1 PROTOCOL SUMMARY

1.1 Synopsis

Title of Study:

An Open-label, Single-Arm, Phase 2 Study to Evaluate Enfortumab Vedotin plus Pembrolizumab for Bladder Preservation in Participants with Muscle-invasive Bladder Cancer

Short Title (Plain Language Title)

A study to find out if enfortumab vedotin given with pembrolizumab helps people with muscle-invasive bladder cancer keep their bladder

Regulatory Agency Identifier Number(s): Study 7465-CL-0209; IND 116360

Planned Total Number of Study Sites and Location(s):

Approximately 150 study sites in North America, EU and APAC

Rationale:

Enfortumab vedotin combined with pembrolizumab has demonstrated significant clinical benefit in LA/mUC, with improved ORRs, prolonged PFS, and OS, as shown in completed and ongoing studies. Based on data from EV-303 (KEYNOTE-905), perioperative enfortumab vedotin in combination with pembrolizumab has also shown positive results in cisplatin-ineligible MIBC with pCR rate of 57.1% and an overall survival advantage compared to surgery alone.

Not all patients are eligible for or choose to have a RC. There remains a critical unmet need for effective bladder preservation strategies beyond the current standard of care trimodal therapy. This applies particularly to those patients with a CR to enfortumab vedotin and pembrolizumab who may benefit from continuing treatment and not undergoing a RC. Here we evaluate the outcome of these responding patients who are eligible for but choose not to have a cystectomy.

Study Objectives, Endpoints and Estimands:

Objectives	Endpoints
Primary	
• To evaluate: 1) the overall cCR rate after treatment with enfortumab vedotin in combination with pembrolizumab and 2) the 2-year BI-EFS rate in participants who had cCR	• Overall cCR rate after treatment with enfortumab vedotin in combination with pembrolizumab as assessed by investigator (FAS) • 2-year BI-EFS rate after treatment with enfortumab vedotin in combination with pembrolizumab as assessed by investigator (FAS1 analysis set)
Secondary	
• To evaluate: 1) the overall cCR rate after 4 cycles of treatment with enfortumab vedotin in combination with pembrolizumab, and 2) the 2-year BI-EFS rate in participants who had cCR after 4 cycles	• Overall cCR rate after 4 cycles of treatment with enfortumab vedotin in combination with pembrolizumab as assessed by investigator (FAS) • 2-year BI-EFS rate after treatment with enfortumab vedotin in combination with pembrolizumab as assessed by investigator (FAS2 analysis set)
• To evaluate other measures of efficacy of enfortumab vedotin in combination with pembrolizumab in participants who had cCR	• OS (FAS1 analysis set) • DFS as assessed by investigator (FAS1 analysis set) • MFS as assessed by investigator (FAS1 analysis set)

• To evaluate the safety and tolerability of enfortumab vedotin in combination with pembrolizumab	• Type, incidence, relatedness, severity and seriousness of safety variables (AEs and laboratory tests) • Treatment discontinuation rate due to AEs
Exploratory	
• To evaluate other measures of efficacy of enfortumab vedotin in combination with pembrolizumab in participants who had cCR after 4 cycles	• OS (FAS and FAS2 analysis sets) • DFS as assessed by investigator (FAS2 analysis set) • MFS as assessed by investigator (FAS2 analysis set)
• To evaluate genomic, proteomic and/or other biomarkers that may correlate with treatment outcome, including Nectin-4 expression	• Measurements of genomic and protein biomarkers, resulting from analysis of peripheral blood and/or tumor tissue samples
• To evaluate association of ctDNA status with clinical outcomes, and profile resistance	• Measurement of ctDNA MRD levels from longitudinal sample collection
• To capture participant perspectives on treatment with enfortumab vedotin in combination with pembrolizumab, including expectations and lived experience of treatment • To understand how participants describe bladder functionality over time, including but not limited to, key themes such as continence, urgency, nocturia, sexual health, and the practical impact on daily life	• Semi-structured qualitative interviews to identify key participant themes, perspectives of treatment, and bladder functionality.

AE: adverse event; BI-EFS: bladder-intact event-free survival; cCR: clinical complete response; ctDNA: circulating tumor deoxyribonucleic Acid; DFS: disease-free survival; FAS: full analysis set; MFS: metastatic-free survival; MRD: minimum residual disease; OS: overall survival

Primary Estimand

In this phase 2 study to evaluate enfortumab vedotin in combination with pembrolizumab, the estimands for the primary endpoints are defined by the following attributes.

Treatment:
Enfortumab vedotin in combination with pembrolizumab in the perioperative MIBC setting.

Population:
Adult participants with histologically confirmed MIBC (stage cT2–T4aN0M0 or T1-T4aN1M0) who are eligible for RC and who have not received prior systemic therapy or radiotherapy for MIBC.

Endpoints:
The primary endpoints of this study are overall cCR rate in FAS and BI-EFS in FAS1:

- cCR is defined as:
  - No visible tumor detected on cystoscopy or no residual tumor on TURBT; no evidence of malignancy, except for the presence of Ta (low grade), and
  - No radiographic evidence of residual or metastatic disease on imaging (MRU or CTU if contraindicated). Bladder wall thickening on imaging is acceptable if not associated with malignancy, except for the presence of Ta (low grade), and
  - Negative urine cytology
- BI-EFS is defined as the time from first dose to any of the following events:

- Histologically confirmed recurrent MIBC
- Disease progression
- Cystectomy
- Death from any cause

Population-level Summary (primary):

- cCR rate: overall cCR rate (as assessed up to cycle 9) prior to initiation of new anti-cancer therapy in all enrolled participants.
- BI-EFS: 2-year BI-EFS rate in participants who achieve cCR after completing up to 9 cycles of treatment with enfortumab vedotin and/or pembrolizumab.

Study Population:

Participants with MIBC who are eligible for radical cystectomy.

Number of Participants:

Approximately 240 participants will be enrolled.

Study Design Overview:

This is a global, open-label, phase 2 study in adult participants with histologically confirmed MIBC (stage cT2–T4aN0M0 or T1-T4aN1M0) who are eligible for RC and who have not received prior systemic therapy or radiotherapy for MIBC. Participants may be eligible or ineligible for cisplatin chemotherapy. Approximately 240 participants will be enrolled to have approximately 160 participants who achieve cCR after treatment with enfortumab vedotin in combination with pembrolizumab, assuming a 67% cCR rate.

The study will consist of 3 periods:

- Screening/Baseline period: for a maximum of 28 days prior to cycle 1 day 1.
- Treatment period: beginning at cycle 1 day 1 and subsequent cycles until participant discontinues study intervention.
- Follow-up period: beginning after participant discontinues study intervention.

Screening/Baseline Period

After informed consent has been obtained, participants will be evaluated for eligibility by review of medical history, physical exam, AEs, eye exam, ECOG performance status, imaging assessments, TURBT, blood sample collection (including biomarkers), vital signs, ECG and tumor sample collection (fresh or archival). Screening assessments may be repeated within the 28-day screening period. Participants may only be rescreened once.

Treatment Period

Participants will receive enfortumab vedotin at 1.25 mg/kg, administered as an IV infusion on days 1 and 8 of every 3-week (21-day) cycle and pembrolizumab 200 mg as an IV infusion on day 1 of every 3-week (21-day) cycle, after completion of the enfortumab vedotin infusion. Pembrolizumab 400 mg administered every 6 weeks is allowed from cycle 10 onwards. An exception to weight-based dosing of enfortumab vedotin will be made for participants weighing greater than 100 kg; doses will be based on 100 kg for these individuals. The maximum dose permitted on this study will be 125 mg. The first on-study disease assessment for cCR will be performed after the participant has completed 4 cycles of enfortumab vedotin in combination with pembrolizumab. If the participant discontinues either enfortumab vedotin or pembrolizumab before cycle 4 (e.g., for toxicity) and continues with enfortumab vedotin or pembrolizumab monotherapy, the participant will still be assessed for cCR and remain on study treatment. This disease assessment will include MRI/CT imaging, cystoscopy/TURBT +/- biopsy, and urine cytology. Participants who discontinue all study treatment before completing 4 cycles of treatment with enfortumab vedotin in combination with

pembrolizumab will receive SoC and enter the survival follow-up period; they will not be eligible for cCR assessment.

cCR After 4 Cycles

For participants who achieve cCR after 4 cycles of study intervention, treatment with enfortumab vedotin will continue for a maximum of 5 additional cycles and pembrolizumab for a maximum of 13 additional cycles or until discontinuation criteria are met, upon study termination, or study completion, whichever occurs first. If the participant transitions to 400 mg Q6W from cycle 10 onwards, the maximum number of cycles of 200 mg Q3W will be 9 cycles followed by a maximum of 4 cycles of 400 mg Q6W. Disease assessment for the participants that achieve cCR will occur every 12 weeks (± 2 weeks) for 2 years, and every 24 weeks (± 2 weeks) thereafter until the participant has recurrent MIBC or progression outside bladder including nodal/distant metastases requiring initiation of new anti-cancer therapy or cystectomy, dies, withdraws consent, is lost to follow-up or the study closes, whichever occurs first. Disease assessments will stop after 5 years, or until study is stopped, and participants will be assessed according to local standard practice in the investigators' institutes.

Non-cCR After 4 Cycles

For participants who do not achieve cCR at the on-study disease assessment following the completion of 4 cycles of treatment with enfortumab vedotin in combination with pembrolizumab, the investigator will determine the appropriate treatment option for the participant. The options are outlined below.

Non-cCR participants with clinical downstaging to T2 or lower

- Providing the participant is eligible to continue therapy by the investigator, they may select to continue participants with enfortumab vedotin and pembrolizumab treatment for up to 5 additional cycles. These participants will undergo repeated disease assessment after 12 weeks (± 2 weeks) and no later than after cycle 9 to determine if they have achieved cCR. Participants who discontinue both enfortumab vedotin and pembrolizumab (e.g., for toxicity) before cycle 9 should have a cCR assessment within 28 days of stopping treatment.
    - For participants that achieve cCR after up to 9 cycles of study intervention, treatment with pembrolizumab will continue for 8 additional cycles, or until discontinuation criteria are met, upon study termination, or study completion, whichever occurs first. The subsequent disease assessment schedule for these participants with cCR after up to 9 cycles will be the same as that for participants who achieved cCR after 4 cycles of study intervention.
    - For participants who do not achieve cCR at the on-study disease assessment following the completion of up to 9 cycles of treatment with enfortumab vedotin in combination with pembrolizumab, the participant will be off-treatment and the investigator will determine the appropriate treatment option for the participant based on current standard treatment practice in their institute/region (this may include undergoing RC or receiving other SoC treatments). The participants will enter the survival follow-up period.
- The investigator may select RC for the participants, in which case the participants will enter the 30-day safety follow-up period then survival follow-up. Disease assessments for these participants after they have received RC will be performed according to local standard practice in the investigators' institutes. The investigator may also select the participant to continue on adjuvant enfortumab vedotin for 5 additional cycles and pembrolizumab for 13 additional cycles as part of SoC. In order to provide continued access for these participants, enfortumab vedotin and pembrolizumab may be provided as IMP if approved but not accessible in their local institute/region. If the participant receives sponsor-provided enfortumab vedotin and pembrolizumab (IMP/AxMP), the end of treatment (EOT) is defined

at the conclusion of the adjuvant phase and they will enter the 30-day safety follow-up followed by survival follow-up. All AEs, SAEs, and other reportable safety events will be collected in this group of participants. If the participant receives locally sourced enfortumab vedotin and pembrolizumab, the adjuvant treatment is not considered as the study intervention but considered as subsequent anti-cancer therapy. In this case, the EOT visit and the 30-day follow-up must occur before initiating adjuvant therapy. AEs occurring during this use are not captured under the protocol but are instead reported via post-marketing surveillance mechanisms (i.e., spontaneous reports).

- The investigator may also select other appropriate SoC options for participants based on current standard practice in their institute/region, in which case the participants will enter the survival follow-up period.

Non-cCR participants without clinical downstaging.

- The investigator may select RC for the participants, in which case the participants will enter the 30-day safety follow-up then survival follow-up. The investigator may also select the participant to continue on adjuvant enfortumab vedotin for 5 additional cycles and pembrolizumab for 13 additional cycles. Enfortumab vedotin and pembrolizumab may be provided as IMP if approved but not accessible in their local institute/region. If continuing treatment with adjuvant enfortumab vedotin and pembrolizumab, EOT and follow-up are the same as above regarding sponsor-supplied or locally sourced enfortumab vedotin and pembrolizumab.
- The investigator may also select other appropriate SoC options for participants based on current standard practice in their institute/region, in which case the participants will enter the survival follow-up period.

The EOT visit must occur within 7 days of the last study intervention (including adjuvant enfortumab vedotin and/or pembrolizumab if supplied by the sponsor and administered following RC per investigator discretion) or when the decision is made by the investigator to discontinue the participant from study intervention, or prior to the initiation of another anti-cancer therapy, whichever occurs first.

Follow-up Period

Participants will have follow-up visits as below:

- Thirty-day Safety Follow-up: 30 days (+ 7 days) after their last dose of study intervention (including adjuvant enfortumab vedotin and/or pembrolizumab if supplied by the sponsor and administered following RC per investigator discretion) or decision to discontinue (whichever is later), or before the initiation of another anti-cancer therapy, whichever comes first, for safety assessments (applies to all participants who received study intervention). The 30-day Safety Follow-up assessments should be completed prior to the initiation of another anti-cancer therapy.
- Post Treatment Follow-up: Every 12 weeks (± 2 weeks) (participants with cCR only) after their last dose of study intervention.
    - If a participant completes treatment or discontinues study intervention prior to BI-EFS event as determined by investigator assessment, the participant should enter the post-treatment follow-up period and continue to undergo disease assessments every 12 weeks (± 2 weeks) for 2 years and every 24 weeks (± 2 weeks) thereafter until BI-EFS event is documented, or the participant starts a subsequent anti-cancer treatment, whichever occurs first. Disease assessments will stop after 5 years, or until study is

stopped, and participants will be assessed based on standard treatment practice in their institute/region.

- Survival Follow-up: Every 12 weeks (± 2 weeks) after their last dose of study intervention. This applies to all participants.
    - Participants with cCR, following a BI-EFS event, will enter the survival follow-up period and be followed every 12 weeks (± 2 weeks) for survival status until death, lost to follow-up, withdrawal of study consent, or study termination by sponsor.
    - Participants who do not achieve cCR and discontinue study treatment will enter survival follow-up and be followed every 12 weeks (± 2 weeks) for survival status until death, lost to follow-up, withdrawal of study consent, or study termination by sponsor.

Collection of efficacy data (except OS) for ongoing participants will cease upon completion of final efficacy analysis; the OS data will be collected until study closure. Participants will be eligible to continue receiving study intervention in this study until they complete the maximum cycles of study intervention per protocol, meet a discontinuation criterion or upon study termination, or study completion, whichever occurs first.

Study Intervention Groups and Duration:

Intervention Label	Enfortumab vedotin	Pembrolizumab
Intervention Name	Enfortumab vedotin	Pembrolizumab
Type	Drug	Drug
Pharmaceutical Dose Form	Powder for concentrate for solution for infusion	Solution for injection
Unit Dose Strength	30 mg	100 mg
Dosage Level	1.25 mg/kg (maximum dose 125 mg) on days 1 and 8 of a 21-day cycle	200 mg on day 1 of each 21-day cycle[1]
Route of Administration	IV infusion	IV infusion
IMP and NIMP/AxMP	IMP	IMP
Use	Experimental	Experimental
Intended Sourcing[2]	Provided centrally by sponsor[2]	Provided locally by study site or provided by sponsor according to local regulation[2]
Packaging and Labeling	Supplied as lyophilized powder in single-dose vial for reconstitution	Refer to package insert

AxMP: auxiliary medicinal product; IMP: investigational medicinal product; NIMP: noninvestigational medicinal product
1. Pembrolizumab 400 mg administered every 6 weeks is allowed from cycle 10 onwards.
2. Planned sourcing may be subject to change based on product availability.
Note SPECIFIC TO JAPAN: In Japan, the study drugs are used accordingly as defined in Japan GCP.

The anticipated duration of the study for each participant, including screening and follow-up, is approximately 48 months.

4.4 Start and End of Study Definitions

First act of recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date the first participant signs the ICF and will be the study start date.

Study Completion

Study completion is defined as the conclusion of data collection for the defined study endpoints. The study will close after the third analysis of the primary endpoint of BI-EFS is complete.

End of study

The end of the study is defined as the last visit or assessment shown in the schedule of assessments [Section 1.3] for the last participant in the study. A participant is considered to have completed the study if the participant has completed all periods of the study including the last assessment shown in the schedule of assessments. The study may be closed within a participating country per local regulations once the study has completed. In addition, the sponsor may prematurely terminate the study for reasonable cause at any time.

5 STUDY POPULATION

The study population will include participants with MIBC who are eligible for RC.

All screening assessments must be completed and reviewed to confirm the potential participant meets all eligibility criteria. Prospective approval of protocol deviations to eligibility criteria (also known as protocol waivers or exemptions) is not permitted.

5.1 Inclusion Criteria

Participants are eligible for participation in the study if all of the following apply:

Age

1. Participant is ≥ 18 years of age at the time of signing the ICF.

Type of Participant and Disease Characteristics

2. Participant has histologically-confirmed MIBC, stage cT2–T4aN0M0 or T1-T4aN1M0.
   NOTE: UCs not originating from the bladder (e.g., 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.
3. Participant has predominant UC histology (≥ 50%).
   NOTE: Participants with mixed histology are eligible provided the urothelial component is ≥ 50% (participants whose tumors contain predominant [≥ 50%]

plasmacytoid variant are not eligible). Participants whose tumors contain any neuroendocrine histology are not eligible.

4. Participant is deemed eligible for RC and PLND by a urologist and/or oncologist.
5. Participant has accessible archival tumor tissue from the primary tumor, for which source and availability have been confirmed prior to study intervention. If no archival tumor tissue is available, the participant will have a biopsy to obtain tumor tissue prior to study intervention.
6. Participant has ECOG performance status of 0 to 2.
7. Participant has the following baseline laboratory data. If a participant has received a recent blood transfusion, the hematology tests must be obtained ≥ 14 days after any blood transfusion.
    - ANC ≥ 1.5×10^9/L
    - Platelet count ≥ 100×10^9/L
    - Hemoglobin ≥ 9 g/dL
    - GFR ≥ 30 mL/min as estimated per Cockcroft-Gault criteria or as measured by 24-hour urine collection
    - Serum TBL ≤ 1.5 × ULN or ≤ 3 × ULN for participants with Gilbert's disease
    - ALT and AST ≤ 2.5 × ULN
    - INR or PT and aPTT both ≤ 1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within the therapeutic range of intended use of anticoagulants. PTT may be used if local lab is unable to perform aPTT.

Sex and Contraceptive Requirements

8. Female participant:
    - is not pregnant (see [Section 10.2]) and at least 1 of the following conditions apply:
        a. Not a WOCBP (see [Section 10.2])
        b. WOCBP who has a negative urine or serum pregnancy test at screening or within 7 days prior to day 1 or for sites in Japan, with a medical interview and agrees to follow the contraceptive guidance (see [Section 10.2]) from the time of informed consent through at least 6 months after final study intervention administration.
    - Must not be breastfeeding or lactating starting at screening and throughout the investigational period and for at least 6 months after final study intervention administration.
    - Must not donate ova starting at first administration of study intervention and throughout the investigational period and for 6 months after final study intervention administration.
9. Male participant:
    - Must agree to use contraception (see [Section 10.2]) with female partner(s) of childbearing potential (including breastfeeding partner) throughout the treatment period and for 4 months after final study intervention administration.

- Must agree to remain abstinent or use a condom with pregnant partner(s) for the duration of the pregnancy throughout the investigational period and for 4 months after final study intervention administration.
- Must not donate sperm during the treatment period and for 4 months after final study intervention administration.

Informed Consent

10. The participant has provided informed consent which includes compliance with the requirements and restrictions listed in the ICF and protocol.

Diagnostic Assessments

11. Have a TUR of a bladder tumor within 60 days (+14 days) prior to screening (from the date of ICF signature).

Other Inclusion Criteria

12. Participant agrees not to participate in another interventional study while receiving study intervention in the present study.

5.2 Exclusion Criteria

Participants will be excluded from participation in the study if any of the following apply:

Medical Conditions

1. Participant has preexisting sensory or motor neuropathy Grade ≥ 2.
2. Participant has ≥ N2 disease or metastatic disease (M1) as identified by imaging
3. Participant has a history of uncontrolled diabetes mellitus within 3 months prior to screening. Uncontrolled diabetes (within 3 months before first dose) is defined as HbA1c ≥ 8% or HbA1c between 7% and < 8% with associated diabetes symptoms (polyuria or polydipsia) that are not otherwise explained. The lowest HbA1c during the screening period will be used to determine eligibility.
4. Participant has a second malignancy diagnosed within 3 years before first dose of study intervention, or any evidence of residual disease from a previously diagnosed malignancy. Participant with non-melanoma skin cancer, localized prostate cancer treated with curative intent with no evidence of progression, low-risk or very low-risk (per standard guidelines) localized prostate cancer under active surveillance/watchful waiting without intent to treat, or carcinoma in situ of any type (if complete resection was performed) are allowed.
5. Participant has had an allogeneic tissue/solid organ transplant.
6. Participant who has known active HBV (defined as HBsAg-positive and/or anti-HBV core antibody-positive) or known active HCV (defined as HCV RNA [qualitative] detected) infection.
    - Participant with HBsAg-positivity and/or anti-HBV core antibody-positivity but with a negative HBV DNA PCR assay is permitted with appropriate antiviral prophylaxis or routine monitoring according to local practice. Participant who has

been curatively treated for HCV infection is permitted if they have documented sustained virologic response of 12 weeks.
- Testing for HBV and HCV is required if mandated by country health authority.

7. Participant has known history of HIV infection (HIV 1 or 2). No HIV testing is required unless mandated by local health authority.
8. Participant has major surgery within 4 weeks prior to first dose of study intervention.
9. Participant has known active keratitis or corneal ulcerations. Participant with superficial punctate keratitis is allowed if the disorder is being adequately treated in the opinion of the investigator.
10. Participant has a history of (non-infectious) pneumonitis/ILD that required steroids or has current pneumonitis/ILD.
11. Participant has a history of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan.
12. Participant has an active infection requiring systemic therapy. Routine antimicrobial prophylaxis is permitted.
13. Participant has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study intervention. Inhaled or topical steroids are permitted in the absence of active autoimmune disease. Physiologic replacement doses of corticosteroids are permitted for participants with adrenal insufficiency.
14. Participant has active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs).
    a) Replacement therapy (e.g., thyroxine, insulin, physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
    b) Brief (< 7 days) use of systemic corticosteroids is allowed when use is considered SoC.
    c) Participant with vitiligo, psoriasis, type 1 diabetes mellitus, hypothyroidism, or resolved childhood asthma/atopy will not be excluded.
    d) Participant requiring intermittent use of bronchodilators, inhaled steroids, or local steroid injections will not be excluded.
    e) Participant with hypothyroidism that is stable with HRT or Sjögren's syndrome will not be excluded.

Prior/Concomitant Therapy

15. Participant 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 (e.g., CTLA-4, OX-40, CD137).
16. Participant has received prior systemic anti-cancer therapy for MIBC/NMIBC, or received prior systemic anti-cancer therapy including investigational agents (including enfortumab vedotin or other MMAE-based ADCs) within 3 years prior to screening.

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/PD-L1 treatment with pembrolizumab, etc.) received for NMIBC is not permitted.

17. Participant has received a live or live attenuated vaccine within 30 days of first dose of study intervention. Administration of killed vaccines are allowed.
18. Participant has received a partial cystectomy of the bladder to remove any NMIBC or MIBC.
19. Participant has received any prior radiotherapy to the bladder.

Prior/Concurrent Clinical Study Experience

20. Participant has received any investigational therapy within 28 days or 5 half-lives, whichever is longer, prior to screening.

Other Exclusion Criteria

21. Participant has known hypersensitivity to enfortumab vedotin or to any excipient contained in the drug formulation of enfortumab vedotin (including histidine, trehalose dihydrate and polysorbate 20) OR participant has known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells.
22. Participant has severe hypersensitivity (≥ Grade 3) to pembrolizumab and/or any of its excipients.
23. Participant has any condition, which, in the investigator's opinion, makes the participant unsuitable for study participation.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

There are no meal or 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

A screen failure is defined as a potential participant who signed the ICF, but did not meet 1 or more criteria required for participation in the study and was not enrolled.

For screen failures, the demographic data, date of signing the ICF, inclusion and exclusion criteria, AEs up to the time of screen failure and reason for screen failure will be collected in the eCRF.