



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 September 2026
EMADOC-1700519818-3286435
Committee for Medicinal Products for Human Use (CHMP)
EMA/VR/0000336191

Assessment report

Invented name: Padcev

International non-proprietary name: Enfortumab vedotin

Procedure No. EMA/VR/0000336191

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
AE	adverse event
AUC	area under the concentration-time curve
BCI	Bladder Cancer Index
BICR	blinded independent central review
CAP	College of American Pathologists
cCR	clinical complete response
cHL	classic Hodgkin lymphoma
CI	confidence interval
CPS	combined positive score
CR	complete response
CrCl	creatinine clearance
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C _{trough}	trough concentration
DCO	data cutoff
ddMVAC	dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin
DFS	disease-free survival
DOR	duration of response
ECOG PS	Eastern Cooperative Oncology Group performance status
EFS	event-free survival
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items
EQ-5D-5L	European Quality of Life Five Dimensions 5 Levels Questionnaire
E-R	exposure-response
EU	European Union
EV	enfortumab vedotin
FAS	full analysis set

Abbreviation	Definition
FDA	Food and Drug Administration
GC	gastric cancer
HCC	hepatocellular carcinoma
HNSCC	head and neck squamous cell carcinoma
HR	hazard ratio
HRQoL	health-related quality of life
IA1	interim analysis 1
ITT	intent to treat
IV	intravenous
KM	Kaplan-Meier
Ia	locally advanced
LA-HNSCC	locally advanced head and neck squamous cell carcinoma
MIBC	muscle-invasive bladder cancer
MIUC	muscle-invasive urothelial carcinoma
MOW	most of world
MRI	magnetic resonance imaging
MSI-H	microsatellite instability high
mUC	metastatic urothelial carcinoma
MVAC	methotrexate, vinblastine, doxorubicin, and cisplatin.
NCCN	National Comprehensive Cancer Network
NE	not evaluable
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
pDS	pathologic downstaging
PFS	progression-free survival

Abbreviation	Definition
PK	pharmacokinetic
PLND	pelvic lymph node dissection
PMBCL	primary mediastinal large B cell lymphoma
PR	partial response
PRO	patient-reported outcome
qwx	every X weeks
QoL	quality of life
RC	radical cystectomy
RDI	relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
RT	radiotherapy
SAP	statistical analysis plan
SC	subcutaneous
SOC	standard of care
TNM	Tumor, Node, Metastasis
UC	urothelial carcinoma
US	United States
VAS	visual analogue scale

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Astellas Pharma Europe B.V. submitted to the European Medicines Agency on 09 March 2026 an application for a variation.

The following changes were proposed:

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

Extension of indication to include Padcev, in combination with pembrolizumab, as neoadjuvant treatment and then continued after radical cystectomy as adjuvant treatment, is indicated for the treatment of adults with muscle invasive bladder cancer (MIBC) who are eligible for cisplatin-containing chemotherapy, based on the results from Interim Analysis 1 of the pivotal Study KN-B15 (EV-304); this is a phase 3, randomized, open-label study to evaluate perioperative enfortumab vedotin plus pembrolizumab (MK-3475) versus neoadjuvant gemcitabine and cisplatin in cisplatin-eligible participants with Muscle-Invasive Bladder Cancer. As consequence, sections 4.1, 4.2, 4.8, and 5.1 of the SmPC have been updated; the Package Leaflet is updated accordingly. Version 6.1 of the RMP is submitted, to reflect the updated data.

The requested variation(s) 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 EMEA-002299- PIP01-17; Decision Number: P/0114/2018) product-specific waiver/class waiver covering the extension of indication for the treatment of urothelial carcinoma.

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: Mette Linnert Jensen

Timetable	Actual dates
Submission date	9 March 2026
Start of procedure:	28 March 2026
CHMP Rapporteur's preliminary assessment report circulated on:	21 May 2026
Joint Rapporteur's updated assessment report circulated on:	18 June 2026
Request for supplementary information and extension of timetable adopted by the CHMP on:	25 June 2026
MAH's responses submitted to the CHMP on:	15 July 2026
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	18 August 2026
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	9 September 2026
PRAC RMP advice and assessment overview adopted by PRAC	3 September 2026
CHMP opinion:	17 September 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The applied indication is:

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

Epidemiology

Bladder cancer is the ninth most common cancer globally. Incidence varies across regions, with highest crude rates in Europe and North America¹. The disease is most common in male. The most important risk factor for bladder cancer is tobacco smoking, followed by occupational exposure to aromatic amines and ionising radiation². Lynch syndrome may also predispose to urothelial cancer.

¹ Global Cancer Observatory (GCO): Cancer Today [Internet]. Lyon (France): International Agency for Research on Cancer (IARC); c1965-2025. Incidence, both sexes, in 2022: bladder; [cited 2025 Jan 6]; [about 2 screens]. Available from: <https://gco.iarc.fr/today/home>.

² Burger M, Catto JW, Dalbagni G, et al. Epidemiology and risk factors of urothelial bladder cancer. Eur Urol. 2013;63(2):234-241.

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 carcinomas³.

Clinical presentation

Approximately 70% of patients with bladder cancer are initially diagnosed with non-muscular invasive bladder cancer (NMIBC), which can generally be treated with local procedures and carries overall good prognosis. Approximately 25% are diagnosed with muscular invasive bladder cancer (MIBC) at presentation and another 10% will progress from non-muscle-invasive tumors. Approximately 5% of patients have metastatic disease at the time of diagnosis⁴.

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 prognosis⁵. 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 prognosis⁶.

Management

Radical cystectomy (RC) with pelvic lymph node dissection (PLND) with its associated urinary diversion is the standard treatment of resectable MIBC with curative intent⁷. 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. For those who have received neoadjuvant chemotherapy, there is no role for adjuvant treatment (chemotherapy or RT). Neoadjuvant chemotherapy is preferred, as there is weak evidence to support the use of adjuvant cisplatin-based chemotherapy in patients who did not receive neoadjuvant therapy⁸. Adjuvant nivolumab for 1 year versus placebo after radical resection showed DFS improvement vs placebo in CHECKMATE-274⁹, leading to EU approval in April 2022 in muscle invasive urothelial carcinoma with tumour cell PD-L1 $\geq 1\%$, who are at high risk of recurrence after undergoing radical resection¹⁰. The NIAGARA phase III study showed a statistically significant improvement in EFS and OS with perioperative durvalumab plus neoadjuvant cisplatin + gemcitabine compared with neoadjuvant cisplatin + gemcitabine followed by RC + PLND (EFS: HR 0.68; 95% CI: 0.56, 0.82;

³ NCCN guidelines Bladder Cancer v 2.2025

⁴ Kamat AM, Hahn NM, Efsthathiou 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 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.

¹⁰ EMA/155845/2022 Opdivo EMEA/H/C/003985/II/0100 https://www.ema.europa.eu/en/documents/variation-report/opdivo-h-c-003985-ii-0100-epar-assessment-report-variation_en.pdf

$p < 0.001$; OS: HR 0.75; 95% CI: 0.59, 0.93; $p = 0.01$)¹¹, leading to the approval of this regimen in the EU in July 2025¹².

Approximately 50% of all newly diagnosed patients with MIBC are considered eligible to receive cisplatin-based chemotherapy¹³. Cisplatin ineligibility is defined as meeting at least one of the following globally accepted criteria: GFR $\leq$ 60 mL/min; ECOG $\geq$ 2; CTCAE v4 Grade $\geq$ 2 for audiometric hearing loss or peripheral neuropathy; or NYHA Class III heart failure¹⁴.

Despite the latest improvements in EFS and OS, recurrence rates and mortality of patients with cisplatin-eligible MIBC are high, and therefore effective therapies with improved long-term outcomes are relevant.

2.1.2. About the product

Pharmacotherapeutic action

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

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

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

Previously approved indications

Padcev is approved for the following indications:

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

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

¹¹ 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.

¹² EMA/196723/2025 IMFINZI EPAR EMEA/H/C/004771/II/0073 https://www.ema.europa.eu/en/documents/variation-report/imfinzi-h-c-004771-ii-0073-epar-assessment-report-variation_en.pdf

¹³ Thompson RH, Boorjian SA, Kim SP, Cheville JC, Thapa P, Tarrel R, Dronca R, Costello B, Frank I. Eligibility for neoadjuvant/adjuvant cisplatin-based chemotherapy among radical cystectomy patients. BJU Int. 2014 May;113(5b):E17-21.

¹⁴ 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.

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

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

Table 1 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
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 <u>Cohort 1:</u> Subjects with la/mUC who have previously received a PD-1/ PD-L1 inhibitor and a platinum-containing chemotherapy <u>Cohort 2:</u> 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/m ² or vinflunine 320 mg/m ² (all IV) on Day 1 of a 21-day cycle	Ongoing
EV-103 (KEYNOTE-896/SGN22E-002/MK-3475-869) Cohorts H and L: See Enfortumab Vedotin + Pembrolizumab Studies for further details					
Enfortumab vedotin + Pembrolizumab Studies					

Study No.	Phase	Description/Design	Enrolled	Dosage Regimen	Study Status
EV-103 (EV-103/SGN22E-002/MK-3475-869)	Phase 1b/2	<p>Enfortumab vedotin as monotherapy or in combination with other anticancer therapies for the treatment of UC</p> <p><u>LA/mUC</u> 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</p> <p><u>MIBC</u> Cohort H: neoadjuvant in cisplatin-ineligible EV monotherapy Cohort L: perioperative cisplatin-ineligible EV monotherapy</p>	<p><u>LA/mUC</u> Dose-escalation: 10 Cohort A: 40 Cohort K: 151</p> <p><u>MIBC</u> 58/60 Cohort H: 22 Cohort L: 41</p> <p>Participants with la/mUC or MIBC. Cohort specific requirements for cisplatin eligibility and PD-1/PD-L1/PD-L2 inhibitor naïve.</p>	<p>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</p>	<p><u>LA/mUC</u> Ongoing; enrollment closed</p> <p><u>MIBC</u> Ongoing; enrollment closed</p>
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	<p>886</p> <p>Participants with previously untreated la/mUC who were eligible for platinum as 1L treatment</p>	<p><u>Arm A:</u> 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</p> <p><u>Arm B:</u> Gemcitabine 1000 mg/m² IV on Days 1 and 8 of a 21-day cycle; either cisplatin (70 mg/m²) or carboplatin (AUC 5 or 4.5 mg/mL/min) (both IV) on Day 1 of each cycle.</p>	Ongoing; enrollment closed

Study No.	Phase	Description/Design	Enrolled	Dosage Regimen	Study Status
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	<u>Treatment Arm A</u> Preoperative pembrolizumab 200 mg IV q3w for 3 cycles + cystectomy + postoperative pembrolizumab 200mg IV q3w for 14 cycles <u>Treatment Arm B</u> Cystectomy + postoperative observation <u>Treatment Arm C</u> 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	<u>Treatment Arm 1</u> 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 <u>Treatment Arm 2</u> Preoperative gemcitabine 1000 mg/m ² on Days 1 and 8 + cisplatin 70 mg/m ² on Day 1 q3w for 4 cycles + cystectomy + postoperative observation	Ongoing; enrollment closed
1L=first-line; 2L=second-line; AUC=area under the curve; CPS=combined positive score; EFS=event-free survival; IV=intravenous; la/mUC=locally advanced or metastatic urothelial carcinoma; MIBC=muscle-invasive bladder cancer; NMIBC=non-muscle-invasive bladder cancer; ORR=objective response rate; OS=overall survival; PD-1= programmed cell death protein 1; PD-L1= programmed cell death ligand 1; PFS=progression-free survival; PLND=pelvic lymph node dissection; q3w=every 3 weeks; RC=radical cystectomy; UC=urothelial carcinoma.					

2.1.4. General comments on compliance with GCP

The MAH states that the clinical studies were conducted in accordance with current standard research approaches regarding the design, conduct, and analysis of such studies including the archiving of essential documents. All studies were conducted following appropriate Good Clinical

Practice standards and considerations for the ethical treatment of human participants that were in place at the time the studies were performed.

2.2. *Non-clinical aspects*

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

2.2.1. Ecotoxicity/environmental risk assessment

No updated environmental risk assessment (ERA) was performed within the present extension of the indication application.

2.2.2. Discussion on non-clinical aspects

Previously evaluated ERA data considered all patients with bladder cancer as eligible for treatment with enfortumab vedotin. As the present application does not alter any of the parameter used for the ERA of the previous extension of indication application (EMA/VR/0000312495), the corresponding conclusion that no environmental risk is expected from the therapeutic use of enfortumab vedotin remains applicable.

2.2.3. Conclusion on the non-clinical aspects

Based on the updated data submitted in the application EMA/VR/0000312495, the extended indication does not lead to a significant increase in environmental exposure further to the use of enfortumab vedotin. Enfortumab vedotin is not expected to pose risk to the environment.

2.3. *Clinical aspects*

2.3.1. Introduction

GCP

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

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

2.3.2. Clinical Pharmacology

2.3.3. Pharmacokinetics

Not applicable – no new data was submitted

2.3.4. Pharmacodynamics

Not applicable – no new data was submitted.

2.3.5. Discussion on clinical pharmacology

No new clinical pharmacology analyses beyond those conducted previously for enfortumab vedotin and pembrolizumab have been submitted, and no labeling revisions for the Clinical Pharmacology section of the EU SmPC for each respective approved product are proposed.

PK and immunogenicity of enfortumab vedotin and pembrolizumab from Ia/mUC studies EV-302 and EV-103, and from the MIBC study KEYNOTE-905, demonstrate that the administration of pembrolizumab in combination with enfortumab vedotin has no impact on the PK or immunogenicity of enfortumab vedotin

2.4. Clinical efficacy

2.4.1. Dose response study

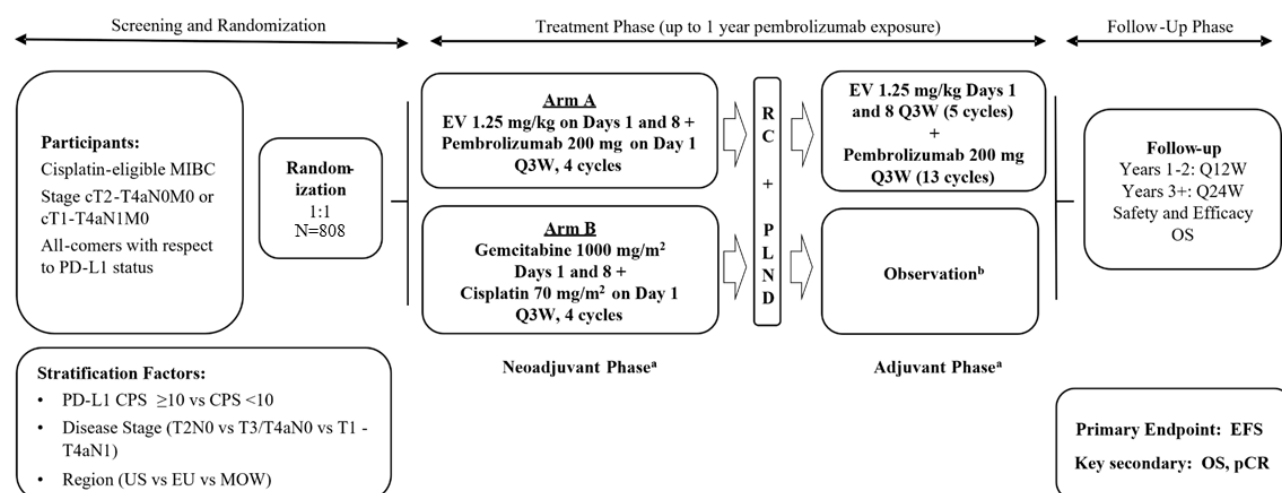
No dose-response studies were submitted as part of this application. The dosing regimen of enfortumab vedotin 1.25 mg/kg (up to a maximum of 125 mg for patients ≥ 100 kg) on Days 1 and 8 of a 21-day cycle in combination with pembrolizumab 200 mg q3w used in KEYNOTE-B15 is consistent with the approved doses used in Ia/mUC and MIBC studies.

2.4.2. Main study

KEYNOTE-B15/ EV-304 study

A Phase 3, Randomized, Open-Label Study to Evaluate Perioperative Enfortumab Vedotin Plus Pembrolizumab (MK-3475) Versus Neoadjuvant Gemcitabine and Cisplatin in Cisplatin-Eligible Participants with Muscle-Invasive Bladder Cancer (KEYNOTE-B15/EV-304)

Figure 1. KEYNOTE-B15 Study Design



CPS=Combined Positive Score; EFS=event-free survival; EU=European Union; EV=enfortumab vedotin; MIBC=muscle-invasive bladder cancer; MOW=most of world; OS=overall survival; pCR=pathological complete response; PD-L1=programmed cell death ligand 1; PLND=pelvic lymph node dissection; Q3/12/24W=every 3/12/24 weeks; RC=radical cystectomy; US=United States.

a The neoadjuvant phase of the study is the pre-surgery component. The adjuvant phase of the study is the post-surgery component.

b For Arm B participants at high risk of recurrence after RC + PLND, adjuvant nivolumab may be used per the approved product label if locally available and provided nivolumab is deemed appropriate for the participant by the investigator. Note: Imaging must continue per protocol after starting adjuvant nivolumab.

Methods

Study participants

Key inclusion criteria:

1. Histologically confirmed diagnosis of MIBC (clinical stage T2-T4aN0M0 or T1-T4aN1M0) with predominant ($\geq 50\%$) urothelial histology confirmed by BICR (central pathology and imaging) and PD-L1 expression (CPS ≥ 10 or CPS < 10) confirmed by BICR (central pathology).
2. Clinically nonmetastatic bladder cancer (N ≤ 1 , M0) determined by imaging (CT or MRI of the chest/abdomen/pelvis), confirmed by BICR.
3. Deemed eligible for RC + PLND by a urologist and/or oncologist and agreed to undergo curative intent standard RC + PLND (including prostatectomy, if applicable) as per AUA/ASTRO/ASCO/SUO guidelines.
4. Transurethral resection of a bladder tumor (obtained within 60 days [+14 days] before enrolment [documented informed consent]) that was submitted for central pathology assessment and adequate to determine urothelial histology and PD-L1 expression.
5. Male or female, and at least 18 years of age, at the time of providing documented informed consent.
6. ECOG performance status of 0 or 1.

Key exclusion criteria:

- Known additional nonurothelial malignancy that was progressing or had required active anticancer treatment ≤ 3 years of study randomization.
- $\geq N2$ disease or metastatic disease (M1) as identified by imaging.
- Prior systemic treatment, chemoradiation, and/or radiation therapy for MIBC or NMIBC.
 - Prior treatment for NMIBC with intravesical instillation therapy such as BCG or intravesical chemotherapy was permitted.
- Prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or coinhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).
- Cisplatin-ineligible, as defined by meeting any 1 of the following criteria:
 - Impaired renal function with measured or calculated creatinine clearance < 60 mL/min
 - ECOG performance status ≥ 2
 - CTCAE v.5.0 Grade ≥ 2 peripheral neuropathy
 - CTCAE v 5.0 Grade ≥ 2 audiometric hearing loss
 - NYHA Class III or greater heart failure
- Prior radiotherapy to the bladder.
- Partial cystectomy of the bladder to remove any NMIBC or MIBC.

- Has 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 intervention. Inhaled or topical steroids are permitted in the absence of active autoimmune disease. Physiologic replacement (10 mg/day prednisone equivalent) doses of corticosteroids are permitted for participants with adrenal insufficiency.
- Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal, pituitary insufficiency, etc.) is not considered a form of systemic treatment and is allowed.

Additional details are available in the study protocol.

Treatments

Patients were randomized 1:1 into one of the two arms to receive:

Arm A: 4 cycles of neoadjuvant EV + pembrolizumab, followed by RC + PLND, followed by 5 cycles of adjuvant EV + 13 cycles of adjuvant pembrolizumab.

Arm B: 4 cycles of neoadjuvant chemotherapy (gemcitabine + cisplatin), followed by RC+ PLND, followed by observation. For participants in Arm B at high risk of recurrence after RC + PLND, adjuvant nivolumab may be used per the approved product label, if locally available, and provided nivolumab is deemed appropriate for the participant by the investigator.

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/Treatment Period	Use
Arm A	Pembrolizumab (MK-3475)	100 mg/4 mL (25 mg/mL) solution in a single-dose vial	200 mg	IV Infusion	Neoadjuvant Phase: Day 1 q3w for 4 cycles Adjuvant Phase: Day 1 q3w for 13 cycles	Test Product
Arm A	Enfortumab vedotin	30 mg single-dose vial	1.25 mg/kg	IV Infusion	Neoadjuvant Phase: Days 1 and 8 q3w for 4 cycles Adjuvant Phase: Days 1 and 8 q3w for 5 cycles	Test Product
Arm B	Cisplatin	Variable	70 mg/m ²	IV Infusion	Neoadjuvant Phase: Day 1 q3w for 4 cycles	Comparator
Arm B	Gemcitabine	Variable	1000 mg/m ²	IV Infusion	Neoadjuvant Phase: Days 1 and 8 q3w for 4 cycles	Comparator

IV=intravenous; q3w=every 3 weeks.

Objectives Outcomes/endpoints

Primary Objective	Primary Endpoint
<p>Objective: To compare EFS in Arm A (perioperative EV + pembrolizumab and RC + PLND) versus Arm B (neoadjuvant gemcitabine + cisplatin and RC + PLND)</p> <p>Hypothesis (H1): Perioperative EV + pembrolizumab and RC + PLND (Arm A) will achieve superior EFS compared with neoadjuvant gemcitabine + cisplatin and RC + PLND (Arm B)</p>	<p>EFS, defined as the time from randomization to the first of the following events:</p> <ul style="list-style-type: none"> -Radiographic disease progression precluding a curative intent surgery as assessed by BICR prior to RC + PLND -Failure to undergo surgery for participants with residual muscle-invasive disease and any radiographic disease present, biopsy proven MIBC will be considered an event regardless of radiographic findings -Gross residual disease left behind at time of surgery (surgeon unable to complete curative intent surgery due to unresectable tumor or newly discovered metastatic disease) -Local or distant recurrence post-RC + PLND as assessed by CT or MRI by BICR and/or biopsy. If biopsy is not feasible due to participant safety, CT/MRI alone will be sufficient -Death from any cause <p>NOTE: A non-urothelial 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.</p>
Secondary Objectives	Secondary Endpoints
<p>Objective: To compare pCR rates obtained in Arm A (preoperative EV + pembrolizumab and RC + PLND) versus Arm B (neoadjuvant gemcitabine + cisplatin and RC + PLND)</p> <p>Hypothesis (H2): Preoperative EV + pembrolizumab and RC + PLND (Arm A) will achieve superior pCR rates compared with neoadjuvant gemcitabine + cisplatin and RC + PLND (Arm B)</p>	<p>pCR, defined as absence of viable tumor (pT0N0) in examined tissue from RC + PLND, as assessed by blinded central pathologic review</p>
<p>Objective: To compare the OS in Arm A (perioperative EV + pembrolizumab and RC + PLND) versus Arm B (neoadjuvant gemcitabine + cisplatin and RC + PLND)</p>	<p>OS, defined as the time from randomization to death due to any cause</p>

Hypothesis (H3): Perioperative EV + pembrolizumab and RC + PLND (Arm A) will achieve superior OS compared with neoadjuvant gemcitabine + cisplatin and RC + PLND (Arm B)	
Objective: To assess DFS in participants from Arm A (perioperative EV + pembrolizumab and RC + PLND) and Arm B (neoadjuvant gemcitabine + cisplatin 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 by BICR and/or biopsy -Death from any cause
Objective: To assess the rate of pDS in Arm A (preoperative EV + pembrolizumab and RC + PLND) and Arm B (neoadjuvant gemcitabine + cisplatin and RC + PLND)	pDS, defined as participants with <pT2 (includes pT0, pTis, pTa, and pT1) and N0 in examined tissue from RC + PLND, based on central pathologic review
Objective: To evaluate the safety and tolerability of perioperative EV + pembrolizumab + RC + PLND in Arm A	-Participants experiencing adverse events (AEs) -Participants discontinuing study drug due to AEs -Participants experiencing perioperative complications
Objective: To evaluate changes from baseline in HRQoL, using 2 general instruments (EORTC QLQ-C30, and EQ-5D-5L), and 1 disease-specific instrument (BCI)	Change from baseline in: -The global health status/quality of life of the EORTC QLQ-C30 (Items 29 and 30) -The physical functioning scale of the EORTC QLQ-C30 -The role functioning scale of the EORTC QLQ-C30 -BCI: urinary, bowel, and sexual domains -EQ-5D-5L VAS

Study assessments:

All patients underwent baseline screening imaging (CT or MRI of the chest, abdomen, pelvis) for clinical staging, which was centrally evaluated using expedited imaging review by BICR, prior to randomization to confirm eligibility. Patients in both treatment arms completed 4 cycles of neoadjuvant study intervention,

followed by repeat imaging studies (same modality as screening) within ≤5 weeks (35 days +7 days) prior to the planned RC + PLND to exclude disease progression (confirmed by BICR), which might preclude curative intent surgery.

Patients who remained radiographically free of distant metastases proceeded to surgery within 6 weeks of the last dose of neoadjuvant treatment. Patients might proceed to surgery outside of this period if the delays were due to an AE. Participants with surgery delays (beyond 12 weeks after the last dose of neoadjuvant treatment) for any reason, other than for an AE, may be considered with Sponsor consultation. Any occurrence of distant disease progression, per site-assessed imaging, at the pre-surgery timepoint (or during the neoadjuvant treatment phase) should be submitted as soon as possible to the iCRO for verification of progression by BICR. Radiographic disease progression precluding a curative intent surgery noted prior to RC + PLND (verified by BICR), failure to undergo surgery for patients 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, local or distant recurrence as assessed radiographically by BICR and/or confirmed with biopsy (local pathology review), or death from any cause will be considered events and such patients will not receive further therapy on study but will transition into survival follow-up.

All RC + PLND surgical specimens (performed at main study site or another facility) were assessed by BICR pathology to determine pathologic response.

For patients who initially do not undergo RC + PLND within the protocol-specified window and subsequently undergo surgery at main study site or another facility, sites should collect and submit RC + PLND specimens for assessment by central pathology.

Following RC + PLND, all participants would have the post-surgery imaging at 6 weeks (± 14 days), using the same imaging modality as at initial screening. Following the post-surgery baseline scan, imaging to be performed Q12W (± 7 days) until end of Year 1 and 2 then; every 24 weeks in Year 3 and beyond.

Biomarker assessment:

Patients enrolled in KEYNOTE-B15 were required to provide tumor tissue from a TUR specimen that was obtained up to 60 days (± 14 days) prior to 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 CPS scoring was utilized for exploratory analyses such as Nectin-4 IHC.

PDL-1 (CPS ≥ 10 or CPS < 10) status was assessed by the blinded central pathology review. According to the protocol Individual participant PDL1 status will not be disclosed to investigative sites or study participants. PD-L1 22C3 IHC testing was done using Agilent PD-L1 22C3 IHC pharmDx (Agilent Technologies, Dako) at a central testing laboratory, which is CE marked and approved as a companion diagnostic to identify UC patients for treatment with pembrolizumab.

The Nectin-4 IHC assay was performed retrospectively on available samples of KEYNOTE-B15 from the 2 treatment groups. Fresh cut slides from FFPE blocks or slides that were within a 9-month stability window were tested, as established during the analytical validation process. A validated IHC assay (for research use only [RUO] using an anti-Nectin-4 antibody [clone M22-321b41.1]) was used to assess expression of Nectin-4 in FFPE tumor tissue at Q2 Solutions. The assay was previously used to assess Nectin-4 IHC expression in other EV clinical studies, including EV-302, KEYNOTE-905 and EV-103/KEYNOTE-869 studies. 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 using the equation:

$$\text{H-score} = (1 \times \text{PI-1}) + (2 \times \text{PI-2}) + (3 \times \text{PI-3}).$$

Nectin-4 IHC was reported on a continuous H-score scale ranging from 0 to 300; as such, no pathologist training was conducted around a validated specified cutoff value. Nectin-4 IHC H-scores of <150, ≥150 to <225, and ≥225 were used to define the subgroups.

Sample size

The study enrolled 808 participants randomized in a 1:1 ratio.

For the EFS endpoint, based on a target number of 325 events at the final EFS analysis and 2 interim analyses at ~75% and 89% of the target number of events, the study has ~88.5% power to detect a HR of 0.7 at the allocated $\alpha=0.025$ (1-sided).

Based on ~808 randomized participants, the power for the pCR rate endpoint at the α level of 0.001/0.025 (1-sided) is >99% to detect a 22-percentage point difference between an underlying 28% pCR rate in the chemotherapy arm and a 50% pCR rate in the EV + pembrolizumab arm.

For the OS endpoint, based on a target number of 277 events and 3 interim analyses at ~51%, 70%, and 83% of the target number of events, the study has ~82.7%/83.1% power to detect a HR of 0.7 at the α level of 0.024/0.025 (1-sided).

Note that the above power calculations for EFS and OS are based on a constant hazard ratio assumption. The interim analysis timing and spending have been designed to ensure the final alpha available is maximized to make testing most sensitive when follow-up is available across both early and late parts of the survival and EFS distributions.

Based on the published studies, Neoadjuvant Chemotherapy plus Cystectomy Compared with Cystectomy Alone for Locally Advanced Bladder Cancer by H. Barton Grossman, et al [5] and Comparative Effectiveness of gemcitabine plus Cisplatin versus Methotrexate, Vinblastine, Doxorubicin, plus Cisplatin as Neoadjuvant Therapy for Muscle-Invasive Bladder Cancer by Galsky, et al [6], the above sample size and power calculations for EFS and OS assume the following:

- * EFS follows an exponential distribution with a median of 43 months for the control group.
- * OS follows an exponential distribution with a median of 66 months for the control group.
- * Enrollment period of ~31 months
- * An annual dropout rate of 10% for EFS and 1% for OS

Randomisation

Intervention randomization will be stratified according to the following factors:

1. PD-L1 CPS ≥10 vs CPS <10 (Note: if PD-L1 is not evaluable based on the submitted specimen, the participant will be assigned to the CPS <10 group)
2. Tumor stage (T2N0 vs T3/T4aN0 vs T1-T4aN1)
3. Geographic regions (US vs EU vs MOW)

Note: PD-L1 status determined by the central vendor will not be disclosed to investigators and participants

Blinding (masking)

The study is open labelled.

Statistical methods

Study population

The ITT population was planned to serve as the analysis population for EFS, pCR rate, pDS rate and OS and consists of all randomized participants whether or not treatment was administered. Participants in the ITT population were planned to be included in the treatment group to which they are randomized.

Primary endpoint, estimand and analysis

EFS was planned as the primary endpoint for the study. No estimand was defined in the study although a definition was provided post hoc. Briefly, the primary estimand is intended to contrast the effect of perioperative EV + pembrolizumab relative to neoadjuvant gemcitabine + cisplatin using a treatment policy strategy, under which endpoints are assessed regardless of the occurrence of intercurrent events. Three IEs of interest were defined as IE1) discontinuation of perioperative EV + pembrolizumab or neoadjuvant gemcitabine + cisplatin, IE2) use of new anticancer therapy, and IE3) failure to undergo surgery. IE1 and IE2 were handled via treatment policy strategy, while IE3 (failure to undergo surgery) was handled via "Treatment policy strategy (adjusted) - * Participants who did not undergo surgery and had not experienced an EFS event were censored at the last disease assessment within 16 weeks after last dose of neoadjuvant treatment or randomization."

The non-parametric 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 a single treatment covariate and Efron's method of tie handling was planned to be used to assess the magnitude of the treatment difference (ie, HR) between the treatment arms. The HR and its 95% CI from the stratified Cox model with a single covariate of treatment arm was planned to be reported.

Participants who refuse or are unable to undergo RC without a protocol-defined event were planned 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 refuse or are unable to undergo surgery and who develop a protocol-defined event at any time were planned to be counted as events. Participants who refuse or are unable to undergo surgery, but without a post-screening scan were planned to be censored at Day 1 from randomization.

Table 2. Censoring Rules for Primary and Sensitivity Analyses of EFS

Situation	Primary Analysis	Sensitivity Analysis
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
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 assessment and new anticancer therapy (excluding the use of adjuvant nivolumab in Arm B), if any
No PD, no recurrence, and no death and new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment
No PD, no recurrence, and no death; new anticancer treatment is initiated ^a	Censored at last disease assessment	Censored at last disease assessment before new anticancer treatment (excluding the use of adjuvant nivolumab in Arm B)
In participants who refuse or are unable to undergo surgery:		
MIBC ^{b,c} , locally advanced disease ^d , 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
MIBC ^{b,c} , locally advanced disease ^d , 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
No MIBC ^{b,c} , no locally advanced disease ^d , no distant PD or 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
No post-screening scan available	Censored at Day 1 from randomization	Censored at Day 1 from randomization
CT=computed tomography; EFS=event-free survival; MIBC=muscle-invasive bladder cancer; MRI=magnetic resonance imaging; NMIBC=non-muscle invasive bladder cancer; PD=progressive disease. ^a Includes cases with high-risk prostate cancer found at surgery who require subsequent anticancer treatment. ^b Includes high-grade NMIBC of the upper tract. ^c Presence of MIBC needs to be confirmed with imaging demonstrating radiographic disease present and a positive post-baseline cystoscopy with biopsy. ^d Participants with T4b, N2/N3 disease as identified by imaging and confirmed by BICR.		

Sensitivity analyses

Since disease assessment is performed periodically, events such as progression and recurrence can occur any time in the time interval between the last assessment where the event was not documented and the assessment when the event is documented. In order to evaluate the robustness of the EFS endpoint, a sensitivity analysis with a different set of censoring rules was

considered. The sensitivity analysis was planned as the same as the primary analysis except that events after 2 consecutive missed disease assessments or after new anticancer therapy if any should be censored at last disease assessment prior to the earlier date of ≥ 2 consecutive missed disease assessments and new anticancer therapy.

Key secondary endpoints and estimands

pCR (pathological Complete Response) rates (pCRR) and OS were planned as key secondary endpoints for the study.

The stratified Miettinen and Nurminen method with strata weighting by sample size was planned to be used for the comparison of pCR rates between treatment arms. The difference in pCR rates, its 95% CI, and the corresponding p-value from the stratified Miettinen and Nurminen method with strata weighting by sample size were planned to be reported.

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

OS was planned to be analysed as EFS. The stratification factors used for randomization were planned to be applied to both the stratified log-rank test and the stratified Cox model. Participants without documented death at the time of analysis were planned to be censored at the date the participant was last known to be alive.

Subgroup analyses

The following subgroup analyses were prespecified:

- PD-L1 CPS (<10 , ≥ 10)
- Disease stage (T2N0, T3/T4aN0, T1-T4aN1)
- Geographic region (US, EU, MOW)
- Age category (<65 years, ≥ 65 years)
- Sex (female, male)
- Race (white, all others)
- Smoking status (never, former, current)

Interim and multiplicity for primary and key-secondary endpoints

Three interim analyses are planned in addition to the final analysis for this study. All randomized participants will be included. Results of the interim analyses will be reviewed by the DMC. Details of the boundaries for establishing statistical significance with regard to efficacy are presented under "Multiplicity".

If EFS was significant at any IA, then the next IA(s) was planned to be triggered by OS events. If the OS event accrual is much slower than expected and the final targeted number of events cannot be reached by the end of year 6 after last participant randomized, then the final OS analysis may be performed at the end of year 6 after last participant randomized at the latest.

Table 3. Summary of Interim and Final Analyses Strategy

Analyses	Key Endpoints	Timing	Estimated Time after First Participant Randomized	Primary Purpose of Analysis
IA1	EFS pCR OS	All participants having had the opportunity for RC + PLND with pCR evaluation and ~ 244 EFS events have been observed and ~ 18 months after last participants randomized.	~ 49 months	<ul style="list-style-type: none"> Interim EFS analysis Interim OS analysis Final pCR analysis
IA2	EFS OS	~ 290 EFS events have been observed and ~ 31 months after last participant randomized	~ 62 months	<ul style="list-style-type: none"> Interim EFS analysis Interim OS analysis
IA3	EFS OS	~ 325 EFS events have been observed	~ 74 months	<ul style="list-style-type: none"> Final EFS analysis Interim OS analysis
FA	OS	~ 277 OS events have been observed	~ 87 months	<ul style="list-style-type: none"> Final OS analysis.

EFS=event-free survival; FA=final analysis; IA1=interim analysis 1; IA2=interim analysis 2; IA3=interim analysis 3; OS=overall survival; pCR=pathologic complete response; PLND= pelvic lymph node dissection; RC=radical cystectomy.

Note that at IA1, if EFS event accrual is slower than expected, the Sponsor may conduct the analysis at ~ 18 months after last participant randomized.

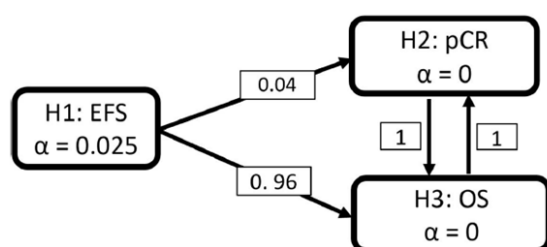
Note that if EFS is significant at IA1, then IA2 will be performed when ~ 193 OS events have been observed. If the OS event accrual is slower than expected, the Sponsor may conduct the analysis at ~ 31 months follow-up after last participant randomized.

Note that if EFS is significant at IA1 or IA2, then IA3 will be performed when ~ 230 OS events have been observed. If the OS event accrual is slower than expected, the Sponsor may conduct the analysis with an additional ~ 15 months of follow-up after IA2.

Note that for FA, if the final targeted number of events cannot be reached by the end of year 6 after last participant randomized, the final OS analysis may be conducted at the end of year 6 after last participant randomized at the latest.

Multiplicity

The study uses the graphical method of Maurer and Bretz [Maurer, W. and Bretz, F. 2013].

Figure 2. Multiplicity Diagram for Type I Error Control

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

EFS

The study was planned to test EFS (H1) at IA1, IA2, and IA3 (FA for EFS). The study allocates $\alpha=0.025$ to test EFS. Boundaries for EFS were derived using a Lan-DeMets spending function approximating O'Brien-Fleming bounds. The final row (IA3) of the table below indicates the total power to reject the null hypothesis for EFS. If the actual numbers of EFS events at the interim and final analyses were to differ from those specified in the table, the bounds were planned to be updated using this spending function evaluated at the observed information fraction at each analysis (i.e., the observed number of events at an analysis divided by the expected number of events at the final analysis), with correlations determined by the observed event counts at this and

previous analyses. The final analysis was planned to use the remaining Type I error that has not been spent at the earlier analyses.

Table 4. Efficacy Boundaries and Properties for Event-free Survival Analyses (H1)

Analysis	Value	$\alpha=0.025$
IA1: 75%* N=808 Events: 244 Month: 49 ⁺	Z	2.3383
	p (1-sided) ^a	0.0097
	HR at bound ^b	0.7410
	P(Cross) if HR=1 ^c	0.0097
	P(Cross) if HR=0.7 ^d	0.6705
IA2: 89%* N=808 Events: 290 Month: 62 ⁺	Z	2.1739
	p (1-sided) ^a	0.0149
	HR at bound ^b	0.7744
	P(Cross) if HR=1 ^c	0.0177
	P(Cross) if HR=0.7 ^d	0.8147
IA3 N=808 Events: 325 Month: 74 ⁺	Z	2.0679
	p (1-sided) ^a	0.0193
	HR at bound ^b	0.7948
	P(Cross) if HR=1 ^c	0.0250
	P(Cross) if HR=0.7 ^d	0.8850
HR=hazard ratio; IA=interim analysis. The number of events and timings are estimated. * Percentage of total planned events at the interim analysis. ⁺ The analysis timeline is projected based on blinded clinical data monitoring. ^a p (1-sided) is the nominal α for group sequential testing. ^b HR at bound is the approximate HR required to reach an efficacy bound. ^c P(Cross if HR=1) is the probability of crossing a bound under the null hypothesis. ^d P(Cross if HR=0.7) is the probability of crossing a bound under the alternative hypothesis.		

pCR

The study was planned to test pCR rate (H2) only when EFS is significant. The test statistics of pCR rate was planned to be computed at IA1. If superiority for EFS is declared at IA2 or later, the test statistic previously computed at IA1 for H2 was planned to be used for inferential testing. Note that if superiority is achieved for the EFS hypothesis, α was planned to be rolled over to the pCR rate hypothesis and the pCR rate hypothesis was planned to be tested with an α level of 0.001. If superiority is achieved for both the EFS and OS hypotheses, $\alpha=0.024$ was planned to be rolled over to the hypothesis for pCR rate and the pCR rate hypothesis was planned to be tested with an updated alpha level of 0.025.

OS

The study was planned to test OS (H3) at IA1, IA2, IA3 and FA. There is no alpha initially allocated to test OS. Note that if superiority is achieved for the EFS hypothesis only, α was planned to be rolled over to the OS hypothesis and the OS hypothesis was planned to be tested with an α level of 0.024. If superiority is achieved for both the pCR rate and EFS hypotheses, α was planned to be rolled over to the OS hypothesis and the OS hypothesis was planned to be tested with an α level of 0.025. Possible α levels were derived using a Lan-DeMets spending function approximating O'Brien-Fleming bounds. The final row of the table below (FA) indicates the total power to reject the null hypothesis for OS. Adaptations of alpha level in case the information fraction available at IA

differed from what expected were planned as described for EFS. The final analysis was planned to use the remaining Type I error that has not been spent at the earlier analyses.

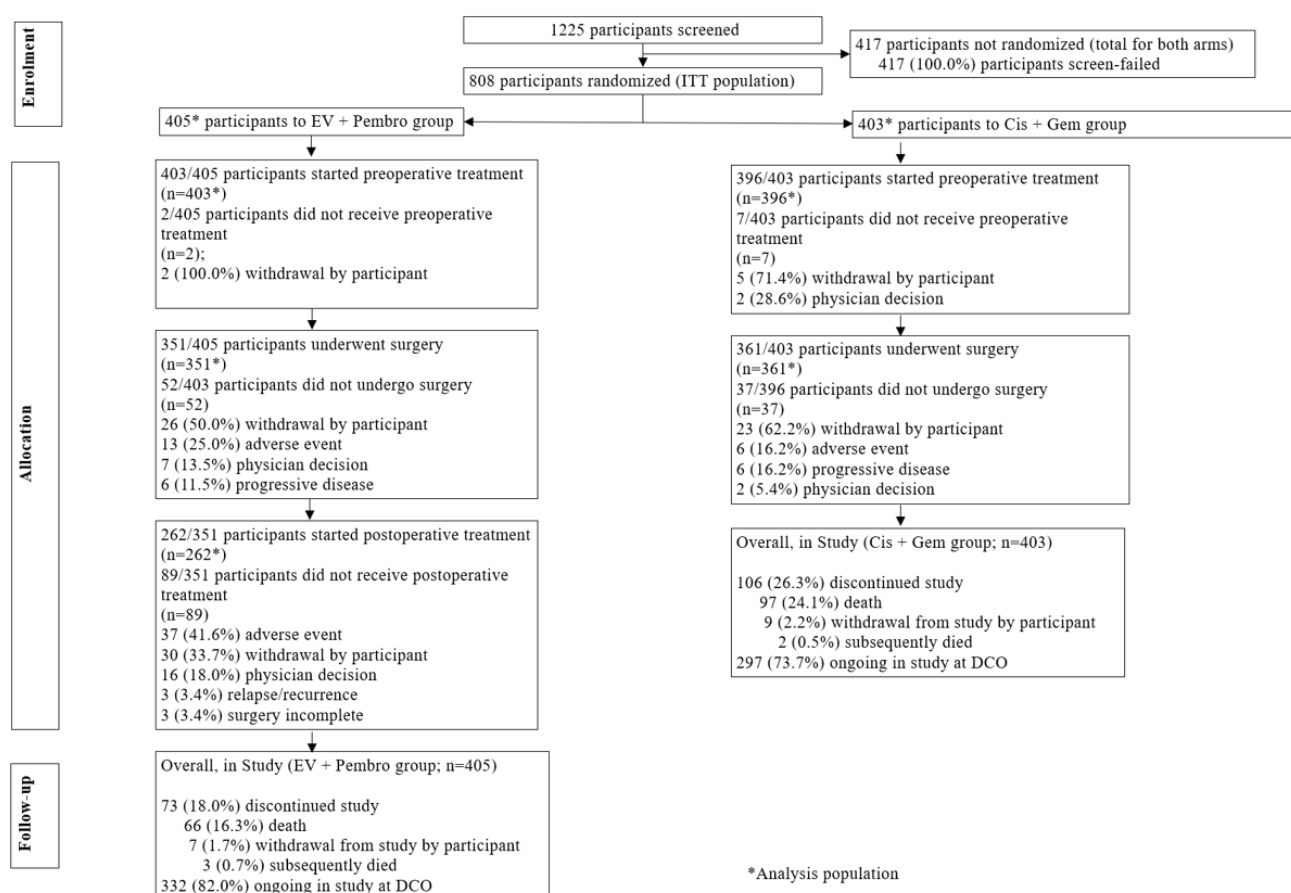
Table 5. Efficacy Boundaries and Properties for Overall Survival Analyses (H3)

Analysis	Value	$\alpha=0.024$	$\alpha=0.025$
IA1: 51%* N=808 Events: 142 Month: 49 ⁺	Z	2.9442	2.9209
	p (1-sided) ^a	0.0016	0.0017
	HR at bound ^b	0.6097	0.6120
	P(Cross) if HR=1 ^c	0.0016	0.0017
	P(Cross) if HR=0.70 ^d	0.2048	0.2112
IA2: 70%* N=808 Events: 193 Month: 62 ⁺	Z	2.4924	2.4728
	p (1-sided) ^a	0.0063	0.0067
	HR at bound ^b	0.6982	0.7001
	P(Cross) if HR=1 ^c	0.0069	0.0072
	P(Cross) if HR=0.70 ^d	0.4972	0.5048
IA3: 83%* N=808 Events: 230 Month: 74 ⁺	Z	2.2867	2.2689
	p (1-sided) ^a	0.0111	0.0116
	HR at bound ^b	0.7394	0.7411
	P(Cross) if HR=1 ^c	0.0132	0.0139
	P(Cross) if HR=0.70 ^d	0.6732	0.6795
FA N=808 Events: 277 Month: 87 ⁺	Z	2.0609	2.0448
	p (1-sided) ^a	0.0197	0.0204
	HR at bound ^b	0.7804	0.7818
	P(Cross) if HR=1 ^c	0.0240	0.0250
	P(Cross) if HR=0.70 ^d	0.8270	0.8310
FA=final analysis; HR=hazard ratio; IA=interim analysis. The number of events and timings are estimated. * Percentage of total planned events at the interim analysis. ⁺ The analysis timeline is projected based on blinded clinical data monitoring. ^a p (1-sided) is the nominal α for group sequential testing. ^b HR at bound is the approximate HR required to reach an efficacy bound. ^c P (Cross if HR=1) is the probability of crossing a bound under the null hypothesis. ^d P (Cross if HR=0.7) is the probability of crossing a bound under the alternative hypothesis.			

Results

Participant flow

Figure 3. Consort Diagram KEYNOTE-B15



A total of 1225 participants were screened. All 417 non-randomized participants were screen failures; the most common reason for ineligibility was the tumor staging criterion not being met, did not provide informed consent, N2 disease or metastatic bladder cancer (data in CSR).

Table 6. Disposition of Participants (ITT Population)

	EV + Pembro		Cis + Gem	
	n	(%)	n	(%)
Participants in population	405		403	
Status for Trial				
Started	405		403	
Discontinued	73	(18.0)	106	(26.3)
Death	66	(16.3)	97	(24.1)
Withdrawal By Subject	7	(1.7)	9	(2.2)
Subsequently died	3	(0.7)	2	(0.5)
Ongoing	332	(82.0)	297	(73.7)
Status for All Study Treatment (Preoperative/Surgical + Postoperative)				
Started	403		398	
Completed	208	(51.6)	350	(87.9)
Discontinued	195	(48.4)	48	(12.1)
Adverse Event	84	(20.8)	6	(1.5)
Physician Decision	30	(7.4)	2	(0.5)

Progressive Disease	6	(1.5)	6	(1.5)
Recurrence/Relapse	7	(1.7)	0	(0.0)
Surgery Incomplete	3	(0.7)	9	(2.3)
Withdrawal By Subject	65	(16.1)	25	(6.3)
Status for Participants Randomized but did not Receive Preoperative Study Medication				
Randomized But Not Treated	2		7	
Physician Decision	0	(0.0)	2	(28.6)
Withdrawal By Subject	2	(100.0)	5	(71.4)
Status for Preoperative Study Medications				
Started	403		396	
Completed	344	(85.4)	352	(88.9)
Discontinued	59	(14.6)	44	(11.1)
Adverse Event	49	(12.2)	31	(7.8)
Physician Decision	3	(0.7)	4	(1.0)
Progressive Disease	2	(0.5)	0	(0.0)
Withdrawal By Subject	5	(1.2)	9	(2.3)
Status for Participants Received Preoperative Study Medications but did not Undergo Surgery				
Received Preoperative Study Medications But Did Not Undergo Surgery	52		37	
Adverse Event	13	(25.0)	6	(16.2)
Physician Decision	7	(13.5)	2	(5.4)
Progressive Disease	6	(11.5)	6	(16.2)
Withdrawal By Subject	26	(50.0)	23	(62.2)
Status for Surgery				
Started	351		361	
Complete Resection	346	(98.6)	352	(97.5)
Incomplete Resection	5	(1.4)	9	(2.5)
Newly Discovered Metastatic Disease	0	(0.0)	1	(0.3)
Unresectable Tumor	2	(0.6)	4	(1.1)
Other	3	(0.9)	4	(1.1)
Status for Participants Underwent Surgery but did not Receive Postoperative Study Medications				
Underwent Surgery But Did Not Receive Postoperative Study Medications	89		NA	
Adverse Event	37	(41.6)	NA	
Physician Decision	16	(18.0)	NA	
Recurrence/Relapse	3	(3.4)	NA	
Surgery Incomplete	3	(3.4)	NA	
Withdrawal By Subject	30	(33.7)	NA	
Status for Postoperative Study Medications				
Started	262		0	
Completed	208	(79.4)	0	(0.0)
Discontinued	54	(20.6)	0	(0.0)
Adverse Event	34	(13.0)	0	(0.0)
Physician Decision	7	(2.7)	0	(0.0)
Recurrence/Relapse	4	(1.5)	0	(0.0)
Withdrawal By Subject	9	(3.4)	0	(0.0)
<p>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.</p> <p>Status for all study treatment (preoperative/surgical + postoperative): [for EV + Pembro] Completed indicates a participant received at least 1 cycle of preoperative study medications, underwent surgery, and received 5 postoperative cycles of EV or 13 postoperative cycles of pembrolizumab. [for Cis +</p>				

Gem] Completed indicates a participant received at least 1 cycle of preoperative study medications and completed surgery.

Status for preoperative study medications: Completed indicates a participant received 4 preoperative cycles of at least one of the two study medications (EV or pembrolizumab) or (cisplatin or gemcitabine). Discontinued indicates a participant did not receive 4 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 5 postoperative cycles of EV or 13 postoperative cycles of pembrolizumab.

Database Cutoff Date: 27OCT2025.

Table 7 Summary of Follow-Up Duration (ITT Population)

Follow-up duration (months) ^a	EV + Pembro (N=405)	Cis + Gem (N=403)	Total (N=808)
Median (Range)	31.3 (0.5, 53.6)	30.6 (0.8, 53.3)	30.8 (0.5, 53.6)
Mean (SD)	32.0 (11.5)	30.2 (11.8)	31.1 (11.6)
^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: 27OCT2025			

Table 8. Disposition of Participants (ITT Population – Participants Who Did Not Undergo Surgery)

	EV + Pembro		Cis + Gem	
	n	(%)	n	(%)
Participants in population	54		42	
Status for Trial				
Started	54		42	
Discontinued	21	(38.9)	21	(50.0)
Death	16	(29.6)	15	(35.7)
Withdrawal By Subject	5	(9.3)	6	(14.3)
Subsequently died	3	(5.6)	2	(4.8)
Ongoing	33	(61.1)	21	(50.0)
Status for Preoperative Study Medications				
Started	52		37	
Completed	32	(61.5)	29	(78.4)
Discontinued	20	(38.5)	8	(21.6)
Adverse Event	15	(28.8)	6	(16.2)
Physician Decision	1	(1.9)	0	(0.0)
Progressive Disease	2	(3.8)	0	(0.0)
Withdrawal By Subject	2	(3.8)	2	(5.4)
Status for Participants who did not Undergo Surgery				
Did Not Undergo Surgery	54		42	
Adverse Event	13	(24.1)	6	(14.3)
Physician Decision	7	(13.0)	4	(9.5)
Progressive Disease	6	(11.1)	6	(14.3)
Withdrawal By Subject	28	(51.9)	26	(61.9)
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 preoperative study medications: Completed indicates a participant received 4 preoperative cycles of at least one of the two study medications (EV or pembrolizumab) or (cisplatin or gemcitabine). Discontinued indicates a participant did not receive 4 cycles of any preoperative study medications. Participants who discontinued preoperative study medications may still undergo surgery.				
Database Cutoff Date: 27OCT2025.				

Table 9. Disposition of Participants With Reason for Not Undergoing Surgery (ITT Population – Participants Who Did Not Undergo Surgery)

	EV + Pembro		Cis + Gem	
	n	(%)	n	(%)
Participants in population	54		42	
Reason for Participants who did not Undergo Surgery				
Adverse Event	13	(24.1)	6	(14.3)
Physician Decision	7	(13.0)	4	(9.5)
Surgery was declined after being informed of post-treatment disease assessments in favor of proceeding with different therapy	0	(0.0)	1	(2.4)
Surgery was declined after being informed of post-treatment disease assessments in favor of proceeding with surveillance	2	(3.7)	0	(0.0)
Surgery was declined because of administrative reasons	2	(3.7)	1	(2.4)
Surgery was declined because of concerns related to surgery	2	(3.7)	0	(0.0)
Unknown	1	(1.9)	2	(4.8)
Progressive Disease	6	(11.1)	6	(14.3)
Withdrawal By Subject	28	(51.9)	26	(61.9)
Surgery was declined after being informed of post-treatment disease assessments in favor of proceeding with different therapy	0	(0.0)	1	(2.4)
Surgery was declined after being informed of post-treatment disease assessments in favor of proceeding with surveillance	8	(14.8)	6	(14.3)
Surgery was declined because of administrative reasons	3	(5.6)	3	(7.1)
Surgery was declined because of concerns related to surgery	15	(27.8)	12	(28.6)
Unknown	2	(3.7)	4	(9.5)
Participants in population is used as the denominator for the percentage calculation.				
Database Cutoff Date: 27OCT2025.				

Recruitment

KEYNOTE B-15/ EV-304 is an ongoing multinational phase 3 study was conducted at 188 centres in 26 countries: Argentina, Australia, Bulgaria, Canada, China, Colombia, Croatia, Czech Republic,

France, Germany, Greece, Hungary, Israel, Italy, Japan, Malaysia, Poland, Portugal, Romania, Russia, South Korea, Spain, Taiwan, United Kingdom, Ukraine, and US.

First patient first visit: 21-APR-2021

Data cut-off: 27-OCT-2025

Study is still ongoing

Conduct of the study

Protocol amendments

Table 10. Protocol Amendments for KEYNOTE-B15

Document	Date of Issue	Overall Rationale
Amendment 05	11-DEC-2024	To revise the statistical analysis plan to ensure sufficient follow-up time for EFS and OS analyses based on a recently published study in the same patient population.
Amendment 04	17-NOV-2023	To allow collection of late-onset peripheral neuropathy data to fulfill an FDA postmarketing requirement for EV, and to ensure consistency between the definition of EFS in the primary endpoint and the statistical analysis plan for this endpoint.
Amendment 03	06-FEB-2023	pCR is revised to a key secondary endpoint and EFS is the only primary endpoint. As a result, the multiplicity strategy is updated to allocate all initial alpha to EFS to test the EFS endpoint more robustly. In addition, adjuvant nivolumab is permitted in Arm B when clinically indicated and per the label, dose modification recommendations for pneumonitis/ILD related to enfortumab vedotin were added, changes were made to align with the EU CTR, and other minor updates and clarifications were made.
Amendment 02	04-APR-2022	Added additional guidance on management of certain Grade 2 skin reactions and any grade bullous lesions.
Amendment 01	14-MAY-2021	Added updated dose modification and supportive care guidelines for rash related to enfortumab vedotin, harmonized the presentation of safety information across all FDA-approved PD-1/L1 antibody prescribing information, made additional minor changes throughout the protocol, and updated the SAP.
Original Protocol	04-NOV-2020	Not applicable

EFS=event-free survival; EU CTR=European Union Clinical Trials Regulation; EV=enfortumab vedotin; FDA=Food and Drug Administration; ILD=interstitial lung disease; OS=overall survival; pCR=pathological complete response; PD-L1=programmed cell death ligand 1; SAP=statistical analysis plan.

Source: [16.1.1](#)

In Amendment 03 (dated 06-FEB-2023), pCR was downgraded from primary to key secondary endpoint. In initial protocol versions, an alpha of 0.001 was attributed to pCR, while 0.024 was attributed to EFS.

In Amendment 05 (dated 11-DEC-2024), follow-up time for EFS and OS was updated (based on the NIAGARA publication) and the sample size was updated from 784 to 808 participants (while maintaining 325 events) to reflect the actual enrolment. Timings and power of IA were adjusted,

and one additional OS IA was added. Furthermore, the original primary pCR analysis was moved to sensitivity analysis.

Protocol deviations

Important (i.e. 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) were reported for 47 (11.6%) participants in the EV + pembrolizumab group and 38 (9.4%) participants in the cis + gem group. None was considered clinically important and none was classified as a serious GCP compliance issue.

There were 3 protocol-defined overdoses (2 overdoses of enfortumab vedotin and 1 overdose of gemcitabine). None were associated with AEs.

Protocol deviations associated with the COVID-19 pandemic were reported for 11 (2.7%) participants in the EV + pembrolizumab group and 16 (4%) participants in the cis + gem group.

Baseline data

Table 11. Participant Characteristics (ITT Population)

	EV + Pembro		Cis + Gem		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	405		403		808	
Sex						
Male	327	(80.7)	327	(81.1)	654	(80.9)
Female	78	(19.3)	76	(18.9)	154	(19.1)
Age (Years)						
< 65	158	(39.0)	156	(38.7)	314	(38.9)
≥ 65	247	(61.0)	247	(61.3)	494	(61.1)
Mean	65.4		65.8		65.6	
SD	8.5		8.2		8.4	
Median	66.0		66.0		66.0	
Range	35 to 83		37 to 85		35 to 85	
Race						
American Indian Or Alaska Native	3	(0.7)	2	(0.5)	5	(0.6)
Asian	63	(15.6)	74	(18.4)	137	(17.0)
Black Or African American	5	(1.2)	5	(1.2)	10	(1.2)
Multiple	5	(1.2)	6	(1.5)	11	(1.4)
American Indian Or Alaska Native, Black Or African American	0	(0.0)	3	(0.7)	3	(0.4)
American Indian Or Alaska Native, White	5	(1.2)	2	(0.5)	7	(0.9)
Black Or African American, Native Hawaiian Or Other Pacific Islander	0	(0.0)	1	(0.2)	1	(0.1)
White	329	(81.2)	314	(77.9)	643	(79.6)
Missing	0	(0.0)	2	(0.5)	2	(0.2)
Ethnicity						
Hispanic Or Latino	35	(8.6)	30	(7.4)	65	(8.0)
Not Hispanic Or Latino	363	(89.6)	366	(90.8)	729	(90.2)
Not Reported	3	(0.7)	3	(0.7)	6	(0.7)
Unknown	4	(1.0)	4	(1.0)	8	(1.0)

Age (Years)					
< 65	158	(39.0)	156	(38.7)	314 (38.9)
65 - 74	199	(49.1)	200	(49.6)	399 (49.4)
75 - 84	48	(11.9)	46	(11.4)	94 (11.6)
85+	0	(0.0)	1	(0.2)	1 (0.1)
Region					
US	59	(14.6)	59	(14.6)	118 (14.6)
EU	206	(50.9)	205	(50.9)	411 (50.9)
MOW	140	(34.6)	139	(34.5)	279 (34.5)
ECOG at Baseline					
0	317	(78.3)	310	(76.9)	627 (77.6)
1	88	(21.7)	93	(23.1)	181 (22.4)
PD-L1 Status at Baseline					
CPS≥10	233	(57.5)	230	(57.1)	463 (57.3)
CPS<10	171	(42.2)	173	(42.9)	344 (42.6)
Missing	1	(0.2)	0	(0.0)	1 (0.1)
Disease Stage at Baseline					
T2N0	79	(19.5)	77	(19.1)	156 (19.3)
T3/T4aN0	293	(72.3)	293	(72.7)	586 (72.5)
T1-T4aN1	33	(8.1)	33	(8.2)	66 (8.2)
Histology of Tumor					
Urothelial Carcinoma	370	(91.4)	353	(87.6)	723 (89.5)
Urothelial Carcinoma with Glandular Differentiation	9	(2.2)	12	(3.0)	21 (2.6)
Urothelial Carcinoma with Squamous Differentiation	17	(4.2)	22	(5.5)	39 (4.8)
Urothelial Carcinoma with Variant Histology	9	(2.2)	16	(4.0)	25 (3.1)
Smoking Status					
Never Smoker	92	(22.7)	98	(24.3)	190 (23.5)
Former Smoker	191	(47.2)	201	(49.9)	392 (48.5)
Current Smoker	122	(30.1)	104	(25.8)	226 (28.0)
Weight (kg)					
≤ 100 kg	366	(90.4)	350	(86.8)	716 (88.6)
> 100 kg	39	(9.6)	53	(13.2)	92 (11.4)
Participants with data	405		403		808
Mean	79.7		80.1		79.9
SD	16.6		17.2		16.9
Median	79.0		78.0		78.8
Range	39 to 168		42 to 139		39 to 168
Body Mass Index (kg/m2)					
< 25 kg/m2	144	(35.6)	136	(33.7)	280 (34.7)
25 to < 30 kg/m2	163	(40.2)	157	(39.0)	320 (39.6)
≥ 30 kg/m2	98	(24.2)	110	(27.3)	208 (25.7)
Participants with data	405		403		808
Mean	26.6		27.0		26.8
SD	4.6		5.1		4.8
Median	26.0		26.0		26.0
Range	15 to 46		16 to 51		15 to 51
Renal Function Based on CrCl (mL/min or mL/min/1.73m2)					
CrCl: ≥ 90	149	(36.8)	156	(38.7)	305 (37.7)
CrCl: ≥ 60 and < 90	252	(62.2)	245	(60.8)	497 (61.5)

CrCl: ≥ 30 and < 60	4	(1.0)	2	(0.5)	6	(0.7)
HbA1c (%)						
< 5.7%	181	(44.7)	202	(50.1)	383	(47.4)
$\geq 5.7\%$ and $< 6.5\%$	166	(41.0)	123	(30.5)	289	(35.8)
$\geq 6.5\%$	39	(9.6)	60	(14.9)	99	(12.3)
Missing	19	(4.7)	18	(4.5)	37	(4.6)
Participants with data	386		385		771	
Mean	5.8		5.7		5.8	
SD	0.6		0.8		0.7	
Median	5.7		5.6		5.7	
Range	2 to 8		3 to 8		2 to 8	
SD=Standard deviation. EU includes participants from the 27 EU countries; participants from the UK are included in MOW. CPS=combined positive score, CrCl=creatinine clearance, ECOG=Eastern Cooperative Oncology Group, EU=European Union, HbA1c=hemoglobin A1c, MIBC=muscle invasive bladder cancer, MOW=Most of World, PD-L1=programmed cell death-ligand 1, UK=United Kingdom, US=United States. kg=kilogram, mL/min=milliliters per minute, m2=square meter, umol/L=micromole per liter. Database Cutoff Date: 27OCT2025.						

Table 12. Summary of Surgical Procedures (ITT Population – Participants Who Underwent Surgery)

	EV + Pembro		Cis + Gem	
	n	(%)	n	(%)
Participants in population	351		361	
Type of Radical Cystectomy				
Laparoscopic Radical Cystectomy	2	(0.6)	10	(2.8)
Robotic Assisted Laparoscopic Radical Cystectomy	158	(45.0)	175	(48.5)
Open Radical Cystectomy	184	(52.4)	169	(46.8)
Unknown	7	(2.0)	7	(1.9)
Type of Urinary Diversion				
Continent Cutaneous Pouch	22	(6.3)	39	(10.8)
Neo-Bladder	95	(27.1)	103	(28.5)
Ileal Conduit	226	(64.4)	207	(57.3)
Ureterocutaneostomy	0	(0.0)	3	(0.8)
Not Applicable	1	(0.3)	2	(0.6)
Unknown	7	(2.0)	7	(1.9)
Type of Pelvic Lymph Nodes Dissection				
Extended	70	(19.9)	65	(18.0)
Standard	271	(77.2)	280	(77.6)
Not Applicable	0	(0.0)	3	(0.8)
Not Done	3	(0.9)	6	(1.7)
Unknown	7	(2.0)	7	(1.9)
Not applicable: procedure was not applicable. Not done: procedure was applicable but not performed. Unknown: procedure was performed with no information available. Database Cutoff Date: 27OCT2025.				

Table 13. Summary Statistics for Time to Surgery (ITT Population – Participants Who Underwent Surgery)

	EV + Pembro	Cis + Gem
Participants in population	351	361
Time from randomization to surgery (weeks)		
Participants with data	351	361
Mean	16.6	16.6
SD	4.5	5.1
Median	15.7	15.9
Range	6.0 to 55.1	7.6 to 73.1
Time from last dose of preoperative treatment to surgery (weeks)		
Participants with data	351	359
Mean	6.6	6.3
SD	4.4	4.9
Median	5.4	5.3
Range	1.0 to 44.0	1.4 to 63.9
Time from surgery to first dose of postoperative treatment (weeks)		
Participants with data	262	.
Mean	9.6	.
SD	4.1	.
Median	8.5	.
Range	5.0 to 46.7	.
SD=Standard deviation. Database Cutoff Date: 27OCT2025.		

Table 14. Reasons for Surgery Delay (ITT Population – Participants Who Underwent Surgery)

	EV + Pembro		Cis + Gem	
	n	(%)	n	(%)
Participants in population	351		361	
Status for Surgery Delay				
No surgery delay	292	(83.2)	309	(85.6)
Surgery Delay	59	(16.8)	52	(14.4)
Adverse Experience	26	(7.4)	16	(4.4)
Patient Non-Compliance	1	(0.3)	2	(0.6)
Scheduling Change	27	(7.7)	28	(7.8)
Other	5	(1.4)	6	(1.7)
Participants in population is used as the denominator for the percentage calculation. Surgery delay is defined as time from last preoperative treatment or randomization (if no preoperative treatment received) to surgery > 8 weeks Database Cutoff Date: 27OCT2025.				

Table 15. Participants With Subsequent Oncologic Therapies by Surgery Status (Incidence > 0% in One or More Treatment Groups) (ITT Population)

	EV + Pembro		Cis + Gem	
	n	(%)	n	(%)
Participants in population	405		403	
with one or more subsequent oncologic therapies	64	(15.8)	128	(31.8)
with no subsequent oncologic therapies	341	(84.2)	275	(68.2)
Participants Who Did Not Undergo Surgery	20	(4.9)	20	(5.0)
Metastatic	7	(1.7)	11	(2.7)
Combination Therapy	5	(1.2)	4	(1.0)
Anti-PD-1/PD-L1 plus Chemotherapy	1	(0.2)	0	(0.0)
Chemotherapy	3	(0.7)	1	(0.2)
EV plus Pembrolizumab	1	(0.2)	1	(0.2)
Other	0	(0.0)	2	(0.5)
Monootherapy	3	(0.7)	6	(1.5)
Anti-PD-1/PD-L1	1	(0.2)	4	(1.0)
Chemotherapy	2	(0.5)	0	(0.0)

EV	0	(0.0)	1	(0.2)
Other	0	(0.0)	1	(0.2)
Radiation Therapy	4	(1.0)	5	(1.2)
Non-Metastatic	16	(4.0)	15	(3.7)
Combination Therapy	5	(1.2)	2	(0.5)
Chemotherapy	3	(0.7)	2	(0.5)
EV plus Pembrolizumab	2	(0.5)	0	(0.0)
Monotherapy	7	(1.7)	5	(1.2)
Chemotherapy	4	(1.0)	4	(1.0)
Other	3	(0.7)	1	(0.2)
Radiation Therapy	10	(2.5)	14	(3.5)
Second Primary Malignancy	2	(0.5)	0	(0.0)
Combination Therapy	1	(0.2)	0	(0.0)
Chemotherapy	1	(0.2)	0	(0.0)
Monotherapy	1	(0.2)	0	(0.0)
Chemotherapy	1	(0.2)	0	(0.0)
Participants Who Underwent Surgery	44	(10.9)	108	(26.8)
Adjuvant	5	(1.2)	29	(7.2)
Combination Therapy	4	(1.0)	1	(0.2)
Chemotherapy	4	(1.0)	1	(0.2)
Monotherapy	1	(0.2)	28	(6.9)
Anti-PD-1/PD-L1	0	(0.0)	28	(6.9)
Avelumab	0	(0.0)	1	(0.2)
Nivolumab	0	(0.0)	25	(6.2)
Pembrolizumab	0	(0.0)	2	(0.5)
Chemotherapy	1	(0.2)	0	(0.0)
Incomplete Resection	2	(0.5)	4	(1.0)
Combination Therapy	2	(0.5)	1	(0.2)
Chemotherapy	2	(0.5)	0	(0.0)
Other	0	(0.0)	1	(0.2)
Monotherapy	1	(0.2)	2	(0.5)
Anti-PD-1/PD-L1	0	(0.0)	1	(0.2)
Chemotherapy	1	(0.2)	1	(0.2)
Radiation Therapy	0	(0.0)	2	(0.5)
Other	5	(1.2)	4	(1.0)
Combination Therapy	5	(1.2)	1	(0.2)
Chemotherapy	5	(1.2)	0	(0.0)
Other	0	(0.0)	1	(0.2)
Monotherapy	0	(0.0)	2	(0.5)
Anti-PD-1/PD-L1	0	(0.0)	1	(0.2)
Chemotherapy	0	(0.0)	1	(0.2)
EV	0	(0.0)	1	(0.2)
Radiation Therapy	0	(0.0)	2	(0.5)
Recurrent/Metastatic	36	(8.9)	74	(18.4)
Combination Therapy	31	(7.7)	34	(8.4)
Anti-PD-1/PD-L1 plus Chemotherapy	3	(0.7)	1	(0.2)
Chemotherapy	28	(6.9)	20	(5.0)
EV plus Pembrolizumab	0	(0.0)	9	(2.2)
Other	1	(0.2)	5	(1.2)
Monotherapy	14	(3.5)	49	(12.2)
Anti-PD-1/PD-L1	4	(1.0)	42	(10.4)
Chemotherapy	6	(1.5)	10	(2.5)
EV	2	(0.5)	18	(4.5)
Other	4	(1.0)	3	(0.7)
Radiation Therapy	11	(2.7)	18	(4.5)
Second Primary Malignancy	3	(0.7)	4	(1.0)
Combination Therapy	3	(0.7)	4	(1.0)
Anti-PD-1/PD-L1 plus Chemotherapy	0	(0.0)	1	(0.2)
Chemotherapy	2	(0.5)	3	(0.7)
Other	1	(0.2)	1	(0.2)
Monotherapy	0	(0.0)	2	(0.5)

Chemotherapy	0 (0.0)	2 (0.5)
<p>Every participant is counted a single time for each applicable subsequent oncologic therapy. A participant with multiple subsequent oncologic therapies within a category is counted a single time for that category.</p> <p>Participants who did not undergo surgery: report subsequent oncologic therapies received for participants who did not undergo surgery. Metastatic: oncologic therapies to treat metastatic disease (outside the pelvis); Non-Metastatic: oncologic therapies to treat non-metastatic disease (within the pelvis); Second Primary Malignancy: oncologic therapies to treat second primary malignancy.</p> <p>Participants who underwent surgery: report subsequent oncologic therapies received after surgery for participants who underwent surgery. Adjuvant: oncologic therapies to reduce the risk of disease recurrence after complete resection; Incomplete Resection: oncologic therapies after incomplete resection due to unresectable tumor; Other: oncologic therapies received prior to or during surgery; Recurrent/Metastatic: oncologic therapies after surgery to treat recurrent/metastatic disease; Second Primary Malignancy: oncologic therapies to treat second primary malignancy.</p> <p>Database Cutoff Date: 27OCT2025.</p>		

In the control arm, 25 patients received adjuvant nivolumab (i.e. 6.9% of the 361 patients who underwent surgery).

Numbers analysed

Table 16. Study Population

	EV + Pembro	Cis + Gem	Total
Number of Participants Screened			1225
Number of Participants Randomized (Planned Treatment) (ITT)	405	403	808
Number of Participants Randomized and Did not Receive Study Medication	2	7	9
Number of Participants Randomized and Received Study Medication (Actual Treatment) (APaT)	403	396	799
Number of Participants Who Received Study Medication and Underwent Surgery (APrS)	351	359	710
Number of Participants Who Were Disease Free After Surgery	339	330	669
Number of Participants Who Did Not Undergo Surgery	54	42	96
Number of Participants Who Did Not Undergo Surgery and Achieved cCR	8	3	11
Database Cutoff Date: 27OCT2025.			

2.4.2.1. Outcomes and estimation

2.4.2.1.1. Primary endpoint: EFS by BICR

EFS (based on BICR assessment) was formally tested with the multiplicity-adjusted p-value boundary of 0.0082 at IA1

Table 17. Analysis of Event-Free Survival (Primary Censoring Rule) Based on BICR Assessment (ITT Population)

	EV + Pembro (N=405)	Cis + Gem (N=403)
Number of Events (%)	87 (21.5)	146 (36.2)
Number of Censored (%)	318 (78.5)	257 (63.8)
Kaplan-Meier Estimates (months) ^a		
Median (95% CI)	NR (NR, NR)	48.5 (43.3, NR)
(Q1, Q3)	(38.5, NR)	(12.5, NR)
Person-months	10498.2	9307.4
Event Rate / 100 Person-months	0.8	1.6
vs Cis + Gem		
Hazard Ratio (95% CI) ^b	0.53 (0.41, 0.70)	
p-value ^c	<0.0001	
EFS Rate at month 6 (%) (95% CI)	94.1 (91.3, 96.1)	91.5 (88.2, 93.9)
EFS Rate at month 12 (%) (95% CI)	86.0 (82.1, 89.1)	75.4 (70.8, 79.4)

EFS Rate at month 18 (%) (95% CI)	82.2 (78.0, 85.7)	68.8 (63.9, 73.2)
EFS Rate at month 24 (%) (95% CI)	79.4 (74.9, 83.1)	66.2 (61.2, 70.8)
EFS Rate at month 30 (%) (95% CI)	78.7 (74.1, 82.5)	63.4 (58.1, 68.2)

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

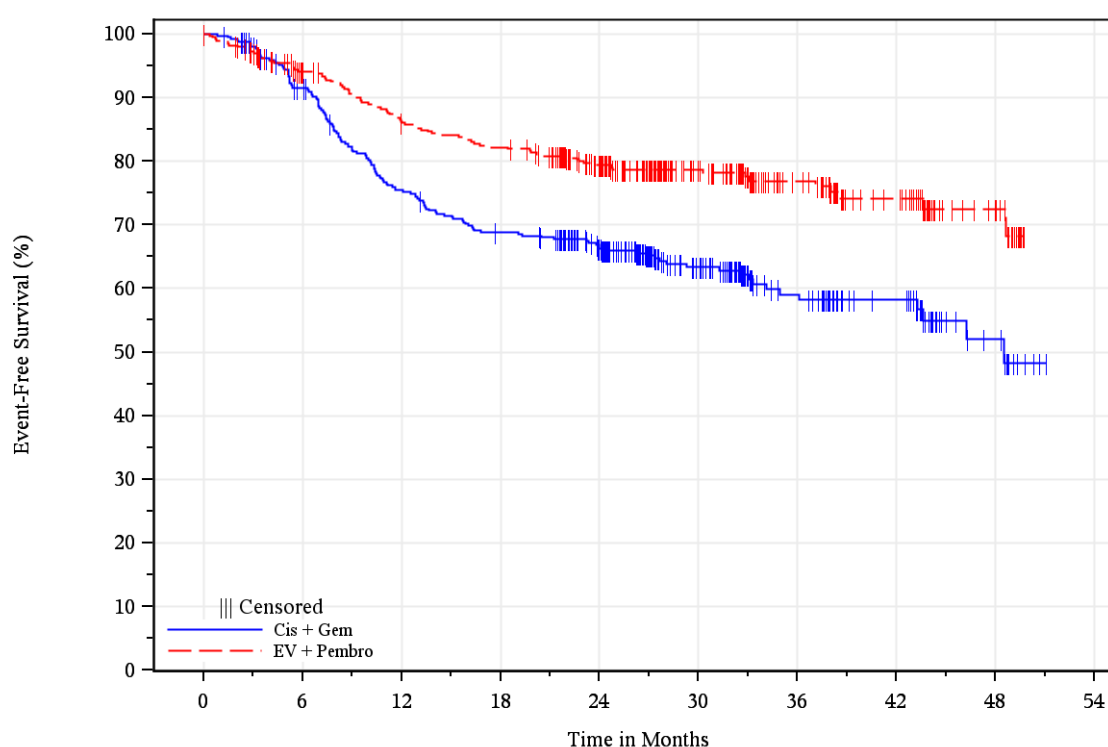
^b Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by baseline PD-L1 (CPS<10 vs CPS≥10), tumor stage (T2N0 vs T3/T4aN0 vs T1-T4aN1), and geographic regions (US vs EU vs MOW) with small strata collapsed as pre-specified in the sSAP.

^c One-sided p-value based on log-rank test stratified by baseline PD-L1 (CPS<10 vs CPS≥10), tumor stage (T2N0 vs T3/T4aN0 vs T1-T4aN1), and geographic regions (US vs EU vs MOW) with small strata collapsed as pre-specified in the sSAP.

NR = Not reached.

Database Cutoff Date: 27OCT2025

Figure 4. Kaplan-Meier Plot of Event-Free Survival (Primary Censoring Rule) Based on BICR Assessment (ITT Population)



Number of Participants at Risk

Cis + Gem	403	350	286	259	216	131	70	45	16	0
EV + Pembro	405	351	317	303	257	154	100	63	23	0

Database Cutoff Date: 27OCT2025.

Source: [PB15V01MK3475: adam-adsl; adtte]

As per protocol EFS primary censoring rules, participants who did not undergo RC + PLND and did not meet an EFS event were censored within 16 weeks of the last dose of neoadjuvant treatment, consistent with the timing of the early censoring observed in the EFS KM curve.

Table 18. Summary of First EFS Event Types Based on BICR Assessment (ITT Population - Participants with Events or Censored During the First 6 Months)

	EV + Pembro n (%)	Cis + Gem n (%)
Participants in Population	405	403
With EFS event	87 (21.5)	146 (36.2)
Distant PD	9 (2.2)	18 (4.5)
Locally advanced disease ^a	2 (0.5)	0 (0.0)
Residual MIBC ^b	1 (0.2)	0 (0.0)
Incomplete resection	2 (0.5)	5 (1.2)
Disease recurrence ^b	43 (10.6)	90 (22.3)
Death	30 (7.4)	33 (8.2)
No EFS event	318 (78.5)	257 (63.8)
Last assessment showing no progression	286 (70.6)	236 (58.6)
Last assessment within 16 weeks of last dose of neoadjuvant treatment or randomization showing no progression	28 (6.9)	15 (3.7)
Randomization	4 (1.0)	6 (1.5)
^a Participants with T4b, N2/N3 disease as identified by imaging and confirmed by BICR.		
^b Includes high-risk NMIBC of the upper-tract/remaining urothelium.		
Database Cutoff Date: 27OCT2025		

Event types for EFS are shown below:

Table 19. Summary of First EFS Event Types Based on BICR Assessment (ITT Population)

	EV + Pembro n (%)	Cis + Gem n (%)
Participants in Population	405	403
With EFS event	87 (21.5)	146 (36.2)
Distant PD	9 (2.2)	18 (4.5)
Locally advanced disease ^a	2 (0.5)	0 (0.0)
Residual MIBC ^b	1 (0.2)	0 (0.0)
Incomplete resection	2 (0.5)	5 (1.2)
Disease recurrence ^b	43 (10.6)	90 (22.3)
Death	30 (7.4)	33 (8.2)
No EFS event	318 (78.5)	257 (63.8)
Last assessment showing no progression	286 (70.6)	236 (58.6)
Last assessment within 16 weeks of last dose of neoadjuvant treatment or randomization showing no progression	28 (6.9)	15 (3.7)
Randomization	4 (1.0)	6 (1.5)
^a Participants with T4b, N2/N3 disease as identified by imaging and confirmed by BICR.		
^b Includes high-risk NMIBC of the upper-tract/remaining urothelium.		
Database Cutoff Date: 27OCT2025		

Note that the term “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.

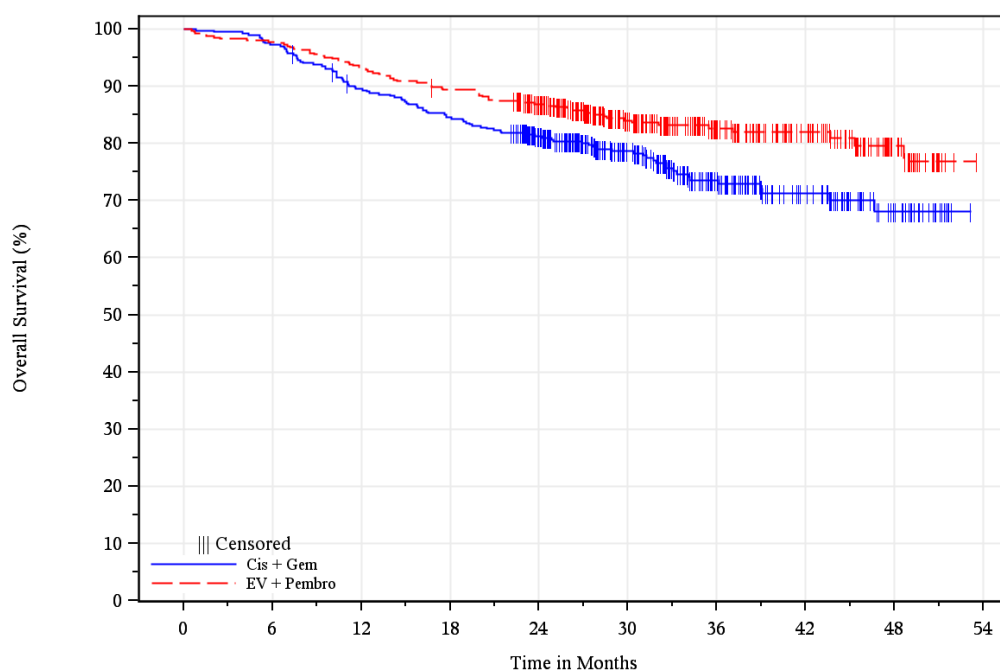
Secondary Efficacy Endpoints

Overall Survival

Since the EFS null hypothesis was rejected, OS was formally tested at IA1 with the multiplicity adjusted p-value boundary of 0.0038.

Table 20. Analysis of Overall Survival (ITT Population)

	EV + Pembro (N=405)	Cis + Gem (N=403)
Number of Events (%)	69 (17.0)	99 (24.6)
Number of Censored (%)	336 (83.0)	304 (75.4)
Kaplan-Meier Estimates (months) ^a		
Median (95% CI)	NR (NR, NR)	NR (NR, NR)
(Q1, Q3)	(NR, NR)	(33.3, NR)
Person-months	12840.6	11995.0
Event Rate / 100 Person-months	0.5	0.8
vs Cis + Gem		
Hazard Ratio (95% CI) ^b	0.65 (0.48, 0.89)	
p-value ^c	0.0029	
OS Rate at month 6 (%) (95% CI)	97.8 (95.8, 98.8)	97.3 (95.1, 98.5)
OS Rate at month 12 (%) (95% CI)	93.1 (90.1, 95.2)	89.6 (86.1, 92.2)
OS Rate at month 18 (%) (95% CI)	89.4 (86.0, 92.0)	84.5 (80.6, 87.7)
OS Rate at month 24 (%) (95% CI)	86.9 (83.2, 89.8)	81.3 (77.1, 84.8)
OS Rate at month 30 (%) (95% CI)	84.0 (79.9, 87.3)	78.7 (74.2, 82.5)
^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 baseline PD-L1 (CPS<10 vs CPS≥10), tumor stage (T2N0 vs T3/T4aN0 vs T1-T4aN1), 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 baseline PD-L1 (CPS<10 vs CPS≥10), tumor stage (T2N0 vs T3/T4aN0 vs T1-T4aN1), and geographic regions (US vs EU vs MOW) with small strata collapsed as pre-specified in the sSAP.		
NR = Not reached.		
Database Cutoff Date: 27OCT2025		

Figure 5. Kaplan-Meier Plot of Overall Survival (ITT Population)**Number of Participants at Risk**

Cis + Gem	403	392	358	338	295	201	119	67	29	0
EV + Pembro	405	396	377	361	325	215	142	90	34	0

Database Cutoff Date: 27OCT2025.

During the first 5 months post-randomization, more deaths were observed in the perioperative EV + pembrolizumab group compared with the cis + gem group (8 vs 4). A summary of all causes of death that occurred during the first 5 months post-randomization for the 2 treatment groups is provided below:

Table 21. Summary of All Deaths For Participants Who Died Within the First 5 Months (ITT Population)

	EV + Pembro		Cis + Gem	
	n	(%)	n	(%)
Participants in population	405		403	
Participants who died	8	(2.0)	4	(1.0)
Cardiac Arrest	1	(0.2)	0	(0.0)
Cardiac Failure	0	(0.0)	1	(0.2)
Covid-19 Pneumonia	1	(0.2)	0	(0.0)
Death	0	(0.0)	1	(0.2)
Malignant Neoplasm Progression	1	(0.2)	0	(0.0)
Multiple Organ Dysfunction Syndrome	2	(0.5)	0	(0.0)
Pneumonia	1	(0.2)	1	(0.2)
Sepsis	0	(0.0)	1	(0.2)
Septic Shock	1	(0.2)	0	(0.0)
Urosepsis	1	(0.2)	0	(0.0)
For treated participants, actual treatment groups were used in the summary. For randomized but not treated participants, planned treatment groups were used in the summary Database Cutoff Date: 27OCT2025.				

Pathological Complete Response Rate

Since the EFS null hypothesis was rejected, pCR (based on BICR) was formally tested with the multiplicity adjusted p-value boundary of 0.001

Table 22. Analysis of Pathological Complete Response Based on BICR Assessment (ITT Population)

Treatment	N	Number of Responses	Response Rate	Difference in % vs. Cis + Gem	
			(%) (95% CI)	Estimate % (95% CI) ^a	p-Value ^b
EV + Pembro	405	226	55.8 (50.8, 60.7)	23.4 (16.7, 29.8)	<0.0001
Cis + Gem	403	131	32.5 (28.0, 37.3)		
^a Based on Miettinen & Nurminen method stratified by baseline PD-L1 (CPS<10 vs CPS≥10), tumor stage (T2N0 vs T3/T4aN0 vs T1-T4aN1), 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: 27OCT2025.					

Pathological Downstaging

Table 23. Analysis of Pathological Downstaging Response Based on BICR Assessment (ITT Population)

Treatment	N	Number of Responses	Response Rate	Difference in % vs. Cis + Gem	
			(%) (95% CI)	Estimate % (95% CI) ^a	p-Value ^b
EV + Pembro	405	258	63.7 (58.8, 68.4)	18.6 (11.8, 25.2)	<0.0001
Cis + Gem	403	182	45.2 (40.2, 50.2)		
^a Based on Miettinen & Nurminen method stratified by baseline PD-L1 (CPS<10 vs CPS≥10), tumor stage (T2N0 vs T3/T4aN0 vs T1-T4aN1), 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: 27OCT2025.					

Disease-Free Survival

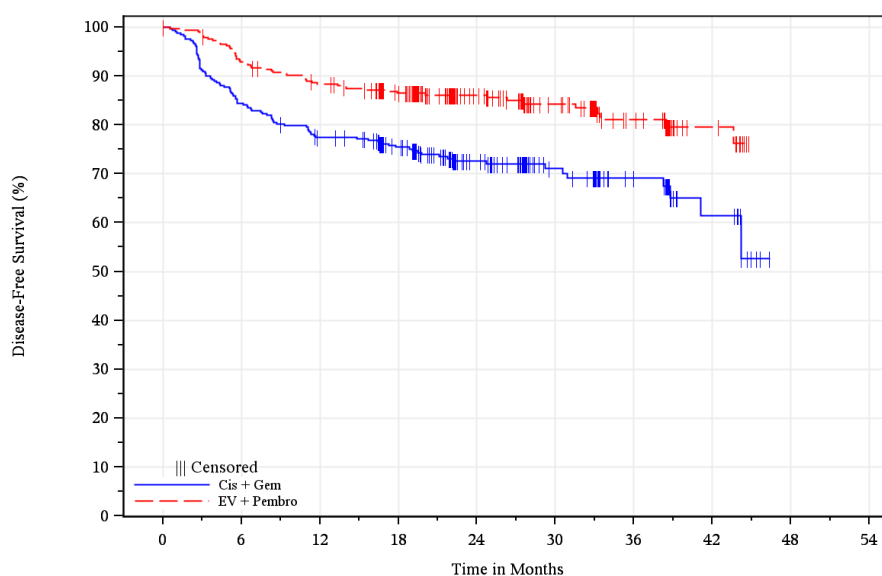
In total after surgery, 339 participants in the perioperative EV + pembrolizumab group and 330 participants in the cis + gem group were included in the analysis of DFS.

In total after surgery, 339 participants in the perioperative EV + pembrolizumab group and 330 participants in the cis + gem group were included in the analysis of DFS.

Table 24. Analysis of Disease-Free Survival (Primary Censoring Rule) Based on BICR Assessment (ITT Population - Participants Who Are Disease Free After Surgery)

	EV + Pembro (N=339)	Cis + Gem (N=330)
Number of Events (%)	54 (15.9)	95 (28.8)
Number of Censored (%)	285 (84.1)	235 (71.2)
Kaplan-Meier Estimates (months) ^a Median (95% CI) (Q1, Q3)	NR (NR, NR) (NR, NR)	NR (44.2, NR) (19.1, NR)
Person-months	8298.0	7075.1
Event Rate / 100 Person-months	0.7	1.3
vs Cis + Gem Hazard Ratio (95% CI) ^b	0.50 (0.36, 0.70)	
DFS Rate at month 6 (%) (95% CI)	92.9 (89.6, 95.2)	84.5 (80.1, 88.0)
DFS Rate at month 12 (%) (95% CI)	88.4 (84.5, 91.4)	77.4 (72.5, 81.6)
DFS Rate at month 18 (%) (95% CI)	86.5 (82.4, 89.8)	75.5 (70.4, 79.8)
DFS Rate at month 24 (%) (95% CI)	86.1 (81.9, 89.4)	72.6 (67.3, 77.2)
DFS Rate at month 30 (%) (95% CI)	84.3 (79.6, 88.0)	71.1 (65.4, 76.0)
^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: 27OCT2025		

Figure 6 Kaplan-Meier Plot of Disease-Free Survival (Primary Censoring Rule) Based on BICR Assessment (ITT Population - Participants Who Are Disease Free After Surgery)



Number of Participants at Risk

Cis + Gem	330	277	251	214	128	71	45	17	0	0
EV + Pembro	339	313	295	260	156	101	62	24	0	0

Database Cutoff Date: 27OCT2025

Patient-reported outcomes

Three PRO questionnaires were used: EORTC QLQ-C30, BCI and EQ-5D-5L VAS.

The baseline PRO assessment was defined as the neoadjuvant Cycle 1 assessment. The mean change from baseline to post-surgery Week 42 was evaluated. Post-surgery Week 42 was the latest time point at which the completion rate was ~60% and the compliance rate was ~80% based on the blinded data review prior to database lock for any PRO analysis.

Definitive TTD was defined as the time from baseline to the first onset of deterioration (e.g., ≥ 10 points deterioration for EORTC QLQ-C30 global health status/QoL score from baseline) with confirmation deterioration at all subsequent timepoints.

No clinically meaningful differences in HRQoL were observed between perioperative EV + pembrolizumab compared with cis + gem with respect to:

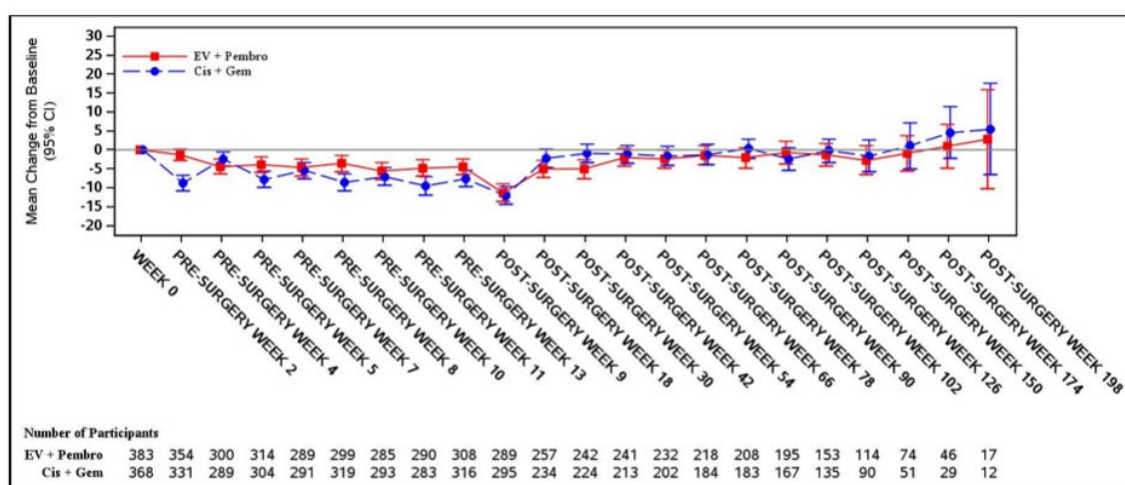
- EORTC QLQ-C30 (global health status/QoL [Items 29 and 30]), physical functioning, and role functioning
- BCI: urinary, bowel, and sexual domains
- EQ-5D-5L VAS

Table 25. Analysis of Change from Baseline to Post-surgery Week 42 in EORTC QLQ-C30 Global Health Status/QoL (PRO FAS Population)

Treatment	Baseline		Post-surgery Week 42		Change from Baseline to Post-surgery Week 42	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI) ^a
EV + Pembro	383	74.37 (18.33)	250	73.47 (17.37)	403	-1.58 (-3.54, 0.38)
Cis + Gem	368	72.92 (19.00)	227	72.43 (16.52)	394	-2.43 (-4.45, -0.41)
Pairwise Comparison					Difference in LS Means ^a (95% CI)	p-Value ^a
EV + Pembro vs. Cis + Gem					0.85 (-1.74, 3.44)	0.5191

^a Based on a cLDA model with the PRO scores as the response variable with covariates for treatment, time, the treatment by time interaction, and stratification factors (PD-L1 (CPS ≥10 vs CPS <10), Tumor stage (cT2N0 vs cT3/T4aN0 vs cT1-T4aN1), and Geographic regions (US, EU, MOW)) as covariates. The p-value is two-sided.
For baseline and Post-surgery Week 42, N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of participants in the analysis population in each treatment group.
Database Cutoff Date: 27OCT2025

Figure 7. Line Plot of Empirical Mean Change from Baseline and 95% CI for the EORTC QLQ-C30 Global Health Status/QoL Over Time by Treatment Group (PRO FAS Population)



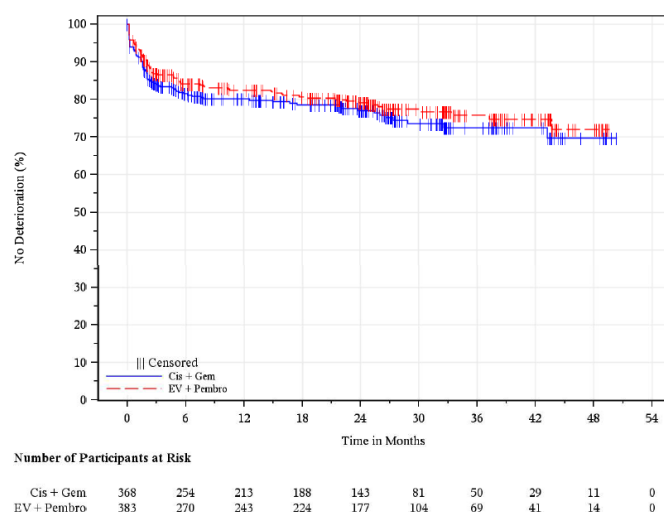
Database Cutoff Date: 27OCT2025

Table 26. Analysis of Time to Definitive Deterioration in EORTC QLQ-C30 Global Health Status/QoL (PRO FAS Population with Baseline)

Treatment	N	Number of Events (%)	Median Deterioration ^a (months) (95% CI)
EV + Pembro	383	79 (20.6)	NR (NR, NR)
Cis + Gem	368	84 (22.8)	NR (NR, NR)
Pairwise Comparisons		Hazard Ratio (95% CI) ^b	p-Value ^c
EV + Pembro vs. Cis + Gem		0.84 (0.61, 1.14)	0.2650

^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 PD-L1 (CPS ≥ 10 vs CPS < 10), Tumor stage (cT2N0 vs cT3/T4aN0 vs cT1-T4aN1), and Geographic regions (US, EU, MOW) as pre-specified in the sSAP.
^c Two-sided p-value based on log-rank test stratified by PD-L1 (CPS ≥ 10 vs CPS < 10), Tumor stage (cT2N0 vs cT3/T4aN0 vs cT1-T4aN1), and Geographic regions (US, EU, MOW) as pre-specified in the sSAP.
NR = Not reached.
Definitive Deterioration is defined as the time from baseline to the first onset of deterioration with confirmation deterioration at all subsequent timepoints.
Database Cutoff Date: 27OCT2025.

Figure 8. Kaplan-Meier Plot of Time to Definitive Deterioration in EORTC QLQ-C30 Global Health Status/QoL (PRO FAS Population with Baseline)



Database Cutoff Date: 27OCT2025.

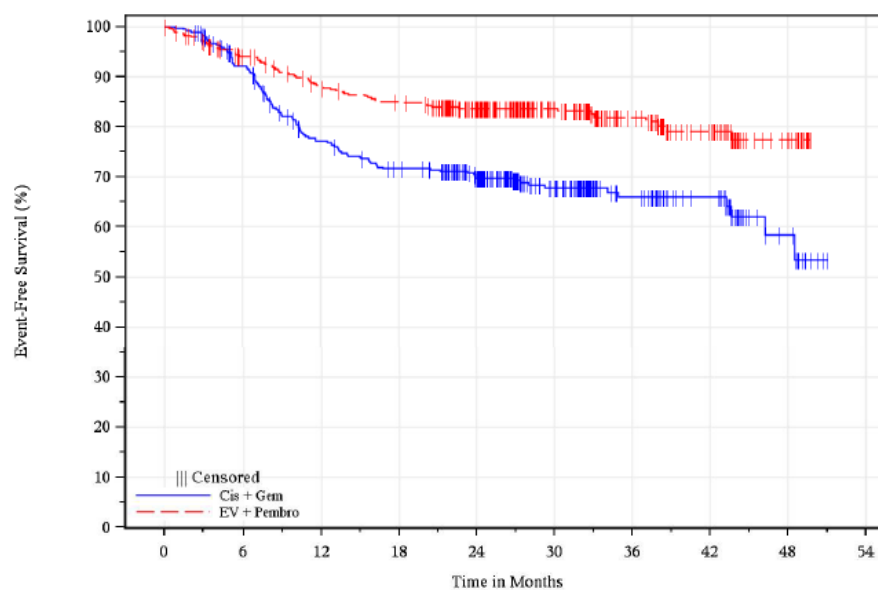
Ancillary analyses

Prespecified sensitivity analyses of primary endpoint

Table 27 Analysis of Event-Free-Survival (Sensitivity Censoring Rule 1) Based on BICR Assessment (ITT population)

	EV + Pembro (N=405)	Cis + Gem (N=403)
Number of Events (%)	69 (17.0)	121 (30.0)
Number of Censored (%)	336 (83.0)	282 (70.0)
Kaplan-Meier Estimates (months) ^a		
Median (95% CI)	NR (NR, NR)	NR (46.2, NR)
(Q1, Q3)	(NR, NR)	(13.5, NR)
Person-months	10838.0	9124.1
Event Rate / 100 Person-months	0.6	1.3
vs Cis + Gem		
Hazard Ratio (95% CI) ^b	0.50 (0.37, 0.67)	
p-value ^c	<0.0001	
EFS Rate at month 6 (%) (95% CI)	94.2 (91.3, 96.1)	92.1 (88.9, 94.4)
EFS Rate at month 12 (%) (95% CI)	88.0 (84.4, 90.9)	77.2 (72.6, 81.1)
EFS Rate at month 18 (%) (95% CI)	85.1 (81.1, 88.3)	71.7 (66.8, 76.0)
EFS Rate at month 24 (%) (95% CI)	83.7 (79.6, 87.1)	69.8 (64.8, 74.2)
EFS Rate at month 30 (%) (95% CI)	83.7 (79.6, 87.1)	67.8 (62.6, 72.5)
^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 baseline PD-L1 (CPS<10 vs CPS≥10), tumor stage (T2N0 vs T3/T4aN0 vs T1-T4aN1), and geographic regions (US vs EU vs MOW) with small strata collapsed as pre-specified in the ESAB .		
^c One-sided p-value based on log-rank test stratified by baseline PD-L1 (CPS<10 vs CPS≥10), tumor stage (T2N0 vs T3/T4aN0 vs T1-T4aN1), and geographic regions (US vs EU vs MOW) with small strata collapsed as pre-specified in the ESAB .		
NR = Not reached.		
Database Cutoff Date: 27OCT2025		

Figure 9 Kaplan Meier Plot of Event-Free-Survival (Sensitivity Censoring Rule 1) Based on BICR Assessment (ITT population)



Number of Participants at Risk

Cis + Gem	403	345	280	256	210	127	67	43	14	0
EV + Pembro	405	359	329	315	270	164	106	66	22	0

Database Cutoff Date: 27OCT2025.

Table 28 Analysis of Event-Free-Survival (Primary Censoring Rule) Based on Investigator Assessment (ITT population)

	EV + Pembro (N=405)	Cis + Gem (N=403)
Number of Events (%)	88 (21.7)	141 (35.0)
Number of Censored (%)	317 (78.3)	262 (65.0)
Kaplan-Meier Estimates (months) ^a		
Median (95% CI)	NR (NR, NR)	NR (46.2, NR)
(Q1, Q3)	(43.7, NR)	(12.8, NR)
Person-months	10457.3	9384.6
Event Rate / 100 Person-months	0.8	1.5
vs Cis + Gem		
Hazard Ratio (95% CI) ^b	0.57 (0.43, 0.74)	
p-value ^c	<0.0001	
EFS Rate at month 6 (%) (95% CI)	93.6 (90.7, 95.6)	91.7 (88.5, 94.1)
EFS Rate at month 12 (%) (95% CI)	86.0 (82.1, 89.2)	76.7 (72.2, 80.6)
EFS Rate at month 18 (%) (95% CI)	81.7 (77.4, 85.3)	70.1 (65.2, 74.4)
EFS Rate at month 24 (%) (95% CI)	77.9 (73.4, 81.8)	67.2 (62.2, 71.6)
EFS Rate at month 30 (%) (95% CI)	77.9 (73.4, 81.8)	64.3 (59.1, 69.0)
^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 baseline PD-L1 (CPS<10 vs CPS≥10), tumor stage (T2N0 vs T3/T4aN0 vs T1-T4aN1), and geographic regions (US vs EU vs MOW) with small strata collapsed as pre-specified in the ESAB . ^c One-sided p-value based on log-rank test stratified by baseline PD-L1 (CPS<10 vs CPS≥10), tumor stage (T2N0 vs T3/T4aN0 vs T1-T4aN1), and geographic regions (US vs EU vs MOW) with small strata collapsed as pre-specified in the ESAB . NR = Not reached. Database Cutoff Date: 27OCT2025		

Table 29 Analysis of Event-Free-Survival (Sensitivity Censoring Rule 1) Based on Investigator Assessment (ITT population)

	EV + Pembro (N=405)	Cis + Gem (N=403)
Number of Events (%)	72 (17.8)	121 (30.0)
Number of Censored (%)	333 (82.2)	282 (70.0)
Kaplan-Meier Estimates (months) ^a Median (95% CI) (Q1, Q3)	NR (NR, NR) (NR, NR)	NR (46.2, NR) (13.7, NR)
Person-months	10887.6	9325.8
Event Rate / 100 Person-months	0.7	1.3
vs Cis + Gem Hazard Ratio (95% CI) ^b p-value ^c	0.53 (0.39, 0.71) <0.0001	
EFS Rate at month 6 (%) (95% CI)	93.6 (90.7, 95.7)	92.1 (88.9, 94.4)
EFS Rate at month 12 (%) (95% CI)	88.1 (84.5, 91.0)	78.5 (74.0, 82.3)
EFS Rate at month 18 (%) (95% CI)	84.7 (80.7, 87.9)	72.3 (67.4, 76.5)
EFS Rate at month 24 (%) (95% CI)	82.5 (78.2, 85.9)	70.0 (65.1, 74.4)
EFS Rate at month 30 (%) (95% CI)	82.5 (78.2, 85.9)	67.8 (62.6, 72.4)
^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 baseline PD-L1 (CPS<10 vs CPS≥10), tumor stage (T2N0 vs T3/T4aN0 vs T1-T4aN1), and geographic regions (US vs EU vs MOW) with small strata collapsed as pre-specified in the SSA . ^c One-sided p-value based on log-rank test stratified by baseline PD-L1 (CPS<10 vs CPS≥10), tumor stage (T2N0 vs T3/T4aN0 vs T1-T4aN1), and geographic regions (US vs EU vs MOW) with small strata collapsed as pre-specified in the SSA . NR = Not reached. Database Cutoff Date: 27OCT2025		

EFS by pCR

Table 30 Event-Free Survival Based on BICR Assessment by pCR Status for KEYNOTE-B15 (ITT Population)

pCR Status	Treatment Group	N	Number of Events (%)	Median (95% CI) (months) ^a	Hazard Ratio (95% CI) ^b vs Cis + Gem
Yes	EV + Pembro	226	16 (7.1)	NR (NR, NR)	0.54 (0.27, 1.07)
	Cis + Gem	131	16 (12.2)	NR (NR, NR)	
No	EV + Pembro	179	71 (39.7)	37.1 (22.7, NR)	0.90 (0.68, 1.21)
	Cis + Gem	272	130 (47.8)	31.2 (19.1, 43.3)	

CI=confidence interval; cis + gem=cisplatin + gemcitabine; EV=enfortumab vedotin; NR=not reached, pCR=pathological complete response; pembro=pembrolizumab.

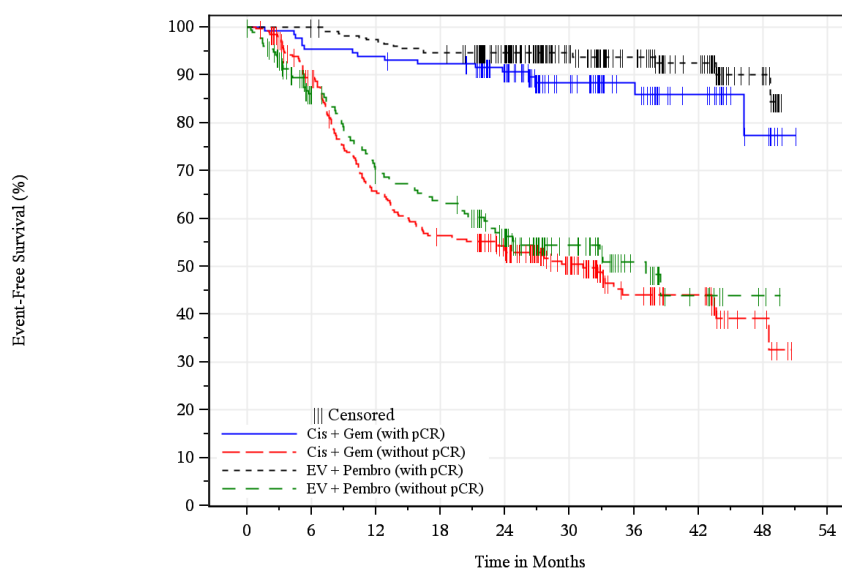
^a From product-limit (Kaplan-Meier) method for censored data.

^b Based on Cox regression model with Efron’s method of tie handling with treatment as a covariate.

Source: [Ref. 5.3.5.1: PB15V01MK3475: Table 14.2-17, 14.2-18]

Database Cutoff Date: 27-OCT-2025

Figure 10 Kaplan-Meier Plot of Event-Free Survival (Primary Censoring Rule) Based on BICR Assessment by Treatment and pCR Status (ITT Population)



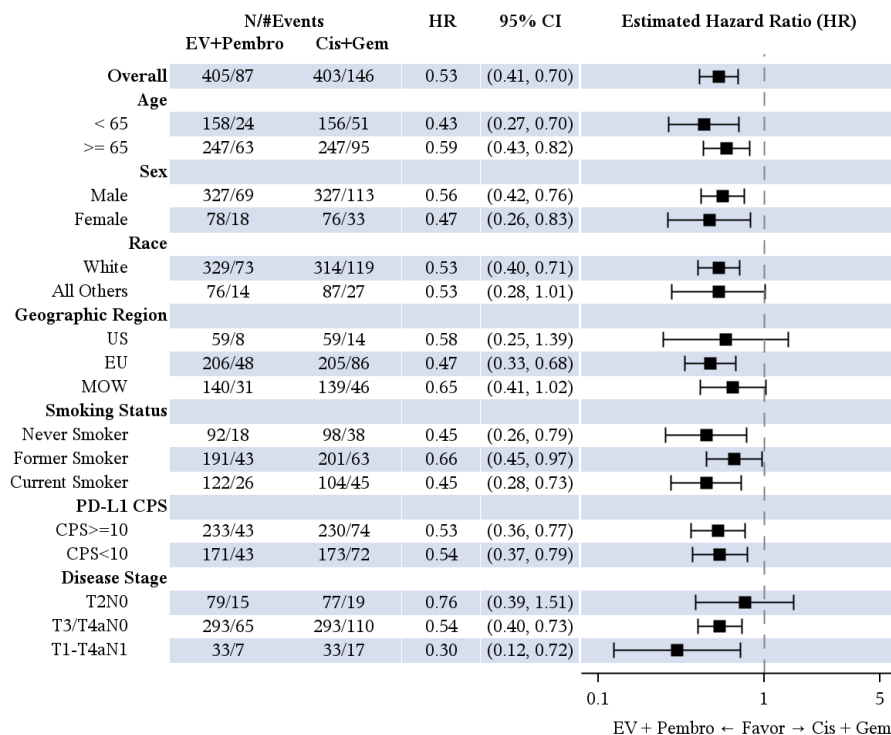
Number of Participants at Risk

Cis + Gem (with pCR)	131	125	123	120	99	57	35	20	8	0
Cis + Gem (without pCR)	272	225	163	139	117	74	35	25	8	0
EV + Pembro (with pCR)	226	225	218	212	189	113	81	55	21	0
EV + Pembro (without pCR)	179	126	99	91	68	41	19	8	2	0

Subgroup analyses

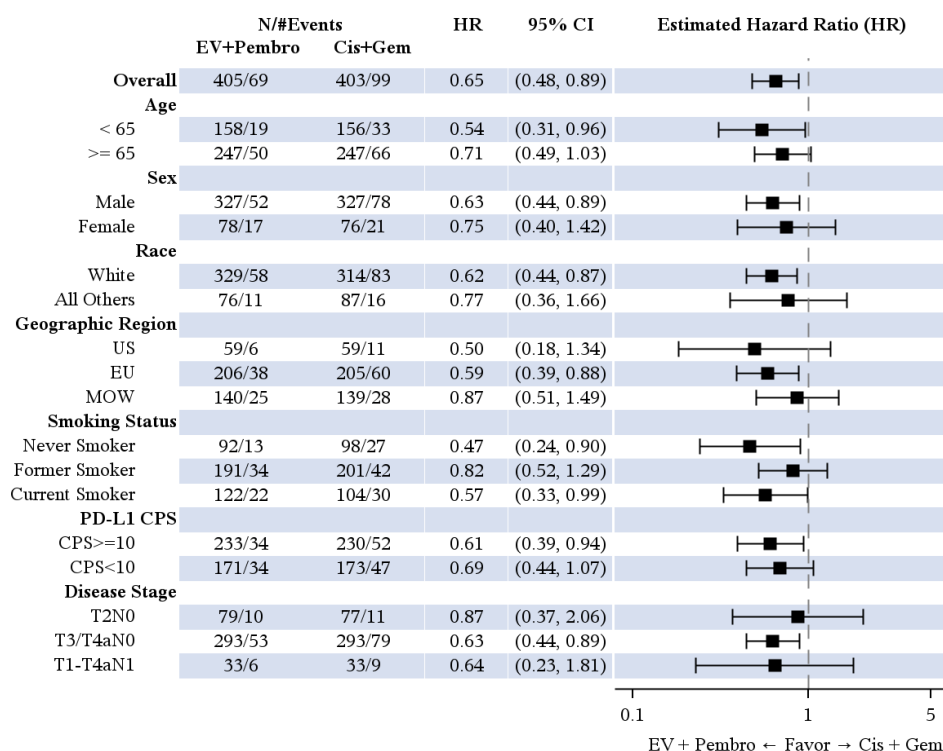
EFS, OS and pCR results across pre-specified subgroups are shown in the figures below:

Figure 11 Forest Plot of Event-Free Survival Hazard Ratio by Subgroup Factors Based on BICR Assessment (ITT Population)



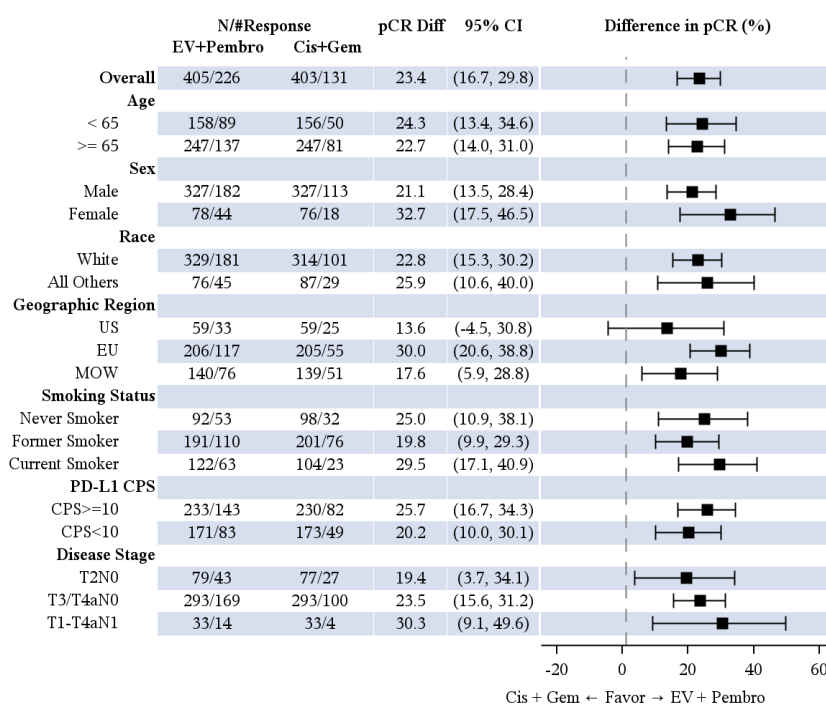
For overall population, analysis is based on stratified Cox regression model with treatment as a covariate. For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate. If a subgroup variable has two levels and one level of the subgroup has less than 10 events, then this subgroup variable is not displayed in the plot. Database Cutoff Date: 27OCT2025.

Figure 12 Forest Plot of Overall Survival Hazard Ratio by Subgroup Factors (ITT 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: 27OCT2025.

Figure 13 Forest Plot of Difference in Pathological Complete Response Rate by Subgroup Factors Based on BICR Assessment (ITT Population)



For overall population, analysis is based on stratified Miettinen & Nurminen method. For subgroup analyses, analysis is based on unstratified Miettinen & Nurminen method. If a subgroup variable has two levels and one level of the subgroup has less than 30 participants, then this subgroup variable is not displayed in the plot. Database Cutoff Date: 27OCT2025.

Subgroup analysis by disease stage

Table 31 Subgroup analysis of Event-Free Survival based on BICR assessment (ITT population)

	EV + Pembro		Cis + Gem		EV + Pembro vs Cis + Gem Hazard Ratio ^a (95% CI) ^a
	N	Number of Events (%)	N	Number of Events (%)	
Disease Stage					
T2N0	79	15 (19.0)	77	19 (24.7)	0.76 (0.39, 1.51)
T3/T4aN0	293	65 (22.2)	293	110 (37.5)	0.54 (0.40, 0.73)
T1-T4aN1	33	7 (21.2)	33	17 (51.5)	0.30 (0.12, 0.72)

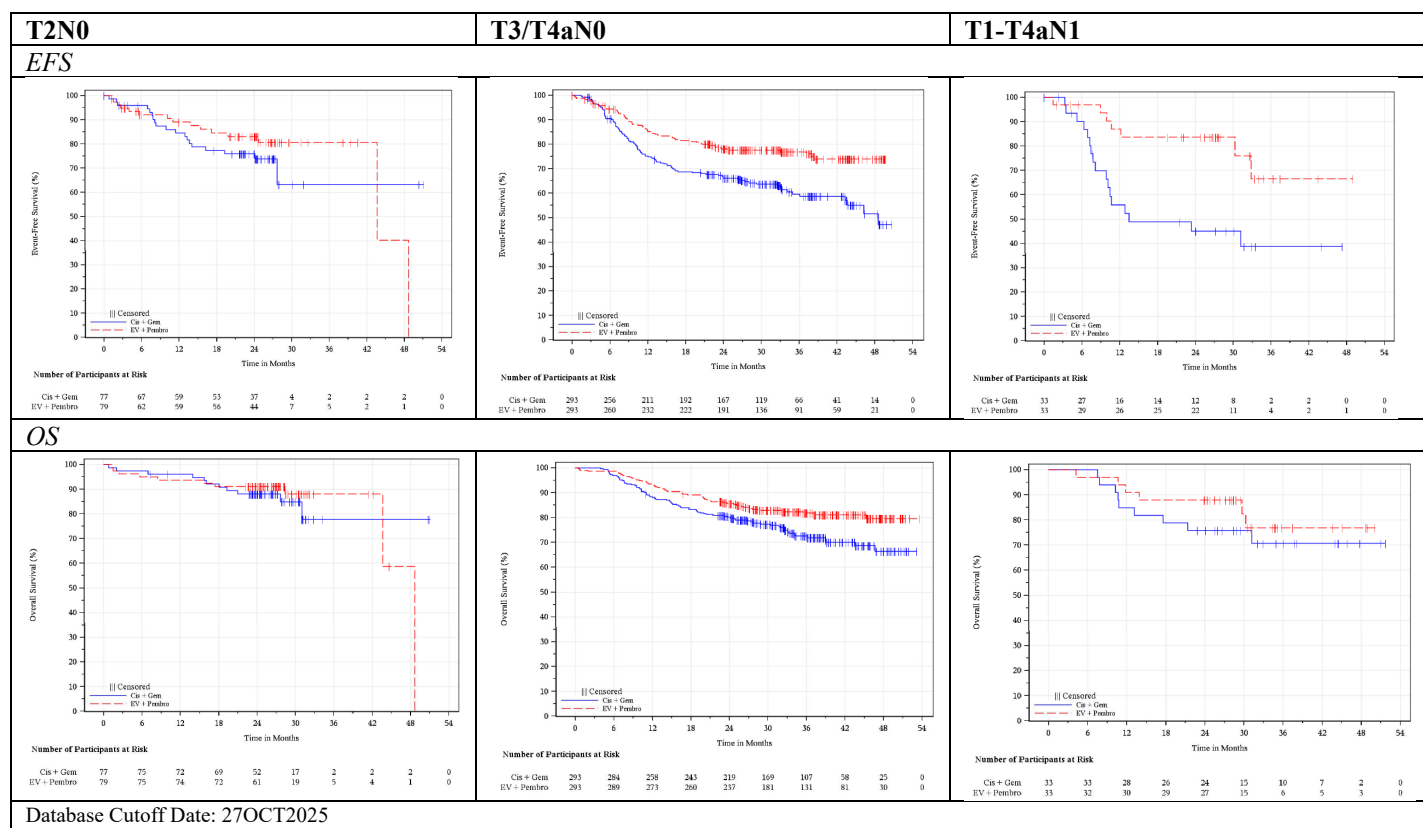
^aFor overall population, analysis is based on stratified Cox regression model with treatment as a covariate. For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate.
If the number of events in a category of a subgroup variable is less than 10, the subgroup analysis will not be performed for this category of the subgroup variable.
Database cutoff date: 27OCT2025

Table 32 Subgroup analysis of Overall Survival (ITT population)

Disease Stage	EV + Pembro		Cis + Gem		EV + Pembro vs Cis + Gem Hazard Ratio ^a (95% CI) ^a
	N	Number of Events (%)	N	Number of Events (%)	
T2N0	79	10 (12.7)	77	11 (14.3)	0.87 (0.37, 2.06)
T3/T4aN0	293	53 (18.1)	293	79 (27.0)	0.63 (0.44, 0.89)
T1-T4aN1	33	6 (18.2)	33	9 (27.3)	0.64 (0.23, 1.81)

^aFor 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 the number of events in a category of a subgroup variable is less than 10, the subgroup analysis will not be performed for this category of the subgroup variable.
Database cutoff date: 27OCT2025

Figure 14 Kaplan-Meier plots of EFS based on BICR and OS by disease stage



Exploratory analysis by Nectin-4

An exploratory analysis was conducted to assess the distribution of Nectin-4 expression in tissue samples collected in KEYNOTE-B15 to further investigate the relationship of Nectin-4 expression with outcomes with perioperative enfortumab vedotin + pembrolizumab compared with neoadjuvant cisplatin + gemcitabine.

The Nectin-4 IHC assay was performed retrospectively on available samples, using a validated IHC assay (for research use only [RUO] using an anti-Nectin-4 antibody [clone M22-321b41.1]) in FFPE tumor tissue at Q2 Solutions. Nectin-4 expression was calculated by estimating the staining intensities of all tumor cells on the slide and the percentage of tumor cells that were positive at a particular intensity, deriving a continuous H-score scale ranging from 0 to 300. The exploratory cutoff H-score values for subgroup analysis were: <150, 150 to <225, ≥225.

Table 33 Participant Characteristics by Nectin-4 H-Score in Tumor Tissue (ITT Population)

	EV + Pembro		Cis + Gem		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	405		403		808	
Nectin4 H Score Total Score						
< 150	43	(10.6)	28	(6.9)	71	(8.8)
150 to < 225	65	(16.0)	84	(20.8)	149	(18.4)
≥ 225	286	(70.6)	132	(32.8)	418	(51.7)
Missing	11	(2.7)	159	(39.5)	170	(21.0)
Participants with data	394		244		638	
Mean	242.9		217.1		233.0	
SD	68.3		65.1		68.2	
Median	265.0		230.0		252.0	
Q1 to Q3	218 to 293		186 to 260		200 to 288	
Range	0 to 300		0 to 300		0 to 300	
SD=Standard deviation; Q1=First quartile, Q3=Third quartile. Missing Nectin-4 data is due to sample adequacy or availability. Database Cutoff Date: 27OCT2025.						

Table 34 Subgroup Analysis of Event-Free Survival Based on BICR Assessment by Nectin-4 H-Score in Tumor Tissue (ITT Population)

	EV + Pembro		Cis + Gem		EV + Pembro vs Cis + Gem Hazard Ratio ^a (95% CI) ^a
	N	Number of Events (%)	N	Number of Events (%)	
Overall	405	87 (21.5)	403	146 (36.2)	0.53 (0.41, 0.70)
Nectin-4 H-score in Tumor Tissue					
< 150	43	11 (25.6)	28	14 (50.0)	0.43 (0.20, 0.96)
150 to < 225	65	14 (21.5)	84	40 (47.6)	0.42 (0.23, 0.78)
≥ 225	286	59 (20.6)	132	47 (35.6)	0.50 (0.34, 0.73)
Missing	11	3 (27.3)	159	45 (28.3)	1.05 (0.32, 3.38)
^a 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. Database cutoff date: 27OCT2025					

Table 35 Subgroup Analysis of Overall Survival by Nectin-4 H-Score in Tumor Tissue (ITT Population)

	EV + Pembro		Cis + Gem		EV + Pembro vs Cis + Gem Hazard Ratio ^a (95% CI) ^a
	N	Number of Events (%)	N	Number of Events (%)	
Overall	405	69 (17.0)	403	99 (24.6)	0.65 (0.48, 0.89)
Nectin-4 H-score in Tumor Tissue					
< 150	43	9 (20.9)	28	10 (35.7)	0.54 (0.22, 1.34)
150 to < 225	65	10 (15.4)	84	30 (35.7)	0.43 (0.21, 0.88)
≥ 225	286	47 (16.4)	132	33 (25.0)	0.59 (0.38, 0.92)
Missing	11	3 (27.3)	159	26 (16.4)	1.96 (0.59, 6.53)
^a 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. Database cutoff date: 27OCT2025					

Table 36 Subgroup Analysis of Pathological Complete Response Based on BICR Assessment by Nectin-4 H-Score in Tumor Tissue (ITT Population)

	EV + Pembro		Cis + Gem		EV + Pembro vs Cis + Gem Rate Difference ^a (95% CI) ^a
	N	Number of Responses (pCR%)	N	Number of Responses (pCR%)	
Overall	405	226 (55.8)	403	131 (32.5)	23.4 (16.7, 29.8)
Nectin-4 H-score in Tumor Tissue					
< 150	43	24 (55.8)	28	7 (25.0)	30.8 (7.2, 50.5)
150 to < 225	65	35 (53.8)	84	26 (31.0)	22.9 (6.9, 37.9)
≥ 225	286	162 (56.6)	132	41 (31.1)	25.6 (15.5, 34.9)
Missing	11	5 (45.5)	159	57 (35.8)	9.6 (-16.1, 37.4)
^a For overall population, analysis is based on stratified Miettinen & Nurminen method. For subgroup analyses, analysis is based on unstratified Miettinen & Nurminen method. Database cutoff date: 27OCT2025					

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 37: Summary of Efficacy for trial

Title: A Phase 3, Randomized, Open-Label Study to Evaluate Perioperative Enfortumab Vedotin Plus Pembrolizumab (MK-3475) Versus Neoadjuvant Gemcitabine and Cisplatin in Cisplatin-Eligible Participants with Muscle-Invasive Bladder Cancer (KEYNOTE-B15 / EV-304)		
Study identifier	KEYNOTE-B15; EV-304; PB15V01MK3475 EudraCT: 2020-003106-31 EU CT: 2023-505615-21-00	
Design	Randomized, active-controlled, parallel-group, multisite, open-label study	
	Duration of main phase:	Approximately 88 months
	Duration of Run-in phase:	Not applicable
	Duration of Extension phase:	Not applicable
Hypothesis	Primary hypothesis: superiority	
Treatment groups	Arm A Perioperative EV + pembrolizumab	4 cycles of neoadjuvant EV 1.25 mg/kg on Days 1 and 8 every 3 weeks (q3w) + 4 cycles of neoadjuvant pembrolizumab 200 mg on Day 1 q3w, followed by RC + PLND, followed by 5 cycles of adjuvant EV 1.25 mg/kg on Days 1 and 8 q3w + 13 cycles of adjuvant pembrolizumab 200 mg on Day 1 q3w
	Arm B Cis + gem	4 cycles of neoadjuvant chemotherapy with cisplatin 70 mg/m ² on Day 1 q3w + gemcitabine 1000 mg/m ² on Days 1 and 8 q3w, followed by RC + PLND

			N=403
Endpoints and definitions	Primary endpoint	Event free survival (EFS) by blinded independent central review (BICR)	<p>EFS, defined as the time from randomization to the first of the following events:</p> <p>Radiographic disease progression precluding a curative-intent surgery as assessed by blinded independent central review (BICR) prior to RC + PLND</p> <p>Failure to undergo surgery for participants with residual muscle-invasive disease and any radiographic disease present, biopsy-proven muscle-invasive bladder cancer (MIBC) will be considered an event regardless of radiographic findings</p> <p>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)</p> <p>Local or distant recurrence post-RC + PLND as assessed by computed tomography (CT) or magnetic resonance imaging (MRI) by BICR and/or biopsy. If biopsy is not feasible due to participant safety, CT/MRI alone will be sufficient</p> <p>Death from any cause</p>
	Key secondary endpoints	Overall survival (OS)	OS, defined as the time from randomization to death due to any cause
		Pathological complete response (pCR)	pCR, defined as absence of viable tumor (pT0N0) in examined tissue from RC + PLND, as assessed by BICR
Database lock	24-NOV-2025; interim analysis 1 (IA1) data cutoff date was 27-OCT-2025		
Results and Analysis			
Analysis description	Primary analysis		
Analysis population and time point description	Intent to treat (ITT): all randomized participants whether or not treatment was administered		
	Time point data cutoff: 27-OCT-2025, study ongoing Interim Analysis 1		
Descriptive statistics and estimate variability	Treatment group	Perioperative EV + pembrolizumab	Cis + gem
	Number of participants	405	403
	Number of events, n (%)	87 (21.5)	146 (36.2)
	Median EFS, months (95% CI)	NR (NR, NR)	48.5 (43.3, NR)
	Hazard ratio:	0.53	

Effect estimate per comparison	95% CI:	0.41, 0.70	
	p-value (1-sided)	<0.0001 (p-value boundary of 0.0082)	
Notes	Abbreviations: CI=confidence interval; NR=not reached		
Analysis description	Key secondary endpoints: OS and pCR		
Analysis population and time point description	ITT: all randomized participants whether or not treatment was administered		
	Treatment group	Perioperative EV + pembrolizumab	Cis + gem
	OS		
Descriptive statistics and estimate variability	Number of participants	405	403
	Number of deaths, n (%)	69 (17.0)	99 (24.6)
	Median OS, months (95% CI)	NR (NR, NR)	NR (NR, NR)
Effect estimates per comparison	Hazard ratio:	0.65	
	95% CI:	0.48, 0.89	
	p-value (1-sided)	0.0029 (p-value boundary of 0.0038)	
	pCR (by BICR)		
Descriptive statistics and estimate variability	Number of responders	226	131
	pCR response rate, % (95% CI)	55.8 (50.8, 60.7)	32.5 (28.0, 37.3)
Effect estimates per comparison	Difference in pCR rate %:	23.4	
	95% CI:	16.7, 29.8	
	p-value (1-sided)	<0.0001 (p-value boundary of 0.001)	
Notes	EFS was statistically significant at IA1. Therefore, key secondary endpoints (OS and pCR) were formally tested according to the multiplicity strategy, and at IA1, OS and pCR were statistically significant. Abbreviations: CI=confidence interval; NR=not reached		

Clinical studies in special populations

Table 38 clinical studies in special populations

	Controlled Studies^a	Noncontrolled Studies
Participants with renal impairment ^b	590/2038	77/121
Age 65-74	936/2038	52/121
Age 75-84	425/2038	30/121
Age ≥85	26/2038	10/121
Other	651/2038	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 KEYNOTE-B15, EV-302, and KEYNOTE-905. Non-controlled studies include EV-103 (dose escalation, Cohort A, and Cohort K).

Source: (KN-B15 CSR: PB15V01MK3475); (EV-302 CSR: PA39V01MK3475); (KN-905 CSR: P905V01MK3475); (EV-103 CSR: P869MK3475)

Supportive study(ies)

The MAH has provided indirect comparison of results across the studies listed below to support for the contribution of each individual component to the overall efficacy of the perioperative enfortumab vedotin + pembrolizumab combination.

Table 39 Supporting Studies

Study Number/Identifier (Status as of Report DCO)	Number of Participants (N)	Study Design	Key Eligibility Criteria	Regimen	Efficacy Endpoints	Efficacy Analysis Population
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 chemotherapy	<u>Primary:</u> PFS by BICR OS <u>Key Secondary:</u> 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 +	1L Cis-IE la/mUC	EV + pembrolizumab or EV	<u>Primary:</u> ORR by BICR <u>Key Secondary:</u> DOR by BICR	FAS (all participants who received ≥1 dose of study medication)

Study Number/Identifier (Status as of Report DCO)	Number of Participants (N)	Study Design	Key Eligibility Criteria	Regimen	Efficacy Endpoints	Efficacy Analysis Population
		pembrolizumab (200 mg IV q3w)				
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	<u>Primary:</u> PFS by BICR OS <u>Key Secondary:</u> 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	<u>Primary:</u> ORR by BICR	APaT (all enrolled participants who received ≥1 dose of pembrolizumab)
MIBC						
KEYNOTE-905 NCT03924895 (ongoing; DCO: 06-JUN-2025)	595	Phase 3 open-label randomized study of perioperative pembrolizumab (200 mg IV q3w) plus RC + PLND and perioperative EV (1.25 mg/kg IV D1, D8 q3w) + pembrolizumab (200 mg IV q3w) with RC + PLND vs. RC + PLND	Cis-IE MIBC	Arm A: Perioperative pembrolizumab vs. Arm B: SOC vs. Arm C: Perioperative EV + pembrolizumab	<u>Primary:</u> EFS by BICR in ITT2 <u>Key Secondary:</u> EFS by BICR in ITT1 pCR by BICR in ITT2 and ITT1 OS in ITT2 and ITT1	ITT2 (all participants randomized to Arm B and Arm C in Stage 2) ITT1 (all participants randomized to Arm A and Arm B in Stages 1 and 2 until Arm

Study Number/Identifier (Status as of Report DCO)	Number of Participants (N)	Study Design	Key Eligibility Criteria	Regimen	Efficacy Endpoints	Efficacy Analysis Population
						A enrollmen t stopped, except in France)
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 UC. 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	<u>Primary:</u> pCR <u>Key</u> <u>Secondary:</u> EFS by BICR EFS by INV	FAS (all participants who received ≥1 dose of study intervention)

1L=first-line; APaT=all participants as treated; BICR=blinded independent central review; cis=cisplatin; cis-E=cisplatin eligible; cis-IE=cisplatin ineligible; D=day; DCO=data cutoff date; DOR=duration of response; EFS=event-free survival; EV=enfortumab vedotin; FAS=full analysis set; gem=gemcitabine; INV=investigator assessment; ITT=intent to treat; IV=intravenous; la=locally advanced; MIBC=muscle-invasive bladder cancer; mUC=(metastatic) urothelial carcinoma; ORR=objective response rate; OS=overall survival; pCR=pathological complete response; PFS=progression-free survival; plat=platinum; q3w=every 3 weeks; PLND=pelvic lymph node dissection; RC=radical cystectomy; SOC=standard of care.

Table 40 Comparison of Efficacy Results Across 1L la/mUC Studies EV-302, EV-103 (Cohort K), KEYNOTE-361, and KEYNOTE-052 Studies (selection)

	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

	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
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)
<p>"+" indicates there is no progressive disease at the minimum and/or maximum follow-up for DOR.</p> <p>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.</p> <p>Source: (EV-302 CSR: PA39V01MK3475); (EV-103 Cohort K: data on file); (KN-361 CSR: P361MK3475); (KN-052 CSR: P052MK3475)</p> <p>DCO Date: 08-AUG-2023 (EV-302); 20-NOV-2024 (EV-103 Cohort K); 15-SEP-2022 (KN-361); 18-FEB-2022 (KN-052)</p>					

Table 41 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 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 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; MIBC=muscle-invasive bladder cancer; 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 enfortumab vedotin in combination with Keytruda for the perioperative treatment of resectable muscle invasive bladder cancer (MIBC) in adults eligible for cisplatin-based chemotherapy, based on the results from the pivotal trial KEYNOTE-B15/EV-304.

Design and conduct of clinical studies

KEYNOTE-B15/ EV-304 is an ongoing Phase 3, randomized, active-controlled, parallel-group, multisite, open-label study comparing perioperative enfortumab vedotin + pembrolizumab with neoadjuvant cisplatin + gemcitabine in participants with muscle invasive bladder cancer (MIBC) and with cT2-T4aN0M0 or cT1-T4aN1M0. All patients should have been eligible to cisplatin, thus the experimental combination has been compared to 4 cycles of neoadjuvant cisplatin + gemcitabine given before radical surgery. In the control arm, participants initially received no adjuvant therapy, although adjuvant nivolumab was allowed if deemed appropriate by the investigator after protocol Amendment 3, implemented one year after starting enrolment due to the approval of such treatment. The control treatment is deemed overall appropriate. Adjuvant nivolumab was used only in 25 patients in the control arm, therefore it is not possible to have a robust characterisation of the specific contribution of adjuvant nivolumab to EFS in the target population, nor to conclude regarding the benefit of perioperative EV + pembrolizumab relative to the current adjuvant standard of care.

The study was open-label; the primary endpoint of event-free survival (EFS) was based on blinded independent central review (BICR) assessment, which is appropriated in an open-label setting to support the objectivity of the primary endpoint evaluation. The EFS definition is considered acceptable from a clinical perspective. EFS definition was clarified with Amendments 04 and 05 specifying that, in case of failure to undergo surgery, biopsy proven MIBC was considered an event regardless of radiographic findings. Biopsy confirmation was systematically required to evaluate residual muscle invasive disease in the bladder, and this clarification did not result in the reclassification of EFS events relative to prior versions of the protocol.

In Amendment 3, pCR was downgraded from primary to key secondary endpoint. This is clinically acceptable, as relationship with long-term outcomes such as EFS and OS has not been sufficiently validated in MIBC, further pCR is relevant only for the neoadjuvant part of the treatment.

Overall, the methods have been chosen appropriately with respect to the study objectives, and modifications introduced during the duration of the study were appropriately justified and are not considered critical.

Survival endpoints(RFS and OS) were planned to be analysed using Kaplan-Maier curves and log-rank test, while pCR was planned to be analysed using the Miettinen and Nurmien method. This is in principle agreeable. However, overlapping/crossing of the EFS and OS curves was observed within the first six months; in the same time frame, a high number of censoring events was observed. The early censoring was justified according to the censoring rules for participants who did not undergo surgery and did not experience an event and is further discussed below. A requested restricted mean survival time (RMST) analysis was conducted for both EFS and OS. The analysis consistently showed that, while the EFS curves separate early (Month 12) and decisively, the separation for OS doesn't happen until much later (Month 30) and remains numerically modest. This is aligned with the results of the primary analyses.

No estimands were originally defined in the trial, although the primary estimand for EFS was provided post-hoc during the assessment. Several scenarios for participants who did not undergo surgery ("refused or were unable to") were presented, including for scenarios in which the

neoadjuvant therapy successfully reduced the tumor ("No MIBC, no locally advanced disease, no distant PD or no death, whether or not new anticancer therapy is initiated"). Participants undergoing this scenario were "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)". The rationale for the 16 weeks was clarified by the MAH, i.e. to avoid attributing favorable long-term outcomes to participants who may have declined surgery due to an absence of detectable disease following neoadjuvant treatment (the 16-week window reflects the time when participants would have had surgery). Additional sensitivity analyses confirmed the results of the study.

Three interim analyses (IAs) and one final analysis (FA) were planned. Each IA was scheduled to take place only after at least 75% of the expected EFS events had occurred, all participants had the opportunity to undergo RC+PLND, and the last participant had been randomized for a minimum of 18 months. These requirements ensured sufficient maturity of the EFS data at each analysis and minimized the risk that the interim results could influence the conduct or design of the ongoing study. Statistical boundaries were established using a Lan-DeMets alpha-spending function and were adjusted according to the observed information fraction, which is considered appropriate.

The study underwent five protocol amendments. The most substantial amendment, where study design and SAP were adjusted was amendment 3 (reported above). In Amendment 05, the MAH states that follow-up time was increased; this increase was due to a slower than expected accrual time and impacted on the timing of the EFS and OS analyses, but not on the number of events needed for each IA and FA. Overall, the protocol amendments are acceptable and should not affect the study integrity and reliability of the results. There were several important protocol deviations, which were fairly balanced between the arms [in 47 (11.6%) vs. 38 (9.4%) patients in arms A and B, respectively] and mostly related to a safety event not being reported per the timelines outlined in the protocol. The important protocol deviations related to COVID-19 pandemic were infrequent in both treatment arms of the KEYNOTE-B15/EV-304. The number and character of the important protocol deviations do not give rise to concerns about a potential impact on the study data.

Baseline characteristics: A total of 1225 patients were screened and 808 randomized in the experimental (n=405) and control (n=403) arm, stratified by region, stage and PD-L1 status.

The demographic and clinical characteristics of the patients at baseline were generally balanced in both arms of study KEYNOTE-B15/EV-304 and are considered representative of the overall patient population with resectable MIBC eligible for cisplatin-containing chemotherapy in Europe. The median age was 66 years, with range of 35 to 83. The majority of patients were men (81%), white (77%) and had an ECOG performance status of 0 (77.6%). Tumours expressing PD-L1 with a CPS ≥ 10 were observed in 57.3% of patients. Most patients had T3/T4aN0 disease (72.5%), while 8.2% had T1-4aN1 disease. "Pure" urothelial carcinoma histology was present in 89.5% of tumours. Patients were primarily enrolled in the EU (50.9%) and most of the world (34.5%), with 14.6% enrolled in the US.

Patient's disposition and study conduct.

Most of the patients who started neoadjuvant treatment completed the planned 4 cycles (85.4% vs 88.9%), although there were more discontinuations in the experimental arm due to adverse event (12.2% in the EV + pembrolizumab group and 7.8% in the cis + gem group). Overall, fewer patients (351 vs 361) participants in the perioperative EV + pembrolizumab group vs in the cis + gem group underwent surgery (including 2 participants who did not receive neoadjuvant study medication), while more patients did not undergo surgery after neoadjuvant treatment (52 vs 37 participants, 13% vs 9%), in the experimental arm. The analysis of detailed reasons for not

undergoing surgery did not suggest bias due to the open-label design in terms of physician/patient's decision. Compared with the control arm, fewer patients in the experimental arm did not proceed to surgery due to disease progression (11.1% vs 14.3%). However, more patients did not proceed to surgery due to AE (24.1% vs 14.3%), confirming the toxicity of the EV + pembrolizumab combination. Surgical resection was complete in almost all patients, and the type of surgical procedure was similar in both treatment arms. Surgery was more frequently delayed due to AE in the pembrolizumab + EV arm, however the median time from randomization to surgery and from the end of neoadjuvant treatment to surgery was comparable between arms.

In the pembrolizumab +EV arm, 262 out of 351 patients (i.e. 75% of the total) who underwent surgery received adjuvant treatment. The remaining 89 patients (25%) did not proceed to adjuvant treatment (89/351), being adverse event, the most common reason followed by participant's withdrawal. Most of the patients starting adjuvant treatment were however able to complete the planned treatment with AE again the most common reason for discontinuation (13%). Overall, data reflects the toxicity of the combination and the need for careful patient selection, as the perioperative EV+pembro regimen appears to be more toxic (higher rates of discontinuation due to AE at any study phase; see safety discussion) than neoadjuvant cis+gem followed by surgery.

Regarding post-study treatments, more patients received following therapies considering all settings in the control arm, as expected (15.8% vs 31.8%).

Efficacy data and additional analyses

Primary endpoint: At the IA1, median survival follow-up was 30.8 months (range 0.5, 53.6). No patients were still under active treatment. At this timepoint, EFS events occurred in 21.5% vs 36.2% of the population in the experimental vs control arm. The study demonstrated a statistically significant improvement in **EFS by BICR**: HR 0.53, 95%CI 0.41, 0.70, $p < 0.0001$. KM curves were almost overlapping during the first 6 months including several censorings in both arms, then started to separate: the improvement in EFS rate is approximately 10% at month 12 (86% vs 75.4%), and 13% at month 18 (82.2 vs 68.8%), and is maintained long-term, acknowledging that curves are still highly censored afterwards. Median EFS is reached only in the control arm, but this data is not yet interpretable. Pre-specified EFS sensitivity analyses and EFS by investigator assessment were consistent with the primary EFS analysis by BICR.

Secondary endpoints: since the EFS null hypothesis was rejected, **OS** was formally tested at IA1 showing a statistically significant survival advantage for the perioperative pembrolizumab + EV vs neoadjuvant cisplatin-based chemotherapy. With 17% vs 24.6% of OS events, HR was 0.65 (95%CI 0.48, 0.89), $p = 0.0029$. KM curves separated after month 6 and remained separated afterwards, although highly censored from month 20. Medians were not reached in either arm, but approximately 5% increase in OS rate is observed (i.e. OS rate at month 12: 93.1% vs 89.6%; OS rate at 18 months 89.4% vs 84.5%). In the initial part of the OS curve however, more deaths were observed in the perioperative EV + pembrolizumab group compared with the cis + gem group (8 vs 4) during the first 5 months post-randomization. However, the small numbers of death events in this timeframe precludes to draw definitive conclusions about the possible risk factors of early deaths in the pembrolizumab + EV arm. The interim OS results are considered promising; however their interpretation is limited by the low data maturity (~21%). The final OS results are expected to be submitted post-authorization to further characterise the efficacy in this early setting (**REC**).

pCR was also formally tested per multiplicity strategy, showing a statistically significant 23.4% (95%CI 16.7-29.8, $p < 0.0001$) improvement for pembrolizumab+EV over standard cis+gem

(55.8% vs 32.5%). The absolute pCR rate was similar to the pCR of 57.1% achieved after neoadjuvant pembrolizumab+EV in the cisplatin-ineligible population of KEYNOTE-905 (EMA/VR/0000312515). Consistently, **pathological downstaging** was in favour of the pembrolizumab+EV neoadjuvant treatment (63.7% vs 45.2%).

DFS based on BICR evaluating the risk of local or distant recurrence or death in patients who were disease free after surgery (339 vs 330) was also in favour of the pembrolizumab+EV arm (HR 0.50 (95% CI: 0.36, 0.70), thus supporting the overall result.

The **patient-reported outcomes** did not suggest meaningful differences in the endpoints analysed.

A prespecified exploratory analysis of EFS by pCR outcome was provided, however, as this is based on post-randomization outcomes, the results need to be interpreted with caution.

Subgroup analyses: subgroup analyses suggested consistent benefit of perioperative pembrolizumab + EV vs neoadjuvant cis-gem across prespecified subgroups. In patients with lower disease stage T2N0 and expected better prognosis (19.3% of the ITT population), the advantage in EFS and OS appears more limited [OS HR 0.87 (0.37, 2.06); EFS HR 0.76 (0.39, 1.51)] compared to higher disease stages, however T2N0 subgroup is small with few OS events occurring: considering that HRs are <1, and CIs are large, the overall data do not justify an exclusion of those patients from the indication. Results of subgroup analyses are included in the EPAR.

Regarding molecular biomarkers, consistent results are observed in patients with **PD-L1** expression CPS <10 and CPS ≥10. Results in the CPS <1 subgroup need to be interpreted with caution due to the exploratory nature of the analysis, the small sample size of this subset (32 vs 30) and the lack of a clear trend in all endpoints.

The potential significance of Nectin-4 expression was evaluated as an exploratory endpoint using leftover tissue samples from 638 out of 808 patients, following assessment of PDL-1 expression and histological confirmation. The mean Nectin-4 H score was 233 (SD 68.2) across both treatment arms, and most patients had a score of 225 or higher, although there was an imbalance between the two treatment arms. The results showed that Nectin-4 expression did not impact EFS, OS, or the ability to achieve a pathological complete response, suggesting no correlation between Nectin-4 expression and the likelihood of responding to perioperative treatment with EV+pembro.

Contribution of components (CoC): The study design does not allow to formally evaluate the contribution of each component (EV and pembrolizumab) of the combination, as well as the contribution of each phase of treatment (neoadjuvant and adjuvant). Nonetheless, the combination of EV and pembrolizumab from the metastatic setting and the clear superiority of the combination shown in KEYNOTE-B15 study attenuates the concern around the individual contribution of each component.

Wording of indication

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

During the procedure, the indication for muscle-invasive bladder cancer was editorially revised to refer to adults with muscle-invasive bladder cancer irrespective of cisplatin eligibility, reflecting the combined evidence from KEYNOTE-905 (cisplatin-ineligible patients; EC-approved under EMA/VR/0000312515) and KEYNOTE-B15 (cisplatin-eligible patients; the current procedure). This revision consolidated the cisplatin-ineligible population and the cisplatin-eligible population into a

single cisplatin agnostic indication. The distinction between the two indications (cisplatin ineligible vs eligible) is maintained in the instructions for duration of therapy in section 4.2 of the SmPC since there is a difference in the number of neoadjuvant and adjuvant treatment cycles for the two indications (cisplatin-ineligible vs cisplatin-eligible) based on the two pivotal studies KEYNOTE-905 and KEYNOTE-B15. Furthermore, these studies are discussed separately in section 5.1. In conclusion, the proposed wording of the indication is acceptable.

The final agreed indication wording was updated as:

Padcev, in combination with pembrolizumab, as neoadjuvant treatment and then continued after radical cystectomy as adjuvant treatment, is indicated for the treatment of adults with resectable muscle invasive bladder cancer (MIBC).

2.4.4. Conclusions on the clinical efficacy

The **KEYNOTE-B15/EV-304** study met its primary and key secondary endpoints, showing a statistically significant and clinically meaningful improvement in EFS and OS with perioperative enfortumab-vedotin in combination with pembrolizumab, administered as neoadjuvant treatment followed by adjuvant treatment after radical cystectomy in patients with resectable MIBC, who are eligible for neoadjuvant cisplatin.

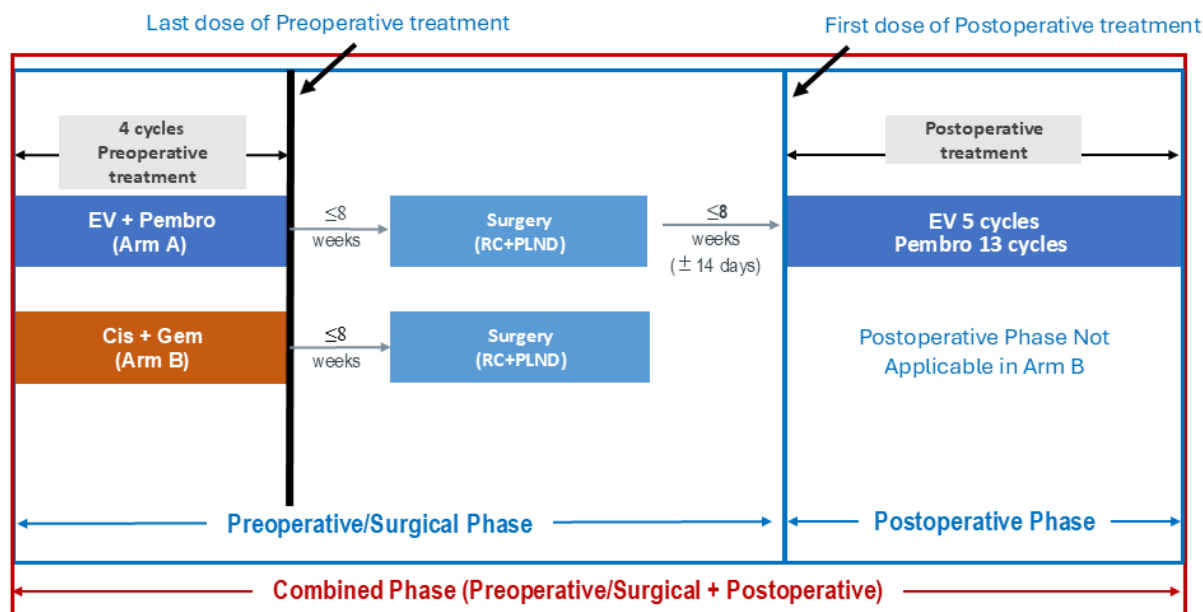
Although the results are based on the first interim analysis, more mature data are not considered needed for the present assessment, however as this is an early curative setting, final OS study results are expected to be submitted post-approval to further characterise the efficacy **(REC)**.

2.5. Clinical safety

Introduction

The safety evaluation of neoadjuvant and adjuvant EV + pembrolizumab in patients with cisplatin-eligible MIBC is based on data from the KEYNOTE-B15 study. Safety analyses were conducted using the APaT population, which included all randomized participants who received at least 1 dose of study treatment as of the DCO 27-OCT-2025 and were analyzed according to the study treatment that they received.

Safety Analysis Phases Schematic Diagram



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

Note: Arm A (perioperative EV + pembrolizumab) includes neoadjuvant and adjuvant treatment with enfortumab vedotin and pembrolizumab and the Surgical Phase. Arm B (cis + gem) includes only neoadjuvant treatment with cis + gem and the surgical phase.

Reference safety data from studies of enfortumab vedotin or pembrolizumab monotherapies are included to enable a comparison of the safety data of enfortumab vedotin in combination with pembrolizumab to the established safety profiles of the respective monotherapies.

Table 42 Summary of Clinical Safety Datasets and Nomenclature

Dataset	Population	Nomenclature in Tables	Nomenclature in Text
KEYNOTE-B15 perioperative enfortumab vedotin plus pembrolizumab	(N=403) Safety data from participants with cisplatin-eligible MIBC in KEYNOTE-B15 with previously untreated MIBC receiving neoadjuvant pembrolizumab + enfortumab vedotin, followed by RC + PLND, followed by adjuvant pembrolizumab + enfortumab vedotin	KN-B15 EV + Pembro	Perioperative EV + pembrolizumab group
KEYNOTE-B15 preoperative cisplatin + gemcitabine	(N=396) Safety data from participants with cisplatin-eligible MIBC in KEYNOTE-B15 receiving neoadjuvant cisplatin plus gemcitabine, followed by RC + PLND	KN-B15 Cis + Gem	cis + gem group
Enfortumab vedotin in combination with pembrolizumab 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/KEYNOTE-869 Cohorts K, A and dose escalation, and EV-302/KEYNOTE-A39	EV + Pembro Combo ISD	EV + pembrolizumab ISD ^a
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/KEYNOTE-869 Cohort K EV monotherapy	EV Mono ISD	EV mono ISD ^a

	arm, EV-201, EV-203, and EV-301		
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; 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 ^a
<p>CRC=colorectal carcinoma; EV=enfortumab vedotin; HL=Hodgkin lymphoma; HNSCC=head and neck squamous cell carcinoma; ISD=integrated safety dataset; 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; UC=urothelial carcinoma</p> <p>^a The list of studies and database cutoff dates for the EV + pembrolizumab ISD, EV mono ISD, and pembrolizumab RSD are provided in [Error! Reference source not found.] [Error! Reference source not found.] [Error! Reference source not found.]</p>			

Patient exposure

At DCO (27-OCT-2025) 403 participants received at least 1 dose of perioperative EV + pembrolizumab and 396 participants received at least 1 dose of cis + gem in KEYNOTE-B15. The last dose of study treatment was administered on 08-MAY-2025, thus all participants were off study treatment at the time of DCO.

The dosing regimen in KEYNOTE-B15 was as follows:

Treatment Arm 1: Neoadjuvant enfortumab vedotin 1.25 mg/kg on Days 1 and 8 q3w for 4 cycles + pembrolizumab 200 mg IV q3w for 4 cycles + RC + PLND + adjuvant 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: Neoadjuvant cisplatin 70 mg/m² on Day 1 q3w for 4 cycles + gemcitabine 1000 mg/m² on Days 1 and 8 + RC + PLND

Table 43 Summary of drug exposure

	KN-B15 EV + Pembro (N=403)	KN-B15 Cis + Gem (N=396)	EV + Pembro Combo ISD (N=564)	EV Mono ISD (N=793)	Pembro Mono RSD (N=7631)
Duration On Treatment (months)^a					
n	403	396	564	793	7631
Mean (SD)	9.5 (5.4)	3.6 (1.3)	12.3 (9.4)	6.8 (7.7)	7.9 (6.9)
Median	10.2	3.5	9.4	4.7	5.8
Range	0.03 to 25.5	0.03 to 16.8	0.3 to 45.9	0.3 to 65.4	0.03 to 38.0
Number of Cycles^b					
n	403	396	564	NA	7631
Mean (SD)	10.4 (6.2)	3.8 (0.6)	16.2 (12.6)		12.3 (10.1)
Median	10.0	4.0	12.0		9.0
Range	1.0 to 17.0	1.0 to 4.0	1.0 to 54.0		1.0 to 59.0
^a Duration on Treatment (months): For KN-B15 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). For KN-B15, treatment includes study medications and surgery. Database cutoff date for KN-B15: 27OCT2025.					

Table 44 Drug exposure by duration for EV

	KN-B15 EV + Pembro (N=403)	EV + Pembro Combo ISD (N=564)
Number of Cycles		
n	403	564
Mean (SD)	6.1 (2.8)	12.5 (10.5)
Median	6.0	9.0
Range	1.0 to 9.0	1.0 to 54.0
Each participant is counted once on each applicable cycle category row. Number of dosing cycles are not summarized for 'EV Mono ISS' due to different number of days per cycle (i.e., 21 days per cycle in EV-103/EV-302, 28 days per cycle in the other studies). Database cutoff date for KN-B15: 27OCT2025.		

Table 45 Drug exposure by duration for pembrolizumab

	KN-B15 EV + Pembro (N=403)	EV + Pembro Combo ISD (N=564)	Pembro Mono RSD (N=7631)
Number of Cycles			
n	403	564	7631
Mean (SD)	10.1 (6.4)	14.7 (11.8)	12.3 (10.1)
Median	10.0	10.0	9.0
Range	1.0 to 17.0	1.0 to 35.0	1.0 to 59.0
Each participant is counted once on each applicable cycle category row. Database cutoff date for KN-B15: 27OCT2025.			

Table 46 Exposure by duration (Combined Phases – Preoperative/Surgical + Postoperative)

	EV + Pembro (N=403)		Cis + Gem (N=396)	
	n	Person-years	n	Person-years
Duration of Exposure				
> 0 m	403	317.6	396	119.9
≥ 1 m	394	317.2	390	119.7
≥ 3 m	338	306.4	333	107.8
≥ 6 m	263	281.4	6	4.9
≥ 9 m	220	254.3	2	2.8
≥ 12 m	188	227.4	2	2.8
≥ 15 m	49	67.9	2	2.8
Each participant is counted once on each applicable duration category row. Duration on exposure is calculated as the last treatment date – the first treatment date +1. Treatment includes study medications and surgery. The duration of exposure in person time is calculated as the total of all individual participant duration values in days divided by days per year (1 Year = 365.24 Days). 1 Month = 30.4367 Days Database Cutoff Date: 27OCT2025.				

Adverse events

AEs in KEYNOTE-B15 were coded using MedDRA (version 28.1) and reported according to NCI CTCAE version 5.0.

Table 47 Adverse Event Summary (APaT Population)

	KN-B15 EV + Pembro		KN-B15 Cis + Gem		EV + Pembro Combo ISD		EV Mono ISD		Pembro Mono RSD	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	403		396		564		793		7,631	
with one or more adverse events	395	(98.0)	389	(98.2)	563	(99.8)	786	(99.1)	7,375	(96.6)
with no adverse event	8	(2.0)	7	(1.8)	1	(0.2)	7	(0.9)	256	(3.4)
with drug-related ^a adverse events	388	(96.3)	372	(93.9)	550	(97.5)	747	(94.2)	5,462	(71.6)
with toxicity grade 3-5 adverse events	305	(75.7)	266	(67.2)	435	(77.1)	565	(71.2)	3,514	(46.0)
with toxicity grade 3-5 drug-related adverse events	187	(46.4)	184	(46.5)	329	(58.3)	404	(50.9)	1,208	(15.8)
with serious adverse events	255	(63.3)	190	(48.0)	295	(52.3)	363	(45.8)	2,742	(35.9)
with serious drug-related adverse events	95	(23.6)	42	(10.6)	155	(27.5)	162	(20.4)	840	(11.0)
who died	17	(4.2)	11	(2.8)	30	(5.3)	56	(7.1)	346	(4.5)
who died due to a drug-related adverse event	2	(0.5)	1	(0.3)	9	(1.6)	17	(2.1)	42	(0.6)
discontinued any drug due to an adverse event	172	(42.7)	62	(15.7)	279	(49.5)	168	(21.2)	1,066	(14.0)
discontinued Pembrolizumab	133	(33.0)	NA		177	(31.4)	NA		1,066	(14.0)
discontinued EV	126	(31.3)	NA		238	(42.2)	168	(21.2)	NA	
discontinued any drug due to a drug-related adverse event	142	(35.2)	44	(11.1)	252	(44.7)	120	(15.1)	639	(8.4)
discontinued Pembrolizumab	105	(26.1)	NA		148	(26.2)	NA		639	(8.4)
discontinued EV	99	(24.6)	NA		209	(37.1)	120	(15.1)	NA	
discontinued any drug due to a serious adverse event	87	(21.6)	20	(5.1)	84	(14.9)	80	(10.1)	714	(9.4)
discontinued Pembrolizumab	79	(19.6)	NA		82	(14.5)	NA		714	(9.4)
discontinued EV	61	(15.1)	NA		59	(10.5)	80	(10.1)	NA	
discontinued any drug due to a serious drug-related adverse event	60	(14.9)	7	(1.8)	62	(11.0)	45	(5.7)	347	(4.5)
discontinued Pembrolizumab	55	(13.6)	NA		60	(10.6)	NA		347	(4.5)
discontinued EV										

^a Determined by the investigator to be related to the drug.

For KN-B15, treatment includes study medications and surgery.
For KN-B15, 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.
For KN-B15, grades are based on NCI CTCAE version 5.0.
Database cutoff date for KN-B15: 27OCT2025.
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 48 Participants with Adve

rse Events by Decreasing Frequency of Preferred Term (Incidence ≥ 10% in One or More Treatment Groups) (APaT Population)

	KN-B15 EV + Pembro		KN-B15 Cis + Gem		EV + Pembro Combo ISD		EV Mono ISD		Pembro Mono RSD	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	403		396		564		793		7,631	
with one or more adverse events	395	(98.0)	389	(98.2)	563	(99.8)	786	(99.1)	7,375	(96.6)
with no adverse events	8	(2.0)	7	(1.8)	1	(0.2)	7	(0.9)	256	(3.4)
Pruritus	186	(46.2)	18	(4.5)	236	(41.8)	265	(33.4)	1,435	(18.8)
Diarrhoea	137	(34.0)	65	(16.4)	227	(40.2)	310	(39.1)	1,678	(22.0)
Alopecia	127	(31.5)	44	(11.1)	217	(38.5)	378	(47.7)	118	(1.5)
Anaemia	126	(31.3)	223	(56.3)	153	(27.1)	232	(29.3)	982	(12.9)
Decreased appetite	115	(28.5)	72	(18.2)	195	(34.6)	374	(47.2)	1,312	(17.2)
Nausea	114	(28.3)	185	(46.7)	166	(29.4)	300	(37.8)	1,534	(20.1)
Fatigue	111	(27.5)	111	(28.0)	232	(41.1)	371	(46.8)	2,368	(31.0)
Constipation	107	(26.6)	147	(37.1)	158	(28.0)	229	(28.9)	1,179	(15.5)
Rash	101	(25.1)	11	(2.8)	16	(2.8)	92	(11.6)	1,175	(15.4)
Urinary tract infection	101	(25.1)	84	(21.2)	131	(23.2)	125	(15.8)	511	(6.7)
Dysgeusia	100	(24.8)	37	(9.3)	138	(24.5)	241	(30.4)	150	(2.0)
Aspartate aminotransferase increased	98	(24.3)	20	(5.1)	91	(16.1)	136	(17.2)	538	(7.1)
Alanine aminotransferase increased	97	(24.1)	39	(9.8)	98	(17.4)	102	(12.9)	572	(7.5)
Asthenia	92	(22.8)	94	(23.7)	99	(17.6)	82	(10.3)	880	(11.5)
Weight decreased	87	(21.6)	25	(6.3)	210	(37.2)	200	(25.2)	628	(8.2)
Rash maculo-papular	83	(20.6)	14	(3.5)	204	(36.2)	187	(23.6)	295	(3.9)
Neuropathy peripheral	69	(17.1)	12	(3.0)	0	(0.0)	33	(4.2)	146	(1.9)
Hyperglycaemia	60	(14.9)	22	(5.6)	95	(16.8)	118	(14.9)	360	(4.7)
Neutropenia	59	(14.6)	218	(55.1)	61	(10.8)	60	(7.6)	82	(1.1)
Pyrexia	59	(14.6)	40	(10.1)	104	(18.4)	148	(18.7)	934	(12.2)

Peripheral sensory neuropathy	55	(13.6)	15	(3.8)	308	(54.6)	305	(38.5)	83	(1.1)
Dry skin	54	(13.4)	7	(1.8)	103	(18.3)	173	(21.8)	394	(5.2)
	KN-B15 EV + Pembro		KN-B15 Cis + Gem		EV + Pembro Combo ISD		EV Mono ISD		Pembro Mono RSD	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Vomiting	54	(13.4)	54	(13.6)	81	(14.4)	148	(18.7)	945	(12.4)
Prostate cancer	53	(13.2)	48	(12.1)	1	(0.2)	0	(0.0)	5	(0.1)
Blood creatinine increased	50	(12.4)	73	(18.4)	51	(9.0)	83	(10.5)	358	(4.7)
Hypothyroidism	48	(11.9)	3	(0.8)	65	(11.5)	7	(0.9)	937	(12.3)
Insomnia	47	(11.7)	28	(7.1)	62	(11.0)	101	(12.7)	528	(6.9)
Abdominal pain	43	(10.7)	27	(6.8)	72	(12.8)	122	(15.4)	671	(8.8)
Lacrimation increased	43	(10.7)	0	(0.0)	57	(10.1)	109	(13.7)	55	(0.7)
COVID-19	40	(9.9)	21	(5.3)	76	(13.5)	14	(1.8)	6	(0.1)
Dry eye	40	(9.9)	4	(1.0)	82	(14.5)	101	(12.7)	142	(1.9)
Hypokalaemia	39	(9.7)	36	(9.1)	57	(10.1)	88	(11.1)	324	(4.2)
Cough	36	(8.9)	13	(3.3)	76	(13.5)	104	(13.1)	1,392	(18.2)
Haematuria	36	(8.9)	29	(7.3)	82	(14.5)	101	(12.7)	189	(2.5)
Arthralgia	35	(8.7)	15	(3.8)	99	(17.6)	95	(12.0)	1,449	(19.0)
Back pain	27	(6.7)	11	(2.8)	75	(13.3)	91	(11.5)	847	(11.1)
Oedema peripheral	27	(6.7)	18	(4.5)	98	(17.4)	138	(17.4)	630	(8.3)
Hyponatraemia	26	(6.5)	26	(6.6)	57	(10.1)	90	(11.3)	387	(5.1)
Dyspnoea	24	(6.0)	13	(3.3)	86	(15.2)	102	(12.9)	1,130	(14.8)
Headache	23	(5.7)	27	(6.8)	47	(8.3)	49	(6.2)	946	(12.4)
Dry mouth	22	(5.5)	6	(1.5)	60	(10.6)	65	(8.2)	388	(5.1)
Dizziness	17	(4.2)	25	(6.3)	66	(11.7)	92	(11.6)	564	(7.4)
Hypomagnesaemia	13	(3.2)	41	(10.4)	28	(5.0)	68	(8.6)	184	(2.4)
Leukopenia	13	(3.2)	75	(18.9)	20	(3.5)	9	(1.1)	52	(0.7)
Rash macular	10	(2.5)	0	(0.0)	64	(11.3)	21	(2.6)	49	(0.6)
Thrombocytopenia										
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 KN-B15, treatment includes study medications and surgery.										
For KN-B15, 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.										
Database cutoff date for KN-B15: 27OCT2025.										

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.

2.5.1. Grade ≥ 3 adverse events

Table 49 Particip

ants With Grade 3-5 Adverse Events by Decreasing Frequency of Preferred Term (Incidence $\geq 1\%$ in One or More Treatment Groups) (APaT Population)

	KN-B15 EV + Pembro		KN-B15 Cis + Gem		EV + Pembro Combo ISD		EV Mono ISD		Pembro Mono RSD	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	403		396		564		793		7,631	
with one or more adverse events	305	(75.7)	266	(67.2)	435	(77.1)	565	(71.2)	3,514	(46.0)
with no adverse events	98	(24.3)	130	(32.8)	129	(22.9)	228	(28.8)	4,117	(54.0)
Urinary tract infection	40	(9.9)	38	(9.6)	38	(6.7)	38	(4.8)	85	(1.1)
Neutropenia	30	(7.4)	131	(33.1)	36	(6.4)	46	(5.8)	21	(0.3)
Anaemia	26	(6.5)	61	(15.4)	52	(9.2)	77	(9.7)	275	(3.6)
Hyperglycaemia	19	(4.7)	1	(0.3)	45	(8.0)	58	(7.3)	83	(1.1)
Rash maculo-papular	19	(4.7)	0	(0.0)	54	(9.6)	43	(5.4)	23	(0.3)
Alanine aminotransferase increased	18	(4.5)	0	(0.0)	13	(2.3)	7	(0.9)	97	(1.3)
Sepsis	18	(4.5)	12	(3.0)	15	(2.7)	24	(3.0)	60	(0.8)
Urosepsis	18	(4.5)	12	(3.0)	9	(1.6)	4	(0.5)	25	(0.3)
Acute kidney injury	16	(4.0)	10	(2.5)	34	(6.0)	36	(4.5)	65	(0.9)
Rash	15	(3.7)	1	(0.3)	1	(0.2)	13	(1.6)	44	(0.6)
Pruritus	13	(3.2)	0	(0.0)	10	(1.8)	14	(1.8)	16	(0.2)
Aspartate aminotransferase increased	12	(3.0)	0	(0.0)	10	(1.8)	13	(1.6)	95	(1.2)
Hypertension	11	(2.7)	7	(1.8)	11	(2.0)	22	(2.8)	148	(1.9)
Pneumonia	10	(2.5)	7	(1.8)	15	(2.7)	34	(4.3)	270	(3.5)
Weight decreased	10	(2.5)	1	(0.3)	22	(3.9)	7	(0.9)	35	(0.5)
Diarrhoea	9	(2.2)	4	(1.0)	30	(5.3)	36	(4.5)	114	(1.5)
Gamma-glutamyltransferase increased	8	(2.0)	1	(0.3)	5	(0.9)	8	(1.0)	56	(0.7)
Hepatitis	8	(2.0)	0	(0.0)	3	(0.5)	0	(0.0)	23	(0.3)
Hydronephrosis	8	(2.0)	7	(1.8)	4	(0.7)	4	(0.5)	11	(0.1)
Lipase increased	8	(2.0)	1	(0.3)	24	(4.3)	24	(3.0)	34	(0.4)
Pneumonitis	8	(2.0)	0	(0.0)	13	(2.3)	3	(0.4)	97	(1.3)
Hyponatraemia	7	(1.7)	1	(0.3)	30	(5.3)	47	(5.9)	169	(2.2)

Intestinal obstruction	7	(1.7)	1	(0.3)	2	(0.4)	1	(0.1)	20	(0.3)
Pulmonary embolism	7	(1.7)	7	(1.8)	18	(3.2)	11	(1.4)	101	(1.3)
Pyelonephritis	7	(1.7)	11	(2.8)	5	(0.9)	3	(0.4)	9	(0.1)
Wound dehiscence	7	(1.7)	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.0)
Fatigue	6	(1.5)	3	(0.8)	32	(5.7)	59	(7.4)	166	(2.2)
Haematuria	6	(1.5)	2	(0.5)	16	(2.8)	17	(2.1)	19	(0.2)
Ileus	6	(1.5)	2	(0.5)	0	(0.0)	2	(0.3)	13	(0.2)
Neuropathy peripheral	6	(1.5)	1	(0.3)	0	(0.0)	2	(0.3)	4	(0.1)
Pyelonephritis acute	6	(1.5)	4	(1.0)	3	(0.5)	1	(0.1)	4	(0.1)
Urinary tract obstruction	6	(1.5)	2	(0.5)	5	(0.9)	6	(0.8)	12	(0.2)
Urticaria	6	(1.5)	0	(0.0)	0	(0.0)	2	(0.3)	4	(0.1)
Abdominal pain	5	(1.2)	1	(0.3)	8	(1.4)	8	(1.0)	65	(0.9)
Asthenia	5	(1.2)	6	(1.5)	12	(2.1)	16	(2.0)	70	(0.9)
Diabetes mellitus	5	(1.2)	0	(0.0)	6	(1.1)	6	(0.8)	12	(0.2)
Peritonitis	5	(1.2)	2	(0.5)	0	(0.0)	0	(0.0)	3	(0.0)
Prostate cancer	5	(1.2)	1	(0.3)	0	(0.0)	0	(0.0)	3	(0.0)
Small intestinal obstruction	5	(1.2)	2	(0.5)	2	(0.4)	7	(0.9)	17	(0.2)
Colitis	4	(1.0)	1	(0.3)	7	(1.2)	8	(1.0)	74	(1.0)
Decreased appetite	4	(1.0)	2	(0.5)	9	(1.6)	31	(3.9)	77	(1.0)
Dehydration	4	(1.0)	1	(0.3)	7	(1.2)	15	(1.9)	70	(0.9)
Dry skin	4	(1.0)	0	(0.0)	2	(0.4)	1	(0.1)	0	(0.0)
Hyperkalaemia	4	(1.0)	6	(1.5)	1	(0.2)	8	(1.0)	30	(0.4)
Kidney infection	4	(1.0)	4	(1.0)	3	(0.5)	3	(0.4)	2	(0.0)
Leukocytosis	4	(1.0)	0	(0.0)	2	(0.4)	2	(0.3)	16	(0.2)
Nausea	4	(1.0)	2	(0.5)	8	(1.4)	14	(1.8)	58	(0.8)
Stevens-Johnson syndrome	4	(1.0)	0	(0.0)	0	(0.0)	1	(0.1)	3	(0.0)

Amylase increased	3	(0.7)	0	(0.0)	14	(2.5)	14	(1.8)	17	(0.2)
Hypertransaminasaemia	3	(0.7)	0	(0.0)	6	(1.1)	0	(0.0)	6	(0.1)
Hypokalaemia	3	(0.7)	2	(0.5)	16	(2.8)	15	(1.9)	70	(0.9)
Hypotension	3	(0.7)	3	(0.8)	11	(2.0)	15	(1.9)	35	(0.5)
Pancreatitis	3	(0.7)	0	(0.0)	6	(1.1)	1	(0.1)	14	(0.2)
Syncope	3	(0.7)	2	(0.5)	11	(2.0)	9	(1.1)	43	(0.6)
Dyspnoea	2	(0.5)	1	(0.3)	7	(1.2)	14	(1.8)	145	(1.9)

Immune-mediated hepatitis	2	(0.5)	0	(0.0)	7	(1.2)	0	(0.0)	3	(0.0)
Lymphocyte count decreased	2	(0.5)	1	(0.3)	7	(1.2)	11	(1.4)	33	(0.4)
Multiple organ dysfunction syndrome	2	(0.5)	0	(0.0)	2	(0.4)	8	(1.0)	6	(0.1)
Peripheral sensory neuropathy	2	(0.5)	1	(0.3)	22	(3.9)	25	(3.2)	2	(0.0)
Rash macular	2	(0.5)	0	(0.0)	9	(1.6)	1	(0.1)	2	(0.0)
Atrial fibrillation	1	(0.2)	1	(0.3)	2	(0.4)	8	(1.0)	28	(0.4)
Back pain	1	(0.2)	0	(0.0)	6	(1.1)	12	(1.5)	72	(0.9)
Cellulitis	1	(0.2)	0	(0.0)	2	(0.4)	11	(1.4)	36	(0.5)
Hypophosphataemia	1	(0.2)	0	(0.0)	16	(2.8)	27	(3.4)	52	(0.7)
Leukopenia	1	(0.2)	17	(4.3)	5	(0.9)	5	(0.6)	7	(0.1)
Rash papular	1	(0.2)	0	(0.0)	7	(1.2)	1	(0.1)	0	(0.0)
Thrombocytopenia	1	(0.2)	36	(9.1)	4	(0.7)	4	(0.5)	23	(0.3)
Urinary tract infection bacterial	1	(0.2)	0	(0.0)	0	(0.0)	16	(2.0)	1	(0.0)
Vomiting	1	(0.2)	1	(0.3)	8	(1.4)	12	(1.5)	52	(0.7)
Cataract	0	(0.0)	0	(0.0)	4	(0.7)	11	(1.4)	14	(0.2)
Chronic kidney disease	0	(0.0)	1	(0.3)	9	(1.6)	7	(0.9)	6	(0.1)
Drug eruption	0	(0.0)	0	(0.0)	0	(0.0)	11	(1.4)	2	(0.0)
Febrile neutropenia	0	(0.0)	1	(0.3)	4	(0.7)	11	(1.4)	11	(0.1)
Hypercalcaemia	0	(0.0)	0	(0.0)	5	(0.9)	9	(1.1)	55	(0.7)

Hyperuricaemia	0	(0.0)	0	(0.0)	4	(0.7)	12	(1.5)	15	(0.2)
Hypoxia	0	(0.0)	0	(0.0)	3	(0.5)	10	(1.3)	25	(0.3)
Malignant neoplasm progression	0	(0.0)	0	(0.0)	0	(0.0)	14	(1.8)	6	(0.1)
Myelosuppression	0	(0.0)	4	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)
Neutrophil count decreased	0	(0.0)	0	(0.0)	14	(2.5)	39	(4.9)	10	(0.1)
Peripheral motor neuropathy	0	(0.0)	0	(0.0)	5	(0.9)	8	(1.0)	2	(0.0)
Peripheral sensorimotor neuropathy	0	(0.0)	0	(0.0)	10	(1.8)	3	(0.4)	0	(0.0)
Pleural effusion	0	(0.0)	0	(0.0)	1	(0.2)	6	(0.8)	73	(1.0)
Rash erythematous	0	(0.0)	0	(0.0)	3	(0.5)	13	(1.6)	1	(0.0)
White blood cell count decreased	0	(0.0)	0	(0.0)	3	(0.5)	13	(1.6)	5	(0.1)

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 KN-B15, treatment includes study medications and surgery.

For KN-B15, 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.

For KN-B15, grades are based on NCI CTCAE version 5.0.

Database cutoff date for KN-B15: 27OCT2025.

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.

Serious adverse event/deaths/other significant events

**Table 50 Participants With Serious Adverse Events by Decreasing Frequency of Preferred Term (Incidence $\geq$ 1% in One or More Treatment Groups)
(APaT Population)**

	KN-B15 EV + Pembro		KN-B15 Cis + Gem		EV + Pembro Combo ISD		EV Mono ISD		Pembro Mono RSD	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	403		396		564		793		7,631	
with one or more adverse events	255	(63.3)	190	(48.0)	295	(52.3)	363	(45.8)	2,742	(35.9)
with no adverse events	148	(36.7)	206	(52.0)	269	(47.7)	430	(54.2)	4,889	(64.1)
Prostate cancer	40	(9.9)	31	(7.8)	0	(0.0)	0	(0.0)	5	(0.1)
Urinary tract infection	37	(9.2)	36	(9.1)	25	(4.4)	31	(3.9)	67	(0.9)
Urosepsis	18	(4.5)	11	(2.8)	9	(1.6)	4	(0.5)	27	(0.4)
Sepsis	16	(4.0)	12	(3.0)	13	(2.3)	24	(3.0)	56	(0.7)
Acute kidney injury	14	(3.5)	8	(2.0)	34	(6.0)	50	(6.3)	65	(0.9)
Pneumonitis	11	(2.7)	0	(0.0)	14	(2.5)	2	(0.3)	136	(1.8)
Pneumonia	9	(2.2)	7	(1.8)	15	(2.7)	30	(3.8)	272	(3.6)
Intestinal obstruction	7	(1.7)	2	(0.5)	2	(0.4)	1	(0.1)	19	(0.2)
Diarrhoea	6	(1.5)	1	(0.3)	19	(3.4)	17	(2.1)	70	(0.9)
Hepatitis	6	(1.5)	0	(0.0)	2	(0.4)	0	(0.0)	13	(0.2)
Pyelonephritis acute	6	(1.5)	5	(1.3)	3	(0.5)	1	(0.1)	4	(0.1)
Wound dehiscence	6	(1.5)	1	(0.3)	0	(0.0)	0	(0.0)	2	(0.0)
Hydronephrosis	5	(1.2)	5	(1.3)	2	(0.4)	3	(0.4)	8	(0.1)
Ileus	5	(1.2)	1	(0.3)	0	(0.0)	2	(0.3)	14	(0.2)
Peritonitis	5	(1.2)	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.0)
Pulmonary embolism	5	(1.2)	5	(1.3)	9	(1.6)	5	(0.6)	78	(1.0)
Pyelonephritis	5	(1.2)	11	(2.8)	5	(0.9)	3	(0.4)	10	(0.1)
Rash	5	(1.2)	0	(0.0)	1	(0.2)	7	(0.9)	13	(0.2)
Rash maculo-papular	5	(1.2)	0	(0.0)	8	(1.4)	7	(0.9)	8	(0.1)
Small intestinal obstruction	5	(1.2)	1	(0.3)	2	(0.4)	7	(0.9)	19	(0.2)
Urinary tract obstruction	5	(1.2)	2	(0.5)	2	(0.4)	4	(0.5)	9	(0.1)
Colitis	4	(1.0)	1	(0.3)	5	(0.9)	7	(0.9)	71	(0.9)

Kidney infection	4	(1.0)	4	(1.0)	2	(0.4)	2	(0.3)	2	(0.0)
Neutropenia	4	(1.0)	5	(1.3)	1	(0.2)	9	(1.1)	3	(0.0)
Abdominal pain	3	(0.7)	2	(0.5)	9	(1.6)	11	(1.4)	43	(0.6)
Dehydration	3	(0.7)	1	(0.3)	4	(0.7)	9	(1.1)	44	(0.6)
Hyponatraemia	3	(0.7)	1	(0.3)	7	(1.2)	9	(1.1)	43	(0.6)
Anaemia	2	(0.5)	9	(2.3)	6	(1.1)	7	(0.9)	65	(0.9)
COVID-19	2	(0.5)	1	(0.3)	8	(1.4)	0	(0.0)	0	(0.0)
COVID-19 pneumonia	2	(0.5)	0	(0.0)	6	(1.1)	0	(0.0)	2	(0.0)
Decreased appetite	2	(0.5)	1	(0.3)	8	(1.4)	11	(1.4)	20	(0.3)
Fatigue	2	(0.5)	0	(0.0)	5	(0.9)	8	(1.0)	22	(0.3)
Hyperglycaemia	2	(0.5)	0	(0.0)	8	(1.4)	17	(2.1)	12	(0.2)
Pyrexia	2	(0.5)	3	(0.8)	9	(1.6)	12	(1.5)	79	(1.0)
Alanine aminotransferase increased	1	(0.2)	0	(0.0)	6	(1.1)	2	(0.3)	16	(0.2)
Atrial fibrillation	1	(0.2)	1	(0.3)	2	(0.4)	12	(1.5)	28	(0.4)
Cellulitis	1	(0.2)	0	(0.0)	4	(0.7)	11	(1.4)	36	(0.5)
Haematuria	1	(0.2)	1	(0.3)	12	(2.1)	15	(1.9)	17	(0.2)
Urinary tract infection bacterial	1	(0.2)	0	(0.0)	0	(0.0)	15	(1.9)	1	(0.0)
Aspartate aminotransferase increased	0	(0.0)	0	(0.0)	7	(1.2)	2	(0.3)	17	(0.2)
Dyspnoea	0	(0.0)	1	(0.3)	5	(0.9)	13	(1.6)	91	(1.2)
Febrile neutropenia	0	(0.0)	1	(0.3)	4	(0.7)	11	(1.4)	8	(0.1)
Hypotension	0	(0.0)	3	(0.8)	6	(1.1)	6	(0.8)	13	(0.2)
Malignant neoplasm progression	0	(0.0)	0	(0.0)	0	(0.0)	14	(1.8)	6	(0.1)
Nausea	0	(0.0)	2	(0.5)	4	(0.7)	10	(1.3)	30	(0.4)
Pleural effusion	0	(0.0)	0	(0.0)	1	(0.2)	4	(0.5)	88	(1.2)
Thrombocytopenia	0	(0.0)	4	(1.0)	0	(0.0)	3	(0.4)	10	(0.1)
Vomiting	0	(0.0)	0	(0.0)	6	(1.1)	14	(1.8)	32	(0.4)

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 KN-B15, treatment includes study medications and surgery.

For KN-B15, 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 KN-B15: 27OCT2025.

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.

Deaths

Table 51 Participants with Adverse Events Resulting in Death by Decreasing Frequency of Preferred Term (Incidence > 0% in One or More Treatment Groups) (APaT Population)

	KN-B15 EV + Pembro		KN-B15 Cis + Gem		EV + Pembro Combo ESD		EV Mono ESD		Pembro Mono RSD	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	403		396		564		793		7,631	
with one or more adverse events	17	(4.2)	11	(2.8)	30	(5.3)	37	(4.7)	346	(4.5)
with no adverse events	386	(95.8)	385	(97.2)	534	(94.7)	756	(95.3)	7,285	(95.5)
Cardiac arrest	2	(0.5)	0	(0.0)	2	(0.4)	2	(0.3)	9	(0.1)
Death	2	(0.5)	1	(0.3)	3	(0.5)	0	(0.0)	49	(0.6)
Multiple organ dysfunction syndrome	2	(0.5)	0	(0.0)	2	(0.4)	6	(0.8)	6	(0.1)
Pneumonia	2	(0.5)	2	(0.5)	1	(0.2)	2	(0.3)	40	(0.5)
COVID-19 pneumonia	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Duodenal ulcer perforation	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pancreatitis acute	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Renal failure	1	(0.2)	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.0)
Sepsis	1	(0.2)	4	(1.0)	3	(0.5)	4	(0.5)	11	(0.1)
Septic shock	1	(0.2)	0	(0.0)	1	(0.2)	1	(0.1)	11	(0.1)
Small cell lung cancer	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Toxic shock syndrome	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Urosepsis	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Abdominal sepsis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Accidental death	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Acute coronary syndrome	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Acute graft versus host disease	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Acute kidney injury	0	(0.0)	1	(0.3)	0	(0.0)	2	(0.3)	3	(0.0)
Acute myeloid leukaemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Acute myocardial infarction	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
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	(0.0)	1	(0.0)

Fatal AEs: 9 out of 17 death occurred in the perioperative EV + pembrolizumab participants and were cause by multiple organ dysfunction syndrome COVID-19 pneumonia, cardiac arrest, sepsis, septic shock, and urosepsis. This included 2 participants with fatal AEs assessed as drug-related by the investigator (2 cases of Multiple organ dysfunction syndrome).

All 11 participants with AEs resulting in death in the cis + gem group in the Combined Phases, including the participant with a fatal AE assessed as drug-related by the investigator (1 case of pneumonia), had AE onset in the Preoperative/Surgical Phase

Adverse events of special interest (AESI) for Enfortumab Vedotin

**Table 52 Participants With Adverse Events of Special Interest (AESI) for EV by AESI Category and Subcategory - All Grades and Grade 3-5
(Incidence > 0% in One or More Treatment Groups) (APaT Population)**

	KN-B15 EV + Pembro (N=403)		KN-B15 Cis + Gem (N=396)		EV + Pembro Combo ISD (N=564)		EV Mono ISD (N=793)	
	All Grade	Grade 3-5	All Grade	Grade 3-5	All Grade	Grade 3-5	All Grade	Grade 3-5
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Skin Reactions	266 (66.0)	59 (14.6)	51 (12.9)	1 (0.3)	395 (70.0)	99 (17.6)	452 (57.0)	108 (13.6)
Rash	249 (61.8)	54 (13.4)	35 (8.8)	1 (0.3)	368 (65.2)	95 (16.8)	415 (52.3)	100 (12.6)
Severe cutaneous adverse reactions	78 (19.4)	15 (3.7)	19 (4.8)	0 (0.0)	161 (28.5)	20 (3.5)	199 (25.1)	33 (4.2)
Peripheral Neuropathy	176 (43.7)	12 (3.0)	45 (11.4)	4 (1.0)	380 (67.4)	41 (7.3)	422 (53.2)	41 (5.2)
Peripheral neuropathy motor events	19 (4.7)	4 (1.0)	6 (1.5)	2 (0.5)	91 (16.1)	18 (3.2)	124 (15.6)	13 (1.6)
Peripheral neuropathy sensory events	169 (41.9)	8 (2.0)	42 (10.6)	2 (0.5)	355 (62.9)	26 (4.6)	386 (48.7)	32 (4.0)
Hyperglycemia	79 (19.6)	27 (6.7)	29 (7.3)	3 (0.8)	112 (19.9)	53 (9.4)	133 (16.8)	61 (7.7)
Ocular Disorders	123 (30.5)	1 (0.2)	14 (3.5)	0 (0.0)	182 (32.3)	0 (0.0)	277 (34.9)	3 (0.4)
Blurred Vision	25 (6.2)	0 (0.0)	11 (2.8)	0 (0.0)	50 (8.9)	0 (0.0)	84 (10.6)	0 (0.0)
Corneal Disorders	5 (1.2)	1 (0.2)	0 (0.0)	0 (0.0)	15 (2.7)	0 (0.0)	46 (5.8)	0 (0.0)
Dry Eye	101 (25.1)	0 (0.0)	5 (1.3)	0 (0.0)	160 (28.4)	0 (0.0)	238 (30.0)	3 (0.4)
Infusion Related Reactions	10 (2.5)	0 (0.0)	18 (4.5)	0 (0.0)	22 (3.9)	1 (0.2)	50 (6.3)	7 (0.9)
<p>Every participant is counted a single time for each applicable specific adverse event. Only the highest reported grade of a given event is counted for the individual participant.</p> <p>For KN-B15, treatment includes study medications and surgery.</p> <p>For KN-B15 and EV + Pembro Combo ISD, non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.</p> <p>For EV Mono ISD, non-serious adverse events and serious adverse events up to 30 days of the last treatment are included.</p> <p>For KN-B15, grades are based on NCI CTCAE version 5.0.</p> <p>Database cutoff date for KN-B15: 27OCT2025.</p> <p>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.</p>								



Skin reactions

Table 53 Adverse Event Summary AESI for EV - Skin Reactions (APaT Population)

	KN-B15 EV + Pembro		KN-B15 Cis + Gem		EV + Pembro Combo ISD		EV Mono ISD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	403		396		564		793	
with one or more adverse events	266	(66.0)	51	(12.9)	395	(70.0)	452	(57.0)
with no adverse event	137	(34.0)	345	(87.1)	169	(30.0)	341	(43.0)
with drug-related ^a adverse events	256	(63.5)	33	(8.3)	378	(67.0)	402	(50.7)
with toxicity grade 3-5 adverse events	59	(14.6)	1	(0.3)	99	(17.6)	108	(13.6)
with toxicity grade 3-5 drug-related adverse events	57	(14.1)	1	(0.3)	96	(17.0)	106	(13.4)
with serious adverse events	25	(6.2)	0	(0.0)	30	(5.3)	34	(4.3)
with serious drug-related adverse events	24	(6.0)	0	(0.0)	30	(5.3)	34	(4.3)
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	36	(8.9)	0	(0.0)	38	(6.7)	25	(3.2)
discontinued Pembrolizumab	23	(5.7)	NA		21	(3.7)	NA	
discontinued EV	32	(7.9)	NA		33	(5.9)	25	(3.2)
discontinued any drug due to a drug-related adverse event	36	(8.9)	0	(0.0)	38	(6.7)	25	(3.2)
discontinued Pembrolizumab	23	(5.7)	NA		21	(3.7)	NA	
discontinued EV	32	(7.9)	NA		33	(5.9)	25	(3.2)
discontinued any drug due to a serious adverse event	15	(3.7)	0	(0.0)	8	(1.4)	13	(1.6)
discontinued Pembrolizumab	11	(2.7)	NA		6	(1.1)	NA	
discontinued EV	14	(3.5)	NA		7	(1.2)	13	(1.6)
discontinued any drug due to a serious drug-related adverse event	15	(3.7)	0	(0.0)	8	(1.4)	13	(1.6)
discontinued Pembrolizumab	11	(2.7)	NA		6	(1.1)	NA	
discontinued EV	14	(3.5)	NA		7	(1.2)	13	(1.6)

^a Determined by the investigator to be related to the drug.
For KN-B15, treatment includes study medications and surgery.
For KN-B15 and EV + Pembro Combo ISD, 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 KN-B15, grades are based on NCI CTCAE version 5.0.
Database cutoff date for KN-B15: 27OCT2025.

Table 54. Participants with Adverse events of special interest (AESI) for EV-Skin Reactions (Incidence > 0% in one or more treatment groups (APaT Population))

	KN-B15 EV + Pembro		KN-B15 Cis + Gem		EV + Pembro Combo ISD		EV Mono ISD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	403		396		564		793	
with one or more adverse events	266	(66.0)	51	(12.9)	395	(70.0)	452	(57.0)
with no adverse events	137	(34.0)	345	(87.1)	169	(30.0)	341	(43.0)
Rash	249	(61.8)	35	(8.8)	368	(65.2)	415	(52.3)
Rash	101	(25.1)	11	(2.8)	16	(2.8)	92	(11.6)
Rash maculo-papular	83	(20.6)	14	(3.5)	204	(36.2)	187	(23.6)
Erythema	24	(6.0)	3	(0.8)	21	(3.7)	32	(4.0)
Rash pruritic	18	(4.5)	0	(0.0)	10	(1.8)	18	(2.3)
Dermatitis	10	(2.5)	2	(0.5)	28	(5.0)	6	(0.8)
Eczema	10	(2.5)	0	(0.0)	32	(5.7)	12	(1.5)
Rash macular	10	(2.5)	0	(0.0)	64	(11.3)	21	(2.6)
Blister	7	(1.7)	0	(0.0)	18	(3.2)	30	(3.8)
Rash erythematous	7	(1.7)	1	(0.3)	22	(3.9)	37	(4.7)
Rash papular	7	(1.7)	0	(0.0)	43	(7.6)	17	(2.1)
Dermatitis bullous	6	(1.5)	1	(0.3)	27	(4.8)	26	(3.3)
Toxic skin eruption	6	(1.5)	0	(0.0)	6	(1.1)	1	(0.1)
Dermatitis contact	5	(1.2)	0	(0.0)	3	(0.5)	5	(0.6)
Drug eruption	4	(1.0)	2	(0.5)	1	(0.2)	31	(3.9)
Stevens-Johnson syndrome	4	(1.0)	0	(0.0)	0	(0.0)	1	(0.1)
Dermatitis atopic	3	(0.7)	0	(0.0)	1	(0.2)	0	(0.0)
Neurodermatitis	2	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
Palmar-plantar erythrodysesthesia syndrome	2	(0.5)	0	(0.0)	8	(1.4)	15	(1.9)
Rash vesicular	2	(0.5)	0	(0.0)	8	(1.4)	10	(1.3)
Seborrhoeic dermatitis	2	(0.5)	0	(0.0)	2	(0.4)	0	(0.0)
Symmetrical drug-related intertriginous and flexural exanthema	2	(0.5)	0	(0.0)	2	(0.4)	0	(0.0)
Drug reaction with eosinophilia and systemic symptoms	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Eczema nummular	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Immune-mediated dermatitis	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Intertrigo	1	(0.2)	0	(0.0)	1	(0.2)	4	(0.5)
Pemphigoid	1	(0.2)	0	(0.0)	5	(0.9)	2	(0.3)
Rash morbilliform	1	(0.2)	0	(0.0)	2	(0.4)	0	(0.0)
Skin irritation	1	(0.2)	0	(0.0)	1	(0.2)	2	(0.3)
Blister rupture	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)
Blood blister	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.3)
Dermatitis allergic	0	(0.0)	1	(0.3)	2	(0.4)	2	(0.3)
Dyshidrotic eczema	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Erythema multiforme	0	(0.0)	0	(0.0)	6	(1.1)	6	(0.8)

Fixed eruption	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)
Hand dermatitis	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Lichen planus pemphigoides	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Pemphigus	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.3)
Plantar erythema	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Prurigo	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)
Rash maculovesicular	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)
SJS-TEN overlap	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Stasis dermatitis	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.1)
Superficial inflammatory dermatosis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)
Toxic epidermal necrolysis	0	(0.0)	0	(0.0)	3	(0.5)	0	(0.0)
Toxic erythema of chemotherapy	0	(0.0)	0	(0.0)	2	(0.4)	0	(0.0)
Severe cutaneous adverse reactions	78	(19.4)	19	(4.8)	161	(28.5)	199	(25.1)
Conjunctivitis	22	(5.5)	0	(0.0)	37	(6.6)	37	(4.7)
Skin exfoliation	12	(3.0)	0	(0.0)	17	(3.0)	35	(4.4)
Stomatitis	10	(2.5)	15	(3.8)	53	(9.4)	63	(7.9)
Skin toxicity	8	(2.0)	0	(0.0)	5	(0.9)	1	(0.1)
Blister	7	(1.7)	0	(0.0)	18	(3.2)	30	(3.8)
Dermatitis bullous	6	(1.5)	1	(0.3)	27	(4.8)	26	(3.3)
Dermatitis exfoliative generalised	6	(1.5)	0	(0.0)	4	(0.7)	5	(0.6)
Toxic skin eruption	6	(1.5)	0	(0.0)	6	(1.1)	1	(0.1)
Drug eruption	4	(1.0)	2	(0.5)	1	(0.2)	31	(3.9)
Stevens-Johnson syndrome	4	(1.0)	0	(0.0)	0	(0.0)	1	(0.1)
Acute generalised exanthematous pustulosis	2	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
Exfoliative rash	2	(0.5)	0	(0.0)	1	(0.2)	2	(0.3)
Symmetrical drug-related intertriginous and flexural exanthema	2	(0.5)	0	(0.0)	2	(0.4)	0	(0.0)
Cutaneous vasculitis	1	(0.2)	0	(0.0)	1	(0.2)	0	(0.0)
Drug reaction with eosinophilia and systemic symptoms	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Epidermolysis bullosa	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Noninfective conjunctivitis	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Pemphigoid	1	(0.2)	0	(0.0)	5	(0.9)	2	(0.3)
Blister rupture	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)
Dermatitis exfoliative	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.1)
Erythema multiforme	0	(0.0)	0	(0.0)	6	(1.1)	6	(0.8)
Fixed eruption	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)
Lichen planus pemphigoides	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Mouth ulceration	0	(0.0)	0	(0.0)	8	(1.4)	7	(0.9)
Pemphigus	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.3)
SJS-TEN overlap	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Skin erosion	0	(0.0)	2	(0.5)	1	(0.2)	0	(0.0)
Toxic epidermal necrolysis	0	(0.0)	0	(0.0)	3	(0.5)	0	(0.0)
Every participant is counted a single time for each applicable specific adverse event. A participant with multiple adverse events within a bolded term is counted a single time for that bolded term.								
For KN-B15, treatment includes study medications and surgery.								
For KN-B15 and EV + Pembro Combo ISD, 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 KN-B15: 27OCT2025								

Cutaneous rash was the most frequent skin reaction reported (EV+ Pembro: 61.8%, Ev+ Pembro combo ISD 65.2%, EV Mono ISD 52.3%), while severe reactions were registered in the 19.4% of the EV+ Pembro arm: conjunctivitis (5.5%) and skin exfoliation (3%) were the most frequently reported severe skin reactions. Four cases of Steven Johnson syndrome (1%) and 6 of dermatitis bullous (1.5%) were included in the skin severe reaction PT. In the reference datasets, the reported rates of severe cutaneous skin reactions were 28.5% in the EV+ Pembro ISD and 25.1% in the EV Mono ISD.

Clinical AEs of **skin hyperpigmentation** include skin discoloration, skin hyperpigmentation, and pigmentation disorder. The percentage of participants with skin hyperpigmentation was 3.5% in the perioperative EV + pembrolizumab group, with no events reported in the cis + gem group. The percentage of participants with skin hyperpigmentation observed in the perioperative EV + pembrolizumab group (3.5%) was similar to that of the EV + pembrolizumab ISD (6.9%) and EV mono ISD (10.0%). All AEs of skin hyperpigmentation were Grade ≤ 2 events and nonserious across all the analyzed groups.

Peripheral neuropathy

Table 55 Adverse Event Summary AESI for EV - Peripheral Neuropathy (APaT Population)

	KN-B15 EV + Pembro		KN-B15 Cis + Gem		EV + Pembro Combo ISD		EV Mono ISD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	403		396		564		793	
with one or more adverse events	176	(43.7)	45	(11.4)	380	(67.4)	422	(53.2)
with no adverse event	227	(56.3)	351	(88.6)	184	(32.6)	371	(46.8)
with drug-related ^a adverse events	145	(36.0)	28	(7.1)	364	(64.5)	381	(48.0)
with toxicity grade 3-5 adverse events	12	(3.0)	4	(1.0)	41	(7.3)	41	(5.2)
with toxicity grade 3-5 drug-related adverse events	8	(2.0)	1	(0.3)	37	(6.6)	38	(4.8)
with serious adverse events	1	(0.2)	1	(0.3)	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	27	(6.7)	2	(0.5)	119	(21.1)	55	(6.9)
discontinued Pembrolizumab	4	(1.0)	NA		16	(2.8)	NA	
discontinued EV	27	(6.7)	NA		119	(21.1)	55	(6.9)
discontinued any drug due to a drug-related adverse event	27	(6.7)	2	(0.5)	117	(20.7)	53	(6.7)
discontinued Pembrolizumab	4	(1.0)	NA		15	(2.7)	NA	
discontinued EV	27	(6.7)	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 KN-B15, treatment includes study medications and surgery. For KN-B15 and EV + Pembro Combo ISD, 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 KN-B15, grades are based on NCI CTCAE version 5.0. Database cutoff date for KN-B15: 27OCT2025.								

Table 56 Participants with Adverse events of special interest (AESI) for EV-Peripheral Neuropathy (Incidence> 0% in one or more treatment groups (APaT Population))

	KN-B15 EV + Pembro		KN-B15 Cis + Gem		EV + Pembro Combo ISD		EV Mono ISD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	403		396		564		793	
with one or more adverse events	176	(43.7)	45	(11.4)	380	(67.4)	422	(53.2)
with no adverse events	227	(56.3)	351	(88.6)	184	(32.6)	371	(46.8)
Peripheral neuropathy motor events	19	(4.7)	6	(1.5)	91	(16.1)	124	(15.6)
Muscular weakness	15	(3.7)	5	(1.3)	41	(7.3)	58	(7.3)
Peripheral motor neuropathy	2	(0.5)	0	(0.0)	37	(6.6)	54	(6.8)
Peroneal nerve palsy	2	(0.5)	0	(0.0)	3	(0.5)	6	(0.8)
Motor dysfunction	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)
Multifocal motor neuropathy	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)
Muscle atrophy	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)
Peripheral sensorimotor neuropathy	0	(0.0)	0	(0.0)	23	(4.1)	19	(2.4)
Peripheral neuropathy sensory events	169	(41.9)	42	(10.6)	355	(62.9)	386	(48.7)
Neuropathy peripheral	69	(17.1)	12	(3.0)	0	(0.0)	33	(4.2)
Peripheral sensory neuropathy	55	(13.6)	15	(3.8)	308	(54.6)	305	(38.5)
Paraesthesia	26	(6.5)	11	(2.8)	37	(6.6)	35	(4.4)
Hypoaesthesia	11	(2.7)	3	(0.8)	19	(3.4)	19	(2.4)
Neurotoxicity	7	(1.7)	0	(0.0)	5	(0.9)	5	(0.6)
Neuralgia	4	(1.0)	1	(0.3)	3	(0.5)	7	(0.9)
Polyneuropathy	4	(1.0)	0	(0.0)	0	(0.0)	6	(0.8)
Dysaesthesia	3	(0.7)	1	(0.3)	4	(0.7)	4	(0.5)
Gait disturbance	2	(0.5)	4	(1.0)	20	(3.5)	40	(5.0)
Burning sensation	1	(0.2)	0	(0.0)	0	(0.0)	3	(0.4)
Peripheral nerve paresis	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Demyelinating polyneuropathy	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.3)
Immune-mediated neuropathy	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Sensory loss	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.1)
Skin burning sensation	0	(0.0)	0	(0.0)	1	(0.2)	3	(0.4)
Every participant is counted a single time for each applicable specific adverse event. A participant with multiple adverse events within a bolded term is counted a single time for that bolded term.								
For KN-B15, treatment includes study medications and surgery.								
For KN-B15 and EV + Pembro Combo ISD, 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 KN-B15: 27OCT2025.								

Hyperglycemia

Hyperglycemia was recorded in 19.6% of subjects in the EV+Pembro arm; overall rate of hyperglycemia resulted similar to the Pembro-EV (19.9%) and mono EV ISDs (16.8%). Most of the reported cases were grade 1-2, accounting for the 12.9% of the events and were mostly represented by transient hyperglycemia. When incidence was adjusted for exposure, it resulted similar to what reported in the EV+ Pembro ISD and mono EV ISD (2.47, 2.62 and 4.19 respectively).

Table 57 Adverse Event Summary AESI for EV -Hyperglycemia (APaT population)

	KN-B15 EV + Pembro		KN-B15 Cis + Gem		EV + Pembro Combo ISD		EV Mono ISD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	403		396		564		793	
with one or more adverse events	79	(19.6)	29	(7.3)	112	(19.9)	133	(16.8)
with no adverse event	324	(80.4)	367	(92.7)	452	(80.1)	660	(83.2)
with drug-related ^a adverse events	53	(13.2)	10	(2.5)	76	(13.5)	86	(10.8)
with toxicity grade 3-5 adverse events	27	(6.7)	3	(0.8)	53	(9.4)	61	(7.7)
with toxicity grade 3-5 drug-related adverse events	21	(5.2)	0	(0.0)	37	(6.6)	46	(5.8)
with serious adverse events	10	(2.5)	3	(0.8)	11	(2.0)	20	(2.5)
with serious drug-related adverse events	9	(2.2)	1	(0.3)	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	5	(1.2)	1	(0.3)	1	(0.2)	5	(0.6)
discontinued Pembrolizumab	5	(1.2)	NA		1	(0.2)	NA	
discontinued EV	2	(0.5)	NA		1	(0.2)	5	(0.6)
discontinued any drug due to a drug-related adverse event	5	(1.2)	1	(0.3)	1	(0.2)	5	(0.6)
discontinued Pembrolizumab	5	(1.2)	NA		1	(0.2)	NA	
discontinued EV	2	(0.5)	NA		1	(0.2)	5	(0.6)
discontinued any drug due to a serious adverse event	5	(1.2)	0	(0.0)	1	(0.2)	5	(0.6)
discontinued Pembrolizumab	5	(1.2)	NA		1	(0.2)	NA	
discontinued EV	2	(0.5)	NA		1	(0.2)	5	(0.6)
discontinued any drug due to a serious drug-related adverse event	5	(1.2)	0	(0.0)	1	(0.2)	5	(0.6)
discontinued Pembrolizumab	5	(1.2)	NA		1	(0.2)	NA	
discontinued EV	2	(0.5)	NA		1	(0.2)	5	(0.6)

^a Determined by the investigator to be related to the drug.
For KN-B15, treatment includes study medications and surgery.
For KN-B15 and EV + Pembro Combo ISD, 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 KN-B15, grades are based on NCI CTCAE version 5.0.
Database cutoff date for KN-B15: 27OCT2025.

Table 58 Participants with Adverse events of special interest (AESI) for EV-Hyperglycemia (Incidence > 0% in one or more treatment groups (APaT Population))

	KN-B15 EV + Pembro		KN-B15 Cis + Gem		EV + Pembro Combo ISD		EV Mono ISD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	403		396		564		793	
with one or more adverse events	79	(19.6)	29	(7.3)	112	(19.9)	133	(16.8)
with no adverse events	324	(80.4)	367	(92.7)	452	(80.1)	660	(83.2)
Hyperglycemia	79	(19.6)	29	(7.3)	112	(19.9)	133	(16.8)
Hyperglycaemia	60	(14.9)	22	(5.6)	95	(16.8)	118	(14.9)
Diabetes mellitus	9	(2.2)	1	(0.3)	9	(1.6)	8	(1.0)
Blood glucose increased	3	(0.7)	3	(0.8)	3	(0.5)	7	(0.9)
Type 1 diabetes mellitus	3	(0.7)	0	(0.0)	1	(0.2)	0	(0.0)
Diabetic ketoacidosis	2	(0.5)	0	(0.0)	0	(0.0)	1	(0.1)
Blood glucose abnormal	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Diabetic metabolic decompensation	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Fulminant type 1 diabetes mellitus	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Glucose tolerance impaired	1	(0.2)	1	(0.3)	7	(1.2)	5	(0.6)
Diabetes mellitus inadequate control	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)
Diabetic hyperglycaemic coma	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Glycosylated haemoglobin increased	0	(0.0)	1	(0.3)	1	(0.2)	2	(0.3)
Hyperglycaemic hyperosmolar nonketotic syndrome	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)
Impaired fasting glucose	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Type 2 diabetes mellitus	0	(0.0)	3	(0.8)	7	(1.2)	4	(0.5)
<p>Every participant is counted a single time for each applicable specific adverse event. A participant with multiple adverse events within a bolded term is counted a single time for that bolded term.</p> <p>For KN-B15, treatment includes study medications and surgery.</p> <p>For KN-B15 and EV + Pembro Combo ISD, non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.</p> <p>For EV Mono ISD, non-serious adverse events and serious adverse events up to 30 days of the last treatment are included.</p> <p>Database cutoff date for KN-B15: 27OCT2025.</p>								

Ocular disorders

Analysis of ocular disorders was focused on three established subsets for which an association with EV was already evaluated: dry eye (identified risk), corneal disorders (potential risk) and blurred vision (potential risk).

Table 59 Exposure-Adjusted Adverse Event Summary of AESI for EV – Ocular disorders (Including Multiple Occurrences of Events) (APaT Population)

	KN-B15 EV + Pembro		KN-B15 Cis + Gem		EV + Pembro Combo ISD		EV Mono ISD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	403		396		564		793	
with one or more adverse events	123	(30.5)	14	(3.5)	182	(32.3)	277	(34.9)
with no adverse event	280	(69.5)	382	(96.5)	382	(67.7)	516	(65.1)
with drug-related* adverse events	94	(23.3)	6	(1.5)	134	(23.8)	199	(25.1)
with toxicity grade 3-5 adverse events	1	(0.2)	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	0	(0.0)	0	(0.0)	1	(0.2)	2	(0.3)
with serious drug-related adverse events	0	(0.0)	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	2	(0.5)	0	(0.0)	1	(0.2)	1	(0.1)
discontinued Pembrolizumab	0	(0.0)	NA		1	(0.2)	NA	
discontinued EV	2	(0.5)	NA		1	(0.2)	1	(0.1)
discontinued any drug due to a drug-related adverse event	2	(0.5)	0	(0.0)	1	(0.2)	1	(0.1)
discontinued Pembrolizumab	0	(0.0)	NA		1	(0.2)	NA	
discontinued EV	2	(0.5)	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)

* Determined by the investigator to be related to the drug.
For KN-B15, treatment includes study medications and surgery.
For KN-B15 and EV + Pembro Combo ISD, 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 KN-B15, grades are based on NCI CTCAE version 5.0.
Database cutoff date for KN-B15: 27OCT2025.
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.

Infusion-Related Reactions

The percentage of participants with IRR events was similar in the perioperative EV + pembrolizumab group (2.5%) compared with the cis + gem group (4.5%), the EV + pembrolizumab ISD (3.9%) and the EV mono ISD (6.3%); all AEs were ≤Grade 3 and nonserious for participants in the perioperative EV + pembrolizumab group. No IRR events in the perioperative EV + pembrolizumab led to dose reductions or discontinuation of any study drug or enfortumab vedotin.

ILD/pneumonitis

The mechanism for enfortumab vedotin-induced pneumonitis is not known; pneumonitis/ILD events are considered an important identified risk for both pembrolizumab and enfortumab vedotin.

Table 60 Adverse Event Summary Other Risk for EV – Pneumonitis/ Interstitial Lung Disease (APaT Population)

	KN-B15 EV + Pembro		KN-B15 Cis + Gem		EV + Pembro Combo ISD		EV Mono ISD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	403		396		564		793	
with one or more adverse events	31	(7.7)	3	(0.8)	62	(11.0)	26	(3.3)
with no adverse event	372	(92.3)	393	(99.2)	502	(89.0)	767	(96.7)
with drug-related ^a adverse events	26	(6.5)	0	(0.0)	59	(10.5)	21	(2.6)
with toxicity grade 3-5 adverse events	10	(2.5)	1	(0.3)	23	(4.1)	6	(0.8)
with toxicity grade 3-5 drug-related adverse events	10	(2.5)	0	(0.0)	23	(4.1)	5	(0.6)
with serious adverse events	14	(3.5)	1	(0.3)	26	(4.6)	6	(0.8)
with serious drug-related adverse events	14	(3.5)	0	(0.0)	25	(4.4)	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	15	(3.7)	1	(0.3)	30	(5.3)	4	(0.5)
discontinued Pembrolizumab	15	(3.7)	NA		30	(5.3)	NA	
discontinued EV	6	(1.5)	NA		14	(2.5)	4	(0.5)
discontinued any drug due to a drug-related adverse event	15	(3.7)	0	(0.0)	30	(5.3)	3	(0.4)
discontinued Pembrolizumab	15	(3.7)	NA		30	(5.3)	NA	
discontinued EV	6	(1.5)	NA		14	(2.5)	3	(0.4)
discontinued any drug due to a serious adverse event	9	(2.2)	1	(0.3)	16	(2.8)	3	(0.4)
discontinued Pembrolizumab	9	(2.2)	NA		15	(2.7)	NA	
discontinued EV	5	(1.2)	NA		8	(1.4)	3	(0.4)
discontinued any drug due to a serious drug-related adverse event	9	(2.2)	0	(0.0)	16	(2.8)	2	(0.3)
discontinued Pembrolizumab	9	(2.2)	NA		15	(2.7)	NA	
discontinued EV	5	(1.2)	NA		8	(1.4)	2	(0.3)

^a Determined by the investigator to be related to the drug.
For KN-B15, treatment includes study medications and surgery.
For KN-B15 and EV + Pembro Combo ISD, 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 KN-B15, grades are based on NCI CTCAE version 5.0.
Database cutoff date for KN-B15: 27OCT2025.
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.

Anemia

Table 61 Adverse Event Summary Other Risk for EV – Anemia (APaT Population)

	KN-B15 EV + Pembro		KN-B15 Cis + Gem		EV + Pembro Combo ISD		EV Mono ISD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	403		396		564		793	
with one or more adverse events	131	(32.5)	223	(56.3)	153	(27.1)	232	(29.3)
with no adverse event	272	(67.5)	173	(43.7)	411	(72.9)	561	(70.7)
with drug-related* adverse events	46	(11.4)	181	(45.7)	88	(15.6)	150	(18.9)
with toxicity grade 3-5 adverse events	26	(6.5)	61	(15.4)	52	(9.2)	77	(9.7)
with toxicity grade 3-5 drug-related adverse events	6	(1.5)	44	(11.1)	25	(4.4)	38	(4.8)
with serious adverse events	2	(0.5)	9	(2.3)	6	(1.1)	7	(0.9)
with serious drug-related adverse events	0	(0.0)	6	(1.5)	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	0	(0.0)	3	(0.8)	2	(0.4)	0	(0.0)
discontinued Pembrolizumab	0	(0.0)	NA		1	(0.2)	NA	
discontinued EV	0	(0.0)	NA		2	(0.4)	0	(0.0)
discontinued any drug due to a drug-related adverse event	0	(0.0)	2	(0.5)	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)	1	(0.3)	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)

* Determined by the investigator to be related to the drug.
For KN-B15, treatment includes study medications and surgery.
For KN-B15 and EV + Pembro Combo ISD, 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 KN-B15, grades are based on NCI CTCAE version 5.0.
Database cutoff date for KN-B15: 27OCT2025.

Table 62 Participants with Adverse events of special interest (AESI) for EV-Anemia- (Incidence> 0% in one or more treatment groups (APaT Population))

	KN-B15 EV + Pembro		KN-B15 Cis + Gem		EV + Pembro Combo ISD		EV Mono ISD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	403		396		564		793	
with one or more adverse events	131	(32.5)	223	(56.3)	153	(27.1)	232	(29.3)
with no adverse events	272	(67.5)	173	(43.7)	411	(72.9)	561	(70.7)
Anemia	131	(32.5)	223	(56.3)	153	(27.1)	232	(29.3)
Anaemia	126	(31.3)	223	(56.3)	153	(27.1)	232	(29.3)
Haemoglobin decreased	4	(1.0)	0	(0.0)	0	(0.0)	1	(0.1)
Anaemia macrocytic	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Microcytic anaemia	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Normocytic anaemia	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Haematocrit decreased	0	(0.0)	1	(0.3)	1	(0.2)	0	(0.0)
Reticulocyte count decreased	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)

Every participant is counted a single time for each applicable specific adverse event. A participant with multiple adverse events within a bolded term is counted a single time for that bolded term.
For KN-B15, treatment includes study medications and surgery.
For KN-B15 and EV + Pembro Combo ISD, 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 KN-B15: 27OCT2025.

Neutropenia

Table 63 Adverse Event Summary Other Risk for EV – Neutropenia (APaT Population)

	KN-B15 EV + Pembro		KN-B15 Cis + Gem		EV + Pembro Combo ISD		EV Mono ISD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	403		396		564		793	
with one or more adverse events	59	(14.6)	220	(55.6)	82	(14.5)	134	(16.9)
with no adverse event	344	(85.4)	176	(44.4)	482	(85.5)	659	(83.1)
with drug-related ^a adverse events	50	(12.4)	216	(54.5)	77	(13.7)	124	(15.6)
with toxicity grade 3-5 adverse events	30	(7.4)	133	(33.6)	50	(8.9)	91	(11.5)
with toxicity grade 3-5 drug-related adverse events	26	(6.5)	130	(32.8)	47	(8.3)	83	(10.5)
with serious adverse events	4	(1.0)	7	(1.8)	7	(1.2)	23	(2.9)
with serious drug-related adverse events	4	(1.0)	6	(1.5)	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	2	(0.5)	13	(3.3)	0	(0.0)	1	(0.1)
discontinued Pembrolizumab	0	(0.0)	NA		0	(0.0)	NA	
discontinued EV	2	(0.5)	NA		0	(0.0)	1	(0.1)
discontinued any drug due to a drug-related adverse event	2	(0.5)	12	(3.0)	0	(0.0)	1	(0.1)
discontinued Pembrolizumab	0	(0.0)	NA		0	(0.0)	NA	
discontinued EV	2	(0.5)	NA		0	(0.0)	1	(0.1)
discontinued any drug due to a serious adverse event	0	(0.0)	1	(0.3)	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 KN-B15, treatment includes study medications and surgery.
For KN-B15 and EV + Pembro Combo ISD, 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 KN-B15, grades are based on NCI CTCAE version 5.0.
Database cutoff date for KN-B15: 27OCT2025.

Table 64 Participants with Adverse events of special interest (AESI) for EV-Neutropenia- (Incidence> 0% in one or more treatment groups (APaT Population))

	KN-B15 EV + Pembro		KN-B15 Cis + Gem		EV + Pembro Combo ISD		EV Mono ISD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	403		396		564		793	
with one or more adverse events	59	(14.6)	220	(55.6)	82	(14.5)	134	(16.9)
with no adverse events	344	(85.4)	176	(44.4)	482	(85.5)	659	(83.1)
Neutropenia	59	(14.6)	220	(55.6)	82	(14.5)	134	(16.9)
Neutropenia	59	(14.6)	218	(55.1)	61	(10.8)	60	(7.6)
Febrile neutropenia	0	(0.0)	1	(0.3)	4	(0.7)	12	(1.5)
Neutropenic sepsis	0	(0.0)	1	(0.3)	1	(0.2)	0	(0.0)
Neutrophil count decreased	0	(0.0)	0	(0.0)	22	(3.9)	69	(8.7)
Every participant is counted a single time for each applicable specific adverse event. A participant with multiple adverse events within a bolded term is counted a single time for that bolded term.								
For KN-B15, treatment includes study medications and surgery.								
For KN-B15 and EV + Pembro Combo ISD, 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 KN-B15: 27OCT2025.								

Nausea, vomiting and diarrhoea

Table 65 Adverse Event Summary Other Risk for EV - Nausea, Vomiting, Diarrhea (APaT Population)

	KN-B15 EV + Pembro		KN-B15 Cis + Gem		EV + Pembro Combo ISD		EV Mono ISD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	403		396		564		793	
with one or more adverse events	257	(63.8)	262	(66.2)	391	(69.3)	562	(70.9)
with no adverse event	146	(36.2)	134	(33.8)	173	(30.7)	231	(29.1)
with drug-related ^a adverse events	159	(39.5)	222	(56.1)	274	(48.6)	418	(52.7)
with toxicity grade 3-5 adverse events	24	(6.0)	9	(2.3)	48	(8.5)	67	(8.4)
with toxicity grade 3-5 drug-related adverse events	11	(2.7)	4	(1.0)	32	(5.7)	40	(5.0)
with serious adverse events	12	(3.0)	5	(1.3)	30	(5.3)	39	(4.9)
with serious drug-related adverse events	6	(1.5)	1	(0.3)	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	6	(1.5)	2	(0.5)	10	(1.8)	0	(0.0)
discontinued Pembrolizumab	6	(1.5)	NA		10	(1.8)	NA	
discontinued EV	1	(0.2)	NA		6	(1.1)	0	(0.0)
discontinued any drug due to a drug-related adverse event	6	(1.5)	2	(0.5)	8	(1.4)	0	(0.0)
discontinued Pembrolizumab	6	(1.5)	NA		8	(1.4)	NA	
discontinued EV	1	(0.2)	NA		5	(0.9)	0	(0.0)
discontinued any drug due to a serious adverse event	2	(0.5)	0	(0.0)	3	(0.5)	0	(0.0)
discontinued Pembrolizumab	2	(0.5)	NA		3	(0.5)	NA	
discontinued EV	1	(0.2)	NA		2	(0.4)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	2	(0.5)	0	(0.0)	3	(0.5)	0	(0.0)
discontinued Pembrolizumab	2	(0.5)	NA		3	(0.5)	NA	
discontinued EV	1	(0.2)	NA		2	(0.4)	0	(0.0)
^a Determined by the investigator to be related to the drug.								
For KN-B15, treatment includes study medications and surgery.								
For KN-B15 and EV + Pembro Combo ISD, 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 KN-B15, grades are based on NCI CTCAE version 5.0.								
Database cutoff date for KN-B15: 27OCT2025.								

Table 66 Adverse Event Summary Other Risk for EV - Nausea, Vomiting, Diarrhea (APaT Population)

	KN-B15 EV + Pembro		KN-B15 Cis + Gem		EV + Pembro Combo ISD		EV Mono ISD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	403		396		564		793	
with one or more adverse events	257	(63.8)	262	(66.2)	391	(69.3)	562	(70.9)
with no adverse events	146	(36.2)	134	(33.8)	173	(30.7)	231	(29.1)
Nausea, Vomiting, Diarrhea	257	(63.8)	262	(66.2)	391	(69.3)	562	(70.9)
Diarrhoea	137	(34.0)	65	(16.4)	227	(40.2)	310	(39.1)
Nausea	114	(28.3)	185	(46.7)	166	(29.4)	300	(37.8)
Constipation	107	(26.6)	147	(37.1)	158	(28.0)	229	(28.9)
Vomiting	54	(13.4)	54	(13.6)	81	(14.4)	148	(18.7)
Abdominal pain	43	(10.7)	27	(6.8)	72	(12.8)	122	(15.4)
Abdominal pain lower	19	(4.7)	3	(0.8)	7	(1.2)	15	(1.9)
Abdominal pain upper	18	(4.5)	17	(4.3)	20	(3.5)	36	(4.5)
Abdominal distension	13	(3.2)	9	(2.3)	15	(2.7)	28	(3.5)
Flatulence	10	(2.5)	2	(0.5)	5	(0.9)	17	(2.1)
Non-cardiac chest pain	3	(0.7)	4	(1.0)	10	(1.8)	14	(1.8)
Eructation	2	(0.5)	4	(1.0)	2	(0.4)	4	(0.5)
Faeces soft	2	(0.5)	0	(0.0)	2	(0.4)	0	(0.0)
Frequent bowel movements	2	(0.5)	0	(0.0)	1	(0.2)	0	(0.0)
Anorectal discomfort	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Epigastric discomfort	1	(0.2)	0	(0.0)	0	(0.0)	2	(0.3)
Abdominal discomfort	0	(0.0)	2	(0.5)	5	(0.9)	12	(1.5)
Aerophagia	0	(0.0)	1	(0.3)	1	(0.2)	0	(0.0)
Defaecation urgency	0	(0.0)	0	(0.0)	2	(0.4)	3	(0.4)
Gastrointestinal pain	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)
Gastrointestinal sounds abnormal	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)
Oesophageal pain	0	(0.0)	1	(0.3)	1	(0.2)	0	(0.0)
Overflow diarrhoea	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
<p>Every participant is counted a single time for each applicable specific adverse event. A participant with multiple adverse events within a bolded term is counted a single time for that bolded term.</p> <p>For KN-B15, treatment includes study medications and surgery.</p> <p>For KN-B15 and EV + Pembro Combo ISD, non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.</p> <p>For EV Mono ISD, non-serious adverse events and serious adverse events up to 30 days of the last treatment are included.</p> <p>Database cutoff date for KN-B15: 27OCT2025.</p>								

• **Pembrolizumab**

Table 67 Participants With Adverse Events of Special Interest by AEOSI Category and Preferred Term for pembrolizumab (Incidence > 0% in One or More Treatment Groups) (APaT Population)

	KN-B15 EV + Pembro		KN-B15 Cis + Gem		EV + Pembro Combo ISD		Pembro Mono RSD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	403		396		564		7,631	
with one or more adverse events	192	(47.6)	21	(5.3)	264	(46.8)	2,095	(27.5)
with no adverse events	211	(52.4)	375	(94.7)	300	(53.2)	5,536	(72.5)
Adrenal Insufficiency	7	(1.7)	1	(0.3)	13	(2.3)	74	(1.0)
Addison's disease	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Adrenal insufficiency	7	(1.7)	0	(0.0)	13	(2.3)	69	(0.9)
Adrenocortical insufficiency acute	0	(0.0)	1	(0.3)	0	(0.0)	2	(0.0)
Secondary adrenocortical insufficiency	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Arthritis	0	(0.0)	0	(0.0)	3	(0.5)	5	(0.1)
Autoimmune arthritis	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Immune-mediated arthritis	0	(0.0)	0	(0.0)	3	(0.5)	1	(0.0)
Cholangitis Sclerosing	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Cholangitis sclerosing	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Colitis	11	(2.7)	1	(0.3)	19	(3.4)	159	(2.1)
Autoimmune colitis	0	(0.0)	0	(0.0)	0	(0.0)	6	(0.1)
Colitis	7	(1.7)	1	(0.3)	15	(2.7)	134	(1.8)
Colitis microscopic	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Enterocolitis	1	(0.2)	0	(0.0)	1	(0.2)	11	(0.1)
Immune-mediated enterocolitis	3	(0.7)	0	(0.0)	3	(0.5)	6	(0.1)
Encephalitis	1	(0.2)	0	(0.0)	1	(0.2)	5	(0.1)
Encephalitis	1	(0.2)	0	(0.0)	0	(0.0)	4	(0.1)
Encephalitis	1	(0.2)	0	(0.0)	1	(0.2)	5	(0.1)
Encephalitis autoimmune	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Immune-mediated encephalitis	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Exocrine Pancreatic Insufficiency	1	(0.2)	0	(0.0)	0	(0.0)	5	(0.1)
Pancreatic failure	1	(0.2)	0	(0.0)	0	(0.0)	5	(0.1)
Gastritis	5	(1.2)	2	(0.5)	9	(1.6)	57	(0.7)
Gastritis	5	(1.2)	2	(0.5)	7	(1.2)	52	(0.7)
Gastritis erosive	0	(0.0)	0	(0.0)	1	(0.2)	7	(0.1)
Haemorrhagic erosive gastritis	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Guillain-Barre Syndrome	0	(0.0)	1	(0.3)	0	(0.0)	6	(0.1)
Axonal neuropathy	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Demyelinating polyneuropathy	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Guillain-Barre syndrome	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Multifocal motor neuropathy	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)
Haemolytic Anaemia	0	(0.0)	0	(0.0)	1	(0.2)	2	(0.0)
Autoimmune haemolytic anaemia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Haemolytic anaemia	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.0)
Hepatitis	17	(4.2)	0	(0.0)	17	(3.0)	80	(1.0)
Autoimmune hepatitis	1	(0.2)	0	(0.0)	5	(0.9)	35	(0.5)
Drug-induced liver injury	0	(0.0)	0	(0.0)	1	(0.2)	8	(0.1)
Hepatitis	14	(3.5)	0	(0.0)	5	(0.9)	34	(0.4)
Encephalitis	1	(0.2)	0	(0.0)	1	(0.2)	5	(0.1)
Encephalitis autoimmune	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Immune-mediated encephalitis	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Exocrine Pancreatic Insufficiency	1	(0.2)	0	(0.0)	0	(0.0)	5	(0.1)
Pancreatic failure	1	(0.2)	0	(0.0)	0	(0.0)	5	(0.1)
Gastritis	5	(1.2)	2	(0.5)	9	(1.6)	57	(0.7)
Gastritis	5	(1.2)	2	(0.5)	7	(1.2)	52	(0.7)
Gastritis erosive	0	(0.0)	0	(0.0)	1	(0.2)	7	(0.1)
Haemorrhagic erosive gastritis	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Guillain-Barre Syndrome	0	(0.0)	1	(0.3)	0	(0.0)	6	(0.1)
Axonal neuropathy	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Demyelinating polyneuropathy	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Guillain-Barre syndrome	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Multifocal motor neuropathy	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)
Haemolytic Anaemia	0	(0.0)	0	(0.0)	1	(0.2)	2	(0.0)
Autoimmune haemolytic anaemia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Haemolytic anaemia	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.0)
Hepatitis	17	(4.2)	0	(0.0)	17	(3.0)	80	(1.0)
Autoimmune hepatitis	1	(0.2)	0	(0.0)	5	(0.9)	35	(0.5)
Drug-induced liver injury	0	(0.0)	0	(0.0)	1	(0.2)	8	(0.1)
Hepatitis	14	(3.5)	0	(0.0)	5	(0.9)	34	(0.4)

Infusion Reactions	12	(3.0)	8	(2.0)	12	(2.1)	165	(2.2)
Cytokine release syndrome	0	(0.0)	0	(0.0)	0	(0.0)	8	(0.1)
Drug hypersensitivity	4	(1.0)	1	(0.3)	3	(0.5)	24	(0.3)
Hypersensitivity	1	(0.2)	2	(0.5)	1	(0.2)	49	(0.6)
Infusion related reaction	6	(1.5)	5	(1.3)	8	(1.4)	75	(1.0)
Myasthenic Syndrome	1	(0.2)	0	(0.0)	3	(0.5)	8	(0.1)
Myasthenia gravis	1	(0.2)	0	(0.0)	3	(0.5)	5	(0.1)
Myasthenic syndrome	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Myelitis	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Myelitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Myelitis transverse	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Myocarditis	2	(0.5)	0	(0.0)	5	(0.9)	9	(0.1)
Immune-mediated myocarditis	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Myocarditis	2	(0.5)	0	(0.0)	4	(0.7)	9	(0.1)
Myositis	3	(0.7)	0	(0.0)	8	(1.4)	34	(0.4)
Dermatomyositis	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Myopathy	1	(0.2)	0	(0.0)	0	(0.0)	8	(0.1)
Myositis	2	(0.5)	0	(0.0)	6	(1.1)	22	(0.3)
Necrotising myositis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Rhabdomyolysis	0	(0.0)	0	(0.0)	2	(0.4)	3	(0.0)
Nephritis	5	(1.2)	1	(0.3)	6	(1.1)	37	(0.5)
Nephritis	5	(1.2)	1	(0.3)	6	(1.1)	37	(0.5)
Acute kidney injury	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Autoimmune nephritis	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Glomerulonephritis	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.0)
Glomerulonephritis acute	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Glomerulonephritis membranous	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Immune-mediated nephritis	0	(0.0)	0	(0.0)	3	(0.5)	0	(0.0)
Nephritis	3	(0.7)	0	(0.0)	0	(0.0)	10	(0.1)
Nephrotic syndrome	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Renal failure	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Tubulointerstitial nephritis	1	(0.2)	1	(0.3)	3	(0.5)	14	(0.2)
Optic Neuritis	0	(0.0)	0	(0.0)	2	(0.4)	2	(0.0)
Optic neuritis	0	(0.0)	0	(0.0)	2	(0.4)	2	(0.0)
Pancreatitis	6	(1.5)	0	(0.0)	9	(1.6)	28	(0.4)
Autoimmune pancreatitis	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.0)
Immune-mediated pancreatitis	2	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
Pancreatitis	4	(1.0)	0	(0.0)	7	(1.2)	24	(0.3)
Pancreatitis acute	1	(0.2)	0	(0.0)	1	(0.2)	4	(0.1)
Pericarditis	0	(0.0)	0	(0.0)	0	(0.0)	11	(0.1)
Autoimmune pericarditis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pericarditis	0	(0.0)	0	(0.0)	0	(0.0)	9	(0.1)
Pleuropericarditis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pneumonitis	28	(6.9)	1	(0.3)	57	(10.1)	324	(4.2)
Autoimmune lung disease	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Immune-mediated lung disease	3	(0.7)	0	(0.0)	8	(1.4)	4	(0.1)
Interstitial lung disease	1	(0.2)	0	(0.0)	5	(0.9)	29	(0.4)
Organising pneumonia	0	(0.0)	0	(0.0)	2	(0.4)	3	(0.0)
Pneumonitis	24	(6.0)	1	(0.3)	42	(7.4)	291	(3.8)
Sarcoidosis	1	(0.2)	0	(0.0)	2	(0.4)	20	(0.3)
Cutaneous sarcoidosis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pulmonary sarcoidosis	0	(0.0)	0	(0.0)	1	(0.2)	2	(0.0)
Sarcoidosis	1	(0.2)	0	(0.0)	1	(0.2)	18	(0.2)
Severe Skin Reactions	69	(17.1)	2	(0.5)	111	(19.7)	130	(1.7)
Cutaneous vasculitis	1	(0.2)	0	(0.0)	1	(0.2)	0	(0.0)
Dermatitis bullous	6	(1.5)	1	(0.3)	27	(4.8)	9	(0.1)
Dermatitis exfoliative	0	(0.0)	0	(0.0)	1	(0.2)	5	(0.1)
Dermatitis exfoliative generalised	6	(1.5)	0	(0.0)	4	(0.7)	2	(0.0)
Erythema multiforme	0	(0.0)	0	(0.0)	6	(1.1)	8	(0.1)
Exfoliative rash	2	(0.5)	0	(0.0)	1	(0.2)	2	(0.0)
Lichen planus	1	(0.2)	0	(0.0)	0	(0.0)	6	(0.1)
Lichen planus pemphigoides	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Oral lichen planus	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pemphigoid	1	(0.2)	0	(0.0)	5	(0.9)	3	(0.0)
Pemphigus	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Pruritus	13	(3.2)	0	(0.0)	10	(1.8)	16	(0.2)
Pruritus genital	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)

Severe Skin Reactions	69	(17.1)	2	(0.5)	111	(19.7)	130	(1.7)
Rash	15	(3.7)	1	(0.3)	1	(0.2)	44	(0.6)
Rash erythematous	0	(0.0)	0	(0.0)	3	(0.5)	1	(0.0)
Rash maculo-papular	19	(4.7)	0	(0.0)	54	(9.6)	23	(0.3)
Rash pruritic	2	(0.5)	0	(0.0)	1	(0.2)	4	(0.1)
Rash pustular	1	(0.2)	0	(0.0)	1	(0.2)	2	(0.0)
SJS-TEN overlap	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Skin necrosis	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Stevens-Johnson syndrome	4	(1.0)	0	(0.0)	0	(0.0)	4	(0.1)
Toxic epidermal necrolysis	0	(0.0)	0	(0.0)	3	(0.5)	0	(0.0)
Toxic skin eruption	6	(1.5)	0	(0.0)	6	(1.1)	4	(0.1)
Thyroiditis	6	(1.5)	0	(0.0)	5	(0.9)	74	(1.0)
Autoimmune thyroiditis	0	(0.0)	0	(0.0)	1	(0.2)	22	(0.3)
Immune-mediated thyroiditis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Silent thyroiditis	1	(0.2)	0	(0.0)	1	(0.2)	0	(0.0)
Thyroid disorder	2	(0.5)	0	(0.0)	0	(0.0)	3	(0.0)
Thyroiditis	3	(0.7)	0	(0.0)	3	(0.5)	50	(0.7)
Type 1 Diabetes Mellitus	6	(1.5)	0	(0.0)	1	(0.2)	34	(0.4)
Diabetic ketoacidosis	2	(0.5)	0	(0.0)	0	(0.0)	15	(0.2)
Fulminant type 1 diabetes mellitus	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Type 1 diabetes mellitus	3	(0.7)	0	(0.0)	1	(0.2)	25	(0.3)
Uveitis	4	(1.0)	0	(0.0)	1	(0.2)	25	(0.3)
Chorioretinitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)

	KN-B15 EV + Pembro		KN-B15 Cis + Gem		EV + Pembro Combo ISD		Pembro Mono RSD	
	n	(%)	n	(%)	n	(%)	n	(%)
Uveitis	4	(1.0)	0	(0.0)	1	(0.2)	25	(0.3)
Iridocyclitis	1	(0.2)	0	(0.0)	0	(0.0)	5	(0.1)
Iritis	1	(0.2)	0	(0.0)	0	(0.0)	4	(0.1)
Uveitis	2	(0.5)	0	(0.0)	1	(0.2)	16	(0.2)
Vasculitis	1	(0.2)	0	(0.0)	0	(0.0)	5	(0.1)
Giant cell arteritis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Vasculitis	1	(0.2)	0	(0.0)	0	(0.0)	4	(0.1)

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

For KN-B15, treatment includes study medications and surgery.

For KN-B15, 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.

Database cutoff date for KN-B15: 27OCT2025.

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.

In the perioperative EV + pembrolizumab group, 4 G-4 events (3 cases of Stevens-Johnson syndrome and 1 of dermatitis bullous) were reported; the median time to onset of first AEOSI of severe skin reaction in the perioperative EV + pembrolizumab group, EV + pembrolizumab ISD, and pembrolizumab RSD were 12.0 days, 79.0 days, and 85.0 days, respectively. At DCO, events for most participants with severe skin reactions (58/69 [84.1%]) were considered resolved. Severe skin reactions led to discontinuation of any study drug, enfortumab vedotin, and pembrolizumab for 5.5%, 5.0%, and 3.2%, respectively.

Analysis per treatment phases

Preoperative/Surgical Phase

Table 68 Participants with Adverse Events (Sorted by Decreasing Incidence) (Incidence ≥ 10% in One or More Treatment Groups) (Preoperative/Surgical Phase) (APaT Population)

	EV + Pembro		Cis + Gem	
	n	(%)	n	(%)
Participants in population	403		396	
with one or more adverse events	395	(98.0)	389	(98.2)
with no adverse events	8	(2.0)	7	(1.8)
Pruritus	162	(40.2)	18	(4.5)
Alopecia	119	(29.5)	44	(11.1)
Anaemia	108	(26.8)	223	(56.3)
Diarrhoea	105	(26.1)	65	(16.4)
Fatigue	102	(25.3)	111	(28.0)
Nausea	100	(24.8)	185	(46.7)
Decreased appetite	90	(22.3)	72	(18.2)
Alanine aminotransferase increased	88	(21.8)	39	(9.8)
Aspartate aminotransferase increased	86	(21.3)	20	(5.1)
Dysgeusia	86	(21.3)	37	(9.3)
Rash	86	(21.3)	11	(2.8)
Constipation	85	(21.1)	147	(37.1)
Asthenia	74	(18.4)	94	(23.7)
Rash maculo-papular	73	(18.1)	14	(3.5)
Urinary tract infection	71	(17.6)	84	(21.2)
Weight decreased	70	(17.4)	25	(6.3)
Neuropathy peripheral	55	(13.6)	12	(3.0)
Hyperglycaemia	54	(13.4)	22	(5.6)
Neutropenia	54	(13.4)	218	(55.1)
Prostate cancer	53	(13.2)	48	(12.1)
Peripheral sensory neuropathy	41	(10.2)	15	(3.8)
Pyrexia	39	(9.7)	40	(10.1)
Vomiting	39	(9.7)	54	(13.6)
Blood creatinine increased	37	(9.2)	73	(18.4)
Hypomagnesaemia	11	(2.7)	41	(10.4)
Leukopenia	11	(2.7)	75	(18.9)
Thrombocytopenia	7	(1.7)	113	(28.5)
<p>Every participant is counted a single time for each applicable row and column.</p> <p>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.</p> <p>Treatment includes preoperative study medications and surgery.</p> <p>Preoperative/surgical phase starts the date when the first treatment is administered and continues until the date the first postoperative study medications are administered.</p> <p>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.</p> <p>MedDRA V28.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.</p> <p>Database Cutoff Date: 27OCT2025.</p>				

Drug-related AEs, as assessed by the investigator, were similar in the perioperative EV + pembrolizumab group (93.8%) and the cis + gem group (93.9%). The most frequently reported drug-related AEs within each group (incidence ≥20%) were:

- **Perioperative EV + pembrolizumab:** pruritus (38.7%), alopecia (27.8%), rash (20.8%), and dysgeusia (20.1%)
- **Cis + gem:** neutropenia (54.0%), anemia (45.7%), nausea (43.2%), thrombocytopenia (26.5%), and fatigue (25.3%).

In general, these drug-related AEs were primarily Grade 1 or 2.

Grade 3- 5 AEs were reported in the 37.2% of the perioperative EV + pembrolizumab group and 46.5% in the cis + gem group (46.5%).

- **Perioperative EV + pembrolizumab:** neutropenia (6.2%), rash maculopapular (4.0%), rash (3.5%), and ALT increased, hyperglycemia, and pruritus (2.5% each)
- **Cis + gem:** neutropenia (32.3%), anemia (11.1%), thrombocytopenia (8.3%), and leukopenia (4.0%)

Adverse Events Leading to Surgery Delay or Cancellation

The median time from randomization to surgery in the perioperative EV + pembrolizumab group was 15.7 weeks (range: 6.0 to 55.1 weeks) and 15.9 weeks (range: 7.6 to 73.1 weeks) in the cis + gem group. The median time from last dose of neoadjuvant treatment to surgery was 5.4 weeks (range: 1.0 to 44.0 weeks) in the perioperative EV + pembrolizumab group and 5.3 weeks (range: 1.4 to 63.9 weeks) in the cis + gem group.

A delay in the undergoing surgery was defined as time from last neoadjuvant treatment to surgery [or time from randomization to surgery if no neoadjuvant treatment received] >8 weeks; it was registered in the 16.8% in the perioperative EV + pembrolizumab group and 14.4% in the cis + gem group.

Table 69 Participants With Adverse Events Resulting in Surgery Delay (Sorted by Decreasing Incidence) (Incidence > 0% in One or More Treatment Groups) (APrS Population)

	EV + Pembro		Cis + Gem	
	n	(%)	n	(%)
Participants in population	351		359	
with one or more adverse events	26	(7.4)	16	(4.5)
with no adverse events	325	(92.6)	343	(95.5)
Pneumonitis	4	(1.1)	0	(0.0)
Colitis	3	(0.9)	0	(0.0)
COVID-19	2	(0.6)	2	(0.6)
Stevens-Johnson syndrome	2	(0.6)	0	(0.0)
Arteriosclerosis	1	(0.3)	0	(0.0)
Asthenia	1	(0.3)	0	(0.0)
Decubitus ulcer	1	(0.3)	0	(0.0)
Dermatitis bullous	1	(0.3)	0	(0.0)
Diarrhoea	1	(0.3)	1	(0.3)
Haemorrhoidal haemorrhage	1	(0.3)	0	(0.0)
Hepatitis	1	(0.3)	0	(0.0)
Hypertransaminaemia	1	(0.3)	0	(0.0)
Ileus	1	(0.3)	0	(0.0)
Immune-mediated hepatitis	1	(0.3)	0	(0.0)
Immune-mediated pancreatitis	1	(0.3)	0	(0.0)
Influenza like illness	1	(0.3)	0	(0.0)
Neutropenia	1	(0.3)	1	(0.3)
Pneumonia	1	(0.3)	1	(0.3)
Pyrexia	1	(0.3)	0	(0.0)
Silent thyroiditis	1	(0.3)	0	(0.0)
Anaemia	0	(0.0)	1	(0.3)
Anaphylactic reaction	0	(0.0)	1	(0.3)
Aortic valve disease	0	(0.0)	1	(0.3)
COVID-19 pneumonia	0	(0.0)	1	(0.3)
Cardiac failure	0	(0.0)	1	(0.3)
Cardiac failure congestive	0	(0.0)	1	(0.3)
Cerebrovascular accident	0	(0.0)	1	(0.3)
Coronavirus infection	0	(0.0)	1	(0.3)
Endocarditis	0	(0.0)	1	(0.3)
Hepatic cancer	0	(0.0)	1	(0.3)
Myocardial infarction	0	(0.0)	1	(0.3)
Pulmonary embolism	0	(0.0)	3	(0.8)
Renal failure	0	(0.0)	1	(0.3)
SARS-CoV-2 test positive	0	(0.0)	1	(0.3)
Thrombocytopenia	0	(0.0)	1	(0.3)
Urosepsis	0	(0.0)	1	(0.3)
Every participant is counted a single time for each applicable row and column.				
Surgery delay is defined as time from last preoperative treatment to surgery > 8 weeks.				
Database Cutoff Date: 27OCT2025.				

The number of surgical cancellations was 52/403 in the perioperative EV + pembrolizumab group and 37/396 in the cis + gem group; those related to AEs are reported in the table below.

Table 70 Participants With Adverse Events Resulting in Surgery Cancellation (Sorted by Decreasing Incidence) (Incidence > 0% in One or More Treatment Groups) (ITT Population)

	EV + Pembro		Cis + Gem	
	n	(%)	n	(%)
Participants in population	403		396	
with one or more adverse events	13	(3.2)	6	(1.5)
with no adverse events	390	(96.8)	390	(98.5)
Multiple organ dysfunction syndrome	2	(0.5)	0	(0.0)
Adenocarcinoma of colon	1	(0.2)	0	(0.0)
COVID-19 pneumonia	1	(0.2)	0	(0.0)
Cardiac arrest	1	(0.2)	0	(0.0)
Chronic obstructive pulmonary disease	1	(0.2)	0	(0.0)
Coronary artery disease	1	(0.2)	0	(0.0)
Glomerulonephritis	1	(0.2)	0	(0.0)
Immune-mediated lung disease	1	(0.2)	0	(0.0)
Myocarditis	1	(0.2)	0	(0.0)
Pneumonia	1	(0.2)	1	(0.3)
Pneumonitis	1	(0.2)	0	(0.0)
Urosepsis	1	(0.2)	0	(0.0)
Angioedema	0	(0.0)	1	(0.3)
Cardiac failure	0	(0.0)	1	(0.3)
Cerebral infarction	0	(0.0)	1	(0.3)
Myocardial infarction	0	(0.0)	1	(0.3)
Pulmonary fibrosis	0	(0.0)	1	(0.3)
Every participant is counted a single time for each applicable row and column. Database Cutoff Date: 27OCT2025.				

AESI during the Preoperative/Surgical phase

Skin reactions: 62.0% in the perioperative EV + pembrolizumab group and 12.9% in the cis + gem group. Serious skin reactions were reported for 5.5% of participants.

Peripheral neuropathy: 34.2% in the perioperative EV + pembrolizumab group and 11.4% in the cis + gem group. Sensory (32.8%) were more common than motor events (3.0%); Serious events of peripheral neuropathy were reported for 1 participant (0.2%).

Hyperglycemia: 16.6% in the perioperative EV + pembrolizumab group and 7.3% in the cis + gem group. Serious events of hyperglycemia were reported for 1.5% of participants

Ocular disorders: 23.6% in the perioperative EV + pembrolizumab group and 3.5% in the cis + gem group. There were no participants with serious ocular disorders.

IRR: 1.2% in the perioperative EV + pembrolizumab group and 4.5% in the cis + gem group. There were no serious IRR events.

Adverse Events in the Surgical Phase and Surgical Mortality

Surgical Phase was defined as the period from the time of surgery until 30/90 days after surgery for nonserious AEs/SAEs, or until the start of adjuvant study medication (applicable for the perioperative EV + pembrolizumab group only).

Table 71 Adverse Event Summary (Surgical Phase) (APrS Population)

	EV + Pembro		Cis + Gem	
	n	(%)	n	(%)
Participants in population	351		359	
with one or more adverse events	248	(70.7)	234	(65.2)
with no adverse event	103	(29.3)	125	(34.8)
with drug-related ^a adverse events	38	(10.8)	14	(3.9)
with toxicity grade 3-5 adverse events	127	(36.2)	127	(35.4)
with toxicity grade 3-5 drug-related ^a adverse events	7	(2.0)	2	(0.6)
with serious adverse events	137	(39.0)	143	(39.8)
with serious drug-related ^a adverse events	5	(1.4)	3	(0.8)
who died	2	(0.6)	9	(2.5)
who died due to a drug-related ^a adverse event	0	(0.0)	0	(0.0)
discontinued any drug due to an adverse event	7	(2.0)	1	(0.3)
discontinued pembrolizumab	5	(1.4)	0	(0.0)
discontinued EV	5	(1.4)	0	(0.0)
discontinued any drug due to a drug-related ^a adverse event	5	(1.4)	0	(0.0)
discontinued pembrolizumab	3	(0.9)	0	(0.0)
discontinued EV	3	(0.9)	0	(0.0)
discontinued any drug due to a serious adverse event	5	(1.4)	1	(0.3)
discontinued pembrolizumab	5	(1.4)	0	(0.0)
discontinued EV	3	(0.9)	0	(0.0)
discontinued any drug due to a serious drug-related ^a adverse event	3	(0.9)	0	(0.0)
discontinued pembrolizumab	3	(0.9)	0	(0.0)
discontinued EV	1	(0.3)	0	(0.0)
^a Determined by the investigator to be related to any drug. Non-serious adverse events up to 30 days of surgery and serious adverse events up to 90 days of surgery and prior to the postoperative study medication (if applicable) are included. MedDRA V28.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded. Grades are based on NCI CTCAE version 5.0. Database Cutoff Date: 27OCT2025.				

Table 72 Participants with Adverse Events (Sorted by Decreasing Incidence) (Incidence > 2% in One or More Treatment Groups) (Surgical Phase) (APrS Population)

	EV + Pembro		Cis + Gem	
	n	(%)	n	(%)
Participants in population	351		359	
with one or more adverse events	248	(70.7)	234	(65.2)
with no adverse events	103	(29.3)	125	(34.8)
Anaemia	55	(15.7)	35	(9.7)
Prostate cancer	51	(14.5)	47	(13.1)
Urinary tract infection	29	(8.3)	44	(12.3)
Constipation	25	(7.1)	30	(8.4)
Hypoalbuminaemia	23	(6.6)	13	(3.6)
Decreased appetite	22	(6.3)	9	(2.5)
Procedural pain	18	(5.1)	20	(5.6)
Nausea	14	(4.0)	11	(3.1)
Abdominal pain	13	(3.7)	20	(5.6)
Asthenia	13	(3.7)	7	(1.9)
Fatigue	13	(3.7)	2	(0.6)
Urosepsis	13	(3.7)	10	(2.8)
Weight decreased	13	(3.7)	3	(0.8)
Vomiting	12	(3.4)	7	(1.9)
Diarrhoea	11	(3.1)	12	(3.3)
Hydronephrosis	11	(3.1)	7	(1.9)
Pyrexia	11	(3.1)	22	(6.1)
Hypocalcaemia	10	(2.8)	8	(2.2)
Acute kidney injury	9	(2.6)	10	(2.8)
Blood creatinine increased	9	(2.6)	12	(3.3)
Wound dehiscence	9	(2.6)	1	(0.3)
Ileus	8	(2.3)	5	(1.4)
Sepsis	8	(2.3)	12	(3.3)
Urinary incontinence	8	(2.3)	8	(2.2)
Abdominal pain lower	7	(2.0)	1	(0.3)
Erectile dysfunction	7	(2.0)	5	(1.4)
Ileus paralytic	7	(2.0)	6	(1.7)
Pneumonia	7	(2.0)	5	(1.4)
Abdominal distension	6	(1.7)	4	(1.1)
Hypertension	6	(1.7)	3	(0.8)
Hypokalaemia	6	(1.7)	14	(3.9)
Neuropathy peripheral	6	(1.7)	0	(0.0)
Pyelonephritis acute	6	(1.7)	5	(1.4)

Postsurgical adverse events

Table 73 Participants with Adverse Events (Sorted by Decreasing Incidence) (Incidence $\geq 10\%$) (Postoperative Phase) (APaT Population – Participants Who Received Postoperative EV/Pembrolizumab)

	EV + Pembro	
	n	(%)
Participants in population	262	
with one or more adverse events	252	(96.2)
with no adverse events	10	(3.8)
Pruritus	65	(24.8)
Diarrhoea	64	(24.4)
Urinary tract infection	50	(19.1)
Decreased appetite	35	(13.4)
Anaemia	34	(13.0)
Asthenia	34	(13.0)
Constipation	30	(11.5)
Nausea	29	(11.1)
Rash	29	(11.1)

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 V28.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 27OCT2025.

Table 74 Participants with Grade 3-5 Adverse Events (Sorted by Decreasing Incidence) (Incidence $\geq 5\%$) (Postoperative Phase) (APaT Population – Participants Who Received Postoperative EV/Pembrolizumab)

	EV + Pembro	
	n	(%)
Participants in population	262	
with one or more adverse events	124	(47.3)
with no adverse events	138	(52.7)
Urinary tract infection	21	(8.0)

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 V28.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 5.0.
Database Cutoff Date: 27OCT2025.

The median time to onset of the first Grade 3 to 5 AE for the perioperative EV + pembrolizumab group in the Postoperative Phase was 74.0 days (range: 1 to 362 days). **Drug-related 3-5 AEs** were reported in the 21.4%, in absence of events reported with incidence $\geq 2\%$. **SAE:** 35.1% of participants experienced SAEs. The most frequently reported SAEs (incidence $\geq 2\%$) in the perioperative EV + pembrolizumab group were UTI (8.0%) and sepsis (2.7%). SAE considered drug-related were described in the 11.8% of participants in the perioperative EV + pembrolizumab; No drug-related SAEs were reported with frequency $\geq 2\%$. No deaths due to AEs in the Postoperative Phase were assessed as drug-related by the Investigator.

Adverse Events Resulting in Treatment Discontinuation in the postoperative phase

Overall, 28.6%, 21.8%, and 13.7% of participants in the perioperative EV + pembrolizumab group experienced AEs resulting in discontinuation of any study drug, discontinuation of pembrolizumab, and discontinuation of enfortumab vedotin, respectively.

AEs resulting in discontinuation of any study drug and pembrolizumab for $\geq 2\%$ of participants were diarrhea and pneumonitis (2.3% each), respectively. All AEs resulting in discontinuation of enfortumab vedotin occurred in $<2\%$ of participants.

Diarrhoea and pneumonitis were identified as the commonly reported drug-related AEs leading to any drug discontinuation for pembrolizumab, while peripheral neuropathy was the most common reported in the EV (1.1%).

Adverse Events Resulting in Treatment Interruption in the postoperative phase

Overall, 43.9%, 37.4%, and 29.8% of participants in the perioperative EV + pembrolizumab group experienced AEs resulting in interruption of any study drug, interruption of pembrolizumab, and interruption of enfortumab vedotin, respectively. AEs resulting in interruption of any study drug, interruption of pembrolizumab, and interruption of enfortumab vedotin for $\geq 2\%$ of participants in the perioperative EV + pembrolizumab group were:

- Any drug: diarrhea (6.5%), UTI (6.1%), COVID-19 (2.7%), and pyrexia (2.3%)
- Pembrolizumab: diarrhea (5.3%), UTI (5.0%), and COVID-19 (2.3%)
- Enfortumab vedotin: UTI (4.6%), diarrhea (4.2%), and COVID-19 (2.3%)

Diarrhea was the most common reported Drug-related AEs resulting in interruption in the any study drug, pembrolizumab (4.6% each), and enfortumab vedotin (3.1%).

Adverse Events Resulting in Dose reduction in the postoperative phase

In the Postoperative Phase, 4.6% of participants in the perioperative EV + pembrolizumab group experienced AEs resulting in dose reduction of enfortumab vedotin. All AEs resulting in dose reduction of enfortumab vedotin occurred in $<1\%$ of participants.

Laboratory findings

Haematology

See sections on AESIs anaemia and neutropenia.

Clinical chemistry

Laboratory abnormalities were generally consistent with the EV + pembrolizumab ISD and individual safety datasets 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. See also section on AESI hyperglycemia.

Liver chemistry

Table 75 Participants with Liver Function Laboratory findings that met predetermined criteria (APaT Population)

Criteria	KN-B15 EV + Pembro		KN-B15 Cis + Gem		EV + Pembro Combo ISD		EV Mono ISD	
	n/m	(%)	n/m	(%)	n/m	(%)	n/m	(%)
Participants in population	403		396		564		793	
Alanine Aminotransferase								
≥3 x ULN	72/403	(17.9)	11/393	(2.8)	85/563	(15.1)	31/785	(3.9)
≥5 x ULN	34/403	(8.4)	2/393	(0.5)	33/563	(5.9)	9/785	(1.1)
≥10 x ULN	14/403	(3.5)	2/393	(0.5)	9/563	(1.6)	2/785	(0.3)
≥20 x ULN	3/403	(0.7)	1/393	(0.3)	4/563	(0.7)	0/785	(0.0)
Aspartate Aminotransferase								
≥3 x ULN	65/403	(16.1)	6/393	(1.5)	85/562	(15.1)	59/784	(7.5)
≥5 x ULN	32/403	(7.9)	3/393	(0.8)	33/562	(5.9)	17/784	(2.2)
≥10 x ULN	11/403	(2.7)	1/393	(0.3)	10/562	(1.8)	2/784	(0.3)
≥20 x ULN	3/403	(0.7)	1/393	(0.3)	4/562	(0.7)	0/784	(0.0)
Aminotransferase (ALT or AST)								
≥3 x ULN	84/403	(20.8)	13/393	(3.3)	106/563	(18.8)	68/785	(8.7)
≥5 x ULN	42/403	(10.4)	3/393	(0.8)	45/563	(8.0)	20/785	(2.5)
≥10 x ULN	19/403	(4.7)	2/393	(0.5)	13/563	(2.3)	3/785	(0.4)
≥20 x ULN	4/403	(1.0)	1/393	(0.3)	4/563	(0.7)	0/785	(0.0)
Bilirubin								
≥2 x ULN	15/403	(3.7)	7/393	(1.8)	13/563	(2.3)	13/785	(1.7)
Alkaline Phosphatase								
≥1.5 x ULN	51/403	(12.7)	29/393	(7.4)	144/563	(25.6)	151/785	(19.2)
Aminotransferase (ALT or AST) and Bilirubin								
AT ≥3 x ULN and BILI ≥1.5 x ULN	7/403	(1.7)	2/393	(0.5)	12/563	(2.1)	8/785	(1.0)
Aminotransferase (ALT or AST) and Bilirubin								
AT ≥3 x ULN and BILI ≥2 x ULN	5/403	(1.2)	1/393	(0.3)	7/563	(1.2)	6/785	(0.8)
Aminotransferase (ALT or AST) and Bilirubin and Alkaline Phosphatase								
AT ≥3 x ULN and BILI ≥2 x ULN and ALP <2 x ULN	2/403	(0.5)	0/393	(0.0)	2/563	(0.4)	3/785	(0.4)
<p>n = Number of participants with postbaseline test results (or combination of test results from the same day) that met predetermined criteria.</p> <p>m = Number of participants with at least one postbaseline test result or combination of test results from the same day.</p> <p>ALP = Alkaline phosphatase; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; AT = Aminotransferase (ALT or AST); BILI = Bilirubin; ULN = Upper limit of normal range.</p> <p>Database cutoff date for KN-B15: 27OCT2025.</p>								

Safety in special populations

• Age

Table 76 Adverse Event Summary by Age Category (< 65, 65-74, 75-84, >= 85 Years) (APaT Population)

Adverse Event Summary by Age Category (< 65, >= 65 Years)
(APaT Population)

	KN-B15 EV + Pembro		KN-B15 Cis + Gem		EV + Pembro Combo ISD		EV Mono ISD	
	<65	>=65	<65	>=65	<65	>=65	<65	>=65
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Participants in population	157	246	154	242	173	391	279	514
with one or more adverse events	155 (98.7)	240 (97.6)	151 (98.1)	238 (98.3)	173 (100.0)	390 (99.7)	278 (99.6)	508 (98.8)
with no adverse event	2 (1.3)	6 (2.4)	3 (1.9)	4 (1.7)	0 (0.0)	1 (0.3)	1 (0.4)	6 (1.2)
with drug-related* adverse events	151 (96.2)	237 (96.3)	144 (93.5)	228 (94.2)	168 (97.1)	382 (97.7)	266 (95.3)	481 (93.6)
with toxicity grade 3-5 adverse events	113 (72.0)	192 (78.0)	95 (61.7)	171 (70.7)	114 (65.9)	321 (82.1)	188 (67.4)	377 (73.3)
with toxicity grade 3-5 drug-related adverse events	66 (42.0)	121 (49.2)	65 (42.2)	119 (49.2)	81 (46.8)	248 (63.4)	128 (45.9)	276 (53.7)
with serious adverse events	91 (58.0)	164 (66.7)	65 (42.2)	125 (51.7)	64 (37.0)	231 (59.1)	121 (43.4)	242 (47.1)
with serious drug-related adverse events	34 (21.7)	61 (24.8)	14 (9.1)	28 (11.6)	31 (17.9)	124 (31.7)	55 (19.7)	107 (20.8)
who died	2 (1.3)	15 (6.1)	1 (0.6)	10 (4.1)	8 (4.6)	22 (5.6)	14 (5.0)	42 (8.2)
who died due to a drug-related adverse event	1 (0.6)	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	9 (2.3)	5 (1.8)	12 (2.3)
discontinued any drug due to an adverse event	57 (36.3)	115 (46.7)	20 (13.0)	42 (17.4)	80 (46.2)	199 (50.9)	50 (17.9)	118 (23.0)
discontinued any drug due to a drug-related adverse event	49 (31.2)	93 (37.8)	15 (9.7)	29 (12.0)	71 (41.0)	181 (46.3)	33 (11.8)	87 (16.9)
discontinued any drug due to a serious adverse event	25 (15.9)	62 (25.2)	1 (0.6)	19 (7.9)	19 (11.0)	65 (16.6)	24 (8.6)	56 (10.9)
discontinued any drug due to a serious drug-related adverse event	20 (12.7)	40 (16.3)	0 (0.0)	7 (2.9)	12 (6.9)	50 (12.8)	12 (4.3)	33 (6.4)
discontinued any drug due to a serious drug-related adverse event	20 (12.7)	29 (14.6)	11 (22.9)	0 (0.0)	0 (0.0)	4 (2.1)	2 (4.3)	1 (100.0)

	Pembro Mono RSD			
	<65	65-74	75-84	>=85
	n (%)	n (%)	n (%)	n (%)
Participants in population	4,524	2,173	824	110
with one or more adverse events	4,364 (96.5)	2,097 (96.5)	805 (97.7)	109 (99.1)
with no adverse event	160 (3.5)	76 (3.5)	19 (2.3)	1 (0.9)
with drug-related* adverse events	3,231 (71.4)	1,552 (71.4)	594 (72.1)	85 (77.3)
with toxicity grade 3-5 adverse events	1,917 (42.4)	1,071 (49.3)	457 (55.5)	69 (62.7)
with toxicity grade 3-5 drug-related adverse events	629 (13.9)	391 (18.0)	163 (19.8)	25 (22.7)
with serious adverse events	1,457 (32.2)	839 (38.6)	387 (47.0)	59 (53.6)
with serious drug-related adverse events	451 (10.0)	265 (12.2)	105 (12.7)	19 (17.3)
who died	158 (3.5)	113 (5.2)	63 (7.6)	12 (10.9)
who died due to a drug-related adverse event	21 (0.5)	13 (0.6)	7 (0.8)	1 (0.9)
discontinued any drug due to an adverse event	554 (12.2)	327 (15.0)	168 (20.4)	17 (15.5)
discontinued any drug due to a drug-related adverse event	333 (7.4)	206 (9.5)	92 (11.2)	8 (7.3)
discontinued any drug due to a serious adverse event	366 (8.1)	214 (9.8)	120 (14.6)	14 (12.7)

	EV + Pembro Combo ISD				EV Mono ISD			
	<65	65-74	75-84	>=85	<65	65-74	75-84	>=85
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
discontinued any drug due to a serious drug-related adverse event	12 (6.9)	34 (13.8)	14 (11.2)	2 (10.5)	12 (4.3)	17 (5.5)	13 (7.1)	3 (15.0)
discontinued any drug due to a serious drug-related adverse event	177 (3.9)	113 (5.2)	52 (6.3)	5 (4.5)				

*Determined by the investigator to be related to the drug.

For KN-B15, treatment includes study medications and surgery.

For KN-B15, 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.

For KN-B15, grades are based on NCI CTCAE version 5.0.

Database cutoff date for KN-B15: 27OCT2025.

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 77 Adverse Event Summary by Sex (Male, Female) (APaT Population)

	KN-B15 EV + Pembro				KN-B15 Cis + Gem				EV + Pembro Combo ISD				EV Mono ISD			
	M		F		M		F		M		F		M		F	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	325		78		320		76		432		132		584		209	
with one or more adverse events	319	(98.2)	76	(97.4)	314	(98.1)	75	(98.7)	431	(99.8)	132	(100.0)	580	(99.3)	206	(98.6)
with no adverse event	6	(1.8)	2	(2.6)	6	(1.9)	1	(1.3)	1	(0.2)	0	(0.0)	4	(0.7)	3	(1.4)
with drug-related* adverse events	313	(96.3)	75	(96.2)	300	(93.8)	72	(94.7)	422	(97.7)	128	(97.0)	547	(93.7)	200	(95.7)
with toxicity grade 3-5 adverse events	245	(75.4)	60	(76.9)	216	(67.5)	50	(65.8)	334	(77.3)	101	(76.5)	412	(70.5)	153	(73.2)
with toxicity grade 3-5 drug-related adverse events	149	(45.8)	38	(48.7)	147	(45.9)	37	(48.7)	261	(60.4)	68	(51.5)	296	(50.7)	108	(51.7)
with serious adverse events	208	(64.0)	47	(60.3)	157	(49.1)	33	(43.4)	234	(54.2)	61	(46.2)	272	(46.6)	91	(43.5)
with serious drug-related adverse events	77	(23.7)	18	(23.1)	34	(10.6)	8	(10.5)	126	(29.2)	29	(22.0)	123	(21.1)	39	(18.7)
who died	14	(4.3)	3	(3.8)	8	(2.5)	3	(3.9)	22	(5.1)	8	(6.1)	40	(6.8)	16	(7.7)
who died due to a drug-related adverse event	2	(0.6)	0	(0.0)	0	(0.0)	1	(1.3)	7	(1.6)	2	(1.5)	14	(2.4)	3	(1.4)
discontinued any drug due to an adverse event	135	(41.5)	37	(47.4)	49	(15.3)	13	(17.1)	223	(51.6)	56	(42.4)	125	(21.4)	43	(20.6)
discontinued any drug due to a drug-related adverse event	109	(33.5)	33	(42.3)	37	(11.6)	7	(9.2)	206	(47.7)	46	(34.8)	94	(16.1)	26	(12.4)
discontinued any drug due to a serious adverse event	68	(20.9)	19	(24.4)	12	(3.8)	8	(10.5)	72	(16.7)	12	(9.1)	57	(9.8)	23	(11.0)
discontinued any drug due to a serious drug-related adverse event	46	(14.2)	14	(17.9)	5	(1.6)	2	(2.6)	57	(13.2)	5	(3.8)	35	(6.0)	10	(4.8)

	Pembro Mono RSD			
	M		F	
	n	(%)	n	(%)
Participants in population	4,889		2,742	
with one or more adverse events	4,711	(96.4)	2,664	(97.2)
with no adverse event	178	(3.6)	78	(2.8)
with drug-related* adverse events	3,457	(70.7)	2,005	(73.1)
with toxicity grade 3-5 adverse events	2,265	(46.3)	1,249	(45.6)
with toxicity grade 3-5 drug-related adverse events	814	(16.6)	394	(14.4)
with serious adverse events	1,797	(36.8)	945	(34.5)
with serious drug-related adverse events	566	(11.6)	274	(10.0)
who died	240	(4.9)	106	(3.9)
who died due to a drug-related adverse event	27	(0.6)	15	(0.5)
discontinued any drug due to an adverse event	695	(14.2)	371	(13.5)
discontinued any drug due to a drug-related adverse event	418	(8.5)	221	(8.1)
discontinued any drug due to a serious adverse event	473	(9.7)	241	(8.8)
discontinued any drug due to a serious drug-related adverse event	233	(4.8)	114	(4.2)

*Determined by the investigator to be related to the drug.
For KN-B15, treatment includes study medications and surgery.
For KN-B15, 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.
For KN-B15, grades are based on NCI CTCAE version 5.0.
Database cutoff date for KN-B15: 27OCT2025.

- **Race**

Table 78 Adverse Event Summary by Race (White, All Others, Null) (APaT Population)

	KN-B15 EV + Pembro						KN-B15 Cis + Gem					
	White		All Others		Null		White		All Others		Null	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	327		76		0		307		87		2	
with one or more adverse events	319	(97.6)	76	(100.0)	0	(0.0)	302	(98.4)	85	(97.7)	2	(100.0)
with no adverse event	8	(2.4)	0	(0.0)	0	(0.0)	5	(1.6)	2	(2.3)	0	(0.0)
with drug-related* adverse events	312	(95.4)	76	(100.0)	0	(0.0)	286	(93.2)	84	(96.6)	2	(100.0)
with toxicity grade 3-5 adverse events	243	(74.3)	62	(81.6)	0	(0.0)	201	(65.5)	64	(73.6)	1	(50.0)
with toxicity grade 3-5 drug-related adverse events	149	(45.6)	38	(50.0)	0	(0.0)	131	(42.7)	52	(59.8)	1	(50.0)
with serious adverse events	206	(63.0)	49	(64.5)	0	(0.0)	151	(49.2)	38	(43.7)	1	(50.0)
with serious drug-related adverse events	76	(23.2)	19	(25.0)	0	(0.0)	31	(10.1)	10	(11.5)	1	(50.0)
who died	13	(4.0)	4	(5.3)	0	(0.0)	10	(3.3)	1	(1.1)	0	(0.0)
who died due to a drug-related adverse event	2	(0.6)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)
discontinued any drug due to an adverse event	143	(43.7)	29	(38.2)	0	(0.0)	51	(16.6)	11	(12.6)	0	(0.0)
discontinued any drug due to a drug-related adverse event	116	(35.5)	26	(34.2)	0	(0.0)	34	(11.1)	10	(11.5)	0	(0.0)
discontinued any drug due to a serious adverse event	71	(21.7)	16	(21.1)	0	(0.0)	19	(6.2)	1	(1.1)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	47	(14.4)	13	(17.1)	0	(0.0)	6	(2.0)	1	(1.1)	0	(0.0)

	EV + Pembro Combo ISD						EV Mono ISD					
	White		All Others		Null		White		All Others		Null	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	410		154		0		527		225		41	
with one or more adverse events	409	(99.8)	154	(100.0)	0	(0.0)	524	(99.4)	224	(99.6)	38	(92.7)
with no adverse event	1	(0.2)	0	(0.0)	0	(0.0)	3	(0.6)	1	(0.4)	3	(7.3)
with drug-related* adverse events	399	(97.3)	151	(98.1)	0	(0.0)	499	(94.7)	214	(95.1)	34	(82.9)
with toxicity grade 3-5 adverse events	312	(76.1)	123	(79.9)	0	(0.0)	366	(69.4)	177	(78.7)	22	(53.7)
with toxicity grade 3-5 drug-related adverse events	234	(57.1)	95	(61.7)	0	(0.0)	251	(47.6)	138	(61.3)	15	(36.6)
with serious adverse events	206	(50.2)	89	(57.8)	0	(0.0)	249	(47.2)	100	(44.4)	14	(34.1)
with serious drug-related adverse events	97	(23.7)	58	(37.7)	0	(0.0)	103	(19.5)	51	(22.7)	8	(19.5)
who died	23	(5.6)	7	(4.5)	0	(0.0)	35	(6.6)	15	(6.7)	6	(14.6)
who died due to a drug-related adverse event	6	(1.5)	3	(1.9)	0	(0.0)	12	(2.3)	4	(1.8)	1	(2.4)
discontinued any drug due to an adverse event	213	(52.0)	66	(42.9)	0	(0.0)	121	(23.0)	39	(17.3)	8	(19.5)
discontinued any drug due to a drug-related adverse event	192	(46.8)	60	(39.0)	0	(0.0)	81	(15.4)	33	(14.7)	6	(14.6)
discontinued any drug due to a serious adverse event	63	(15.4)	21	(13.6)	0	(0.0)	60	(11.4)	16	(7.1)	4	(9.8)
discontinued any drug due to a serious drug-related adverse event	45	(11.0)	17	(11.0)	0	(0.0)	31	(5.9)	12	(5.3)	2	(4.9)

ECOG Status

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

	KN-B15 EV + Pembro				KN-B15 Cis + Gem			
	[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	317		86		305		91	
with one or more adverse events	313	(98.7)	82	(95.3)	300	(98.4)	89	(97.8)
with no adverse event	4	(1.3)	4	(4.7)	5	(1.6)	2	(2.2)
with drug-related* adverse events	309	(97.5)	79	(91.9)	290	(95.1)	82	(90.1)
with toxicity grade 3-5 adverse events	240	(75.7)	65	(75.6)	208	(68.2)	58	(63.7)
with toxicity grade 3-5 drug-related adverse events	152	(47.9)	35	(40.7)	141	(46.2)	43	(47.3)
with serious adverse events	200	(63.1)	55	(64.0)	144	(47.2)	46	(50.5)
with serious drug-related adverse events	78	(24.6)	17	(19.8)	33	(10.8)	9	(9.9)
who died	9	(2.8)	8	(9.3)	5	(1.6)	6	(6.6)
who died due to a drug-related adverse event	2	(0.6)	0	(0.0)	0	(0.0)	1	(1.1)
discontinued any drug due to an adverse event	130	(41.0)	42	(48.8)	49	(16.1)	13	(14.3)
discontinued any drug due to a drug-related adverse event	110	(34.7)	32	(37.2)	34	(11.1)	10	(11.0)
discontinued any drug due to a serious adverse event	63	(19.9)	24	(27.9)	16	(5.2)	4	(4.4)
discontinued any drug due to a serious drug-related adverse event	47	(14.8)	13	(15.1)	5	(1.6)	2	(2.2)

	EV + Pembro Combo ISD				EV Mono ISD			
	[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	273		258		284		485	
with one or more adverse events	273	(100.0)	257	(99.6)	281	(98.9)	481	(99.2)
with no adverse event	0	(0.0)	1	(0.4)	3	(1.1)	4	(0.8)
with drug-related* adverse events	271	(99.3)	250	(96.9)	271	(95.4)	456	(94.0)
with toxicity grade 3-5 adverse events	209	(76.6)	199	(77.1)	193	(68.0)	354	(73.0)
with toxicity grade 3-5 drug-related adverse events	174	(63.7)	135	(52.3)	149	(52.5)	244	(50.3)
with serious adverse events	130	(47.6)	148	(57.4)	111	(39.1)	240	(49.5)
with serious drug-related adverse events	80	(29.3)	66	(25.6)	53	(18.7)	105	(21.6)
who died	7	(2.6)	19	(7.4)	11	(3.9)	40	(8.2)
who died due to a drug-related adverse event	2	(0.7)	5	(1.9)	3	(1.1)	12	(2.5)
discontinued any drug due to an adverse event	143	(52.4)	117	(45.3)	62	(21.8)	100	(20.6)
discontinued any drug due to a drug-related adverse event	132	(48.4)	102	(39.5)	52	(18.3)	64	(13.2)
discontinued any drug due to a serious adverse event	44	(16.1)	35	(13.6)	21	(7.4)	54	(11.1)
discontinued any drug due to a serious drug-related adverse event	35	(12.8)	23	(8.9)	15	(5.3)	27	(5.6)

	Pembro Mono RSD			
	[0] Normal Activity		[1] Symptoms, but ambulatory	
	n	(%)	n	(%)
Participants in population	4,016		3,440	
with one or more adverse events	3,883	(96.7)	3,324	(96.6)
with no adverse event	133	(3.3)	116	(3.4)
with drug-related* adverse events	3,072	(76.5)	2,295	(66.7)
with toxicity grade 3-5 adverse events	1,540	(38.3)	1,866	(54.2)
with toxicity grade 3-5 drug-related adverse events	623	(15.5)	555	(16.1)
with serious adverse events	1,157	(28.8)	1,491	(43.3)
with serious drug-related adverse events	442	(11.0)	381	(11.1)
who died	93	(2.3)	237	(6.9)
who died due to a drug-related adverse event	13	(0.3)	29	(0.8)
discontinued any drug due to an adverse event	515	(12.8)	522	(15.2)
discontinued any drug due to a drug-related adverse event	379	(9.4)	247	(7.2)
discontinued any drug due to a serious adverse event	296	(7.4)	397	(11.5)
discontinued any drug due to a serious drug-related adverse event	184	(4.6)	156	(4.5)

*Determined by the investigator to be related to the drug.
For KN-B15, treatment includes study medications and surgery.
For KN-B15, 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.
For KN-B15, grades are based on NCI CTCAE version 5.0.
Database cutoff date for KN-B15: 27OCT2025.
The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Source: [ISS: adam-adsl; adae]

	Pembro Mono RSD					
	White		All Others		Null	
	n	(%)	n	(%)	n	(%)
Participants in population	5,838		1,122		671	
with one or more adverse events	5,661	(97.0)	1,078	(96.1)	636	(94.8)
with no adverse event	177	(3.0)	44	(3.9)	35	(5.2)
with drug-related* adverse events	4,182	(71.6)	749	(66.8)	531	(79.1)
with toxicity grade 3-5 adverse events	2,762	(47.3)	530	(47.2)	222	(33.1)
with toxicity grade 3-5 drug-related adverse events	928	(15.9)	182	(16.2)	98	(14.6)
with serious adverse events	2,155	(36.9)	414	(36.9)	173	(25.8)
with serious drug-related adverse events	605	(10.4)	153	(13.6)	82	(12.2)
who died	276	(4.7)	67	(6.0)	3	(0.4)
who died due to a drug-related adverse event	32	(0.5)	10	(0.9)	0	(0.0)
discontinued any drug due to an adverse event	812	(13.9)	158	(14.1)	96	(14.3)
discontinued any drug due to a drug-related adverse event	464	(7.9)	91	(8.1)	84	(12.5)
discontinued any drug due to a serious adverse event	553	(9.5)	119	(10.6)	42	(6.3)
discontinued any drug due to a serious drug-related adverse event	255	(4.4)	60	(5.3)	32	(4.8)

*Determined by the investigator to be related to the drug.
For KN-B15, treatment includes study medications and surgery.
For KN-B15, 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.
For KN-B15, grades are based on NCI CTCAE version 5.0.
Database cutoff date for KN-B15: 27OCT2025.

• Region

Table 80 Adverse Event Summary by Region (US, EU, MOW) (APaT Population)

	KN-B15 EV + Pembro						KN-B15 Cis + Gem						EV + Pembro Combo ISD					
	US		EU		MOW		US		EU		MOW		US		EU		MOW	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	58		205		140		59		198		139		191		158		215	
with one or more adverse events	58	(100.0)	200	(97.6)	137	(97.9)	59	(100.0)	195	(98.5)	135	(97.1)	191	(100.0)	157	(99.4)	215	(100.0)
with no adverse event	0	(0.0)	5	(2.4)	3	(2.1)	0	(0.0)	3	(1.5)	4	(2.9)	0	(0.0)	1	(0.6)	0	(0.0)
with drug-related* adverse events	57	(98.3)	197	(96.1)	134	(95.7)	58	(98.3)	181	(91.4)	133	(95.7)	185	(96.9)	155	(98.1)	210	(97.7)
with toxicity grade 3-5 adverse events	51	(87.9)	143	(69.8)	111	(79.3)	45	(76.3)	125	(63.1)	96	(69.1)	157	(82.2)	114	(72.2)	164	(76.3)
with toxicity grade 3-5 drug-related adverse events	31	(53.4)	91	(44.4)	65	(46.4)	26	(44.1)	81	(40.9)	77	(55.4)	117	(61.3)	82	(51.9)	130	(60.5)
with serious adverse events	42	(72.4)	125	(61.0)	88	(62.9)	34	(57.6)	92	(46.5)	64	(46.0)	100	(52.4)	80	(50.6)	115	(53.5)
with serious drug-related adverse events	12	(20.7)	54	(26.3)	29	(20.7)	8	(13.6)	21	(10.6)	13	(9.4)	48	(25.1)	41	(25.9)	66	(30.7)
who died	1	(1.7)	10	(4.9)	6	(4.3)	0	(0.0)	8	(4.0)	3	(2.2)	14	(7.3)	4	(2.5)	12	(5.6)
who died due to a drug-related adverse event	0	(0.0)	1	(0.5)	1	(0.7)	0	(0.0)	1	(0.5)	0	(0.0)	5	(2.6)	1	(0.6)	3	(1.4)
discontinued any drug due to an adverse event	25	(43.1)	96	(46.8)	51	(36.4)	9	(15.3)	36	(18.2)	17	(12.2)	98	(51.3)	85	(53.8)	96	(44.7)
discontinued any drug due to a drug-related adverse event	20	(34.5)	77	(37.6)	45	(32.1)	6	(10.2)	25	(12.6)	13	(9.4)	92	(48.2)	80	(50.6)	80	(37.2)
discontinued any drug due to a serious adverse event	10	(17.2)	52	(25.4)	25	(17.9)	2	(3.4)	15	(7.6)	3	(2.2)	26	(13.6)	24	(15.2)	34	(15.8)

	EV Mono ISD						Pembro Mono RSD					
	US		EU		MOW		US		EU		MOW	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	414		120		259		2,296		2,430		2,905	
with one or more adverse events	412	(99.5)	117	(97.5)	257	(99.2)	2,244	(97.7)	2,328	(95.8)	2,803	(96.5)
with no adverse event	2	(0.5)	3	(2.5)	2	(0.8)	52	(2.3)	102	(4.2)	102	(3.5)
with drug-related* adverse events	392	(94.7)	109	(90.8)	246	(95.0)	1,674	(72.9)	1,683	(69.3)	2,105	(72.5)
with toxicity grade 3-5 adverse events	291	(70.3)	80	(66.7)	194	(74.9)	1,119	(48.7)	1,051	(43.3)	1,344	(46.3)
with toxicity grade 3-5 drug-related adverse events	208	(50.2)	48	(40.0)	148	(57.1)	333	(14.5)	364	(15.0)	511	(17.6)
with serious adverse events	185	(44.7)	55	(45.8)	123	(47.5)	863	(37.6)	838	(34.5)	1,041	(35.8)
with serious drug-related adverse events	77	(18.6)	22	(18.3)	63	(24.3)	195	(8.5)	266	(10.9)	379	(13.0)
who died	26	(6.3)	10	(8.3)	20	(7.7)	79	(3.4)	110	(4.5)	157	(5.4)
who died due to a drug-related adverse event	10	(2.4)	4	(3.3)	3	(1.2)	5	(0.2)	10	(0.4)	27	(0.9)
discontinued any drug due to an adverse event	90	(21.7)	33	(27.5)	45	(17.4)	294	(12.8)	337	(13.9)	435	(15.0)
discontinued any drug due to a drug-related adverse event	65	(15.7)	23	(19.2)	32	(12.4)	156	(6.8)	215	(8.8)	268	(9.2)
discontinued any drug due to a serious adverse event	41	(9.9)	18	(15.0)	21	(8.1)	202	(8.8)	225	(9.3)	287	(9.9)

	KN-B15 EV + Pembro			KN-B15 Cis + Gem			EV + Pembro Combo ISD											
	US	EU	MOW	US	EU	MOW	US	EU	MOW									
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)								
discontinued any drug due to a serious drug-related adverse event	7	(12.1)	34	(16.6)	19	(13.6)	2	(3.4)	4	(2.0)	1	(0.7)	20	(10.5)	20	(12.7)	22	(10.2)

	EV Mono ISD			Pembro Mono RSD								
	US	EU	MOW	US	EU	MOW						
	n	(%)	n	(%)	n	(%)						
discontinued any drug due to a serious drug-related adverse event	25	(6.0)	9	(7.5)	11	(4.2)	84	(3.7)	118	(4.9)	145	(5.0)

*Determined by the investigator to be related to the drug.
For KN-B15, treatment includes study medications and surgery.
For KN-B15, 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.
For KN-B15, grades are based on NCI CTCAE version 5.0.
EU includes participants from the 27 EU countries; participants from the UK are included in MOW.
EU=European Union, MOW=Most of World, UK=United Kingdom, US=United States.
Database cutoff date for KN-B15: 27OCT2025.

Safety related to drug-drug interactions and other interactions

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

Discontinuation due to adverse events

Table 81 Participants With Adverse Events Resulting in Any Drug Discontinuation by Decreasing Frequency of Preferred Term (Incidence > 0% in One or More Treatment Groups) (APaT Population)

	KN-B15 EV + Pembro		KN-B15 Cis + Gem		EV + Pembro Combo ISD		EV Mono ISD		Pembro Mono RSD	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	403		396		564		793		7,631	
with one or more adverse events	172	(42.7)	62	(15.7)	279	(49.5)	168	(21.2)	1,066	(14.0)
with no adverse events	231	(57.3)	334	(84.3)	285	(50.5)	625	(78.8)	6,565	(86.0)
Death	1	(0.2)	1	(0.3)	2	(0.4)	0	(0.0)	27	(0.4)
Dermatitis contact	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Diabetic ketoacidosis	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.1)	4	(0.1)
Drug reaction with eosinophilia and systemic symptoms	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Dry eye	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Dry skin	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Duodenal ulcer perforation	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Eczema	1	(0.2)	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)
Enterocolitis infectious	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Erythema	1	(0.2)	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)
Fatigue	1	(0.2)	2	(0.5)	4	(0.7)	5	(0.6)	19	(0.2)
Fulminant type 1 diabetes mellitus	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Gamma-glutamyltransferase increased	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Hepatic failure	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Ileus	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Immune-mediated dermatitis	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Immune-mediated hypophysitis	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Immune-mediated lung disease	1	(0.2)	0	(0.0)	6	(1.1)	0	(0.0)	3	(0.0)
Interstitial lung disease	1	(0.2)	0	(0.0)	3	(0.5)	2	(0.3)	11	(0.1)
Iridocyclitis	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Kidney infection	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Leukopenia	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Lichenoid keratosis	1	(0.2)	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)
Mucinous adenocarcinoma of appendix	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Mucosal inflammation	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Myalgia	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Myocardial infarction	1	(0.2)	2	(0.5)	0	(0.0)	0	(0.0)	8	(0.1)
Myocarditis	1	(0.2)	0	(0.0)	2	(0.4)	0	(0.0)	5	(0.1)
Nephropathy toxic	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Neurotoxicity	1	(0.2)	0	(0.0)	2	(0.4)	0	(0.0)	0	(0.0)
Pancreatitis	1	(0.2)	0	(0.0)	1	(0.2)	0	(0.0)	4	(0.1)
Pancreatitis acute	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Paraesthesia	1	(0.2)	0	(0.0)	6	(1.1)	1	(0.1)	0	(0.0)
Pemphigoid	1	(0.2)	0	(0.0)	3	(0.5)	0	(0.0)	0	(0.0)
Pneumonia	1	(0.2)	1	(0.3)	2	(0.4)	3	(0.4)	34	(0.4)
Polymyalgia rheumatica	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Proctitis	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pulmonary embolism	1	(0.2)	1	(0.3)	0	(0.0)	1	(0.1)	14	(0.2)
Pyelonephritis acute	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pyrexia	1	(0.2)	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.0)
Rash papular	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)
Rash pruritic	1	(0.2)	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)
Rash vesicular	1	(0.2)	0	(0.0)	1	(0.2)	1	(0.1)	0	(0.0)
Renal failure	1	(0.2)	2	(0.5)	2	(0.4)	0	(0.0)	6	(0.1)
Renal haematoma	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Retinal detachment	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Retinal haemorrhage	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Skin toxicity	1	(0.2)	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)
Small cell lung cancer	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Small intestinal obstruction	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)
Symmetrical drug-related intertriginous and flexural exanthema	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Tubulointerstitial nephritis	1	(0.2)	0	(0.0)	1	(0.2)	0	(0.0)	6	(0.1)
Type 1 diabetes mellitus	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	8	(0.1)
Urinary fistula	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Urinary incontinence	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Urticaria	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Visual acuity reduced	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Weight decreased	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.1)	2	(0.0)
Abdominal distension	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Abdominal pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Abdominal pain upper	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Abdominal sepsis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Accidental death	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Acute coronary syndrome	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Acute myeloid leukaemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Acute myocardial infarction	0	(0.0)	0	(0.0)	2	(0.4)	0	(0.0)	2	(0.0)
Acute respiratory failure	0	(0.0)	0	(0.0)	1	(0.2)	2	(0.3)	5	(0.1)
Addison's disease	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Adenocarcinoma gastric	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Adrenal insufficiency	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	13	(0.2)
Amylase increased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Anaemia	0	(0.0)	3	(0.8)	2	(0.4)	0	(0.0)	3	(0.0)
Anaphylactoid reaction	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)

The overall rates of drug related AEs leading to any drug discontinuation was 35.2% in the EV+Pembro, 11.1% in the cis-gem, 44.7% in the EV+Pembro ISD, 21.2% in the EV Mono ISD and 14% in the Pembro mono RSD.

Adverse Events Resulting in Any Drug Interruption by System Organ Class and Preferred Term (Incidence > 0% in One or More Treatment Groups) (APaT Population)

The percentage of participants with AEs resulting in discontinuation of any drug was higher in the perioperative EV + pembrolizumab group (42.7%) compared with the cis + gem group (15.7%). When adjusted for exposure the event rate of discontinuation of any drug remained higher in the perioperative EV + pembrolizumab group. AEs resulting in discontinuation of any study drug in the perioperative EV + pembrolizumab group for $\geq 2\%$ of participants were neuropathy peripheral (3.7%), pneumonitis (3.2%), peripheral sensory neuropathy (2.5%), ALT increased and rash (2.0% each). The only AE resulting in discontinuation of any study drug in the cis + gem group was neutropenia (3.3%). The percentage of participants with AEs resulting in discontinuation of any drug was similar in the perioperative EV + pembrolizumab group (42.7%) compared with the EV + pembrolizumab ISD (49.5%). Drug-related AEs resulting in discontinuation of any drug in $\geq 2\%$ of participants in the perioperative EV + pembrolizumab group were peripheral neuropathy (3.7%), pneumonitis (3.2%), peripheral sensory neuropathy (2.5%), and rash (2.0%).

The analysis of discontinuations and interruptions per treatment phases is reported in the specific section above.

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 summarized in the Periodic Safety Update Report covering the period of 18-DEC-2024 through 17-DEC-2025. The cumulative number of patients receiving enfortumab vedotin since the launch of the product through 17-DEC-2025 is estimated as 153,295.

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

2.5.2. Discussion on clinical safety

The safety assessment of perioperative EV+pembrolizumab in the proposed indication is based on data from the pivotal trial EV-304. The EV-304 safety set consists of 403 patients treated with EV+pembrolizumab and 396 treated with neoadjuvant gemcitabine+cisplatin. Additional safety data for the EV+pembrolizumab combination are available for 564 patients from KEYNOTE-869/ EV-103 and KEYNOTE-A39/ EV-302, and safety data for EV monotherapy are available for 793 patients. The median **duration of exposure** to the combination regimen was 10.2 months in the EV+pembrolizumab arm, which is similar to the EV+pembrolizumab combination safety pool and, as expected, longer than the median duration of exposure in the cisplatin+gemcitabine arm (3.5 months). These safety pools are considered of sufficient size and treatment duration for characterisation of the safety profile of the EV+pembrolizumab combination, although rare adverse drug reactions may not have been detected.

Pooled reference safety data from studies of enfortumab vedotin (EV mono ISD) or pembrolizumab (pembrolizumab RSD) monotherapies are also included to enable a comparison of the safety data of enfortumab vedotin + pembrolizumab to the established safety profiles of the respective monotherapies. This is considered important for a proper evaluation of the safety profile of each

drug in the experimental combination. Moreover, to isolate the contribution of each phase of treatment, data were presented separately for each phase of treatment.

Baseline characteristics were overall well-balanced between treatment arms in KEYNOTE-B15 (see discussion on clinical efficacy).

The **collection of safety data** was generally acceptable, although the reporting window of non-serious adverse events of 30 days after treatment cessation is on the shorter side for an ADC plus checkpoint inhibitor combination therapy, where 90 days would have been preferable. Importantly, serious adverse events were reported for 90 days after treatment cessation, which is considered appropriate. However, the narrow reporting window for non-serious AEs has likely led to underreporting of some events and is therefore considered to constitute an uncertainty about unfavourable effects.

In KEYNOTE-B15, 98% of patients in both treatment arms experienced at least one **adverse event**. The incidence of **grade ≥ 3 adverse events** was higher in the EV+pembrolizumab arm (75.7%) than in the cisplatin+gemcitabine arm (67.2%), which could be explained by the longer duration of exposure in the EV+pembrolizumab arm. The most common adverse events of any grade in the EV + pembrolizumab arm were pruritus (46.2%), diarrhoea (34.0%), alopecia (31.5%), anaemia (31.3%), decreased appetite (28.5%), nausea (28.3%), fatigue (27.5%), constipation (26.6%), rash (25.1%), and urinary tract infection (25.1%). The most common **grade ≥ 3 adverse events** were urinary tract infection (9.9%), neutropenia (7.4%), anaemia (6.5%), hyperglycemia (4.7%), and maculo-papular rash (4.7%). Incidences of all-grade AEs and grade ≥ 3 AEs were generally similar between the KEYNOTE-B15 EV + pembrolizumab arm and the EV + pembrolizumab ISD. The incidence of **serious adverse events** 63.3% in the EV + pembrolizumab arm of KEYNOTE-15, which was higher than the observed 48% in the cisplatin + gemcitabine arm, and 47.7% in the EV + pembrolizumab ISD. Not all SAEs were considered drug related (23.6% in the EV+ pembro arm and 10.6% in the cis-gem arm). This is not unexpected considering that this category included serious events typically associated with the surgical intervention of radical cystectomy. In both arms, the most reported SAEs were infectious (UTI, urosepsis, sepsis, pneumonitis) and genitourinary complications (prostate cancer, acute kidney injury).

Adverse events leading to death were more frequent in the EV + pembrolizumab arm (4.2%) than the cisplatin + gemcitabine arm (2.8%), and most events were related to infections/sepsis or unexplained cardiac arrest. The rate of AEs resulting in death was similar across datasets (for datasets see Table 44). However, the comparisons are limited by differences in indication, line of therapy, and treatment (monotherapy), which preclude the identification of specific risk factor for deaths. Absence of a specific correlation between age and risk of death can be noted. In general, the information reported in the SmPC about the risk of infectious complications is considered sufficient to address the risk of complications during the perioperative phase.

Adverse events of special interest to enfortumab vedotin were (numbers in the following are for the EV+pembrolizumab arm of KEYNOTE-B15):

Skin reactions (66% all-grade, 6.2% serious events), including 6 (1.5%) cases of bullous dermatitis, 4 (1.0%) cases of Steven-Johnson syndrome, and 2 (0.5%) cases of acute generalised exanthematous pustulosis. 7.9% of patients discontinued EV due to skin reactions.

Peripheral neuropathy (43.7% all grade, 3% grade ≥ 3). 6.7% of patients discontinued EV due to peripheral neuropathy. Most events were sensory (41.9%).

Hyperglycaemia (19.6%, 2.2% serious). Three events of type 1 diabetes mellitus and two events of grade 4 diabetic ketoacidosis were observed.

Ocular disorders (30.5%, only one event was grade ≥ 3). Most events were dry eye (25.1%) and blurred vision 6.2%).

ILD/pneumonitis (7.7%, 3.5% serious, 0 fatal). 6 (1.5%) events led to discontinuation of EV.

Haematological events (anaemia and neutropenia). Incidences were lower in the EV+pembrolizumab arm than in the cisplatin + gemcitabine arm.

Nausea, vomiting, and diarrhoea (63%, 6% grade ≥ 3 events, 3% serious events). Most events were diarrhoea (34%).

Skin hyperpigmentation (3.5%).

Rates of AESIs were generally similar between the KEYNOTE-B15 EV+pembrolizumab arm and the EV+pembrolizumab combination therapy ISD.

Analysis per **treatment phase** allows isolating the contribution of each phase to the general safety evaluation. In particular, the first treatment phase is considered the most critical determinant of whether patients can proceed to the treatment plan.

In the preoperative treatment phase, the nature and frequency of AEs were similar to what was observed throughout the entire observation period of the study and reflects the specific safety profile of both treatments. The reduced frequency of grade 3-5 AEs showed in the pretreatment phase is expected considering the exclusion of the events related to the surgical phase. Slightly more patients in the EV + pembrolizumab arm experienced a delay in undergoing surgery (16.8% vs. 14.4%), but the difference was minimal.

During the surgical phase, the type of AEs reflects the surgical intervention; the number of deaths was higher in the cis-gem arm (9 vs 2) with infectious complications as the main cause of death.

There were slightly more postsurgical adverse events in the EV + pembrolizumab arm (70.7%) than in the cisplatin + gemcitabine arm (65.2%), but similar rates of grade ≥ 3 events (36.2% vs. 35.4%) and serious adverse events (39.0% vs. 39.8%). Fewer patients died from adverse postsurgical events in the EV + pembrolizumab arm (0.6%) than in the cisplatin + gemcitabine arm (2.5%).

AEOSI for EV

Skin reactions were the most frequently AEOSI identified for EV (66%) followed by Peripheral Neuropathy (43.7%) Ocular Disorders (30.5%), Hyperglycemia (19.6%) and Infusion related reactions (2.5%). The overall incidence of AEOSI for EV (66%) resulted similar for what reported in the EV+ pembro ISD (70%) and higher in respect to the monotherapy dataset, as expected (57%).

Cutaneous rash was the most frequent skin reaction reported; the cutaneous toxicity of EV is explained considering that the target of enfortumab vedotin, Nectin-4, is expressed in epidermal keratinocytes and skin appendages (eg, sweat glands and hair follicles) and was already reported in the safety profile of EV. The comparison with the ISDs did not show an increased incidence when EV is combined with pembrolizumab (also when incidence was adjusted for exposure), so it could be inferred that risk of skin toxicity does increase non-linearly when both drugs are used in combination.

Peripheral neuropathy, explained by the known effects of MMAE included in EV, was registered in 43.7% of patients in the experimental arm; most of registered cases were defined as sensitive events (41.9%) and mild in grade (2% of grade 3-5). The comparison with other ISDs dataset showed a lower incidence of events (EV+ Pembro ISD 67.4%, EV mono 53.2%); this difference is

maintained also in the exposure adjusted dataset. A possible explanation can be identified in the different duration of therapy in respect to the monotherapy setting, in which a longer exposure to EV is permitted and, in respect to EV + Pembro ISD, in the difference in terms of enrolled population, considering that the EV+ Pembro ISD included subjects with a lower ECOG performance status and with a previous chemotherapy before the disease relapse.

The percentage of participants with AEs in the any gastrointestinal nonspecific symptoms group (nausea, vomiting, diarrhea) was similar to the one reported in the reference datasets. Gastrointestinal tract is subjected to EV specific toxicity considering both the nectin-4 expression in various parts of the tract and the specific toxicity due to the MMAE ADCs.

AEOSI for Pembrolizumab

The incidence of AEOSI for pembrolizumab (47.6%) resulted substantially similar to what reported in the Ev+Pembro ISD (46.8%) and, as expected, higher when compared to the monotherapy of pembrolizumab RSD (27.5%). These findings were similar when incidence was adjusted for exposure. The median time to onset was 46 days (1-449) with a median duration of 77 days (1-1419+). At last follow up, the majority of AEOSI resulted resolved (65.1%) although a 22.9% of subjects were reported with AEOSI not resolved.

In the context of immunotherapy-based treatment, AEOSIs are relevant to the benefit-risk assessment because of their potential effect on treatment continuation, adherence and surgery. The overall number of subjects in which AEOSI were not resolved at the last DCO was 44 (10.9%) in the perioperative EV + pembrolizumab group and 1 (0.3%) in the cis + gem group. The effects of these unresolved AEOSI on the overall treatment plan is deemed negligible, as in the experimental arm treatment discontinuation of any study drug due to them accounted for 1.2% of participants (1.0% discontinuation of pembrolizumab and 0.5% enfortumab vedotin), while dose interruptions of any study drug, pembrolizumab, and enfortumab vedotin occurred in 4 (1.0%) participants, 3 (0.7%) participants, and 4 (1.0%) participants, respectively. The most common not resolved AEOSIs for pembrolizumab were hypothyroidism (6.2%) and severe skin reactions (1.2%), while for EV peripheral neuropathy (17.6%), ocular disorders (6.2%), skin reactions (5.0%) and hyperglycemia (4.5%) were the most commonly reported. Peripheral neuropathy was the only AEOSI that was associated with discontinuation with any study drug (2.7%).

AEOSI had a minor impact on drug discontinuations: 14.9% of drug related AEOSI led to discontinuation at any point of the experimental combined treatment.

Corticosteroid was required in the 54.2% of subjects, with 35.4% of subjects who need high starting dose for AE control.

Laboratory abnormalities were generally consistent with those observed in the EV + pembrolizumab ISD, although more patients had aminotransferase elevations ($\geq 10 \times \text{ULN}$: 4.7% vs. 2.3%, respectively).

The frequency of **adverse events leading to discontinuation** of any drug was considerably higher in the EV + pembrolizumab arm than the cisplatin + gemcitabine arm of KEYNOTE-B15 (42.7% vs. 15.7%), but similar to that in the EV + pembrolizumab ISD (49.5%).

Safety in special population

Most of enrolled subjects presented an age < 75 years (88% in both arms), with a minority of subjects between 75-84 years; only 1 subject was > 85 years old and was enrolled in the experimental arm. In general, the incidence of AEs was similar between the three age categories (< 65, 65-74, 75-84, > 85) as well as G 3-5 AEs, while drug-related G 3-5 AE and SAE were higher

in the age 75-84 subgroup. This trend can be noted also in the comparator arm and in the pembrolizumab monotherapy dataset, probably reflecting an age-dependant susceptibility in developing AEs. Similarly, the rate of discontinuations was higher in subjects aged > 75 years (50% vs 36.3% in < 65 years). Similar considerations can be applied to ECOG performance status: most of subjects enrolled in the trial had ECOG PS 0 (78.6% in the experimental arm and 77% in the control arm). Numerical difference between ECOG PS 0 and 1 makes comparisons difficult: in general, no substantial difference can be noted between subjects with ECOG PS 0 and 1: discontinuations due to drug related AEs were numerically higher in ECOG PS 1 in absence of a clear trend in higher discontinuation rates overall. No clinically relevant differences can be noted in terms of gender, race and region of origin.

2.5.3. Conclusions on clinical safety

The safety profile of EV + pembrolizumab in the proposed indication is overall similar to the profile of this combination known from the already approved indication. No new safety concerns were identified.

2.5.4. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version 6.3 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 6.3 is acceptable.

The CHMP endorsed the Risk Management Plan version 6.3 with the following content

Safety concerns

Table 82 Summary of safety concerns

Summary of safety concerns	
Important identified risks	<ul style="list-style-type: none"> ○ Skin reactions ○ Hyperglycemia ○ Pneumonitis/Interstitial lung disease
Important potential risks	None
Missing information	None

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

Pharmacovigilance plan

Table 83 Summary table of additional pharmacovigilance activities

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

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

Risk minimisation measures

Table 84 Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Skin reactions	<p>Routine risk communication:</p> <ul style="list-style-type: none"> EU-SmPC Sections 4.2, 4.4 and 4.8; PL Sections 2 and 4 <p>Routine risk minimization activities recommending specific clinical measures to address the risk:</p> <ul style="list-style-type: none"> Recommendations are provided in the EU-SmPC Section 4.4 to monitor for severe skin reactions starting with the first cycle 	<p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</p> <ul style="list-style-type: none"> None <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> NI-PASS category 3 study to assess evaluation of patients' understanding and awareness of the content of the patient card related to risks of skin reactions and patient behaviours to minimize the risk.

Safety concern	Risk minimization measures	Pharmacovigilance activities
	<p>and throughout enfortumab vedotin treatment.</p> <ul style="list-style-type: none"> Recommendations are provided in the EU-SmPC Section 4.2 for treatment interruption, dose reduction and treatment discontinuation of enfortumab vedotin. <p>Additional risk minimization measures:</p> <ul style="list-style-type: none"> Patient card 	
Hyperglycemia	<p>Routine risk communication:</p> <ul style="list-style-type: none"> EU-SmPC Sections 4.2, 4.4 and 4.8 PL Sections 2 and 4 <p>Routine risk minimization activities recommending specific clinical measures to address the risk:</p> <ul style="list-style-type: none"> Recommendations are provided in the EU-SmPC Section 4.4 to monitor blood glucose levels prior to dosing and periodically throughout the course of treatment. Recommendations are provided in EU-SmPC Section 4.2 for treatment interruption and when to resume treatment of enfortumab vedotin. <p>Additional risk minimization measures:</p> <ul style="list-style-type: none"> None 	<p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</p> <ul style="list-style-type: none"> None <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> None
Pneumonitis/Interstitial lung disease	<p>Routine risk communication:</p> <ul style="list-style-type: none"> EU-SmPC Sections 4.2, 4.4 and 4.8; PL Sections 2 and 4 	<p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</p> <ul style="list-style-type: none"> None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	<p>Routine risk minimization activities recommending specific clinical measures to address the risk:</p> <ul style="list-style-type: none"> For Grade 2 pneumonitis/interstitial lung disease, withhold enfortumab vedotin until Grade ≤ 1, then resume at the same dose level or consider dose reduction by one dose level. Permanently discontinue enfortumab vedotin for Grade ≥ 3 pneumonitis/interstitial lung disease <p>Additional risk minimization measures:</p> <ul style="list-style-type: none"> None 	<p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> None

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

The pharmacovigilance plan and risk minimisations activities remain unchanged.

2.7. Update of the Product information

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

Changes were also made to the PI to bring it in line with the current Agency/QRD template version 10.4, SmPC guideline and to align with the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' regarding the polysorbate 20 content.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

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

2.7.2. Additional monitoring

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

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The final indication is:

Padcev, in combination with pembrolizumab, as neoadjuvant treatment and then continued after radical cystectomy as adjuvant treatment, is indicated for the treatment of adult patients with resectable muscle invasive bladder cancer (MIBC).

3.1.2. Available therapies and unmet medical need

Radical cystectomy and pelvic lymph node dissection (RC + PLND) is the mainstay of curative treatment for resectable MIBC {Dong X, et al, UroPrecision. 2023;1:141–61; Matsumoto H, et al, 2019 Int J Urol. 2020) preceded by neoadjuvant cisplatin-based chemotherapy for patients who can receive it. Adjuvant nivolumab for 1 year showed DFS improvement vs placebo in CHECKMATE-274, leading to EU approval in muscle invasive urothelial carcinoma with tumour cell PD-L1 $\geq 1\%$, who are at high risk of recurrence after undergoing radical resection (Bajorin DF et al N Engl J Med. 2021 Aug 26;385(9):864). More recently, the results of the Phase 3 NIAGARA study provided a new treatment option for patients with cisplatin-eligible MIBC. The study showed a statistically significant improvement in EFS and OS with perioperative durvalumab plus neoadjuvant chemotherapy (cisplatin + gemcitabine) compared with neoadjuvant cisplatin + gemcitabine followed by RC + PLND (EFS: HR 0.68; 95% CI: 0.56, 0.82; $p < 0.001$; OS: HR 0.75; 95% CI: 0.59, 0.93; $p = 0.01$) (Powles T, et al, N Engl J Med. 2024). Despite the improvement in outcomes demonstrated in the above studies, there remains an unmet need in this setting and the opportunity to further improve clinical outcomes in this patient population.

3.1.3. Main clinical studies

The pivotal study is KEYNOTE-B15/ EV-304 study, an ongoing Phase 3, randomized, controlled, parallel-group, multisite, open-label study comparing perioperative enfortumab vedotin + pembrolizumab with neoadjuvant cisplatin + gemcitabine in participants with cisplatin-eligible muscle invasive bladder cancer (MIBC) and with cT2-T4aN0M0 or cT1-T4aN1M0 tumors. A total of 808 adult patients with previously untreated MIBC who were deemed eligible for RC + PLND and planned to undergo standard surgery with curative intent were randomized in a 1:1 ratio to receive perioperative enfortumab vedotin + pembrolizumab (Arm A) or neoadjuvant cis + gem (Arm B). Stratification factors were PD-L1 expression (CPS ≥ 10 vs < 10), disease stage (T2N0 vs T3/T4aN0 vs T1-T4aN1), and region (US vs EU vs MOW). The primary endpoint of KN-B15/EV-304 was event free survival (EFS) by blinded independent central review (BICR). Key secondary endpoints were pathological Complete Response (pCR) and overall survival (OS). The results submitted are from the IA1 with DCO of 27-Oct-2025.

3.2. Favourable effects

- The primary endpoint EFS by BICR per RECIST 1.1 demonstrated a statistically significant improvement for the perioperative pembrolizumab + EV treatment compared to standard neoadjuvant cisplatin + gemcitabine. EFS events occurred in 21.5% vs 36.2% of participants, showing HR 0.53 (95%CI 0.41, 0.70) $p < 0.0001$. Kaplan-Meier curves separated from months 6 onwards and remained separated over time, with EFS rates at 12 and 18 months of 86.6% and 82.2% in EV + pembrolizumab arm vs 75.4% and 68.8% in cis-gem arm. Prespecified EFS sensitivity analyses were reported as generally consistent with the primary analysis, including consistency between investigator and BICR-assessed EFS.
- OS results were statistically significant in favour of the perioperative EV + pembrolizumab arm, with HR 0.65 (95%CI 0.48, 0.89; $p = 0.0029$), after 17% vs 24.6% of OS events occurred. After month 6 curves divided with a 5% improvement in OS rate (OS rate at month 12 93.1 vs 89.6%, OS rate at month 18 89.4 vs 84.5%), with medians not reached in either arm.
- pCR was also statistically significant showing improvement for pembrolizumab + EV over standard cis+gem (55.8% vs 32.5%; $p < 0.0001$). The absolute pCR rate for pembrolizumab + EV was similar to the pCR of 57.1% achieved in the cisplatin-ineligible population of KEYNOTE-905.

3.3. Uncertainties and limitations about favourable effects

The study design does not allow to formally evaluate the contribution of each component (EV and pembrolizumab) of the combination, as well as the contribution of each phase of treatment (neoadjuvant and adjuvant). Nonetheless, the combination of EV and pembrolizumab from the metastatic setting and the clear superiority of the combination shown in KEYNOTE-B15/ EV-304 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 in KEYNOTE-B15/ EV-304 and although more mature data are not considered necessary for this assessment, the final OS results are expected to be submitted post-authorization to further characterize the efficacy in the context of an early curative setting (**REC**).

3.4. Unfavourable effects

Almost all subjects treated with the combination EV+ pembrolizumab experienced at least one adverse event during treatment (98%) and most of them were classified as drug related (96.3%).

63.3% experienced at least one **serious adverse events**. The most common adverse events of any grade were pruritus (46.2%), diarrhoea (34.0%), alopecia (31.5%), anaemia (31.3%), decreased appetite (28.5%), nausea (28.3%), fatigue (27.5%), constipation (26.6%), rash (25.1%), and urinary tract infection (25.0%). The most common **grade ≥ 3 adverse events** were urinary tract infection (9.9%), neutropenia (7.4%), anaemia (6.5%), hyperglycaemia (4.7%), and maculopapular rash (4.7%).

4.2% of patients experienced an **adverse event leading to death**, but most events were related to infections/sepsis or unexplained cardiac arrest.

Adverse events of special interest to enfortumab vedotin are well-known and include skin reactions (of which some can be severe, including 4 cases of Steven-Johnson syndrome), peripheral neuropathy, hyperglycaemia, ocular disorders, ILD/pneumonitis, anaemia, neutropenia, diarrhoea,

vomiting, skin hyperpigmentation. Perioperative EV + pembrolizumab did not appear to adversely affect time to surgery or surgical outcomes compared to gemcitabine + cisplatin.

The frequency of **adverse events leading to discontinuation** of any drug was considerably higher in the EV + pembrolizumab arm than the cisplatin + gemcitabine arm of KEYNOTE-B15 (42.7% vs. 15.7%).

3.5. Uncertainties and limitations about unfavourable effects

Non-serious adverse events were only collected for 30 days after treatment cessation, which is considered suboptimal for a checkpoint inhibitor + ADC combination where later adverse drug reactions may be expected. Serious adverse events were collected for 90 days, which is a more appropriate time window which is a more appropriate and reassuring timeframe for analysis of safety.

3.6. Effects Table

Table 85: Effects Table for KEYNOTE- B15/EV-304 Study: Padcev in combination with pembrolizumab for resectable MIBC in cisplatin-eligible patients (data cut-off: 27-October-2025)

Effect	Short description	Unit	Treatment	Control	Uncertainties /	Refer ences
pembrolizumab +EV followed by RC + PLND, followed by adjuvant pembrolizumab + EV						
neoadjuvant chemotherapy (gemcitabine + cisplatin), followed by RC+ PLND, followed by observation						
Strength of evidence						
Favourable Effects						
EFS	Per RECIST 1.1 by BICR	Median months (95%CI)	NR (NR, NR)	48.5 (43.3, NR)	Statistically significant	CSR KN B15
		HR (95%CI)	0.53 (0.41, 0.70) p<0.0001			
OS		Median months (95%CI)	NR (NR, NR)	NR (NR, NR)	Statistically significant	
		HR (95%CI)	0.65 (0.48, 0.89) p=0.0029			
pCR	by BICR	% (95%CI)	55.8% (50.8,60.7)	32.5% (28, 37.3)	Statistically significant	
			p<0.0001			
Unfavourable Effects						
Grade 3-5 AE		%	75.7	67.2	Higher rate in the Perioperative EV + pembrolizumab arm. Overall low tolerability (high discontinuation rate) and higher toxicity in elderly.	CSR KNB15, ISS
SAE		%	63.3	48		

Effect	Short description	Unit	Treatment pembrolizumab + EV followed by RC + PLND, followed by adjuvant pembrolizumab + EV	Control neoadjuvant chemotherapy (gemcitabine + cisplatin), followed by RC+ PLND, followed by observation	Uncertainties / Strength of evidence	References
					Higher rate in the Perioperative EV + pembrolizumab arm. Overall low tolerability (high discontinuation rate) and higher toxicity in elderly	
AE resulting in deaths		%	4.2	2.8	Higher rate in the Perioperative EV + pembrolizumab arm; rates of deaths higher in the experimental arm during the first 5 months, mostly due to AEs.	
Discontinuation due to AE		%	42.7	15.7	Higher rate in the Perioperative EV + pembrolizumab arm; different treatment duration between the two arms may have had an influence on the crude incidence	

Abbreviations: EFS: event free survival, OS: overall survival, BICR: blinded independent central review, N: not reached, HR: hazard ratio, CI: confidence intervals,

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Overall, KEYNOTE-B15/EV-304 provides evidence of a clinically meaningful benefit of perioperative enfortumab vedotin plus pembrolizumab compared with neoadjuvant cisplatin/gemcitabine in cisplatin-eligible patients with resectable MIBC undergoing radical cystectomy. At the first pre-specified interim analysis, the study met its primary endpoint of EFS by BICR and the key secondary endpoint of OS, with statistically significant and clinically meaningful effects. The significantly higher pCR rate further supports the greater activity of neoadjuvant enfortumab vedotin plus pembrolizumab. The findings were consistent across predefined subgroups and sensitivity and supplementary analyses, and no adverse effect on the feasibility or completion of surgery was observed. Although the results are based on an interim analysis, the available data are considered sufficient for assessment. Given the early curative setting, the final study results, including final OS data, will be submitted post-authorisation (**REC**). The study methods were appropriately selected, and changes to the study design and statistical analysis were adequately justified and are not considered to have materially affected the results.

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-B15/EV-304 - study attenuates the concern around the individual contribution of EV. 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 combination in other and more advanced metastatic settings. No new safety signals were observed.

During the first five months of follow-up, a higher number of deaths due to AEs is reported in the experimental arm: infectious complications remain the main causes of deaths due to AEs in this restricted timeframe. The small number of events during this time frame however does not allow definitive conclusions to be drawn.

3.7.2. Balance of benefits and risks

KEYNOTE-B15/EV-304 study showed statistically significant and clinically relevant EFS and OS benefit of perioperative EV + pembrolizumab compared to standard neoadjuvant cisplatin-based chemotherapy in cisplatin-eligible patients with resectable MIBC undergoing radical cystectomy. The risks related to the toxicity of the combination appear counterbalanced by a clinical benefit in the targeted setting.

3.8. Conclusions

The overall B/R is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

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

Extension of indication to include Padcev, in combination with pembrolizumab, as neoadjuvant treatment and then continued after radical cystectomy as adjuvant treatment, is indicated for the treatment of adults with resectable muscle invasive bladder cancer (MIBC) who are eligible for cisplatin-containing chemotherapy, based on the results from Interim Analysis 1 of the pivotal Study KN-B15 (EV-304); this is a phase 3, randomized, open-label study to evaluate perioperative enfortumab vedotin plus pembrolizumab (MK-3475) versus neoadjuvant gemcitabine and cisplatin in cisplatin-eligible participants with Muscle-Invasive Bladder Cancer. As consequence, sections 4.1, 4.2, 4.8, and 5.1 of the SmPC have been updated; the Package Leaflet is updated accordingly. Version 6.3 of the RMP is agreed. In addition, the MAH took the opportunity to bring the PI in line with the latest QRD template version 10.4 and to align with the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' regarding the polysorbate 20 content.

Amendments to the marketing authorisation

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