21 May 2026
EMADOC-1700519818-3005612
Committee for Medicinal Products for Human Use CHMP

Assessment report

Invented name: Keytruda

International non-proprietary name: pembrolizumab

Procedure No. EMA/VR/0000312515

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

Abbreviation	Definition
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

Abbreviation	Definition
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

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency on 11 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 in combination with enfortumab vedotin, as neoadjuvant treatment and then continued after radical cystectomy as adjuvant treatment of adults with muscle invasive bladder cancer (MIBC) who are ineligible for cisplatin containing chemotherapy for KEYTRUDA, 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 51.1 of the RMP has also been submitted.

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 P/0043/2018 on the agreement of a paediatric investigation plan (PIP) for malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue).

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

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Paolo Gasparini

Timetable	Actual dates
Submission date	11 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:	2 February 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:	18 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 applied indication is:

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

Epidemiology and risk factors, screening tools/prevention

Bladder cancer is the ninth most common cancer globally. Incidence varies across regions, with highest crude rates in Europe (77 per 100000) and North America (78 per 100000)[1]. The disease is most common in male. The most important risk factor for bladder cancer is tobacco smoking, followed by

[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.

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, diagnosis and stage/prognosis

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, 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

[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.
[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.

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.

[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

Pembrolizumab is a humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. This blockade can result in activation of existing antitumor T-cells in the presence of antigen and subsequent tumor regression.

Pembrolizumab is approved in Europe in several indications as described in the SmPC (https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf).

For the current submission in neoadjuvant and adjuvant treatment of cisplatin-ineligible MIBC, patients should be treated with neoadjuvant KEYTRUDA in combination with enfortumab vedotin for 3 doses of 200 mg every 3 weeks or until disease progression that precludes radical cystectomy or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA in combination with enfortumab vedotin for 14 doses of 200 mg every 3 weeks or 7 doses of 400 mg every 6 weeks or until disease recurrence or unacceptable toxicity.

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,	Treatment Arm 1 (Monotherapy): Pembrolizumab 200 mg q3w Treatment Arm 2 (Combination): Pembrolizumab + cisplatin/carboplatin + gemcitabine	Complete

Study No.	Phase	Description/Design	Enrolled	Dosage Regimen	Study Status
			(3) combination chemotherapy only	Treatment Arm 3 (Chemotherapy only): Cisplatin/carboplatin + gemcitabine	
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
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					
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	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
		cisplatin-ineligible EV monotherapy Cohort L: perioperative cisplatin-ineligible EV monotherapy			
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**
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

Study No.	Phase	Description/Design	Enrolled	Dosage Regimen	Study Status
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.					

The MAH did not seek Scientific Advice from CHMP for KEYNOTE-905 study. A pre-submission meeting was also not requested by the MAH.

2.1.4. General comments on compliance with GLP, GCP

No issues of GCP compliance are raised after the assessment of the dossier.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

Pembrolizumab is a protein composed of natural amino acids. Proteins are expected to biodegrade in the environment and not be a significant risk for the environment. As a protein, pembrolizumab is exempt from submitting environmental risk assessment studies in line with the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/S/4447/00 Rev. 1-Corr.). Keytruda and the product excipients do not pose a significant risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Study ID	Phase	Country/ Region	Study Title	Study Design	Dosing Regimen	Study Population	Participant Exposure
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. Pharmacokinetics

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

Substantial characterization of the PK and immunogenicity of pembrolizumab 200 mg Q3W have been provided in previous submissions. In particular, pembrolizumab PK disposition has been characterized via pooled population PK analyses using serum concentration-time data contributed from subjects across various clinical studies using a time-dependent PK (TDPK) model. The PK reference dataset for monotherapy includes all available PK data from subjects enrolled on KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, KEYNOTE-010, and KEYNOTE-024, with an overall sample size of 2993. This serves as the PK reference analysis to support descriptions of pembrolizumab pharmacokinetics in the USPI and EU SmPC.

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

MK-3475A (pembrolizumab and berahyaluronidase alfa [MK-5180], a variant of human hyaluronidase used as a permeation enhancer) is for SC administration in the abdomen or thigh. The original application for MK-3475A supported the 790 mg q6w and 395 mg q3w dosing regimens of MK-3475A for all approved pembrolizumab IV adult indications. This was based on demonstration of PK non-inferiority between pembrolizumab 400 mg q6w IV and pembrolizumab 790 mg q6w SC administered as MK-3475A with respect to Cycle 1 AUC0-6 wks and steady-state (Cycle 3) Ctrough, and comparable efficacy (ORR, PFS, OS), and safety data from the final analysis of the pivotal study MK-3475A-D77 in 1L metastatic NSCLC patients[23]. Based on consistent PK of pembrolizumab across tumor types, treatment settings (monotherapy or combination) and a flat exposure-response relationship for efficacy and safety over a 5-fold dose range, any inferences on comparability of PK, efficacy and safety between SC and IV administration from MK-3475A-D77 can also be applied to other pembrolizumab indications[24].

Additionally, based on clinical data from Phase 1 study MK-3475A-C18, where the 395 mg q3w dosing regimen of MK-3475A was administered, and also based on modeling and simulation data, the PK exposures of pembrolizumab 395 mg q3w SC were shown to be consistent with those of 790 mg q6w SC and can be expected to have similar efficacy and safety profiles. The PK exposures for the 395 mg q3w SC regimen were also shown to be consistent with those for the 200 mg q3w IV regimen based on modeling and simulation[26].

Absorption

Pembrolizumab is immediately and completely bioavailable if it is dosed via the intravenous rout, while following subcutaneous administration of pembrolizumab, the mean bioavailability (CV %) of pembrolizumab is approximately 60% (14%).

[23] Felip E, Rojas CI, Schenker M, Kowalski DM, Casarini IA, Csoszi T, et al. Subcutaneous versus intravenous pembrolizumab, in combination with chemotherapy, for treatment of metastatic non small-cell lung cancer: the phase III 3475A-D77 trial. Ann Oncol. 2025;36(7):775-85.

Distribution

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

Elimination

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

- ***Pharmacokinetic in target population***

Considering that an extensive characterization of the PK and immunogenicity profile of pembrolizumab have been provided in previous submissions, in this one the focus is on the data related to the characterization of the pharmacology for the combination of pembrolizumab with enfortumab vedotin, as neoadjuvant treatment and then continued after radical cystectomy as adjuvant treatment of adults with muscle invasive bladder cancer (MIBC) who are ineligible for cisplatin containing chemotherapy for KEYTRUDA

PK Data KEYNOTE-905

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. (See Figure 3).

Participants with previously untreated MIBC who are ineligible for or decline cisplatin-based chemotherapy were randomized into Arm A (hereafter, perioperative pembrolizumab group) and Arm B (hereafter, RC + PLND alone) in a 1:1 ratio in Stage 1. With the subsequent addition of Arm C (hereafter, 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).

PK Analysis Pembrolizumab

The objectives of the PK analysis were:

- To evaluate pembrolizumab serum concentrations after neoadjuvant and adjuvant treatment with EV in combination with pembrolizumab in KEYNOTE-905 Arm C participants.
- To compare KEYNOTE-905 Arm C observed PK data with reference model (time-dependent pharmacokinetics [TDPK] model based) predicted pharmacokinetics (PK).

Table 3 Overview of Pembrolizumab Cohorts included in KEYNOTE-905

Study	Cancer Type	Treatment	Analyte	Number of participants providing PK [a]
KEYNOTE-905 Arm C	MIBC	EV [b] + Pembrolizumab 200 mg q3w	MK-3475	167
Total number of participants				167

[a] Unique participants providing PK samples; not all participants had Cycle 1 day 1 samples.
[b] EV was to be administered at 1.25 mg/kg as an intravenous infusion on Days 1 and 8 of each 3-week cycle
EV = enfortumab vedotin
MIBC = Muscle-invasive bladder cancer
q3w = every 3 weeks

The PK analysis dataset (adpcmk) includes pembrolizumab PK samples with a PK/ADA cutoff date of April 8, 2025, measured for a total of 171 participants in KEYNOTE-905 Arm C.

All participants with at least one dose administration in Arm C were included resulting in 167 unique participants providing PK samples.

The PK analysis dataset was constructed from the final locked SDTM datasets using SAS version 9.4 and contains observed pembrolizumab serum concentrations and actual elapsed blood sampling times relative to the corresponding time of dose.

PK sampling schedule in KEYNOTE-905 for pembrolizumab was as follows: pre infusion pembrolizumab serum concentrations (Ctrough) were obtained within 4 hours prior to dosing at neoadjuvant (preoperative) treatment Cycle 1, and 2 and adjuvant (postoperative) treatment Cycle 1, 2 and 6. Postdose samples (Cmax) were drawn at neoadjuvant treatment Cycle 1, and adjuvant treatment Cycle 1 and Cycle 6, approximately 10 minutes after the end of pembrolizumab infusion.

Phoenix™ WinNonlin® (Version 8.6.0) software was used for pharmacokinetic analysis.

Summary descriptive statistics of the pre-dose and post-dose concentrations by cycle are presented in the following table:

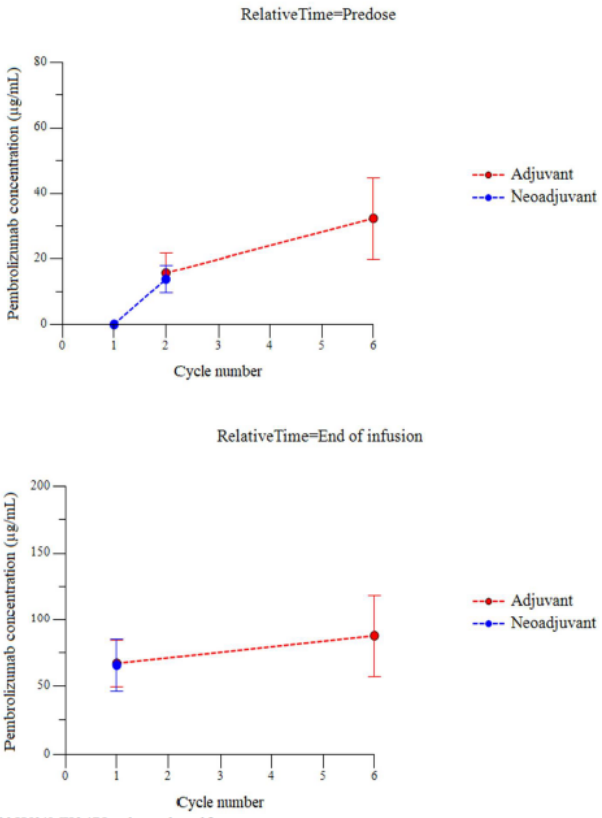
Table 4 Summary statistic of Pembrolizumab Serum concentration following treatment with EV in combination with 200mg q3w pembrolizumab in KEYNOTE-905 Arm C participants

Period	Visit	Relative Time	N	GM(%CV)	AM (SD)	Min	Median	Max
				(µg/mL)				
Neoadjuvant	Cycle 1 Day 1	Predose	161	-	0.00 (0)	0.00	0.00	0.00
	Cycle 1 Day 1	End of infusion	145	62.9 (29.5)	65.5 (19.5)	19.2	64.2	184
	Cycle 2 Day 1	Predose	146	13.2 (29.9)	13.8 (4.1)	6.13	13.1	25.2
Adjuvant	Cycle 1 Day 1	End of infusion	79	64.7 (26.9)	66.9 (17.4)	25.4	64.6	127
	Cycle 2 Day 1	Predose	88	14.6 (42.8)	15.7 (6.0)	2.80	15.1	37.3
	Cycle 6 Day 1	Predose	57	29.9 (43)	32.3 (12.4)	7.72	30.4	71.0
	Cycle 6 Day 1	End of infusion	59	82.2 (38.7)	87.7 (30.8)	28.8	82.8	177

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

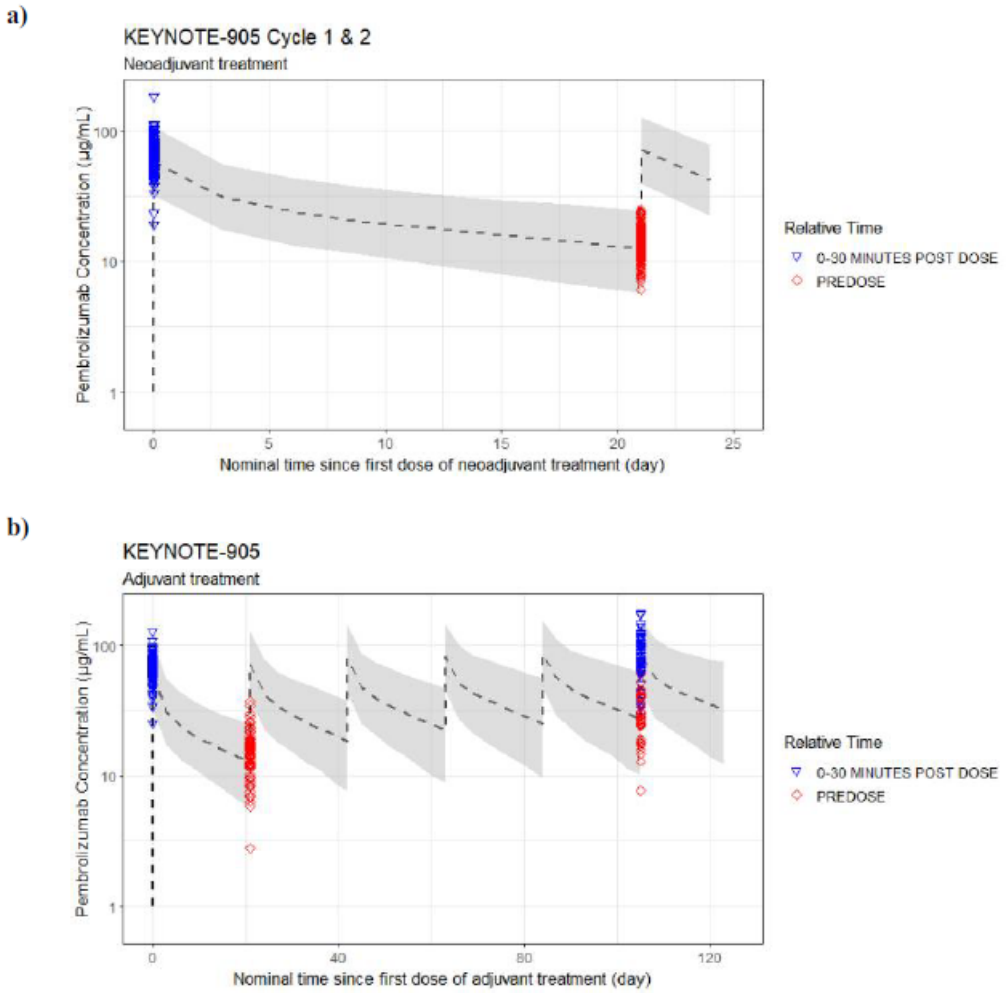
Mean ± SD predose and end of infusion serum pembrolizumab concentration-time profiles, stratified by treatment period, are shown in the following figure:

Figure 1 Arithmetic Mean ± SD pre-dose and end of infusion serum pembrolizumab concentration-time profiles following treatment with EV in combination with pembrolizumab in KEYNOTE-905 Arm C participants, linear scale



Observed pembrolizumab concentration data in KEYNOTE-905 for pembrolizumab are overlaid on the simulated profile using the reference PK model (both at early cycles and steady-state) as shown in the following figure:

Figure 2 Observed pembrolizumab concentration data in KEYNOTE-905 Arm C participants receiving EV treatment in combination with pembrolizumab with reference model predictive PK profile for 200 mg q3w IVD dose



Note: Pembrolizumab model predictions and observed concentration data for KEYNOTE-905 Arm C participants a) After 1st dose of neoadjuvant treatment; b) after 1st, 2nd and 6th dose of adjuvant period, with a 28 day time since last dose sample cut off. Symbols are individual observed data (nominal time); black dashed line is median predicted concentrations from the model for a regimen of 200 mg q3w and the grey shaded area represents the 90% prediction interval; plots are displayed on log scale.

Data Source: [P905V01MK3475: adam-adpcmk]

2.3.3. Pharmacodynamics

Mechanism of action

KEYTRUDA is an antibody that binds to the programmed death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. KEYTRUDA potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment.

Primary and secondary pharmacology

An immunogenicity evaluation after treatment with pembrolizumab in combination with enfortumab vedotin has been performed in the context of this EoI, using data from KEYNOTE-905 in Participants with muscle invasive bladder cancer (MIBC).

In KEYNOTE-905, the evaluation of pembrolizumab (200 mg MK-3475 q3w) immunogenicity included ADA samples from 172 participants from KEYNOTE-905 with an ADA sample cut-off date of April 8, 2025.

A subset of the subjects was not assessable for drug-induced immunogenicity analysis, because only a pre-treatment ADA sample was available (n=11), 4 subjects were not enrolled in Arm C, and 3 subjects were not dosed with pembrolizumab. The remaining 154 subjects were assessable for drug-induced immunogenicity analysis.

Table 5 Overview of the subjects included in the immunogenicity analysis of Pembrolizumab in KEYNOTE-905

Study	Cohort	Treatment	Number of Subjects	
			Subjects Providing ADA Samples	Assessable Subjects Dosed with MK-3475 and Post-Treatment Samples
KEYNOTE-905	Arm C	EV [a] + Pembrolizumab 200 mg q3w	172	154
Total Number of Assessable Subjects				154

[a] EV was to be administered at 1.25 mg/kg as an intravenous infusion on Days 1 and 8 of each 3-week cycle
EV = enfortumab vedotin
Q3W = every 3 weeks

An overview of the immunogenicity status of all assessable participants is reported in the following table:

Table 6 summary of Subject immunogenicity results for pembrolizumab after treatment with EV in combination with pembrolizumab in KEYNOTE-905 Arm C

Assessable subjects[a]	154
Evaluable subjects[c]	**154**
Inconclusive subjects[b]	3 (1.9%)
Negative[d]	143 (92.9%)
Non-Treatment emergent positive[d]	0
Neutralizing negative	0
Neutralizing positive	0
Treatment emergent positive[d]	8 (5.2%)
Neutralizing negative	3 (1.9%)
Neutralizing positive	5 (3.2%)

[a] Included are subjects with at least one ADA sample available after treatment with pembrolizumab;
[b] Inconclusive subjects are the number of participants with no positive ADA samples present and the drug concentration in the last sample above the drug tolerance level;
[c] Evaluable subjects are the total number of negative and positive subjects (non-treatment emergent and treatment emergent;

2.3.4. PK/PD modelling

No new information regarding PK/PD modelling for pembrolizumab is available within this extension of indication.

2.3.5. Discussion on clinical pharmacology

In this application, the focus is on PK data related to pembrolizumab in combination with enfortumab vedotin, as neoadjuvant treatment and then continued after radical cystectomy as adjuvant treatment of adults with muscle invasive bladder cancer (MIBC) who are ineligible for cisplatin containing chemotherapy for KEYTRUDA.

The PK sampling schedule in KEYNOTE-905 includes pre-infusion pembrolizumab serum concentrations (Ctrough) obtained within 4 hours prior to dosing at neoadjuvant (preoperative) treatment Cycle 1, and 2 and adjuvant (postoperative) treatment Cycle 1, 2 and 6. Moreover, postdose samples (Cmax) were drawn at neoadjuvant treatment Cycle 1, and adjuvant treatment Cycle 1 and Cycle 6, approximately 10 minutes after the end of pembrolizumab infusion.

PK data from study KEYNOTE-905 show that the observed pembrolizumab serum concentration values after neoadjuvant and adjuvant treatment in combination with EV in KEYNOTE-905 Arm C participants with MIBC who are ineligible for or decline cisplatin-based chemotherapy are contained within the 90% CI of the reference PK model, which indicate consistency with the historical data, both at early cycles and at steady state.

In KEYNOTE-905, the evaluation of pembrolizumab (200 mg MK-3475 q3w) immunogenicity included ADA samples from 172 participants from KEYNOTE-905 with an ADA sample cut-off date of April 8, 2025, but only 154 subjects were assessable for drug-induced immunogenicity analysis.

The observed incidence of treatment-emergent ADA in evaluable subjects is 5.2% (8 out of 154), based on 8 subjects with confirmed treatment-emergent positive status, 3 subjects with an inconclusive status, and 143 subjects with a negative immunogenicity status. Among the 8 treatment-emergent positive subjects, 5 had antibodies with neutralizing capacity, resulting in a treatment-emergent neutralizing positive rate of 3.2% (5 out of 154), confirming the low potential of pembrolizumab to elicit the formation of ADA also when it is co-administered with enfortumab vedotin in the perioperative setting.

In conclusion, PK and ADA results from participants in KEYNOTE-905 were consistent with the previously reported data, confirming that pembrolizumab PK disposition is not affected by coadministration of EV.

2.3.6. Conclusions on clinical pharmacology

Pembrolizumab PK disposition is not affected by the coadministration with enfortumab vedotin in the perioperative setting in patients with MIBC who are ineligible for or decline cisplatin-based chemotherapy. Observed concentrations from KEYNOTE-905 overlaid on the reference model predicted median concentrations both at early cycles and at steady state and are consistent with other globally approved studies in different cancer indications. In the same way, the known immunogenicity profile of pembrolizumab is not affected by the co-administration of EV.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No dose-response studies were submitted as part of this application.

2.4.2. Main study

Title of Study

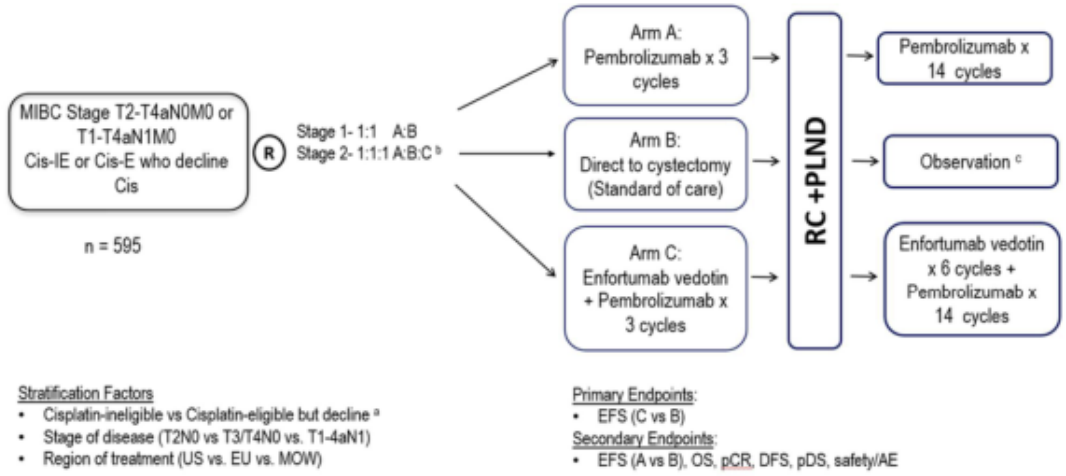
A Phase 3 Randomized Study of Cystectomy plus Perioperative Pembrolizumab versus Cystectomy Alone in Cisplatin-ineligible Participants with Muscle-invasive Bladder Cancer (KEYNOTE-905)

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

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 3 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).

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

Arm A: Pembrolizumab was administered IV 200 mg every three weeks (Q3W) in the neoadjuvant phase for 3 cycles prior to surgery. Following cystectomy and PLND, pembrolizumab was continued in the adjuvant phase for 14 cycles, provided that the participant met protocol-defined criteria for continuation.

Arm B: comparator control arm. The intervention consisted solely of radical cystectomy (RC) with pelvic lymph node dissection, performed according to institutional standard therapy practices.

Arm C: Enfortumab vedotin was administered by intravenous infusion 1.25 mg/kg on Days 1 and 8 of each 21-day cycle, for three cycles in the neoadjuvant phase prior to surgery and six cycles in the adjuvant phase following surgery. Pembrolizumab was administered at 200 mg IV on Day 1 of each 21-day cycle, for three cycles in the neoadjuvant phase and up to fourteen cycles in the adjuvant phase, subject to protocol-defined criteria.

Table 7 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 and 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 prior to RC+PLND assessed by BICR - 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 and/or biopsy. CT or MRI will be assessed by BICR. If biopsy is not feasible due to participant safety, CT/MRI alone will be sufficient - Death from any cause NOTE: A nonurothelial second primary malignancy is not considered an event. Participants who develop high-risk NMIBC (in addition to muscle-invasive cancer) of the upper-tract/remaining urothelium after RC + PLND will be considered as having an event.
Secondary Objective	**Secondary Endpoint**
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
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
Objective: To compare the rates of pathological downstaging (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 was 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. 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 included ~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 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 enrolment 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 is open label.

Statistical methods

Analysis sets

ITT1: all participants randomized to Arm A and Arm B in Stage 1 and Stage 2 from the beginning of the study until Arm A enrollment stopped, regardless of whether or not treatment was administered. ITT1 population was used to compare Arm A and Arm B.

ITT2: all participants randomized to Arm C and Arm B in Stage 2, regardless of whether treatment was administered. ITT2 population was used to compare Arm C and Arm B.

DFS analysis population: participants who are disease-free at the post-surgery baseline scan.

Primary endpoint: primary analysis

No estimands were defined in the study.

The nonparametric Kaplan-Meier method was planned to be used to estimate the EFS curve in each treatment group. The treatment difference in EFS was planned to be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling was planned to be used to assess the magnitude of the treatment difference (ie, HR) between each experimental arm and the control arm. The HR and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate were planned to be reported. 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 decline) and geographic regions (US vs EU vs MOW)) were planned to be applied to both the stratified log-rank test and the stratified Cox model.

Participants who refused or were unable to undergo radical cystectomy without a protocol-defined event were to be censored at the last disease assessment within 16 weeks of last dose of neoadjuvant treatment (or within 16 weeks of the randomization date for participants who do not receive any treatment). Participants who refused or were unable to undergo surgery and who develop a protocol-defined event were to be counted as events. Participants who refused or were unable to undergo surgery, but without a postscreening scan were to be censored at Day 1 from randomization.

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

Primary endpoint: sensitivity analyses

Sensitivity analysis 1 was the same as the primary analysis except that events occurring after 2 consecutive missed disease assessments or after new anticancer therapy if any, were censored at last disease assessment prior to the earlier date of these events. The difference between sensitivity analyses 1 and 2 is that the use of adjuvant nivolumab in Arm B for high-risk participants was not to be considered as new anticancer therapy in sensitivity analysis 1, but would be considered as new anticancer therapy in sensitivity analysis 2.

Table 8 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 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
No post-screening scans available	Censored at Day 1 from randomization	Censored at Day 1 from randomization	Censored at Day 1 from randomization

Abbreviations: 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.

Secondary endpoints analyses

Overall survival (OS)

The analysis of OS was planned like the analysis of EFS, including the definition of OS (time from randomisation to death due to any cause) and the sensitivity analysis with PD-L1 expression (CPS ≥10 versus CPS<10) as a covariate in the stratified Cox proportional hazard model. Participants without documented death at the time of analysis were to be censored at the date of the last known to be alive.

Pathological complete response rate (pCR rate / pCRR)

The stratified Miettinen and Nurminen method with strata weighting by sample size was to be used for the comparison of pCR rates between each experimental arm and the control arm. The difference in pCR rates and its 95% CI from the stratified Miettinen and Nurminen method with strata weighting by sample size was to be reported. 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 decline) and geographic regions (US vs EU vs MOW)) applied to the analysis.

Participants who were discontinued from the study treatment and continued with other treatment not specified by the study prior to definitive surgery were to be classified as not having a pCR (nonresponders) in the efficacy analyses, regardless of the results obtained from the surgery. Participants who refused or were unable to undergo surgery and participants with relevant data missing were considered non-responders. For participants who refused or were unable to undergo surgery and achieve cCR (per Section 8.2.3), sensitivity analyses could be conducted in which 1) participants with cCR were excluded from the pCR analysis, or 2) participants with cCR were considered responders.

Other secondary efficacy endpoints

Pathological downstaging rate (pDSR) was planned to be analysed the same way as pCR.

Disease-free survival (DFS) was planned to be analysed descriptively using the Kaplan-Meier method.

Interim analyses

The eDMC served as the primary reviewer of the results of the IAs and could make recommendations for discontinuation of the study or modification to an Executive Oversight Committee (EOC) of the Sponsor. EOC and limited Sponsor personnel could have been unblinded to the treatment-level results of the interim analysis(es), if required, in order to act on the recommendations of the eDMC or facilitate regulatory filing.

Treatment-level results of the efficacy IAs were planned to be provided by an internal unblinded statistician to the eDMC.

Prior to final study unblinding, the internal unblinded statistician was planned not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the IAs.

Table 9 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.

At the time of an analysis, the observed number of events might have differed 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 planned to be adopted. At the IA, the information fraction used in Hwang-Shih-DeCani (HSD) spending function to determine the alpha spending at the IA was planned to be 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 is less than the expected number of events at a given analysis, the information fraction was planned 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 planned to be calculated as the expected number of events at the interim analysis over the target number of events at FA.

The final analysis was planned to use the remaining Type I error that has not been spent at the earlier analyses. The event counts for all analyses was planned to be used to compute correlations.

For further details on the parameters and margins, see below under *Multiplicity*.

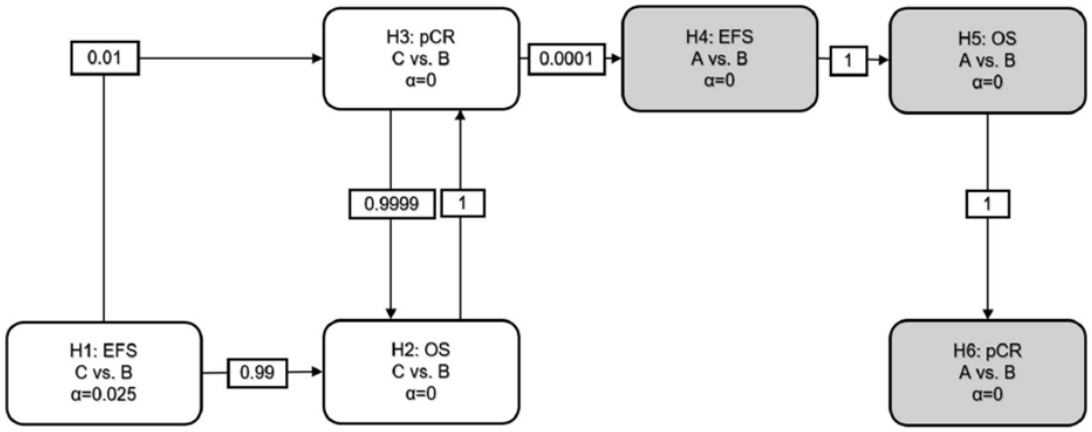
The IA plan was amended across the duration of the trial:

- According to the original protocol, three IA for EFS and four IA for OS in the comparison of Arm A vs Arm B were planned;
- In Amendment 01, with the addition of Arm C, the number of IA per endpoint was reduced of one (i.e. two IA for EFS and three IA for OS), but the criteria for triggering the IA included both the number of events for the ITT1 population (Arm A vs Arm B) and for the ITT2 population (Arm C vs Arm B);
- In Amendment 05, the design went back to four IA overall, but with different schedules for EFS/OS and ITT1/ITT2 comparisons;

- In Amendment 08, the design went back to three IA overall, but all of them limited to the ITT2 comparisons;
- Finally, in Amendment 10, one IA for EFS/OS population was dropped, and estimated timings for the final analyses of EFS and OS were anticipated.

Multiplicity

Figure 4 Multiplicity Graph for Type I error control of study endpoints



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

Event-Free Survival (EFS)

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 16 and Table 17 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 as described above.

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 then will be used in the final EFS analysis in ITT2.

Table 10 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.

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

[b] 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.

[c] p (1-sided) is the α for testing

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

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

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

Overall Survival (OS)

No α has been initially allocated to test OS. For Arm C versus Arm B, if the null hypothesis for H1 is rejected, α=2.475% is reallocated to H2. If the null hypotheses for H1 and H3 are rejected, almost the full α of 2.5% is reallocated to H2. For Arm A versus Arm B, if the null hypotheses for H1, H2, H3 and H4 are rejected, α=2.5% is reallocated to H5. Table 18 and Table 19 show the boundary properties for the planned interim and final analyses of OS in different populations and different comparison groups derived using a HSD α-spending function with γ=-4.

Note that if the null hypothesis for EFS in ITT2 (H1) is rejected 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.

Table 11 Boundary properties for planned analyses of OS based on potential alpha-levels to be used for testing (H2, Arm C vs Arm B)

Analysis	Value	α=2.475%	α=2.5%
IA1: 63%[a]	Z	2.5571	2.5536
N: 344	p (1-sided)[c]	0.0053	0.0053
Events: 110	HR at bound[d]	0.6135	0.6138
Month: 69[b]	P(Cross) if HR=1[e]	0.0053	0.0053
	P(Cross) if HR=0.59[f]	0.5788	0.5799
IA2: 83%[a]	Z	2.3134	2.3094
N: 344	p (1-sided)[c]	0.0104	0.0105
Events: 145	HR at bound[d]	0.6804	0.6808
Month: 81[b]	P(Cross) if HR=1[e]	0.0123	0.0124
	P(Cross) if HR=0.59[f]	0.8108	0.8117
Final: 100%[a]	Z	2.0314	2.0270
N: 344	p (1-sided)[c]	0.0211	0.0213
Events: 174	HR at bound[d]	0.7348	0.7353
Month: 92[b]	P(Cross) if HR=1[e]	0.0248	0.0250
	P(Cross) if HR=0.59[f]	0.9295	0.9300

Abbreviations: H=hypothesis; HR=hazard ratio; IA=interim analysis; ITT=intention-to-treat; OS=overall survival.

[a] Percentage of target no. of events at final analysis needed at interim analysis

[b] 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.

[c] p (1-sided) is the α for testing

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

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

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

The specific strategy to adjust for multiplicity was updated along with the protocol amendments, but the approach always followed the proposal by Maurer and Bretz [Maurer, W. 2013].

Subgroup analyses

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoints was planned to be estimated and plotted within each category of the following classification variables.

- 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 versus CPS <10)
- Age category (<65 vs ≥65 years)
- Sex (female vs male)
- Race (white vs all others)
- Smoking status (never vs former vs current)

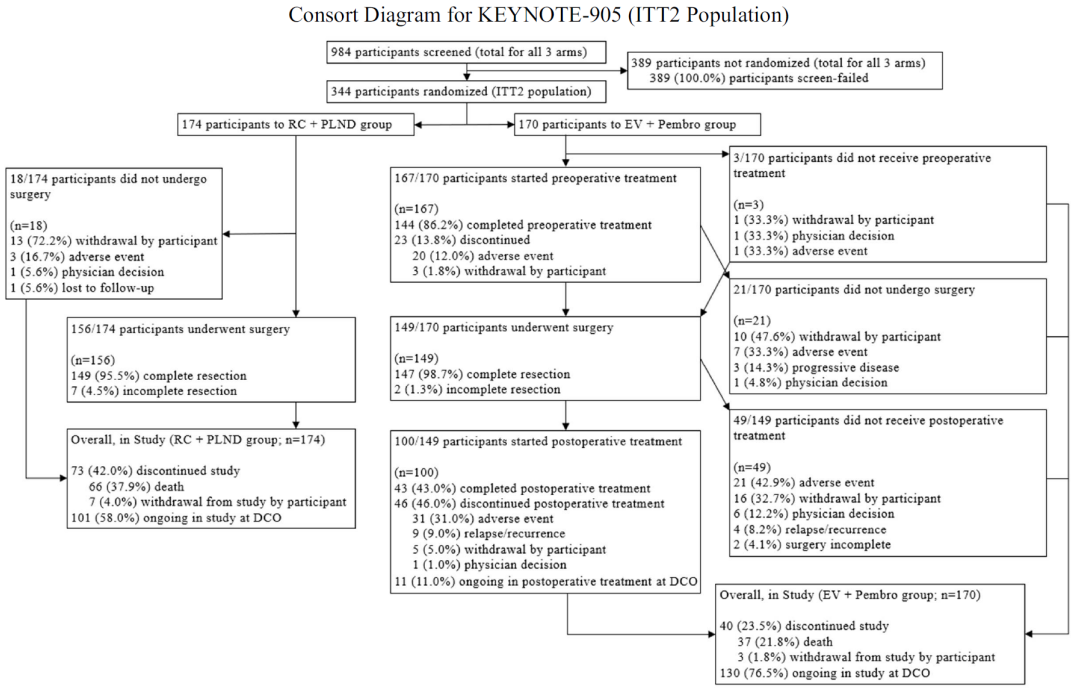
Summary efficacy statistics were planned to be described in terms of the primary and key secondary endpoints by geographic region of enrolling site (for example and including: Asia vs non Asia, EU vs non-EU, US vs non-US).

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 participants, 170 in arm C and 174 in arm B.

Figure 5 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 12 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 Postoperative Study Medications	49		0	
Adverse Event	21	(42.9)	0	(0.0)
Physician Decision	6	(12.2)	0	(0.0)
Relapse/Recurrence	4	(8.2)	0	(0.0)
Surgery Incomplete	2	(4.1)	0	(0.0)
Withdrawal By Subject	16	(32.7)	0	(0.0)
Status for Participants Who Received Postoperative Study Medications				
Started	100		0	
Completed	43	(43.0)	0	(0.0)
Discontinued	46	(46.0)	0	(0.0)
Adverse Event	31	(31.0)	0	(0.0)
Physician Decision	1	(1.0)	0	(0.0)
Relapse/Recurrence	9	(9.0)	0	(0.0)
Withdrawal By Subject	5	(5.0)	0	(0.0)
Ongoing	11	(11.0)	0	(0.0)

If the overall count of participants is calculated and displayed within a section in the first row, then it is used as the denominator for the percentage calculation. Otherwise, participants in population is used as the denominator for the percentage calculation.

Status for all study treatment (preoperative/surgical + postoperative): [for EV + Pembro] Completed indicates a participant received at least 1 cycle of preoperative study medications, had complete

resection, and received 6 postoperative cycles of EV or 14 postoperative cycles of pembrolizumab. [for RC + PLND] Completed indicates a participant had complete resection.

Status for preoperative study medications: Completed indicates a participant received 3 preoperative cycles of at least one of the two study medications (EV or pembrolizumab). Discontinued indicates a participant did not receive 3 cycles of any preoperative study medications. Participants who discontinued preoperative study medications may still undergo surgery.

Status for postoperative study medications: Completed indicates a participant received 6 postoperative cycles of EV or 14 postoperative cycles of pembrolizumab.

Database Cutoff Date: 06JUN2025

Table 13 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 14 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

Protocol 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 (Table below).

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 15 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.

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 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 16 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.				

Table 17 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.

Table 18 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 19 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 Native	0	(0.0)	1	(0.6)	1	(0.3)
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 Variant Histology	3	(1.8)	4	(2.3)	7	(2.0)
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.

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 Efficacy Endpoint: Event-free Survival (EFS)

EFS was formally tested in the ITT2 population with the multiplicity-adjusted, 1-sided *p*-value boundary of 0.00968 at IA1.

Table 20 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 6 Kaplan-Meier Plot of Event-Free Survival (Primary Censoring Rule) Based on BICR Assessment (ITT2 Population) Database Cutoff Date: 06JUN2025.

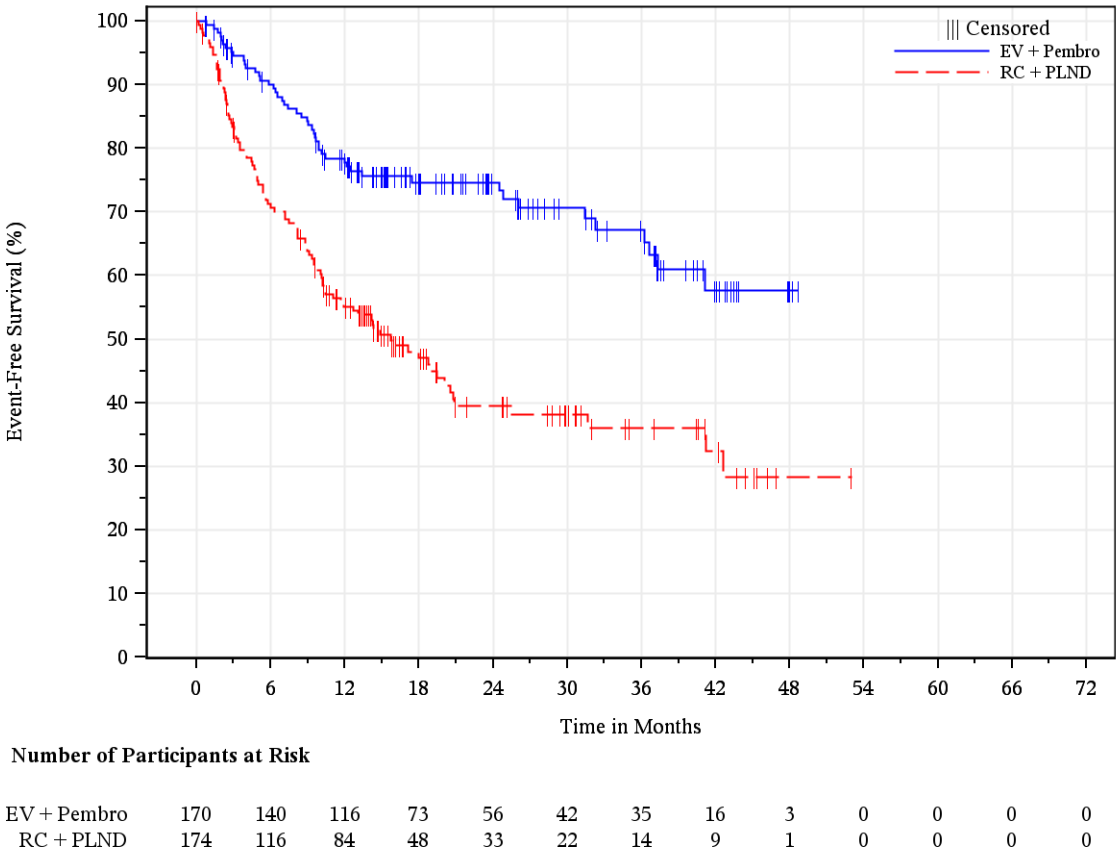


Table 21 Summary of First EFS Event Types Based on BICR Assessment (ITT2 Population) Database Cutoff Date: 06JUN2025

	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

"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 Efficacy 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 22 Analysis of Overall Survival (ITT2 Population) Database Cutoff Date: 06JUN2025

	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.

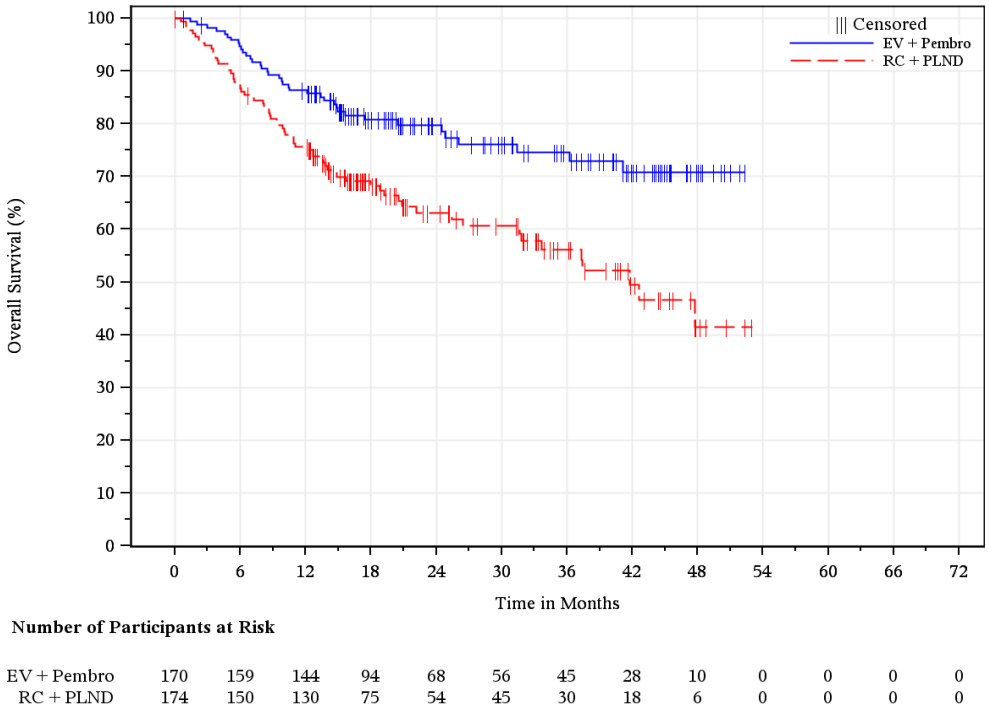
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by cisplatin status (cisplatin-ineligible vs cisplatin-eligible but declined), tumor stage (T2N0 vs T3/T4aN0 vs T1-4aN1), and geographic regions (US vs EU vs MOW) with small strata collapsed 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 7 Kaplan-Meier Plot of Overall Survival (ITT2 Population) Database Cutoff Date: 06JUN2025



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 23 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 24 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.

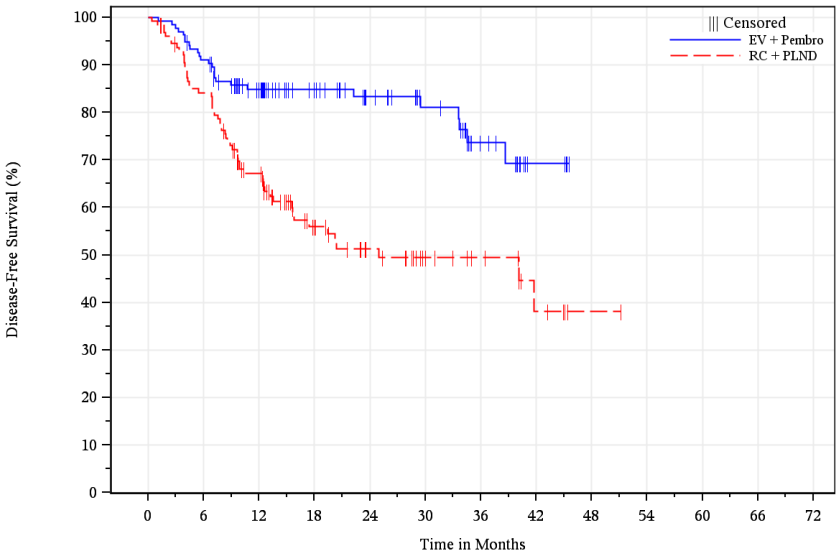
Table 25 Analysis of Disease-Free Survival (Primary Censoring Rule) Based on BICR Assessment (ITT2 Population - Participants Who Are Disease Free After Surgery) Database Cutoff Date: 06JUN2025

	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 8 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



Number of Participants at Risk

EV + Pembro	135	122	96	65	45	36	19	5	0	0	0	0	0
RC + PLND	129	106	75	40	28	18	13	6	1	0	0	0	0

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.

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 (results presented for the FACT-G total score).

Figure 9 Bar Plot of Empirical Mean Change from Baseline to Post-Surgery Week 18 and 95% CI in FACT-G Total Score (PRO FAS2 Population)

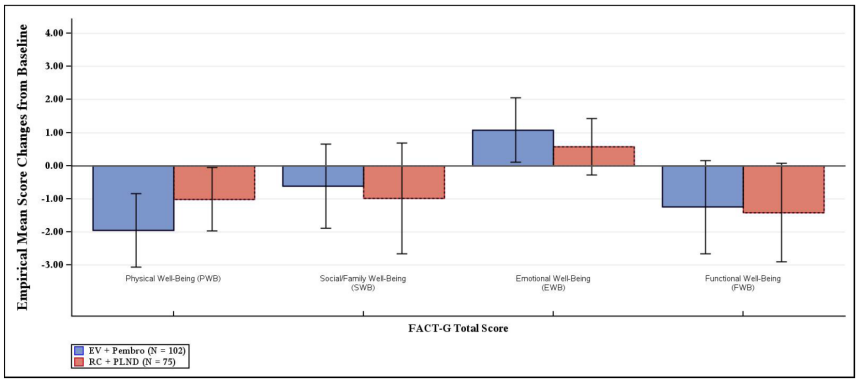


Figure 10 Line Plot of Empirical Mean Change from Baseline and 95% CI for the FACT-G Total Score Over Time (PRO FAS2 Population - EV + Pembro Arm) Database Cutoff Date: 06JUN2025

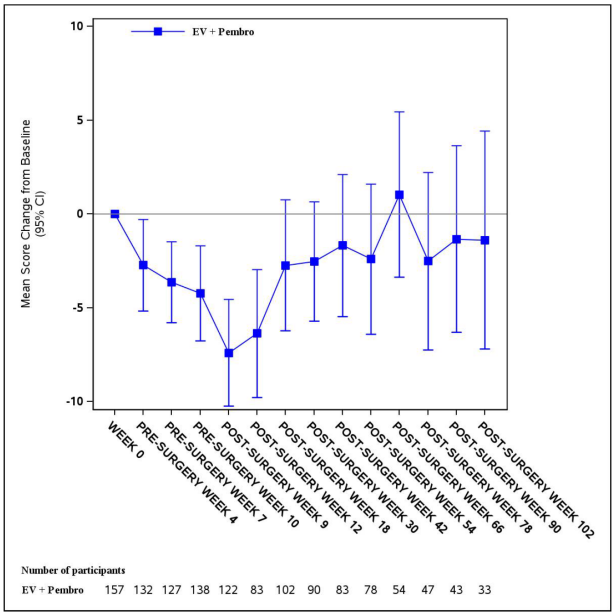
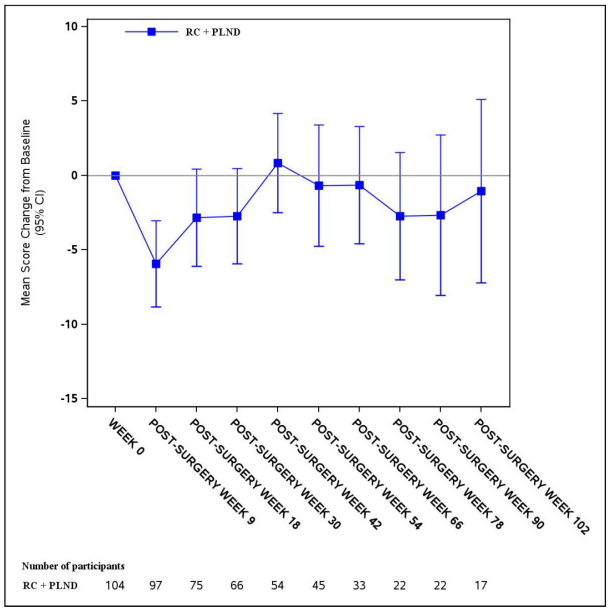


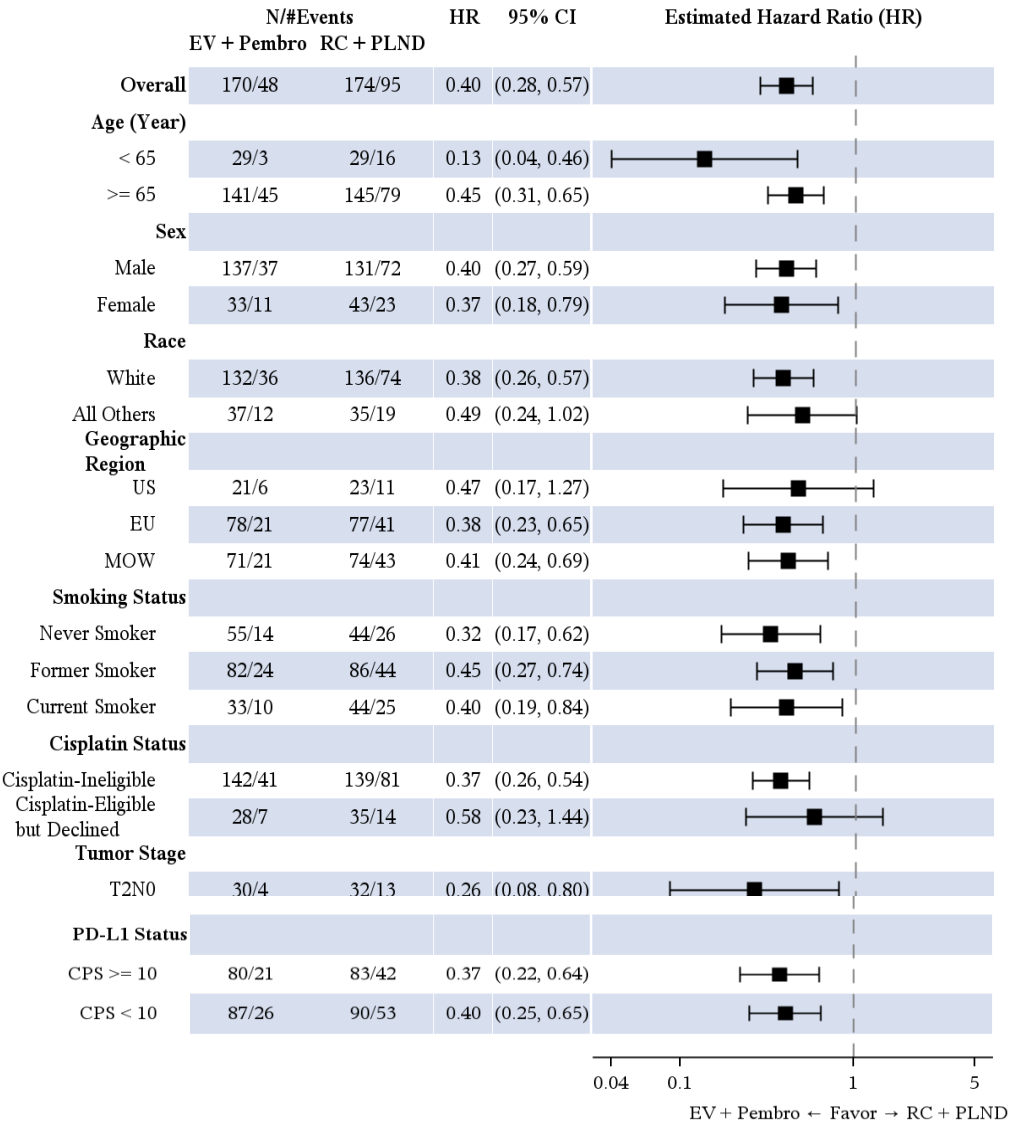
Figure 11 Line Plot of Empirical Mean Change from Baseline and 95% CI for the FACT-G Total Score Over Time (PRO FAS2 Population - RC + PLND Arm)



Ancillary analyses

EFS subgroup analyses

Figure 12 Forest Plot of Event-Free Survival Hazard Ratio by Subgroup Factors Based on BICR Assessment (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.

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 26 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 13 Kaplan-Meier Plot of Event-Free Survival (Sensitivity Censoring Rule 2) Based on BICR Assessment (ITT2 Population) Cutoff date: 06 June 2025

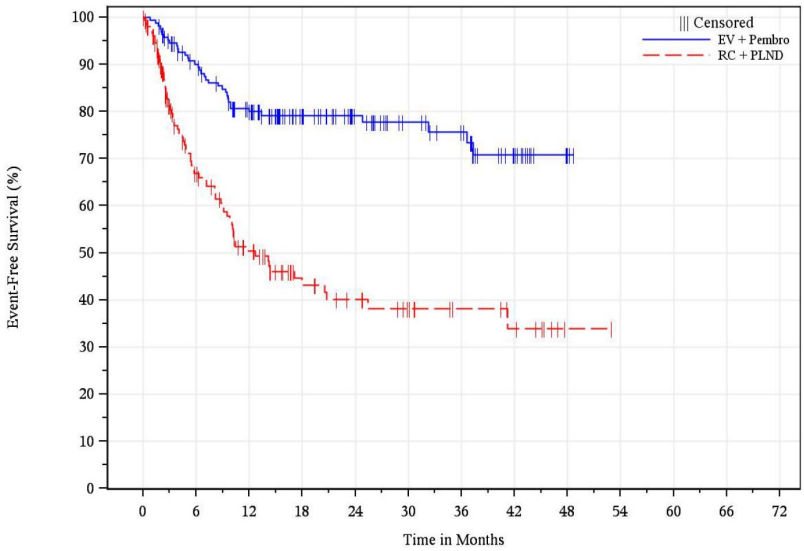


Table 27 Analysis of Event-Free Survival (Primary Censoring Rule) Based on Investigator Assessment (ITT2 Population) Cutoff date: 06 June 2025

	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.
Database Cutoff Date: 06JUN2025.

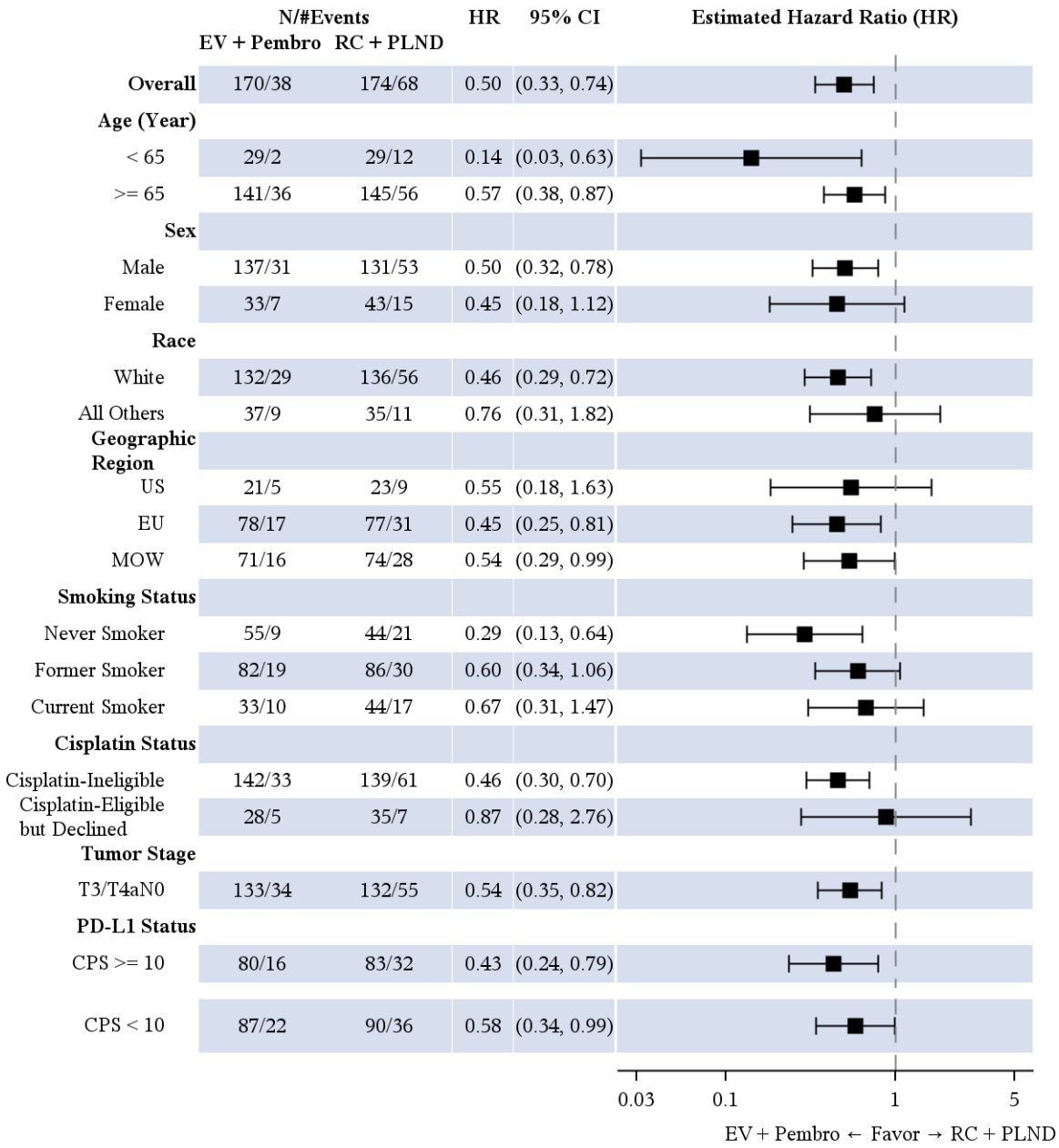
Table 28 Concordance of EFS Events (Investigator vs BICR Assessment) (ITT2 Population) Cutoff date: 06 June 2025

	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 14 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 29 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)

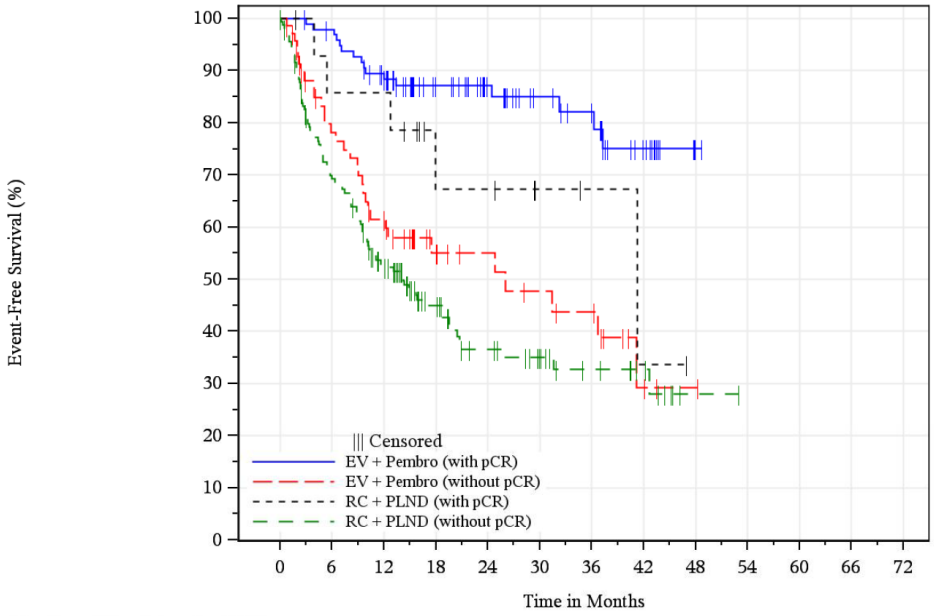
[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
NR = Not reached.
Database Cutoff Date: 06JUN2025.

Table 30 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 15 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 31 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 32 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 33 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

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).

Summary of main study(ies)

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 34 Summary of Efficacy for trial KEYNOTE-905

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-Invasive Bladder Cancer (KEYNOTE-905/EV-303)		
Study identifier	KEYNOTE 905; EV-303; P905V01MK3475 EudraCT: 2018-003809-26 EU CT: 2023-504932-16	
Design	Randomized, active-controlled, parallel-group, multisite, open-label study	
	Duration of main phase:	Approximately 92 months
	Duration of Run-in phase:	Not applicable
	Duration of Extension phase:	Not applicable
Hypothesis	Superiority	
Treatment groups	Perioperative EV + pembrolizumab group	3 cycles of preoperative EV 1.25 mg/kg, D1 and 8 q3w + pembrolizumab 200 mg q3w followed by RC + PLND, followed by 6 cycles of postoperative EV 1.25 mg/kg, D1 and 8 q3w + 14 cycles of postoperative pembrolizumab 200 mg q3w N=170

	RC + PLND alone group		Standard of care RC + PLND N=174
Endpoints and definitions	Primary endpoint	EFS	EFS is defined as the time from the date of randomization to the date of first record of any of the following events: • Radiographic disease progression • 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 surgery • 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
	Key secondary endpoints	Pathological complete response (pCR)	pCR is defined as absence of viable tumor (pT0N0) in examined tissue from RC + PLND
		Overall Survival (OS)	OS is defined as the time from randomization to death due to any cause
Database lock	09-JUL-2025; Interim Analysis 1 (IA1) data cutoff date 06-JUN-2025		
Results and Analysis			
Analysis Description	**Primary Analysis** **Primary Endpoint: EFS (by BICR)**		
Analysis population and time point description	Intent-to-treat population 2 (ITT2 population): All participants concurrently randomized to the perioperative EV + pembrolizumab group and to the RC + PLND alone group.		
Descriptive statistics and estimate variability	**Treatment group**	**Perioperative EV + Pembrolizumab**	**RC + PLND Alone Group**
	Number of participants	170	174
	Number of events, n(%)	48 (28.2)	95 (54.6)
	Median EFS, months (95% CI)	NR (37.3, NR)	15.7 (10.3, 20.5)
	EFS rate at 12 months, % (95% CI)	77.8 (70.4, 83.5)	55.1 (47.2, 62.4)
	EFS rate at 24 months, % (95% CI)	74.7 (66.9, 80.8)	39.4 (31.0, 47.8)

Effect estimate per comparison	Hazard ratio:	0.40	
	95% CI:	0.28, 0.57	
	p-value	<0.0001 (1-sided *p*-value boundary 0.00968)	
Analysis description	**Key Secondary Endpoints: OS and pCR**		
Analysis population and time point description	ITT2 population		
Descriptive statistics and estimate variability	**Treatment group**	**Perioperative EV + Pembrolizumab**	**RC + PLND alone Group**
	OS		
	Number of participants	170	174
	Number of deaths, n (%)	38 (22.4)	68 (39.1)
	Median OS, months (95% CI)	NR (NR, NR)	41.7 (31.8, NR)
	OS rate at 12 months, % (95% CI)	86.3 (80.1, 90.7)	75.7 (68.5, 81.4)
	OS rate at 24 months, % (95% CI)	79.7 (72.5, 85.3)	63.1 (54.7, 70.4)
Effect estimates per comparison	Hazard ratio:	0.50	
	95% CI:	0.33, 0.74	
	p-value	0.0002 (1-sided *p*-value boundary 0.00488)	
Descriptive statistics and estimate variability	**pCR (by BICR)**		
	Number of responders	97	15
	pCR % (95% CI)	57.1 (49.3, 64.6)	8.6 (4.9, 13.8)
Effect estimates per comparison	Difference in pCR rate %:	48.3	
	95% CI:	39.5, 56.5	
	p-value	<0.000001 (1-sided *p*-value boundary 0.00025)	
Notes	CI=confidence interval; NR=not reached At IA1, the success criterion was met for the primary endpoint (EFS) and for the key secondary endpoints OS and pCR in the ITT2 population.		

Supportive studies

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 35 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-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)
KEYNOTE-361 NCT02853305 (completed: 15-SEP-2022)	1010	Phase 3 open-label randomized study evaluating pembrolizumab (200 mg IV q3w) ± SOC chemotherapy (plat + gem) vs. SOC chemotherapy alone	1L Cis-E/IE la/mUC	Pembrolizumab +/- SOC chemotherapy vs. SOC chemotherapy	Primary: PFS by BICR OS Key Secondary: ORR by BICR	ITT (all randomized participants)
KEYNOTE-052 NCT02335424 (completed: 18-FEB-2022)	374	Phase 2 open-label single-arm study evaluating pembrolizumab (200 mg IV q3w)	1L Cis-IE la/mUC	Pembrolizumab monotherapy	Primary: ORR by BICR	APaT (all enrolled participants who received ≥1 dose of pembrolizumab)
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)

Contribution of component in 1L locally advanced/metastatic urothelial carcinoma (LA/mUC)

Contribution of EV:

- EV-302 (EV + pembrolizumab) vs KEYNOTE-361 (pembrolizumab mono) and KEYNOTE-052 (pembrolizumab mono)
- The efficacy of EV mono in 1L la/mUC is demonstrated in EV-103 Cohort K (EV mono).

Contribution of pembrolizumab:

- EV-302 (EV + pembrolizumab) and EV-103 Cohort K (EV + pembrolizumab) vs EV-103 Cohort K (EV monotherapy)
- The efficacy of pembrolizumab monotherapy in 1L la/mUC is demonstrated in KEYNOTE-361 and KEYNOTE-052.

Contribution of Components in Cisplatin-ineligible MIBC (Perioperative Setting):

Contribution of EV:

- KEYNOTE-905 Arm C (EV + pembrolizumab) vs KEYNOTE 905 Arm A (pembrolizumab monotherapy)

- The efficacy of EV monotherapy in MIBC is demonstrated in EV 103 Cohort L.

Contribution of pembrolizumab:

- KEYNOTE-905 Arm A (pembrolizumab monotherapy) vs KEYNOTE-905 Arm B (RC + PLND alone) and KEYNOTE-905 Arm C (EV + pembrolizumab) vs EV-103 Cohort L (EV monotherapy)
- The efficacy of pembrolizumab monotherapy in MIBC is demonstrated in KEYNOTE-905 Arm A.

Table 36 Comparison of Efficacy Results Across la/mUC Studies EV-302, EV-103 (Cohort K), KEYNOTE-361, and KEYNOTE-052 Studies

	EV-302 (Arm A)	EV-103 (Cohort K)		KN-361	KN-052
	EV + Pembro N=437	EV + Pembro N=76	EV Mono N=73	Pembro Mono N=307	Pembro Mono N=370
Median duration of follow-up, months	17.2	44.8	43.7	15.6	11.4
Range	0.07-37.16	0.56-55.59	0.53-55.89	0.4-69.5	0.1-80.5
ORR (confirmed CR or PR), n (%)	296 (67.7)	50 (65.8)	33 (45.2)	93 (30.3)	107 (28.9)
95% CI	63.1, 72.1	54.0, 76.3	33.5, 57.3	25.2, 35.8	24.3, 33.8
DOR, median (95% CI), months	NR (20.2, NR)	38.7 (20.93, NE)	13.2 (6.14, NE)	27.5 (2.1+, 63.7+)	33.4 (NE, NE)
Min, Max	2.04+, 28.32+	1.18, 52.83+	1.51+, 40.94+	NE, NE	1.4+, 67.7+
Ongoing responses at 12 months (%) (95% CI)	67.3 (61.1, 72.7)	67.1 (50.60, 79.14)	60.7 (39.93, 76.23)	60.0 (NE, NE)	68 (NE, NE)
PFS by BICR, median (95% CI), months	12.5 (10.4, 16.6)	29.0 (8.31, 48.10)	8.2 (6.05, 15.28)	4.0 (2.3, 5.5)	2.5 (2.1, 3.4)
Rate at 6 months (%) (95% CI)	72.8 (68.3, 76.8)	73.8 (62.01, 82.42)	64.2 (51.09, 74.69)	44.0 (38.2, 49.5)	34.0 (29.2, 38.8)
Rate at 12 months (%) (95% CI)	50.7 (45.6, 55.5)	54.5 (41.74, 65.61)	40.6 (27.03, 53.80)	NE	22.9 (18.7, 27.3)
OS, median (95% CI), months	31.5 (25.4, NR)	30.7 (20.73, 44.85)	22.8 (16.30, 28.42)	15.6 (12.1, 17.9)	11.3 (9.7, 13.1)
Rate at 6 months (%) (95% CI)	90.2 (87.0, 92.6)	88.2 (78.48, 93.65)	83.6 (72.87, 90.31)	74.3 (69.0, 78.8)	67.0 (62.0, 71.5)
Rate at 12 months (%) (95% CI)	78.2 (73.9, 81.9)	81.6 (70.89, 88.65)	69.9 (57.93, 79.01)	56.0 (50.3, 61.4)	46.9 (41.8, 51.9)

"+" indicates there is no progressive disease at the minimum and/or maximum follow-up for DOR.

BICR=blinded independent central review; CI=confidence interval; CR=complete response; CSR=clinical study report; DCO=database cutoff; DOR=duration of response; EV=enfortumab vedotin; KN=KEYNOTE; Mono=monotherapy; NE=not evaluated; NR=not reached; ORR=objective response rate; OS=overall survival; Pembro=pembrolizumab; PFS=progression-free survival; PR=partial response.

Source: (EV-302 CSR); (EV-103 Cohort K: data on file); (KN-361 CSR: P361MK3475); (KN-052 CSR: P052MK3475)

DCO Date: 08-AUG-2023 (EV-302); 20-NOV-2024 (EV-103 Cohort K); 15-SEP-2022 (KN-361); 18-FEB-2022 (KN-052)

Table 37 Comparison of Efficacy Results Across MIBC Studies KEYNOTE-905 (ITT Population - Concurrently Randomized for All Arms) and EV-103 (Cohort L)

	KN-905			EV-103
	Arm A	Arm B	Arm C	Cohort L
	Pembro Mono N=83	RC + PLND N=87	EV + Pembro N=85	EV Mono N=51
Median duration of follow-up, months	32.0	32.1	37.8	32.0
Range	0.8-51.5	1.0-53.7	1.4-52.6	1.22-43.10
EFS by BICR, median (95% CI), months	28.7 (13.9, NR)	15.7 (9.5, 31.6)	NR (41.2, NR)	37.5 (13.96, NR)
HR (KN-905 Arm C vs Arm A) (95% CI)	0.55 (0.33, 0.91)	-	-	-
HR (KN-905 Arm A vs Arm B) (95% CI)	-	0.71 (0.47, 1.07)	-	-
Rate at 6 months (%) (95% CI)	77.9 (67.2, 85.4)	68.7 (57.5, 77.5)	90.0 (81.0, 94.9)	76.6 (61.67, 86.34)
Rate at 12 months (%) (95% CI)	66.4 (55.0, 75.6)	55.0 (43.6, 65.0)	77.2 (66.2, 85.0)	69.5 (53.84, 80.74)
Rate at 18 months (%) (95% CI)	58.5 (46.8, 68.5)	47.4 (36.2, 57.8)	75.8 (64.8, 83.9)	62.2 (46.24, 74.67)
Rate at 24 months (%) (95% CI)	55.8 (44.1, 66.0)	41.0 (30.2, 51.5)	75.8 (64.8, 83.9)	62.2 (46.24, 74.67)
OS, median (95% CI), months	51.0 (32.0, NR)	41.7 (26.4, NR)	NR (NR, NR)	NR (34.76, NR)
Rate at 6 months (%) (95% CI)	91.6 (83.1, 95.9)	82.8 (73.0, 89.2)	94.0 (86.3, 97.5)	90.0 (77.70, 95.73)
Rate at 12 months (%) (95% CI)	78.2 (67.6, 85.6)	74.6 (64.1, 82.5)	83.3 (73.5, 89.8)	85.8 (72.57, 92.99)
Rate at 18 months (%) (95% CI)	71.9 (60.8, 80.4)	66.3 (55.2, 75.2)	78.4 (68.0, 85.8)	75.4 (60.70, 85.21)
Rate at 24 months (%) (95% CI)	66.9 (55.5, 76.0)	62.6 (51.4, 71.9)	78.4 (68.0, 85.8)	73.1 (58.15, 83.43)
pCR Rate (%) (95% CI)	25.3 (16.4, 36.0)	10.3 (4.8, 18.7)	58.8 (47.6, 69.4)	34.0 (21.2, 48.8)

BICR=blinded independent central review; CI=confidence interval; EFS=event-free survival; EV=enfortumab vedotin; HR=hazard ratio; ITT=intent-to-treat; KN=KEYNOTE; Mono=monotherapy; NR=not reached; OS=overall survival; pCR=pathological complete response; Pembro=pembrolizumab; RC+PLND=radical cystectomy and pelvic lymph node dissection.

Source: data on file.

Database Cutoff Date: 06-JUN-2025 (KN-905); 20-NOV-2024 (EV-103 Cohort L).

2.4.3. Discussion on clinical efficacy

The scope of this variation is to support the extension of indication of pembrolizumab 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 application is supported by KEYNOTE-905, a Phase 3, randomized, multicentre, open-label study conducted in participants with previously untreated, non-metastatic muscle-invasive bladder cancer who were ineligible for, or declined, cisplatin-based chemotherapy and were planned for curative-intent radical cystectomy with pelvic lymph node dissection.

Presently, the treatment standard for patients in Europe who are deemed cisplatin-ineligible and have resectable MIBC is based on surgery with radical cystectomy and pelvic lymph node dissection (RC + PLND), and nivolumab for the high-risk presentations. This is a setting of limited therapeutic options and dismal prognosis, related to intrinsic patient characteristics and the limited options that have proved to improve outcomes. 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.

The study initially randomized participants 1:1 to perioperative pembrolizumab plus RC + PLND (Arm A) versus RC + PLND alone (Arm B). A subsequent protocol amendment introduced a third arm evaluating perioperative enfortumab vedotin in combination with pembrolizumab plus RC + PLND (Arm C) and modified randomization to 1:1:1. Following Protocol Amendment 08 (01 November 2022), randomization to the pembrolizumab-only arm was stopped (except in France), and the study focus and multiplicity strategy were revised such that **the primary efficacy evaluation was centred on the comparison of Arm C versus Arm B**. The ITT2 population, which forms the primary efficacy population for the Arm C versus Arm B comparison, comprised 344 randomized participants (170 in Arm C and 174 in Arm B). Baseline demographic and disease characteristics in ITT2 were generally balanced between treatment groups and were representative of an elderly MIBC population, with a median age of 73 years and the majority being cisplatin-ineligible (81.7%).

In ITT2, among participants who underwent surgery, subsequent therapy data indicate a higher proportion of off-study adjuvant therapy in Arm B than in Arm C (21.8% vs 4.7%), with nivolumab reported as the most frequently used adjuvant therapy in Arm B (18.6%). A total of 29/156 (18.6%) participants in the Arm B received adjuvant nivolumab. 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 used 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. The study was open-label; however, the primary endpoint of event-free survival (EFS) was based on blinded independent central review (BICR) assessment, supporting objectivity. EFS was defined as time from randomization to the first occurrence of protocol-specified events spanning the full perioperative pathway, including radiographic progression precluding curative surgery (BICR), failure to undergo surgery with residual muscle-invasive disease (including biopsy-proven MIBC under specified conditions), gross residual disease at surgery, local or distant recurrence after RC + PLND (with imaging assessed by BICR where applicable), or death from any cause. This definition is considered acceptable from a clinical perspective.

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.

From a methodological perspective, the study was particularly critical because of the many (and, sometimes, late) substantial amendments to key aspects of the trial: study treatment, study

population, primary comparison, interim analyses, hierarchy of endpoints (and multiplicity strategy), definition of the primary endpoint, sample size. All these amendments occurred in an open-label setting, which increases the concerns about the integrity of the study. Additional analyses convincingly corroborated the MAH's statement that all modifications to the study protocol were driven by external factor and not by insights on the data results.

Subsequently to Amendment 08 randomization to arm A (pembrolizumab monotherapy) was closed and as a consequence, the study design is unable to formally establish the magnitude of the benefit conferred by adding EV to pembrolizumab. Supportive data from the ITT1 population of KEYNOTE 905 encompassing those patients initially enrolled to receive neoadjuvant pembrolizumab vs upfront surgery did not show a statistically significant EFS improvement (HR 0.80; 95% CI: 0.60–1.06) at this interim analysis, with no clear improvement in OS (HR 0.87; 95% CI: 0.64–1.19), although some evidence of antitumour activity is reflected by higher rates of pCR (27.1% vs 9.3%) and pathological downstaging (35.5% vs 14%) compared with surgery alone. Data according to PD-L1 in the ITT1 suggests lack of efficacy for PD-L1 negative (i.e. PD-L1 < 1) patients, however the cut-off 1 was not prespecified, moreover the number of patients with CPS<1 is very low to draw any conclusion.

The MAH has also provided an overview of studies in support of the contribution of each component to the combination therapy from the metastatic setting. 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 Keytruda EMEA/H/C/003820/II/0150).

In conclusion, 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 for the combination EV+pembrolizumab may be of less impact. Relevantly, the change in stratification factor was addressed by including an additional sensitivity analysis using PD-L1 status (CPS $\geqslant$ 10 vs CPS <10) as covariate in the analysis.

Amendments

The definition of primary endpoint EFS as the time from randomisation to any event indicative of failure to cure (failure to undergo surgery due to disease progression, inability to completely resect the tumour during surgery, recurrence of disease, death), was modified in Amendment 10 at the request of the FDA in order to explicitly clarify the evidence necessary to establish an EFS event, and this change had no impact on the adjudication of EFS events.

Due to the perioperative treatment, time to surgery was longer in Arms A and C versus Arm B (planned at ~12 weeks vs within ~2–9 weeks post-randomisation) with an observed difference of approximately 7.5 weeks. This design feature could artificially increase the difference in EFS between Arm C and Arm B. However, additional simulations and tipping point analyses clarified that the difference due to the study design had a negligible impact on the treatment effect, and corroborated the robustness of the trial conclusions.

To accommodate the study design amendments, several changes were made to the Interim Analysis (IA) plan as the trial was ongoing. Although chosen spending function (Hwang-Shih-DeCani) allow a certain flexibility to add or remove interim analyses, it was not fully clear how such major modifications might have impacted the alpha spending throughout the trial. Multiple substantial amendments (01, 05, 08, 10) modified key elements (population, intervention, endpoint, hypotheses), in an open-label setting, raising concerns on trial integrity. Additional discussion and analyses clarified that the amendments were unlikely to have been implemented because of insights in the results.

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 conduct of the study indicates that most participants in Arm C initiated treatment and that the majority completed the protocol-specified three preoperative cycles. The proportions of participants undergoing surgery were similar between groups (149/170 in Arm C and 156/174 in Arm B). Although neoadjuvant treatment inherently implied longer time to resection, the proportion of patients who did not undergo planned surgery was balanced (~10% in Arm B and ~12% in Arm C), suggesting that neoadjuvant treatment did not appear to impair surgery in comparison to no neoadjuvant treatment. Complete resection was achieved in 98.7% of operated participants in Arm C and 95.5% in Arm B. 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, in the combination Arm C the proportion of patents that completed the planned neoadjuvant treatment was 86.2% and there appeared to be no detriment in resectability.

Discontinuations from study treatment in Arm C occurred primarily due to adverse events and withdrawal by participant, consistent with the presence of perioperative systemic therapy in that arm; Arm B did not include study drug exposure.

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[25] [26], who are typically older, more comorbid, and less likely to receive neoadjuvant therapy.

At the first interim analysis (IA1; data cutoff 06 June 2025), median survival follow-up was 20.4 months in Arm C and 17.1 months in Arm B at IA1. The primary efficacy analysis of EFS in the ITT2 population showed a statistically significant improvement for enfortumab vedotin plus pembrolizumab compared with RC + PLND alone. EFS events occurred in 28.2% of participants in Arm C and 54.6% in Arm B, with a hazard ratio 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 were reported as generally consistent with the primary analysis, including consistency between investigator-assessed EFS and BICR-assessed EFS.

Following rejection of the EFS null hypothesis, overall survival (OS) was formally tested in accordance with the prespecified multiplicity strategy. OS results were statistically significant in favour of perioperative enfortumab vedotin plus pembrolizumab, with a hazard ratio of 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.

In addition to time-to-event endpoints, the protocol defines pathologic complete response (pCR) as absence of viable tumour (pT0N0) in examined tissue from RC + PLND based on blinded central pathology review and pathologic downstaging (pDS) as <pT2 and N0. The protocol describes that pCR was formally tested contingent upon a positive EFS result after the Amendment 08 revision, and that the IA1 conclusions include improvement in pCR with perioperative enfortumab vedotin plus pembrolizumab versus RC + PLND alone. The clinical relevance of pCR comparison between patients who received neoadjuvant treatment vs patients who proceed directly to surgery is limited.

Subgroup analyses

For participants defined as "cisplatin-eligible but declined", although the HR point estimates for EFS and OS were higher than in the ITT population, the subgroup was small (18%). In addition, the positive results of perioperative EV+pembro in the cisplatin-eligible population in KEYNOTE-B15[27] alleviate the concern. Regarding biomarkers, the benefit in EFS and OS of EV+pembro over surgery alone was consistent between PD-L1 CPS<10 and ≥10 subgroups, although pCR for EV+pembro was lowed in CPS<10 (68.8% vs 47.1%). Nectin-4 expression analyses of EFS and OS across pre-specified H-score ranges as well as a continuous variable overall support the view that the efficacy of perioperative EV plus pembrolizumab is broadly consistent across the observed range of Nectin-4 expression and does not suggest the presence of a clinically relevant Nectin-4 threshold for patient selection.

[25] 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.
[26] 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.
[27] Galsky M et al. Neoadjuvant and adjuvant enfortumab vedotin (EV) plus pembrolizumab (pembro) for participants with muscle-invasive bladder cancer (MIBC) who are eligible for cisplatin: Randomized, open-label, phase 3 KEYNOTE-B15 study. Clin Oncol 44, LBA630(2026) Volume 44, Number 7_suppl DOI: 10.1200/JCO.2026.44.7_suppl.LBA630

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 + pembrolizumab 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 EV could affect the suitability for subsequent therapy.

Wording of indication

Patients had to be deemed resectable to be included in the protocol and thus the perioperative EV + pembrolizumab regimen is not indicated for downsizing an unresectable tumour. The MAH added "resectable" to the indication wording:

*Keytruda, in combination with enfortumab vedotin, 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

In the ITT2 population of the pivotal KEYNOTE-905 study, perioperative enfortumab vedotin plus pembrolizumab showed a clinically meaningful and statistically significant improvement in EFS compared with RC + PLND alone, with early and sustained separation of Kaplan–Meier curves and a substantial absolute reduction in EFS events. This benefit translated into a statistically significant improvement in OS, reinforcing the clinical relevance of the EFS findings and supporting a favourable benefit-risk profile in this setting. 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).

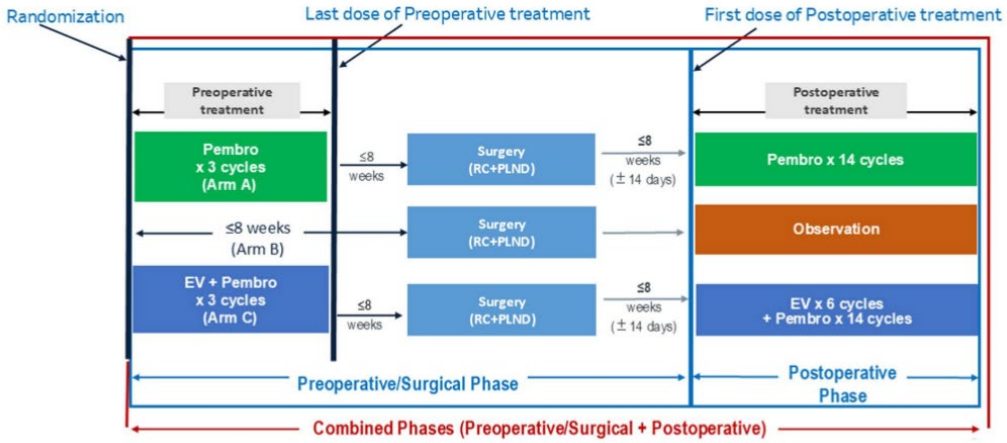
Reference safety data from studies enfortumab vedotin in combination with pembrolizumab have been provided to assess the consistency of the safety of the combination emerged in KEYNOTE-905 study, as well as of enfortumab vedotin or pembrolizumab monotherapies to enable a comparison of the safety data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

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

Dataset	Population	Nomenclature in Tables	Nomenclature in Text
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.			

Figure 16 Safety Analysis Phases Schematic Diagram



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

Note: Arm C (perioperative EV + pembrolizumab) includes preoperative and postoperative treatment with enfortumab vedotin and pembrolizumab as well as the surgical phase. Arm B (RC + PLND alone) includes only the surgical phase. Arm A (perioperative pembrolizumab) includes preoperative and postoperative treatment with pembrolizumab as well as the surgical phase.

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. Participants were analyzed according to the study treatment that they received. As of the DCO, 167 participants received at least 1 dose of perioperative EV + pembrolizumab, and 163 participants received at least 1 dose of pembrolizumab in KEYNOTE-905. Participants in the RC + PLND alone group (surgery only) did not receive study medications. Eleven participants were still receiving study treatment in the perioperative EV + pembrolizumab group at the time of DCO.

Table 39 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).

Table 40 Summary of Drug Exposure for EV (APaT Population)

	KN-905 EV + Pembro (N=167)	EV + Pembro Combo ISD (N=564)	EV Mono ISD (N=793)
Duration on EV[a] (months)			
n	167	564	793
Mean (SD)	5.0 (3.6)	9.8 (8.2)	6.8 (7.7)
Median	5.5	7.0	4.7
Range	0.03 to 14.1	0.3 to 45.9	0.3 to 65.4

[a] Duration on individual treatment EV (months): For EV + Pembro in KN905, duration = (last administration date of EV – first administration of EV + 1) / 30.4367; For EV 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.

Table 41 Summary of Drug Exposure for Pembrolizumab (APaT Population)

	KN-905 EV + Pembro (N=167)	KN-905 Pembro mono (N=163)	EV + Pembro Combo ISD (N=564)	Pembro Mono RSD (N=7631)
Duration on Pembrolizumab[a] (months)				
n	167	163	564	7631
Mean (SD)	6.9 (5.8)	7.9 (5.8)	11.2 (8.8)	7.9 (6.9)
Median	5.7	7.9	8.3	5.8
Range	0.03 to 19.7	0.03 to 19.8	0.3 to 32.3	0.03 to 38.0

[a] Duration on Treatment (months): For KN905 and Pembro Mono RSD, duration = (last dose date of pembrolizumab – first administration of pembrolizumab+ 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.

Patient characteristics

Table 42 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.

Adverse events

AEs were coded using MedDRA (version 28.0) and reported according to NCI CTCAE version 4.03.

Table 43 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)

	KN-905 EV + Pembro		KN-905 Pembro mono		KN-905 Cystectomy		EV + Pembro Combo ISD		EV Mono ISD		Pembro Mono RSD	
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 Pembrolizumab	57	(34.1)	45	(27.6)	NA		177	(31.4)	NA		1,066	(14.0)
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)

	KN-905 EV + Pembro		KN-905 Pembro mono		KN-905 Cystectomy		EV + Pembro Combo ISD		EV Mono ISD		Pembro Mono RSD	
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 44 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 45 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	159	-97.5	152	-62.8	563	-99.8	785	-99	7,375	-96.6
with no adverse events	0	0	4	-2.5	90	-37.2	1	-0.2	8	-1	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	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
Fatigue	54	-32.3	26	-16	12	-5	232	-41.1	371	46.8	2,368	-31
Anaemia	51	-30.5	50	-30.7	29	-12	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	138	-24.5	241	30.4	150	-2
Constipation	46	-27.5	24	-14.7	20	-8.3	158	-28	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	16	-9.8	2	-0.8	91	-16.1	136	-17.2	538	-7.1
Urinary tract infection	40	-24	46	-28.2	22	-9.1	131	-23.2	125	-15.8	511	-6.7
Weight decreased	33	-19.8	18	-11	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

	KN-905 EV + Pembro		KN-905 Pembro mono		KN-905 Cystectomy		EV + Pembro Combo ISD		EV Mono ISD		Pembro Mono RSD	
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	8	-4.9	1	-0.4	103	-18.3	173	-21.8	394	-5.2
Hypothyroidism	24	-14.4	27	-16.6	0	0	65	-11.5	7	-0.9	937	-12.3
Peripheral sensory neuropathy	23	-13.8	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	83	-10.5	358	-4.7
Prostate cancer	19	-11.4	18	-11	22	-9.1	1	-0.2	0	0	5	-0.1
Pyrexia	19	-11.4	18	-11	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	101	-12.7	528	-6.9
Abdominal pain	17	-10.2	13	-8	17	-7	72	-12.8	122	-15.4	671	-8.8
Neuropathy peripheral	17	-10.2	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	57	-10.1	109	-13.7	55	-0.7
Neutropenia	16	-9.6	4	-2.5	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	9	-5.5	8	-3.3	81	-14.4	148	-18.7	945	-12.4
Dizziness	12	-7.2	6	-3.7	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

	KN-905 EV + Pembro		KN-905 Pembro mono		KN-905 Cystectomy		EV + Pembro Combo ISD		EV Mono ISD		Pembro Mono RSD	
Arthralgia	10	-6	7	-4.3	1	-0.4	99	-17.6	95	-12	1,449	-19
Dry eye	10	-6	3	-1.8	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	47	-8.3	49	-6.2	946	-12.4
Hyperthyroidism	8	-4.8	19	-11.7	0	0	26	-4.6	2	-0.3	398	-5.2
Back pain	5	-3	9	-5.5	1	-0.4	75	-13.3	91	-11.5	847	-11.1
Rash macular	0	0	1	-0.6	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.

Table 46 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 47 Participants With Grade 3-5 Adverse Events by Decreasing Frequency of Preferred Term (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.

Table 48 Participants With Drug-Related Grade 3-5 Adverse Events by Decreasing Frequency of Preferred Term (Incidence ≥ 1% 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	76	(45.5)	38	(23.3)	0	(0.0)	330	(58.5)	404	(50.9)	1,208	(15.8)
with no adverse events	91	(54.5)	125	(76.7)	242	(100.0)	234	(41.5)	389	(49.1)	6,423	(84.2)
Neutropenia	9	(5.4)	0	(0.0)	0	(0.0)	34	(6.0)	43	(5.4)	13	(0.2)
Diarrhoea	5	(3.0)	3	(1.8)	0	(0.0)	24	(4.3)	26	(3.3)	75	(1.0)
Pruritus	5	(3.0)	0	(0.0)	0	(0.0)	10	(1.8)	13	(1.6)	13	(0.2)
Rash	5	(3.0)	0	(0.0)	0	(0.0)	0	(0.0)	13	(1.6)	37	(0.5)
Anaemia	4	(2.4)	0	(0.0)	0	(0.0)	25	(4.4)	38	(4.8)	33	(0.4)
Fatigue	4	(2.4)	0	(0.0)	0	(0.0)	26	(4.6)	52	(6.6)	75	(1.0)
Rash maculo-papular	4	(2.4)	2	(1.2)	0	(0.0)	52	(9.2)	43	(5.4)	21	(0.3)
Asthenia	3	(1.8)	0	(0.0)	0	(0.0)	9	(1.6)	9	(1.1)	26	(0.3)
Hyperglycaemia	3	(1.8)	1	(0.6)	0	(0.0)	30	(5.3)	41	(5.2)	20	(0.3)
Hypothyroidism	3	(1.8)	0	(0.0)	0	(0.0)	3	(0.5)	0	(0.0)	8	(0.1)
Acute kidney injury	2	(1.2)	2	(1.2)	0	(0.0)	14	(2.5)	10	(1.3)	16	(0.2)
Aspartate aminotransferase increased	2	(1.2)	5	(3.1)	0	(0.0)	10	(1.8)	10	(1.3)	47	(0.6)
Colitis	2	(1.2)	1	(0.6)	0	(0.0)	7	(1.2)	5	(0.6)	67	(0.9)
Constipation	2	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Febrile neutropenia	2	(1.2)	0	(0.0)	0	(0.0)	4	(0.7)	9	(1.1)	0	(0.0)
Hepatic function abnormal	2	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	4	(0.1)
Hepatitis	2	(1.2)	2	(1.2)	0	(0.0)	3	(0.5)	0	(0.0)	20	(0.3)
Hypophosphataemia	2	(1.2)	0	(0.0)	0	(0.0)	8	(1.4)	13	(1.6)	15	(0.2)
Peripheral sensory neuropathy	2	(1.2)	0	(0.0)	0	(0.0)	21	(3.7)	24	(3.0)	2	(0.0)
Renal impairment	2	(1.2)	0	(0.0)	0	(0.0)	2	(0.4)	1	(0.1)	2	(0.0)
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)	3	(0.5)	3	(0.4)	0	(0.0)
Urticaria	2	(1.2)	1	(0.6)	0	(0.0)	0	(0.0)	2	(0.3)	1	(0.0)

Serious adverse event/deaths/other significant events

2.5.1. SAEs

Table 49 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 50 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 51 Participants With Adverse Events Resulting in Death by Decreasing Frequency of Preferred Term (Incidence > 0% in One or More KN-905 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.

Adverse Events Leading to Surgery Delay or Cancellation

AEs leading to surgery delay were reported for 6 participants (4.0%) in the perioperative EV + pembrolizumab group and 1 participant (0.6%) in the RC + PLND alone group (participants may have had more than 1 AE leading to surgery delay) as follows:

- Perioperative EV + pembrolizumab: acute myocardial infarction, ALT increased, AST increased, atrial fibrillation, autoimmune hepatitis, cardiac failure, endocarditis, myocarditis, and pulmonary edema (1 participant [0.7%] each).
- RC + PLND alone: respiratory tract infection (1 participant [0.6%]).

AEs resulting in surgery cancellation were reported for 7 participants (4.1%) in the perioperative EV + pembrolizumab group and 3 participants (1.7%) in the RC + PLND alone group:

- Perioperative EV + pembrolizumab: acute myocardial infarction, bile duct cancer, colon cancer, myasthenia gravis, respiratory distress, toxic epidermal necrolysis, and UTI (1 participant [0.6%] each).

- RC + PLND alone: cerebrovascular accident, suicidal ideation, and urosepsis (1 participant [0.6%] each).

2.5.3. Adverse events of special interest

2.5.3.1. Adverse Events of Special Interest for Pembrolizumab

AEOSI are immune-mediated events and infusion-related reactions causally associated with pembrolizumab.

Table 52 Adverse Event Summary AEOSI Overall for Pembrolizumab (APaT Population)

	KN-905 EV + Pembro		KN-905 Pembro mono		KN-905 Cystectomy		EV + Pembro Combo ISD		Pembro Mono RSD	
	n	(%)	N	(%)	n	(%)	n	(%)	n	(%)
Participants in population	167		163		242		564		7,631	
with one or more adverse events	72	(43.1)	63	(38.7)	3	(1.2)	264	(46.8)	2,095	(27.5)
with no adverse event	95	(56.9)	100	(61.3)	239	(98.8)	300	(53.2)	5,536	(72.5)
with drug-relateda adverse events	64	(38.3)	50	(30.7)	0	(0.0)	254	(45.0)	1,815	(23.8)
with toxicity grade 3-5 adverse events	30	(18.0)	23	(14.1)	1	(0.4)	132	(23.4)	543	(7.1)
with toxicity grade 3-5 drug-related adverse events	30	(18.0)	21	(12.9)	0	(0.0)	129	(22.9)	475	(6.2)
with serious adverse events	14	(8.4)	18	(11.0)	1	(0.4)	77	(13.7)	527	(6.9)
with serious drug-related adverse events	14	(8.4)	18	(11.0)	0	(0.0)	74	(13.1)	462	(6.1)
who died	2	(1.2)	2	(1.2)	0	(0.0)	3	(0.5)	13	(0.2)
who died due to a drug-related adverse event	2	(1.2)	2	(1.2)	0	(0.0)	3	(0.5)	13	(0.2)
discontinued any drug due to an adverse event	22	(13.2)	19	(11.7)	0	(0.0)	73	(12.9)	363	(4.8)
discontinued Pembrolizumab	20	(12.0)	19	(11.7)	NA		66	(11.7)	363	(4.8)
discontinued EV	17	(10.2)	NA		NA		38	(6.7)	NA	
discontinued any drug due to a drug-related adverse event	22	(13.2)	19	(11.7)	0	(0.0)	73	(12.9)	356	(4.7)
discontinued Pembrolizumab	20	(12.0)	19	(11.7)	NA		66	(11.7)	356	(4.7)
discontinued EV	17	(10.2)	NA		NA		38	(6.7)	NA	
discontinued any drug due to a serious adverse event	8	(4.8)	14	(8.6)	0	(0.0)	31	(5.5)	231	(3.0)
discontinued Pembrolizumab	7	(4.2)	14	(8.6)	NA		30	(5.3)	231	(3.0)
discontinued EV	7	(4.2)	NA		NA		15	(2.7)	NA	
discontinued any drug due to a serious drug-related adverse event	8	(4.8)	14	(8.6)	0	(0.0)	31	(5.5)	229	(3.0)
discontinued Pembrolizumab	7	(4.2)	14	(8.6)	NA		30	(5.3)	229	(3.0)
discontinued EV	7	(4.2)	NA		NA		15	(2.7)	NA	

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 53 Participants With Adverse Events of Special Interest by AEOSI Category and Preferred Term by Maximum Toxicity Grade (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		Pembro Mono RSD	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	167		163		242		564		7,631	
with one or more adverse events	72	(43.1)	63	(38.7)	3	(1.2)	264	(46.8)	2,095	(27.5)
Grade 1	16	(9.6)	11	(6.7)	1	(0.4)	41	(7.3)	496	(6.5)
Grade 2	26	(15.6)	29	(17.8)	1	(0.4)	91	(16.1)	1,056	(13.8)
Grade 3	26	(15.6)	18	(11.0)	1	(0.4)	114	(20.2)	465	(6.1)
Grade 4	2	(1.2)	3	(1.8)	0	(0.0)	15	(2.7)	65	(0.9)
Grade 5	2	(1.2)	2	(1.2)	0	(0.0)	3	(0.5)	13	(0.2)
with no adverse events	95	(56.9)	100	(61.3)	239	(98.8)	300	(53.2)	5,536	(72.5)

The two Grade 5 (fatal) AEOSI events in the EV + pembrolizumab group were myasthenic syndrome and Severe skin reactions (toxic epidermal necrolysis).

Table 54 Participants With Adverse Events of Special Interest by AEOSI Category and 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		Pembro Mono RSD	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	167		163		242		564		7,631	
with one or more adverse events	72	(43.1)	63	(38.7)	3	(1.2)	264	(46.8)	2,095	(27.5)
with no adverse events	95	(56.9)	100	(61.3)	239	(98.8)	300	(53.2)	5,536	(72.5)
Adrenal Insufficiency	1	(0.6)	2	(1.2)	0	(0.0)	13	(2.3)	74	(1.0)
Arthritis	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.5)	5	(0.1)
Cholangitis Sclerosing	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Colitis	4	(2.4)	3	(1.8)	0	(0.0)	19	(3.4)	159	(2.1)
Encephalitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	5	(0.1)
Exocrine Pancreatic Insufficiency	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Gastritis	4	(2.4)	2	(1.2)	3	(1.2)	9	(1.6)	57	(0.7)
Guillain-Barre Syndrome	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	6	(0.1)
Haemolytic Anaemia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	2	(0.0)
Hepatitis	6	(3.6)	5	(3.1)	0	(0.0)	17	(3.0)	80	(1.0)
Hyperthyroidism	8	(4.8)	19	(11.7)	0	(0.0)	26	(4.6)	398	(5.2)
Hypoparathyroidism	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Hypophysitis	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.9)	52	(0.7)
Hypothyroidism	24	(14.4)	27	(16.6)	0	(0.0)	66	(11.7)	939	(12.3)
Infusion Reactions	1	(0.6)	0	(0.0)	0	(0.0)	12	(2.1)	165	(2.2)
Myasthenic Syndrome	1	(0.6)	2	(1.2)	0	(0.0)	3	(0.5)	8	(0.1)
Myelitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Myocarditis	1	(0.6)	3	(1.8)	0	(0.0)	5	(0.9)	9	(0.1)
Myositis	1	(0.6)	4	(2.5)	0	(0.0)	8	(1.4)	34	(0.4)
Nephritis	4	(2.4)	1	(0.6)	0	(0.0)	6	(1.1)	37	(0.5)
Optic Neuritis	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.4)	2	(0.0)

Pancreatitis	0	(0.0)	0	(0.0)	0	(0.0)	9	(1.6)	28	(0.4)
Pericarditis	0	(0.0)	2	(1.2)	0	(0.0)	0	(0.0)	11	(0.1)
Pneumonitis	6	(3.6)	3	(1.8)	0	(0.0)	57	(10.1)	324	(4.2)
Sarcoidosis	0	(0.0)	1	(0.6)	0	(0.0)	2	(0.4)	20	(0.3)
Severe Skin Reactions	23	(13.8)	2	(1.2)	0	(0.0)	111	(19.7)	130	(1.7)
Thyroiditis	5	(3.0)	0	(0.0)	0	(0.0)	5	(0.9)	74	(1.0)
Type 1 Diabetes Mellitus	0	(0.0)	3	(1.8)	0	(0.0)	1	(0.2)	34	(0.4)
Uveitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	25	(0.3)
Vasculitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)

Every participant is counted a single time for each applicable row and column.
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.
Database cutoff date for KN905: 06JUN2025.

Table 55 Time to Onset and Duration of AEOSI (APaT Population)

	KN-905 EV + Pembro	KN-905 Pembro mono	KN-905 Cystectomy	EV + Pembro Combo ISD	Pembro Mono RSD
Participants in population	167	163	242	564	7631
Participants with AEOSI, n (%)	72 (43.1)	63 (38.7)	3 (1.2)	264 (46.8)	2095 (27.5)
Time to Onset of First AEOSI[a] (day)					
Mean (SD)	110.5 (116.7)	122.1 (105.6)	5.0 (3.6)	121.4 (132.3)	118.8 (121.6)
Median	70.0	97.0	6.0	77.0	78.0
Range	1 to 456	16 to 499	1 to 8	1 to 762	1 to 796
Total number of episodes of AEOSI	97	82	3	449	2979
Average number of episodes of AEOSI per participant	1.3	1.3	1.0	1.7	1.4
Episode Duration[b] (day)					
Median	94.0	146.0	103.0	46.0	103.0
Range	2 to 1271+	1+ to 1949+	1 to 1033+	1 to 2018+	1 to 1915+

Table 56 Summary of Outcome for Participants With AEOSI (APaT Population)

	Outcome	KN-905 EV + Pembro	KN-905 Pembro mono	KN-905 Cystectomy	EV + Pembro Combo ISD	Pembro Mono RSD
		n (%)	n (%)	n (%)	n (%)	n (%)
Participants in population		167	163	242	564	7631
With one or more AEOSI	**Overall**	**72 (43.1)**	**63 (38.7)**	**3 (1.2)**	**264 (46.8)**	**2095 (27.5)**
	Fatal	2 (2.8)	2 (3.2)	0 (0.0)	3 (1.1)	13 (0.6)
	Not Resolved	20 (27.8)	19 (30.2)	1 (33.3)	92 (34.8)	909 (43.4)
	Resolving	9 (12.5)	9 (14.3)	0 (0.0)	54 (20.5)	182 (8.7)
	Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	30 (1.4)
	Sequelae	0 (0.0)	1 (1.6)	0 (0.0)	6 (2.3)	67 (3.2)
	Resolved	41 (56.9)	32 (50.8)	2 (66.7)	109 (41.3)	894 (42.7)

Table 57 Summary of Concomitant Corticosteroid Use for AEOSI (APaT Population)

	KN-905 EV + Pembro		KN-905 Pembro mono		KN-905 Cystectomy		EV + Pembro Combo ISD		Pembro Mono RSD	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	167		163		242		564		7631	
Participants with one or more events	72		63		3		264		2095	
Treated with systemic corticosteroid	28	(38.9)	21	(33.3)	0	(0.0)	136	(51.5)	730	(34.8)
High starting dose	18	(25.0)	16	(25.4)	0	(0.0)	NA		530	(25.3)
Low starting dose	10	(13.9)	5	(7.9)	0	(0.0)	NA		197	(9.4)
Missing starting dose	0	(0.0)	0	(0.0)	0	(0.0)	NA		3	(0.1)
Not treated with systemic corticosteroid	44	(61.1)	42	(66.7)	3	(100.0)	128	(48.5)	1365	(65.2)

2.5.3.2. Adverse Events of Special Interest for Enfortumab Vedotin

AESI analyses are based on a predefined list of preferred AE terms deemed clinically relevant for enfortumab vedotin.

2.5.3.2.1. Skin Reactions

The target of enfortumab vedotin, Nectin-4, is expressed in epidermal keratinocytes and skin appendages (eg, sweat glands and hair follicles); clinical AEs of skin reactions have been observed.

Table 58 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 59 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)

Median time to onset of first AESI Skin Reactions for EV was 0.46 months (range 0.033 to 8.411).

Table 60 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).

2.5.3.2.2. Peripheral neuropathy

Table 61 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 62 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).

2.5.3.2.3. Hyperglycemia

Table 63 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 64 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 65 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 66 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 67 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)**

2.5.3.2.4. Ocular disorders

Table 68 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 69 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.

2.5.3.2.5. Infusion-related Reactions

Table 70 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.

Pneumonitis/Interstitial Lung Disease

The mechanism for enfortumab vedotin-induced pneumonitis is not known. Pneumonitis/ILD events is considered an important identified risk of enfortumab vedotin.

Table 71 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.

In the EV plus pembrolizumab group, 6 patients experienced pneumonitis and one pulmonary toxicity. No cases of ILD were reported.

Table 72 Participants With Adverse Events of Other Risk for EV - Pneumonitis/Interstitial Lung Disease 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	7	(4.2)	0	(0.0)	62	(11.0)	26	(3.3)
Grade 1	4	(2.4)	0	(0.0)	14	(2.5)	9	(1.1)
Grade 2	3	(1.8)	0	(0.0)	25	(4.4)	11	(1.4)
Grade 3	0	(0.0)	0	(0.0)	17	(3.0)	4	(0.5)
Grade 4	0	(0.0)	0	(0.0)	3	(0.5)	2	(0.3)
Grade 5	0	(0.0)	0	(0.0)	3	(0.5)	0	(0.0)
with no adverse events	160	(95.8)	242	(100.0)	502	(89.0)	767	(96.7)

In the EV plus pembrolizumab group, median time to onset of first event of Pneumonitis/Interstitial Lung Disease was 2.497 months (range 1.938 to 9.692).

2.5.3.2.6. Anemia and Neutropenia

Table 73 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 74 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 75 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 76 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)

2.5.3.2.7. 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 77 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 78 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 79 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)

2.5.3.2.8. 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 80 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 81 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 82 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 83 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 findingsAll laboratory parameters of the pivotal trial were submitted with this procedure however they are not reproduced entirely in this assessment report.

2.6.1. 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 84 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)

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	(%)
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 85 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.
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.

Sex

Table 86 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 87 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.

Table 88 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.

Discontinuation due to adverse events

Table 89 Participants With Adverse Events Resulting in Any Drug Discontinuation (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	81	(48.5)	45	(27.6)	0	(0.0)	279	(49.5)	168	(21.2)	1,066	(14.0)
with no adverse events	86	(51.5)	118	(72.4)	242	(100.0)	285	(50.5)	625	(78.8)	6,565	(86.0)

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)

Table 90 Participants With Adverse Events Resulting in Dose Reduction for EV (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)	0	(0.0)	250	(44.3)	301	(38.0)
with no adverse events	139	(83.2)	242	(100.0)	314	(55.7)	492	(62.0)

Dose reductions were only applicable for enfortumab vedotin. No dose reductions were permitted for pembrolizumab per protocol. By treatment phase, patients in the perioperative EV + pembrolizumab group who experienced AEs resulting in dose reduction of enfortumab vedotin, were 13.8% in the Preoperative/Surgical phase, and 7% in the postoperative phase.

2.1. Immunogenicity

The incidence rate for treatment-emergent ADA for pembrolizumab in the KEYNOTE-905 study population treated with enfortumab vedotin in combination with pembrolizumab was low, at 5.2% (8 out of 154 evaluable subjects) (see table 6 Clinical pharmacology).

Blood samples for enfortumab vedotin-related ADA were collected for patients recruited to the EV + Pembro arm of the KN-905 trial resulting in 159/167 evaluable participants (see table below).

Table 91 Summary of enfortumab vedotin 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

Enfortumab vedotin 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 safety profile of enfortumab vedotin was most recently described in the Periodic Safety Update Report covering the period of 18-DEC-2024 through 17-JUN-2025. The cumulative number of patients receiving enfortumab vedotin since the launch of the product through 17-JUN-2025 is estimated as 121,411 patients.

There are no records of any enfortumab vedotin registration being revoked or withdrawn for safety reasons in any country.

Pembrolizumab was first approved for marketing in the United States (US) on 04-SEP-2014.The safety profile of pembrolizumab was summarized in the Periodic Safety Update Report covering the period 04-SEP-2023 through 03-SEP-2024, approximately 369,482 patient-years of treatment with pembrolizumab. Cumulatively, there were approximately 1,518,204 patient-years of treatment with pembrolizumab.

There are no records of any pembrolizumab registration being revoked or withdrawn for safety reasons in any country.

2.1.1. Discussion on clinical safety

The safety analysis of the perioperative (neoadjuvant EV + pembrolizumab for 3 cycles Q3W then adjuvant EV for 6 cycles +pembrolizumab for 14 cycles) combination of enfortumab vedotin with pembrolizumab and RC + PLND is based on the IA1 data of the pivotal Phase 3 Study KEYNOTE-905/EV-303 in participants with MIBC who are ineligible for or decline cisplatin-based chemotherapy (n=167). This is compared to patients in the control arm where patients were treated only with surgery RC + PLND (n=242), and to those enrolled in the pembrolizumab monotherapy arm who received the perioperative pembrolizumab alone with RC + PLND (n=163). Additional comparisons with the reference datasets (ISD) including prior clinical trials data of EV + pembrolizumab (n=564), EV monotherapy (n=793) and pembrolizumab monotherapy (n=7631) allow a good contextualization of the safety profile.

Overall, the incidence of adverse reactions for pembrolizumab in combination with enfortumab vedotin was observed to be higher than for pembrolizumab monotherapy reflecting the contribution of enfortumab vedotin. Adverse reactions were generally similar to those occurring in patients with unresectable or metastatic urothelial carcinoma treated with pembrolizumab in combination with enfortumab vedotin and the inclusion of the adverse reactions observed in KEYNOTE-905/EV-303 in table 2: "Adverse reactions in patients treated with pembrolizumab" of section 4.8 of the SmPC didn't change the frequency nor new adverse reactions were observed.

Baseline demographics of participants in the perioperative EV + pembrolizumab group were similar to the other arms of KEYNOTE-905 while showed some differences with respect to EV + pembrolizumab ISD, EV mono ISD, and pembrolizumab RSD, e.g. more male participants, ≥65 years old, ECOG PS 2, CrCl ≥30 and <60 mL/min, likely reflective of the cisplatin ineligible population with MIBC enrolled in KEYNOTE-905.

The overall incidences of AE, drug-related AE, SAE, death, discontinuation due to AE, in the perioperative EV + pembrolizumab group were obviously higher than in the RC + PLND group as patients received no systemic treatment in the latter, while higher incidences were reported in drug-related AE (all and G3-5) and discontinuation due to AE as compared to the pembrolizumab monotherapy arm. Of note, the safety of the EV + pembrolizumab group of KEYNOTE-905 appears

generally similar to the reference EV + pembrolizumab dataset, including in terms of toxicity grade of AE, with EV mono showing generally worse toxicity than pembrolizumab monotherapy.

When analysed by treatment phase, in the preoperative/surgical phase the incidence of AE was higher in the EV + pembrolizumab than in the surgical arm (99% vs 65%), as expected. Most of the patients (80%) in the EV + pembrolizumab arm also experienced drug-related AE in the post-operative phase, with 7 cases (7%) of death, none considered drug-related. Of note, however, treatment-related AE led to the death of two patients in the neoadjuvant phase before curative surgery. AE was also a common reason for discontinuing systemic any drug in the EV + pembrolizumab arm (48.5%), 27% in the neoadjuvant and up to 37% in the adjuvant phase, confirming the limited overall tolerability of the EV + pembrolizumab regimen.

In the perioperative EV + pembrolizumab group, the most common AE (>20%) were pruritus, alopecia, diarrhoea, fatigue, anemia, decreased appetite, dysgeusia, constipation, nausea, rash, AST increased, UTI, while the most common G3-5 AEs (>4%) were UTI, anemia, neutropenia, AKI, diarrhoea and hyperglicemia. Events like UTI and AKI were usually considered not drug related and attributable to the underlying tumor, indeed occurred, also in the RC + PLND group, although at lower frequency in the control arm. Overall, the type and frequency of each AEs was similar to the EV + pembrolizumab ISD. Most common SAE EV + pembrolizumab group were also mostly related to the bladder tumor (UTI, AKI, urosepsis, pyelonephritis), while most common drug-related SAE were AKI and diarrhoea (3 patients each).

Regarding death related to AE, the incidence was similar in the 3 treatment arms of KEYNOTE-905 (7.8% vs 9.8% vs 5% in EV + pembrolizumab, pembrolizumab and surgery arm, respectively). Among those, the cases which were considered drug-related by the investigator in KN-905 study were 2 (1.2%) in the EV + pembrolizumab arm (myasthenia gravis, toxic epidermal necrosis), 2 (1.2%) in the pembrolizumab mono arm (myasthenia gravis, diabetic ketoacidosis), and no cases in the cystectomy group. The death due to myasthenia gravis in the EV + pembrolizumab arm occurred after only one cycle of EV and pembrolizumab in the neoadjuvant phase, and this event was considered an AEOSI related to pembrolizumab. Similarly, the death due to myasthenia gravis in the pembrolizumab mono arm occurred after only one cycle of pembrolizumab, and was associated with myocarditis and myositis. In this latter case, in addition to corticosteroid, the patient was treated with plasmapheresis, although with no success. Myasthenic Syndrome including myastenia gravis is a known AEOSI for pembrolizumab already reported in sections 4.4 and 4.8 of the Keytruda SmPC. The death due to toxic epidermal necrolysis occurred after one cycle of EV + pembrolizumab and was considered by the Sponsor related to both EV and pembrolizumab; TEN is clearly reported in the SmPC of both Keytruda and Padcev. Diabetic ketoacidosis, occurred after two cycles of pembrolizumab, is also a known AEOSI for Keytruda. It is of note that all drug-related deaths occurred after one-two cycles of treatment in the neoadjuvant setting. Therefore, all the AEs leading to deaths observed in KEYNOTE-905 are known and not unexpected events related to Keytruda and/or Padcev, although highlighting the possibility that the toxicity of neoadjuvant treatment might cause the death of patients who otherwise may have been treated with curative surgery for their baseline tumor.

Overall, AEs resulting in surgery cancellation were reported for 7 participants (4.1%) in the perioperative EV + pembrolizumab group and 3 participants (1.7%) in the RC + PLND alone group. No drug-related AE leading to death occurred in the post-operative phase.

With regard to adverse events specifically related to each drug of the combination, in the EV + pembrolizumab arm of KEYNOTE-905 the overall incidence of immune-mediated adverse events (AEOSI) causally associated with pembrolizumab was similar to the EV + pembrolizumab ISD; the most frequently reported (incidence ≥5%) AEOSI categories in the perioperative EV + pembrolizumab group were hypothyroidism (14.4%) and severe skin reactions (13.8%), similarly than in the combo

reference dataset. The incidence of AEOSI in the EV + pembrolizumab group was also similar to the pembrolizumab mono group of KN-905 while higher than in the pembrolizumab mono ISD. However, in the pembrolizumab mono arm, thyroid disfunctions (hyperthyroidism and hypothyroidism) were the mostly reported AEOSI.

Severe skin reactions were reported for 13.8% participants in the perioperative EV + pembrolizumab group. The higher frequency of severe skin reactions between the perioperative EV + pembrolizumab group versus the pembrolizumab RSD was likely due to a contribution of both drugs. In the perioperative EV + pembrolizumab group, 2 Grade 4 events (toxic epidermal necrolysis and toxic skin eruption) and 1 Grade 5 event (toxic epidermal necrolysis) were reported. The median time to onset of first AEOSI of severe skin reactions in the perioperative EV + pembrolizumab group, EV + pembrolizumab ISD, and pembrolizumab RSD were 11 days, 79 days, and 85 days, respectively. Overall, 60.9% of the participants with severe skin reactions in the perioperative EV + pembrolizumab group were treated with systemic corticosteroids, similar to the EV + pembrolizumab ISD and the pembrolizumab RSD. At DCO, most Severe Skin Reactions events (73.9%) were considered resolved. Both Grade 4 events resolved (after 1.15 months for the toxic epidermal necrolysis and after 3.78 months for the toxic skin eruption). Severe skin reactions led to discontinuation of any drug, enfortumab vedotin, and pembrolizumab for 6.6%, 6.6%, and 5.4% of participants in the perioperative EV + pembrolizumab group, respectively. Skin toxicity was however known, and already described in both Padcev and Keytruda SmPCs. Other known AESI for EV are peripheral neuropathy, hyperglycaemia, ocular disorders, IRR, anemia and neutropenia; the incidence of each of those class of events was overall similar to both the EV + pembrolizumab ISD and EV ISD. With regard to the AESI Interstitial Lung Disease - AEOSI pneumonitis, this occurred in a quite lower frequency in the EV + pembrolizumab group than in the EV + pembrolizumab dataset.

Laboratory abnormalities in the perioperative EV + pembrolizumab group were generally consistent with the prior experience with EV in combination with pembrolizumab, and EV + pembrolizumab ISD and individual safety profiles of enfortumab vedotin monotherapy and pembrolizumab monotherapy. There were no specific trends in laboratory abnormalities in the perioperative EV + pembrolizumab group that suggest any new safety concern.With regard to safety by age, toxicity in the EV + pembrolizumab arm seems slightly worse in older patients ≥65 years, especially in G3-5 AEs and discontinuation due to AE, although the limited number of younger (<65y) subjects should be noted in this arm, the same trend is observed in the EV + pembrolizumab ISD. On the contrary, safety by ECOG PS appears roughly similar in each subgroup, as well as by region. 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.

Immunogenicity data showed low potential of pembrolizumab to elicit the formation of ADA also when it is co-administered with enfortumab vedotin in the perioperative setting. (see clinical pharmacology section).

2.1.2. Conclusions on clinical safety

Overall, the safety profile of the perioperative EV + pembrolizumab group in KEYNOTE 905 was generally consistent with prior experience of the enfortumab vedotin + pembrolizumab combination, the known safety profiles of the respective monotherapies, the underlying disease and/or surgery, or preexisting comorbidities of the study population. No new safety concerns were identified.

It is of note that all deaths due to drug-related AE in the EV + pembrolizumab and pembrolizumab arms of KEYNOTE-905 occurred after one-two cycles of treatment in the neoadjuvant setting, therefore precluding patients to be treated with curative surgery. The discontinuation rates highlight the overall limited tolerability of the EV + pembrolizumab association, with worse toxicity with increasing age.

2.1.3. 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.

2.2. 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 48.0 is acceptable. In addition, minor revisions were recommended to be taken into account with the next RMP update, as follows:

The MAH should bring the key elements in annex 6 of the RMP in line with the approved key elements presented in annex IID of the SmPC.

Safety concerns

Table 92 Summary of Safety Concerns

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

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

Pharmacovigilance plan

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

Risk minimisation measures

Table 93 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

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

The risk minimisation activities remain unchanged.

2.3. Update of the Product information

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

2.3.1. 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: there are no other proposed changes to the content of the package leaflet except to listing the new indication of urothelial carcinoma; in particular the key messages for the safe use of the medicinal product are not impacted. Furthermore, the design, layout and format of the package leaflet will not be affected by the proposed revisions.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The final indication is:

KEYTRUDA, in combination with enfortumab vedotin, 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.

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[28].

According to ESMO guidelines, for patients eligible to cisplatin-combination chemotherapy, 3-4 cycles of cisplatin-based neoadjuvant ChT should be given for MIBC[29] [30]. Adjuvant cisplatin-based ChT in patients who did not receive neoadjuvant therapy remains an area of debate[31].

Up to 50% of patients with MIBC are however considered unable to receive cisplatin-based chemotherapy due to comorbidities[32]. Carboplatin-based neoadjuvant regimens for cisplatin-ineligible patients with MIBC have demonstrated limited clinical response[33], and it is not recognized as standard neoadjuvant regimen[34].

Adjuvant nivolumab for 1 year showed DFS improvement vs placebo in CHECKMATE-274[35], 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[36]) 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

[28] NCCN guidelines Bladder Cancer v 2.2025
[29] 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.
[30] 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/
[31] 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.
[32] 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.
[33] 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.
[34] 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.
[35] 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.
[36] 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.

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[37].

Up to 50% of patients with MIBC who undergo RC + PLND alone experience local or distant recurrence within 2 to 3 years[38], with five-year survival in about 50% of patients[39]. 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).

Post-hoc analyses and additional studies, including data from the perioperative pembrolizumab monotherapy arm, have been presented as supportive evidence of the contribution of individual components EV and pembrolizumab and contribution of phases to the combination.

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 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.

[37] 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.
[38] 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.
[39] Stein, J.P., et al. Radical cystectomy for invasive bladder cancer: long-term results of a standard procedure. World J Urol, 2006. 24: 296.

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 pembrolizumab and EV 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

- The overall incidences of AE (100% vs 62.8%; G3-5 71.3% vs 40.5%), drug-related AE (92.2% vs 0%), SAE (58.1% vs 38.8%) and death (7.8% vs 5%) in the perioperative EV + pembrolizumab group were, as expected, higher than in the RC + PLND group, as patients received no systemic treatment in the latter arm.
- The safety of the EV + pembrolizumab group of KEYNOTE-905 appears generally similar to the reference EV + pembrolizumab dataset, with EV monotherapy showing generally worse toxicity than pembrolizumab monotherapy.
- In the perioperative EV + pembrolizumab group, the most common AE (>20%) were pruritus, alopecia, diarrhoea, fatigue, anemia, decreased appetite, dysgeusia, constipation, nausea, rash, AST increased, UTI, while the most common G3-5 AEs (>4%) were UTI, anemia, neutropenia, AKI, diarrhoea and hyperglicemia. Most common SAE in the EV + pembrolizumab group were mostly related to the bladder tumor (UTI, AKI, urosepsis, pyelonephritis), while most common drug-related SAE were AKI and diarrhoea (3 patients each).
- Of the 13 deaths due to AE in the EV + pembrolizumab arm, two were considered drug related: myasthenia gravis (related to pembrolizumab), and toxic epidermal necrosis (related to EV and pembrolizumab). Of note, both deaths occurred after only one cycle of treatment in the neoadjuvant phase, thus precluding the possibility for patients to undergo curative surgery for their bladder cancer.
- The overall incidence of AEOSI (immune-mediated AE related to pembrolizumab) was similar in the EV + pembrolizumab arm of KEYNOTE-905 and in the EV + pembrolizumab reference dataset, but higher than in the pembrolizumab monotherapy dataset (43.1% vs 46.8% vs 27.5%). The most frequently reported AEOSI categories in the perioperative EV + pembrolizumab group were hypothyroidism (14.4%) and severe skin reactions (13.8%), similarly than in the combination reference dataset, contrary to pembrolizumab monotherapy where thyroid disfunctions (hyperthyroidism and hypothyroidism) were the mostly reported AEOSI.
- Skin reactions occurred similarly in the EV + pembrolizumab arm as compared to the EV + pembrolizumab ISD and EV monotherapy ISD (61.1% vs 70% vs 57%). The higher frequency of severe skin reactions in the perioperative EV + pembrolizumab group versus the pembrolizumab RSD was likely due to a contribution of both drugs. Skin toxicity is a known risk of the combination which is already well described in Keytruda and Padcev labels.

- Toxicity in the EV + pembrolizumab arm seems slightly worse in older patients ≥65 years, especially in G3-5 AEs and discontinuation due to AE; although the limited number of younger (<65y) subjects should be noted in this arm, the same trend is observed in the EV + pembrolizumab ISD. On the contrary, safety by ECOG PS appears roughly similar in each subgroup, as well as by region.

3.5. Uncertainties and limitations about unfavourable effects

None.

3.6. Effects Table

Table 94 Effects Table for perioperative Keytruda in combination with Padcev for resected (RC+PLDN) cisplatin-ineligible MIBC (KEYNOTE-905, interim analysis, ITT2 population, data cut-off: 6 Jun 2025)

Effect	Short description	Unit	Treatment EV+pembro N=170	Control Surgery N=174	Uncertainties / Strength of evidence
Favourable effects					
EFS	Per RECIST 1.1 by BICR	Median (months)	NR (37.3, NR)	15.7 (10.3, 20.5)	Statistically significant and clinically relevant
		HR (95%CI)	0.40 (0.28, 0.57) p<0.0001		
OS		Median (months)	NR (NR, NR)	41.7 (31.8, NR)	Statistically significant and clinically relevant
		HR (95%CI)	0.50 (0.33, 0.74) p=0.0002		
	Short description	**Unit**	**EV + Pembro n=167**	**Surgery (alone) n=242**	**Uncertainties / Strength of evidence**
Unfavourable effects					
	TEAEs (any grade)	%	100	68.2	Perioperative EV + pembrolizumab arm toxicity worse than surgery alone but consistent with known EV + pembrolizumab reference safety dataset. Overall low tolerability (high discontinuation rate) and higher toxicity in elderly.
	Grade ≥3 AEs		71.3	40.5	
	SAE		58.1	28.8	
	Deaths due to TEAE		7.8	5	
	Discontinuation of any drug		48.5	0	

Abbreviations: HR: hazard ratio; CI: confidence interval; EFS: event free survival; OS: overall survival; Ref: reference; CSR: clinical study report; KN905: KEYNOTE-905; BICR: blinded independent central review; ISS: integrated summary of safety; TEAE: treatment emergent adverse event; SAE: serious adverse event.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Overall, KEYNOTE-905 provides compelling evidence of a clinically meaningful benefit for perioperative enfortumab vedotin plus pembrolizumab compared with surgery alone in cisplatin-ineligible patients with resectable MIBC, based on relevant time to event endpoints EFS by BICR and OS. While a statistically significant increase in pCR was also shown, the comparison with patients who proceed directly to surgery and the lack of validation in this disease setting limit its interpretability and informativeness. Although based on an interim analysis, current data are considered sufficient for assessment; final results of KEYNOTE-905 are expected post-approval, given the early curative setting (REC).

Although a formal comparison would have been ideal in the perioperative setting to assess the contribution of each component to the combination, the supportive evidence for the efficacy of 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 pembrolizumab. 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. However, 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.

Overall, the safety profile of the perioperative EV + pembrolizumab in KEYNOTE 905 was generally consistent with prior experience with EV + pembrolizumab combination, the known safety profiles of the respective monotherapies, the underlying disease and surgery, or preexisting comorbidities of the study population, with no new safety concerns were identified. Safety results confirm the toxicity and the scarce tolerability of the combination, especially in older patients. The toxicity in the neoadjuvant phase (two treatment-related deaths in the combo arm) which can preclude the curative surgery should be considered.

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 Keytruda 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:

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 KEYTRUDA in combination with enfortumab vedotin, 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 48.0 of the RMP has also been agreed.

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

Amendments to the marketing authorisation

In view of the data submitted with the variation procedure, amendments to Annex(es) 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.