An Open-label, Single-Arm, Phase 2 Study to Evaluate Enfortumab Vedotin plus Pembrolizumab for Bladder Preservation in Participants with Muscle-invasive Bladder Cancer
(EV-209)

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

ISN/Protocol 7465-CL-0209

Version 2.0

Amendment 1 [Nonsubstantial]

26 Nov 2025

IND 116360

IND Grantor: CDER

EU CT Number 2025-524488-18

Sponsor:

Astellas Pharma Global Development Inc.

Northbrook, IL 60062, US

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 $\geq$ 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 $\geq 8\%$ 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.