vs MOW) with small strata collapsed as pre-specified in the sSAP.
[b] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
Database Cutoff Date: 06JUN2025.

Pathological downstaging

The pDS rate based on BICR (defined as downstaging to non-muscle invasive disease) was higher for the perioperative EV + pembrolizumab group compared with the RC + PLND alone group. The pDS results based on investigator assessment were consistent with those based on BICR alone.

Table 27 Analysis of Pathological Downstaging Based on BICR Assessment (ITT2 Population) Database Cutoff Date: 06JUN2025.

Treatment	N	Number of Pathological Downstaging	Pathological Downstaging Rate (%) (95% CI)	Difference in % vs. RC + PLND	
				Estimate % (95% CI)[a]	p-Value[b]
EV + Pembro	170	112	65.9 (58.2, 73.0)	53.1 (44.0, 61.2)	<0.000001
RC + PLND	174	22	12.6 (8.1, 18.5)		

[a] Based on Miettinen & Nurminen method stratified by cisplatin status (cisplatin-ineligible vs cisplatin-eligible but declined), tumor stage (T2N0 vs T3/T4aN0 vs T1-4aN1), and geographic regions (US vs EU vs MOW) with small strata collapsed as pre-specified in the sSAP.
[b] p-value is nominal.
Database Cutoff Date: 06JUN2025.

Disease-free Survival

DFS was evaluated in participants who are disease-free at the post-surgery baseline scan. In total after surgery, 135 participants in the perioperative EV + pembrolizumab group and 129 participants in the RC + PLND alone group were included in the analysis of DFS.

Table 28 Analysis of Disease-Free Survival (Primary Censoring Rule) Based on BICR Assessment (ITT2 Population - Participants Who Are Disease Free After Surgery) Database Cutoff Date: 06JUN2025.

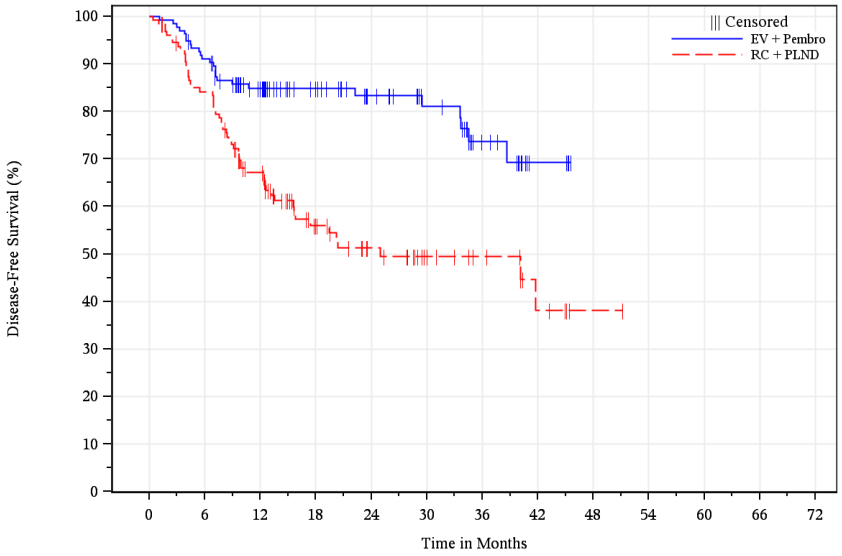
	EV + Pembro (N=135)	RC + PLND (N=129)
Number of Events (%)	26 (19.3)	57 (44.2)
Number of Censored (%)	109 (80.7)	72 (55.8)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	23.6 (13.7, NR)
[Q1, Q3]	[33.2, NR]	[7.0, NR]
Person-months	2534.1	1893.5
Event Rate / 100 Person-months	1.0	3.0
vs RC + PLND		
Hazard Ratio (95% CI)[b]	0.37 (0.23, 0.59)	

DFS Rate at month 6 (%) (95% CI)	88.0 (81.2, 92.5)	78.6 (70.4, 84.8)
DFS Rate at month 12 (%) (95% CI)	84.9 (77.5, 90.0)	62.0 (52.6, 70.1)
DFS Rate at month 18 (%) (95% CI)	84.9 (77.5, 90.0)	56.0 (46.1, 64.7)
DFS Rate at month 24 (%) (95% CI)	83.2 (75.1, 88.9)	49.6 (39.0, 59.3)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
NR = Not reached.
Database Cutoff Date: 06JUN2025.

The sensitivity analysis results of DFS that was measured from the date of surgery were consistent with the primary analysis results.

Figure 11 Kaplan-Meier Plot of Disease-Free Survival (Primary Censoring Rule) Based on BICR Assessment (ITT2 Population - Participants Who Are Disease Free After Surgery) Database Cutoff Date: 06JUN2025.



Database Cutoff Date: 06JUN2025.

Patient-reported Outcomes

The PRO FAS2 population comprised participants in the perioperative EV + pembrolizumab group (N=157) and the RC + PLND alone group (N=104) who were randomized in Stage 2, had PRO assessments available at both baseline and the specified post-baseline timepoint for the specific endpoint, and had received any study intervention.

PROs were assessed using validated instruments, including FACT-G, FACT-Bl-Cys (including TOI), BCI (urinary, bowel and sexual domains), and EQ-5D-5L (including VAS), in the PRO FAS2 population (results presented for the FACT-G total score).

Participants maintained HRQoL while receiving perioperative enfortumab vedotin + pembrolizumab. The FACT-G total score, FACT-Bl-Cys, FACT-Bl-Cys TOI, BCI urinary domain score, and EQ-5D-5L VAS scores remain stable for patients receiving perioperative enfortumab vedotin + pembrolizumab. The BCI bowel and sexual domain scores declined in both treatment arms, likely due to surgery.

Figure 12 Bar Plot of Empirical Mean Change from Baseline to Post-Surgery Week 18 and 95% CI in FACT-G Total Score (PRO FAS2 Population)

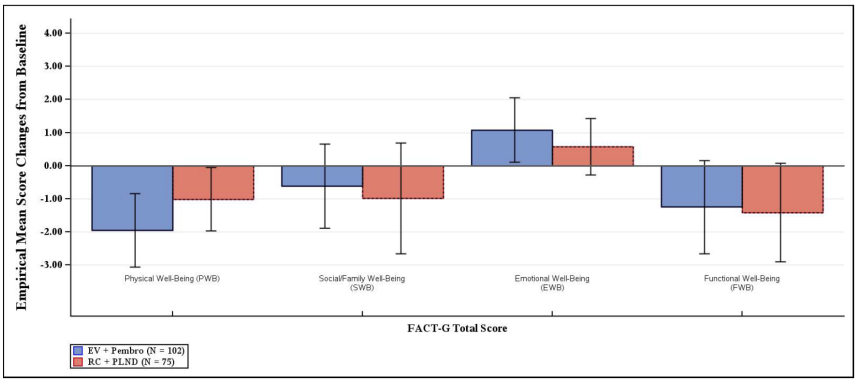


Figure 13 Line Plot of Empirical Mean Change from Baseline and 95% CI for the FACT-G Total Score Over Time (PRO FAS2 Population - EV + Pembro Arm) Database Cutoff Date: 06JUN2025

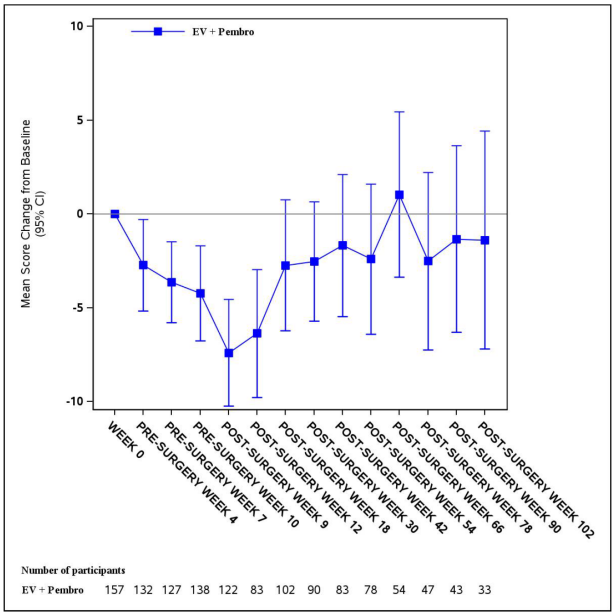
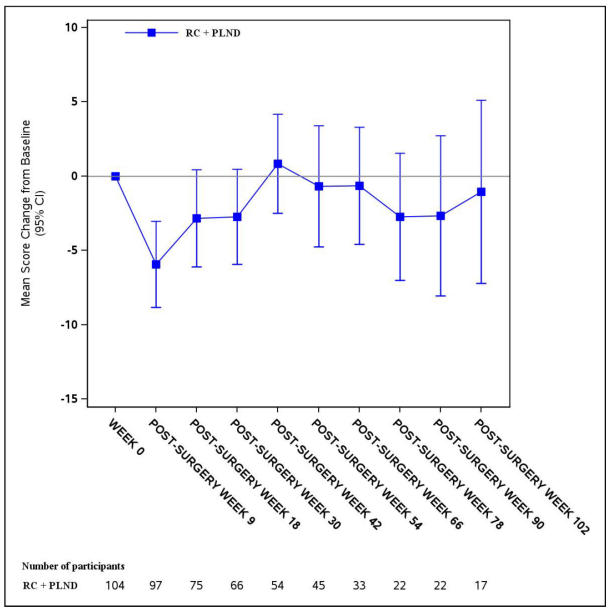


Figure 14 Line Plot of Empirical Mean Change from Baseline and 95% CI for the FACT-G Total Score Over Time (PRO FAS2 Population - RC + PLND Arm)

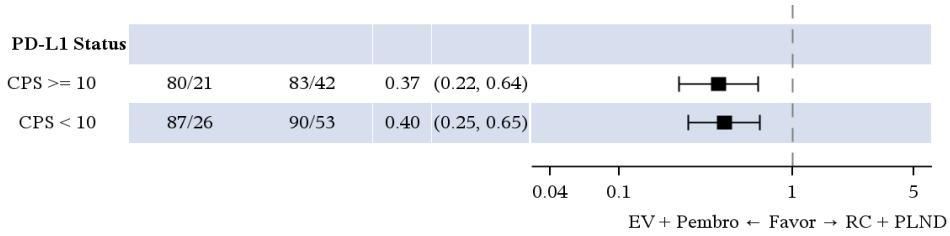


Ancillary analyses

Event-Free Survival Subgroup Analyses

Figure *15 Forest Plot of Event-Free Survival Hazard Ratio by Subgroup Factors Based on BICR Assessment (ITT2 Population)*

	N/#Events EV + Pembro	N/#Events RC + PLND	HR	95% CI	Estimated Hazard Ratio (HR)
Overall	170/48	174/95	0.40	(0.28, 0.57)	
Age (Year)					
< 65	29/3	29/16	0.13	(0.04, 0.46)	
>= 65	141/45	145/79	0.45	(0.31, 0.65)	
Sex					
Male	137/37	131/72	0.40	(0.27, 0.59)	
Female	33/11	43/23	0.37	(0.18, 0.79)	
Race					
White	132/36	136/74	0.38	(0.26, 0.57)	
All Others	37/12	35/19	0.49	(0.24, 1.02)	
Geographic Region					
US	21/6	23/11	0.47	(0.17, 1.27)	
EU	78/21	77/41	0.38	(0.23, 0.65)	
MOW	71/21	74/43	0.41	(0.24, 0.69)	
Smoking Status					
Never Smoker	55/14	44/26	0.32	(0.17, 0.62)	
Former Smoker	82/24	86/44	0.45	(0.27, 0.74)	
Current Smoker	33/10	44/25	0.40	(0.19, 0.84)	
Cisplatin Status					
Cisplatin-Ineligible	142/41	139/81	0.37	(0.26, 0.54)	
Cisplatin-Eligible but Declined	28/7	35/14	0.58	(0.23, 1.44)	
Tumor Stage					
T2N0	30/4	32/13	0.26	(0.08, 0.80)	
T3/T4aN0	133/41	132/75	0.43	(0.29, 0.63)	
T1-4aN1	7/3	10/7	0.35	(0.09, 1.40)	



For overall population, analysis is based on stratified Cox regression model with treatment as a covariate. For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate. If a subgroup variable has two levels and one level of the subgroup has less than 10 events, then this subgroup variable is not displayed in the plot.

EFS pre-specified sensitivity analyses

Sensitivity censoring rule 1 per BICR Assessment: EFS analysis according to censoring rule 1 (see table 8) showed consistent results with the primary analysis HR 0.32 (95%CI 0.21, 0.48).

Sensitivity Censoring Rule 2 per BICR Assessment: In sensitivity analysis 2, the new anticancer therapy includes the use of adjuvant nivolumab in Arm B (including adjuvant nivolumab for those settings where this use is authorized, was classified as initiation of a new anticancer therapy).

Table 29 Table. Analysis of Event-Free Survival (Sensitivity Censoring Rule 2) Based on BICR Assessment (ITT2 Population). Cutoff date: 06 June 2025

	EV + Pembro (N=170)	RC + PLND (N=174)
Number of Events (%)	36 (21.2)	71 (40.8)
Number of Censored (%)	134 (78.8)	103 (59.2)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	12.7 (9.1, 20.7)
[Q1, Q3]	[36.7, NR]	[4.4, NR]
Person-months	3284.6	1741.7
Event Rate / 100 Person-months	1.1	4.1
vs RC + PLND		
Hazard Ratio (95% CI)[b]	0.29 (0.19, 0.43)	
p-value[c]	<0.0001	
EFS Rate at month 6 (%) (95% CI)	90.1 (84.3, 93.8)	66.9 (57.9, 74.3)
EFS Rate at month 12 (%) (95% CI)	80.0 (72.7, 85.5)	50.4 (41.0, 59.0)
EFS Rate at month 18 (%) (95% CI)	79.2 (71.8, 84.8)	43.2 (33.6, 52.4)
EFS Rate at month 24 (%) (95% CI)	79.2 (71.8, 84.8)	40.1 (30.4, 49.6)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by cisplatin status (cisplatin-ineligible vs cisplatin-eligible but declined), tumor stage (T2N0 vs T3/T4aN0 vs T1-4aN1), and geographic regions (US vs EU vs MOW) with small strata collapsed as pre-specified in the sSAP.
[c] One-sided p-value based on log-rank test stratified by cisplatin status (cisplatin-ineligible vs cisplatin-eligible but declined), tumor stage (T2N0 vs T3/T4aN0 vs T1-4aN1), and geographic regions (US vs EU vs MOW) with small strata collapsed as pre-specified in the sSAP.
NR = Not reached.
Database Cutoff Date: 06JUN2025.

Figure 16 Kaplan-Meier Plot of Event-Free Survival (Sensitivity Censoring Rule 2) Based on BICR Assessment (ITT2 Population) Cutoff date: 06 June 2025

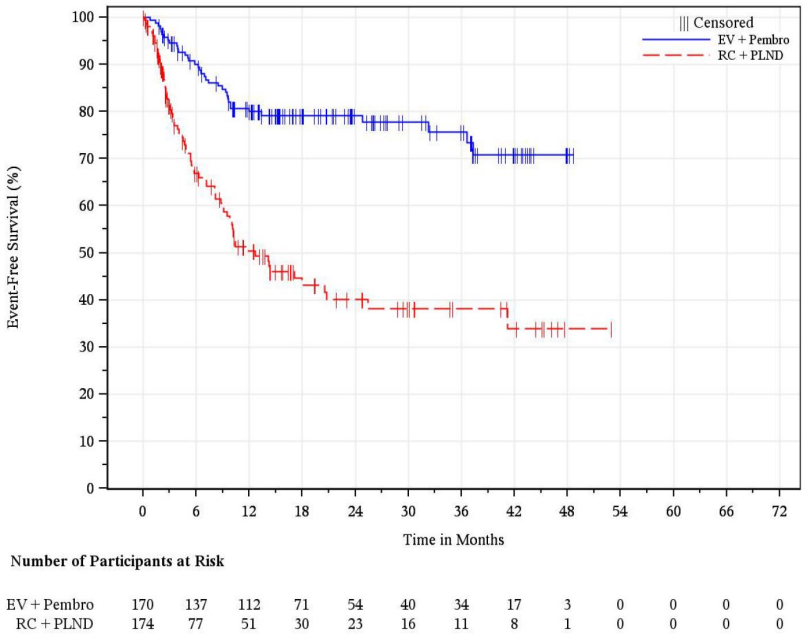


Table 30 Analysis of Event-Free Survival (Primary Censoring Rule) Based on Investigator Assessment (ITT2 Population) Cutoff date: 06 June 2025

	EV + Pembro (N=170)	RC + PLND (N=174)
Number of Events (%)	46 (27.1)	98 (56.3)
Number of Censored (%)	124 (72.9)	76 (43.7)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (41.2, NR)	15.6 (11.0, 20.0)
[Q1, Q3]	[20.5, NR]	[5.4, 47.3]
Person-months	3369.1	2446.0
Event Rate / 100 Person-months	1.4	4.0
vs RC + PLND		
Hazard Ratio (95% CI)[b]	0.36 (0.26, 0.52)	
p-value[c]	<0.0001	
EFS Rate at month 6 (%) (95% CI)	92.5 (87.2, 95.7)	72.4 (64.9, 78.5)
EFS Rate at month 12 (%) (95% CI)	80.2 (73.0, 85.6)	56.9 (48.9, 64.0)
EFS Rate at month 18 (%) (95% CI)	75.4 (67.6, 81.6)	46.9 (38.7, 54.6)
EFS Rate at month 24 (%) (95% CI)	74.3 (66.2, 80.7)	38.3 (29.9, 46.7)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by cisplatin status (cisplatin-ineligible vs cisplatin-eligible but declined), tumor stage (T2N0 vs T3/T4aN0 vs T1-4aN1), and geographic regions (US vs EU vs MOW) with small strata collapsed as pre-specified in the sSAP.
[c] One-sided p-value based on log-rank test stratified by cisplatin status (cisplatin-ineligible vs cisplatin-eligible but declined), tumor stage (T2N0 vs T3/T4aN0 vs T1-4aN1), and geographic regions (US vs EU vs MOW) with small strata collapsed as pre-specified in the sSAP.
NR = Not reached.

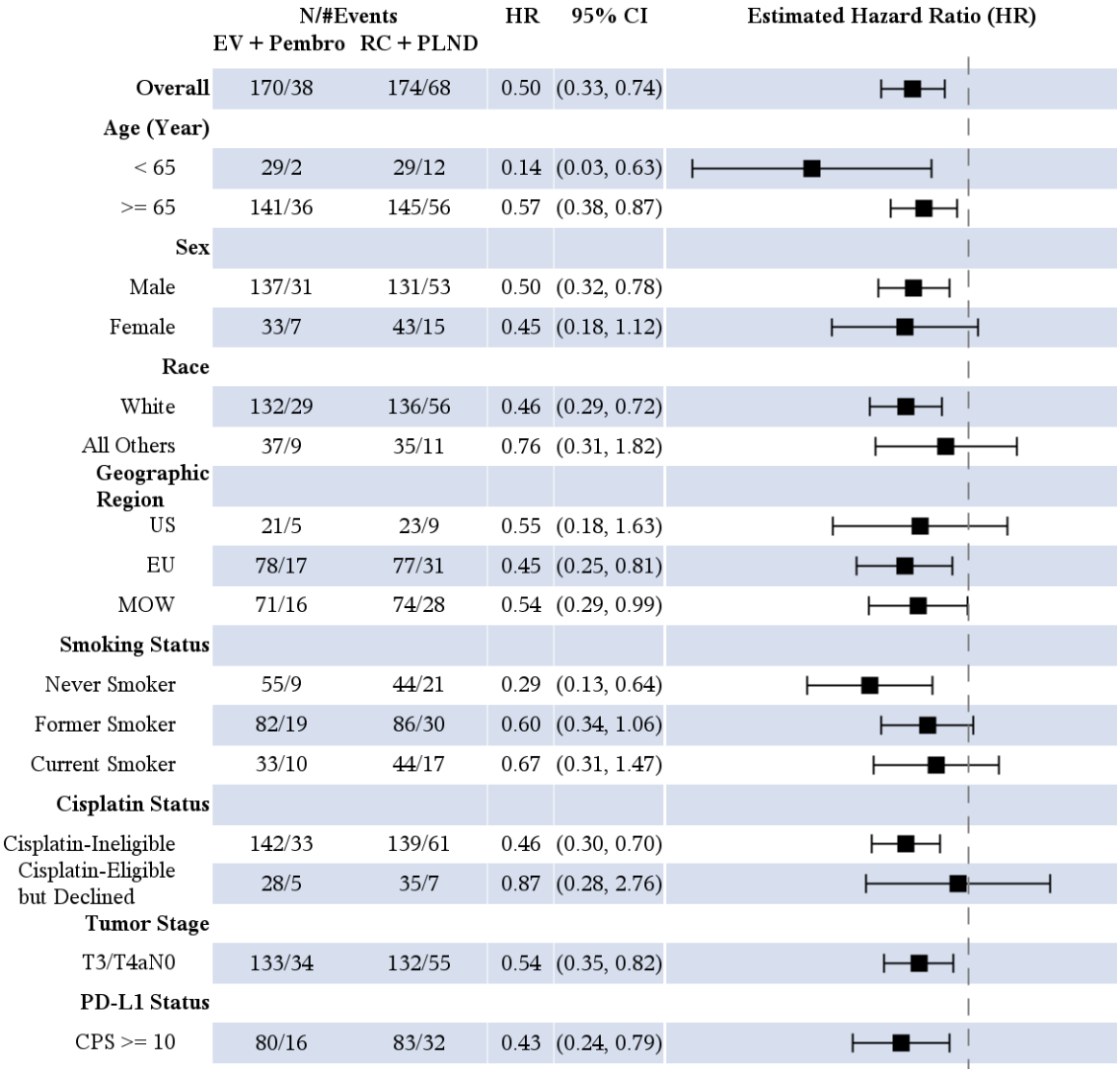
Table 31 Concordance of EFS Events (Investigator vs BICR Assessment) (ITT2 Population) Cutoff date: 06 June 2025

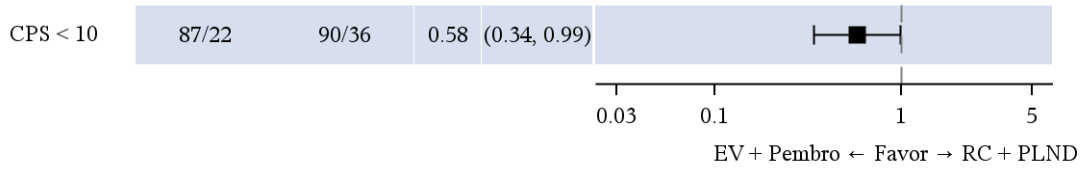
	EV + Pembro n (%)	RC + PLND n (%)
Participants in Population	170	174
Investigator Assessment - Event	46	98
BICR Agreed	46 (100.0)	93 (94.9)
BICR Disagreed	0 (0.0)	5 (5.1)
No BICR Assessment	0 (0.0)	0 (0.0)
Investigator Assessment - Non-Event	122	74
BICR Agreed	120 (98.4)	72 (97.3)
BICR Disagreed	2 (1.6)	2 (2.7)
No BICR Assessment	0 (0.0)	0 (0.0)
No Investigator Assessment	2	2

BICR: Blinded Independent Central Review; EFS=event free survival.
Database Cutoff Date: 06JUN2025

Overall survival subgroup analyses

Figure 17 **Forest Plot of Overall Survival Hazard Ratio by Subgroup Factors (ITT2 Population)**





For overall population, analysis is based on stratified Cox regression model with treatment as a covariate. For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate.
If a subgroup variable has two levels and one level of the subgroup has less than 10 events, then this subgroup variable is not displayed in the plot.
Database Cutoff Date: 06JUN2025.

Exploratory analyses have been provided for patients achieving or not achieving pCR in ITT2.

Table 32 Analysis of Event-Free Survival (Primary Censoring Rule) Based on BICR Assessment (ITT2 Population – Participants With pCR) Cutoff date: 06 June 2025

	EV + Pembro (N=97)	RC + PLND (N=15)
Number of Events (%)	16 (16.5)	5 (33.3)
Number of Censored (%)	81 (83.5)	10 (66.7)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	41.2 (12.7, NR)
[Q1, Q3]	[NR, NR]	[17.9, NR]
Person-months	2308.7	311.6
Event Rate / 100 Person-months	0.7	1.6
vs RC + PLND		
Hazard Ratio (95% CI)[b]	0.43 (0.16, 1.16)	
EFS Rate at month 6 (%) (95% CI)	97.9 (91.9, 99.5)	85.7 (53.9, 96.2)
EFS Rate at month 12 (%) (95% CI)	88.4 (80.0, 93.4)	85.7 (53.9, 96.2)
EFS Rate at month 18 (%) (95% CI)	87.2 (78.5, 92.5)	67.3 (33.0, 86.9)
EFS Rate at month 24 (%) (95% CI)	87.2 (78.5, 92.5)	67.3 (33.0, 86.9)

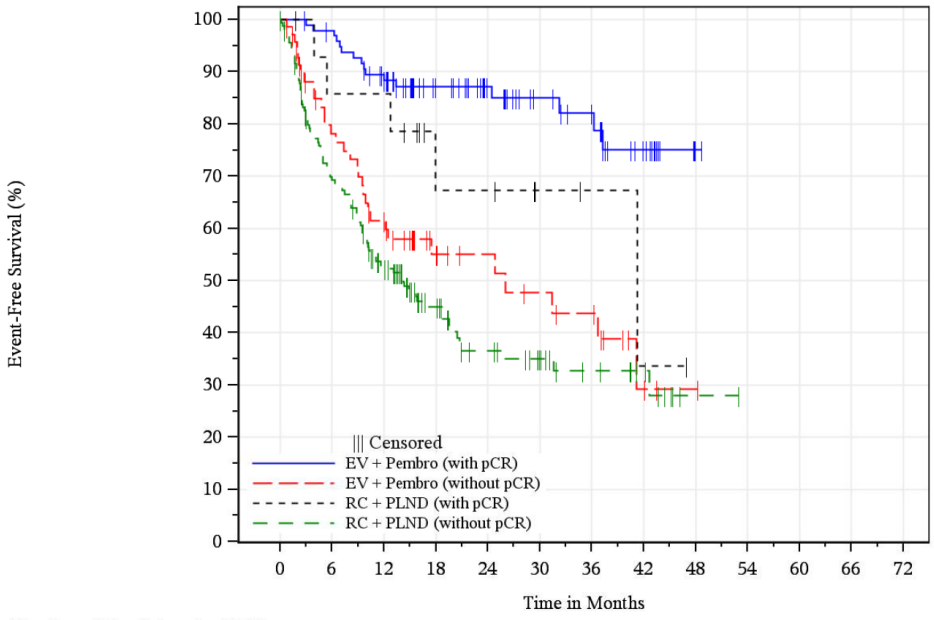
[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
NR = Not reached.
Database Cutoff Date: 06JUN2025.

Table 33 Analysis of Event-Free Survival (Primary Censoring Rule) Based on BICR Assessment (ITT2 Population – Participants Without pCR) Cutoff date: 06 June 2025

	EV + Pembro (N=73)	RC + PLND (N=159)
Number of Events (%)	32 (43.8)	90 (56.6)
Number of Censored (%)	41 (56.2)	69 (43.4)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	26.1 (10.1, 41.2)	14.2 (10.1, 19.5)
[Q1, Q3]	[7.4, NR]	[4.9, NR]
Person-months	1038.5	2141.8
Event Rate / 100 Person-months	3.1	4.2
vs RC + PLND		
Hazard Ratio (95% CI)[b]	0.76 (0.51, 1.14)	
EFS Rate at month 6 (%) (95% CI)	78.2 (65.9, 86.5)	69.2 (61.2, 75.9)
EFS Rate at month 12 (%) (95% CI)	61.5 (48.2, 72.3)	52.2 (43.9, 59.9)
EFS Rate at month 18 (%) (95% CI)	55.0 (41.1, 66.9)	44.9 (36.5, 53.1)
EFS Rate at month 24 (%) (95% CI)	55.0 (41.1, 66.9)	36.5 (27.8, 45.3)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
NR = Not reached.
Database Cutoff Date: 06JUN2025.

Figure 18 Kaplan-Meier Plot of Event-Free Survival by pCR Status (Primary Censoring Rule) Based on BICR Assessment (ITT2 Population) Cutoff date: 06 June 2025



Number of Participants at Risk

EV + Pembro (with pCR)	97	93	80	54	41	30	25	13	2	0	0	0	0
EV + Pembro (without pCR)	73	47	36	19	15	12	10	3	1	0	0	0	0
RC + PLND (with pCR)	15	12	12	6	6	3	2	1	0	0	0	0	0
RC + PLND (without pCR)	159	104	72	42	27	19	12	8	1	0	0	0	0

Exploratory Efficacy Subgroup Analysis of Nectin-4 Expression by H-score.

Participants enrolled in KEYNOTE-905 were required to provide tumor tissue from a TUR specimen that was obtained up to 60 days (+14 days) before being enrolled into the study. Tumor tissue was collected as either FFPE blocks (preferred) or unstained slides. The tissue that remained after conducting the clinical diagnosis of MIBC and PD-L1 expression was used for exploratory analyses such as Nectin-4 IHC. For the nectin expression assessment, a minimum of 100 viable tumor cells were required for tissue to be acceptable for Nectin-4 testing. Nectin-4 staining was scored by pathologists trained on the Nectin-4 IHC assay. Nectin-4 expression was calculated by estimating the staining intensities of all tumor cells on the slide (3=strong, 2=moderate, 1=low, 0=negative) and the percentage of tumor cells that were positive at a particular intensity (PI-0, PI-1, PI-2, PI-3). An H-score ranging from 0 to 300 was derived for each tumor tissue sample.

Table 34 Participant Characteristics by Nectin-4 H-score in Tumor Tissue (ITT2 Population) Cutoff date: 06 June 2025

	EV + Pembro		RC + PLND	
	n	(%)	n	(%)
Participants in population	170		174	
Nectin4 H Score Total Score				
< 150	18	(10.6)	17	(9.8)
150 to < 225	34	(20.0)	38	(21.8)
≥ 225	116	(68.2)	79	(45.4)
Missing	2	(1.2)	40	(23.0)
Participants with data	168		134	
Mean	241.3		224.9	
SD	65.7		69.3	
SE	5.1		6.0	
Median	270.0		240.0	
Q1 to Q3	210.0 to 293.0		200.0 to 280.0	
Range	0.0 to 300.0		10.0 to 300.0	

SD=Standard deviation; SE=Standard error; Q1=First quartile, Q3=Third quartile.
Database Cutoff Date: 06JUN2025.

Table 35 Subgroup Analysis of Event-Free Survival Based on BICR Assessment by Nectin-4 H-Score in Tumor Tissue (ITT2 Population) Cutoff date: 06 June 2025

	EV + Pembro		RC + PLND		EV + Pembro vs RC + PLND
	N	Number of Events (%)	N	Number of Events (%)	Hazard Ratio (95% CI)[a]
Overall	170	48 (28.2)	174	95 (54.6)	0.40 (0.28, 0.57)
Nectin-4 H-score in Tumor Tissue					
< 150	18	4 (22.2)	17	10 (58.8)	0.28 (0.09, 0.89)
150 to < 225	34	12 (35.3)	38	25 (65.8)	0.50 (0.25, 1.00)
≥ 225	116	32 (27.6)	79	37 (46.8)	0.43 (0.27, 0.70)
Missing	2	0 (0.0)	40	23 (57.5)	NA

[a]For overall population, the hazard ratio and nominal 95% CI are estimated based on Cox regression model with treatment as a covariate stratified by cisplatin status (cisplatin-ineligible vs cisplatin-eligible but declined), tumor stage (T2N0 vs T3/T4aN0 vs T1-4aN1), and geographic regions (US vs EU vs MOW) with small strata collapsed as pre-specified in the sSAP. For subgroup analyses, the hazard ratio and nominal 95% CI are estimated within each category based on unstratified Cox regression model with treatment as a covariate.
HR estimate for missing category not done as EV + Pembro arm only has 2 participants in this category.
Database cutoff date: 06JUN2025

Table 36 Subgroup Analysis of Overall Survival by Nectin-4 H-Score in Tumor Tissue (ITT2 Population) Cutoff date: 06 June 2025

	EV + Pembro		RC + PLND		EV + Pembro vs RC + PLND
	N	Number of Events (%)	N	Number of Events (%)	Hazard Ratio (95% CI)[a]
Overall	170	38 (22.4)	174	68 (39.1)	0.50 (0.33, 0.74)
Nectin-4 H-score in Tumor Tissue					
< 150	18	3 (16.7)	17	8 (47.1)	0.28 (0.07, 1.05)
150 to < 225	34	12 (35.3)	38	18 (47.4)	0.72 (0.35, 1.50)
≥ 225	116	23 (19.8)	79	26 (32.9)	0.48 (0.27, 0.85)
Missing	2	0 (0.0)	40	16 (40.0)	NA

[a]For overall population, the hazard ratio and nominal 95% CI are estimated based on Cox regression model with treatment as a covariate stratified by cisplatin status (cisplatin-ineligible vs cisplatin-eligible but declined), tumor stage (T2N0 vs T3/T4aN0 vs T1-4aN1), and geographic regions (US vs EU vs MOW) with small strata collapsed as pre-specified in the sSAP. For subgroup analyses, the hazard ratio and nominal 95% CI are estimated within each category based on unstratified Cox regression model with treatment as a covariate.

HR estimate for missing category not done as EV + Pembro arm only has 2 participants in this category.

Database cutoff date: 06JUN2025

Situation	Primary Analysis[a]	Sensitivity Analysis 1[a]	Sensitivity Analysis 2[b]
No post-screening scans available	Censored at Day 1 from randomization	Censored at Day 1 from randomization	Censored at Day 1 from randomization

EFS=event-free survival; PD=progressive disease; MIBC=muscle-invasive bladder cancer; NMIBC=nonmuscle-invasive bladder cancer.

[a] In the primary analysis and sensitivity analysis 1, the new anticancer therapy excludes the use of adjuvant nivolumab in Arm B.

[b] In sensitivity analysis 2, the new anticancer therapy includes the use of adjuvant nivolumab in Arm B.

[c] Includes cases with high-risk prostate cancer found at surgery who require subsequent anticancer treatment and for new anticancer therapy in bladder cancer initiated off-study without evidence of EFS event.

[d] Includes high risk NMIBC of the upper tracts.

[e] Presence of MIBC needs to be confirmed with imaging demonstrating radiographic disease present and a positive post-baseline cystoscopy with biopsy.

[f] Participants with T4b, N2/N3 disease as identified by imaging and confirmed by BICR.

Additional sensitivity analyses were prespecified for EFS and OS, including:

• Add PD-L1 expression (CPS ≥10 versus CPS< 10) as a covariate to the stratified Cox proportional hazard model to assess the impact of PD-L1 expression on efficacy outcomes

• Unstratified log-rank test and unstratified Cox proportional hazard model

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).

Table 1. Summary of Efficacy for trial **KEYNOTE-905/EV-303**

Title:
A Randomized Phase 3 Study Evaluating Cystectomy with Perioperative Pembrolizumab and Cystectomy with Perioperative Enfortumab Vedotin and Pembrolizumab versus Cystectomy Alone in Participants who are Cisplatin-Ineligible or Decline Cisplatin with Muscle

Study identifier	P905V01MK3475 EudraCT: 2018- 003809-26 EU CT: 2023- 504932-16		
Design	Multi-centre, efficacy, safety, parallel assignment, open-label, active comparator intervention		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	1 year not applicable not applicable	
Hypothesis	Superiority (EFS and OS) of perioperative EV + pembrolizumab vs. radical cystectomy and pelvic lymph node dissection alone		
Treatments groups	Arm B	radical cystectomy and pelvic lymph node dissection alone	
	Arm C	Enfortumab vedotin 1.25 mg/kg i.v. days 1 and 8 q3w and Pembrolizumab 200 mg q3w in the neoadjuvant phase and 6 cycles of Enfortumab vedotin and 14 cycles of pembrolizumab in the adjuvant phase.	
Endpoints and definitions	Primary endpoint	EFS	EFS is defined as time from randomisation to any of the following events: Radiographic disease progression precluding a curative intent surgery as assessed by BICR prior to RC + PLND; Failure to undergo surgery for participants with residual muscle invasive disease and any radiographic disease present; Gross residual disease left behind at time of surgery (surgeon unable to complete curative intent surgery due to unresectable tumor or newly discovered metastatic disease); Local or distant recurrence post-RC + PLND as assessed by CT or MRI by BICR and/or biopsy – if biopsy is not feasible due to participant safety, CT/MRI alone will be sufficient; Death from any cause.
	Secondary endpoint	OS	Overall survival
	Secondary endpoint	pCR	Pathological complete response
Database lock	09-JUL-2025		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intention to treat (ITT2)			
Descriptive statistics and estimate variability	Treatment group	Padcev + pembrolizumab	RC + PLND alone	
	Number of subject	170	174	

	Event-free survival **EFS**: Number of patients with events, n (%)	48 (28.2)	95 (54.6)	
	Median in months	NR (37.3, NR)	15.7 (10.3, 20.5)	
	Overall survival **OS**: Number of patients with events, n (%)	38 (22.4)	68 (39.1)	
	Median in months	NR (NR, NR)	41.7 (31.8, NR)	
	Pathological complete response **pCR**: Number of patients with pCR/pCR rate % (95% CI)	97 57.1 (49.3, 64.6)	15 8.6 (4.9, 13.8)	

Effect estimate per comparison	Primary endpoint **EFS**	Comparison groups	Padcev + pembrolizumab versus RC + PLND alone
		Hazard ratio	0.40
		95% confidence interval	(0.28, 0.57)
		P-value	<0.0001
	Secondary endpoint **OS**	Comparison groups	Padcev + pembrolizumab versus RC + PLND alone
		Hazard ratio	0.50
		95% confidence interval	(0.33, 0.74)
		P-value	0.0002
	Secondary Endpoint **pCR**	Comparison groups	Padcev + pembrolizumab versus RC + PLND alone
		Treatment difference estimate (%)	48.3
		(95% CI)	(39.5, 56.5)
		P-value	<0.000001
Notes	For response-related endpoints, response-evaluable dataset per BICR		

Clinical studies in special populations

	Controlled Studies[a]	**Noncontrolled Studies**

Participants with renal impairment[b]	584/1230	77/121
Age 65-74	537/1230	52/121
Age 75-84	331/1230	30/121
Age ≥85	25/1230	10/121
Other	337/1230	29/121

a. Data for the KEYNOTE-905 study are from the ITT2 Population.

b. Renal impairment is defined as having creatinine clearance <60 mL/min.

Note: Controlled studies include EV-302, and KEYNOTE-905. Non-controlled studies include EV-103 (dose escalation, Cohort A, and Cohort K).

Supportive study(ies)

The following supportive studies have been provided by the MAH as evidence supporting the contribution of each individual component to the combination regimen and the contribution of phases/proposed duration of treatment.

Table 37 Supportive studies

la/mUC						
EV-302 NCT04223856 (ongoing; DCO: 08-AUG-2023)	886	Phase 3 open-label randomized study evaluating EV (1.25 mg/kg IV D1,D8 q3w) + pembrolizumab (200 mg IV q3w) vs. SOC (plat + gem)	1L Cis-E/IE la/mUC	EV + pembrolizumab vs. SOC	Primary: PFS by BICR OS Key Secondary: ORR by BICR	PFS/OS: ITT (all randomized participants) ORR: all participants with measurable disease at baseline
EV-201 (SGN22E-001)	Phase 2 Open-label, multicenter study of efficacy and safety as monotherapy/ single-arm	Locally advanced metastatic UC; previously treated with PD-1/PD-L1 n = approx. 200	1.25 mg/kg on days 1, 8 and 15 of a 28-day cycle	Ongoing 219 subjects‡	Data cut for primary analyses: Cohort 1 01 Mar 2019 Cohort 2 08 Sep 2020	
EV-103 Cohort K NCT03288545 (ongoing; DCO: 20-NOV-2024)	151	Phase 1b/2 study of EV (ASG-22CE) as monotherapy or in combination with other anticancer therapies for the treatment of UC. Cohort K is an open-label randomized cohort evaluating EV monotherapy (1.25 mg/kg IV D1,D8 q3w) and EV + pembrolizumab (200 mg IV q3w)	1L Cis-IE la/mUC	EV + pembrolizumab or EV	Primary: ORR by BICR Key Secondary: DOR by BICR	FAS (all participants who received ≥1 dose of study medication)
MIBC						
EV-103 Cohort L NCT03288545 (ongoing; DCO: 20-NOV-2024)	51	Phase 1b/2 study of EV (ASG-22CE) as monotherapy or in combination with other anticancer therapies for the treatment of urothelial cancer. Cohort L is an open-label cohort evaluating perioperative EV monotherapy (1.25 mg/kg IV D1,D8 q3w)	Cis-IE MIBC	Perioperative EV monotherapy	Primary: pCR Key Secondary: EFS by BICR EFS by INV	FAS (all participants who received ≥1 dose of study intervention)

2.4.3. Discussion on clinical efficacy

The scope of this variation is to support the extension of indication of enfortumab vedotin for the perioperative treatment of resectable muscle invasive bladder cancer (MIBC) in adults not eligible for cisplatin-based chemotherapy, based on the results from the pivotal trial KEYNOTE-905/EV-303.

Design and conduct of clinical studies

The KEYNOTE-905/EV-303 study is a Phase 3, randomized, controlled, parallel-group, multisite, open-label study of perioperative pembrolizumab plus radical cystectomy and pelvic lymph node dissection (RC + PLND) (Arm A) and perioperative enfortumab vedotin in combination with pembrolizumab plus RC + PLND (Arm C) versus RC + PLND alone (Arm B) in participants with MIBC (cT2-T4aN0M0 or cT1-T4aN1M0) who are ineligible for or decline cisplatin-based chemotherapy. As perioperative pembrolizumab without enfortumab vedotin (Arm A) is not part of the sought indication for this application, only the comparison between Arm B and Arm C will be discussed in this assessment

For patients, ineligible to cisplatin with resectable MIBC, the current SoC according to the European guideline on MIBC (ESMO 2021) is RC + PLND. Up to 50% of patients with MIBC, who undergo RC + PLND alone, experience local or distant recurrence within 2 to 3 years (Witjes JA, et al, (EAU); 2024. 97p; Mari A, et al, J Urol. 2018;36:157-70). Thus, a relevant unmet medical need is addressed by the trial and the chosen comparator is appropriate. Patients had to have upfront resectable MIBC, defined as cT2-T4aN0M0 or cT1-T4aN1M0. These resectability criteria are in accordance with international guidelines (ESMO 2021, AJCC 2017). The eligibility criteria are considered to appropriately reflect the target population.

Patients in the experimental arm C were treated with Enfortumab vedotin 1.25 mg/kg i.v. days 1 and 8 q3w and Pembrolizumab 200 mg q3w in the neoadjuvant phase and with 6 cycles of Enfortumab vedotin and 14 cycles of pembrolizumab in the adjuvant phase. The recommended dose for the combination treatment is identical to that of Study EV-302 (Keynote-A39), which supported the approved indication of Padcev + pembrolizumab in the metastatic setting of urothelial cancer and is considered acceptable on this basis.

Contribution of components:

Subsequently to Amendment 08 randomization to arm A (pembrolizumab monotherapy) was closed and as a consequence, the study design is unable to establish the magnitude of the benefit conferred by adding EV to pembrolizumab.

The MAH has provided an overview of studies in support of the contribution of each component to the combination therapy from the metastatic setting.

Enfortumab vedotin has shown efficacy in urothelial cancer as monotherapy (EV-103, EV-201, EV-302) and in combination with pembrolizumab (EV-103, EV-302), in both cisplatin eligible and ineligible patients.

Study EV-103 is a phase1/2b study, which was evaluated as supportive evidence for the approval of EV + pembrolizumab in the mUC setting. Study EV-103 provides both EV + Pembrolizumab data and EV monotherapy data in a population of 1L cisplatin-ineligible patients. The contribution of pembrolizumab was supported by comparing EV + Pembrolizumab data from EV-302 to EV monotherapy data from the Cohort K monotherapy arm of the EV-103 study (EPAR EMEA/H/C/005392/II/0013). The MAH has appropriately presented available evidence showing the individual contribution of EV and pembrolizumab in the metastatic setting of urothelial cancer.

Although a formal comparison of the combination therapy to monotherapy has not been performed, the supportive evidence is acknowledged, and the issue is not further pursued.

Phase contribution and treatment duration

The MAH has provided the following justification for the duration of treatment: 3 cycles of pembrolizumab, in the neoadjuvant phase, was based on the preliminary results of the PURE-01 study [Necchi, A., et al 2018]. Additionally, for cisplatin-eligible patients with MIBC, 3 to 4 chemotherapy cycles prior to cystectomy is a well-accepted interval for neoadjuvant treatment prior to surgery for curative intent [Wong, Y. N., et al 2012] [Choueiri, T. K., et al 2014]. The choice of 1-year duration of adjuvant treatment (17 cycles of pembrolizumab) was based on positive results of the KEYNOTE-054 trial, which investigated 1 year of adjuvant pembrolizumab versus placebo for completely resected Stage III melanoma [Suciu, S., et al 2018]. The 1-year duration of therapy was also consistent with ongoing large Phase 3 adjuvant studies in the MIBC setting (AMBASSADOR [KEYNOTE-123] NCT03244384, IMvigor010 NCT02450331, CheckMate 274 NCT02632409). The duration of EV treatment followed that of pembrolizumab. While the rationale provided for the chosen duration of treatment is acknowledged, the study design does not clarify the contribution of the neoadjuvant and adjuvant treatment phase, respectively, and thus cannot be determined based on the available data.

Stratification:

The stratification factors were cisplatin-ineligible versus cisplatin-eligible status, disease stage (T2N0 vs. T37T4aN0 vs. T1-4aN1) and region (US vs. EU vs. Most of World). The choice of stratification factors is endorsed, as they are prognostic or potentially related to treatment outcome. Of note, with Amendment 05 (and the inclusion of cisplatin-eligible patients who declined cisplatin) PD-L1 expression level was replaced by cisplatin eligibility as stratification factor. The rationale for this change is acknowledged, as being cisplatin eligible is prognostically more favourable than being cisplatin-ineligible (Fischer-Valuck BW, J Urol. 2018 Feb; 199:, Li R, Eur Urol Oncol. 2024;7: 614-24) and the predictive role of PD-L1 expression in resectable MIBC may be of less impact. Relevantly, the change in stratification factor was addressed by including an additional sensitivity analysis using PD-L1 status (CPS $\geq$ 10 vs CPS <10) as covariate in the analysis.

Endpoints

The primary endpoint was event free survival (EFS), arm B versus arm C, assessed by independent review (BICR) per RECIST 1.1. Assessment by BICR is considered appropriate in the context of an open-label study. The EFS definition applied in the protocol is acceptable. Given the expected high rate of local recurrence and disease progression in the setting of resectable MIBC, not treated with cisplatin, EFS is considered an appropriate primary endpoint. OS as the key secondary endpoint is endorsed. The downgrading of pCR from a primary endpoint to a secondary endpoint (Amendment 08) is also endorsed, given the greater clinical relevance of EFS.

Amendments

The main amendments were the following:

1) in amendment 01 (June 2020) arm C was added and patients were randomized 1:1:1 between the three arms (stage 2 of the trial).

2) in amendment 05 (Jan 2022) the eligibility criteria were broadened to include cisplatin-eligible patients, who declined cisplatin.

3) in amendment 8 (Nov 2022) randomization to arm A was stopped and instead patients were randomized 1:1 to arm B and arm C. The primary endpoint pCR was converted to a key secondary endpoint, and EFS between arm B and arm C became the new primary endpoint. Further, adjuvant nivolumab was now permitted in arm B when clinically indicated.

Arm C was added to the trial, after preliminary data from EV-103 dose escalation/Cohort A in 1L cisplatin-ineligible la/mUC were released, indicating promising antitumor activity. Although efficacy data from the EV-103 were achieved in a metastatic setting, the rationale for adding arm C in the perioperative setting studied is acknowledged. The broadening of the ITT to include cisplatin-eligible patients who decline cisplatin, is also endorsed. The potential difference in prognosis that being cisplatin-eligible can confer, is relevantly handled by stratifying for cisplatin-eligibility at randomization.

Due to positive results for enfortumab vedotin + pembrolizumab in Study EV-103 Cohort K, enrolment was stopped to the perioperative pembrolizumab group in Protocol Amendment 08 (01-NOV-2022), (except in France due to a request from the French Ethics Committee) and Stage 2 randomization proceeded into arm C and arm B only. The premature termination of randomization to arm A was thus based on external data, and not on the interim results from the Keynote-905/EV-303. Only post hoc descriptive analyses of key efficacy endpoints were performed in all participants who were concurrently randomized to arm A, arm B and arm C. Consequently, the magnitude of the benefit of adding EV to pembrolizumab cannot be formerly established, only supported by a descriptive analysis.

Nivolumab was approved for the adjuvant treatment of patients with MIBC who are at high risk of recurrence after radical surgery by the FDA in AUG-2021 and in the EU (restricted to those with PD-L1 expression level of ≥1%) in APR-2022. Subsequently, as of Protocol Amendment 8, participants in Arm B at high risk of recurrence after RC + PLND could receive adjuvant nivolumab, if locally available; such participants continued in efficacy follow-up. Exploratory descriptive and adjusted analyses separating these participants from those managed with surgery alone were provided; however, interpretation of these data is limited due to the fact that the use of nivolumab was assigned post-randomisation and the small sample size and wide confidence intervals. Consequently, the analyses do not allow a robust characterisation of the specific contribution of adjuvant nivolumab to EFS, nor they permit firm conclusions regarding the incremental benefit of perioperative EV + pembrolizumab relative to the current adjuvant standard of care.

Statistics

Analysis set: All efficacy analyses in this assessment were based on the ITT2 population which comprised all participants randomized to Arm B and Arm C in Stage 2. Participants in efficacy analysis populations were included in the treatment group to which they were randomized. This is endorsed as it aligns with the ITT principle.

For EFS and OS, HRs and corresponding 95% CIs were estimated using a stratified Cox regression model. Event rates over time were estimated within each treatment group using the Kaplan-Meier method. This is endorsed, as it is standard methodology. DFS was analysed by similar methods as EFS and OS, however with no multiplicity control.

The protocol specified detailed assessment and censoring rules for participants not undergoing surgery, including mandatory reassessment within 12 weeks (+4 weeks) after the last neoadjuvant dose and prespecified handling of complete clinical response and residual disease scenarios, ensuring consistent anchoring of EFS at randomization and capture of preoperative and postoperative events

An additional sensitivity analysis included PD-L1 status (CPS ≥ 10 vs CPS <10) as covariate in the analysis and this yielded similar results as the primary analysis. This is deemed relevant in light of the change in stratification from PD-L1 status to cisplatin eligibility in Amendment 05.

Discrepancy between Amendment 08 and Amendment 10 in terms of abandonment of IA1 (107 EFS events), postponement of the final EFS analysis and multiplicity graphs were clarified by the MAH. A sensitivity analysis using the Amendment 08 multiplicity graph and a cutoff date of 15 Oct 2024 supports the primary results based on the multiplicity graph from Amendment 10 (data not shown).

Conduct and disposition

A total of 984 participants were screened and 595 were randomized to the three arms in the KEYNOTE-905/EV-303 study. Of the 611 patients screened for the ITT2, 267 did not meet the eligibility criteria (~ 43%). The reasons for screen failure were disclosed and the single most important reason for not meeting eligibility criteria was the presence of metastatic disease. There were 9% who did not have predominant urothelial histology. Overall, the reasons were diverse and considered pertinent.

The number of withdrawals from trial participation was 3 (1.8%) in arm C and 7 (4.0%) in arm B. Although imbalanced, the difference in drop-out of 2.2% is considered low and without potential to have impacted the study results decisively.

Although neoadjuvant treatment inherently implied longer time to resection, the proportion of patients who did not undergo planned surgery was acceptably balanced (~10% in arm B and ~12% in arm C), meaning that neoadjuvant treatment did not appear to impair surgery in comparison to no neoadjuvant treatment. The majority of participants who underwent surgery achieved complete resection (98.7% in arm C group and 95.5% in arm B) and 1.3% and 4.5%, respectively, had incomplete resection. Reasons for incomplete resection were unresectable tumour (arm C: 0.7%; arm B: 2.6%) and newly discovered metastatic disease (arm C: 0.7%; arm B: 1.3%). The types of surgery received were generally similar in the two arms. Conclusively, the proportion that completed planned neoadjuvant treatment was 86.2% and there appeared to be no detriment in resectability in arm C.

Despite the high proportion of non-completers, the benefit of perioperative EV+ pembrolizumab in the ITT2 is shown.

Efficacy data and additional analyses

Baseline demographic and disease characteristics were generally balanced between treatment groups. Although a relevant rate of screen failure (39%, 389/984), the baseline characteristics of KEYNOTE-905 appear broadly consistent with contemporary real-world cohorts of cisplatin-ineligible patients with MIBC[23] [24], who are typically older, more comorbid, and less likely to receive neoadjuvant therapy.

The study met its primary endpoint event-free survival at IA1 (DCO: 06-June-2025, event maturity 82.8%), showing a statistically significant and clinically relevant improvement in EFS. Median EFS in arm C was not reached (37.3, NR) and was 15.7 months (10.3, 20.5) in arm B, with a hazard

[23] Li R, Nocera L, Rose KM, Raggi D, Naidu S, Mercinelli C, et al. Comparative effectiveness of neoadjuvant pembrolizumab versus cisplatin-based chemotherapy or upfront radical cystectomy in patients with muscle-invasive urothelial bladder cancer. Eur Urol Oncol. 2024;7:614-24.
[24] Fazili A, Jazayeri SB, Rose KM, Guske C, Wen L, Durant A, et al. Cisplatin-ineligible patients with muscle-invasive bladder cancer demonstrate poor long-term survival following immediate radical cystectomy. BJU Int. 2026;137:181-8.

ratio for EFS of **0.40** (95% CI 0.28-0.57, p-value < 0.0001). The median follow-up in arm C was 20.4 months (1.4,52.6) and 17.1 months (0.6, 53.7) in arm B. The Kaplan-Meier curves separate at day 0 and the separation is sustained. The EFS event "distant progressive disease" prior to surgery was ~2% in both arms. Death from any cause was the EFS event for 13.5% in arm C and 20.1% in arm B. Overall disease recurrence was 9.4% in arm C and 29.3% in arm B.

Pre-planned subgroup analyses showed HRs in line with the EFS results for the ITT2 consistently across all important subgroups (geographic region, tumour stage, cisplatin eligibility, PD-L1 status).

Overall survival, the key secondary endpoint, showed a statistically significant and clinically relevant superiority for arm C at IA1 (DCO 06-June-2025, maturity 61.5%). Median OS was not reached (95% CI: NR, NR) for arm C and was 41.7 months (95% CI: 31.8, NR) for arm B. The hazard ratio for death was 0.50 (95% CI: 0.33, 0.74; p=0.0002). The OS KM curves separated from randomization and remained separated over time. The results were consistent across all subgroups. This is considered to represent a robust survival benefit. The final EV-303/KEYNOTE-905 Overall survival study results should be provided post-approval as a Recommendation (REC).

For the cisplatin-eligible group, the HR was below 1 with a HR of 0.87 (95% CI 0.28, 2.76). This subgroup (18.3% of ITT2) has a better prognosis than the cisplatin-ineligible group, constituting a biological rationale which could explain a lower absolute magnitude of benefit. However, the subgroup is also small and therefore the results of this subgroup analysis are not considered robust enough to restrict the sought indication. The results of the OS sensitivity analysis adjusted for PD-L1 expression and unstratified OS analysis were consistent with the results of the primary analysis.

The secondary endpoint pathological complete response was also in favour of arm C. The pCR rate (based on BICR) was 57.1% versus 8.6% (difference in response rates of 48.3%; 95% CI: 39.5, 56.5; p < 0.000001; 1-sided p-value boundary of 0.00025).

Overall, the sensitivity analyses performed are considered appropriate and were supportive and confirmatory of the primary and secondary endpoint results.

Subsequent Oncological Therapies

There was a higher proportion in arm B who received adjuvant therapy and oncologic therapy for recurrent disease. As described, the protocol permitted adjuvant nivolumab in arm B, which can explain the much higher number of adjuvant therapy in arm B. A similar (and small) number received adjuvant chemotherapy in both arms. Among patients who underwent surgery and had recurrence, there were 19 and 63 potential candidates for subsequent therapy in the EV+Pembro arm and in the RC+PLND arm respectively. Of these, there were 8 (42.1%) and 46 (73.0%) respectively, who received subsequent therapy. Due to the small number of potential candidates in the experimental arm, the data do not permit an evaluation of whether Padcev could affect the suitability for subsequent therapy.

Wording of indication

Participants had to be deemed resectable to be included in the protocol and thus the perioperative EV + pembrolizumab regime should not indicated for downsizing an unresectable tumour. The finally agreed indication wording was updated to reflect resectable MIBC:

PADCEV, in combination with pembrolizumab, as neoadjuvant treatment and then continued after radical cystectomy as adjuvant treatment, is indicated for the treatment of adults with ***resectable*** *muscle invasive bladder cancer (MIBC) who are ineligible for cisplatin-containing chemotherapy.*

2.4.4. Conclusions on the clinical efficacy

The EV-303/Keynote-905 study met its primary and key secondary endpoint, showing a statistically significant and robust improvement in EFS and OS with perioperative enfortumab-vedotin in combination with pembrolizumab in patients with resectable MIBC, who are ineligible for or decline neoadjuvant cisplatin. The consistency of results across sensitivity analyses and central review further supports the robustness of the primary findings, notwithstanding the open-label design and the methodological concerns. Although the results are based on the first interim analysis, more mature data are not considered needed for the assessment, however as this is an early curative setting, final study results are expected to be submitted post-approval to further characterise the efficacy **(REC)**.

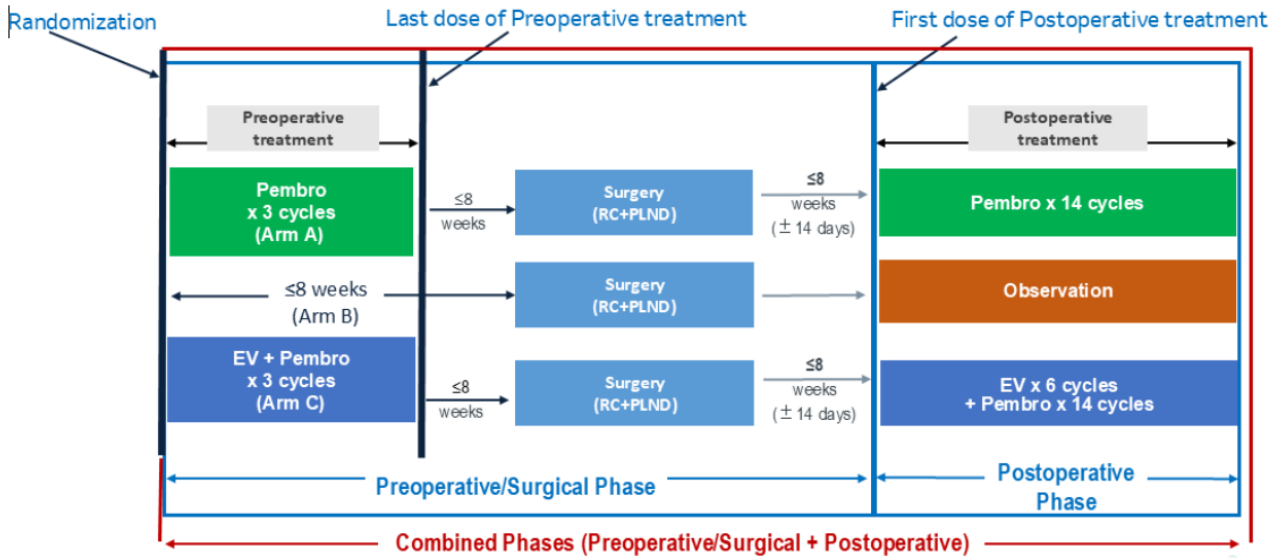
2.5. Clinical safety

Introduction

The MAH has provided the safety data of the perioperative combination of enfortumab vedotin with pembrolizumab and pembrolizumab monotherapy vs RC alone for the treatment of participants with MIBC who are ineligible for or decline cisplatin-based chemotherapy (KEYNOTE-905) based on IA1 (DCO: 06-JUN- 2025). Safety data have been also provided for treatment comparison, reported by phase (Preoperative, Preoperative/Surgical, and Postoperative phases).

Reference safety data from studies enfortumab vedotin in combination with pembrolizumab have been provided to assess the consistency of the safety of the combination emerged in KEYNOTE-905 study, as well as of enfortumab vedotin or pembrolizumab monotherapies to enable a comparison of the safety data of perioperative enfortumab vedotin in combination with pembrolizumab to the established safety profiles of the respective monotherapies.

Figure 19– Safety Analysis Schematic Diagram



EV=enfortumab vedotin, Pembro= pembrolizumab; RC + PLND=radical cystectomy + pelvic lymph node dissection;.

Note: Arm C includes preoperative and postoperative treatment with enfortumab vedotin and pembrolizumab as well as the surgical phase. Arm B includes only the surgical phase, without other perioperative treatment. Arm A includes preoperative and postoperative treatment with pembrolizumab as well as the surgical phase.

For assessment purposes, several segmentations of safety data populations are analysed. These are presented in the below table.

Table 38 Summary of Clinical Safety Datasets and Nomenclature

Dataset	Population	Nomenclature in Tables	Nomenclature in Text
KEYNOTE-905 perioperative enfortumab vedotin in combination with pembrolizumab and cystectomy	**(N=167)** Safety data from participants with MIBC who are ineligible for or decline cisplatin-based chemotherapy in KEYNOTE-905 receiving preoperative enfortumab vedotin + pembrolizumab followed by RC + PLND, followed by postoperative enfortumab vedotin + pembrolizumab	KN-905 EV + Pembro	perioperative EV + pembrolizumab
KEYNOTE-905 perioperative pembrolizumab and cystectomy	**(N=163)** Safety data from participants with MIBC who are ineligible for or decline cisplatin-based chemotherapy in KEYNOTE-905 receiving preoperative pembrolizumab followed by RC + PLND, followed by postoperative pembrolizumab	KN-905 Pembro mono	perioperative pembrolizumab
KEYNOTE-905 radical cystectomy	**(N=242)** Safety data from participants with MIBC who are ineligible for or decline cisplatin-based chemotherapy in KEYNOTE-905	KN-905 cystectomy	RC + PLND alone
Enfortumab vedotin in combination with pembrolizumab integrated safety dataset	**(N=564)** Pooled safety data from participants with locally advanced or metastatic UC who received pembrolizumab in combination with enfortumab vedotin (at the dose of 1.25 mg/kg) in EV-103/KEYNOTE869 Cohort K & A and dose escalation, and EV-302/KEYNOTEA39	EV + Pembro Combo ISD	EV + pembrolizumab ISD
Enfortumab vedotin monotherapy safety dataset	**(N=793)** Pooled safety data from participants with locally advanced or metastatic UC who were treated with enfortumab vedotin monotherapy (at the dose of 1.25 mg/kg) in EV-101, EV-102, EV-103/KEYNOTE869 Cohort K EV monotherapy arm, EV-201, EV-203, and EV-301	EV Mono ISD	EV mono ISD
Pembrolizumab monotherapy reference safety dataset	**(N=7631)** Pooled safety data from participants treated with pembrolizumab monotherapy, including 2559 participants with advanced melanoma from KEYNOTE-001, KEYNOTE-002, and KEYNOTE-006, KEYNOTE-054, and KEYNOTE-716; 2022 participants with NSCLC from KEYNOTE-001, KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042; 909 participants with HNSCC from KEYNOTE-012, KEYNOTE-040, KEYNOTE-048, and KEYNOTE-055; 636 participants with bladder cancer from KEYNOTE-045 and KEYNOTE-052; 488 participants with RCC from KEYNOTE-564; 475 participants with MSI-H tumors from KEYNOTE-158 and KEYNOTE-164; 389 participants with HL from KEYNOTE-013, KEYNOTE-087, and KEYNOTE-204; 153 participants with MSI-H CRC from KEYNOTE-177	Pembro Mono RSD	Pembrolizumab RSD
CRC=colorectal carcinoma; EV=enfortumab vedotin; HL=Hodgkin lymphoma; HNSCC=head and neck squamous cell carcinoma; MIBC=muscle-invasive bladder cancer; Mono=monotherapy; MSI-H=microsatellite instability-high; NSCLC=non-small cell lung cancer; Pembro=pembrolizumab; RC + PLND=radical cystectomy + pelvic lymph node dissection; RCC=renal cell carcinoma; RSD=reference safety dataset; ISD= integrated safety dataset; UC= urothelial carcinoma.			

Patient exposure

Safety analyses were conducted using the all participants as treated (APaT) population, which included all enrolled participants who received study treatment as of the DCO. The same dosing of Padcev (1.25mg/kg IV) was used across all trials in various segmentations of the safety population. When given in combination with pembrolizumab for the treatment of unresectable or metastatic urothelial cancer, the recommended dose of enfortumab vedotin is 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) administered as an intravenous infusion on Days 1 and 8 of every 3-week (21-day) cycle until disease progression or unacceptable toxicity.

Table 39 – Participant characteristics (APaT population)

	KN-905 EV + Pembro		KN-905 Pembro mono		KN-905 Cystectomy		EV + Pembro Combo ISD		EV Mono ISD		Pembro Mono RSD	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	167		163		242		564		793		7,631	
Sex												
Male	135	(80.8)	127	(77.9)	181	(74.8)	432	(76.6)	584	(73.6)	4,889	(64.1)
Female	32	(19.2)	36	(22.1)	61	(25.2)	132	(23.4)	209	(26.4)	2,742	(35.9)
Age (Years)												
<65	29	(17.4)	31	(19.0)	39	(16.1)	173	(30.7)	279	(35.2)	4,524	(59.3)
>=65	138	(82.6)	132	(81.0)	203	(83.9)	391	(69.3)	514	(64.8)	3,107	(40.7)
Mean	72.1		71.7		71.6		68.6		67.6		59.9	
SD	7.9		7.9		7.8		9.2		9.9		13.4	
Median	74.0		72.0		73.0		69.0		69.0		62.0	
Range	47 to 87		54 to 93		46 to 92		37 to 91		24 to 90		15 to 94	
Race												
American Indian Or Alaska Native	0	(0.0)	0	(0.0)	1	(0.4)	2	(0.4)	0	(0.0)	59	(0.8)
Asian	31	(18.6)	15	(9.2)	36	(14.9)	107	(19.0)	191	(24.1)	826	(10.8)
Black Or African American	2	(1.2)	1	(0.6)	4	(1.7)	9	(1.6)	12	(1.5)	146	(1.9)
Multiracial	4	(2.4)	0	(0.0)	6	(2.5)	0	(0.0)	0	(0.0)	86	(1.1)
Native Hawaiian Or Other Pacific Islander	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Not Reportable	0	(0.0)	0	(0.0)	0	(0.0)	22	(3.9)	18	(2.3)	0	(0.0)
Other	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.9)	3	(0.4)	0	(0.0)
Unknown	0	(0.0)	0	(0.0)	0	(0.0)	9	(1.6)	1	(0.1)	0	(0.0)
White	129	(77.2)	146	(89.6)	191	(78.9)	410	(72.7)	527	(66.5)	5,838	(76.5)
Missing	1	(0.6)	1	(0.6)	4	(1.7)	0	(0.0)	41	(5.2)	671	(8.8)
Ethnicity												
Hispanic Or Latino	8	(4.8)	3	(1.8)	13	(5.4)	64	(11.3)	42	(5.3)	604	(7.9)
Not Hispanic Or Latino	157	(94.0)	152	(93.3)	217	(89.7)	467	(82.8)	689	(86.9)	6,064	(79.5)
Not Reportable/Not Reported	2	(1.2)	8	(4.9)	12	(5.0)	22	(3.9)	52	(6.6)	808	(10.6)
Unknown	0	(0.0)	0	(0.0)	0	(0.0)	11	(2.0)	1	(0.1)	145	(1.9)
Missing	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	9	(1.1)	10	(0.1)
Age Category (year)												
<65	29	(17.4)	31	(19.0)	39	(16.1)	173	(30.7)	279	(35.2)	4,524	(59.3)
65-74	61	(36.5)	74	(45.4)	106	(43.8)	247	(43.8)	310	(39.1)	2,173	(28.5)
75-84	73	(43.7)	51	(31.3)	91	(37.6)	125	(22.2)	184	(23.2)	824	(10.8)
>=85	4	(2.4)	7	(4.3)	6	(2.5)	19	(3.4)	20	(2.5)	110	(1.4)
ECOG Performance Status												
[0] Normal Activity	100	(59.9)	73	(44.8)	122	(50.4)	273	(48.4)	284	(35.8)	4,016	(52.6)
[1] Symptoms	46	(27.5)	53	(32.5)	82	(33.9)	258	(45.7)	485	(61.2)	3,440	(45.1)
[2] Ambulatory	21	(12.6)	37	(22.7)	38	(15.7)	33	(5.9)	24	(3.0)	167	(2.2)
Other/Missing	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	8	(0.1)
Geographic Region												
US	21	(12.6)	18	(11.0)	34	(14.0)	191	(33.9)	414	(52.2)	2,296	(30.1)
EU	76	(45.5)	73	(44.8)	99	(40.9)	173	(30.7)	143	(18.0)	2,856	(37.4)
Rest of the World	70	(41.9)	72	(44.2)	109	(45.0)	200	(35.5)	236	(29.8)	2,479	(32.5)

SD=Standard deviation.
Western Europe includes countries in the European Economic Area, United Kingdom, and Switzerland.

Table 40 - Other Participants Baseline Characteristics (APaT Population)

	KN-905 EV + Pembro		KN-905 Pembro mono		KN-905 Cystectomy		EV + Pembro Combo ISD		EV Mono ISD	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	167		163		242		564		793	
Renal function based on CrCL (mL/min)										
CrCL: >= 60 mL/min	67	(40.1)	61	(37.4)	94	(38.8)	292	(51.8)	397	(50.1)
CrCL: >= 30 and < 60 mL/min	100	(59.9)	101	(62.0)	146	(60.3)	263	(46.6)	365	(46.0)
CrCL: < 30 mL/min	0	(0.0)	1	(0.6)	1	(0.4)	9	(1.6)	25	(3.2)
Missing	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	6	(0.8)
Weight (kg)										
<= 100 kg	149	(89.2)	149	(91.4)	229	(94.6)	510	(90.4)	735	(92.7)
> 100 kg	18	(10.8)	14	(8.6)	13	(5.4)	53	(9.4)	58	(7.3)
Missing	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Participants with data	167		163		242		563		793	
Mean	76.5		75.6		75.0		76.4		75.7	
SD	18.2		17.8		15.5		18.3		16.9	
Median	75.0		73.5		73.9		75.9		74.8	
Range	38.0 to 140.0		38.2 to 150.0		43.8 to 142.2		30.4 to 172.3		36.9 to 146.5	
Body Mass Index (kg/m2)										
< 25 kg/m2	66	(39.5)	76	(46.6)	99	(40.9)	258	(45.7)	352	(44.4)
25 to < 30 kg/m2	69	(41.3)	56	(34.4)	93	(38.4)	183	(32.4)	310	(39.1)
>= 30 kg/m2	32	(19.2)	31	(19.0)	50	(20.7)	120	(21.3)	131	(16.5)
Missing	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.5)	0	(0.0)
Participants with data	167		163		242		561		793	
Mean	25.9		25.8		26.0		26.3		26.0	
SD	5.0		5.2		4.5		5.0		4.6	
Median	26.0		25.0		25.0		25.6		25.5	
Range	14.0 to 47.0		16.0 to 43.0		16.0 to 46.0		13.7 to 55.3		15.8 to 43.0	
HbA1c (%)										
Normal: <5.7	68	(40.7)	32	(19.6)	78	(32.2)	262	(46.5)	272	(34.3)
Prediabetes: >=5.7 - < 6.5	67	(40.1)	34	(20.9)	62	(25.6)	210	(37.2)	264	(33.3)
Diabetes: >=6.5	28	(16.8)	14	(8.6)	18	(7.4)	51	(9.0)	83	(10.5)
Missing	4	(2.4)	83	(50.9)	84	(34.7)	41	(7.3)	174	(21.9)
Participants with data	163		80		158		523		619	
Mean	5.9		6.3		5.7		5.5		5.8	
SD	0.7		3.7		0.6		1.0		0.6	
Median	5.8		5.8		5.7		5.6		5.7	
Range	4.4 to 9.1		4.3 to 38.0		4.1 to 7.8		2.5 to 9.7		4.0 to 10.3	

SD=Standard deviation.
CrCl=creatinine clearance, HbA1c=hemoglobin A1c.
kg=kilogram, mL/min=milliliters per minute, m2=square meter.
Database cutoff date for KN905: 06JUN2025.
The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Source: [ISS: adam-adsl]

Table 41 - Summary of Drug Exposure (APaT Population)

	KN-905 EV + Pembro (N=167)	KN-905 Pembro mono (N=163)	EV + Pembro Combo ISD (N=564)	EV Mono ISD (N=793)	Pembro Mono RSD (N=7631)
Duration On Treatment (months)[a]					
n	167	163	564	793	7631
Mean (SD)	7.7 (5.3)	8.2 (5.4)	12.3 (9.4)	6.8 (7.7)	7.9 (6.9)
Median	6.3	7.9	9.4	4.7	5.8
Range	0.03 to 19.7	0.03 to 19.8	0.3 to 45.9	0.3 to 65.4	0.03 to 38.0
Number of Cycles [b]					
n	167	163	564	NA	7631
Mean (SD)	8.3 (6.2)	9.5 (6.4)	16.2 (12.6)		12.3 (10.1)
Median	6.0	8.0	12.0		9.0
Range	1.0 to 17.0	1.0 to 17.0	1.0 to 54.0		1.0 to 59.0

[a] Duration on Treatment (months): For KN905 and Pembro Mono RSD, duration = (last treatment date - first treatment date + 1) / 30.4367; For any drug in EV-103 and EV-302 studies, duration = (min(initial treatment date of the last cycle + 20, cutoff date, death date) - first treatment date + 1) / 30.4375; For other EV studies, duration = (min(initial treatment date of the last cycle + 27, cutoff date, death date)–first treatment date + 1) / 30.4375.
[b] Number of dosing cycles are not summarized for '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).
Database cutoff date for KN905: 06JUN2025.

Adverse events

Table 42 - Adverse Event Summary (APaT Population)

	KN-905 EV + Pembro	KN-905 Pembro mono	KN-905 Cystectomy	EV + Pembro Combo ISD	EV Mono ISD	Pembro Mono RSD

	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	167		163		242		564		793		7,631	
with one or more adverse events	167	(100.0)	159	(97.5)	152	(62.8)	563	(99.8)	786	(99.1)	7,375	(96.6)
with no adverse event	0	(0.0)	4	(2.5)	90	(37.2)	1	(0.2)	7	(0.9)	256	(3.4)
with drug-related[a] adverse events	154	(92.2)	106	(65.0)	0	(0.0)	550	(97.5)	747	(94.2)	5,462	(71.6)
with toxicity grade 3-5 adverse events	119	(71.3)	116	(71.2)	98	(40.5)	435	(77.1)	565	(71.2)	3,514	(46.0)
with toxicity grade 3-5 drug-related adverse events	76	(45.5)	38	(23.3)	0	(0.0)	330	(58.5)	404	(50.9)	1,208	(15.8)
with serious adverse events	97	(58.1)	107	(65.6)	94	(38.8)	295	(52.3)	363	(45.8)	2,742	(35.9)
with serious drug-related adverse events	33	(19.8)	28	(17.2)	0	(0.0)	155	(27.5)	162	(20.4)	840	(11.0)
who died	13	(7.8)	16	(9.8)	12	(5.0)	30	(5.3)	56	(7.1)	346	(4.5)
who died due to a drug-related adverse event	2	(1.2)	2	(1.2)	0	(0.0)	9	(1.6)	17	(2.1)	42	(0.6)
discontinued any drug due to an adverse event	81	(48.5)	45	(27.6)	0	(0.0)	279	(49.5)	168	(21.2)	1,066	(14.0)
discontinued	57	(34.1)	45	(27.6)	NA		177	(31.4)	NA		1,066	(14.0)

Pembrolizumab												
discontinued EV	69	(41.3)	NA		NA		238	(42.2)	168	(21.2)	NA	
discontinued any drug due to a drug-related adverse event	62	(37.1)	32	(19.6)	0	(0.0)	252	(44.7)	120	(15.1)	639	(8.4)
discontinued Pembrolizumab	42	(25.1)	32	(19.6)	NA		148	(26.2)	NA		639	(8.4)
discontinued EV	51	(30.5)	NA		NA		209	(37.1)	120	(15.1)	NA	
discontinued any drug due to a serious adverse event	31	(18.6)	33	(20.2)	0	(0.0)	84	(14.9)	80	(10.1)	714	(9.4)
discontinued Pembrolizumab	26	(15.6)	33	(20.2)	NA		82	(14.5)	NA		714	(9.4)
discontinued EV	27	(16.2)	NA		NA		59	(10.5)	80	(10.1)	NA	
discontinued any drug due to a serious drug-related adverse event	16	(9.6)	20	(12.3)	0	(0.0)	62	(11.0)	45	(5.7)	347	(4.5)
discontinued Pembrolizumab	13	(7.8)	20	(12.3)	NA		60	(10.6)	NA		347	(4.5)
discontinued EV	12	(7.2)	NA		NA		36	(6.4)	45	(5.7)	NA	

[a] Determined by the investigator to be related to the drug.

Treatment includes study medications and surgery.

For KN905, EV + Pembro Combo ISD, and Pembro Mono RSD, non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.

For EV Mono ISD, non-serious adverse events and serious adverse events up to 30 days of the last treatment are included.

For Pembro and EV+Pembro studies, MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

Grades are based on NCI CTCAE version 4.03.

Database cutoff date for KN905: 06JUN2025.

Table 43 - Participants With Adverse Events by Decreasing Frequency of Preferred Term (Incidence ≥ 10% in One or More Treatment Groups) (APaT Population)

	KN-905 EV + Pembro		KN-905 Pembro mono		KN-905 Cystectomy		EV + Pembro Combo ISD		EV Mono ISD		Pembro Mono RSD	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	167		163		242		564		793		7,631	
with one or more adverse events	167	(100.0)	159	(97.5)	152	(62.8)	563	(99.8)	785	(99.0)	7,375	(96.6)
with no adverse events	0	(0.0)	4	(2.5)	90	(37.2)	1	(0.2)	8	(1.0)	256	(3.4)
Pruritus	79	(47.3)	28	(17.2)	1	(0.4)	236	(41.8)	265	(33.4)	1,435	(18.8)
Alopecia	58	(34.7)	1	(0.6)	0	(0.0)	217	(38.5)	378	(47.7)	118	(1.5)
Diarrhoea	57	(34.1)	23	(14.1)	7	(2.9)	227	(40.2)	310	(39.1)	1,678	(22.0)
Fatigue	54	(32.3)	26	(16.0)	12	(5.0)	232	(41.1)	371	(46.8)	2,368	(31.0)
Anaemia	51	(30.5)	50	(30.7)	29	(12.0)	153	(27.1)	232	(29.3)	982	(12.9)
Decreased appetite	47	(28.1)	23	(14.1)	9	(3.7)	195	(34.6)	374	(47.2)	1,312	(17.2)
Dysgeusia	47	(28.1)	5	(3.1)	0	(0.0)	138	(24.5)	241	(30.4)	150	(2.0)
Constipation	46	(27.5)	24	(14.7)	20	(8.3)	158	(28.0)	229	(28.9)	1,179	(15.5)
Nausea	43	(25.7)	21	(12.9)	16	(6.6)	166	(29.4)	300	(37.8)	1,534	(20.1)
Rash	42	(25.1)	16	(9.8)	2	(0.8)	16	(2.8)	92	(11.6)	1,175	(15.4)
Aspartate aminotransferase increased	40	(24.0)	16	(9.8)	2	(0.8)	91	(16.1)	136	(17.2)	538	(7.1)
Urinary tract infection	40	(24.0)	46	(28.2)	22	(9.1)	131	(23.2)	125	(15.8)	511	(6.7)
Weight decreased	33	(19.8)	18	(11.0)	11	(4.5)	210	(37.2)	200	(25.2)	628	(8.2)
Alanine aminotransferase increased	32	(19.2)	14	(8.6)	3	(1.2)	98	(17.4)	101	(12.7)	572	(7.5)
Asthenia	29	(17.4)	23	(14.1)	5	(2.1)	99	(17.6)	82	(10.3)	880	(11.5)
Rash maculo-papular	27	(16.2)	4	(2.5)	1	(0.4)	204	(36.2)	187	(23.6)	295	(3.9)
Dry skin	25	(15.0)	8	(4.9)	1	(0.4)	103	(18.3)	173	(21.8)	394	(5.2)
Hypothyroidism	24	(14.4)	27	(16.6)	0	(0.0)	65	(11.5)	7	(0.9)	937	(12.3)
Peripheral sensory neuropathy	23	(13.8)	0	(0.0)	1	(0.4)	308	(54.6)	305	(38.5)	83	(1.1)
Hyperglycaemia	21	(12.6)	9	(5.5)	2	(0.8)	95	(16.8)	118	(14.9)	360	(4.7)
Blood creatinine increased	19	(11.4)	22	(13.5)	8	(3.3)	51	(9.0)	83	(10.5)	358	(4.7)
Prostate cancer	19	(11.4)	18	(11.0)	22	(9.1)	1	(0.2)	0	(0.0)	5	(0.1)
Pyrexia	19	(11.4)	18	(11.0)	7	(2.9)	104	(18.4)	148	(18.7)	934	(12.2)
Dry mouth	18	(10.8)	3	(1.8)	1	(0.4)	60	(10.6)	65	(8.2)	388	(5.1)
Insomnia	18	(10.8)	3	(1.8)	8	(3.3)	62	(11.0)	101	(12.7)	528	(6.9)
Abdominal pain	17	(10.2)	13	(8.0)	17	(7.0)	72	(12.8)	122	(15.4)	671	(8.8)
Neuropathy peripheral	17	(10.2)	0	(0.0)	0	(0.0)	0	(0.0)	33	(4.2)	146	(1.9)
Hypokalaemia	16	(9.6)	16	(9.8)	8	(3.3)	57	(10.1)	88	(11.1)	324	(4.2)
Lacrimation increased	16	(9.6)	0	(0.0)	0	(0.0)	57	(10.1)	109	(13.7)	55	(0.7)
Neutropenia	16	(9.6)	4	(2.5)	0	(0.0)	61	(10.8)	60	(7.6)	82	(1.1)
Oedema peripheral	16	(9.6)	11	(6.7)	4	(1.7)	98	(17.4)	138	(17.4)	630	(8.3)
Vomiting	15	(9.0)	9	(5.5)	8	(3.3)	81	(14.4)	148	(18.7)	945	(12.4)
Dizziness	12	(7.2)	6	(3.7)	0	(0.0)	66	(11.7)	92	(11.6)	564	(7.4)
Hyponatraemia	12	(7.2)	8	(4.9)	1	(0.4)	57	(10.1)	90	(11.3)	387	(5.1)
Haematuria	11	(6.6)	15	(9.2)	1	(0.4)	82	(14.5)	101	(12.7)	189	(2.5)
Arthralgia	10	(6.0)	7	(4.3)	1	(0.4)	99	(17.6)	95	(12.0)	1,449	(19.0)
Dry eye	10	(6.0)	3	(1.8)	0	(0.0)	82	(14.5)	101	(12.7)	142	(1.9)
Cough	9	(5.4)	8	(4.9)	2	(0.8)	76	(13.5)	104	(13.1)	1,392	(18.2)
Dyspnoea	9	(5.4)	4	(2.5)	3	(1.2)	86	(15.2)	102	(12.9)	1,130	(14.8)
COVID-19	8	(4.8)	15	(9.2)	1	(0.4)	78	(13.8)	14	(1.8)	6	(0.1)
Headache	8	(4.8)	4	(2.5)	0	(0.0)	47	(8.3)	49	(6.2)	946	(12.4)
Hyperthyroidism	8	(4.8)	19	(11.7)	0	(0.0)	26	(4.6)	2	(0.3)	398	(5.2)
Back pain	5	(3.0)	9	(5.5)	1	(0.4)	75	(13.3)	91	(11.5)	847	(11.1)
Rash macular	0	(0.0)	1	(0.6)	0	(0.0)	64	(11.3)	21	(2.6)	49	(0.6)

Every participant is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
For KN905, EV + Pembro Combo ISD, and Pembro Mono RSD, non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.
For EV Mono ISD, non-serious adverse events and serious adverse events up to 30 days of the last treatment are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Database cutoff date for KN905: 06JUN2025.

Table 44 Participants With Drug-Related Adverse Events by Decreasing Frequency of Preferred Term (Incidence ≥4% in KN-905 EV + Pembrolizumab Group) (APaT Population)

	KN-905 EV + Pembro		KN-905 Pembro mono		KN-905 Cystectomy		EV + Pembro Combo ISD		EV Mono ISD		Pembro Mono RSD	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	167		163		242		564		793		7,631	
with one or more adverse events	154	(92.2)	106	(65.0)	0	(0.0)	550	(97.5)	747	(94.2)	5,462	(71.6)
with no adverse events	13	(7.8)	57	(35.0)	242	(100.0)	14	(2.5)	46	(5.8)	2,169	(28.4)
Pruritus	67	(40.1)	18	(11.0)	0	(0.0)	225	(39.9)	243	(30.6)	1,143	(15.0)
Alopecia	54	(32.3)	0	(0.0)	0	(0.0)	204	(36.2)	363	(45.8)	57	(0.7)
Fatigue	44	(26.3)	15	(9.2)	0	(0.0)	197	(34.9)	315	(39.7)	1,476	(19.3)
Dysgeusia	43	(25.7)	2	(1.2)	0	(0.0)	123	(21.8)	233	(29.4)	79	(1.0)
Rash	41	(24.6)	16	(9.8)	0	(0.0)	14	(2.5)	84	(10.6)	884	(11.6)
Diarrhoea	38	(22.8)	11	(6.7)	0	(0.0)	166	(29.4)	228	(28.8)	904	(11.8)
Decreased appetite	33	(19.8)	3	(1.8)	0	(0.0)	157	(27.8)	293	(36.9)	525	(6.9)
Aspartate aminotransferase increased	32	(19.2)	10	(6.1)	0	(0.0)	82	(14.5)	113	(14.2)	312	(4.1)
Nausea	27	(16.2)	2	(1.2)	0	(0.0)	127	(22.5)	243	(30.6)	675	(8.8)
Alanine aminotransferase increased	25	(15.0)	9	(5.5)	0	(0.0)	89	(15.8)	85	(10.7)	336	(4.4)
Hypothyroidism	23	(13.8)	20	(12.3)	0	(0.0)	62	(11.0)	2	(0.3)	810	(10.6)
Rash maculo-papular	23	(13.8)	3	(1.8)	0	(0.0)	196	(34.8)	176	(22.2)	237	(3.1)
Peripheral sensory neuropathy	22	(13.2)	0	(0.0)	0	(0.0)	299	(53.0)	291	(36.7)	35	(0.5)
Dry skin	17	(10.2)	6	(3.7)	0	(0.0)	84	(14.9)	141	(17.8)	218	(2.9)
Neuropathy peripheral	17	(10.2)	0	(0.0)	0	(0.0)	0	(0.0)	31	(3.9)	54	(0.7)
Asthenia	16	(9.6)	8	(4.9)	0	(0.0)	73	(12.9)	55	(6.9)	491	(6.4)
Constipation	14	(8.4)	1	(0.6)	0	(0.0)	42	(7.4)	102	(12.9)	184	(2.4)
Dry mouth	13	(7.8)	3	(1.8)	0	(0.0)	40	(7.1)	44	(5.5)	209	(2.7)
Neutropenia	13	(7.8)	0	(0.0)	0	(0.0)	57	(10.1)	56	(7.1)	49	(0.6)
Weight decreased	13	(7.8)	0	(0.0)	0	(0.0)	113	(20.0)	136	(17.2)	148	(1.9)
Hyperglycaemia	12	(7.2)	2	(1.2)	0	(0.0)	63	(11.2)	74	(9.3)	62	(0.8)
Anaemia	10	(6.0)	2	(1.2)	0	(0.0)	88	(15.6)	150	(18.9)	234	(3.1)
Dry eye	10	(6.0)	0	(0.0)	0	(0.0)	62	(11.0)	79	(10.0)	76	(1.0)
Lacrimation increased	9	(5.4)	0	(0.0)	0	(0.0)	44	(7.8)	88	(11.1)	22	(0.3)
Taste disorder	9	(5.4)	0	(0.0)	0	(0.0)	16	(2.8)	28	(3.5)	35	(0.5)
Paraesthesia	8	(4.8)	1	(0.6)	0	(0.0)	32	(5.7)	30	(3.8)	63	(0.8)

Table 45 - Participants with grade 3 - 5 Adverse Events by decreasing frequency of PT (Incidence ≥ 5% in one or more treatment groups) (APaT Population)

	KN-905 EV + Pembro		KN-905 Pembro mono		KN-905 Cystectomy		EV + Pembro Combo ISD		EV Mono ISD		Pembro Mono RSD	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	167		163		242		564		793		7,631	
with one or more adverse events	119	(71.3)	116	(71.2)	98	(40.5)	435	(77.1)	565	(71.2)	3,514	(46.0)
with no adverse events	48	(28.7)	47	(28.8)	144	(59.5)	129	(22.9)	228	(28.8)	4,117	(54.0)
Urinary tract infection	20	(12.0)	18	(11.0)	18	(7.4)	38	(6.7)	38	(4.8)	85	(1.1)
Anaemia	15	(9.0)	8	(4.9)	15	(6.2)	52	(9.2)	77	(9.7)	275	(3.6)
Neutropenia	10	(6.0)	0	(0.0)	0	(0.0)	36	(6.4)	46	(5.8)	21	(0.3)
Acute kidney injury	7	(4.2)	4	(2.5)	4	(1.7)	34	(6.0)	36	(4.5)	65	(0.9)
Diarrhoea	7	(4.2)	3	(1.8)	2	(0.8)	30	(5.3)	36	(4.5)	114	(1.5)
Hyperglycaemia	7	(4.2)	2	(1.2)	1	(0.4)	45	(8.0)	58	(7.3)	83	(1.1)
Fatigue	4	(2.4)	4	(2.5)	1	(0.4)	32	(5.7)	59	(7.4)	166	(2.2)
Hyponatraemia	4	(2.4)	1	(0.6)	1	(0.4)	30	(5.3)	47	(5.9)	169	(2.2)
Rash maculo-papular	4	(2.4)	2	(1.2)	0	(0.0)	54	(9.6)	43	(5.4)	23	(0.3)

Every participant is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
For KN905, EV + Pembro Combo ISD, and Pembro Mono RSD, non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.
For EV Mono ISD, non-serious adverse events and serious adverse events up to 30 days of the last treatment are included.
For Pembro and EV+Pembro studies, MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.03.
Database cutoff date for KN905: 06JUN2025.

***Table 46* Participants With Adverse Events by Maximum Toxicity Grade (APaT Population)**

	KN-905 EV + Pembro		KN-905 Pembro mono		KN-905 Cystectomy		EV + Pembro Combo ISD		EV Mono ISD		Pembro Mono RSD	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	167		163		242		564		793		7,631	
with one or more adverse events	167	(100.0)	159	(97.5)	152	(62.8)	563	(99.8)	786	(99.1)	7,375	(96.6)
Grade 1	6	(3.6)	10	(6.1)	20	(8.3)	6	(1.1)	18	(2.3)	1,028	(13.5)
Grade 2	42	(25.1)	33	(20.2)	34	(14.0)	122	(21.6)	203	(25.6)	2,833	(37.1)
Grade 3	81	(48.5)	83	(50.9)	66	(27.3)	335	(59.4)	439	(55.4)	2,731	(35.8)
Grade 4	25	(15.0)	17	(10.4)	20	(8.3)	70	(12.4)	70	(8.8)	438	(5.7)
Grade 5	13	(7.8)	16	(9.8)	12	(5.0)	30	(5.3)	56	(7.1)	345	(4.5)
with no adverse events	0	(0.0)	4	(2.5)	90	(37.2)	1	(0.2)	7	(0.9)	256	(3.4)

Table 47 – Tabulated summary of adverse events by frequency category

Frequency	**Monotherapy**	**In combination with pembrolizumab**
Infections and infestations		
Common	Sepsis, pneumonia	Sepsis, pneumonia
Blood and lymphatic system disorders		
Very common	Anaemia	Anaemia
Common	Thrombocytopenia	Thrombocytopenia
Not known[1]	Neutropenia, febrile neutropenia, neutrophil count decreased	Neutropenia, febrile neutropenia, neutrophil count decreased
Endocrine disorders		
Very common		Hypothyroidism
Metabolism and nutrition disorders		
Very common	Hyperglycaemia, decreased appetite	Hyperglycaemia, decreased appetite
Not known[1]	Diabetic ketoacidosis	Diabetic ketoacidosis
Nervous system disorders		
Very common	Peripheral sensory neuropathy, dysgeusia	Peripheral sensory neuropathy, dysgeusia
Common	Neuropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, paraesthesia, hypoaesthesia, gait disturbance, muscular weakness	Neuropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, paraesthesia, hypoaesthesia, gait disturbance, muscular weakness, neurotoxicity
Uncommon	Demyelinating polyneuropathy, polyneuropathy, neurotoxicity, motor dysfunction, dysaesthesia, muscle atrophy, neuralgia, peroneal nerve palsy,	Dysaesthesia, polyneuropathy, myasthenia gravis, neuralgia, peroneal nerve palsy, skin burning sensation

Frequency	Monotherapy	In combination with pembrolizumab
	sensory loss, skin burning sensation, burning sensation	
Eye disorders		
Very common	Dry eye	Dry eye
Respiratory, thoracic and mediastinal disorders		
Common	Pneumonitis/ILD[2]	Pneumonitis/ILD[2]
Gastrointestinal disorders		
Very common	Diarrhoea, vomiting, nausea	Diarrhoea, vomiting, nausea
Skin and subcutaneous tissue disorders		
Very common	Alopecia, pruritus, rash, rash maculo-papular, dry skin	Alopecia, pruritus, rash maculo-papular, dry skin
Common	Drug eruption, skin exfoliation, conjunctivitis, dermatitis bullous, blister, stomatitis, palmar-plantar erythrodysesthesia syndrome, eczema, erythaema, rash erythaematous, rash macular, rash papular, rash pruritic, rash vesicular	Rash, skin exfoliation, conjunctivitis, dermatitis bullous, blister, stomatitis, palmar-plantar erythrodysesthesia syndrome, eczema, erythaema, rash erythaematous, rash macular, rash papular, rash pruritic, rash vesicular, dermatitis
Uncommon	Dermatitis exfoliative generalised, erythaema multiforme, exfoliative rash, pemphigoid, rash maculovesicular, dermatitis, dermatitis allergic, dermatitis contact, intertrigo, skin irritation, stasis dermatitis, blood blister	Drug eruption, dermatitis exfoliative generalised, erythaema multiforme, exfoliative rash, pemphigoid, dermatitis allergic, dermatitis contact, intertrigo, skin irritation, stasis dermatitis
Not known[1]	Toxic epidermal necrolysis, skin hyperpigmentation, skin discolouration, pigmentation disorder, Stevens-Johnson syndrome, epidermal necrosis, symmetrical drug-related intertriginous and flexural exanthaema	Toxic epidermal necrolysis, skin hyperpigmentation, skin discolouration, pigmentation disorder, Stevens-Johnson syndrome, epidermal necrosis, symmetrical drug-related intertriginous and flexural exanthaema
Musculoskeletal and connective tissue disorders		
Uncommon		Myositis
General disorders and administration site conditions		
Very common	Fatigue	Fatigue
Common	Infusion site extravasation	Infusion site extravasation
Investigations		

Frequency	Monotherapy	In combination with pembrolizumab
Very common	Alanine aminotransferase increased, aspartate aminotransferase increased, weight decreased	Alanine aminotransferase increased, aspartate aminotransferase increased, weight decreased
Common		Lipase increased
Injury, poisoning and procedural complications		
Common	Infusion related reaction	Infusion related reaction

[1]Based on global post-marketing experience.

[2]Includes: acute respiratory distress syndrome, autoimmune lung disease, immune-mediated lung disease, interstitial lung disease, lung opacity, organising pneumonia, pneumonitis, pulmonary fibrosis, pulmonary toxicity, pulmonary sarcoidosis and sarcoidosis.

Serious adverse event/deaths/other significant events

2.5.1. SAEs

Table 48 - Participants With Serious Adverse Events by Decreasing Frequency of Preferred Term (Incidence ≥ 2% in One or More Treatment Groups) (APaT Population)

	KN-905 EV + Pembro		KN-905 Pembro mono		KN-905 Cystectomy		EV + Pembro Combo ISD		EV Mono ISD		Pembro Mono RSD	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	167		163		242		564		793		7,631	
with one or more adverse events	97	(58.1)	107	(65.6)	94	(38.8)	295	(52.3)	363	(45.8)	2,742	(35.9)
with no adverse events	70	(41.9)	56	(34.4)	148	(61.2)	269	(47.7)	430	(54.2)	4,889	(64.1)
Urinary tract infection	17	(10.2)	15	(9.2)	17	(7.0)	25	(4.4)	31	(3.9)	67	(0.9)
Acute kidney injury	8	(4.8)	5	(3.1)	3	(1.2)	34	(6.0)	50	(6.3)	65	(0.9)
Urosepsis	7	(4.2)	3	(1.8)	8	(3.3)	9	(1.6)	4	(0.5)	27	(0.4)
Pyelonephritis	6	(3.6)	7	(4.3)	2	(0.8)	5	(0.9)	3	(0.4)	10	(0.1)
Pneumonia	5	(3.0)	5	(3.1)	2	(0.8)	15	(2.7)	30	(3.8)	272	(3.6)
Sepsis	5	(3.0)	7	(4.3)	7	(2.9)	13	(2.3)	24	(3.0)	56	(0.7)
Diarrhoea	4	(2.4)	1	(0.6)	1	(0.4)	19	(3.4)	17	(2.1)	70	(0.9)
Haematuria	4	(2.4)	4	(2.5)	0	(0.0)	12	(2.1)	15	(1.9)	17	(0.2)
Intestinal obstruction	4	(2.4)	4	(2.5)	2	(0.8)	2	(0.4)	1	(0.1)	19	(0.2)
Small intestinal obstruction	4	(2.4)	1	(0.6)	2	(0.8)	2	(0.4)	7	(0.9)	19	(0.2)
Prostate cancer	3	(1.8)	13	(8.0)	11	(4.5)	0	(0.0)	0	(0.0)	5	(0.1)
Hydronephrosis	1	(0.6)	5	(3.1)	3	(1.2)	2	(0.4)	3	(0.4)	8	(0.1)
Hyperglycaemia	1	(0.6)	1	(0.6)	0	(0.0)	8	(1.4)	17	(2.1)	12	(0.2)
Postoperative wound infection	1	(0.6)	4	(2.5)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Pyelonephritis acute	1	(0.6)	4	(2.5)	2	(0.8)	3	(0.5)	1	(0.1)	4	(0.1)
Pneumonitis	0	(0.0)	0	(0.0)	0	(0.0)	14	(2.5)	2	(0.3)	136	(1.8)

Every participant is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
For KN905, EV + Pembro Combo ISD, and Pembro Mono RSD, serious adverse events up to 90 days of last treatment are included. For EV Mono ISD, serious adverse events up to 30 days of the last treatment are included.
For Pembro and EV+Pembro studies, MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Database cutoff date for KN905: 06JUN2025.

Table 49 Participants With Drug-Related Serious Adverse Events by Decreasing Frequency of Preferred Term (Incidence > 0% in KN-905 EV+Pembro Group) (APaT Population)

	KN-905 EV + Pembro		KN-905 Pembro mono		KN-905 Cystectomy		EV + Pembro Combo ISD		EV Mono ISD		Pembro Mono RSD	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	167		163		242		564		793		7,631	
with one or more adverse events	33	(19.8)	28	(17.2)	0	(0.0)	155	(27.5)	162	(20.4)	840	(11.0)
with no adverse events	134	(80.2)	135	(82.8)	242	(100.0)	409	(72.5)	631	(79.6)	6,791	(89.0)
Acute kidney injury	3	(1.8)	2	(1.2)	0	(0.0)	13	(2.3)	14	(1.8)	19	(0.2)
Diarrhoea	3	(1.8)	1	(0.6)	0	(0.0)	13	(2.3)	12	(1.5)	44	(0.6)
Asthenia	2	(1.2)	0	(0.0)	0	(0.0)	4	(0.7)	2	(0.3)	6	(0.1)
Hepatic function abnormal	2	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.3)	4	(0.1)
Toxic epidermal necrolysis	2	(1.2)	0	(0.0)	0	(0.0)	3	(0.5)	0	(0.0)	0	(0.0)
Toxic skin eruption	2	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)
Urinary tract infection	2	(1.2)	0	(0.0)	0	(0.0)	1	(0.2)	3	(0.4)	0	(0.0)
Adrenal insufficiency	1	(0.6)	2	(1.2)	0	(0.0)	2	(0.4)	0	(0.0)	25	(0.3)
Autoimmune colitis	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Autoimmune hepatitis	1	(0.6)	1	(0.6)	0	(0.0)	1	(0.2)	0	(0.0)	23	(0.3)
Blood creatine phosphokinase increased	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Cellulitis	1	(0.6)	0	(0.0)	0	(0.0)	2	(0.4)	6	(0.8)	2	(0.0)
Cholecystitis acute	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)
Dermatitis exfoliative generalised	1	(0.6)	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)
Embolism	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Febrile neutropenia	1	(0.6)	0	(0.0)	0	(0.0)	4	(0.7)	9	(1.1)	0	(0.0)
Gastrooesophageal reflux disease	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Hepatitis	1	(0.6)	2	(1.2)	0	(0.0)	2	(0.4)	0	(0.0)	12	(0.2)
Hypokalaemia	1	(0.6)	0	(0.0)	0	(0.0)	2	(0.4)	1	(0.1)	3	(0.0)
Hypothyroidism	1	(0.6)	0	(0.0)	0	(0.0)	2	(0.4)	0	(0.0)	6	(0.1)
Intestinal obstruction	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Myasthenia gravis	1	(0.6)	1	(0.6)	0	(0.0)	3	(0.5)	0	(0.0)	3	(0.0)
Myocarditis	1	(0.6)	3	(1.8)	0	(0.0)	3	(0.5)	0	(0.0)	9	(0.1)
Pancreatitis chronic	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonia	1	(0.6)	0	(0.0)	0	(0.0)	3	(0.5)	9	(1.1)	19	(0.2)
Pruritus	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Rash	1	(0.6)	0	(0.0)	0	(0.0)	1	(0.2)	7	(0.9)	7	(0.1)
Renal impairment	1	(0.6)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.1)	1	(0.0)
Skin reaction	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Skin toxicity	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Toxic erythema of chemotherapy	1	(0.6)	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)
Tubulointerstitial nephritis	1	(0.6)	0	(0.0)	0	(0.0)	2	(0.4)	0	(0.0)	11	(0.1)
Type 2 diabetes mellitus	1	(0.6)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.1)	2	(0.0)
Urosepsis	1	(0.6)	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)
Vision blurred	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

2.5.2. Deaths

Table 50 - Participants With Adverse Events Resulting in Death by Decreasing Frequency of Preferred Term (Incidence > 0% in One or More Treatment Groups) (APaT Population)

	KN-905 EV + Pembro		KN-905 Pembro mono		KN-905 Cystectomy		EV + Pembro Combo ISD		EV Mono ISD		Pembro Mono RSD	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	167		163		242		564		793		7,631	
with one or more adverse events	13	-7.8	16	-9.8	12	-5	30	-5.3	37	-4.7	346	-4.5
with no adverse events	154	-92.2	147	-90.2	230	-95	534	-94.7	756	-95.3	7,285	-95.5
Sepsis	2	-1.2	2	-1.2	2	-0.8	3	-0.5	4	-0.5	11	-0.1
Small intestinal obstruction	2	-1.2	0	0	0	0	0	0	0	0	0	0
Death	1	-0.6	1	-0.6	3	-1.2	3	-0.5	0	0	49	-0.6
Haemorrhage intracranial	1	-0.6	0	0	0	0	0	0	0	0	1	0
Multiple organ dysfunction syndrome	1	-0.6	0	0	0	0	2	-0.4	6	-0.8	6	-0.1

Myasthenia gravis	1	-0.6	1	-0.6	0	0	0	0	0	0	0	0
Myocardial infarction	1	-0.6	0	0	0	0	0	0	0	0	6	-0.1
Pneumonia pseudomonal	1	-0.6	0	0	0	0	0	0	0	0	0	0
Road traffic accident	1	-0.6	0	0	0	0	0	0	0	0	0	0
Toxic epidermal necrolysis	1	-0.6	0	0	0	0	0	0	0	0	0	0
Urosepsis	1	-0.6	1	-0.6	0	0	0	0	0	0	5	-0.1
Abdominal sepsis	0	0	0	0	0	0	0	0	0	0	1	0
Accidental death	0	0	0	0	0	0	0	0	0	0	1	0
Acute coronary syndrome	0	0	0	0	0	0	0	0	1	-0.1	1	0
Acute graft versus host disease	0	0	0	0	0	0	0	0	0	0	1	0
Acute kidney injury	0	0	0	0	0	0	0	0	2	-0.3	3	0
Acute myeloid leukaemia	0	0	0	0	0	0	0	0	0	0	1	0
Acute myocardial infarction	0	0	0	0	0	0	0	0	0	0	1	0
Acute respiratory failure	0	0	0	0	0	0	2	-0.4	2	-0.3	5	-0.1
Adenocarcinoma gastric	0	0	0	0	0	0	0	0	0	0	1	0
Alcohol poisoning	0	0	0	0	0	0	0	0	0	0	1	0
Anaemia	0	0	0	0	0	0	0	0	0	0	1	0
Anaphylactic shock	0	0	0	0	0	0	0	0	0	0	1	0
Arterial injury	0	0	0	0	0	0	0	0	0	0	1	0
Arteriosclerosis coronary artery	0	0	1	-0.6	0	0	0	0	0	0	0	0
Aspiration	0	0	0	0	0	0	0	0	0	0	4	-0.1
Asthenia	0	0	0	0	0	0	1	-0.2	0	0	0	0
Atypical pneumonia	0	0	0	0	0	0	0	0	0	0	1	0
Autoinflammatory disease	0	0	0	0	0	0	0	0	0	0	1	0
Brain oedema	0	0	0	0	0	0	0	0	1	-0.1	1	0
COVID-19	0	0	0	0	0	0	1	-0.2	0	0	0	0
COVID-19 pneumonia	0	0	1	-0.6	1	-0.4	0	0	0	0	1	0
Cachexia	0	0	0	0	0	0	0	0	0	0	3	0
Cardiac arrest	0	0	1	-0.6	0	0	2	-0.4	2	-0.3	9	-0.1
Cardiac complication associated with device	0	0	0	0	0	0	0	0	0	0	1	0
Cardiac disorder	0	0	0	0	0	0	0	0	1	-0.1	0	0
Cardiac failure	0	0	0	0	0	0	1	-0.2	0	0	4	-0.1
Cardiac failure acute	0	0	1	-0.6	0	0	0	0	0	0	2	0
Cardiac failure congestive	0	0	0	0	0	0	0	0	0	0	2	0

Cardiac tamponade	0	0	0	0	0	0	0	0	0	0	1	0
Cardio-respiratory arrest	0	0	0	0	1	-0.4	1	-0.2	0	0	4	-0.1
Cardiopulmonary failure	0	0	0	0	0	0	0	0	0	0	2	0
Cellulitis	0	0	0	0	0	0	0	0	0	0	1	0
Cerebral haemorrhage	0	0	0	0	0	0	1	-0.2	0	0	1	0
Cerebrovascular accident	0	0	1	-0.6	0	0	0	0	0	0	5	-0.1
Cholangitis acute	0	0	0	0	1	-0.4	0	0	0	0	0	0
Chronic kidney disease	0	0	0	0	0	0	0	0	0	0	1	0
Chronic obstructive pulmonary disease	0	0	0	0	0	0	0	0	0	0	1	0
Clostridium difficile infection	0	0	0	0	0	0	0	0	0	0	1	0
Coma	0	0	0	0	0	0	0	0	0	0	1	0
Completed suicide	0	0	0	0	0	0	0	0	0	0	3	0
Diabetic ketoacidosis	0	0	1	-0.6	0	0	0	0	1	-0.1	0	0
Diarrhoea	0	0	0	0	0	0	1	-0.2	0	0	1	0
Diffuse alveolar damage	0	0	0	0	0	0	0	0	0	0	1	0
Disseminated intravascular coagulation	0	0	0	0	0	0	0	0	0	0	1	0
Diverticulitis	0	0	0	0	0	0	0	0	0	0	1	0
Drug reaction with eosinophilia and systemic symptoms	0	0	0	0	0	0	0	0	0	0	1	0
Duodenal obstruction	0	0	0	0	0	0	0	0	0	0	1	0
Duodenal perforation	0	0	0	0	0	0	0	0	0	0	1	0
Dyspnoea	0	0	0	0	0	0	0	0	2	-0.3	5	-0.1
Embolism	0	0	0	0	0	0	0	0	1	-0.1	5	-0.1
Encephalopathy	0	0	0	0	0	0	0	0	0	0	1	0
Euthanasia	0	0	0	0	0	0	0	0	0	0	1	0
Failure to thrive	0	0	0	0	0	0	0	0	0	0	1	0
Fall	0	0	0	0	0	0	0	0	0	0	1	0
Febrile neutropenia	0	0	0	0	0	0	0	0	0	0	1	0
Gastric haemorrhage	0	0	0	0	0	0	0	0	0	0	2	0
Gastric ulcer haemorrhage	0	0	0	0	0	0	0	0	0	0	2	0
Gastrointestinal perforation	0	0	0	0	0	0	0	0	0	0	2	0
General physical health deterioration	0	0	0	0	0	0	0	0	0	0	9	-0.1
Generalised oedema	0	0	0	0	0	0	0	0	0	0	1	0
Guillain-Barre syndrome	0	0	0	0	0	0	0	0	0	0	1	0

Haemoptysis	0	0	0	0	0	0	0	0	0	0	1	0
Haemorrhagic infarction	0	0	0	0	0	0	0	0	0	0	1	0
Haemorrhagic stroke	0	0	0	0	0	0	0	0	0	0	2	0
Haemothorax	0	0	0	0	0	0	0	0	0	0	1	0
Heat illness	0	0	0	0	0	0	0	0	1	-0.1	0	0
Hepatic failure	0	0	0	0	0	0	0	0	0	0	3	0
Hepatic function abnormal	0	0	0	0	0	0	0	0	1	-0.1	0	0
Hydrocephalus	0	0	0	0	0	0	1	-0.2	0	0	0	0
Hyperglycaemia	0	0	0	0	0	0	0	0	1	-0.1	1	0
Hypovolaemic shock	0	0	0	0	0	0	0	0	0	0	1	0
Hypoxia	0	0	0	0	0	0	0	0	0	0	1	0
Ileus paralytic	0	0	0	0	0	0	0	0	0	0	1	0
Immune-mediated lung disease	0	0	0	0	0	0	1	-0.2	0	0	0	0
Infectious pleural effusion	0	0	0	0	0	0	0	0	0	0	1	0
Interstitial lung disease	0	0	0	0	0	0	0	0	0	0	1	0
Intestinal ischaemia	0	0	0	0	0	0	0	0	0	0	1	0
Intestinal obstruction	0	0	0	0	0	0	0	0	0	0	1	0
Intestinal perforation	0	0	0	0	0	0	0	0	0	0	1	0
Ischaemic cardiomyopathy	0	0	0	0	0	0	0	0	0	0	1	0
Ischaemic stroke	0	0	0	0	0	0	0	0	0	0	1	0
Large intestine perforation	0	0	0	0	0	0	0	0	0	0	2	0
Lung neoplasm malignant	0	0	0	0	0	0	0	0	0	0	1	0
Lymphangiosis carcinomatosa	0	0	0	0	0	0	0	0	0	0	1	0
Malabsorption	0	0	0	0	0	0	0	0	0	0	1	0
Malignant gastrointestinal obstruction	0	0	0	0	0	0	0	0	1	-0.1	0	0
Malignant neoplasm progression	0	0	0	0	0	0	0	0	0	0	4	-0.1
Mental status changes	0	0	0	0	0	0	0	0	0	0	1	0
Metabolic acidosis	0	0	0	0	0	0	0	0	1	-0.1	0	0
Metastatic malignant melanoma	0	0	0	0	0	0	0	0	0	0	1	0
Myocarditis	0	0	0	0	0	0	0	0	0	0	1	0
Myositis	0	0	0	0	0	0	0	0	0	0	1	0
Nervous system disorder	0	0	0	0	0	0	1	-0.2	0	0	0	0
Neutropenic sepsis	0	0	0	0	0	0	0	0	0	0	1	0

Pelvic abscess	0	0	0	0	0	0	0	0	1	-0.1	0	0
Peripheral artery occlusion	0	0	0	0	0	0	0	0	0	0	1	0
Pleural effusion	0	0	0	0	0	0	0	0	0	0	1	0
Pneumocystis jirovecii pneumonia	0	0	0	0	0	0	0	0	0	0	1	0
Pneumonia	0	0	1	-0.6	1	-0.4	1	-0.2	2	-0.3	40	-0.5
Pneumonia aspiration	0	0	1	-0.6	0	0	1	-0.2	1	-0.1	8	-0.1
Pneumonia klebsiella	0	0	0	0	0	0	0	0	0	0	1	0
Pneumonia staphylococcal	0	0	0	0	0	0	0	0	0	0	1	0
Pneumonia streptococcal	0	0	0	0	0	0	0	0	0	0	1	0
Pneumonitis	0	0	0	0	0	0	2	-0.4	0	0	8	-0.1
Pneumothorax	0	0	0	0	0	0	0	0	0	0	1	0
Post procedural haemorrhage	0	0	0	0	0	0	0	0	0	0	1	0
Post procedural infection	0	0	0	0	1	-0.4	0	0	0	0	1	0
Pseudobulbar palsy	0	0	0	0	0	0	0	0	0	0	1	0
Pseudomonal sepsis	0	0	0	0	0	0	0	0	0	0	1	0
Pulmonary artery thrombosis	0	0	0	0	0	0	0	0	0	0	1	0
Pulmonary embolism	0	0	1	-0.6	0	0	0	0	0	0	10	-0.1
Pulmonary haemorrhage	0	0	0	0	0	0	0	0	0	0	5	-0.1
Pulmonary oedema	0	0	1	-0.6	0	0	0	0	0	0	1	0
Pulmonary sepsis	0	0	0	0	0	0	0	0	1	-0.1	2	0
Renal failure	0	0	0	0	0	0	1	-0.2	0	0	1	0
Respiratory distress	0	0	0	0	0	0	0	0	0	0	2	0
Respiratory failure	0	0	0	0	0	0	2	-0.4	2	-0.3	17	-0.2
Respiratory tract infection	0	0	0	0	0	0	0	0	0	0	1	0
Septic shock	0	0	1	-0.6	1	-0.4	1	-0.2	1	-0.1	11	-0.1
Soft tissue infection	0	0	0	0	0	0	0	0	0	0	2	0
Spinal cord compression	0	0	0	0	0	0	0	0	0	0	1	0
Stevens-Johnson syndrome	0	0	0	0	0	0	0	0	0	0	1	0
Sudden death	0	0	0	0	1	-0.4	1	-0.2	0	0	2	0
Superior vena cava syndrome	0	0	0	0	0	0	0	0	0	0	1	0
Traumatic intracranial haemorrhage	0	0	0	0	0	0	0	0	0	0	1	0
Tumour haemorrhage	0	0	0	0	0	0	0	0	0	0	5	-0.1
Type 2 diabetes mellitus	0	0	0	0	0	0	0	0	0	0	1	0

Upper gastrointestinal haemorrhage	0	0	0	0	0	0	0	0	0	0	1	0
Urinary tract obstruction	0	0	0	0	0	0	0	0	1	-0.1	1	0

Every participant is counted a single time for each applicable row and column.

For KN905, EV + Pembro Combo ISD, and Pembro Mono RSD, serious adverse events up to 90 days of last treatment are included. For EV Mono ISD, serious adverse events up to 30 days of the last treatment are included.

For Pembro and EV+Pembro studies, MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

For EV mono studies, disease progressions that are identified based on the sponsor specified search strategy utilizing MedDRA terminology are excluded.

Database cutoff date for KN905: 06JUN2025.

2.5.3. Adverse events of special interest

The protocol pre-specified AESI for enfortumab vedotin were skin reactions, peripheral neuropathy, ocular events, hyperglycaemia and IRR.

2.5.3.1. Skin reactions

Table 51 - Adverse Event Summary AESI for EV - Skin Reactions (APaT Population)

	KN-905 EV + Pembro		KN-905 Cystectomy		EV + Pembro Combo ISD		EV Mono ISD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	167		242		564		793	
with one or more adverse events	102	(61.1)	5	(2.1)	395	(70.0)	452	(57.0)
with no adverse event	65	(38.9)	237	(97.9)	169	(30.0)	341	(43.0)
with drug-related[a] adverse events	96	(57.5)	0	(0.0)	378	(67.0)	402	(50.7)
with toxicity grade 3-5 adverse events	18	(10.8)	0	(0.0)	99	(17.6)	108	(13.6)
with toxicity grade 3-5 drug-related adverse events	18	(10.8)	0	(0.0)	96	(17.0)	106	(13.4)
with serious adverse events	8	(4.8)	0	(0.0)	30	(5.3)	34	(4.3)
with serious drug-related adverse events	8	(4.8)	0	(0.0)	30	(5.3)	34	(4.3)
who died	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to an adverse event	16	(9.6)	0	(0.0)	38	(6.7)	25	(3.2)
discontinued Pembrolizumab	8	(4.8)	NA		21	(3.7)	NA	
discontinued EV	16	(9.6)	NA		33	(5.9)	25	(3.2)
discontinued any drug due to a drug-related adverse event	16	(9.6)	0	(0.0)	38	(6.7)	25	(3.2)
discontinued Pembrolizumab	8	(4.8)	NA		21	(3.7)	NA	
discontinued EV	16	(9.6)	NA		33	(5.9)	25	(3.2)
discontinued any drug due to a serious adverse event	5	(3.0)	0	(0.0)	8	(1.4)	13	(1.6)
discontinued Pembrolizumab	4	(2.4)	NA		6	(1.1)	NA	
discontinued EV	5	(3.0)	NA		7	(1.2)	13	(1.6)
discontinued any drug due to a serious drug-related adverse event	5	(3.0)	0	(0.0)	8	(1.4)	13	(1.6)
discontinued Pembrolizumab	4	(2.4)	NA		6	(1.1)	NA	
discontinued EV	5	(3.0)	NA		7	(1.2)	13	(1.6)

[a] Determined by the investigator to be related to the drug.

For KN905, EV + Pembro Combo ISD, and Pembro Mono RSD, non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.

For EV Mono ISD, non-serious adverse events and serious adverse events up to 30 days of the last treatment are included.

Grades are based on NCI CTCAE version 4.03.

Database cutoff date for KN905: 06JUN2025.

Table 52 Participants With Adverse Events of Special Interest (AESI) for EV - Skin Reactions by Maximum Toxicity Grade (Incidence > 0% in One or More Treatment Groups) (APaT Population)

	KN-905 EV + Pembro		KN-905 Cystectomy		EV + Pembro Combo ISD		EV Mono ISD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	167		242		564		793	
with one or more adverse events	102	(61.1)	5	(2.1)	395	(70.0)	452	(57.0)
Grade 1	41	(24.6)	3	(1.2)	123	(21.8)	183	(23.1)
Grade 2	43	(25.7)	2	(0.8)	173	(30.7)	161	(20.3)
Grade 3	15	(9.0)	0	(0.0)	93	(16.5)	105	(13.2)
Grade 4	2	(1.2)	0	(0.0)	6	(1.1)	3	(0.4)
Grade 5	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
with no adverse events	65	(38.9)	237	(97.9)	169	(30.0)	341	(43.0)

Table 53 Summary of Resolution of AESI for EV - Skin Reactions (APaT Population)

	KN-905 EV + Pembro (N=167)	KN-905 Cystectomy (N=242)	EV + Pembro Combo ISD (N=564)	EV Mono ISD (N=793)
Participants in population	167	242	564	793
Participants with AESI (%)	102 (61.1)	5 (2.1)	394 (69.9)	366 (46.2)
All events resolved[a] , n (%)	85 (83.3)	4 (80.0)	293 (74.4)	223 (60.9)
Some events that either resolved[a] or resolving, n (%)	6 (5.9)	0 (0.0)	73 (18.5)	88 (24.0)
No events that either resolved[a] or resolving, n (%)	11 (10.8)	1 (20.0)	28 (7.1)	55 (15.0)

Median time to resolution was 1.117 months (range 0.033 to 28.057).

2.5.3.2. Peripheral neuropathy

Table 54 - Adverse Event Summary AESI for EV - Peripheral Neuropathy (APaT Population)

	KN-905 EV + Pembro		KN-905 Cystectomy		EV + Pembro Combo ISD		EV Mono ISD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	167		242		564		793	
with one or more adverse events	65	(38.9)	5	(2.1)	380	(67.4)	422	(53.2)
with no adverse event	102	(61.1)	237	(97.9)	184	(32.6)	371	(46.8)
with drug-related[a] adverse events	61	(36.5)	0	(0.0)	364	(64.5)	381	(48.0)
with toxicity grade 3-5 adverse events	5	(3.0)	0	(0.0)	41	(7.3)	41	(5.2)
with toxicity grade 3-5 drug-related adverse events	5	(3.0)	0	(0.0)	37	(6.6)	38	(4.8)
with serious adverse events	0	(0.0)	0	(0.0)	9	(1.6)	17	(2.1)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	7	(1.2)	11	(1.4)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to an adverse event	12	(7.2)	0	(0.0)	119	(21.1)	55	(6.9)
discontinued Pembrolizumab	2	(1.2)	NA		16	(2.8)	NA	
discontinued EV	11	(6.6)	NA		119	(21.1)	55	(6.9)
discontinued any drug due to a drug-related adverse event	12	(7.2)	0	(0.0)	117	(20.7)	53	(6.7)
discontinued Pembrolizumab	2	(1.2)	NA		15	(2.7)	NA	
discontinued EV	11	(6.6)	NA		117	(20.7)	53	(6.7)
discontinued any drug due to a serious adverse event	0	(0.0)	0	(0.0)	2	(0.4)	3	(0.4)
discontinued Pembrolizumab	0	(0.0)	NA		1	(0.2)	NA	
discontinued EV	0	(0.0)	NA		1	(0.2)	3	(0.4)
discontinued any drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	2	(0.4)	3	(0.4)
discontinued Pembrolizumab	0	(0.0)	NA		1	(0.2)	NA	
discontinued EV	0	(0.0)	NA		1	(0.2)	3	(0.4)

[a] Determined by the investigator to be related to the drug.

For KN905, EV + Pembro Combo ISD, and Pembro Mono RSD, non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.

For EV Mono ISD, non-serious adverse events and serious adverse events up to 30 days of the last treatment are included.

Grades are based on NCI CTCAE version 4.03.

Database cutoff date for KN905: 06JUN2025.

Median time to onset of first AESI Peripheral neuropathy for EV was 2.497 months (range 0.066 to 11.565).

Table 55 Summary of Resolution of AESI for EV - Peripheral Neuropathy (APaT Population)

	KN-905 EV + Pembro (N=167)	KN-905 Cystectomy (N=242)	EV + Pembro Combo ISD (N=564)	EV Mono ISD (N=793)
Participants in population	167	242	564	793
Participants with AESI (%)	65 (38.9)	5 (2.1)	376 (66.7)	340 (42.9)
All events resolved[a] , n (%)	21 (32.3)	2 (40.0)	91 (24.2)	48 (14.1)
Some events that either resolved[a] or resolving, n (%)	13 (20.0)	1 (20.0)	153 (40.7)	158 (46.5)
No events that either resolved[a] or resolving, n (%)	31 (47.7)	2 (40.0)	132 (35.1)	134 (39.4)

Median time to resolution was 2.464 months (range 0.033 to 30.719).

2.5.3.3. Ocular events

Table 56 - Adverse Event Summary AESI for EV - Ocular Disorders (APaT Population)

	KN-905 EV + Pembro		KN-905 Cystectomy		EV + Pembro Combo ISD		EV Mono ISD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	167		242		564		793	
with one or more adverse events	38	(22.8)	0	(0.0)	182	(32.3)	277	(34.9)
with no adverse event	129	(77.2)	242	(100.0)	382	(67.7)	516	(65.1)
with drug-related[a] adverse events	29	(17.4)	0	(0.0)	134	(23.8)	199	(25.1)
with toxicity grade 3-5 adverse events	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.4)
with toxicity grade 3-5 drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.4)
with serious adverse events	1	(0.6)	0	(0.0)	1	(0.2)	2	(0.3)
with serious drug-related adverse events	1	(0.6)	0	(0.0)	1	(0.2)	2	(0.3)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to an adverse event	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.1)
discontinued Pembrolizumab	0	(0.0)	NA		1	(0.2)	NA	
discontinued EV	0	(0.0)	NA		1	(0.2)	1	(0.1)
discontinued any drug due to a drug-related adverse event	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.1)
discontinued Pembrolizumab	0	(0.0)	NA		1	(0.2)	NA	
discontinued EV	0	(0.0)	NA		1	(0.2)	1	(0.1)
discontinued any drug due to a serious adverse event	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.1)
discontinued Pembrolizumab	0	(0.0)	NA		1	(0.2)	NA	
discontinued EV	0	(0.0)	NA		1	(0.2)	1	(0.1)
discontinued any drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.1)
discontinued Pembrolizumab	0	(0.0)	NA		1	(0.2)	NA	
discontinued EV	0	(0.0)	NA		1	(0.2)	1	(0.1)

[a] Determined by the investigator to be related to the drug.

For KN905, EV + Pembro Combo ISD, and Pembro Mono RSD, non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.

For EV Mono ISD, non-serious adverse events and serious adverse events up to 30 days of the last treatment are included.

Grades are based on NCI CTCAE version 4.03.

Database cutoff date for KN905: 06JUN2025.

Table 57 - Participants With Adverse Events of Special Interest (AESI) for EV - Ocular Disorders by Maximum Toxicity Grade (Incidence > 0% in One or More Treatment Groups) (APaT Population)

	KN-905 EV + Pembro		KN-905 Cystectomy		EV + Pembro Combo ISD		EV Mono ISD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	167		242		564		793	
with one or more adverse events	38	(22.8)	0	(0.0)	182	(32.3)	277	(34.9)
Grade 1	26	(15.6)	0	(0.0)	137	(24.3)	193	(24.3)
Grade 2	12	(7.2)	0	(0.0)	45	(8.0)	81	(10.2)
Grade 3	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.4)
with no adverse events	129	(77.2)	242	(100.0)	382	(67.7)	516	(65.1)

Dry eye events were the most common type of ocular disorder reported across the analysis subgroups. There were no participants with corneal disorder events.

2.5.3.4. Hyperglycaemia

Table 58 - Adverse Event Summary AESI for EV – Hyperglycemia (APaT Population)

	KN-905 EV + Pembro		KN-905 Cystectomy		EV + Pembro Combo ISD		EV Mono ISD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	167		242		564		793	
with one or more adverse events	28	(16.8)	2	(0.8)	112	(19.9)	133	(16.8)
with no adverse event	139	(83.2)	240	(99.2)	452	(80.1)	660	(83.2)
with drug-related[a] adverse events	16	(9.6)	0	(0.0)	76	(13.5)	86	(10.8)
with toxicity grade 3-5 adverse events	9	(5.4)	1	(0.4)	53	(9.4)	61	(7.7)
with toxicity grade 3-5 drug-related adverse events	5	(3.0)	0	(0.0)	37	(6.6)	46	(5.8)
with serious adverse events	2	(1.2)	0	(0.0)	11	(2.0)	20	(2.5)
with serious drug-related adverse events	1	(0.6)	0	(0.0)	10	(1.8)	18	(2.3)
who died	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.3)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.3)
discontinued any drug due to an adverse event	1	(0.6)	0	(0.0)	1	(0.2)	5	(0.6)
discontinued Pembrolizumab	1	(0.6)	NA		1	(0.2)	NA	
discontinued EV	1	(0.6)	NA		1	(0.2)	5	(0.6)
discontinued any drug due to a drug-related adverse event	1	(0.6)	0	(0.0)	1	(0.2)	5	(0.6)
discontinued Pembrolizumab	1	(0.6)	NA		1	(0.2)	NA	
discontinued EV	1	(0.6)	NA		1	(0.2)	5	(0.6)
discontinued any drug due to a serious adverse event	0	(0.0)	0	(0.0)	1	(0.2)	5	(0.6)
discontinued Pembrolizumab	0	(0.0)	NA		1	(0.2)	NA	
discontinued EV	0	(0.0)	NA		1	(0.2)	5	(0.6)
discontinued any drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	1	(0.2)	5	(0.6)
discontinued Pembrolizumab	0	(0.0)	NA		1	(0.2)	NA	
discontinued EV	0	(0.0)	NA		1	(0.2)	5	(0.6)

[a] Determined by the investigator to be related to the drug.

For KN905, EV + Pembro Combo ISD, and Pembro Mono RSD, non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.

For EV Mono ISD, non-serious adverse events and serious adverse events up to 30 days of the last treatment are included.

Grades are based on NCI CTCAE version 4.03.

Database cutoff date for KN905: 06JUN2025.

Table 59 - Participants With Adverse Events of Special Interest (AESI) for EV - Hyperglycemia by Maximum Toxicity Grade (Incidence > 0% in One or More Treatment Groups)

	KN-905 EV + Pembro		KN-905 Cystectomy		EV + Pembro Combo ISD		EV Mono ISD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	167		242		564		793	
with one or more adverse events	28	(16.8)	2	(0.8)	112	(19.9)	133	(16.8)
Grade 1	11	(6.6)	1	(0.4)	27	(4.8)	32	(4.0)
Grade 2	8	(4.8)	0	(0.0)	32	(5.7)	40	(5.0)
Grade 3	9	(5.4)	1	(0.4)	46	(8.2)	53	(6.7)
Grade 4	0	(0.0)	0	(0.0)	7	(1.2)	6	(0.8)
Grade 5	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.3)
with no adverse events	139	(83.2)	240	(99.2)	452	(80.1)	660	(83.2)

For participants in the perioperative EV + pembrolizumab group with hyperglycemia, the median time to first onset was 0.723 months (range 0.033 to 15.343). The majority of patients with AESI Hyperglycemia events resolved (85.7%), median time to resolution was 1.018 months.

Table 60 -Participants With Adverse Events of Special Interest (AESI) for EV by Pre-existing Condition - Hyperglycemia

	KN-905 EV + Pembro		KN-905 Cystectomy		EV + Pembro Combo ISD		EV Mono ISD	
	Pre-existing Hyperglycemia = Yes	Pre-existing Hyperglycemia = No	Pre-existing Hyperglycemia = Yes	Pre-existing Hyperglycemia = No	Pre-existing Hyperglycemia = Yes	Pre-existing Hyperglycemia = No	Pre-existing Hyperglycemia = Yes	Pre-existing Hyperglycemia = No
Participants in population	51	116	62	180	58	506	231	562
Hyperglycemia	**16 (31.4)**	**12 (10.3)**	**1 (1.6)**	**1 (0.6)**	**14 (24.1)**	**98 (19.4)**	**29 (12.6)**	**104 (18.5)**

Table 61 - Participants With Adverse Events of Special Interest (AESI) for EV by Baseline HbA1c(<5.7, >=5.7 - <6.5, >=6.5), Hyperglycemia

	KN-905 EV + Pembro				KN-905 Cystectomy				EV + Pembro Combo ISD				EV Mono ISD			
	Baseline HbA1c <5.7	Baseline HbA1c >=5.7 - < 6.5	Baseline HbA1c >=6.5	Baseline HbA1c Missing	Baseline HbA1c <5.7	Baseline HbA1c >=5.7 - < 6.5	Baseline HbA1c >=6.5	Baseline HbA1c Missing	Baseline HbA1c <5.7	Baseline HbA1c >=5.7 - < 6.5	Baseline HbA1c >=6.5	Baseline HbA1c Missing	Baseline HbA1c <5.7	Baseline HbA1c >=5.7 - < 6.5	Baseline HbA1c >=6.5	Baseline HbA1c Missing
Participants in population	68	67	28	4	78	62	18	84	262	210	51	41	272	264	83	174
Hyperglycemia	**4 (5.9)**	**15 (22.4)**	**9 (32.1)**	**0 (0.0)**	**1 (1.3)**	**0 (0.0)**	**0 (0.0)**	**1 (1.2)**	**29 (11.1)**	**44 (21.0)**	**28 (54.9)**	**11 (26.8)**	**18 (6.6)**	**54 (20.5)**	**32 (38.6)**	**29 (16.7)**

Table 62 - Participants With Adverse Events of Special Interest (AESI) for EV by Baseline BMI (<30, >=30 kg/m2), Hyperglycemia

	KN-905 EV + Pembro		KN-905 Cystectomy		EV + Pembro Combo ISD		EV Mono ISD	
	Baseline BMI < 30 kg/m2	Baseline BMI >= 30 kg/m2	Baseline BMI < 30 kg/m2	Baseline BMI >= 30 kg/m2	Baseline BMI < 30 kg/m2	Baseline BMI >= 30 kg/m2	Baseline BMI < 30 kg/m2	Baseline BMI >= 30 kg/m2
Participants in population	135	32	192	50	441	120	662	131
Hyperglycemia	**18 (13.3)**	**10 (31.3)**	**2 (1.0)**	**0 (0.0)**	**73 (16.6)**	**38 (31.7)**	**93 (14.0)**	**40 (30.5)**

2.5.3.5. Infusion related reactions (IRR)

Table 63 - Adverse Event Summary AESI for EV – Infusion related reactions (APaT Population)

	KN-905 EV + Pembro		KN-905 Cystectomy		EV + Pembro Combo ISD		EV Mono ISD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	167		242		564		793	
with one or more adverse events	3	(1.8)	0	(0.0)	22	(3.9)	50	(6.3)
with no adverse event	164	(98.2)	242	(100.0)	542	(96.1)	743	(93.7)
with drug-related[a] adverse events	2	(1.2)	0	(0.0)	16	(2.8)	49	(6.2)
with toxicity grade 3-5 adverse events	1	(0.6)	0	(0.0)	1	(0.2)	7	(0.9)
with toxicity grade 3-5 drug-related adverse events	1	(0.6)	0	(0.0)	1	(0.2)	7	(0.9)
with serious adverse events	0	(0.0)	0	(0.0)	1	(0.2)	4	(0.5)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	1	(0.2)	4	(0.5)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to an adverse event	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)
discontinued Pembrolizumab	0	(0.0)	NA		0	(0.0)	NA	
discontinued EV	0	(0.0)	NA		0	(0.0)	1	(0.1)
discontinued any drug due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)
discontinued Pembrolizumab	0	(0.0)	NA		0	(0.0)	NA	
discontinued EV	0	(0.0)	NA		0	(0.0)	1	(0.1)
discontinued any drug due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued Pembrolizumab	0	(0.0)	NA		0	(0.0)	NA	
discontinued EV	0	(0.0)	NA		0	(0.0)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued Pembrolizumab	0	(0.0)	NA		0	(0.0)	NA	
discontinued EV	0	(0.0)	NA		0	(0.0)	0	(0.0)

[a] Determined by the investigator to be related to the drug.

For KN905, EV + Pembro Combo ISD, and Pembro Mono RSD, non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.

For EV Mono ISD, non-serious adverse events and serious adverse events up to 30 days of the last treatment are included.

Grades are based on NCI CTCAE version 4.03.

Database cutoff date for KN905: 06JUN2025.

2.5.3.6. Pneumonitis/Interstitial lung disease

Table 64 - Adverse Event Summary Other Risk for EV - Pneumonitis/Interstitial Lung Disease (APaT Population)

	KN-905 EV + Pembro		KN-905 Cystectomy		EV + Pembro Combo ISD		EV Mono ISD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	167		242		564		793	
with one or more adverse events	7	(4.2)	0	(0.0)	62	(11.0)	26	(3.3)
with no adverse event	160	(95.8)	242	(100.0)	502	(89.0)	767	(96.7)
with drug-related[a] adverse events	7	(4.2)	0	(0.0)	59	(10.5)	21	(2.6)
with toxicity grade 3-5 adverse events	0	(0.0)	0	(0.0)	23	(4.1)	6	(0.8)
with toxicity grade 3-5 drug-related adverse events	0	(0.0)	0	(0.0)	23	(4.1)	5	(0.6)
with serious adverse events	0	(0.0)	0	(0.0)	27	(4.8)	6	(0.8)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	26	(4.6)	5	(0.6)
who died	0	(0.0)	0	(0.0)	3	(0.5)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	3	(0.5)	0	(0.0)
discontinued any drug due to an adverse event	3	(1.8)	0	(0.0)	30	(5.3)	4	(0.5)
discontinued Pembrolizumab	3	(1.8)	NA		30	(5.3)	NA	
discontinued EV	1	(0.6)	NA		14	(2.5)	4	(0.5)
discontinued any drug due to a drug-related adverse event	3	(1.8)	0	(0.0)	30	(5.3)	3	(0.4)
discontinued Pembrolizumab	3	(1.8)	NA		30	(5.3)	NA	
discontinued EV	1	(0.6)	NA		14	(2.5)	3	(0.4)
discontinued any drug due to a serious adverse event	0	(0.0)	0	(0.0)	16	(2.8)	3	(0.4)
discontinued Pembrolizumab	0	(0.0)	NA		15	(2.7)	NA	
discontinued EV	0	(0.0)	NA		8	(1.4)	3	(0.4)
discontinued any drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	16	(2.8)	2	(0.3)
discontinued Pembrolizumab	0	(0.0)	NA		15	(2.7)	NA	
discontinued EV	0	(0.0)	NA		8	(1.4)	2	(0.3)

[a] Determined by the investigator to be related to the drug.

For KN905, EV + Pembro Combo ISD, and Pembro Mono RSD, non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.

For EV Mono ISD, non-serious adverse events and serious adverse events up to 30 days of the last treatment are included.

Grades are based on NCI CTCAE version 4.03.

Database cutoff date for KN905: 06JUN2025.

2.5.3.7. Anemia and Neutropenia

Table 65 Adverse Event Summary Other Risk for EV – Anemia (APaT Population)

	KN-905 EV + Pembro		KN-905 Cystectomy		EV + Pembro Combo ISD		EV Mono ISD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	167		242		564		793	
with one or more adverse events	51	(30.5)	29	(12.0)	153	(27.1)	232	(29.3)
with no adverse event	116	(69.5)	213	(88.0)	411	(72.9)	561	(70.7)
with drug-related[a] adverse events	10	(6.0)	0	(0.0)	88	(15.6)	150	(18.9)
with toxicity grade 3-5 adverse events	15	(9.0)	15	(6.2)	52	(9.2)	77	(9.7)
with toxicity grade 3-5 drug-related adverse events	4	(2.4)	0	(0.0)	25	(4.4)	38	(4.8)
with serious adverse events	2	(1.2)	2	(0.8)	6	(1.1)	7	(0.9)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	3	(0.5)	2	(0.3)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to an adverse event	1	(0.6)	0	(0.0)	2	(0.4)	0	(0.0)
discontinued Pembrolizumab	0	(0.0)	NA		1	(0.2)	NA	
discontinued EV	1	(0.6)	NA		2	(0.4)	0	(0.0)
discontinued any drug due to a drug-related adverse event	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
discontinued Pembrolizumab	0	(0.0)	NA		0	(0.0)	NA	
discontinued EV	0	(0.0)	NA		1	(0.2)	0	(0.0)
discontinued any drug due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued Pembrolizumab	0	(0.0)	NA		0	(0.0)	NA	
discontinued EV	0	(0.0)	NA		0	(0.0)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued Pembrolizumab	0	(0.0)	NA		0	(0.0)	NA	
discontinued EV	0	(0.0)	NA		0	(0.0)	0	(0.0)

[a] Determined by the investigator to be related to the drug.

For KN905, EV + Pembro Combo ISD, and Pembro Mono RSD, non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.

For EV Mono ISD, non-serious adverse events and serious adverse events up to 30 days of the last treatment are included.

Grades are based on NCI CTCAE version 4.03.

Database cutoff date for KN905: 06JUN2025.

Table 66 - Participants With Adverse Events of Other Risk for EV - Anemia by Maximum Toxicity Grade (Incidence > 0% in One or More Treatment Groups) (APaT Population)

	KN-905 EV + Pembro		KN-905 Cystectomy		EV + Pembro Combo ISD		EV Mono ISD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	167		242		564		793	
with one or more adverse events	51	(30.5)	29	(12.0)	153	(27.1)	232	(29.3)
Grade 1	10	(6.0)	2	(0.8)	51	(9.0)	54	(6.8)
Grade 2	26	(15.6)	12	(5.0)	50	(8.9)	101	(12.7)
Grade 3	15	(9.0)	15	(6.2)	50	(8.9)	77	(9.7)
Grade 4	0	(0.0)	0	(0.0)	2	(0.4)	0	(0.0)
with no adverse events	116	(69.5)	213	(88.0)	411	(72.9)	561	(70.7)

Table 67 Adverse Event Summary Other Risk for EV – Neutropenia (APaT Population)

	KN-905 EV + Pembro		KN-905 Cystectomy		EV + Pembro Combo ISD		EV Mono ISD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	167		242		564		793	
with one or more adverse events	18	(10.8)	0	(0.0)	82	(14.5)	134	(16.9)
with no adverse event	149	(89.2)	242	(100.0)	482	(85.5)	659	(83.1)
with drug-related[a] adverse events	15	(9.0)	0	(0.0)	77	(13.7)	124	(15.6)
with toxicity grade 3-5 adverse events	12	(7.2)	0	(0.0)	50	(8.9)	91	(11.5)
with toxicity grade 3-5 drug-related adverse events	11	(6.6)	0	(0.0)	47	(8.3)	83	(10.5)
with serious adverse events	1	(0.6)	0	(0.0)	7	(1.2)	23	(2.9)
with serious drug-related adverse events	1	(0.6)	0	(0.0)	7	(1.2)	21	(2.6)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to an adverse event	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)
discontinued Pembrolizumab	0	(0.0)	NA		0	(0.0)	NA	
discontinued EV	0	(0.0)	NA		0	(0.0)	1	(0.1)
discontinued any drug due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)
discontinued Pembrolizumab	0	(0.0)	NA		0	(0.0)	NA	
discontinued EV	0	(0.0)	NA		0	(0.0)	1	(0.1)
discontinued any drug due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)
discontinued Pembrolizumab	0	(0.0)	NA		0	(0.0)	NA	
discontinued EV	0	(0.0)	NA		0	(0.0)	1	(0.1)
discontinued any drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)
discontinued Pembrolizumab	0	(0.0)	NA		0	(0.0)	NA	
discontinued EV	0	(0.0)	NA		0	(0.0)	1	(0.1)

[a] Determined by the investigator to be related to the drug.

For KN905, EV + Pembro Combo ISD, and Pembro Mono RSD, non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.

For EV Mono ISD, non-serious adverse events and serious adverse events up to 30 days of the last treatment are included.

Grades are based on NCI CTCAE version 4.03.

Database cutoff date for KN905: 06JUN2025.

Among 18 (10.8%) patients with Neutropenia events, 16 (9.6%) had neutropenia and 2 (1.2%) febrile neutropenia.

Table 68 Participants With Adverse Events of Other Risk for EV - Neutropenia by Maximum Toxicity Grade (Incidence > 0% in One or More Treatment Groups) (APaT Population)

	KN-905 EV + Pembro		KN-905 Cystectomy		EV + Pembro Combo ISD		EV Mono ISD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	167		242		564		793	
with one or more adverse events	18	(10.8)	0	(0.0)	82	(14.5)	134	(16.9)
Grade 1	1	(0.6)	0	(0.0)	7	(1.2)	24	(3.0)
Grade 2	5	(3.0)	0	(0.0)	25	(4.4)	19	(2.4)
Grade 3	9	(5.4)	0	(0.0)	44	(7.8)	64	(8.1)
Grade 4	3	(1.8)	0	(0.0)	6	(1.1)	27	(3.4)
with no adverse events	149	(89.2)	242	(100.0)	482	(85.5)	659	(83.1)

2.5.3.8. Nausea, Vomiting, and Diarrhea

Nectin-4 expression has been identified in the esophagus and the stomach (Study ES10-001), and weak staining was observed in the mucosal glands of other gastrointestinal tract organs, including the small intestine, colon, and rectum. The gastrointestinal toxicities of diarrhea, nausea, and vomiting are common events reported with the use of MMAE ADCs, including enfortumab vedotin. The SMQ of gastrointestinal nonspecific symptoms and therapeutic procedures was used to identify these events.

Table 69 Adverse Event Summary Other Risk for EV - Nausea, Vomiting, Diarrhea (APaT Population)

	KN-905 EV + Pembro		KN-905 Cystectomy		EV + Pembro Combo ISD		EV Mono ISD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	167		242		564		793	
with one or more adverse events	101	(60.5)	49	(20.2)	391	(69.3)	562	(70.9)
with no adverse event	66	(39.5)	193	(79.8)	173	(30.7)	231	(29.1)
with drug-related[a] adverse events	59	(35.3)	0	(0.0)	274	(48.6)	418	(52.7)
with toxicity grade 3-5 adverse events	15	(9.0)	5	(2.1)	48	(8.5)	67	(8.4)
with toxicity grade 3-5 drug-related adverse events	7	(4.2)	0	(0.0)	32	(5.7)	40	(5.0)
with serious adverse events	7	(4.2)	4	(1.7)	30	(5.3)	39	(4.9)
with serious drug-related adverse events	3	(1.8)	0	(0.0)	15	(2.7)	20	(2.5)
who died	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
discontinued any drug due to an adverse event	7	(4.2)	0	(0.0)	10	(1.8)	0	(0.0)
discontinued Pembrolizumab	7	(4.2)	NA		10	(1.8)	NA	
discontinued EV	3	(1.8)	NA		6	(1.1)	0	(0.0)
discontinued any drug due to a drug-related adverse event	7	(4.2)	0	(0.0)	8	(1.4)	0	(0.0)
discontinued Pembrolizumab	7	(4.2)	NA		8	(1.4)	NA	
discontinued EV	3	(1.8)	NA		5	(0.9)	0	(0.0)
discontinued any drug due to a serious adverse event	1	(0.6)	0	(0.0)	3	(0.5)	0	(0.0)
discontinued Pembrolizumab	1	(0.6)	NA		3	(0.5)	NA	
discontinued EV	1	(0.6)	NA		2	(0.4)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	1	(0.6)	0	(0.0)	3	(0.5)	0	(0.0)
discontinued Pembrolizumab	1	(0.6)	NA		3	(0.5)	NA	
discontinued EV	1	(0.6)	NA		2	(0.4)	0	(0.0)

[a] Determined by the investigator to be related to the drug.

For KN905, EV + Pembro Combo ISD, and Pembro Mono RSD, non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.

For EV Mono ISD, non-serious adverse events and serious adverse events up to 30 days of the last treatment are included.

Grades are based on NCI CTCAE version 4.03.

Database cutoff date for KN905: 06JUN2025.

Table 70 Participants With Adverse Events of Other Risk for EV - Nausea, Vomiting, Diarrhea (Incidence > 1% in KN-905 EV+Pembro Group) (APaT Population)

	KN-905 EV + Pembro		KN-905 Cystectomy		EV + Pembro Combo ISD		EV Mono ISD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	167		242		564		793	
with one or more adverse events	101	(60.5)	49	(20.2)	391	(69.3)	562	(70.9)
with no adverse events	66	(39.5)	193	(79.8)	173	(30.7)	231	(29.1)
Nausea, Vomiting, Diarrhea	**101**	**(60.5)**	**49**	**(20.2)**	**391**	**(69.3)**	**562**	**(70.9)**
Diarrhoea	57	(34.1)	7	(2.9)	227	(40.2)	310	(39.1)
Constipation	46	(27.5)	20	(8.3)	158	(28.0)	229	(28.9)
Nausea	43	(25.7)	16	(6.6)	166	(29.4)	300	(37.8)
Abdominal pain	17	(10.2)	17	(7.0)	72	(12.8)	122	(15.4)
Vomiting	15	(9.0)	8	(3.3)	81	(14.4)	148	(18.7)
Flatulence	6	(3.6)	2	(0.8)	5	(0.9)	17	(2.1)
Abdominal pain lower	4	(2.4)	1	(0.4)	7	(1.2)	15	(1.9)
Abdominal distension	2	(1.2)	1	(0.4)	15	(2.7)	28	(3.5)
Abdominal pain upper	2	(1.2)	0	(0.0)	20	(3.5)	36	(4.5)
Eructation	1	(0.6)	1	(0.4)	2	(0.4)	4	(0.5)

Table 71 Participants With Adverse Events of Other Risk for EV - Nausea, Vomiting, Diarrhea by Maximum Toxicity Grade (Incidence > 0% in One or More Treatment Groups) (APaT Population)

	KN-905 EV + Pembro		KN-905 Cystectomy		EV + Pembro Combo ISD		EV Mono ISD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	167		242		564		793	
with one or more adverse events	101	(60.5)	49	(20.2)	391	(69.3)	562	(70.9)
Grade 1	48	(28.7)	20	(8.3)	198	(35.1)	290	(36.6)
Grade 2	38	(22.8)	24	(9.9)	145	(25.7)	205	(25.9)
Grade 3	15	(9.0)	5	(2.1)	46	(8.2)	66	(8.3)
Grade 4	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.1)
Grade 5	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
with no adverse events	66	(39.5)	193	(79.8)	173	(30.7)	231	(29.1)

2.5.3.9. Skin Hyperpigmentation

Clinical AEs of skin hyperpigmentation include skin discoloration, skin hyperpigmentation, and pigmentation disorder. The proportion of participants with skin hyperpigmentation was 3.0%, 6.9% in the EV + pembrolizumab ISD and 10% in the EV mono ISD. All AEs of skin hyperpigmentation were Grade 1 or 2 events and nonserious across all the analyzed groups. No AEs of skin hyperpigmentation resulted in study drug dose modifications in the perioperative EV + pembrolizumab group.

2.6. Adverse Events by treatment phases

Table 72 Adverse Event Summary (Preoperative/Surgical Phase) (APaT2 Population)

	EV + Pembro		RC + PLND	
	n	(%)	n	(%)
Participants in population	167		159	
with one or more adverse events	165	(98.8)	103	(64.8)
with no adverse event	2	(1.2)	56	(35.2)
with drug-related[a] adverse events	151	(90.4)	0	(0.0)
with toxicity grade 3-5 adverse events	100	(59.9)	73	(45.9)
with toxicity grade 3-5 drug-related[a] adverse events	62	(37.1)	0	(0.0)
with serious adverse events	76	(45.5)	65	(40.9)
with serious drug-related[a] adverse events	26	(15.6)	0	(0.0)
who died	6	(3.6)	9	(5.7)
who died due to a drug-related[a] adverse event	2	(1.2)	0	(0.0)
discontinued any drug due to an adverse event	45	(26.9)	0	(0.0)
discontinued pembrolizumab	29	(17.4)	0	(0.0)
discontinued EV	43	(25.7)	0	(0.0)
discontinued any drug due to a drug-related[a] adverse event	37	(22.2)	0	(0.0)
discontinued pembrolizumab	22	(13.2)	0	(0.0)
discontinued EV	35	(21.0)	0	(0.0)
discontinued any drug due to a serious adverse event	18	(10.8)	0	(0.0)
discontinued pembrolizumab	15	(9.0)	0	(0.0)
discontinued EV	16	(9.6)	0	(0.0)
discontinued any drug due to a serious drug-related[a] adverse event	12	(7.2)	0	(0.0)
discontinued pembrolizumab	9	(5.4)	0	(0.0)
discontinued EV	10	(6.0)	0	(0.0)

[a] Determined by the investigator to be related to any drug.
Treatment includes preoperative study medications and surgery.
Preoperative/surgical phase starts the date when the first treatment is administered and continues until the date the first postoperative study medications are administered.
Included adverse events in the preoperative/surgical phase. If there are no postoperative study medications, non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.
MedDRA V28.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.03
Database Cutoff Date: 06JUN2025.

Table 73 Adverse Event Summary (Postoperative Phase) (APaT2 Population - Participants Who Received Postoperative EV/Pembrolizumab)

	EV + Pembro	
	n	(%)
Participants in population	100	
with one or more adverse events	99	(99.0)
with no adverse event	1	(1.0)
with drug-related[a] adverse events	80	(80.0)
with toxicity grade 3-5 adverse events	56	(56.0)
with toxicity grade 3-5 drug-related[a] adverse events	25	(25.0)
with serious adverse events	43	(43.0)
with serious drug-related[a] adverse events	8	(8.0)
who died	7	(7.0)
who died due to a drug-related[a] adverse event	0	(0.0)
discontinued any drug due to an adverse event	37	(37.0)
discontinued pembrolizumab	28	(28.0)
discontinued EV	26	(26.0)
discontinued any drug due to a drug-related[a] adverse event	26	(26.0)
discontinued pembrolizumab	20	(20.0)
discontinued EV	16	(16.0)
discontinued any drug due to a serious adverse event	13	(13.0)
discontinued pembrolizumab	11	(11.0)
discontinued EV	11	(11.0)
discontinued any drug due to a serious drug-related[a] adverse event	4	(4.0)
discontinued pembrolizumab	4	(4.0)
discontinued EV	2	(2.0)

[a] Determined by the investigator to be related to any drug.
Treatment includes postoperative study medications.
Postoperative phase starts the date of the first postoperative treatment.
Included adverse events in the postoperative phase. Non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.
MedDRA V28.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.03
Database Cutoff Date: 06JUN2025.

Table 74 Participants With Adverse Events (Sorted by Decreasing Incidence) (Incidence ≥ 10% in One or More Treatment Groups) (Preoperative/Surgical Phase) (APaT2 Population)

	EV + Pembro		RC + PLND	
	n	(%)	n	(%)
Participants in population	167		159	
with one or more adverse events	165	(98.8)	103	(64.8)
with no adverse events	2	(1.2)	56	(35.2)
Pruritus	64	(38.3)	0	(0.0)
Alopecia	54	(32.3)	0	(0.0)
Fatigue	47	(28.1)	7	(4.4)
Dysgeusia	43	(25.7)	0	(0.0)
Diarrhoea	42	(25.1)	5	(3.1)
Anaemia	40	(24.0)	19	(11.9)
Nausea	40	(24.0)	12	(7.5)
Aspartate aminotransferase increased	37	(22.2)	0	(0.0)
Rash	37	(22.2)	1	(0.6)
Decreased appetite	35	(21.0)	3	(1.9)
Constipation	34	(20.4)	13	(8.2)
Urinary tract infection	33	(19.8)	20	(12.6)
Alanine aminotransferase increased	30	(18.0)	2	(1.3)
Rash maculo-papular	23	(13.8)	0	(0.0)
Weight decreased	23	(13.8)	5	(3.1)
Asthenia	20	(12.0)	3	(1.9)
Dry skin	20	(12.0)	1	(0.6)
Prostate cancer	19	(11.4)	15	(9.4)
Hyperglycaemia	18	(10.8)	1	(0.6)
Peripheral sensory neuropathy	18	(10.8)	0	(0.0)

Every participant is counted a single time for each applicable row and column.

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Treatment includes preoperative study medications and surgery.

Preoperative/surgical phase starts the date when the first treatment is administered and continues until the date the first postoperative study medications are administered.

Included adverse events in the preoperative/surgical phase. If there are no postoperative study medications, non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.

MedDRA V28.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.

Database Cutoff Date: 06JUN2025.

Table 75 Participants With Adverse Events (Sorted by Decreasing Incidence) (Incidence ≥10%) (Postoperative Phase) (APaT2 Population - Participants Who Received Postoperative EV/Pembrolizumab)

	EV + Pembro	
	n	(%)
Participants in population	100	
with one or more adverse events	99	(99.0)
with no adverse events	1	(1.0)
Pruritus	28	(28.0)
Diarrhoea	27	(27.0)
Constipation	15	(15.0)
Urinary tract infection	15	(15.0)
Anaemia	14	(14.0)
Decreased appetite	14	(14.0)
Dysgeusia	14	(14.0)
Hypothyroidism	12	(12.0)
Fatigue	11	(11.0)
Weight decreased	11	(11.0)
Asthenia	10	(10.0)

Every participant is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Treatment includes postoperative study medications.
Postoperative phase starts the date of the first postoperative treatment.
Included adverse events in the postoperative phase. Non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.
MedDRA V28.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 06JUN2025.

Laboratory findings

All laboratory parameters of the pivotal trial were submitted with this procedure however they are not reproduced entirely in this assessment report.Haematology

2.6.1.1. Haemoglobin decreased

The rate of grade ≥3 haemoglobin decreased (highest post-baseline) in the EV + Pembro arm of the KN-905 trial was 13.2% compared to 9.3% in the EV + Pembro ISD. All grades were 60.5% compared to 57.5% respectively.

2.6.1.2. Neutrophils decreased

The rate of grade ≥3 neutrophils decreased (highest post-baseline) in the EV + Pembro arm of the KN-905 trial was 7.2% compared to 9.9% in the EV + Pembro ISD. All grades were 13.8% compared to 31.1% respectively, mainly due to a higher grade 2 event rate in the ISD (3.6% vs 12.3%).

2.6.1.3. Platelets decreased

The rate of grade ≥3 platelet decreased (highest post-baseline) in the EV + Pembro arm of the KN-905 trial was 1.2% compared to 1.8% in the EV + Pembro ISD. All grades were 11.4% compared to 22.6% respectively, mainly due to a higher grade 1 event rate in the ISD (9.6% vs 19.4%).

Clinical chemistry

Glucose increased

The rate of grade ≥3 glucose increased (highest post-baseline) in the EV + Pembro arm of the KN-905 trial was 12.0% compared to 14.2% in the EV + Pembro ISD. All grades were 72.5% compared to 67.9% respectively.

Hyper – and hypokalemia

The rate of grade ≥3 potassium decreased (highest post-baseline) in the EV + Pembro arm of the KN-905 trial was 4.2% compared to 6.4% in the EV + Pembro ISD. All grades were 18.0% compared to 29.0% respectively, mainly due to more grade 1 events in the ISD group (13.8% compared to 22.6%).

The rate of grade ≥3 potassium increased (highest post-baseline) in the EV + Pembro arm of the KN-905 trial was 6.6% compared to 1.4% in the EV + Pembro ISD. All grades were 38.9% compared to 25.4% respectively, mainly due to overall more events across all grades in the KN-905 arm.

Liver function

Table 76 - Participants with liver function laboratory findings that met predetermined criteria (APaT Population)

Criteria	KN-905 EV + Pembro		KN-905 Pembro mono		KN-905 Cystectomy		EV + Pembro Combo ISD		EV Mono ISD	
	n/m	(%)	n/m	(%)	n/m	(%)	n/m	(%)	n/m	(%)
Participants in population	167		163		242		564		793	
Alanine Aminotransferase										
≥3 x ULN	23/167	(13.8)	19/163	(11.7)	6/187	(3.2)	85/563	(15.1)	31/785	(3.9)
≥5 x ULN	8/167	(4.8)	12/163	(7.4)	4/187	(2.1)	33/563	(5.9)	9/785	(1.1)
≥10 x ULN	2/167	(1.2)	5/163	(3.1)	1/187	(0.5)	9/563	(1.6)	2/785	(0.3)
≥20 x ULN	0/167	(0.0)	1/163	(0.6)	1/187	(0.5)	4/563	(0.7)	0/785	(0.0)
Aspartate Aminotransferase										
≥3 x ULN	18/167	(10.8)	21/162	(13.0)	6/185	(3.2)	85/562	(15.1)	59/784	(7.5)
≥5 x ULN	10/167	(6.0)	15/162	(9.3)	4/185	(2.2)	33/562	(5.9)	17/784	(2.2)
≥10 x ULN	5/167	(3.0)	5/162	(3.1)	1/185	(0.5)	10/562	(1.8)	2/784	(0.3)
≥20 x ULN	0/167	(0.0)	2/162	(1.2)	1/185	(0.5)	4/562	(0.7)	0/784	(0.0)
Aminotransferase (ALT or AST)										
≥3 x ULN	25/167	(15.0)	23/162	(14.2)	7/186	(3.8)	106/563	(18.8)	68/785	(8.7)
≥5 x ULN	12/167	(7.2)	17/162	(10.5)	5/185	(2.7)	45/563	(8.0)	20/785	(2.5)
≥10 x ULN	6/167	(3.6)	9/162	(5.6)	1/185	(0.5)	13/563	(2.3)	3/785	(0.4)
≥20 x ULN	0/167	(0.0)	2/162	(1.2)	1/185	(0.5)	4/563	(0.7)	0/785	(0.0)
Bilirubin										
≥2 x ULN	2/167	(1.2)	5/163	(3.1)	2/187	(1.1)	13/563	(2.3)	13/785	(1.7)
Alkaline Phosphatase										
≥1.5 x ULN	20/167	(12.0)	25/163	(15.3)	17/185	(9.2)	144/563	(25.6)	151/785	(19.2)
Aminotransferase (ALT or AST) and Bilirubin										
AT ≥3 x ULN and BILI ≥1.5 x ULN	1/167	(0.6)	5/163	(3.1)	2/188	(1.1)	12/563	(2.1)	8/785	(1.0)
Aminotransferase (ALT or AST) and Bilirubin										
AT ≥3 x ULN and BILI ≥2 x ULN	1/167	(0.6)	5/163	(3.1)	2/188	(1.1)	7/563	(1.2)	6/785	(0.8)
Aminotransferase (ALT or AST) and Bilirubin and Alkaline Phosphatase										
AT ≥3 x ULN and BILI ≥2 x ULN and ALP <2 x ULN	0/167	(0.0)	0/163	(0.0)	0/187	(0.0)	2/563	(0.4)	3/785	(0.4)

n = Number of participants with postbaseline test results (or combination of test results from the same day) that met predetermined criteria.

m = Number of participants with at least one postbaseline test result or combination of test results from the same day.

ALP = Alkaline phosphatase; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; AT = Aminotransferase (ALT or AST); BILI = Bilirubin; ULN = Upper limit of normal range.

Database cutoff date for KN905: 06JUN2025.

Safety in special populations

Age

Table 77 - Adverse Event Summary by Age Category (<65, ≥65 Years) (APaT Population)

	KN-905 EV + Pembro				KN-905 Pembro mono				KN-905 Cystectomy				EV + Pembro Combo ISD			
	<65		>=65		<65		>=65		<65		>=65		<65		>=65	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	29		138		31		132		39		203		173		391	
with one or more adverse events	29	(100.0)	138	(100.0)	30	(96.8)	129	(97.7)	21	(53.8)	131	(64.5)	173	(100.0)	390	(99.7)
with no adverse event	0	(0.0)	0	(0.0)	1	(3.2)	3	(2.3)	18	(46.2)	72	(35.5)	0	(0.0)	1	(0.3)
with drug-related[a] adverse events	24	(82.8)	130	(94.2)	20	(64.5)	86	(65.2)	0	(0.0)	0	(0.0)	168	(97.1)	382	(97.7)
with toxicity grade 3-5 adverse events	18	(62.1)	101	(73.2)	17	(54.8)	99	(75.0)	13	(33.3)	85	(41.9)	114	(65.9)	321	(82.1)
with toxicity grade 3-5 drug-related adverse events	7	(24.1)	69	(50.0)	4	(12.9)	34	(25.8)	0	(0.0)	0	(0.0)	81	(46.8)	249	(63.7)
with serious adverse events	17	(58.6)	80	(58.0)	18	(58.1)	89	(67.4)	15	(38.5)	79	(38.9)	64	(37.0)	231	(59.1)
with serious drug-related adverse events	5	(17.2)	28	(20.3)	3	(9.7)	25	(18.9)	0	(0.0)	0	(0.0)	31	(17.9)	124	(31.7)
who died	2	(6.9)	11	(8.0)	1	(3.2)	15	(11.4)	2	(5.1)	10	(4.9)	8	(4.6)	22	(5.6)
who died due to a drug-related adverse event	0	(0.0)	2	(1.4)	0	(0.0)	2	(1.5)	0	(0.0)	0	(0.0)	0	(0.0)	9	(2.3)
discontinued any drug due to an adverse event	11	(37.9)	70	(50.7)	5	(16.1)	40	(30.3)	0	(0.0)	0	(0.0)	80	(46.2)	199	(50.9)
discontinued any drug due to a drug-related adverse event	8	(27.6)	54	(39.1)	4	(12.9)	28	(21.2)	0	(0.0)	0	(0.0)	71	(41.0)	181	(46.3)
discontinued any drug due to a serious adverse event	3	(10.3)	28	(20.3)	4	(12.9)	29	(22.0)	0	(0.0)	0	(0.0)	19	(11.0)	65	(16.6)
discontinued any drug due to a serious drug-related adverse event	0	(0.0)	16	(11.6)	3	(9.7)	17	(12.9)	0	(0.0)	0	(0.0)	12	(6.9)	50	(12.8)

	EV Mono ISD				Pembro Mono RSD			
	<65		>=65		<65		>=65	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	279		514		4,524		3,107	
with one or more adverse events	278	(99.6)	508	(98.8)	4,364	(96.5)	3,011	(96.9)
with no adverse event	1	(0.4)	6	(1.2)	160	(3.5)	96	(3.1)
with drug-related[a] adverse events	266	(95.3)	481	(93.6)	3,231	(71.4)	2,231	(71.8)
with toxicity grade 3-5 adverse events	188	(67.4)	377	(73.3)	1,917	(42.4)	1,597	(51.4)
with toxicity grade 3-5 drug-related adverse events	128	(45.9)	276	(53.7)	629	(13.9)	579	(18.6)
with serious adverse events	121	(43.4)	242	(47.1)	1,457	(32.2)	1,285	(41.4)
with serious drug-related adverse events	55	(19.7)	107	(20.8)	451	(10.0)	389	(12.5)
who died	14	(5.0)	42	(8.2)	158	(3.5)	188	(6.1)
who died due to a drug-related adverse event	5	(1.8)	12	(2.3)	21	(0.5)	21	(0.7)
discontinued any drug due to an adverse event	50	(17.9)	118	(23.0)	554	(12.2)	512	(16.5)
discontinued any drug due to a drug-related adverse event	33	(11.8)	87	(16.9)	333	(7.4)	306	(9.8)
discontinued any drug due to a serious adverse event	24	(8.6)	56	(10.9)	366	(8.1)	348	(11.2)
discontinued any drug due to a serious drug-related adverse event	12	(4.3)	33	(6.4)	177	(3.9)	170	(5.5)

[a]Determined by the investigator to be related to the drug.
Treatment includes study medications and surgery.
For KN905, EV + Pembro Combo ISD, and Pembro Mono RSD, non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.
For EV Mono ISD, non-serious adverse events and serious adverse events up to 30 days of the last treatment are included.
For Pembro and EV+Pembro studies, MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.03.
Database cutoff date for KN905: 06JUN2025.

Sex

Table 78 - Adverse Event Summary by Sex (Male, Female) (APaT Population)

	KN-905 EV + Pembro				KN-905 Pembro mono				KN-905 Cystectomy				EV + Pembro Combo ISD			
	M		F		M		F		M		F		M		F	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	135		32		127		36		181		61		432		132	
with one or more adverse events	135	(100.0)	32	(100.0)	123	(96.9)	36	(100.0)	114	(63.0)	38	(62.3)	431	(99.8)	132	(100.0)
with no adverse event	0	(0.0)	0	(0.0)	4	(3.1)	0	(0.0)	67	(37.0)	23	(37.7)	1	(0.2)	0	(0.0)
with drug-related[a] adverse events	124	(91.9)	30	(93.8)	81	(63.8)	25	(69.4)	0	(0.0)	0	(0.0)	422	(97.7)	128	(97.0)
with toxicity grade 3-5 adverse events	96	(71.1)	23	(71.9)	90	(70.9)	26	(72.2)	71	(39.2)	27	(44.3)	334	(77.3)	101	(76.5)
with toxicity grade 3-5 drug-related adverse events	60	(44.4)	16	(50.0)	30	(23.6)	8	(22.2)	0	(0.0)	0	(0.0)	261	(60.4)	69	(52.3)
with serious adverse events	82	(60.7)	15	(46.9)	82	(64.6)	25	(69.4)	69	(38.1)	25	(41.0)	234	(54.2)	61	(46.2)
with serious drug-related adverse events	26	(19.3)	7	(21.9)	23	(18.1)	5	(13.9)	0	(0.0)	0	(0.0)	126	(29.2)	29	(22.0)
who died	12	(8.9)	1	(3.1)	10	(7.9)	6	(16.7)	7	(3.9)	5	(8.2)	22	(5.1)	8	(6.1)
who died due to a drug-related adverse event	2	(1.5)	0	(0.0)	2	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)	7	(1.6)	2	(1.5)
discontinued any drug due to an adverse event	66	(48.9)	15	(46.9)	37	(29.1)	8	(22.2)	0	(0.0)	0	(0.0)	223	(51.6)	56	(42.4)
discontinued any drug due to a drug-related adverse event	48	(35.6)	14	(43.8)	28	(22.0)	4	(11.1)	0	(0.0)	0	(0.0)	206	(47.7)	46	(34.8)
discontinued any drug due to a serious adverse event	28	(20.7)	3	(9.4)	28	(22.0)	5	(13.9)	0	(0.0)	0	(0.0)	72	(16.7)	12	(9.1)
discontinued any drug due to a serious drug-related adverse event	13	(9.6)	3	(9.4)	19	(15.0)	1	(2.8)	0	(0.0)	0	(0.0)	57	(13.2)	5	(3.8)

	EV Mono ISD				Pembro Mono RSD			
	M		F		M		F	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	584		209		4,889		2,742	
with one or more adverse events	580	(99.3)	206	(98.6)	4,711	(96.4)	2,664	(97.2)
with no adverse event	4	(0.7)	3	(1.4)	178	(3.6)	78	(2.8)
with drug-related[a] adverse events	547	(93.7)	200	(95.7)	3,457	(70.7)	2,005	(73.1)
with toxicity grade 3-5 adverse events	412	(70.5)	153	(73.2)	2,265	(46.3)	1,249	(45.6)
with toxicity grade 3-5 drug-related adverse events	296	(50.7)	108	(51.7)	814	(16.6)	394	(14.4)
with serious adverse events	272	(46.6)	91	(43.5)	1,797	(36.8)	945	(34.5)
with serious drug-related adverse events	123	(21.1)	39	(18.7)	566	(11.6)	274	(10.0)
who died	40	(6.8)	16	(7.7)	240	(4.9)	106	(3.9)
who died due to a drug-related adverse event	14	(2.4)	3	(1.4)	27	(0.6)	15	(0.5)
discontinued any drug due to an adverse event	125	(21.4)	43	(20.6)	695	(14.2)	371	(13.5)
discontinued any drug due to a drug-related adverse event	94	(16.1)	26	(12.4)	418	(8.5)	221	(8.1)
discontinued any drug due to a serious adverse event	57	(9.8)	23	(11.0)	473	(9.7)	241	(8.8)
discontinued any drug due to a serious drug-related adverse event	35	(6.0)	10	(4.8)	233	(4.8)	114	(4.2)

[a]Determined by the investigator to be related to the drug.
Treatment includes study medications and surgery.
For KN905, EV + Pembro Combo ISD, and Pembro Mono RSD, non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.
For EV Mono ISD, non-serious adverse events and serious adverse events up to 30 days of the last treatment are included.
For Pembro and EV+Pembro studies, MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.03.
Database cutoff date for KN905: 06JUN2025.

ECOG

Table 79 Adverse Event Summary by ECOG Status Category (0, 1, 2) (APaT Population)

	KN-905 EV + Pembro						KN-905 Pembro mono					
	[0] Normal Activity		[1] Symptoms		[2] Ambulatory		[0] Normal Activity		[1] Symptoms		[2] Ambulatory	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	100		46		21		73		53		37	
with one or more adverse events	100	(100.0)	46	(100.0)	21	(100.0)	71	(97.3)	53	(100.0)	35	(94.6)
with no adverse event	0	(0.0)	0	(0.0)	0	(0.0)	2	(2.7)	0	(0.0)	2	(5.4)
with drug-related[a] adverse events	96	(96.0)	39	(84.8)	19	(90.5)	56	(76.7)	33	(62.3)	17	(45.9)
with toxicity grade 3-5 adverse events	73	(73.0)	33	(71.7)	13	(61.9)	50	(68.5)	43	(81.1)	23	(62.2)
with toxicity grade 3-5 drug-related adverse events	50	(50.0)	18	(39.1)	8	(38.1)	16	(21.9)	16	(30.2)	6	(16.2)
with serious adverse events	57	(57.0)	29	(63.0)	11	(52.4)	45	(61.6)	42	(79.2)	20	(54.1)
with serious drug-related adverse events	20	(20.0)	10	(21.7)	3	(14.3)	13	(17.8)	12	(22.6)	3	(8.1)
who died	5	(5.0)	6	(13.0)	2	(9.5)	3	(4.1)	9	(17.0)	4	(10.8)
who died due to a drug-related adverse event	0	(0.0)	1	(2.2)	1	(4.8)	1	(1.4)	1	(1.9)	0	(0.0)
discontinued any drug due to an adverse event	49	(49.0)	25	(54.3)	7	(33.3)	18	(24.7)	20	(37.7)	7	(18.9)
discontinued any drug due to a drug-related adverse event	40	(40.0)	17	(37.0)	5	(23.8)	15	(20.5)	13	(24.5)	4	(10.8)
discontinued any drug due to a serious adverse event	15	(15.0)	13	(28.3)	3	(14.3)	10	(13.7)	18	(34.0)	5	(13.5)
discontinued any drug due to a serious drug-related adverse event	9	(9.0)	6	(13.0)	1	(4.8)	7	(9.6)	11	(20.8)	2	(5.4)

	KN-905 Cystectomy						EV + Pembro Combo ISD					
	[0] Normal Activity		[1] Symptoms		[2] Ambulatory		[0] Normal Activity		[1] Symptoms		[2] Ambulatory	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	122		82		38		273		258		33	
with one or more adverse events	75	(61.5)	55	(67.1)	22	(57.9)	273	(100.0)	257	(99.6)	33	(100.0)
with no adverse event	47	(38.5)	27	(32.9)	16	(42.1)	0	(0.0)	1	(0.4)	0	(0.0)
with drug-related[a] adverse events	0	(0.0)	0	(0.0)	0	(0.0)	271	(99.3)	250	(96.9)	29	(87.9)
with toxicity grade 3-5 adverse events	46	(37.7)	36	(43.9)	16	(42.1)	209	(76.6)	199	(77.1)	27	(81.8)
with toxicity grade 3-5 drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	174	(63.7)	136	(52.7)	20	(60.6)
with serious adverse events	45	(36.9)	36	(43.9)	13	(34.2)	130	(47.6)	148	(57.4)	17	(51.5)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	80	(29.3)	66	(25.6)	9	(27.3)
who died	3	(2.5)	6	(7.3)	3	(7.9)	7	(2.6)	19	(7.4)	4	(12.1)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.7)	5	(1.9)	2	(6.1)
discontinued any drug due to an adverse event	0	(0.0)	0	(0.0)	0	(0.0)	143	(52.4)	117	(45.3)	19	(57.6)
discontinued any drug due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	132	(48.4)	102	(39.5)	18	(54.5)
discontinued any drug due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)	44	(16.1)	35	(13.6)	5	(15.2)
discontinued any drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	35	(12.8)	23	(8.9)	4	(12.1)

	EV Mono ISD						Pembro Mono RSD					
	[0] Normal Activity		[1] Symptoms		[2] Ambulatory		[0] Normal Activity		[1] Symptoms		[2] Ambulatory	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	284		485		24		4,016		3,440		167	
with one or more adverse events	281	(98.9)	481	(99.2)	24	(100.0)	3,883	(96.7)	3,324	(96.6)	162	(97.0)
with no adverse event	3	(1.1)	4	(0.8)	0	(0.0)	133	(3.3)	116	(3.4)	5	(3.0)
with drug-related[a] adverse events	271	(95.4)	456	(94.0)	20	(83.3)	3,072	(76.5)	2,295	(66.7)	92	(55.1)
with toxicity grade 3-5 adverse events	193	(68.0)	354	(73.0)	18	(75.0)	1,540	(38.3)	1,866	(54.2)	105	(62.9)
with toxicity grade 3-5 drug-related adverse events	149	(52.5)	244	(50.3)	11	(45.8)	623	(15.5)	555	(16.1)	28	(16.8)
with serious adverse events	111	(39.1)	240	(49.5)	12	(50.0)	1,157	(28.8)	1,491	(43.3)	90	(53.9)
with serious drug-related adverse events	53	(18.7)	105	(21.6)	4	(16.7)	442	(11.0)	381	(11.1)	16	(9.6)
who died	11	(3.9)	40	(8.2)	5	(20.8)	93	(2.3)	237	(6.9)	15	(9.0)
who died due to a drug-related adverse event	3	(1.1)	12	(2.5)	2	(8.3)	13	(0.3)	29	(0.8)	0	(0.0)
discontinued any drug due to an adverse event	62	(21.8)	100	(20.6)	6	(25.0)	515	(12.8)	522	(15.2)	27	(16.2)
discontinued any drug due to a drug-related adverse event	52	(18.3)	64	(13.2)	4	(16.7)	379	(9.4)	247	(7.2)	12	(7.2)
discontinued any drug due to a serious adverse event	21	(7.4)	54	(11.1)	5	(20.8)	296	(7.4)	397	(11.5)	19	(11.4)
discontinued any drug due to a serious drug-related adverse event	15	(5.3)	27	(5.6)	3	(12.5)	184	(4.6)	156	(4.5)	6	(3.6)

[a]Determined by the investigator to be related to the drug.
Treatment includes study medications and surgery.
For KN905, EV + Pembro Combo ISD, and Pembro Mono RSD, non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.
For EV Mono ISD, non-serious adverse events and serious adverse events up to 30 days of the last treatment are included.
For Pembro and EV+Pembro studies, MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.03.
Database cutoff date for KN905: 06JUN2025.
The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Region

Table 80 Adverse Event Summary by Region (US, EU, Rest of the World) (APaT Population)

	KN-905 EV + Pembro						KN-905 Pembro mono						KN-905 Cystectomy					
	US		EU		Rest of the World		US		EU		Rest of the World		US		EU		Rest of the World	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	21		76		70		18		73		72		34		99		109	
with one or more adverse events	21	(100.0)	76	(100.0)	70	(100.0)	18	(100.0)	72	(98.6)	69	(95.8)	28	(82.4)	68	(68.7)	56	(51.4)
with no adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)	3	(4.2)	6	(17.6)	31	(31.3)	53	(48.6)
with drug-related[a] adverse events	21	(100.0)	72	(94.7)	61	(87.1)	13	(72.2)	54	(74.0)	39	(54.2)	0	(0.0)	0	(0.0)	0	(0.0)
with toxicity grade 3-5 adverse events	16	(76.2)	55	(72.4)	48	(68.6)	16	(88.9)	53	(72.6)	47	(65.3)	16	(47.1)	45	(45.5)	37	(33.9)
with toxicity grade 3-5 drug-related adverse events	8	(38.1)	38	(50.0)	30	(42.9)	3	(16.7)	25	(34.2)	10	(13.9)	0	(0.0)	0	(0.0)	0	(0.0)
with serious adverse events	13	(61.9)	43	(56.6)	41	(58.6)	16	(88.9)	50	(68.5)	41	(56.9)	15	(44.1)	45	(45.5)	34	(31.2)
with serious drug-related adverse events	2	(9.5)	15	(19.7)	16	(22.9)	2	(11.1)	19	(26.0)	7	(9.7)	0	(0.0)	0	(0.0)	0	(0.0)
who died	3	(14.3)	3	(3.9)	7	(10.0)	2	(11.1)	6	(8.2)	8	(11.1)	1	(2.9)	5	(5.1)	6	(5.5)
who died due to a drug-related adverse event	1	(4.8)	1	(1.3)	0	(0.0)	0	(0.0)	2	(2.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to an adverse event	10	(47.6)	43	(56.6)	28	(40.0)	8	(44.4)	24	(32.9)	13	(18.1)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to a drug-related adverse event	8	(38.1)	34	(44.7)	20	(28.6)	6	(33.3)	19	(26.0)	7	(9.7)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to a serious adverse event	2	(9.5)	16	(21.1)	13	(18.6)	4	(22.2)	18	(24.7)	11	(15.3)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	1	(4.8)	9	(11.8)	6	(8.6)	2	(11.1)	13	(17.8)	5	(6.9)	0	(0.0)	0	(0.0)	0	(0.0)

	EV + Pembro Combo ISD						EV Mono ISD						Pembro Mono RSD					
	US		EU		Rest of the World		US		EU		Rest of the World		US		EU		Rest of the World	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	191		173		200		414		143		236		2,296		2,856		2,479	
with one or more adverse events	191	(100.0)	172	(99.4)	200	(100.0)	412	(99.5)	139	(97.2)	235	(99.6)	2,244	(97.7)	2,745	(96.1)	2,386	(96.2)
with no adverse event	0	(0.0)	1	(0.6)	0	(0.0)	2	(0.5)	4	(2.8)	1	(0.4)	52	(2.3)	111	(3.9)	93	(3.8)
with drug-related[a] adverse events	185	(96.9)	170	(98.3)	195	(97.5)	392	(94.7)	131	(91.6)	224	(94.9)	1,674	(72.9)	2,018	(70.7)	1,770	(71.4)
with toxicity grade 3-5 adverse events	157	(82.2)	125	(72.3)	153	(76.5)	291	(70.3)	97	(67.8)	177	(75.0)	1,119	(48.7)	1,251	(43.8)	1,144	(46.1)
with toxicity grade 3-5 drug-related adverse events	117	(61.3)	92	(53.2)	121	(60.5)	208	(50.2)	61	(42.7)	135	(57.2)	333	(14.5)	447	(15.7)	428	(17.3)
with serious adverse events	100	(52.4)	88	(50.9)	107	(53.5)	185	(44.7)	70	(49.0)	108	(45.8)	863	(37.6)	1,019	(35.7)	860	(34.7)
with serious drug-related adverse events	48	(25.1)	47	(27.2)	60	(30.0)	77	(18.6)	31	(21.7)	54	(22.9)	195	(8.5)	332	(11.6)	313	(12.6)
who died	14	(7.3)	5	(2.9)	11	(5.5)	26	(6.3)	12	(8.4)	18	(7.6)	79	(3.4)	126	(4.4)	141	(5.7)
who died due to a drug-related adverse event	5	(2.6)	1	(0.6)	3	(1.5)	10	(2.4)	4	(2.8)	3	(1.3)	5	(0.2)	13	(0.5)	24	(1.0)
discontinued any drug due to an adverse event	98	(51.3)	96	(55.5)	85	(42.5)	90	(21.7)	33	(23.1)	45	(19.1)	294	(12.8)	400	(14.0)	372	(15.0)
discontinued any drug due to a drug-related adverse event	92	(48.2)	89	(51.4)	71	(35.5)	65	(15.7)	23	(16.1)	32	(13.6)	156	(6.8)	260	(9.1)	223	(9.0)
discontinued any drug due to a serious adverse event	26	(13.6)	30	(17.3)	28	(14.0)	41	(9.9)	18	(12.6)	21	(8.9)	202	(8.8)	264	(9.2)	248	(10.0)
discontinued any drug due to a serious drug-related adverse event	20	(10.5)	24	(13.9)	18	(9.0)	25	(6.0)	9	(6.3)	11	(4.7)	84	(3.7)	140	(4.9)	123	(5.0)

[a]Determined by the investigator to be related to the drug.
Treatment includes study medications and surgery.
For KN905, EV + Pembro Combo ISD, and Pembro Mono RSD, non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.
For EV Mono ISD, non-serious adverse events and serious adverse events up to 30 days of the last treatment are included.
For Pembro and EV+Pembro studies, MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.03.
Database cutoff date for KN905: 06JUN2025.
The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Safety related to drug-drug interactions and other interactions

As per the SmPC, no formal drug-drug interaction studies with EV have been conducted. Theoretically unbound MMAE might exhibit relevant interactions with strong CYP3A inhibitor/inducers, which would increase/decrease MMAE concentrations. Relevant warnings are included in the SmPC.

Discontinuation due to adverse events

Table 81 - Participants with adverse events resulting in any drug discontinuation (sorted by decreasing incidence) (Incidence 0%) Combined phases - APaT2 Population - participants who received EV/Pembrolizumab

	EV + Pembro	
	n	(%)
Participants in population	167	
with one or more adverse events	81	(48.5)
with no adverse events	86	(51.5)
Diarrhoea	7	(4.2)
Peripheral sensory neuropathy	4	(2.4)
Alanine aminotransferase increased	3	(1.8)
Aspartate aminotransferase increased	3	(1.8)
Neuropathy peripheral	3	(1.8)
Pneumonitis	3	(1.8)
Pruritus	3	(1.8)
Rash	3	(1.8)
Acute kidney injury	2	(1.2)
Arthralgia	2	(1.2)
Dermatitis exfoliative generalised	2	(1.2)
Dysgeusia	2	(1.2)
Fatigue	2	(1.2)
Intestinal obstruction	2	(1.2)
Neurotoxicity	2	(1.2)
Rash maculo-papular	2	(1.2)
Sepsis	2	(1.2)
Skin exfoliation	2	(1.2)
Toxic epidermal necrolysis	2	(1.2)
Acute myocardial infarction	1	(0.6)
Amylase increased	1	(0.6)
Anaemia	1	(0.6)
Autoimmune nephritis	1	(0.6)
Bacterial infection	1	(0.6)
Bile duct cancer	1	(0.6)
Blood creatine phosphokinase increased	1	(0.6)
Blood creatinine increased	1	(0.6)
Colitis	1	(0.6)
Colon cancer	1	(0.6)
Death	1	(0.6)
Dermatitis	1	(0.6)
Dermatitis bullous	1	(0.6)

Every participant is counted a single time for each applicable row and column.
Treatment includes study medications and surgery.
Non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.
MedDRA V28.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 06JUN2025.

In the perioperative EV + pembrolizumab group, in the Combined phases, 48.5%, 41.3%, and 34.1% of participants experienced AEs resulting in discontinuation of any study drug, enfortumab vedotin, or pembrolizumab, respectively. Most AEs (by PT) resulting in discontinuation of study drug occurred in ≤2% of participants. AEs resulting in discontinuation for ≥2% of participants in the perioperative EV + pembrolizumab group were:

- Any drug: diarrhea (4.2%) and peripheral sensory neuropathy (2.4%).

- Enfortumab vedotin: peripheral sensory neuropathy (2.4%).
- Pembrolizumab: diarrhea (4.2%).

In the **Preoperative/Surgical phase**, 26.9%, 25.7%, and 17.4% of participants in the perioperative EV + pembrolizumab group experienced AEs resulting in discontinuation of any study drug, enfortumab vedotin, or pembrolizumab, respectively. All AEs resulting in discontinuation of study drug occurred in <2% of participants. Most common were:

- Enfortumab vedotin: peripheral sensory neuropathy (n=3, 1.8%), dermatitis exfoliative generalised, diarrhoea, dysgeusia, fatigue, pruritus, rash, skin exfoliation, toxic epidermal necrolysis (each n=2, 1.2%).
- Pembrolizumab: alanine aminotransferase increased, aspartate aminotransferase increased, dermatitis exfoliative generalised, diarrhoea, dysgeusia, toxic epidermal necrolysis (each n=2, 1.2%).

In the **Postoperative phase**, 37.0%, 26.0%, and 28.0% of participants in the perioperative EV + pembrolizumab group experienced AEs resulting in discontinuation of any study drug, enfortumab vedotin, or pembrolizumab, respectively. Most AEs resulting in discontinuation of any study drug occurred in <2% of participants. AEs resulting in discontinuation for ≥2% of participants in the perioperative EV + pembrolizumab group were:

- Any drug: diarrhea (5%), acute kidney injury, neuropathy peripheral, neurotoxicity, and pneumonitis (2% each).
- Enfortumab vedotin: neuropathy peripheral and neurotoxicity (2% each).
- Pembrolizumab: diarrhea (5%), acute kidney injury and pneumonitis (2% each)

2.6.2. Dose reductions

Dose reduction was only applicable for EV. No dose reductions were permitted for pembrolizumab per protocol.

Table 82 - Participants With Adverse Events Resulting in Dose Reduction for EV (APaT Population)

	EV + Pembro	
	n	(%)
Participants in population	167	
with one or more adverse events	28	(16.8)
with no adverse events	139	(83.2)
Rash	4	(2.4)
Weight decreased	4	(2.4)
Decreased appetite	3	(1.8)
Fatigue	3	(1.8)
Pruritus	3	(1.8)
Rash maculo-papular	3	(1.8)
Alanine aminotransferase increased	2	(1.2)
Aspartate aminotransferase increased	2	(1.2)
Neutropenia	2	(1.2)
Blepharitis	1	(0.6)
Blood creatinine increased	1	(0.6)
Constipation	1	(0.6)
Drug eruption	1	(0.6)
Dysgeusia	1	(0.6)
Hepatic function abnormal	1	(0.6)
Hyperglycaemia	1	(0.6)
Muscle spasms	1	(0.6)
Muscular weakness	1	(0.6)
Nausea	1	(0.6)
Neurotoxicity	1	(0.6)
Peripheral sensory neuropathy	1	(0.6)
Rash pruritic	1	(0.6)
Renal impairment	1	(0.6)
Skin reaction	1	(0.6)
Urinary tract infection	1	(0.6)
Vision blurred	1	(0.6)

Every participant is counted a single time for each applicable row and column.
Treatment includes study medications and surgery.
Non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.
MedDRA V28.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 06JUN2025.

2.7. Immunogenicity

Blood samples for ADA were collected for patients recruited to the EV + Pembro arm of the KN-905 trial resulting in 159/167 evaluable participants.

Table 83 - Summary of ADA Incidence

Participants:	EV 1.25 mg/kg + Pembro (N = 167)
With a baseline and ≥ 1 post-baseline sample	159
Negative at baseline	156
Positive post-baseline†	2/156 (1.3%)
Positive at baseline	3
Positive post-baseline†	2/3 (66.7%)
Treatment-boosted† ADA	0

ADA: antidrug antibody; EV: enfortumab vedotin; Pembro: pembrolizumab.
†For participants whose ADA status is positive at baseline, a positive post-baseline sample, and titer value that is ≥ 4 times higher than the baseline is considered treatment-boosted ADA.

Post marketing experience

EV was first approved for marketing in the US on 18-DEC-2019 under accelerated approval, and regular approval was granted on 09-JUL-2021. The cumulative number of patients receiving EV is 121.411 patients. There are no records of any EV registration being revoked or withdrawn for safety reasons in any country.

2.7.1. Discussion on clinical safety

The safety assessment of enfortumab vedotin (EV) in combination with pembrolizumab (Pembro) is based on the pivotal trial data from the KEYNOTE-905 trial comparing EV + Pembrolizumab or Pembrolizumab monotherapy or surgery alone in a perioperative setting. One hundred sixty seven (167) patients received at least one dose of enfortumab vedotin 1.25 mg/kg in combination with pembrolizumab in this study.

Patients characteristics within the pivotal trial KN-095 were mostly well-balanced between arms with a median age of 73 (range: 72-74 across arms), race with a 77.2% - 89.6% white majority across arms and with geographic region distribution of 40.9% - 45.5% European, 41.9% - 45.0% rest of the world and 11.0% - 14.0% US.

There were differences in male/female composition within the KN-905 trial with 19.2% in the EV-Pembro arm, 22.1% in the Pembro mono arm and 25.2% in the cystectomy. There was also a difference in ECOG performance status (PS) between arms with the Pembro mono arm having 22.7% with an ECOG-PS of 2 compared to only 12.6% and 15.7% in the EV + Pembro arm and cystectomy arm, respectively. The Pembro mono arm also recruited in lowest proportion of patients with an ECOG-PS of 0 (44.8%) compared to EV + Pembro arm (59.9%) and cystectomy arm (50.4%). Compared to reference safety datasets, KN-905 pivotal trial recruited older patients (median 4-12 years older) with a higher proportion of ECOG 2 (12.6% - 22.75% compared to 5% - 9%). None of these differences are expected to significantly impact safety characterisation. Hyperglycaemia is an important AE of pembro. Important differences were noted in patients with baseline prediabetes and diabetes based on HbA1c with 40.1% and 16.8% in the EV arm compared to 25.6% and 7.4% in the cystectomy arm, respectively. Proportion of missing data were also high. This was due to HbA1c testing not being mandated before amendment 2. Measurements after amendment 2 was implemented, were well balanced and support that pre-treatment risk of hyperglycemia was similar between the arms of the pivotal trial.

The same dosing of Padcev (1.25mg/kg IV) was used across all trials in various segmentations of the safety population. The median **duration of exposure** to study treatment in the KN-905 trial was shorter than the EV + Pembro reference ISD with 6.3 months compared to 9.4 months. The duration of EV exposure alone was similarly shorter for these arms with 5.5 months (5 cycles) compared to 7.0 months (9 cycles). The KN-905 trial specified a fixed regime (maximum planned no. of cycles) compared to the metastatic settings of the reference safety populations (treatment until progression).

In the KN-905 pivotal trial, the overall toxicity profile was comparable to that of the EV + Pembro ISD. However, a significantly lower incidence of peripheral neuropathy (including sensory) was observed in the KN-905 trial compared to the EV + Pembro ISD (24.0% vs. 54.6%). Safety reference trials such as KN-869 and EV-302 also recruited patients without concurrent treatment with cisplatin (although some patients could have received this in the neo-/adjuvant setting) and so the main reason for the lower rate of neuropathy in the KN-905 trial is likely the lower exposure of EV payload MMAE as drug-induced peripheral neuropathy from other microtubule inhibitors (taxanes, vinca alkaloids) exhibits dose-dependency.

The **pre- and postoperative safety profiles** of EV + Pembro in the KN-905 pivotal trial were similar. Incidences of ≥3 grade TEAEs were 59.9% preoperative and 56.0% postoperative and incidences of SAEs were 45.5% and 43%, respectively. There were 6 TEAEs resulting in death preoperatively and 7 postoperative events.

Overall, the safety profile of grade ≥3 TEAEs in the KN-905 was comparable to the EV + Pembro ISD except for the fact that the incidence of urinary tract infection was almost doubled in the pivotal study. However, this is not unexpected given the major surgical procedure incorporated in the trial and the incidence in the surgery alone arm was 7.4%.

The incidence of **SAEs** in patients treated with EV + Pembro was 58.1% compared to 38.8% among patients treated surgery alone. Some added toxicity of EV+ Pembro was observed as the incidence of SAE in the Pembro monotherapy ISD was 45.8%, however within the pivotal KN-905 there were more SAEs in the pembro monotherapy arm than in the EV + Pembro arm (65.6% vs 58.1%). The SAE profile of EV + Pembro in the pivotal KN-905 trial was consistent with the ISD, albeit significantly more pronounced with higher rates of each specific SAE except acute kidney injury. Especially urinary tract infections including sepsis and pyelonephritis were much higher in the KN-905 trial than in the ISD, which was also true for the Pembro monotherapy comparison to the Pembro monotherapy RSD alluding to the major surgical procedure included in the perioperative setting compared to the metastatic and adjuvant (for Pembro) settings of the reference groups.

The incidence of **TEAEs leading to deaths** in patients treated with EV+ Pembro was 7.8% compared to 9.8% among patients treated with Pembro monotherapy and 5.0% among patients who received surgery alone. In the reference safety populations, this was 5.3% for EV + Pembro and 4.5% for the Pembro monotherapy. Review of narrative descriptions of TEAEs leading to death in the KN-905 trial were acceptable and causal conclusions reasonably supported.

Adverse events of special interest were pre-specified in the protocol and included skin reactions, peripheral neuropathy, ocular events, hyperglycaemia and IRR. In addition, pneumonitis is an important identified risk of EV.

Skin reactions were common (61.1% -102 patients out of 167; 20.4% SCAR) in EV + Pembro arm compared to only 2.1% in the surgery alone group. Markedly, reactions were lower, but consistent with the ISD EV + Pembro group (70% skin reaction, 28.5% SCAR). A majority of these skin

reactions included rash and rash maculo-papular. Severe (Grade 3 or 4) skin reactions occurred in 10% (17) of patients (Grade 3: 9%, Grade 4: 1%).

Time to onset of any grade skin reactions were similar for KN-905 and the reference groups.

Peripheral neuropathy was significantly less common in EV + Pembro arm (38.9%) compared the ISD EV + Pembro group (67.4%). Sensory neuropathy was more common than motor neuropathy (36.5% vs 4.8%), which is consistent with a microtubule-disrupting agent and also the ratio observed in the EV + Pembro RSD group (62.9% vs. 16.1%).

The proportion of patients with hyperglycaemia was 16.8% in the EV + Pembro and 0.8% in the surgery alone group. The proportion of patients was generally similar to that observed in the EV + Pembro ISD (19.9%) and the EV monotherapy ISD (16.8%). The incidence of grade ≥3 events were 5.4% in the EV+ Pembro arm and 9.4% in the EV + Pembro ISD. Time to onset and resolution of hyperglycaemia were 0.7/2 months in the KN-905 and 0.7/2 months in the ISD.

Ocular disorders (primary dry eyes) were observed at a lower incidence of 22.8% in the EV + Pembro group compared to 32.3% in the ISD.

The rate of pneumonitis/ILD in the EV+ Pembro arm of the KN-905 trial was 4.2% (7 patients) compared to 11.0% and 3.3% in the EV + Pembro ISD and EV monotherapy ISD respectively. All events were Grade 1-2. Pneumonitis/ILD led to discontinuation of enfortumab vedotin in 0.6% of patients. The median time to onset of any grade pneumonitis/ILD was 2.5 months (range: 1.9 to 9.7 months).

There were no significant differences between major **laboratory parameters** of the EV + Pembro arm of the KN-905 and the referenced safety groups. Haematological parameters of the EV + Pembro arm of the KN-905 study were similar to the EV + Pembro ISD. Events of increased glucose (highest post-baseline) showed similar incidences between the EV + Pembro arm of KN-905 trial and the corresponding ISD group (grade ≥3 glucose 12.0% compared to 14.2%, all grades 72.5% compared to 67.9% respectively), indicating no differences in hyperglycaemia risks when administered in the perioperative setting.

Age-dependant toxicity has been observed for EV combined with Pembrolizumab with higher grade ≥3 TEAEs among patients ≥ 65 years of age (82.1%) compared to patients <65 years of age (65.9%) in the EV + Pembro ISD. This observation was not as pronounced in the KN-905 trial for the combination treatment (62.1% compared to 73.2%) with some uncertainty given that only 29 patients were recruited in the <65 years of age combination treatment arm (and 138 patients ≥65 years). Two patients died in the <65 years of age group (6.9%) compared to 11 patients (8.0%) in ≥ 65 years of age group, which is similar to the ISD group (4.6% and 5.6%). Increased toxicity with increased age was also observed in the EV monotherapy ISD. Tables on specific TEAEs were not presented and given the small number of younger patients, these would not be informative and this is not pursued further.

There was a skewed recruitment in favour of males in the KN-905 Pembro + EV arm, which is expected as males have a higher risk of developing MIBC (32 females and 135 males). The rates of grade ≥ 3 TEAEs and deaths among males and females in the KN-905 study were 71.1% compared to 71.9% and 8.9% (12 deaths) compared to 3.1% (one death). The rate of grade ≥ 3 TEAEs and deaths among males and females EV + Pembro ISD were overall comparable.

No differences in overall toxicity was noted for race.

The incidence of discontinuations of any drug (EV + Pembro arm) in KN-905 pivotal trial was 48.5% and 49.5% in the reference safety group. In the Pembro monotherapy arm this was 27.6%

compared to 14.0% in the Pembro monotherapy RSD. The most common AEs that lead to any drug discontinuation in the EV + Pembro arm of the KN-905 were diarrhoea (4.2%), sensory peripheral neuropathy (2.4%), increased ALT and pneumonitis (each 1.8%). In the EV + Pembro ISD groups these were sensory peripheral neuropathy (15.8%), pneumonitis (3.2%), rash (2.5%), motor peripheral neuropathy (2.0%) and diarrhoea (1.6%). Forty-one percent of patients permanently discontinued enfortumab vedotin for adverse reactions; the most common adverse reaction (≥2%) leading to discontinuation was peripheral sensory neuropathy (2.4%). Adverse reactions leading to dose interruption of enfortumab vedotin occurred in 44% of patients. The most common adverse reactions (≥2%) leading to dose interruption were diarrhoea (4.2%), rash (4.2%), neutropenia (3.6%), fatigue (3%), hyperglycaemia (3%) and pruritus (2.4%). Adverse reactions leading to dose reduction of enfortumab vedotin occurred in 17% of patients. The most common adverse reactions (≥2%) leading to dose reduction were rash (2.4%) and weight decreased (2.4%).

Overall, the immunogenicity findings in KEYNOTE-905 are consistent with previous experience with EV + Pembro in 1L la/mUC studies (EV-103 and EV-302) and in the monotherapy treatment of later line metastatic UC. This is considered acceptable and clinically irrelevant.

2.7.2. Conclusions on clinical safety

Patients treated with EV + Pembro in the KN-905 experienced an overall similar toxicity profile compared to patients treated with the combination in previous clinical trial settings, even with the added burden of surgery. No new safety signals were identified. Notably, the incidence of peripheral neuropathy was almost halved in the perioperative setting compared to later metastatic settings. The discontinuation rates highlight the overall limited tolerability of the EV + pembrolizumab association, with worse toxicity with increasing age.

2.7.3. 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.

2.8. Risk management plan

The MAH submitted an updated RMP version with this application.

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

The PRAC considered that the risk management plan version 5.3 is acceptable.

The CHMP endorsed the Risk Management Plan version 5.3 with the following content

Safety concerns

Table 84 Summary of safety concerns

Summary of safety concerns	
Important identified risks	○ Skin reactions ○ Hyperglycemia ○ Pneumonitis/Interstitial lung disease

Important potential risks	None
Missing information	None

No new safety concerns were identified as a result of the review of the data from this extension of indication.

Pharmacovigilance plan

Table 85 Summary table of additional pharmacovigilance activities

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Protocol 7465-PV-0002 A non-interventional post authorization safety study (NI-PASS) to evaluate effectiveness of the patient card (Ongoing)	To evaluate patients' understanding and awareness of the content of the patient card related to risks of skin reactions and patient behaviours to minimize the risk.	Skin reactions	Submission of final study report to EMA	13 Oct 2025

EMA: European Medicines Agency; NI-PASS: Non Interventional - Post Authorization Safety Study.

Risk minimisation measures

Table 86 Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	**Risk minimization measures**	**Pharmacovigilance activities**
Skin reactions	Routine risk communication: • EU-SmPC Sections 4.2, 4.4 and 4.8; • PL Sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendations are provided in the EU-SmPC Section 4.4 to monitor for severe skin reactions starting with the first cycle and throughout enfortumab vedotin treatment. • Recommendations are provided in the EU-SmPC Section 4.2 for treatment interruption, dose reduction and treatment discontinuation of enfortumab vedotin. Additional risk minimization	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • NI-PASS category 3 study to assess evaluation of patients' understanding and awareness of the content of the patient card related to risks of skin reactions and patient behaviours to minimize the risk.

Safety concern	Risk minimization measures	Pharmacovigilance activities
	measures: • Patient card	
Hyperglycemia	Routine risk communication: • EU-SmPC Sections 4.2, 4.4 and 4.8 • PL Sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendations are provided in the EU-SmPC Section 4.4 to monitor blood glucose levels prior to dosing and periodically throughout the course of treatment. • Recommendations are provided in EU-SmPC Section 4.2 for treatment interruption and when to resume treatment of enfortumab vedotin. Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Pneumonitis/Interstitial lung disease	Routine risk communication: • EU-SmPC Sections 4.2, 4.4 and 4.8; • PL Sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • For Grade 2 pneumonitis/interstitial lung disease, withhold enfortumab vedotin until Grade ≤1, then resume at the same dose level or consider dose reduction by one dose level. • Permanently discontinue enfortumab vedotin for Grade ≥3 pneumonitis/interstitial lung disease Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

EU-SmPC: European Union-Summary of Product Characteristics; NI-PASS: Non-interventional Post-Authorization Safety Studies; PL: Package Leaflet; SJS: Stevens Johnson Syndrome; TEN: Toxic Epidermal Necrolysis.

The pharmacovigilance plan and risk minimisations activities remain unchanged.

2.9. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) which were reviewed and accepted by the CHMP.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representatives of Member States Malta and Κύπρος(Cyprus).

2.9.1. 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 changes do not significantly alter the readability of Padcev PL. Furthermore, since the populations for MIBC and la/mUC are considered to represent the same disease, the results from the previous readability testing remain sufficient to meet the user consultation requirements.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Padcev (enfortumab vedotin) is included in the additional monitoring list as it contains a new active substance.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The final indication is:

PADCEV, in combination with pembrolizumab, as neoadjuvant treatment and then continued after radical cystectomy as adjuvant treatment, is indicated for the treatment of patients with resectable muscle invasive bladder cancer (MIBC) who are ineligible for cisplatin-containing chemotherapy.

3.1.2. Available therapies and unmet medical need

Radical cystectomy (RC) with pelvic lymph node dissection (PLND) with its associated urinary diversion is the standard treatment of resectable MIBC with curative intent[25].

According to ESMO guidelines, for patients eligible to cisplatin-combination chemotherapy, 3-4 cycles of cisplatin-based neoadjuvant ChT should be given for MIBC[26] [27]. Adjuvant cisplatin-based ChT in patients who did not receive neoadjuvant therapy remains an area of debate[28].

Up to 50% of patients with MIBC are however considered unable to receive cisplatin-based chemotherapy due to comorbidities[29]. Carboplatin-based neoadjuvant regimens for cisplatin-ineligible patients with MIBC have demonstrated limited clinical response[30], and it is not recognized as standard neoadjuvant regimen[31].

[25] NCCN guidelines Bladder Cancer v 2.2025
[26] Powles T, Bellmunt J, Comperat E, et al; ESMO Guidelines Committee. Bladder cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022 Mar;33(3):244-258.
[27] EAU Guidelines. Edn. presented at the EAU Annual Congress Madrid 2025. ISBN 978-94-92671-29-5. http://uroweb.org/guidelines/compilations-of-all-guidelines/
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[29] Thompson RH, Boorjian SA, Kim SP et al. Eligibility for neoadjuvant/adjuvant cisplatin-based chemotherapy among radical cystectomy patients. BJU Int 2014;113(5b):E17-21.
[30] Fazili A, Jazayeri SB, Rose KM, et al. Cisplatin-ineligible patients with muscle-invasive bladder cancer demonstrate poor long-term survival following immediate radical cystectomy. BJU Int. 2026 Jan;137(1):181-188.
[31] Holzbeierlein J, Bixler BR, Buckley DI, et al. Treatment of non-metastatic muscle- invasive bladder cancer: AUA/ASCO/SUO guideline (2017; amended 2020, 2024). J Urol. 2024 Jul;212:3-10.

Adjuvant nivolumab for 1 year showed DFS improvement vs placebo in CHECKMATE-274[32], leading to FDA and EMA (only for PD-L1 positive tumors ≥1%) approval of this indication. ESMO guidelines[30] underline that, due to the inconsistency across trials (adjuvant atezolizumab did not improve DFS nor OS[33]) and uncertainty of the relationship between DFS and OS with immunotherapy, OS results are awaited before this treatment can be recommended. Postoperative RT may be an option for the subset of patients with high-risk pathology or presence of positive surgical margins after RC + PLND, and it is not considered standard treatment of patients with MIBC[34].

Up to 50% of patients with MIBC who undergo RC + PLND alone experience local or distant recurrence within 2 to 3 years[35], with five-year survival in about 50% of patients[36]. The literature on outcomes in cisplatin-ineligible MIBC is limited, and the available evidence is primarily from small, single-arm Phase 2 studies, or subset analyses. Effective treatment options for this frailer population are needed.

3.1.3. Main clinical studies

The pivotal study is the KEYNOTE-905/EV-303 study, a Phase 3, randomized, controlled, parallel-group, multisite, open-label study of perioperative pembrolizumab plus radical cystectomy and pelvic lymph node dissection (RC + PLND) (Arm A) and RC + PLND alone (Arm B) and perioperative enfortumab vedotin in combination with pembrolizumab plus RC + PLND (Arm C) in participants with MIBC (cT2-T4aN0M0 or cT1-T4aN1M0) who are ineligible for or decline cisplatin-based chemotherapy.

The pivotal results are based on the comparison between the combination EV + pembrolizumab perioperative strategy (Arm C) vs surgery alone (Arm B) in the ITT2 population (344 participants: 170 in combo arm and 174 in control arm).

The primary endpoint is event free survival (EFS), defined as the time from randomization to either 1) progression assessed by BICR, 2) failure to undergo surgery, 3) gross residual disease after surgery, 4) local or distant disease recurrence or 5) death from any cause. The key secondary endpoint is overall survival (OS).

3.2. Favourable effects

- The primary endpoint EFS per RECIST 1.1 by BICR showed a statistically significant improvement for perioperative EV + pembrolizumab regimen compared with RC + PLND alone. EFS events occurred in 28.2% of participants in Arm C and 54.6% in Arm B, with a HR of 0.40 (95% CI: 0.28, 0.57; one-sided p<0.0001) under the multiplicity-adjusted boundary. Median EFS was not reached in Arm C (95% CI: 37.3, NR) and was 15.7 months in Arm B (95% CI: 10.3, 20.5). The EFS rates at 12 months and 24 months were 77.8% and 74.7% in Arm C compared with 55.1% and 39.4% in Arm B, respectively, and Kaplan–Meier curves separated from randomization and remained separated over time. Prespecified EFS sensitivity analyses

[32] Bajorin DF, Witjes JA, Gschwend JE, et al. Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma. N Engl J Med. 2021 Jun 3;384(22):2102-2114. Erratum in: N Engl J Med. 2021 Aug 26;385(9):864.
[33] Bellmunt J, Hussain M, Gschwend JE, et al. Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma (IMvigor010): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2021;22(4):525-537.
[34] Powles T, Bellmunt J, Comperat E, et al; ESMO Guidelines Committee. Bladder cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022 Mar;33(3):244-258.
[35] Mari A, Campi R, Tellini R, et al. Patterns and predictors of recurrence after open radical cystectomy for bladder cancer: a comprehensive review of the literature. World J Urol. 2018;36:157-70.
[36] Stein, J.P., et al. Radical cystectomy for invasive bladder cancer: long-term results of a standard procedure. World J Urol, 2006. 24: 296.

were reported as generally consistent with the primary analysis, including consistency between investigator-assessed EFS and BICR-assessed EFS.

- OS results were statistically significant in favour of perioperative EV + pembrolizumab, with HR 0.50 (95% CI: 0.33, 0.74; one-sided p=0.0002). Median OS was not reached in Arm C and was 41.7 months in Arm B (95% CI: 31.8, NR). OS rates at 12 months and 24 months were 86.3% and 79.7% in Arm C compared with 75.7% and 63.1% in Arm B, respectively, with separation of Kaplan–Meier curves from randomization.

3.3. Uncertainties and limitations about favourable effects

The study design and amendment (i.e. dropping of the monotherapy arm) do not allow to formally evaluate the contribution of each component (EV and pembrolizumab) of the combination, as well as the contribution of each phase of treatment (neoadjuvant and adjuvant). Nonetheless, the combination of EV and pembrolizumab from the metastatic setting and the clear superiority of the combination shown in KEYNOTE-905 study attenuates the concern around the individual contribution of each component.

The results supporting this application are based on the first interim analysis of study KEYNOTE-905 and although more mature data are not considered necessary for this assessment, the final results are expected to be submitted post-approval to further inform the efficacy in the context of an early curative setting **(REC)**.

3.4. Unfavourable effects

Patients treated with EV+ Pembro in the KN-905 all experienced at least one **treatment emergent adverse event** (100%) and 92.2% experienced at least one treatment-related AE (92.2%).

The most **common adverse events of any grade** in the EV + Pembro were pruritus (47.3%), alopecia (34.7%), diarrhoea (34.1%), fatigue (32.3%), anaemia (30.5%), constipation (27.5%), nausea (25.7%), rash (25.1%), and AST increased and urinary tract infection (24.0% each). Peripheral neuropathy was lower than for reference safety group (24.0% vs. 54.6%, respectively).

The incidence of **grade ≥3 TEAEs** in patients treated with EV+ Pembro in the KN-905 trial was 71.3%, which was 77.1% in the reference safety population. For patients who received surgery alone, the rate of grade ≥3 TEAEs was 40.5%. The most common grade ≥3 TEAEs in of EV+ Pembro in the pivotal trial were urinary tract infection (12.0%), anaemia (9.0%), neutropenia (6.0%), acute kidney injury, diarrhoea and hyperglycaemia (each 4.2%).

The incidence of **SAEs** in patients treated with EV + Pembro in the KN-905 was higher than for the reference safety group (58.1% compared to 45.8%). The most common SAEs were urinary tract infection (10.2%), acute kidney injury (4.8%), urosepsis (4.2%), pyelonephritis (3.6%), pneumonia (3.0%), sepsis (3.0%).

The incidence of **TEAEs leading to deaths** in patients treated with EV+ Pembro was 7.8% (n=13) with 5 five deaths occurring in relation to surgical complications.

Skin reactions were a common **adverse event of special interest** in the KN-905 trial (61.1% skin reactions and 20.4% SCAR events). Grade ≥3 skin reactions were reported for 10.8% of patients. ILD/Pneumonitis of any grade was observed in 4.4%.

The rate of ≥3 and ≥5 ALT increased (highest post-baseline) in the EV + Pembro arm of the KN-905 trial was 13.8% and 4.8%. There were 1 (0.6%) event of Hy' s Law.

The incidence of **discontinuations** of any drug (EV + Pembro arm) was 48.5%. The most common AEs that lead to any drug discontinuation in the EV + Pembro arm of the KN-905 were diarrhoea (4.2%), sensory peripheral neuropathy (2.4%), increased ALT and pneumonitis (each 1.8%).

3.5. Uncertainties and limitations about unfavourable effects

None

3.6. Effects Table

Table 87: Effects Table for *EV-303/Keynote-905 Study: Padcev in combination with pembrolizumab for resectable MIBC in cisplatin-ineligible patients (data cut-off: 06-June-2025)*

Effect	Short description	Unit	Treatment EV + Pembro n=170	Control Surgery n=174	Uncertainties / Strength of evidence
Favourable Effects					
Primary endpoint	EFS by BICR	months	Median EFS not reached (37.3, NR)	Median EFS 15.7 (10.3, 20.5)	HR **0.40** (95% CI 0.28-0.57, p-value < 0.0001)
Key secondary endpoint	OS	months	Median OS was not reached (95% CI: NR, NR)	Median OS 41.7 (95% CI: 31.8, NR)	HR **0.50** (95% CI: 0.33, 0.74; p=0.0002)

Adverse Events	Unit	Treatment	Control	ISD
Unfavourable Effects				
		Pivotal trial – KN905		
		EV + Pembro	Surgery (alone)	EV + Pembro (ISD)
		n = 167	n = 242	n = 564
General				
TEAEs (any grade)	%	100	62.8	99.8
Grade ≥3 AEs	%	71.3	40.5	77.1
SAEs	%	58.1	38.8	52.3
TEAEs leading to death	% (n)	7.8 (13)	5.0 (12)	5.3 (30)
Discontinuations (any)	%	48.5	0	49.5

Abbreviations: HR: hazard ratio; CI: confidence interval; EFS: event free survival; OS: overall survival; KN905: KEYNOTE-905; BICR: blinded independent central review; TEAE: treatment emergent adverse event; SAE: serious adverse event; ISD, integrated safety dataset

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The pivotal study EV 303/Keynote-905 met its primary endpoint EFS by BICR and the key secondary endpoint OS, which were both statistically significant and with clinically meaningful magnitudes of effect in a target population with a high unmet medical need.

The robustness of the results is supported by consistent effects in subgroups and in the sensitivity and supplementary analyses, despite only ~59 % of the ITT2 in arm C initiated adjuvant therapy and just ~25% of the ITT2 in arm C completed the entire planned perioperative regimen. No detrimental effect on the completion of surgery was observed, which is considered of major importance. Final results of KEYNOTE-905 are expected post-approval, given the early curative setting (REC).

The efficacy of the combination of EV and pembrolizumab was derived from studies in the metastatic setting of urothelial cancer. Although a formal comparison to monotherapy would have been ideal in the perioperative setting, the supportive evidence from the metastatic setting and the descriptive results of the monotherapy pembrolizumab arm indicating lower efficacy, are acknowledged. The study design does not allow to disentangle the contribution of each phase (neoadjuvant and adjuvant) to the overall treatment; therefore the peri-operative treatment package should be considered in its entirety.

Substantial amendments to key aspects of the trial were introduced in an open label setting, including (but not limited to) study treatment, study population and primary study comparison. The rationale for the changes of study design and statistical analysis have been sufficiently justified by the MAH and are not considered to have significantly impacted the overall study results.

The safety of EV + pembrolizumab in this setting is overall consistent with this treatment combination in other and more advanced metastatic settings. No new safety signals were observed and the toxicities were manageable. Focusing on the adjuvant setting and the risks of long term and late effect toxicity in cancer survivors, it is of some reassurance that the incidence of peripheral neuropathy was almost halved in the perioperative setting compared to the metastatic settings.

3.7.2. Balance of benefits and risks

KEYNOTE-905 study showed statistically significant and clinically relevant EFS and OS benefit of perioperative EV + pembrolizumab compared to surgery alone in patients with cisplatin-ineligible MIBC. The risks related to the important toxicity of the combination are counterbalanced by meaningful benefit in this setting of limited therapeutic options and dismal prognosis.

3.8. Conclusions

The overall B/R of Padcev 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 changes:

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 changes:

Variation(s) accepted		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include PADCEV in combination with pembrolizumab, as neoadjuvant treatment and then continued after radical cystectomy as adjuvant treatment of adults with resectable muscle invasive bladder cancer (MIBC) who are ineligible for cisplatin containing chemotherapy, based on interim results from study KEYNOTE-905, an open label, randomised, interventional phase 3 study. As consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 5.3 of the RMP has also been agreed.

In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet, and to bring the PI in line with the latest QRD template version 10.4.

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.