Official Protocol Title:	A Randomized Phase 3 Study Evaluating Cystectomy with Perioperative Pembrolizumab and Cystectomy with Perioperative Enfortumab Vedotin and Pembrolizumab versus Cystectomy Alone in Participants who are Cisplatin-Ineligible or Decline Cisplatin with Muscle-Invasive Bladder Cancer (KEYNOTE-905/EV-303)
NCT number:	NCT03924895
Document Date:	08-Apr-2026

TITLE PAGE

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Protocol Title: A Randomized Phase 3 Study Evaluating Cystectomy with Perioperative Pembrolizumab and Cystectomy with Perioperative Enfortumab Vedotin and Pembrolizumab versus Cystectomy Alone in Participants who are Cisplatin-Ineligible or Decline Cisplatin with Muscle-Invasive Bladder Cancer (KEYNOTE-905/EV-303)

Protocol Number: 905-12

Compound Number: MK-3475

Sponsor Name: Merck Sharp & Dohme LLC (hereafter called the Sponsor or MSD)

Legal Registered Address:

126 East Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

NCT	NCT03924895
EU CT	2023-504932-16
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JRCT	2031220686
WHO/UTN	U1111-1290-4057
IND	122753

Approval Date: 08 April 2026

Sponsor Signatory

Typed Name: Title:	Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 12	08-APR-2026	To change the IA2 and FA trigger, based on the targeted number of events needed for hypothesis testing, to be performed in the ITT1 population if all hypotheses are rejected in the ITT2 population at IA1.
Amendment 11	16-JAN-2025	To clarify the EFS endpoint to indicate that any biopsy-proven residual MIBC will be considered an event and change pCR primary analysis to intention-to-treat.
Amendment 10	06-SEP-2024	To align the definition of the EFS endpoint and the statistical analysis plan with the clinical criteria required for evaluating residual MIBC and to revise the statistical analysis plan with updated protocol assumptions based on emerging literature in the target population.
Amendment 09	29-JUN-2023	To implement collection of late-onset peripheral neuropathy AEs and to maintain Arm A open in France. Recommendations regarding management and dose modifications for pneumonitis/ILD in participants receiving enfortumab vedotin were also added.
Amendment 08	01-NOV-2022	To stop randomization in Arm A, change Stage 2 randomization to Arm B and Arm C only in a 1:1 ratio, and remove Stage 3 randomization. To reduce the sample size due to ceasing enrollment in Arm A, updating the multiplicity strategy, and by changing the assumption of hazard ratio of EFS and OS between Arm C versus Arm B from 0.65 to 0.59. To change pCR from a primary to a key secondary objective, update the hypothesis testing to prioritize the Arm C versus Arm B comparison for EFS, and update the analysis timing and multiplicity strategy in the SAP accordingly. In addition, adjuvant nivolumab will be permitted in Arm B when clinically indicated, changes were made to align with the EU CTR, and other minor updates and clarifications were made.

Document	Date of Issue	Overall Rationale
Amendment 07	14-JUN-2022	Ireland-specific amendment: Agency request (HPRA) for Ireland to ensure investigators are aware that fever or flu-like symptoms may be the first sign of a severe skin reaction.
Amendment 06	04-APR-2022	Added additional guidance on management of certain Grade 2 skin reactions and any grade bullous lesions.
Amendment 05	25-JAN-2022	To broaden eligibility criteria and potentially enhance enrollment, changes were made to randomization, sample size, statistical analyses, stratification factors, and the study population to include cisplatin-eligible participants who decline cisplatin-based chemotherapy.
Amendment 04	14-APR-2021	Updated dose modification and supportive care guidelines for rash related to enfortumab vedotin. Updated pembrolizumab dose modification table per FDA request to align with the USPI.
Amendment 03	24-MAR-2021	UK-specific amendment to update enfortumab vedotin dose modification and management guidelines for rash
Amendment 02	05-AUG-2020	Corrected errors in Amendment 01 and updated details on glucose monitoring and contraception while using EV
Amendment 01	22-JUN-2020	To add perioperative EV in combination with pembrolizumab plus RC + PLND (Arm C)
Original Protocol	28-FEB-2019	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Description of Current Amendment:

Reason(s) for Amendment:	Primary: Change In Strategy	Secondary: Not Applicable
Amendment Summary:	To change the IA2 and FA trigger, based on the targeted number of events needed for hypothesis testing, to be performed in the ITT1 population if all hypotheses are rejected in the ITT2 population at IA1.	
Is this amendment likely to have a substantial impact on the safety or rights of the participants?	No	
Is this amendment likely to have a substantial impact on the reliability and robustness of the data generated in the clinical trial?	No	

Overview of Changes in the Current Amendment:

Section # and Name	Description of Change	Brief Rationale for Change
Section 1.1, Synopsis, Number of Participants Section 4.1, Overall Design Section 9.1 Statistical Analysis Plan Summary Section 9.9 Sample Size and Power Calculations	Text was revised to indicate enrollment was complete with 595 participants randomized in the study.	To align language across the protocol for consistency.
Section 8.1.10, Procedures for Discontinuing a Study or One or More Study Arm(s) Without Safety Concerns	Added new section.	To provide actions the Sponsor may implement if determined that the study or one or more study intervention group(s) should be discontinued.

Section # and Name	Description of Change	Brief Rationale for Change
Section 9.1, Statistical Analysis Plan Summary Section 9.7.1, Efficacy Interim Analyses Section 9.8.1, Multiplicity Control for Efficacy Interim Analyses Section 9.8.1.1, Event-Free Survival (EFS) Section 9.8.1.2, Overall Survival (OS)	Updated trigger for IA2 and FA, with additional details for future analyses provided accordingly.	To clarify that if all hypotheses are rejected in the ITT2 population at IA1, then IA2 and FA will be triggered when the targeted number of EFS and OS events in the ITT1 population are observed, respectively.
Section 10.1.6, Compliance with Study Registration and Results Posting Requirements	Added sentence related to submission of results for studies conducted under the EMA Clinical Trials Regulation 536/2014.	To align with Regulation (EU) 536/2014.
Section 10.7.9, Japan-Specific Requirements	Added new section.	To provide country-specific requirements for Japan.
Throughout	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Randomized Phase 3 Study Evaluating Cystectomy with Perioperative Pembrolizumab and Cystectomy with Perioperative Enfortumab Vedotin and Pembrolizumab versus Cystectomy Alone in Participants who are Cisplatin-Ineligible or Decline Cisplatin with Muscle-Invasive Bladder Cancer (KEYNOTE-905/EV-303)

Short Title: A Phase 3 trial of perioperative pembrolizumab or enfortumab vedotin in combination with pembrolizumab in participants who are cisplatin-ineligible or decline cisplatin with MIBC

Acronym: KN905/EV-303

Hypotheses, Objectives, and Endpoints:

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

In male or female participants at least 18 years of age with histologically confirmed muscle-invasive bladder cancer (MIBC) clinical Stage cT2-T4aN0M0 or cT1-T4aN1M0:

Primary Objective	**Primary Endpoint**
Objective: To compare event-free survival (EFS) between Arm C (perioperative enfortumab vedotin in combination with pembrolizumab and radical cystectomy plus pelvic lymph node dissection [RC+PLND]) and Arm B (RC+PLND). Hypothesis (H1): Perioperative enfortumab vedotin in combination with pembrolizumab plus RC+PLND will achieve superior EFS compared with RC+PLND alone.	EFS (defined as the time from randomization to the first of any of the following events): -Radiographic disease progression precluding a curative intent surgery as assessed by BICR prior to RC+PLND -Failure to undergo surgery for participants with residual muscle-invasive disease and any radiographic disease present (for other participants who do not undergo surgery, see Section 8.2.3), 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 computed tomography (CT) or magnetic resonance imaging (MRI) (BICR) and/or biopsy. If biopsy is not feasible due to participant safety, CT/MRI alone will be sufficient -Death from any cause
Secondary Objectives	**Secondary Endpoints**
Objective: To compare EFS between Arm A (perioperative pembrolizumab and RC+PLND) and Arm B (RC+PLND). Hypothesis (H4): Perioperative pembrolizumab plus RC+PLND will achieve superior EFS compared with RC+PLND alone.	EFS

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

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

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	Bladder cancer
Population	Participants with MIBC (cT2-T4aN0M0 or cT1-T4aN1M0) who are ineligible for or decline cisplatin-based chemotherapy.
Study Type	Interventional
Intervention Model	Parallel This is a multi site study.
Type of Control	Active Control Without Placebo
Study Blinding	Unblinded open-label
Blinding Roles	No blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 92 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

At the time of Amendment 10, the study completed enrollment, with 595 participants randomized to receive perioperative pembrolizumab + RC + PLND (Arm A), RC + PLND alone (Arm B), or perioperative enfortumab vedotin in combination with pembrolizumab + RC + PLND (Arm C). After implementation of Amendment 8, enrollment in Arm A was stopped and participants were randomized in a 1:1 ratio to Arm B or Arm C.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Arm A	Pembrolizumab	100 mg/4 mL (25 mg/mL) solution in a single-dose vial	200 mg	IV Infusion	Q3W – 3 cycles neoadjuvant phase; 14 cycles adjuvant phase	Test Product
Arm C	Pembrolizumab	100 mg/4 mL (25 mg/mL) solution in a single-dose vial	200 mg	IV Infusion	Q3W – 3 cycles neoadjuvant phase; 14 cycles adjuvant phase	Test Product
Arm C	Enfortumab vedotin	30 mg single dose vial	1.25 mg/kg	IV Infusion	Days 1 and 8 Q3W- 3 cycles in the neoadjuvant phase and for 6 cycles in the adjuvant phase	Test Product

Total Number of Intervention Groups/Arms	3 arms (2 arms after implementation of Amendment 8)
Duration of Participation	After a screening phase of up to 42 days, all study participants will be stratified and randomized to receive assigned study intervention for up to approximately 1 year. Study participants in Arm A will receive preoperative therapy with pembrolizumab for 3 cycles followed by RC + PLND at Week 12 (84 days ± 7 days) from study randomization. At 8 weeks (56 days ± 14 days) after RC + PLND, study participants in Arm A will receive postoperative pembrolizumab for 14 cycles. In total, the participants on Arm A will receive 17 cycles of pembrolizumab (equivalent to 1 year). After implementation of Amendment 8, enrollment in Arm A was stopped.

	Study participants in Arm B will follow standard of care therapy and undergo RC + PLND within 8 weeks (56 days + 7 days) from randomization. Study participants in Arm C will receive preoperative therapy with enfortumab vedotin and pembrolizumab for 3 cycles followed by a RC + PLND at Week 12 (84 days ± 7 days). At 8 weeks (56 days ± 14 days) after RC + PLND, study participants in Arm C will receive postoperative enfortumab vedotin and pembrolizumab for 6 cycles, then pembrolizumab for 8 more cycles. Enfortumab vedotin must be given 7 days apart in each preoperative and postoperative cycle. After the end-of-treatment, each participant will be followed until meeting criteria for study discontinuation or Sponsor decision. In total, the participants on Arm C will receive 9 cycles of enfortumab vedotin (approximately 6.5 months) on Days 1 and 8 of each cycle and 17 cycles of pembrolizumab (equivalent to one year). Each participant will participate in the study from the time that the participant provides documented informed consent through the final protocol-specified contact. Study intervention will be received until any of the following occur: disease progression is radiographically documented and/or confirmed by biopsy when clinically appropriate, unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, noncompliance with study intervention or procedure requirements or administrative reasons requiring cessation of treatment, as described in Section 7.1. After the end-of-treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy as described under Section 8.4. All participants will be followed by telephone for OS until death, withdrawal of consent, or the end of the study.

Study Governance Committees:

Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No
Steering Committee	No

Study governance considerations are outlined in Appendix 1.

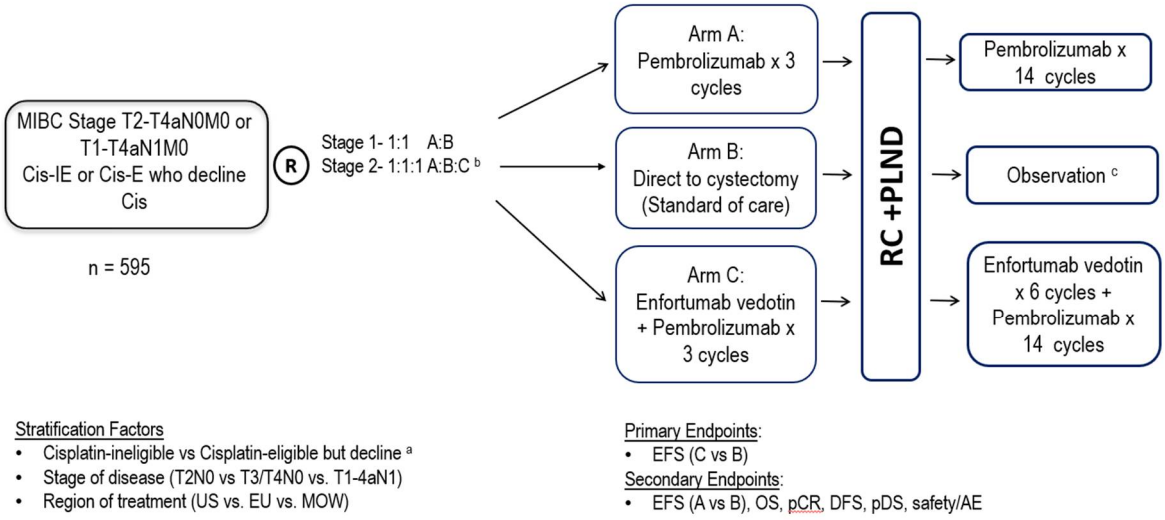
Study Accepts Healthy Participants: No

A list of abbreviations is in Appendix 10.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Design



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

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

1.3 Schedule of Activities

1.3.1 Study Screening and Neoadjuvant Treatment (Preoperative and Operative Phase) – Arm A (Pembrolizumab) and Arm C (Enfortumab Vedotin and Pembrolizumab)

Note: After implementation of Amendment 8, enrollment in Arm A was stopped.

Trial Period	**Screening**	**Neoadjuvant Treatment (Arm A&C)**						**Pre-surgery Imaging/ Safety**	**RC + PLND**	**Post-surgery Follow-Up*** **	**Notes:**
Visit/Procedure		**Preoperative**									***Can be combined with the A1 visit**
Treatment Cycle		**N1****		**N2**		**N3**					****N1-N3 = neoadjuvant Cycle 1, neoadjuvant Cycle 2, neoadjuvant Cycle 3**
Week		**1**		**4**		**7**		**10**	**12**	**18**	*+3-day window for C1D1 neoadjuvant treatment, from randomization
Scheduled Cycle Days	**-42 to -1**	**D1***	**D8**	**D1**	**D8**	**D1**	**D8**				
Window Days		**+3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±7**	**±7**	**±14**	
Administrative Procedures											
Informed Consent	X										
Participant Identification Card	X	X									Add the randomization number at the time of randomization.
Inclusion/Exclusion Criteria	X										
Demographics, Disease Details and Complete Medical History	X										
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	Assess prior medications use for 28 days prior to randomization and concomitant medications up to 30 days after the last dose of study intervention (or for up to 90 days after last dose for SAEs).
Treatment Randomization via IVRS	X										Participant must be deemed eligible based on central pathology and central radiology review prior to randomization.

Trial Period	**Screening**	**Neoadjuvant Treatment (Arm A&C)**						**Pre-surgery Imaging/ Safety**	**RC + PLND**	**Post-surgery Follow-Up***	**Notes:**
Visit/Procedure		**Preoperative**									***Can be combined with the A1 visit
Treatment Cycle		**N1****		**N2**		**N3**					**N1-N3 = neoadjuvant Cycle 1, neoadjuvant Cycle 2, neoadjuvant Cycle 3**
Week		**1**		**4**		**7**		**10**	**12**	**18**	*+3-day window for C1D1 neoadjuvant treatment, from randomization
Scheduled Cycle Days	**-42 to -1**	**D1***	**D8**	**D1**	**D8**	**D1**	**D8**				
Window Days		**+3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±7**	**±7**	**±14**	
Survival Status		←					→				Upon Sponsor request, participants may be contacted for survival sweep status at any time during the study.
Pembrolizumab Administration		X		X		X					Participants may receive pembrolizumab while thyroid function test results are pending.
Enfortumab vedotin Administration		X	X*	X	X*	X	X*				Participants on Arm C will receive enfortumab vedotin on Days 1 and 8 of a 3-week cycle. *Enfortumab vedotin must be infused 7 (Day 8 + 4 days) days apart from each dose.
Cystectomy + PLND[a]									X		**It is recommended that presurgery cystoscopy with repeat TUR not be performed.**
Efficacy Procedures											
CT or MRI of the chest, abdomen & pelvis (CT of the chest is preferred to MRI)[b] Oral contrast is optional. IV contrast is required unless contraindicated.	X							X*		X**	Use same imaging modality for all evaluations. CT/MRI screening scans to be performed ≤28 days before randomization. *Must be performed ≤5 weeks (35 days ± 7 days) prior to cystectomy. ****First (baseline) post-cystectomy scan to be performed at 6 weeks [42 days] ±14 days post-cystectomy.** If the participant does not undergo surgery, scans must be performed within 12 weeks (+4 weeks) after last dose of neoadjuvant treatment.

Trial Period	**Screening**	**Neoadjuvant Treatment (Arm A&C)**						**Pre-surgery Imaging/ Safety**	**RC + PLND**	**Post-surgery Follow-Up***	**Notes:**
Visit/Procedure		**Preoperative**									***Can be combined with the A1 visit
Treatment Cycle		**N1****		**N2**		**N3**					**N1-N3 = neoadjuvant Cycle 1, neoadjuvant Cycle 2, neoadjuvant Cycle 3**
Week		**1**		**4**		**7**		**10**	**12**	**18**	*+3-day window for C1D1 neoadjuvant treatment, from randomization
Scheduled Cycle Days	**-42 to -1**	**D1***	**D8**	**D1**	**D8**	**D1**	**D8**				
Window Days		**+3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±7**	**±7**	**±14**	
Tissue Collection (TUR specimen) for histopathology, T stage and PD-L1 assessment[c]	X										
RC + PLND tissue specimen (for pCR and pDS assessment)									X		Samples to be sent to central vendor for review and confirmation of pCR and pDS.
Pharmacokinetics/Pharmacodynamics/ Biomarkers: <u>For Arm C only</u>											
PK for pembrolizumab[d]		X		X							
PK for enfortumab vedotin[e]		X	X	X							
ADA for pembrolizumab		X		X							Collect predose sample 0-4 h before pembrolizumab administration on D1 of cycles N1 and N2. Collect with plasma samples for PK when feasible.
ADA for enfortumab vedotin		X	X	X							Collect predose sample 0-4 h before enfortumab vedotin administration on D1 and D8 of cycle N1 and D1 of cycle N2. Collect with plasma samples for PK when feasible.
Patient-reported Outcomes											
EQ-5D-5L[f]		X		X		X		X		X	
FACT-Bl-Cys[f]		X		X		X		X		X	
BCI[f]		X		X		X		X		X	

Trial Period	**Screening**	**Neoadjuvant Treatment (Arm A&C)**						**Pre-surgery Imaging/ Safety**	**RC + PLND**	**Post-surgery Follow-Up***	**Notes:**
Visit/Procedure		**Preoperative**									***Can be combined with the A1 visit
Treatment Cycle		**N1****		**N2**		**N3**					**N1-N3 = neoadjuvant Cycle 1, neoadjuvant Cycle 2, neoadjuvant Cycle 3**
Week		**1**		**4**		**7**		**10**	**12**	**18**	*+3-day window for C1D1 neoadjuvant treatment, from randomization
Scheduled Cycle Days	**-42 to -1**	**D1***	**D8**	**D1**	**D8**	**D1**	**D8**				
Window Days		**+3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±7**	**±7**	**±14**	
Clinical Assessments or Procedures											
Full physical examination including neurological examination* and height**	X	X		X		X				X	*If a full neurological examination performed ≤6 weeks prior to randomization, no need to repeat in screening. **Height (screening only)
Ophthalmologic examination[g]	X										
Directed physical examination			X		X		X	X			To include neurological examination if clinically indicated for participants in Arm C.
ECOG Performance Status	X	X		X		X		X		X	For screening, must be performed ≤14 days prior to randomization. Status must be 0, 1, or 2 presurgery. During treatment, ECOG should be assessed on cycle Day 1 prior to dosing.
Weight and Vital Signs	X	X	X	X	X	X	X	X	X	X	Weight should be measured ≤72 hours prior to dosing on D1 and D8 of Cycles N1 to N3 for weight-based dosing.
12-lead ECG (local)	X										
Laboratory Procedures											
Urine or Serum hCG Pregnancy Test (WOCBP only), per local SOP[h]	X	X		X		X				(x)	Required at screening. See Section 8.3.4.2 for details. (x) = pregnancy testing optional unless mandated by local regulations. (Appendix 2). Refer to Appendix 7 for country-specific requirements.

Trial Period	**Screening**	**Neoadjuvant Treatment (Arm A&C)**						**Pre-surgery Imaging/ Safety**	**RC + PLND**	**Post-surgery Follow-Up***	**Notes:**
Visit/Procedure		**Preoperative**									***Can be combined with the A1 visit
Treatment Cycle		**N1****		**N2**		**N3**					**N1-N3 = neoadjuvant Cycle 1, neoadjuvant Cycle 2, neoadjuvant Cycle 3**
Week		**1**		**4**		**7**		**10**	**12**	**18**	*+3-day window for C1D1 neoadjuvant treatment, from randomization
Scheduled Cycle Days	**-42 to -1**	**D1***	**D8**	**D1**	**D8**	**D1**	**D8**				
Window Days		**+3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±7**	**±7**	**±14**	
HIV, hepatitis B and C screening (testing optional per site SOP)	X										Acceptable to be based on history unless required by local authority (see Appendix 2). Refer to Appendix 7 for country-specific requirements. Assessed at Screening ≤28 days prior to randomization, if required.
Hematology[i]	X	X	X*	X	X*	X	X*	X		X	*For participants on Arm C only, collect hematology and chemistry on Days 1 and 8. Participants on Arm A do not require the Day 8 laboratory tests.
Chemistry[i]	X	X	X*	X	X*	X	X*	X		X	N1D1: Not required if Screening samples were collected ≤72 hours before dose.
Finger stick glucose (Arm C only)[j]		X	X	X	X	X	X				
HbA1c (for all participants at screening)[k]	X										
Urinalysis	X	---If Clinically Indicated---									Must be collected ≤14 days prior to randomization and may then be performed as clinically indicated.
Coagulation tests (PT/INR and aPTT or PTT)[l]	X	---If Clinically Indicated---						X	If clinically indicated	If clinically indicated	
ACTH and cortisol[m]	X							X			
Thyroid Function (TSH)[n]	X			X				X		X	*Total T3 is preferred, if not available, free T3 may be tested.

Trial Period	**Screening**	**Neoadjuvant Treatment (Arm A&C)**						**Pre-surgery Imaging/ Safety**	**RC + PLND**	**Post-surgery Follow-Up*** **	**Notes:** ***Can be combined with the A1 visit **N1-N3 = neoadjuvant Cycle 1, neoadjuvant Cycle 2, neoadjuvant Cycle 3
Visit/Procedure		**Preoperative**									
Treatment Cycle		**N1****		**N2**		**N3**					
Week		**1**		**4**		**7**		**10**	**12**	**18**	*+3-day window for C1D1 neoadjuvant treatment, from randomization
Scheduled Cycle Days	**-42 to -1**	**D1***	**D8**	**D1**	**D8**	**D1**	**D8**				
Window Days		**+3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±7**	**±7**	**±14**	
AE/SAE review	X	---Continuous Reporting---									
Sample Collection											
Blood for Genetic Analysis		X									Sample not collected if local regulation prohibits it or IRB/IEC does not approve. Collect ≤72 hours predose for enrolled participants only.
Blood for Serum Biomarker Analyses		X		X				X			All samples will be collected predose. Collect ≤72 hours predose for enrolled participants only.
Blood for ctDNA		X		X				X			All samples will be collected predose. Collect ≤72 hours predose for enrolled participants only.
Tissue Collection for Biomarkers											
Tissue Collection for Biomarker Analysis (tested centrally)	X								X		Tumor tissue from diagnostic TUR specimen and RC+PLND required (FNA not adequate) to identify novel biomarkers.

A=adjuvant cycle; ACTH=adrenocorticotropic hormone; ADA=antidrug antibodies; AE=adverse event; aPTT / PTT=activated partial thromboplastin time / partial thromboplastin time; BCI=Bladder Cancer Index; BICR=blinded independent central review; C=cycle; CT=computed tomography; CTCAE=common terminology criteria for adverse events; ctDNA=circulating tumor deoxyribonucleic acid; D=day; eCRF=electronic case report form; ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group; ePRO=electronic patient-reported outcomes; EQ-5 D-5 L=EuroQoL 5 Dimension Questionnaire; EV=enfortumab vedotin; FACT-Bl-Cys=functional assessment of cancer therapy-bladder cystectomy; FNA=fine needle aspirate; HbA1c=hemoglobin A1c; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; iCRO=imaging contract research organization; IEC=independent ethics committee; INR=international normalized ratio; IRB=institutional review board; IV=intravenous; IVRS=interactive voice response system; MRI=magnetic resonance imaging; N=neoadjuvant cycle; NCI=National Cancer Institute; pCR=pathologic complete response; PD=progressive disease; PD-L1=programmed cell death ligand 1; pDS=pathologic downstaging; PK=pharmacokinetics; PLND=pelvic lymph node dissection; PT=prothrombin time; RC=radical cystectomy; SAE=serious adverse event; SOP=standard operating procedure; T3=T3 thyroid hormone; TSH=thyroid-stimulating hormone; T stage=tumor stage; TUR=transurethral resection; WOCBP=woman of childbearing potential.

[a] In the event there is a delay between preoperative treatment and Week 12 (Day 84 ± 7 days) RC + PLND date for reasons other than an AE, the site must consult with the Sponsor.

Regarding Arm A and Arm C participants who do not undergo RC + PLND, see Sections 1.3.2 and 8.2.3.
Post-surgical complications will be assessed and graded according to NCI CTCAE v4.0.

[b] All imaging scans must be sent to the imaging vendor. Other than the presurgical and post-surgical scans, all other imaging timing should follow calendar days and should not be recalculated based on the date of previous scans and treatment. Results of additional investigative imaging (eg, CT urography) will be reported/collected in the eCRFs and should be submitted to iCRO to be centrally reviewed by BICR.

[c] Samples must have been collected within 60 days (+14 days) prior to enrollment (providing documented informed consent) and be sent to central vendor for review and histological confirmation of urothelial carcinoma pathologic Stage pT2 or pT1 (only if N1) and predominant urothelial histology prior to randomization, and for PD-L1 expression assessment.

[d] Collect predose sample 0-4 h before pembrolizumab administration and postdose sample at the end of infusion (as soon as possible, ideally within 10 minutes) on D1 of cycle N1, and predose sample 0-4 h before pembrolizumab administration on D1 of cycle N2.

[e] Collect predose sample 0-4 h before enfortumab vedotin administration and postdose sample at the end of infusion (as soon as possible, ideally within 10 minutes) on D1 and D8 of cycle N1, and predose sample 0-4 h before enfortumab vedotin administration on D1 of cycle N2.

[f] The ePRO questionnaires should be administered prior to dosing on D1 of neoadjuvant treatment Cycles 1, 2, and 3, and at the presurgery imaging/safety visit and post-surgery follow-up visit.

PROs given by trained site personnel and completed electronically by participants. Participants randomized under the original protocol will follow the original ePRO schedule, N1, N3, presurgery, post-surgery. PROs should be completed in the following order: EQ-5 D-5 L, FACT-Bl-Cys. For participants enrolled after Amendment 1, PROs should be completed in the following order EQ 5 D-5 L, FACT-Bl-Cys, BCI. Perform PRO assessment according to the schedule until confirmed PD or initiation of a new anticancer regimen, withdrawal of consent, or death, whichever occurs first. If ePROs are not completed, Miss Mode form must record the reason.

[g] Ophthalmologic examination should be performed for all participants at study screening. Prior ophthalmologic examination performed within 3 months of enrollment is acceptable provided the participant does not have new symptoms since that examination. Complete ophthalmologic examination, to be performed by a qualified ophthalmologist or optometrist, will include, but is not limited to, visual acuity, slit lamp, tonometry examination, and dilated fundus examination. Ophthalmology assessments should be performed as clinically indicated. Further ophthalmology assessments should be performed for participants in Arm C only per standard of care or if clinically indicated.

[h] Required at ≤24 hours prior to first treatment dose (C1D1). Required ≤72 hours prior to start of each subsequent treatment cycle. Ongoing testing should be conducted where applicable at intervals specified per country or local requirements (administrative letter can be provided if required). If urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required.

[i] Screening laboratory tests must be performed ≤14 days prior to randomization to confirm eligibility. Laboratory tests can be collected ≤72 hours prior to a dose.

[j] Serum glucose should be collected for all participants at screening. After screening, in Arm C only, verify blood glucose is ≤250 mg/dL in clinic prior to dosing. If blood glucose is >250 mg/dL or if participant has Grade 3 or 4 hyperglycemia, withhold EV dosing. If serum glucose is collected and reviewed on the day of the EV dosing, finger stick glucose is not required.

[k] Participants who enter the study with an elevated HbA1c (≥6.5%) at baseline should be referred to an appropriate provider during Cycle 1 for glucose management. See Section 5.2 Exclusion Criteria #16 for the HbA1c limitations for enrollment onto this study.

[l] Check at baseline ≤14 days prior to start of treatment and at presurgery safety visit for all participants. If on anticoagulant(s), test coagulation as clinically indicated. PTT may be performed if laboratory cannot perform aPTT.

[m] Assessed because pembrolizumab can rarely cause adrenal insufficiency. Assessed at Screening ≤42 days prior to randomization. Participants can be randomized while ACTH/Cortisol results are pending.

[n] Screening TSH must be performed ≤14 days prior to randomization. If TSH is abnormal, perform T3* + T4. Participants may receive pembrolizumab (Arm A) or pembrolizumab and enfortumab vedotin (Arm C) treatment while thyroid function test results are pending.

1.3.2 Post-surgery Adjuvant Treatment (Postoperative Phase) - Arm A (Pembrolizumab) and Arm C (Enfortumab Vedotin in Combination With Pembrolizumab)

Note: After implementation of Amendment 8, enrollment in Arm A was stopped.

Post-surgery Adjuvant Treatment (Postoperative Phase): Treatment Arm A = Pembrolizumab x 14 Cycles/ Treatment Arm C = Enfortumab vedotin x 6 Cycles in Combination with Pembrolizumab x 14 Cycles																	
Trial Period	**Postoperative (Adjuvant) Phase (Arm A and C)**														**EOT/ Discon****	**Safety FU**	**Notes:** *** A1-A14 = adjuvant Cycle 1; adjuvant Cycle 2; etc.** *** A1 will occur 8 weeks (±14 days) post-cystectomy and can be combined with the post-surgery follow-up visit.** **** If this occurs ≥30 days after last intervention, it may be combined with the Safety Follow-Up Visit.** **After completion of Cycle A14 or discontinuation of adjuvant treatment, participants will be followed per Section 1.3.4 below (note that Year 1 FU will overlap with the duration of adjuvant treatment). If adjuvant treatment is discontinued, the participant will complete the remaining Year 1 FU before continuing to Year 2 FU and beyond.**
Visit/Procedure																	
Treatment Cycle	**A1***		**A2**		**A3**		**A4**		**A5**		**A6**		**A7**	**A8-14**			
Adjuvant Phase Week	**1**		**4**		**7**		**10**		**13**		**16**		**19**	**22-40**			
Scheduled Cycle Day(s)	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D1**	**At time of last inter-vention/ dose**	**30 days after last interven-tion/ dose**	
Window Days	**±3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±3**	**±3**		**+14**	
Administrative Procedures																	
Prior/Concomitant Meds Review	X		X		X		X		X		X		X	X	X	X	
Survival Status	←													→			Upon Sponsor request, participants may be contacted for survival sweep status at any time during the course of the study.
Study Drug Administration																	
Pembrolizumab Administration	X		X		X		X		X		X		X	X			Participants may receive pembrolizumab while thyroid function test results are pending.
Enfortumab vedotin Administration[a]	X	X*	X	X*	X	X*	X	X*	X	X*	X	X*					*Enfortumab vedotin must be infused 7 (Day 8 + 4 days) days apart from each dose.

Post-surgery Adjuvant Treatment (Postoperative Phase): Treatment Arm A = Pembrolizumab x 14 Cycles/ Treatment Arm C = Enfortumab vedotin x 6 Cycles in Combination with Pembrolizumab x 14 Cycles																	
Trial Period	**Postoperative (Adjuvant) Phase (Arm A and C)**														**EOT/ Discon****	**Safety FU**	**Notes:** *** A1-A14 = adjuvant Cycle 1; adjuvant Cycle 2; etc.** *** A1 will occur 8 weeks (±14 days) post-cystectomy and can be combined with the post-surgery follow-up visit.** **** If this occurs ≥30 days after last intervention, it may be combined with the Safety Follow-Up Visit.** **After completion of Cycle A14 or discontinuation of adjuvant treatment, participants will be followed per Section 1.3.4 below (note that Year 1 FU will overlap with the duration of adjuvant treatment). If adjuvant treatment is discontinued, the participant will complete the remaining Year 1 FU before continuing to Year 2 FU and beyond.**
Visit/Procedure																	
Treatment Cycle	**A1***		**A2**		**A3**		**A4**		**A5**		**A6**		**A7**	**A8-14**			
Adjuvant Phase Week	**1**		**4**		**7**		**10**		**13**		**16**		**19**	**22-40**			
Scheduled Cycle Day(s)	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D1**	**At time of last inter-vention/ dose**	**30 days after last interven-tion/ dose**	
Window Days	**±3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±3**	**±3**		**+14**	
Efficacy Procedures																	
CT or MRI of the chest, abdomen & pelvis (CT of the chest is preferred to MRI)[b] Oral contrast is optional. IV contrast is required unless contraindicated.							X							X*	X**		*Scan will be performed at Adjuvant Cycle 12 D1 (Week 34). **To be performed within ± 4 weeks of discontinuation. If imaging was performed within 4 weeks of treatment discontinuation, then imaging at treatment discontinuation is not necessary.
Tissue collection for confirmation of recurrence[c]	◄													►			
Only for Participants who do not undergo RC + PLND Surgery:																	
Cystoscopy (± biopsy)																X	Refer to Section 8.2.3
Urine Cytology																X	Refer to Section 8.2.3.
CT or MRI																X	Refer to Section 8.2.3. Use same imaging modality for all evaluations.

Post-surgery Adjuvant Treatment (Postoperative Phase): Treatment Arm A = Pembrolizumab x 14 Cycles/ Treatment Arm C = Enfortumab vedotin x 6 Cycles in Combination with Pembrolizumab x 14 Cycles																	
Trial Period	**Postoperative (Adjuvant) Phase (Arm A and C)**														**EOT/ Discon****	**Safety FU**	**Notes:** *** A1-A14 = adjuvant Cycle 1; adjuvant Cycle 2; etc.** *** A1 will occur 8 weeks (±14 days) post-cystectomy and can be combined with the post-surgery follow-up visit.** **** If this occurs ≥30 days after last intervention, it may be combined with the Safety Follow-Up Visit.** **After completion of Cycle A14 or discontinuation of adjuvant treatment, participants will be followed per Section 1.3.4 below (note that Year 1 FU will overlap with the duration of adjuvant treatment). If adjuvant treatment is discontinued, the participant will complete the remaining Year 1 FU before continuing to Year 2 FU and beyond.**
Visit/Procedure																	
Treatment Cycle	**A1***		**A2**		**A3**		**A4**		**A5**		**A6**		**A7**	**A8-14**			
Adjuvant Phase Week	**1**		**4**		**7**		**10**		**13**		**16**		**19**	**22-40**			
Scheduled Cycle Day(s)	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D1**	**At time of last inter-vention/ dose**	**30 days after last interven-tion/ dose**	
Window Days	**±3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±3**	**±3**		**+14**	
Pharmacokinetics/ADA: For Arm C only																	
PK for pembrolizumab[d]	X		X								X						
PK for enfortumab vedotin[e]	X	X	X								X	X					
ADA for pembrolizumab	X		X								X						Collect predose sample 0-4 h before pembrolizumab administration on D1 of Cycles A1, A2 and A6. Collect with plasma samples for PK when feasible.
ADA for enfortumab vedotin	X	X	X								X	X					Collect predose sample 0-4 h before enfortumab vedotin administration on D1 and D8 of Cycles A1 and A6 and D1 of cycle A2. Collect with plasma samples for PK when feasible.

Post-surgery Adjuvant Treatment (Postoperative Phase): Treatment Arm A = Pembrolizumab x 14 Cycles/ Treatment Arm C = Enfortumab vedotin x 6 Cycles in Combination with Pembrolizumab x 14 Cycles																
Trial Period	**Postoperative (Adjuvant) Phase (Arm A and C)**														**EOT/ Discon****	**Safety FU**	**Notes:** *** A1-A14 = adjuvant Cycle 1; adjuvant Cycle 2; etc.** *** A1 will occur 8 weeks (±14 days) post-cystectomy and can be combined with the post-surgery follow-up visit.** **** If this occurs ≥30 days after last intervention, it may be combined with the Safety Follow-Up Visit.** **After completion of Cycle A14 or discontinuation of adjuvant treatment, participants will be followed per Section 1.3.4 below (note that Year 1 FU will overlap with the duration of adjuvant treatment). If adjuvant treatment is discontinued, the participant will complete the remaining Year 1 FU before continuing to Year 2 FU and beyond.**
Visit/Procedure																	
Treatment Cycle	**A1***		**A2**		**A3**		**A4**		**A5**		**A6**		**A7**	**A8-14**			
Adjuvant Phase Week	**1**		**4**		**7**		**10**		**13**		**16**		**19**	**22-40**			
Scheduled Cycle Day(s)	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D1**	**At time of last inter-vention/ dose**	**30 days after last interven-tion/ dose**	
Window Days	**±3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±3**	**±3**		**+14**	
Patient-reported Outcomes																	
EQ-5 D-5 L	X		X				X							X*	X**	X	*During postoperative phase while participants receive adjuvant treatment, the ePRO questionnaires should be administered prior to dosing on D1 of adjuvant treatment Cycle 1, Cycle 2, Cycle 4, Cycle 8, and Cycle 12. Participants randomized under the original protocol will follow the original ePRO schedule, ie, Cycles 1, 3, 7, 11. **The ePRO questionnaire should be administered at time of intervention discontinuation.
FACT-Bl-Cys	X		X				X							X*	X**	X	
BCI[f]	X		X				X							X*	X**	X	
Safety Procedures																	
Full physical examination															X		
Directed physical examination	X		X		X		X		X		X		X	X		X	Include neurological examination if clinically indicated. In Arm C, include ophthalmological examination, if clinically indicated.
ECOG Performance Status	X		X		X		X		X		X		X	X	X	X	

Post-surgery Adjuvant Treatment (Postoperative Phase): Treatment Arm A = Pembrolizumab x 14 Cycles/ Treatment Arm C = Enfortumab vedotin x 6 Cycles in Combination with Pembrolizumab x 14 Cycles																	
Trial Period	**Postoperative (Adjuvant) Phase (Arm A and C)**														**EOT/ Discon****	**Safety FU**	**Notes:** *** A1-A14 = adjuvant Cycle 1; adjuvant Cycle 2; etc.** *** A1 will occur 8 weeks (±14 days) post-cystectomy and can be combined with the post-surgery follow-up visit.** **** If this occurs ≥30 days after last intervention, it may be combined with the Safety Follow-Up Visit.** **After completion of Cycle A14 or discontinuation of adjuvant treatment, participants will be followed per Section 1.3.4 below (note that Year 1 FU will overlap with the duration of adjuvant treatment). If adjuvant treatment is discontinued, the participant will complete the remaining Year 1 FU before continuing to Year 2 FU and beyond.**
Visit/Procedure																	
Treatment Cycle	**A1***		**A2**		**A3**		**A4**		**A5**		**A6**		**A7**	**A8-14**			
Adjuvant Phase Week	**1**		**4**		**7**		**10**		**13**		**16**		**19**	**22-40**			
Scheduled Cycle Day(s)	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D1**	**At time of last inter-vention/ dose**	**30 days after last interven-tion/ dose**	
Window Days	**±3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±3**	**±3**		**+14**	
Weight and Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	If clin indicated	Weight should be obtained ≤72 hours prior to dosing on D1 and D8 of Cycles A1 to A6 for weight-based dosing.
Urine or Serum hCG Pregnancy Test (WOCBP only), per local SOP[g]	X		X		X		X		X		X		X	X	X*	X	See Section 8.3.4.2 for details. *End of study intervention pregnancy testing should be conducted where applicable at intervals specified per country or local requirements (administrative letter provided if required). Refer to Appendix 7 for country-specific requirements.
Hematology	X	X*	X	X*	X	X*	X	X*	X	X*	X	X*	X	X	X	X	Collect ≤72 hours prior to pembrolizumab administration in each cycle. *For participants on Arm C, collect hematology and chemistry on Days 1 and 8.
Chemistry	X	X*	X	X*	X	X*	X	X*	X	X*	X	X*	X	X	X	X	
Urinalysis	----------As Clinically Indicated----------														X	X	
Finger stick glucose (Arm C only)[h]	X	X	X	X	X	X	X	X	X	X	X	X					
Coagulation tests (PT/INR and aPTT or PTT)	----------As Clinically Indicated----------																If on anticoagulant, perform as needed. PTT may be performed if laboratory cannot perform aPTT.

Post-surgery Adjuvant Treatment (Postoperative Phase): Treatment Arm A = Pembrolizumab x 14 Cycles/ Treatment Arm C = Enfortumab vedotin x 6 Cycles in Combination with Pembrolizumab x 14 Cycles																	
Trial Period	**Postoperative (Adjuvant) Phase (Arm A and C)**														**EOT/ Discon****	**Safety FU**	**Notes:** *** A1-A14 = adjuvant Cycle 1; adjuvant Cycle 2; etc.** *** A1 will occur 8 weeks (±14 days) post-cystectomy and can be combined with the post-surgery follow-up visit.** **** If this occurs ≥30 days after last intervention, it may be combined with the Safety Follow-Up Visit.** **After completion of Cycle A14 or discontinuation of adjuvant treatment, participants will be followed per Section 1.3.4 below (note that Year 1 FU will overlap with the duration of adjuvant treatment). If adjuvant treatment is discontinued, the participant will complete the remaining Year 1 FU before continuing to Year 2 FU and beyond.**
Visit/Procedure																	
Treatment Cycle	**A1***		**A2**		**A3**		**A4**		**A5**		**A6**		**A7**	**A8-14**			
Adjuvant Phase Week	**1**		**4**		**7**		**10**		**13**		**16**		**19**	**22-40**			
Scheduled Cycle Day(s)	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D1**	**At time of last inter-vention/ dose**	**30 days after last interven -tion/ dose**	
Window Days	**±3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±3**	**±3**		**+14**	
Thyroid Function (TSH)[i]	X				X				X				X	X	X	X	*Total T3 is preferred, if not available free T3 may be tested
AE/SAE review[j]	----------Continuous Reporting----------																
Biomarkers																	
Blood for Serum Biomarker Analyses	X						X						X		X		All samples will be collected ≤72 hours predose.
Blood for ctDNA	X						X						X		X		

A=adjuvant cycle; ADA=antidrug antibodies; AE=adverse event; aPTT / PTT=activated partial thromboplastin time / partial thromboplastin time; BCI=Bladder Cancer Index; BICR=blinded independent central review; C=cycle; CT=computed tomography; ctDNA=circulating tumor deoxyribonucleic acid; D=day; DC=discontinuation; discon.=discontinuation; eCRF=electronic case report form; ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group; EOT=end-of-treatment; ePRO=electronic patient-reported outcomes; EQ-5 D-5 L=EuroQoL 5 Dimension Questionnaire; EV=enfortumab vedotin; FACT-Bl-Cys=functional assessment of cancer therapy-bladder cystectomy; FU=follow-up; HbA1c=hemoglobin A1c; hCG=human chorionic gonadotropin; iCRO=imaging contract research organization; INR=international normalized ratio; IV=intravenous; MRI=magnetic resonance imaging; N/A=not applicable; PD=progressive disease; PK=pharmacokinetics; PLND=pelvic lymph node dissection; PRO=patient-reported outcome; PT=prothrombin time; RC=radical cystectomy; SAE=serious adverse event; SOP=standard operating procedure; T3=T3 thyroid hormone; TSH=thyroid-stimulating hormone; TUR=transurethral resection; WOCBP=woman of childbearing potential.

[a] Participants on Arm C will receive enfortumab vedotin with pembrolizumab on Days 1 and 8 of a 3-week cycle.

[b] Use same imaging modality for all evaluations. After the post-cystectomy baseline scan, imaging to be performed every 12 weeks (± 7 days) until end of Year 1 post-cystectomy baseline scan. After Year 1, follow Section 1.3.4. Other than the presurgical and post-surgical scans, all other imaging timing should follow calendar days and should not be recalculated based on the date of previous scans and treatment. Results of additional investigative imaging (eg, CT urography) will be reported/collected in the eCRFs and should be submitted to iCRO to be centrally reviewed by BICR.

[c] Mandatory biopsy will be collected and locally assessed to confirm disease recurrence in participants found to have radiographic disease progression. Biopsy sample must also be sent to the central pathology vendor. If biopsy is not feasible due to participant safety, CT/MRI alone will be sufficient to document progression.

[d] Collect predose sample 0-4 h before pembrolizumab administration on D1 of cycles A1, A2, and A6; and postdose sample at the end of infusion (as soon as possible, ideally within 10 minutes) on D1 of cycles A1 and A6.

[e] Collect predose sample 0-4 h before enfortumab vedotin administration on D1 and D8 of cycles A1 and A6 and D1 of cycle A2; and postdose sample at the end of infusion (as soon as possible, ideally within 10 minutes) on D1 and D8 of cycles A1 and A6.

[f] For participants enrolled after Amendment 1, BCI is added and PROs should be completed in the following order: EQ-5 D-5 L, FACT-Bl-Cys, BCI. PROs given by trained site personnel and completed electronically by participants. Perform PRO assessment according to the schedule until confirmed PD or initiation of a new anticancer regimen, withdrawal of consent, or death, whichever occurs first. If ePROs are not completed, Miss Mode form must record the reason.

[g] Required ≤72 hours prior to start of each subsequent treatment cycle, EOT/DC, and Safety FU. Ongoing testing should be conducted where applicable at intervals specified per country or local requirements (administrative letter can be provided if required). This testing will be N/A for many participants as standard RC+PLND surgery includes removal of the uterus. If urine pregnancy test is required and cannot be confirmed as negative, a serum pregnancy test is required.

[h] Serum glucose should be collected for all participants at screening. After screening, in Arm C only, verify blood glucose is ≤250 mg/dL in clinic prior to dosing. If blood glucose is >250 mg/dL or if participant has Grade 3 or 4 hyperglycemia, withhold EV dosing. If serum glucose is collected and reviewed on the day of the EV dosing, finger stick glucose is not required.

[i] If TSH is abnormal, perform T3*+ T4. TSH to be tested on Day 1 of every 2 cycles (ie, Cycles 1, 3, 5, 7, 9, etc,), and more frequently if clinically indicated. Participants may receive pembrolizumab (Arm A) or pembrolizumab and enfortumab vedotin (Arm C) treatment while thyroid function test results are pending.

[j] All AEs up until 30 days post study intervention and SAEs up until 90 days post study treatment or 30 days if participant starts new anticancer therapy, whichever is earlier, should be reported. Treatment-related late toxicity may be collected for up to 5 years. As of Amendment 09, for any participant on Arm C study intervention (or within 30 days of cessation of study intervention), peripheral neuropathy AEs should continue to be reported until new anticancer therapy is initiated and as long as the participant remains in Efficacy Follow-up.

1.3.3 Study Screening, Surgery and Post-Surgery (Control) - Arm B (Cystectomy)

Treatment Arm B: RC + PLND Only											
Trial Period	**Screen-ing**	**Pre-surgery**	**RC + PLND**	**Post-surgery Follow-up**							**Notes:** *** After the visit at Week 30, subsequent clinic visits will occur every 12 weeks [±14 days] (if the participant remains clinically stable) through the end of Year 1 (from the post-cystectomy baseline scan).** **‡ The 6-week post-surgery visit may also serve as the Safety Follow-up Visit (if it occurs 4-6 weeks post-surgery, as noted in the window periods).**
Visit/ Procedure			**Surgery**	**Safety Follow-Up**	**Weeks Post-surgery (Clinical Observation)**						
Week	**≤6 weeks prior to randomization (Days -42 to -1)**	**2 weeks prior to surgery**	**Within 8 weeks from random-ization**	**30 days after study intervention (surgery)**	**6‡**	**12**	**18**	**24**	**30**	***42 to 54**	
Window Days		**±7**	**+7**	**+14**	**±14**	**±7**	**±7**	**±7**	**±7**	**±14**	
Informed Consent	X										
Participant Identification Card	X	X									Add the randomization number at the time of randomization.
Inclusion/ Exclusion Criteria	X										
Demographics, Disease Details and Complete Medical History	X										
Ophthalmologic examination	X										Ophthalmologic examination should be performed for all participants at study screening. Prior ophthalmologic examination performed within 3 months of enrollment is acceptable provided the participant does not have new symptoms during that examination.
Prior/ Concomitant	X	X	X	X							Assess prior medications use for 28 days prior to randomization

Treatment Arm B: RC + PLND Only											
Trial Period	**Screen-ing**	**Pre-surgery**	**RC + PLND**	**Post-surgery Follow-up**							**Notes:** *** After the visit at Week 30, subsequent clinic visits will occur every 12 weeks [±14 days] (if the participant remains clinically stable) through the end of Year 1 (from the post-cystectomy baseline scan).** **‡ The 6-week post-surgery visit may also serve as the Safety Follow-up Visit (if it occurs 4-6 weeks post-surgery, as noted in the window periods).**
Visit/ Procedure			**Surgery**	**Safety Follow-Up**	**Weeks Post-surgery (Clinical Observation)**						
Week	**≤6 weeks prior to randomization (Days -42 to -1)**	**2 weeks prior to surgery**	**Within 8 weeks from random-ization**	**30 days after study intervention (surgery)**	**6‡**	**12**	**18**	**24**	**30**	***42 to 54**	
Window Days		**±7**	**+7**	**+14**	**±14**	**±7**	**±7**	**±7**	**±7**	**±14**	
Medication Review											Concomitant medications will be collected up to 30 days post-surgery and for SAEs up to 90 days post-surgery.
Treatment Randomization via IVRS	X										Participant must be deemed eligible based on central pathology and central radiology review prior to randomization.
Survival Status		←								→	Upon Sponsor request, participants may be contacted for survival sweep status at any time during the course of the study.
Cystectomy + PLND			X								It is recommended that presurgery cystoscopy with repeat TUR not be performed. Should be performed within 8 (+7 days) weeks from time of randomization. Post-surgical complications will be assessed and graded according to NCI CTCAE v4.0.

Treatment Arm B: RC + PLND Only											
Trial Period	**Screen-ing**	**Pre-surgery**	**RC + PLND**	**Post-surgery Follow-up**							**Notes:** *** After the visit at Week 30, subsequent clinic visits will occur every 12 weeks [±14 days] (if the participant remains clinically stable) through the end of Year 1 (from the post-cystectomy baseline scan).** **‡ The 6-week post-surgery visit may also serve as the Safety Follow-up Visit (if it occurs 4-6 weeks post-surgery, as noted in the window periods).**
Visit/ Procedure			**Surgery**	**Safety Follow-Up**	**Weeks Post-surgery (Clinical Observation)**						
Week	**≤6 weeks prior to randomization (Days -42 to -1)**	**2 weeks prior to surgery**	**Within 8 weeks from random-ization**	**30 days after study intervention (surgery)**	**6‡**	**12**	**18**	**24**	**30**	***42 to 54**	
Window Days		**±7**	**+7**	**+14**	**±14**	**±7**	**±7**	**±7**	**±7**	**±14**	
CT or MRI of the chest, abdomen & pelvis. (CT of the chest is preferred to MRI)[a] Oral contrast is optional. IV contrast is required unless contraindicated.	X				X*		X		X	X	Use same imaging modality for all evaluations. CT/MRI Screening scan should be performed ≤28 days prior to randomization. Screening scan: *First (baseline) post-cystectomy scan to occur at 6 weeks (42 days ±14 days) post-cystectomy. Subsequent imaging then to be performed every 12 weeks ±7 days until end of Year 1 post-cystectomy scan. If a new anticancer treatment is started in the absence of disease progression, participants should continue follow-up imaging as per Section 1.3.4.
Tissue Collection (TUR specimen) for histopathology, T stage and PD-L1 assessment[b]	X										
RC+ PLND tissue specimen (for pCR and pDS assessment)			X								Samples to be sent to central vendor for review and confirmation of pCR and pDS.

Treatment Arm B: RC + PLND Only											
Trial Period	**Screen-ing**	**Pre-surgery**	**RC + PLND**	**Post-surgery Follow-up**							**Notes:** *** After the visit at Week 30, subsequent clinic visits will occur every 12 weeks [±14 days] (if the participant remains clinically stable) through the end of Year 1 (from the post-cystectomy baseline scan).** **‡ The 6-week post-surgery visit may also serve as the Safety Follow-up Visit (if it occurs 4-6 weeks post-surgery, as noted in the window periods).**
Visit/ Procedure			**Surgery**	**Safety Follow-Up**	**Weeks Post-surgery (Clinical Observation)**						
Week	**≤6 weeks prior to randomization (Days -42 to -1)**	**2 weeks prior to surgery**	**Within 8 weeks from random-ization**	**30 days after study intervention (surgery)**	**6‡**	**12**	**18**	**24**	**30**	***42 to 54**	
Window Days		**±7**	**+7**	**+14**	**±14**	**±7**	**±7**	**±7**	**±7**	**±14**	
Tissue collection for confirmation of recurrence											Mandatory biopsy will be collected and locally assessed to confirm disease recurrence in participants found to have radiographic disease progression. Biopsy sample must also be sent to the central pathology vendor. If biopsy is not feasible due to participant safety, CT/MRI alone will be sufficient to document progression.
EQ-5 D-5 L[c]		X			X		X		X	X*	*During the preoperative phase, operative phase, and postoperative phase, the ePRO questionnaires should be administered at the presurgery visit (≤2 weeks prior to surgery) and first post-surgery imaging follow-up visit (6 weeks [42 days] after the surgery); every 12 weeks thereafter up to the end of Year 1.
FACT-Bl-Cys		X			X		X		X	X*	
BCI		X			X		X		X	X*	
Full physical examination including neurological examination* and height**	X			X							*If neurological examination ≤6 weeks prior to randomization: no need to repeat in screening. **Height at Screening only.
Directed physical examination		X			X	X	X	X	X	X	Include neurological examination if clinically indicated.

Treatment Arm B: RC + PLND Only											
Trial Period	**Screen-ing**	**Pre-surgery**	**RC + PLND**	**Post-surgery Follow-up**							**Notes:** *** After the visit at Week 30, subsequent clinic visits will occur every 12 weeks [±14 days] (if the participant remains clinically stable) through the end of Year 1 (from the post-cystectomy baseline scan).** **‡ The 6-week post-surgery visit may also serve as the Safety Follow-up Visit (if it occurs 4-6 weeks post-surgery, as noted in the window periods).**
Visit/ Procedure			**Surgery**	**Safety Follow-Up**	**Weeks Post-surgery (Clinical Observation)**						
Week	**≤6 weeks prior to randomization (Days -42 to -1)**	**2 weeks prior to surgery**	**Within 8 weeks from random-ization**	**30 days after study intervention (surgery)**	**6‡**	**12**	**18**	**24**	**30**	***42 to 54**	
Window Days		**±7**	**+7**	**+14**	**±14**	**±7**	**±7**	**±7**	**±7**	**±14**	
ECOG Performance Status	X	X		X	X	X	X	X	X	X	Screening ≤14 days prior to randomization. Status must be 0, 1, or 2 presurgery. ECOG should be assessed at each post-cystectomy visit.
Weight and Vital Signs	X	X	X	X	X	X	X	X	X	X	
12-lead ECG (local)	X										
Urine or Serum hCG Pregnancy Test (WOCBP only), per local SOP[d]	X			(x)				(x)		(x)	Required at screening. See Section 8.3.4.2 for details. (x) = pregnancy testing optional unless mandated by local regulations. (Appendix 2). Refer to Appendix 7 for country-specific requirements.
HIV, hepatitis B and C screen (testing optional per site SOP)	X										Assessed at Screening ≤28 days prior to randomization, if required. Acceptable to be based on history unless required by local authority (see Appendix 2). Refer to Appendix 7 for country-specific requirements.

Treatment Arm B: RC + PLND Only											
Trial Period	**Screen-ing**	**Pre-surgery**	**RC + PLND**	**Post-surgery Follow-up**							**Notes:** *** After the visit at Week 30, subsequent clinic visits will occur every 12 weeks [±14 days] (if the participant remains clinically stable) through the end of Year 1 (from the post-cystectomy baseline scan).** **‡ The 6-week post-surgery visit may also serve as the Safety Follow-up Visit (if it occurs 4-6 weeks post-surgery, as noted in the window periods).**
Visit/ Procedure			**Surgery**	**Safety Follow-Up**	**Weeks Post-surgery (Clinical Observation)**						
Week	**≤6 weeks prior to randomization (Days -42 to -1)**	**2 weeks prior to surgery**	**Within 8 weeks from random-ization**	**30 days after study intervention (surgery)**	**6‡**	**12**	**18**	**24**	**30**	***42 to 54**	
Window Days		**±7**	**+7**	**+14**	**±14**	**±7**	**±7**	**±7**	**±7**	**±14**	
Hematology	X	X		X	--As Clinically Indicated--						Screening laboratory tests must be performed within 14 days prior to randomization. During post-surgery follow-up, laboratory tests should be collected as clinically indicated.
Chemistry	X	X		X	--As Clinically Indicated--						
HbA1c	X										Participants who enter the study with an elevated HbA1c (≥6.5%) at baseline should be referred to an appropriate provider for glucose management. See Section 5.2, Exclusion Criteria #16 for the HbA1c limitations for enrollment onto this study.
Urinalysis	X	As clinically indicated		X	--As Clinically Indicated--						Must be collected ≤14 days prior to randomization and may then be performed as clinically indicated.
Coagulation tests (PT/INR and aPTT or PTT)	X	X	--If Clinically Indicated--								Screening laboratory tests must be performed within 14 days prior to randomization and at presurgery safety visit for all participants. If on anticoagulant(s), test coagulation as clinically indicated. PTT may be performed if laboratory cannot perform aPTT.

Treatment Arm B: RC + PLND Only											
Trial Period	**Screen-ing**	**Pre-surgery**	**RC + PLND**	**Post-surgery Follow-up**							**Notes:** *** After the visit at Week 30, subsequent clinic visits will occur every 12 weeks [±14 days] (if the participant remains clinically stable) through the end of Year 1 (from the post-cystectomy baseline scan).** **‡ The 6-week post-surgery visit may also serve as the Safety Follow-up Visit (if it occurs 4-6 weeks post-surgery, as noted in the window periods).**
Visit/ Procedure			**Surgery**	**Safety Follow-Up**	**Weeks Post-surgery (Clinical Observation)**						
Week	**≤6 weeks prior to randomization (Days -42 to -1)**	**2 weeks prior to surgery**	**Within 8 weeks from random-ization**	**30 days after study intervention (surgery)**	**6‡**	**12**	**18**	**24**	**30**	***42 to 54**	
Window Days		**±7**	**+7**	**+14**	**±14**	**±7**	**±7**	**±7**	**±7**	**±14**	
ACTH and cortisol	X										Assessed at Screening ≤42 days prior to randomization. Participants can be randomized while ACTH/cortisol results are pending.
Thyroid Function (TSH)	X	--If Clinically Indicated--									Screening TSH must be performed ≤14 days prior to randomization. If TSH is abnormal, perform T3* + T4. *Total T3 is preferred, if not available free T3 may be tested.
AE/SAE review	X	--Continuous Reporting--									AE reporting period for Nonserious AE is 30 days and SAE is 90 days from RC +PLND.
Blood for Genetic Analysis		X									Sample not collected if prohibited by local regulation, or if IRB/IEC does not approve.
Blood for Serum Biomarker Analyses		X			X				X		
Blood for ctDNA		X			X				X		

Treatment Arm B: RC + PLND Only											
Trial Period	**Screening**	**Pre-surgery**	**RC + PLND**	**Post-surgery Follow-up**							**Notes:** *** After the visit at Week 30, subsequent clinic visits will occur every 12 weeks [±14 days] (if the participant remains clinically stable) through the end of Year 1 (from the post-cystectomy baseline scan).** **‡ The 6-week post-surgery visit may also serve as the Safety Follow-up Visit (if it occurs 4-6 weeks post-surgery, as noted in the window periods).**
Visit/ Procedure			**Surgery**	**Safety Follow-Up**	**Weeks Post-surgery (Clinical Observation)**						
Week	**≤6 weeks prior to randomization (Days -42 to -1)**	**2 weeks prior to surgery**	**Within 8 weeks from randomization**	**30 days after study intervention (surgery)**	**6‡**	**12**	**18**	**24**	**30**	***42 to 54**	
Window Days		**±7**	**+7**	**+14**	**±14**	**±7**	**±7**	**±7**	**±7**	**±14**	
Tissue Collection for Biomarkers											
Tissue Collection for Biomarker Analysis (tested centrally)	X		X								Tumor tissue from diagnostic TUR specimen and RC+PLND required (FNA not adequate) to identify novel biomarkers.

ACTH=adrenocorticotropic hormone; AE=adverse event; aPTT / PTT=activated partial thromboplastin time / partial thromboplastin time; BCI=Bladder Cancer Index; BICR=blinded independent central review; CT=computed tomography; ctDNA=circulating tumor deoxyribonucleic acid; eCRF=electronic case report form; ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group; ePRO=electronic patient-reported outcomes; EQ-5 D-5 L=EuroQoL 5 Dimension Questionnaire; FACT-Bl-Cys=functional assessment of cancer therapy-bladder cystectomy; FNA=fine needle aspirate; HbA1c=hemoglobin A1c; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; iCRO=imaging contract research organization; IEC=independent ethics committee; INR=international normalized ratio; IRB=institutional review board; IV=intravenous; IVRS=interactive voice response system; MRI=magnetic resonance imaging; pCR=pathologic complete response; PD=progressive disease; PD-L1=programmed cell death ligand 1; pDS=pathologic downstaging; PLND=pelvic lymph node dissection; PT=prothrombin time; RC=radical cystectomy; SAE=serious adverse event; SOP=standard operating procedure; T3=T3 thyroid hormone; TSH=thyroid-stimulating hormone; T stage=tumor stage; TUR=transurethral resection; WOCBP=woman of childbearing potential.

[a] If performed ≤35 days prior to cystectomy, then this will be adequate to serve as the presurgery scan. If performed >35 days prior to scheduled cystectomy date, then a repeat scan will need to be performed if that scan is ≤5 weeks of cystectomy. Other than presurgical and post-surgical scans, all other imaging timing should follow calendar days and not be recalculated based on the date of previous scans and treatment. Results of additional investigative imaging (eg, CT urography) will be reported/collected in the eCRFs and should be submitted to the iCRO to be centrally reviewed by BICR.

[b] Samples must have been collected within 60 days (+14 days) prior to enrollment (providing documented informed consent) and be sent to central vendor for review and histological confirmation of urothelial carcinoma pathologic Stage pT2 or pT1 (only if N1) and predominant urothelial histology prior to randomization, and for PD-L1 expression assessment.

[c] PROs given by trained site personnel and completed PROs should be completed in the following order: EQ-5 D-5 L, FACT-Bl-Cys. For newly enrolled participants after Amendment 1: PROs should be completed in the following order: EQ-5 D-5 L, FACT-Bl-Cys, BCI. Perform PRO assessment according to the schedule until confirmed PD or initiation of a new anticancer regimen, withdrawal of consent, or death, whichever occurs first. If ePROs are not completed, Miss Mode form must record the reason.

[d] Ongoing testing should be conducted where applicable at intervals specified per country or local requirements (administrative letter can be provided if required). This testing will be N/A for many participants as standard RC+PLND surgery includes removal of the uterus. If urine pregnancy test is required and cannot be confirmed as negative, a serum pregnancy test is required.

1.3.4 Efficacy Follow-up Visits (Arms A [Pembrolizumab + Cystectomy], B [Cystectomy], and C [Enfortumab Vedotin in Combination With Pembrolizumab + Cystectomy])

Note: After implementation of Amendment 8, enrollment in Arm A was stopped.

Follow-up Visits (Arms A [Pembrolizumab + Cystectomy], B [Cystectomy], and C [Enfortumab vedotin in combination with Pembrolizumab + Cystectomy])					
Trial Period	**Follow-Up**				**Notes:** †For participants who do not undergo RC + PLND, Year 1 will begin from the EOT scan, if applicable. If EOT scan is not performed, then Year 1 will begin from presurgery scan where applicable. *Year 1 begins from the post-cystectomy baseline scan for all participants who undergo RC + PLND. For Arms A and C, Year 1 will overlap with the duration of adjuvant treatment (Section 1.3.2). If adjuvant treatment is discontinued, the participant will complete the remaining Year 1 FU before continuing to Year 2 FU and beyond. **Applicable to all participants, including those who complete adjuvant treatment.
Visit /Procedure	**Postoperative FU†**			**Survival FU**	
Treatment Cycle/Day	**Year 1***	**Year 2****	**Years 3-beyond****		
Scheduled Time	**Q12 weeks**	**Q12 weeks**	**Q24 Weeks**	**Q12 weeks**	
Windows (Days)	±7 days	±7 days	±14 days	±14 days	
Administrative Procedures					
Prior/Concomitant Medication Review	----If Clinically Indicated------				Concomitant medication recording will follow the reporting period guidelines for AEs and SAEs (see Section 8.4.1).
Anticancer Therapy Status	X	X	X	X	
Survival status/Bladder status	←———	———	———	———→	In Years 3 and beyond during Posttreatment FU, survival status/bladder status will be monitored by phone call Q12W, in between Q24 week visits. Upon Sponsor request, participants may be contacted for survival status at any time during the study.
Efficacy Procedures					
CT or MRI of the chest, abdomen & pelvis[a] (CT of the chest is preferred to MRI)	X	X	X	X***	Use same imaging modality for all evaluations. First (baseline) post-cystectomy scan to occur at 6 weeks (42 days ±14 days) post-cystectomy. Subsequent scans to be performed every 12 weeks ±7 days until end of Year 2 post-cystectomy scan (approximately Weeks 12, 24, 36, 48, 60, 72, 84, and 96) and every 24 weeks ±14 days thereafter until one of the criteria for discontinuation of imaging (Section 8.2.1.3) are met.

Follow-up Visits (Arms A [Pembrolizumab + Cystectomy], B [Cystectomy], and C [Enfortumab vedotin in combination with Pembrolizumab + Cystectomy])					
Trial Period	**Follow-Up**				**Notes:** †For participants who do not undergo RC + PLND, Year 1 will begin from the EOT scan, if applicable. If EOT scan is not performed, then Year 1 will begin from presurgery scan where applicable. *Year 1 begins from the post-cystectomy baseline scan for all participants who undergo RC + PLND. For Arms A and C, Year 1 will overlap with the duration of adjuvant treatment (Section 1.3.2). If adjuvant treatment is discontinued, the participant will complete the remaining Year 1 FU before continuing to Year 2 FU and beyond. **Applicable to all participants, including those who complete adjuvant treatment.
Visit /Procedure	**Postoperative FU†**			**Survival FU**	
Treatment Cycle/Day	**Year 1***	**Year 2****	**Years 3-beyond****		
Scheduled Time	**Q12 weeks**	**Q12 weeks**	**Q24 Weeks**	**Q12 weeks**	
Windows (Days)	±7 days	±7 days	±14 days	±14 days	
Oral contrast is optional. IV contrast is required unless contraindicated.					Other than the pre-surgical and post-surgical scans, all other imaging timing should follow calendar days and should not be recalculated based on the date of previous scans and treatment. *** Participants who have not progressed, but decline participation in Efficacy Follow-up should be encouraged to submit imaging performed as standard of care.
Tissue collection for confirmation of recurrence	◄———		———►		Mandatory biopsy will be collected and assessed locally to confirm disease recurrence in participants found to have radiographic disease progression. Biopsy sample must also be sent to the central pathology vendor. If biopsy is not feasible due to participant safety, CT/MRI alone will be sufficient to document progression.
Only for Participants who do not undergo RC + PLND Surgery:					
Cystoscopy (± biopsy)	X	X	X		Refer to Section 8.2.3.
Urine Cytology	X	X	X		Refer to Section 8.2.3.
CT or MRI	X	X	X	X[$]	Refer to Section 8.2.3. Use same imaging modality for all evaluations. [$]Participants who decline participation in Efficacy Follow-up should be encouraged to submit imaging performed as standard of care.

Follow-up Visits (Arms A [Pembrolizumab + Cystectomy], B [Cystectomy], and C [Enfortumab vedotin in combination with Pembrolizumab + Cystectomy])					
Trial Period	**Follow-Up**				**Notes:** †For participants who do not undergo RC + PLND, Year 1 will begin from the EOT scan, if applicable. If EOT scan is not performed, then Year 1 will begin from presurgery scan where applicable. *Year 1 begins from the post-cystectomy baseline scan for all participants who undergo RC + PLND. For Arms A and C, Year 1 will overlap with the duration of adjuvant treatment (Section 1.3.2). If adjuvant treatment is discontinued, the participant will complete the remaining Year 1 FU before continuing to Year 2 FU and beyond. **Applicable to all participants, including those who complete adjuvant treatment.
Visit /Procedure	**Postoperative FU†**			**Survival FU**	
Treatment Cycle/Day	**Year 1***	**Year 2****	**Years 3-beyond****		
Scheduled Time	**Q12 weeks**	**Q12 weeks**	**Q24 Weeks**	**Q12 weeks**	
Windows (Days)	±7 days	±7 days	±14 days	±14 days	
Patient-reported Outcomes					
EQ-5 D-5 L[b]	X	X			Also includes participants in Arms A and C who received at least one dose of study intervention but did not undergo study surgery.
FACT-Bl-Cys[b]	X	X			
BCI[b]	X	X			
Safety Procedures					
Directed physical examination	X	X	X		Include neurological examination if clinically indicated.
Ophthalmological examination				If clinically indicated	End-of-treatment slit lamp examinations are required for participants who experience corneal AEs during the study and must be performed ≥4 to 12 weeks from last dose.
ECOG Performance Status	X	X	X		Also includes participants in Arms A and C who received at least one dose of study intervention but did not undergo study surgery.
Weight and Vital Signs	----If Clinically Indicated----				
Hematology, Chemistry, Urinalysis	----If Clinically Indicated----				
Coagulation tests (PT/INR and aPTT/PTT)	----If Clinically Indicated----				

<table>
<tr><th colspan="6">Follow-up Visits (Arms A [Pembrolizumab + Cystectomy], B [Cystectomy], and C [Enfortumab vedotin in combination with Pembrolizumab + Cystectomy])</th></tr>
<tr><td>Trial Period</td><td colspan="4">Follow-Up</td><td rowspan="5">Notes:
†For participants who do not undergo RC + PLND, Year 1 will begin from the EOT scan, if applicable. If EOT scan is not performed, then Year 1 will begin from presurgery scan where applicable.
*Year 1 begins from the post-cystectomy baseline scan for all participants who undergo RC + PLND. For Arms A and C, Year 1 will overlap with the duration of adjuvant treatment (Section 1.3.2). If adjuvant treatment is discontinued, the participant will complete the remaining Year 1 FU before continuing to Year 2 FU and beyond.
**Applicable to all participants, including those who complete adjuvant treatment.</td></tr>
<tr><td>Visit /Procedure</td><td colspan="3">Postoperative FU†</td><td>Survival FU</td></tr>
<tr><td>Treatment Cycle/Day</td><td>Year 1*</td><td>Year 2**</td><td>Years 3-beyond**</td><td></td></tr>
<tr><td>Scheduled Time</td><td>Q12 weeks</td><td>Q12 weeks</td><td>Q24 Weeks</td><td>Q12 weeks</td></tr>
<tr><td>Windows (Days)</td><td>±7 days</td><td>±7 days</td><td>±14 days</td><td>±14 days</td></tr>
<tr><td>Thyroid Function (TSH)</td><td colspan="3">----If Clinically Indicated----</td><td></td><td>If TSH is abnormal, perform T3* + T4.
*Total T3 is preferred, if not available free T3 may be tested.</td></tr>
<tr><td>AE/SAE review</td><td colspan="3">----------Continuous Reporting----------</td><td></td><td>All AEs up until 30 days post study treatment and SAEs up until 90 days post study treatment or 30 days if participant starts new anticancer therapy, whichever is earlier, should be reported. Treatment-related late toxicity may be collected for up to 5 years. As of Amendment 09, for any participant on Arm C study intervention (or within 30 days of cessation of study intervention), peripheral neuropathy AEs should continue to be reported until new anticancer therapy is initiated and as long as the participant remains in Efficacy Follow-up.</td></tr>
</table>

AE=adverse event; aPTT / PTT=activated partial thromboplastin time / partial thromboplastin time; BCI=Bladder Cancer Index; CT=computed tomography; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic case report form; EFS=event-free survival; EOT=end-of-treatment; ePRO=electronic patient-reported outcomes; EQ-5 D-5 L=EuroQoL 5 Dimension Questionnaire; FACT-Bl-Cys=functional assessment of cancer therapy-bladder cystectomy; FU=follow-up; iCRO=imaging contract research organization; INR=international normalized ratio; IV=intravenous; MRI=magnetic resonance imaging; PD=progressive disease; PLND=pelvic lymph node dissection; PT=prothrombin time; Q12/24Ws=every 12/24 weeks; RC=radical cystectomy; SAE=serious adverse event; T3=T3 thyroid hormone; TSH=thyroid-stimulating hormone; TUR=transurethral resection.

[a] Results of additional investigative imaging (eg, CT urography) will be reported/collected in the eCRFs and should be submitted to the iCRO to be centrally reviewed by BICR. Participants who have started a new anticancer treatment after RC + PLND will continue imaging assessments, as long as no EFS event is observed, at the posttreatment follow-up visits. After a participant has an EFS event, disease progression, or withdrawal of consent, whichever occurs first, the participant will enter Survival Follow-up.

[b] The ePRO questionnaire should be administered every 12 weeks up to the end of Year 2. PROs given by trained site personnel and completed electronically by participants. PROs should be completed in the following order: EQ-5 D-5 L, FACT-Bl-Cys. For newly enrolled participants after Amendment 1, PROs should be completed in the following order: EQ-5 D-5 L, FACT-Bl-Cys, BCI. Perform PRO assessment according to the schedule until confirmed PD or initiation of a new anticancer regimen, withdrawal of consent, or death, whichever occurs first. If ePROs are not completed, Miss Mode form must record the reason.

2 INTRODUCTION

2.1 Study Rationale

This study is designed to assess the antitumor efficacy and safety of perioperative pembrolizumab and the combination of perioperative enfortumab vedotin (EV) with perioperative pembrolizumab compared with the current standard of care (cystectomy alone) for participants with muscle-invasive urothelial carcinoma (UC) who are ineligible for or decline cisplatin-based chemotherapy.

Bladder cancer is one of the most common malignancies in the world, with over 81,000 new cases diagnosed in the United States (US) alone in 2018 [Siegel, R. L., et al 2020]; urothelial carcinoma is the most frequent histology. Though most new cases of bladder cancer are noninvasive and thus amenable to cystoscopic resection, up to 25% of newly diagnosed cases feature muscle-invasive tumors. The prognosis for muscle-invasive bladder cancer (MIBC) is significantly poorer, with historical 5-year survival rates of approximately 40% to 50%. The current standard of care for patients eligible for cisplatin is neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy plus pelvic lymph node dissection (RC + PLND) based on level 1 evidence. For patients who are ineligible for cisplatin, the standard of care in most of the world is RC + PLND alone [Grossman, H. B., et al 2003] [Yin, M., et al 2016]. Patients who are cisplatin-eligible with high-risk pathology post-RC and did not receive neoadjuvant chemotherapy are recommended to receive adjuvant cisplatin-based chemotherapy, based largely on retrospective data suggesting a possible survival benefit [Seisen, T. 2018] [Galsky, M. D., et al 2016]. Adjuvant therapy is generally not offered to patients who are cisplatin-ineligible. Five-year overall survival (OS) rates for patients with MIBC who receive neoadjuvant cisplatin chemotherapy are improved by approximately 5% to 10% compared with patients receiving surgery alone.

Outcomes in resectable MIBC can vary significantly and depend on several key factors such as treatment received, tumor stage, age/comorbidities, and cisplatin eligibility. Prior randomized, controlled trials of neoadjuvant therapy have primarily been in a cisplatin-eligible population. In the seminal SWOG 8710 study, median OS was 77 months (95% CI, 55, 104) in patients receiving neoadjuvant M-VAC chemotherapy versus 46 months (95% CI, 25, 60) in those undergoing cystectomy alone. Among those with T3 or T4a disease, the median survival in those undergoing RC + PLND alone was 24 months, demonstrating the importance of T stage to prognosis [Grossman, H. B., et al 2003]. When considering real-world MIBC cohorts, which include cisplatin-ineligible patients, the outcomes of those undergoing cystectomy alone are very poor. In a National Cancer Database analysis of octogenarians with MIBC, which included cisplatin-eligible and ineligible patients, those undergoing RC + PLND alone had a median OS of 23.2 months (95% CI 19.8, 26.6) [Fischer-Valuck, B. W., et al 2018]. In a more recent, retrospective cohort study of cisplatin-ineligible patients who underwent RC + PLND alone, the median EFS was ~17 months, with a 3-year EFS of 36.1% (95% CI 28.6, 45.5) [Li, R., et al 2024]. This study had patient characteristics very similar to the KN-905 target population and underscores the very high unmet need in the population.

In addition to cisplatin-ineligible participants, the study population will include those who are cisplatin-eligible, but decline treatment with cisplatin-based chemotherapy. It is expected that the overall clinical outcomes in patients who are eligible or ineligible for cisplatin will be similar, as seen in the metastatic urothelial carcinoma (mUC) setting with first-line treatment with a programmed cell death ligand 1 (PD-L1) inhibitor. There is precedent in UC with this approach, as other perioperative trials that evaluate cisplatin-ineligible MIBC patients allow the enrollment of cisplatin-eligible patients who decline cisplatin-based chemotherapy (eg, CheckMate 274, PIVOT-2 trial, PURE-01 trial). Furthermore, EV and pembrolizumab have demonstrated to be active in both cisplatin-eligible and cisplatin-ineligible UC. More specifically, EV has demonstrated significant clinical activity as a single agent in platinum-eligible patients in later-line therapy in mUC. Pembrolizumab has shown activity in platinum-eligible mUC as well as in cisplatin-eligible MIBC patients (over 80% of the PURE-01 patient population). EV in combination with pembrolizumab has shown encouraging activity (73% objective response rate [ORR]; 95% confidence interval [CI]: 58, 85]) in the EV-103/KEYNOTE-869 (NCT03288545) study in cisplatin-ineligible patients with locally advanced and mUC. Considering these data together, EV in combination with pembrolizumab has the potential to offer similar antitumor activity in cisplatin-eligible MIBC patients who decline cisplatin-based chemotherapy.

Due to the high rates of recurrence and relatively poor OS seen in patients with MIBC receiving RC alone, there is an urgent need to develop new treatment strategies.

Immunotherapy with checkpoint inhibitors targeting the programmed cell death 1 (PD-1)/PD-L1 axis has dramatically changed the landscape of treatment for patients with unresectable locally advanced/mUC. In KEYNOTE-045, a randomized, Phase 3 trial investigating pembrolizumab versus investigator's choice chemotherapy as second-line therapy, the median OS was 10.1 months for pembrolizumab versus 7.3 months for chemotherapy (hazard ratio [HR] 0.70, 95% CI: 0.57, 8.5; p=0.00015). In KEYNOTE-052, a single-arm study investigating pembrolizumab as first-line (1 L) therapy in cisplatin-ineligible patients with mUC, the ORR was 29% (95% CI: 24.3, 33.8) and median OS was 11.3 months (95% CI: 9.7, 13.1) [O'Donnell, P. H., et al 2019]. Furthermore, the median duration of response was 30.1 months (95% CI: 18.1, not reached) with 67% and 52% of patients with a duration of response ≥12 and ≥24 months, respectively; in KEYNOTE-045, the median duration of response in the pembrolizumab arm had not been reached after >2 years follow-up.

PD-L1 expression has emerged as a meaningful biomarker for patients with UC receiving pembrolizumab, however its predictive value is not well established in bladder cancer. In KEYNOTE-052, participants with tumors with PD-L1 combined positive score (CPS) ≥10 had an ORR of 47.3% (95% CI: 37.7, 57.0) compared with 21.1% (95% CI: 16.2, 26.7) for participants with tumors with CPS <10. Although the ORR among participants with CPS ≥10 exceeded that of the overall population, many participants with CPS <10 and CPS <1 in their tumors also responded [Fradet, Y., et al 2019]. In KEYNOTE-361, data suggests that the PD-L1 CPS of at least 10 cutoff alone does not enrich for patients with mUC likely to gain a survival benefit with pembrolizumab monotherapy versus chemotherapy as first-line therapy [Powles, T., et al 2021]. In addition, the use of different PD-L1 assays and cutoff points in

published studies complicates the utility of PD-L1 positivity as a selection biomarker in mUC [Galsky, M. D., et al 2020] [Powles, T., et al 2020].

In KEYNOTE-045, the OS benefit by pembrolizumab treatment was demonstrated regardless of PD-L1 status; however, median OS in the PD-L1 CPS ≥10 subgroup was lower compared with that of CPS <10 group in both the comparable pembrolizumab treated and chemotherapy treated participants, suggesting that high PD-L1 expression may be a negative prognostic factor for survival in second-line treatment of advanced urothelial cancer [Fradet, Y., et al 2019]. Given the promising results in advanced disease, investigating immunotherapy approaches in the neoadjuvant and adjuvant settings of UC is an appropriate next step.

There have been small clinical studies investigating the activity of single-agent immunotherapy as neoadjuvant treatment for MIBC. Data recently presented from 3 of these studies revealed significant clinical activity as measured by pathologic response, with a pathologic complete response (pCR) of 42% [95% CI: 28.2, 56.8] for participants receiving 3 cycles of neoadjuvant pembrolizumab (PURE-01) [Necchi, A., et al 2018] and 29% [95% CI: 18, 42] for participants receiving 2 cycles of atezolizumab [Powles, T., et al 2018]. In both studies, higher levels of PD-L1 expression were associated with higher rates of pCR. Pathologic response was noted to correlate with improved OS in the large Southwest Oncology Group (SWOG) bladder cancer study [Grossman, H. B., et al 2003]. Data regarding the prevalence of high PD-L1 expression is limited in the MIBC population, but the assumption based on the prevalence in the mUC population and the PURE-01 study [Necchi, A., et al 2018] is that approximately 50% of the MIBC patients will be PD-L1 positive (CPS ≥10).

The activity of a single-agent immunotherapy as adjuvant treatment for MIBC was investigated in CheckMate 274. This Phase 3, multicenter, double-blind, randomized, controlled trial evaluated nivolumab (anti-PD-1) compared with placebo in participants with MIBC at high risk of recurrence after undergoing radical surgery [Bajorin, D. F., et al 2021]. A total of N=709 participants were assigned in a 1:1 ratio to receive either nivolumab 240 mg (n=353) or placebo (n=356) intravenously (IV) every 2 weeks for up to 1 year. Neoadjuvant cisplatin-based chemotherapy prior to randomization was allowed. Eligible participants must have had radical surgery within 120 days before randomization with a high risk of recurrence; participants who received neoadjuvant cisplatin with pathological stage ypT2 to ypT4a or ypN+ and participants not eligible for or who declined adjuvant cisplatin-based combination chemotherapy with pathological stage pT3, pT4a, or pN+ were eligible. The 2 primary endpoints were disease-free survival (DFS) among all randomized participants (the intention-to-treat [ITT] population) and among participants with a tumor PD-L1 expression level of ≥1%. Secondary endpoints included survival free from recurrence outside the urothelial tract, OS, and disease-specific survival.

In CheckMate 274, DFS was longer with adjuvant nivolumab than with placebo in the ITT population and among participants with PD-L1 expression of ≥1%. The medium DFS in the ITT population was 20.8 months (95% CI: 16.5 to 27.6) with nivolumab and 10.8 months (95% CI: 8.3 to 13.9) with placebo. The percentage of participants who were alive and disease-free at 6 months was 74.9% with nivolumab and 60.3% with placebo (HR for disease

recurrence or death, 0.70; 98.22% CI: 0.55, 0.90; $p<0.001$). Among participants with a PD-L1 expression level of ≥1%, the percentage who were alive and disease-free at 6 months was 74.5% with nivolumab and 55.7% with placebo (HR, 0.55; 98.72% CI: 0.35, 0.85; $p<0.001$).

Based on these findings, in AUG-2021, the US Food and Drug Administration (FDA) approved nivolumab for the adjuvant treatment of patients with MIBC who are at high risk of recurrence after radical surgery regardless of PD-L1 expression levels. In APR-2022, the European Commission approved adjuvant nivolumab treatment in patients with MIBC who are at high risk of recurrence after radical surgery restricted to those with tumor cell PD-L1 expression level of ≥1%.

The evaluation of EV in combination with pembrolizumab is ongoing in the EV-103/ KEYNOTE-869 study Cohort A and Cohort K (n=126 total participants in cisplatin-ineligible participants with locally advanced or mUC in the 1 L setting) [Rosenberg, J. E., et al 2020]. As of data cutoff 13-OCT-2020, EV-103 Cohort A (n=45 in the Full Analysis Set [FAS]) shows an ORR of 73.3% for the overall population [Friedlander, T. W., et al 2021]. When reviewing the results by CPS, participants with a CPS ≥10 had an ORR of 78.6% and those with CPS <10 had an ORR of 63.2% [Rosenberg, J. E., et al 2020].The median duration of response (DOR) is 25.6 months (95% CI: 8.3, -). The median progression-free survival (PFS) was 12.3 months and the median OS had not been reached [Friedlander, T. W., et al 2021]. EV-103 Cohort K (n=76) showed an ORR of 64.5% for the overall population. When reviewing the results by CPS, participants with a CPS ≥10 had an ORR of 67.7% and those with CPS <10 had an ORR of 61.4%. The median DOR was not reached with 65.4% of responders still responding at 12 months [Rosenberg, J. E., et al 2022]. For both Cohort A and Cohort K the majority of participants, 93.0% in Cohort A and 97.1% in Cohort K, had tumor reduction regardless of PD-L1 status. EV in combination with pembrolizumab in cisplatin-ineligible participants with locally advanced or mUC in the 1 L setting is being further evaluated in the Phase 3 confirmatory trial EV-302.

The EV-302/KEYNOTE-A39 Phase 3 study evaluates the combination of EV plus pembrolizumab versus platinum-based chemotherapy in 1L la/mUC. Results at the first interim analysis showed that PFS was prolonged with EV plus pembrolizumab versus platinum chemotherapy, reducing the risk of progression or death by 55% (median PFS: 12.5 months versus 6.3 months, respectively; HR 0.45 [95% CI: 0.38 to 0.54]; $p<0.001$). OS was significantly prolonged with EV plus pembrolizumab, reducing the risk of death by 53% (median OS: 31.5 months versus 16.1 months, respectively; HR 0.47 [95% CI: 0.38 to 0.58]; $p<0.001$) [Powles, T., et al 2024].

These extremely promising results are expected to be reproduced in an earlier disease setting and could therefore represent a possible treatment option for patients who are ineligible for or decline cisplatin-based chemotherapy in MIBC. The clinical need for improved therapies in MIBC and the evidence of clinical activity in mUC noted above provide a robust rationale for investigating perioperative pembrolizumab and perioperative pembrolizumab in combination with EV in the setting of cisplatin-ineligible or cisplatin-eligible, but decline cisplatin-based chemotherapy in MIBC.

2.2 Background

2.2.1 Pembrolizumab

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. KEYTRUDA® (pembrolizumab) is indicated for the treatment of patients across several indications. For more details on specific indications refer to the IB.

2.2.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, M. L. 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer, hepatocellular carcinoma, malignant melanoma, and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 that has been shown to negatively regulate antigen receptor signaling on engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald, R. J., et al 2005] [Okazaki, T., et al 2001].

The structure of murine PD-1 has been resolved [Zhang, X., et al 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an IgV–type domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. After T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ, and ZAP70, which are involved in the CD3 T-cell signaling cascade [Okazaki, T., et al 2001] [Chemnitz, J. M., et al 2004] [Sheppard, K-A, et al 2004] [Riley, J. L. 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry, R. V., et al 2005] [Francisco, L. M., et al 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in MIBC.

2.2.1.2 Preclinical Studies

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a monotherapy or in combination with other treatment modalities. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses as a monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, MEL and colorectal carcinoma [Nomi, T., et al 2007] [Blank, C. and Mackensen, A. 2007] [Iwai, Y., et al 2002] [Tsushima, F., et al 2006] [Korman, A., et al 2007]. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of IFN-γ promoted CD8+ T-cells and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [Nomi, T., et al 2007]. Experiments have confirmed the in vivo efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the IB).

2.2.2 Enfortumab Vedotin Background

EV is an antibody-drug conjugate (ADC) comprised of a fully human anti-Nectin-4 immunoglobulin G1 (IgG1) kappa monoclonal antibody conjugated to the small molecule microtubule disrupting agent, monomethyl auristatin E (MMAE), via a protease cleavable maleimidocaproyl valine-citrulline (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.

EV binds to the V domain of Nectin-4 protein [Challita-Eid, P. M., et al 2016]. In the presumed mechanism of action, the drug binds to the Nectin-4 protein on the cell surface and is internalized, causing proteolytic cleavage of the vc linker and intracellular release of MMAE. Free MMAE subsequently disrupts tubulin polymerization and leads to mitotic arrest.

Information about mode of action, chemical structure, and posology of EV are provided in the EV IB.

2.2.2.1 Enfortumab Vedotin Monotherapy in Urothelial Cancer

EV monotherapy has been evaluated in multiple Phase 1, Phase 2, and Phase 3 studies. Study EV-101 is a Phase 1 study to evaluate the safety and pharmacokinetics of escalating doses of EV given as monotherapy in participants with mUC and other malignant solid tumors that express Nectin-4 [Rosenberg, J. E., et al 2019] and identified 1.25 mg/kg of EV as the recommended monotherapy dose in mUC. Study EV-201 is an ongoing, Phase 2, single-arm, open-label, multicenter study to evaluate EV monotherapy in participants with locally advanced or mUC who previously received systemic therapy with a PD-1 or PD-L1 inhibitor [Rosenberg, J. E., et al 2019a]. The results of these trials supported the accelerated approval of EV, under the trade name PADCEV in the US, in DEC-2019 for the treatment of adult patients with locally advanced or mUC who previously received a PD-1/PD-L1 inhibitor, and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting. Study EV-301 is a Phase 3 confirmatory trial comparing EV

monotherapy and chemotherapy in participants with locally advanced or mUC who previously received platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor. The primary endpoint was OS and secondary endpoints included PFS, ORR, DOR, disease control rate, safety and tolerability, and quality-of-life parameters. EV-301 met its primary objective of demonstrating improved OS compared with chemotherapy in patients with locally advanced or mUC. Based on the results of EV-201 and EV-301, on 09-JUL-2021, the FDA approved an expanded indication for PADCEV for adult patients with locally advanced or mUC who have previously received a PD-1 or PD-L1 inhibitor and platinum-containing chemotherapy or are ineligible for cisplatin-containing chemotherapy and have previously received one or more prior lines of therapy [Powles, T., et al 2021a] [Yu, E. Y., et al 2021].

2.2.2.1.1 EV-101 (ASG-22CE-13-2)

As of the 25-OCT-2018 data cutoff, 112 participants with mUC treated with EV at 1.25 mg/kg (mUC Total Analysis Set), ORR was 43% (95% CI: 33.6%, 52.5%), with 5 participants (4.5%) achieving complete response (CR), and a median DOR of 7.4 months (95% CI: 5.6, 9.6). The median OS was 12.3 months (95% CI: 9.3, 15.3) [Rosenberg, J., et al 2020].

In the safety population of all participants who received any amount of EV (n=201), the most common AEs of any grade were fatigue (56%), nausea (45%), decreased appetite (43%), and alopecia (41%). The incidence of Grade 3 or higher AEs was 59%, and those reported in ≥5% of participants included anemia (7%), hyperglycemia (7%), hyponatremia (6%), urinary tract infection (UTI) (5%), and sepsis (5%).

2.2.2.1.2 EV-201 (SGN22E-001)

As of the data cutoff date of 01-MAR-2019, for participants previously treated with a PD-1/PD-L1 inhibitor and platinum-containing chemotherapy, treatment with EV resulted in an ORR per blinded independent central review (BICR) of 44% (95% CI: 35.1%, 53.2%), including a CR for 15 participants (12%). Activity was observed in participants with poor prognostic features such as liver metastases (ORR 38%; 95% CI: 24.7%, 52.8%) and prior PD-1/PD-L1 nonresponse (ORR 41%; 95% CI: 31.3%, 51.3%). Responses to EV were observed in participants with both high (PD-L1 CPS ≥10) and low PD-L1 (CPS <10) expression, with an ORR 36% and 47%, respectively. Observed responses were durable, with median response duration of 7.6 months (95% CI: 6.34, not reached; range: 0.95 months, 11.3+ months). Median PFS was 5.8 months (95% CI: 4.9 months, 7.5 months) and median OS was 11.7 months (95% CI: 9.1 months, not reached).

The most common AEs of any grade in were fatigue (55%), decreased appetite (52%), alopecia (50%), nausea (45%), peripheral sensory neuropathy (43%), diarrhea (42%), and dysgeusia (42%). The incidence of Grade 3 or higher AEs was 73%, and those reported in >5% of participants included anemia (14%), neutropenia (9%), hyperglycemia (7%), and fatigue and hyponatremia (6% each). SAEs were reported for 58 participants (46%).

2.2.2.1.3 EV-301 (7465-CL-0301)

The Phase 3 EV-301 trial of EV met its primary end point of OS compared with chemotherapy in patients with locally advanced or mUC. Two analyses were planned; interim analysis at 285 deaths of the estimated 600 patients to be enrolled, and a final analysis at 439 deaths. At the prespecified interim analysis, OS was longer in the EV group than in the chemotherapy group (median OS 12.88 vs 8.97 months; HR for death, 0.70; 95% CI: 0.56 to 0.89; p=0.001). EV also demonstrated a statistically significant benefit for PFS of 1.8 months (HR 0.62, p<0.0001), and 40.6% of patients had an overall response on EV therapy compared with 17.9% of patients who received chemotherapy. Treatment-related adverse events of special interest to EV included skin reactions, peripheral neuropathy (PN), and hyperglycemia, which were generally mild to moderate in severity [Powles, T., et al 2021b].

2.2.2.2 Enfortumab Vedotin in Combination With Pembrolizumab in Urothelial Cancer

PD-1/PD-L1 inhibitors unleash the antitumor activity of T-lymphocytes by targeting the T-cell inhibition pathway [Sonpavde, G. 2017]and have shown effective antitumor activity as a single agent in locally advanced or mUC. Although these agents are able to induce durable responses, most patients do not respond to PD-1/PD-L1 monotherapy. Combining PD-1/PD-L1 inhibitors with a novel therapy, such as EV, may improve patient outcomes. Data from preclinical studies of brentuximab vedotin (a CD30-directed ADC comprising the same linker and MMAE payload as EV), shows potential to induce immunogenic cell death (ICD), antigen presentation, and tumor immune infiltration [Gardai, S. J., et al 2015]. These results suggest that the effects are due to MMAE. Treatment with brentuximab vedotin in vitro and in preclinical models has been shown to induce hallmarks of ICD. ICD is characterized by induction of the endoplasmic reticulum stress response and subsequent surface presentation of danger-associated molecular patterns (DAMPs) immune stimulatory molecules. These DAMPs induce innate immune migration and activation into the tumor cell activation [Cao, A. T., et al 2017] [Cao, A. T., et al 2018].

Based on the potential enhancement of immune response, it is hypothesized that combining EV with a PD-1 inhibitor will result in improved response leading to prolonged PFS and OS in patients with locally advanced or mUC with minimal overlapping toxicities between the 2 agents.

2.2.2.2.1 EV-103 (SGN22E-002)/KEYNOTE-869

Study EV-103/KEYNOTE-869 is an ongoing, Phase 1b/2 study evaluating the safety and antitumor activity of EV monotherapy or in combination with pembrolizumab and/or platinum drugs for the 1 L treatment of locally advanced or mUC and treatment of MIBC. EV-103/KEYNOTE-869 Cohort A/Cohort K evaluates EV (1.25 mg/kg) on Days 1 and 8 in combination with pembrolizumab (200 mg) on Day 1 of 3-week cycles in cisplatin-ineligible participants with locally advanced or mUC in the 1 L setting. As of the data cutoff of 17-DEC-2021, 126 participants were enrolled: n=50 in Cohort A and n=76 in Cohort K.

2.2.2.2.1.1 Preliminary Safety

The EV-103 Cohort A/Cohort K preliminary safety data as of the data cutoff 17-DEC-2021 show that overall, 125 of 126 (99.2%) participants reported at least 1 treatment-emergent adverse event (TEAE). The most common TEAEs (≥30%) were fatigue (57.9%), alopecia (50.0%), peripheral sensory neuropathy (50.0%), diarrhea (45.2%), rash maculopapular (41.3%), weight decreased (38.9%), pruritus (38.1%), decreased appetite (35.7%), nausea (34.1%), and dysgeusia (32.5%). Overall, 20 of the 126 (15.9%) participants experienced TEAEs that led to discontinuation of study drug. Of these, only peripheral sensory neuropathy (4 of 126 [3.2%] participants) and peripheral motor neuropathy (2 of 126 [1.6%] participants) occurred in more than 1 participant.

Seventy-two (57.1%) participants experienced a treatment-related Grade ≥3 TEAE. The most common (≥10%) were rash maculopapular (15 of 126 [11.9%] participants) and lipase increased (13 of 126 [10.3%] participants). Fifty-two (41.3%) participants experienced a serious TEAE. The most common serious TEAE was acute kidney injury in 10 participants (7.9%). Seven (5.6%) participants experienced a TEAE leading to death: 1 case each of cardiac arrest, metastases to meninges, multiple organ dysfunction syndrome, pneumonitis, respiratory failure, sepsis, and septic shock.

In Cohort K at the data cutoff of 10-JUN-2022, the majority of EV treatment-related AEs of special interest (AESIs) were Grade ≤2: skin reactions 67.1% any grade, 21.1% Grade ≥3; peripheral neuropathy 60.5% any grade, 2.6% Grade ≥3; ocular disorders (dry eye, blurred vision, corneal disorders) 26.3% any grade, 0 Grade ≥3; hyperglycemia 14.5% any grade, 6.6% Grade ≥3; and infusion-related reactions (IRRs) 3.9% any grade, 0 Grade ≥3. Pembrolizumab TEAEs of special interest were consistent with previously observed safety data with pembrolizumab monotherapy, except for severe skin reactions, which were reported with a higher incidence (27.6% any grade, 19.7% Grade ≥3) [Rosenberg, J. E., et al 2022].

The EV-103 Cohort A/Cohort K safety profile to date appears tolerable and manageable and generally consistent with the known safety profile of EV in combination with pembrolizumab. See the EV IB for details.

2.2.2.2.1.2 Preliminary Efficacy

The EV-103 Cohort A preliminary efficacy data of EV 1.25 mg/kg in combination with pembrolizumab in cisplatin-ineligible participants with locally advanced or mUC in the 1 L setting are summarized for the FAS (n=45), defined as all treated participants who had at least 2 post-baseline response assessments or discontinued treatment by the time of data cutoff 13-OCT-2020 (Table 1). The confirmed ORR per investigator per Response Evaluation Criteria in Solid Tumors (RECIST) was 73.3% (95% CI: 58.1%, 85.4%), including 7 (15.6%) confirmed CRs and 26 (57.8%) confirmed partial responses (PRs). The majority of participants (93.0%) had tumor shrinkage, regardless of PD-L1 status. The ORR for patients with CPS ≥10 was 78.6% and for patients with CPS <10 was 63.2% [Rosenberg, J. E., et al 2020].

Table 1 Summary of Best Overall Response per Investigator per RECIST 1.1 – Full Analysis Set

	EV-103 Cohort A 1 L EV 1.25 mg/kg + Pembro N=45 n (%)
Best Overall Response[a], n (%)	
Confirmed Complete Response (CR)	7 (15.6)
Confirmed Partial Response (PR)	26 (57.8)
Stable Disease (SD)	9 (20.0)
Progressive Disease (PD)	1 (2.2)
Not Evaluable (NE)	2 (4.4)
Confirmed ORR (CR or PR)	33 (73.3)
95% CI[b] for ORR	(58.1, 85.4)
Disease Control (CR or PR or SD)	42 (93.3)
95% CI[b] for DCR	(81.7, 98.6)

1 L: first-line; CI: confidence interval; DCR: disease control rate; ORR: objective response rate; RECIST: Response Evaluation Criteria in Solid Tumors; EV: enfortumab vedotin.

[a] Best overall response according to RECIST v1.1.

[b] Computed using the Clopper-Pearson method [Clopper, C. J. and Pearson, E. S. 1934].

As of the data cutoff 13-OCT-2020, median DOR in Cohort A was 25.6 months (95% CI: 8.3, -). Fifty-three percent of the responders had DOR at 24 months and the DCR was 93.3%. The combination also shows a favorable PFS trend with median PFS of 12.3 months (95% CI: 8.0, -) and the median OS was not reached. The OS rate at 24 months was 56.3% (95% CI: 39.8, 69.9) [Friedlander, T. W., et al 2021].

In EV-103 Cohort K, preliminary efficacy data of EV 1.25 mg/kg in combination with pembrolizumab in cisplatin-ineligible participants with locally advanced or mUC in the 1 L setting (n=76), as of data cutoff 10-JUN-2022, confirmed ORR was 64.5% (95% CI: 52.7%, 75.1%), including 10.5% CR and 53.9% PR. Stable disease occurred in 22.4% and progressive disease in 7.9% (3.9% not evaluable and 1.3% with no assessment). Median time to ORR was 2.1 months. The median DOR was not reached; 65.4% of responders were still responding at 12 months. The majority of assessable participants (97.1%) had tumor reduction regardless of PD-L1 status. The ORR for participants with CPS ≥10 was 67.7% (21/31) and for participants with CPS <10 was 61.4% (27/44) [Rosenberg, J. E., et al 2022].

EV-103 Cohort A/Cohort K preliminary efficacy data showed a high ORR with rapid responses and median DOR not reached in cisplatin-ineligible participants with locally advanced or mUC in the 1 L setting. This data supports the investigation of EV in combination with pembrolizumab in cisplatin-ineligible participants with MIBC.

2.2.2.2.2 EV-302/KEYNOTE-A39

The EV-302/KEYNOTE-A39 Phase 3 study evaluates the combination of EV plus pembrolizumab versus platinum-based chemotherapy. A total of 886 patients underwent randomization: 442 to the EV plus pembrolizumab group and 444 to the chemotherapy group. PFS was prolonged with EV plus pembrolizumab versus platinum chemotherapy, reducing the risk of progression or death by 55% (median PFS: 12.5 months versus 6.3 months, respectively; HR 0.45 [95% CI: 0.38 to 0.54]; $p<0.001$). OS was significantly prolonged with EV plus pembrolizumab, reducing the risk of death by 53% (median OS: 31.5 months versus 16.1 months, respectively; HR 0.47 [95% CI: 0.38 to 0.58]; $p<0.001$). Additionally, the ORR of EV plus pembrolizumab was 67.7% [95% CI: 63.1 to 72.1; $p<0.001$], consistent with prior studies [Powles, T., et al 2024].

Treatment-related AEs of Grade 3 or higher occurred in 55.9% of the patients in the EV + pembrolizumab group and in 69.5% of those in the chemotherapy group. The most common treatment-related AEs in the EV plus pembrolizumab group were peripheral sensory neuropathy (50%), pruritus (39.8%), and alopecia (33.2%), while the most common treatment-related AEs of Grade 3 or higher were maculopapular rash (7.7%), hyperglycemia (5.0%), and neutropenia (4.8%). Overall, the EV + pembrolizumab regimen was demonstrated to be tolerable, with manageable toxicities [Powles, T., et al 2024].

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

In this study, participants randomized to treatment Arm A will receive perioperative pembrolizumab as opposed to RC + PLND alone in Arm B, which is the standard of care for cisplatin-ineligible patients with MIBC. Pembrolizumab has known antitumor efficacy in UC in the advanced/metastatic setting, and there are early data to suggest efficacy in the neoadjuvant setting as well. Although there are the risks of pembrolizumab-related AEs as well as the delay in potentially curative surgery, the effective downstaging of MIBC to pT0N0 and pT1/TIS/TaN0 suggests improvements in EFS and recurrence-free survival, and ultimately, OS when neoadjuvant therapy is used [Bandini, M., et al 2020]. The further addition of pembrolizumab adjuvant therapy in Arm A will allow for the treatment of any micrometastatic disease that may be present. Due to the 40–50% recurrence rate seen in patients with MIBC when RC + PLND alone is used, the addition of pembrolizumab may offer significant benefits despite the toxicities associated with this treatment.

Participants in this study may also be randomized to treatment Arm C and will receive perioperative EV plus pembrolizumab as opposed to RC + PLND alone in Arm B in the management of MIBC. The promising combination data of EV and pembrolizumab demonstrated a dramatic improvement in ORR in a 1 L locally advanced or metastatic cisplatin-ineligible patient population suggests the potential for improved efficacy in the neoadjuvant setting as well. Given the high recurrence rate/mortality for MIBC patients

treated with RC + PLND alone, adding EV combined with pembrolizumab in this setting offers significant potential benefits, including possible cure.

Participants in this study may also be randomized to Arm B and will undergo RC + PLND alone followed by observation. Adjuvant nivolumab may be used per the approved product label in participants randomized to Arm B at high risk of recurrence after RC + PLND, if locally available, and provided the participant is deemed appropriate by the investigator. Note: Imaging must continue per protocol after starting adjuvant nivolumab.

Additional details regarding specific benefits and risks for participants in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

In male or female participants at least 18 years of age with histologically confirmed muscle-invasive bladder cancer (MIBC) clinical Stage cT2-T4aN0M0 or cT1-T4aN1M0:

Primary Objective	**Primary Endpoint**
Objective: To compare event-free survival (EFS) between Arm C (perioperative enfortumab vedotin in combination with pembrolizumab and radical cystectomy plus pelvic lymph node dissection [RC+PLND]) and Arm B (RC+PLND). Hypothesis (H1): Perioperative enfortumab vedotin in combination with pembrolizumab plus RC+PLND will achieve superior EFS compared with RC+PLND alone.	EFS (defined as the time from randomization to the first of any of the following events): -Radiographic disease progression precluding a curative intent surgery as assessed by BICR prior to RC+PLND -Failure to undergo surgery for participants with residual muscle-invasive disease and any radiographic disease present (for other participants who do not undergo surgery, see Section 8.2.3), 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 computed tomography (CT) or magnetic resonance imaging (MRI) (BICR) and/or biopsy. If biopsy is not feasible due to participant safety, CT/MRI alone will be sufficient -Death from any cause
Secondary Objectives	**Secondary Endpoints**
Objective: To compare EFS between Arm A (perioperative pembrolizumab and RC+PLND) and Arm B (RC+PLND). Hypothesis (H4): Perioperative pembrolizumab plus RC+PLND will achieve superior EFS compared with RC+PLND alone.	EFS

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

Objective: To compare the rates of pathologic downstaging (pDS) between Arm A (perioperative pembrolizumab and RC+PLND) and Arm B (RC+PLND) and between Arm C (perioperative enfortumab vedotin in combination with pembrolizumab and RC+PLND) and Arm B.	pDS is defined as participants with <pT2 (includes pT0, pTis, pTa, pT1) and N0 in examined tissue from RC+PLND
Objective: To evaluate the safety and tolerability of perioperative pembrolizumab with RC+PLND and perioperative enfortumab vedotin in combination with pembrolizumab with RC+PLND.	Participants experiencing adverse events (AEs) Participants discontinuing study drug due to AEs Participant experiencing perioperative complications
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
Objective: To evaluate the mean change from baseline in Functional Assessment of Cancer Therapy – Bladder Cystectomy (FACT-Bl-Cys), Bladder Cancer Index (BCI), and EuroQol 5-dimension questionnaire (EQ-5 D-5 L) instruments.	Mean change from baseline in: -The total score of Functional Assessment of Cancer Therapy – General (FACT-G) -The total score of Bl-Cys, the bladder cancer-specific subscale/symptom index -FACT-Bl-Cys-Trial Outcome Index (TOI) -BCI: urinary, bowel, and sexual domains -EQ-5 D-5 L utility score -EQ-5 D-5 L visual analog score (VAS)
Objective: To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab or pembrolizumab + enfortumab vedotin.	Germline genetic variation, genetic (DNA) mutations from tumor, tumor and blood RNA variation, proteomics and immunohistochemistry (IHC), and other biomarkers

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 3, randomized, controlled, parallel-group, multisite, open-label study of perioperative pembrolizumab plus RC + PLND and perioperative EV in combination with pembrolizumab plus RC + PLND versus RC + PLND alone in participants with MIBC who are ineligible for or decline cisplatin-based chemotherapy. Planned IAs will occur throughout the course of this study.

Approximately 608 participants with previously untreated MIBC were planned to be randomized in 2 stages. The study originally had 2 arms, and participants were enrolled into Arm A and Arm B in a 1:1 ratio. With the subsequent addition of Arm C, participants began to enroll into Arms A, B, and C in a 1:1:1 ratio. After implementation of Amendment 8, Stage 2 randomization was under Arms B and C only (randomization under Arm A was stopped except in France). At the time of Amendment 10, the study completed enrollment, with 595 participants randomized in 2 stages:

- Stage 1, includes ~84 participants randomized to each arm (Arm A and Arm B in a 1:1 ratio);
- Stage 2, includes ~85 participants randomized to each arm (Arms A, B, and C in a 1:1:1 ratio) until implementation of Amendment 8. After implementation of Amendment 8, the study no longer randomized participants to Arm A (except France), and randomized ~86 additional participants to each arm (Arms B and C in a 1:1 ratio).

Note that the updates to study randomization in Amendment 8 do not impact participants already randomized to the study.

At screening, a tumor specimen from a transurethral resection of bladder tumor (TURBT) or biopsy performed within 60 days (+14 days) prior to enrollment (documented informed consent) will be submitted for central pathology review including confirmation of histology, presence of muscle invasion (at least T2 disease), or presence of nonmuscle-invasive tumor (T1 disease) in N1 patients prior to randomization. This tissue will also be sent for PD-L1 determination by IHC. T1N1M0 represents a nonmuscle-invasive bladder cancer (NMIBC) patient population and are considered to have Stage IIIA disease. Participants with T1N1M0 disease are included in this study because it is biologically more like T3-T4aN0M0 bladder cancer in its progression, OS, cancer-specific survival, and management [National Comprehensive Cancer Network 2020]. T1 disease (eligible only with N1 disease) and T2 disease will be confirmed by central pathology review. T3, T4, N0, and N1 disease will be confirmed by central imaging review (where nodal biopsy / fine needle aspirate [FNA] is possible and available N1 disease will be confirmed by central pathology review for participants with T1 disease). All participants will undergo baseline screening imaging studies (CT or MRI of the chest/abdomen/pelvis) for clinical staging; these studies will be centrally evaluated in real time by BICR prior to randomization to confirm eligibility. As noted in the inclusion criteria (Section 5.1), all participants must be deemed eligible for RC + PLND and planned to undergo standard curative intent surgery to enroll in this study. Any

participant refusing surgery will no longer receive any study treatment. Sponsor consultation is required for participants who do not undergo RC + PLND. Participants who refuse or do not undergo surgery who have achieved a clinical complete response (cCR) or have been downstaged to NMIBC (<T2 disease) will be followed observationally for EFS with disease assessments at designated intervals (see Sections 1.3 and 8.2.3).

At the time of Amendment 8 implementation, randomization under Arm A was stopped and eligible participants were randomized in a 1:1 ratio to Arms C and B only, to receive either 3 cycles of neoadjuvant EV in combination with pembrolizumab (Arm C) or proceed directly to RC + PLND (Arm B). Participants will be stratified based on centrally determined clinical T stage (T2N0 or T3/T4aN0 or T1-4aN1), geographic region (US or European Union [EU] or Most of World [MOW]), and cisplatin eligibility (cisplatin-ineligible or cisplatin-eligible but decline). Stratification by cisplatin eligibility applies to randomization Stage 2. Prior to Amendment 5, participants were stratified by PD-L1 status. PD-L1 status determined by the central vendor will not be disclosed to investigators and participants.

The planned total treatment with pembrolizumab in Arm A is 17 doses (approximately 1 year) including the neoadjuvant and adjuvant phase combined (3 cycles in the neoadjuvant phase and 14 cycles in the adjuvant phase).

The planned total treatment with EV in Arm C is 18 doses (9 cycles) including 3 cycles in the neoadjuvant phase on Day 1 and Day 8 of each cycle and 6 cycles in the adjuvant phase on Day 1 and Day 8 of each cycle. The EV doses must be given 7 days apart in each cycle. The planned total treatment with pembrolizumab in Arm C is 17 doses (approximately 1 year) including 3 cycles in the neoadjuvant phase (all of the neoadjuvant cycles will be given with EV) and 14 cycles in the adjuvant phase (6 of the adjuvant cycles will be with EV).

Treatment will be discontinued if the participant experiences unacceptable AE(s), intercurrent illness that prevents further administration of treatment, the investigator's decision to withdraw the participant; the participant withdraws consent, pregnancy of the participant, noncompliance with study treatment or procedure requirements or the maximum number of cycles has been received for each treatment component individually (Section 7.1).

Participants in Arm A will complete 3 cycles of pembrolizumab, followed by repeat imaging studies (same modality as screening) within ≤5 weeks prior to cystectomy to exclude disease progression, which would preclude curative intent surgery. Participants in Arm A who remain radiographically free of distant metastases will proceed to surgery at Week 12 (84 days ± 7 days) from study randomization. Participants in Arm A are allowed to proceed to surgery outside this time frame if the delays are due to an AE. Participants with delays other than for an AE may be considered with Sponsor consultation.

Participants in Arm B will undergo surgery within 8 weeks (56 days + 7 days) from randomization. If ≥5 weeks has elapsed between screening imaging studies and the scheduled surgery date, repeat imaging studies must be obtained, such that the interval between the most recent imaging studies and surgery is ≤5 weeks prior to cystectomy. Participants in Arm B are allowed to proceed to surgery outside this time frame if the delays are due to an AE. Participants with delays other than for an AE may be considered with Sponsor consultation.

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 the participant is deemed appropriate by the investigator. Note: Imaging must continue per protocol after starting adjuvant nivolumab.

Participants in Arm C will complete 3 cycles of EV and pembrolizumab followed by repeat imaging studies (same modality as screening) within ≤5 weeks prior to cystectomy to exclude disease progression, which would preclude curative intent surgery. Participants in Arm C who remain radiographically free of distant metastases will proceed to surgery at Week 12 (84 days ± 7 days) from study randomization. Participants in Arm C are allowed to proceed to surgery outside this time frame if the delays are due to an AE. Delays other than for an AE may be considered with Sponsor consultation. In Arm C, participants who experience unacceptable toxicity that is attributable only to pembrolizumab may continue on EV monotherapy up to 9 cycles until a protocol-defined reason for study discontinuation. Participants who experience toxicity that is attributable only to EV may continue on pembrolizumab monotherapy up to a maximum of 17 cycles until a protocol-defined reason for study discontinuation.

All participants must be intended to undergo a standard RC + PLND. RC + PLND will be performed and all surgical specimens will be assessed by central pathology to determine pathologic response. Radiographic disease progression precluding a curative intent surgery noted prior to RC + PLND, failure to undergo surgery for participants with residual muscle-invasive disease and any radiographic disease present, gross residual disease left behind at time of surgery, local or distant recurrence post-surgery as assessed radiographically and/or confirmed with biopsy (local pathology review), or death from any cause will be considered events and such participants will not receive further therapy on study. Participants who have not yet had a BICR-verified EFS event will continue in Efficacy Follow-up until BICR verification. All other participants with events other than death will transition into Survival Follow-up. For more details regarding participants who do not undergo surgery, see Section 8.2.3.

At 6 weeks ± 14 days after RC + PLND, all participants will have repeat imaging (same modality as screening); participants with new recurrent/metastatic disease at this time will have met the primary endpoint (ie, had an “event”) and will not receive further therapy on study, but will transition into Survival Follow-up. All imaging should continue to be submitted (even retrospectively) to BICR until BICR-verified PD or death (see Section 8.2.1.3). Participants in Arm A who remain radiographically disease-free and have recovered adequately from the morbidity and/or complications from the surgery will continue to receive pembrolizumab (up to 14 cycles in the adjuvant phase, beginning 8 weeks ± 14 days post-cystectomy) to complete approximately 1 year of total therapy. If additional recovery time is required, this may be discussed with the Sponsor using a Sponsor consultation form. Participants in Arm C who remain radiographically disease-free and have recovered adequately from the morbidity and/or complications from the surgery will continue to receive EV and pembrolizumab (up to 14 cycles of pembrolizumab and 6 cycles of EV in the adjuvant phase, beginning 8 weeks ± 14 days post-cystectomy) to complete approximately 1 year of total therapy. If additional recovery time is required, this may be discussed with the Sponsor using a Sponsor consultation form.

All participants will have serial imaging and office visits as per the SoA (Section 1.3). At any time during the post-RC surveillance period, if a participant develops suspected radiographic disease progression/recurrence, a mandatory biopsy to confirm disease progression/recurrence will be performed and reviewed locally (biopsy sample to be sent to central pathology vendor). Biopsy samples that demonstrate secondary malignancy should not be sent to central pathology vendor. If it is not feasible to obtain a biopsy for participant safety, the reason for omitting biopsy must be documented in the participant's medical record and electronic case report form (eCRF). Participants who are found to have disease progression will not receive further study treatment and will transition into Survival Follow-up. When biopsy confirms recurrent disease (local review), the date of recurrence will be documented as the date when progression/recurrence was initially noted radiographically.

Participants who discontinue treatment for reasons other than an EFS event will have posttreatment follow-up for disease status until an EFS event occurs; during this period, participants will continue study-related disease assessments including imaging per the SoA (for more details regarding participants who do not undergo surgery, see Section 8.2.3). All participants will be followed for OS until death, withdrawal of consent, or notification to the investigator by the Sponsor to discontinue follow-up, or end of study, whichever comes first.

Specific procedures to be performed during the study, including prescribed times and associated visit windows, are outlined in Section 1.3 of the SoA. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

Approximately 40% of patients with MIBC are cisplatin-ineligible and represent a significant unmet medical need. The current standard of care for patients with MIBC who are deemed cisplatin-ineligible is RC + PLND followed by observation. This study is designed to demonstrate improvements in clinical outcomes for participants with MIBC via pathologic downstaging and improvement in EFS [Cajipe, M., et al 2020].

The proof of concept for the activity of neoadjuvant single-agent PD-1/PD-L1 axis targeting therapy (ie, pembrolizumab and atezolizumab) in MIBC has been established, with investigator-initiated studies (including both cisplatin-ineligible and cisplatin-eligible participants) revealing significant pathological response rates [Necchi, A., et al 2018] [Powles, T., et al 2018]. The evidence of clinical activity provides a robust rationale for investigating perioperative pembrolizumab in patients with cisplatin-ineligible MIBC. Pembrolizumab will be combined with EV in this study due to the dramatic improvement in ORR in locally advanced and metastatic UC noted in the EV-103/KEYNOTE-869 study [Hoimes, C. J., et al 2019] showing the potential for use in the perioperative setting.

In Arm A, 3 cycles of neoadjuvant pembrolizumab (200 mg every 3 weeks [Q3W] on Day 1 of each cycle) will be administered. This duration of therapy is similar to established neoadjuvant chemotherapy regimens (3-4 cycles) in cisplatin-eligible participants.

In Arm C, 3 cycles of neoadjuvant pembrolizumab (200 mg Q3W on Day 1 of each cycle) and EV (1.25 mg/kg on Days 1 and 8 – separated by at least 7 days) will be administered. Three cycles of EV were chosen for the neoadjuvant portion of this study based on a similar established number of neoadjuvant chemotherapy regimens (3-4 cycles) in cisplatin-eligible participants as well as on the observation that the majority of the responses in EV-103/KEYNOTE-869 occurred at the first tumor assessment (Week 9 ± 1 week) [Rosenberg, J. E., et al 2020].

After surgery, participants randomized to Arm A will continue to receive adjuvant pembrolizumab to complete approximately 1 year of immunotherapy in total. Participants in Arm C will also continue to receive adjuvant pembrolizumab and adjuvant EV; pembrolizumab will be given for the equivalent of 1 year, while EV will be given for 6 more cycles. The pembrolizumab treatment duration is comparable to 3 large Phase 3 studies investigating single-agent adjuvant checkpoint blockade in MIBC (AMBASSADOR, IMvigor 010, and CheckMate 274).

This study provides neoadjuvant immunotherapy, which offers a theoretical advantage to adjuvant therapy alone [Schmid, P., et al 2020]. The administration of immunotherapy in the neoadjuvant setting with the primary tumor in place in Arm A and Arm C will allow the activated T-cells to encounter more tumor cells, potentially gaining the ability to identify and destroy similar tumor cells in the future (ie, “memory”). The adjuvant immunotherapy is intended to continue to stimulate immune surveillance and the eradication of any residual micrometastatic disease. CheckMate 274 is a Phase 3 study that evaluated adjuvant immunotherapy (nivolumab, anti-PD-1) compared with placebo in participants with MIBC at high risk of recurrence after undergoing radical surgery. The study found that DFS was longer with adjuvant nivolumab than with placebo in the ITT population and among participants with PD-L1 expression of ≥1% [Bajorin, D. F., et al 2021]. Based on these findings, adjuvant nivolumab may be used per the approved product label in Arm B participants at high risk of recurrence after RC + PLND, if locally available, and provided that the participant is deemed appropriate by the investigator. Note: Imaging must continue per protocol after starting adjuvant nivolumab.

The combination of EV and pembrolizumab in the neoadjuvant setting with the primary tumor in place in Arm C will allow for tumor antigen release from the Nectin-4-associated tumor lysis to further activate T-cells [Cao, A., et al 2016]. The adjuvant combination therapy is intended to continue to stimulate immune surveillance and eradication of any micrometastases of UC as well as eradicate any micrometastatic disease expressing Nectin-4.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

The primary efficacy endpoint is EFS for Arm C versus Arm B comparison.

Event-Free Survival (EFS)

- EFS (defined as the time from randomization to the first of any of the following events):
  - Radiographic disease progression precluding a curative intent surgery prior to RC+PLND assessed by BICR
  - Failure to undergo surgery for participants with residual muscle-invasive disease and any radiographic disease present (for other participants who do not undergo surgery, see Section 8.2.3), biopsy-proven MIBC will be considered an event regardless of radiographic findings
  - Gross residual disease left behind at time of surgery (surgeon unable to complete curative intent surgery due to unresectable tumor or newly discovered metastatic disease)
  - Local or distant recurrence post-RC+PLND as assessed by CT or MRI and/or biopsy. CT or MRI will be assessed by BICR. If biopsy is not feasible due to participant safety, CT/MRI alone will be sufficient
  - Death from any cause

    NOTE: A nonurothelial second primary malignancy is not considered an event. Participants who develop high-risk NMIBC (in addition to muscle-invasive cancer) of the upper tract/remaining urothelium after RC + PLND will be considered as having an event.

EFS is a common surrogate endpoint for OS that is used to evaluate the efficacy of perioperative cancer therapy and is frequently used as a primary endpoint. EFS represents a clinically significant endpoint for participants with MIBC, given the high rate of local recurrence and disease progression.

The secondary efficacy endpoints include OS, pCR, DFS, pDS, and EFS for Arm A versus Arm B comparison.

Overall Survival (OS)

- OS is defined as the time from randomization to death due to any cause.

OS is a key endpoint in this study and is included in the multiplicity analysis.

The use of OS as the primary endpoint in this study would considerably lengthen the study interval, and possibly delay access to improved therapeutic options for this population; thus, OS is being evaluated as a secondary endpoint and included in the multiplicity analysis.

Pathologic Complete Response (pCR)

- Pathologic CR is defined as the absence of viable tumor (pT0N0) in examined tissue from RC and PLND.

In this study pCR is being used as a surrogate for survival in MIBC participants treated with neoadjuvant pembrolizumab. A SWOG study (8710) investigating neoadjuvant chemotherapy in MIBC found that pCR, whether achieved by neoadjuvant chemotherapy plus cystectomy or cystectomy alone, significantly correlated with improved OS [Grossman, H. B., et al 2003]. There is also prospective data from clinical trials in breast cancer that demonstrate a significant correlation between pCR rates and improved EFS [Yee, D., et al 2017].

Disease-free Survival (DFS)

- DFS is defined as the time from post-surgery baseline scan (revealing no recurrent/metastatic disease) until the first occurrence of either:
  - Local or distant recurrence as assessed by CT or MRI (BICR) and/or biopsy
  - Death from any cause

DFS is a common surrogate endpoint for OS that is used to evaluate the efficacy of adjuvant cancer therapies. DFS is a widely accepted endpoint in oncology clinical studies as prolonged DFS constitutes clinically meaningful benefit for participants.

Pathologic Downstaging (pDS)

- pDS is defined as participants with <pT2 (includes pT0, pTis, pTa, pT1) and N0 in examined tissue from RC + PLND).

Data from multiple studies in MIBC have shown that improved clinical outcomes correlate with pathologic downstaging, with greater benefit associated with a greater degree of downstaging [Sonpavde, G., et al 2009] [Rosenblatt, R., et al 2012].

4.2.1.2 Safety Endpoints

Safety parameters frequently used for evaluating investigational-systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/SAEs, and changes in vital signs and laboratory values. AEs will be assessed as defined by CTCAE, Version 4.0.

4.2.1.3 Patient-reported Outcomes

Symptomatic improvement is considered a clinical benefit and accepted by health authorities. As part of the analyses for this study, participants will provide information regarding their health-related quality of life (HRQoL) via the following assessment tools: FACT-Bl-Cys, EQ-5 D-5 L, and BCI. These PROs measures are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

4.2.1.3.1 EQ-5 D-5 L

The EQ-5 D-5 L is a standardized instrument for use as a measure of health outcome and will provide data to develop health utilities for use in health economic analyses [Rabin, R. and de Charro, F. 2001]. The 5 health state dimensions in this instrument include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a five-point scale from 1 (no problem) to 5 (unable to/extreme problems). The EQ-5 D-5 L also includes a graded (0 to 100) vertical VAS on which the participant rates his or her general state of health at the time of the assessment. This instrument has been used extensively in cancer studies and published results from these studies support its validity and reliability [Pickard, A. S., et al 2007].

4.2.1.3.2 Functional Assessment of Cancer Therapy-Bladder-Cystectomy (FACT-Bl-Cys)

The Functional Assessment of Chronic Illness Therapy (FACIT) is a general collection of quality-of-life questionnaires, which are focused on the management of chronic illness. Included in these questionnaires are the FACT Assessments. The FACT-Bl-Cys was developed using input from experts in the treatment of bladder cancer and patients who previously underwent radical cystectomy and urinary diversion. FACT-Bl-Cys contains 17 items on the bowel, bladder, and sexual symptoms after cystectomy; and it is to be administered in conjunction with the FACT-G. The FACT-G questionnaire is a validated and reliable tool that measures generic HRQoL in patients being treated for cancer a 27-item questionnaire. The FACT-G subscales include Physical Well-Being (PWB), Social/Family Well-Being (SWB), Emotional Well-Being (EWB), and Functional Well-Being (FWB). All items are scored on a 5-point Likert scale of 0 to 4, with higher scores indicating higher HRQoL. The total score can range from 0 to 68 and 10 questions are reverse scored.

4.2.1.3.3 Bladder Cancer Index

The BCI is a validated, condition-specific health questionnaire assessing quality of life among patients with bladder cancer [Gilbert, S. M., et al 2010] [Gilbert, S. M., et al 2007]. The BCI contains 36 items, which assess 3 domains (urinary, bowel, and sexual) with function and bother subdomains. Scores range from 0 to 100 with higher scores corresponding to better functioning and HRQoL. The minimally important difference thresholds indicating clinically significant changes or differences were recently established for radical cystectomy-treated MIBC patients as 6 to 9, 5 to 8, and 7 to 11 points for urinary, bowel, and sexual domains, respectively [Peyton, C. C., et al 2019].

4.2.1.4 Planned Exploratory Biomarker Research

Cancer immunotherapies represent an important and novel class of antitumor agents. However, the mechanism of action of these exciting new therapies is not completely understood and much remains to be learned regarding how best to leverage these new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer immunotherapy and other treatments administered, as well as determinants of AEs in the course of our clinical studies. These efforts may identify novel predictive/pharmacodynamic biomarkers and generate information that may better guide single-agent and combination therapy with immuno-oncology drugs. To identify novel biomarkers, biospecimens (ie, blood components, tumor material) will be collected to support analyses of cellular components (eg, protein, DNA, RNA, metabolites) and other circulating molecules. Investigations may include, but are not limited to:

Germline (blood) genetic analyses (eg, SNP analyses, whole exome sequencing, whole genome sequencing)

This research may evaluate whether genetic variation within a clinical study population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or AEs, the data might inform optimal use of therapies in the patient population. Furthermore, it is important to evaluate germline DNA variation across the genome to interpret tumor-specific DNA mutations. Finally, MSI may be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer).

Genetic (DNA) analyses from tumor

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (ie, mutations, methylation status, microsatellite instability). Key molecular changes of interest to immuno-oncology drug development include the mutational burden of tumors and the clonality of T-cells in the tumor microenvironment. Increased mutational burden (sometimes called a ‘hyper-mutated’ state) may generate neoantigen presentation in the tumor microenvironment. To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Thus, genome-wide approaches may be used for this effort. Note that to understand tumor-specific mutations, it is necessary to compare the tumor genome with the germline genome. Microsatellite instability may also be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer). Circulating tumor DNA and/or RNA may also be evaluated from blood samples.

Tumor and/or blood RNA analyses

Both genome-wide and targeted mRNA expression profiling and sequencing in tumor tissue and/or in blood may be performed to define gene signatures that correlate to clinical response to treatment with pembrolizumab or other immunotherapies. Pembrolizumab induces a response in tumors that likely reflects an inflamed/immune phenotype. Specific immune-related gene sets (ie, those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Individual genes related to the

immune system may also be evaluated (eg, IL-10). MicroRNA profiling may also be pursued as well as exosomal profiling.

Proteomics and IHC using blood and/or tumor

Tumor and/or blood samples from this study may undergo proteomic analyses (eg, PD-L1 IHC). PD-L1 protein level in tumor sections, assessed by IHC, has been shown to correlate with response to pembrolizumab in patients with NSCLC, and an IVD device has been developed for use with pembrolizumab in NSCLC. Preliminary data indicates that this association may also be true in additional cancer types (ie, triple negative breast cancer, head and neck, and gastric). Additional tumor or blood-derived proteins may also correlate with response to pembrolizumab. Therefore, tumor tissue may be subjected to proteomic analyses using a variety of platforms that could include, but are not limited to, immunoassays and liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for pembrolizumab (MK-3475) therapy.

Other blood-derived biomarkers

In addition to expression on the tumor tissue, PD-L1 and other tumor derived proteins can be shed from tumor and released into the blood. Assays such as ELISA measure such proteins in serum. Correlation of expression with response to pembrolizumab therapy may identify new approaches for predictive biomarkers in blood, representing a major advance from today's reliance on assessing tumor biomarkers. This research would serve to develop such assays for future clinical use.

Other molecular changes of interest include the subtype of T-cells in the tumor microenvironment. The T-cell repertoire from tumor tissue and blood components may be evaluated.

4.2.2 Rationale for the Use of Comparator/Placebo

The study design does not include the use of a placebo. In this study, RC + PLND is the standard of care (SOC) for MIBC participants who cannot receive neoadjuvant cisplatin-based chemotherapy. For participants in this study randomized to the SOC arm (Arm B), RC + PLND alone followed by observation, adjuvant nivolumab may be used per the approved product label in participants at high risk of recurrence after RC + PLND, if locally available, and provided the participant is deemed appropriate by the investigator. Note: imaging must continue per protocol after starting adjuvant nivolumab. The design of this study is open-label, as delay in time to surgery for placebo treatment is not acceptable.

The study design also does not include a placebo for EV in Arm A (perioperative pembrolizumab) as the AE profile of EV would effectively unblind the treatment to the study participants, the investigators, and the Sponsor.

4.3 Justification for Dose

Pembrolizumab

The planned dose of pembrolizumab for this study is 200 mg Q3W. Based on the totality of data generated in the KEYTRUDA® development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W), clinical data showing meaningful improvement in benefit-risk including OS at 200 mg Q3W across multiple indications, and pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically based PK [PBPK] analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and NSCLC, covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q3W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2, and KN006). These studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer, and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed-dose and 2 mg/kg Q3W dose. Supported by these PK characteristics and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

Enfortumab vedotin

EV will be administered at a dose of 1.25 mg/kg (up to a maximum dose of 125 mg) as an intravenous infusion over approximately 30 minutes on Days 1 and 8 of each 3-week cycle.

In the monotherapy setting, EV is administered on Days 1, 8, and 15 of every 4-week cycle. Based on PK data from previous studies, the half-life of EV is approximately 3 to 4 days. No notable intracycle accumulation (<30%) of ADC was observed with this monotherapy dosing regimen at any dose level. Minimal intracycle accumulation (<50%) of MMAE was observed.

When comparing the same dose level, the average weekly total exposure of EV after administration on Days 1 and 8 of each 21-day cycle is predicted to be similar to that observed for dosing on Days 1, 8, and 15 of a 28-day cycle. Thus, it is anticipated that the dosing schedule in the current combination study will achieve ADC exposures over each 3-week cycle that may lead to a favorable balance of antitumor activity and safety similar to that observed in the Phase 2 Study EV-201.

The safety and antitumor activity of EV 1.25 mg/kg administered on Days 1 and 8 (dosed 7 days apart) of every 3-week cycle in combination with pembrolizumab is currently being evaluated in the ongoing EV-103/KEYNOTE-869 trial described in Section 2.2.2.2.1. Safety data from the combination of EV and pembrolizumab shows the combination to be tolerable. The evaluation of the maximum duration of EV therapy has been determined to be a total of 9 cycles. Pembrolizumab will be used for a total of 17 cycles, including 8 cycles without EV.

4.3.1 Starting Dose for This Study

For participants in Arms A and C, a single dose of pembrolizumab (200 mg Q3W) will be used. For participants in Arm C, EV will be administered at 1.25 mg/kg on Days 1 and 8 of each 3-week cycle. EV will be given prior to pembrolizumab (200 mg Q3W) on Day 1 of each cycle and will be given as monotherapy on Day 8 of each cycle. EV doses should be given 7 days apart in each treatment cycle.

4.3.2 Maximum Dose Exposure for This Study

It is planned that participants enrolled in the pembrolizumab treatment arm (Arm A) will receive up to a total of 17 cycles of treatment (3 cycles in the neoadjuvant phase and 14 cycles in the adjuvant phase). Participants in the EV and pembrolizumab treatment arm (Arm C) will receive up to a total of 17 cycles of treatment with pembrolizumab (3 cycles of therapy in the neoadjuvant phase and 14 cycles of therapy in the adjuvant phase) and up to a total of 9 cycles of treatment with EV (3 cycles of therapy in the neoadjuvant phase and 6 cycles of therapy in the adjuvant phase).

4.3.3 Rationale for Dose Interval and Study Design

For the neoadjuvant portion of the study, 3 cycles of pembrolizumab will be administered to participants in Arm A, as this schedule appears to have significant activity based on the preliminary results of the PURE-01 study [Necchi, A., et al 2018].

Additionally, in patients with MIBC deemed cisplatin-eligible, 3 to 4 chemotherapy cycles prior to cystectomy is a well-accepted interval for neoadjuvant treatment prior to surgery for curative intent [Wong, Y. N., et al 2012] [Choueiri, T. K., et al 2014]. There is literature, which suggests delay in time from diagnosis to surgery for MIBC ≥12 weeks leads to worsened outcomes; the study schedule for both arms will allow participants to undergo surgery in less than 12 weeks from diagnosis [Gore, J. L., et al 2009] [Lee, C. T., et al 2006].

The duration of therapy in the adjuvant setting is 14 cycles. Therefore, as noted above, participants in the study will receive up to 17 cycles of pembrolizumab with an approximate duration of 1 year. KEYNOTE-054 (a randomized Phase 3 trial) investigated 1 year of adjuvant pembrolizumab versus placebo for completely resected Stage III melanoma and demonstrated a significant recurrence-free survival benefit [Suciu, S., et al 2018]. Investigating a 1-year duration of therapy is also consistent with ongoing large Phase 3 adjuvant studies in the MIBC setting (AMBASSADOR [KEYNOTE-123] NCT03244384, IMvigor010 NCT02450331, CheckMate 274 NCT02632409).

The neoadjuvant and adjuvant portions of Arm C will include the same treatment schedules of pembrolizumab with the addition of EV given on Days 1 and 8 of each 3-week cycle (with the doses given 7 days apart in each cycle) based upon the data from the EV-103/KEYNOTE-869 study [Hoimes, C. J., et al 2019]. The duration of EV treatment is capped at 9 total cycles (3 neoadjuvant cycles plus 6 adjuvant cycles).

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

If the study includes countries in the European Economic Area (EEA), the local start of the study in the EEA is defined as First Site Ready (FSR) in any Member State.

The Sponsor estimates that the maximum duration of the study from first participant entered through long-term follow-up will be 92 months (approximately 2 to 3 years after study intervention has been completed) to attain the final assessment of the study (eg, to evaluate safety and/or long-term efficacy) for all evaluable participants. Refer to the Synopsis, Section 1.1, for the duration of participation of participants.

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects is such that the risk/benefit ratio to the study population is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped as described in Section 10.1.10.

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Section 10.1.1) this study includes participants of varying age, race, ethnicity, and sex. The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

Male and female participants of at least 18 years with MIBC clinical Stage T2-T4aN0M0 or T1-4aN1M0 will be enrolled in this study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

An individual is eligible for inclusion in the study if the individual meets all of the following criteria:

Type of Participant and Disease Characteristics

1. Have a histologically confirmed diagnosis of urothelial carcinoma/MIBC (cT2-T4aN0M0 or T1-T4aN1M0) with predominant (≥50%) urothelial histology to be confirmed by BICR (central pathology and/or imaging):

- T1 disease (eligible only with N1 disease) and T2 disease will be confirmed by central pathology review and T3, T4a, N0, and N1 disease will be confirmed by central imaging review.
- Note: N1 disease will be confirmed by central imaging review. Where nodal biopsy / FNA is possible and available, N1 disease will be confirmed by central pathology review for participants with T1 disease.
- Participants with mixed histology are eligible provided the urothelial component is ≥50% as noted above (participants whose tumors contain predominant [≥50%] plasmacytoid variant are not eligible).
- Participants whose tumors contain any neuroendocrine histology are not eligible.
- UCs not originating from the bladder (eg, upper tract [ureters, renal pelvis], urethra) are not eligible. UCs invading into the prostatic stroma with no histologic muscle invasion is allowed, provided that the extent of disease is confirmed via imaging.

2. Have clinically nonmetastatic bladder cancer (N≤1M0) determined by imaging (CT or MRI of the chest/abdomen/pelvis), confirmed by BICR.
3. Be deemed eligible for RC + PLND by a urologist and/or oncologist and agree to undergo curative intent standard RC + PLND (including prostatectomy if applicable) as per AUA/ASTRO/ASCO/SUO guidelines referenced in Appendix 9 in Section 10.9.

4. Be ineligible for treatment with cisplatin, as defined by meeting at least **one** of the following criteria listed below OR be eligible for treatment with cisplatin, but decline treatment with cisplatin-based chemotherapy.

- Impaired renal function with measured or calculated CrCl 30 to 59 mL/min (calculated by Cockcroft-Gault method, Modification of Diet of Renal Disease (MDRD) equations, or measured by 24-hour urine collection)
- ECOG Performance Status 2
- CTCAE v.4 Grade ≥2 audiometric hearing loss.
  - Note: Audiometric abnormalities without corresponding clinical symptoms of Grade ≥2 hearing loss will not be grounds for exclusion
- New York Heart Association (NYHA) Class III heart failure

See Appendix 7 for country-specific requirements.

5. Have a transurethral resection (TUR) of a bladder tumor (obtained within 60 days [+ 14 days] prior to study enrollment [documented informed consent]) that is submitted for central pathology assessment and adequate to determine urothelial histology and PD-L1 expression assessment.

   Note: For confirmation of T1 disease (with N1) it is recommended that TUR biopsy sample include detrusor muscle. For confirmation of T2, TUR biopsy samples must include detrusor muscle, without which tumor samples will not be evaluated by central vendor.

   Formalin-fixed, paraffin-embedded (FFPE) tissue blocks are preferred to slides (details pertaining to tumor tissue submission can be found in the Procedures Manual).
6. Must have an ECOG performance status of 0, 1, or 2.
7. Demonstrate adequate organ function as defined in Table 2 (all screening laboratory tests should be performed within 14 days prior to randomization). Refer to Appendix 7 for country-specific requirements.

Table 2 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 cells/µL
Platelets	≥100,000 cells/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Measured or calculated creatinine clearance (CrCl)[b] (GFR can also be used in place of CrCl)	≥30 mL/min
Hepatic	
Serum total bilirubin	≤1.5 × ULN **OR**
	Direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT) **OR** Partial Thromboplastin Time (PTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic-pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic-oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.

[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.

[b] CrCl should be calculated using one of the following methods: Cockcroft-Gault method, Modification of Diet in Renal Disease equations (MDRD), or 24-hour urine collection. The same method for CrCl calculation should be used consistently for a participant over the course of the study.

Demographics

8. Participant is male or female at least 18 years of age, at the time of providing informed consent.

Male Participants

9. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 180 days after the last dose of enfortumab vedotin:

- Refrain from donating sperm

  PLUS:

- Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Appendix 5]) as detailed below:
  - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

  If the male participants are receiving pembrolizumab only or undergoing surgery only, there are no contraception requirements.

- Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.

Female Participants

10. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 120 days after the last dose of pembrolizumab and 180 days after the last dose of enfortumab vedotin, whichever comes last, and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.
- A WOCBP must have a negative highly sensitive pregnancy test within 24 hours before the first dose of study intervention.
- Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.4.2.

- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.
- Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.

Informed Consent

11. The participant (or legally acceptable representative if applicable) provides documented informed consent/assent for the study.

5.2 Exclusion Criteria

An individual must be excluded from the study if the individual meets any of the following criteria:

Medical Conditions

1. Has a known additional nonurothelial malignancy that is progressing or has required active anticancer treatment ≤3 years of study randomization.

   Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, breast carcinoma, cervical cancer) who have undergone potentially curative therapy are not excluded. Participants with curatively treated localized prostate cancer are not excluded; Sponsor consultation is required prior to randomization to determine eligibility in these participants.

2. Participants with ≥N2 disease or metastatic disease (M1) as identified by imaging.
3. Has received any prior systemic treatment, chemoradiation, and / or radiation therapy for MIBC or NMIBC.
   Note: Prior treatment for NMIBC with intravesical instillation therapy such as *Bacillus* Calmette-Guérin or intravesical chemotherapy is permitted. Prior systemic treatment (including, but not limited to, anti-PD 1/L1 treatment with pembrolizumab, etc,) received for NMIBC is not permitted.

Prior/Concomitant Therapy

4. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or coinhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).
5. Has received prior systemic anticancer therapy including investigational agents (including enfortumab vedotin or other MMAE-based ADCs) within 3 years prior to randomization.

   Note: Participants must have recovered from all AEs due to previous therapies (received >3 years prior to randomization) to ≤ Grade 1 or baseline. Participants with <Grade 2 neuropathy may be eligible.

   Note: If a participant has had major surgery, recovery from any toxicity and/or complications from surgery is required prior to starting study intervention.
6. Has received any prior radiotherapy to the bladder.
7. Has received a partial cystectomy of the bladder to remove any NMIBC or MIBC.
8. Received a live or live-attenuated vaccine within 30 days before the first dose of study intervention. Administration of killed vaccines are allowed.
   Refer to Section 6.5 for information on COVID-19 vaccines.

Prior/Concurrent Clinical Study Experience

9. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study intervention.

   Note: Participants who have entered the Follow-up Phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.

Diagnostic Assessments

10. Has ongoing sensory or motor neuropathy Grade 2 or higher.
11. 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 drug. Inhaled or topical steroids are permitted in the absence of active autoimmune disease. Physiologic replacement doses of corticosteroids are permitted for participants with adrenal insufficiency.
12. Has hypersensitivity to monoclonal antibodies (including pembrolizumab) and/or any of their excipients.
13. Has known severe hypersensitivity (≥ Grade 3) to enfortumab vedotin or any excipient contained in the drug formulation of enfortumab vedotin (including histidine, trehalose dihydrate, and polysorbate 20). Refer to Appendix 7 for country-specific requirements.
14. Has active keratitis or corneal ulcerations. Participants with superficial punctate keratitis are allowed if the disorder is being adequately treated in the opinion of the investigator.

15. Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
16. Has uncontrolled diabetes. Uncontrolled diabetes is defined as hemoglobin A1c (HbA1c) ≥8% or HbA1c 7% to <8% with associated diabetes symptoms (polyuria or polydipsia) that are not otherwise explained.
17. Has a history of (noninfectious) pneumonitis that required steroids or has current pneumonitis.
18. Has an active infection (viral, bacterial, or fungal) requiring systemic therapy. Participants may be rescreened once after resolution of the infection. Refer to Appendix 7 for country-specific requirements.

    Note: Routine antimicrobial prophylaxis is permitted and participants with asymptomatic chronic infections on prophylactic treatments are allowed.
19. Has a known history of human immunodeficiency virus (HIV) infection. No HIV testing is required unless mandated by local health authority. Refer to Appendix 7 for country-specific requirements.
20. Has a known history of hepatitis B (defined as hepatitis B surface antigen [HBsAg] reactive) or known active hepatitis C virus (defined as detectable HCV RNA via qualitative nucleic acid testing) infection. Refer to Appendix 7 for country-specific requirements.

    Note: No testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.
21. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.
22. Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.

Other Exclusions

23. Has had an allogeneic tissue/solid organ transplant.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

There are no caffeine, alcohol, or tobacco restrictions.

5.3.3 Activity Restrictions

There are no study mandated activity restrictions.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently randomized in the study. A minimal set of screen-failure information is required to ensure transparent reporting of screen-failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen-failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention will not be replaced.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies will be packaged to support enrollment as required. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in Table 3.

Table 3 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Arm A	Experimental	Pembrolizumab	Biological/ Vaccine	Solution	100 mg/4 mL (25 mg/mL) solution in a single-dose vial	200 mg	IV Infusion	Q3W – 3 cycles neoadjuvant phase; 14 cycles adjuvant phase	Test Product	IMP	CENTRAL
Arm C	Experimental	Pembrolizumab	Biological/ Vaccine	Solution	100 mg/4 mL (25 mg/mL) solution in a single-dose vial	200 mg	IV Infusion	Q3W – 3 cycles neoadjuvant phase; 14 cycles adjuvant phase	Test Product	IMP	CENTRAL
Arm C	Experimental	Enfortumab vedotin	Biological/ Vaccine	Solution	30 mg single dose vial	1.25 mg/kg	IV Infusion	Days 1 and 8 Q3W- 3 cycles in the neoadjuvant phase and for 6 cycles in the adjuvant phase	Test Product	IMP	CENTRAL

EEA=European Economic Area; IMP=investigational medicinal product; IV=intravenous; N/A=not applicable; NIMP/AxMP=noninvestigational/auxiliary medicinal product; PLND=pelvic lymph node dissection; Q3W=every 3 weeks; RC=radical cystectomy.
The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.
Study intervention = study treatment.
In this protocol, RC + PLND is considered part of the assigned study treatment for Arms A, B, and C. For additional details, refer to Sections 10.9.

All study interventions will be administered on an outpatient basis.

All products indicated in Table 3 will be provided centrally by the Sponsor or locally by the study site, subsidiary, or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the study site, subsidiary, or designee, every attempt will be made to source these supplies from a single lot/batch number. The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

Refer to Section 8.1.8 for details regarding administration of the study intervention.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual.

Details on the preparation and administration of EV are provided in the Pharmacy Manual.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Treatment randomization will occur centrally using an interactive response technology (IRT) system. There are 3 study treatment arms. Until implementation of Amendment 8, participants will be assigned randomly in a 1:1:1 ratio to Arm A (perioperative pembrolizumab + RC + PLND), Arm B (RC + PLND), and Arm C (perioperative EV in combination with pembrolizumab + RC +PLND). After implementation of Amendment 8, participants were assigned randomly in a 1:1 ratio to Arm B or Arm C, and randomization to Arm A was stopped. Refer to Appendix 7 for country-specific requirements.

6.3.2 Stratification

Participants will be stratified by:

- Tumor clinical Stage (T2N0 vs T3/T4aN0 vs T1-T4aN1)
- Cisplatin eligibility (cisplatin-ineligible or cisplatin-eligible but decline)
- Geographic regions (US vs EU vs MOW)

Note: Stratification by cisplatin eligibility applies to randomization Stage 2. Prior to Amendment 5, participants were stratified by PD-L1 status.

6.3.3 Blinding

There is no blinding in this study.

6.4 Study Intervention Compliance

If there are interruptions in the study intervention schedule or infusion/injection was stopped, the details of and reason for any interruption or infusion/injection cessation of study intervention will be documented in the participant's medical record.

Refer to Section 6.6.1 for Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations and for other allowed dose interruptions.

See Section 6.6.2 for dose modifications for EV.

6.5 Concomitant Therapy

6.5.1 Prohibited Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study (until discontinuation of study intervention). If there is a clinical indication for any medication or vaccination specifically prohibited, discontinuation from study therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor's Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

Listed below are specific restrictions for concomitant therapy or vaccination during the course of the study:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Investigational agents other than pembrolizumab, EV, or any ADCs
- Radiation therapy
- Live or live-attenuated vaccines within 30 days before the first dose of study intervention and while participating in the study. Refer to Appendix 7 for country-specific requirements.

Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, replication-incompetent adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.

Investigational vaccines (ie, those not licensed or approved for Emergency Use) are not allowed.

- Systemic glucocorticosteroids, except for the purposes listed in Section 6.5.2, are prohibited.
- Any medication prohibited in combination with EV (for participants in Arm C), as described in the respective product labels.
- Participants who are receiving strong CYP3A4 inhibitors or P-glycoprotein inhibitors concomitantly with EV should be monitored for adverse reactions.

If the investigator determines that a participant requires any of the aforementioned treatments for any reason, study intervention must be discontinued.

It is recommended that antidiabetic medications such as pioglitazone should not be prescribed due to evidence suggesting an increased risk of bladder cancer associated with its use.

6.5.2 Accepted Concomitant Therapy

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the eCRF including all prescription, over-the-counter products, herbal supplements, and intravenous (IV) medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

All concomitant medications received within 28 days prior to time of study intervention allocation/randomization and up to 30 days after cessation of study intervention should be recorded. If participants experience an SAE or event of clinical interest (ECI), all concomitant medications administered 30 days after the last dose of study intervention are to be recorded as defined in Section 8.4.

- Systemic glucocorticoids are allowed for the following cases:
  - To mediate potential immune-related AEs as noted in Table 4.
  - As pre/post-medication to prevent AEs associated with IV contrast.
  - Brief, limited use of systemic corticosteroids (≤7 days) is permitted where such use is considered SOC (eg, for asthma or chronic obstructive pulmonary disease exacerbation). For use >7 days, consultation with the Clinical Director is required.
  - Replacement doses of steroids (eg, prednisone 5 to 7.5 mg daily) are permitted while on study, as is the use of topical steroids.
    - Intra-articular steroid injections are permitted.
  - Administration of granulocyte colony-stimulating factor (G-CSF; eg, filgrastim or peg-filgrastim) following institutional guidelines is strongly encouraged to avoid dose delays or reductions. G-CSF may be administered on or after Day 9 of each treatment cycle for neutropenia prevention/treatment according to local guidelines for Arm C only.

Standard of care medications routinely administered for surgery (anesthetic medications, muscle relaxants, IV fluids, etc,) do not need to be recorded in the eCRF. Concomitant medications should be recorded for any SAEs and AEs related to surgery.

6.5.2.1 Premedication

For participants in Arms A and C, pembrolizumab and EV do not need to be given with premedications, though noncorticosteroid premedications may be introduced on an as-needed basis per investigator discretion.

6.5.3 Rescue Medications and Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator.

Suggested supportive care measures for the management of AEs associated with study intervention are outlined along with the dose modification guidelines in Section 6.6.

Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab or EV, the investigator does not need to follow the treatment guidance. Refer to Table 4 in Section 6.6.1 for guidelines regarding dose modification and supportive care.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

6.6 Dose Modification (Escalation/Titration/Other)

Dose modifications and interruptions in response to treatment-related AEs are permitted in order to keep the participant on study medication, when appropriate. Details on the modifications for each study intervention are provided in the sections below.

Action (dose reduction, interruption or discontinuation) may be taken independently for each component of study treatment.

Pembrolizumab dose reductions are not permitted. Pembrolizumab treatment may be interrupted or discontinued due to toxicity.

In Arm C (EV + pembrolizumab), participants who experience unacceptable toxicity that is attributable only to pembrolizumab may continue on EV monotherapy until a protocol-defined reason for study discontinuation or maximum of 9 cycles (neoadjuvant + adjuvant phase). Participants who experience toxicity that is attributable only to EV may continue on pembrolizumab monotherapy up to a maximum of 17 cycles (neoadjuvant + adjuvant phase).

Dose interruptions (EV and pembrolizumab) may be allowed for situations other than treatment-related AEs such as medical/surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 21 days (3 weeks) of the originally scheduled dose and within 42 days (6 weeks) of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the eCRF.

Note that the permitted dose interruption time applies to the neoadjuvant and adjuvant periods separately, and adjuvant treatment must start within 8 weeks (± 14 days) post cystectomy per the SoA (Section 1.3.2).

6.6.1 Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue)

Dose Modification and Toxicity Management for Immune-Related AEs Associated With Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids, and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids.

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 4.

Refer to Appendix 7 for country-specific requirements.

Table 4 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated With Pembrolizumab Monotherapy, Coformulations, or IO Combinations

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab monotherapy, coformulations or IO combinations must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab monotherapy, coformulations or IO combinations have been withheld, treatment may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Recurrent Grade 2 or Grade 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST / ALT Elevation or Increased Bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [a]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [a]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or Permanently discontinue [a]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue [b]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT=alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] The decision to withhold or permanently discontinue pembrolizumab monotherapy, coformulations or IO combinations is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab monotherapy, coformulations or IO combinations may be resumed.

[b] Events that require discontinuation include, but are not limited to: Guillain-Barre Syndrome, encephalitis, myelitis, DRESS, SJS, TEN and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab-associated infusion reaction are provided in Table 5.

Table 5 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator	None
Grade 2 Requires therapy or infusion interruption, but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	Stop Infusion Additional appropriate medical therapy may include, but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise, dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug intervention.	Participant may be premedicated 1.5 h (±30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include, but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug intervention.	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

Other Allowed Dose Interruption for Pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to the study intervention. However, study intervention is to be restarted within 21 days (3 weeks) of the originally scheduled dose and within 42 days (6 weeks) of the previously administered dose unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the participant's study record.

Note that the permitted dose interruption time applies to the neoadjuvant and adjuvant periods separately, and adjuvant treatment must start within 8 weeks (± 14 days) post-cystectomy per the SoA (Section 1.3.2).

6.6.2 Dose Modification of Enfortumab Vedotin (Arm C Only)

Dose modification recommendations for EV-associated toxicity (hematologic and nonhematologic, by CTCAE v4.0 grade) are presented in Table 6, Table 7, and Table 8.

Table 6 Enfortumab Vedotin Dose Reductions

Dose Level	Enfortumab Vedotin
0	1.25 mg/kg
-1	1.0 mg/kg
-2	0.75 mg/kg

Dose reduction or delay for other EV-associated toxicity is permitted at the discretion of the site investigator. Dose reduction from 1.25 mg/kg to 1 mg/kg, or to 0.75 mg/kg should a second dose reduction be required, will be allowed depending on the type and severity of toxicity. Participants requiring a dose reduction may be re-escalated by 1 dose level (ie, participants reduced to 0.75 mg/kg may only be re-escalated to 1 mg/kg) provided the toxicity does not require study drug discontinuation and has returned to baseline or ≤ Grade 1. If the toxicity recurs, re-escalation will not be permitted. Participants with ≥ Grade 2 corneal AEs will not be permitted to dose re-escalate.

If a dose interruption is required, an interruption of all Day 1 doses (both EV and pembrolizumab in Arm C) must be considered at investigator discretion. The Day 1 and Day 8 doses of EV must be given 7 days apart. The Day 8 dose of EV must be given within 4 days of the planned dose (ie, Day 8 + 4 days). If toxicities warranting a dose delay occur after Day 1 dosing and are not resolved prior to Day 8 dosing (up to Day 12), Day 8 EV administration must be skipped rather than delayed. A dose delay may last up to 6 weeks (2 cycles). Dose delays for participants who are deriving clinical benefit from treatment may be extended beyond 6 weeks, if the participant's toxicity does not otherwise require permanent discontinuation. If there is a dose delay, the schedule for response assessments will not be adjusted.

EV may be delayed for situations other than treatment-related AEs such as medical/surgical events or logistical reasons not related to study therapy. Participants should resume study therapy as soon as clinically safe as assessed by the investigator. For delays longer than 6 weeks, the medical monitor should be consulted before resuming study therapy. The reason for delay should be documented in the participant's CRF.

Note that the permitted dose interruption time applies to the neoadjuvant and adjuvant periods separately, and adjuvant treatment must start within 8 weeks (± 14 days) post-cystectomy per the SoA (Section 1.3.2).

Table 7 Recommended Dose Modification for Enfortumab Vedotin-Associated Hematologic Toxicity

Grade 1	Grade 2	Grade 3	Grade 4
Continue at same dose level.	Continue at same dose level. For Grade 2 thrombocytopenia, withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose level.	Withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose level or consider dose reduction by 1 dose level. Transfusions or growth factors may be used as indicated per institutional guidelines. Administration of G-CSF (eg, filgrastim or peg-filgrastim) following institutional guidelines is strongly encouraged to avoid dose delays or reductions.	Withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then reduce dose by 1 dose level and resume treatment or discontinue at the discretion of the investigator. Transfusions or growth factors may be used as indicated per institutional guidelines. For Grade 4 anemia, treatment discontinuation should be strongly considered.
Note: Hematologic toxicity refers to anemia, thrombocytopenia, neutropenia, and febrile neutropenia.			

Table 8 Recommended Dose Modifications for Enfortumab Vedotin-Associated Nonhematologic Toxicity

Toxicity	**Grade**			
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Skin reactions	Any Grade			
	For suspected Stevens-Johnson Syndrome (SJS) or suspected toxic epidermal necrolysis (TEN), or bullous lesions, immediately withhold EV and refer the participant to a dermatologist/specialist for diagnosis and specialized care. For confirmed SJS or TEN, permanently discontinue treatment. If SJS or TEN is ruled out, see recommendations provided below for skin reactions.			
	For Grade 1 rash or skin reactions, may continue at same dose level. See also Section 6.6.2.2 for recommended management of rash.	For Grade 2 rash or skin reactions, continue at same dose level. For worsening rash or skin reactions or skin reactions with concomitant fever, withhold EV until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose level or consider dose reduction by 1 level. Consider referral of the participant to a dermatologist/ specialist for diagnosis and specialized care. See also Section 6.6.2.2 for recommended management of rash.	For Grade 3 rash or skin reactions, withhold EV until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose level or consider dose reduction by 1 level. Consider referral of the participant to a dermatologist/ specialist for diagnosis and specialized care. See also Section 6.6.2.2 for recommended management of rash. Participants who have confirmed SJS or recurrent Grade 3 rash events should have therapy permanently discontinued.	For confirmed SJS or TEN, or Grade 4 rash, permanently discontinue treatment.

Toxicity	**Grade**			
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Ocular	Continue at same dose level. If ocular symptoms and/or changes in vision are identified, the participant should be evaluated by an optometrist or ophthalmologist.	For Grade 2 corneal AEs, withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose level. For the second occurrence of Grade 2 corneal AEs, withhold dose until toxicity is ≤ Grade 1, then reduce the dose by 1 dose level and resume treatment. If ocular symptoms and/or changes in vision are identified, the participant should be evaluated by an optometrist or ophthalmologist.	For Grade 3 corneal AEs, discontinue treatment at the discretion of the investigator. If ocular symptoms and/or changes in vision are identified, the participant should be evaluated by an optometrist or ophthalmologist.	For Grade 4 AEs, discontinue treatment.
Neuropathy	Continue at same dose level.	For Grade 2 neuropathy AEs, withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose level. For the second occurrence of Grade 2 neuropathy AEs, withhold dose until toxicity is ≤ Grade 1, then reduce the dose by 1 dose level and resume treatment.	For Grade 3 neuropathy AEs, discontinue treatment at the discretion of the investigator.	For Grade 4 AEs, discontinue treatment.

Toxicity	Grade			
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Gastrointestinal	Continue at same dose level.	Continue at same dose level.	Withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose level or consider dose reduction by 1 dose level.	For Grade 4 AEs, discontinue treatment. Grade 4 vomiting and/or diarrhea that improves to ≤ Grade 2 within 72 hours with supportive management does not require discontinuation.
Hyperglycemia	Continue at same dose level.	Continue at same dose level.	For Grade 3 hyperglycemia/ elevated blood glucose, withhold EV treatment. Resume treatment once hyperglycemia/ elevated blood glucose has improved to ≤ Grade 2 and participant is clinically and metabolically stable. See also pembrolizumab dose modification recommendations for hyperglycemia in Table 4.	For Grade 4 hyperglycemia/ elevated blood glucose, withhold EV treatment and undertake a full evaluation of the hyperglycemia to determine the underlying diagnosis. Once blood glucose returns to ≤ Grade 2, drug dosing may resume at the same dose level with close monitoring after consultation with the medical monitor. See also pembrolizumab dose modification recommendations for hyperglycemia in Table 4.
Pneumonitis/ ILD	Continue at same dose level.	Withhold dose until ≤Grade 1, then resume at the same dose level or consider dose reduction by 1 dose level.	Permanently discontinue treatment.	Permanently discontinue treatment.

Toxicity	Grade			
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
All Other (not previously mentioned)	Continue at same dose level.	Continue at same dose level.	Withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose level or consider dose reduction by 1 dose level[a]	For Grade 4 AEs, discontinue treatment[a]

AEs=adverse events; EV=enfortumab vedotin; ILD=interstitial lung disease; SJS=Stevens-Johnson Syndrome; TEN=toxic epidermal necrolysis.

[a] Grade 3 to 4 electrolyte imbalances/laboratory abnormalities, except hyperglycemia, that are not associated with clinical sequelae or are corrected with supplementation/appropriate management within 72 h of their onset do not require discontinuation (eg, Grade 4 hypouricemia). Grade 3 or 4 elevations of amylase or lipase, if asymptomatic do not require treatment delay.

6.6.2.1 Management of Hyperglycemia

Investigators should monitor blood glucose levels and are advised to perform additional assessments if any symptoms of hyperglycemia are observed, including a thorough evaluation for infection. In addition, if steroids are used to treat any other condition, blood glucose levels may require additional monitoring. If elevated blood glucose levels are observed, participants should be treated according to local SOC and referral to endocrinology may be considered.

Participants, especially those with a history of or ongoing diabetes mellitus or hyperglycemia, should be advised to immediately notify their physician if their glucose level becomes difficult to control or if they experience symptoms suggestive of hyperglycemia such as frequent urination, increased thirst, blurred vision, fatigue, and headache.

Participants who enter the study with an elevated HbA1c (≥6.5%) at baseline should be referred to an appropriate provider during Cycle 1 for glucose management, regardless of the Study Arm for which they are randomized. Participants with a history of uncontrolled diabetes, defined as HbA1c ≥8% or HbA1c 7% to <8% with associated diabetes symptoms (polyuria or polydipsia) that are not otherwise explained, should not be enrolled onto this study. Blood glucose should be checked prior to each EV dosing as per SoA (Section 1.3.1) and dose should be withheld for blood glucose >250 mg/dL (Grade 3 or higher). EV dosing may continue once the participant's blood glucose has improved to ≤250 mg/dL and participant is clinically and metabolically stable. The use of insulin is permitted as part of SOC. Blood glucose >500 mg/dL (Grade 4) considered related to EV requires drug interruption and a full evaluation of the hyperglycemia to determine the underlying diagnosis. Once hyperglycemia/elevated blood glucose has improved to ≤250 mg/dL, dosing may resume with close monitoring after consultation with the Sponsor.

6.6.2.2 Management of Rash

EV is a Nectin-4 directed ADC. Nectin-4 is a cell adhesion molecule that is highly expressed in urothelial carcinoma. Low to moderate levels of Nectin-4 are also expressed on normal tissues, including skin keratinocytes, sweat glands, and hair follicles; thus, skin reactions are anticipated events. As such, skin reactions are adverse events of interest in all clinical studies with EV.

A cumulative review of postmarketing safety data from 18-DEC-2019 (the approval date of EV in the US) through 22-OCT-2020 identified reports of severe cutaneous adverse reactions (SCAR) in 15 patients receiving EV, some of whom had fatal outcomes. These reactions occurred predominantly during the first cycle of treatment. Adverse events reported in these cases included SJS (5 cases), blister (3 cases), dermatitis bullous (3 cases), symmetrical drug-related intertriginous and flexural exanthema (2 cases), and 1 case each of dermatitis exfoliative, exfoliative rash, epidermal necrosis, oropharyngeal blistering, stomatitis, and TEN.

In EV monotherapy studies of urothelial carcinoma, SAEs of SCAR were reported in 11 of 749 participants (1.5%) and included dermatitis bullous (0.4%), drug eruption (0.4%), blister (0.1%), conjunctivitis (0.1%), SJS (0.1%), stomatitis (0.1%), and toxic skin eruption (0.1%).

Participants should be informed that rashes and severe skin reactions have occurred after administration of EV, and to contact the investigator immediately if they have signs and symptoms of skin reactions, oral mucosal, and ocular abnormalities, including mucositis or conjunctivitis. Fever or flu like symptoms may be the first sign of a severe skin reaction, and participants should be observed, if this occurs. Starting in the first cycle and throughout treatment, closely monitor participants for skin reactions. For mild to moderate skin reactions, consider appropriate treatment, such as topical corticosteroids and antihistamines as clinically indicated. For recommendations regarding dose modifications for skin reactions, refer to Table 8.

For the EV and pembrolizumab study treatment arm (Arm C), if the rash or skin reaction is determined by the investigator to be related to study treatment, initial management actions (ie, to withhold or discontinue study treatment) should apply to both study treatments and the investigator should follow the most conservative dose modification recommendations described in Sections 6.6.1 (Table 4) and 6.6.2 (Table 8). However, for Grade 2 skin reactions that are stable (not worsening and in the absence of fever) with supportive measures and not limiting the participant's activities of daily living (ADLs), continued dosing of EV may be considered following consultation with the Sponsor. Neither EV nor pembrolizumab should be administered in the setting of a Grade ≥3 skin reaction.

6.6.2.3 Management of Infusion Reactions

An infusion-related reaction (IRR) may occur during the infusion of study treatment with EV. The infusion should be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. All supportive measures consistent with optimal patient care should be given throughout the study according to institutional standards [Polovich, M., et al 2014] [Perez Fidalgo, J. A., et al 2012]. Supportive measures may include administering medications for IRRs.

Premedications for IRRs may include pain medication (eg, acetaminophen or equivalent), an antihistamine (eg, diphenhydramine hydrochloride), and a corticosteroid administered approximately 30–60 minutes prior to each EV infusion and after the pembrolizumab infusions. Should a participant experience IRRs in the setting of premedication, continued treatment must be discussed with the medical monitor prior to the next planned dose. Prophylactic premedication prior to combination treatment on Cycle 1 Day 1 for prevention of IRRs may not be administered.

If anaphylaxis occurs, study treatment administration should be immediately and permanently discontinued.

6.6.2.4 Management of Pneumonitis/Interstitial Lung Disease-Related to Enfortumab Vedotin

Severe, life-threatening, or fatal pneumonitis/ILD have occurred in patients receiving EV. Monitor participants for signs and symptoms indicative of pneumonitis/ILD such as hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams. For all participants, including participants with asymptomatic/Grade 1 pneumonitis/ILD, clinical monitoring and supportive measures consistent with local medical guidelines should be followed as appropriate throughout the study. Medical intervention per standard of care should be considered for Grade≥2 events (eg, corticosteroids initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper). For recommendations regarding dose modifications for pneumonitis/ILD due to EV, refer to Section 6.6.2.

6.6.2.5 Overlapping Adverse Reactions

The IBs for EV and pembrolizumab individually describe AEs frequently observed relative to individual study treatment, as well as less common serious findings. Some AEs, including rash or skin reactions or pneumonitis/ILD, may represent overlapping toxicities for EV and pembrolizumab, and attribution to an individual study treatment may be difficult. For overlapping AEs of skin reaction or pneumonitis/ILD, the management actions (ie, to withhold or discontinue study treatment) should apply to both EV and pembrolizumab and the investigator should follow the most conservative dose modification guidelines as described in Sections 6.6.1 (Table 4) and 6.6.2 (Table 8). However, for Grade 2 skin reactions that are stable (not worsening and in the absence of fever) with supportive measures and not limiting the participant's ADLs, continued dosing of EV may be considered following consultation with the Sponsor.

6.7 Intervention After the End of the Study

There is no study-specified intervention after the end of the study.

6.8 Clinical Supplies Disclosure

This study is open-label; therefore, the participant, the study site personnel, the Sponsor and/or designee are not blinded. Study treatment (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

6.9 Standard Policies

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period will still continue to be monitored in this study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.1.9 unless the participant has withdrawn from the study.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

A participant must be discontinued from study intervention, but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- Any prolonged interruption of study intervention beyond the permitted periods, for irAE management or other allowed dose interruptions, as noted in Section 6.6.1, require Sponsor consultation prior to restarting treatment. If treatment will not be restarted, the participant will continue to be monitored in the study and the reason for discontinuation of study intervention will be recorded in the medical record.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 6.6.
- The participant has an EFS event.
- Investigator's decision to withdraw participant.
- Unacceptable adverse experiences.
- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment.

- Prohibited medication or vaccination required, and agreement between Sponsor, investigator, and participant to discontinue study therapy.
- Refusal of RC + PLND (study mandated curative intent surgery).
- The maximum number of cycles has been received for each treatment component individually (Arms A and C).
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment.
  Note: For participants where local intervention (eg, surgery) is required, please discuss with Sponsor.

7.2 Participant Withdrawal From the Study

It has been well documented that a higher rate of withdrawal can render a study uninterpretable; therefore, unnecessary withdrawal of participants should be avoided.

As clinical event data are important study endpoints, participants who discontinue study intervention prior to completion of the treatment period should be encouraged to continue all remaining study visits for follow-up and vital status assessment as outlined in the SoA and Section 8.12.3.

The investigator is to inform the participants that:

- They may discontinue from study intervention at any time during the study, and
- They are encouraged to continue visits in the study for follow-up, imaging, and vital status assessment.

If participants elect to stop study procedures, they are encouraged to continue to be followed, which allows periodic Survival Follow-up and vital status data to be collected.

If a participant fails to return for scheduled visits and/or if the study site is unable to contact the participant after multiple attempts (ie, is lost to follow-up), the procedures to be performed are outlined in Section 7.3.

If a participant decides not to continue receiving study intervention, the participant is to be encouraged to continue visits in the study for follow-up, imaging, and vital status assessment.

Participants who withdraw consent during the study

If the participant or participant's legally acceptable representative withdraws consent, the participant must be withdrawn from the study.

Section 8.1.9 delineates the specific procedures performed at the time of withdrawal.

Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before providing documented informed consent may be utilized for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.
- Information regarding the maximum amount of blood collected from each participant over the duration of the study can be found in the Procedures Manual.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant (or their legally acceptable representative) prior to participating in this clinical study. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place. Refer to Appendix 7 for country-specific requirements.

8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant (or their legally acceptable representative) before participation in the study.

The initial ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or the participant's legally acceptable representative's dated signature.

Specifics about the study and the study population are to be included in the study informed consent form.

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study-site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent. At the time of intervention/randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant ID card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The medical history will collect all active conditions and any condition diagnosed within the prior

10 years that the investigator considers to be clinically significant. A full smoking history will also be collected at screening. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

If a medical condition is diagnosed at the time of screening due to the physical examination, laboratory tests, radiologic assessment, other assessment, and/or a combination of these evaluations, the medical condition is to be recorded as a baseline condition along with the participant's other medical history unless due to any protocol-specified intervention (eg, procedure, washout, or run-in treatment including placebo run-in).

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days prior to randomization. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study through the Safety Follow-up Visit.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur before randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants. One rescreening will be allowed.

8.1.7 Assignment of Randomization Number

All eligible participants will be randomly allocated and will receive a randomization number. The randomization number identifies the participant for all procedures occurring after randomization. Once a randomization number is assigned to a participant, it can never be re-assigned to another participant.

A single participant cannot be assigned more than 1 randomization number.

8.1.8 Study Intervention Administration

Study treatment should begin within 3 days of and as close as possible to the date on which the participant is randomized. Administration of pembrolizumab and EV must be performed by qualified personnel.

Additional details on the administration of pembrolizumab and EV are provided in the Pharmacy Manual.

8.1.8.1 Timing of Dose Administration

Study treatment should be administered after all procedures/assessments have been completed.

In Arm A, pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons except for N1D1, where the acceptable window is +3 days from randomization. Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes -5 min/+10 min).

In Arm C, EV (1.25 mg/kg) will be administered as an IV infusion over approximately 30 minutes on Days 1 and 8 of a Q3W cycle. Weight-based dosing is based on the participant's actual body weight. Doses must be adjusted for participants who experience a ≥10% change in weight from baseline or previous cycle. Participant's weight must be measured during all relevant assessment windows as described in the SoA as well as per institutional standards, if applicable. Other dose adjustments for changes in body weight <10% are permitted per institutional standard. An exception to weight-based dosing of EV is made for participants weighing greater than 100 kg; doses will be based on 100 kg for these individuals. The maximum dose permitted on study is 125 mg.

At least 7 days must have elapsed between EV doses. The Day 8 dose of EV must be given within 4 days of the planned dose (Day 8 + 4 days). In the absence of infusion-related reactions, the infusion rate for all participants should be calculated in order to achieve a 30-minute infusion period. EV must not be administered as an IV push or bolus. EV should not be mixed with other medications during administration.

Pembrolizumab 200 mg will be administered as an IV infusion approximately 30 minutes after completion of EV on Cycle 1 Day 1. A delay of 15 minutes may be used for subsequent infusions if the Cycle 1 Day 1 infusion was well tolerated. Pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons except for N1D1, where the acceptable window is +3 days from randomization.

The participant should be observed during EV administration and for at least 60 minutes after the infusion during the first 3 cycles. All supportive measures consistent with optimal participant care should be given throughout the study according to institutional standards [Polovich, M., et al 2014] [Perez Fidalgo, J. A., et al 2012].

The infusion site should be monitored closely for redness, swelling, pain, and infection during and at any time after administration. Participants should be advised to report redness or discomfort promptly at the time of administration or after infusion. Institutional guidelines will be followed for the administration of chemotherapy agents and precautions taken to prevent extravasation per institutional standards [Polovich, M., et al 2014] [Perez Fidalgo, J. A., et al 2012]. In case of EV extravasation, the combination drug(s) should be held until consultation and further discussion with the Sponsor.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.12.3.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the final study visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.10 Procedures for Discontinuing a Study or One or More Study Arm(s) Without Safety Concerns

If the Sponsor determines that the study or one or more study intervention group(s) should be discontinued (eg, due to a futility analysis, a DMC recommendation/EOC decision, the availability of new data, a Sponsor decision after the final analysis, or the study not demonstrating statistically significant efficacy results per protocol-specified analyses), and there are no urgent safety issues, the Sponsor may implement one or more of the following actions for the study or the affected study group(s):

- Discontinue participants assigned to a specific cohort, control group, or intervention group from the study and transition them to standard of care
- Discontinue the submission of imaging to the iCRO for BICR analysis
- Reduce the frequency of efficacy assessments (eg, imaging) to align with standard of care
- Discontinue the collection of PROs
- Reduce the frequency at which chemistry, hematology, and urinalysis samples are collected to align with standard of care
- Transition laboratory analyses from the central to the local laboratory
- Transition participants into an extension study that is using study intervention (if available) if participants are eligible and are deriving clinical benefit
- Discontinue all further pre-specified analyses
- Discontinue analyses of exploratory objectives

If any of these actions will be implemented, participating sites will be notified via a formal memo from the Sponsor communicating the decision to discontinue the study or one or more study intervention group(s) and the specific actions from the list above that are to be implemented. The investigator or designee must rapidly inform each participant of their study's or treatment group's discontinuation and discuss treatment options. The investigator or designee must also inform their IRB/IEC of the Sponsor's formal memo and retain it in the study binder.

8.1.11 Participant Blinding/Unblinding

This is not applicable as this is an open-label study.

8.1.12 Domiciling

Participants will not be domiciled.

8.1.13 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Efficacy Assessments

8.2.1 Tumor Imaging and Assessment of Disease

Throughout this section, the term 'scan' refers to any medical imaging data used to assess tumor burden and may include cross-sectional imaging (such as CT or MRI), medical photography, or other methods as specified in this protocol.

The process for image collection and transmission to the central imaging vendor can be found in the Site Imaging Manual. Tumor imaging is strongly preferred to be acquired by CT. CT is the preferred imaging modality for the chest. Contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. MRI is the strongly preferred modality for imaging the brain. The site imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging. Note: for the purposes of assessing tumor imaging, the term "investigator" refers to the local investigator at the site and/or the radiological reviewer at the site or at an offsite facility.

Other imaging modalities that may be collected, submitted to the imaging contract research organization (iCRO), and included in response assessment include brain imaging, CT urography, and bone scans. Other types of medical imaging (such as ultrasound) should not

be submitted to the iCRO and will not be included in response assessment. All scheduled imaging for all study participants will be submitted to the iCRO. In addition, imaging that is obtained at an unscheduled time point, for any reason (including suspicion of progression or other clinical reason), should also be submitted to the iCRO if it shows progression, or if it is used to support a response assessment. All imaging acquired within the protocol-specified window of time around a scheduled imaging visit can be classified as pertaining to that visit.

When the investigator declares disease progression/recurrence (whether before or after RC + PLND and including participants who do not undergo RC+PLND), the iCRO will perform expedited BICR verification of progression/recurrence and communicate results to the study site and Sponsor via email. BICR verification of progression/recurrence process was removed from Protocol Amendments 02 through 09 but reinstated for Amendment 10. Scans with examination dates after country protocol approval may be submitted for BICR verification of progression/recurrence.

Investigator sites should continue submitting scans (even retrospectively) for participants until BICR-verified disease progression/recurrence.

8.2.1.1 Initial Tumor Scans

Imaging of the chest, abdomen, and pelvis with optional oral and mandatory IV contrast (unless noted to the Sponsor to be intolerable) will be performed within ≤28 days prior to randomization. Any imaging obtained after Cycle 1 Day 1 of treatment cannot be included in the screening assessment. The screening images must be submitted to the iCRO to confirm absence of T4b disease, distant metastases (M1 disease) and ≥N2 disease (prior to randomization). These imaging results will be evaluated by BICR in real time.

At screening, imaging scans performed as part of routine clinical management are acceptable for use as the screening imaging scan if they are of diagnostic quality, can be assessed by the iCRO and performed within the imaging window of ≤28 days prior to randomization.

For Arm B participants, if the screening scan is performed ≤35 days prior to cystectomy, then this will be adequate to serve as the presurgery baseline scan.

If brain imaging is performed to evaluate for the presence of metastases, MRI should be used if possible. If MRI is medically contraindicated, CT with contrast is an acceptable alternative.

8.2.1.2 Tumor Scans During the Study

Imaging of the chest, abdomen, and pelvis will be performed using optional oral and mandatory IV contrast (unless noted to the Sponsor to be intolerable) ≤5 weeks (35 days ±7 days) prior to cystectomy and 6 weeks (42 days ±14 days) post-cystectomy. Then, scans will be performed every 12 weeks (84 days ±7 days) up to 96 weeks from the post-cystectomy baseline scan, and at discontinuation; then, every 24 weeks (168 days ±14 days) in Year 3 and beyond.

Other than imaging performed prior to cystectomy and first imaging performed after cystectomy, imaging timing should follow calendar days and should not be adjusted for

delays in cycle starts. Imaging should continue to be performed as per Section 1.3 until BICR-verified disease progression/recurrence, pregnancy, death, or withdrawal of consent, whichever occurs first.

NOTE: Participants who have started a new anticancer treatment after RC + PLND will continue imaging assessments, as long as no EFS event is observed, at the posttreatment follow-up visits.

8.2.1.3 End-of-treatment and Follow-up Tumor Scans

For participants who discontinue study intervention, tumor imaging should be performed at the time of treatment discontinuation (±4-week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory.

For participants who discontinue study intervention without documented BICR-verified disease progression/recurrence, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment (every 12 weeks in Years 1 and 2 and every 24 weeks Year 3 and beyond) until BICR-verified disease progression/recurrence, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first. Participants who discontinue due to an EFS event will be transitioned to Survival Follow-up as per Sections 1.3 and 4.1.

NOTE: For participants who have started a new anticancer therapy for reasons other than documented BICR-verified disease progression/recurrence, imaging assessments will continue as indicated in SoA Section 1.3. Where allowed, participants who do not have documented BICR-verified progression, but have declined participation in study-specific imaging in Efficacy Follow-up should be encouraged to submit imaging performed as standard of care (even retrospectively) in the Survival Follow-up Phase.

8.2.1.4 RECIST 1.1 Assessment of Disease

The principles of RECIST 1.1 will be used by BICR to determine eligibility.

Any scans demonstrating site-assessed progression/recurrence should be submitted immediately for BICR verification of progression/recurrence. Ongoing study intervention should be withheld while waiting for BICR verification of disease recurrence/progression results. The site will be notified of the BICR result upon completion of the central read. For timing of imaging, refer to Sections 1.3 and 4.1.

8.2.2 Determination of Disease Recurrence

Guidance for determining disease recurrence is presented in Table 9.

Table 9 Disease Recurrence

Local Imaging[a]	Central Imaging[a]	Biopsy[b]	Disease Recurrence
Negative	N/A	N/A	No
Positive	Negative	Positive	Yes
Positive	Negative	Negative/Not performed	No
Positive	Positive	Positive	Yes
Positive (one site)	Positive (one site)	Negative	Yes
Positive (multiple sites)	Positive (multiple sites)	Negative (multiple sites biopsied)	Yes
Positive	Positive	Refused/Inconclusive	Yes

[a] Positive imaging = suspicious lesion based on RECIST 1.1 criteria, to be specified in Radiology charter table.

[b] Positive biopsy = urothelial carcinoma present.

If a participant develops suspected radiographic disease recurrence, a mandatory biopsy to confirm disease recurrence (which will be reviewed locally) will be performed. Biopsy samples should be sent to the central pathology vendor. Biopsy samples that demonstrate secondary malignancy should not be sent to the central pathology vendor.

When biopsy confirms recurrent disease, the date of recurrence will be documented as the date when recurrence was initially noted radiographically.

Note: Participants diagnosed with a second primary malignancy and with no evidence of urothelial cancer recurrence or progression may remain on study and continue on study treatment as long as no active treatment is planned to treat the secondary malignancy and the investigator considers continued participation on study treatment to be in the interest of the participant.

8.2.3 Participants Who Do Not Undergo RC + PLND

In this study all participants are expected to undergo curative intent RC + PLND as noted in the inclusion criteria (Section 5.1). However, some participants may refuse surgery or be unable to undergo surgery for a variety of reasons [Herr, H. W. 2008] [Sternberg, C. N., et al 2003]. Sponsor consultation is required for participants who do not undergo RC + PLND. Any participant who refuses or is unable to undergo surgery in Arm A or Arm C will no longer receive any study treatment, but will be followed as described below.

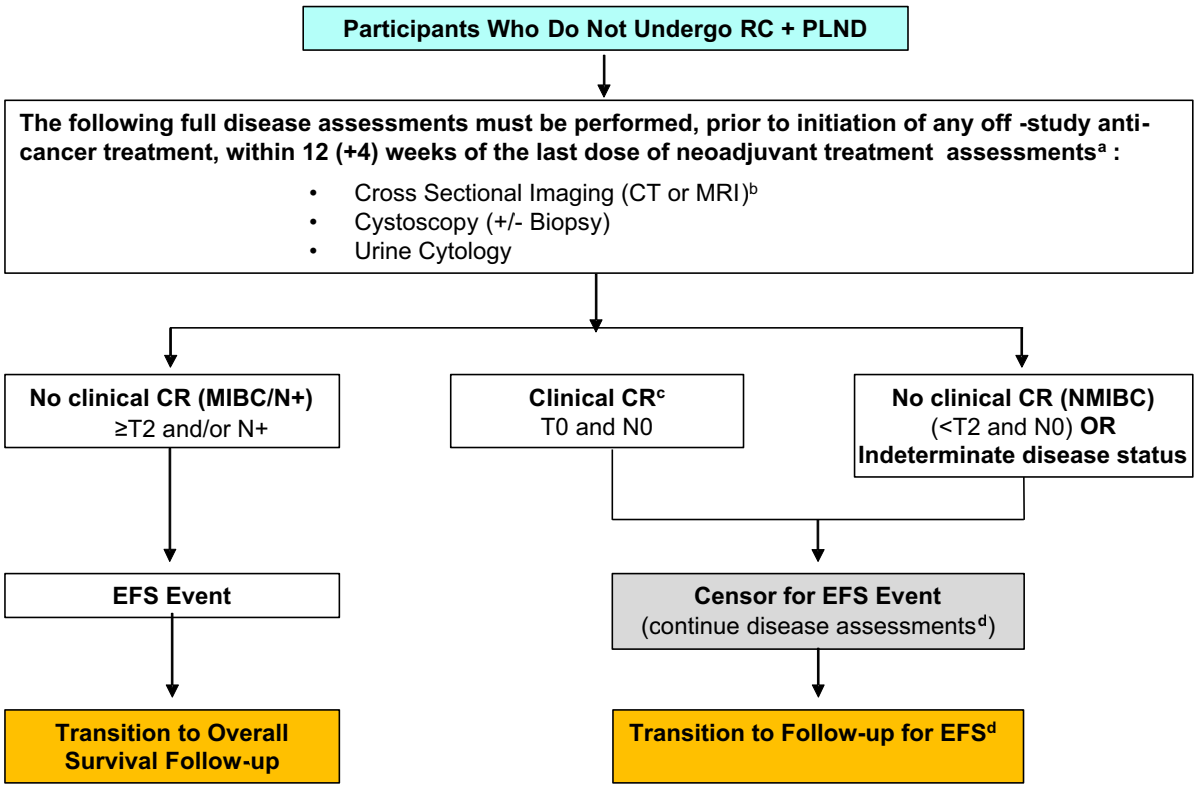
Participants in Arm A and Arm C who do not undergo surgery must repeat a full disease assessment with cross-sectional imaging (CT or MRI), cystoscopy (± biopsy), and urine cytology. These tests should be performed within 12 weeks (+4 weeks) after last dose of neoadjuvant treatment to determine the disease status and are assessed by local review and sent to iCRO (Figure 2). For participants with no radiographic evidence of disease per imaging by investigator assessment, who do not undergo RC + PLND, and who subsequently had cystoscopy (± biopsy) and urine cytology assessments performed off-study, study sites should obtain the results of the assessments and enter the data in the eCRFs.

Participants who do not undergo surgery and have achieved a cCR (defined as no disease on cross-sectional imaging [CT or MRI], negative cystoscopy [± biopsy] and negative urine cytology) [Meyer, A., et al 2014] [Robins, D., et al 2018] will be censored for EFS and will be followed with serial disease assessments for efficacy analyses with cross-sectional imaging (CT or MRI), cystoscopy (± biopsy) and urine cytology every 12 weeks for 2 years, then every 24 weeks for Year 3 and beyond (as noted in Section 1.3.4). These participants will be included in the OS analysis. Participants with persistent MIBC (≥T2 and/or N+) and radiographic evidence of disease by investigator assessment who refuse or are unable to undergo surgery will be counted as an EFS event and transitioned to Survival Follow-up.

Participants with residual non-muscle-invasive disease (<T2), nodal downstaging (<N1 disease), or indeterminate disease status (ie, missing cross-sectional imaging, cystoscopy, cytology) who refuse or are unable to undergo surgery will be censored for EFS and will be followed with serial disease assessments (as noted in Section 1.3) for efficacy analyses. These participants will proceed to the exploratory Follow-up Phase and continue cross-sectional imaging (CT or MRI), cystoscopy (± biopsy), and urine cytology every 12 weeks for 2 years, then every 24 weeks for Year 3 and beyond (as noted in Section 1.3.4). These participants will be included in the OS analysis.

For participants treated with TUR, the pathology stage on TUR as assessed by local review, must be entered in the eCRFs.

Figure 2 Disposition Schema for Participants Who Do Not Undergo RC + PLND (Arm A or Arm C)



CR=complete response; CT=computed tomography; EFS=event-free survival; MRI=magnetic resonance imaging; MIBC=muscle-invasive bladder cancer; NMIBC=nonmuscle-invasive bladder cancer; N+=presence of nodal disease; PLND=pelvic lymph node dissection; RC=radical cystectomy.

[a] If any assessment is missing/not performed, the participant may be considered as having indeterminate disease status.

[b] Investigator assessment. Use same imaging modality for all evaluations. If residual MIBC and/or nodal disease was confirmed by CT/MRI, then cystoscopy (± biopsy) and/or cytology should be performed per investigator discretion and assessed locally.

[c] No disease on CT/MRI, negative cystoscopy (± biopsy; if biopsy is performed results should demonstrate no evidence of residual disease), and negative urine cytology.

[d] Participants to be followed with serial disease assessments for efficacy analyses: Cross-sectional imaging (CT or MRI), cystoscopy ± biopsy, urine cytology every 12 weeks for 2 years, then every 24 weeks for Year 3 and beyond (as per Section 1.3.4). Participants will also be included in the OS analysis. Refer to Section 1.3.4 for required additional procedures.

Note: Participants who do not undergo surgery with radiographic evidence of disease ≥T2 and/or N+ based on investigator assessment of imaging performed within 12 weeks (+4 weeks) from last dose of neoadjuvant treatment are not required to undergo cystoscopy (± biopsy) or urine cytology and will be counted as an EFS event.

For participants in Arm B who do not undergo surgery, cross-sectional imaging (CT or MRI) should be performed prior to initiation of any off-study anti-cancer therapy, within 12 (+4) weeks of randomization:

Participants are to be followed with serial cross-sectional imaging (CT or MRI) for efficacy analyses every 12 weeks for 2 years, then every 24 weeks for Year 3 and beyond (as per Section 1.3.4). Additionally, any cystoscopy +/- biopsy results in Arm B participants that are performed as standard of care to assess for residual MIBC should be collected. Participants will also be included in the OS analysis.

8.2.3.1 Bladder Status

For participants who do not undergo RC + PLND, new anticancer treatments will be assessed at the End-of-Treatment Visit and at any Follow-up visits along with bladder status (ie, intact vs removed/cystectomy performed, stage at cystectomy/removal, and rationale for not removing bladder if medically indicated). This information will be recorded in the eCRF.

8.2.4 Patient-reported Outcomes

The EQ-5 D-5 L, FACT-Bl-Cys, (for participants enrolled prior to Amendment 1), and BCI questionnaires (for all newly enrolled participants after Amendment 1) will be administered by trained site personnel in order and completed electronically by participants.

PROs should be completed in the following order: EQ-5 D-5 L, FACT-Bl-Cys for all enrolled participants; for newly enrolled participants after this protocol amendment, PROs should be completed in the following order: EQ-5 D-5 L, FACT-Bl-Cys, BCI.

For participants in Arms A and C, the questionnaires should be administered prior to dosing on D1 of neoadjuvant treatment Cycle 1, Cycle 2, and Cycle 3, at the presurgery imaging/safety visit and post-surgery follow-up visit, prior to dosing on D1 of adjuvant treatment Cycle 1, Cycle 2, Cycle 4, Cycle 8, and Cycle 12, and at treatment discontinuation; every 12 weeks thereafter up to the end of Year 2. For neoadjuvant treatment, participants randomized under the original protocol will follow the original ePRO schedule, N1, N3, presurgery, post-surgery. For adjuvant treatment, participants randomized under the original protocol will follow the original ePRO schedule of adjuvant treatment, ie, Cycles 1, 3, 7, 11, etc, For participants in Arm B, the questionnaires should be administered at the presurgery visit (≤2 weeks prior to surgery) and first post-surgery follow-up visit (around 4 weeks after the surgery); every 12 weeks from radical cystectomy thereafter up to the end of Year 2. Perform PRO assessment according to the schedule until confirmed progressive disease (PD) or initiation of a new anticancer regimen, withdrawal of consent or death, whichever occurs first.

It is best practice and strongly recommended that ePROs are administered to randomized participants before drug administration, AE evaluation, and disease status notification. If the participant does not complete the ePROs at a scheduled time point, the MISS_MODE form must be completed to capture the reason the assessment was not performed.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in the Procedures Manual.

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard, as noted in Section 1.3. Height and weight will also be measured and recorded.

Brief directed physical examinations will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard, as noted in Section 1.3.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.1.1 Full Physical Examination

The investigator or qualified designee will perform a complete physical examination during the Screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exams are described in Section 1.3. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

8.3.1.2 Directed Physical Examination

For cycles that do not require a full physical examination as defined in Section 1.3, the investigator or qualified designee will perform a directed physical examination as clinically indicated prior to the administration of the study intervention.

For participants in Arm C, a neurological examination will be performed prior to each EV dose if clinically indicated. New clinically significant abnormal findings should be recorded as AEs.

Ophthalmologic assessment for all participants is required at screening. Prior ophthalmologic examination performed within 3 months of screening is acceptable provided symptoms are not new since the examination.

For participants in Arm C, ophthalmology assessments should be performed per SOC or if clinically indicated throughout the study intervention phase. End-of-treatment slit lamp examinations are required for participants who experience corneal AEs during the study and

must be performed ≥4 to 12 weeks after last dose. New clinically significant abnormal findings should be recorded as AEs.

8.3.2 Vital Signs

- Temperature (oral, tympanic, rectal, axillary, skin, or temporal artery), pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in a semisupine or sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions.
- Vital signs will be measured in a semisupine or seated position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse and respiratory rate.

8.3.3 Electrocardiograms

Single 12-lead electrocardiogram (ECG) will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

8.3.4 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation In the study or within 30 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

Details regarding specific laboratory procedures/assessments to be performed in this study are provided below. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant can be found in the Study Procedures Manual. Refer to the SoA (Section 1.3) for the timing of laboratory assessments.

8.3.4.1 Laboratory Safety Evaluations (Hematology, Chemistry, and Urinalysis)

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 2. Serum blood glucose should be checked at screening for all participants and prior to each EV dosing (Arm C only). If serum glucose is not collected and reviewed on the day of EV dosing, then a fingerstick glucose is required. EV dose should be withheld for blood glucose >250 mg/dL. Participants with HbA1c (≥6.5%) at baseline should be referred to an appropriate provider for blood glucose management.

8.3.4.2 Pregnancy Test

Pregnancy testing:

- Pregnancy testing requirements for study inclusion are described in Section 5.1.
- Pregnancy testing (urine as required by local regulations) should be conducted at screening for Arms A, B, and C.
- Pregnancy testing (urine as required by local regulations) should be conducted ≤24 hours prior to first treatment dose (C1D1) in Arm A and Arm C. It should also be conducted ≤72 hours prior to start of each subsequent treatment cycle in Arm A and Arm C.
- Pregnancy testing (urine as required by local regulations) should be conducted at EOT/DC and Safety FU in Arm A and Arm C.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

Refer to Appendix 7 for country-specific requirements.

8.3.5 Performance Assessments

8.3.5.1 Eastern Cooperative Oncology Group Performance Status

The investigator or qualified designee will assess ECOG at screening (within ≤14 days prior to randomization). ECOG score at screening must be 0, 1, or 2. ECOG performance status must be assessed prior to the administration of each dose of study intervention and during the follow-up period as specified in the SoA (Section 1.3).

8.3.6 Ophthalmologic Examination

Ophthalmologic assessment for all participants is required at screening. Prior ophthalmologic examination performed within 3 months of enrollment is acceptable provided symptoms are not new since the examination. For participants on study in Arm C, ophthalmology assessments should be performed per SOC or if clinically indicated throughout study intervention phase. End-of-treatment slit lamp examinations are required for participants who experience corneal AEs during the study and must be performed ≥4 to 12 weeks after last dose. New clinically significant abnormal findings should be recorded as AEs.

8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3. Guidance for evaluating AEs is also presented in Table 10.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse.

Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3. The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity, and causality.

Table 10 Evaluating Adverse Events

An investigator, who is a qualified physician, will evaluate all AEs as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life-threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of study intervention that:	
	†**Results in death**; or	
	†**Is life-threatening; or** places the participant, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of participant taking the product regardless of time to diagnosis); or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a nonserious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life-threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the study intervention to be discontinued?	
Relationship to test drug	Did the study intervention cause the adverse event? The determination of the likelihood that the study intervention caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the study intervention and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:	
	Exposure	Is there evidence that the participant was actually exposed to the study intervention such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the study intervention? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
Relationship to Study Intervention (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the study intervention discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the study intervention; or (3) the trial is a single-dose drug trial); or (4) study intervention(s) is/are only used one time.)
	Rechallenge	Was the participant re-exposed to the study intervention in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) study intervention(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE STUDY INTERVENTION, OR IF RE-EXPOSURE TO THE STUDY INTERVENTION POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the study intervention or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a study intervention relationship).**	
Yes, there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.	
No, there is not a reasonable possibility of Sponsor's product relationship	Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)	

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention allocation/randomization, must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of intervention allocation/randomization through 30 days after cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention allocation/randomization through 90 days after cessation of study intervention or 30 days after cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.
- As of Amendment 09, for any participant on Arm C study intervention (or within 30 days of cessation of study intervention), peripheral neuropathy AEs should continue to be reported until new anticancer therapy is initiated and as long as the participant remains in efficacy follow up.
- All pregnancies and exposure during breastfeeding, from the time of intervention allocation/randomization through the time required to eliminate systemic exposure after cessation of study intervention as described in Section 5.1, or 30 days after cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside the time specified above must be reported immediately to the Sponsor if the event is considered related to study intervention.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 11.

Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.

Table 11 Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor:**
Nonserious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
Serious Adverse Event (SAE) including Cancer and Overdose[a]	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential drug-induced liver injury (DILI) - require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

[a] No longer considering clinically insignificant prostate cancer a SAE.

DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event.

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AE and/or SAE and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Note: To meet EU CTR requirements, the Sponsor will report SUSARs to the Eudravigilance database via E2B(R3) electronic ICSR form in compliance with CTR 536/2014.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee), including the pregnancy of a male participant's female partner, that occurs during the study are reportable to the Sponsor. Any pregnancy complication will be reported as an AE or SAE.

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of ectopic pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (important medical events). If the pregnancy continues to term, the outcome (health of infant) must also be reported. Infants should be followed for a minimum of 8 weeks.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 9.4.1.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression/recurrence of the cancer under study.

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the participants in the study. Any suspected endpoint, which upon review is not progression of the cancer under study, will be forwarded to Global Pharmacovigilance as an SAE within 24 hours of determination that the event is not progression of the cancer under study.

8.4.7 Events of Clinical Interest

Selected serious and nonserious AEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

- An overdose of Sponsor's product, as defined in Section 8.5, that is not associated with clinical symptoms or abnormal laboratory results.
- Potential DILI events defined as an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

  *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).

8.4.8 Adverse Events of Special Interest (AESIs) for Enfortumab Vedotin (Arm C Only)

Selected nonserious and SAEs related to EV must be reported. AESIs for EV include the following:

- Skin reactions
- Peripheral neuropathy
- Ocular events
- Hyperglycemia
- IRR

8.5 Treatment of Overdose

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater.

No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

Weight-based dosing for EV is based on the participant's actual body weight, with the exception of participants weighing greater than 100 kg, for whom doses will be based on 100 kg. **The maximum dose calculated per infusion (Day 1 and Day 8/cycle) in this study is 125 mg.**

In the event of an overdose of EV >10%, study personnel should:

- Care for and medically stabilize the participant until there is no immediate risk of complications or death, if applicable. There is currently no known antidote for an overdose of EV.
- Notify the Medical Monitor as soon as they become aware of the overdose, to discuss details of the overdose (eg, exact amount of EV administered, participant weight) and AEs, if any.

8.6 Pharmacokinetics

With the combination of EV and pembrolizumab in Arm C, this protocol is evaluating the combined exposure and immunogenicity by sample collections for analysis of PK and antidrug antibodies (ADA). The PK and ADA are being collected for both EV and pembrolizumab and are shown in the SoA (Section 1.3). Blood samples will be obtained to measure PK and ADA of serum pembrolizumab. Blood samples will be obtained to measure PK and ADA of EV. The samples collected may be stored at this time. Analysis may be performed, as required. If ongoing PK and/or ADA results are consistent with historical data

and further PK and/or ADA data are deemed to be unnecessary by the Sponsor, it may be decided to discontinue or reduce further sample collection in this study. Should this occur, it will be communicated by an administrative memo. If PK and/or ADA analyses are performed, the results of these analyses will be reported separately. Sample collection, storage, and shipment instructions for plasma samples will be provided in the laboratory manual.

8.7 Pharmacodynamics

Not applicable.

8.8 Biomarkers

To identify novel biomarkers, the following biospecimens to support exploratory analyses of cellular components (eg, protein, RNA, DNA, metabolites) and other circulating molecules will be collected from all participants as specified in the SoA:

- Tissue Collection for Biomarker Analysis (tissue from TURBT and RC + PLND timepoints)
- Blood for Genetic Analysis
- Blood for ctDNA
- Blood for Serum biomarker analysis

The planned genetic analysis sample should be collected for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes.

8.9 Future Biomedical Research Sample Collection

Not applicable.

8.10 Medical Resource Utilization and Health Economics

All-cause hospitalizations and emergency room visits must be reported in the eCRF, from the time of treatment allocation/randomization through 90 days following cessation of study intervention, or 30 days following cessation of study intervention, if the participant initiates new anticancer therapy, whichever is earlier.

8.11 Tumor Tissue Collection

Characterization of PD-L1 expression will be evaluated by a central laboratory for all participants as part of screening. Biopsy from bladder TURBT or newly obtained core or excisional biopsy of bladder tumor lesion (not previously irradiated) must be provided to the central laboratory for testing and be deemed adequate for evaluation. Newly obtained biopsies are preferred to archived tissue. FFPE tissue blocks are preferred to slides. If

submitting unstained slides, the slides should be freshly cut and submitted to the testing laboratory. If the sample is determined to be nonevaluable prior to testing by the central laboratory, a new sample should be submitted, if available. Individual participant PD-L1 status will not be disclosed to investigative sites or study participants. The tissue analysis will include PD-L1 expression and other biomarkers aligned with the objectives of the protocol. Detailed instructions for tissue collection, processing, and shipment are provided in the Procedures/Laboratory Manual.

8.12 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.12.1 Screening

Documented informed consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the participant providing documented informed consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 42 days prior to the first dose of study intervention except as described below. See Section 1.3.1 for Arms A and C and Section 1.3.3 for Arm B.

- Disease assessments or imaging scans performed as part of routine clinical management are acceptable for use as the screening imaging scan if they are of diagnostic quality and performed within the imaging window of ≤28 days prior to randomization.
- Most laboratory tests are to be performed within 14 days prior to randomization. Hepatitis/HIV testing may be performed up to 28 days, and ACTH and cortisol testing may be performed up to 42 days prior to randomization.
- Imaging studies are to be performed within 28 days prior to randomization.
- Evaluation of ECOG is to be performed within 14 days prior to randomization.
- For women of reproductive potential, a urine or serum pregnancy test will be performed within 24 hours prior to the first dose of study intervention. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).
- Tumor tissue submitted from a TURBT performed within 60 days (+14 days) prior to enrollment (providing documented informed consent).
- Ophthalmologic assessment for all participants is required at screening. Prior ophthalmologic examination performed within 3 months of enrollment is acceptable provided symptoms are not new since the examination.

Participants may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the corresponding inclusion/exclusion criteria is met. Participants who are rescreened will retain their original screening number.

8.12.2 Treatment Period

Visit requirements are outlined in the SoA (Section 1.3), Sections 1.3.1 and 1.3.2 for Arms A and C, and Section 1.3.3 for Arm B. Specific procedure-related details are provided in Section 8.1.

8.12.3 Discontinued Participants Continuing to be Monitored in the Study

The investigator or qualified designee should clarify what a participant is withdrawing from, ie, treatment, follow-up visits and/or contact. Given the importance of EFS and OS in this study, efforts should be made to clarify if participants are willing to continue with efficacy assessments (if the EFS endpoint has not yet been met) and be followed for survival and/or whether review of public records is acceptable.

8.12.4 Posttreatment Visit

The Discontinuation Visit should occur at the time study treatment is discontinued for any reason (Section 1.3.2 for Arms A and C). If the Discontinuation Visit occurs ≥30 days after the last dose of study treatment, the Safety Follow-up Visit is not required. Additional details regarding participant treatment discontinuation can be found in Section 7.1.

8.12.5 Safety Follow-Up Visit

The mandatory Safety Follow-up Visit should be conducted approximately 30 days after cessation of study intervention or before the initiation of a new anticancer treatment, whichever comes first. See Section 1.3.2 for Arms A and C and Section 1.3.3 for Arm B).

8.12.5.1 Follow-Up Visits

Participants who discontinue study intervention for a reason other than disease progression and/or recurrence will move into the Follow-up Phase and should be assessed to monitor disease status (Section 1.3.4 for Arms A, B, and C). Every effort should be made to collect information regarding disease status until disease progression and/or recurrence, death, withdrawal of consent or end of study, whichever occurs first. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated.

Note: Participants who have started a new anticancer treatment after RC + PNLD will continue imaging assessments, as long as no EFS event is observed, at the posttreatment follow-up visits.

8.12.5.2 Survival Follow-Up

Participants who experience disease progression and/or recurrence will move into the Survival Follow-up Phase and should be contacted approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first (Section 1.3.4 for Arms A, B, and C). The first Survival Follow-up contact should be scheduled as described below:

- For participants who discontinue treatment intervention and who will not enter the Efficacy Follow-up Phase, the first Survival Follow-up contact will be scheduled 12 weeks after the Discontinuation Visit and/or Safety Follow-up Visit (whichever is last).
- For participants who completed assessments in the Efficacy Follow-up Phase, the first Survival Follow-up contact will be scheduled 12 weeks after the last efficacy assessment follow-up visit has been performed.

8.12.6 Survival Status

To ensure current and complete survival data is available at the time of interim analyses and database lock, updated survival status may be requested during the course of the study by the Sponsor. For example, updated survival status may be requested prior to, but not limited to an external Data Monitoring Committee (eDMC) review, interim and/or final analysis. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a previously recorded death event in the collection tool).

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but prior to the conduct of any analysis, will be documented in a supplemental Statistical Analysis Plan (sSAP) and referenced in the Clinical Study Report (CSR) for the study. A separate biomarker analysis plan will be provided. Post hoc exploratory analyses will be clearly identified in the CSR. The PRO analysis plan will be included in the sSAP.

9.1 Statistical Analysis Plan Summary

Key elements of the SAP are summarized below; the comprehensive plan is provided in Section 9.2 through Section 9.12.

Study Design Overview	A Randomized Phase 3 Study Evaluating Cystectomy with Perioperative Pembrolizumab and Cystectomy with Perioperative Enfortumab Vedotin and Pembrolizumab versus Cystectomy Alone in Participants who are Cisplatin-Ineligible or Decline Cisplatin with Muscle-Invasive Bladder Cancer (KEYNOTE-905/EV-303)
Treatment Assignment	At the time of Amendment 10, the study completed enrollment, with 595 participants randomized in 2 stages as follows: 1. Stage 1, ~168 participants are randomized in a 1:1 ratio under Arm A and Arm B, followed by 2. Stage 2, participants are randomized in a 1:1:1 ratio under Arm A, Arm B and Arm C. After implementation of Amendment 8, enrollment of Arm A stops (except France), and participants are randomized in a 1:1 ratio under Arm B and Arm C. A total of ~427 participants are randomized in Stage 2 under Arm A, Arm B and Arm C. A total of ~344 participants are randomized in Stage 2 in a 1:1 ratio under Arm B and Arm C. The 2 stages of randomization are designed to be sequential and seamless. (Arm A) Perioperative pembrolizumab in combination with RC + PLND (Arm B) RC + PLND followed by observation (Arm C) Perioperative EV in combination with pembrolizumab + RC + PLND Stratification factors are as follows: 1) Cisplatin eligibility (cisplatin-ineligible vs cisplatin-eligible but decline) 2) Tumor Stage (T2N0 vs T3/T4aN0 vs T1-4aN1) 3) Geographic regions (United States [US] vs European Union [EU] vs Most of World [MOW]) This study will be conducted as an unblinded, open-label study.
Analysis Populations	• Efficacy: Intention-to-Treat (ITT). ITT1 consists of all participants that are randomized to Arm A and Arm B in Stage 1 and Stage 2 until Arm A enrollment stopped (ie, until the implementation of Amendment 8 except France; ~338 participants) and ITT2 consists of all participants that are randomized to Arm B and Arm C in Stage 2 (~344 participants). • Safety: All Participants as Treated (APaT), All Participants receiving Surgery (APrS)

Primary Endpoints	• Event-free survival (EFS)
Key Secondary Endpoints	• Overall survival (OS) • Pathological complete response (pCR) rate
Statistical Methods for Key Efficacy Analyses	• Treatment comparisons for time-to-event endpoints such as EFS and OS will be evaluated using a stratified log-rank test. The HR will be estimated using a stratified Cox model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier Method. • Treatment comparisons of the pCR rate will be performed using the stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985] with strata weighting by sample size. The between-treatment difference in percentages, its 95% CI and p-value will be provided.
Statistical Methods for Key Safety Analyses	For analyses in which 95% CIs will be provided for the between-treatment differences in the percentage of participants with events, these analyses will be provided using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985].
Interim and Final Analyses	Two efficacy interim analyses (IAs) and one final analysis will be performed. Results will be reviewed by an external Data Monitoring Committee (eDMC). Details are provided in Section 9.7 Interim Analyses. **Efficacy IAs:** • First Interim Analysis (IA1) o Timing: All ITT2 participants have had the opportunity for RC + PLND with pCR evaluation, and ~133 EFS events have been observed in ITT2 and ~12 months from last participant randomized o Primary Purpose: Final pCR analysis, interim EFS analysis, and interim OS analysis for comparison of Arm C versus Arm B and Arm A versus Arm B • Second Interim Analysis (IA2) o Timing: When ~173 EFS events have been observed in ITT2 o Primary Purpose: Final EFS analysis and interim OS analysis for comparison of Arm C versus Arm B and Arm A versus Arm B • Final Analysis (FA) o Timing: When ~174 OS events have been observed in ITT2 o Primary Purpose: Final OS analysis for comparison of Arm C versus Arm B and Arm A versus Arm B If all hypotheses (EFS, OS, and pCR) in ITT2 are rejected at IA1, then IA2 and FA will be performed when the targeted number of EFS (~213 EFS events) and OS (~214 OS events) events have been observed in ITT1, respectively. **Safety IAs:** An interim safety analysis will be performed and reviewed by the eDMC 6 months after the first participant is randomized. Afterwards, the eDMC will review safety data periodically in the study. Details will be specified in the DMC charter.
Multiplicity	The overall type I error rate is strongly controlled at 2.5% (1-sided) by the Hwang-Shih-DeCani [Hwang, I. K., et al 1990] group sequential methods using the graphical approach of Maurer and Bretz [Maurer, W. and Bretz, F. 2013].

Sample Size and Power	The study completed enrollment, with 595 participants randomized in 2 stages under 3 arms. The sample size for comparing Arm A versus Arm B (ITT1) is ~338, and the sample size for comparing Arm C versus Arm B (ITT2) is ~344. For Arm C versus Arm B, the study is ~93% powered to detect a HR in EFS of 0.59 with α=2.5% (one-sided). For Arm A versus Arm B, the study is ~87.7% powered to detect a HR in EFS of 0.65 with α=2.5% (one-sided) if H1, H2 and H3 are rejected. For Arm C versus Arm B, the study is ~93% powered to detect a HR in OS of 0.59 with α=2.475% (one-sided) if H1 is rejected. For Arm A versus Arm B, the study is ~87.6% powered to detect a HR in OS of 0.65 with α=2.5% (one-sided) if H1, H2, H3 and H4 are rejected. For Arm C versus Arm B, the study is ~99% powered to detect a difference in pCRR of 27% at α=0.025% (one-sided) if H1 is rejected. For Arm A versus Arm B, the study is ~87% powered to detect a difference in pCRR of 13.5% at α=2.5% (one-sided) if H1, H2, H3, H4, and H5 are rejected.

9.2 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics Department of the Sponsor. The Sponsor will generate the randomized allocation schedule(s) for study treatment assignment for this protocol, and the randomization will be implemented in IRT.

This study will be conducted as an unblinded, open-label study. Although the study is open-label, analyses or summaries generated by randomized treatment assignment or actual treatment received will be limited and documented. Further documentation will be provided in the sSAP. Central imaging and central pathology reviews will be performed on all imaging and surgical specimens, respectively.

Blinding issues related to the planned IAs are described in Section 9.7.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3 – Hypotheses, Objectives, and Endpoints.

9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed below.

9.4.1 Efficacy Endpoints

9.4.1.1 Primary Endpoint

The primary efficacy endpoint is EFS for Arm C versus Arm B comparison.

Event-Free Survival (EFS)

Event-free survival is defined as the time from randomization to the first occurrence of any of the following events:

- Radiographic disease progression precluding a curative intent surgery as assessed by BICR prior to RC+PLND.
- Failure to undergo surgery for participants with residual muscle-invasive disease and any radiographic disease present (for other participants who do not undergo surgery, see Section 8.2.3), biopsy-proven MIBC will be considered an event regardless of radiographic findings.
- Gross residual disease left behind at time of surgery (surgeon unable to complete curative intent surgery due to unresectable tumor or newly discovered metastatic disease).
- Local or distant recurrence post-RC+PLND as assessed by CT or MRI (BICR) and/or biopsy. If biopsy is not feasible due to participant safety, CT/MRI alone will be sufficient.
- Death due to any cause.

(Note: A nonurothelial second primary malignancy will not be counted as 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).

See Section 9.6.1 for the definition of censoring.

9.4.1.2 Secondary Endpoints

Event-Free Survival (EFS)

EFS (as defined in Section 9.4.1.1) for Arm A versus Arm B comparison.

Overall Survival

Overall survival is defined as the time from randomization to death due to any cause.

Pathological Complete Response Rate (pCRR)

Pathological complete response rate is defined as the proportion of participants having pCR. pCR is defined as the absence of viable tumor (pT0N0) in examined tissue from RC + PLND, as determined centrally.

Pathologic Downstaging (pDS) Rate

Pathologic downstaging rate is defined as the proportion of participants having pDS. pDS is defined as participants with <pT2 (includes pT0, pTis, pTa, pT1) and N0 in examined tissue from RC + PLND.

Disease-Free Survival (DFS)

Disease-free survival is defined as the time from post-surgery baseline scan until the first occurrence of any of the following events:

- Local or distant recurrence as assessed by CT or MRI (BICR) and/or biopsy;
- Death due to any cause.

9.4.2 Safety Endpoints

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, SAEs, fatal AEs, laboratory tests, and vital signs as described in Section 8.4. Furthermore, specific events will be collected and designated as ECIs as described in Section 8.4.7.

9.4.3 PRO Endpoints

The following key PRO endpoints will be evaluated as described in Section 4.2.1.3.

Change of PRO from baseline in:

- The total score of FACT-G
- Bl-Cys, the bladder cancer-specific subscale/symptom index
- FACT-Bl-Cys TOI
- EQ-5 D-5 L utility score
- EQ-5 D-5 L VAS
- BCI: urinary, bowel, and sexual domains

Details will be provided in the sSAP.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Population

The participants will be randomized in 2 stages as described in Section 9.9. The ITT population will serve as the analysis population for EFS, pCR, pDS, and OS. The ITT1 population will be used to compare Arm A and Arm B. ITT1 consists of all participants that are randomized to Arm A and Arm B in Stage 1 and Stage 2 from the beginning of the study until Arm A enrollment stopped, regardless of whether or not treatment was administered. The ITT2 population will be used to compare Arm C and Arm B. ITT2 consists of all participants that are randomized to Arm B and Arm C in Stage 2, regardless of whether or not treatment was administered. Any participant who receives a randomization number will be considered to have been randomized, and they will be included in the treatment group to

which they are randomized. The DFS analysis population will be those participants who are disease-free at the post-surgery baseline scan.

9.5.2 Safety Analysis Population

The safety analysis population is defined as the APaT population, which consists of all randomized participants who received at least one dose of study intervention. For Arm B participants, RC+PLND is considered as study intervention. At any interim analysis, the participants who are randomized in Arm B, but waiting for the surgery, although not treated, will be included in the safety analysis. Participants will be included in the treatment group corresponding to the study intervention they actually received for the analysis of safety data using the APaT population. This will be the treatment group to which they are randomized except for participants who receive incorrect study intervention for the entire treatment period; such participants will be included in the treatment group corresponding to the study intervention actually received. Any participant who receives the incorrect study intervention for one cycle, but receives the randomized study intervention for all other cycles, will be analyzed according to the randomized treatment group, and a narrative will be provided for any events that occur during the cycle for which the participant is incorrectly dosed.

For the analysis of perioperative complications, the APrS population will be used, which consists of all randomized participants who undergo surgery.

At least 1 laboratory or vital sign measurement obtained after randomization is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

9.5.3 Patient-reported Outcomes (PRO) Analysis Population

The PRO analyses are based on the PRO FAS population, defined as all randomized participants who have at least one PRO assessment available for the specific endpoint and have received any of the study intervention. Participants will be analyzed in the treatment group to which they are randomized.

9.6 Statistical Methods

9.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. Methods related to additional objectives addressing PROs, as well as exploratory objectives, will be described in the sSAP(s).

The stratification factors used for randomization (ie, tumor clinical stage (T2N0 vs T3/T4aN0 vs T1-T4aN1), cisplatin eligibility (cisplatin-ineligible vs cisplatin-eligible but decline) and geographic regions (US vs EU vs MOW) will be applied to all stratified analyses, in particular, the stratified log-rank test, stratified Cox model, and stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]. In the event that there are small strata, for the purpose of analysis, strata will be combined to ensure sufficient number of participants and events in each stratum. Details regarding the pooling strategy will

be prespecified in the sSAP prior to the database lock for the first analysis when each applicable endpoint will be analyzed, and decisions regarding the pooling will be based on a blinded review of participants and event counts by stratum.

Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 9.8 – Multiplicity. Nominal p-values may be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity.

9.6.1.1 Event-Free Survival (EFS)

The nonparametric Kaplan-Meier method will be used to estimate the EFS curve in each treatment group. The treatment difference in EFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, HR) between each experimental arm and the control arm. The HR and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors used for randomization (ie, tumor clinical stage (T2N0 vs T3/T4aN0 vs T1-T4aN1), cisplatin eligibility (cisplatin-ineligible vs cisplatin-eligible but decline) and geographic regions (US vs EU vs MOW) will be applied to both the stratified log-rank test and the stratified Cox model.

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 by the central imaging vendor, sensitivity analyses with a different set of censoring rules will be performed. Sensitivity analysis 1 is 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. The difference between sensitivity analyses 1 and 2 is that the usage of adjuvant nivolumab in Arm B for high-risk participants will not be considered as new anticancer therapy in sensitivity analysis 1, but will be considered as new anticancer therapy in sensitivity analysis 2.

In the primary EFS analysis, participants who refuse or are unable to undergo RC without a protocol-defined event (Table 12) will 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 (Table 12) will be counted as events. Participants who refused or were unable to undergo surgery, but without a post-screening scan will be censored at Day 1 from randomization.

The censoring rules are summarized in Table 12 and details of the sensitivity analysis will be provided in the sSAP.

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

Table 12 Censoring Rules for Primary and Sensitivity Analyses of EFS

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

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

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

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

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

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

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

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

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

9.6.1.2 Overall Survival (OS)

The nonparametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the HR) between each experimental arm and the control arm. The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for randomization (ie, tumor clinical stage (T2N0 vs T3/T4aN0 vs T1-T4aN1), cisplatin eligibility (cisplatin-ineligible vs cisplatin-eligible but decline) and geographic regions (US vs EU vs MOW) will be applied to both the stratified log-rank test and the stratified Cox model. Participants without documented death at the time of analysis will be censored at the date of the last known to be alive.

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

9.6.1.3 Pathological Complete Response Rate (pCRR)

The stratified Miettinen and Nurminen method with strata weighting by sample size will be used for the comparison of pCR rates between each experimental arm and the control arm. The difference in pCR rates and its 95% CI from the stratified Miettinen and Nurminen method with strata weighting by sample size will be reported. The stratification factors used for randomization (ie, tumor clinical stage (T2N0 vs T3/T4aN0 vs T1-T4aN1), cisplatin eligibility (cisplatin-ineligible vs cisplatin-eligible but decline) and geographic regions (US vs EU vs MOW) will be applied to the analysis.

Participants who are discontinued from the study treatment and continue with other treatment not specified by the study prior to definitive surgery will be classified as not having a pCR (nonresponders) 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 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.

9.6.1.4 Pathological Downstaging Rate (pDSR)

The stratified Miettinen and Nurminen method with strata weighting by sample size will be used for the comparison of pDS rates between each experimental arm and the control arm. The difference in pDS rates and its 95% CI from the stratified Miettinen and Nurminen method with strata weighting by sample size will be reported. The stratification factors used for randomization (ie, tumor clinical stage (T2N0 vs T3/T4aN0 vs T1-T4aN1), cisplatin eligibility (cisplatin-ineligible vs cisplatin-eligible but decline) and geographic regions (US vs EU vs MOW) will be applied to the analysis.

Participants who are discontinued from the study treatment and continue with other treatment not specified by the study prior to definitive surgery will be classified as not having a pDS in the efficacy analyses, regardless of the results obtained from the surgery. Participants who refuse or unable to undergo surgery and participants with relevant data missing are considered as not having a pDS.

9.6.1.5 Disease-Free Survival (DFS)

DFS will be summarized descriptively for each treatment arm using the Kaplan-Meier method. Only those participants who are confirmed to be disease-free at the initial post-surgery scan will be included in the analysis.

9.6.1.6 Summary of Statistical Methods for Efficacy

Table 13 summarizes the primary analysis approach for primary and key secondary efficacy endpoints. Sensitivity analysis methods are described above for each endpoint as applicable.

The strategy to address multiplicity issues with regard to multiple efficacy endpoints, multiple populations, and IAs is described in Section 9.7 – Interim Analyses and in Section 9.8 – Multiplicity.

Table 13 Analysis Strategy for Key Efficacy Endpoints

Endpoint/ Variable (Description, Time Point)	Statistical Method[a]	Analysis Population	Missing Data Approach
Primary:			
EFS	Test: stratified Log-rank test Estimation: stratified Cox model with Efron's tie handling method	ITT1 and ITT2	• Primary censoring rule • Sensitivity analysis (More details are provided in Table 12 of Section 9.6.1.1)
Key Secondary:			
OS	Test: stratified Log-rank test Estimation: stratified Cox model with Efron's tie handling method	ITT1 and ITT2	Censored at last known alive date
pCR rate	Stratified M&N method [b]	ITT1 and ITT2	Participants with relevant data missing are considered nonresponders

Abbreviations: EFS=event-free survival; ITT=intention-to-treat; M&N=Miettinen and Nurminen; OS=overall survival; pCR=pathological complete response.

[a] Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomization (ie, tumor clinical stage (T2N0 vs T3/T4aN0 vs T1-T4aN1), cisplatin eligibility (cisplatin-ineligible vs cisplatin-eligible but decline) and geographic regions (US vs EU vs MOW) will be applied to the analysis model.

[b] Miettinen and Nurminen method with strata weighting by sample size.

9.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of AEs and other relevant parameters, including laboratory tests, vital signs, and surgical complications.

The overall safety evaluation will include a summary by treatment group of the number and percentage of participants with at least one AE, drug-related AE, serious AE, serious drug-related AE, Grade 3-5 AE, drug-related Grade 3-5 AE, discontinuation from study intervention due to an AE, interruption of study intervention due to an AE, an AE leading to dose reduction, and an AE resulting in death.

The number and percentage of participants with specific AEs will also be provided. Point estimate and 95% CIs for the difference between treatment groups in the percentage of participants with specific AEs will be provided for AEs that occur in at least 10% of participants in any treatment group. The threshold of at least 10% of participants was chosen because the population enrolled in this study is in critical condition and usually experiences various AEs of similar types regardless of treatment; events reported less frequently than 10% of participants would obscure the assessment of the overall safety profile and add little to the interpretation of potentially meaningful treatment differences. In addition, difference in the percentage of participants with specific Grade 3-5 AEs (≥2% of participants in any treatment group) and SAEs (≥2% of participants in any treatment group) will also be

summarized by point estimate and 95% CI. Rainfall plots with point estimates and 95% CIs will be displayed for specific AEs, specific Grade 3-5 AEs, and specific SAEs that meet the corresponding predefined threshold rules.

CIs for between treatment group differences will be provided using the M&N method [Miettinen, O. and Nurminen, M. 1985a]. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as helpful descriptive measures for the review of the safety profile and not as a formal method for assessing the statistical significance of the between-group differences.

The number and percentage of participants with laboratory toxicity grade increased from baseline will be summarized by the post-baseline maximum toxicity grade per CTCAE V5.0 for each gradable laboratory test.

For continuous safety measures, such as changes from baseline in laboratory and vital signs, summary statistics for baseline, on treatment, and change from baseline values will be provided by treatment group in table format.

The primary approach to the analysis of the safety parameters combines both the preoperative/surgical and postoperative phases. Adverse events will also be evaluated separately in the preoperative/surgical and postoperative phases using descriptive statistics only.

Assessment of Safety Topics of Special Interest

AEs that are immune-mediated or potentially immune-mediated will be evaluated separately. These events have been characterized consistently throughout the pembrolizumab clinical development program. Point estimates and 95% CIs for between-group difference is not expected to add value to the safety evaluation, and hence only number and percentage of participants with such a pembrolizumab AEOSI will be provided, as well as the number and percentage of participants with corticosteroid administration to treat an AEOSI. Summary statistics will be provided for the analysis of time from first dose to the onset of an AEOSI.

Adverse event of special interest (AESI) for EV will be evaluated separately. AESI are medical concepts of composite terms based on the search criteria (standard MedDRA query [SMQ] or sponsor specified query [SSQ]). The search criteria for AESI will be maintained in a separate document and finalized prior to database lock for the primary analyses. Treatment-emergent AESI will be summarized by preferred term and maximum severity. In addition, serious treatment-emergent AESI; treatment-related, treatment-emergent AESI; and AESI leading to study drug dose interruption, reduction, and discontinuation will be summarized.

Table 14 summarizes the analysis strategy for safety endpoints in this study.

Table 14 Analysis Strategy for Safety Parameters

Analysis Part	Safety Endpoint	95% between-group CI (Graphical display)	Descriptive Statistics
Overall Safety Assessment	Specific Grade 3-5 AE (incidence ≥2% of participants in any treatment group)	X	X
	Specific serious AE (incidence ≥2% of participants in any treatment group)	X	X
	Specific AEs (incidence ≥10% of participants in any treatment group)	X	X
	Any AE		X
	Any Grade 3-5 AE		X
	Any Serious AE		X
	Any Drug-Related AE		X
	Any Serious and Drug-Related AE		X
	Any Grade 3-5 and Drug-Related AE		X
	Discontinuation of study treatment due to AE		X
	Interruption of study treatment due to AE		X
	AE that resulted in dose reduction		X
	AE that resulted in death		X
	Specific AEs, SOCs (incidence > 0% of participants in all of the treatment groups)		X
	Laboratory toxicity grade increase from baseline		X
	Change from baseline results (vital signs)		X
Assessment of safety topics of special interest	Pembrolizumab AEOSI		X
	EV AESI		X

9.6.3 Statistical Methods for Patient-Reported Outcome Analyses

Details of PRO analyses will be described in the sSAP.

9.6.4 Summaries of Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized, and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables (eg, age, race, etc,), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

9.7 Interim Analyses

The eDMC will serve as the primary reviewer of the results of the IAs and will make recommendations for discontinuation of the study or modification to an Executive Oversight Committee (EOC) of the Sponsor. Depending on the recommendation of the eDMC, the Sponsor may prepare a regulatory submission.

If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, this EOC may be unblinded to study results at the treatment level in order to act on these recommendations or facilitate regulatory filing. Limited additional Sponsor personnel may also be unblinded to the treatment-level results of the interim analysis(es), if required, in order to act on the recommendations of the eDMC or facilitate regulatory filing. The extent to which individuals are unblinded with respect to results of IAs will be documented. Additional logistical details, revisions to the above plan and data monitoring guidance will be provided in the eDMC Charter.

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

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

9.7.1 Efficacy Interim Analyses

Two efficacy IAs are planned in addition to the final analysis for this study. Results of the IAs will be reviewed by an eDMC. If the EFS null hypotheses are rejected prior to the final analysis, the eDMC may recommend stopping the study early for EFS follow-up; however, in this case OS follow-up would continue. This study is not planned to be stopped for futility. Therefore, no futility bound is provided. Details on how the above planned analyses are incorporated into establishing statistical significance and the boundaries with regard to efficacy are discussed further in Section 9.8 – Multiplicity.

At the time of an analysis, the observed number of events may differ substantially from the expected. To avoid overspending at an interim analysis and leave reasonable alpha for the final analysis, the minimum α spending strategy will be adopted. At the IA, the information fraction used in Hwang-Shih-DeCani (HSD) spending function to determine the alpha spending at the IA will be based on the minimum of the expected information fraction and the actual information fraction at each analysis. Specifically,

- In the scenario that the events accrue slower than expected and the observed number of events is less than the expected number of events at a given analysis, the information fraction will be calculated as the observed number of events at the interim analysis over the target number of events at FA.

- In the scenario that the events accrue faster than expected and the observed number of events exceeds the expected number of events at a given analysis, then the information fraction will be calculated as the expected number of events at the interim analysis over the target number of events at FA.

The FA will use the remaining Type I error that has not been spent at the earlier analyses. The event counts for all analyses will be used to compute correlations. The planned analyses, endpoints evaluated, and drivers of the timing are summarized in Table 15.

If all hypotheses (EFS, OS and pCR) in ITT2 are rejected at IA1, then IA2 and FA will be performed when the targeted number of EFS (~213 events) and OS (~214 events) events have been observed in ITT1, respectively.

Following Amendment 12, all future analyses (including FA) in ITT2 will be descriptive without multiplicity adjustment, since the study hypotheses tests in ITT2 were significant for EFS, OS, and pCR at the first interim analysis (IA1) with a data cutoff of 06-JUN-2025. IA1 is the final analysis for hypothesis testing for EFS, OS, and pCR in ITT2. If the final targeted number of OS events cannot be reached by end of year 4 after last participant was randomized, the Sponsor will conduct the FA approximately 4 years after last participant randomized at the latest.

Table 15 Analyses Planned, Endpoints Evaluated, and Drivers of Timing

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

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

If all hypotheses (EFS, OS and pCR) in ITT2 are rejected at IA1, then IA2 and FA will be performed when the targeted number of EFS (~213 EFS events) and OS (~214 OS events) events have been observed in ITT1, respectively.

Note that if all hypotheses in ITT2 are rejected at IA1, and EFS in ITT1 is statistically significant at IA2 and corresponding information fraction of OS in ITT1 is ~97% or greater, IA2 will also be the final OS analysis in ITT1.

Note that if all hypotheses in ITT2 are rejected at IA1 and the final targeted number of EFS or OS events are not reached in ITT1 by end of year 4 after last ITT2 participant was randomized, the Sponsor will conduct the final analysis approximately 4 years after last ITT2 participant randomized at the latest.

9.7.2 Safety Interim Analyses

The DMC will be responsible for periodic interim safety reviews as specified in the DMC charter. An interim safety analysis will be performed 6 months since first participant is randomized. Afterwards, the eDMC will review safety data periodically in the study. Interim safety analyses will also be performed at the time of interim efficacy analyses. Details will be specified in the DMC charter.

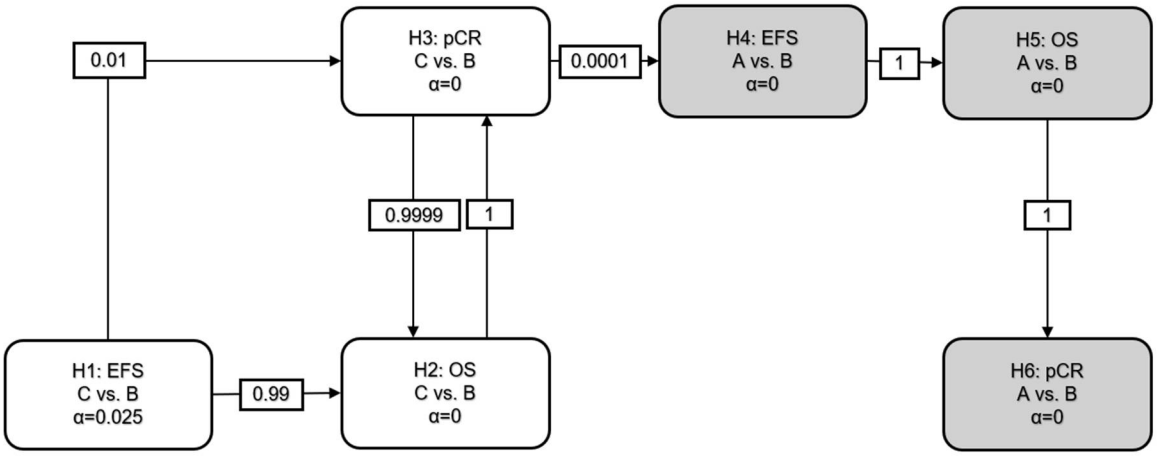
9.8 Multiplicity

The study uses the method of Maurer and Bretz [Maurer, W. and Bretz, F. 2013] to provide strong multiplicity control for multiple hypotheses as well as IAs [Miettinen, O. and Nurminen, M. 1985]. According to this approach, study hypotheses may be tested more than once, and when a particular null hypothesis is rejected, the α allocated to that hypothesis can be reallocated to other hypothesis tests.

Figure 3 shows the initial 1-sided α allocation and transition strategy for each hypothesis. Initially, all of the α=0.025 is allocated to the primary endpoint H1. When H1 is rejected, 99% of the α (=0.02475) is reallocated to H2, 1% of the α (=0.00025) is reallocated to H3. H2 and H3 will only have a chance to be tested when H1 is rejected. When H3 is rejected, 99.99% of its α will be recycled to H2. When H2 is rejected, all of its α is reallocated to H3. When H2 and H3 are both rejected, all of their α is reallocated to H4. H4 will only have a chance to be tested when H3 is rejected. When H4 is rejected, all of its α is reallocated to H5. H5 will only have a chance to be tested when H4 is rejected. When H5 is rejected, all of its reallocated to H6. H6 will only have a chance to be tested when H5 is rejected..

The weights for reallocation from each hypothesis to the others are represented in the small boxes on the arrows connecting hypotheses, and the directions of reallocation are represented by the arrows. This is further explained in Section 9.8.1.

Figure 3 Multiplicity Graph for Type I Error Control of Study Hypotheses



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

9.8.1 Multiplicity Control for Efficacy Interim Analyses

Following Amendment 12, all future analyses (including FA) in ITT2 will be descriptive without multiplicity adjustment, since the study hypotheses tests in ITT2 were significant for EFS, OS, and pCR at the first interim analysis (IA1) with a data cutoff of 06-JUN-2025. IA1 is the FA for hypothesis testing for EFS, OS and pCR in ITT2.

9.8.1.1 Event-Free Survival (EFS)

For Arm C versus Arm B, the study initially allocates all α=2.5% to H1. For Arm A versus Arm B, the study initially allocates α=0 to H4. If the null hypotheses for H1, H2 and H3 are all rejected, α=2.5% is reallocated to H4. Table 16 and Table 17 show the boundary properties for the planned interim and final analyses of EFS, derived using an HSD α-spending function with γ=-4. Note that the final row indicates the total power to reject the null hypothesis for EFS at the α level. If the actual number of EFS events at the IAs differ from those specified in the tables, the bounds will be adjusted using the HSD α-spending function as described in Section 9.7.1. More details will be discussed in the sSAP.

Note that if all hypotheses in ITT2 are rejected at IA1, then IA2 will be performed when the final targeted number of EFS events in ITT1 have been observed. If the final targeted number of EFS events in ITT1 cannot be reached by end of year 4 after last ITT2 participant was randomized, the Sponsor will conduct the analysis approximately 4 years after last ITT2 participant randomized at the latest. In this situation, all of the remaining available alpha by then will be used in the final EFS analysis (ie, IA2) in ITT1.

Table 16 Boundary Properties for Planned Analyses of EFS Based on Potential α-Levels to be Used for Testing (H1, Arm C vs Arm B)

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

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

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

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

[c] p (1-sided) is the α for testing

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

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

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

Table 17 Boundary Properties for Planned Analyses of EFS Based on Potential α-Levels to be Used for Testing (H4, Arm A vs Arm B)

Analysis	Value	α=2.5%
IA1: 89%[a]	Z	2.1396
N: 338	p (1-sided) [b]	0.0162
Events: 190	HR at bound [c]	0.7331
Month: 69	P(Cross) if HR=1[d]	0.0162
	P(Cross) if HR=0.65[e]	0.7979
IA2: 100%[a]	Z	2.0279
N:338	p (1-sided) [b]	0.0213
Events: 213	HR at bound [c]	0.7571
Month: 81	P(Cross) if HR=1[d]	0.0250
	P(Cross) if HR=0.65[e]	0.8770

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

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

[b] p (1-sided) is the α for testing

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

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

[e] P(Cross if HR=0.65) is the probability of crossing a bound under the alternative hypothesis

9.8.1.2 Overall Survival (OS)

No α has been initially allocated to test OS. For Arm C versus Arm B, if the null hypothesis for H1 is rejected, α=2.475% is reallocated to H2. If the null hypotheses for H1 and H3 are rejected, almost the full α of 2.5% is reallocated to H2. For Arm A versus Arm B, if the null hypotheses for H1, H2, H3, and H4 are rejected, α=2.5% is reallocated to H5. Table 18 and Table 19 show the boundary properties for the planned interim and final analyses of OS in different populations and different comparison groups derived using an HSD α-spending function with γ=-4. Note that the final row indicates the total power to reject the null hypothesis for OS at each α level. If the actual number of OS events at the IAs differ from those specified in the tables, the bounds will be adjusted using the HSD α-spending function as described in Section 9.7.1. More details will be provided in the sSAP.

Note that if all hypotheses in ITT2 are rejected at IA1, EFS in ITT1 is statistically significant at IA2 and corresponding information fraction of OS in ITT1 is ~97% or greater, IA2 will also be the final OS analysis in ITT1. In this situation, all of the remaining available alpha by then will be used in the final OS analysis in ITT1.

Note that if the final targeted number of OS events in ITT1 cannot be reached by end of year 4 after last ITT2 participant was randomized, the Sponsor will conduct the analysis approximately 4 years after last ITT2 participant randomized at the latest. In this situation, all of the remaining available alpha by then will be used in the final OS analysis (ie, FA) in ITT1.

Table 18 Boundary Properties for Planned Analyses of OS Based on Potential α-Levels to be Used for Testing (H2, Arm C vs Arm B)

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

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

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

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

[c] p (1-sided) is the α for testing

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

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

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

Table 19 Boundary Properties for Planned Analyses of OS Based on Potential α-Levels to be Used for Testing (H5, Arm A vs Arm B)

Analysis	**Value**	**α=2.5%**
IA1: 79%[a]	Z	2.3074
N: 338	p (1-sided)[b]	0.0105
Events: 169	HR at bound[c]	0.7009
Month: 69	P(Cross) if HR=1[d]	0.0105
	P(Cross) if HR=0.65[e]	0.6892
IA2: 91%[a]	Z	2.1850
N: 338	p (1-sided)[b]	0.0144
Events: 195	HR at bound[c]	0.7310
Month: 81	P(Cross) if HR=1[d]	0.0174
	P(Cross) if HR=0.65[e]	0.8073
Final: 100%[a]	Z	2.0492
N: 338	p (1-sided)[b]	0.0202
Events: 214	HR at bound[c]	0.7554
Month: 92	P(Cross) if HR=1[d]	0.0250
	P(Cross) if HR=0.65[e]	0.8760

Abbreviations: H=hypothesis; HR=hazard ratio; IA=interim analysis; OS=overall survival.

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

[b] p (1-sided) is the α for testing

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

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

[e] P(Cross if HR=0.65) is the probability of crossing a bound is shown under the alternative hypothesis

9.8.1.3 Pathological Complete Response Rate (pCRR)

For Arm C versus Arm B, the study initially allocates α=0 to H3. If the null hypothesis for H1 is rejected, α=0.025% is reallocated to H3. If the null hypotheses for H1 and H2 are both rejected, α=2.5% is reallocated to H3. Only data from IA1 will be used to test the pCRR. However, if the test does not reach statistical significance at IA1, the p-value from IA1 can be compared to an updated α-level if the null hypothesis for OS in H2 is rejected at a later time.

For Arm A versus Arm B, the study initially allocates α=0 to H6. If the null hypotheses for H1, H2, H3, H4 and H5 are all rejected, α=2.5% is reallocated to H6. Similarly, only data from IA1 will be used to test the pCRR.

The sample size is ~338 and ~344 for Arm A + Arm B and Arm C + Arm B. The pCRR based on the ITT population in Arm A, Arm B, and Arm C are assumed as 27%, 13.5%, 40.5%, respectively, taking into account 10% participants with no disease who did not undergo surgery. Testing powers as well as the approximate treatment difference required to reach the bound (ΔpCRR) are shown in Table 20 and Table 21.

Table 20 Possible α-Levels and Approximate pCRR Difference Required to Demonstrate Efficacy for pCRR (H3, Arm C vs Arm B)

α	~Δ pCRR	Power (ΔpCRR=0.27)
0.00025	0.1666	0.988
0.025	0.0938	0.999

Abbreviations: H=hypothesis; pCRR=pathological complete response rate; RC + PLND=radical cystectomy + pelvic lymph node dissection.

Assumes a 10% dropout rate from participants with no disease who refuse surgery from a total of 344 participants.

Assumes enrollment is complete with all participants having had the opportunity for RC + PLND with pCRR evaluation

The assumption for pCRR in Arm B is 13.5%

Table 21 Possible α-Levels and Approximate pCRR Difference Required to Demonstrate Efficacy for pCRR (H6, Arm A vs Arm B)

α	~Δ pCRR	Power (ΔpCRR=0.135)
0.025	0.0857	0.874

Abbreviations: H=hypothesis; pCRR=pathological complete response rate; RC + PLND=radical cystectomy + pelvic lymph node dissection.

Assumes a 10% dropout rate from participants with no disease who refuse surgery from a total of 338 participants.
Assumes enrollment is complete with all participants having had the opportunity for RC + PLND with pCRR evaluation

The assumption for pCRR in Arm B is 13.5%

9.8.2 Multiplicity Control for Safety Interim Analyses

The eDMC has responsibility for assessment of overall risk: benefit. When prompted by safety concerns, the eDMC can request corresponding efficacy data. The eDMC review of efficacy data to assess the overall risk: benefit to study participants will not require a multiplicity adjustment typically associated with a planned efficacy IA. However, to account for any multiplicity concerns raised by the eDMC review of unplanned efficacy data when prompted by safety concerns, a sensitivity analysis for pCRR, EFS, and OS adopting a conservative multiplicity adjustment will be prespecified in the sSAP.

9.9 Sample Size and Power Calculations

The study is event-driven. The study has completed enrollment and 595 participants have been randomized in 2 stages as follows:

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

Approximately 427 participants were randomized in Stage 2 under Arm A, Arm B, and Arm C. This included ~85 participants in each arm before enrollment in Arm A stopped with the implementation of Amendment 8 (except France). After enrollment in Arm A stopped, Stage 2 continued in a 1:1 ratio under Arm B and Arm C with ~86 participants in each arm. The enrollment of Stage 2 stopped when ~344 total participants were randomized under Arm B and Arm C, and this was not impacted by when enrollment in Arm A stopped or by the number of participants enrolled in Arm A.

The 2 stages of randomization are designed to be sequential and seamless. The time to stop Arm A enrollment in Stage 2 depends on the time of implementation of Amendment 8, but not on number of participants randomized. For analysis comparing Arm A and Arm B, all participants who are randomized in Stage 1 and Stage 2 before Arm A enrollment stop will be included, which will consist of ~168 participants randomized in Stage 1 and ~170 participants randomized in Arm A and Arm B in Stage 2. The sample size for Arm A and Arm B prior to Amendment 8 implementation (except France) is ~338. For analysis comparing Arm C and Arm B, all participants who are randomized in Stage 2 will be included, which is ~344 participants. The total study sample size is 595.

For Arm C versus Arm B, for the EFS endpoint based on 344 participants and a target number of 173 events and 1 IA at ~77% of the target number of events, the study has ~93% power to detect a HR of 0.59 at an overall α level of 2.5% (1 sided) within a group sequential setting.

For Arm A versus Arm B, for the EFS endpoint based on 338 participants and a target number of 213 events and 1 IA at ~89% of the target number of events, the study has ~87.7% power to detect a HR of 0.65 at an overall α level of 2.5% (1 sided) within a group sequential setting.

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

For Arm A versus Arm B, for the OS based on 338 participants and a target number of 214 events and 2 IAs at ~79%, and 91% of the target number of events, the study has ~87.6% power to detect a HR of 0.65 at an overall α level of 2.5% (1 sided) within a group sequential setting.

For Arm C versus Arm B, based on 344 participants, the study has ~99% power to detect a treatment difference of 27 percentage points assuming an underlying pCRR of 13.5% in the RC + PLND + observation arm at an overall α level of 0.025% (1-sided) by taking into account 10% participants without disease who do not undergo surgery.

For Arm A versus Arm B, based on 338 participants, the study has ~87% power to detect a treatment difference of 13.5 percentage points assuming an underlying pCRR of 13.5% in the RC + PLND + observation arm at an overall α level of 2.5% (1-sided) by taking into account 10% participants without disease who do not undergo surgery.

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

- EFS follows an exponential distribution with a median of 27 months for the control group.
- OS follows an exponential distribution with a median of 37 months for the control group.
- Enrollment period of 20 months with constant enrollment rate of ~9 participants per month for Stage 1, 27 months with constant enrollment rate of ~9 participants per month for Stage 2 before the implementation of Amendment 8, and 15 months with constant enrollment rate of ~12 participants per month for Stage 2 after the implementation of Amendment 8.
- A yearly dropout rate of 5.0% for EFS and 1% for OS.

The median EFS and OS assumptions for the control arm are estimated to approximate the outcomes for the target population from a comprehensive review of the literature, including data from randomized, controlled trials in MIBC, large real-world datasets, and newly described cohorts of cisplatin-ineligible patients undergoing radical cystectomy [Grossman, H. B., et al 2003] [Pfister, C., et al 2024] [Li, R., et al 2024] [Fischer-Valuck, B. W., et al 2018].

The sample size and power calculation were performed using gsDesign.

9.10 Subgroup Analyses

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

- Cisplatin eligibility (cisplatin-ineligible vs cisplatin-eligible but decline)
- Tumor Stage (T2N0 vs T3/T4aN0 vs T1-4aN1)
- Geographical regions (US vs EU vs MOW)
- PD-L1 (CPS ≥10 versus CPS <10)
- Age category (<65 vs ≥65 years)
- Sex (female vs male)
- Race (White vs all others)
- Smoking status (never vs former vs current)

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

9.11 Compliance (Medication Adherence)

Drug accountability data for study treatment will be collected during the study. Any deviation from protocol-directed administration will be reported.

9.12 Extent of Exposure

The extent of exposure will be summarized as duration of treatment in cycles. Summary statistics will be provided on Extent of Exposure for the APaT population.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

I. Introduction

A. Purpose

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD), through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to conducting these trials in compliance with the highest ethical and scientific standards. Trial conduct includes processes from design to reporting, including planning, initiating, performing, recording, oversight, evaluation, analysis and reporting activities as appropriate. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with MSD's global standards, local and/or national regulations (including all applicable data protection laws and regulations), Regulation (EU) 536/2014, the International Council for Harmonisation Good Clinical Practice (ICH GCP) E6 and ICH General Considerations for Clinical Studies E8, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (eg, contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy, and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (ie, participant population, duration, statistical power, randomization, and blinding) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. Input may be considered from a broad range of

stakeholders, including patient advocacy groups/patients representing the trial population, caregivers, and health care providers to ensure operational feasibility. The use of innovative digital health technologies will be considered. Factors critical to the quality of the trial should also be identified. These factors are attributes of a trial that are fundamental to the protection of participants, the reliability and interpretability of the trial results and the decisions made based on those trial results. Risks to critical to quality factors should be managed prospectively and adjusted when new or unanticipated issues arise once the trial has begun. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease-related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial. Individuals involved in trial conduct receive training commensurate with their role prior to their becoming involved in the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source records according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the prespecified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are

intended to be hypothesis generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations and ICH Guidelines. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Informed consents include relevant aspects of the trial, such as trial design, anticipated benefits and risks of medical intervention(s), trial setting, and the potential use of technology. Trial designs include procedures and systems for the identification, monitoring, and reporting of safety concerns. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

During trial planning, the need for an independent Data Monitoring Committee (DMC) is assessed.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

E. Trial Results

At the time of providing informed consent and in accordance with local laws and regulations, participants should be informed about the plans for availability of trial results.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on medical record review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (eg, to scientific meetings, investigator meetings, etc) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for financial disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide their financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, frequently known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The Sponsor has EU-approved Binding Corporate Rules since 2017, covering all aspects of its Global Privacy Program (Corporate Policy 20), and is self-certified pursuant to the EU-US Data Privacy Framework.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee, affiliated institution, and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution, and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked before transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules, and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

10.1.4.1 Executive Oversight Committee

The EOC is comprised of members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the eDMC regarding the study.

10.1.4.2 External Data Monitoring Committee

To supplement the routine study monitoring outlined in this protocol, an eDMC will monitor the interim data from this study. The voting members of the committee are external to the Sponsor. The members of the eDMC must not be involved with the study in any other way (eg, they cannot be study investigators) and must have no competing interests that could affect their roles with respect to the study.

The eDMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the eDMC will review interim study results, consider the overall risk and benefit to study participants (see Section 9.7 – Interim Analyses) and recommend to the EOC if the study should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the study governance structure; and requirements for and proper documentation of eDMC reports, minutes, and recommendations will be described in the eDMC charter that is reviewed and approved by all the eDMC members.

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trials Regulation 536/2014, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu, https://euclinicaltrials.eu, or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. For studies conducted under the EMA Clinical Trials Regulation 536/2014, a summary of the study results will be submitted in compliance with the regulation**.** MSD entries are not limited to FDAAA or the EMA clinical trials Regulation 536/2014 mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials Regulation 536/2014, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol, generally accepted standards of GCP (eg, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP), and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this Appendix under the Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

For investigators located in countries with serious breach reporting requirements, investigator will promptly report to the Sponsor any serious breach or suspected serious breach that occurs in compliance with those requirements. Unless more specifically defined in the applicable requirements, a serious breach is any breach of the applicable clinical trial regulation or of the clinical trial protocol which is likely to affect to a significant degree: (i) the safety or rights of a trial participant, or (ii) the reliability and robustness of the data generated in the clinical trial.

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding data management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period (eg, EU CTR: 25 years after the end of the study). No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 Study and Site Closure

The Sponsor or its designee may stop the study or study-site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

All laboratory tests will be performed by a central laboratory. Prior to study treatment administration, specific laboratory tests may be performed locally as clinically indicated per investigator assessment, in parallel to central laboratory testing, if necessary, to ensure participant's safety prior to treatment. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of study treatment.

- Treatment decisions may be made based on local laboratory results.
- However, if local laboratory tests are used, it is important that the samples for central analysis be obtained in parallel.
- Additionally, if the local laboratory results significantly disagree with those results obtained from the central laboratory and that a patient management decision was made based on local laboratory value(s), then the value(s) supporting the patient management decision are required to be entered in the relevant eCRF, as applicable.
- The tests detailed in Table 22 will be performed by the central laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 22 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Coagulation	PT/INR and aPTT or PTT: If on anticoagulant, test coagulation as clinically indicated. PTT may be performed if laboratory cannot perform aPTT.			
Chemistry	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate	Chloride	Phosphorus
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (nonfasting) HbA1C	Calcium	Alkaline phosphatase	
Finger stick glucose	To be performed prior to each dose of EV for participants in Arm C. If nonfasting serum glucose is collected and reviewed on the day of EV dosing, a nonfasting finger stick glucose is not required			
Endocrine	TSH, T3 (preferably total T3), T4, ACTH, cortisol			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Pregnancy Testing	• Urine hCG pregnancy test (as needed for WOCBP) Note: Urine pregnancy tests will be performed by the local laboratory. If the urine test result is positive or inconclusive, serum samples will be submitted to the central laboratory.			
Other Screening Tests	• FSH (as needed in WONCBP only) • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus [defined as detectable HCV RNA via qualitative nucleic acid testing])			
NOTES: If available as SOC in your region. The carbon dioxide may be either a measurement of CO_2 or bicarbonate as an electrolyte. BUN Blood urea nitrogen is preferred; if not available urea may be used.				

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic intentional, excessive use of a medicinal product for a perceived psychological or physiological reward or desired nontherapeutic effect.

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- Note: For purposes of AE definition, study intervention includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol-specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death
b. Is life-threatening
   - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization
   - Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. Results in persistent or significant disability/incapacity
   - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
   - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect
   - In offspring of participant taking the product regardless of time to diagnosis.

f. Other important medical events
   - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
   - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.4 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same time frame as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a new cancer (that is not the cancer under study)

  Note: Pathologically insignificant prostate cancer (organ confined disease with Gleason score 7 [3+4] or less) incidentally found at the time of radical cystoprostatectomy will be reported as a non-serious adverse event.
- Is associated with an overdose

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.
  - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
  - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
  - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
  - Grade 4: Life-threatening consequences; urgent intervention indicated.
  - Grade 5: Death related to AE.

Assessment of causality

- Did the study intervention cause the adverse event?
- The determination of the likelihood that the study intervention caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the adverse event based upon the available information.
- **The following components are to be used to assess the relationship between the study intervention and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the adverse event:
  - **Exposure:** Is there evidence that the participant was actually exposed to the study intervention such as: reliable history, acceptable compliance assessment (pill count, diary, etc,), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the study intervention? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
  - **Dechallenge:** Was the study intervention discontinued or dose/exposure/frequency reduced?
    - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
    - If no, this is a negative dechallenge.

      (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the study intervention; (3) the trial is a single-dose drug trial); or (4) study intervention(s) is/are only used one time.)

  - **Rechallenge:** Was the participant re-exposed to the study intervention in this trial?
    - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
    - If no, this is a negative rechallenge.

      (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) study intervention(s) is/are used only one time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE STUDY INTERVENTION, OR IF RE-EXPOSURE TO THE STUDY INTERVENTION POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.

- **Consistency with Study Treatment Profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the study intervention or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a study intervention relationship).
  - Yes, there is a reasonable possibility of study intervention relationship:
    - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.
  - No, there is not a reasonable possibility of study intervention relationship:
    - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each adverse event causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the adverse event to the single agent.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.6 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
  - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure email of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Medical Device and Drug–Device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  For individuals with permanent infertility due to an alternate medical cause other than the above (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.
  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraceptive Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
Progestogen-only subdermal contraceptive implant[b,c] IUS[c] Nonhormonal IUD Bilateral tubal occlusion
Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Sexual Abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. b If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. c IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

Not applicable.

10.7 Appendix 7: Country-specific Requirements

10.7.1 UK-Specific Requirements

The UK has country-specific requirements for the protocol, which are summarized below.

Section 1.3 – Schedule of Activities

In addition to the assessments and procedures indicated in Section 1.3 – Schedule of Activities, participants in the UK should have the following procedures/assessments performed (Table 23 for Arms A and C and Table 24 for Arm B):

Table 23 UK-Specific Schedule of Activities – Arms A and C

Study Period	Screening Phase	Preoperative / Operative Phase		Postoperative Phase	Follow-up Phase		Notes
		Neoadjuvant Treatment	Post-surgery Follow-up	Adjuvant Treatment	End-of-Treatment/ Discontinuation (DC)	Safety Follow-up Visit	
Cycle/Visit Title	Screening	N1 to N3	Week 16	A1 to A14			
Cycle Day		1	4 Weeks post-surgery	1	At time of DC	30 days post last dose	
Scheduling Window (Days)	-42 to -1	±3	±7	±3		+14	
Laboratory Procedures							
Urine or Serum hCG Pregnancy Test (WOCBP only), per local SOP	X	X	X	X	X	X	Required at screening. Required at ≤24 hours prior to first treatment dose (C1D1). Required ≤72 hours prior to start of each subsequent treatment cycles. Ongoing pregnancy testing should be conducted where applicable at the intervals specified. This testing will be N/A for many participants as standard RC+PLND surgery includes removal of the uterus. If urine pregnancy test is required and cannot be confirmed as negative, a serum pregnancy test is required.
HIV Testing	X						
Hepatitis B and C Testing	X						

Table 24 UK-Specific Schedule of Activities – Arm B

Study Period	Screening Phase	Presurgery/Surgical Phase		Post-surgery	Notes
Visit Title	Screening	Presurgery	Surgery	Safety Follow-up Visit	
Week		≤2 weeks prior to surgery	≤8 weeks post-randomization	30 days post study intervention (surgery)	
Scheduling Window (Days)	-42 to -1	±7	±7	+14	
Laboratory Procedures					
Urine or Serum hCG Pregnancy Test (WOCBP only), per local SOP	X			X	Required at screening and Safety Follow-up Visit. Ongoing pregnancy testing should be conducted where applicable at the intervals specified. This testing will be N/A for many participants as standard RC+PLND surgery includes removal of the uterus. If urine pregnancy test is required and cannot be confirmed as negative, a serum pregnancy test is required.
HIV Testing	X				
Hepatitis B and C Testing	X				

Section 5.2 – Exclusion Criteria

For Exclusion Criterion #19 (HIV infection) and #20 (hepatitis B and hepatitis C infection), testing for HIV, hepatitis B, and hepatitis C must be performed in the UK during screening to determine a participant's eligibility for the study.

Section 6.5 – Concomitant Therapy

In addition to all restrictions on concomitant medications listed in Section 6.5 – Concomitant Therapy, the following restriction applies to participants in the UK:

- Live vaccines within 30 days prior to the first dose of study treatment, while receiving study treatment, and for 90 days after the last dose of study treatment, are prohibited.

Section 8.3.4.2 – Pregnancy Testing

Repeated pregnancy test should be conducted as described above.

10.7.2 Germany-Specific Requirements

Germany has country-specific requirements for the protocol, which are summarized below.

Section 1.3 – Schedule of Activities

In addition to the assessments and procedures indicated in Section 1.3 – Schedule of Activities, participants in Germany should have the following procedures/assessments performed (Table 25 for Arms A and C and Table 26 for Arm B):

Table 25 Germany-Specific Schedule of Activities – Arms A and C

Study Period	Screening Phase	Preoperative / Operative Phase		Postoperative Phase	Follow-up Phase		Notes
		Neoadjuvant Treatment	Post-surgery Follow-up	Adjuvant Treatment	End-of-Treatment/ Discontinuation (DC)	Safety Follow-up Visit	
Cycle/Visit Title	Screening	N1 to N3	Week 16	A1 to A14			
Cycle Day		1	4 Weeks post-surgery	1	At time of DC	30 days post last dose	
Scheduling Window (Days)	-42 to -1	±3	±7	±3		+14	
Laboratory Procedures							
Urine or Serum hCG Pregnancy Test (WOCBP only), per local SOP	X	X	X	X	X	X	Required at screening. Required at ≤24 hours prior to first treatment dose (C1D1). Required ≤72 hours prior to start of each subsequent treatment cycles. Ongoing pregnancy testing should be conducted where applicable at the intervals specified. This testing will be N/A for many participants as standard RC+PLND surgery includes removal of the uterus. If urine pregnancy test is required and cannot be confirmed as negative, a serum pregnancy test is required.
HIV Testing	X						
Hepatitis B and C Testing	X						
Lipase & Amylase	X	←----------As Clinically Indicated----------→					

Table 26 Germany-Specific Schedule of Activities – Arm B

Study Period	Screening Phase	Presurgery/Surgical Phase		Post-surgery	Notes
Visit Title	Screening	Presurgery	Surgery	Safety Follow-up Visit	
Week		≤2 weeks prior to surgery	≤8 weeks post-randomization	30 days post study intervention (surgery)	
Scheduling Window (Days)	-42 to -1	±7	±7	+14	
Laboratory Procedures					
Urine or Serum hCG Pregnancy Test (WOCBP only), per local SOP	X			X	Required at screening and Safety Follow-up Visit. Ongoing pregnancy testing should be conducted where applicable at the intervals specified. This testing will be N/A for many participants as standard RC+PLND surgery includes removal of the uterus. If urine pregnancy test is required and cannot be confirmed as negative, a serum pregnancy test is required.
HIV Testing	X				
Hepatitis B and C Testing	X				
Lipase & Amylase	X	←----------As Clinically Indicated----------→			

Section 5.1 – Inclusion Criteria

For inclusion criterion #7 (Adequate Organ Function) testing for amylase and lipase must be performed in Germany within 14 days of randomization and results for both tests must be ≤1.5 x ULN for participant to be eligible for this study.

Section 5.2 – Exclusion Criteria

For Exclusion Criterion #13: Has known hypersensitivity (any grade) to enfortumab vedotin and/or any excipient contained in the drug formulation of enfortumab vedotin (including histidine, trehalose dihydrate, and polysorbate 20).

Section 5.2 – Exclusion Criteria

For Exclusion Criterion #19 (HIV infection) and #20 (hepatitis B and hepatitis C infection), testing for HIV, hepatitis B, and hepatitis C must be performed in Germany during screening in order to determine a participant's eligibility for the study.

Section 6.6.1 – Dose Modification

For occurrences of immune-related asymptomatic increased serum amylase or lipase, follow the pembrolizumab dose modification and toxicity management guidelines shown below:

Immune-related AEs	Toxicity Grade or Conditions (CTCAEv4.0)	Study Medication	Action Taken with Study Medication	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-Up
Asymptomatic Amylase or Lipase Increased	**Grade 3**	**Pembrolizumab**	**May continue treatment with MSD Clinical Director approval**		• Permanently discontinue if clinical signs and symptoms of pancreatitis develop (abdominal pain, nausea, vomiting). • If toxicity does not resolve within 12 weeks of last dose after an interruption, must permanently discontinue unless approved by the medical monitor to continue. • If Grade 4 lipase/amylase elevation is asymptomatic and abdominal imaging suggests no pathology, study drug administration dosing may continue with medical monitor approval.
	Grade 4	**Pembrolizumab**	**Withhold until toxicity resolves to Grade 0 to 1**		

Section 8.3.4.2 – Pregnancy Testing

Repeated pregnancy test should be conducted as described above.

Legally Acceptable Representative

In order for a participant to be eligible to participate in Germany, they must be capable of providing documented informed consent; therefore, all references to a participant's "legally acceptable representative" in the protocol are not applicable for participants in Germany.

10.7.3 Belgium-Specific Requirements

Belgium has country-specific requirements for the protocol, which are summarized below.

Section 1.3 – Schedule of Activities

In addition to the assessments and procedures indicated in Section 1.3 – Schedule of Activities, participants in Belgium should have the following procedures/assessments performed (Table 27 for Arms A and C and Table 28 for Arm B):

Table 27 Belgium-Specific Schedule of Activities – Arms A and C

Study Period	Screening Phase	Preoperative / Operative Phase		Postoperative Phase	Follow-up Phase		Notes
		Neoadjuvant Treatment	Post-surgery Follow-up	Adjuvant Treatment	End-of-Treatment/ Discontinuation (DC)	Safety Follow-up Visit	
Cycle/Visit Title	Screening	N1 to N3	Week 16	A1 to A14			
Cycle Day		1	4 Weeks post-surgery	1	At time of DC	30 days post last dose	
Scheduling Window (Days)	-42 to -1	±3	±7	±3		+14	
Laboratory Procedures							
Urine or Serum hCG Pregnancy Test (WOCBP only), per local SOP	X	X	X	X	X	X	Required at screening. Required at ≤24 hours prior to first treatment dose (C1D1). Required ≤72 hours prior to start of each subsequent treatment cycles. Ongoing pregnancy testing should be conducted where applicable at the intervals specified. This testing will be N/A for many participants as standard RC+PLND surgery includes removal of the uterus. If urine pregnancy test is required and cannot be confirmed as negative, a serum pregnancy test is required.

Table 28 Belgium-Specific Schedule of Activities – Arm B

Study Period	Screening Phase	Presurgery/Surgical Phase		Post-surgery	Notes
Visit Title	Screening	Presurgery	Surgery	Safety Follow-up Visit	
Week		≤2 weeks prior to surgery	≤8 weeks post-randomization	30 days post study intervention (surgery)	
Scheduling Window (Days)	-42 to -1	±7	±7	+14	
Laboratory Procedures					
Urine or Serum hCG Pregnancy Test (WOCBP only), per local SOP	X			X	Required at screening and Safety Follow-up Visit. Ongoing pregnancy testing should be conducted where applicable at the intervals specified. This testing will be N/A for many participants as standard RC+PLND surgery includes removal of the uterus. If urine pregnancy test is required and cannot be confirmed as negative, a serum pregnancy test is required.

Section 8.3.4.2 – Pregnancy Testing

Repeated pregnancy test should be conducted as described above.

10.7.4 France-Specific Requirements

Section 5.1 – Inclusion Criteria

For inclusion criterion #4, participants in France will only be eligible to participate in the study if they are considered ineligible for treatment with cisplatin, as defined by meeting at least one of the criteria listed (Section 5.1). Participants in France that decline treatment with cisplatin-based chemotherapy will not be eligible to participate.

For inclusion criterion #4, cisplatin ineligibility is defined as meeting any one of a number of criteria including:

- CTCAE v.4 Grade ≥2 audiometric hearing loss (Threshold shift of > 25 dB averaged at 2 consecutive test frequencies in at least 1 ear)

For France, audiometric assessments should be performed by a qualified audiologist, investigator, or qualified designee for all participants at Screening (within 6 weeks prior to randomization) per local institutional practice. As part of the screening assessment, the audiologist, investigator, or qualified designee will assess hearing aid use prior to the start of study treatment. If auditory symptoms develop after the screening assessment and prior to treatment initiation, the audiometric assessments should be repeated prior to treatment initiation. Additional comprehensive audiometric assessments should be conducted as deemed appropriate by the audiologist, investigator, or qualified designee and following local cisplatin product label (for France) to provide continued safety assessment. Documented routine audiometric testing performed within 6 weeks of trial treatment is acceptable and does not need to be repeated in Screening.

For inclusion criterion #7, adequate organ function laboratory values:

1) Measured or calculated creatinine clearance* (CrCl) ≥30 mL/min for participants with creatinine >1.5 institutional ULN or 2) CrCl ≥30 mL/min AND creatinine ≤1.5 x ULN. Both CrCl and creatinine level will be applicable when local guidelines require both assessments. GFR can also be used in place of CrCl or creatinine.

*CrCl should be calculated using one of the following methods: Cockcroft-Gault method, Modification of Diet in Renal Disease equations (MDRD), or 24-hour urine collection. The same method for CrCl calculation should be used consistently for a participant over the course of the study.

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 cells/µL
Platelets	≥100,000 cells/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal[b]	
Measured or calculated creatinine clearance (CrCl) OR CrCl AND Creatinine	≥30 mL/min for participants with creatinine >1.5 x institutional upper limit of normal (ULN) ≥30 mL/min ≤1.5 x ULN
Hepatic	
Serum total bilirubin	≤1.5 × ULN **OR** Direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT) **OR** Partial Thromboplastin Time (PTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic-pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic-oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.

[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.

[b] Both CrCl and creatinine level will be applicable when local guidelines require both assessments. GFR can also be used in place of CrCl or creatinine. CrCl should be calculated using one of the following methods: Cockcroft-Gault method, Modification of Diet in Renal Disease equations (MDRD), or 24-hour urine collection. The same method for CrCl calculation should be used consistently for a participant over the course of the study.

Section 6.3.1 Intervention Assignment

Treatment randomization will occur centrally using an interactive response technology (IRT) system. There are 3 study treatment arms. Participants will be assigned randomly in a 1:1:1 ratio to Arm A (perioperative pembrolizumab + RC + PLND), Arm B (RC + PLND), and Arm C (perioperative EV in combination with pembrolizumab + RC + PLND).

10.7.5 Italy-Specific Requirements

In addition to the assessments and procedures indicated in Section 1.3 – Schedule of Activities, participants in Italy should have the following procedures/assessments performed (Table 29 and Table 30 for Arms A and C, and Table 31 for Arm B).

Table 29 Study Screening and Neoadjuvant Treatment (Preoperative and Operative Phase) – Arm A (Pembrolizumab) and Arm C (Enfortumab Vedotin and Pembrolizumab)

Trial Period	**Screening**	**Neoadjuvant Treatment (Arm A&C)**						**Pre-surgery Imaging / Safety**	**RC + PLND**	**Post-surgery Follow-Up*** **	**Notes:** *****Can be combined with the A1 visit** ****N1-N3 = neoadjuvant Cycle 1, neoadjuvant Cycle 2, neoadjuvant Cycle 3**
Visit/Procedure		**Preoperative**									
Treatment Cycle		**N1****		**N2**		**N3**					
Week		**1**		**4**		**7**		**10**	**12**	**18**	*+3-day window for C1D1 neoadjuvant treatment, from randomization
Scheduled Cycle Days	**-42 to -1**	**D1***	**D8**	**D1**	**D8**	**D1**	**D8**				
Window Days		**+3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±7**	**±7**	**±14**	
Laboratory Procedures											
Urine or Serum hCG Pregnancy Test (WOCBP only), per local SOP	X	X		X		X				X	Pregnancy testing by Urine or Serum beta-human chorionic gonadotropin (β-hCG) for women of childbearing potential (WOCBP) is required at screening. Required at ≤24 hours prior to first treatment dose (C1D1). Required ≤72 hours prior to start of each subsequent treatment cycles.
HIV Testing	X										
Hepatitis B and C Testing	X										

Table 30 Post-Surgery Adjuvant Treatment (Postoperative Phase): Treatment Arm A = Pembrolizumab x 14 Cycles/ Treatment Arm C = Enfortumab Vedotin x 6 Cycles in Combination With Pembrolizumab x 14 Cycles

Trial Period	**Postoperative (Adjuvant) Phase (Arm A and C)**														**EOT/ Discon****	**Safety FU**	**Notes :**
Visit/Procedure																	
Treatment Cycle	**A1***		**A2**		**A3**		**A4**		**A5**		**A6**		**A7**	**A8-14**			***A1- A14 = adjuvant Cycle 1 ; adjuvant Cycle 2 ; etc.** *** A1 will occur 8 weeks (±14 days) post-cystectomy and can be combined with the post-surgery follow-up visit.** **** If this occurs ≥30 days following last intervention, it may be combined with the Safety Follow-Up visit.** **Following completion of Cycle A14 participants will be followed per Section 1.3.4 below.**
Adjuvant Phase Week	**1**		**4**		**7**		**10**		**13**		**16**		**19**	**22-40**			
Scheduled Cycle Day(s)	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D1**	**At time of last intervention/ dose**	**30 days after last intervention/dose**	
Window Days	**±3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±3**	**±3**		**+14**	
Safety Procedures																	
Urine or Serum hCG Pregnancy Test (WOCBP only), per local SOP	X		X		X		X		X		X		X	X	X*	X	Pregnancy testing by Urine or Serum beta-human chorionic gonadotropin (β-hCG) for women of childbearing potential (WOCBP) is required at screening. Required at ≤24 hours prior to first treatment dose (C1D1). Required ≤72 hours prior to start of each subsequent treatment cycles. Required at the time of treatment discontinuation and one month after the last dose of study treatment.

Table 31 Study Screening, Surgery, and Post-Surgery (Control) – Arm B (Cystectomy)

Treatment Arm B: RC + PLND Only											
Trial Period	**Screening**	**Pre-surgery**	**RC + PLND**	**Post-surgery Follow-up**							**Notes:** *** Following the visit at Week 30, subsequent clinic visits will occur every 12 weeks [±14 days] (if the participant remains clinically stable) through the end of Year 1 (from the post-cystectomy baseline scan).** **‡ The 6-week post-surgery visit may also serve as the Safety Follow-up Visit (if it occurs 4-6 weeks post-surgery, as noted in the window periods).**
Visit/ Procedure											
Week			**Surgery**	**Safety Follow-Up**	**Weeks Post-surgery (Clinical Observation)**						
	≤6 weeks prior to randomization (Days -42 to -1)	**2 weeks prior to surgery**	**Within 8 weeks from randomization**	**30 days after study intervention (surgery)**	**6‡**	**12**	**18**	**24**	**30**	***42 to 54**	
Window Days		**±7**	**+7**	**+14**	**±14**	**±7**	**±7**	**±7**	**±7**	**±14**	
Urine or Serum hCG Pregnancy Test (WOCBP only), per local SOP	X		(x)	(x)				(x)		(x)	Required at screening. Ongoing pregnancy testing should be conducted where applicable at the intervals specified. This testing will be N/A for many participants as standard RC+PLND surgery includes removal of the uterus. If urine pregnancy test is required and cannot be confirmed as negative, a serum pregnancy test is required. (x) = pregnancy testing (optional unless mandated by local regulations). (Appendix 2).
HIV Testing	X										
Hepatitis B and C Testing	X										

Section 5.2 – Exclusion Criteria

For Exclusion Criterion #19 (HIV infection) and #20 (hepatitis B and hepatitis C infection), testing for HIV, hepatitis B, and hepatitis C must be performed in Italy during screening in order to determine a participant's eligibility for the study.

10.7.6 Ireland-Specific Requirements

In addition to the assessments and procedures indicated in Section 1.3 – Schedule of Activities, participants in Ireland should have the following procedures/assessments performed (Table 32 and Table 33 for Arms A and C, and Table 34 for Arm B).

Table 32 Study Screening and Neoadjuvant Treatment (Preoperative and Operative Phase) – Arm A (Pembrolizumab) and Arm C (Enfortumab Vedotin and Pembrolizumab)

Trial Period	**Screening**	**Neoadjuvant Treatment (Arm A&C)**						**Pre-surgery Imaging/ Safety**	**RC + PLND**	**Post-surgery Follow-Up***	**Notes:** ***Can be combined with the A1 visit **N1-N3 = neoadjuvant Cycle 1, neoadjuvant Cycle 2, neoadjuvant Cycle 3**
Visit/Procedure		**Preoperative**									
Treatment Cycle		**N1****		**N2**		**N3**					
Week		**1**		**4**		**7**		**10**	**12**	**18**	*+3-day window for C1D1 neoadjuvant treatment, from randomization
Scheduled Cycle Days	**-42 to -1**	**D1***	**D8**	**D1**	**D8**	**D1**	**D8**				
Window Days		**+3**	**+4**	**±3**	**+4**	**±3**	**+4**	**±7**	**±7**	**±14**	
Laboratory Procedures											
Urine or Serum hCG Pregnancy Test (WOCBP only), per local requirements	X	X		X		X				(x)	Pregnancy testing by Urine or Serum beta-human chorionic gonadotropin (β-hCG) for women of childbearing potential (WOCBP) is required at screening. Required at ≤24 hours prior to first treatment dose (C1D1). Required ≤72 hours prior to start of each subsequent treatment cycles. (x) = pregnancy testing optional unless mandated by local regulations. (Appendix 2).
HIV, hepatitis B and C screening	X										Assessed at Screening ≤28 days prior to randomization.

Table 33 Post-Surgery Adjuvant Treatment (Postoperative Phase): Treatment Arm A = Pembrolizumab x 14 Cycles/ Treatment Arm C = Enfortumab Vedotin x 6 Cycles in Combination With Pembrolizumab x 14 Cycles

Trial Period	**Postoperative (Adjuvant) Phase (Arm A and C)**														**EOT/ Discon****	**Safety FU**	**Notes:**
Visit/Procedure																	
Treatment Cycle	**A1***		**A2**		**A3**		**A4**		**A5**		**A6**		**A7**	**A8-14**			***A1- A14 = adjuvant Cycle 1; adjuvant Cycle 2; etc.** *** A1 will occur 8 weeks (±14 days) post-cystectomy and can be combined with the post-surgery follow-up visit.** **** If this occurs ≥30 days following last intervention, it may be combined with the Safety Follow-Up visit.** **Following completion of Cycle A14 participants will be followed per Section 1.3.4 below.**
Adjuvant Phase Week	**1**		**4**		**7**		**10**		**13**		**16**		**19**	**22-40**			
Scheduled Cycle Day(s)	**D1**	**D8**	**D 1**	**D 8**	**D 1**	**D 8**	**D 1**	**D 8**	**D 1**	**D 8**	**D 1**	**D 8**	**D1**	**D1**	**At time of last interventi on/ dose**	**30 days after last interven-tion/dose**	
Window Days	**± 3**	**+ 4**	**± 3**	**+ 4**	**± 3**	**+ 4**	**± 3**	**+ 4**	**± 3**	**+ 4**	**± 3**	**+ 4**	**±3**	**±3**		**+14**	
Safety Procedures																	
Urine or Serum hCG Pregnancy Test (WOCBP only), per local requirements	X		X		X		X		X		X		X	X	X*	X	Pregnancy testing by Urine or Serum beta-human chorionic gonadotropin (β-hCG) for women of childbearing potential (WOCBP) is required at screening. Required at ≤24 hours prior to first treatment dose (C1D1). Required ≤72 hours prior to start of each subsequent treatment cycles. Required at the time of treatment discontinuation and one month after the last dose of study treatment.

Table 34 Study Screening, Surgery, and Post-Surgery (Control) – Arm B (Cystectomy)

Treatment Arm B: RC + PLND Only											
Trial Period	**Screening**	**Pre-surgery**	**RC + PLND**	**Post-surgery Follow-up**							**Notes:** *** Following the visit at Week 30, subsequent clinic visits will occur every 12 weeks [±14 days] (if the participant remains clinically stable) through the end of Year 1 (from the post-cystectomy baseline scan).** **‡ The 6-week post-surgery visit may also serve as the Safety Follow-up Visit (if it occurs 4-6 weeks post-surgery, as noted in the window periods).**
Visit/ Procedure											
Week			**Surgery**	**Safety Follow-Up**	**Weeks Post-surgery (Clinical Observation)**						
	≤6 weeks prior to randomization (Days -42 to -1)	**2 weeks prior to surgery**	**Within 8 weeks from randomization**	**30 days after study intervention (surgery)**	**6‡**	**12**	**18**	**24**	**30**	***42 to 54**	
Window Days		**±7**	**+7**	**+14**	**±14**	**±7**	**±7**	**±7**	**±7**	**±14**	
Urine or Serum hCG Pregnancy Test (WOCBP only), per local requirements	X		(x)	(x)				(x)		(x)	Required at screening. Ongoing pregnancy testing should be conducted where applicable at the intervals specified. This testing will be N/A for many participants as standard RC+PLND surgery includes removal of the uterus. If urine pregnancy test is required and cannot be confirmed as negative, a serum pregnancy test is required. (x) = pregnancy testing (optional unless mandated by local regulations). (Appendix 2)
HIV, hepatitis B and C screening	X										Assessed at Screening ≤28 days prior to randomization.

10.7.7 South Africa-Specific Requirements

In addition to the assessments and procedures indicated in Section 1.3 – Schedule of Activities, participants in South Africa should have the following procedures/assessments performed (Table 35 for Arms A and C and Table 36 for Arm B).

Table 35 South Africa-Specific Schedule of Activities – Arms A and C

Study Period	Screening Phase	Preoperative / Operative Phase		Postoperative Phase	Follow-up Phase		Notes
		Neoadjuvant Treatment	Post-surgery Follow-up	Adjuvant Treatment	End-of-Treatment/ Discontinuation (DC)	Safety Follow-up Visit	
Cycle/Visit Title	Screening	N1 to N3	Week 16	A1 to A14			
Cycle Day		1	4 Weeks post-surgery	1	At time of DC	30 days post last dose	
Scheduling Window (Days)	-42 to -1	±3	±7	±3		+14	
Laboratory Procedures							
HIV Testing	X						
TB Testing	X						Local standards at screening and every 6 months in an SoA.

Table 36 South Africa-Specific Schedule of Activities – Arm B

Study Period	Screening Phase	Presurgery/Surgical Phase		Post-surgery	Notes
Visit Title	Screening	Presurgery	Surgery	Safety Follow-up Visit	
Week		≤2 weeks prior to surgery	≤8 weeks post-randomization	30 days post study intervention (surgery)	
Scheduling Window (Days)	-42 to -1	±7	±7	+14	
Laboratory Procedures					
HIV Testing	X				
TB Testing	X				Local standards at screening and every 6 months in an SoA.

Section 5.2 – Exclusion Criteria

For Exclusion Criteria #19 (HIV infection) testing for HIV must be performed in South Africa during screening in order to determine a participant's eligibility for the study.

Has an active TB infection. Participants must be tested at screening and then every 6 months for a TB infection.

10.7.8 Argentina-Specific Requirements

Argentina has country-specific requirements for the protocol, which are summarized below.

Section 1.3 – Schedule of Activities

In addition to the assessments and procedures indicated in Section 1.3 – Schedule of Activities, participants in Argentina should have the following procedures/assessments performed (Table 37 for Arms A and C and Table 38 for Arm B).

Table 37 Argentina-Specific Schedule of Activities – Arms A and C

Study Period	Screening Phase	Preoperative / Operative Phase		Postoperative Phase	Follow-up Phase		Notes
Cycle/Visit Title	Screening	Neoadjuvant Treatment N1 to N3	Post-surgery Follow-up Week 16	Adjuvant Treatment A1 to A14	End-of-Treatment/ Discontinuation (DC)	Safety Follow-up Visit	
Cycle Day		1	4 Weeks post-surgery	1	At time of DC	30 days post last dose	
Scheduling Window (Days)	-42 to -1	±3	±7	±3		+14	
Laboratory Procedures							
Urine or Serum hCG Pregnancy Test (WOCBP only), per local SOP	X	X	X	X	X	X	Required at screening. Required at ≤24 hours prior to first treatment dose (C1D1). Required ≤72 hours prior to start of each subsequent treatment cycles. Ongoing pregnancy testing should be conducted where applicable at the intervals specified. This testing will be N/A for many participants as standard RC+PLND surgery includes removal of the uterus. If urine pregnancy test is required and cannot be confirmed as negative, a serum pregnancy test is required.
HIV Testing	X						
Hepatitis B and C Testing	X						

Table 38 Argentina-Specific Schedule of Activities – Arm B

Study Period	Screening Phase	Presurgery/Surgical Phase		Post-surgery	Notes
Visit Title	Screening	Presurgery	Surgery	Safety Follow-up Visit	
Week		≤2 weeks prior to surgery	≤8 weeks post-randomization	30 days post study intervention (surgery)	
Scheduling Window (Days)	-42 to -1	±7	±7	+14	
Laboratory Procedures					
Urine or Serum hCG Pregnancy Test (WOCBP only), per local SOP	X			X	Required at screening and Safety Follow-up Visit. Ongoing pregnancy testing should be conducted where applicable at the intervals specified. This testing will be N/A for many participants as standard RC+PLND surgery includes removal of the uterus. If urine pregnancy test is required and cannot be confirmed as negative, a serum pregnancy test is required.
HIV Testing	X				
Hepatitis B and C Testing	X				

Section 5.2 – Exclusion Criteria

For Exclusion Criterion #19 (HIV infection) and #20 (hepatitis B and hepatitis C infection), testing for HIV, hepatitis B, and hepatitis C must be performed in Argentina during screening to determine a participant's eligibility for the study.

Section 8.3.4.2 – Pregnancy Testing

Repeated pregnancy test should be conducted as described above.

10.7.9 Japan-Specific Requirements

Throughout the Protocol

After marketing approval of Enfortumab Vedotin and MK-3475 for cisplatin-ineligible or decline cisplatin with muscle-invasive bladder cancer in Japan, the term of "clinical study" and "clinical trial" should be replaced with "post marketing clinical trial" and the study will be continued.

All applicable laws, rules, and regulations related to the conduct of the clinical trial mentioned in these sections include Japan-specific local regulation, Good Post-Marketing Study Practice (GPSP) in Japan.

10.8 Appendix 8: Description of the iRECIST Process for Assessment of Disease Progression

Not applicable.

10.9 Appendix 9: Surgery

Surgical Guidelines:

Surgical approach for RC+PLND (eg, open, laparoscopic with robot-assistance) and urinary diversion (eg, ileal conduit, neobladder) is per discretion of the treating urologist and the participant.

RC + PLND will be performed in accordance with the AUA/ASCO/ASTRO/SUO guidelines*, as follows:

"When performing a standard RC, clinicians should remove the bladder, prostate, and seminal vesicles in males and should remove the bladder, uterus, fallopian tubes, ovaries, and anterior vaginal wall in females. When performing bilateral pelvic lymphadenectomy, clinicians should remove, at a minimum, the external and internal iliac and obturator lymph nodes (standard lymphadenectomy)." In the case of neobladder reconstruction, sparing of female sex organs may be allowed based on SOC and the treating urologist's judgment. Any deviation from this guidance should be documented in the medical record and eCRFs.

All postoperative complications will be reported and graded, if applicable, in the same way as other AEs (CTCAE version 4.0) and will be identified by the investigator and/or surgeon as post-surgical complications.

* https://www.auanet.org/guidelines/bladder-cancer-non-metastatic-muscle-invasive-(2017)

10.10 Appendix 10: Abbreviations

Abbreviation	Expanded Term
A1	Adjuvant Cycle 1
ACTH	adrenocorticotropic hormone
ADA	antidrug antibodies
ADC	antibody-drug conjugate
ADL	activities of daily living
AE	adverse event
AESI/AEOSI	adverse events of special interest
AKI	acute kidney injury
ALT	alanine transaminase
ANC	absolute neutrophil count
APaT	all participants as treated
APrS	all participants receiving surgery
aPTT	activated partial thromboplastin time
AST	aspartate transaminase
BCI	Bladder Cancer Index
BICR	blind independent central review
C1	Cycle 1
cCR	clinical Complete Response
CD28	cluster of differentiation 28
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
CPS	combined positive score
CR	complete response
CrCl	creatinine clearance
CRF	Case Report Form
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events

Abbreviation	Expanded Term
ctDNA	circulating tumor DNA
CTLA4	cytotoxic T lymphocyte associated protein 4
CYP3A4	cytochrome P450 3A4
D	day
D1	Day 1
DAMPs	danger-associated molecular patterns
dB	decibels
DC	discontinued
DCR	disease control rate
DFS	disease-free survival
DILI	drug-induced liver injury
DKA	diabetic ketoacidosis
DLT	dose limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
ECD	extracellular domain
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data collection
eDMC	External Data Monitoring Committee
EEA	European Economic Area
EFS	event-free survival
ELISA	enzyme linked immunoassay
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EOT	end of treatment
ePRO	electronic patient-reported outcomes

Abbreviation	Expanded Term
EU	European Union
EU CT	European Union Clinical Trials
EU CTR	European Union Clinical Trials Regulation
EV	enfortumab vedotin
Exp	experimental
FA	final analysis
FACT-Bl-Cys	Functional Assessment of Cancer Therapy – Bladder – Cystectomy
FACT-G	Functional Assessment of Cancer Therapy – General
FAS	full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FFPE	formalin-fixed paraffin-embedded
FNA	fine needle aspirate
FSH	follicle-stimulating hormone
FSR	first site ready
FU	follow-up
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GFR	glomerular filtration rate
GI	gastrointestinal
HA	health authority
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotrophin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
HRT	hormone replacement therapy
HSD	Hwang Shih-DeCani

Abbreviation	Expanded Term
IA	interim analysis
IB	Investigator's Brochure
ICD	immunogenic cell death
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iCRO	imaging contract research organization
ICSR	individual case safety report
IEC	Independent Ethics Committee
Ig	immunoglobulin
IHC	immunohistochemistry
ILD	interstitial lung disease
IND	Investigational New Drug
INR	international normalized ratio
IMP	investigational medicinal product
irAE	immune-related adverse event
IRB	Institutional Review Board
IRR	infusion-related reaction
IRT	interactive response technology
ITT	intention-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IVD	in vitro diagnostic
jRCT	Japan Registry for Clinical Trials
1 L	first-line
M&N	Miettinen and Nurminen
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MDRD	Modification of Diet in Renal Disease equations

Abbreviation	Expanded Term
MIBC	muscle-invasive bladder cancer
MID	minimally important difference
MMAE	monomethyl auristatin E
MOW	most of world
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
mUC	metastatic urothelial carcinoma
N1	Neoadjuvant Cycle 1
N/A	not applicable
NCI	National Cancer Institute
NDA	New Drug Application
NMIBC	nonmuscle-invasive bladder cancer
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PBPK	physiologically-based pharmacokinetics
pCR	pathologic complete response
pCRR	pathologic complete response rate
PD	progressive disease
PD-1	programmed cell death 1
PD-L1/2	programmed cell death ligand 1/2
pDS	pathologic down staging
PFS	progression-free survival
PK	pharmacokinetic
PKCθ	protein kinase C theta
PLND	pelvic lymph node dissection
PN	peripheral neuropathy
PR	partial response
PRO	patient-reported outcome

Abbreviation	Expanded Term
PSA	prostate-specific antigen
PT	prothrombin time
Q2/3W	every 2 to 3 weeks
RC	radical cystectomy
RCTs	randomized clinical trials
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RNA	ribonucleic acid
SAE	serious adverse event
SCAR	severe cutaneous adverse reactions
SoA	schedule of activities
SOC	standard of care
SOP	standard operating procedure
sSAP	supplemental statistical analysis plan
ST	standard therapy
SUSAR	suspected unexpected serious adverse reaction
SWOG	Southwest Oncology Group
TB	tuberculosis
TEAE	treatment-emergent adverse event
TMDD	target-mediated drug disposition
TOI	Trial Outcome Index
TSH	thyroid-stimulating hormone
TTD	time to deterioration
TUR	transurethral resection
TURBT	transurethral resection of bladder tumor
UC	urothelial carcinoma
US	United States
UTI	urinary tract infection
VAS	visual analog scale
WOCBP	woman/women of childbearing potential
ZAP70	zeta chain associated protein kinase

11 REFERENCES

[Bajorin, D. F., et al 2021]	Bajorin DF, Witjes JA, Gschwend JE, Schenker M, Valderrama BP, Tomita Y, et al. Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma. N Engl J Med. 2021 Jun 3;384(22):2102-14.	[07W3S5]
[Bandini, M., et al 2020]	Bandini M, Gibb EA, Gallina A, Raggi D, Marandino L, Bianchi M, et al. Does the administration of preoperative pembrolizumab lead to sustained remission post-cystectomy? First survival outcomes from the PURE-01 study. Ann Oncol. 2020;31(12):1755-63.	[05R9VM]
[Blank, C. and Mackensen, A. 2007]	Blank C, Mackensen A. Contribution of the PD-L1/PD-1 pathway to T-cell exhaustion: an update on implications for chronic infections and tumor evasion. Cancer Immunol Immunother. 2007 May;56(5):739-45.	[00VMND]
[Cajipe, M., et al 2020]	Cajipe M, Wang H, Elshabrawy A, Kaushik D, Liss M, Svatek R, et al. Pathological downstaging following radical cystectomy for muscle-invasive bladder cancer: survival outcomes in the setting of neoadjuvant chemotherapy versus transurethral resection only. Urol Oncol. 2020;38:231-9.	[05H4JY]
[Cao, A. T., et al 2017]	Cao AT, Law CL, Gardai SJ, Heiser RA. Brentuximab vedotin-driven immunogenic cell death enhances antitumor immune responses, and is potentiated by PD1 inhibition in vivo [abstract]. Presented at: American Association for Cancer Research (AACR) Annual Meeting; 2017 Apr 1-5; Washington, DC. Cancer Res. 2017;77(13 suppl): Abstract no. 5588.	[05CPGS]

[Cao, A. T., et al 2018]	Cao AT, Higgins S, Stevens N, Gardai SJ, Sussman D. Additional mechanisms of action of ladiratuzumab vedotin contribute to increased immune cell activation within the tumor [abstract]. Presented at: American Association for Cancer Research (AACR) Annual Meeting; 2018 Apr 14-18; Chicago, IL. Cancer Res. 2018;78(13 suppl): Abstract no. 2742.	[05CPGV]
[Cao, A., et al 2016]	Cao A, Heiser R, Law CL, Gardai SJ. Auristatin-based antibody drug conjugates activate multiple ER stress response pathways resulting in immunogenic cell death and amplified T-cell responses [abstract]. Presented at: American Association for Cancer Research (AACR) 107th Annual Meeting; 2016 Apr 16-20; New Orleans, LA. Cancer Res. 2016 Jul;76(14 suppl). Abstract no. 4914.	[05H77B]
[Challita-Eid, P. M., et al 2016]	Challita-Eid PM, Satpayev D, Yang P, An Z, Morrison K, Shostak Y, et al. Enfortumab vedotin antibody-drug conjugate targeting nectin-4 is a highly potent therapeutic agent in multiple preclinical cancer models. Cancer Res. 2016 May 15;76(10):3003-13.	[05CDGL]
[Chemnitz, J. M., et al 2004]	Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol 2004;173:945-54.	[00VMPN]
[Choueiri, T. K., et al 2014]	Choueiri TK, Jacobus S, Bellmunt J, Qu A, Appleman LJ, Tretter C, et al. Neoadjuvant dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin with pegfilgrastim support in muscle-invasive urothelial cancer: pathologic, radiologic, and biomarker correlates. J Clin Oncol. 2014 Jun 20;32(18):1889-94.	[054M7N]

[Clopper, C. J. and Pearson, E. S. 1934]	Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. Biometrika 1934;26(4):404-13.	[03RMKM]
[Disis, M. L. 2010]	Disis ML. Immune regulation of cancer. J Clin Oncol 2010;28(29):4531-8.	[058SQL]
[Dudley, M. E., et al 2005]	Dudley ME, Wunderlich JR, Yang JC, Sherry RM, Topalian SL, Restifo NP, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23(10):2346-57.	[00VMPR]
[Fischer-Valuck, B. W., et al 2018]	Fischer-Valuck BW, Rao YJ, Rudra S, Przybysz D, Germino E, Samson P, et al. Treatment patterns and overall survival outcomes of octogenarians with muscle invasive cancer of the bladder: an analysis of the national cancer database. J Urol. 2018 Feb;199:416-23.	[08N2SQ]
[Fradet, Y., et al 2019]	Fradet Y, Bellmunt J, Vaughn DJ, Lee JL, Fong L, Vogelzang NJ, et al. Randomized phase III KEYNOTE-045 trial of pembrolizumab versus paclitaxel, docetaxel, or vinflunine in recurrent advanced urothelial cancer: results of >2 years of follow-up. Ann Oncol. In press 2019.	[05890S]
[Francisco, L. M., et al 2010]	Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 2010;236:219-42.	[058SQP]

[Friedlander, T. W., et al 2021]	Friedlander TW, Milowsky MI, Bilen MA, Srinivas S, McKay RR, Flaig TW, et al. Study EV-103: update on durability results and long term outcome of enfortumab vedotin + pembrolizumab in first line locally advanced or metastatic urothelial carcinoma (la/mUC) [abstract]. Poster session presented at: 2021 American Society of Clinical Oncology (ASCO) Annual Meeting; 2021 Jun 4-8; [online meeting]. J Clin Oncol. 2021;39(15 suppl).	[07ZP4H]
[Galsky, M. D., et al 2016]	Galsky MD, Stensland KD, Moshier E, Sfakianos JP, McBride RB, Tsao CK, et al. Effectiveness of adjuvant chemotherapy for locally advanced bladder cancer. J Clin Oncol. 2016 Mar 10;34(8):825-32. Authors disclosures of potential conflicts of interest; Appendix, Tables A1-3, Figure A1; 5 p.	[050RJL]
[Galsky, M. D., et al 2020]	Galsky MD, Arija JAA, Bamias A, Davis ID, De Santis M, Kikuchi E, et al. Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): a multicentre, randomised, placebo-controlled phase 3 trial. Lancet. 2020 May 16;395:1547-57.	[05JB79]
[Gardai, S. J., et al 2015]	Gardai SJ, Epp A, Law CL. Brentuximab vedotin-mediated immunogenic cell death [abstract]. Presented at: American Association for Cancer Research (AACR) 106th Annual Meeting; 2015 Apr 18-22; Philadelphia, PA. Cancer Res. 2015;75(15 suppl). Abstract no. 2469.	[05CPGX]
[Gilbert, S. M., et al 2007]	Gilbert SM, Wood DP, Dunn RL, Weizer AZ, Lee CT, Montie JE, et al. Measuring health-related quality of life outcomes in bladder cancer patients using the Bladder Cancer Index (BCI). Cancer. 2007 May 1;109(9):1756-62.	[058B3P]

[Gilbert, S. M., et al 2010]	Gilbert SM, Dunn RL, Hollenbeck BK, Montie JE, Lee CT, Wood DP, et al. Development and validation of the bladder cancer index: a comprehensive, disease specific measure of health related quality of life in patients with localized bladder cancer. J Urol. 2010 May;183:1764-70.	[05892T]
[Gore, J. L., et al 2009]	Gore JL, Lai J, Setodji CM, Litwin MS, Saigal CS. Mortality increases when radical cystectomy is delayed more than 12 weeks: results from a Surveillance, Epidemiology, and End Results-Medicare analysis. Cancer. 2009 Mar 1;115:988-96.	[050SDH]
[Greenwald, R. J., et al 2005]	Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol 2005;23:515-48.	[00VMQL]
[Grossman, H. B., et al 2003]	Grossman HB, Natale RB, Tangen CM, Speights VO, Vogelzang NJ, Trump DL, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med. 2003 Aug 28;349(9):859-66. Erratum in: N Engl J Med. 2003 Nov 6;349(19):1880.	[050DTJ]
[Herr, H. W. 2008]	Herr HW. Outcome of patients who refuse cystectomy after receiving neoadjuvant chemotherapy for muscle-invasive bladder cancer. Eur Urol. 2008;54:126-32.	[054H9M]
[Hoimes, C. J., et al 2019]	Hoimes CJ, Rosenberg JE, Srinivas S, Petrylak DP, Milowsky M, Merchan JR, et al. EV-103: initial results of enfortumab vedotin plus pembrolizumab for locally advanced or metastatic urothelial carcinoma [abstract]. Presented at: European Society for Medical Oncology (ESMO) 2019 Congress; 2019 Sep 27-Oct 1; Barcelona (Spain). Ann Oncol. 2019;30(suppl 5):v356-402. Abstract no. 9010.	[05CPH0]

[Hunder, N. N., et al 2008]	Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med 2008;358(25):2698-703.	[00VMPX]
[Hwang, I. K., et al 1990]	Hwang IK, Shih WJ, De Cani JS. Group sequential designs using a family of type I error probability spending functions. Stat Med 1990;9:1439-45.	[03R4J4]
[Iwai, Y., et al 2002]	Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci U S A 2002;99(19):12293-7.	[00VMNR]
[Korman, A., et al 2007]	Korman A, Chen B, Wang C, Wu L, Cardarelli P, Selby M. Activity of anti-PD-1 in murine tumor models: role of "host" PD-L1 and synergistic effect of anti-PD-1 and anti-CTLA-4 [Abstract]. J Immunol 2007;178:48.37.	[00VMPZ]
[Lee, C. T., et al 2006]	Lee CT, Madii R, Daignault S, Dunn RL, Zhang Y, Montie JE, et al. Cystectomy delay more than 3 months from initial bladder cancer diagnosis results in decreased disease specific and overall survival. J Urol. 2006 Apr;175:1262-7.	[050SF7]
[Li, R., et al 2024]	Li R, Nocera L, Rose KM, Raggi D, Naidu S, Mercinelli C, et al. Comparative effectiveness of neoadjuvant pembrolizumab versus cisplatin-based chemotherapy or upfront radical cystectomy in patients with muscle-invasive urothelial bladder cancer. Eur Urol Oncol. 2024;7:614-24.	[08N2HY]
[Maurer, W. and Bretz, F. 2013]	Maurer W and Bretz F. Multiple testing in group sequential trials using graphical approaches. Stat Biopharm Res 2013;5(4):311-20.	[03XQVB]

[Meyer, A., et al 2014]	Meyer A, Ghandour R, Bergman A, Castaneda C, Wosnitzer M, Hruby G, et al. The natural history of clinically complete responders to neoadjuvant chemotherapy for urothelial carcinoma of the bladder. J Urol. 2014 Sep;192:696-701.	[054HBD]
[Miettinen, O. and Nurminen, M. 1985]	Miettinen O and Nurminen M. Comparative analysis of two rates. Stat Med 1985;4:213-26.	[00VMQY]
[Miettinen, O. and Nurminen, M. 1985a]	Miettinen O and Nurminen M. Comparative Analysis of Two Rates. Stat Med 1985;4:213-26.	[03QCDT]
[National Comprehensive Cancer Network 2020]	National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: bladder cancer; version 6.2020. Plymouth Meeting (PA): National Comprehensive Cancer Network (NCCN); 2020. 118 p.	[05KNBJ]
[Necchi, A., et al 2018]	Necchi A, Anichini A, Raggi D, Briganti A, Massa S, Luciano R, et al. Pembrolizumab as neoadjuvant therapy before radical cystectomy in patients with muscle-invasive urothelial bladder carcinoma (PURE-01): an open-label, single-arm, phase II study. J Clin Oncol. 2018 Dec 1;36(34):3353-60.	[055TLY]
[Nomi, T., et al 2007]	Nomi T, Sho M, Akahori T, Hamada K, Kubo A, Kanehiro H, et al. Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. Clin Cancer Res 2007;13(7):2151-7.	[00VMNS]

[O'Donnell, P. H., et al 2019]	O'Donnell PH, Balar AV, Vuky J, Castellano DE, Bellmunt J, Powles T, et al. KEYNOTE-052: phase 2 study evaluating first-line pembrolizumab (pembro) in cisplatin-ineligible advanced urothelial cancer (UC) - updated response and survival results [abstract]. Presented at: 2019 American Society of Clinical Oncology (ASCO) Annual Meeting; 2019 May 31-Jun 4; Chicago, IL. J Clin Oncol. 2019;37(15 suppl). Abstract no. 4546.	[058MTS]
[Okazaki, T., et al 2001]	Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci U S A 2001;98(24):13866-71.	[00VMQ6]
[Parry, R. V., et al 2005]	Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Mol Cell Biol 2005;25(21):9543-53.	[00VMQ7]
[Perez Fidalgo, J. A., et al 2012]	Perez Fidalgo JA, Garcia Fabregat L, Cervantes A, Margulies A, Vidall C, Roila F. Management of chemotherapy extravasation: ESMO-EONS clinical practice guidelines. Ann Oncol. 2012 Oct;23(suppl 7):vii167-73.	[05CPWH]
[Peyton, C. C., et al 2019]	Peyton CC, Henriksen C, Reich RR, Azizi M, Gilbert SM. Estimating minimally important differences for the Bladder Cancer Index using distribution and anchor based approaches. J Urol. 2019 Apr;201:709-14.	[058B59]
[Pfister, C., et al 2024]	Pfister C, Gravis G, Flechon A, Chevreau C, Mahammedi H, Laguerre B, et al. Perioperative dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin in muscle-invasive bladder cancer (VESPER): survival endpoints at 5 years in an open-label, randomised, phase 3 study. Lancet Oncol. 2024 Feb;25:255-64.	[08N2HW]

[Pickard, A. S., et al 2007]	Pickard AS, Wilke CT, Lin H-W, Lloyd A. Health utilities using the EQ-5D in studies of cancer. Pharmacoeconomics 2007;25(5):365-84.	[03RLHG]
[Polovich, M., et al 2014]	Polovich M, Olsen M, LeFebvre KB. Chemotherapy and biotherapy guidelines and recommendations for practice. 4th ed. Pittsburgh (PA): Oncology Nursing Society; c2014. Chapter 8, Infusion-related complications; p. 155-70.	[05CQ34]
[Powles, T., et al 2018]	Powles T, Rodriguez-Vida A, Duran I, Crabb SJ, Van Der Heijden MS, Pous AF, et al. A phase II study investigating the safety and efficacy of neoadjuvant atezolizumab in muscle invasive bladder cancer (ABACUS) [abstract]. Presented at: 2018 American Society of Clinical Oncology (ASCO) Annual Meeting; 2018 Jun 1-5; Chicago, IL. J Clin Oncol. 2018;36(15 suppl). Abstract no. 4506.	[050RK0]
[Powles, T., et al 2020]	Powles T, van der Heijden MS, Castellano D, Galsky MD, Loriot Y, Petrylak DP, et al. Durvalumab alone and durvalumab plus tremelimumab versus chemotherapy in previously untreated patients with unresectable, locally advanced or metastatic urothelial carcinoma (DANUBE): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol. 2020 Dec;21:1574-88. Erratum in: Lancet Oncol. 2021 Jan;22:e5.	[05PV4S]
[Powles, T., et al 2021]	Powles T, Csoszi T, Ozguroglu M, Matsubara N, Geczi L, Cheng SYS, et al. Pembrolizumab alone or combined with chemotherapy versus chemotherapy as first-line therapy for advanced urothelial carcinoma (KEYNOTE-361): a randomised, open-label, phase 3 trial. Lancet Oncol. 2021 Jul;22:931-45.	[06FS3T]

[Powles, T., et al 2021a]	Powles T, Rosenberg JE, Sonpavde GP, Loriot Y, Duran I, Lee JL, et al. Enfortumab vedotin in previously treated advanced urothelial carcinoma. N Engl J Med. 2021 Mar 25;384(12):1125-35.	[07WNZD]
[Powles, T., et al 2021b]	Powles T, Rosenberg JE, Sonpavde GP, Loriot Y, Duran I, Lee JL, et al. Enfortumab vedotin in previously treated advanced urothelial carcinoma. N Engl J Med. In press 2021.	[05QVYT]
[Powles, T., et al 2024]	Powles T, Valderrama BP, Gupta S, Bedke J, Kikuchi E, Hoffman-Censits J, et al. Enfortumab vedotin and pembrolizumab in untreated advanced urothelial cancer. N Engl J Med. 2024 Mar 7;390(10):875-88.	[08KP20]
[Rabin, R. and de Charro, F. 2001]	Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med 2001;33:337-43.	[03XLS2]
[Riley, J. L. 2009]	Riley JL. PD-1 signaling in primary T cells. Immunol Rev 2009;229:114-25.	[00VMQ9]
[Robins, D., et al 2018]	Robins D, Matulay J, Lipsky M, Meyer A, Ghandour R, DeCastro G, et al. Outcomes following clinical complete response to neoadjuvant chemotherapy for muscle-invasive urothelial carcinoma of the bladder in patients refusing radical cystectomy. Urology. 2018;111:116-21.	[054HCM]
[Rosenberg, J. E., et al 2019]	Rosenberg JE, Ballman KV, Halabi S, Watt C, Hahn OM, Steen PD, et al. CALGB 90601 (alliance): randomized, double-blind, placebo-controlled phase III trial comparing gemcitabine and cisplatin with bevacizumab or placebo in patients with metastatic urothelial carcinoma [abstract]. Presented at: 2019 American Society of Clinical Oncology (ASCO) Annual Meeting; 2019 May 31-Jun 4; Chicago, IL. J Clin Oncol. 2019;37(15 suppl). Abstract no. 4503.	[05CNR6]

[Rosenberg, J. E., et al 2019a]	Rosenberg JE, O'Donnell PH, Balar AV, McGregor BA, Heath EI, Yu EY, et al. Pivotal trial of enfortumab vedotin in urothelial carcinoma after platinum and anti-programmed death 1/programmed death ligand 1 therapy. J Clin Oncol. 2019;37(29):2592-600.	[05D23H]
[Rosenberg, J. E., et al 2020]	Rosenberg JE, Flaig TW, Friedlander TW, Milowsky MI, Srinivas S, Petrylak DP, et al. Study EV-103: preliminary durability results of enfortumab vedotin plus pembrolizumab for locally advanced or metastatic urothelial carcinoma [abstract]. Presented at: American Society of Clinical Oncology (ASCO) 2020 Gastrointestinal Cancers Symposium; 2020 Feb 13-15; San Francisco, CA. J Clin Oncol. 2020;38(6 suppl). Abstract no. 441.	[05H4MP]
[Rosenberg, J. E., et al 2022]	Rosenberg JE, Milowsky MI, Ramamurthy C, Mar N, Friedlander TW, McKay RR, et al. Study EV-103 cohort K: antitumor activity of enfortumab vedotin monotherapy or in combination with pembrolizumab in previously untreated cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer (la/mUC). Slides presented at: European Society for Medical Oncology (ESMO) Congress; 2022 Sep 9-13; Paris, France.	[085BFS]
[Rosenberg, J., et al 2020]	Rosenberg J, Sridhar SS, Zhang J, Smith D, Ruether D, Flaig TW, et al. EV-101: a phase I study of single-agent enfortumab vedotin in patients with nectin-4-positive solid tumors, including metastatic urothelial carcinoma. J Clin Oncol. 2020;38(10):1041-9.	[05GVN8]
[Rosenblatt, R., et al 2012]	Rosenblatt R, Sherif A, Rintala E, Wahlqvist R, Ullen A, Nilsson S, et al. Pathologic downstaging is a surrogate marker for efficacy and increased survival following neoadjuvant chemotherapy and radical cystectomy for muscle-invasive urothelial bladder cancer. Eur Urol. 2012;61:1229-38.	[050SFN]

[Schmid, P., et al 2020]	Schmid P, Cortes J, Pusztai L, McArthur H, Kummel S, Bergh J, et al. Pembrolizumab for early triple-negative breast cancer. N Engl J Med. 2020 Feb 27;382(9):810-21.	[05GBCT]
[Seisen, T. 2018]	Seisen T. Examining the role of centralisation of radical cystectomy for bladder cancer. BJU Int. 2018 Feb;121(2):165-7.	[054HF0]
[Sheppard, K-A, et al 2004]	Sheppard K-A, Fitz LJ, Lee JM, Benander C, George JA, Wooters J, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS Lett. 2004;574:37-41.	[00VMQC]
[Siegel, R. L., et al 2020]	Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020 Jan-Feb;70(1):7-30.	[05F2SG]
[Sonpavde, G. 2017]	Sonpavde G. PD-1 and PD-L1 inhibitors as salvage therapy for urothelial carcinoma. N Engl J Med. 2017 Mar 16;376(11):1073-4.	[05CDGR]
[Sonpavde, G., et al 2009]	Sonpavde G, Goldman BH, Speights VO, Lerner SP, Wood DP, Vogelzang NJ, et al. Quality of pathologic response and surgery correlate with survival for patients with completely resected bladder cancer after neoadjuvant chemotherapy. Cancer. 2009 Sep 15;115:4104-9.	[050RHV]
[Sternberg, C. N., et al 2003]	Sternberg CN, Pansadoro V, Calabro F, Schnetzer S, Giannarelli D, Emiliozzi P, et al. Can patient selection for bladder preservation be based on response to chemotherapy? Cancer. 2003 Apr 1;97(7):1644-52.	[054HC7]
[Suciu, S., et al 2018]	Suciu S, Eggermont AMM, Lorigan P, Kirkwood JM, Markovic SN, Garbe C, et al. Relapse-free survival as a surrogate for overall survival in the evaluation of stage II-III melanoma adjuvant therapy. J Natl Cancer Inst. 2018 Jan;110(1):87-96.	[04V9XX]

[Tsushima, F., et al 2006]	Tsushima F, Tanaka K, Otsuki N, Youngnak P, Iwai H, Omura K, et al. Predominant expression of B7-H1 and its immunoregulatory roles in oral squamous cell carcinoma. Oral Oncol 2006;42:268-74.	[00VMNY]
[Wong, Y. N., et al 2012]	Wong YN, Litwin S, Vaughn D, Cohen S, Plimack ER, Lee J, et al. Phase II trial of cetuximab with or without paclitaxel in patients with advanced urothelial tract carcinoma. J Clin Oncol 2012;30(28):3545-51.	[03XLPN]
[Yee, D., et al 2017]	Yee D, DeMichele A, Isaacs C, Symmans F, Yau C, Albain KS, et al. Pathological complete response predicts event-free and distant disease-free survival in the I-SPY2 TRIAL [abstract]. Presented at: 2017 San Antonio Breast Cancer Symposium (SABCS); 2017 Dec 5-9; San Antonio, TX. Cancer Res. 2018 Feb;78(4 suppl). Abstract no. GS3-08.	[050RLB]
[Yin, M., et al 2016]	Yin M, Joshi M, Meijer RP, Glantz M, Holder S, Harvey HA, et al. Neoadjuvant chemotherapy for muscle-invasive bladder cancer: a systematic review and two-step meta-analysis. Oncologist. 2016;21:708-15.	[054M7P]
[Yu, E. Y., et al 2021]	Yu EY, Petrylak DP, O'Donnell PH, Lee JL, van der Heijden MS, Loriot Y, et al. Enfortumab vedotin after PD-1 or PD-L1 inhibitors in cisplatin-ineligible patients with advanced urothelial carcinoma (EV-201): a multicentre, single-arm, phase 2 trial. Lancet Oncol. 2021 Jun;22:872-82.	[07W59P]
[Zhang, X., et al 2004]	Zhang X, Schwartz J-CD, Guo X, Bhatia S, Cao E, Chen L, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity 2004;20:337-47.	[00VMQJ]